Pain 124 (2006) 126–133

PAIN

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How prior experience shapes placebo analgesia

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Received 9 November 2005; received in revised form 21 February 2006; accepted 3 April 2006

Abstract

Some studies indicate that placebo analgesia is stronger when pre-conditioning with effective analgesic treatments is performed, thereby suggesting that the placebo response is a learning phenomenon. Here we further tested this hypothesis in order to better understand when and how previous experience affects the placebo analgesic response. To do this, we used a conditioning procedure whereby the intensity of painful stimulation was reduced surreptitiously, so as to make the subjects believe that an analgesic treatment was effective. This procedure induced strong placebo responses after minutes, and these responses, albeit reduced, lasted up to 4–7 days. In addition, in a second group of subjects we repeated the same conditioning procedure 4–7 days after a totally ineffective analgesic treatment, and found that the placebo responses were remarkably reduced compared to the first group. Thus we obtained small, medium and large placebo responses, depending on several factors, such as the previous positive or negative experience of an analgesic treatment and the time lag between the treatment and the placebo responses. We also ran extinction trials, and found that these effects did not undergo extinction in a time span of several minutes. These findings indicate that placebo analgesia is finely tuned by prior experience and these effects may last, albeit reduced, several days. These results emphasize that the placebo effect is a learning phenomenon in which many factors come into play, and may explain the large variability of the placebo responses that is found in many studies.
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Keywords: Placebo analgesia; Learning; Expectation; Conditioning

1. Introduction

Several studies suggest that the placebo effect is a learning phenomenon whereby previous experience of a therapeutic outcome plays an important role. In fact, robust placebo responses can be obtained after repeated exposure to effective treatments. Conversely, although verbal suggestions alone may elicit placebo responses as well, these responses are smaller (Amanzio and Benedetti, 1999). The enhancing effect of prior positive experience is not well understood, but conditioning and/or expectations seem to play a role (Kirsch, 2004a; Williams-Stewart and Podd, 2004; Colloca and Benedetti, 2005).

Although this has been studied in many conditions, such as Parkinson's disease (de la Fuente-Fernandez et al., 2001; Benedetti et al., 2004), hormone secretion (Benedetti et al., 2003), immune responses (Olness and Ader, 1992; Giang et al., 1996; Goebel et al., 2002; Ader, 2003) and depression (Mayberg et al., 2002), most of the research has focused on the placebo analgesic response (Colloca and Benedetti, 2005; Finniss and Benedetti, 2005). For example, it has been shown that robust placebo analgesic responses may be induced through a conditioning procedure but they are actually mediated by expectation (Montgomery and Kirsch, 1997; Benedetti et al., 2003). This is in keeping with alternative theories of learning which suggest that cognitive elements are involved in Pavlovian conditioning. In

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doi:10.1016/j.pain.2006.04.005

other words, conditioning would lead to the expectation that a given event will follow another event, and this occurs on the basis of the information that the conditioned stimulus provides about the unconditioned stimulus (Reiss, 1980; Rescorla, 1988; Kirsch et al., 2004b).

The prior experience of a subject, both in the experimental setting and in the clinical setting, is not easy to be assessed. This uncertainty about the previous therapeutic experience, either positive or negative, of a subject might account for the variability of the magnitude of the placebo analgesic responses, ranging from small in some studies to large in some others (Hrobjartsson and Gotzsche, 2001, 2004; Vase et al., 2002, 2005).

On the basis of these considerations, we wanted to better understand the role of either positive or negative previous experience, and of the relative time lags, on the magnitude of the placebo response. To do this, we induced either positive or negative analgesic experiences in healthy volunteers in the experimental setting, in order to investigate their effects on a subsequent (with both short and long time lags) placebo-induced analgesic response.

2. Methods

2.1. Subjects

A total of 30 healthy right-handed volunteers participated in the study after they signed a written informed consent to participate in either one or two experimental sessions. The experimental procedure was also described, and the subjects were told that a new analgesic procedure was assessed. They were also told that this procedure consisted in the electric stimulation of the middle finger which, in turn, induced analgesia on the back of the hand. Each subject underwent a medical examination in order to rule out the presence of any kind of disease. All the experimental procedures were conducted in conformance with the policies and principles contained in the Declaration of Helsinki. The subjects were subdivided into 3 groups, whose characteristics are shown in Table 1.

