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# Placebo analgesia and beyond: a melting pot of concepts and ideas for neuroscience

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**Purpose of review**

In the last two decades, some of the neuroanatomical and neurophysiological substrates of the placebo effect have been elucidated. What has emerged is the multifactorial nature of the placebo effect, such that there is not a single placebo effect but many. Here we report recent advances in our understanding of this phenomenon, with particular emphasis on its use as an experimental model to better clarify different brain mechanisms.

**Recent findings**

One of the most interesting findings in the past few years is that the placebo effect is a learning phenomenon, which is powerfully influenced by the manipulation of different variables. The involvement of opioid mechanisms is supported by several studies on pain, but also by the exploration of new fields such as memory and cognition. Non-opioid mechanisms have been described as well, e.g. in pain, Parkinson's disease and anxiety. Recent evidence confirms and extends previous findings on the key role of prefrontal regions in the placebo response.

**Summary**

The study of the placebo effect is paying dividends and bodes well for the future. Whereas in clinical practice it can increase the efficacy of a therapy, in the experimental setting it represents an excellent tool for neuroscience.

**Keywords**

Placebo, endogenous opioids, cholecystokinin, dopamine, serotonin, learning, prefrontal cortex

## Introduction

Over the past years, different definitions of the placebo effect, or response, have been offered. For example, it has been labeled as a variable to control and minimize in the clinical trial setting, or a powerful therapeutic tool in medical practice, or an experimental model to better understand how our brains work. Based on recent work, a more articulated and complete model of the placebo effect, as well as its opposite nocebo effect, has been proposed [1-4]. According to this model, the placebo effect is a genuine neurobiological and behavioral modification that occurs following the simulation of a therapy. A treatment is not administered in a vacuum, but in a context of words and rituals that, on the whole, represents the placebo. With this conceptualization in mind, the therapeutic outcome of any medical act, be it pharmacological or not, is influenced by the patient's cognitive and affective state.

Pain is certainly the most fruitful field for placebo investigation, yet other conditions have been analyzed, such as Parkinson's disease [5-7], endocrine [8] and immune systems [9,10], depression [11-13], anxiety [14,15] and itch [16*]. In the present review, we want to emphasize how placebo research is today a wide field of research which helps understand a number of brain mechanisms, ranging from learning to anxiety, from endogenous opioids to dopamine, and from genetics to prefrontal functioning.

## Learning as a key mechanism

Different studies support the idea that the placebo effect is, at least in part, a learning phenomenon. One of the most effective procedures to induce a robust placebo effect is classical conditioning. Any classical conditioning protocol consists of two different steps: the acquisition and evocation phases. During the acquisition phase, the active treatment (unconditioned stimulus, US) is repeatedly associated with one or more contextual cues (conditioned stimuli, CS). In the evocation phase the CS alone is able to induce a conditioned response (CR) [17]. Following this schema, the psychosocial context surrounding a treatment represents a CS that, after the repeated association with a pharmacological or procedural therapy (US), induces a conditioned placebo response. A common procedure to induce conditioned placebo analgesia consists in pairing a specific CS (e.g. the application of a placebo cream, or the presentation of a visual cue) with the surreptitious reduction of an experimental pain stimulus (US). In this way, the pain decrease is attributed to the CS. Using this experimental method, Morton et al. [18] investigated the long term changes after the

exposure to a placebo treatment. After 30 US-CS pairings, a reduction of pain rating was observed in two different sessions separated by 2-6 weeks and accompanied by changes in laser-evoked potentials (LEP). Confirming previous findings [19-20], the LEP N2-P2 complex was reduced during the evaluation phase in both sessions, providing a reproducible index of pain reduction. Moreover, a decrease of the anticipatory component (stimulus-preceding-negativity, SPN) was observed after 2-6 weeks suggesting that a learning process occurs and produces enduring cognitive effects.

Several studies have been designed to explore the factors that can influence learning. A crucial factor is the number of US-CS pairings. Recently, Colloca et al. [21] investigated the relationship between the number of acquisition trials and the resistance to extinction of both placebo and nocebo pain responses. Using the above mentioned conditioning procedure, either one or four acquisition trials were administered in order to either decrease or increase the perceived intensity of tactile and painful stimuli. A single acquisition trial was enough to induce both placebo and nocebo responses, but these effects extinguished over time. Conversely, four acquisition trials induced robust placebo and nocebo responses that persisted over the entire experiment. These findings suggest that a CS can mimic an active procedure, and that its strength is related to the number of pairings.

A second important variable for the induction of a placebo response is the effect of the treatment during the acquisition phase. In a clinical study on patients with chronic neuropathic pain [22**], the authors compared the placebo effect induced by sham repetitive transcranial magnetic stimulation (rTMS) that either preceded or followed a successful or unsuccessful active rTMS. Three placebo groups were studied: the first received no conditioning because the sham session preceded the active rTMS (plac1); the second and third groups received ineffective (plac2ineff) or effective (plac2eff) active treatment before the sham session. Therefore, plac2 groups experienced either negative or positive acquisition phases. The results showed that the sham rTMS induced a pain relief of 11% when applied after a successful active rTMS, whereas the same procedure increased the pain scores by 6% when preceded by inefficacious active rTMS. No effects were observed without the conditioning procedure, underlining a limited effect of expectancy. Hence, the effect of a conditioned placebo response strongly depends on the effect of the previous treatment.

