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# Placebo, Nocebo, and Learning Mechanisms

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## Abstract

Recent substantial laboratory and theoretical research hints for different learning mechanisms regulating the formation of placebo and nocebo responses. Moreover, psychological and biological variants may play a role as modulators of learning mechanisms underlying placebo and nocebo responses. In this chapter, we present pioneering and recent human and nonhuman research that has impressively increased our knowledge of learning mechanisms in the context of placebo and nocebo effects across different physiological processes and pathological conditions.

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**Keywords**

Conditioning • Expectation • Verbal suggestion • Observational learning • Drug-mimic effects • Vicarious hypoalgesia

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## 1 Introduction

Behavioral and neurobiological placebo and nocebo responses are formed by processing verbal instructions, conditioning, and social cues including observations and complex interpersonal interactions (Colloca et al. 2013a, b; Colloca and Miller 2011b). Verbal communication through suggestions of benefits from a certain treatment via persuasive words can induce placebo responses (Amanzio and Benedetti 1999). Conversely, verbal suggestion of harm creates an opposite phenomenon, by invoking a nocebo response (Benedetti et al. 2007a; Colloca and Miller 2011c). The experience of varying degrees of benefit through prior pharmacological and non-pharmacological conditioning creates subsequent behavioral and neurobiological placebo and nocebo responses depending respectively upon the positive or negative effect of the treatment (Colloca and Benedetti 2006; Colloca et al. 2008a). Finally, observing and interacting with other persons play a role in the formation of placebo and nocebo responses (Colloca and Benedetti 2009; Vogtle et al. 2013). Placebo and nocebo responses are elicited without any practice and direct experience, which are essential aspects in optimizing learning capabilities and probably survival mechanisms. It is likely that verbal conditioning and social cues are processed by the brain to generate dynamically updated expectations that, in turn, shape different symptoms and neurobiological responses.

We describe central concepts and learning mechanisms underpinning the formation of placebo and nocebo responses, and suggest promising future laboratory investigations to help expand our knowledge and provide valuable evidence of the effectiveness of placebo and nocebo responses in contexts other than pain.

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## 2 Pharmacological Conditioning

In this section, we present a series of studies that illustrate how different forms of learning impact placebo and nocebo responses in animals and humans.

Classical conditioning has been the prevalent paradigm to explain the genesis of placebo and nocebo responses in terms of learning principles and mechanisms. Therefore, we use the terms and concepts derived from Pavlov's classical experiments, demonstrating that dogs would salivate (conditioned response, CR) in response to a bell (conditioned stimulus, CS) that had previously been paired with the administration of food (unconditioned stimulus, US) (Pavlov 1927). These learned responses indicated that a ringing bell implied food, hence the salivary reaction upon hearing the bell. Similar to the conditioned stimulus of ringing a bell,

visual, tactile, and gustatory stimuli associated with the efficacy of a medication can also become conditioned stimuli through their repeated association with the unconditioned stimuli in the form of different active medication. Placebos given along with the presentation of CS and subsequently the US elicit CRs that are similar to the response to medication (Ader 1987).

## 2.1 Pharmacological Conditioning and Placebo Responses in Animals

A pioneering study by Alvarez-Buylla and Carrasco-Zanini (1960) investigated hypoglycemic conditioning by using insulin for eight consecutive days and then replacing insulin with saline solution in dogs. There were no appreciable differences in the magnitude of the hypoglycemic response to insulin compared to those induced by the conditioning stimulus saline given along with a metronome's sound. Interestingly, the authors tested for the different CS components, extinction, and mechanisms underlying the conditioned hypoglycemia. After having established the CR, the injection alone did not produce any CR, while the auditory stimulus elicited a hypoglycemic effect which was as great as that produced by the combination of injection and sound. When tested for extinction, the conditioned hypoglycemia diminished progressively and was totally extinguished on the fifth day. The CR was also tested in alloxan diabetic dogs and depancreatized dogs, respectively. Both presented a CR suggesting that the conditioned reflex was not related to the disease or the pancreas activity (Alvarez-Buylla and Carrasco-Zanini 1960).

A few years later, Woods and colleagues extended these pioneering observations by varying the number of conditioning trials and the CS nature to define the optimal values for a conditioned hypoglycemic reflex (Woods et al. 1969). Rats were tested with and without a menthol cue. The menthol cue consisted in an odor of menthol through a gauze pack taped to the inside of the chambers where the animals were kept between blood drawings. When the menthol cue was used, the acquisition of the conditioning was more rapid, the CR larger, and the development of a detectable CR faster compared to the conditioning without menthol cue (Woods et al. 1969).

Another study entitled "Placebo effect in the rat" by R.J. Herrnstein demonstrated that a pharmacological conditioning with 14 administrations of scopolamine paired with sweetened milk was able to induce a placebo response following the presentation of the pure sweetened milk alone (Herrnstein 1962). Herrnstein was one of the first scientists who interpreted the effect of the pharmacological conditioning as a placebo response in which the presentation of the conditioned stimulus (e.g., the sweetened milk) caused a scopolamine-like alteration of behavior such as the decrease in rates of a lever-pressing task (Herrnstein 1962).

