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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

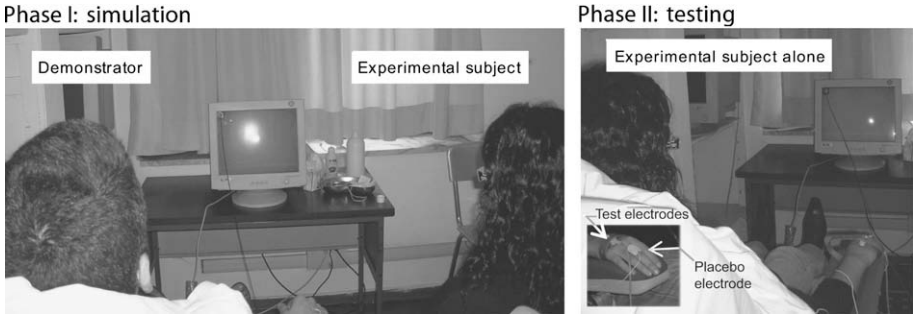

Fig. 1. Experimental setting of the social observational learning. An experimental subject sits beside a demonstrator who rates as painful red-associated stimuli and as non-painful green-associated stimuli (Phase I). Then a phase of testing is run, whereby the experimental subject receives a series of 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.

demonstrator's reports). This observational phase lasted about 12 minutes (Phase I of Fig. 1). At the end of this phase, the subjects were asked to undergo a similar experimental session (Phase II of Fig. 1). After t and T assessment, stimulus intensity was set at 2T for both the green- and the red-stimuli.

2.3.2. Group 2

In order to assess the effect of direct experience of benefit, the placebo responses were tested after a conditioning phase according to the procedure used in our previous studies [14,15]. Subjects were informed that the green- and red-lights indicated the activation and deactivation, respectively, of the electrode on their middle finger which, in turn, would induce an analgesic effect by delivering a sub-threshold electrical shock. However, this electrode never delivered electrical pulses (placebo electrode).

A total of 36 stimuli (18 red + 18 green) were delivered according to the same pseudorandom sequence of Group 1. In this case, subjects received a pseudorandom series of 12 red-stimuli at 2T and 12 green-stimuli at T-2 (T minus 2 mA), so that they had a first-hand experience of green light-associated non-painful stimulation. It is important to stress that the stimulus intensity was surreptitiously reduced, so that the subjects believed that the green light anticipated analgesic effects. This conditioning phase was followed by a testing period whereby the intensity of green light was increased up to 2T.

2.3.3. Group 3

As in Group 2, subjects were informed that green- and red-lights would indicate the activation and deactivation, respectively, of the electrode on their middle finger. In fact, the subjects were told that a green light would anticipate a stimulus that was made analgesic by delivering a sub-threshold electrical shock on their middle finger. Conversely, a red light would anticipate the deactivation of this electrode and thus a painful stimulation on the dorsum of the hand. Actually, all the stimuli were set at 2T. A total of 36 stimuli (18 red + 18 green) were delivered according to the same pseudorandom sequence of Groups 1 and 2.

2.4. Psychophysical scale and empathy questionnaire

In all the experimental groups, the subjects rated pain intensity at the end of each stimulus by means of Numerical Rating Scale (NRS) ranging from 0 = no pain to 10 = maximum imaginable pain. Subjects were also required to complete the Interpersonal Reactivity Index [IRI; 18] a commonly used trait empathy questionnaire which includes the following four subscales: Perspective Taking (PT), Fantasy Score (FS), Empathic Concern (EC) and Personal Distress (PD).

2.5. Cardiac data analysis

Heart rate (HR) was obtained by recording conventional electrocardiogram (ECG) from the arms. ECG signals were amplified, digitalized and stored. Cardiac data analysis was performed on beat-to-beat series which did not present ectopic beats or artifacts. After the extrapolation of R–R intervals (Spectrum Cartoon Galileo, EBNeuro, Firenze, Italy), heart rate (HR) was calculated by transforming them into frequency (1/R–R). We evaluated 10 R–R intervals immediately preceding and following each stimulus. Because the testing phase in Group 2 consisted of 6 red + 6 green-stimuli, we restricted the cardiac data analysis to the initial 6 red + 6 green testing series in all the experimental groups.

