PERSPECTIVES

SCIENCE AND SOCIETY

Placebos and painkillers: is mind as real as matter?

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Abstract | Considerable progress has been made in our understanding of the neurobiological mechanisms of the placebo effect, and most of our knowledge originates from the field of pain and analgesia. Today, the placebo effect represents a promising model that could allow us to shed new light on mind–body interactions. The mental events induced by placebo administration can activate mechanisms that are similar to those activated by drugs, which indicates a similarity between psychosocial and pharmacodynamic effects. These new neurobiological advances are already changing our conception of how clinical trials and medical practice must be viewed and conducted.

All medical procedures are associated with a complex psychosocial context that might affect the therapeutic outcome[1–7]. To analyse the effects of the psychosocial context on the patient, we need to eliminate the specific action of a therapy (for example, a drug) and to reproduce a context that is similar in all respects to that of real drug administration, without the specific action of the drug itself. To do this, a dummy treatment (the placebo) is given, which the patient believes is an effective therapy, and so expects a reduction in symptoms. The placebo effect, or response, is the outcome that follows the dummy treatment. Therefore, the study of the placebo effect is essentially the study of the psychosocial context that surrounds the patient[8].

It is important to stress, and there is confusion on this point, that the real placebo response is a psychobiological phenomenon that can be due to different mechanisms, which include the expectation of clinical benefit[9–17] and Pavlovian conditioning[16–22]. In other words, there is not one single placebo effect, there are many, so we need to look for different mechanisms in different conditions. As there is experimental evidence that expectations have a fundamental role in placebo-induced analgesia[12,16], most of this article is devoted to the link between expectancy and pain — an interesting model with which to study mind–body interactions.

So far, the placebo effect has been considered a troublesome artefact and a nuisance in clinical research, in which the validation of a new treatment requires comparison with a placebo treatment. In recent years — partly due to advances in laboratory research, both in patients and in healthy volunteers — the placebo effect has been transformed from a nuisance factor in the setting of clinical research to a target of scientific inquiry. The results of recent neuropharmacological, neurophysiological and neuroimaging studies promise to cast direct light on the neural mechanisms that are involved in this phenomenon, not only for pain but also for other conditions. It is worth noting that in order to be certain that we are dealing with a psychobiological effect, we must rule out other phenomena, such as the spontaneous remission of a symptom or symptoms (BOX 1).

It should also be recognized that, despite the recent explosion of neurobiological study on the placebo effect, research in this area is still in its infancy and many questions remain unresolved — for example, how and when opioid and non-opioid mechanisms come into play in placebo analgesia. However, there is compelling reason to believe that, in light of the rapid advances in placebo research in recent times, the coming years will be characterized by a real attempt to place the placebo effect in an emerging neuroscience of mind–brain–body interactions. In this review, we describe these new neurobiological insights into placebo mechanisms, their clinical applications and the ethical and social implications. So far, the interest in and the success of placebo research resides in its multifaceted meaning, which involves key issues in modern science — from neurobiology to philosophy, from ethics to social psychology, and from clinical trial design to medical practice.

An emerging uncertainty principle

Today, the gold standard in clinical trial design is the double-blind randomized placebo-controlled study with two arms[23–24]. One arm of the trial consists of a group of randomized patients who are given the active treatment, whereas the second arm consists of a group that is given the placebo — an inert treatment that mimics the active one in all respects. This is done according to a double-blind design, in which neither the doctors nor the patients know what is being given. The patients are told that they could receive either the active treatment or the placebo, with a chance of 50%. In order to conclude that the active treatment is effective, the outcome that follows its administration must be better than that of the placebo. This approach is necessary because the placebo group might itself show a clinical improvement (BOX 1). The key question is: is this design appropriate to enable us to conclude that a therapy is effective?

Box 1 | **Identifying real psychobiological placebo responses**

The investigation of the placebo response is full of pitfalls because, for a placebo response to be shown, several other phenomena must be ruled out. The placebo itself is not always the cause of the effect that is observed[8,80,81]. For example, people experience spontaneous variations in pain intensity in most painful conditions, which is known as 'natural history'[82,83]. If a patient takes a placebo just before his or her pain starts to decrease, he or she might believe that the placebo is effective, even though the decrease would have occurred anyway. Another example is represented by the regression to the mean — a statistical phenomenon that assumes that individuals tend to receive their initial pain assessment when the pain is near its greatest intensity, and that their pain level is likely to be lower when they return for a second assessment[84]. A further source of confusion might be represented by false positive errors, which, according to signal detection theory, are based on the occurrence of errors in the detection of ambiguous signals, such as pain[85]. Sometimes it is a co-intervention that is responsible for the reduction of pain — for example, the analgesic effect that is induced by the mechanical stimulation of a syringe needle for injecting a solution[8]. Such examples show that the placebo is not necessarily the cause of the improvement that is observed. All of these possibilities must be ruled out through adequate controls. For example, to rule out spontaneous remission, a group taking the placebo is compared with a group receiving no treatment, the latter of which gives information about the natural course of the symptom(s). The difference between the placebo group and the no-treatment group represents the real psychobiological placebo response[82]. As all these factors cannot be adequately controlled in clinical trials, placebo mechanisms need to be studied in the laboratory setting under strictly controlled experimental conditions[86]. In fact, in a meta-analysis of the power of placebos[87], small placebo effects were found in some clinical trials. This was probably due, among other factors, to the fact that a 50% chance of getting a placebo was openly communicated to the patients. When only the experimental placebo studies were considered, in which the information about the placebo was 'you will be given a powerful analgesic drug', larger placebo effects were observed[88]. Therefore, manipulating the degree of expectation in the laboratory setting changes the degree of the placebo effect.

