Physiol Rev 93: 1207–1246, 2013
doi:10.1152/physrev.00043.2012

PLACEBO AND THE NEW PHYSIOLOGY OF THE DOCTOR-PATIENT RELATIONSHIP

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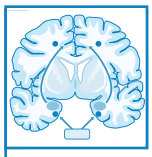

Benedetti, Fabrizio. Placebo and the New Physiology of the Doctor-Patient Relationship. *Physiol Rev* 93: 1207–1246, 2013; doi:10.1152/physrev.00043.2012.—Modern medicine has progressed in parallel with the advancement of biochemistry, anatomy, and physiology. By using the tools of modern medicine, the physician today can treat and prevent a number of diseases through pharmacology, genetics, and physical interventions. Besides this materia medica, the patient's mind, cognitions, and emotions play a central part as well in any therapeutic outcome, as investigated by disciplines such as psychoneuroendocrinoimmunology. This review describes recent findings that give scientific evidence to the old tenet that patients must be both cured and cared for. In fact, we are today in a good position to investigate complex psychological factors, like placebo effects and the doctor-patient relationship, by using a physiological and neuroscientific approach. These intricate psychological factors can be approached through biochemistry, anatomy, and physiology, thus eliminating the old dichotomy between biology and psychology. This is both a biomedical and a philosophical enterprise that is changing the way we approach and interpret medicine and human biology. In the first case, curing the disease only is not sufficient, and care of the patient is of tantamount importance. In the second case, the philosophical debate about the mind-body interaction can find some important answers in the study of placebo effects. Therefore, maybe paradoxically, the placebo effect and the doctor-patient relationship can be approached by using the same biochemical, cellular and physiological tools of the materia medica, which represents an epochal transition from general concepts such as suggestibility and power of mind to a true physiology of the doctor-patient interaction.

I. WHAT IS A PLACEBO RESPONSE?

A. Placebos Were Introduced to Validate the Efficacy of Medical Treatments

Ancient physicians have always used bizarre and odd treatments to cure their patients, with scarce, if any, knowledge of anatomy and physiology. As the anatomical and physiological details of both the animal and the human body started emerging, the need of a scientific explanation of many medical treatments became an imperative objective of physicians and the scientific community. An important historical period whereby scientific skepticism emerged about the efficacy of some medical remedies is approximately in the second half of 1700 and involved treatments like mesmerism, perkinism, and homeopathy (178).

To take mesmerism as an example, this was introduced in the second half of 1700 by Franz Anton Mesmer, who claimed to have discovered a healing fluid which he called animal magnetism. To assess the very nature and the efficacy of mesmerism in treating many diseases and symptoms, Louis XVI appointed a commission that was headed by Benjamin Franklin. This commission performed what can be considered one of the first blind assessments and sham (placebo) interventions in the history of medicine. Some women were blindfolded and asked where the mesmeric energy was being applied. As reported by the members of the commission themselves, "while the woman was permitted to see the operation, she placed her sensations precisely in the part towards which it was directed; that on the other hand, when she did not see the operation, she placed them at hazard, and in parts very distant from those which were the object of magnetism. It was natural to conclude that these sensations, real or pretended, were determined by the imagination" (133, 178). Real mesmerism was found to work as well as sham mesmerism in a subsequent series of experiments, thus leading to the conclusion that the mesmeric fluid had no existence and any effect was attributable to imagination.

In the same period, Elisha Perkins introduced perkinism, a kind of healing procedure whereby two metal rods were

supposed to conduct pathogenic fluid away from the body. As done with mesmerism, one of the first sham (placebo) devices in the history of medicine was devised by replacing the two metal rods with two sham wooden rods. Again, it was found that both the metal and the wooden rods had the same probability to induce clinical improvement (160, 178), which indicates that the metal rods had no specific therapeutic effects. Likewise, to test the efficacy of homeopathy, a novel therapeutic approach introduced by Samuel Hahnemann, whereby the belief was that a disease can be cured by very small amounts of the same substances that cause it, in the first half of 1800, bread pills (placebo) were used by informing the patients that they were a homeopathic treatment (323, 178). A positive effect of bread pills was found, and this was attributed to the natural course of disease and to imagination.

