How placebo responses are formed: a learning perspective

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Despite growing scientific interest in the placebo effect and increasing understanding of neurobiological mechanisms, theoretical conceptualization of the placebo effect remains poorly developed. Substantial mechanistic research on this phenomenon has proceeded with little guidance by any systematic theoretical paradigm. This review seeks to present a theoretical perspective on the formation of placebo responses. We focus on information processing, and argue that different kinds of learning along with individuals’ genetic make-up evolved as the proximate cause for triggering behavioural and neural mechanisms that enable the formation of individual expectations and placebo responses. Conceptualizing the placebo effect in terms of learning offers the opportunity for facilitating scientific investigation with a significant impact on medical care.

Keywords: conditioning; expectation; evolution; nocebo; social learning; verbal suggestion

1. INTRODUCTION

Recent human and non-human research has impressively increased our knowledge of neurobiological mechanisms underlying placebo effects in different medical conditions and physiological processes. It has emerged that very different neurobiological pathways mediate the formation of placebo responses depending on the medical condition of subjects and the outcomes investigated. On what basis can we describe this diversity on the neurobiological level as reflecting a single phenomenon, known as the placebo response? There are relatively few comprehensive theories about how beliefs and psychosocial messages are decoded to form a placebo response. The most extensively accepted theories are expectation and conditioning, involving both conscious and unconscious information processing.

Is there a way of understanding the formation of behavioural and biological placebo changes as a coherent phenomenon with important implications for laboratory research and medical care?

This review attempts to orchestrate common themes in the placebo literature with the aim of articulating a unified account of the phenomenon through a learning perspective.

The first section describes the placebo phenomenon in terms of Peirce’s theory of signs and introduces the reader to the different ways of forming placebo responses on the basis of information processing. The core of the review focuses on behavioural and neurobiological evidence of placebo (and nocebo) responses formed by verbal instruction, conditioning and social observation and interactions. In the final part, we present a general account of the concept of expectations as central to the formation of placebo responses, develop speculations relating to the evolution of placebo responses, and discuss implications of the learning perspective for future clinically oriented research.

We suggest that interpreting, critiquing and formally modelling the existing experimental and clinical research on placebo (and nocebo) effects in terms of learning as the process of decoding information and creating expectations is promising for future laboratory investigation and translational patient-oriented placebo research.

2. PLACEBOS AND SIGNALS

Placebo interventions, such as sugar pills or saline injections, can be vehicles of therapeutic responses, but not by virtue of containing medication or internal properties with the power to produce beneficial health outcomes. Instead, the placebo intervention—a placebo pill, saline injection, and the invasive procedure or device that works by virtue of the placebo effect—should be understood as a signal, or set of signals, which convey information. A placebo intervention is usually delivered within and surrounded by a context, which includes a host of cues that convey information...
with potential for producing therapeutic (and also counter-therapeutic nocebo) responses. In addition to the treatment ritual, these include the therapist’s white coat, diagnostic instruments, the appearance of the therapist’s office or hospital room, the words communicated by the therapist, the therapist’s disposition in listening and responding to the patient, gestures and touch.

The patient does not come to the clinical encounter as a blank slate but with a history of experiences and memories evoked by prior responses to signals related to the milieu of therapy, some of which may influence the way in which the patient processes the information from signals emanating from the present clinical encounter. It is important to recognize that placebo responses are not limited to ‘inert’ placebo interventions. Proven effective treatments also function as signals, in addition to producing therapeutic effects based on their inherent pharmacological or physiological characteristics; and they are administered in the clinical encounter, with a potential to generate placebo responses that enhance the therapeutic benefit of the treatment.

On the philosophical level, Miller & Colloca [2] suggested that Peirce’s theory of signs [3] can illuminate the placebo response as deriving from processes of decoding psychosocial signals. Peirce developed his theory of signs in an effort to provide a systematic understanding of logic, and his semiotic theory seems to apply to all forms of communication and learning, not only by humans but also other animals [3]. According to Peirce’s theory, signs convey information about objects to an interpreter. There is a triadic relationship between (i) the sign vehicle, (ii) the object it signifies and (iii) the interpreter who consciously or unconsciously decodes information produced by the sign. Peirce classifies signs into three types: (i) indices, signs which are dynamically connected with their objects, and with the senses or memory of the individuals for whom they serve as stimuli; (ii) symbols, signs which refer to the object that it denotes by virtue of a conventional rule, which causes the symbol to be interpreted as referring to that object, as in the use of symbolic communication; and (iii) icons, signs that signify their objects by virtue of a likeness between the sign and the object, as observation are detected by the brain and interpreted and translated into neural input events and behavioural changes. Learning allows human individuals (and to some extent non-human animals) to combine distinctive elements of environmental and social cues with internal higher order functions (motivation, emotions and beliefs), which contribute to generating expectations and placebo responses.