In 1995, we ran a classical clinical trial of postoperative pain, in which the cholecystokinin antagonist proglumide was shown to be better than the placebo, and the placebo was shown to be better than no treatment for relieving pain[25] (FIG. 1a). According to classical clinical trial methodology, these results indicate that proglumide is a good painkiller that acts on the pain pathways, whereas the placebo reduces pain by inducing the expectation of analgesia, which activates expectation pathways (FIG. 1a). However, this conclusion proved to be erroneous, as a hidden injection of proglumide — a procedure in which participants were completely unaware that a treatment was being administered — was totally ineffective (FIG. 1b). Therefore, the likely interpretation of the mechanism of action of proglumide is that it does not act on pain pathways at all, but, rather, on expectation pathways, which enhances the placebo analgesic response (FIG. 1b). In other words, proglumide induces a reduction in pain if, and only if, it is associated with a placebo procedure. We now know that proglumide is not a painkiller, and that it acts on placebo-activated opioid mechanisms (see below). Importantly, cholecystokinin has been found to play a part in the interaction between complex environmental–social stimuli, such as safety cues, and the endogenous opioid systems[26], which emphasizes the involvement of cholecystokinin–opioid systems in cognitive processes.

We believe that the trial described above is the best example with which to explain our urgent need to understand the neurobiological mechanisms of the placebo response. By borrowing the Heisenberg uncertainty principle from physics[27], which imposes limits on the precision of a measurement, we can apply a similar principle to the outcomes of clinical trials. In the same way that the uncertainty principle states that a dynamical disturbance is necessarily induced in a system by a measurement, a dynamical disturbance might be induced in the brain in clinical trials by almost any type of drug. The very nature of this dynamical disturbance is the interference of the injected drug with the expectation pathways, which affects both the outcome measures and the interpretation of the data. In other words, as in the Heisenberg uncertainty principle, the disturbance is the cause of the uncertainty. A pharmacological analgesic treatment, for instance, has a pharmacodynamic effect on pain pathways, but might also interfere with the mechanisms of top-down pain control (FIG. 1c). As we have no *a priori* knowledge of which substances act on pain pathways and which on expectation mechanisms — and almost all drugs might interfere with the top-down mechanisms — this uncertainty cannot be resolved using the standard clinical trial design. The only way to partially resolve this problem is to make the expectation pathways 'silent'. This can be achieved by the hidden administration of drugs (see below).

In the following sections we focus our attention on the nature of the placebo-activated expectation pathways, their biochemistry and their localization in the brain. This understanding is crucial and fundamental to our understanding of the dynamical disturbance that drugs might produce in expectation mechanisms (FIG. 1c).

Biochemistry of placebo analgesia

So far, most studies investigating the placebo analgesic response have used verbal suggestions of analgesia, and verbally induced expectations of pain reduction have been found to play a crucial part in placebo analgesia, even though a conditioning procedure has previously been carried out[16]. In fact, the association between the context in which a patient is treated (conditioned stimulus) and a painkiller (unconditioned stimulus) can be learned consciously through the expectation that the conditioned stimulus brings about the occurrence or nonoccurrence of the unconditioned stimulus[16,28,29]. However, it is worth noting that the distinction between conditioning and expectation goes beyond the understanding of the placebo effect itself, as it relates to the more general problem of whether conditioning in humans can occur at all in the absence of consciousness[30].

Several lines of evidence indicate that the administration of a placebo, combined with the suggestion that it is a painkiller (verbal context), can reduce pain by both opioid and non-opioid mechanisms (FIG. 2). In the first case, placebo analgesia is typically blocked by the opioid antagonist naloxone[31–34], whereas in the second case it is not[12,35]. Which of these mechanisms is used depends on the procedure that is applied to induce the placebo analgesic response[12]. In a model of human experimental ischaemic arm pain, the placebo response can be blocked by naloxone if it is induced by strong expectation cues; if the expectation cues are reduced, the placebo response is insensitive to naloxone. In addition, if the placebo response is obtained after exposure to opioid drugs, it can also be blocked by naloxone. By contrast, if the placebo response occurs after exposure to non-opioid drugs, it is naloxone-insensitive. These data indicate that opioid and non-opioid mechanisms come into play under different circumstances. The placebo-activated