Other authors have also pursued this line of research providing proof of concepts for the area of placebo research across different domains. Notably, Robert Ader introduced the concept that the immune system can be conditioned with potential

clinical benefits (Ader 1987; Ader et al. 1987, 1990, 1995). For example, Ader and Cohen used a schedule of pharmacological conditioning in which a novel saccharine-flavored solution was paired with the immunosuppressant, cyclophosphamide (Ader and Cohen 1982). The authors observed that merely giving a placebo such as saccharine solution following the administration of cyclophosphamide induced immunosuppression in rats. Interestingly, there was a dose–response effect: rats that received two doses of cyclophosphamide during the conditioning phase had greater conditioned immunosuppression responses than those which received one dose of cyclophosphamide, supporting the notion that the stronger the US effect, the more robust the CR. Ader and colleagues have also demonstrated that the antibody production can be conditioned using an antigen as an unconditioned stimulus of the immune system (Ader et al. 1993). Mice received repeated immunizations with keyhole limpet hemocyanin (KLH) paired with a gustatory conditioned stimulus. Subsequently, mice were reexposed to the gustatory stimulation alone and a conditioned enhancement of anti-KLH antibodies was found (Ader et al. 1993).

In a more recent experiment, Pacheco-López et al. conditioned rats with 0.2 % saccharin given just before the administration of the immunosuppressive drug cyclosporin A, which specifically inhibits calcineurin (Pacheco-Lopez et al. 2009). This experiment confirmed that the pharmacological properties of cyclosporin A could be elicited by the neutral stimulus behaviorally. Furthermore, the authors found that these effects were not limited to behaviors but impacted activity at the level of splenocytes. In fact, there was a change in the production of Th1-cytokine when the rats were reexposed to the saccharin alone. Therefore, the calcineurin activity in CD4 (+) T lymphocytes was identified as the intracellular target for inducing placebo immunosuppression after cyclosporin A exposure, suggesting that the use of placebos after a pharmacological conditioning triggers specific neurobiological pathways (Pacheco-Lopez et al. 2009).

More recently, Guo et al. investigated the effect of prior pharmacological opioid and non-opioid exposure in mice using a model of a hot-plate test (Guo et al. 2010). Conditioned cues were paired with either the opioid agonist morphine hydrochloride or non-opioid aspirin. Placebo analgesic responses evoked by morphine pharmacological conditioning were antagonized by naloxone suggesting that the opioidergic system mediates this effect. By contrast, after aspirin conditioning, the placebo responses were not blocked by naloxone indicating that the substance used during the conditioning phase triggers the underlying systems leading to a specific effect (Guo et al. 2010). In another study, the authors investigated the relation between receptors at the level of rACC and placebo analgesia finding that rACC is the key brain region involved in opioid-mediated placebo analgesia with a determinant role of  $\mu$ -opioid receptors (Zhang et al. 2013). Placebo analgesia has an effect that is transferable to other domains. After being conditioned with 10 mg of morphine in a model of pharmacologically induced placebo analgesia, plasma levels of corticosterone and ACTH were reduced and the effect produced significant changes to stress in a behavioral despair test (Guo et al. 2011).

Caution is urged in generalizing this knowledge. Pre-drug cues can also elicit conditioned compensatory responses (CCRs) that are opposite in direction to the US when tolerance, a decrease response to a drug within the course of administrations, is present. An early study by Subkov and Zilov (1937) showed that dogs treated with epinephrine every few days presented tachycardia that decreased over time developing tolerance. On a final test, epinephrine was replaced by inert Ringer's solution and an opposite bradycardic response was observed. Many other studies have shown that when tolerance occurs, pre-drug cues can elicit paradoxical CCRs on pharmacological tolerance likewise because pharmacological stimulations initiate adaptive responses that compensate for the primary drug effect (Siegel et al. 2000).

## **2.2 Pharmacological Conditioning and Placebo Responses in Humans**

The above-described studies in animals have been partially repeated in human patients with immune disorders. Based on these findings, the pharmacological conditioning of the immune system appears to be an important result because it is suggestive of potential influences of conditioned placebo responses during the course of specific symptoms and the response to a pharmacological immune therapy. Importantly, Ader and colleagues have attempted to provide proof-of-concept evidence that a schedule of pharmacological reinforcement with immunosuppressors associated with placebos actually works in maintaining good clinical outcomes in patients suffering from immune disorders. For example, a child with lupus erythematosus was treated with cyclophosphamide given in association with a taste and smell beverage (Olness and Ader 1992). Remarkably, successful clinical outcomes were obtained by using taste and smell beverages alone on half of the monthly chemotherapeutic sessions. In another study, multiple sclerosis patients received four intravenous treatments with cyclophosphamide in association with anise-flavored syrup. Peripheral leukocyte count was assessed following the syrup alone, and eight out of ten patients displayed decreased peripheral leukocytes, an effect that mimicked that of cyclophosphamide (Giang et al. 1996).