Many experiments and assessments of this kind were performed in the following years, and they were refined more and more over time. Physicians became aware that the outcome of many therapies was nothing more than spontaneous remission or imagination, and they realized that rigorous trials were necessary to validate the efficacy of a medicament. The use of the word "placebo" (which in Latin means "I shall please") in clinical research emerged gradually over time to indicate a control group that receives a sham treatment, as was done with sham mesmerism, sham rods in perkinism, and sham homeopathy. Therefore, the word *sham* was gradually replaced with the word *placebo*. Another important point that was crucial for the modern use of placebos in clinical trials was the emerging awareness that even physicians and clinical investigators were susceptible to imagination and biases. This led to the use of the double-blind design, in which neither the investigator nor the patient knew the nature of the tested therapy (it could be either real or sham).

With these elements in their hands, modern clinical investigators use the randomized double-blind placebo-controlled trial, which represents today the tenet of clinical research for the validation of a therapy. It contains most of the elements that are necessary to control for suggestion, imagination, and biases of both patient and investigator, and to control for other confounding factors such as the spontaneous fluctuations of diseases and symptoms.

B. Today the Placebo Effect, or Response, Is an Excellent Model to Understand How the Brain Works

Not only have placebos been used for the validation of therapies, but they have also traditionally taken as an example of the powerful interaction between mind and body. For example, in mesmerism and perkinism, the main conclusion was that imagination played a major role in the therapeutic outcome, thus emphasizing the important role of mind in the modulation of a number of physiological functions. Following this psychological perspective of the placebo phenomenon, the placebo concept has permeated the psychology literature for many years (76, 156, 292, 293 340).

Today placebo researchers tend to use the terms *placebo effect* and *placebo response* interchangeably. Accordingly, throughout this article I use these two terms as synonyms. In the course of the years, several factors have been considered to be important in the placebo effect. For example, many elements are at work during a placebo response, such as the relationship between the doctor and his patient, the patient's expectations and needs, the patient's personality and psychological state, the severity and discomfort of the symptoms, the type of verbal instructions, the preparation characteristics, and the environmental milieu (281).

The importance of the mind-body interaction in the placebo effect clearly emerges in the definition by Brody (76), who defines the placebo effect as a change in the body, or the body-mind unit, that occurs as a result of the symbolic significance which one attributes to an event or object in the healing environment. It is important to emphasize that the psychological conceptualization of the placebo has been very important in drawing our attention on what is really important (the meaning and the symbols of the healing environment), and deflecting it from what is not (the inert medical treatments) (239, 240). Therefore, whereas in the clinical trial setting the conceptualization of placebo focuses on distal and external factors, such as inert treatments and inert substances, in the context of psychology the concept of placebo focalizes on proximal, and internal, factors, like symbolic representation and mind-body relationship (269).

The merits of the psychological conceptualization of the placebo effect as a mind-body phenomenon reside in the fact that it makes us understand that the placebo effect is due to the psychosocial context around the patient and the therapy. When a placebo (sham treatment), e.g., an inert substance like water, is administered, what matters is not the water, of course, but its symbolic significance, which can be attached to practically anything (76). In this sense, the concept of placebo has shifted from the "inert" content of the placebo agent to the concept of a simulation of an active therapy within a psychosocial context.

On the basis of these considerations, when a treatment is given to a patient, be it sham or real, it is not administered in a vacuum, but in a complex set of psychological states that vary from patient to patient and from situation to situation. For example, when a placebo is given to relieve pain, it is administered along with a complex set of psychosocial stimuli which tell the patient that a clinical improvement should be occurring shortly **(FIGURE 1)**. These psycho-