2.2. Pain induction

The pain stimulus was an electric shock that was 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. After the skin had been cleaned with alcohol, the two electrodes were applied by means of a strap and separated 1 cm from each other. Stimuli were square pulses delivered by a somatosensory stimulator (Galileo Mizar NT, EBNeuro, Florence, Italy), with a duration of 100 μs. Depending on the experimental design (see below), the intensity, expressed in mA, was set either above or below the pain threshold.

2.3. Experimental design

The experimental session started with the determination of pain threshold (T) according to the method of the limits (Gracely, 1994). An ascending series of stimuli in steps of 1 mA was delivered starting from sub-tactile threshold until pain sensation was induced. After determination of T, each subject was randomly assigned to 1 of 3 experimental groups, as shown in Fig. 1.

Group 1 (Fig. 1A). Two blocks of 12 pain stimuli each at twice the pain threshold (2T) were delivered. The interval between the two blocks was 3 min. Each stimulus was delivered at the end of a 12 s presentation of a red light (displayed on a computer screen). The subjects were told that the red light anticipated the delivery of a painful stimulus. Therefore, in this group, 24 associations (12 for each block) red light-pain stimuli were performed. At the end of each association, the subjects reported their perceived pain intensity according to a numerical rating scale (NRS) ranging from 0 = no pain to 10 = unbearable pain. This group was used as a control for possible sensitization and habituation effects. In other words, this group represents the natural history group.

Table 1
Characteristics of the subjects

Subject	Group 1		Group 2			Group 3		
	Age (years)	Sex	Age (years)	Sex	Time lag* (days)	Age (years)	Sex	Time lag* (days)
1	29	M	21	M	5	21	F	5
2	25	F	22	F	5	23	M	4
3	21	F	21	F	5	23	F	4
4	29	F	22	F	5	22	F	5
5	27	M	22	F	5	23	F	5
6	25	F	23	M	4	23	F	4
7	21	F	21	F	4	21	F	7
8	21	F	21	F	5	21	F	4
9	23	F	21	F	7	21	F	4
10	26	F	22	F	7	21	F	5
$\bar{X}$	24.70		21.60		5.20	21.90		4.70
SD	3.13		0.70		1.03	0.99		0.95

* The time lag reported is between session 1 and 2.

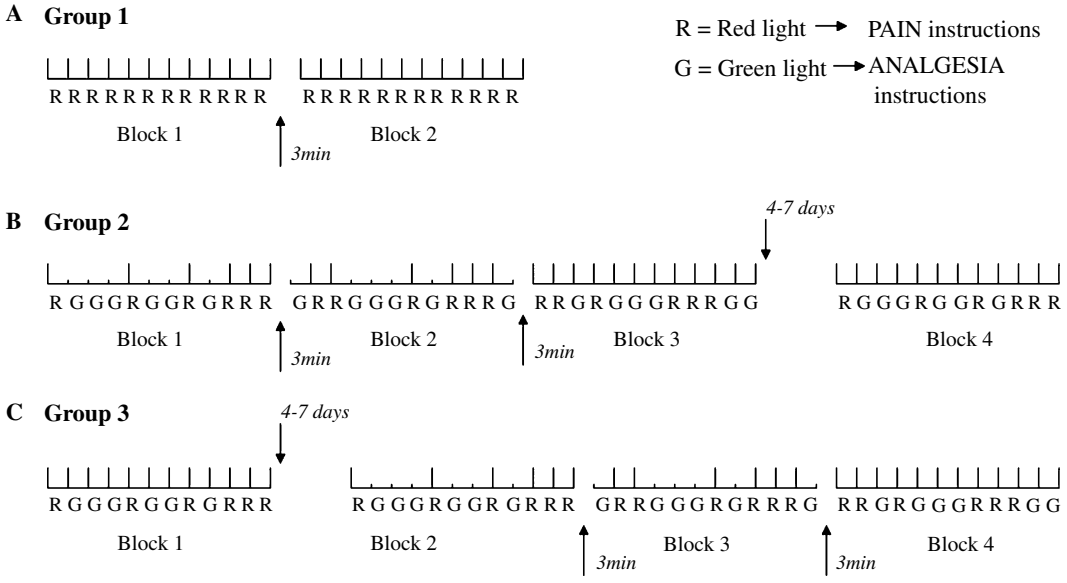

Fig. 1. Experimental paradigm for Groups 1, 2 and 3. In all the conditions, a red light means "pain", and is always associated to a painful stimulus (long vertical bar). Conversely, a green light means "analgesia", and is associated either to a non-painful tactile stimulus (short vertical bar) to train the subjects or to a painful stimulus to test placebo responses.