Gobel et al. performed a similar experiment in which healthy subjects received cyclosporin A along with a strawberry-flavored milk drink (Goebel et al. 2002). The effects of conditioned immunosuppression were assessed by measuring interleukin-2 (IL-2) and interferon gamma (IFN-gamma) mRNA expression, in vitro release of IL-2 and IFN-gamma, and lymphocyte proliferation. A placebo given with the flavored drink significantly suppressed the immune functions in terms of interleukin-2 (IL-2) and interferon gamma (IFN-gamma) mRNA expression, in vitro release of IL-2 and IFN-gamma, as well as lymphocyte proliferation, revealing for the first time the mechanisms underlying conditioned immune responses (Goebel et al. 2002).

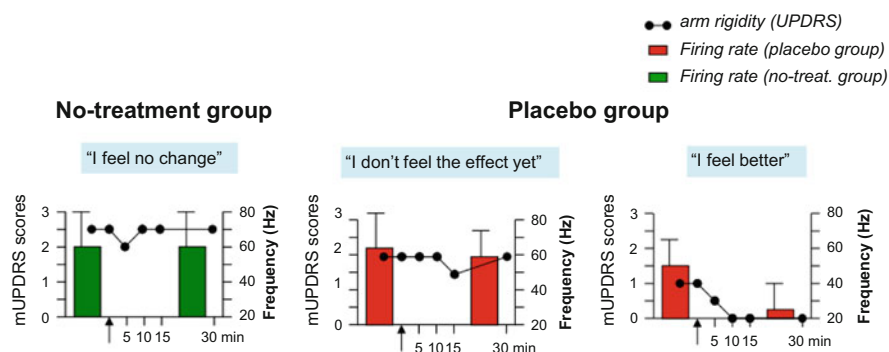
Conditioned placebo responses have also been demonstrated in conditions other than the immune system in human and animal experimental settings. Benedetti

et al. (2007a, b) demonstrated that a pharmacological conditioning with morphine induced robust placebo analgesic responses when morphine is replaced with a placebo (Benedetti et al. 2007b). Morphine was given twice at intervals of 1 week. The placebo without prior morphine conditioning induced a small but significant increase in pain tolerability, which indicates smaller effects when a placebo is given for the first time compared with its administration after pharmacological conditioning (Benedetti et al. 2007b). Amanzio and Benedetti had also shown that the administration of morphine for two consecutive days produced substantial placebo responses when the placebo is given on the third day (Amanzio and Benedetti 1999). Therefore, it is important to note that different schedules of pharmacological conditioning influenced elicited morphine-like effects, and that these effects last at least in a range of days and weeks. Interestingly, these observations suggest that a pharmacological conditioning procedure creates a memory of the learned response that can be re-evoked over time.

The effects of conditioning have been explored using other drugs such as the serotonin agonist of the 5-HT<sub>1B/1D</sub> receptors, sumatriptan, which stimulates growth hormone (GH) and inhibits cortisol secretion (Benedetti et al. 2003). The administration of a placebo after the repetitive administration of sumatriptan produced similar hormonal responses. Indeed, the placebo-induced GH increases and cortisol decreases (Benedetti et al. 2003).

Some additional human studies have adopted a pharmacological conditioning with drugs such as the dopamine agonist, apomorphine (Benedetti et al. 2004, 2009). A subcutaneous placebo was given after three repetitive subcutaneous administration of the dopaminergic agonist, apomorphine, to explore conditioned placebo responses at the level of single neurons in patients suffering from Parkinson's disease who underwent surgical implantation of electrodes for high-frequency deep brain stimulation. Notably, patients who showed a clear-cut conditioned placebo response, depicted clinically by a significant decrease of arm rigidity and subjective reports of well-being, presented a significant decrease of the neuronal discharge recorded at the level of the subthalamic region (Fig. 1). Nonresponders showed no differences in clinical assessment of rigidity, self-reports, and neuronal discharge characteristics. This study was the first one documenting a pharmacologically induced conditioned effect at the level of specific neuronal populations in Parkinson patients (Benedetti et al. 2004). The CR produced by the administration of the placebo induced effects similar to the neural patterns of activity elicited by apomorphine (Levy et al. 2001; Stefani et al. 2002). It remains obscure why only some patients respond to the pharmacological conditioning procedures.

