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Understanding the mechanisms of placebo and nocebo effects

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Summary

Although placebos have long been considered a nuisance in clinical research, over recent years they have become an active and productive field of research. Indeed, the placebo effect represents an elegant model to understand how the brain works. It is worth knowing that there is not a single but many placebo effects, with different mechanisms across different systems, medical conditions and therapeutic interventions. For example, brain mechanisms of expectation, anxiety and reward are all involved, as well as a variety of learning phenomena. There is also some experimental evidence of different genetic variants in placebo responsiveness. Pain and Parkinson's disease represent the most productive models to better understand the neurobiology of the placebo effect. In these medical conditions the neural networks involved have indeed been identified: that is, opioid, cannabinoid, cholecystokinin, cyclooxygenase, and dopamine modulatory networks in pain; and part of the basal ganglia circuitry in Parkinson's disease. Overall, there is today compelling evidence that placebos and drugs share common biochemical pathways and activate the same receptor pathways, which suggests possible interference between social stimuli and therapeutic rituals on one hand and pharmacological agents on the other. The same holds true for the nocebo effect, the opposite phenomenon of placebo. The assessment of patients' expectations should become the rule in clinical trials in order to allow us a better interpretation of therapeutic outcomes when comparing placebo and active treatment groups. Administering drugs covertly is another way to identify the placebo psychobiological component without the administration of any placebo, and this provides important information on the role of patient's expectations in the therapeutic outcome. A further in-depth analysis of placebo and nocebo phenomena will certainly provide important information in the near future for a better understanding of human biology, medicine and society.

Keywords: *placebo*, *nocebo*, *pain*, *Parkinson's disease*, *depression*, *immune system*, *endocrine system*, *clinical trials*

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Definition

The placebo effect is the reduction of a symptom or a change in a physiological parameter when an assumingly inert treatment (the placebo) is administered along with a complex set of psychosocial stimuli that tell the patient that a benefit may occur. The placebo effect, so far considered a nuisance in clinical research when a new treatment is tested, has now become a target of scientific investigation into a better understanding of the physiological and neurobiological mechanisms that associate a complex mental activity to different functions of the body. Usually, the terms placebo effect and response are used interchangeably by both clinical researchers, who run clinical trials, and by neuroscientists, who want to understand the underlying mechanisms. It is important to realise that there is not a single placebo effect but many, which occur through different mechanisms in different conditions, systems and diseases [1–4].

A placebo effect is not easy to recognise and its study is full of pitfalls. Indeed, the effect that follows the administration of a placebo can be due to many factors, such as spontaneous remission, regression to the mean, symptom detection ambiguity and other biases. All these phenomena need to be ruled out by means of control groups. The possibility of spontaneous remission (the natural course of a disease or a symptom) can be avoided by means of a no-treatment group. Regression to the mean (the statistical phenomenon stating that if a symptom is near its greatest intensity during the first assessment, it will be of lower intensity at the second assessment) can be controlled by using an experimental model in healthy volunteers. Symptom detection ambiguity and patient's or experimenter's biases can be ruled out by using objective physiological measurements. It is also important to exclude possible effects of co-interventions; for example, an unidentified concomitant diet may be responsible for the clinical improvement during a placebo treatment.

The Hawthorne effect should also be considered in any clinical trial since it potentially affects the therapeutic outcome and its interpretation. It describes those changes in patients' baseline values occurring even before they have received a treatment, due to the mere act of being recruited

into a clinical trial [5]. When all these phenomena are ruled out and the correct methodological approach is used, the real placebo effect can be detected, which is attributable only to the psychobiological changes in the patient's brain and is mediated by neurobiological mechanisms worthy of scientific inquiry [6–8].

Basic mechanisms

In the investigation of the placebo effects the psychosocial context should be considered. This context surrounds the patient and any medical treatments (e.g., the therapist's words, the hospital environment, the sight of complex machines, the colour, shape and odour of a pill, and other sensory inputs). Conscious anticipation and unconscious conditioning represent two of the main mechanisms through which the context may produce a therapeutic effect. In the first case, expectation and anticipation of clinical benefit have sometimes been shown to induce a real clinical improvement. In the second case, contextual cues (e.g., taste and smell of a drink, colour and shape of a pill) may act as a conditioned stimulus that, after repeated associations with an unconditioned stimulus (the active pharmacological agent contained in the drink or in the pill), are capable alone of inducing a clinical improvement. The neural mechanisms underlying the placebo effects are only partially understood and most of our knowledge comes from pain, Parkinson's disease, hypoxia, and immune and endocrine responses, whereas we have only a few pieces of information for other conditions such as neuropsychiatric disorders. Today we know that in each of these conditions different mechanisms are at play, so that we cannot talk of a single placebo effect but many [7].

