Brain mechanisms underlying the placebo effect in neurological disorders

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Summary

The potential of placebo treatments to alleviate a variety of medical conditions has long been recognised. Although the placebo effect is widely known, the physiological mechanisms underlying this phenomenon are not well understood. This review focuses on the existing evidence for placebo responses in different neurological conditions, including pain, Parkinson's disease, depression, sleep and immune-mediated disorders. Special attention is paid to the neural changes associated with placebo treatments, as revealed by in vivo neurophysiological and functional neuroimaging studies. Converging evidence suggests that placebo analgesia is linked to the activation of the endogenous opioid analgesia network, whilst dopaminergic pathways seem to play a central role in the placebo effect in movement disorders and neuroimmunomodulation. Further research on the placebo response is needed, both to improve the efficacy of its application in clinical practice and to shed more light on the complexity of mind-body interactions.

KEY WORDS: depression, nocebo effect, pain, Parkinson’s disease, placebo effect.

Introduction

The term “placebo” comes from a Latin word, literally meaning “I shall please.” It was first used in the medical setting in the eighteenth century to mean a medicine that pleases a patient rather than giving a real benefit. The modern concept of the “placebo effect”, meaning an actual change in the illness status induced by the medicine’s symbolic value rather than as a result of specific therapeutic effects, evolved only in the last century (1). The placebo effect is currently understood by the medical community as a healing response induced by non-specific verbal or behavioural procedures that operate through the patient’s belief in the therapeutic power of the placebo (2). Conversely, the nocebo effect is the phenomenon whereby a patient who believes that a treatment will cause harm actually does experience adverse effects (3). It has been claimed that the nocebo phenomenon could offer new insights into the aetiopathological mechanisms of some non-specific side effects of active medications (4). On the other hand, the placebo effect cuts across a wide range of pathological conditions, and therefore provides us with a privileged window onto the biological bases of mind-brain and brain-body interactions (3).

Conceptual and methodological problems make accurate estimation of the placebo effect difficult in clinical settings, as not all changes occurring after placebo treatments can reasonably be interpreted as “true” placebo effects (5). For instance, the severity of the signs and symptoms reported by the subject can vary over time due to a number of processes that are independent of any placebo intervention, processes that include the natural course of the disease and the regression to the mean. The latter, a well-known statistical phenomenon, is the tendency of a clinical parameter found to be extreme on one measurement to be closer to the mean (i.e. clinically improved) on subsequent measurements (6). Despite these well-recognised difficulties, our understanding of the brain processes involved in the placebo effect has considerably improved over the last few years, with neuroimaging techniques opening up new avenues in the scientific exploration of this phenomenon.

Generally, the placebo effect plays a central role in the therapeutic management of several neurological conditions, because the central nervous system acts as a common interface between mental states (including placebo-induced beliefs) and physical states. As outlined in figure 1, both classical conditioning and conscious expectancy processes have been thought to be involved in the interaction between mental states and physiological mechanisms.

![Figure 1 - Theoretical model of the putative processes mediating placebo-induced physiological changes.](image-url)
The present paper looks briefly at a few selected neurological conditions that may serve as models for neurobiological, neurophysiological, and neuroimaging investigations into the brain mechanisms underlying the placebo effect: pain conditions (including headache), movement disorders (particularly Parkinson’s disease), depression, insomnia, immune-mediated disorders such as multiple sclerosis, and epilepsy.

**Placebo analgesia**

Pain relief is one of the most common clinical applications of the placebo effect. Placebo analgesia is the situation in which a substance known to be non-analgesic (usually a biologically inactive substance administered orally, intramuscularly or endovenously) produces an analgesic response in a subject who has been told that it is a painkiller (7). The existence of an analgesic effect induced by placebo procedures has long been documented in the literature and placebo analgesia is widely used in everyday clinical practice (3). Moreover, the insights we have into the brain mechanisms underlying the placebo effect come mostly from studies on pain conditions. Study of the neurobiology of placebo began about 30 years ago, when Levine et al. (8) demonstrated that naloxone, a potent mu-opioid antagonist, causes a significant reduction in placebo analgesia. These findings constituted the first suggestion that placebo analgesia is somehow mediated by the release of endogenous opioids, which in turn are responsible for the diminished pain perception. Conversely, ten years ago, Benedetti et al. (9) showed that the nocebo effect can be reduced through the hidden administration of proglumide, a cholecystokinin antagonist, thus suggesting that cholecystokinin is implicated in the neurobiological mechanisms mediating nocebo-induced hyperalgesia.