Overall, these studies suggest that learned placebo responses following the exposure to drugs represent specific effects depending on the kind of drug exposure that is originally performed. These responses can be potentially relevant for clinical practice if we understand the underpinning mechanisms. Conditioned drug effects can be therapeutically exploited in routine clinical practice by integrating placebos in schedules of reinforcement, so that conditioned stimuli acquire properties and characteristics of USs. These effects, if generalizable, may become part of the



**Fig. 1** Placebo responses at the level of single neuronal activity. After a pharmacological conditioning with apomorphine, a placebo was given and variations in frequency of discharge of subthalamic single neuronal activity, report of self-being, and rigidity scores were assessed. Three representative patients with Parkinson Disease are depicted. The *first graph* represents the neurophysiological, clinical, and subjective responses for a patient assigned to the natural history group. No changes were observed for all the measures in the first graph. The *second and third graphs* show the responses measured from a placebo nonresponder and a placebo responder, respectively. No changes were observed in patients who were nonresponders. In contrast, those who responded to the placebo given after the pharmacological conditioning with apomorphine presented a change in the neurophysiological, clinical, and subjective outcomes [Data from Benedetti et al. (2004)]

pharmacotherapeutic protocol preserving therapeutic benefits while costs and side effects are likely reduced (Colloca and Miller 2011a).

In line with these considerations, a recent clinical trial showed that a schedule of conditioning with corticosteroids was effective in reducing the relapse of symptoms in patients with psoriasis (Ader et al. 2010). Patients with mild-to-moderate psoriasis received medication that was followed by unconditioned effects of the drug (100 % reinforcement schedule), or placebo medication that was never reinforced by the active medication. Indeed, the results were clinically comparable to the reduction in symptoms induced by a full dose of corticosteroids (Ader et al. 2010).

Recent research in children with Attention Deficit Hyperactivity Disorder indicates that placebo effects may have potential therapeutic applications (Sandler et al. 2008, 2010; Sandler and Bodfish 2008). Children were randomly assigned to 1 of 3 schedules of 8-week treatments: (1) reduction of amphetamine dose by pairing drug with placebos; (2) reduction of amphetamine without placebo substitution; or (3) full dose of amphetamine treatment. Children in arm 1 received an open placebo pill paired with 50 % reduced dose of amphetamine. The same reduction of treatment was performed in arm 2 but without placebos as cue (control group). Pairing a conditioned stimulus with amphetamines produced conditioned placebo responses that allowed children with ADHD to be treated effectively with a lower dose of psychostimulant medication. The placebo treatment was overtly described to both parents and children transparently (Sandler and Bodfish 2008). Parents and children were informed that placebos consisted of a pill with no

medication in it, thus overcoming the ethical problem of deception and consistent with requirements of informed consent.

Taken together, these studies in patients and research with placebos given after active pharmacological treatment suggest that placebo substitution may be understood as a specific way for promoting placebo effects. According to conditioning mechanisms, placebo effects can be strategically elicited on the basis of a planned sequence of drug and conditioned stimuli. A still open question is whether pharmacological conditioning produces side effects similar to those induced by the active treatment. It is plausible to think that side effects can be elicited as part of the conditioning processes. With this regard, Benedetti and colleagues used repeated administrations of analgesic doses of buprenorphine in postoperative patients, a treatment that produces a mild reduction of ventilation, to study the role of pharmacological conditioning on side effects. Placebos given after repetitive administration of buprenorphine produced mild reduction of ventilation mimicking the buprenorphine respiratory depressant response (Benedetti et al. 1998). This effect was reversible by the administration of naloxone, indicating the release of endogenous opioids that can account for the reduction in ventilation (Benedetti et al. 1999). Thus, conditioned placebo effects may expand to adverse events and this possibility deserves further investigation.

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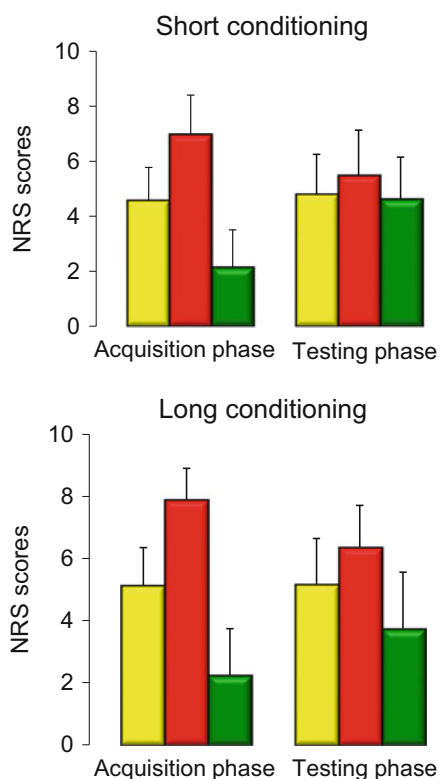
### **3 Non-pharmacological Conditioning and Placebo Responses**

Potentially, any CS-USs can induce strong placebo responses and the driving force for these effects is represented by the experience of efficacy and mastery induced by the USs during the conditioning phases. Based on this concept, simulation of efficacious treatments, such as surreptitiously reducing the intensity of painful stimulations delivered after a placebo cream, has been extensively used to produce models of studying placebo responses in various laboratory environments (Reiss 1980).

