Mechanisms of Placebo and Placebo-Related Effects Across Diseases and Treatments

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Abstract

The placebo effect has evolved from being thought of as a nuisance in clinical and pharmacological research to a biological phenomenon worthy of scientific investigation in its own right. It is now clear that the term placebo effect is too restrictive and, in fact, many placebo-related effects have recently been investigated. A placebo effect differs from a placebo-like effect in that the former follows the administration of a placebo, whereas in the latter no placebo is administered. However, in both cases, the psychosocial context around the treatment plays a key role. In recent years, placebo and placebo-related effects have been analyzed with sophisticated biological tools that have uncovered specific mechanisms at both the biochemical and cellular level. This recent research has revealed that these psychosocial-induced biochemical changes in a patient's brain and body in turn may affect the course of a disease and the response to a therapy.

INTRODUCTION

Natural history: the natural course of a symptom; if a symptom subsides naturally, this represents the spontaneous remission of the symptom

By looking through PubMed and inserting the search word "placebo," more than 115,000 papers can be found. Most of the papers are clinical trials in which an active treatment is compared with a placebo, some are reviews about placebo effects in pharmacotherapy and psychotherapy, and others are papers dealing with both social and philosophical implications of the placebo phenomenon. In recent years, an increasing number of studies have approached the placebo effect as a psychobiological phenomenon worthy of scientific inquiry and have investigated it with sophisticated neurobiological tools, from neuropharmacology to neuroimaging and from single-neuron recordings in awake patients to in vivo receptor binding. Indeed, in recent times, the placebo effect has passed from a nuisance in clinical research to a target of investigation, and our understanding of its underlying mechanisms is improving, as more and more researchers get involved in its study.

The widespread use of the word placebo in the medical literature, and its use in many experimental procedures, is clear evidence of the importance of this phenomenon in modern biomedical sciences. If one considers that the current clinical approach of evidence-based medicine, which in most cases is related to therapeutics, relies on the superiority of a treatment compared with a placebo, the central role of the placebo emerges even more. Although any treatment that is used in routine medical practice, be it pharmacological or not, should be better than a placebo, this holds true mainly in mainstream medicine. By contrast, there are many circumstances in which this methodological and ethical principle is partially or completely ignored. Many over-the-counter drugs as well as complementary and alternative treatments are marketed even though there are serious doubts that they are more efficacious than placebos; thus, mainstream science often consider them nothing but placebos, i.e., inert.

Knowledge of placebo effects is therefore essential in modern medicine, and the crucial questions to be answered are "where," "when," and "how" placebo effects work. Pharmacological research, particularly clinical pharmacology, is involved in this issue more than other disciplines, as the use of placebos for the validation of drug effectiveness represents one, if not most, of the tenets of many therapeutic trials.

However, in spite of the widespread use of the terms placebo and placebo effect, they undoubtedly represent a source of confusion and misconception, and their meaning is often used inappropriately and confused with other phenomena (1). For example, when a placebo is given to a group of subjects in a clinical trial, the reduction of a symptom that follows its administration can be due to many causes, such as the natural history and the regression to the mean of the symptom. The former is the spontaneous remission of the symptom and occurs regardless of any treatment being administered. The latter is a statistical phenomenon whereby a measurement in a clinical trial tends to be higher at a first evaluation compared with a second assessment. Because of the occurrence of these different phenomena, the reduction of a symptom following placebo administration in a clinical trial can be caused by multiple factors and may therefore represent the sum of spontaneous remission plus regression to the mean, the true placebo response (i.e., a real psychobiological phenomenon), or some other factors (e.g., the patient's biases).

For the sake of simplicity and clarity, people that study the placebo effect tend to use the terms placebo effect and placebo response interchangeably to mean a real psychobiological phenomenon, having nothing to do with other phenomena, including spontaneous remission, regression to the mean, and patient bias. Therefore, the placebo effect, or response, is a biological phenomenon that is due to the psychosocial context of the patient and the therapy. It is important to point out that contextual and social stimuli may affect the patient's brain and body in many ways, such that there is not a single placebo effect but instead many, each with different mechanisms and in different systems and diseases (1, 2). Recently, it has also emerged that the term placebo effect is too restrictive and should be extended to related phenomena that share similar mechanisms. Thus, as described throughout this review, besides classical placebo effects, one can describe several placebo-related effects which are characterized by the fact that no placebo is administered.

Although many placebo and placebo-related effects have been described in different diseases and therapeutic interventions, in this review I consider only those effects for which we know at least some neurobiological mechanisms (**Table 1**). In addition, there are numerous studies in which clinical placebo effects have been described but

Table 1 Summary of the mechanisms of placebo and placebo-related effects across diseases/systems and treatments

Disease/System	Treatment	Mechanism
Pain	Placebo administration Nocebo administration Verbal suggestions Open versus hidden administration	Expectation-induced activation of endogenous opioids and cholecystokinin as well as of several brain regions
Parkinson's disease	Placebo administration Nocebo administration Verbal suggestions Open versus hidden administration	Expectation-induced release of dopamine in the striatum and changes of firing pattern of subthalamic nucleus neurons
Depression	Placebo administration	Changes of metabolic responses in different brain regions (inhibition of serotonin reuptake?)
Anxiety	Placebo administration Open versus hidden diazepam	Change of activity of some brain regions
Addiction	Expected versus unexpected methylphenidate	Changes of metabolic activity in different brain regions
Autonomic responses to deep brain stimulation	Open versus hidden deep brain stimulation	Change of neuronal excitability in associative/limbic regions
Cardiovascular system	Placebo administration	Reduction of β-adrenergic activity of the heart
Respiratory system	Pharmacological preconditioning with buprenorphine	Conditioning of opioid receptors in the respiratory centers
Immune system	Pharmacological preconditioning with immunosuppressive drugs (e.g., cyclophosphamide and cyclosporin A)	Conditioning of some immune mediators (e.g., IL-2, IFN-γ, lymphocytes)
Endocrine system	Pharmacological preconditioning with 5-HT_{1B-1D} receptor agonists (sumatriptan)	Conditioning of some hormones (e.g., growth hormone, cortisol)

the underlying mechanisms are completely unknown. These studies, albeit interesting and promising, are awaiting confirmation and a better mechanistic understanding, and therefore are not considered in this review.

PLACEBO EFFECTS

By definition, a placebo effect is the effect that occurs following the administration of a placebo, that is, of an inert treatment. Therefore, any psychobiological effect on the brain and/or the body that follows the administration of a placebo can be called, in its own right, a placebo effect or placebo response. It is important to stress that the inert treatment is given along with verbal suggestions of clinical improvement thereby making the patient believe that the treatment is real and effective. Albeit apparently obvious, it is crucial to note that the inert treatment (e.g., a sugar pill or a saline solution) never acquires therapeutic properties, so a pharmacologically inert substance will always remain inert. What matters is the verbal suggestion of clinical benefit or other sensory stimuli in the therapeutic context (e.g., the sight of a syringe) that anticipate the benefit (1, 3, 4). Recent meta-analyses indicate that placebo effects are not always present (5, 6), and that their mechanisms should be investigated under strictly controlled conditions in an experimental, rather than in the clinical trial, setting (7).

Expectation of Benefit

The patient's expectation of clinical benefit has been found to play a critical role in many placebo effects (8, 9), and this may occur in association with emotions (10). In a typical study of this kind, a placebo is given along with verbal suggestions that clinical improvement should be expected shortly. To rule out other phenomena, such as spontaneous remission, the group that receives the placebo is compared with a group that does not receive treatment, the so-called no-treatment or natural history group. The latter gives us information about the natural course of the symptoms or disease. Therefore, the difference between the outcome in the placebo group and in the natural history group represents a measure of the biological placebo effect or response.

Pain. A modulation of pain perception by placebos that is dependent on expectation has been shown by many studies (8, 9, 11). In one study (11), one group of subjects were administered a pharmacological preconditioning with ketorolac, a nonopioid analgesic, for two consecutive days and ketorolac was then replaced with a placebo on the third day along with verbal suggestions of analgesia. This procedure induced a strong placebo analgesic response. To see whether this placebo response was due to the pharmacological preconditioning, in a second group of subjects the same preconditioning procedure with ketorolac was carried out but the placebo was given on the third day along with verbal suggestions that the drug was a hyperalgesic agent. These verbal instructions were enough not only to block completely placebo analgesia, but also to produce hyperalgesia. These findings clearly show that placebo analgesia

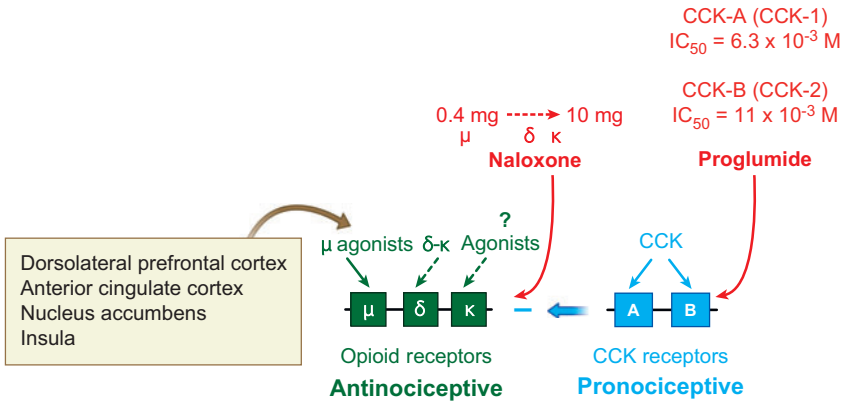

Figure 1

Placebo administration induces the activation of μ-opioid neurotransmission in the dorsolateral prefrontal cortex, anterior cingulate cortex, nucleus accumbens, and insula (12). Because high doses of naloxone are necessary to block the placebo analgesic effect, δ and κ receptors may also be involved (15). This placebo-activated antinociceptive opioid system (*green*) is antagonized by a CCKergic pronociceptive system (*blue*, represented by the minus sign). In fact, the CCK-antagonist, proglumide, is capable of potentiating placebo analgesia (18). Proglumide is a nonspecific CCK-A/B receptor antagonist, as shown by the similar binding affinity, expressed as the concentration required to inhibit by 50% the specific binding of ^{125}I-Bolton-Hunter CCK-8 (IC_{50}), for CCK-A and CCK-B receptors.

depends on expectation of a decrease in pain, even though a preconditioning analgesic procedure is done.