Group 2 (Fig. 1B). This group underwent 2 experimental sessions in 2 different days. On the first day, 3 blocks of 12 stimuli each were delivered. The first block consisted of 6 painful stimuli at 2T associated to the red light and 6 tactile stimuli (the intensity was surreptitiously lowered by 2 mA below T (T-2 mA)) associated to a green light. In the latter case, as done in previous studies (Voudouris et al., 1989, 1990; Montgomery and Kirsch, 1997; Price et al., 1999), the subjects did not know that the intensity had been reduced. In fact, a sham electrode was applied to the middle finger of the hand that received the pain stimuli, and the subjects were told that the green light anticipated the activation of this electrode that, in turn, induced an analgesic effect. The second block was the same as the first one. In the third block, the same random sequence of red and green lights was used, but all the 12 stimuli were painful (2T). Pain intensity was reported according to the NRS as in Group 1. It should be noted that this third block was actually an extinction trial, in that the green light was paired with the painful stimuli. Therefore, we also tested whether extinction occurred within a sequence as long as 12 stimuli. After 4–7 days (see Table 1), a fourth block of 12 painful stimuli was delivered, which was exactly the same as block 3. This group was used to assess both the short-lasting (minutes) and the long-lasting (days) effects of a conditioning procedure.

Group 3 (Fig. 1C). This group underwent 2 experimental sessions in 2 different days. On day 1 one block of 12 stimuli was delivered (block 1), as in block 4 of Group 2. The subjects were told that a red light would anticipate a pain stimulus (6 stimuli) while a green light anticipated a painful stimulus that was made analgesic by the stimulation of the middle finger (6 stimuli). Actually, all the 12 stimuli were painful, as they were set at 2T. After 4–7 days, 3 blocks of 12 stimuli each were delivered, as in the first session of Group 2. In other words, the 2 sessions of Group 3 were reversed compared to those of Group 2. It should be noted that, in this case also, we run an extinction trial, so that we assessed extinction in this group as well.

2.4. Statistical analysis

After testing the data for normal distribution with the Kolmogorov–Smirnov test, we performed statistical comparisons by means of repeated measures ANOVA. In fact, in no case we found a significant difference between our data set and a normal distribution. Sphericity condition, which assesses the validity of F statistics, was verified by using the Mauchly's test. When the sphericity condition was not verified, the Greenhouse–Geisser correction was applied (Greenhouse and Geisser, 1959). The F-tests were followed by simple contrasts and the Bonferroni and the Dunnett post hoc tests for multiple comparisons. All the analyses were carried out using SPSS for Windows software, version 12.0 (SSPS Inc., Chicago, Illinois, USA). The level of significance was set at $P < 0.05$.

3. Results

The time course of pain perception to the electrical stimuli across the 24 stimuli in the 2 blocks of the natural history group (Group 1) was analyzed in order to control for possible sensitization or habituation effects. Fig. 2 shows that no significant difference was found across the 24 stimuli ($F(23) = 0.947$, $P = 0.535$), which indicates stable experimental conditions in a sequence as long as 24 pain stimuli.

In Group 2 we found variability in the subjective reports of pain, particularly when the re-test at 4–7 days was performed. In fact, a significant difference was present across the blocks for the red light-associated pain

