Pain 136 (2008) 211–218

PAIN

www.elsevier.com/locate/pain

The role of learning in nocebo and placebo effects

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Received 26 September 2007; received in revised form 10 December 2007; accepted 4 February 2008

Abstract

The nocebo effect consists in delivering verbal suggestions of negative outcomes so that the subject expects clinical worsening. Here we show that nocebo suggestions, in which expectation of pain increase is induced, are capable of producing both hyperalgesic and allodynic responses. By extending previous findings on the placebo effect, we investigated the role of learning in the nocebo effect by means of a conditioning procedure. To do this, verbal suggestions of pain increase were given to healthy volunteers before administration of either tactile or low-intensity painful electrical stimuli. This nocebo procedure was also carried out after a pre-conditioning session in which two different conditioned visual stimuli were associated to either pain or no-pain. Pain perception was assessed by means of a Numerical Rating Scale raging from 0 = tactile to 10 = maximum imaginable pain. We found that verbal suggestions alone, without prior conditioning, turned tactile stimuli into pain as well as low-intensity painful stimuli into high-intensity pain. A conditioning procedure produced similar effects, without significant differences. Therefore, in contrast to placebo analgesia, whereby a conditioning procedure elicits larger effects compared to verbal suggestions alone, learning seems to be less important in nocebo hyperalgesia. Overall, these findings indicate that, by defining hyperalgesia as an increase in pain sensitivity and allodynia as the perception of pain in response to innocuous stimulation, nocebos can indeed produce both hyperalgesic and allodynic effects. These results also suggest that learning is not important in nocebo hyperalgesia compared to placebo analgesia.

Keywords: Learning; Nocebo; Placebo; Allodynia; Hyperalgesia; Conditioning; Expectation

1. Introduction

Nocebo hyperalgesia represents the best model to study the mechanisms of the nocebo effect. However, there has been far less investigation of the nocebo effect compared with the placebo phenomenon, even though the clinical implications may carry the same degree of importance as those of the placebo effect [7,8].

Several studies indicate that negative verbal suggestions may result in the amplification of pain [19,30] and in the alteration of somatosensory perception [33]. In order to try to disentangle the effects of positive and negative cues on pain processing, several authors used brain imaging [16,20,23]. Expectation of pain increase has been found to enhance the activation of the thalamus, insula, prefrontal cortex, and anterior cingulate cortex. Conversely, expectation of decreased pain reduces the activation of pain-related brain regions [20]. Likewise, Lorenz et al. [23] described a negative and positive expectation-induced modulation of pain by using source localization analysis of brain electrical activity, showing that the dipole in the secondary somatosensory cortex was reduced when pain decrease was expected and enhanced when pain increase was expected. Furthermore, by using two visual cues, each conditioned to one of two noxious thermal stimuli (high and low), Keltner et al. [16] found that subjects' pain report and brain responses were higher when the noxious stimulation was anticipated by the high-intensity visual cue.

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0304-3959/$34.00
doi:10.1016/j.pain.2008.02.006

It is also worth noting that, by using tonic pain stimulation (ischemic arm pain) and by studying clinical pain (postoperative), along with the administration of an inert substance that the subjects believed to be a hyperalgesic drug, Benedetti et al. [4,6] showed robust nocebo responses to verbal suggestions alone, which were mediated by cholecystokinin.

Whereas the differential contribution of expectation and conditioning in nocebo hyperalgesia is not known, in placebo analgesia it has been tested in many studies [for a review see Ref. 8]. There is now general agreement that placebo analgesia is stronger when the subjects have had prior positive experiences with effective analgesics. For example, we showed that both small, medium, and large placebo responses can be obtained, depending on the past positive or negative experience of an analgesic treatment. In addition, these placebo responses lasted four-seven days [9]. In a second group of volunteers of the same study, the same procedure was repeated four–seven days after a totally ineffective analgesic treatment. In this case, the placebo responses were remarkably reduced in comparison to the first group, pointing out that the placebo effect is a learning phenomenon.

