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Seeing facial expressions enhances placebo analgesia

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ABSTRACT

The strength of the placebo effect is influenced by social contexts and individual personality. Although facial expressions provide important contextual cues, no study of their influence on the placebo response has been performed hitherto. Here we tested (1) whether the observation of facial expressions with different emotional content (Neutral, Pain, and Happy) affects the magnitude of placebo analgesia, and (2) whether interindividual differences in personality traits interact with any modulation of placebo response induced by facial expression. Twenty-seven healthy participants underwent classical placebo conditioning, and subsequently rated the intensity and unpleasantness of their pain experience associated with nociceptive-specific laser pulses delivered to the right hand dorsum. On each trial, different visual cues signalled the occurrence of a laser stimulus alone or of a laser stimulus accompanied by a sham analgesic treatment. In the conditioning period, cues signalling the sham treatment were followed by laser stimuli whose intensity was surreptitiously lowered. In the test period, either cue was followed by laser stimuli of the same intensity. The observation of facial expressions with different emotional content enhanced significantly the placebo analgesia. In particular, a significantly greater analgesic effect was observed when facial expressions with emotional content were presented concomitantly to the nociceptive stimulation. The enhancement of placebo analgesia during the observation of facial expressions was not correlated with personality traits like empathy and behavioural activation/inhibition. These findings quantify for the first time the effect of facial expressions on the magnitude of placebo analgesia.

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1. Introduction

One of the most studied placebo effects is placebo analgesia, where the administration of either a pharmacologically inert substance or a sham procedure has a pain-relieving effect [25,28,34]. Unconscious learning and conscious expectations are the most well-studied mechanisms of placebo analgesia. The process of pairing an unconditioned stimulus (e.g., a surreptitious reduction of the intensity of a noxious stimulus) with a conditioned stimulus (e.g., the presentation of a green cue) can lead to a conditioned response (e.g., analgesia), even when the conditioned stimulus is no longer paired with the unconditioned stimulus [2,9]. The analgesic effect of the unconditioned stimulus is also influenced by prior exposure to an effective analgesic treatment [19,26], number of learning trials [12], desire of pain relief [34], and anxiety [1]. Regardless of whether unconscious learning or conscious expectations better explain the placebo effect [12,27], there seems to be a general consensus on the notion that the placebo phenomenon is not caused by the administration of an inert or sham treatment *per se*, but rather by the social context suggesting to the patient that a beneficial treatment is being administered [15]. In fact, saline solutions or sugar pills may fail as placebos in patients if the relevant surrounding psychosocial context is absent [5,24]. It is known, for example, that the establishment of a placebo effect is susceptible to the effect of external observation and assessment (Hawthorne effects) [23], or the treatment procedure rituality [20], and of the patient–practitioner interaction and proxemics [21]. Yet, surprisingly little information about whether similar social factors affect the placebo effect in the controlled experimental setting is currently available. Indeed, to the best of our knowledge, the only study focusing on this issue explored whether social *learning* could significantly modulate placebo analgesia, and showed an increase of placebo analgesia during the observation of the beneficial effects of an analgesic procedure in another individual [11]. It

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is known that expectations are dramatically shaped by verbal and nonverbal interpersonal communication [35]. Facial expressions are highly salient signals that effectively modulate pain perception during social interactions [32,37,38]. Considering the importance of facial expressions of caregivers and doctors during health care, it is surprising that there is no experimental evidence on whether facial expressions affect placebo analgesia. In addition, the possible effects of facial expressions may be mediated by the onlooker's personality traits [7].

In this study, we used a classic paradigm of placebo conditioning to assess (1) whether the passive observation of facial expressions (Neutral, Pain, and Happy) affects the magnitude of placebo analgesia, and if so, (2) whether personality traits influence the modulatory effect of facial expressions.

2. Methods

2.1. Participants

Twenty-seven healthy participants (12 female) aged between 18 and 34 years (mean ± SD, 22.8 ± 5.0) participated in the study. All had normal or corrected-to-normal vision and were naïve as to the purpose of the experiment. None of the participants had a history of neurological or psychiatric conditions, or of conditions potentially interfering with pain sensitivity (e.g., drug intake or skin diseases). Participants gave written informed consent after reading an information sheet that partly overlapped with experimental instructions (see Appendix A). Participants were debriefed at the end of the experiment. All experimental procedures were approved by the ethics committee of University College London and were in accordance with the standards of the Declaration of Helsinki.