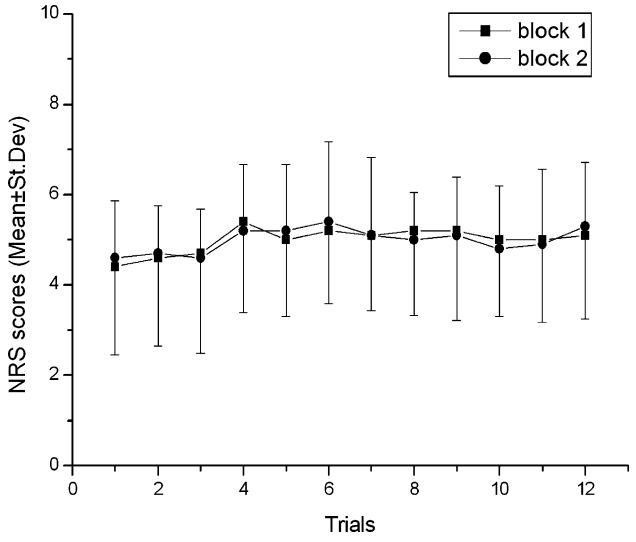

Fig. 2. Intra-block and inter-block pain reports in Group 1. Note that pain perception did not change across the 24 stimuli of the two blocks.

stimuli ($F(3,27) = 7.599$, $p < 0.001$). A post hoc Bonferroni test for multiple comparisons showed that the red light-associated pain reports were different in block 4 with respect to both block 2 ($p < 0.05$) and block 3 ($p < 0.05$) and in block 3 with respect to block 1 ($p < 0.05$). Likewise, there was a significant variability across different blocks for the green light-associated pain reports ($F(3,27) = 8.295$, $p < 0.001$) (Fig. 3). The post hoc Bonferroni test showed that block 1 was significantly different from both blocks 3 ($p < 0.05$) and 4 ($p < 0.05$).

Due to this inter-block variability, we expressed the placebo analgesic effect as the difference between red-associated and green-associated pain reports within a single block. The ANOVA indicated significant main effects for blocks ($F(3,27) = 29.631$, $p < 0.001$, $\eta^2 = 0.688$) and for block/time interaction ($F(15,135) = 3.692$, $p < 0.008$, $\eta^2 = 0.316$), which indicates significant differences between red and green lights in each block, whereas there was no significant main effect for time ($F(5,45) = 1.331$, $p = 0.289$, $\eta^2 = 0.455$), thus indicating constant responses over time to both red and green lights in all the blocks. Whereas these differences were obviously expected for blocks 1 and 2, in which the stimulus intensity was surreptitiously reduced in association with the green light, it should be remembered that in blocks 3 and 4 both red- and green-associated stimuli were painful, which indicates that a placebo response was present in both blocks 3 and 4. However, simple contrast with Bonferroni adjustment for multiple comparisons showed that the difference between the red- and green-associated pain reports was smaller in block 4 compared to block 3 ($p < 0.025$), thus indicating the placebo analgesic response, albeit present at 4–7 days after the extinction trial of block 3, decreased over time.