Placebo-induced analgesia has been found to activate the endogenous opioid systems in some circumstances. For example, in vivo receptor-binding techniques with the radiotracer carfentanil, a mu-opioid agonist, have shown that a placebo procedure activates μ-opioid neurotransmission in the dorsolateral prefrontal cortex, the anterior cingulate cortex, the insula, and the nucleus accumbens (12) (**Figure 1**). Indeed, some placebo analgesic responses can be blocked either partially or totally by the opioid antagonist naloxone (13–16). Interestingly, the dose of naloxone necessary to block placebo analgesia is as large as 10 mg, which suggests the involvement of other opioid receptors, such as the δ and κ receptors (**Figure 1**). The binding affinity of naloxone for these receptors is approximately 10–15 times lower than for the μ receptors, thus the large doses of naloxome may antagonize δ and κ receptors as well.

The activation of the opioid antinociceptive system by placebos has been shown to be counteracted by a pronociceptive system that involves cholecystokinin (CCK). The nonspecific CCK-A/B receptor antagonist proglumide has been found to potentiate placebo analgesia (17, 18), and this may occur from the antiopioid action of CCK (19) (**Figure 1**). These data suggest that the opioid and CCK systems have opposing actions on pain perception, and may participate in the complex cognitive modulation of nociception.

The involvement of the opioid systems in placebo analgesia is also shown by the activation of some brain regions, such as the anterior cingulate cortex, by both

CCK: cholecystokinin

μ-opioid agonists, for example, remifentanil, and placebos, which suggests that opioids and placebos share common mechanisms of action (20). Other brain imaging studies have demonstrated the involvement of different regions in placebo analgesia, for example, reduced brain activity in key areas involved in pain transmission, such as the thalamus and insula (21–23).

The endogenous opioid systems are not the only mechanisms involved in placebo analgesia; however, very little is known about such effects on nonopioid neurotransmission. One example of nonopioid-mediated placebo response is represented by previous exposure to a nonopioid drug, such as ketorolac (15). When ketorolac is administered for two consecutive days and then replaced with a placebo on the third day, the placebo analgesic response is not reversed by naloxone, which suggests that specific pharmacological mechanisms are involved in a learned placebo response, depending on the previous exposure to opioid or nonopioid substances. Another placebo analgesic effect that is not mediated by opioids has been described in irritable bowel syndrome patients (24).

Deep brain stimulation: therapeutic electrical stimulation of different regions of the brain, which is performed by implanting electrodes in the brain

Parkinson's disease: a movement disorder caused by the degeneration of the nigrostriatal dopaminergic pathway, whose main symptoms are tremor, muscle rigidity, and bradykinesia (movements slow down)

Parkinson's disease. Expectation plays a key role in Parkinson's disease as well. Expectation of either good or bad motor performance has been found to modulate the therapeutic effects of deep brain stimulation in Parkinson patients (25, 26) and this effect is independent of previous conditioning (11). In a typical placebo procedure in Parkinson patients, a placebo is administered along with verbal suggestions of motor improvement. Parkinson's disease is a movement disorder in which at least three motor symptoms are involved: tremor, muscle rigidity, and bradykinesia (movements slow down). In a brain imaging experiment with positron emission tomography (PET), the release of endogenous dopamine was assessed by using raclopride, a radiotracer that binds to dopamine D2 and D3 receptors (27). After administration of a placebo that the patient believed to be apomorphine, a powerful anti-Parkinsonian agent, dopamine was released in the striatum, corresponding to a change of 200% or more in extracellular dopamine concentration and comparable to the response to amphetamine in subjects with an intact dopamine system. The release of dopamine in the motor striatum (putamen and dorsal caudate) was greater in patients who reported clinical improvement (**Figure 2**). In a more recent study (28), these findings have been confirmed by using sham transcranic magnetic stimulation as a placebo.

Interestingly, although in the studies by de la Fuente-Fernandez et al. (27, 29) all patients showed dopamine placebo responses, only half of them reported motor improvement. These patients also released larger amounts of dopamine in the dorsal motor striatum, suggesting a relationship between the amount of dorsal striatal dopamine release and clinical benefit. This relationship was not present in the ventral striatum in which all patients showed increased dopamine release, irrespective of whether they perceived any improvement. Compared with the dorsal motor striatum, the ventral striatum is involved in motivation and reward anticipation. Accordingly, the authors proposed that the dopamine released in the ventral striatum was associated with the patients' expectation of improvement in their symptoms, which could in turn be considered a form of reward (**Figure 2**).

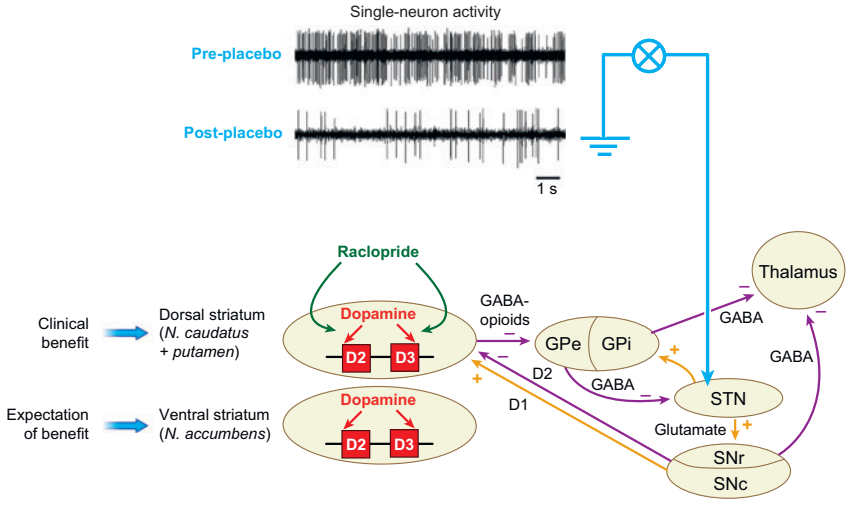

Figure 2

The basal ganglia circuitry involved in Parkinson's disease following placebo administration. By using raclopride, which competes with endogenous dopamine for D2 and D3 receptors, a release of dopamine in both the ventral and dorsal striatum has been demonstrated (27). The former is associated with expectation of clinical benefit, whereas the latter with the benefit itself. In a different study, the neurons of the subthalamic nucleus (STN) have been found to decrease their firing rate and to change from a bursting to a nonbursting activity (30). GPe, external globus pallidus; GPi, internal globus pallidus; SNr, substantia nigra pars reticulata; SNc, substantia nigra pars compacta.

In a different experiment in Parkinson patients undergoing the implantation of two electrodes for deep brain stimulation, the electrical activity from single neurons was recorded in the subthalamic nucleus of awake patients after administration of a placebo, which the patients believed to be apomorphine (30). The authors found a change in the firing pattern of the subthalamic nucleus neurons during the placebo response (**Figure 2**): There was a decrease in firing rate as well as a change from bursting to nonbursting activity. These changes were correlated with both the patients' subjective reports of well-being and the muscle rigidity reduction at the wrist, as assessed by a neurologist unaware of the nature of treatment each patient received. Although it is tempting to speculate that these neuronal changes are due to dopamine release in the striatum, the dopamine release and the single-neuron changes were observed in two separate studies, thus no definitive conclusion can be drawn. Nonetheless, on the basis of our knowledge about the basal ganglia circuitry (**Figure 2**), it is plausible that a release of dopamine acting on the inhibitory D2 receptors disinhibits the GABA neurons of the external globus pallidus, which, in turn, increase their inhibition onto the subthalamic nucleus.

Depression. Evidence of significant and increasing rates of placebo responses in antidepressant trials has been documented in several studies (31–33). Unlike single-dose

trials of an intervention, such as the intravenous analgesia or anti-Parkinson acute therapy studies described above, antidepressants do not work acutely, requiring on average a minimum of 2–3 weeks to see clinical effects. Therefore, investigating placebo effects in depression is more problematic from both an ethical and methodological point of view.

