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REVIEW ARTICLE

Placebo-Induced Improvements: How Therapeutic Rituals Affect the Patient's Brain

Fabrizio Benedetti [1,2,*]

[1] *Department of Neuroscience, University of Turin Medical School, Turin, Italy*
[2] *National Institute of Neuroscience, Turin, Italy*

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Abstract
The placebo effect has evolved from being thought of as a nuisance in clinical research to a biological phenomenon worthy of scientific investigation. The study of the placebo effect and of its evil twin, the nocebo effect, is basically the study of the therapeutic ritual around the patient, and it plays a crucial role in the therapeutic outcome. In recent years, different types of placebo responses have been analyzed with sophisticated biological tools that have uncovered specific mechanisms at the neuroanatomical, neurophysiological, biochemical, and cellular levels. Most of our knowledge about the neurobiological mechanisms of the placebo response comes from pain and Parkinson's disease, whereby the neuronal networks involved in placebo responsiveness have been identified. In the first case, opioid, cannabinoid, and cholecystokinin circuits have been found to be involved. In the second case, dopaminergic activation in the striatum and neuronal changes in basal ganglia have been described. This recent research has revealed that these placebo-induced biochemical and cellular changes in a patient's brain are very similar to those induced by drugs. This new way of thinking may have profound implications in clinical trials and medical practice both for pharmacological interventions and for nonpharmacological treatments such as acupuncture.

1. Introduction

Any pharmacological or nonpharmacological treatment has two components, one related to the specific effects of the treatment itself and the other related to the perception that the therapy is being administered [1]. The latter is called placebo effect or placebo response. Placebo is the Latin word of "I shall please." The study of the placebo

* Department of Neuroscience, University of Turin Medical School, Corso Raffaello 30, 10125 Turin, Italy.
E-mail: fabrizio.benedetti@unito.it

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effect is basically the analysis of the relationship between the complex psychosocial context surrounding the patient, which constitutes the ritual of the therapeutic act, and its effects on the patient's brain [2,3]. Two terms are commonly encountered in placebo literature: placebo effect and placebo response. Although they are often used interchangeably, technically they refer to different concepts. The placebo effect is that observed in the placebo arm of a clinical trial, and is produced by the placebo psychobiological phenomenon in addition to other factors, such as spontaneous remission, regression to the mean, biases, and judgment errors. The placebo response, on the other hand, designates the psychobiological phenomenon in isolation, and can best be studied in specifically designed experimental protocols. The definition of nocebo effect also needs to be stated precisely. The term nocebo (Latin for "I shall harm") is the result of negative expectations, in contrast to the placebo effect, which is related to positive expectations. Moerman [4] has proposed to substitute the term *placebo response* with *meaning response*, to underscore the importance of the patient's beliefs about the treatment. At the limit, a physical substance or treatment needs not be administered at all—that is, a placebo/nocebo effect can also be induced by raising expectations in the complete absence of a treatment, just by inducing expectations. These effects are sometimes called "placebo/nocebo-related" effects [5].

2. Psychological mechanisms

Different explanatory mechanisms have been proposed for both placebo and nocebo effects, each supported by experimental evidence. They need not be mutually exclusive and can actually be at work simultaneously. The first theory considers the placebo effect as an example of classical conditioning. As described in the studies on conditioned reflexes by the Russian physiologist Ivan Pavlov, the repeated co-occurrence of an unconditioned response to an unconditioned stimulus (e.g., salivation after the sight of food) with a conditioned stimulus (e.g., a bell ringing) induces a conditioned response (i.e., salivation that is induced by bell ringing alone). Likewise, aspects of the clinical setting (e.g., color, taste, shape of a pill, as well as concurrent aspects of the therapeutic environment, such as white coats or the peculiar hospital smell) can also act as conditioned stimuli, eliciting a therapeutic response in the absence of an active principle, just because they have been paired with it in the past [6—9]. Similarly, the conditioned response can also occur for a nocebo effect. For example, nausea can be elicited by the sight of the environment where chemotherapy has been administered in the past.