In a pioneering study, Price et al. used painful stimuli and a placebo cream to study placebo analgesia in healthy subjects (Price et al. 1999). The testing subjects were randomized to three experimental conditions receiving either a strong placebo (A), a weak placebo (B), or a control agent (C). The authors manipulated the intensity of the painful stimulation by decreasing it to 67 % in condition A and 17 % in condition B. No reduction was performed under condition C serving as control. Therefore, the placebo analgesic responses were contrasted with the experience of relief given during the conditioning phase. Those who received the strong placebo experienced the largest placebo analgesic response when a control level of pain was delivered. Conversely a lower placebo analgesic response was observed in condition B in which subjects were conditioned with small pain reduction (Price et al. 1999). The findings indicate that previous exposure to distinct intensities of the US determined the magnitude of the placebo effect.



**Fig. 2** Relationship between the number of conditioning trials and placebo and nocebo responses. *On the left*, runs of short and long conditioning schedules (acquisition phase) with high, medium, and low of pain are shown. Each square corresponds respectively to 10 (short conditioning) and 40 (long conditioning) trials of conditioning. *On the right*, placebo and nocebo responses are shown (testing phase). A short conditioning elicited modest placebo (*green*) and nocebo (*red*) responses as compared to a control condition (*yellow*). These effects showed extinction over time. By contrast a longer schedule of conditioning induced both robust placebo and nocebo responses that lasted over the entire experimental session [Data from Colloca et al. (2010)]



Notably, a recent study showed that the number of CS-US pairings impacts placebo responses. Colloca et al. used different schedules of full conditioning in which 10 vs. 40 CS-US pairings were delivered during the conditioning phase. Interestingly, there was a net relation between the magnitude of placebo and nocebo responses and the number of trials used for the conditioning (Colloca et al. 2010). The increase in number of associations during the conditioning resulted in robust placebo and nocebo responses that persisted over the entire experimental session as depicted in Fig. 2 (Colloca et al. 2010).

Research has also shown that prior experiences via conditioning impact placebo responsiveness (Colloca and Benedetti 2006; Kessner et al. 2013). For example, a positive, full-conditioning procedure induces robust analgesic responses of a subsequent placebo, but the identical procedure performed after an ineffective experience does not significantly impact the formation of placebo effects (Colloca and Benedetti 2006). The simulated effective intervention induced by reducing the intensity of painful stimulations induced robust analgesic responses in Group 1. A second group of subjects in the same study underwent a simulation of ineffective intervention with no reduction of intensity of painful stimulation, and after a time lag of 4–7 days, received the same effective manipulation as Group 1. As a result, the prior experience of ineffectiveness negatively impacted the effects of the

subsequent effective procedure suggesting that placebo analgesia is finely tuned by prior experience (either positive or negative), and that the effect of an initial intervention may influence the formation of future placebo responses (Colloca and Benedetti 2006).

Similar findings have been recently reported by Kessner et al. who used the same design to test the effect of intervention history in an fMRI study (Kessner et al. 2013). The placebo analgesia related to the tested intervention was lower in the negative intervention history group as compared to the positive. The negative prior experience reduced the effect of the following positive one and this reduction was maintained in the brain by a higher activation of the bilateral posterior insulae and regions related to afferent nociceptive processing, and a lower activation of the right dorsolateral prefrontal cortex that is also involved in nociceptive inhibition processes and placebo analgesia. The above and many other similar studies indicate that conditioning via pharmacological or biologically significant prior exposures is a key modulating factor of the placebo effect owing to the fact that learning mechanisms account for a wealth of behavioral and clinical placebo and nocebo responses (Kessner et al. 2013).

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#### **4 Verbal Communication, Reserve Information, and Memories**

It is necessary to clarify that the ability of one stimulus (CS) to evoke the original response by prior pairing with the US may only partially explain conditioned response in humans. Humans learn to anticipate relationships among events so that they can represent their own environment via verbal suggestions and observation. Therefore, while pairing and contiguity are determinant components, learning depends strongly on both the information that the CS provides about the US and the acquired awareness of a relation among events (Colloca and Miller 2011b; Kirsch 1985; Rescorla 1988a, b). This concept is well illustrated by studies focusing on the interactions of verbal suggestions and conditioned placebo effects.