Pain

Most of our knowledge about the neurobiological mechanisms that mediate placebo responses comes from the field of pain and analgesia. Specifically, there is now compelling experimental evidence that the endogenous opioid systems play an important role in some circumstances (fig. 1A). A combination of both imaging and pharmacological studies has produced several lines of evidence indicating that placebo analgesia is mediated by a descending pain-modulating circuit, which uses endogenous opioids as neuromodulators. In fact, by using positron emission tomography (PET), it was found that the very same regions of the brain in the cerebral cortex and in the brainstem are affected by both a placebo and the opioid agonist remifentanil, suggesting a related mechanism in placebo-induced and opioid-induced analgesia [9]. In particular, the administration of a placebo induces the activation of three important brain regions: the dorsolateral prefrontal cortex (DLPFC), the rostral anterior cingulate cortex (rACC), and the periaqueductal grey (PAG) (fig. 1F). Moreover, there is a significant covariation in activity between the rACC and the rostral ventromedial medulla (RVM), and a sub-significant covariation between the rACC and the PAG, thus suggesting that the descending rACC/PAG/RVM pain-modulating circuit is involved in placebo analgesia. In another functional magnetic resonance imaging (fMRI) experiment, it was shown that placebo administration also induced the inhibition of those regions involved in pain processing, such as the mid and posterior cingulate cortex (MCC, PCC), insula and thalamus [10]. Therefore, the PET and fMRI studies tell us that placebo analgesia and opioid analgesia share a common neural mechanism and that pain transmission is inhibited by placebos. The regions activated and deactivated during placebo analgesia are shown in figure 2. However, a recent meta-analysis of brain imaging studies has shown that placebo analgesia activates a complex network of areas that influence pain related regions, while it only partially affect areas involved in pain processing [11].

In support of the involvement of endogenous opioids in the descending circuit there are several pharmacological studies that show that placebo analgesia is antagonised by the opioid antagonist naloxone [12–14]. For example, in 2005 a PET study used *in vivo* receptor binding to show that placebos induce the activation of mu-opioid receptors in different brain areas, such as the dorsolateral prefrontal cortex, nucleus accumbens, insula and rACC (fig. 1A) [13].

Besides their action on pain transmission, the placebo-activated endogenous opioids have been found to induce respiratory depression, which in turn could be prevented by the opioid antagonist naloxone [7]. Likewise, a reduction of beta-adrenergic system activity, which is blocked by naloxone, has been found during placebo analgesia [7]. Even though it is not known whether the placebo-activated opioid systems act only through a descending modulating network, these reported findings indicate that they have a broad range of action, influencing pain, respiration and the autonomic nervous system.

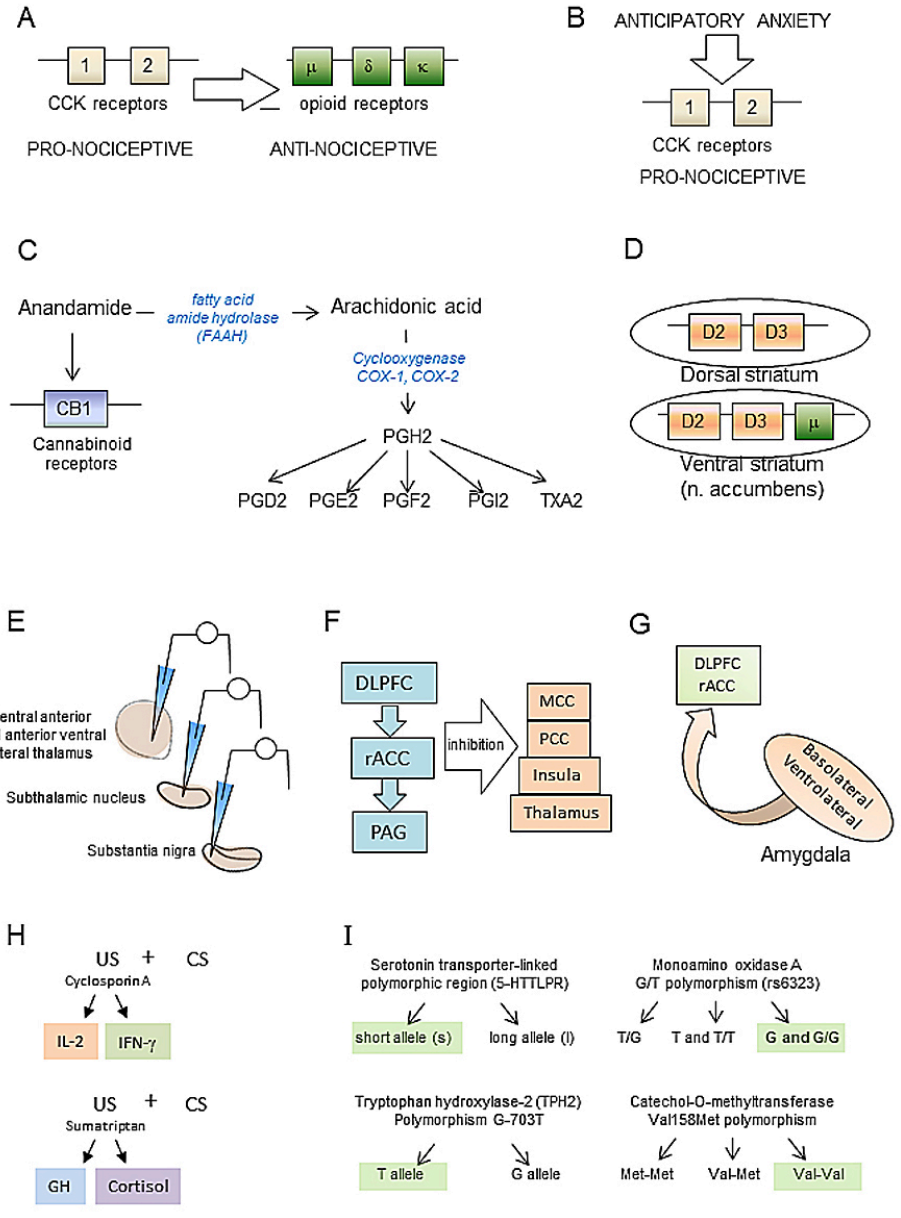
The placebo-activated endogenous opioids have also been shown to interact with endogenous substances that are involved in pain transmission. On the basis of the anti-opioid action of the octapeptide cholecystokinin (CCK), CCK antagonists have been shown to enhance placebo analgesia, thus suggesting that the placebo-activated opioid systems are counteracted by CCK during a placebo procedure: when CCK activity outweighs opioid activity, placebo analgesia is reduced, and the opposite situation leads to increased placebo analgesic responses (fig. 1A) [1].