The second explanation centers on expectations, generated as the product of cognitive engagement, when the patient consciously foresees a positive/negative outcome, based on factors such as verbal instructions, environmental clues, emotional arousal, previous experience, and the interaction with care-providers. By grading the degree of expectation, graded responses can be obtained: the same placebo cream applied onto three contiguous skin areas induces a progressively stronger analgesia, according to the strength of the accompanying words ("it is a powerful/weak analgesic cream") [10]. This is true also in the clinical setting, where changing the symbolic meaning of a basal physiological infusion in postoperative patients resulted in different additional painkiller request [11]. The expectation of forthcoming pain can be further modulated by a number of emotional and cognitive factors, like desire and self-efficacy [12]. A related proposed mechanism posits that anxiety reduction also plays a role in placebo responses, because the subject interpretation of ambiguous sensations is turned from harmful and threatening to benign and unworthy of attention. Accordingly, Vase and collaborators [13] found decreased anxiety levels in patients with irritable bowel syndrome who received a placebo treatment.

A particular type of expectation which has been suggested as a contributor to the genesis of placebo effects is the expectation of reward. Our brain is endowed with a so-called reward system, which—through the activation of the mesolimbic and mesocortical pathways and the release of dopamine—fulfills its natural task to provide pleasurable feelings in response to life sustaining functions, such as eating, drinking, or sex, in order to encourage repetition of those functions. It has been argued that placebos have reward properties, associated with the beneficial outcome they provide. In other words, the expected clinical benefit is a form of reward, which triggers the placebo response [14].

3. Biological mechanisms in pain

The past decade has witnessed the beginning of clarification of neurochemical and pharmacological details of placebo analgesia (Fig. 1). There is now compelling evidence that the secretion of endogenous opioids in the brain is the key event in placebo pain modulation [15]. Placebo responders had levels of β-endorphin in the

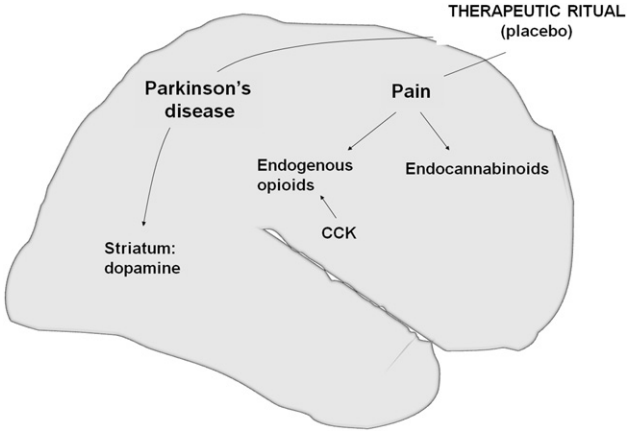

Figure 1 The neurobiological mechanisms of the placebo effect are better understood in pain and Parkinson's disease. In pain, either endogenous opioids or endocannabinoids can be activated, depending on the previous exposure to opioid or non-opioid drugs, respectively. Cholecystokinin (CCK) antagonizes the action of opioids. In Parkinson's disease, a release of dopamine takes place in the striatum after placebo administration.

cerebrospinal fluid which were more than double those of nonresponders; opioids released by a placebo procedure displayed the same side effects as exogenous opiates; naloxone-sensitive cardiac effects could be observed during placebo-induced expectation of analgesia. Indirect support also came from the placebo-potentiating role of the cholecystokinin (CCK) antagonist proglumide. In fact, the CCK system effects counteract those of opioids, delineating a picture where the placebo effect seems to be under the opposing influence of facilitating opioids and inhibiting CCK [15]. In some situations, however, a placebo effect can still occur after blockade of opioid mechanisms by naloxone, indicating that systems other than opioids are also implicated. For example, with a morphine conditioning and/or expectation-inducing protocol, naloxone was able to completely reverse placebo analgesia induced in experimental ischemic arm pain. Conversely, with the use of ketorolac (a nonopioid analgesic) in the same protocol, naloxone was ineffective, whereas the CB1 cannabinoid receptor antagonist rimonabant completely blocked placebo analgesia [16]. These results indicate that both opioid and cannabinoid mechanisms are involved in the placebo analgesic response, depending on the drug (either opioid or nonopioid) which was used in the preconditioning phase.