2.6. Statistical analysis

The normal distribution of data was tested with the Kolmogorov–Smirnov test. As in no case we found a significant difference between our data set and a normal distribution, statistical comparisons were performed by means of ANOVA for repeated measures. Sphericity condition was assessed and when it was not verified, the Greenhouse–Geisser correction was applied. In Groups 1 and 3, ANOVA included the following within-subjects factors: treatment (red- and green-stimuli) and time (trials). In Group 2, ANOVA was performed with the factors: treatment (red- and green-stimuli), run (1, 2, and 3) and time (trials). In this case, the *F*-tests were followed by the Bonferroni post hoc tests for multiple comparisons. In addition, a series of single-sample paired *t*-tests were performed on red against green ratings to determine whether each green-stimulus was rated as analgesic or not. In order to compare the effects of the different conditions, we expressed the placebo responses as the difference between green-associated and red-associated NRS scores and performed a supplementary ANOVA with Group as between factor. Linear regression analysis was done to correlate IRI scores with placebo responses. Linear regressions were also used to examine the relationship between the ratings by the demonstrator and the placebo responses in Group 1. Finally, HR changes were estimated by performing repeated measures ANOVA with treatment (red- and green-stimuli), phase (pre- and post-stimuli) and time (six trials), as within factors. All the analyses were carried out using SPSS software package (SSPS Inc., Chicago, Illinois, USA). The level of significance was set at $p < 0.05$.

3. Results

3.1. Psychophysical data

3.1.1. Group 1

Repeated measures ANOVA of the NRS scores revealed a main effect for treatment ($F_{(1,15)} = 87.677$, $p < 0.0001$) but not for time ($F_{(17,255)} = 1.222$, $p = 0.247$), indicating that the subjects who had observed the analgesic effect in the demonstrator rated the green-stimuli consistently less painful than the red-stimuli. An additional series of single-sample paired *t*-tests were performed to determine whether each green-associated stimulus was rated as analgesic or not. We found that all the 18 green-stimuli were deemed less painful compared to the red-associated stimuli, which indicates stable conditions of the responses over the entire experimental session, with neither habituation nor sensitization effects ($p < 0.01$ for all the 18 pairs; Fig. 2A). We also examined the relationship between demonstrator's and subjects' reports. The correlation between the differences in demonstrator's and participant's NRS scores (red–green values) did not show any significance ($r = 0.135$; $p = 0.617$), which suggests that the subjects rated their own perception rather than repeating what they heard from the demonstrator.

In order to test whether empathy itself modulated these socially learned placebo responses, we correlated the differences in NRS with IRI scores. We found a positive correlation for EC ($r = 0.555$, $p < 0.026$; see Fig. 3), but not for the other IRI subscales [PT ($r = 0.154$; $p = 0.569$), FS ($r = 0.172$; $p = 0.523$), PD ($r = -0.084$; $p = 0.756$) and total IRI ($r = 0.42$; $p = 0.106$)]. Thus social observational learning induced placebo responses that were independent of the demonstrator's NRS reports. Rather, they were linked to the individual empathy trait.

3.1.2. Group 2

After first-hand experience of analgesia by means of the conditioning procedure, the green-associated stimuli were rated significantly less painful compared with the red-associated stimuli. In this case, we performed a repeated measures ANOVA of the NRS scores, including both conditioning (runs 1 and 2) and testing (run 3) phases. We found a main effect for treatment ($F_{(1,15)} = 197.08$,