2.2. Personality measures

Dispositional empathy was measured by means of the Interpersonal Reactivity Index [14], a self-report questionnaire composed of 4 subscales that assess both the cognitive and the emotional components of empathy. The 2 cognitive components are: (1) *perspective taking* (PT), which measures the reported disposition to adopt another person's view (e.g., "I sometimes try to understand my friends better by imagining how things looks from their perspective"); and (2) *fantasy* (FS), which instead measures the propensity of an individual to become imaginatively involved with fictional characters and situations (e.g., "When I am reading an interesting story or novel I imagine how I would feel if the events in the story were happening to me"). The 2 affective components are (3) *empathic concern* (EC) and (4) *personal distress* (PD). The EC scale quantifies the tendency to experience feelings of sympathy and compassion for others engaged in negative experiences (e.g., "I often have tender, concerned feelings for people less fortunate than me"). The PD scale quantifies the extent to which an individual feels anxiety and discomfort as a result of witnessing another's negative experience (e.g., "When I see someone who badly needs help in an emergency, I go to pieces"). It is noteworthy that while the PT scale consistently relates to measures of interpersonal functioning, social competence, and high self-esteem, the EC scale is associated to measures of affective empathy [14].

Given that previous studies demonstrated a strong relationship between dopaminergic neurotransmission and measures of approach and avoidance behaviours such as novelty seeking, behavioural drive, and reward anticipation [30,31], participants were also asked to complete the Behavioral Inhibition Scale (BIS) and the Behavioral Activation Scale (BAS) [8], 2 questionnaires that assess personality measures related to behavioural inhibition/anxiety (BIS) and reward sensitivity (BAS). The BIS measures self-perceived proneness to anxiety in the presence of threat cues (e.g., "I feel pretty worried or upset when I think or know somebody is angry at me"). The BAS measures 3 distinct factors [8]: *Drive* (e.g., "When I want something I usually go all-out to get it"), which reflects energetic pursuit of rewards; *Reward responsiveness* (e.g., "When I get something I want, I feel excited and energized"), which reflects positive emotional reactivity to rewarding events; *Fun seeking* (e.g., "If I see a chance to get something I want I move on it right away"), which reflects sensitivity to potential new rewards.

2.3. Visual stimuli

Visual stimuli consisted of short video clips where Neutral, Pain, and Happy facial expressions were performed by professional actors. The video clips were taken from a standardized set developed and validated by Simon et al. [33]. Six different video clips, 3 with a woman and 3 with a man, were used.

2.4. Nociceptive stimulation

Nociceptive heat stimuli were pulses generated by an infrared neodymium yttrium aluminium perovskite (Nd:YAP) laser with a wavelength of 1.34 μm (El.En., Florence, Italy). The duration of laser pulses was 4 ms. These pulses activate selectively and directly the Aδ and C-fibre nociceptive terminals located in the superficial layers of the skin [4]. The laser beam was transmitted via an optic fibre, and its diameter was set at approximately 6 mm (~28 mm^2) by focusing lenses. Laser pulses were delivered on a squared area (5 × 5 cm) defined on the right hand dorsum before the beginning of the experimental session. To prevent increases in baseline skin temperature, and fatigue or sensitization of the nociceptors, the position of the laser beam was changed after each pulse. An infrared thermometer (KT22 radiation pyrometer; Heitronics, Wiesbaden, Germany) was used to collect temperature of the stimulated skin district, before the beginning of the experiment and after each laser pulse. Temperature fluctuations never exceeded 1°C.

Participants were informed about the study using the same set of sentences (see Appendix A), and instructed to use the numerical (0-100) scales to describe verbally the intensity (how strong) and the unpleasantness (how uncomfortable) of the painful percepts. Participants were allowed to give decimal ratings over the entire numerical scale.

To familiarize participants with the nociceptive stimulus, a small number of low-energy laser pulses were delivered to the right hand dorsum. The energy of the stimulus was then adjusted using a staircase procedure. The procedure required one increase series and one decrease series in steps of 0.5 Joules (J), followed by an increase series in steps of 0.25 J until a clear pricking/burning pain sensation was reported (50 on the 0-100 numerical rating scale). Lastly, random energies within 0.5 J below and above the energy eliciting the pricking/burning pain sensation were delivered to test the reliability of the intensity ratings. Importantly, the experimental design implied the use of 2 stimulation energies: a *conditioning* energy, eliciting a sensation ranging from no pain to low pain (median 12.7; range 1–30) and a *test* energy eliciting a sensation ranging from moderate to high pain (median 54.5; range 31–70).

2.5. Induction of placebo analgesia

The volunteers were verbally informed (using the script reported in Appendix A) that a red cue would have been followed

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by a laser stimulus delivered on their right hand dorsum in isolation. In contrast, a green cue would have been followed by the same laser stimulus associated to a sub-threshold electric current, delivered by 2 surface disc electrodes and applied on the volar aspect of the wrist, that would induce analgesia (i.e., the sham analgesic procedure). Identical or similar procedures have been used by previous studies [19,22]. In contrast with these previous works, to make the cover story convincing, we delivered, during the induction phase, a real non-nociceptive electrical stimulation, first using a clearly perceivable intensity (9 to 14 mA), and subsequently reducing the intensity until the participant was not able to perceive it. This preliminary procedure aimed to strengthen the expectation of pain relief associated to the sham treatment. During the experimental phase, no electrical stimulation was delivered.

