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Partial reinforcement, extinction, and placebo analgesia

Siu Tsin Au Yeung [a], Ben Colagiuri [a,b,*], Peter F. Lovibond [b], Luana Colloca [c]

[a] School of Psychology, University of Sydney, Sydney, Australia
[b] School of Psychology, University of New South Wales, Sydney, Australia
[c] National Institute of Mental Health and National Center for Complementary and Alternative Medicine (NCCAM), National Institutes of Health, Bethesda, MD, USA

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ABSTRACT

Numerous studies indicate that placebo analgesia can be established via conditioning procedures. However, these studies have exclusively involved conditioning under continuous reinforcement. Thus, it is currently unknown whether placebo analgesia can be established under partial reinforcement and how durable any such effect would be. We tested this possibility using electrocutaneous pain in healthy volunteers. Sixty undergraduates received placebo treatment (activation of a sham electrode) under the guise of an analgesic trial. The participants were randomly allocated to different conditioning schedules, namely continuous reinforcement (CRF), partial reinforcement (PRF), or control (no conditioning). Conditioning was achieved by surreptitiously reducing pain intensity during training when the placebo was activated compared with when it was inactive. For the CRF group, the placebo was always followed by a surreptitious reduction in pain during training. For the PRF group, the placebo was followed by a reduction in pain stimulation on 62.5% of trials only. In the test phase, pain stimulation was equivalent across placebo and no placebo trials. Both CRF and PRF produced placebo analgesia, with the magnitude of initial analgesia being larger after CRF. However, although the placebo analgesia established under CRF extinguished during test phase, the placebo analgesia established under PRF did not. These findings indicate that PRF can induce placebo analgesia and that these effects are more resistant to extinction than those established via CRF. PRF may therefore reflect a novel way of enhancing clinical outcomes via the placebo effect.

1. Introduction

A wealth of research indicates that placebo effects can ameliorate both experimental [5,7,12,13,15,16,22,34,36,38,41–44] and clinical pain [26,32,40]. Recent neuroimaging studies demonstrate that placebo analgesia is accompanied by modulation of brain activity in regions known to process pain [8,44]. Furthermore, some of the neurobiological mechanisms underlying placebo analgesia are beginning to be understood, particularly the importance of endogenous opioids in placebo analgesia established via instruction [5,6,32]. Despite these advances, significant gaps remain in our knowledge of the optimal conditions for producing and maintaining placebo analgesia.

Most modern accounts view the placebo effect as a learning phenomenon in which verbal instruction and prior experience combine to produce a placebo effect [14,28,29]. Although numerous studies have confirmed that conditioning either alone or in combination with verbal suggestion can produce placebo effects [4,5,12,15,16,24,30,34,36,41–43], these studies have almost exclusively used conditioning schedules in which presentation of the placebo is always followed by analgesia during acquisition, referred to as continuous reinforcement [10,19]. Thus, it is currently unknown whether placebo effects can be established with variable conditioning schedules in which the placebo is only followed by analgesia on some occasions, referred to as partial reinforcement [10,19]. This is particularly interesting because in practice, patients are likely to experience fluctuations in both the severity of their symptoms and the efficacy of their treatments.

In addition, few studies have investigated how long placebo effects last once established [12,15,34], which may well differ depending on how the effect is established. A number of animal studies indicate a partial reinforcement extinction effect, whereby partial reinforcement leads to more durable responding than continuous reinforcement [23,25,27,35]. Thus, partial reinforcement may be one way to increase the longevity of placebo analgesia. Understanding the durability of placebo analgesia and placebo

* Corresponding author at: School of Psychology, A18, University of Sydney, NSW 2006, Australia. Tel.: +61 2 9351 4589; fax: +61 2 9351 5223.
E-mail address: ben.colagiuri@sydney.edu.au (B. Colagiuri).

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effects more generally is essential for determining the extent to which placebo effects could be used to enhance outcomes in clinical practice.

This study addressed these gaps by comparing the magnitude and durability of placebo analgesia after continuous and partial reinforcement schedules using experimentally induced pain. In terms of magnitude, we hypothesized that both continuous and partial reinforcement would induce placebo analgesia, but that this effect would be stronger after continuous reinforcement. This is because partial reinforcement provides some experience of the placebo not working, which weakens the association between placebo and analgesia. In terms of extinction, consistent with the animal literature [23,25,27,35], we hypothesized that if partial reinforcement did induce placebo analgesia, then it would be more resistant to extinction than the placebo analgesia established under continuous reinforcement. This is because the lack of reinforcement during training may make it harder for the partial reinforcement group to detect a shift from training to testing compared with the continuous reinforcement group. To our knowledge, this is the first attempt to establish a placebo analgesic effect using partial reinforcement in humans.

2. Methods

2.1. Participants

Sixty-six (39 female; mean age = 19.8, SD = 3.82) healthy undergraduate psychology students from the University of Sydney participated to gain course credit. The study was advertised on an online system within the School of Psychology where the students could choose from a number of different studies. To be included in this study, participants had to be at least 18 years old, fluent in English, and not have any current or previous heart problems. The study had approval from the University of Sydney's Human Research Ethics Committee.

2.2. Design

The key variable in this study was the between-subjects manipulation of conditioning schedule as shown in Table 1. Participants were recruited under the guise of a trial investigating the analgesic properties of transcutaneous electrical nerve stimulation (TENS). They were then randomized to 1 of 3 groups: continuous reinforcement (CRF), partial reinforcement (PRF), or no conditioning (control). The 2 conditioning groups were told that they would receive a series of painful stimuli with (placebo) and without (no placebo) activation of the TENS machine. No TENS was actually delivered at any stage. Instead, a placebo device was used that involved an electrode being placed on the participant's forearm, with "activation" signaled by tactile and auditory cues. Conditioning was achieved by surreptitiously reducing the intensity of the painful stimuli on placebo relative to no placebo trials. The conditioning phase consisted of 32 trials in total: 16 with activation of the placebo device and 16 without activation of the placebo device presented in quasirandom order for each participant. In the CRF group, pain stimuli were reduced on all trials on which the placebo was activated in the conditioning phase. In the partial reinforcement group, pain stimuli were reduced on only 62.5% of the trials on which the placebo was activated in the conditioning phase. The test phase occurred immediately after the conditioning phase, with no break or signal that a new phase had begun. In this phase, the conditioning groups underwent a further 16 placebo and 16 no placebo trials with pain stimuli at full intensity on all trials, providing the test of placebo analgesia and whether or not it extinguishes after reinforcement has been withdrawn.