It is important to point out that some types of placebo analgesia appear to be insensitive to naloxone, thus suggesting that neuromodulators other than opioids can be involved in some circumstances. For example, if a placebo is given after repeated administrations (pre-conditioning) of the non-opioid painkiller ketorolac, the placebo analgesic response is not blocked by naloxone but by rimonabant, a CB1 cannabinoid receptor antagonist, which suggests the involvement of endocannabinoids in placebo analgesia (fig.1 C) [15]. Interestingly, there is now compelling experimental evidence that the whole lipidic pathway (involving arachidonic acid, anandamide, prostaglandins and thromboxane) is important in the modulation of the placebo response in pain. For example, by using high-altitude headache as a model, it has been found that a placebo can modulate cyclooxygenase activity and the synthesis of prostaglandins and thromboxane leading to a reduction of headache pain [16–18].

Dopamine also plays a role in placebo analgesia responsiveness. In particular, an increase in dopamine binding to D2/D3 receptors and in opioid binding to μ receptors occurs in the nucleus accumbens, which is part of the ventral striatum [19, 20]. Since the nucleus accumbens is in-

volved in motivation and reward anticipation processing, dopamine release in this brain region is associated with patient expectation of improvement in symptoms, which could in turn be considered a form of reward.

Figure 1: Principal neurobiological mechanisms of the placebo response that have been identified across a variety of conditions. (A) The anti-nociceptive opioid system is activated in placebo analgesia in some circumstances, and the mu opioid receptors play a crucial role. The pro-nociceptive cholecystokinin (CCK) system antagonises the opioid system, thus blocking placebo analgesia. (B) The pro-nociceptive CCK system is activated by anticipatory anxiety in nocebo hyperalgesia, with some evidence that the CCK-2 receptors are more important. (C) Different lipidic mediators have been identified in placebo analgesia and nocebo hyperalgesia. Whereas placebos activate the CB1 cannabinoid receptors and inhibit prostaglandins (PG) synthesis in some circumstances, nocebos increase PG synthesis. In addition, different genetic variants of FAAH affect the magnitude of placebo analgesia. (D) The activation of D2-D3 dopamine receptors in the striatum is related to the placebo response in Parkinson's disease. Likewise, in placebo analgesia there is an activation of D2-D3 receptors and mu opioid receptors in the nucleus accumbens, whereas in nocebo hyperalgesia there is a deactivation of D2-D3 and μ receptors. (E) Placebo administration in Parkinson patients produces a decrease of firing rate and bursting activity of the subthalamic nucleus neurons. It also produces a decrease of firing rate in the substantia nigra pars reticulata and an increase in the ventral anterior and anterior ventral lateral thalamus. (F) The neuroanatomy of placebo analgesia has been described trough brain imaging. Different regions are modulated by both placebos and nocebos, but the most studied and understood regions are the dorsolateral prefrontal cortex (DLPFC), the rostral anterior cingulate cortex (rACC), and the periaqueductal gray (PAG), which represent a descending pain modulating network. This, in turn, inhibits those regions that are involved in pain processing, such as the mid and posterior cingulate cortex (MCC, PCC), insula and thalamus. (G) In social anxiety disorder, placebos affect the basolateral and ventrolateral amygdala as well as its projections to DLPFC and rACC. (H) In the immune and endocrine system, the mechanism of the placebo response is classical conditioning, whereby an unconditioned stimulus (US) is paired with a conditioned stimulus (CS). For example, after pairing a CS with either ciclosporin or sumatriptan, the CS alone can mimic the responses to cyclosporine and sumatriptan. (I) Different polymorphisms have been found to be associated to low (coloured squares) or high placebo responsiveness. From Benedetti F. Placebo effects: from the neurobiological paradigm to translational implications. Neuron. 2014;84:623–37 (permission not required).