2.6. Experimental procedure

The experimental procedure is summarized in Fig. 1. Participants were comfortably seated, with their right hand resting on a table, ~40 cm right of the body midline. A wooden frame blocked the sight of their right arm and of the stimulation devices. Participants were asked to relax and fixate the centre of the computer screen placed in front of them. The background of the computer screen was black throughout the experiment. The experiment consisted of 2 stimulation blocks, a conditioning block followed by a test block. Each block lasted between 15 and 20 minutes, and an interval of 10 minutes separated the 2 blocks. Each block consisted of 48 trials. Each trial consisted of either a red or a green visual cue, followed by a laser stimulus delivered during the presentation of a video clip representing neutral (Neutral), grimacing (Pain), or smiling (Happy) facial expressions. During the conditioning block, the laser energy following the green cue was lower ("low" energy: 2.2 ± 0.6 J) than the laser energy following the red cue ("high" energy: 3.3 ± 0.6 J). During the test block, the energy of the laser stimuli following either the green or the red cue was the same, that is, it was always "high." Each type of facial expression was presented an equal number of times during each block. In each block, 24 trials started with a red disk (Red trials) and the remaining 24 trials with a green disk (Green trials). The order of presentation of the different facial expressions was balanced, with the constraint that the same cue (green or red) was never coupled with the same facial expression in more than 4 consecutive trials. Participants were told that the electrical stimulation inducing the pain relief would have been delivered only in the Green trials during the presentation of the video clip, and that pain intensity and unpleasantness ratings would have been requested verbally after each trial (Fig. 1).

The timing of each trial was as follows. Each trial started with the cue (either red or green) displayed at the centre of the screen for 4 seconds. Immediately after the disappearance of the cue, the video clip (representing the Neutral, Pain, or Happy expression) was displayed for 4 seconds. Laser stimuli were jittered with a rectangular distribution in the time window between 1.8 and 2.9 seconds after the onset of the video clip, and always after the start of the facial expression in the Pain and Happy conditions. At the end of the video clip, a black background was displayed for a variable time interval ranging between 15 and 20 seconds. The average