The control group was told that they had been allocated to receive no treatment and would experience a series of pain stimuli without any TENS stimulation. To control for any possible analgesic effect of the activation of the device, participants were exposed to the device activated, but did not receive the placebo instructions and were merely told that the researchers were piloting a new way of assessing skin conductance. The control group received a total of 64 control stimulations: 32 with the device activated and 32 with the device inactive. Blocks with full and reduced pain stimuli were used such that the control group experienced high and low pain similarly to the CRF and PRF groups, except that this was not contingent upon whether or not the device was activated. The dependent variable was pain report after each painful stimulus.

2.3. Materials

2.3.1. Verbal instructions

All participants were given an information sheet on arrival that described TENS only briefly as involving passing an electrical current through the skin, with no suggestion of how this might affect their pain. The 2 conditioning groups receive more substantial information on TENS as follows. Before the placebo device being attached, they received a 1-page handout including sections "What is TENS used for?", "How does TENS work?", and "What's so good about TENS?". The handout suggested that TENS was effective for reducing pain by "sending stimulation to block or reduce pain signals going to the brain" and was accompanied by references to journal articles on TENS for pain. The conditioning groups were also given oral instructions that supported this as the placebo device was being attached to their arm. These instructions were:

> This is the TENS electrode *[researcher shows participant the placebo device]*. TENS stands for transcutaneous electrical nerve stimulation. TENS can reduce pain by inhibiting the pain signals that travel up your arm and into your brain. The TENS itself is not painful, but you will feel a small sensation when it's turned on. I'll give you an example of what it feels like now.

Table 1
Summary of study design.

Group	Instruction	Conditioning	Extinction
CRF (n = 20)	Told receiving TENS to reduce pain	16 Placebo → 60% 16 No placebo → 100%	16 Placebo → 100% 16 No placebo → 100%
PRF (n = 20)	Told receiving TENS to reduce pain	10 Placebo → 60% 6 Placebo → 100% 16 No placebo → 100%	16 Placebo → 100% 16 No placebo → 100%
Control (n = 20)	Told no treatment controls	16 Active + 16 inactive → 60% 16 Active + 16 inactive → 100%	

In the CRF and PRF groups, the participants were led to believe that the placebo device was a TENS machine that would reduce their pain. In the control group, the participants were told that the same device was a method of measuring skin conductance, with no mention of any potential effects on pain. The device was active on half the trials and inactive on the other half. The active trials in the CRF and PRF groups constituted the placebo trials.
CRF, continuous reinforcement; PRF, partial reinforcement; TENS, transcutaneous electrical nerve stimulation.

The control group were given no additional information about TENS other than the brief mention in the initial information sheet. They did not receive the TENS handout. They only received oral instructions suggesting that a device measuring skin conductance was being attached to their arm. The instructions were:

> You have been allocated to the control group, which means that you will not receive TENS. But, your skin conductance will still be measured. This is the electrode that measures skin conductance *[researcher shows participant the device]*. Skin conductance is a measure of autonomic arousal. You will feel a slight sensation when the skin conductance is being recorded, but it won't be painful. Because the skin conductance electrode can interfere with other equipment, we will only turn it on half the time. I'll give you an example of what it feels like now.

2.3.2. Placebo device

No TENS was actually delivered to the participant. TENS was simply used as a cover story for the placebo effect. The placebo device was a stimulus isolator (model FE180, ADInstruments, Sydney, NSW) that generated tactile stimulation via direct currents. Two electrodes, 4 cm apart from each other, were attached to the dorsal forearm of the nondominant hand. Activation of the device involved the delivery of 16 consecutive square pulses with pulse width of 0.2 ms and series of coinciding tones. Intensity of the stimulation was calibrated for each participant to a level he or she found just perceptible. This was done by giving all participants an example of the activation of the placebo device before testing and in the absence of any pain stimuli. The initial stimulation was originally set at 1 mA and was increased by 1 mA until it became noticeable to the participant, creating a very gentle vibration on the participants' skin at the site of the electrode.

2.3.3. Pain stimuli

Pain was induced via electrocutaneous stimulation similar to that used in other studies on placebo analgesia [12,15]. Each stimulus consisted of an electrical shock delivered to the back of the participant's nondominant hand via 2 silver chloride electrodes, each approximately 1 cm apart. Stimuli were generated by a pain stimulator (model SHK1, Contact Precision Instruments, Cambridge, MA). The stimuli were square pulses with duration of 0.5 seconds and a frequency of 100 Hz.

The intensity of the pain stimuli was calibrated for each participant individually before testing. This was done by initially delivering stimuli at a very low and usually imperceptible level and then increasing the intensity of the stimuli in steps until participants reached a level that they felt was "definitely painful, but tolerable". To ensure this was at least somewhat painful and to avoid potential floor effects, when this level was reached, the participant was asked to verbally report their pain on a scale of 1 to 10. If their reported pain was less than 6 of 10, then they were asked whether they felt comfortable trying a higher intensity, such that participants' pain ratings at the end of calibration were at least 6 of 10 on a verbally reported scale. The level of intensity reached at the end of calibration was labelled as the 100% intensity for that particular participant. Intensity of each stimulus during the experiment was determined on the individual's 100% intensity level, their experimental condition, and particular trial.

2.3.4. Pain ratings

Participants were asked to rate their pain after each painful stimulus on a 100-point computerized visual analogue scale (VAS). Three anchors were used, with 0 (no pain) and 100 (very painful) on the left and right extremes, respectively, and 50 (moderately painful) in the middle.