By taking all these considerations into account, we wanted to investigate the role of learning in nocebo hyperalgesia, as we did for placebo analgesia [9]. To do this, we compared the magnitude of the nocebo hyperalgesic effect following verbal suggestions alone and following a conditioning procedure, in order to see whether, as occurs in placebo analgesia, prior experience shapes the nocebo responses.

2. Materials and methods

2.1. Subjects

A total of 116 female healthy volunteers (mean age 22.3 ± 2.4) were recruited from the University of Turin and all signed an informed consent prior to the study. All the experimental procedures were conducted in conformance with the declaration of Helsinki. The subjects were subdivided into four experimental conditions and randomly assigned to one of eight groups (Table 1). The three nocebo conditions were aimed at studying the modulation of low tactile, high tactile and low-intensity painful stimuli. In addition, we included a fourth condition with two additional placebo groups, which reproduces part of the study by Colloca and Benedetti [9].

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 $= 1 \times 2.5$ cm) connected to a constant current unit, thus avoiding the variability of skin-electrode impedance, according to the procedure by Colloca and Benedetti [9]. 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 lasting 7 s, repetitively (6 red + 6 green) and randomly administered (Fig. 1). Depending on the experimental condition, the intensity, expressed in mA, was set either above or below the pain threshold (T) (see Table 1).

2.3. Experimental procedure

We first assessed tactile (stimulus detection) and pain threshold (T) according to the following procedure. An ascending series of stimuli (steps of 1 mA) was delivered starting at sub-tactile threshold, until tactile sensation (detection threshold $= t$) and pain sensation (pain threshold $= T$) were induced. After determination of T, each subject was randomly assigned to one of the four experimental conditions and then to either the verbal suggestion or the conditioning group (Table 1). Before each session started, the green- and red-stimuli were delivered once in order to make the subjects familiarize with the experimental protocol.

As to the verbal suggestion groups of the three nocebo conditions, verbal instructions of pain increase were given to the volunteers before administration of a low tactile stimulus at T minus 4 mA ($T-4$) (condition 1, Group 1), high tactile stimulus at T minus 2 ($T-2$) (condition 2, Group 3) or a painful stimulus at $1.5T$ (condition 3, Group 5). The subjects were told that a green light would anticipate a stimulus that was made painful by the stimulation of the middle finger. In fact, a sham electrode was applied to the middle finger of the experimental hand, and the subjects were told that the green light anticipated the activation of this electrode that, in turn, induced a hyperalgesic effect [see Ref. 9 for further details]. The subjects were also informed that a red light would anticipate a low tactile (Group 1), high tactile (Group 3), or low-intensity painful stimulus (Group 5). Actually, all the stimuli were set at $T-4$ (low tactile, Group 1), $T-2$ (high tactile, Group 3), $1.5T$ (painful, Group 5), respectively (see Fig. 1).

In order to assess the effect of prior experience, the nocebo procedure was carried out after a pre-conditioning session in Groups 2, 4, and 6 (Fig. 1). In this case, the first and second block of stimuli consisted of six low tactile (condition 1, Group 2), high tactile (condition 2, Group 4), or painful at $1.5T$ (condition 3, Group 6) stimuli associated to the red light and six painful stimuli, whose intensity was surreptitiously increased to $2T$ (Groups 2 and 4) and to $3T$ (Group 6), associated to the green light. In the third block, we used the same random sequence of red and green lights, but all the 12 stimuli were set at $T-4$ (low tactile, Group 2), $T-2$ (high tactile, Group 4), $1.5T$ (painful, Group 6).

The fourth condition consisted in two groups (Fig. 1). The first received placebo verbal suggestions alone and the second received placebo verbal suggestion after a pre-conditioning procedure. In this case, the subjects were told that a green light would anticipate a stimulus that was made analgesic by the stimulation of the middle finger where a sham electrode had been applied [see Ref. 9 for further details]. They were also told that a red light would anticipate a painful stimulation. In the case of verbal suggestions alone, all the 12 stimuli were set at $2T$ (condition 4, Group 7). Subjects assigned to the placebo conditioning group (condition 4, Group 8) received a first and second block of 6 painful stimuli at $2T$ that were associated to the red light and six tactile stimuli at $T-2$ that were