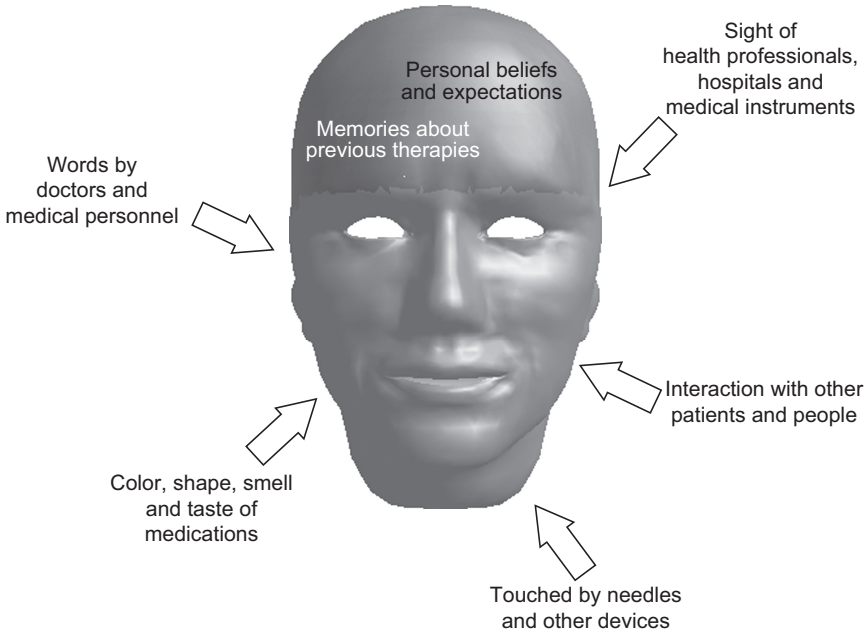

FIGURE 1. The psychosocial context around the patient and the therapy. When a medical treatment is administered, several sensory and social stimuli, as well as personal beliefs and memories, tell the patient that a therapy is being performed. The whole context constitutes the ritual of the therapeutic act, which is at the very heart of placebo and nocebo responses.

social stimuli represent the context around the therapy and the patient, and such a context may be as important as the specific effect of a drug. The contextual factors that might affect the therapeutic outcome can be represented by the characteristics of the treatment (color and shape of a pill), the patient's and provider's characteristics (treatment and illness beliefs, status, sex), the patient-provider relationship (suggestion, reassurance, and compassion), the healthcare setting (home or hospital, and room layout) (103). Thus the context is made up of anything which surrounds the patient under treatment, like doctors, nurses, hospitals, syringes, pills, and machines **(FIGURE 1)**, but certainly doctors, nurses, and health professionals represent a very important component of the context, as they can transmit a lot of information to the patient through their words, attitudes, and behaviors (41). Balint (27) called this context the whole atmosphere around the treatment.

This line of reasoning paved the way for the neuroscientific investigation of the placebo response. Starting from the first biological investigations of the placebo effect, for example, in the early 1960s in animals (169) and in the late 1970s in humans (212), today placebo research is a complex field of investigation which ranges from psychology to psychophysiology, from pharmacology to neurophysiology, and from cellular/molecular analysis to modern neuroimaging techniques.

What neuroscientists have learned from the psychological and social approach is that placebos are not inert substances. Instead, they are constituted of different words and therapeutic rituals as well as of different symbolic elements which, in turn, can influence the patient's brain; thus they are amenable to classic neuroscientific investigation. Neuroscientists use the placebo response as a model to understand how our brain works, and indeed, it is emerging as an excellent approach to understand several higher brain functions, such as expectation and reward. The placebo response is today a melting pot of ideas for neuroscience. In fact, there is not a single but many placebo effects, and there is not a single but many mechanisms across different conditions and interventions (43, 44, 119). In fact, sometimes anxiety mechanisms are involved, whereas reward mechanisms are involved in other circumstances. Likewise, different types of learning and genetic variants may be important.

C. Appropriate Controls Are Necessary to Rule Out Other Phenomena

Not all improvements observed after placebo administration are attributable to real psychobiological phenomena. In fact, many improvements can be due to different factors, such as the natural history of the disease, regression to the mean, biases by experimenters and patients, as well as unidentified cointerventions **(FIGURE 2)**. Therefore, the placebo effect is approached differently by the clinical trialist and the neuroscientist, because the former is not interested in the cause of the improvement following the administration of the inert substance, whereas the latter is interested only in the psychobiological factors that lead to the improvement.

In pragmatic clinical trials, the trialist only needs to establish whether the true treatment is better than a placebo, regardless