2.3.5. Trial structure and conditioning manipulation

Each trial consisted of a single pain stimulus followed by a pain rating. Within a given trial, each pain stimulus was signaled by a 10-second countdown culminating in an X appearing on the computer screen, 0.5 seconds after which the stimulation was delivered. After each stimulus, participants rated the intensity of the pain on the computerized VAS. Between trials, participants had a rest of 10 to 15 seconds. On placebo trials, the placebo device was activated for 8 seconds during the countdown. On no placebo trials, the placebo device remained inactive.

The conditioning phase included 16 placebo and 16 no placebo trials. The CRF group received a surreptitious reduction in painful stimulation on all 16 placebo trials. This was achieved by lowering the pain intensity to 60% on placebo trials, a similar-sized reduction to those previously used on conditioned placebo analgesia studies [20]. The PRF group received the same surreptitious reduction in painful stimulation, but only on 62.5% of placebo trials; that is, pain intensity was lowered in 10 of the 16 placebo trials, as shown in Table 1. The placebo trials were intermixed with no placebo trials in quasirandomized order within participants, such that there were no more than 2 placebo or no placebo trials in a row. This trial order was used to ensure that the different trials were distributed across the test session both within and across participants. The test/extinction phase consisted of 32 trials (16 placebo and 16 no placebo) in which the intensity of painful stimuli was set at 100% on both placebo and no placebo trials.

For the control group, the conditioning and extinction phases were identical. Participants in this group received half of their trials at 100% pain intensity and the other half at 60% pain intensity, but this was unrelated to whether or not the device was activated. Although control groups in most previous studies received the same 100% shock throughout the experiment (eg, [12,34]), we included the variation in pain intensity to ensure the control group had experience with the 2 levels of painful stimulation and using different levels of pain ratings. This meant the control group experienced 16 active and 16 inactive trials with 100% painful stimulation and 16 active and 16 inactive trials with 60% painful stimuli. These trials were presented in 8 blocks of 8 trials (4 with the device active and 4 with the device inactive) with 4 blocks being at 100% intensity and 4 at 60% intensity. The blocked design was intended to prevent potential superstitious conditioning, even though the 2 events were noncontingent.

2.3.6. Exit questionnaire

An exit questionnaire was used to test whether participants guessed the true nature of the study, as well as their knowledge of the placebo-shock reduction contingency across groups. The first question asked, "What do you think the study was about?" with an open response. The second and third questions assessed contingency knowledge for the first and second half of the experiment, respectively. The questions read, "In the first [or second] half of the experiment, did you notice any reduction in pain when TENS was turned on compared with when it was not turned on?". Participants had to make a forced-choice response, either yes or no, and then rate how consistent they thought this relationship was on a 10-point scale ranging from 1 (not at all) to 10 (very consistent). The same questions were asked of the control group, except they concerned the relationship between pain reduction and the supposed skin conductance measurements.

2.4. Procedure

Participants attended a single 1-hour session and were tested individually in an isolated cubicle. Upon arrival, they were given an information sheet that described the study as a test of the acute effect of TENS on psychophysiological responses to pain. The 2

conditioning groups were then told that they had been allocated to receive TENS and were given the handout on TENS. The control group were told that they had been allocated to receive no treatment and simply rested for 2 minutes. The placebo device was then introduced and attached to the participant, during which each group was given the relevant oral instructions.

The experimenter then explained the trial structure to the participant, left the room, and then initiated the computerized program that controlled the delivery of the pain stimuli, activation of the "TENS" device, and pain ratings. The conditioning phase was initiated and was followed immediately by the test/extinction phase without any notification to the participant. At the end of the test/extinction phase, participants completed the exit questionnaire assessing their beliefs about the study. A debrief statement was sent to all participants via e-mail at the completion of the study.

2.5. Data handling and analysis

Participants (n = 6) were excluded if their average pain rating on no placebo (CRF and PRF) or device inactive trials (control group) at 100% pain intensity was <20 of 100. Analysis of variance and χ^2 tests of independence tested for baseline differences in age and sex. We checked the normality of the pain ratings across each of the 64 trials within each group. Deviations from normality were rare (only 15 of 192 tests, ie, 8%) and consistent with the type I error rate of .05 (5%) in these tests, suggesting acceptable levels of normality.

For the main analysis, conditioning and test phases were analyzed separately. In each phase, the groups were compared by calculating difference scores between pain with and without the "TENS" device activated that were analyzed via mixed analyses of covariance with group and trial as factors, controlling for age and sex. For the test phase, we followed up with within-groups analysis of placebo analgesia using repeated-measures analysis of covariance with treatment and trial as factors, again controlling for age and sex. The critical test of the magnitude of the placebo effect established under each conditioning schedule was the difference in pain ratings on the first placebo trial and no placebo trial in the test/extinction phase, ie, trial 17. We expected that the strongest placebo analgesic effect would occur immediately after the conditioning phase. This is because the first test trial occurs before any extinction has taken place. To explore changes over time and compare rates of extinction across the groups, we tested linear trends whenever trial was included as a factor. To isolate the effects of the different conditioning schedules, we conducted planned pairwise comparisons between each group. All analyses were conducted in IBM SPSS Statistics 20.0, covariates were mean centered to reduce multicollinearity, Greenhouse-Geisser corrections were made whenever the sphericity assumption was not met (unadjusted degrees of freedom are reported), and results were considered statistically significant when $P < .05$.

3. Results

There were no differences in age or sex across the 3 groups, $F_{2,57} = .26$, $P = .775$ and χ^2 (df = 2, N = 60) = 1.67, $P = .435$, respectively.