A positron emission tomography (PET) study showed overlapping in the brain activation pattern generated by opioid-induced analgesia (by the μ-agonist remifentanil) and by placebo-induced analgesia [17]. Common activated areas included the rostral anterior cingulate cortex and the orbitofrontal cortex. Direct demonstration of endogenous opioid release was obtained through [^{11}C]carfentanil displacement by the activation of opioid neurotransmission, with the decrease in binding correlating with placebo reduction of pain intensity reports. Recently, naloxone was observed to block placebo-induced responses in pain modulatory cortical structures and in key structures of the descending pain control system [18]. For a review on neuroimaging studies, see the report of Zubieta and Stohler [19].

Interestingly, the areas involved in placebo analgesia, including those related to placebo acupuncture, are part of a general circuit underlying the voluntary regulation of affective responses (see [20—22]). In this direction, both placebo analgesia [17,23,24] and emotional regulation [25] are associated with increased activation in a modulatory network that includes the rostral anterior cingulate cortex and the ventrolateral prefrontal cortex. This suggests a functional—anatomical relationship between placebo analgesia and emotional regulation in which top—down modulation of the pain or emotional network is implemented. This is particularly well studied in placebo acupuncture studies [21,22].

4. The nocebo hyperalgesic effect

Compared to placebo effect research, the investigation of the nocebo effect raises more ethical difficulties, especially in the clinical setting. However, in recent times a few experimental studies have begun to shed light on this phenomenon, focusing mainly on the model of nocebo hyperalgesia. In the protocols used, an inert treatment is given along with verbal suggestions of pain worsening, resulting in exacerbation of pain. It has been suggested that the anticipatory anxiety about the impending pain, brought about by negative expectations, triggers the activation of CCK, which in turn facilitates pain transmission and results in hyperalgesia. Accordingly, this hyperalgesia can be blocked by proglumide, a nonspecific CCK-1 and CCK-2 antagonist, in a dose-dependent manner. The proglumide block is related specifically to nocebo/anxiety-induced hyperalgesia rather than to the more general process of nocebo-induced anxiety, as it is selectively exerted on nocebo hyperalgesia but not on the concurrent stress-induced hypothalamic—pituitary—adrenal axis hyperactivity.

As noted before, proglumide also exhibited placebo-potentiating effects, raising the question of how the two endogenous systems, CCK and opioids, may interact in producing negative or positive outcomes. It can be speculated that the placebo—nocebo phenomenon is a continuum, with opioid and CCK-ergic systems acting as the mediators of opposing effects.

As for placebo analgesia, neuroimaging techniques have also brought important contributions to the knowledge of nocebo hyperalgesia [26]. Here, again, expectations without the physical administration of a nocebo treatment have sometimes been exploited ("nocebo-like" effects). Inducing negative expectations resulted in both amplified unpleasantness of innocuous stimuli as assessed by psychophysical pain measures (subject report) and increased functional magnetic resonance imaging responses in ACC, insula, hypothalamus, secondary somatosensory areas, and prefrontal cortex. From these studies, it appears that the circuitry underlying nocebo hyperalgesia largely involves, with opposite modulation, the same areas engaged by placebo analgesia [5].

5. Parkinson's disease

The neurobiological mechanisms of placebos have also been studied in conditions other than pain. Parkinson's disease is particularly interesting because different approaches, ranging from PET to micromapping methods (microrecording and microstimulation), have significantly increased the body of knowledge of the placebo effect.

By using PET imaging, de la Fuente-Fernández and colleagues [27,28] detected a significant drop in [^{11}C] raclopride binding potential when Parkinson patients were injected with a saline solution along with the suggestion of motor improvement. A reduction in [^{11}C]raclopride binding is indicative of an increase in extracellular dopamine concentration. In the studies by de la Fuente-Fernández et al [27,28], it occurred in the dorsal and ventral striatum (Fig. 1). As the patients who experienced symptomatic benefit released more dopamine in the dorsal striatum than those who did not, the degree of placebo-induced dopamine release in the dorsal striatum seems to be related to the degree of perceived improvement by the patient [27]. Conversely, the level of placebo-dopamine release in the ventral striatum is independent of perception of clinical benefit [28]. As the ventral striatum (NAc) is involved in the circuitry of reward mechanisms, de la Fuente-Fernández

et al [27,28] suggested that placebo-induced dopamine release might be related to expectation of reward. In the case of the placebo effect, the reward would be the clinical improvement. These results have been confirmed by subsequent studies [29].