Table 1
Characteristics of subjects for each experimental group

Condition	Group	*n*	Age	Procedure	Intensity of stimulation
1	1	14	22.71 ± 3.56	Nocebo verbal suggestion	$T-4$
	2	15	23.13 ± 3.36	Nocebo verbal suggestion after pre-conditioning	$T-4$
2	3	14	21.57 ± 1.34	Nocebo verbal suggestion	$T-2$
	4	15	22.87 ± 2.75	Nocebo verbal suggestion after pre-conditioning	$T-2$
3	5	14	21.43 ± 0.76	Nocebo verbal suggestion	$1.5T$
	6	15	22.40 ± 1.76	Nocebo verbal suggestion after pre-conditioning	$1.5T$
4	7	14	22.57 ± 2.31	Placebo verbal suggestion	$2T$
	8	15	22.33 ± 2.44	placebo verbal suggestion after pre-conditioning	$2T$

T = pain threshold expressed in mA.
$T-2$ = pain threshold minus 2 mA.
$T-4$ = pain threshold minus 4 mA.
$1.5T$ = pain threshold × 1.5.
$2T$ = pain threshold × 2.

associated to the green light. In this way, the green light simulated an analgesic effect [9]. In the third block, all the 12 stimuli were painful ($2T$), as shown in Fig. 1.

The mean values of stimulus intensity were the following: $T-4 = 5.9 \pm 2.4$ mA; $T-2 = 8.15 \pm 5.3$ mA; $1.5T = 17 \pm 11.1$ mA; $2T = 25.4 \pm 10.6$ mA. In all the experimental conditions, at the end of each stimulation, tactile and pain intensity was assessed by means of Numerical Rating Scale (NRS), ranging from 0 = tactile to 10 = maximum imaginable pain.

2.4. 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. Within-subjects ANOVAs were used to assess the effects of treatment (levels 2) and time (levels 6) in Groups 1, 3, 5 and 7. The within-subjects ANOVA included the factor treatment (levels 2), blocks (levels 3) and time (levels 6) in the case of Groups 2, 4, 6, and 8. The *F*-tests were followed by simple contrasts and the Bonferroni *post-hoc* tests for multiple comparisons. In order to compare the effects induced by verbal suggestion alone and conditioning for each condition, we expressed the nocebo/placebo responses as the difference between green-associated and red-associated NRS scores within each single block. We performed a supplementary ANOVA for repeated measures on the difference between green-associated and red-associated NRS scores with group as between- factor. Finally, we performed a 2 × 3 ANOVA on nocebo-test blocks of conditions 1, 2 and 3, whose between-factors were prior experience (conditioning/no-conditioning) and stimulation level ($T-4$, $T-2$, $1.5T$). The level of significance was set at $p < 0.05$. All the analyses were carried out by using SPSS for Windows software, version 12.0 (SSPS Inc, Chicago, Illinois, USA).

3. Results

3.1. Condition 1

Group 1. Repeated measures ANOVA of the NRS scores revealed a main effect for treatment ($F_{(1,13)} = 11.469$, $p < 0.005$) demonstrating that subjects rated a low tactile stimulus consistently as painful when they expected a noxious stimulus (Fig. 2), although an intra-trial variability was present ($F_{(5,65)} = 3.585$, $p = 0.006$) with an interaction treatment × trials not significant ($F_{(5,65)} = 0.574$, $p = 0.719$).

Group 2. After conditioning, in block 3, green-associated stimuli were rated as significantly painful compared with red-associated stimuli (Fig. 2). We found a main effect for treatment ($F_{(1,14)} = 183.417$, $p < 0.0001$) and blocks ($F_{(2,28)} = 65.874$, $p < 0.0001$), with a significant interaction between the two factors ($F_{(2,28)} = 65.117$, $p < 0.0001$). The intra-trial effects were not significant ($F_{(5,70)} = 0.660$, $p = 0.655$), thus confirming the stable conditions of the responses over time, with neither habituation nor sensitization effects. The *post-hoc* Bonferroni test for multiple comparisons shows that the difference between green-associated and red-associated NRS reports of block 3 was different with respect to block 1 ($p < 0.0001$) and block 2 ($p < 0.0001$), whereas no difference was present between blocks 1 and 2 ($p = 1.000$).