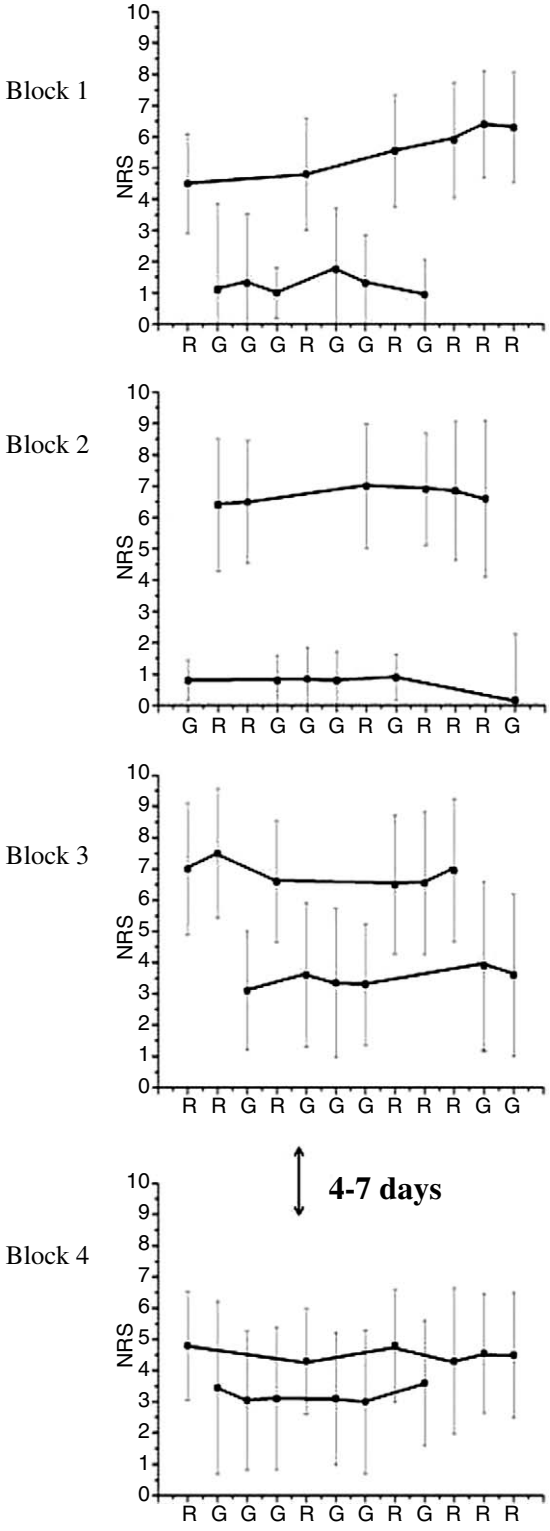

Fig. 3. Intra-block and inter-block pain reports in Group 2. Due to some inter-block variability of the absolute pain scores, placebo analgesia is expressed as the difference between red-associated and green-associated pain reports within each block. In blocks 1 and 2, the surreptitious reduction of stimulus intensity, which was associated to the green light, induced a decrease of pain reports only when the green light was presented. Despite in blocks 3 and 4 all the stimuli being painful, the green light induced reduced pain reports (placebo analgesic responses). Note that no intra-block (blocks 3 and 4) extinction occurred.

As far as Group 3 is concerned (Fig. 4), we found variability in the subjective reports of pain, as in Group 2. In fact, a significant difference was present across the blocks for the red light-associated pain stimuli ($F(3,27) = 3.194$, $p < 0.04$). A post hoc Bonferroni test for multiple comparisons showed that the red light-associated pain reports were different between blocks 1 and 4 ($p < 0.05$). Similarly, there was a significant variability across different blocks for the green light-associated pain reports ($F(3,27) = 22.131$, $p < 0.001$) (Fig. 4). The post hoc Bonferroni test showed that block 1 was significantly different from both blocks 2 ($p < 0.05$) and 3 ($p < 0.05$) and that block 4 was significantly different from blocks 2 ($p < 0.05$) and 3 ($p < 0.05$). Therefore, in this case also, we expressed placebo analgesia as the difference between red- and green-associated pain reports. We found that the differences between red and green lights were significant for blocks ($F(3,27) = 22.160$, $p < 0.001$, $\eta^2 = 0.656$), whereas no significant block/time interaction was present ($F(15,135) = 1.483$, $p = 0.226$, $\eta^2 = 0.277$). Moreover, there was no significant main effect for time ($F(5,45) = 0.797$, $p = 0.517$, $\eta^2 = 0.667$). As in Group 2, this indicates significant differences between red and green lights in each block and constant responses over time to both red and green lights in all the blocks.

Thus verbal suggestions alone were ineffective in inducing significant placebo responses. It should be remembered that in block 1 of Fig. 4 all the stimuli were painful. Therefore, this block represented a negative analgesic experience whereby the expectations about the verbal analgesic suggestions were not fulfilled. Whereas a red–green difference was obviously expected for blocks 2 and 3, in which the stimulus intensity was surreptitiously reduced in association with the green light, it should be remembered that in block 4 both red- and green-associated stimuli were painful. Simple contrast with Bonferroni adjustment for multiple comparisons showed that no difference was present between block 1 and 4 ($p = 1$), which indicates that no placebo response was present in block 4. Therefore, the negative analgesic experience of block 1 antagonized completely the effects of the conditioning procedure.