The subthalamic nucleus (STN) is now the major target in the surgical therapy of Parkinson's disease, and its identification can require the recording of intranuclear electrical activity. The possibility of studying patients with Parkinson's disease who are implanted with electrodes for deep brain stimulation has been exploited to record from single neurons after the administration of a placebo. Benedetti et al [30] investigated for the first time the placebo effect at the level of single neurons. These authors recorded the activity from single neurons in the STN before and after placebo administration to test whether neuronal changes were linked to the clinical placebo response. Those patients who showed a clear-cut clinical placebo response—as assessed by means of both the decrease in arm rigidity and the subjective report of well-being—also showed a significant decrease in neuronal discharge compared to the pre-placebo condition. None of the placebo nonresponders showed these differences. Benedetti et al [30] also found that the STN neurons of all the placebo responders shifted significantly from a pattern of bursting activity to a pattern of non-bursting discharge. None of the placebo nonresponders showed any difference in the number of bursting neurons before and after placebo injection. Neuronal activity changes were also found in the substantia nigra pars reticulata and in the thalamus [31] (Fig. 2).

Indeed, several studies have reported apomorphine-induced changes in the STN firing pattern of patients with PD [32,33]. Although Levy et al [32] found a certain variability on the firing rates of single neurons under the effect of apomorphine, Stefani et al [33] reported that the administration of apomorphine is invariably followed by reduction of firing activity from 40.4 to 27.2 Hz. Similarly, in the study of Benedetti et al [30,31], a reduction of firing rate was induced by a placebo.

6. Depression

The neural mechanisms of placebo treatments have also been studied in psychiatric disorders, such as depression and drug addiction, although only a few pieces of information are available in this case. There is a clear explanation for this. Unlike single-dose trials of an intervention, such as oral or intravenous analgesia or anti-Parkinson acute therapy studies, antidepressants do not work acutely, requiring on average a minimum of 2—3 weeks to see clinical effects. Therefore, investigating placebo effects in depression is more problematic from both an ethical and a methodological point of view. In fact, if one wants to see what happens in the patient's brain via