Group 1 versus Group 2. By expressing the nocebo hyperalgesic responses as the difference between green- and red-associated NRS reports, Group1 was not different from block 3 of Group 3 ($F_{(1,27)} = 0.127$, $p = 0.725$), which indicates that prior experience did not enhance the allodynic effects of verbal suggestions.

3.2. Condition 2

Group 3. The subjects rated a high tactile stimulus constantly as painful when they expected a noxious stimulus [Fig. 2; main effect for treatment ($F_{(1,13)} = 15.808$, $p < 0.002$) and no effect for time ($F_{(5,65)} = 0.915$, $p = 0.477$)].

Group 4. We found a main effect for treatment ($F_{(1,14)} = 118.199$, $p < 0.0001$) and blocks ($F_{(2,28)} = 67.750$, $p < 0.0001$) with a significant interaction treatment × blocks ($F_{(2,28)} = 65.117$, $p < 0.0001$). No intra-trials differences were present ($F_{(5,70)} = 0.872$, $p = 0.505$). The *post-hoc* Bonferroni test showed that block

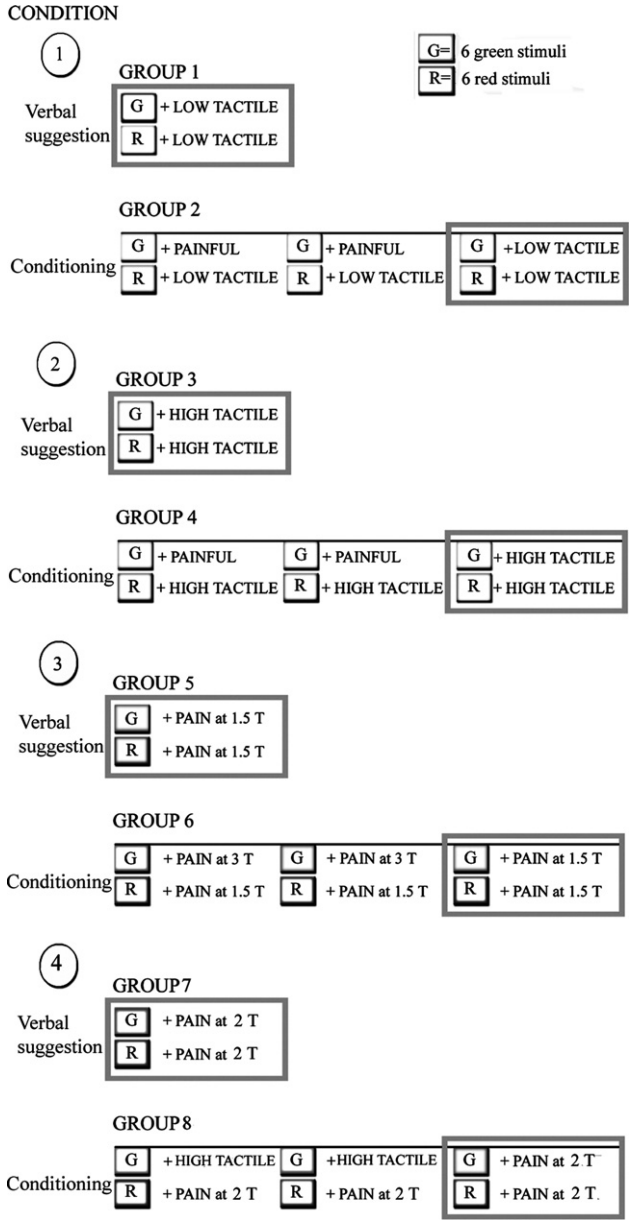

Fig. 1. Experimental conditions and groups used in the present study. It can be seen that there were three nocebo conditions (1, 2, 3) and one placebo condition (4). The grey panels show the experimental trials used for studying the differential role of verbal suggestion and learning in the nocebo and placebo responses.

3 was different with respect to block 1 ($p < 0.0001$) and block 2 ($p < 0.0001$) and no differences were present between blocks 1 and 2 ($p = 1.000$).