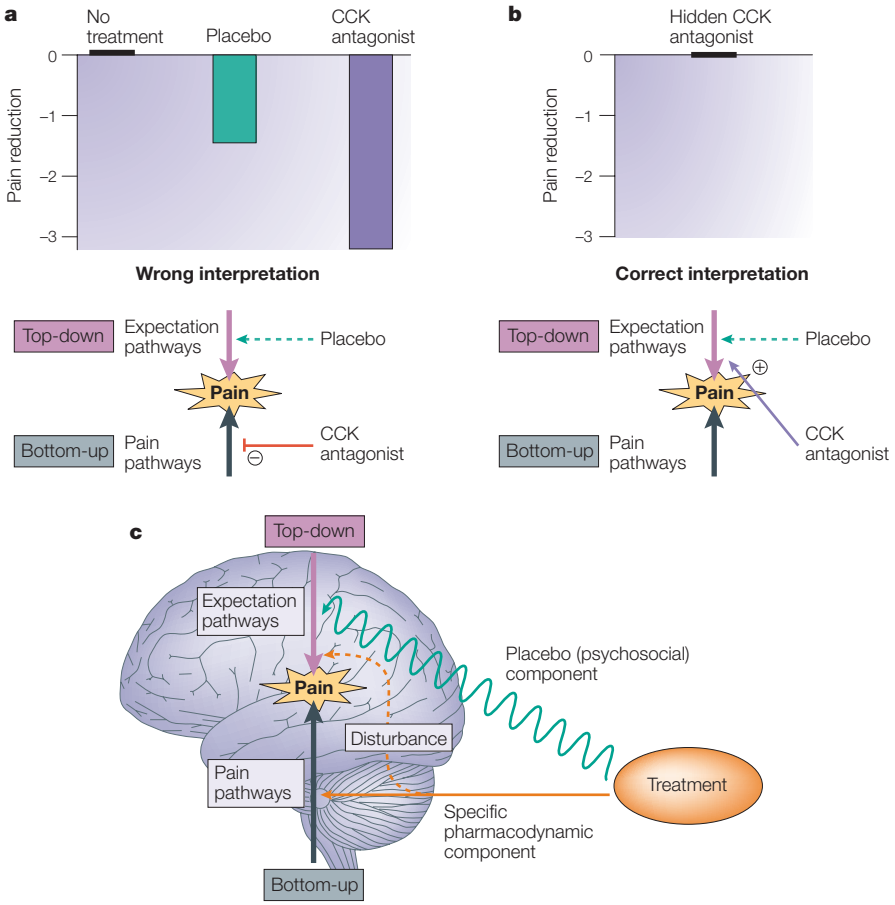

Figure 1 | **An emerging uncertainty principle imposes limitations on our understanding of the effects of a therapeutic agent. a** | A clinical trial with 3 arms shows that a placebo is better than no treatment, and that proglumide, an antagonist of cholecystokinin (CCK), is better than a placebo in relieving pain. According to classical clinical trial methodology, this leads to the erroneous belief that the cholecystokinin antagonist acts specifically on pain pathways (the bottom-up action) whereas the placebo acts on expectation pathways (the top-down control). **b** | The interpretation in (**a**) is incorrect because if the same cholecystokinin antagonist is given covertly, so that the patient is completely unaware that a drug is being administered and, therefore, has no expectations, the drug has no effect at all. As the drug has analgesic effects only in association with a placebo procedure, its action is not directed specifically to the pain pathways, but to the expectation pathways, which enhances the placebo analgesic response. **c** | Any analgesic treatment consists of two components: the specific pharmacodynamic component and the placebo component. The latter is induced by the psychosocial context in which the treatment is given and elicits expectations of therapeutic benefit. The uncertainty principle in a clinical trial is represented by the fact that a drug might act on expectation pathways (broken arrow) rather than pain pathways, which makes it extremely difficult to conclude whether or not a pharmacological substance is a real painkiller. The only way in which this uncertainty can be partially resolved, and the identity of the real pharmacodynamic effect of a painkiller established, is through the elimination of the placebo component, and, therefore, of the expectation pathways, by hidden treatments. Data in panels **a** and **b** taken from REF. 25. Anatomical image in panel **c** adapted, with permission, from REF. 99 © (1996) Appleton & Lange.

endogenous opioid systems have been shown to have a precise and somatotopic organization. Highly specific placebo responses can be obtained in specific parts of the body[13,36,37] and these local placebo responses can be blocked by naloxone[13].

Further experimental evidence to support the role of endogenous opioids in placebo analgesia comes from the cholecystokinin-antagonist trial that is described above[25]. On the basis of the anti-opioid action of cholecystokinin[38], the cholecystokinin antagonist proglumide is able to enhance the placebo analgesic effect through the potentiation of the placebo-activated opioid systems[25,34]. Therefore, the placebo analgesic response seems to result from a balance between endogenous opioids and endogenous cholecystokinin (FIG. 2). In another study on patients with chronic pain, it was found that placebo responders showed a higher concentration of endorphins in the cerebrospinal fluid than placebo non-responders[39].