More recently, the relationship between placebo analgesia and the endogenous opioid system has been investigated using functional imaging methods, such as positron emission tomography (PET) and magnetic resonance imaging (MRI). Converging evidence suggests that a pivotal role in both exogenous opioid and placebo analgesia is played by the rostral portion of the anterior cingulate cortex (rACC), which is strategically positioned to form a loop linking the brainstem with limbic and medial prefrontal regions, and is densely populated with mu-opioid receptors (10). The ACC, along with the brainstem and the dorsolateral and orbitofrontal cortices, are the sites most commonly investigated in placebo imaging studies (11-16). Although there is general consensus on the regions involved in placebo analgesia, the exact location of the activation peak in the ACC is debated (Table I). However, most authors agree that

<table>
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<th>Study [ref.]</th>
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<td>Petrovic et al. 2002 [11]</td>
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<td>Orbital frontal cortex, rACC, brainstem (PAG, lower pons and medulla)</td>
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<td>Pariente et al. 2005 [13]</td>
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<td>Dorsolateral prefrontal cortex, pregenual ACC, anterior insula, nucleus accumbens</td>
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Abbreviations: PET=positron emission tomography; fMRI=functional magnetic resonance imaging; rACC=rostral anterior cingulate cortex; PAG=periaqueductal grey; ACC=anterior cingulate cortex. * During anticipation of pain
the rACC, when activated during placebo procedures, enhances descending pain control systems. In fact, the rACC could act as the main interface between the cognitive elaboration of analgesia expectation and endogenous opioid release.

Several neurological conditions are associated with pain and have good potential to benefit from placebo treatments. In particular, placebo analgesia in patients suffering from headache has proved to be a powerful and consistent phenomenon. A recent meta-analysis by de Craen et al. (17) revealed a significant placebo effect in 26-32% of patients with migraine. Overall, results from placebo-controlled clinical trials aimed at the development of new drugs for the abortive treatment of migraine (triptans) have confirmed that placebo effects are highly variable and often substantial in migraine populations (18). From a clinical perspective, a better knowledge of the neurochemical mechanisms underlying placebo analgesia could be helpful, first in detecting placebo-responders and second in refining the use of this additional tool for the treatment of complicated headaches (19).

**Placebo in movement disorders**

Although the neurobiological processes bringing about the placebo response were first described and have traditionally been investigated in pain conditions, new clinical models have emerged in recent years (20). These models now include several movement disorders, in particular Parkinson’s disease. Unlike pain conditions, in which the patient’s subjective report of pain perception is the main parameter for the assessment of clinical improvement, in Parkinson’s disease the response to treatment can also be assessed objectively by the examiner, and this direct measurability allows a more precise evaluation of the placebo effect. Placebo effects may occur whenever patients are given an inert substance and are told that it is an antiparkinsonian drug that will produce an improvement in their motor performance. Although all the classical Parkinsonian symptoms show a clinical response to placebo procedures, there is a trend for a greater effect on bradykinesia than on tremor or gait/balance disturbances (21,22). It has recently been proposed that these differences in expectation-induced clinical variations support the notion of a dopamine-mediated process underlying the expectation response (23).

A preliminary PET study by de la Fuente-Fernandez and colleagues (24) on patients with Parkinson’s disease who had undergone placebo treatment showed an increase in the endogenous release of dopamine in the basal ganglia circuitry. In further studies, the same group provided evidence for dopamine release in the ventral striatum/nucleus accumbens (a region involved in reward mechanisms) and argued that the clinical benefit perceived by the patients is linked to placebo-induced reward experiences (25-27).

Moreover, it has been found that expecting a poor versus a good motor performance modulates the therapeutic effect of subthalamic nucleus stimulation in patients chronically implanted with electrodes for deep brain stimulation. In fact, analyzing the effect of subthalamic stimulation on the speed of right-hand movements, these movements were found to be faster when the patients anticipated a good motor performance. These effects occurred within minutes, suggesting that expectations can induce neural changes in the basal ganglia circuitries relatively quickly (28). The strong placebo responses in Parkinson’s disease and the possibility to study patients who are implanted with electrodes for deep brain stimulation have been recently exploited by Benedetti et al. (29) to record the activity from single neurons in the subthalamic nucleus after placebo administration. In this study, the activity was recorded both before and after placebo administration to see whether neural changes were linked to the clinical response to the placebo (a saline solution given to patients who believed it to be an antiparkinsonian drug). It was found that the placebo responders showed a significant decrease of neuronal discharge and the disappearance of bursting activity of subthalamic neurons, whereas the placebo non-responders did not.