3.1. Training phase

Pain ratings during training are shown in Fig. 1 (trials 1 to 16). The training phase was separated into trials on which the PRF group were reinforced in the presence of the placebo vs the nonreinforced placebo trials. For the reinforced trials, the 2-way analysis with group and trial as factors revealed a significant main effect of group ($F_{2,55} = 72.7$, $P < .001$). Pairwise comparisons revealed that the differences in pain ratings on placebo vs no placebo trials were significantly greater in both the CRF group and the PRF group relative to the equivalent control trials ($F_{1,55} = 114.5$, $P < .001$ and $F_{1,55} = 101.5$, $P < .001$, respectively), confirming that the conditioning manipulation effectively reduced pain on the relevant trials. Importantly, there was no difference in magnitude of the pain reduction on reinforced trials between the CRF and PRF groups ($F < 1$). There was also a significant main effect of trial ($F_{9,495} = 11.6$, $P < .001$). A significant linear trend indicated that the differences in pain ratings on placebo vs no placebo trials increased over the training phase, averaged across groups ($F_{1,55} = 31.8$, $P < .001$). Interaction contrasts comparing linear trends between groups revealed significant interactions in linear trends for CRF vs control and for PRF vs control ($F_{1,55} = 11.9$, $P = .001$ and $F_{1,55} = 20.2$, $P < .001$, respectively). These results indicated that the magnitude of pain relief caused by the surreptitious reduction increased across trials. There was, importantly, no difference in linear trends between the CRF and PRF groups ($F_{1,55} = 1.12$, $P = .294$). For the trials in which subjects in the PRF group were not reinforced, there was also a main effect of group ($F_{2,55} = 111.1$, $P < .001$) with pairwise comparisons between groups revealing that the difference in pain ratings was significantly larger for the CRF group compared with both the PRF group and the control group ($F_{1,55} = 198.9$, $P < .001$ and $F_{1,55} = 126.2$, $P < .001$, respectively), which was unsurprising because the pain intensity of the former group was at 60%, whereas the latter group was at 100%. The reduction in pain on placebo trials in the PRF group was larger than equivalent trials in the control group even when these trials were all at 100% intensity ($F_{1,55} = 7.10$, $P = .01$), confirming evidence of a placebo effect during training. Neither the main effect nor the overall linear trend for trial reached statistical significance ($F_{5,275} = 2.18$, $P = .07$ and $F_{1,55} = 1.60$, $P = .21$, respectively). The trial-by-group interaction also was not significant ($F_{2,55} = 2.05$, $P = .13$), nor were any of the pairwise group-by–linear trend interactions, although the linear trends for CRF vs control bordered significance ($F_{1,55} = 4.00$, $P = .05$). Thus, the training data confirmed that the surreptitious reduction effectively reduced pain, and importantly, that the magnitude of this reduction was equivalent for the CRF and PRF groups.

3.2. Test phase

3.2.1. Intergroup comparisons

In order to compare pain ratings across groups, we calculated difference scores between pain in trials when the "TENS" device was active compared with when it was inactive. This adjusts for the variability in shock intensities experienced over the course of the test phase among the experimental groups. These differences are shown in Fig. 2.

On the initial test trial, there was a significant main effect of group ($F_{2,55} = 4.00$, $P = .05$). Pairwise comparisons revealed a placebo effect in the CRF group, with the pain reduction induced by the placebo treatment 15.8 points greater than control ($F_{1,55} = 20.5$, $P < .001$). There also was a placebo effect in the PRF group, with the pain reduction induced by the placebo treatment being 8.6 points greater than control ($F_{1,55} = 5.96$, $P = .02$). Further, these comparisons revealed that the placebo analgesia induced by CRF was 7.2 points larger than that induced by PRF ($F_{1,55} = 4.16$, $P = .046$).

The 2-way group-by-trial analysis over the entire test phase revealed a significant main effect of group ($F_{2,55} = 6.42$, $P = .003$). Pairwise comparisons confirmed the placebo analgesia observed on the first test trial for CRF vs control and PRF vs control were evident when averaged across all test trials ($F_{1,55} = 10.5$, $P = .002$ and $F_{1,55} = 8.50$, $P = .005$, respectively). However, in this case, there

