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Placebo analgesia induced by social observational learning

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ABSTRACT

Although it has long been known that psychosocial factors play a crucial role in placebo responses, no attempt has been made to understand if social observation shapes the placebo analgesic effect. To address this question, we compared placebo analgesia induced through social observation (Group 1) with first-hand experience via a typical conditioning procedure (Group 2) and verbal suggestion alone (Group 3). In Group 1, subjects underwent painful stimuli and placebo treatment after they had observed a demonstrator (actually a simulator) showing analgesic effect when the painful stimuli were paired to a green light. In Group 2, subjects were conditioned according to previous studies, whereby a green light was associated to the surreptitious reduction of stimulus intensity, so as to make them believe that the treatment worked. In Group 3, subjects received painful stimuli and were verbally instructed to expect a benefit from a green light. Pain perception was assessed by means of a Numerical Rating Scale (NRS) ranging from 0 = no pain to 10 = maximum imaginable pain. Empathy trait and heart rate were also measured. We found that observing the beneficial effects in the demonstrator induced substantial placebo analgesic responses, which were positively correlated with empathy scores. Moreover, observational social learning produced placebo responses that were similar to those induced by directly experiencing the benefit through the conditioning procedure, whereas verbal suggestions alone produced significantly smaller effects. These findings show that placebo analgesia is finely tuned by social observation and suggest that different forms of learning take part in the placebo phenomenon.

1. Introduction

Placebo effects are known to be mediated by a variety of mechanisms, such as expectation, reward, and conditioning [11,13,28,39,40]. However, a common factor that appears to be present across different conditions is represented by learning, as previous experience has been found to powerfully modulate the magnitude of placebo responses. For example, early clinical observations [1,7,27,31,32] as well as more recent experimental findings [2,9,14–16,29,33,37,38,41–43] indicate that prior experience can either lead to conditioned responses or reinforce expectations. Placebo effects might also occur without a history of actual first-hand experience, because other signaling systems such as language and/or observation may convey information that are necessary to build up learned responses. On the basis of these considerations, it is worth investigating the potential of other forms of learning in the modulation of placebo responses. So far, only conditioning and reinforced expectations have been tested, whereas no attempt has been made to understand whether social observation influences placebo analgesia. Social learning refers to instances of learning where the behavior of a demonstrator, or its by-products, modifies the subsequent behavior of an observer [21], and a substantial body of work highlights its critical function in a wide range of models, both human, and non-human for reviews see [24,25,34]. In addition, Bootzin and Caspi [12] postulated the possible involvement of social learning in placebo responsiveness.

In the present study, we investigated the role of observational social learning in placebo analgesia in a human experimental setting, whereby subjects learn by observing the analgesic experience of others. In order to compare these observation-induced effects with other kinds of learning, we replicated our earlier findings (e.g. [14]) demonstrating that learning, via a typical conditioning procedure, can elicit placebo responses that are substantially larger than those induced by verbal suggestions alone.

2. Materials and methods

2.1. Subjects

A total of 48 healthy female volunteers (mean age 22.6 ± 4.7 years) were recruited from the University of Turin Medical School, Turin, Italy, to participate in a research on pain mechanisms. They were randomly assigned to one of three experimental groups: social learning, through the observation of another subject (Group 1), conditioning (Group 2), and verbal suggestions alone

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Table 1
Characteristics of subjects for each experimental group.

Group	Experimental procedure	*n*	Sex	Age	IRI				
					PT	FS	EC	PD	Total IRI
1	Social observation	16	F	21.7 ± 3.4	20.8 ± 2.6	22.4 ± 2.4	24.1 ± 3	15.9 ± 3.3	83.3 ± 5.7
2	Conditioning	16	F	22.8 ± 3.1	22.7 ± 4.7	21.5 ± 3.7	23.7 ± 2.5	14.2 ± 3.1	82.1 ± 6.4
3	Verbal suggestion	16	F	23.5 ± 6.9	21.8 ± 4	22.7 ± 2.4	23.6 ± 3.8	15.1 ± 3.3	83.2 ± 6.8

IRI, Interpersonal Reactivity Index; PT, Perspective Taking; FS, Fantasy Score; EC, Empathic Concern; PD, Personal Distress.

(Group 3) Table 1. None of them had any kind of disease or were taking any type of medication. All the experimental procedures were conducted in conformance with the policies and principles contained in the Declaration of Helsinki. Subjects gave their written informed consent to receive repeated phasic painful and non-painful stimuli for a study on a procedure of pain inhibition. Those who were enrolled in Group 1 were informed that the experimental details would be shown by one of the experimenters. Conversely, subjects who were assigned to Groups 2 and 3 were deceptively informed that a red light would anticipate painful electrical stimuli, whereas a green light would anticipate a stimulus that would be made less painful through a sub-threshold stimulation of a different body part. All the subjects were debriefed at the end of the study.