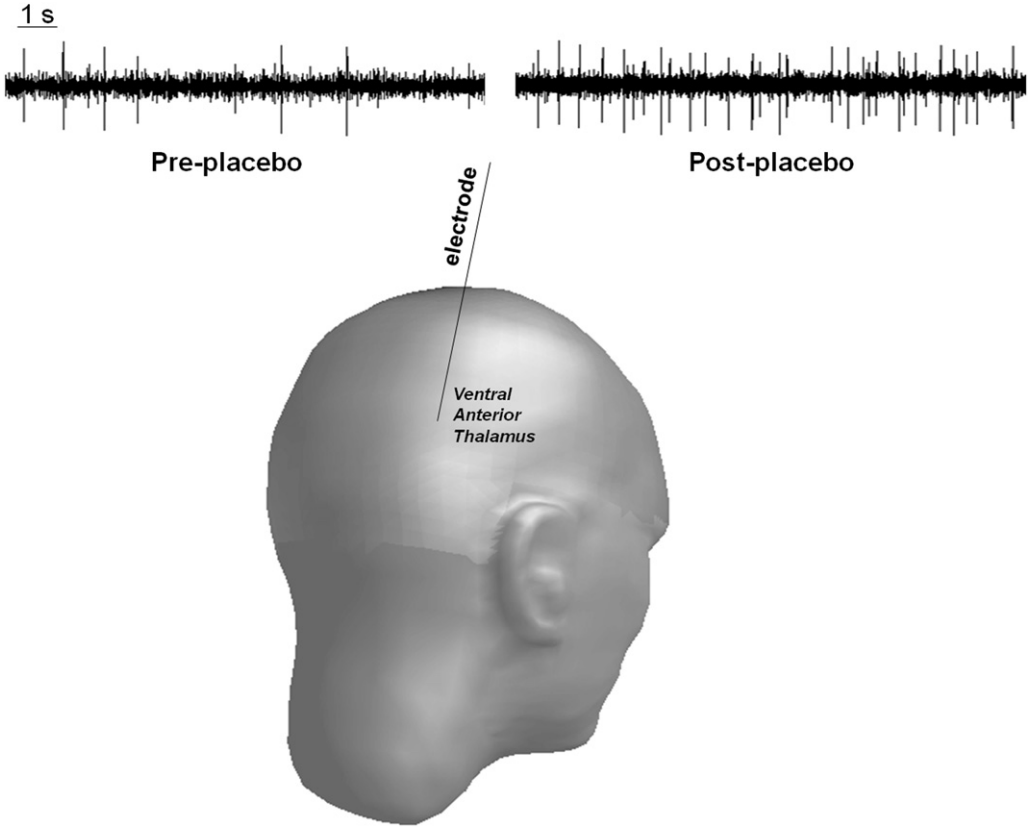

Figure 2 Single neuron recording from a thalamic neuron before and after placebo administration in Parkinson patients. Note the increase in firing rate following placebo administration, which is correlated to clinical improvement.

neuroimaging techniques, it is necessary to follow the patient for a long period or, otherwise, to devise pre- and post-treatment assessment with adequate control groups. Of course, if one wants to compare a placebo group with a no-treatment group to rule out spontaneous remission, this requires that some patients should not be treated for a long period, with the inherent ethical problems and limitations. This is one of the main reasons why depression, albeit an interesting and exciting model to study placebo effects, has not been investigated in detail so far.

Depressed patients who undergo a placebo treatment have been found to show both electrical and metabolic changes in the brain. Placebos induced electroencephalogram changes in the prefrontal cortex of patients with major depression, particularly in the right hemisphere. In fact, Leuchter et al [34,35] found distinct neurophysiological patterns in the placebo responders behind the prefrontal region by using an offline elaboration of electroencephalogram recordings, labeled *cordance*. By using PET, changes in brain glucose metabolism have also been documented in patients with unipolar depression [36]. Compared to baseline patterns, patients treated with drug (fluoxetine), regardless of response, showed changes in subcortical areas, including the brainstem, hippocampus, and cortical regions, including the posterior cingulate, the dorsolateral prefrontal cortex (DLPFC), the premotor cortex, the dorsal anterior cingulate cortex, and the inferior parietal posterior cortex. It was possible to note a suppression of activity in the subgenual cingulate (area 25). The placebo responders showed similar activity patterns in the cortex as compared to the drug responders, but the magnitude of change was smaller in patients who received placebo.

7. Drug addiction

Another example of the powerful role of expectation in drug responses is the work by Volkow et al [37,38], who investigated the effect of placebos in both cocaine abusers and non-drug-abusing individuals. In particular, they described the effects of methylphenidate on brain glucose metabolism, as measured by [^{18}F]deoxyglucose-PET, when participants expected (1) to receive the drug and indeed received the drug; (2) to receive the drug but they received the placebo; (3) to receive placebo but they received the drug; (4) to receive placebo and indeed received placebo. The researchers found that when the participants expected to receive drug, the effects were about 50% greater than when the participants did not expect the drug. In other words, unexpected methylphenidate induced smaller changes in the thalamic and cerebellar metabolism, thus indicating that expectation potentiates the pharmacological action of methylphenidate [37]. In non-drug-abusing participants, the changes in brain glucose metabolism occurred in regions involved in emotional reactivity and reward, such as the ventral gyrus (BA 25) and NAc [38]. The different findings in cocaine abusers and non-cocaine abusers suggest that in the first case, the enhanced thalamic and cerebellar responses reflect conditioned responses, whereas the changes in the striatum observed in the non drug-abusing participants may indicate the prevalence of expectations in the absence of prior experience.