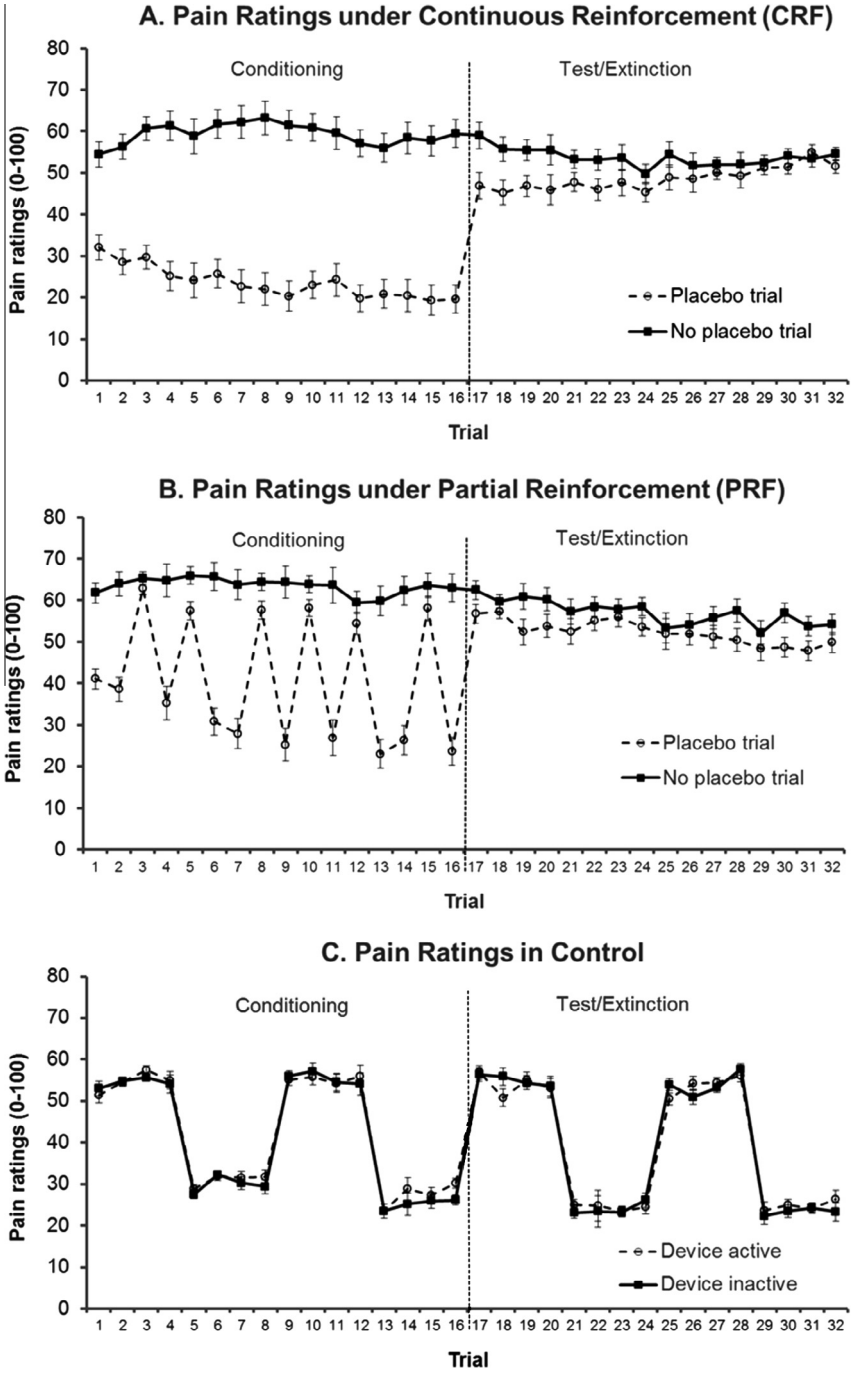

Fig. 1. Covariate (age, sex) adjusted mean (±SE of mean difference) pain ratings with the device active vs inactive for (A) the continuous reinforcement group (CRF), which showed a significant placebo effect that extinguished over the course of the test phase. (B) Partial reinforcement group (PRF), which also showed a significant placebo effect, although weaker than that of the continuous reinforcement group, which did not appear to extinguish. (C) Control group, which received no conditioning and no placebo instruction, showed no difference between active and inactive trials.

was no difference in the magnitude of the placebo analgesia between CRF and PRF when averaged over all test trials ($F < 1$). There was not a significant main effect of trial overall ($F_{15,825} = 1.40$, $P = .18$), but there was a significant linear trend indicating that the difference in pain ratings between placebo and no placebo trials decreased across the test phase ($F_{1,55} = 13.6$, $P = .001$). There was also a significant trial-by-group interaction ($F_{30,825} = 1.61$, $P = .05$). The pairwise comparisons revealed significant interactions of linear trends between the CRF group and the control group and between the CRF group and the PRF group ($F_{1,55} = 17.4$, $P < .001$ and $F_{1,55} = 20.8$, $P < .001$, respectively), indicating that the placebo analgesia in the CRF group decreased relative to both control and PRF, indicating extinction. There was, however, no significant interaction of linear trends between the PRF group and control ($F < 1$), suggesting that the placebo analgesia induced via PRF did not extinguish. Confirmation of these effects can be seen by analyzing differences between placebo and no placebo trials within the CRF and PRF groups, as discussed later.

3.2.2. CRF group

In the CRF group, there was clear evidence of placebo analgesia on the initial test trial, with pain rated as 12.3 (SD = 14.2) lower in

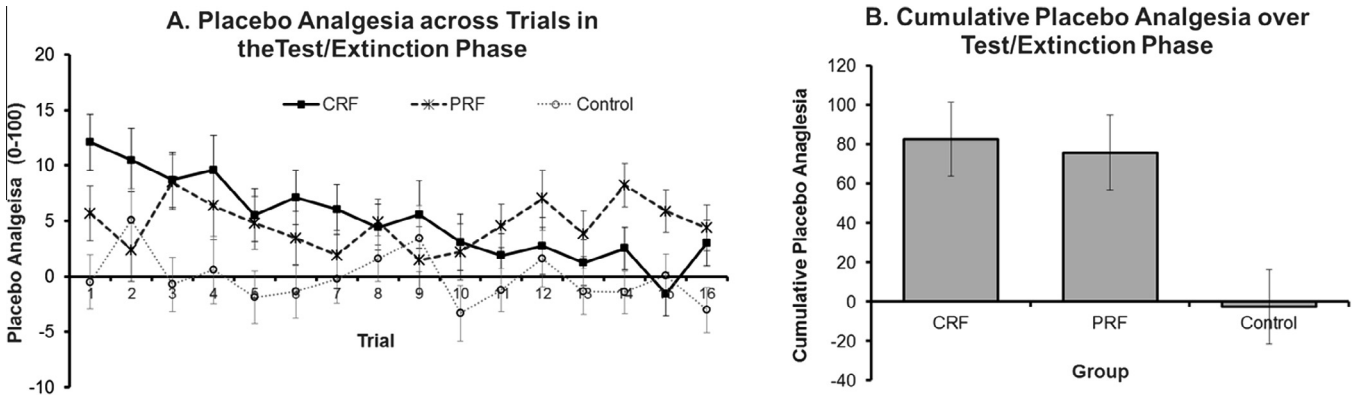

Fig. 2. Covariate (age, sex) adjusted mean difference (±SE) in pain ratings with the device active and inactive during the test/extinction phase across groups for each individual trial (A) and cumulatively over the entire test/extinction phase (B). Higher scores indicate less pain with the device active. The continuous reinforcement group (CRF) showed a significant placebo effect of the first test trial that extinguished over the course of the test phase. The partial reinforcement group (PRF) also showed a significant placebo effect on the first test trial, although significantly weaker than that of the CRF, but this did not seem to extinguish over the test phase.

the presence of the placebo compared with no placebo, despite shock level being at 100% on both trials ($F_{1,17}$ = 13.8, P = .002), as can be seen in Fig. 1A. The 2-way analysis of trial-by-treatment over the entire test phase revealed a significant main effect of treatment, with pain on placebo trials being lower than that on no placebo trials ($F_{1,17}$ = 11.4, P = .004). There was no main effect of trial, nor a significant linear trend in trials when averaged across treatments (both F < 1). However, there was a significant overall trial-by-treatment interaction ($F_{15,255}$ = 2.73, P = .02), which was accompanied by a significant interaction in linear trends, indicating that difference in pain ratings between placebo and no placebo trials gradually decreased over the test phase with extinction of the placebo analgesia ($F_{1,17}$ = 17.1, P = .001).