Each of these three forms of signs can be seen as operating in the formation of placebo responses. For example, in the domain of pain, the most important area of investigation of the placebo effect [4–6], an experimental subject or a patient who experiences pain relief after being presented with a placebo described as an analgesic medication (‘This is a powerful painkiller’) is responding to this symbolic communication and other signals (including index signs) that constitute the treatment ritual. Understanding this symbolic communication, the patient anticipates pain relief and may experience analgesia simply by virtue of this anticipation. The interpretation of symbols in communication between therapist and patient can also relieve anxiety, which often exacerbates suffering from illness. In the context of conditioning, a conditioned stimulus (CS) becomes an index which conveys information. Its object is the unconditioned stimulus (US), with which the CS has been paired. In general, by detecting the CS and learning the relation between it and the US, the subject anticipates the US and exhibits the conditioned response (CR). Thus, the conditioned placebo effect is a response to an index sign that leads the individual to learn to experience a beneficial outcome, such as pain relief. Finally, icons are signs that signify their objects by virtue of a likeness between the sign and the object. An experimental observer who forms a placebo response following the observation of a simulator who demonstrates pain relief in response to a sham treatment can be understood as responding to an iconic sign that conveys information about analgesia to the subject that leads him to produce a similar response (figure 1).

The exact mechanisms that transform the detection of signs into placebo responses are unknown: we can speculate that when placebo responses occur, the sign (or set of signs) that trigger these responses are interpreted and translated into neural input events and behaviour changes. Although there are differences across physiological systems and diseases, the diversity of placebo responses can be understood as generated by neural and psychobiological mechanisms based primarily on information processing and learning principles. Learning allows human individuals (and to some extent non-human animals) to combine distinctive elements of environmental and social cues with internal higher order functions (motivation,

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**Figure 1.** A learning perspective on placebo responses. The scheme shows how a set of signs including (i) indices (signs which are dynamically connected with their objects, and with the senses or memory of the individuals for whom they serve as conditioned stimuli); (ii) symbols (signs which refer to the object that it denotes by virtue of a conventional rule, which causes the symbol to be interpreted as referring to that object, as in the use of symbolic communication); and (iii) icons (signs that signify their objects by virtue of a likeness between the sign and the object, as observation) are detected by the brain and interpreted and translated into neural input events and behavioural changes. Learning allows human individuals (and to some extent non-human animals) to combine distinctive elements of environmental and social cues with internal higher order functions (motivation, emotions and beliefs), which contribute to generating expectations and placebo responses.
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3. VERBALLY INDUCED PLACEBO (AND NOCEBO) RESPONSES

Experimentally, the studies documenting the contribution of cognitive and emotional elements for obtaining placebo responses have been performed by using verbal suggestions of benefit and persuasive communication. Here, we present some examples of placebo responses induced by communication, as a form of instructional learning. Although verbal suggestions and conditioning often overlap, it remains useful to differentiate verbally induced and conditioned placebo responses as involving distinct learning modalities.

Different sets of verbal instructions result in the modulation (enhancement and/or reversal) of a variety of clinical outcomes and specific perceptions. After the early experimental studies by Wolf [7] indicating that placebo effects could mimic, mask, enhance or prevent beneficial responses to active drugs, more systematic experimental evidence has supported the intuition that verbally induced expectations can markedly influence the response to drugs and other interventions. Earlier studies by Luparello et al. [8,9] indicated 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. The same patients were able to reverse airway obstruction by inhaling the identical substance presented as a medicine with beneficial effects on asthma [8]. Similarly, the effects of the bronchoconstrictor carbachol were higher when it was administered along with the information that it was a bronchodilator than when subjects were told it was a bronchoconstrictor [9].

Verbal suggestions produced different outcomes in healthy subjects randomized to receive decaffeinated coffee under two different verbal descriptions: group 1, in which participants were told that they would receive either regular or decaffeinated coffee according to a double-blind design; and group 2, in which decaffeinated coffee was presented as real coffee. Placebo responses were higher in group 2 rather than group 1, suggesting a difference in expectations [10].