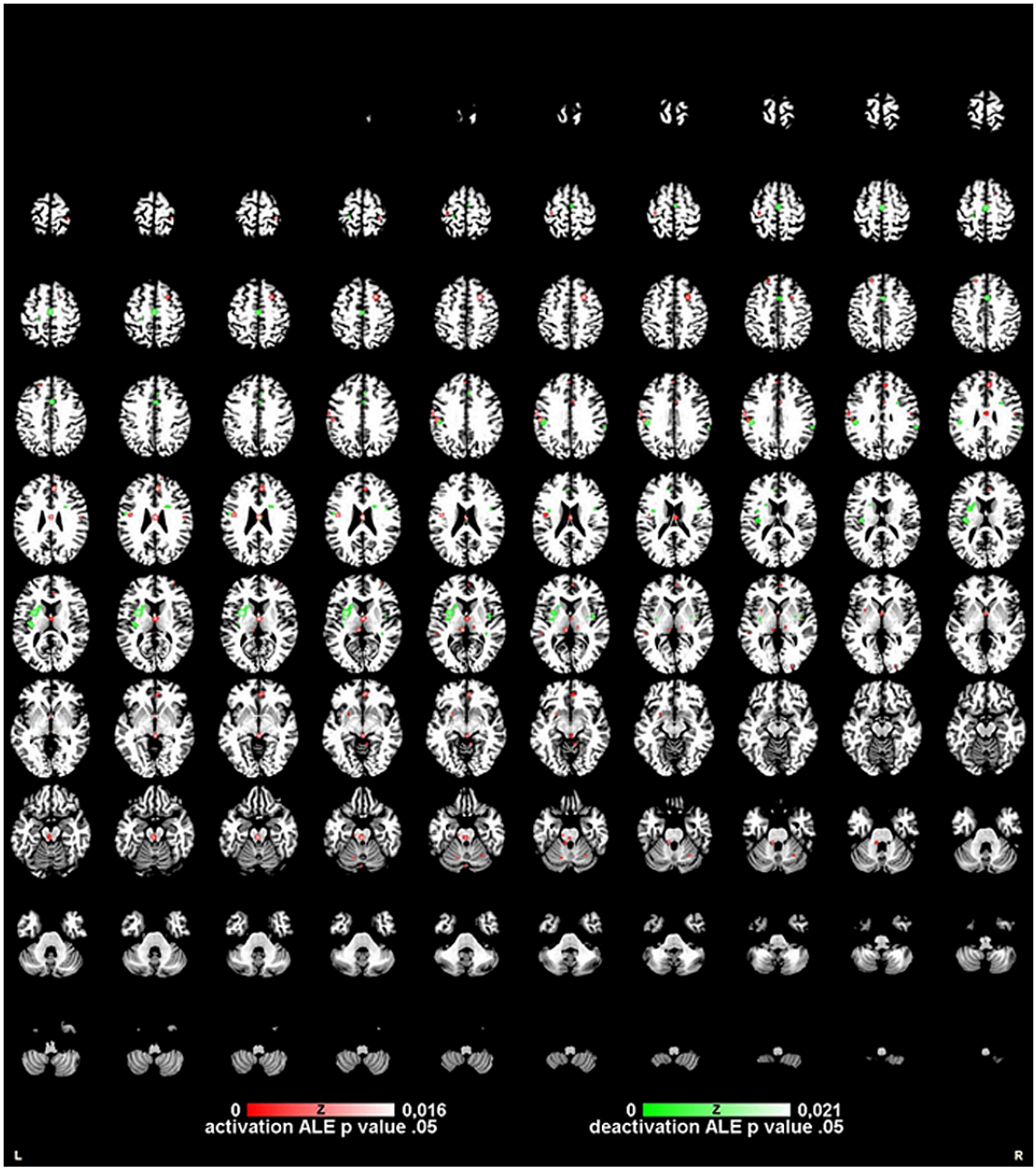
Parkinson's disease

As with pain, also in motor disorders, such as Parkinson's disease, a placebo procedure can be followed by the release of endogenous substances. In particular, the high rate of the placebo response in Parkinson's disease clinical trials provided the impetus for investigating the underlying mechanisms.