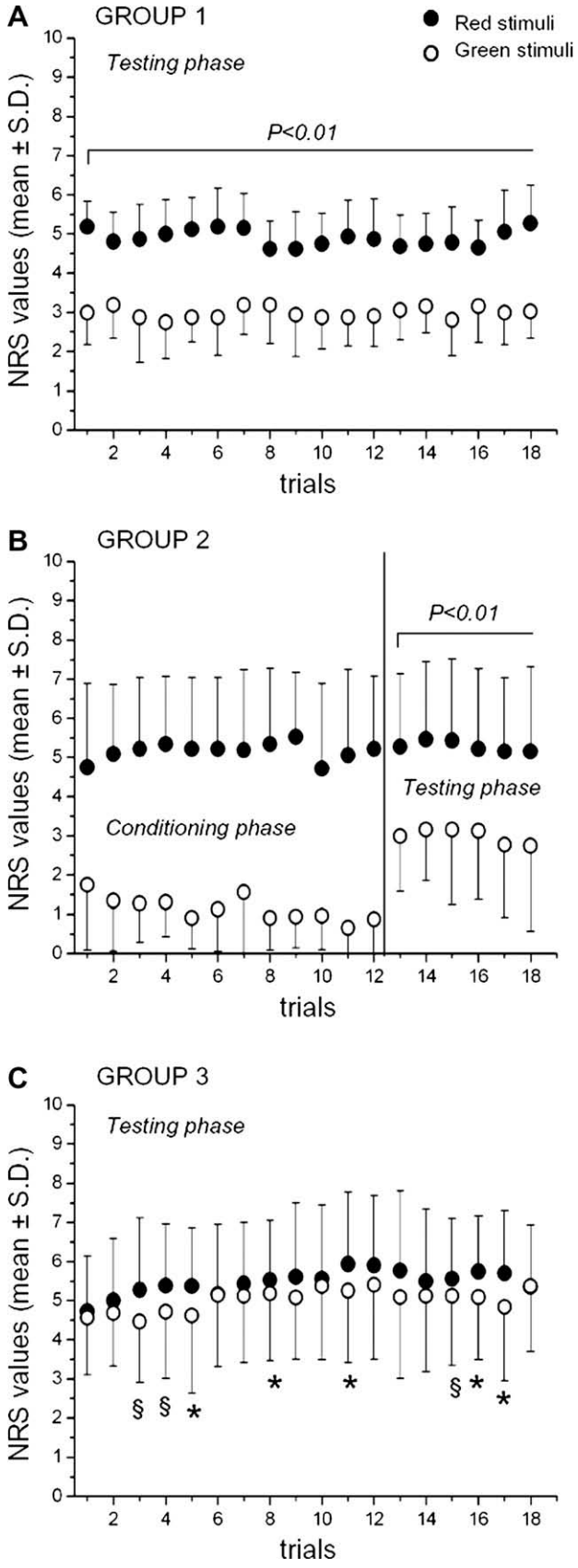

Fig. 2. The graphics show the placebo responses following prior observation (A), first-person experience of benefit (B, testing phase), and verbal suggestions of benefit (C). Stimuli that were paired to the green light were constantly rated as non-painful in Groups 1 and 2 (testing phase). Conversely, verbal suggestions alone produced smaller and more variable placebo responses ($^{\S}p < 0.01$; $^{*}p < 0.05$).

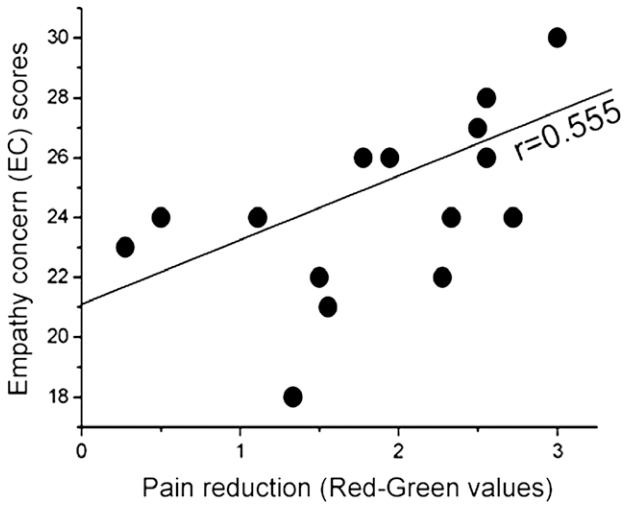

Fig. 3. Correlations between EC scores and NRS differences in Group 1. Note that the placebo analgesic responses were positively correlated with the subjects' empathy trait.

$p < 0.0001$) and run ($F_{(2,30)} = 10.598$, $p < 0.0001$) with a significant interaction between the two factors ($F_{(2,30)} = 30.813$, $p < 0.0001$), indicating variability across the three experimental runs, as expected. The post hoc Bonferroni test for multiple comparisons showed that the NRS reports of run 3 were different with respect to run 1 ($p < 0.036$) and run 2 ($p < 0.0001$); no difference was present between runs 1 and 2 ($p = 1.000$). A separate analysis in the testing run demonstrated that subjects rated noxious stimuli consistently less painful when they expected an analgesic effect following the green light (treatment: $F_{(1,15)} = 94.433$, $p < 0.0001$; time: $F_{(5,75)} = 0.972$, $p = 0.440$). The single-sample t-tests confirmed that each green-associated stimulus of the testing series was rated less painful with respect to the red-stimuli ($p < 0.01$ for all the six pairs; Fig. 2B).