2.2. Tactile and painful stimuli

The stimulus was an electric shock delivered to the back of the non-dominant hand through two silver chloride electrodes (size = 1 × 2.5 cm) connected to a constant current unit, thus avoiding the variability of skin-electrode impedance, according to the procedure previously used by Colloca and Benedetti [14], by and Colloca et al. [15]. Stimuli were square pulses delivered by a somatosensory stimulator (Galileo Mizar NT, EBNeuro, Florence, Italy), with a duration of 100 μs. The stimuli were delivered at the end of either a red or a green light, repetitively (18 red + 18 green) and randomly administered.

2.3. Design and procedures

We first assessed tactile (t) and pain threshold (T) according to the following procedure: an ascending series of stimuli (steps of 1 mA) were delivered starting at sub-tactile threshold, until tactile sensation and pain sensation were induced. After determination of T, each subject was randomly assigned to one of the three experimental groups. Depending on the experimental group, the stimulus paired to the green light had either the same intensity as the stimulus following the red light (Groups 1 and 3) or a surreptitiously reduced intensity with respect to the stimulus intensity following the red light (Group 2, conditioning phase).

The placebo was administered according to the following procedure: a placebo electrode was applied to the middle finger of the non-dominant hand, but it was not connected to any pulse generator, and no electric shock was ever delivered. However, the subjects believed that the stimulation of the middle finger through this electrode, which was anticipated by the green light on the computer screen, was analgesic, thus they expected a green light-associated non-painful stimulus. By contrast, the red light indicated that the electrode was not activated, thus they expected a red light-associated painful stimulus. Each trial lasted about 20 s. Either the red or the green light was presented for 5 s and ended with the electric shock. The inter-stimulus interval (ISI) was about 15 s. Before each session started, the green- and red- stimuli were delivered once in order to make the subjects familiarize with the experimental protocol.

2.3.1. Group 1

To evaluate the effects of observational social learning, the subjects were asked to sit beside a demonstrator (actually a simulator) who underwent the whole experimental session (Fig. 1). The demonstrator was the same for all the experimental subjects: he was a 26-year-old male Ph.D. student visiting our laboratory from the University of Sydney, Australia, carefully trained to simulate the experimental session. To do this, two silver chloride electrodes were applied to the back of the non-dominant hand, and a sham electrode was pasted above his middle finger. The demonstrator received a total of 36 stimuli (18 red + 18 green) delivered according to a pseudorandom sequence. He always rated as painful the stimuli paired to red light and as non-painful the stimuli paired to green light. In this way, he simulated an analgesic benefit following the presentation of the green light. The experimental subjects had to pay attention to the lights displayed on a monitor, with particular regard to their meaning. To be sure that attention was kept constant throughout the experimental session, the subjects were asked to furnish some details about the experiment (total number of red and green lights as well as evaluation of

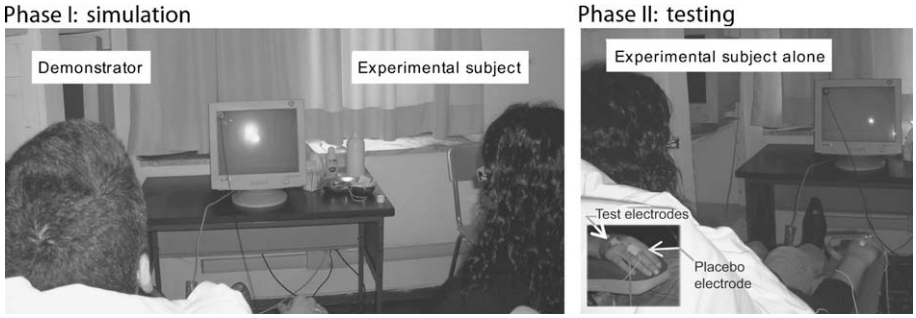

Fig. 1. Experimental setting of the social observational learning. An experimental subject sits beside a demonstrator who rates as painful red-associated stimuli and as non-painful green-associated stimuli (Phase I). Then a phase of testing is run, whereby the experimental subject receives a series of red- and green-associated stimuli in the same way as the demonstrator, but the intensity of all the stimuli is set at twice the pain threshold (Phase II). The insert (bottom right) shows some details of the placebo electrode on the middle finger and the test electrodes on the dorsum of the same hand. The subjects believe that the stimulation of the middle finger induces analgesia on the dorsum of the hand.