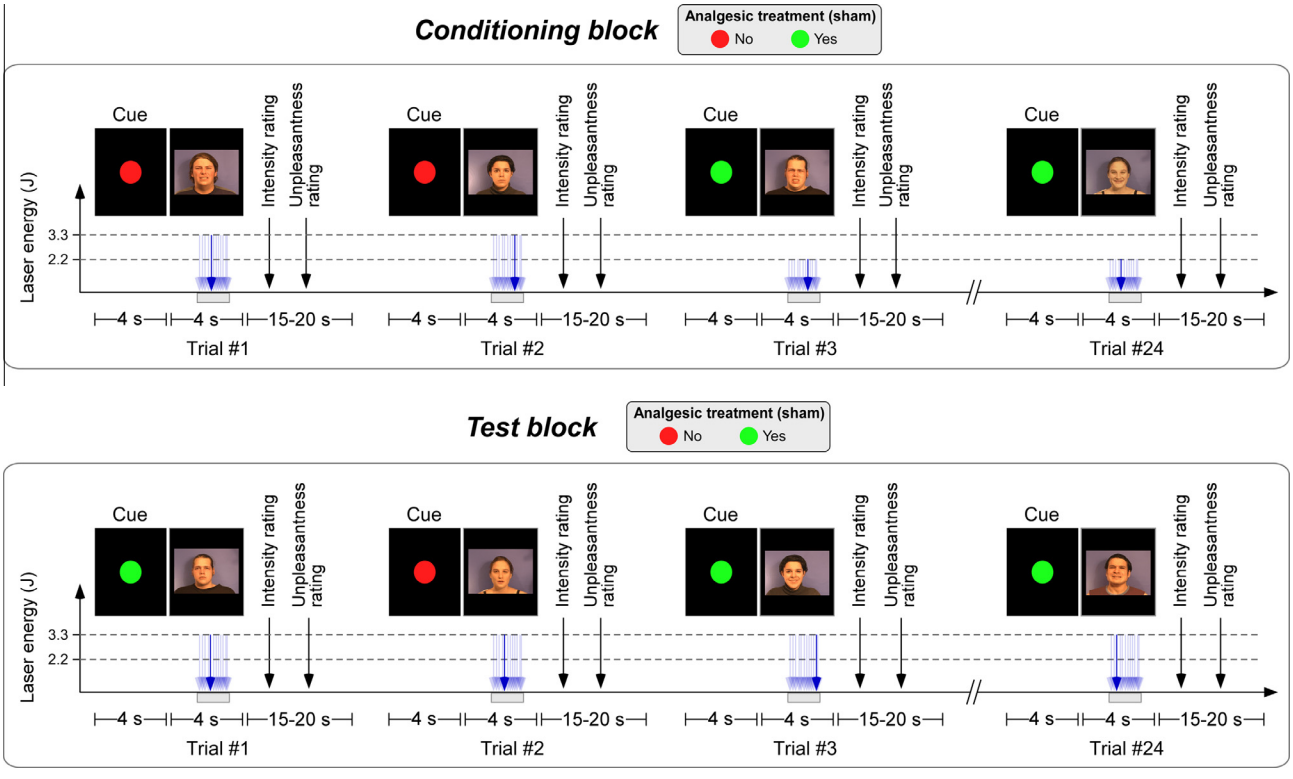

Fig. 1. Experimental design. Subjective ratings of pain intensity and unpleasantness elicited by nociceptive laser pulses delivered to the hand dorsum were collected in 2 blocks. During the preliminary conditioning block, laser pulses were delivered using either low energy eliciting nonpainful sensations (Green trials) or high energy eliciting clearly painful sensations (Red trials). Conversely, during the test block, the laser energy in Green trials was set to the same high energy level used in Red trials. Each trial started with either a red (Red trials) or a green (Green trials) visual warning cue displayed on a black screen for 4 seconds. The cue was followed by a video clip lasting 4 seconds and representing neutral (Neutral), grimacing (Pain), or smiling (Happy) facial expressions. During the video clip, a single laser pulse was delivered. The onset of the laser pulse was jittered between 1.8 and 2.9 seconds with respect to the onset of the video clip. Three seconds after the end of the video clip, participants were required to verbally rate both pain intensity and pain unpleasantness using a numerical scale ranging from 0 ("no pain/not unpleasant at all") to 100 ("intolerable pain/intolerable unpleasantness"). The order of the 2 ratings was counterbalanced across participants. Note that such within-subject design allowed us to estimate the placebo effect as the difference in ratings obtained during Red and Green trials in the test block.

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duration of each trial was 25.5 seconds. Three seconds after the end of the video clip, participants were verbally asked to provide a rating of the intensity and unpleasantness of the perceived pain, using a numerical rating scale ranging from 0 (“no pain/not unpleasant at all”) to 100 (“intolerable pain/intolerable unpleasantness”). The order of the 2 ratings was counterbalanced across participants.

During the calibration phase, the group average skin temperature was 34.0 ± 0.6°C. During the conditioning and the test blocks, the group average skin temperature was 34.2 ± 0.7°C and 34.3 ± 0.9°C, respectively.

2.7. Data analysis

Single-subject differences in pain intensity and unpleasantness between the Red and the Green trials (i.e., the reductions in pain intensity and unpleasantness in the Green, as compared to the Red trials) in the test block were taken as a measure of the placebo effect. Statistical analyses were performed using Statistica 8.0 (StatSoft Inc., Tulsa, OK, USA). The level of significance was set at $P < 0.05$. We reported partial eta squared (η^2) as measure of effect size of significant main effects and interactions.

2.7.1. Analysis of variance

A 2-way analysis of variance was conducted separately on the conditioning and test blocks, with “cue” (2 levels: Red and Green), and “expression” (3 levels: Neutral, Happy, and Pain) as main effects. Mauchly’s test was applied to assess possible violations of sphericity. If the assumption of sphericity was violated ($P < 0.01$), the degrees of freedom were adjusted consequently ($\varepsilon < 0.75$: Greenhouse-Geisser correction, $\varepsilon > 0.75$: Huynh and Feldt correction). Newman-Keuls tests were used to perform post hoc pairwise comparisons.

2.7.2. Correlation analysis

To test whether the possible modulatory effect of facial expressions on the placebo analgesia was different in participants with different personality traits, we correlated self-reported personality scores with the magnitude of placebo analgesia for both pain intensity and pain unpleasantness. This was obtained by subtracting, for each subject, the subjective ratings obtained during the Green trials from those obtained during the Red trials. To this purpose we computed Pearson’s r correlation coefficients. The level of significance was set at $P < 0.05$.

3. Results

3.1. Pain intensity

3.1.1. Conditioning block

Mauchly’s test revealed no violations of sphericity for both main effect of face ($P = 0.23$) and the interaction ($P = 0.83$). There was a significant main effect of “cue” [$F(1,26) = 313.97$; $P < 0.001$; partial $\eta^2 = 0.92$], with lower ratings of pain intensity in Green trials than in Red trials. This result is explained by the lower laser energy used in Green trials in this block. There was no main effect of “expression” [$F(2,52) = 1.76$; $P = 0.18$], and no interaction between “cue” and “expression” [$F(2,52) = 1.08$; $P = 0.35$].

3.1.2. Test block

Subjective ratings of pain intensity are shown in Fig. 2 (left graph). Mauchly’s test revealed no violations of sphericity for both main effect of face ($P = 0.23$) and the interaction ($P = 0.87$).