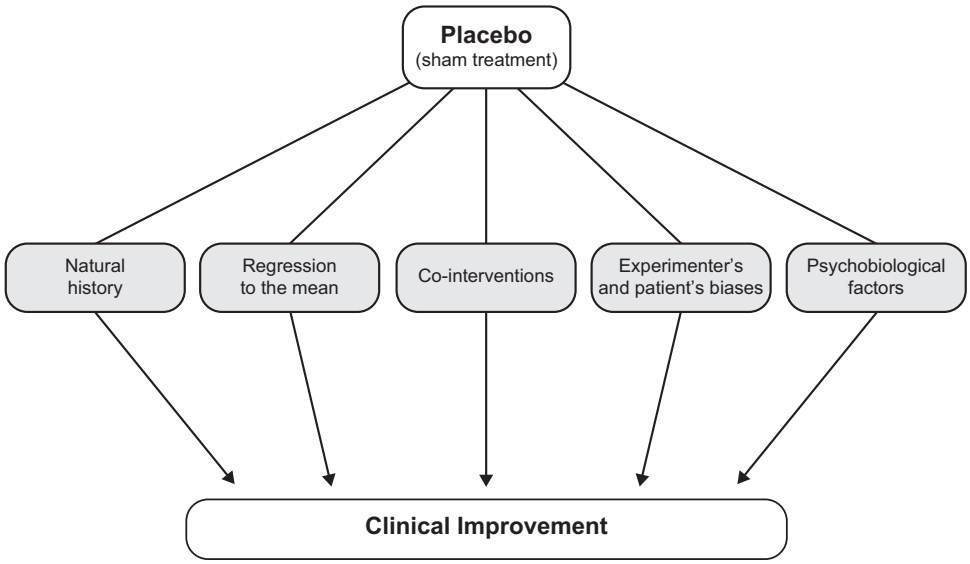

FIGURE 2. The clinical improvement that may be observed after placebo administration is due to many factors. The real placebo response is attributable only to the psychobiological factors, namely, to psychological and physiological changes in the patient's brain.

of the causes behind the placebo improvement. Although this pragmatic approach is useful in clinical trials, if one is interested in the mechanisms of the real psychobiological placebo effect, it is necessary to separate it from other phenomena such as spontaneous remission, regression to the mean, biases (43, 44). For example, spontaneous remission is frequently and erroneously defined placebo effect. In fact, in many chronic conditions there is a spontaneous variation in symptom intensity that is known as natural history (128). If a subject takes a placebo just before his symptom starts decreasing, one may believe that the placebo is effective, although that decrease would have occurred anyway. Clearly, this is not a placebo effect but a misinterpretation of the cause-effect relationship. To avoid this mistake, the natural history must be compared with a placebo treatment and an active treatment. Whereas the difference between the natural history and the placebo treatment represents the real psychological placebo component of the therapy, the difference between the placebo treatment and the active treatment represents the specific component of the therapy.

Similarly, regression to the mean is a statistical phenomenon that is often misinterpreted as a psychological placebo response. It assumes that individuals tend to have extreme values of a physiological parameter, e.g., glucose, when enrolled in a clinical trial, and then these extreme values tend to be lower at a second measurement (97). In this case also, the improvement cannot be attributed to any intervention they might have undergone. An important factor in the regression to the mean phenomenon is represented by the inclusion criteria in a clinical trial, which are often represented by extreme physiological values.

Signal detection ambiguity can sometimes explain symptom reduction. In fact, according to the signal detection theory, a false-positive error made by either the patient or the physician may explain the illusory improvement occurring in some circumstances (12, 86). Likewise, sometimes patients and doctors give biased reports of the clinical condition. For example, there is some evidence that patients often want to please doctors for their time and effort to help them so that some exaggeration of their feelings of clinical improvement may be reported (184). This can be overcome by using objective measurements, such as electrophysiological responses or blood markers. Finally, cointerventions can sometimes be the cause of improvement. For example, an unidentified concomitant diet may be responsible for the clinical improvement during a placebo treatment.

For all these reasons, classical clinical trials are not good for understanding the mechanisms of real psychological placebo effects, for all these phenomena are present in a clinical trial. As the context surrounding the patient and the therapy is the crucial factor in placebo responsiveness, and psychological factors are at the core of its magnitude, we should not be surprised that placebo effects in clinical trials are highly variable. Again, this emphasizes the usefulness of the neuroscientific approach in the laboratory setting to clarify the biology of different placebo responses, for in the laboratory it is possible to manipulate the context and the patient's psychological state under strictly controlled conditions.

D. The Nocebo Effect Is the Opposite of the Placebo Effect

Nocebos are opposite to placebo phenomena, for they involve the pathogenic effects of imagination and negative expectations. Nocebo phenomena were first described

within an anthropological context in tribal societies, and taken as a good example of the power of mind. For example, in some aboriginal people of Australia, pointing a bone at someone may lead to negative outcomes, and in Latin America and Africa, voodoo death has sometimes been related to the belief of being bewitched (79). It should be emphasized that many of these phenomena are anecdotal (215); nonetheless, they can be explained as a stress-induced activation of the sympathetic nervous system (79). Some anthropologists go further by proposing a sociocultural model of illness and healing, whereby placebos and nocebos are crucially involved (152, 153).