In order to summarize all these data, we considered the mean difference between red- and green-associated pain reports in each block. By expressing the placebo analgesic response as the intra-block difference between red and green lights, in Fig. 5 it can be seen that small, medium and large placebo responses could be obtained, depending on the circumstances. For example, a surreptitious conditioning procedure may result in either large (block 3 of Group 2) or small non-significant (block 4 of Group 3) placebo responses, depending on the previous negative analgesic experience of 4–7 days before. Likewise, verbal suggestions alone may result in significant placebo responses (block 4 of Group 2) or no response

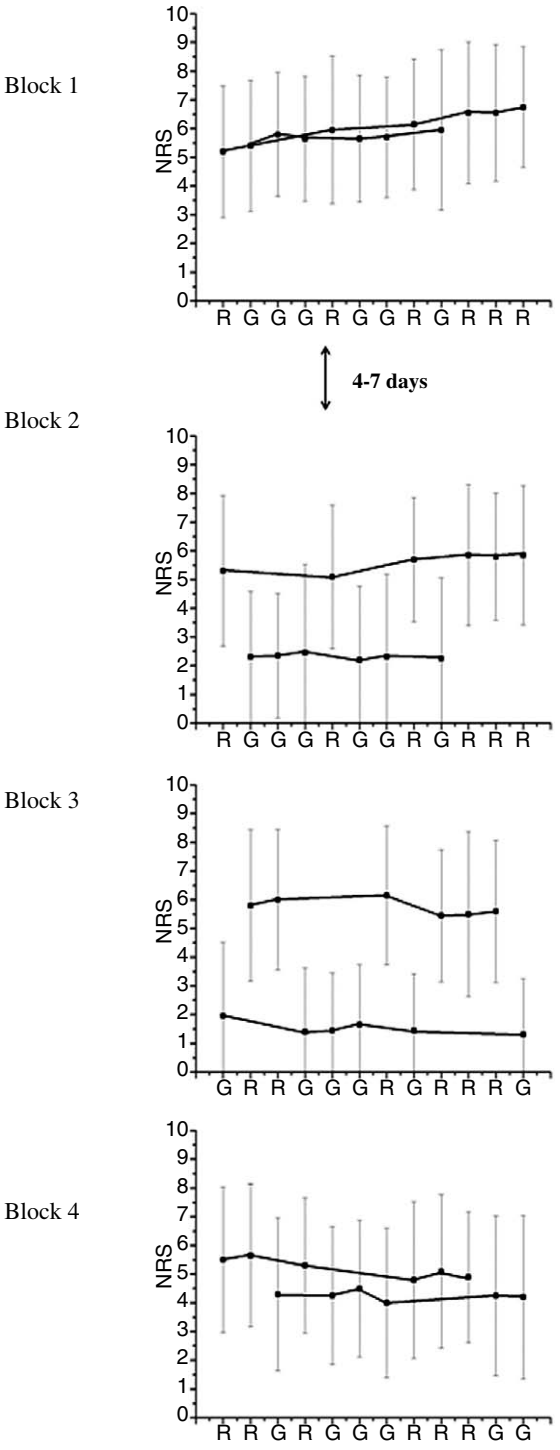

Fig. 4. Intra-block and inter-block pain reports in Group 3. As in Fig. 3, placebo analgesia is expressed as the difference between red-associated and green-associated pain reports within each block. In block 1 all the stimuli were painful but the red light anticipated pain whilst the green light anticipated analgesia. In this condition, no placebo analgesic responses were elicited. In blocks 2 and 3, the surreptitious reduction of stimulus intensity, which was associated to the green light, induced a decrease of pain reports only when the green light was presented. Block 4 did not differ from block 1. Note that no intra-block (block 4) extinction occurred.

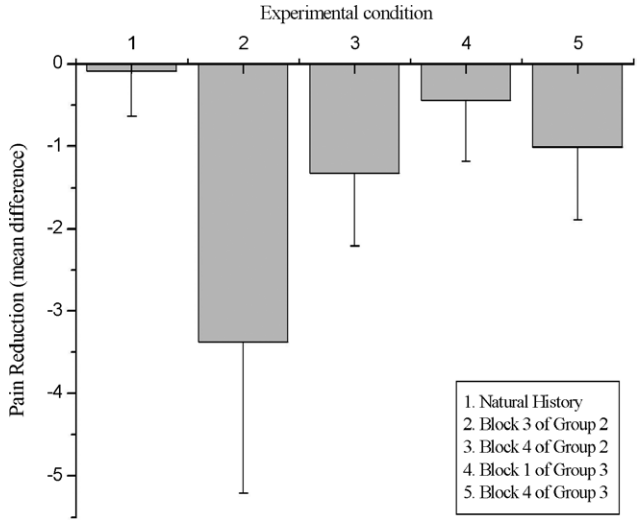

Fig. 5. Summary of the results, in which placebo pain reduction is expressed as the mean difference between red light- and green light-associated pain reports. Note that different degrees of placebo responses (small, medium and large) could be elicited, depending on the experimental condition.