In an earlier study, Voudouris and colleagues tested the effects of verbal suggestions and conditioning procedures (Voudouris et al. 1990). Healthy subjects underwent an iontophoretic pain stimulation attending four sessions during four consecutive days. During the first session, half the subjects were told that a topical cream was a powerful painkiller and would provide pain relief and the other half was told that the cream was a placebo. During the second session, half of the subjects received a cream (placebo) and the other half were given none. In the third session, half the subjects were conditioned by surreptitiously reducing the pain intensity after the application of placebo cream. The other half received the same pain stimulus. Thus, Group 1 received a combination of verbal suggestions and conditioning manipulation; Group 2 received verbal suggestions alone; Group 3 received conditioning alone; and Group 4 represented the control group. There was an enhancement of placebo responses in both Groups 1 and 3, but conditioning

was effective in eliciting placebo analgesia with and without verbal suggestions (Voudouris et al. 1990).

When studied at the level of both N1 and biphasic N2-P2 components of scalp laser-evoked potentials (LEPs), verbal suggestions and conditioning clearly show that conditioning modulates placebo analgesia (Colloca et al. 2008b; Wager et al. 2006). N1 is generated in the second somatosensory area, while N2-P2 is a biphasic negative–positive complex obtained at the vertex which originates in the bilateral operculo-insular areas and in the cingulate gyrus. It was observed that verbal suggestions induced modest LEP changes occurring without subjective perception of pain reduction, whilst N2-P2 amplitude reductions induced by the conditioning, were robust and occurred along with a subjective self-report of pain relief (Colloca et al. 2008b).

Recently, Fiorio and colleagues showed that while a conditioning manipulation influences tactile perception and the late components (N140 and P200) of the somatosensory evoked potentials (SEPs) (Fiorio et al. 2012), verbal suggestions alone did not change SEPs (Fiorio et al. 2014).

While it is clear that conditioning is the most effective procedure to elicit a placebo response, it is interesting to note that reverse verbal suggestions communicating conflicting and opposite information about the US can influence clinical outcomes and behaviors (Chung et al. 2007; Flaten et al. 1999; Luparello et al. 1970).

Luparello and coworkers reported significant increases in airway resistance in nearly half the asthmatic patients under investigation when they inhaled a nebulized saline solution along with the information that it was an allergen with irritant properties. Interestingly, these patients reversed their airway obstruction by inhaling the same substance presented as a medicine with beneficial effects on asthma. Similarly, the effects of the bronchoconstrictor carbachol were higher when it was administered along with the information that it was a bronchoconstrictor than when subjects were told it was a bronchodilator (Luparello et al. 1970).

Different outcomes were found in healthy participants who were given decaffeinated coffee under two different verbal suggestions: participants in Group 1 were told that they would receive either regular or decaffeinated coffee according to a double-blind design, while participants in Group 2 received decaffeinated coffee presented as real coffee. Placebo responses were higher in Group 2 rather than Group 1, suggesting that verbal suggestions may shape perception and sensation (Kirsch and Weixel 1988). Moreover, Flaten et al. showed that carisoprodol, a centrally acting muscle relaxant, resulted in opposite outcomes, either relaxant or stimulant, depending on the interaction of verbal suggestions and given drug, suggesting that instructional learning can strongly shape experiences based on a priori expectations (Flaten et al. 1999).

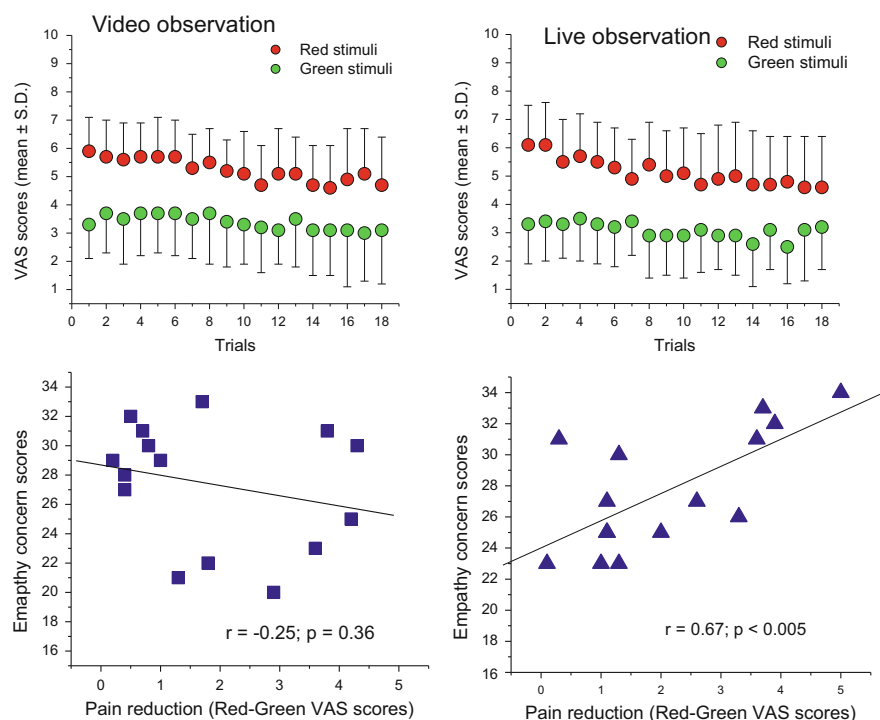
Communication can influence experience with negative outcomes (Colloca and Finniss 2012). Healthy participants were alerted to the hyperalgesic effect of a treatment perceived pain despite the intensity of stimulation was ranging from no-painful to low painful levels (Colloca et al. 2008a). Negative suggestions produced allodynic effects, whereby non-painful tactile stimuli become painful.