Group 3 versus Group 4. Group 3 was not different from block 3 of Group 4 ($F_{(1,27)} = 0.345$, $p = 0.562$), which indicates that prior experience did not enhance the allodynic effects of verbal suggestions.

3.3. Condition 3

Group 5. Low painful stimuli were rated as more painful when the subjects expected a high-intensity noxious stimulus [main effect for treatment ($F_{(1,13)} = 10.307$, $p < 0.007$); no intra-trials differences ($F_{(5,65)} = 1.859$, $p = 0.114$); see Fig. 2].

Group 6. After conditioning, the low painful stimulus was rated as more painful [Fig. 2; main effect for treatment ($F_{(1,14)} = 96.261$, $p < 0.0001$), for blocks ($F_{(2,28)} = 15.741$, $p < 0.0001$) with a significant interaction treatment × blocks ($F_{(2,28)} = 12.434$, $p < 0.0001$). The *post-hoc* Bonferroni test showed that block 3 differed from both block 1 ($p < 0.0001$) and block 2 ($p < 0.0001$), whereas no difference was present between blocks 1 and 2 ($p = 1.000$). Neither habituation nor sensitization was present, as indicated by no intra-trial differences ($F_{(5,70)} = 0.477$, $p = 0.792$)].

Group 5 versus Group 6. Group 5 was not different from block 3 of Group 6 ($F_{(1,27)} = 1.185$, $p = 0.286$), which again indicates that prior experience did not enhance the hyperalgesic effects of verbal suggestions.

3.4. Condition 4

Group 7. Verbal placebo suggestions were ineffective in inducing significant placebo responses, and we found only a tendency to significance [main effect for treatment ($F_{(1,13)} = 4.121$, $p < 0.063$)].

Group 8. After conditioning, we found that green-associated stimuli were rated as significantly analgesic compared with red-associated stimuli [main effect for treatment ($F_{(1,14)} = 193.521$, $p < 0.0001$), blocks ($F_{(2,27)} = 11.117$, $p < 0.0001$), with a significant interaction ($F_{(2,28)} = 28.121$, $p < 0.0001$)]. No intra-trials differences were present ($F_{(5,70)} = 1.034$, $p = 0.405$). *The post-hoc* Bonferroni test showed that block 3 was different with respect to block 1 ($p < 0.0001$) and block 2 ($p < 0.0001$), with no differences between blocks 1 and 2 ($p = 1.000$)].

Group 7 versus Group 8. By expressing the placebo analgesic responses as the difference between green- and red-associated NRS reports, block 3 of Group 8 showed placebo responses that were significantly different from Group 7 ($F_{(1,27)} = 42.857$, $p < 0.0001$), which indicates that prior experience was crucial to induce placebo responses (Fig. 2).

We summarized the effects of the different experimental procedures, by averaging the differences between green- and red-associated NRS reports in each group, as shown in Fig. 3. It can be seen that, whereas no significant differences between verbal suggestion alone and conditioning were present in the three nocebo conditions, the conditioning procedure was fundamental to induce the placebo analgesic responses. Thus, whereas learning was important in placebo analgesia, it had no different effects with respect to verbally-induced responses on nocebo effect. In order to explain this finding, we further tested the role of prior experience on nocebo effects by performing a 2×3 ANOVA, with