Verbal suggestions, alone or in combination with preconditioning, are also very effective in inducing placebo responses [Amanzio et al, 1999; Colloca&Benedetti2006,] confirming the key role of learning. Recently, verbal suggestions have been studied in a new experimental model, in which both placebo and nocebo responses to itch could be induced by changing the verbal information provided to participants, (van Laarhoven et al. [16]).

Thus, a placebo response is modulated by learning and the magnitude of the response is related to different variables, such as the duration of the acquisition phase and the effect of the conditioning procedure. In the design of a placebo protocol these variables need to be considered in order to enhance or reduce the response.

**Opioid mechanisms: from pain to memory**

Different studies have provided compelling evidence of the involvement of opioid systems in the placebo response, combining behavioral outputs with neuroimaging and/or pharmacological approaches. In an fMRI work [23], the regions involved in the descending pain control (primary and secondary somatosensory cortices, prefrontal cortex, rostral anterior cingulate cortex, amygdala, insula, thalamus, hypothalamus, periaqueductal grey, and rostroventromedial medulla) were monitored in two different conditions: after a conditioning manipulation, subjects received either saline solution (opioid placebo condition) or the μ-opioid-antagonist naloxone (opioid block condition). A strong pain rating decrease (36%) was observed in the opioid placebo condition along with dorsolateral prefrontal cortex and subgenual rostral anterior cingulate cortex activation and a placebo-enhanced coupling between anterior cingulate cortex and periaqueductal grey. Naloxone administration disrupted the analgesic effect at both behavioral and neural levels, demonstrating the involvement of opioid mechanisms. A disruption of opioid-induced placebo responses has been also reported in a recent pharmacological study using the anti-opioid action of cholecystokinin (CCK) [24] in which CCK-2 receptor activity was enhanced by means of the CCK agonist pentagastrin. Pain was induced experimentally with a tourniquet technique and the subjects received a morphine preconditioning. As expected, the substitution of morphine with a saline solution induced a placebo response that was completely disrupted by pentagastrin administration. Thus, pentagastrin and naloxone appear to have similar effects on opioid placebo analgesia due to their opioid-blocking action. These data are also in good agreement with placebo analgesia enhancement by CCK antagonists [25].

Support for the opioid role in mediating placebo effects in a field other than pain has been recently provided [26**]. With a novel approach, the authors investigated the placebo effect in short memory tasks, opening placebo research to cognitive domains. After a baseline run of memory tasks, the placebo group received an intravenous saline injection along with expectation of memory boosting, whereas a control group received the same treatment without any information. Objective short memory performances were measured by scores in recall and delayed-recognition tasks. Moreover, subjective performance estimation was assessed. Both objective and subjective increase in memory recall tasks were observed after placebo, and the boosting was naloxone-reversible.

These results indicate that the placebo effect modulates cognitive performance through opioid mechanisms.

**Non-opioid mechanisms: pain, Parkinson's disease and anxiety**

Although there is general agreement on the key role of endogenous opioids, the placebo response is not always opioid-mediated. In fact, different mechanisms seem to be at play. Indeed, it has been demonstrated that some placebo responses are naloxone-insensitive [27,28] in humans. Recently, Guo et al. [29*] have supplied similar findings in mice. Using the standardized procedure of the hot-plate test, either the opioid agonist morphine hydrochloride or the non-opioid acetylsalicylic acid were administered during the acquisition phase, along with contextual cues. As expected, both morphine and acetylsalicylic acid conditioning evoked placebo responses, but only the placebo analgesia induced by morphine was naloxone-reversible. The results show that non-opioid analgesic placebo responses can be obtained in animals as well and may serve as a model for future studies. Further evidence for non-opioid mechanisms comes from a re-analysis [30-31] of two previous studies of placebo analgesia [32-33]. The authors showed that, despite consistent overlapping of regions, a double dissociation of brain responses occurred during opioid and placebo analgesia: the rostral anterior cingulate cortex and anterior insula were more extensively activated during opioid administration, while placebo analgesia produced greater responses in the lateral orbitofrontal cortex and venrolateral prefrontal cortex. The proposed explanation is that a placebo produces an analgesic effect through the activation of mechanisms that partly differ from those involved in an opioidergic reduction of pain. During placebo analgesia, discrepancy between actual pain and expectancy of pain relief occurs, whereas this error signal is not present during opioid analgesia, in which pain decrease matches expectation. According to the model, the discrepancy activates prefrontal regions and produces the placebo effect. Even if further confirmation to this hypothesis is required, the study supports the interpretation of placebo response as a unique and active phenomenon involving the activation of specific brain pathways which are not completely opioid.