In addition, low-intensity painful stimuli were perceived as high-intensity stimuli after negative verbal suggestion, with or without preconditioning, indicating that nocebos can also induce hyperalgesic effects, whereby low-intensity painful stimuli are perceived as high-intensity stimuli (Colloca et al. 2008a). Rodriguez-Raecke et al. showed that contextual information given once at the beginning of the investigation indicating that repeated painful stimulations over several days would increase pain sensation from day to day, impacted pain perception over 8- and 90-day periods with brain changes at the level of the insula (Rodriguez-Raecke et al. 2010).

#### 4.1 Beyond Direct Experience: Learning from Others

Beyond firsthand experience, humans and animals learn by observing others in the absence of any direct reinforcement. Colloca and Benedetti first demonstrated that placebo analgesic effects could be elicited by observing the experience of another person (a demonstrator) who was carefully trained to simulate the analgesic experience (Colloca and Benedetti 2009). In the experiment, two silver chloride electrodes were applied to the back of the nondominant hand and a sham electrode was pasted above the subject's middle finger while a set of painful and non-painful stimuli were delivered. The demonstrator rated audibly the painful stimuli that were paired to a red light and the non-painful stimuli paired to a green light and the simulation of efficacious treatment. The experimental subjects paid attention to the entire session and at the end of this observational phase were asked to undergo a similar experimental session. However, the stimulus intensities were set at their painful level for both the green and the red stimuli. Interestingly, all the green painful stimuli were deemed less painful compared to the red-associated stimuli, indicating that observing a beneficial treatment in another person elicited placebo analgesia. The observed effects were stable over the entire experimental session (a total of 18 stimuli), showing no extinction and indicating implicit acquisition and retention of behavioral output. The effect size of observationally induced placebo analgesic responses was comparable to those induced by direct prior experience of analgesia via a conditioning schedule. The information drawn from observational learning may have established a self-projection into the future outcome boosting expectation of analgesia. The higher observationally induced placebo responses were reported by those subjects who had higher empathy scores suggesting that empathy might predict placebo analgesia elicited by observational learning (Colloca and Benedetti 2009).

We have further studied observationally induced placebo analgesia by looking at different components such as the live interaction with a demonstrator as compared to merely observing a video (Hunter et al. 2014). Testing subjects were randomized to watch either the video of the demonstrator or the same live demonstrator showing an analgesic benefit following the presentation of the green light. The subjects then received the same set of painful stimuli after the brief presentation of either a red or green light. The live face-to-face observation vs. a video replay induced similar



**Fig. 3** Observationally induced placebo analgesia and empathy. *At the top*, placebo analgesic scores induced by video and live face-to-face observation are depicted. Placebo analgesia was similarly induced by observing a video or a live demonstrator. *At the bottom*, correlations with empathetic scores are shown. A positive correlation with empathy was found for the live face-to-face observation only [Data from Hunter et al. (2014)]

placebo analgesic effects in terms of magnitude emphasizing that observation conveys potential cues to induce expectations of benefit and activate specific mechanisms independently of the social interactions. However, empathy strongly correlated with placebo analgesic responses in the live observation group only, but not in the video replay group (Fig. 3) (Hunter et al. 2014). These findings suggest that observation induces placebo analgesia and that empathy may facilitate these effects when live interactions are involved but without being a driving factor. Two recent studies confirming and extending the findings on vicarious learning have adopted during the observational phase, either a video reply (Vögtle et al. 2013) or live demonstrators (Swider and Babel 2013). Observationally induced changes in pain were correlated with the empathy scores only when live demonstrators were involved in the experimental settings, confirming that empathy predicts these effects when interpersonal interactions are involved. It is worth noting that the effect of observation and modeling applies to nocebo effect as well.

Vögtle et al. have studied young women, randomly assigning them to one of three conditions: (1) control condition in which subjects received information that

an ointment would have no effect on pain perception; (2) verbal suggestion condition, in which subjects received information that the ointment would increase pain sensitivity; and (3) observational learning condition, in which subjects were asked to watch a video in which a demonstrator displayed more pain when ointment was applied (Vogtle et al. 2013). Subsequently, all subjects were exposed to three pressure painful stimuli on their hands. One side was tested before the observational learning and served as within-subject control. Pain reports in the control and verbal suggestion groups were at the same level with and without ointment. Interestingly, subjects in the observational group reported higher pain after watching the demonstrator and these responses were higher than in the control group with and without ointment (Vogtle et al. 2013). The nocebo responses induced by observational learning correlated with pain catastrophizing scores, indicating the importance of studying the mechanisms underlying observational learning, psychological traits, and nocebo hyperalgesia (Vogtle et al. 2013).