Similar findings have been observed in some clinical settings of post-operative pain [11] and visceral somatic pain [12,13]. In the former, thoracotomized patients were treated with buprenorphine on request for three consecutive days together with a basal intravenous infusion of saline solution, and three different sets of verbal instructions were given to the patients. The first group was told nothing about the analgesic effect (natural history). The second group was told that the basal infusion was either a powerful painkiller or a placebo according to a double-blind paradigm. The third group was informed that the basal infusion was a potent painkiller (full-deceptive administration). The placebo response was measured by recording the doses of buprenorphine requested over the three day treatment. Buprenorphine requests decreased in the double-blind group by 20.8 per cent compared with natural history, and by 33.8 per cent in the deceptive administration group [11]. These results indicated that differences in instructions trigger a dramatic change of behaviour leading to a clinically significant reduction of buprenorphine opioid intake.

In the latter setting, patients with irritable bowel syndrome (IBS) exposed to painful rectal balloon distension under no treatment, rectal placebo or rectal lidocaine conditions showed a higher analgesia when the active rectal lidocaine was administered along with the information that they were given an agent which is known to significantly reduce pain in some patients as compared with the patients that were informed that they may receive either an active pain reducing medication or an inert placebo agent [12,13].

Communication and verbally induced expectations can also produce negative responses, commonly labelled as nocebo effects [14]. Negative information given verbally once can induce nocebo responses as strong as those which are induced by direct experience of negative outcomes [15,16]. After informing healthy subjects about the hyperalgesic effect of a treatment, they perceived no-painful and low-intensity painful stimuli as painful and higher intensity painful stimuli, respectively, thus indicating that expectations derived from verbal suggestions produced both allodynic and hyperalgesic effects [15]. In line with these findings, Rodriguez-Raecke et al. [16] showed that informing healthy subjects once at the beginning of the investigation that ‘repeated pain over several days will increase your pain sensation over time, e.g. from day to day’, elicited immediate hyperalgesia. Additionally, as compared with the control group, this information interfered at the level of the neural opercular region with the natural course of habituation in pain perception over 8 and 90 day periods. At the neurochemistry level, verbal suggestions of hyperalgesia trigger the activation of cholecystokinin pathways [17] with a possible involvement of dopaminergic and opioidergic systems as well [18].

4. CONDITIONING AND PRIOR EXPERIENCE

(a) Classical conditioning

The analysis of the placebo effect in terms of learning has for the most part been discussed with respect to classical conditioning [19–24], even though other forms of learning also play a crucial role. Expectancy placebo mechanisms have been typically distinguished sharply from conditioning [25]; however, Kirsch, author of a general model of expectancy [26], recognized that conditioning underlies the formation of expectancies which, in turn, mediate placebo effects [27].

The classical example is Pavlov’s conditioning experiments with dogs, which salivated (CR) in response to a bell (CS) that had previously been paired with the administration of food (US) [28]. The formation of these CRs in the dogs suggests that they learned that the ringing bell anticipated food and thus exhibited the salivary reaction when hearing the bell. According to this view, the visual, tactile and gustatory stimuli associated with the ingestion of a medication can become CSs through their repeated association with the delivery of active medication, the
USs. Placebos given along with the presentation of CSs and subsequently without the USs may elicit CRs that are similar to the response to medication. Thus, classical conditioning has been the prevalent paradigm to explain the genesis of (unconscious) placebo responses by learning mechanisms. The initial support for a classical conditioning interpretation of the placebo effect arises from some studies in animals [20,29]. Herrnstein demonstrated that after 14 pairings of scopolamine with sweetened milk, the presentation of the CS caused scopolamine-like alteration of behaviour (depression of rates of a lever-pressing) [20]. Ader & Cohen [29] found that pairing a novel saccharine-flavoured solution with the immunosuppressant cyclophosphamide induced immunosuppression in the rats which were presented with saccharine solution alone. Rats that received two doses of cyclophosphamide during the conditioning showed greater conditioned immunosuppression than those given one dose; hence, the stronger the US, the more robust the CR is. The evidence of conditioned placebo responses in the immune system has been extensively investigated in human models with promising clinical implications [19,30].

Human placebo responses in the immune and endocrine systems, which are not accessible consciously, do not differ, other than in degree of complexity, from those in non-human animals. For example, Benedetti et al. [31] observed that the pharmacological exposure to a serotonin agonist of 5-HT1B/1D receptors, stimulating growth hormone and inhibiting cortisol secretion, produced similar responses when drug was replaced by a placebo treatment. Furthermore, these responses were not influenced by verbal instructions.