In the case of Parkinson patients, the placebo procedure consists of administering an inert substance (placebo) along with the information that it is an anti-parkinsonian drug that produces an improvement in motor performance. In 2001, the first brain imaging study of the placebo effect by means of PET was conducted [21]. In this study, patients were aware that they would be receiving an injection of either active drug (apomorphine, a dopamine receptor agonist) or placebo (an inert substance that the patient believed to be apomorphine), according to classic clinical trials methodology. The authors assessed the competition for D_2/D_3 receptors between endogenous dopamine and [^{11}C]-raclopride, a method that allows identification of endogenous dopamine release. After placebo administration, a release of dopamine was found in the striatum (both dorsal and ventral), corresponding to a change of 200% or more in extracellular dopamine concentration (fig. 1 D). However, whereas dopamine release in the dorsal striatum was greater in those patients who reported clinical improvement, its release in the ventral striatum was associated with patient expectation of improvement in symptoms [21, 22].

The placebo response in Parkinson's disease is associated with changes in activity of neurons in the subthalamic nucleus, substantia nigra pars reticulata and motor thalamus

Figure 2: Activation likelihood estimation (ALE) meta-analysis of brain imaging data showing the regions activated (red) and deactivated (green) during placebo analgesia.



[23–25]. Indeed, the possibility to record from single neurons during the implantation of electrodes for deep brain stimulation makes Parkinson's disease an excellent model for investigating the placebo mechanisms occurring when patients expect a therapeutic benefit. In particular, placebo administration in Parkinson patients affects the activity of the neurons in the subthalamic nucleus, a brain region belonging to the basal ganglia circuitry and whose activity is increased in Parkinson's disease. Verbal suggestions of motor improvement during a placebo procedure are capable of reducing the firing rate and abolishing bursting activity of subthalamic nucleus neurons. These effects also produce a decrease of firing rate in the substantia nigra pars reticulata, followed by an increase in the ventral anterior and anterior ventral lateral thalamus, and resulting in clinical improvement (fig. 1E). Although patients' expectations are recognised as a major mediator of placebo responses, recent research suggests that learning is even more important in Parkinson's disease. Placebos given for the first time to naïve Parkinson's disease patients induce neither clinical nor neuronal improvement. However, this lack of placebo responsiveness may be turned into substantial placebo responses following previous exposure to repeated administrations of the anti-Parkinson agent apomorphine [26, 27].

Depression and social anxiety

Both electroencephalographic and metabolic changes have been observed in the brain of depressed patients who receive a placebo treatment. Electroencephalogram changes were found in the prefrontal cortex of patients with major depression [28, 29]. Changes in brain glucose metabolism were documented by using PET in subjects with unipolar depression who were treated for 6 weeks with either placebo or the selective serotonin reuptake inhibitor fluoxetine [30]. The authors showed that both placebo and fluoxetine treatment induced metabolic increases in the prefrontal, anterior cingulate, premotor, parietal and posterior cingulate cortices, and posterior insula, and metabolic decreases in the subgenual cingulate, thalamus and parahippocampus. The magnitude of regional changes with fluoxetine was generally greater than those induced by a placebo. However, fluoxetine responses were associated with additional changes in the striatum, parahippocampus and anterior insula. Therefore, since the brain changes associated with placebo response most closely match those of fluoxetine, a possible role for serotonin in placebo-induced antidepressant effects is suggested. Interestingly, ventral striatal (nucleus accumbens) and orbital frontal changes were found in both placebo and drug responders well before clinical benefit, namely at 1 week of treatment. These changes are thus associated with expectation and anticipation of the clinical benefit, rather than to clinical response.

In social anxiety disorder, PET imaging has been used to assess regional cerebral blood flow during an anxiogenic public speaking task, before and after 6–8 weeks of treatment with selective serotonin reuptake inhibitors (SSRIs) under double-blind conditions [31, 32]. The authors found that both SSRIs and placebo responders show a common attenuation of regional cerebral blood flow in the basolateral and ventrolateral amygdala, as well as in its projections to DLPFC and rACC (fig. 1G). This pattern correlates with behavioural measures of reduced anxiety, and indicates that in this specific clinical condition drugs and placebos act on common amygdala targets and amygdala-frontal connections.