In short, Parkinson’s disease is a useful clinical model for investigating the intricate relationship between expectation, reward, and neural systems. In particular, the possibility of recording from single neurons offers us the chance to identify the neuronal changes that take place in the basal ganglia circuitry during the placebo response. Interestingly, other movement disorders thought to be associated with dysfunction of dopaminergic neurotransmission in either the nigrostriatal or the mesocorticolimbic dopamine pathways also seem to be susceptible to the placebo effect. These conditions include dystonia, tremors, akathisia, tardive dyskinesia, restless legs syndrome, and Gilles de la Tourette syndrome (30). However, definite conclusions about the mechanism of the placebo effect are hard to reach from these disorders, because many of them are heterogeneous in nature and in most of them it is still uncertain whether the underlying pathophysiology is due to a primary hyperdopaminergic or hypodopaminergic state (or to some combination of the two).

**Placebo in other neurological conditions**

The placebo response has been widely recognised in neuropsychiatric disorders, especially depression. In trials of antidepressants it is commonly found that about 35% of the patients receiving placebo show some improvement, although according to a few authors the rate of the placebo response is even higher. For example, Kirsch and Sapirstein (31) concluded from their meta-analysis of 19 trials of antidepressants that about 75% of the effectiveness of these drugs derives from the placebo effect. Depressed patients receiving a placebo treatment show both electrical and metabolic changes in the brain. A study by Leuchter et al. (32) demonstrated that depressed patients who respond to placebo antidepressants show a specific pattern of prefrontal activation as detected by quantitative electroencephalography measures, particularly in the right hemisphere. In this study, placebo responders also showed faster cognitive processing times, as assessed by neuropsychological testing, and gave fewer reports of late insomnia. On the basis of these data, the authors suggested a combination of clinical, neurophysiological, and cognitive assess-
ments for identifying depressed subjects who are likely to be placebo responders. Moreover, changes in brain glucose metabolism were measured using PET in subjects with unipolar depression who were taking placebo antidepressants. Placebo treatments were associated with metabolic increases in the prefrontal, anterior cingulate, premotor, parietal, posterior insular, and posterior cingulate cortex, and metabolic decreases in the subgenual cingulate cortex, parahippocampus, and thalamus. Interestingly, these regions showed similar changes in metabolic activity after the administration of a selective serotonin reuptake inhibitor, fluoxetine, thus suggesting a role for serotonin in placebo-induced antidepressant effects (33).

Perlis et al. in 2005 (34) reviewed the literature on the placebo effect in primary insomnia, revealing an important role for placebo in the clinical management of this condition. It is a common finding within randomized clinical trials on patients suffering from insomnia that placebos produce significant changes in self-reported sleep continuity measures. In a recent meta-analysis of these studies, McCall and colleagues (35) estimated the magnitude of the pre- versus post-placebo change in sleep latency and total sleep time measures to be approximately 20%. Longer-term trials (both intermittent and nightly dosing) show that these effects are not only stable, but that clinical improvements continue to occur over time.

Placebo has been found to demonstrate efficacy also in immune-mediated neurological disorders such as multiple sclerosis, even though the potency of its effect varies among studies. In a review of placebo-controlled randomized clinical trials on patients with multiple sclerosis, La Mantia et al. (36) showed that in the placebo arm the frequency of relapse in relapsing-remitting patients decreases during follow up, and disability in progressive cases increases more slowly than before enrolment. Therefore, the role played by the placebo effect should be taken into due account when evaluating the impact of experimental drugs on the natural course of multiple sclerosis. Ader (37) observed placebo-induced changes in blood cell counts in eight out of ten patients with multiple sclerosis included in a cyclophosphamide therapy protocol. Animal models of placebo-induced immune-suppression support the notion that the immune system can be modulated by brain processes, which could have implications as regards the possible role of placebos in disorders associated with altered immunological functioning (38). Several neurotransmitters, including dopamine, have been implicated in neuroimmunomodulation (39). The nigrostriatal and mesolimbic dopamine pathways, as well as other central pathways (e.g. tuberoinfundibular) and peripheral dopamine systems, are known to influence immune responses. Indeed, direct dopamine agonists seem to exert a beneficial effect in several autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus, thus providing indirect evidence that dopaminergic systems play a first-line role in immune system modulation (40).