More recently, Guo et al. [32] investigated the effect of prior pharmacological opioid and non-opioid exposure in mice by using a model of hot-plate test. Conditioned cues were paired with either opioid agonist morphine hydrochloride or non-opioid aspirin. Placebo analgesic responses evoked by morphine-based pharmacological conditioning were completely antagonized by naloxone. By contrast, after conditioning the placebo responses were not blocked by naloxone [32]. Therefore, the responses evoked were either naloxone-reversible or naloxone-insensitive depending on previous drug exposure, confirming parallel early results in humans [33]. Some more recent human studies adopting a pharmacological conditioning with drugs such as the immunosuppressant cyclosporin A [34,35], dopamine agonist apomorphine [36], benzodiazepine receptor agonist midazolam and antagonist flumazenil [37] found that the conditioned placebo responses mimic drug effects, supporting the notion that such placebo responses depend on the kind of drug exposure that is originally performed.

Additionally, acquired CRs can be evoked without any reinforcement [38], at least, when people have had prior experience of specific symptoms. An interesting observation relevant to this aspect of CS response was early reported by MacKenzie in 1896, who noted that some people with allergy to flowers showed an allergic reaction when presented with something that superficially looks like a flower, but contains no pollen (an artificial flower) [39]. With respect to Peirce’s theory of signs, the fake flower is an icon suggesting the presence of a real flower which in the past has produced allergy symptoms.

Paradoxical and contrasting results have also been reported on conditioned hypo- and hyperglycaemia [21]. However, hyperglycaemia post-insulin administration can be viewed as a compensatory physiological response in the presence of hypoglycaemic blood levels, emphasizing the need for a correct interpretation of unconditioned responses [40].

(b) Beyond classical conditioning

The traditional conception of conditioning based on non-human responses as the acquired ability of one stimulus (CS) to evoke the original response by means of the pairing with the US may only partially explain conditioned response in humans. Rescorla [41] described conditioning as the learning of relations among events so as to allow the organism to represent its environment. According to this definition, pairing and contiguity remain a central concept, but conditioning depends on both the information that the CS provides about the US and the learning of relations among events. Many theories have been formulated about the organism’s way of coding these relations, suggesting that classical conditioning is not a mindless process by which the organism forms associations between any two stimuli that happen to co-occur; rather, it is a process by which the organism uses logical and perceptual relations among the events to form a sophisticated representation of its world [41–44].

Reward-learning has also been described as another form of learning [45] which accounts for the formation of placebo responses [46], with a predominant role of the ventral striatum. Dopaminergic activation, underlying the experience of reward, was observed in the ventral basal ganglia in Parkinsonian patients and healthy subjects during pain manipulation [18,47–49]. Confirmation of the role of reward learning in forming placebo responses is reflected in the following experimental results: dopamine released in the nucleus accumbens accounted for 25 per cent of the variance in placebo analgesic effects [18]; dopamine-related personality traits predicted the magnitude of the placebo analgesic responses [49]; and beliefs relating to the probability of receiving active drugs directly modulated dopamine release [48].

The physician’s appearance, demeanor and the vehicles of treatment (e.g. syringe or tablets), which encompass the ritual of the clinical encounter, may produce separately or together a result that mimics the physiological and therapeutic actions of a specific drug that would otherwise have required some specific chemical agent. Some authors have argued that the elicitation of a specific reaction by environmental stimuli, such as the abatement of a symptom after the mere sight of a physician wearing a white coat and his medicines, involves simple conditioning of the sort originally demonstrated by Pavlov with animals [20,23]. However, it is important to note that the stimuli in the clinical encounter that are hypothesized to promote placebo responses by means of
conditioning often also have a symbolic meaning, derived from cultural dimensions, which may also contribute to learned placebo responses. In other words, index signs and symbols may work together to produce placebo (and nocebo) responses.

(c) Prior experience and sequential effects

In general, learning via prior experience has been increasingly emphasized as a modulating factor of the placebo effect [50] owing to the awareness that a previous direct experience of benefit via pharmacological or biologically significant cue exposure can powerfully change behaviour and clinical outcomes.