Immune and endocrine responses

The mechanisms of the placebo effect in the immune and endocrine systems are related to conditioning [33–36]. If the active drug is replaced by a placebo after being administered repeatedly, the placebo is capable of evoking immune or hormonal responses comparable to those obtained by the previously administered drug. For example, immunosuppressive placebo responses can be induced in humans by repeated administration of ciclosporin (unconditioned stimulus) associated with a flavoured drink (conditioned stimulus), as assessed by interleukin-2 and interferon-γ mRNA expression, *in vitro* release of interleukin-2 and interferon-γ, and lymphocyte proliferation [37]. Furthermore, if a placebo is given after repeated administrations of sumatriptan, a serotonin agonist of the 5-$HT_{1B/1D}$ receptors that stimulates growth hormone and inhibits cortisol (glucocorticoids) secretion, a placebo growth hormone increase and a placebo cortisol decrease can be found (fig. 1H) [38]. These hormonal and immune responses represent the best examples of unconscious placebo effects, that is, placebo effects that take place in the absence of conscious cognitive processes.

Genes

Although genetic studies of placebos are still at the beginning, different polymorphisms have been found to be associated with low or high placebo responsiveness, and the analysis of genetic variants has been centred around different systems, such as the dopamine, opioid, serotonin and endocannabinoid systems [39–41]. For example, patients affected by social anxiety disorder were genotyped for the serotonin transporter-linked polymorphic region (5-HTTLPR) and the G-703T polymorphism in the tryptophan hydroxylase-2 (TPH2) gene promoter (fig. 1I) [42]. The fMRI analysis showed that robust placebo responses and reduced activity in the amygdala only occurred in those patients who were homozygous for the long allele of the 5-HTTLPR or the G variant of the TPH2 G-703T polymorphism. In another study, catabolic enzymes catechol-O-methyltransferase and monoamine oxidase A polymorphisms were examined in patients affected by major depressive disorder [43]. Small placebo responses were found in those patients with monoamine oxidase A polymorphisms coding for the highest activity form of the enzyme, and in those patients with the catechol-O-methyltransferase polymorphisms coding for a lower-activity form of the enzyme. Interestingly, catechol-O-methyltransferase val158met polymorphisms have also been associated with placebo responsiveness in the irritable bowel syndrome [44].

Nocebo effect

Whereas a positive context may elicit positive expectations and lead to positive outcomes, namely placebo effects, a negative context may elicit negative expectations and lead to negative outcomes, that is, nocebo effects [1, 2, 7, 45].

Typical nocebo effects are those deriving from the administration of an inert substance along with negative expectations of adverse events. If the inert substance is administered along with verbal suggestions of pain increase it may induce a hyperalgesic effect. Since the induction of nocebo responses is a stressful and anxiogenic procedure, much less is known about nocebo hyperalgesia than placebo analgesia, mainly because of ethical limitations. Nocebo hyperalgesia has been found to be blocked by proglumide, a non-specific CCK-1/2 receptor antagonist, even though it is not a specific painkiller. This suggests that CCK mediates the nocebo hyperalgesic response. This effect is not antagonised by naloxone, thus ruling out the involvement of endogenous opioids. In addition, since the nocebo procedure represents an anxiogenic stimulus and previous studies showed a role for cholecystokinin in anxiety, nocebo hyperalgesia may be due to a cholecystokinin-dependent increase of anxiety (fig. 1B) [46, 47]. The regions activated and deactivated during nocebo hyperalgesia are shown in figure 3.

Nocebo effects represent a source of confusion and misinterpretation in clinical trials, and adverse events described in informed consent forms can actually lead to negative outcomes. The information provided to clinical trial participants about the nature of the expected side effects may thus influence the types of side effects occurring in the placebo arm. For example, in clinical trials for anti-migraine drugs, it has been shown that the adverse events described specifically for each drug out of three different classes (non-steroid anti-inflammatory drugs, triptans and anticonvulsants) corresponded to the adverse events observed in each respective placebo arm [48]. Similar findings were observed in a meta-analysis on nocebo effect in depression: a total of 143 placebo-controlled trials SSRIs were analysed, showing that reported rate of adverse events was influenced by their assessment, so that a more systematic assessment led to higher rates in comparison to a less systematic assessment [49].

Implications for clinical trials and medical practice

According to the classical methodology of clinical trials, any drug must be compared with a placebo in order to assess its effectiveness. When those patients who take the drug show a larger clinical improvement than those who take the placebo, the drug is considered to be effective. However, in light of the recent advances in placebo research, some caution is necessary in the interpretation of classical clinical trials. In fact, by consideration of the complex cascade of biochemical events induced by placebo administration, any drug that is tested in a clinical trial may interfere with these placebo-/expectation-activated mechanisms involving endogenous opioids, endocannabinoids, dopamine and serotonin. Indeed, what is emerging from the recent physiological understanding of the placebo response is related to the common biochemical pathways that are modulated by social stimuli and therapeutic rituals on the one hand and by drugs on the other. For example, expectations of analgesia or expectations of motor improvement modulate the very same receptor pathways as those modulated by real pharmacological agents. Assessing patients' expectations should become the rule in any clinical trial. This would allow us to better interpret therapeutic outcomes when comparing placebo and active treatment groups [50].