Gender effects influence the magnitude of nocebo induced by observational learning (Swider and Babel 2013). Subjects (men and women) were assigned to observational experimental groups in which either a male or a woman was respectively observed. Subjects rated red-associated stimuli as more painful than the ratings of subjects from control groups who did not observe a demonstrator before receiving the same pain stimuli. Also, regardless of the sex of the subject, nocebo hyperalgesia was greater after a male demonstrator was observed (Swider and Babel 2013).

It has been also recently reported that observation may trigger nocebo mass psychogenic illness (Mazzoni et al. 2010). Healthy subjects were invited to self-administer an intranasal product containing a suspected environmental toxin, which can cause headache, nausea, itchy skin, and drowsiness. Half of the subjects observed an actor who inhaled the product. Those who had observed the actor displaying signs of illness reported a significant increase of the four described symptoms, suggesting that observational learning is likely involved in mass psychogenic illnesses (Mazzoni et al. 2010). Interestingly, empathic stress responses modulated the HPA-axis activity and such a modulation is shaped by the familiarity between observer and target (partners vs. strangers), and the modality of observation (real-life vs. virtual). The exposure to a psychosocial stressor induced in the observer (26 %) physiologically significant cortisol increases. This effect was larger in intimate observer-target dyads (40 %) and during the real-life representation of the stressor (30 %) (Engert et al. 2014).

One may argue that these self-reported scores represent biases generated by the subjects' wishes to please the researcher or fit in with the perceived experimental proposition (Hrobjartsson et al. 2011). However, the experimental settings include control groups (e.g., verbal suggestion and natural history groups) that have received the same instruction about what to expect, and there was no analgesic or hyperalgesic response, indicating that biases are unlikely to account for the difference in the placebo and nocebo effects found in observational learning models. Observation of the demonstrator's benefit may have acted as a US, indicating possible commonalities between observational learning and classical conditioning.

Attempts to analyze observational learning within an associative learning framework have been made for aversive and fear models. In rats, observational aversive learning fails to show blocking, latent inhibition, and overshadowing that are three characteristics of classical conditioning (Galef and Durlach 1993). By contrast, studies in humans have found that observational aversive learning is characterized by features of classing conditioning including overshadowing and blocking (Lanzetta and Orr 1980). We can speculate that humans alter and adapt their behaviors, due to their ability to use symbols, thus setting them apart from the limited stimulus–response world of animals. Further behavioral and brain imaging studies are needed to illustrate the mechanisms involved in the observationally induced placebo and nocebo phenomena.

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## 5 Conclusions

Aspects of conditioning, instructional, and observational learning are likely to combine promoting expectations of benefits and anticipations of negative outcomes (e.g., increase of pain). Expectations are central to the formation of placebo and nocebo responses, are influenced by emotions, and are dynamically shaped by the prior experiences and likelihood of positive or negative outcomes (Colloca and Miller 2011b; Kirsch 1985).

Expectations can be induced explicitly by suggestions of positive or negative outcomes and implicitly by individual previous experience. It is imperative to keep away from any strict dichotomy between conditioning and expectation mechanisms, as the former involves information processing by which a subject expects a future event, which may or may not be conscious. Conversely, expectations formed on the basis of instructions are often associated with unconscious prior experience and thus involving different grades of awareness.

When a perception, such as pain relief, is consciously accessible, verbal instructions become a crucial modulator of placebo effects. By contrast, conditioned placebo responses are shaped by unconscious conditioning but are not affected by verbal instructions and such an event cannot be experienced and perceived by human cognition (e.g., changes in cortisol levels).

If learning mechanisms are understood as processes generating expectations and conditioned responses in humans and animals without being mediated by consciousness, it follows that expectations are not necessarily conscious (Colloca and Miller 2011b). However, it is reasonable to assume that by and large, the closer the phylogenetic distance to human, the larger the role of cognition and emotions. Conscious and unconscious expectations in forming placebo responses are partially an open question and deserve further investigation.

In conclusion, this chapter has explored a wealth of research serving to elucidate the mechanisms responsible for activating learning mechanisms and placebo and nocebo responses. In particular, learning mechanisms have been demonstrated to be a key mediator of expectations and placebo and nocebo responses. We formally systemized here a large body of evidence, integrating behavioral and

neurobiological literature and reframing the placebo effect as a complex emotional and learning phenomenon. This approach has the potential to guide future research opening new avenue in placebo and nocebo investigation. Viewing the placebo effect via a learning perspective will endorse a better knowledge of the phenomenon also in health care. In fact, the ramifications of such approach are of paramount importance to the study of symptom management, given the potential capacity of the placebo and nocebo responses in affecting clinical outcomes across different pathological conditions.

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