In laboratory settings, numerous studies have found that conditioning is more effective than verbal suggestions in producing placebo responses [15,22,51–57]. By using a CS reinforced on 100 per cent of trials with different numbers of CS–US pairings, Colloca et al. [58] found that the persistence of placebo and nocebo responses was firmly connected to the length of exposures to effective (and ineffective) treatments. They demonstrated a causal relation between the number of learning trials and the resistance to extinction of the ensuing placebo and nocebo responses.

Bootzin & Caspi [59, p. 203] suggested that ‘therapeutic interventions that change performance directly and provide experiences of mastery will have the strongest effect on efficacy expectations and on subsequent behaviour’.

In this regard, Price et al. [55] applied a pain stimulus and placebo cream to healthy volunteers under two experimental conditions, A (strong placebo) and B (weak placebo) and a control agent, C. During the conditioning procedure, the intensity of the stimulus was decreased 67 per cent in A and 17 per cent in B. There was no reduction in C (control). Expectancies were also assessed after the trials of intensity manipulation. In comparison to the pre-treatment condition, subjects experienced a large and small reduction, as well as no reduction in the three areas on the ventral part of the forearm, which had corresponding labels of A, B and C [55]. The findings were congruent with what the subjects previously perceived, thus the feedback probably graded different expectation levels so that graded placebo analgesic effects were obtained. Feedback about cognitive performance in a double-blind randomized placebo-controlled trial of therapeutic interventions distorted measures of the effectiveness of the intervention. Colaguri & Boakes [60] manipulated participants’ beliefs about whether they had been allocated to the active treatment or placebo by giving false feedback about cognitive performance. They found different participants’ performance (accuracy and reaction times), if they were led to believe that they were taking part in testing a cognitive-enhancing drug or not.

Prior positive experience also induces increased analgesic responses of a subsequent placebo, whereas ineffective previous experiences influence negatively the formation of placebo responses [51]. In one group, a simulation of effective treatment (surreptitious reduction of intensity of painful stimulation) was performed to create expectations of benefit. After this procedure, the administration of a placebo induced robust analgesic responses. A second group of subjects of the same study received a placebo after an ineffective treatment (no reduction of intensity of painful stimulation) and there were no placebo effects. After a time lag of 4 to 7 days, both the groups were shifted to either effective or ineffective procedures. Interestingly, the placebo responses following an effective procedure in the second group were remarkably reduced compared with the first group. The ineffective treatment given after the treatment perceived as effective resulted as effective resulted in higher placebo responses as compared with the second group. These findings suggest that placebo analgesia is finely tuned by prior experience (either positive or negative), and that the effect of initial treatment influences the magnitude of subsequent placebo responses after several days.

The power of placebos is finely tuned by expectations which are dynamically built up during the exposure to effective treatment. Lui et al. [61] found that brain activities overlapped in the right dorsolateral prefrontal cortex when healthy subjects expected analgesia (i.e. anticipatory phase of CSs), experienced analgesic effects (i.e. manipulation of intensity, USs) and perceived conditioned placebo analgesic effects (i.e. CRs in the post-manipulation phase), thus suggesting that a common brain network takes part in the different phases of conditioned placebo analgesia.

However, learning effects may differ in patient populations from those of non-patients. Klinge et al. [53] examined conditioned and verbally induced placebo effects in patients with atopic dermatitis compared with healthy controls. They showed that conditioning supports the maintenance of placebo responses in a patient population. Additionally, the authors demonstrated that the patient’s history plays an important role in the formation of placebo responses [53]. Patients have a completely different history of exposure to medications and healing experiences, suggesting that the prior experience of those who interpret placebos as sign vehicles have differential impacts on the formation of placebo responses. Additionally, cognitive and emotional factors can also shape conditioned placebo responses.

5. OBSERVATIONAL AND SOCIAL LEARNING

Beyond direct first-hand experience, people can learn by observing others. Likewise, placebo responses can be formed by means of observational learning in a social context without any deliberate reinforcement.

Colloca & Benedetti [62] investigated the role of observational social learning in placebo analgesia in healthy subjects who learned by observing the experience of a demonstrator who simulated an analgesic benefit. Substantial placebo analgesic responses were found following observation of the demonstrator, suggesting that the information drawn from observation of another person may establish a self-projection into the future outcome. These effects exhibited no extinction over the entire experimental session, indicating implicit acquisition and retention of behavioural
output. The magnitude of observationally induced placebo responses was similar to those induced by directly experiencing the benefit through a conditioning procedure in which subjects underwent first-hand experience of benefit. Interestingly, the more pronounced observationally induced placebo responses were found in those subjects who presented higher empathy scores. This suggests a link between the ability to modify behaviours following mere observation, the formation of placebo analgesia responses and empathy. These observations emphasize that social interactions are potential cues to induce expectations of benefit and might activate specific brain-body mechanisms.