The placebo-activated endogenous opioids have also been shown to produce a typical side effect of opioids — respiratory depression[40,41]. After repeated administration of analgesic doses of buprenorphine in the postoperative phase, which induces a mild decrease in ventilation, a placebo is able to mimick the same respiratory-depressant response. Remarkably, this respiratory placebo response can be completely blocked by naloxone[41]. Therefore, not only do placebo-activated opioid systems act on pain mechanisms, they also act on the respiratory centres (FIG. 2). The involvement of other systems during placebo analgesia is further supported by a recent study in which the sympathetic control of the heart was analysed during placebo analgesia in both the clinical and laboratory settings[42]. It was found that placebo analgesia was accompanied by a reduced heart rate and a decreased β-adrenergic response — an effect that was reversed by naloxone. These findings indicate that opioid-mediated placebo analgesia also affects the cardiovascular system (FIG. 2).

In recent years, attempts have been made to identify the different neurochemical systems that are involved in placebo analgesia. For example, the analgesic drug sumatriptan, a serotonin agonist of the 5-$HT_{1B/1D}$ receptors that stimulates growth hormone and inhibits cortisol secretion, has been used as a preconditioning drug to induce placebo responses[16]. In this study, participants were given sumatriptan repeatedly before a placebo was administrated in the absence of the drug. The placebo was found to be more likely to induce an increase in growth hormone secretion and a decrease in cortisol secretion — outcomes that would have been caused by sumatriptan — in participants who had previously been treated with sumatriptan. Therefore, a placebo procedure that involves sumatriptan preconditioning might affect serotonin-dependent hormone secretion, which indicates that neurotransmission other than that mediated by the opioid pathway might be responsible for some placebo effects.

Where the biochemical events occur

Although the pharmacological approach with agonist and antagonist drugs has provided important information about the biochemical events that are triggered by placebos, it has not allowed identification of the specific brain regions that are involved.

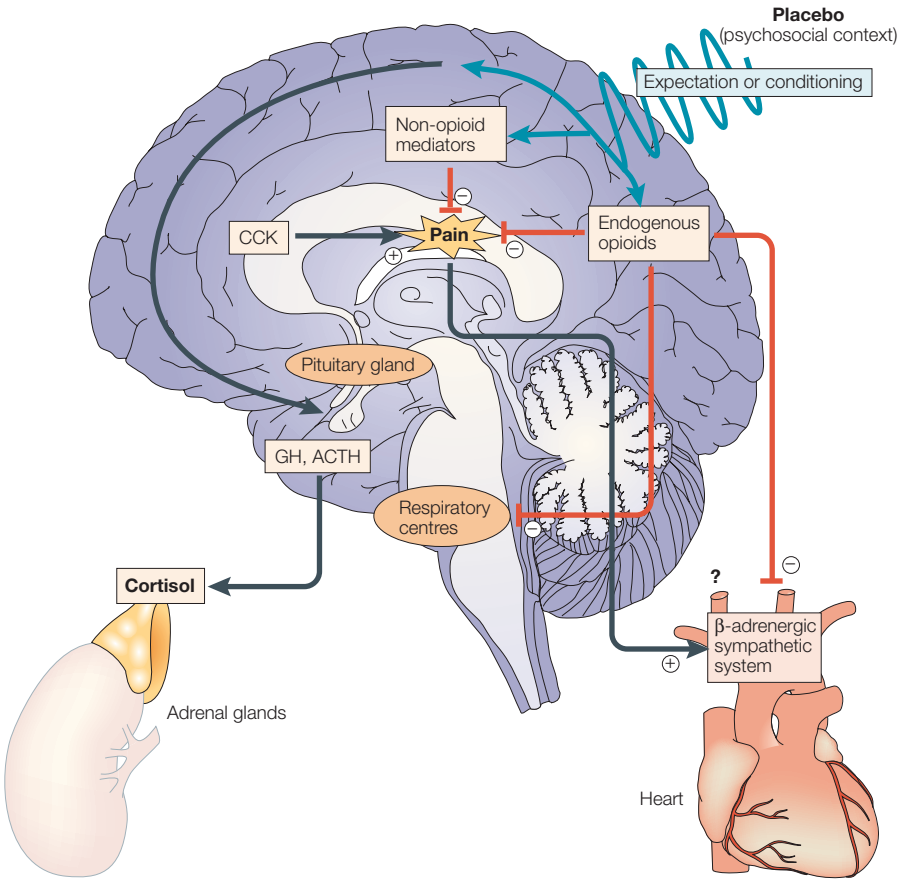

Figure 2 | **Putative cascade of biochemical events in the brain after placebo administration.** Placebo administration, combined with the verbal suggestion of analgesia (psychosocial context) might reduce pain through opioid and/or non-opioid mechanisms by expectation and/or conditioning mechanisms. The respiratory centres might also be inhibited by opioid mechanisms. The β-adrenergic sympathetic system of the heart is also inhibited during placebo analgesia, although the underlying mechanism is not known and could occur through the reduction of the pain itself and/or the direct action of endogenous opioids. Cholecystokinin (CCK) counteracts the effects of the endogenous opioids, thereby antagonizing placebo analgesia. Placebos can also act on serotonin-dependent hormone secretion, in both the pituitary and adrenal glands, thereby mimicking the effect of the analgesic drug sumatriptan. ACTH, adrenocorticotrophic hormone; GH, growth hormone. Anatomical brain image adapted, with permission, from REF. 99 © (1996) Appleton & Lange.