Another approach to rule out the possible pharmacological interference is to eliminate the placebo psychobiological component and to maintain the specific effects of the treatment, providing important information on the role of patient's expectations in the therapeutic outcome. This can be achieved by administering drugs covertly; to make this possible, drugs are administered through hidden infusions by machines. A hidden drug infusion can be performed through a computer-controlled infusion pump that is preprogrammed 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 drug automatically, without a doctor or nurse in the room and without the patient being aware that a treatment has been started [51, 52].

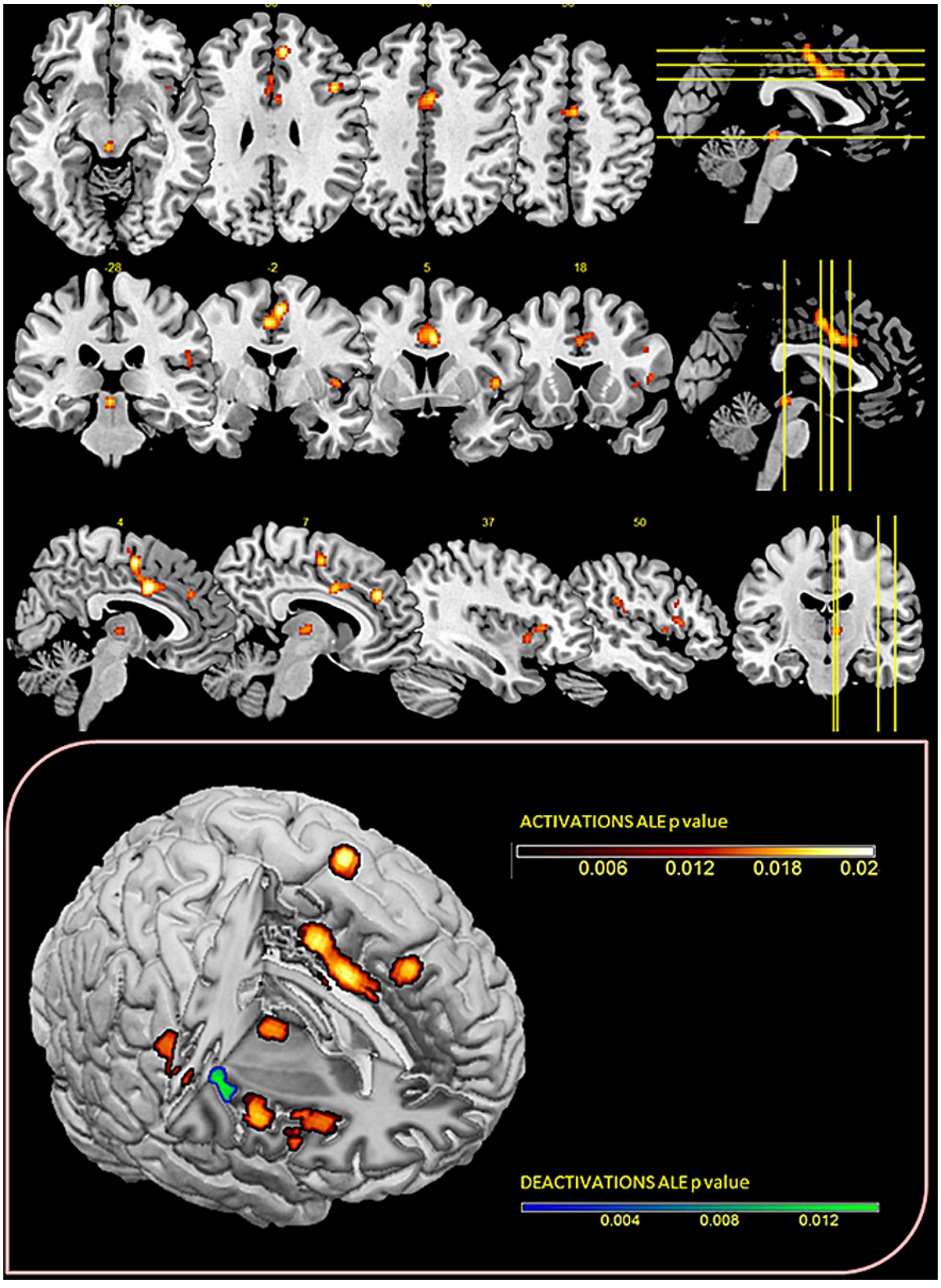
The analysis of different treatments, either pharmacological or not, in different conditions has shown that an open (expected) therapy, carried out in full view of the patient, is more effective than a hidden one (unexpected). Whereas the hidden injection represents the real pharmacodynamic effect of the drug, free of any psychological contamination, the open injection represents the sum of the pharmacodynamic effect plus the psychological component of the treatment. The latter can be considered to represent the placebo component of the therapy, even though it cannot be called placebo effect, as no placebo has been given. It is important to realise that, by using hidden administration of drugs, it is possible to study the placebo effect without the administration of any placebo. For example, in a postoperative setting it has been shown that the analgesic dose used to reduce pain by 50% was higher with hidden than with open administrations of four different painkillers (buprenorphine, tramadol, ketorolac, metamizole) and the reported pain was higher after a hidden analgesic infusion compared with an open one [53].