3.2.3. PRF group

As with the CRF group, there was evidence of placebo analgesia on the initial test trial in the PRF group, with pain rated as 5.5 (SD = 10.1) lower in the presence of the placebo compared with no placebo, despite shock level being at 100% on both trials ($F_{1,17}$ = 4.68, P = .045), as shown in Fig. 1B. The 2-way analysis of trial-by-treatment over the entire test phase revealed a significant main effect of treatment, with pain rated as lower on placebo trials compared with no placebo trials ($F_{1,17}$ = 10.9, P = .004). There was a main effect of trial ($F_{15,255}$ = 3.53, P = .003), with a significant linear trend suggesting a decrease in pain across the test phase when averaged across treatment ($F_{1,17}$ = 13.3, P = .002). Importantly, however, there was no overall interaction between trial and treatment, nor a significant interaction in linear trends (both F < 1), suggesting that the placebo analgesia in the PRF group was maintained over the test phase.

3.2.4. Control group

There was no difference between the training and test phases for this group. Therefore, the control group data were analyzed over the entire study session, but separately for 60% and 100% shock intensity. At 60% intensity, there was a trend toward a significant main effect of treatment, suggesting that pain ratings in fact tended to be higher on device-active trials compared with trials in which the device was inactive ($F_{1,17}$ = 3.91, P = .065), as shown in Fig. 1C. The main effect of trial was marginally nonsignificant ($F_{15,255}$ = 2.76, P = .053), as was the linear trend ($F_{1,17}$ = 3.79, P = .068), suggesting a tendency for pain ratings to decrease across trials when averaged over treatment. There was no interaction between trial and treatment (both F < 1). At 100% intensity, there was no main effect of treatment or trial (both F < 1), nor any significant interactions between the 2 (highest $F_{15,255}$ = 1.30, P = .27). This indicated that there was no difference in pain between active and inactive trials and no change in the magnitude of pain across trials in the control group at 100% pain intensity. Overall, this indicated that activation of the device used as a placebo in the CRF and PRF groups had no inherent analgesic effects.

3.3. Exit questionnaire

Participants seemed to find the cover story credible. Sixty percent of participants reported that the aim of the study was to test the effect of TENS on pain, specifically. The remaining participants generally gave very brief responses that were consistent with the cover story, usually that the aim was to test pain tolerance, without mentioning TENS specifically (26.7%). Only 1 participant mentioned anything vaguely related to the placebo effect, which was that the study aimed to test the effect of a "pre-hint" on pain. There were no differences in beliefs about the cover story between the CRF and PRF groups.

4. Discussion

The current study tested the effect of different reinforcement schedules on the magnitude and durability of placebo analgesia. Four novel and important findings emerged. The first is that placebo analgesia can be established under partial reinforcement. The second is that the placebo analgesia established under partial reinforcement was weaker than that established under continuous reinforcement. The third is that the placebo analgesia established under continuous reinforcement extinguished. The fourth, and perhaps most interesting, is that the placebo analgesia established under partial reinforcement seemed resistant to extinction. These findings have a number of important practical and theoretical implications.

The initial pain relief we observed in the test phase after continuous reinforcement, ie, when placebo treatment was always followed by a surreptitious reduction in pain during conditioning, is consistent with numerous previous studies using conditioning to produce placebo analgesia [5,12,15,16,30,34,36,41–43]. However, we extended this previous research by demonstrating that placebo analgesia can also be induced after partial reinforcement, ie, when placebo treatment was usually but not always followed by a surreptitious reduction in pain during training, which has not been tested previously. It is important to emphasize, however, that the magnitude of the initial placebo analgesia established under partial reinforcement was weaker than the placebo analgesia established

under continuous reinforcement. This is consistent with animal conditioning studies demonstrating weaker conditioned responding after partial reinforcement compared with continuous reinforcement [1,2,21]. Thus, although partial reinforcement can induce placebo analgesia, it seems that continuous reinforcement will produce stronger initial placebo analgesia.

Perhaps most interestingly, the durability of the placebo analgesia differed depending on the reinforcement schedule under which it was established. Although the placebo effect established under continuous reinforcement extinguished relative to both the control group and the PRF group over the test phase, the placebo effect established under partial reinforcement was maintained relative to both the control group and the CRF group. Therefore, this study provides the first evidence of a partial reinforcement extinction effect for placebo analgesia. That is, placebo analgesia established under partial reinforcement seems more durable than placebo analgesia established under continuous reinforcement. Although no previous studies have compared continuous vs partial reinforcement training schedules for placebo effects in humans, the current finding is consistent with animal studies demonstrating greater resistance to extinction after partial reinforcement [35].

There are a number of possibilities to explain such an effect. The most parsimonious is probably a Bayesian account in which the shift from training to extinction is harder to detect in the partial reinforcement group compared with the continuous reinforcement group because in the former, the probability of reinforcement during training is more similar to the test phase [17]. Other accounts make similar predictions based on learning phenomena such as generalization decrement [35]. Generalization decrement refers to when conditioned responding becomes weaker as the eliciting cue or context becomes more dissimilar from the originally trained cue or context. According to this account of the partial reinforcement extinction effect, the nonreinforced trials during training under partial reinforcement serve as contextual cues themselves, which are encoded as part of the context. This means that in test phase, when no trials are reinforced, the context is more similar to training for those who received partial reinforcement compared with those who received continuous reinforcement, because the latter have never previously experienced nonreinforced trials. This results in less generalization decrement and hence slower extinction after partial reinforcement [35].