In a placebo-controlled study of fluoxetine, a serotonin reuptake inhibitor, PET scans were acquired before and 1 and 6 weeks after treatment (34). Anatomically concordant metabolic changes observed by PET were associated with clinical response (6 weeks of treatment relative to baseline) in both the fluoxetine-treated and placebo groups (**Figure 3**). These changes were characterized by increased activity in prefrontal, parietal, and posterior cingulate cortex, and decreases in subgenual cingulate cortex. The magnitude of change observed with fluoxetine was generally greater than with placebo. Unique to fluoxetine were additional increases in the activity of the pons and decreases in caudate, insula, and hippocampus, that is, in regions with efferent connections to both subgenual cingulate and prefrontal cortex in which changes were seen in both groups. There were no regional changes unique to placebo after 6 weeks of treatment. Although no natural history group was run in these studies, psychotherapy has been noted to induce brain changes that were different from both fluoxetine and placebo treatment (2, 34). These differences rule out the hypothesis

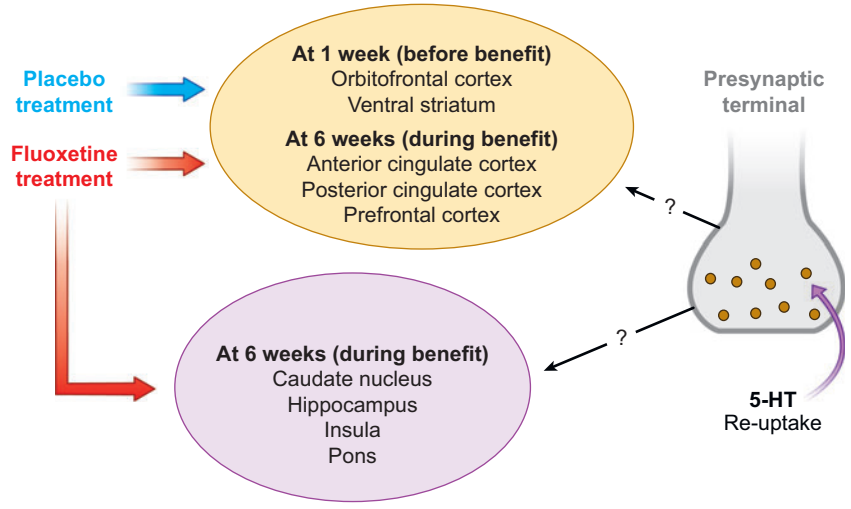

Figure 3

Therapy with placebo or fluoxetine of depressed patients has similar effects on the orbitofrontal cortex and ventral striatum after 1 week of treatment and on anterior/posterior cingulate cortex and prefrontal cortex after 6 weeks of treatment. By contrast, the caudate nucleus, hippocampus, insula, and pons are affected by fluoxetine treatment only (34). Because fluoxetine is a serotonin reuptake inhibitor, serotonin might be involved in the placebo treatment. However, an alternative explanation is that serotonin reuptake inhibition may occur in those regions affected by fluoxetine only, thus placebo treatment might act by a completely different mechanism.

that placebo responses are mediated by changes in a common antidepressant response pathway. Moreover, they suggest that the antidepressant effect of placebo is not the result of uncontrolled, nonspecific psychological treatment effects, as brain changes associated to placebo therapy match those observed with the active drug.

Interestingly, there were unique ventral striatal and orbital frontal changes in both placebo and drug responders after 1 week of treatment, that is, well before clinical benefit (**Figure 3**). Thus these changes are not associated with the clinical response, but rather appropriately to the expectation and anticipation of clinical benefit. Such changes were seen neither in the eventual drug nonresponders nor after 6 weeks when the antidepressant response was well established, consistent with an expectation pattern of response (2, 34).

Because fluoxetine is an inhibitor of serotonin reuptake, it is tempting to speculate that serotonergic mechanisms may be involved in the antidepressant effect produced by placebos. However, as shown in **Figure 3**, at least two hypotheses can be envisaged. First, serotonin reuptake inhibition could be a common mechanism shared by fluoxetine and placebo-induced expectation of clinical improvement. Second, serotonin reuptake could be involved only in those brain regions that are affected by fluoxetine, the placebo response being mediated by different mechanisms. Although the long latency of the antidepressant action limits the ethical experimental approach to the study of the placebo effect in depression, it should be of interest to devise new experiments to better understand these mechanisms.

Anxiety. Some information is available regarding the mechanisms that underlie the effect of placebos in anxiety. In one brain imaging study, it was found that treatments with placebo can modulate emotional perception in the same way as occurs with pain perception (35). On the first day of the experiment, subjects were treated with either the benzodiazepine midazolam or the benzodiazepine receptor antagonist flumazenil before the presentation of unpleasant pictures. As expected, midazolam reduced the unpleasantness and flumazenil had an opposite effect. Therefore, on the first day, a robust expectation of the treatment effect was induced. On the second day, the subjects were told that they would be treated either with the same anxiolytic drug or the anxiolytic blocker as administered the previous day. However, instead of receiving the drugs, they received a placebo. The investigators found a significant and robust placebo response (reduced unpleasantness) when the subjects thought they had been treated with the anxiolytic drug, whereas no response occurred if they thought they had received the anxiolytic blocker. In the same study (35), functional magnetic resonance imaging (fMRI) showed that regional blood flow changed in both the anterior cingulate cortex and lateral orbitofrontal cortex. Interestingly, this same circuit is also involved in placebo analgesia (20, 21), which suggests that similar mechanisms are involved in the placebo response of both emotional stimuli and analgesia.

Cardiovascular system. What is known regarding placebo mechanisms in the cardiovascular system is the result of placebo analgesia studies. In one study, heart rate during placebo-induced expectation of analgesia was found to be reduced (36). The opioid antagonist naloxone completely antagonized both placebo analgesia and the

concomitant reduction in heart rate, whereas the β-blocker propranolol antagonized the placebo-promoted reduction in heart rate but not placebo analgesia. By contrast, both placebo responses were present during blockade of muscarinic cholinergic receptors with atropine, indicating no involvement of the parasympathetic system. A spectral analysis of the heart rate variability for the identification of the sympathetic and parasympathetic components showed that the β-adrenergic sympathetic component was reduced during placebo analgesia, an effect that was reversed by naloxone. These findings, although in the context of placebo analgesia, indicate that the placebo analgesic response is accompanied by a complex cascade of events that affect the cardiovascular system through the autonomic nervous system.

β-adrenergic sympathetic system: part of the autonomic nervous system that is involved in the stress response and whose effect on the heart is the increase of both frequency and strength of contraction

CS: conditioned stimulus

US: unconditioned stimulus

CR: conditioned response

Immunosuppressive drugs: pharmacological agents that inhibit immune responses

Classical Conditioning

In many situations, classical conditioning plays a key role in the placebo effect. It has been suggested that, whereas expectation is important when conscious physiological functions, such as pain and motor performance, are involved, conditioning plays a role in unconscious physiological functions, such as immune and hormonal responses (11). In classical conditioning, after repeated associations between a conditioned stimulus (CS), which can be represented by several contextual cues (e.g., color and shape of a pill), and an unconditioned stimulus (US) (e.g., the active agent inside the pill), the CS alone can induce a conditioned response (CR) that is similar to that induced by the active drug. This can be considered a placebo effect in all respects, as the CS per se is inert. Although pharmacologists have long been aware of pharmacoconditioning effects (37–40), conditioning in pharmacotherapy has only recently been better conceptualized in terms of the placebo effect (39, 41, 42).

Immune responses. One of the most interesting observations on the placebo effect in the immune system was reported in 1896 by MacKenzie (43), who showed that some people who are allergic to flowers show an allergic reaction when presented with an object that looks like a flower but contains no pollen (an artificial flower). Some of the first evidence that immunological placebo responses can be obtained by pairing a CS (a solution of sodium saccharin) with a US (the immunosuppressive drug cyclophosphamide) was obtained with mice. Mice treated in this way show conditioned immunosuppression, that is, immune responses to sodium saccharin alone (44). It was also shown that a conditioned enhancement of antibody production is possible using an antigen as US of the immune system. Mice were given repeated immunizations with keyhole limpet hemocyanin paired with a gustatory CS. A classically conditioned enhancement of antikeyhole limpet hemocyanin antibodies was observed when the mice were reexposed to the gustatory stimulation alone (45).

These animal studies have been repeated in humans (46). For example, a clinical case study of a child with lupus erithematosus has been described (47). The child received cyclophosphamide (US) paired with taste and smell stimuli (US), according to the conditioning procedure used in animals. During the course of 12 months, a clinically successful outcome was obtained by using taste and smell stimuli alone on half the monthly chemotherapy sessions. In another study, multiple sclerosis patients received

intravenous treatments with cyclophosphamide (US) paired with anise-flavored syrup (CS), and eight out of ten patients displayed decreased peripheral leukocyte counts following the syrup alone, an effect that mimics that of cyclophosphamide (48).

As shown in **Figure 4*a***, repeated associations between cyclosporin A (US) and a flavored drink (CS) induced conditioned immunosuppression (CR), in which the flavored drink alone produced a suppression of the immune functions, as assessed by assays of interleukin-2 (IL-2) and interferon-γ (IFN-γ) mRNA expression, in vitro release of IL-2 and IFN-γ, as well as lymphocyte proliferation (49).

Hormone secretion. Findings similar to those observed in the immune system have also been obtained in the endocrine system. In one study (11), the effects of opposing verbal suggestions on hormonal secretion were tested and it was found that verbally induced expectations of increase/decrease of growth hormone (GH) and cortisol did not have any effect on their secretion. However, if a preconditioning was performed for two consecutive days with sumatriptan, a 5-$HT_{1B/1D}$ agonist that stimulates GH and inhibits cortisol secretion, a significant increase of GH and decrease of cortisol plasma concentrations were found after placebo administration on the third day (**Figure 4*b***). These conditioned effects occurred regardless of the verbal suggestions the subjects received. In other words, the placebo mimicked the sumatriptan-induced GH increase, even though the subjects expected a GH decrease. Likewise, the placebo mimicked the sumatriptan-induced cortisol decrease, even though the subjects expected a cortisol increase. In this case, the CS was represented by the act of injecting the pharmacological agent (i.e., the context around the treatment).

Respiratory system. In a clinical study on the effects of narcotics on respiratory depression, respiratory depressant responses to placebo were described (50). A placebo was given after repeated administrations of buprenorphine, which induces mild respiratory depression. The placebo mimicked the respiratory depressant effect of buprenorphine, even though the patients did not expect any effect and did not notice any decrease in ventilation. The best explanation for this response is a conditioning mechanism in which the act of giving the drug represented the CS. These respiratory depressant responses to placebo could be prevented by the opioid antagonist naloxone, which suggests the involvement of endogenous opioids in respiratory centers (50).