There was a significant main effect of the factor “cue” [$F(1,26) = 6.57$; $P = 0.02$; partial $\eta^2 = 0.20$], with lower ratings of pain intensity in Green trials than in Red trials. This result indicates a significant placebo analgesia across the participants. Conversely, there was no significant main effect of “expression” [$F(2,52) = 0.29$; $P = 0.75$]. Importantly, however, there was a significant interaction between “cue” and “expression” [$F(2,52) = 3.70$; $P = 0.03$; partial $\eta^2 = 0.12$], reflecting (1) a larger reduction of pain intensity during the observation of Happy facial expressions in Green trials than during Red trials ($P < 0.001$), and (2) a larger reduction of pain intensity during the observation of Pain facial expressions in Green trials than during Red trials ($P = 0.01$) (Fig. 2, left panel). In Green trials, there were no significant differences in the pain intensity ratings during observation of facial expressions (Happy vs. Neutral: $P = 0.13$; Happy vs. Pain: $P = 0.17$; Pain vs. Neutral: $P = 0.59$). Importantly, there were no significant differences in the pain intensity ratings during observation of facial expressions in the Red trials (Happy vs. Neutral: $P = 0.21$; Happy vs. Pain: $P = 0.79$; Pain vs. Neutral: $P = 0.16$). This pattern of results indicates that facial expressions did not significantly modulate pain intensity *per se*, but specifically increased the magnitude of the placebo analgesia (Table 1).

3.2. Effects on pain unpleasantness

3.2.1. Conditioning block

Mauchly’s test revealed no violations of sphericity for both main effect of face ($P = 0.77$) and the interaction ($P = 0.77$). There was a significant main effect of “cue” [$F(1,26) = 131.66$; $P < 0.001$; partial $\eta^2 = 0.83$], with lower ratings of pain unpleasantness in Green trials than in Red trials. This result is explained by the lower laser energy used in Green trials in this block. In contrast with what was observed in the pain intensity ratings, there was a significant main effect of “expression” [$F(2,52) = 6.12$; $P = 0.004$; partial $\eta^2 = 0.19$], with higher ratings of pain unpleasantness during observation of Pain facial expressions as compared to Neutral ($P = 0.006$) and Happy ($P = 0.007$) facial expressions. Finally, there was no interaction between “cue” and “expression” [$F(2,52) = 1.16$; $P = 0.32$].

3.2.2. Test block

Subjective ratings of pain unpleasantness are shown in Fig. 2 (right graph). Mauchly’s test revealed no violations of sphericity for both main effect of face ($P = 0.42$) and the interaction ($P = 0.99$).

Differently from what was observed for pain intensity ratings, the factor “cue” just approached significance [$F(1,26) = 4.15$; $P = 0.05$; partial $\eta^2 = 0.14$]. In addition, there was no significant main effect of the factor “expression” [$F(2,52) = 2.03$; $P = 0.14$]. There was, however, an interaction between “cue” and “expression” [$F(2,52) = 3.95$; $P = 0.02$; partial $\eta^2 = 0.13$], indicating a larger reduction of pain unpleasantness during the observation of Happy facial expressions in Green trials than during Red trials ($P < 0.001$; Fig. 2, right panel). In Green trials, pain unpleasantness ratings during observation of Happy facial expressions were significantly different from Neutral ($P = 0.02$) and Pain ($P = 0.01$), whereas no difference was observed between Pain and Neutral conditions ($P = 0.59$). There were no significant differences in the pain unpleasantness ratings during the observation of different facial expressions in the Red trials (Happy vs. Neutral: $P = 0.14$; Happy vs. Pain: $P = 0.39$; Pain vs. Neutral: $P = 0.06$). Altogether, this interaction indicates a significant reduction in unpleasantness during the passive observation of Happy facial expressions and the concomitant expectation of placebo analgesia (Table 1).

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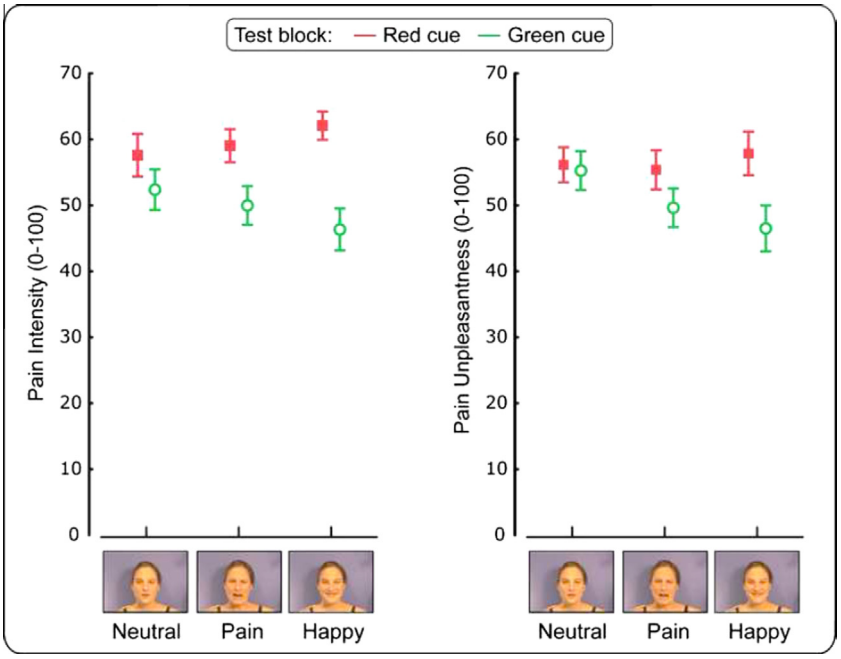