The extinction we observed in the continuous reinforcement group differs from that reported in other studies that have tested the durability of placebo analgesia and found no evidence of extinction [12,34]. One potential reason for evidence of extinction in the current study compared with the lack of evidence in Colloca and Benedetti's [12] study, which also used continuous reinforcement to establish placebo analgesia, is the difference in the length of the test phases across these studies. In the current study, we tested extinction over 16 test trials, whereas Colloca and Benedetti [12] tested it over 6 trials, the latter of which may not have been sufficient to detect extinction. The pattern of results in Fig. 2A supports this possibility, with the placebo inducing analgesia relative to the control on the 6th test trial (ie, trial 22) that had clearly diminished by the 16th test trial (ie, trial 32). Thus, longer test phases may be required to demonstrate extinction. Montgomery and Kirsch [34] found no evidence of extinction in a group of participants given suggestion of placebo analgesia without conditioning. Their experimental design also differed in terms of the type of placebo (inert cream) and number of test trials (10). Moreover, it is plausible that placebo effects established via suggestion alone extinguish differently from those established via suggestion with conditioning, the latter of which was the focus here, which could explain the apparent differences in results. Furthermore, the current result is consistent with the broader learning literature, in which there is a large body of evidence that demonstrates a gradual reduction in conditioned responding after reinforcement is withdrawn, ie, extinction [9,33]

At this point, it is also worth noting that some investigators have used data from double-blind placebo-controlled clinical trials in which placebo-treated patients reported ongoing improvement as evidence against extinction of placebo effects, including for rheumatoid arthritis [39] and pain due to irritable bowel syndrome [11]. There is also evidence of prolonged (50 days) placebo analgesia in a case study of a chronic pain patient [31]. However, such findings are limited in that double-blind placebo-controlled trials do not include natural history groups, meaning that any improvement observed in the placebo group could be attributable to other factors, such as regression to the mean or spontaneous recovery, and case studies of single patients may not generalize to other patients. In addition, the durability of a placebo effect may vary depending on the specific condition being treated and the psychological processes underlying the effect.

The differences in the magnitude and durability of placebo effects established under different reinforcement schedules have some important clinical implications. The current results suggest that continuous reinforcement is the most effective training schedule to induce a large one-off placebo effect. However, partial reinforcement seems the most effective in terms of inducing a more durable placebo effect. One interesting application of this finding is for drug dose reductions/discontinuation. It may be possible to use partial reinforcement schedules when delivering active drugs in which the active treatment is occasionally replaced by a placebo [3,18,37]. Although these findings need to be replicated in clinical pain with active treatments, pharmacological partial reinforcement schedules could lead to a reduction in the total amount of active painkillers required to maintain the same treatment effect while reducing tolerance and side effects. Furthermore, in the case of drugs that lead to discontinuation effects, such a schedule could produce more durable placebo effects that attenuate withdrawal effects during dose reduction.

There were some potential limitations to the current study worth noting. First, although placebo effect established under partial reinforcement seemed to be maintained over the course of the test phase, suggesting nonextinction, it could be the case that with further test trials, this effect would extinguish. Nonetheless, it is clear from the results that over the course of the 16 test trials, the rate of extinction was much more rapid after continuous reinforcement compared with partial reinforcement, whether or not the latter would have eventually extinguished with more test trials. Second, there was an asymmetry between the continuous and partial reinforcement groups in terms of the total number of reinforced trials they each experienced during training. This was an intentional decision in order to match the total length of training across the 2 groups. However, it would be interesting for future studies to compare different reinforcement schedules on placebo effects matched on the number of reinforced trials compared with matching for training length. Third, extinction was tested within a single test phase consisting of 16 placebo and inactive trials each, ie, trials 17 to 32. As such, it would be worth testing the extent to which the current findings generalize to a clinical setting in which both training and testing occur over a number of days, rather than in a single session. Finally, we did not assess participants' expectancies over the course of the study. Assessing participant expectancies in future studies would provide interesting data on how different reinforcement schedules affect expectancies and the extent to which these mediate the differences in placebo analgesia observed across the schedules. Indeed, one potentially important difference between conditioning processes in humans compared with those in animals insofar as they relate to placebo analgesia, is how consciously accessible and verbalizable expectancies might affect conditioning procedures in humans.

In conclusion, the current study provides novel evidence that placebo analgesia can be established under partial reinforcement and that such effects, although weaker initially, are more durable than placebo analgesia established under continuous reinforcement. These findings support recent suggestions that partial reinforcement could be an interesting method of reducing total drug dosages while maintaining therapeutic benefit.

Conflict of interest statement

The authors declare no conflict of interest.