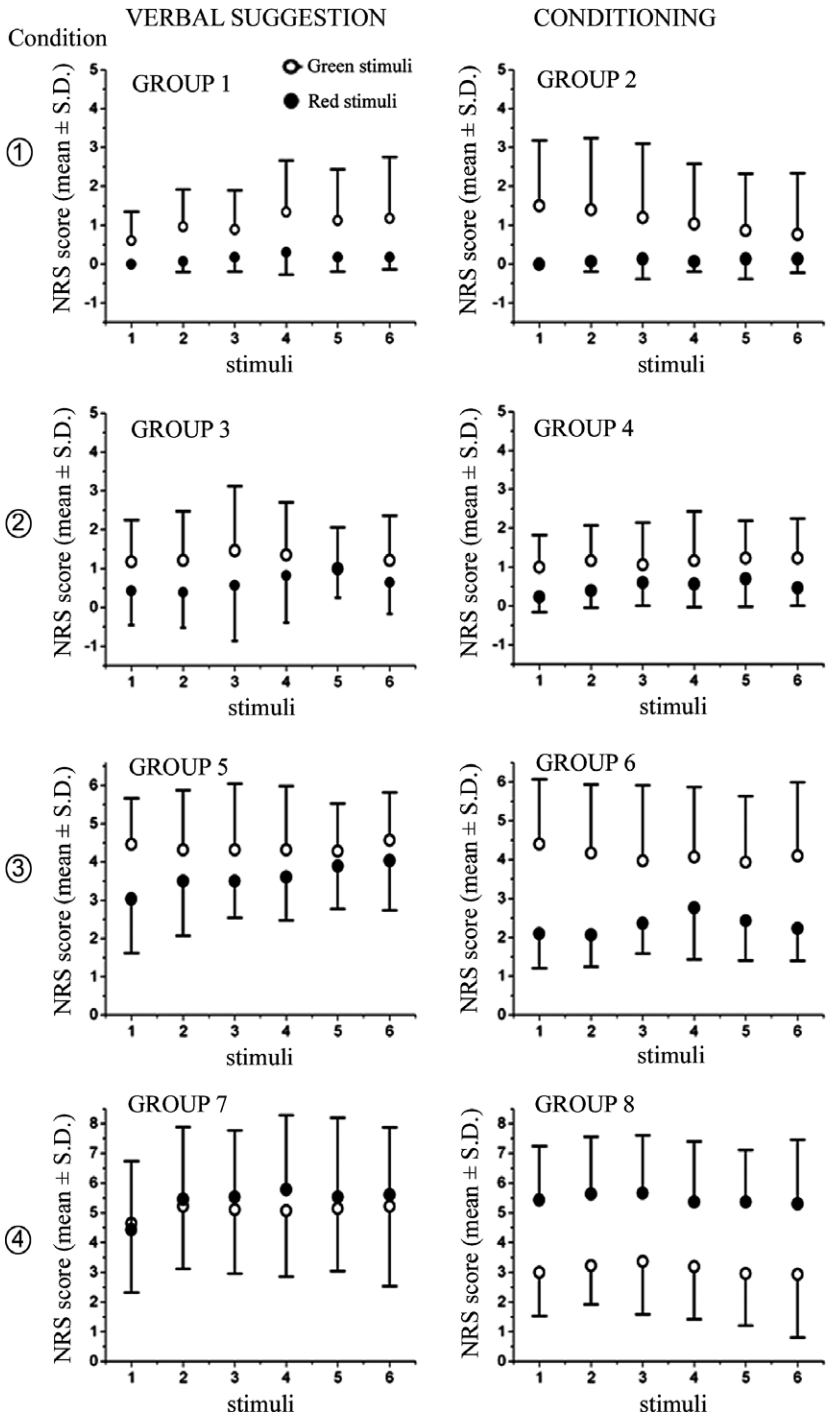

Fig. 2. The graphics show the nocebo (conditions 1, 2, 3) and placebo (condition 4) responses following verbal suggestions alone (Groups 1, 3, 5, 7) and conditioning (Groups 2, 4, 6, 8). Note that, whereas no differences are present between verbal suggestions alone and conditioning in the nocebo conditions, a significant increase after conditioning occurs in the placebo condition.

nocebo-test blocks (see the panels of Fig. 1), whose between-factors were prior experience (conditioning/no-conditioning) and stimulation level ($T-4$, $T-2$, $1.5T$) across conditions 1, 2 and 3. Again, we found that prior experience did not influence the nocebo responses ($F_{(1,81)} = 0.506$, $p = 0.479$). However, the responses were sensible to the level of stimulation ($F_{(2,81)} = 3.245$, $p < 0.044$). The interaction between prior experience and stimulation level was not significant ($F_{(2,81)} = 0.678$, $p = 0.510$), suggesting that, at least in this experimental situation, the effects of learning do not depend on the levels of stimulation.