Nocebo Effects

The nocebo effect is a placebo effect because an inert substance is administered. However, to induce a nocebo effect, the inert substance is given along with verbal suggestions of clinical worsening, so as to induce negative expectations about the outcome. To investigate the neurobiological basis of the nocebo effect one studies the effects of such negative psychosocial contexts on the patient's brain and body.

Pain. Much less is known about nocebo hyperalgesia compared with placebo analgesia owing to ethical limitations. Whereas the induction of placebo responses is acceptable in many circumstances (51), the induction of nocebo responses represents

IL-2: interleukin 2

IFN-γ: interferon gamma

GH: growth hormone

Sumatriptan: agonist of serotonin 5-HT_{1B-1D} receptors that is used in the treatment of migraine attacks, and whose hormonal effects are the increase of GH and a biphasic response (first increase, then decrease) of cortisol

Buprenorphine: opioid drug that is used to treat different types of pain

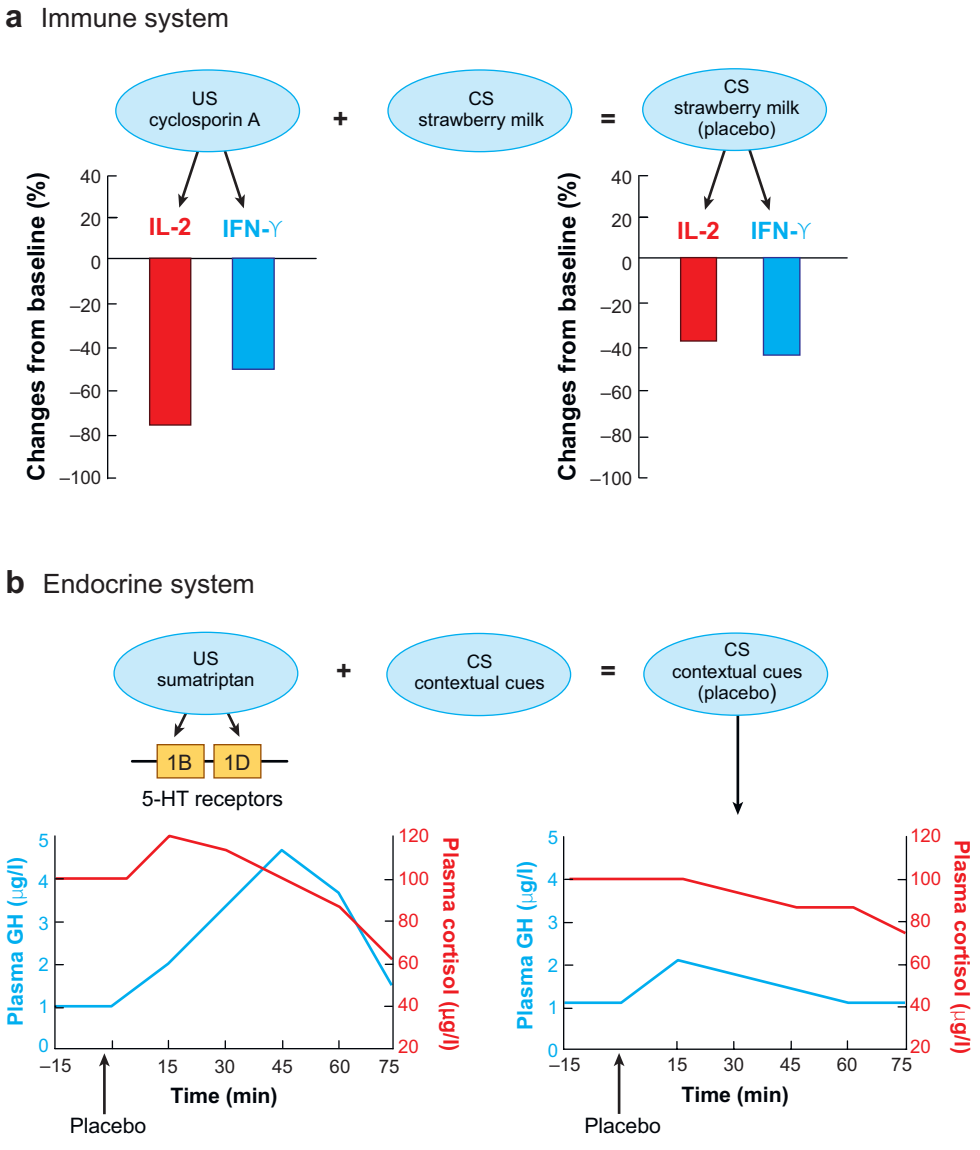

Figure 4

Placebo responses in which classical conditioning plays a major role. (*a*) Repeated associations between the immunosuppressive drug cyclosporin A (US, unconditioned stimulus), which inhibits both IL-2 and IFN-γ, and strawberry milk (CS, conditioned stimulus) induce conditioned responses in which the CS alone (a placebo in all respects) is capable of inhibiting both IL-2 and IFN-γ (49). (*b*) Repeated associations between the 5-$HT_{1B\text{-}1D}$ receptor antagonist sumatriptan (US), which increases growth hormone (GH) and decreases cortisol, and contextual cues (CS) induce conditioned responses in which the CS alone is capable of increasing GH and decreasing cortisol (11).

a stressful and anxiogenic procedure in that nocebo hyperalgesia is produced by giving an inert treatment along with verbal suggestions of an increase in pain.

In 1997, a trial in postoperative patients was run with the nonspecific CCK-A/B receptor antagonist proglumide in a setting that induced expectations of pain worsening (52). It was found that proglumide prevented nocebo hyperalgesia in a dose-dependent manner, even though it is not a specific painkiller, thus suggesting that the nocebo hyperalgesic effect is mediated by CCK. A dose as low as 0.05 mg was ineffective, whereas a dose ranging from 0.5 to 5 mg proved to be effective. Because CCK is also involved in anxiety mechanisms, it was hypothesized that proglumide affects anticipatory anxiety (52, 53). Importantly, this effect was not antagonized by naloxone. However, owing to ethical constraints, these effects were not investigated further.

To better understand the mechanisms underlying nocebo hyperalgesia and to overcome the ethical constraints that are inherent in the clinical approach, a similar procedure was used in healthy volunteers by inducing experimental pain (54). Oral administration of an inert substance, along with verbal suggestions of hyperalgesia, induced both hyperalgesia and hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis, as assessed by adrenocorticotropic hormone (ACTH) and cortisol plasma concentrations. Both nocebo-induced hyperalgesia and HPA hyperactivity were blocked by the benzodiazepine diazepam, which suggests the involvement of anxiety mechanisms. By contrast, the administration of the mixed CCK type-A/B receptor antagonist, proglumide, completely blocked nocebo hyperalgesia, but had no effect on HPA hyperactivity, thus suggesting a specific involvement of CCK in the hyperalgesic but not in the anxiety component of the nocebo effect. Interestingly, both diazepam and proglumide did not show analgesic properties on baseline pain, as they only acted on the nocebo-induced pain increase. These data suggest that a close relationship between anxiety and nocebo hyperalgesia exists, but that proglumide does not act by blocking anticipatory anxiety, as previously hypothesized (52, 53). Instead, proglumide appears to interrupt a CCKergic link between anxiety and pain. Therefore, as shown in **Figure 5**, in contrast to the anxiolytic action of diazepam, proglumide blocks a CCKergic pronociceptive system that is activated by anxiety and is responsible for anxiety-induced hyperalgesia. Support of this conclusion comes from a social-defeat model of anxiety in rats, in which CI-988, a selective CCK-B receptor antagonist, prevents anxiety-induced hyperalgesia (55).

Nocebo hyperalgesia is thus an interesting model to access when and how endogenous pronociceptive systems are activated. The pronociceptive and antiopioid action of CCK has been documented in many brain regions (19, 56, 57), and it has been shown that CCK reverses opioid analgesia by acting at the level of the rostral ventromedial medulla (58, 59) and activates pain facilitating neurons within the rostral ventromedial medulla (60). The similarity of the pain facilitating action of CCK on brainstem neurons in animals and nocebo mechanisms in humans may represent a starting point for further research into the neurochemical mechanisms of nocebo-induced hyperalgesia.

Parkinson's disease. Whereas nocebo hyperalgesia has been studied from both a behavioral and a biochemical point of view, the neural mechanisms of the nocebo

Hypothalamic-pituitary-adrenal (HPA) axis: endocrine system connecting the hypothalamus, the pituitary gland, and the adrenal glands, and which is generally hyperactive during stress and anxiety

ACTH: adrenocorticotropic hormone

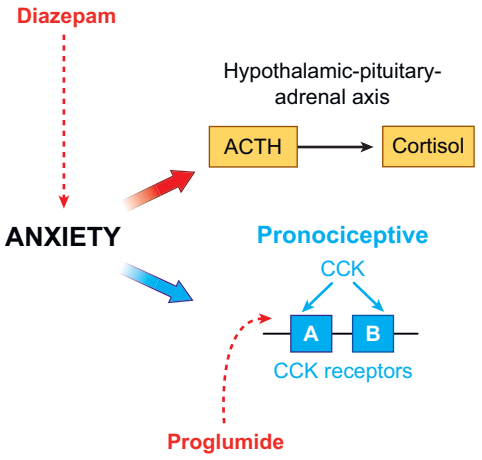

Figure 5

A nocebo procedure induces anxiety, which, in turn, activates the hypothalamic-pituitary-adrenal (HPA) axis and a CCKergic pronociceptive system, thus amplifying pain. Diazepam blocks anxiety and, therefore, both HPA hyperactivity and hyperalgesia. Conversely, the CCK-antagonist proglumide only blocks the CCKergic link between anxiety and pain, thus it has no effect on anxiety itself (54).

effect in conditions other than pain are poorly understood. In one study (11), Parkinson patients who had undergone the implantation of two electrodes for deep brain stimulation were tested for the velocity of movement of their right hand by means of a movement analyzer. After the stimulator had been turned off several times (at 4 and 2 weeks) before the test session, on the day of the experimental session, even though the stimulation was maintained, the patients were told that the stimulator had been turned off, so as to induce negative expectations of motor worsening (nocebo). It was found that, although the stimulator was on, motor performance worsened and mimicked the worsening of the previous days. Recently, these findings have been replicated (26), and it was also found that this effect occurred for bradykinesia but not for tremor and rigidity. No neurobiological mechanism is as yet known for this nocebo bradykinesia. However, in light of the findings on the placebo effect in Parkinson's disease described above, it will be interesting to extend these findings to the nocebo effect as well.