Fig. 2. Group-level average (±SEM) ratings (y axis) of pain intensity (left panel) and pain unpleasantness (right panel) in the 3 experimental conditions (x axis). Displayed results were obtained in the test block. Ratings collected in Red and Green trials are represented in red and green, respectively. Crucially, in the test block the energy of the laser pulses in the Green trials was identical to the energy of the laser pulses in the Red trials. Thus, the difference between pain rating in Red and Green trials provided a measure of the placebo analgesia. Both negative (Pain) and positive (Happy) expressions reduced ratings of both pain intensity and pain unpleasantness (i.e., increased the magnitude of the placebo analgesia). Notably, Happy facial expressions appeared to enhance most significantly the placebo analgesia only when there was a placebo expectation (Green trials).

Table 1
Post hoc comparisons of the interaction between the experimental factors "cue" and "expression" in the test block.

	Pain intensity Means (±SD)	Pain unpleasantness Means (±SD)
Effect of cue within facial expression		
Red Neutral vs. Green Neutral	46.9 (12.8) vs. 45.3 (12.8)*	40.1 (17.6) vs. 39.3 (16.6)
Red Pain vs. Green Pain	48.6 (11.1) vs. 44.7 (12.4)***	42.8 (16.1) vs. 39.9 (16.5)*
Red Happy vs. Green Happy	48.9 (11.8) vs. 43.0 (13.8)****	41.8 (17.0) vs. 36.5 (17.2)****
Effect of expression within cue		
Red Neutral vs. Red Pain	46.9 (12.8) vs. 48.6 (11.1)*	40.1 (17.6) vs. 42.8 (16.1)*
Red Neutral vs. Red Happy	46.9 (12.8) vs. 48.9 (11.8)	40.1 (17.6) vs. 41.8 (17.0)*
Red Pain vs. Red Happy	48.6 (11.1) vs. 48.9 (11.8)	42.8 (16.1) vs. 41.8 (17.0)
Green Neutral vs. Green Pain	45.3 (12.8) vs. 44.7 (12.4)	39.3 (16.6) vs. 39.9 (16.5)
Green Neutral vs. Green Happy	45.3 (12.8) vs. 43.0 (13.8)*	39.3 (16.6) vs. 36.5 (17.2)**
Green Pain vs. Green Happy	44.7 (12.4) vs. 43.0 (13.8)*	39.9 (16.5) vs. 36.5 (17.2)***

*$P \leqslant 0.20$, **$P \leqslant 0.05$, ***$P \leqslant 0.01$, ****$P \leqslant 0.001$.

3.3. Correlation between personality traits and subjective ratings

There were no significant correlations between personality scales and pain intensity or unpleasantness ratings. These correlation analyses are summarized in Table 2.

4. Discussion

This study investigates for the first time whether placebo effects are influenced by the observation of facial expressions displayed by stranger models. By coupling verbal suggestions with a simple Pavlovian conditioning procedure, we obtained significant placebo analgesia. In particular, passive observation of facial expressions with negative and positive valence content (grimacing – "Pain," and smiling – "Happy") significantly interacted with the placebo analgesia, with both expressions leading to an increase of the analgesic effect (Fig. 2). Moreover, the enhancement of placebo analgesia was maximal when observing smiling facial expressions.

4.1. Facial expressions affect the magnitude of placebo analgesia: emotional arousal, distraction, or expectation?

That passive observation of facial expressions induces a significant increase of placebo analgesia (Fig. 2) may reflect changes in *emotional arousal*. Indeed, the observation of smiling and grimacing expressions may have induced a positive or negative arousal in the

Table 2
Pearson's *r* coefficients and *P* values representing the correlation between difference scores (Green-Red trials) of pain intensity and pain unpleasantness, and personality variables, during the test block.