8. Implications for clinical practice

The administration of placebos is widespread all over the world, as demonstrated by the high percentage of physicians surveyed who reported the use of placebo, usually to calm patients, avert requests for unnecessary medication, or as a supplemental treatment [39,40]. Deception is not necessarily involved in the use of a placebo, and this can represent an effective treatment which it would be unethical to withdraw [41,42]. There is also ample space for placebo use in less direct ways. For example, the therapeutic environment is a complex context, in which the active principle contained in a drug is not the sole agent acting on the patient body. In fact, any treatment administered in routine health care can be regarded as having two components: one pharmacodynamic, the other psychosocial. As described throughout this chapter, expectations have a central role in determining this second component (placebo or nocebo), and as they can be elicited by any aspect of the therapeutic context, it is in its optimization that the knowledge on placebo/nocebo mechanisms can both fruitfully and ethically be applied. To the extreme, total elimination of the context-induced expectations can be achieved with hidden drug administration carried out by a machine unbeknownst to the patient. In this case, dose requirements for the achievement of a given level of analgesia are invariably higher than in the open condition [43].

The first and foremost aspect of the psychosocial context is the patient—provider interaction. Indeed, the placebo effect has recently been defined as a form of interpersonal healing [44]. A list of eight specific clinical actions has been proposed: speak positively about treatments, provide encouragement, develop trust, provide reassurance, support relationships, respect uniqueness, explore values, and create ceremony [45]. Moreover, nonverbal clues intentionally or unintentionally conveyed by the therapist are important [46]. Equal attention should be paid to avoid nocebo suggestions [47,48]. Language incorporating negative suggestions should be changed to offer positive hints (e.g., from "Here's your pain medicine" to "Here's some medicine to help you get better"), in order to minimize anxiety [49,50].

Another important aspect is what the context can teach us about other patients' experiences. Just by watching others, it is possible to obtain useful information (the so-called social observational learning). Just like other forms of learning (prior experience, conditioning, expectation induced by verbal communication), social observational learning can also induce placebo/nocebo responses [51].

9. Implications for clinical trials

In clinical trials, the desired goal is just the opposite as in clinical practice, namely, to limit and reduce placebo effects as much as possible, in order to isolate the specific effect of the active principle under scrutiny. Research on placebo mechanisms has at least two important implications for clinical trials: (1) The design of protocols that circumvent the need of a placebo arm. An example is the "open/hidden" protocol, where the placebo component

stands out as the difference between overt or covert drug administration, with no patients receiving sham treatment. (2) The reevaluation of clinical trial methodology. In fact, patient expectations are not usually among the controlled variables but they have the potential to differentially influence improvement in both control (placebo) and drug arms, thus invalidating the attempt at separating the pharmacodynamic effect. For example, a study on acupuncture has showed that results could be drastically reversed by redistributing the participants according to what they believed was their group of assignment. In other words, no differences were found with the standard grouping, but the participants expecting real acupuncture reported significant less pain than those believing to be in the sham group, regardless of the real assignment [52]. Similar results were obtained in another study [53].

The large numbers of randomized controlled clinical trials have drawn the attention of some authors to the need to improve the design of such trials [54—56]. In particular, adequate methodology is a critical issue in their planning and execution, as different methodological approaches can translate into different results. The side effects observed in both the active medication arm and the placebo arm are often influenced by nonspecific factors. This issue can be quantified by using a systematic review approach to study the rates of adverse events reported in the placebo arms of clinical trials [57,58]. The participants recruited to take part in a typical randomized, double-blind clinical trial know they will receive either an active medication or a placebo, and they are informed about the possible adverse events they may experience. This information is provided in the informed consent form and in the instructions given by the investigator. Informing the participants about the possible adverse events they may experience has a significant impact on their expectations. In particular, an expectation of negative symptoms, in terms of adverse effects, may be considered an important element in eliciting negative outcomes [57]. These nocebo phenomena may help us better understand the occurrence of psychologically driven adverse symptoms, as well as to improve clinical trial designs and patient—provider communication.

Therefore, understanding the placebo effect, its biological underpinnings and its use in clinical trials, represents a scientific challenge which not only will give insights into human biology, but it will also generate new designs and interpretations of the clinical trials that are currently carried out [59,60].

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