Correlation analyses between the differences in NRS and IRI scores did not show any significance [EC ($r = -0.144$, $p = 0.608$), PT ($r = 0.08$; $p = 0.778$), FS ($r = 0.06$, $p = 0.828$), PD ($r = -0.01$; $p = 0.967$) and total IRI ($r = 0.04$; $p = 0.875$)].

3.1.3. Group 3

Repeated measures ANOVA of the NRS scores showed that subjects rated a green-associated painful stimulus less painful than a red-associated pain stimulus [main effect for treatment ($F_{(1,15)} = 16.977$, $p < 0.001$) and for time ($F_{(17,255)} = 1.883$, $p < 0.02$), with a non-significant interaction between the two factors ($F_{(17,255)} = 1.166$, $p = 0.293$)]. However, this effect was smaller and less consistent over time (Fig. 2C). Indeed, paired t-tests revealed that only some of the 18 green-associated stimuli were rated less painful than the red-associated stimuli (Fig. 2C). No correlation was present between NRS and IRI subscale scores [EC ($r = 0.03$, $p = 0.919$), PT ($r = -0.393$; $p = 0.132$), FS ($r = -0.04$; $p = 0.876$), PD ($r = 0.284$; $p = 0.286$) and total IRI ($r = -0.1$; $p = 0.714$)].

In order to compare the effects of the three placebo conditions, after expressing the pain reports as the difference between red- and green-stimuli, we calculated the ANOVA with Group as between factor. We found a significant difference between Groups 1, 2, and 3 ($F_{(2,45)} = 26.543$, $p < 0.0001$). The post hoc Bonferroni test for multiple comparisons showed that Group 1 was not different from Group 2 ($p = 1.000$), whereas both Groups 1 and 2 differed from Group 3 (Group 1 versus 3, $p < 0.0001$; Group 2 versus 3 $p < 0.0001$). As shown in Fig. 4A, the mean difference between red and green pain reports was 1.92 ± 0.82 in Group 1, 2.29 ± 0.94 in Group 2, and 0.46 ± 0.45 in Group 3, which

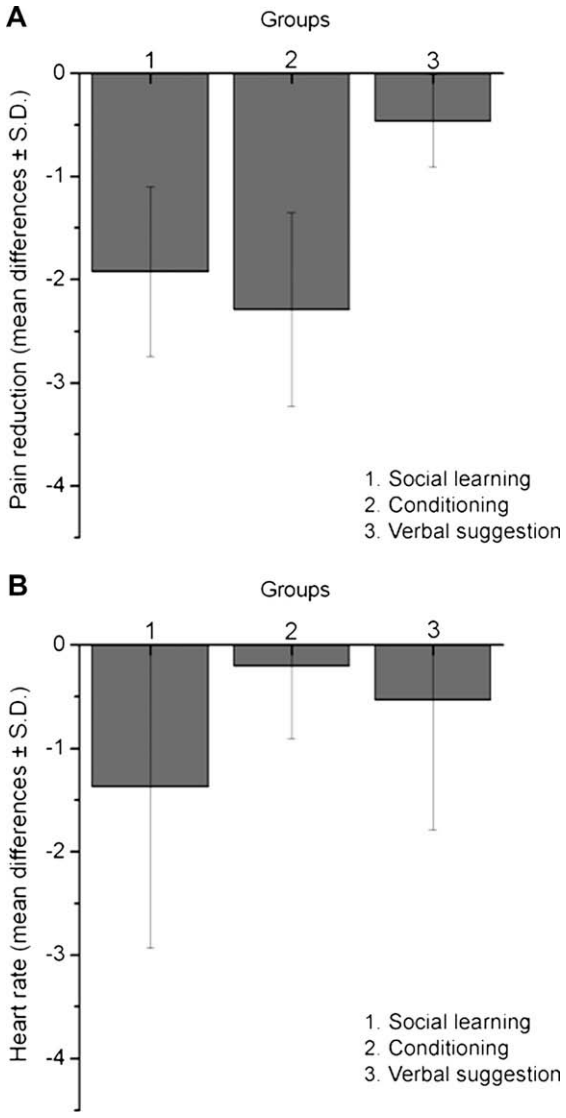

Fig. 4. (A) Pain reduction in each experimental group. The mean differences (red–green values) in Group 1 were not different from those found in Group 2. Both Group 1 and Group 2 showed a substantial difference in the magnitude of placebo responses with respect to Group 3 (Group 1 versus 3, $p < 0.01$; Group 2 versus 3, $p < 0.01$). (B) HR changes in each experimental group. The bars represent the HR mean difference (red–green values) during the anticipation of the red- and green-associated stimuli in the testing phase. The presentation of green-associated stimuli resulted in heart rate acceleration, whereas heart rate deceleration was found during presentation of red-associated stimuli in all the three experimental groups. However, only HR changes of Group 1 reached significance ($p < 0.026$).

corresponds to a percentage reduction of 39.18% in Group 1, 43.35% in Group 2, and 8.42% in Group 3.

