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Partial reinforcement, extinction, and placebo analgesia

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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

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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.