PLACEBO-RELATED EFFECTS

By definition, if no placebo is administered, the effect that follows its administration cannot be called a placebo effect. However, it has become clear in recent times that this definition is too restrictive and does not aid in understanding the underlying mechanisms (3). Indeed, there are several placebo-like effects in which no placebo is given, and these effects are attributable to the influence of the context surrounding the treatment on the patient's brain.

Verbal Suggestions

A placebo is usually given along with verbal suggestions of clinical improvement. However, verbal suggestions of either improvement or worsening can be given alone, so as to induce expectancies about the outcome.

Top-down control: psychological (cognitive and emotional) modulation of incoming sensory inputs in brain regions

Pain. Modern brain imaging techniques have been fundamental in the understanding of the neurobiology of positive and negative expectations. Typically, the experimenter tells the subject about the forthcoming pain so as to make the subject expect either a low-intensity or a high-intensity painful stimulation. Overall, negative (or positive) expectations may result in the amplification (or reduction) of pain along with activation (or inhibition) of several brain regions (61–67). For example, in one study (65), as the magnitude of expected pain increased, activation increased in the thalamus, insula, prefrontal cortex, and anterior cingulate cortex. By contrast, expectations of decreased pain reduced activation of pain-related brain regions, including the primary somatosensory cortex, the insular cortex, and anterior cingulate cortex.

In another study, the level of expected pain intensity was found to alter perceived pain intensity along with the activation of different brain regions (67). By using two visual cues, each conditioned to one of two noxious thermal stimuli of differing intensity, the investigators showed that subjects reported higher pain when the noxious stimulus was preceded by the high-intensity visual cue. By comparing the brain activations produced by the two visual cues, these authors found significant differences in the ipsilateral caudal anterior cingulate cortex, the head of the caudate, the cerebellum, and the contralateral nucleus cuneiformis. Thus, expectation of either low- or high-intensity painful stimuli has a strong influence on the perceived pain, regardless of the concomitant administration of a placebo.

Parkinson's disease. Similar to what has been observed for painful stimuli, in Parkinson's disease, placebo administration is not a necessary condition to modulate the therapeutic outcome. In one study (25), the velocity of movements was analyzed in Parkinson patients who had been implanted with electrodes in the subthalamic nuclei for deep brain stimulation. The patients were tested under two opposite conditions: in the first condition, they expected a good motor performance, whereas in the second, they expected a bad motor performance. The results indicated that these two opposite expectations can modulate the therapeutic effect of stimulation of the subthalamic nucleus. Analysis of the effect of subthalamic stimulation on the velocity of movement of the right hand with a movement analyzer revealed that the hand movement was faster when the patients expected a good motor performance than when they expected a bad performance.

Sensory stimuli. Overall, many sensory modalities undergo a top-down control of the sensory inputs, in which expectations of a future outcome can shape the global perceptual experience (68–70). For example, when subjects are led to believe that a highly aversive bitter taste would be less distasteful than it actually is, they report it to be less aversive than when they have accurate information about the taste. This

is associated with a reduced activation of the primary taste cortex, that is, the insula and operculum (71). Such findings imply that in the clinical setting, the modulation of sensory stimuli by expectations may be relevant to the perception of a symptom in many circumstances.

Open (Expected) versus Hidden (Unexpected) Treatments

One of the best pieces of evidence that underscores the crucial role of expectation in the therapeutic outcome is the decreased effectiveness of hidden treatments. This can be accomplished by eliminating the placebo (psychosocial) component and then analyzing the pharmacodynamic effect of the treatment, free of any psychological contamination, by making the patient unaware that a medical therapy is being carried out (1, 72). To do this, drugs are administered through hidden infusions by machines. Such infusions can be administered using computer-controlled infusion pumps that are preprogrammed to deliver drugs at a desired time. The crucial factor is that the patients do not know that the drug is being injected, so they ought not have expectations of a therapeutic response. This contrasts with open administration, which is used in routine medical practice in which drugs are given overtly and the patients expect a clinical benefit. Therefore, an open injection of a drug provides an expected treatment, whereas a hidden injection represents an unexpected therapy. The difference between the outcomes following the administration of the expected and unexpected therapy is the placebo (psychological) component, even though no placebo has been given (1, 72–74).

Pain. In postoperative pain following the extraction of the third molar (75, 76), a hidden injection of a 6–8 mg intravenous dose of morphine corresponds to an open intravenous injection of saline solution in full view of the patient (placebo). In other words, telling the patient that a painkiller is being injected (when a saline solution is actually injected) is as potent as 6–8 mg of morphine. The investigators concluded that an open injection of morphine in full view of the patient is more effective than a hidden one because the placebo component is absent in the latter situation.

A careful analysis of the differences between open (expected) and hidden (unexpected) injections in the postoperative setting has been performed for five widely used painkillers (morphine, buprenorphine, tramadol, ketorolac, metamizol) (72, 73, 77). In one analysis (73), it was found that the analgesic dose needed to reduce the pain by 50% was much higher with hidden infusions than with open ones, thus indicating that a hidden administration is less effective than an open one. In another analysis of the same study, it was found that pain rating was significantly higher with a hidden injection than with an open one.

The difference between open and hidden injections was also investigated in the laboratory setting by using the experimental model of ischemic arm pain in healthy volunteers (73) (**Figure 6*a***). As occurs in the clinical setting, it was found that a hidden injection of the nonopioid analgesic ketorolac (a non-steroidal anti-inflammatory drug), was less effective than an open injection. Interestingly, when the opioid antagonist naloxone was added to the open injection of ketorolac, the effect was the same

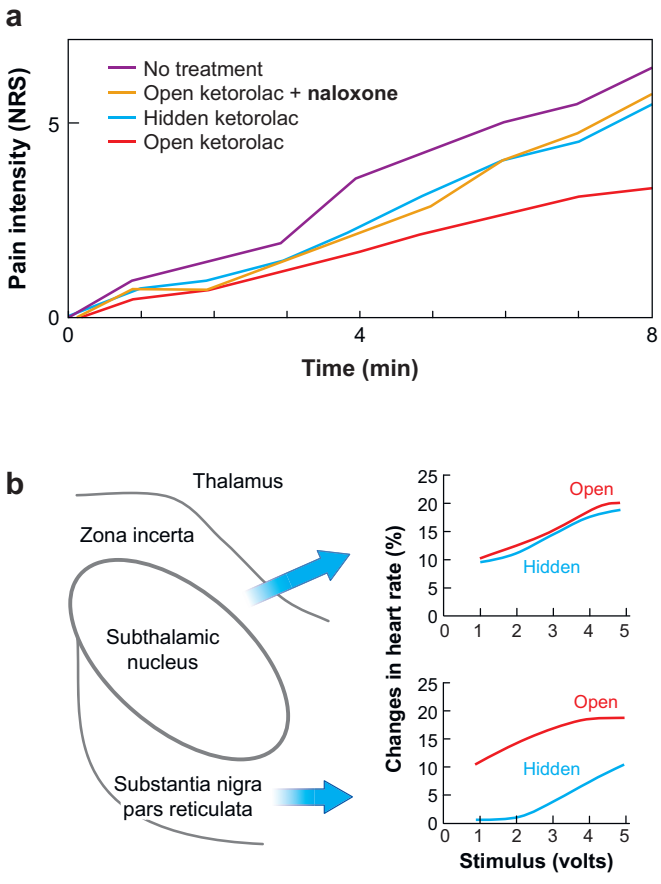

Figure 6

Open versus hidden administration of treatments. (*a*) An open (expected) administration of the analgesic ketorolac reduces experimental ischemic arm pain (*red line*) compared with the natural history of pain (*purple line*). A hidden (unexpected) injection of the same dose of ketorolac (*blue line*) is much less effective in reducing pain than the open injection. However, if the open injection of ketorolac is performed together with the opioid antagonist naloxone (*yellow line*), no difference is present between open and hidden administration. This suggests that the larger effect of open ketorolac is due to the activation of endogenous opioid systems (73). (*b*) The stimulation of the zona incerta produces a stimulus-response curve that is the same in the open and hidden condition. Conversely, the stimulation of the substantia nigra pars reticulata produces a stimulus-response curve that is different in the open and hidden conditions. This suggests a change of neuronal excitability in the two conditions in specific brain regions (79).

as that produced by a hidden injection. This suggests that an open injection (i.e., in full view of the patient) activates endogenous opioids that enhance the effects of the injected painkiller.

In addition to the expected (open) and unexpected (hidden) administration of analgesics, open and hidden interruptions were also investigated. For example, it has

been shown that the relapse of pain occurs faster and the pain intensity is larger with an open interruption of morphine compared with a hidden one, thus indicating that the hidden interruption prolongs postinterruption analgesia (57, 72, 77). A possible explanation for this effect is the patient's negative expectation of pain relapse (i.e., a nocebo-like effect).