3.2. Heart rate responses

3.2.1. Group 1

Repeated measures ANOVA showed a trend for HR to be differently affected by treatment [$F_{(1,12)} = 4.475$, $p = 0.056$] and experimental phase [$F_{(1,12)} = 8.251$, $p < 0.014$]. The interaction between the two factors was not significant [$F_{(1,12)} = 0.282$, $p = 0.605$]. Thus we performed a separate analysis of HR responses to red- and green-associated stimuli in the anticipatory and in the post-stimulus phases. We found a main effect of treatment only during the anticipatory phase [$F_{(1,12)} = 6.425$, $p < 0.026$]. Presentation of green-associated stimuli resulted in heart rate acceleration, whereas heart rate deceleration was found during presentation of red-associated stimuli. Fig. 4B shows the HR mean difference (red–green values) during the anticipation of the red- and green-associated stimuli. HR changes did not correlate with NRS differences (anticipation phase: $r = -0.06$, $p = 0.844$; post-stimulus phase: $r = -0.105$, $p = 0.720$).

3.2.2. Group 2

HR did not present differences related to either red- or green-associated stimuli [$F_{(1,13)} = 0.307$, $p = 0.589$]. It should be noted that this group underwent repetitive stimulation during the conditioning phases, thus habituation may have occurred. Conversely, a significant HR increase was observed in the post-stimulus phase with respect to the anticipatory phase [$F_{(1,13)} = 25.756$, $p < 0.0001$].

3.2.3. Group 3

As in Group 2, HR showed a difference between pre- and post-stimulus [$F_{(1,13)} = 55.887$, $p < 0.0001$], but not with respect to either red- or green-associated stimulus [$F_{(1,13)} = 0.287$, $p = 0.601$].

4. Discussion

This is the first study which investigates the effects of observational social learning on placebo analgesia in the experimental setting. Bootzin and Caspi [12] postulated the involvement of social learning in placebo responsiveness as one of the underlying mechanisms. Indeed we found substantial placebo responses following observation of another subject undergoing a beneficial treatment. These responses were positively correlated with EC scores of the empathy questionnaire, suggesting that emphatic concern may modulate socially learned placebo analgesic responses. Interestingly, observational social learning produced placebo responses that were similar in magnitude to those induced by directly experiencing the benefit through the conditioning procedure. In addition, these two conditions induced placebo responses that were significantly larger than those induced by verbal suggestions alone. These findings extend and confirm our previous works [14,15], demonstrating the key role of different forms of learning in the placebo phenomenon.

Today several lines of research indicate that the placebo analgesic response is a learned phenomenon. In a previous study [14], we showed that a conditioning manipulation can produce substantial placebo responses that lasted several days and that depended on prior experience. In fact, after exposure to an effective treatment, we observed that conditioned placebo responses were present after both a few minutes and four to seven days. Conversely, when the same conditioning procedure was repeated after a totally ineffective verbal suggestion procedure, the placebo responses were remarkably reduced compared to the first group, pointing out that prior experience, both effective and ineffective, may have long-lasting effects on the outcome of a subsequent treatment.

The importance of previous experience in placebo responsiveness is also confirmed by recent findings illustrating the effects of conditioning and verbal suggestions at the level of central early nociceptive processing. Compared to natural history, conditioning produced more robust reductions in the amplitudes of N2-P2 components of laser evoked potentials (LEPs) than verbal suggestions alone [16]. In the case of placebo analgesia conditioning elicits larger reductions in pain than verbal suggestions alone, whereas in nocebo hyperalgesia both negative verbal suggestions and conditioning induce significant nocebo responses [15], suggesting the presence of some distinctly different neural mechanisms in placebo and nocebo phenomenon [35], for a review see [19].