Not only does a recent brain imaging study provide information about the brain regions that are involved in placebo analgesia, it also supports the opioid hypothesis. Using positron emission tomography (PET), it was found that the same regions of the brain are affected by both a placebo and the opioid agonist remifentanil[43,44], which indicates a related mechanism in placebo-induced (psychosocial effect) and opioid-induced (pharmacodynamic effect) analgesia (FIG. 3a). In particular, the administration of a placebo induced the activation of the rostral anterior cingulate cortex (rACC), the orbitofrontal cortex (OrbF), and the anterior insula (aINS); there was also a significant co-variation in activity between the rACC and the lower pons and medulla, and a sub-significant co-variation between the rACC and the periacqueductal grey (PAG). The data indicate that a descending rACC–PAG–pons–medulla pain-modulating circuit is involved in placebo analgesia, and support the previous suggestion that the PAG–pons–medulla-modulating circuit might be involved in complex cognitive functions, such as placebo analgesia[45]. In fact, an opioid neuronal network in the cerebral cortex and the brainstem has been described as a descending pain-modulating pathway that connects the cerebral cortex, either directly or indirectly, to the brainstem[14,45,46,47]. In particular, the rACC and OrbF project to the PAG which, in turn, modulates the activity of the rostral ventromedial medulla (RVM). All of these regions are rich in opioid receptors[48–51], so this pain-modulating circuit is probably the same as that activated by placebo analgesia.

Another study used functional magnetic resonance imaging to analyse the brain regions that are involved in placebo analgesia (FIG. 3b,c). This study showed that the activity of pain regions, particularly the thalamus, aINS and caudal rACC, was decreased by a placebo treatment, which indicates that placebos reduce nociceptive transmission along the pain pathways[52]. Furthermore, during the anticipation phase of the placebo analgesic response, activation of the dorsolateral prefrontal cortex (DLPFC), OrbF, rostral medial and anterior anterior prefrontal cortex (rmAPC and aAPC), superior parietal cortex (SPC) and the PAG was found, which indicates that a cognitive-evaluative network is activated just before the placebo response[52–53]. The increased activity of the PAG indicates that the release of endogenous opioids might be activated in the anticipatory phase of the placebo response[54].

Reduced efficacy of hidden treatments

The best evidence to indicate that expectation is involved in the therapeutic outcome is the decreased effectiveness of covert therapies[55]. It is possible to eliminate the placebo (psychosocial) component and analyse the pharmacodynamic effects of a treatment, free of any psychological contamination. To eliminate the context in which a treatment is given, the patient is not made aware that a medical therapy is being carried out. To make this possible, drugs are administered through hidden infusions by machines[33,35,55–58]. A hidden drug infusion can be performed through a computer-controlled infusion pump that is pre-programmed to deliver the drug at the desired time. It is crucial that the patient does not know that any drug is being injected, so that he or she does not expect anything. The computer-controlled infusion pump can deliver a painkiller automatically, without a doctor or nurse in the room, and without the patient being aware that an analgesic treatment has been started.

In postoperative pain following oral surgery, a hidden injection of 6–8 mg of morphine was found to correspond to an open injection of saline solution in full view of the patient (placebo)[33,56]. In other words, telling a patient that a painkiller is being injected (actually a saline solution) is as potent as 6–8 mg of morphine. An analgesic effect stronger than the placebo was only observed when the hidden morphine dose was increased to 12 mg. This indicates that an open injection of morphine in full view of the patient, which is the usual medical practice, is more effective than a hidden injection, because in the latter the placebo component is absent.

A careful analysis of the differences between open and hidden injections in the postoperative setting has recently been performed for four widely used painkillers (buprenorphine, tramadol, ketorolac and metamizol)[57]. The open injection was carried out by a doctor at the bedside who told the patient that the injection was a powerful analgesic and that the pain would subside in a few minutes. By contrast, the hidden injection of the same analgesic dose was performed by an automatic infusion machine, which started the painkilling infusion without a doctor or nurse in the room, so that patients were completely unaware that an analgesic therapy had started. In one analysis, the analgesic dose required to reduce the pain by 50% (AD_{50}) was much higher for hidden infusions than for open ones, which indicates that a hidden administration is less effective than an open one. In another analysis, the intensity of postoperative pain was found to be much higher in patients who had received a hidden injection of analgesic than in those that had received an open one[57]. In the same study, it was shown that the difference between open and hidden administrations could be eliminated by blocking the opioid receptors with naloxone, which indicates that an open injection activates the endogenous opioid systems, presumably through the expectation pathways. Therefore, the opioid mechanisms described above are also likely to be activated during the routine therapist–patient interaction.