	IRI PT	IRI FS	IRI EC	IRI PD	BAS DRIVE	BAS FUN	BAS REW	BIS
INT Neutral	$r = -0.24$	$r = -0.13$	$r = -0.23$	$r = -0.24$	$r = -0.03$	$r = -0.05$	$r = 0.30$	$r = 0.09$
INT Pain	$r = -0.19$	$r = -0.004$	$r = -0.22$	$r = -0.25$	$r = -0.05$	$r = -0.12$	$r = 0.22$	$r = 0.10$
INT Happy	$r = -0.07$	$r = -0.09$	$r = -0.18$	$r = -0.20$	$r = 0.14$	$r = 0.08$	$r = 0.27$	$r = 0.03$
UNP Neutral	$r = -0.03$	$r = -0.12$	$r = -0.34^{*}$	$r = -0.18$	$r = -0.26$	$r = -0.12$	$r = 0.09$	$r = 0.21$
UNP Pain	$r = -0.04$	$r = -0.01$	$r = -0.36^{*}$	$r = -0.13$	$r = -0.28$	$r = -0.08$	$r = -0.004$	$r = 0.12$
UNP Happy	$r = 0.01$	$r = -0.001$	$r = -0.23$	$r = -0.08$	$r = -0.16$	$r = 0.01$	$r = 0.03$	$r = 0.07$

IRI, Interpersonal Reactivity Index; PT; Perspective Taking; FS, Fantasy Scale; EC, Empathic Concern; PD, Personal Distress; BAS, Behavioral Activation Scale; BIS, Behavioral Inhibition Scale; FUN, fun seeking; REW, reward responsiveness; INT, pain intensity; UNP, pain unpleasantness.
The level of significance was set at $P < 0.05$.
* $P \leqslant 0.10$.

onlooker. However, changes in the emotional arousal of opposite valence directions should exert opposite perceptual modulation (i.e., higher pain ratings/lower placebo analgesia for the negative valence expression – "Pain," vs. lower pain ratings/higher placebo analgesia for the positive valence expression – "Happy"), particularly in the case that emotional contagion is at play [17]. Both these interpretations may find theoretical support in the affect-as-information approach, which suggests that affective processes occur outside awareness, and can modulate the value of nonaffective feelings [9]. In the context of the current experiment, the positive affect induced by happy facial expressions may have enhanced the placebo analgesia.

Importantly, an interpretation based on emotional arousal would imply an increase of pain ratings *per se* (i.e., already in the conditioning block) during the observation of facial expression of pain. However, a simple emotional "congruency" account would predict that negative and positive valence information enhances negative and positive valence experience, respectively (e.g., [29]). This was not the case in this study, where facial expressions did not modulate the intensity of perceived pain in the conditioning block, but only in the test block when the green cues were presented (ie, when participants were expecting the placebo analgesia; Fig. 2). In contrast, an emotional "congruency" account should ensue in no significant analgesia during the observation of pain expressions in the Green trials of the test block, or at least in absence of statistical difference between the placebo analgesia during the observation of pain and neutral expressions. Given that placebo analgesia was stronger when participants observed pain expressions than when they observed neutral expressions (Fig. 2), both these hypotheses (emotional arousal and emotional congruency) can be rejected.

An alternative explanation might be that mere exposure to strangers' facial expressions may have *distracted* the participants. Given that the intensity of perceived pain depends on the available attentional resources [36], the reduction of attention towards the nociceptive stimulation might have increased the analgesic effect related to the placebo manipulation. However, the distracting effect of facial expressions should also be manifest as reduced ratings of pain reported during Red trials, which were instead not significantly different across conditions. Thus, the reduction in pain ratings during the observation of facial expressions was specifically related to placebo analgesia.

It is also worth noting that participants could have anticipated the occurrence of the nociceptive stimulus on the basis of the information conveyed by the cue, which influenced the participants' expectation about the impending laser stimulus. Therefore, a third explanation of the enhancement of placebo analgesia induced by facial expressions may call *expectation* into play [4]. This explanation is also supported by the evidence that the amount of placebo analgesia is significantly increased by desire for and expectation of pain relief (see [18] and [27] for a comprehensive discussion).

Interestingly, a recent study suggested that placebo analgesia may not depend on mere attentional orientation, and that expectation and attention may have independent effects on pain control [6]. Thus, these 2 factors may interact in modulating the magnitude of placebo analgesia. In both Green and Red trials, expectation about the sensation elicited by the incoming nociceptive input may interact with the attentional capture exerted by the emotional valence associated with the different facial expressions. For example, the positive valence of the Happy facial expression may reinforce the expected pain relief predicted by green cues and thus enhance the placebo analgesic effect. The observation of Pain expression, instead, contrasted with the expected relief from pain predicted by green cues. While such incongruence may reduce the expectancy of relief determined by the green cue, the attentional load related to incongruity detection may determine a distraction-related analgesic effect. In contrast, neutral faces were neither congruent nor incongruent with the expected relief from pain predicted by the green cue. As to the effect of red cues, one may posit that their coupling with facial expressions of pain simply confirms the expected pain and that a Happy face following the red cue does not elicit a distraction effect. This is consistent with the notion that happy faces are judged significantly less arousing than facial expressions of pain [33].