Autonomic responses to deep brain stimulation. A detailed analysis of autonomic responses to intraoperative stimulation of different brain regions has been carried out in Parkinson patients during electrode implantation for deep brain stimulation (78, 79). The stimulation of the most dorsal part of the subthalamic region, which includes the zona incerta, produced autonomic responses that did not differ in the hidden and the open condition. By contrast, the stimulation of the most ventral region, which includes the substantia nigra pars reticulata, produced autonomic responses that varied according to the open or hidden stimulation. Moreover, the hidden (unexpected) stimulation was less effective, so that an increase of the stimulus intensity was necessary to induce an autonomic response. The stimulus-response curves in the dorsal and ventral subthalamic region are shown in **Figure 6*b***. It can be seen that the curves are different in the hidden and open condition only in the ventral part, a region that is involved in associative-limbic functions. This suggests that expectation may change the neuronal excitability in limbic structures (79).

Anxiety. In a study in postoperative patients with high anxiety scores, the anxiolytic diazepam was administered either overtly or covertly (72, 77). Whereas in the open group there was a clear-cut decrease of anxiety, in the hidden group diazepam was totally ineffective, which indicates that anxiety reduction after the open administration of diazepam was a placebo effect. With respect to interruption of diazepam, in the open condition anxiety increased significantly after 4 and 8 h, whereas in the hidden condition it did not change. Therefore, the relapse of anxiety after the expected interruption of diazepam could be attributed to the negative expectation of such relapse (nocebo-like effect).

Addiction. The outcome of methylphenidate on brain glucose metabolism has been analyzed in different conditions in cocaine abusers (80). In one condition they expected to receive, and then received, the drug. In a second condition, they expected to receive a placebo, but actually received the drug. This paradigm is rather similar to the open-hidden design, as in the first case methylphenidate is expected, whereas in the second case its administration is unexpected. In the former case, the effect on brain glucose metabolism was larger than in the latter, which indicates that expectation can enhance the action of methylphenidate.

Expectations in Clinical Trials

Recent experimental evidence suggests that expectations can have a large influence on the outcome of a clinical trial. Indeed, what the subjects expect in a clinical trial may influence the outcome, regardless of whether they belong to the placebo group

or to the active treatment group. Because expectations of benefit are involved, the underlying mechanisms are likely akin to those described above. However, to date, no neurobiological investigation has been done in this context.

Pain. In one clinical trial, real acupuncture, in which the needle was really inserted into the skin, was compared with sham acupuncture, in which the needle did not enter the skin. Patients were then asked whether they thought they were in the placebo or the real treatment group. Those patients who believed they were in the real treatment group experienced larger clinical improvement than those patients who believed they were in the placebo group (81). In another clinical trial, patients were asked whether they considered acupuncture to be an effective therapy in general and what they personally expected from the treatment. Patients with higher expectations about acupuncture treatment experienced larger clinical benefits than those with lower expectations, regardless of their allocation to real or sham acupuncture (82). Thus it did not really matter whether the patients received the real or sham procedure. Rather, what mattered was whether they believed in acupuncture and expected a benefit from it.

Parkinson's disease. In a clinical trial of human fetal mesencephalic transplantation, which is being assessed as a possible treatment for Parkinson's disease, investigators studied the effect of this treatment compared with placebo treatment for a twelve-month period. They also assessed the patient's perceived assignment to either the active (fetal tissue implant) or placebo (sham surgery) treatment. There were no differences between the transplant and sham surgery groups on several outcome measures, such as physical and quality of life scores. However, the perceived assignment between the treatment groups had a beneficial impact on the overall outcome, and this difference was still present at twelve months after surgery. Patients who believed they received transplanted tissue had significant improvements in both quality of life and motor outcomes, regardless of whether they received sham surgery or fetal tissue implantation (83).

Smoking cessation. In a trial of nicotine replacement treatment for smoking reduction, smokers were randomly assigned to receive nicotine, placebo products, or no intervention. After 6 months, the participants were asked to guess the group to which they believed they belonged (either nicotine or placebo). Regardless of actual treatment, smokers who believed they had received nicotine had significantly better outcome than those who believed they had received placebo (84).

COGNITIVE MODULATION OF DRUG ACTION

All the mechanisms described above indicate that several social stimuli within the context of a particular treatment can activate neurotransmitters and modulators that bind to the same receptors to which drugs bind and can trigger biochemical pathways that are similar to those activated by pharmacological agents. Present knowledge is

insufficient for us to understand whether the activation of specific receptors is a feature of a specific placebo procedure. For example, we do not know whether placebo-induced expectation of analgesia activates only endogenous opioids, whereas expectation of motor improvement activates only dopamine, although a very recent study found dopamine activation in placebo analgesia (85). Future research will hopefully answer this important issue.

Even without that information, one can conclude that different psychosocial contexts are capable of activating several biochemical pathways through anticipatory and expectancy mechanisms and/or classical conditioning. A summary of various targets and pathways involved in these psychosocial responses is shown in **Figure 7**. On the basis of the experimental results presented in this review, it is clear that for many types of treatments, whenever a medical treatment is carried out, a complex biochemical matrix is activated by several social stimuli. Such biochemical cascades of events will inevitably contribute to responses observed with drug administration. In other words, drugs are not administered in a vacuum but rather in a complex biochemical environment that varies according to the patient's cognitive/affective state and to previous exposure to other pharmacological agents (conditioning). **Figure 7** shows that drugs given for specific conditions may act on a set of receptors that could have been modified by the therapeutic context.

This concept led Colloca & Benedetti to propose a principle based on uncertainty in human pharmacology (1). This principle asserts that one can never be sure regarding the action of a pharmacological agent, as its pharmacodynamic action is perturbed

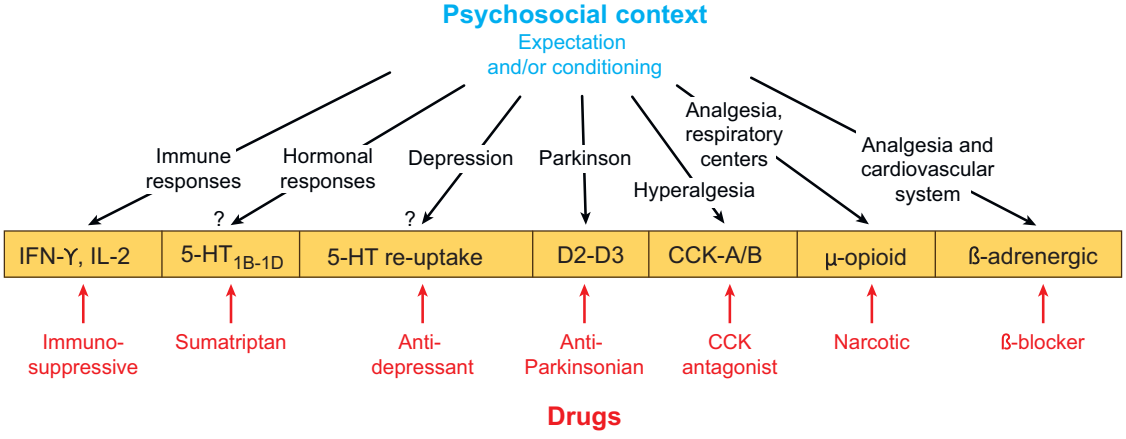

Figure 7

The psychosocial context around the treatment activates, through expectation and/or conditioning mechanisms, a number of receptor pathways in different diseases and treatments (the involvement of 5-HT receptors in hormonal responses and depression is not definitive). These receptors are the same to which different drugs bind, thus indicating that cognitive and affective factors are capable of modulating the action of drugs. This interference has profound implications for our understanding of drug action: When a drug is given, the act of administering (i.e., the psychosocial context) may perturb the system and change the response to the drug.

by the act of administering it. In other words, in the same way that the Heisenberg uncertainty principle in physics asserts that the act of measuring perturbs the system under measurement, in pharmacology, the act of giving a drug perturbs the system (brain and body) in which the measurement (therapeutic outcome) is undertaken. Such uncertainty may contribute to the variability in clinical trials. A new approach that divides subjects in a clinical trial on the basis of their expectation about the therapeutic outcome shows how the perceived assignment to a group (either placebo or active treatment) may have a higher impact on outcome than the actual assignment (81–84).

Figure 7 predicts that if one wants to test a new drug for the relief of pain, the act of its administration can impact its real pharmacodynamic effects. For example, negative expectation may activate CCKergic systems or, conversely, positive expectation may activate opioid receptors and thus may modify the overall action of the drug under study. A partial solution to this interference between social stimuli and drugs is to "silence" the psychosocial biochemical pathways. As discussed above, this is possible with unexpected, or hidden, administration of medical treatments. In this way, a drug may be given, at least in part, free of psychologically induced activation of receptor pathways. In a trial that was performed in 1995 (18), a group taking a placebo was compared with a group taking proglumide. The proglumide group showed more analgesia than the placebo group, suggesting that proglumide is an analgesic. However, this conclusion is erroneous because a hidden injection of proglumide was totally ineffective, demonstrating that it is not an analgesic, but instead, that the drug enhances placebo-activated release or response to endogenous opioids (1). Therefore, an analgesic that is tested according to the classical methodology of clinical trials can give a better response than a placebo even though it lacks analgesic properties.

In conclusion, placebo research has evolved from early investigations, such as the influential study by Beecher in 1955 (86), to the recent sophisticated biological investigations of placebo and placebo-like effects in humans. These years of research in the field of placebo have taught us that complex cognitive/affective factors are capable of modulating the action of drugs through the activation, at least in some cases, of the same receptors to which drugs bind. From an evolutionary perspective, it is tempting to speculate that social stimuli may have drug-like therapeutic properties because this is advantageous for a member of a social group. If you trust an authoritative member of your social group, be he a modern doctor or a primitive shaman, you have better chances to survive and to improve your quality of life. This "endogenous pharmacy" is made up of biochemical pathways described throughout this review that are activated by various social stimuli. Although this evolutionary perspective is only speculative, these issues are worthy of further scrutiny, as they seem likely to lead to fundamental insights into both human biology and therapeutics.