Recently, Mazzoni et al. [63] reported observationally induced responses in a model of nocebo mass psychogenic illness. Healthy subjects were asked to inhale a sample of normal air which was presented as a product containing a suspected environmental toxin known to cause headache, nausea, itchy skin and drowsiness. Half of the healthy subjects also observed a confederate who inhaled the product. Those who watched another who displayed signs of illness reported a significant increase of the four described symptoms, suggesting that social learning might also play a role in clinical contexts.

Attempts to analyse observationally induced effects within the associative learning framework have been made in human and non-human models. Studies on observational aversive learning in rats failed to find blocking, latent inhibition and overshadowing—three well-documented features of classical conditioning [64]; however, studies in humans reported classical conditioning features for social aversive learning, including overshadowing and blocking [65], implying that observation might serve as a US.

Beyond these attempts to categorize observational learning, the ability to change behaviours without any practice and direct reinforcement is part of the large repertoire of prosocial behaviours (e.g. ability to share others’ feelings, imitation, mimicry) which allows humans and non-humans to draw information from the social environment and make inference about a future outcome [66].

The strength of social learning in placebo health-promoting processes is demonstrated by studies focusing on contextual cues in clinical settings and the patient–provider relationship. Aspects of conditioning, instructional learning and observational learning are likely to combine in the clinical encounter to promote socially induced placebo responses.

A way to understand the weight of psychosocial components is to compare the effects of medication administered in the manner of routine clinical practice with a hidden administration of the same medication (for a review see [67]) and the effects of business-like placebo responses versus an augmented patient–doctor relationship [68].

Patients hospitalized after surgery who received an injection of analgesic drugs administered by a physician and were told that this injection contained a powerful painkiller, which should produce pain relief in a few minutes, required a much lower dose of medication to reduce pain by 50 per cent than those who received analgesic medication from a preprogrammed infusion machine without being told when they would be given the medication [67,69,70].

Patients with IBS enrolled in a run-in phase of a randomized trial comparing verum and sham acupuncture reported greater symptom relief when they received an augmented sham acupuncture intervention arm consisting of a longer and more empathetic initial conversation with the practitioner, as compared with a more business-like sham intervention whereby communication between practitioner and patient was reduced to a minimum. Both sham acupuncture groups reported superior outcomes relating to symptoms compared with those in a no-treatment waiting-list group. When augmented by supportive communication, the ritual of treatment produces an enhanced and sustained placebo response in a difficult-to-treat patient population [68].

These findings make some inroads into revealing the cognitive and emotional appraisal of a situation, based on human–social interactions, in the generation and maintenance of placebo effects. Conceptually, the placebo responses derived from the patient–doctor relationship may be viewed as learned healing whereby the patient learns to produce placebo responses by interaction with a healer [71]. In this regard the etymological meaning of ‘doctor’ as teacher is suggestive. The doctor may ‘teach’ not only by making a diagnosis and giving instructions on how to take treatment and promote healthy behaviour. The doctor promotes healing by means of clinical attention (including the ritualistic element of administering treatment) and communicative interaction with the patient, including reassurance, verbal suggestions for positive therapeutic expectations, empathic listening, and encouragement. The doctor–patient relationship is a process of interaction in which patients and doctors continually, mutually and reciprocally influence each other. The doctor learns to understand and co-regulate his behaviour as a healer depending on a patient’s behaviour and response. The doctor’s belief in the effectiveness of treatment may influence the patient’s expectation of benefit.