A more parsimonious interpretation could highlight the lack of a significant reduction of pain during observation of neutral faces in the Green trials compared to the Red trials. Indeed, it cannot be excluded that viewing "emotional" facial expressions decreases pain ratings (e.g., by one of the above-mentioned mechanisms), but only when such expressions are preceded by a "safety" cue (i.e., the green cue).

4.2. Do personality variables modulate the magnitude of placebo analgesia?

It has been suggested that pain is not only a private and personal experience, but also includes a social dimension that may imply interpersonal sharing of pain [16]. Accordingly, a recent study reported that the corticospinal excitability of subjects with high levels of cognitive empathy is reduced while they observe a needle penetrating a stranger's hand. Conversely, this is not observed in subjects with high levels of personal distress [3]. This finding indicates a greater inhibition of the motor system in individuals who are able to take the perspective of others. Furthermore, it has been shown that differences in personality traits explain part of the variability in the brain responses elicited by the observation of emotional faces [7]. Although we explicitly investigated the possible relationship between personality traits and the effect of watching a stranger's facial expression on the

magnitude of placebo analgesia, we did not detect any significant correlation between the magnitude of placebo effect and the personality scores during the observation of different facial expressions. One possible explanation for the lack of correlations between personality variables and modulation of placebo effects may reside in the small sample size used in this study (n = 27).

4.3. Methodological remarks

The observation of others' facial expressions significantly increased the magnitude of placebo analgesia in the onlookers. In addition, individual differences in personality traits did not seem to determine the magnitude of placebo analgesia. These findings highlight the need for additional research to identify the social and personality factors determining the appearance and size of the placebo effect. Importantly, our findings were obtained using a within-subject design in which participants served as their own controls. This methodological advantage makes it unlikely that the current results are consequent to sensory habituation and/or regression to the mean. Indeed, these 2 effects would be similarly distributed throughout the experimental blocks, and similarly affect the pain ratings reported both in Red trials (expectation of no analgesic treatment) and Green trials (expectation of analgesic treatment). However, we cannot exclude a potential effect of response bias on these results because self-reported measures are inherently sensitive to, for example, social desirability bias [19].

A further caveat, which also applies to results from several previous studies of placebo analgesia [10–13,22], is that the analgesic effect observed here stems from inadvertent conditioning of the colour green with safety or pain relief because sham analgesic stimulation was always preceded by green cues in this study design. However, had the analgesia observed in Green trials been largely due to the safety meaning of the green cue, a similar effect would have been observed regardless of the type of facial expression, which was not the case in the current study. Future studies may formally address this issue by associating red cues to the sham analgesic stimulation in half of the experimental sample, and thus explore a possible main effect of the semantic property of the colour. Additionally, future studies may investigate whether the presentation of faces in the conditioning phase is crucial for obtaining the interaction with the placebo analgesia or whether the presentation of faces elicits a modulatory effect sufficiently robust to take place during the placebo-testing phase only.

Finally, it is worth noting that watching a noninformative stranger's face in the context of an experiment conducted in a research laboratory has surely less emotional impact than watching the face of a caregiver in a medical setting (i.e., the face of a relative or of a health professional in a hospital environment). Thus, although speculatively, we suggest that the effect of facial expressions on the magnitude of placebo analgesia would be enhanced in the clinical setting.

Conflict of interest statement

The authors declare no conflicts of interest.

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Appendix A.

A.1. Instruction script

You will participate in a study in which we will be testing the efficacy of a new analgesic technique on the subjective experience of pain. During the experiment we will deliver two types of sensory stimulation, thermal (laser) and electrical. The thermal stimulus elicits pain, while the electrical stimulus is the analgesic technique that reduces pain.

When occurring concomitantly with laser stimulation, very low electrical stimulation has been observed to reduce the pain sensation elicited by the laser. Importantly, the electrical stimulation will be so low that you will not perceive it. Thus, you will not be aware of this electrical stimulation. Both laser and the electrical stimuli will be delivered on your right hand. Only one laser intensity will be used throughout the experiment and we will establish it before starting the experiment. In some of the trials the laser pulse will be preceded by the electrical stimulus (so you will not feel the laser as much painful), while in other trials the laser pulse will not be preceded by the electrical stimulus (so you will feel the real painful sensation caused by the laser pulse). You will be informed by the appearance of a green circle on the screen when the laser stimulus will be preceded by the electrical pain-relieving stimulus. In contrast, the appearance of a red circle will inform you that no preceding analgesic electrical treatment will be delivered before the laser stimulus.

At the end of each trial we will ask you to report two numerical values describing the intensity and the unpleasantness of pain sensation you experienced. The values you can choose from range from 0 (“no pain/not unpleasant at all”) to 100 (“intolerable pain/intolerable unpleasantness”).

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