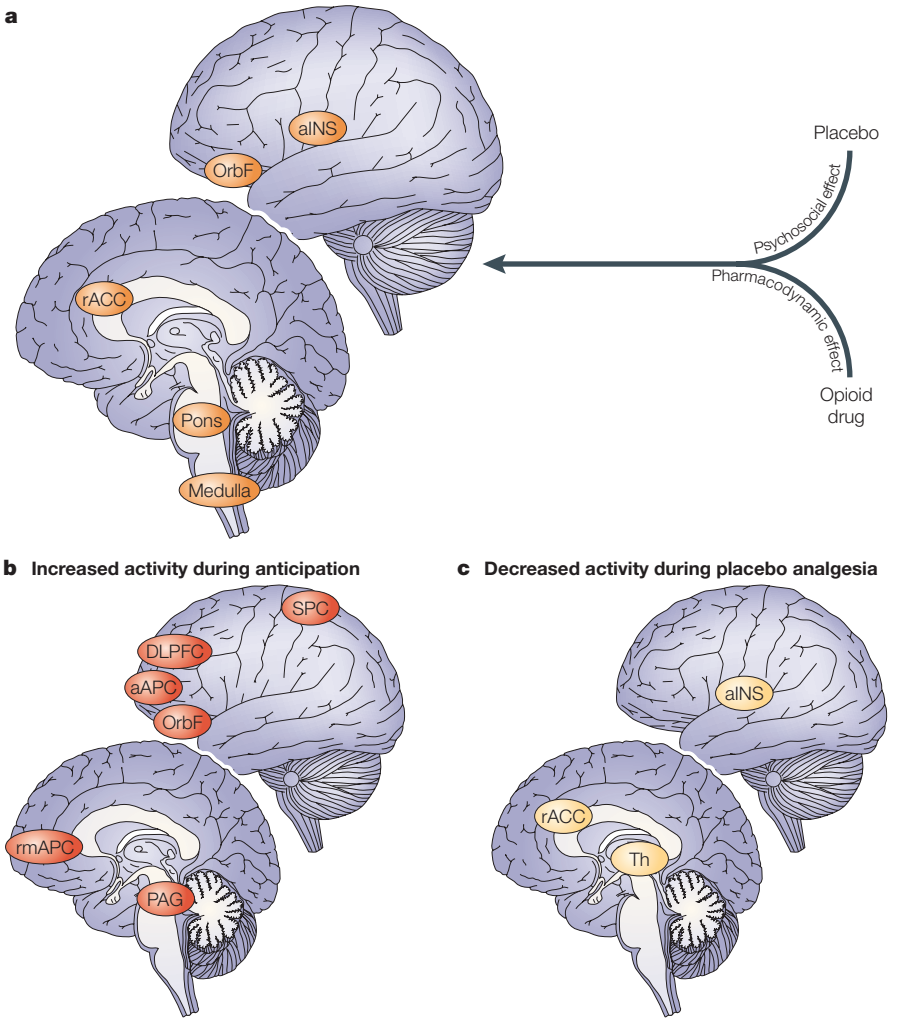

Figure 3 | **Summary of brain imaging studies showing the different brain regions that are involved in placebo analgesia. a** | Brain regions activated by both the administration of a placebo and the administration of an opioid drug, which indicates that mental events (psychosocial effect) and painkillers (pharmacodynamic effect) might have similar effects on the brain. **b** | Detailed representation of the brain regions that are activated by the administration of a placebo. During the anticipatory phase, the activated brain regions are likely to represent the activation of a cognitive-evaluative network. **c** | During placebo analgesia, there is a decrease in the activity of different brain areas that are involved in pain processing, which indicates an effect of the placebo on pain transmission. aAPC, anterior anterior prefrontal cortex; aINS, anterior insula; DLPFC, dorsolateral prefrontal cortex; OrbF, orbitofrontal cortex; PAG, periacqueductal grey; rACC, rostral anterior cingulate cortex; rmAPC, rostral medial anterior prefrontal cortex; SPC, superior parietal cortex; Th, thalamus. Data in panel **a** taken from REFS 43 and 44. Data in panel **b** taken from REFS 52 and 54. Anatomical image adapted, with permission, from REF. 99 © (1996) Appleton & Lange.

Beyond pain

The placebo response is not limited to the field of pain — it is also present in many other conditions[59]. The integration of our understanding of the placebo mechanisms in pain and analgesia and in other illnesses is fundamental to identifying similarities and differences that might help us to better appreciate the complexity of the placebo effect. We would like to focus our attention on three aspects of the placebo response in conditions other than pain that are relevant to placebo analgesia: conditioning, reward and hidden treatments.

Immunosuppressive placebo responses can be induced by repeated administration of an immunosuppressive drug[60–62]. For example, repeated associations between cyclosporin A (unconditioned stimulus) and a flavoured drink (conditioned stimulus) induced conditioned immunosuppression in humans, in which the flavoured drink alone produced suppression of immune functions, as assessed by interleukin-2 (IL-2) and interferon-γ (IFNγ) mRNA expression, *in vitro* release of IL-2 and IFNγ, and lymphocyte proliferation[61]. This study supports a conditioning mechanism in immunosuppressive placebo responses, although, as discussed above, further research is needed to allow us to better understand the roles of conditioning and expectation.