SUMMARY POINTS

1. The placebo effect is the effect that follows the administration of an inert treatment (the placebo), whereas in a placebo-related effect no inert treatment is given.

2. There are many placebo effects with different biological mechanisms that are triggered by the psychosocial context of the therapy.
3. The placebo analgesic effect is mediated by the endogenous opioid systems and antagonized by cholecystokinin in some circumstances.
4. The placebo effect in Parkinson's disease is mediated by dopamine release in the striatum and is associated with neuronal changes in the subthalamic nucleus.
5. In depression, treatment with fluoxetine or a placebo treatment affect similar brain regions.
6. The placebo effect in the immune and endocrine system is primarily a conditioned response, whereby classical conditioning plays a key role.
7. The nocebo hyperalgesic effect, which is opposite to the placebo analgesic effect, is mediated by anxiety-induced activation of cholecystokinin.
8. Because social stimuli may activate the same receptor pathways upon which drugs act, several cognitive and affective factors can modulate the action of drugs.

FUTURE ISSUES

1. We need to know where, when, and how placebos work across different diseases and therapeutic interventions.
2. It would be fruitful to test the effects of pharmacological conditioning on placebo responses for different drug classes, such as immunosuppressive and hormone-stimulating agents.
3. The role and the mechanisms of the placebo effect across different alternative and complementary therapies need to be explored.
4. It is necessary to know the contribution of expectation and conditioning in different types of placebo responses.
5. An unresolved issue is why some subjects respond to placebos, whereas other subjects do not.
6. The social, psychological, neurobiological, and genetic determinants of the different placebo effects need to be identified.

DISCLOSURE STATEMENT

The author is not aware of any biases that might be perceived as affecting the objectivity of this review.

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LITERATURE CITED

1. **Colloca L, Benedetti F. 2005. Placebos and painkillers: Is mind as real as matter? *Nat. Rev. Neurosci.* 6:545–52**
2. Benedetti F, Mayberg HS, Wager TD, Stohler CS, Zubieta JK. 2005. Neurobiological mechanisms of the placebo effect. *J. Neurosci.* 25:10390–402
3. Moerman DE. 2002. *Meaning, Medicine and the Placebo Effect*. Cambridge, MA: Cambridge Univ. Press
4. Di Blasi Z, Harkness E, Ernst E, Georgiou A, Kleijnen J. 2001. Influence of context effects on health outcomes: a systematic review. *Lancet* 357:757–62
5. Hrobjartsson A, Gøtzsche PC. 2001. Is the placebo effect powerless? An analysis of clinical trials comparing placebo with no treatment. *N. Engl. J. Med.* 344:1594–602
6. Hrobjartsson A, Gøtzsche PC. 2004. Is the placebo effect powerless? Update of a systematic review with 52 new randomized trials comparing placebo with no treatment. *J. Int. Med.* 256:91–100
7. Vase L, Riley JL III, Price DD. 2002. A comparison of placebo effects in clinical analgesic trials versus studies of placebo analgesia. *Pain* 99:443–52
8. Kirsch I, ed. 1999. *How Expectancies Shape Experience*. Washington, DC: Am. Psychol. Assoc.
9. Price DD, Milling LS, Kirsch I, Duff A, Montgomery GH, et al. 1999. An analysis of factors that contribute to the magnitude of placebo analgesia in an experimental paradigm. *Pain* 83:147–56
10. **Price DD, Finniss DG, Benedetti F. 2008. A comprehensive review of the placebo effect: recent advances and current thought. *Annu. Rev. Psychol.* 59: In press**
11. Benedetti F, Pollo A, Lopiano L, Lanotte M, Vighetti S, et al. 2003. Conscious expectation and unconscious conditioning in analgesic, motor, and hormonal placebo/nocebo responses. *J. Neurosci.* 23:4315–23
12. **Zubieta JK, Bueller JA, Jackson LR, Scott DJ, Xu Y, et al. 2005. Placebo effects mediated by endogenous opioid activity on μ-opioid receptors. *J. Neurosci.* 25:7754–62**
13. Levine JD, Gordon NC, Fields HL. 1978. The mechanisms of placebo analgesia. *Lancet* 2:654–57
14. Grevert P, Albert LH, Goldstein A. 1983. Partial antagonism of placebo analgesia by naloxone. *Pain* 16:129–43
15. Amanzio M, Benedetti F. 1999. Neuropharmacological dissection of placebo analgesia: expectation-activated opioid systems versus conditioning-activated specific subsystems. *J. Neurosci.* 19:484–94

1. A review on the placebo effect in which the uncertainty principle in pharmacology is described.

10. The most recent review in which the placebo effect is approached primarily from a psychological perspective.

12. The first direct evidence that placebos activate endogenous opioids.

16. Benedetti F, Arduino C, Amanzio M. 1999. Somatotopic activation of opioid systems by target-directed expectations of analgesia. *J. Neurosci.* 9:3639–48
17. Benedetti F. 1996. The opposite effects of the opiate antagonist naloxone and the cholecystokinin antagonist proglumide on placebo analgesia. *Pain* 64:535–43
18. Benedetti F, Amanzio M, Maggi G. 1995. Potentiation of placebo analgesia by proglumide. *Lancet* 346:1231
19. Benedetti F. 1997. Cholecystokinin type-A and type-B receptors and their modulation of opioid analgesia. *News Physiol. Sci.* 12:263–68

20. The first brain imaging study of placebo analgesia.

20. Petrovic P, Kalso E, Petersson KM, Ingvar M. 2002. Placebo and opioid analgesia—imaging a shared neuronal network. *Science* 295:1737–40

21. Wager T, Rilling JK, Smith EE, Sokolik A, Casey KL, et al. 2004. Placebo-induced changes in fMRI in the anticipation and experience of pain. *Science* 303:1162–67
22. Kong J, Gollub RL, Rosman IS, Webb JM, Vangel MG, et al. 2006. Brain activity associated with expectancy-enhanced placebo analgesia as measured by functional magnetic resonance imaging. *J. Neurosci.* 26:381–88
23. Price DD, Craggs J, Verne GN, Perlstein WM, Robinson ME. 2007. Placebo analgesia is accompanied by large reductions in pain-related brain activity in irritable bowel syndrome patients. *Pain* 127:63–72
24. Vase L, Robinson ME, Verne GN, Price DD. 2005. Increased placebo analgesia over time in irritable bowel syndrome (IBS) patients is associated with desire and expectation but not endogenous opioid mechanisms. *Pain* 115:338–47
25. Pollo A, Torre E, Lopiano L, Rizzone M, Lanotte M, et al. 2002. Expectation modulates the response to subthalamic nucleus stimulation in Parkinsonian patients. *NeuroReport* 13:1383–86
26. Mercado R, Constantoyannis C, Mandat T, Kumar A, Schulzer M, et al. 2006. Expectation and the placebo effect in Parkinson's disease patients with subthalamic nucleus deep brain stimulation. *Mov. Disord.* 21:1457–61

27. In this study, the release of dopamine in the striatum is demonstrated for the first time in Parkinson's disease.

27. de la Fuente-Fernandez R, Ruth TJ, Sossi V, Schulzer M, Calne DB, Stoessl AJ. 2001. Expectation and dopamine release: mechanism of the placebo effect in Parkinson's disease. *Science* 293:1164–66

28. Strafella AP, Ko JH, Monchi O. 2006. Therapeutic application of transcranial magnetic stimulation in Parkinson's disease: the contribution of expectation. *Neuroimage* 31:1666–72
29. de la Fuente-Fernandez R, Phillips AG, Zamburlini M, Sossi V, Calne DB, et al. 2002. Dopamine release in human ventral striatum and expectation of reward. *Behav. Brain Res.* 136:359–63

30. This is the first study analyzing the placebo effect at the single-neuron level in Parkinson patients.

30. Benedetti F, Colloca L, Torre E, Lanotte M, Melcarne A, et al. 2004. Placebo-responsive Parkinson patients show decreased activity in single neurons of subthalamic nucleus. *Nat. Neurosci.* 7:587–88

31. Andrews G. 2001. Placebo response in depression: Bane of research, boon to therapy. *Br. J. Psychiatry* 178:192–94
32. Khan A, Warner HA, Brown WA. 2000. Symptom reduction and suicide risk in patients treated with placebo in antidepressant clinical trials: An analysis of the FDA database. *Arch. Gen. Psychiatry* 57:311–17