Finally, a few studies have focused on the relationship between placebo and epilepsy. In 2002, Burneo et al. (41) assessed the magnitude of the placebo effect in randomized trials of antiepileptic drugs, revealing that 9.3-16.6% of patients in the placebo arm had a >50% reduction in seizure frequency. This effect represents 20-50% of the overall effect observed with active agents. The exact mechanisms by which the administration of placebo can modulate cortical excitability, and ultimately raise the seizure threshold, are still unclear and need to be elucidated through further research.

Concluding remarks

Over the past few years, converging evidence from neurophysiological and functional imaging studies has suggested that placebo procedures raise expectations about future events and can trigger different neural pathways affecting not only pain perception, but also movement, mood, and immunomodulation. Multiple biochemical substrates seem to be involved in the placebo responses observed in different neurological conditions. There is also a body of evidence suggesting that placebo analgesia is linked to the activation of the endogenous opioid analgesia network, with the rostral portion of the anterior cingulate cortex playing a central role. Recent studies on Parkinson’s disease and other movement disorders have led to the formulation of the theory that the placebo effect is mediated by the dopaminergic reward mechanisms and is related to the expectation of clinical benefit. Moreover, nigrostriatal and mesolimbic dopamine pathways seem to be involved in placebo-induced neuroimmunomodulation. Finally, clinical studies on depressed subjects suggest a possible role for the serotonergic system in the well-recognized placebo-induced antidepressant effects.

Placebos are not thought to work uniformly across acute and chronic disorders: generally, anxiety and pain, autonomic nervous system involvement, and immunobiological processes are believed to respond favourably to placebo. In particular, Evans (42) has recently proposed that the placebo effect could act at a subcellular level, inhibiting the acute phase of the inflammatory process, which cuts across several placebo-susceptible pathologies.

Overall, the new insights into the brain mechanisms underlying placebo responses support the view that the widespread use of the placebo effect for therapeutic goals (particularly with regard to neurological disorders) is both a real possibility and a legitimate approach. It has been shown that there is a percentage of placebo responders in most clinical entities, although reliable data quantifying the placebo effect are available only for a few conditions, partly due to methodological difficulties in the identification of the placebo response. For instance, a study by McQuay et al. (43) examined five placebo-controlled trials of painkillers conducted between 1981 and 1990 and found that the individual pain relief scores of those taking placebos ranged from 0 to 100%. However, there is little doubt that the traditional figure of “35% of the general population” susceptible to placebo, originally reported by Beecher in his influential paper published in 1955 (44) and quoted for decades afterwards, needs to be replaced by more accurate measures of placebo responders for each clinical population. Regardless of the real size of the placebo effect, a recent study on the clinical practice of physicians in Israel found that 60% of them use placebos, most commonly in order to “fend off” requests for unjustified medications or as a means of calming patients (45). Of the physi-
cians who reported using placebos, 68% told patients they were receiving actual medication and 28% saw placebos as a diagnostic tool that would help them to determine whether the patient’s symptoms were real, or whether the patient was malingered. Both critics and defenders of the exploitation of the placebo effect in clinical practice agree that such behaviour is unethical. In fact, the issue of the clinical application of placebo treatment mirrors the ethical debate about the primacy of the principle of patient autonomy (which would probably limit the use of the placebo effect in clinical practice) and the principle of trust in medical expertise (which would justify its use) (46). Placebo administration may prove useful in some specific cases where recommended drugs cannot be used. For example, patients with respiratory problems often cannot be prescribed opioids as painkillers, as these can cause further respiratory depression. In such cases, placebo injections can provide real pain relief if patients are told that they are being given a powerful dose of painkillers. Moreover, placebos and drugs can be expected to show a reciprocally potentiating effect in several neurological conditions, since the same brain areas have been shown to be involved in both the placebo effect and pharmacological treatment.

From a different perspective, these findings suggest that the placebo effect could represent a useful model for investigation of mind-brain interactions. Furthermore, they provide a new conceptual framework in which to reformulate the ancient philosophical question of whether mental states (res cogitans, in Descartes’ words) can be regarded as the real cause of any physical response (res extensa) (47). It is expected that further steps in the neuroscientific exploration of the brain mechanisms underlying the placebo effect will provide us with new insights into some of these unanswered problems.

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