6. EXPECTATIONS
By reviewing the above-described body of studies on placebo and nocebo effects, we have indicated that expectations can be related to verbal suggestions (e.g. suggestions of positive or negative outcomes), influenced by individual previous experience, graded by perceived likelihood of an outcome and modulated by emotional appraisal of a situation (e.g. anticipation of a dangerous event). In other words, we suggest that, across the board, expectations play a role in the formation of placebo responses. If this is correct, then it is necessary to overcome any strict dichotomy between conditioning and expectation mechanisms, as the former involves information processing by which a subject anticipates (i.e. expects) a future event, which may or may not be conscious. Conversely, expectations formed on the basis of communication or observation may often be associated with prior experience and thus involve elements of conditioning.
Expectations can derive from information learned from the environment, via personal experiences and from other forms of learning which are dynamically connected with individual beliefs and internal states, leading to the formation of a placebo (and nocebo) response. When a perception, and more generally a change in the mind-body unit, such as pain relief is consciously accessible, verbal instructions become a crucial modulator of placebo effects. However, many modifications in the body are not consciously accessible. For example, endocrine placebo responses are not affected by verbal instructions. A persuasive communication that cortisol (or growth factor) is going to change by means of the power of a specific treatment (actually an inert medication) does not produce any effect [31]. Thus, an event that cannot be experienced and perceived by human cognition (e.g. growth factor secretion) appears not to be influenced by self-cognition.

Owing to the difficulty in defining the boundaries of consciousness, delineating the role of conscious and unconscious expectancies in forming placebo responses is challenging. Some authors have defined expectations as consciously accessible mental entities [25,72], but others have suggested that unconscious expectations also exist [73]. If conditioning is understood as generating expectations and CRs (in humans and non-human animals) can occur without being mediated by consciousness, it follows that expectations are not necessarily conscious. However, it is reasonable to assume that, by and large, the higher the phylogenetic level, the larger the role of conscious cognition and the smaller the role of unconscious conditioning processes.

7. EVOLUTION AND LEARNED PLACEBO RESPONSES

In evaluating the hypothesis that the placebo effect predominantly relies on learning, it is worth asking the reasons for human and non-human ability to release endogenous substances with health-promoting effects in the context of nature and how this may have evolved. We have previously inquired into the evolution of human placebo responses with a strong foundation in patient–healer interactions, suggesting a biological function of the phenomenon as a form of interpersonal healing, which favours survival in the face of immediate threats to life and ameliorates symptoms that are not counteracted by the body's automatic mechanisms of self-healing [71]. In this parallel attempt to reconstruct the evolutionary meaning of the placebo responses, we briefly rely on the social behaviour of non-human primates, naturalistic and ecological contexts, and potential genetic contribution to selection.

Like other animals, humans have the innate capacity to enhance adaptation to the environment by learning. Thus, the capacity to modulate endogenous systems and heal by learning presumably would enhance survival. Placebo effects may be favoured directly by natural selection. In particular, genetic make-up and social context may interact in controlling behaviours and promoting adaptation via proximal causes. Genes modify an organism’s vulnerability to environmental features and situations. Despite many factors and variables that combine to induce a placebo response, making the placebo effect a highly complex phenomenon, recent evidence supports the idea that placebo responses may be associated with specific polymorphisms. For example, serotonin-related gene polymorphisms have been found to influence the individual placebo response in social anxiety, both at the behavioural and neural levels (as indicated by amygdala activity during a stressful public speaking task) [74]. Also, genetic polymorphisms modulating monoaminergic tone (catabolic enzymes catechol-O-methyltransferase and monoamine oxidase A) have been related to degree of placebo responsiveness in major depressive disorder [75]. However, genetic investigation can only partially elucidate the formation of learned placebo effects.

The propensity to be conditioned and the potential for placebo interventions to modify disease by means of classical conditioning may also be part of our biological heritage. Pavlovian conditioning may be one of the evolutionarily oldest systems which humans share with other species and relatively simple invertebrates. We reviewed above experiments indicating conditioning-mediated placebo responses in mice and rats. Indeed, an organism with a simple nervous system such as Aplysia californica learns via classical and instrumental conditioning [76].

Interestingly, the phenomenon of observationally induced placebo responses finds support in the wide occurrence of social learning across different species [77]. The ability to imitate and learn from others’ behaviours appears advantageous because it is a rapid form of learning, saving cost and time, in terms of effort and risk, leading the animal or individual to acquire appropriate information without risks of trial-and-error learning. For example, great apes and capuchin monkeys show that imitation positively affects subsequent social interactions [78,79]. Therefore, social learning may be an evolutionary adaption that prevents errors, selects strategies useful for survival and facilitates group living.

Viewed as activated by conditioning and observational processing, the placebo effect would represent a form of learned responses that antedated the emergence of language. However, human placebo responses appear strongly moulded by the social environment in which linguistic communication is prominent. Speaking in terms of ontogenesis, neocortical structures are evolved in processing language, social attitudes and all the elements of interpersonal context. On one hand, humans have the peculiar option of using language to recode and re-represent their experience. Patients who are given inert treatments along with the verbal suggestion that they are powerful remedies have shown an improvement in a variety of symptoms. In the doctor–patient relationship, the way in which doctors inform patients about diagnoses and/or prognoses may result not only in good compliance with treatment and patients’ satisfaction but also in placebo responses promoting healing processes.