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References

[1] Ader R. Conditioned immunopharmacological effects in animals: implications for a conditioning model of pharmacotherapy. In: White L, Tursky B, Schwartz GE, editors. Placebo: theory, research, and mechanisms. New York: Guilford Press; 1985. p. 306–23.
[2] Ader R, Cohen N. Behaviorally conditioned immunosuppression. Psychosom Med 1975;37:333–40.
[3] Ader R, Mercurio MG, Walton J, James D, Davis M, Ojha V, Kimball AB, Fiorentino D. Conditioned pharmacotherapeutic effects: a preliminary study. Psychosom Med 2010;72:192–7.
[4] Albring A, Wendt L, Benson S, Witzke O, Kribben A, Engler H, Schedlowski M. Placebo effects on the immune response in humans: the role of learning and expectation. PLoS One 2012;7:e49477.
[5] Amanzio M, Benedetti F. Neuropharmacological dissection of placebo analgesia: expectation-activated opioid systems vs conditioning-activated specific subsystems. J Neurosci 1999;19:484–94.
[6] Benedetti F. The opposite effects of the opiate antagonist naloxone and the cholecystokinin antagonist proglumide on placebo analgesia. PAIN® 1996; 64:535–43.
[7] Benedetti F, Mayberg HS, Wager TD, Stohler CS, Zubieta J-K. Neurobiological mechanisms of the placebo effect. J Neurosci 2005;25:10390–402.
[8] Bingel U, Wanigasekera V, Wiech K, Ni Mhuircheartaigh R, Lee MC, Ploner M, Tracey I. The effect of treatment expectation on drug efficacy: imaging the analgesic benefit of the opioid remifentanil. Sci Transl Med 2011;3:70ra14.
[9] Bouton ME. Context, ambiguity, and unlearning: sources of relapse after behavioral extinction. Biol Psychiatry 2002;52:976–86.
[10] Bouton ME. Learning and behavior: a contemporary synthesis. Sunderland, MA: Sinauer Associates; 2007.
[11] Chey WD, Chey WY, Heath AT, Dukes GE, Carter EG, Northcutt A, Ameen VZ. Long-term safety and efficacy of alosetron in women with severe diarrhea-predominant irritable bowel syndrome. Am J Gastroenterol 2004;99: 2195–203.
[12] Colloca L, Benedetti F. How prior experience shapes placebo analgesia. PAIN® 2006;124:126–33.
[13] Colloca L, Benedetti F. Nocebo hyperalgesia: how anxiety is turned into pain. Curr Opin Anaesthesiol 2007;20:435–9.
[14] Colloca L, Miller FG. Harnessing the placebo effect: the need for translational research. Philos Trans R Soc Lond B Biol Sci 2011;366:1922–30.
[15] Colloca L, Petrovic P, Wager TD, Ingvar M, Benedetti F. How the number of learning trials affects placebo and nocebo responses. PAIN® 2010;151:430–9.
[16] Colloca L, Sigaudo M, Benedetti F. The role of learning in nocebo and placebo effects. PAIN® 2008;136:211–8.
[17] Courville AC, Daw ND, Touretzky DS. Bayesian theories of conditioning in a changing world. Trends Cogn Sci 2006;10:294–300.
[18] Doering BK, Rief W. Utilizing placebo mechanisms for dose reduction in pharmacotherapy. Trends Pharmacol Sci 2012;33:165–72.
[19] Domjan M. The principles of learning and behavior: active learning edition. Belmont, CA: Thomson Wadsworth; 2006.
[20] Eippert F, Bingel U, Schoell ED, Yacubian J, Klinger R, Lorenz J, Büchel C. Activation of the opioidergic descending pain control system underlies placebo analgesia. Neuron 2009;63:533–43.
[21] Fitzgerald RD. Effects of partial reinforcement with acid on the classically conditioned salivary response in dogs. J Comp Physiol Psychol 1963;56: 1056–60.
[22] Geers AL, Wellman JA, Fowler SL, Helfer SG, France CR. Dispositional optimism predicts placebo analgesia. PAIN® 2010;11:1165–71.
[23] Haselgrove M, Aydin A, Pearce JM. A partial reinforcement extinction effect despite equal rates of reinforcement during Pavlovian conditioning. J Exp Psychol Anim Behav Process 2004;30:240–50.
[24] Herrnstein R. Placebo effect in the rat. Science 1962;138:677–8.
[25] Jenkins WO, Stanley JC. Partial reinforcement: a review and critique. Psychol Bull 1950;47:193–234.
[26] Kaptchuk TJ, Stason WB, Davis RB, Legedza ART, Schnyer RN, Kerr CE, Stone DA, Nam BH, Kirsch I, Goldman RH. Sham device v inert pill: randomised controlled trial of two placebo treatments. Br Med J 2006;332:391–7.
[27] Kimble GA. Hilgard and Marquis' conditioning and learning. New York: Appleton-Century-Crofts; 1961.
[28] Kirsch I. Response expectancy as a determinant of experience and behaviour. Am Psychol 1985;40:1189–202.
[29] Kirsch I. How expectancies shape experience. Washington: American Psychological Association; 1999.
[30] Klinger R, Soost S, Flor H, Worm M. Classical conditioning and expectancy in placebo hypoalgesia: a randomized controlled study in patients with atopic dermatitis and persons with healthy skin. PAIN® 2007;128:31–9.
[31] Kupers R, Maeyaert J, Boly M, Faymonville M, Laureys S. Naloxone-insensitive epidural placebo analgesia in a chronic pain patient. Anesthesiology 2007; 106:1239–42.
[32] Levine JD, Gordon NC, Fields HL. The mechanism of placebo analgesia. Lancet 1978;2:654–7.
[33] Lovibond PF. Cognitive processes in extinction. Learn Mem 2004;11: 495–500.
[34] Montgomery GH, Kirsch I. Classical conditioning and the placebo effect. PAIN® 1997;72:107–13.
[35] Pearce JM, Redhead ES, Aydin A. Partial reinforcement in appetitive Pavlovian conditioning with rats. Q J Exp Psychol B 1997;50:273–94.
[36] Price DD, Milling LS, Kirsch I, Duff A, Montgomery GH, Nicholls SS. An analysis of factors that contribute to the magnitude of placebo analgesia in an experimental paradigm. PAIN® 1999;83:147–56.
[37] Sandler AD, Glesne CE, Bodfish JW. Conditioned placebo dose reduction: a new treatment in attention-deficit hyperactivity disorder? J Dev Behav Pediatr 2010;31:369–75.
[38] Tang CW, Colagiuri B. Can an educational handout enhance placebo analgesia for experimentally-induced pain? PLoS One 2013;8:e77544.
[39] Traut EF, Passarelli EW. Placebo in the treatment of rheumatoid arthritis and other rheumatic conditions. Ann Rheum Dis 1957;16:18–22.
[40] Vase L, Robinson ME, Verne G, Price DD. Increased placebo analgesia over time in irritable bowel syndrome (IBS) patients is associated with desire and expectation but not endogenous opioid mechanisms. PAIN® 2005;115: 338–47.
[41] Voudouris NJ, Peck CL, Coleman G. Conditioned placebo responses. J Pers Soc Psychol 1985;48:47–53.
[42] Voudouris NJ, Peck CL, Coleman G. Conditioned response models of placebo phenomena: further support. PAIN® 1989;38:109–16.
[43] Voudouris NJ, Peck CL, Coleman G. The role of conditioning and verbal expectancy in the placebo response. PAIN® 1990;43:121–8.
[44] Wager TD, Matre D, Casey KL. Placebo effects in laser-evoked pain potentials. Brain Behav Immun 2006;20:219–30.