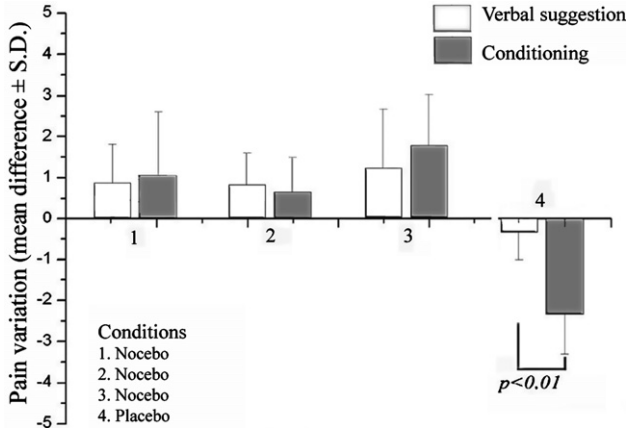

Fig. 3. Average of the responses in each group. It can be seen that the mean response in the groups that received verbal suggestions alone (1, 3, 5) was not different from those in the groups that underwent conditioning (2, 4, 6) in the three nocebo conditions. By contrast, in the placebo condition, Group 7 (verbal suggestions) did not show significant responses whereas Group 8 (conditioning) showed substantial placebo responses.

4. Discussion

The aim of the present study was to delineate the differential contribution of verbal suggestions alone and learning to nocebo and placebo responses. At least three findings emerge. First, stimuli associated to the green light along with the verbal suggestion of worsening, with or without pre-conditioning, were capable of turning both low and high non-painful tactile stimuli into pain. Thus nocebos can produce allodynic effects, whereby non-painful tactile stimuli become painful. Second, low-intensity painful stimuli were perceived as high-intensity stimuli after verbal suggestion of worsening, with or without pre-conditioning, indicating that nocebos can induce hyperalgesic effects, whereby low-intensity painful stimuli are perceived as high-intensity stimuli. Third, stimuli associated to the green light along with verbal suggestion of analgesia were ineffective to induce placebo responses, whereas a pre-conditioning procedure proved to be effective. Therefore, whereas learning did not matter in nocebo responses, it proved to be fundamental in placebo responses, in line with our previous study on placebo analgesia [9].

We would like to underline some terminological clarifications which are relevant to the present study. In fact, it is worth noting that we described our findings in terms of allodynia, hyperalgesia, and analgesia. Usually, allodynia and hyperalgesia refer to inflammatory and neuropathic pain, and their mechanisms are known to take place in the spinal cord. For example, allodynia can be produced through the activation of low-threshold myelinated Aβ fibres on an altered central nervous system and by a reduction in the threshold of peripheral nociceptor terminals. Likewise, hyperalgesia is the result of abnormal processing of nociceptor inputs [40]. Besides the underlying neurophysiological mechanisms, allodynia and hyperalgesia can be defined on the basis of psychophysical properties. Allodynia is the sensation of pain elicited by a non-noxious stimulus and hyperalgesia is an increased pain response to a suprathreshold noxious stimulus. Consistent with the psychophysical definition, we found that stimuli that would never normally produce pain began to do so after verbal suggestions of hyperalgesia. Similarly, noxious stimuli evoked greater pain following verbal suggestion of pain increase.

Another clarification that needs to be made concerns the meaning of learning. In fact, it should be stressed that the term learning refers to the influences of prior experience on a subsequent outcome. Therefore, as we did previously [9], a conditioning procedure was meant as a manipulation of the subject's experience. For example, some authors claim that conditioning plays an important role in the placebo response [1,34–39] and some others have tried to differentiate the role of expectation and conditioning [2,5,9,17,25,29,37], as well as the effect of learning in short- and long-lasting placebo responses [9,14,21,22]. However, cognitive interpretations of conditioning should also be taken into consideration [18,31,32]. For example, Montgomery and Kirsch [25], Benedetti et al. [5] and Colloca and Benedetti [9] found that previous experience with an effective analgesic can be reversed by subsequent verbal suggestions, thus indicating that, even following a conditioning procedure, expectation plays a key role.