In recent years, Parkinson's disease has been used as a model to enable us to understand the neurobiological mechanisms of the placebo response, which might help us to better understand placebo analgesia. Placebo-induced expectation of motor improvement in patients with Parkinson's disease has been shown to activate endogenous dopamine in the striatum[63] and change the firing pattern of the neurons of the subthalamic nucleus[64]. It has been proposed that the placebo-induced release of dopamine represents a mechanism of reward. According to this hypothesis, dopamine release in response to the expectation of reward — in this case the expectation of clinical benefit — could represent a common biochemical substrate in many conditions, including pain. It is worth noting that there is an important interaction

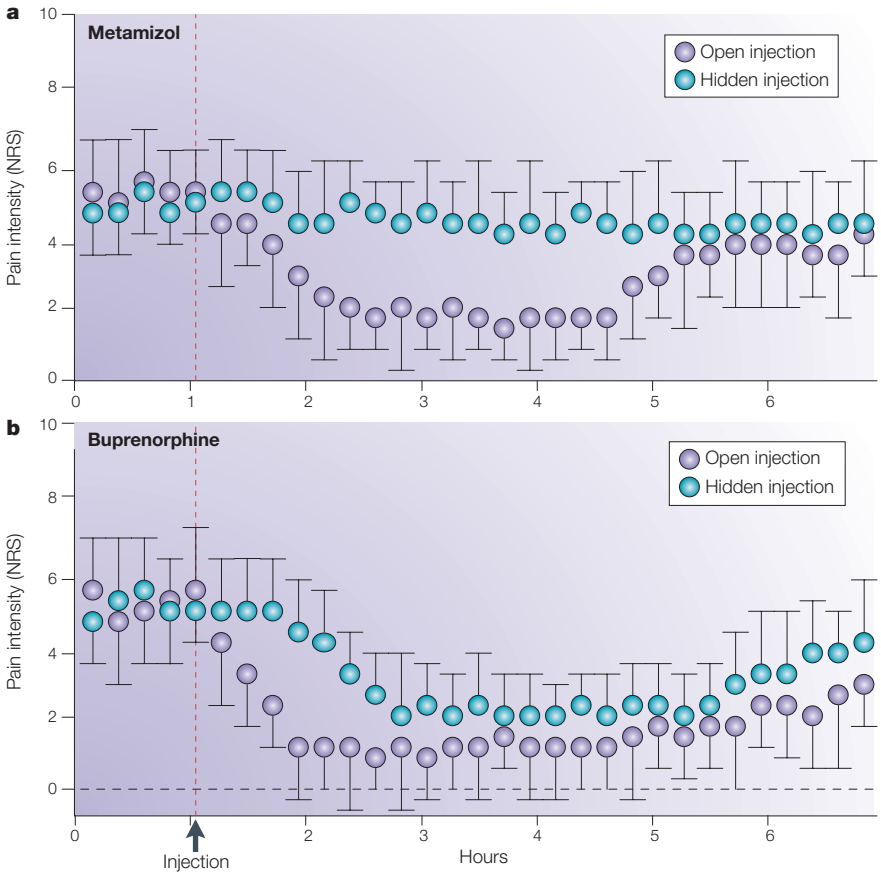

Figure 4 | **Examples of two clinical trials that used the open–hidden paradigm, revealing an ineffective and an effective treatment.** In a clinical trial of this type, the larger the difference between the open and hidden administration, the larger the placebo component and, therefore, the smaller the active effect of the treatment being investigated. Conversely, the smaller the difference, the greater the specific effects of the treatment. **a** | In this trial, a 300-mg dose of metamizol was tested in 10 patients to investigate whether it is effective in relieving post-thymectomy pain. One group of patients received an open injection of metamizol combined with the information that the pain would soon subside. The patients in the other group knew that metamizol was going to be administered, but they did not know when. To do this, a computer-controlled infusion pump was pre-programmed to deliver the drug at the desired time, out of view of the patient. The figure shows that a hidden injection was totally ineffective in reducing pain, which indicates that the positive outcome of the open administration was only a placebo effect. **b** | In this trial, a 0.2-mg dose of buprenorphine was tested in 12 patients to investigate whether it is effective in relieving post-thoracoscopy pain. The figure shows that the difference between the open and hidden conditions was small, which indicates that buprenorphine is an effective analgesic. However, note the slower decrease of pain in the hidden patient group compared with the open one, which indicates that most of the initial benefit in the open group was due to a placebo effect. Using this approach, the real pharmacodynamic effect of the drug and the placebo component can be assessed without the administration of a placebo. NRS, numerical rating scale.

between dopamine and opioid systems, and that endogenous opioids are also involved in reward mechanisms[65–67].

Finally, the reduced effect of hidden treatments occurs not only for pain, but also for other conditions, such as Parkinson's disease and anxiety[55]. Recently, the effect of methylphenidate on glucose metabolism in the brain was analysed in two different conditions: when cocaine abusers expected to receive the drug and when they did not. The effect in the former was ~50% greater than in the latter, which indicates that expectation enhanced the pharmacological effect of the drug[68].