In different domains, the role of specific non opioid neurotransmitters has been reported. For example, dopamine has been found to play a role in placebo analgesia, particularly in relation to the activation of the reward mechanisms in the nucleus accumbens [34-35]. Likewise, in Parkinson's disease, the placebo effect is associated with the release of endogenous dopamine in both nigrostriatal and mesoaccumbens pathways, and the amount of dopamine release is associated with the clinical motor improvement [6,36]. Recently, Lidstone *et al.* [37*] also reported a relationship

between the dopamine release and the strength of expectations. In particular, only when subjects were informed that they had a 75% probability of receiving active medication, when in fact they always received a placebo, did a significant dopamine release occur.

A second example of non-opioid neurotransmitters comes from a study on the modulation of serotonin in social anxiety disorder [38]. Brain activity was assessed by PET during an anxiety-inducing task (a public speech), before and after an eight-week placebo treatment that the subject believed to be an anxiolytic. The patients were genotyped with respect to the serotonin transporter-linked polymorphic region (5-HTTLPR) and the G-703T polymorphism in the tryptophan hydroxylase-2 (TPH2) gene promoter. Results showed that the reduced stress-related activity in the amygdala which accompanied the placebo response could be observed only in subjects who were homozygous for the long allele of the 5-HTTLPR or the G variant of the TPH2 G-703T polymorphism. In addition, the TPH2 polymorphism was a significant predictor of the clinical placebo response.

**Prefrontal control**

Different works have suggested the involvement of prefrontal regions in the placebo effect [23,32,33,39,40]. Recently, different approaches have confirmed this finding. Bingel *et al.* [41**] reported the fMRI activation of the dorsolateral prefrontal cortex in a condition of expected analgesia. Using an open-hidden paradigm [42,43], the analgesic remifentanil was injected along with different expectations of analgesia: no expectation (hidden administration), positive expectation (open administration after analgesic preconditioning) or negative expectation (hidden administration after hyperalgesic preconditioning). Hidden remifentanil administration resulted in a reduction of pain, associated with a decreased activity in several pain-matrix regions, such as the primary somatosensory cortex, the insula, the anterior cingulate cortex and the thalamus. Positive expectations doubled the hidden analgesic effect and were associated with a reduction of the pain-matrix activity together with reduced activity in the pregenual anterior cingulate cortex and the dorsolateral prefrontal cortex. Conversely, negative expectancy completely reversed both the behavioral and the neural analgesic remifentanil effect, and was associated with increased activity in the hippocampus. This study provides an elegant demonstration of how different meanings ascribed to the same analgesic treatment produce different behavioral and brain changes [44].

Another recent fMRI study suggests that placebo conditioning takes place in these prefrontal regions [45**]. Conditioned analgesia was induced by pairing reduction or increase of pain intensity with green or red lights respectively, in two separate sessions. In the test session, stimuli of the same intensity were administered and, as expected, pain reduction (33%) was reported for

stimuli associated with the green light. During the acquisition phase, anticipation of analgesia was accompanied by signal increase over time in the medial prefrontal cortex and dorsolateral prefrontal cortex, suggesting a progressive build-up of the association between analgesic effect and green light. These areas were adjacent to, and partly overlapped with the frontal loci activated for green lights in the test phase, confirming that similar neural activity occurs in the same prefrontal areas during the learning and the testing periods. The top-down frontal modulation of pain experience has been reported also in a condition of visceral pain induced by esophageal balloon distension [46]. In this study, placebo analgesia was enhanced by a conditioning procedure consisting in the association between a hidden reduction of balloon distension and a saline solution that the subject believed to be an analgesic. fMRI activity showed that during the evocation phase placebo analgesia was associated to a reduction of pain-matrix activity and an activation of the ventrolateral prefrontal cortex during the anticipation phase. Prefrontal activity was also correlated with the degree of placebo analgesia [41,45,46], suggesting a close relationship between prefrontal control and placebo response. These data are in agreement with a recent reanalysis reported by Wager *et al.* [47], in which the increased anticipatory activity in the frontoparietal network strongly predicts the analgesic response.

In line with these neuroimaging findings, Krummenacher *et al*. [48**] demonstrated that the artificial inhibition of prefrontal regions disrupts placebo analgesia. In a heat pain protocol, increased pain threshold and tolerance were induced with a conditioning procedure whereby the surreptitious reduction of pain intensity was associated with auditory and visual feedback. The analgesic effect that followed the learning session was completely abolished when a transitory depression of cortical excitability in the dorsolateral prefrontal cortex was induced by transcranial magnetic stimulation, suggesting that the prefrontal regions are necessary to induce placebo analgesia. This study is in agreement with the disruption of placebo analgesia in pathological conditions that affect prefrontal connectivity, such as Alzheimer's disease [49].

## Conclusions

Today the placebo effect can be considered a melting pot of concepts and ideas for basic and clinical neuroscience. It is both an excellent model to better understand a variety of brain mechanisms and a valid tool in medical practice. Therefore, it is not hazardous to anticipate that its use as a model in both basic and clinical sciences will lead to substantial advances both in human biology and in medicine.

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