at all (block 1 of Group 3), depending on whether they are given for the first time or after a conditioning procedure. In addition, placebo responses are more effective after minutes from the conditioning procedure (block 3 of Group 2) than after days and after an extinction trial (block 4 of Group 2). Therefore, both prior positive or negative experiences and time lags affect the magnitude of placebo analgesia. By performing a Dunnett test for multiple comparisons, we found that the experimental conditions 2 and 3 of Fig. 5 were significantly different from condition 1 (natural history group) ($p < 0.001$ and $p < 0.03$, respectively), thus indicating the occurrence of a significant placebo effect, whereas the experimental conditions 4 and 5 did not differ from the natural history group ($p = 0.601$ and $p = 0.137$, respectively).

4. Discussion

In this study, at least two interesting findings emerge. First, prior experience of a therapeutic intervention shapes the magnitude of the analgesic effect induced by the administration of a placebo. This modulation occurs for both positive and negative experiences, so that the placebo responses can be large in the former case and small in the latter. Second, the effects of a conditioning procedure have both short- and long-lasting effects, which may last several days. Overall, these findings suggest that the placebo effect is a learning phenomenon and that the large variability of the placebo responses in different studies might depend, at least in some circumstances, on previous different therapeutic experiences.

We would like to emphasize some important methodological considerations that emerge from the present study. One of the reasons why we chose this experimental paradigm is that we wanted to compare painful stimuli with non-painful stimuli in each block, without relying on absolute scores across different blocks. In other words, we preferred to measure the difference between red light-associated and green light-associated subjective reports in order to overcome the possible, and indeed real, variability across different sessions. Indeed, the present work shows that, whereas absolute pain reports varied over time, relative analgesic responses, as obtained by the continuous comparison between a baseline pain stimulus (red light) and a test stimulus (green light), were more reliable in assessing placebo effects.

Some limitations of the general implications of this study need to be mentioned and discussed. For example, in our work prior experience of a therapeutic intervention, either positive or negative, was represented by a simulation (surreptitious reduction of stimulus intensity) in healthy volunteers. Thus it does not necessarily reflect a real situation in the clinical setting. In fact, a clinical situation is certainly different from the present one, and the concept of prior positive or negative therapeutic experience in our experimental conditions requires some caution in the interpretation of the results. However, it should be noted that many similarities have been found in previous studies between the experimental and the clinical setting, and indeed most of the phenomenological and physiological understanding of placebo analgesia has been achieved in experimental healthy subjects (Benedetti et al., 2005; Colloca and Benedetti, 2005; Finniss and Benedetti, 2005). A second limitation is represented by the fact that we used a phasic stimulation with pain stimuli of very short duration. In this case also, this type of pain is very different from the clinical situation, whereby pain is typically persistent and of long duration. A third limitation is that we did not assess subject expectancies, so that no definitive conclusion about the role of subjects' expectations can be drawn. However, it should be stressed that the main aim of this work was to study different circumstances in which a placebo response could be elicited, and to see whether these different conditions elicited similar or different responses.

Despite these limitations, that are inherent to the experimental setting, it should be emphasized that early clinical observations had already found the important role of prior therapeutic experience in the responsiveness to placebos. For example, a placebo given before an active treatment is less effective than when given after an effective treatment (Lasagna et al., 1954; Kantor et al., 1966; Batterman and Lower, 1968; Laska and Sunshine, 1973; Ader, 1997). Likewise, prior exposure to effective pharmacological agents has been found to

produce very strong placebo responses in different pathological conditions, such as Parkinson's disease (de la Fuente-Fernandez et al., 2001; Benedetti et al., 2004), immune response (Olness and Ader, 1992; Giang et al., 1996; Goebel et al., 2002; Ader, 2003), hormonal secretion (Benedetti et al., 2003) and respiratory depression (Benedetti et al., 1998, 1999). In addition, a very recent study emphasized the role of learning in the placebo effect in an experimental paradigm in which anxiety was assessed (Petrovic et al., 2005).