33. Walsh BT, Seidman SN, Sysko R, Gould M. 2002. Placebo response in studies of major depression: variable, substantial, and growing. *JAMA* 287:1840–47
34. Mayberg HS, Silva AJ, Brannan SK, Tekell JL, Mahurin RK, et al. 2002. The functional neuroanatomy of the placebo effect. *Am. J. Psychiatry* 159:728–37
35. Petrovic P, Dietrich T, Fransson P, Andersson J, Carlsson K, et al. 2005. Placebo in emotional processing-induced expectations of anxiety relief activate a generalized modulatory network. *Neuron* 46:957–69
36. Pollo A, Vighetti S, Rainero I, Benedetti F. 2003. Placebo analgesia and the heart. *Pain* 102:125–33
37. Herrnstein RJ. 1962. Placebo effect in the rat. *Science* 138:677–78
38. Ader R. 1985. Conditioned immunopharmacological effects in animals: Implications for a conditioning model of pharmacotherapy. In *Placebo: Theory, Research, and Mechanisms*, ed. L White, B Tursky, GE Schwartz, pp. 306–23, New York: Guilford Press
39. Ader R. 1997. The role of conditioning in pharmacotherapy. In *The Placebo Effect: An Interdisciplinary Exploration*, ed. A Harrington, pp. 138–65, Cambridge, MA: Harvard Univ.
40. Siegel S. 1985. Drug-anticipatory responses in animals. In *Placebo: Theory, Research, and Mechanisms*, ed. L White, B Tursky, GE Schwartz, pp. 288–305, New York: Guilford Press
41. Siegel S. 2002. Explanatory mechanisms for placebo effects: Pavlovian conditioning. In *The Science of the Placebo: Toward an Interdisciplinary Research Agenda*, ed. HA Guess, A Kleinman, JW Kusek, LW Engel, pp. 133–57, London: BMJ Books
42. Stewart-Williams S, Podd J. 2004. The placebo effect: dissolving the expectancy versus conditioning debate. *Psychol. Bull.* 130:324–40
43. McKenzie JN. 1896. The production of the so-called 'rose-cold' by means of an artificial rose. *Am. J. Med. Sci.* 91:45
44. Ader R, Cohen N. 1982. Behaviorally conditioned immunosuppression and murine systemic lupus erythematosus. *Science* 215:1534–36
45. Ader R, Kelly K, Moynihan JA, Grota LJ, Cohen N. 1993. Conditioned enhancement of antibody production using a antigen as the unconditioned stimulus. *Brain Behav. Immun.* 7:334–43
46. Pacheco-Lopez G, Engler H, Niemi MB, Schedlowski M. 2006. Expectations and associations that heal: Immunomodulatory placebo effects and its neurobiology. *Brain Behav. Immun.* 20:430–46
47. Olness K, Ader R. 1992. Conditioning as an adjunct in the pharmacotherapy of lupus erythematosus. *J. Dev. Behav. Pediatr.* 13:124–25
48. Giang DW, Goodman AD, Schiffer RB, Mattson DH, Petrie M, et al. 1996. Conditioning of cyclophosphamide-induced leukopenia in humans. *J. Neuropsychiatry Clin. Neurosci.* 8:194–201
49. Goebel MU, Trebst AE, Steiner J, Xie YF, Exton MS, et al. 2002. Behavioral conditioning of immunosuppression is possible in humans. *FASEB J.* 16:1869–73
50. Benedetti F, Amanzio M, Baldi S, Casadio C, Maggi G. 1999. Inducing placebo respiratory depressant responses in humans via opioid receptors. *Eur. J. Neurosci.* 11:625–31

46. This review is particularly devoted to behavioral conditioning and placebo responses in the immune system.

51. Benedetti F, Colloca L. 2004. Placebo-induced analgesia: methodology, neurobiology, clinical use, and ethics. *Rev. Analg.* 7:129–43
52. Benedetti F, Amanzio M, Casadio C, Oliaro A, Maggi G. 1997. Blockade of nocebo hyperalgesia by the cholecystokinin antagonist proglumide. *Pain* 71:135–40
53. Benedetti F, Amanzio M. 1997. The neurobiology of placebo analgesia: from endogenous opioids to cholecystokinin. *Prog. Neurobiol.* 52:109–25
54. Benedetti F, Amanzio M, Vighetti S, Asteggiano G. 2006. The biochemical and neuroendocrine bases of the hyperalgesic nocebo effect. *J. Neurosci.* 26:12014–22
55. Andre J, Zeau B, Pohl M, Cesselin F, Benoliel J-J, Becker C. 2005. Involvement of cholecystokininergic systems in anxiety-induced hyperalgesia in male rats: Behavioral and biochemical studies. *J. Neurosci.* 25:7896–904
56. Hebb ALO, Poulin J-F, Roach SP, Zacharko RM, Drolet G. 2005. Cholecystokinin and endogenous opioid peptides: Interactive influence on pain, cognition, and emotion. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* 29:1225–38
57. Benedetti F, Lanotte M, Lopiano L, Colloca L. 2007. When words are painful—unraveling the mechanisms of the nocebo effect. *Neuroscience*. In press
58. Mitchell JM, Lowe D, Fields HL. 1998. The contribution of the rostral ventromedial medulla to the antinociceptive effects of systemic morphine in restrained and unrestrained rats. *Neuroscience* 87:123–33
59. Heinricher MM, McGaraughty S, Tortorici V. 2001. Circuitry underlying antipioid actions of cholecystokinin within the rostral ventromedial medulla. *J. Neurophysiol.* 85:280–86
60. Heinricher MM, Neubert MJ. 2004. Neural basis for the hyperalgesic action of cholecystokinin in the rostral ventromedial medulla. *J. Neurophysiol.* 92:1982–89
61. Chua P, Krams M, Toni I, Passingham R, Dolan R. 1999. A functional anatomy of anticipatory anxiety. *Neuroimage* 9:563–71
62. Ploghaus A, Tracey I, Gati JS, Clare S, Menon RS, et al. 1999. Dissociating pain from its anticipation in the human brain. *Science* 284:1979–81
63. Sawamoto N, Honda M, Okada T, Hanakawa T, Kanda M, et al. 2000. Expectation of pain enhances responses to nonpainful somatosensory stimulation in the anterior cingulated cortex and parietal operculum/posterior insula: An event-related functional magnetic resonance imaging study. *J. Neurosci.* 20:7438–45
64. Porro CA, Cettolo V, Francescato MP, Baraldi P. 2003. Functional activity mapping of the mesial hemispheric wall during anticipation of pain. *Neuroimage* 19:1738–47
65. Koyama T, McHaffie JG, Laurienti PJ, Coghill RC. 2005. The subjective experience of pain: Where expectations become reality. *Proc. Natl. Acad. Sci. USA* 102:12950–55
66. Lorenz J, Hauck M, Paur RC, Nakamura Y, Zimmermann R, et al. 2005. Cortical correlates of false expectations during pain intensity judgments—a possible manifestation of placebo/nocebo cognitions. *Brain Behav. Immun.* 19:283–95

54. The CCKergic link between anxiety and hyperalgesia is demonstrated in relation to the nocebo effect.

67. Keltner JR, Furst A, Fan C, Redfern R, Inglis B, Fields HL. 2006. Isolating the modulatory effect of expectation on pain transmission: a functional magnetic resonance imaging study. *J. Neurosci.* 26:4437–43
68. Frith C, Dolan RJ. 1997. Brain mechanisms associated with top-down processes in perception. *Philos. Trans. R. Soc. London B Biol. Sci.* 352:1221–30
69. Mesulam MM. 1998. From sensation to cognition. *Brain* 121:1013–52
70. Pessoa L, Kastner S, Ungerleider LG. 2003. Neuroimaging studies of attention: From modulation of sensory processing to top-down control. *J. Neurosci.* 23:3990–98
71. Nitschke JB, Dixon GE, Sarinopoulos I, Short SJ, Cohen JD, et al. 2006. Altering expectancy dampens neural response to aversive taste in primary taste cortex. *Nat. Neurosci.* 9:435–42
72. Colloca L, Lopiano L, Lanotte M, Benedetti F. 2004. Overt versus covert treatment for pain, anxiety and Parkinson's disease. *Lancet Neurol.* 3:679–84
73. Amanzio M, Pollo A, Maggi G, Benedetti F. 2001. Response variability to analgesics: A role for nonspecific activation of endogenous opioids. *Pain* 90:205–15
74. Price DD. 2001. Assessing placebo effects without placebo groups: An untapped possibility? *Pain* 90:201–3
75. Levine JD, Gordon NC, Smith R, Fields HL. 1981. Analgesic responses to morphine and placebo in individuals with postoperative pain. *Pain* 10:379–89
76. Levine JD, Gordon NC. 1984. Influence of the method of drug administration on analgesic response. *Nature* 312:755– *56*
77. Benedetti F, Maggi G, Lopiano L, Lanotte M, Rainero I, et al. 2003. Open versus hidden medical treatments: The patient's knowledge about a therapy affects the therapy outcome. *Prev. Treat.* 6(1)
78. Benedetti F, Colloca L, Lanotte M, Bergamasco B, Torre E, Lopiano L. 2004. Autonomic and emotional responses to open and hidden stimulations of the human subthalamic region. *Brain Res. Bull.* 63:203–11
79. Lanotte M, Lopiano L, Torre E, Bergamasco B, Colloca L, Benedetti F. 2005. Expectation enhances autonomic responses to stimulation of the human subthalamic limbic region. *Brain Behav. Immun.* 19:500–9
80. Volkow ND, Wang G-J, Ma Y, Fowler JS, Zhu W, et al. 2003. Expectation enhances the regional brain metabolic and the reinforcing effects of stimulants in cocaine abusers. *J. Neurosci.* 23:11461–68
81. Bausell RB, Lao L, Bergman S, Lee WL, Berman BM. 2005. Is acupuncture analgesia an expectancy effect? Preliminary evidence based on participants' perceived assignments in two placebo-controlled trials. *Eval. Health Prof.* 28:9–26
82. Linde K, Witt CM, Streng A, Weidenhammer W, Wagenpfeil S, et al. 2007. The impact of patient expectations on outcomes in four randomised controlled trials of acupuncture in patients with chronic pain. *Pain* 128:264–71
83. McRae C, Cherin E, Yamazaki G, Diem G, Vo AH, et al. 2004. Effects of perceived treatment on quality of life and medical outcomes in a double-blind placebo surgery trial. *Arch. Gen. Psychiatry* 61:412–20

72. This paper reviews all the studies comparing open versus hidden administrations of different treatments.

84. Dar R, Stronguin F, Etter JF. 2005. Assigned versus perceived placebo effects in nicotine replacement therapy for smoking reduction in Swiss smokers. *J. Consult. Clin. Psychol.* 73:350–53
85. Scott DS, Srohler CS, Egnatvk CM, Wang H, Koeppe RA, et al. 2007. Individual differences in reward responding explain placebo-induced expectations and effects. *Neuron* 55:325–36
86. Beecher HK. 1955. The powerful placebo. *JAMA* 159:1602–6

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