In the present study, we extend these findings on learning by demonstrating for the first time that robust placebo analgesic

responses can be evoked through social observation in the experimental setting. On the one hand, it has long been known that social and contextual cues and the whole atmosphere around the patient [5], such as words, attitudes, providers' behavior, drug's color and smell, medical devices, all contribute to evoke placebo responses [8]. On the other hand, an extensive literature investigating prosocial behaviors (e.g. ability to share the others' feelings, imitation, mimicry) suggests that social modeling is critical in developing learning processes across species [24,25,34], including social influences on psychophysical judgments of pain [17].

In our experimental condition, subjects constantly reported as less painful those stimuli that were paired to the analgesic procedure during the demonstrator's simulation (i.e., the green light), suggesting that the information drawn from observation of another person may establish a self-projection into the future outcome. These effects exhibited no extinction over the entire experimental session, indicating implicit acquisition and retention of behavioral output. It is also worth noting that the participants' NRS ratings did not correlate with those provided by the demonstrator, indicating that they evaluated their own perception rather than reporting merely what they heard during the simulation.

The larger HR changes for green-associated versus red-associated stimuli replicate earlier findings on heart rate responses to low- and high-painful stimuli [36].

At least in our experimental conditions, the magnitude of observation-induced placebo responses was similar to that found in Group 2, in which subjects underwent first-hand experience of the conditioning procedure. This suggests that observation of the demonstrator's benefit served as a US, underscoring some possible similarities between social learning and classical conditioning. Indeed, attempts to analyze social learning phenomena within an associative learning framework have been made in the field of fear. Some studies on observational aversive learning in rats fail to find blocking, latent inhibition, and overshadowing – three well-documented features of classical conditioning [22,44], whilst studies in humans reported classical conditioning features for social aversive learning, including overshadowing and blocking [30]. By contrast, other theories move beyond classical learning interpretation. Humans might alter their behavior without any practice and direct reinforcement, due to their ability to use symbols, thus setting them apart from the limited stimulus–response world of animals [6].

In our study, major gains in social learning occurred when the experimental subjects presented high EC scores of the empathy questionnaire. In fact, the analgesic placebo responses acquired through observation were highly correlated with EC scores, demonstrating a link between prosocial features and placebo effects. This is in line with several studies investigating inter-individual differences in trait measures of empathy in questionnaires such as IRI, as well as in pain modulation for reviews, see [23,26]. Usually, the higher the subjects scored on IRI, the higher the activation of part of the neural pain network was. Results of recent neuroimaging studies show that the neural system involved in the perception of pain in others partially overlap with some areas such as anterior cingulate, insular, and somatosensory cortices, which are activated by the first-hand perception of noxious stimuli [26]. Nevertheless, it is important to note that where these studies investigated the affective link between the empathizer and person in pain, our present work focused on instances of learning in which the behavior of a demonstrator modifies the subsequent behavior of an experimental subject. This type of cognitive processing likely requires the involvement of the medial prefrontal cortex which has a predominant role in making inferences and in social cognition [3].

Some limitations of our study need to be discussed. First, this work is based on phasic and acute experimental pain, whilst clinical pain is usually chronic and long-lasting. A second limitation is represented by the fact that we did not assess expectations and motivation, thus limiting our understanding about the weight of subject's expectations on potential outcomes. A third limitation is about the involvement of a male subject as a demonstrator and female subjects as experimental subjects, thus not allowing definitive conclusions about possible gender differences in empathy. In fact, there is some experimental evidence that gender (of both experimenter and experimental subject) is important in both placebo responsiveness and pain reports [4,18–20]. It is also worth discussing the relative magnitude of placebo responses induced by verbal suggestions alone. The duration of the experimental pain and the placebo instruction set may have been critical factors. For example, in previous studies we observed a substantial effect of suggestions on the submaximal effort tourniquet technique [2,10], but not on electrical shock [14,15]. Moreover, different types of placebos, such as an intra-muscular saline injection [10] versus the application of a sham electrode [14,15], can make a difference.

The main point that emerges from this work is that social learning, which humans share with many other species, is important in placebo analgesia. Thus many forms of learning appear to be involved in placebo responsiveness, making the placebo effect a highly complex phenomenon which is attributable to the intricate interplay of many factors. Further investigations of the neural mechanisms underlying socially-induced placebo responses are essential to integrate observational learning into the neurobiological placebo literature. From a clinical point of view, a better understanding of social learning in the placebo phenomenon may have important implications in the everyday clinical setting, whereby social interactions of patients with healthcare providers and other patients represent routine medical practice.

5. Conflicts of interest

We have no conflicts of interest.

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