Imaging studies have shown different brain activity for open and hidden administrations of analgesic drugs. In fact, it has been observed that the open infusion of the analgesic remifentanil (told, remifentanil, got remifentanil) induced stronger analgesic effects than its hidden infusion (told saline, got remifentanil), and these effects were associated with activity in the dorsolateral prefrontal cortex and pregenual anterior cingulate cortex. Interestingly, the negative expectation of drug interruption (told interruption, got remifentanil) completely blocked the analgesic effects of remifentanil and was associated with activity in the hippocampus [54].

The implications of placebo research are not related to clinical trials only, but to medical practice as well. In fact, whereas we need to reduce placebo responses in the setting of clinical trials, we want to increase them in medical practice [55]. Conversely, we need to reduce nocebo responses both in clinical trials and in medical practice [56]. It could be argued that today's ethical restrictions prevent the widespread use of placebos that was commonplace in ancient times. Still, its practice is common, and physicians surveyed in many countries reported using placebos to calm patients, avert requests for unnecessary medications or as a

supplementary treatment, thereby emphasising that placebo effects can be easily elicited in routine clinical practice [8]. But from what we know today, deception is not necessarily involved in the use of placebo, as shown by many recent studies, in which non-deceptive (open label) placebo administration might induce substantial clinical improvements [57–59]. We have learned that anything inducing expectation of benefit (e.g., analgesia) can act as a placebo, positively impacting on the patient's (pain) brain circuitry. In fact, every real treatment administered in routine health care has two distinct components: the active constituent and the placebo (psychosocial) factor. Every effort should be made to enhance the latter to maximise the benefit of the therapeutic act. This behaviour is perfectly acceptable and

Figure 3: Activation likelihood estimation (ALE) meta-analysis of brain imaging data showing the regions activated (yellow/orange) and deactivated (green) during nocebo hyperalgesia. In the lower panel a 3-D reconstruction of the brain is also shown.



does not challenge ethical imperatives. Central in the psychosocial context is the patient-provider relationship, with empathy, perceived skill, correct attitudes and words, ceremony and encouragement all contributing to a positive outcome.

The reverse actions represent nocebos, and they may lessen the effectiveness of therapeutic agents. Although the harmful effect of natural situations such as the impact of negative diagnoses or the patient's disbelief in a therapy are sometimes difficult to circumvent, care should be given to at least eliminate negligence and minimise distrust. Even a seemingly innocuous act such as communicating to the patient that a therapy is going to be interrupted can have a negative impact, as showed by the faster and larger intensity relapse of pain after open versus hidden interruption of morphine analgesic therapy.

Prefrontal control and placebo response

A common finding across different neuroimaging studies on placebo analgesia is the predominant activity of prefrontal regions such as the dorsolateral prefrontal cortex, suggesting their crucial role in placebo responses. Data coming from studies on patients, neuroimaging and neuromodulation support this idea. Since in patients affected by Alzheimer's disease the frontal lobes appear to be severely compromised, this neurodegenerative disorder has been used as a model to test placebo responsiveness. Indeed, in these patients, it has been found that placebo analgesia is positively correlated with cognitive status and functional connectivity between different brain areas and, conversely, the more impaired the prefrontal activity the smaller the observed placebo response [60]. More recently, it has been shown that stronger placebo analgesia is associated with stronger connectivity between PAG and both rACC and DLPC [61]. Finally, in healthy volunteers, repetitive transcranial magnetic stimulation has been used to inactivate the left and right prefrontal cortex during placebo analgesia. This prefrontal inactivation resulted in a complete blockade of the placebo response [62]. Collectively, these studies confirm that the placebo response is directly correlated to prefrontal control: when this activity is abolished, no placebo response occurs.

Conclusions

Placebo and nocebo effects are today an active and productive field of research and, because of the involvement of many mechanisms ranging from expectation to conditioning and from neuromodulation to genetics, they represent a melting pot of concepts and ideas for neuroscience. Besides their role for better understanding the human brain and more in general human biology, placebo and nocebo effects have several implications both in medical practice and in the setting of clinical trials.

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