On the other hand, social attitudes and elements of interpersonal context seem to be important determinants of the formation of a human placebo response.
The ability to experience placebo responses may be a byproduct of the social solidarity of early human communities and the prolonged nurturance of human infants, both of which have a survival value. There are some analogues to this in human precursors like macaque monkeys that spend a large time in parental nurturing and in inter-animal practices of grooming to build up alliances and reciprocal altruism [80]. Also relevant in humans is the prolonged process of dependency in infancy and childhood that gives more salience to parental nurturing, thus laying a strong foundation for projecting the relief of suffering that children receive from their parents’ intervention onto the interaction with healers. This may explain why some internal mechanisms of symptoms’ relief so often take the intervention of a healer [71] and do not kick in spontaneously when an animal or an individual is at rest and is doing what is needed to avoid further damage to the organism.

Humphrey [81] posed the key question about the social dimension of the placebo effect from an evolutionary perspective. He suggested the need of the emotional trigger of hope for relief in order to activate internal healing mechanisms to counteract the otherwise biologically useful defence mechanisms such as pain and anxiety reactions. It is plausible to think that basic emotions generate the tendency to engage in the projection of positive (or negative) future events and mediate the effective integration and regulation of learning processes and social interactions.

Cultural processes may facilitate the spread of adaptive knowledge over generations, by being able to recognize vital life skills, to cultivate successful social relations and prosocial behaviours. Thus, it is possible to argue that the human placebo effect is based on an innate ability to learn with obvious survival value, which is made use of in healing in light of the human situation of prolonged dependency, social interactions and features of cultural evolution.

8. IMPLICATIONS AND FUTURE DIRECTIONS
Research on the formation of placebo responses via conditioning has important implications for clinical practice. Learned placebo responses following the exposure to drugs can be successfully exploited in routine clinical practice by integrating placebos in a schedule of reinforcements, so that conditioned stimuli acquire properties and characteristics of USs. These effects can become part of the pharmacotherapeutic protocol, preserving therapeutic benefits while side effects are reduced. An example has been recently provided by Ader et al. [82], who showed that a reinforced partial schedule of amounts of corticosteroids was effective in suppressing symptoms of psoriasis similarly to the full-dose treatment.

Instructional learning and techniques of promoting placebo responses by physician–patient communication also deserve attention in clinically oriented research, because verbal and non-verbal communication can also influence the responses to active medication. For example, Flaten et al. [83] showed that carisoprodol, a centrally acting muscle relaxant, resulted in different outcomes, either relaxant or stimulant, depending on the combination of verbal suggestion and drug administered (included the placebo), thus suggesting the potential utility of standardized verbal information in the context of clinical trials evaluation of new drugs.

Research has only begun to indicate the specific ways in which placebo effects can be generated and enhanced in clinical practice settings. Of particular clinical interest is whether the use of a treatment ritual is necessary to optimally produce placebo responses. Randomized trials comparing the use of placebo treatments with strategies of clinical attention without discrete treatment interventions, accompanied by various forms of verbally induced expectations, hold promise in generating knowledge that can guide clinicians in promoting placebo responses in routine medical practice.

Finally, looking at observational learning, we have seen that social interactions are also involved in the formation of placebo responses by integrating the basic emotions with environmental and contextual cues. Although, the investigation of social learning is only in its infancy, and more mechanistic research is needed, future clinically oriented research in this area may be promising. Patients are, inevitably, not only confronted with their own expectations and experiences but are strongly influenced by beliefs of their families, peers, clinicians, and cultural elements. Gathering knowledge regarding the role of social observational learning across different bodily systems and diseases may represent an important and clinically relevant extension of placebo research.

9. CONCLUSION
Learning and associated mechanisms have been demonstrated to be key mediators of expectations and placebo responses. In this paper, we have formally systematized a large body of research, integrating behavioural and neurobiological literature, in terms of information processing, reframing the placebo effect as a learning phenomenon. We have argued that learning processes guide the changes of behaviour and expectations that, in turn, lead to the formation of placebo responses. Seeing the placebo effect through a learning perspective may foster scientific investigation promoting a deeper and better knowledge of the phenomenon in healthcare.

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