Some limitations need also to be discussed. For example, the phasic electrical stimulation does not necessarily reproduce clinical pain. In fact, allodynia and hyperalgesia in patients can persist long after the initiating event. Although our approach is different from a real clinical condition, it offers the chance to overcome the ethical problem of investigating the nocebo effect in patients. A second limitation is represented by the fact that we did not assess expectations, thus limiting our understanding about the weight of subject's expectation on the pain reports. A third limitation is about the possible involvement of some personality traits in placebo/nocebo responsiveness, which we have not addressed in the present study. For example, we did not consider that pessimists might respond to nocebo suggestions more than optimists [12]. A fourth limitation is represented by the number of conditioning trials. In fact, we do not know whether the lack of difference between verbal suggestions and conditioning in the nocebo conditions is attributable to the number of pairings between the conditioned (visual) and the unconditioned (painful) stimulus. However, it should be noted that an equal number of conditioning trials produce a significant effect on placebo responses, as shown in the present study and in the study by Colloca and Benedetti [9]. Another possible

limitation is the comparison of the nocebo conditions with a single placebo condition that used a different stimulus intensity (2*T*). The reason why we used one placebo condition only is that we have already performed a detailed analysis of learning in placebo analgesia [9]. As to the possible effects of stimulus intensity, we found that the level of stimulation induced differences in nocebo responses, but did not interact with prior experience. Thus the difference between verbal suggestions and conditioning in the nocebo conditions is independent of the level of stimulation. Another limitation is represented by the subjective nature of the outcome measures, thus signal detection effect as well as biases cannot be ruled out completely.

It should be emphasized that several imaging studies have already investigated negative expectations and modulation of perception of visual, auditory, gustative and somatosensory processing [11,24,26,27]. As to the somatosensory system, recently, brain imaging studies have shed light on the neuroanatomical areas that are involved in the painful perception of an innocuous stimulus [33] and in the exacerbation of pain when subjects expect a high-intensity noxious stimulus [16,20,23,28]. From these studies, what emerges is the existence of overlapping brain areas that are engaged in the non-painful and painful perceptual experience. The increased anxiety and alertness levels might enhance perceptual processing leading to perceive non-painful tactile stimuli as painful and low-intensity painful stimuli as more painful. This is supported by some experimental evidence on the neurochemistry of the nocebo effect. Studies in humans [4,6] and animals [for reviews see Ref. 7,10,13] have suggested the important role of cholecystokinin (CCK) systems in linking anxiety and hyperalgesia. The selective CCK-B receptor antagonist, CI-988, has been found to prevent anxiety-induced hyperalgesia in a social-defeat model of anxiety in rats [3] and the non-specific CCK-antagonist for both CCK-A and CCK-B receptors, proglumide, has been found to interrupt the link between anxiety and pain, thus blocking nocebo-induced hyperalgesia [6].

It should also be pointed out that not only did we use negative suggestions of pain increase, but also an inert treatment, thus reproducing a true nocebo phenomenon. In fact, the sham stimulation of the third finger represents a real nocebo. In this regard, it is interesting that sham devices (e.g. sham needle for acupuncture) have shown greater effects than placebo pills on self-reported pain and severity of symptoms [15], and although we did not compare specifically our sham nocebo treatment with nocebo pills, it will be interesting to consider the possibility to perform this comparison in future studies.

Within this context, the findings of the present study show that learning is less important in nocebo hyperalgesia compared to placebo analgesia. It is plausible that nocebo expectations in response to electrical stimulation are strong enough without any prior experience because subjects interpret a shock as dangerous and potentially painful. Conversely, analgesic effects produced by an electrode may need to experience to be believed.

From a clinical point of view, these results have important implications for daily practice. If nocebo verbal suggestions are really powerful in eliciting a negative response, it is licit to think that the doctor's words and attitudes can induce immediate worsening of the severity of symptoms. From an evolutionary perspective, nocebo (aversive responses) and placebo (safety responses) pathways may represent two opposite contexts that coexist in the organism. Nocebos may induce short-term innate responses which are aimed at enhancing the perceptual processing and at anticipating negative outcomes, which helps initiate potentially defensive behavioral reactions. On the other hand, long-term responses based on learning may favorite the consolidation of expected outcomes, with a reduction of the severity of symptoms.

Acknowledgements

This work was supported by grants from Istituto San Paolo di Torino and from Regione Piemonte.

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