In the present study, the advantage of investigating an experimental situation in healthy volunteers was represented by the fact that both pain stimuli and time lags were strictly controlled. We used different time intervals between the conditioning procedure and the assessment of the placebo responses in order to analyze both short- and long-lasting effects. Indeed, one of the most interesting findings in our work is that the effects of a conditioning procedure lasted, albeit reduced, several days. This occurred for both a positive therapeutic experience (conditioning in Group 2) and a negative experience (Group 3). It should be noted, however, that the reduction of the placebo effect could also be due to the extinction trial (e.g., block 3 of Group 2). It should also be pointed out that no intra-block extinction occurred in blocks 3 and 4 of Group 2, and in block 4 of Group 3. In fact, in these blocks, the green light was associated to painful stimuli. This represents an interesting finding, as it shows that, at least in our experimental conditions, no short-term (within minutes) extinction occurs.

Another advantage of studying prior experience in the experimental setting was represented by the fact that either positive or negative experience could be tracked back in time with precision, both qualitatively and quantitatively. It will be interesting in future research and under strictly controlled conditions to assess how effective and ineffective drugs shape subsequent placebo responses in both the experimental and clinical setting. In fact, although some experimental evidence suggests that effective drugs shape the magnitude of subsequent placebo responses (Goebel et al., 2002; Benedetti et al., 2003; Benedetti et al., 2004; Petrovic et al., 2005), evidence for the opposite effect is scanty or completely lacking.

Overall, our work shows that small, medium, large placebo responses, or no response at all, can be obtained in different circumstances, even though the same procedure is apparently used. For example, as shown in Fig. 5, a surreptitious conditioning procedure may result in either large or small placebo responses, depending on the previous negative analgesic experience of 4–7 days before. Similarly, verbal suggestions alone may result in significant placebo responses or no response at all, depending on whether they are given for the first time or after a conditioning procedure. In this regard, our present results, in contrast with previous studies (for a review, see Colloca and Benedetti, 2005), show that verbally induced expectations of analgesia alone are not enough to evoke a significant placebo effect (block 1 of Fig. 4). This may be due to our different experimental conditions. For example, a sequence as long as 12 painful stimuli may not represent the appropriate experimental approach to evoke significant verbally induced effects.

It goes without saying that in the clinical setting and in clinical trials it is extremely difficult to understand the previous experiences of the patients, so that a large variability of the placebo responses can remain unexplained in most of the studies. In addition, it should be stressed again that our study shows that placebo responses are more effective after minutes from the conditioning procedure than after days. Thus, although the type of prior therapeutic experience certainly matters, the time interval also plays a crucial role, as the effects of prior experience fade over time.

According to the present work, the placebo analgesic effect is a learning phenomenon that relies on prior experience, although the underlying mechanisms are not yet clear (either expectation or conditioning). However, many lines of evidence indicate that, at least for analgesia, expectation plays a crucial role (Montgomery and Kirsch, 1997; Benedetti et al., 2003), which is in agreement with recent theories of classical conditioning. These suggest that cognitive elements are involved in Pavlovian conditioning on the basis of the information that the conditioned stimulus provides about the unconditioned stimulus (Reiss, 1980; Rescorla, 1988; Kirsch et al., 2004b). In other words, the conditioning procedure we used produced increased expectations of benefit. This concept is supported by the long-lasting effects of block 1 in Group 3, whereby reduced expectations of a positive effect, because of a negative therapeutic experience, lasted several days and antagonized the effects of a conditioning procedure.

We believe that any investigation of the placebo effect as well any therapeutic procedure in clinical practice and clinical trials should take these findings into consideration, as the implications might be very important. For example, in the clinical trial setting, different results could be obtained if no scrupulous retrospective analysis of therapeutic successes and failures is performed. Similarly, in medical practice early therapeutic failures may affect the response to subsequent treatments. We understand that in routine medical practice the assessment of early therapeutic experiences is extremely difficult to perform, but we believe that this way of reasoning is worthy of further analysis.

Acknowledgements

This work was supported by the Italian Ministry of University and Research with a FIRB grant (RBNE01SZB) and a COFIN2004 grant.

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