Do we need to change clinical trials?

An important implication of placebo research in clinical trials is illustrated in FIG. 1. When we give a painkiller, we cannot be certain that it acts on the pain pathways, as it might also, or only, act on the expectation pathways (the uncertainty principle). Indeed, almost all pharmacological substances might act on the neurotransmission of the expectation pathways — the cholecystokinin antagonist proglumide represents the best example[25] (FIG. 1). Therefore, in light of the fact that some substances might interfere with placebo-activated endogenous opioids, we must consider the possibility that a new drug might have no analgesic properties, but might enhance placebo-activated endogenous opioids[69].

We believe that this new way of considering the action of a drug might have an important impact on the design of clinical trials. For example, we can only be certain of the real pharmacodynamic effect of a drug if it is administered covertly, free of any type of psychological contamination. The similarity between the pharmacodynamic action of an opioid drug and the psychological action of a placebo (FIG. 3a) poses several problems for the interpretation of a clinical trial. So the question is: can we separate the pharmacodynamic effects of a drug on pain pathways from its effects on expectation pathways? A partial solution to this question can be achieved by using an open–hidden paradigm, whereby drugs, or medical treatments in general, can be given covertly. To overcome the ethical constraints of the hidden administration of a treatment, the experimental design might consist of an unknown temporal sequence of drug administration, in which subjects know that a painkiller will be administered but they do not know when. If the painkiller is really effective, pain reduction should be correlated with the timing of drug administration[55]. FIGURE 4 shows a totally ineffective drug and an effective drug, tested using this approach. The open–hidden paradigm might serve to decrease the debate on the use of placebos in clinical trials, as no placebo is administered in this procedure[70,71]. This would provide a good alternative to placebo-controlled trials, and would keep within the World Medical Association's (WMA) 'Declaration of Helsinki' ethical guidelines[72].

Another important point is represented by the role of expectations and subsequent neurobiological changes in clinical trial design. In a recent double-blind study that addressed the perceived assignment of treatment in human fetal mesencephalic transplantation for Parkinson's disease, it was found that the perceived assignment of treatment (either active or placebo) had a more powerful impact on both quality of life and motor function than did the actual treatment[73]. In other words, which group participants believed they belonged to was more important than the group to which they were actually assigned (active treatment or placebo). This study raises a crucial question about how a clinical trial should be conceived: should we consider the perceived assignment to an arm of the trial rather than the actual assignment[74]? These results were

Box 2 | **The potential negative impact of placebo research on society**

Although placebo research is aimed at understanding mind–body interactions, improving clinical practice and the patient's quality of life, and developing new clinical trial designs, its impact on society is not necessarily always positive. Placebo research underscores the instability (or meta-stability) of the human mind and its somewhat dangerous tendency to be manipulated, particularly by verbal suggestion. For example, the assertion that placebos, fake therapies, fresh water and sugar pills could positively affect the brain biochemistry in the appropriate psychosocial context might lead to a dangerous justification for deception, lying and quackery[89,90]. Interestingly, although most research is devoted to the placebo effect, it is worth mentioning that pain perception can be modulated in the opposite direction by negative verbal suggestions, which give rise to a nocebo effect[16,91–94]. Likewise, the subjective emotional responses to deep brain stimulation of the limbic system can be modulated in different directions, as they depend on the participant's psychological traits and concerns, and on the ongoing psychosocial context[95,96]. If future research leads to a full understanding of the mechanisms of suggestibility of the human mind, an ethical debate will then be required, aimed at avoiding the misuse of placebos and nocebos. There are, therefore, potentially negative outcomes of placebo research that need to be discussed and considered from an ethical perspective[97,98].

recently repeated in a study on pain. It was found that the perceived assignment in an acupuncture trial had a greater impact on the analgesic outcome than did the actual treatment[75]. Both these studies highlight how clinical trials might be viewed from a theoretical perspective and conducted from a practical viewpoint, whereby the power of patients' expectations underscores the importance of perceived assignment rather than actual assignment[76].

Future perspectives

The future challenges for placebo research encompass neuroscience, clinical practice and social psychology. By using new experimental designs and techniques, such as *in vivo* receptor binding[48,49], recording from neurons in awake humans[64], and a combination of imaging and electrophysiological techniques, it will be possible to better clarify the relationship between a complex mental activity (such as expectancy) and different neuronal systems. This could allow us to create a new strategic approach to the mind–body problem, not only for pain but also for other conditions (such as psychiatric illnesses)[77–79]. At the same time, we need to develop new clinical trial designs that will allow us to better understand the mechanisms of action of different drugs, and new therapeutic protocols that exploit the drug–placebo association, with the aim of reducing the intake of toxic drugs, and so reducing side effects[15]. Finally, we need to further explore the impact of placebo research on society in order to identify both the positive and negative aspects of the suggestibility of the human mind (BOX 2). We believe that these issues are worthy of intense scientific scrutiny, as they will lead to fundamental insights into human biology.

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Competing interests statement

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