Nocebo phenomena and the impact of negative expectations and imagination are not limited to the past and to tribal societies, but they are also present in western societies. For example, many side effects both in clinical trials and in clinical practice are psychological, and many health warnings by the media may induce negative expectations and negative outcomes (18, 244, 277). Similarly, anticipatory nausea and vomiting in cancer chemotherapy, the negative effects of negative diagnoses, and patients' distrust towards conventional medicine, all represent examples of nocebo and nocebo-like phenomena in western societies (159, 309)

The term *nocebo* (Latin "I shall harm") was introduced to describe the negative effects of placebos (259). However, it is important to stress that in modern terminology true nocebo effects are considered as the result of negative expectations. This conceptualization of nocebo effects is particularly useful from a neuroscientific perspective, because nocebo administration induces negative expectations and these, in turn, are anxiogenic. In other words, a nocebo is a stressor. Therefore, the nocebo response is a good model to understand anxiety, particularly anticipatory anxiety.

Not surprisingly, our knowledge about the mechanisms of the nocebo response still lags behind the more detailed understanding of the placebo counterpart, mainly due to ethical constraints. Inducing negative expectations and inflicting pain is certainly unethical; thus many studies are carried out on healthy volunteers rather than on patients, and negative expectations are triggered without actual administration of any substance (61, 90).

II. WHAT IS THE DOCTOR-PATIENT RELATIONSHIP?

Different disciplines have approached the doctor-patient relationship, often also labeled patient-provider interaction or therapist-patient encounter, from different perspectives, including psychology, sociology, philosophy, and health policy. What has emerged in the course of the years is that not only should health professionals learn technical skills, but they also should develop appropriate social skills to better interact and communicate with their patients. With the recent advances of neuroscience, today we are in a better position to approach the doctor-patient relationship from a biological perspective and to consider it as a special type of social interaction. Indeed, this new biological approach is quite interesting because the neurosciences are interested in understanding how brains work, and this special social encounter may uncover the mechanisms of higher brain functions, such as expectations, beliefs, trust, hope, empathy, and compassion. In addition, since any biological system is a product of evolution which has emerged in animals and humans with a precise purpose, an evolutionary understanding of why and how these social mechanisms have emerged and evolved is of paramount importance, for they give us insights into the relationship between the first social interactions in non-human primates and early hominids and subsequent medical care.

A. The Doctor-Patient Relationship Has Emerged During Evolution as a Unique Social Interaction

Many simple behavioral repertoires are aimed at protecting the body from possible damage. For example, the withdrawal reflex and the scratch reflex protect from threatening stimuli, and they are present in both invertebrates and vertebrates, including humans. However, from an evolutionary perspective, the two reflexes differ for at least one important aspect. In fact, the scratch reflex is particularly interesting because, differently from the withdrawal reflex, the movement is aimed at targeting the potential noxious stimulus and at removing it from the body. This represents an important evolutionary step toward the more complex behavior of grooming, which involves behaviors such as scratching, licking, preening, rubbing, nibbling, and wallowing (46). Interestingly, whereas the scratch reflex is triggered by cutaneous stimuli, such as a bug's bite, grooming is a self-directed behavior that does not require the peripheral stimulation of the skin, for its biological function is the care of the body surface (49, 304). The more complex function of grooming is also evidenced by the involvement of supraspinal centers, whilst the scratch reflex only requires the spinal cord. The evolutionary step from the peripherally driven scratch reflex to the centrally driven grooming behavior shows how the nervous system developed from a simple reflex act to a complex motor pattern for the care of the whole body surface.

But the big evolutionary jump to social behavior is represented by allogrooming, i.e., taking care of the skin of others. In fact, not only do animals scratch, rub, and lick themselves, but they scratch and rub their companions as well. Social grooming has a function in the regulation of social relationships, and it is not only involved in the care of body surface (304). Individuals who are virtually free of parasites still solicit for and submit themselves to being groomed.

Allogrooming time correlates with social group size, which suggests that it has to do with intense social relationships (109). In contrast to scratch reflexes and self-grooming, which require neuronal circuits in the spinal cord and in the brain stem, respectively, allogrooming is related to the cerebral cortex.

Two actors take part in social grooming: the one being groomed and the groomer. Whereas the former benefits from it in a number of ways, such as the pleasure, relaxation, and hygiene induced by touch, it is less clear what the benefits are for the latter. Since there are no immediate benefits to the groomer, for he spends energies and time to the advantage of others, the act of grooming can be considered an early form of altruistic behavior such as reciprocal altruism. In fact, the roles of the groomer and the groomee are related, because any individual can be either a groomer or a groomee. Therefore, if there is no immediate advantage to the groomer, the service can be returned by the one who is being groomed. Reciprocal altruism explains cases of altruism among nonkin organisms (322).

From social grooming, prosocial behavior in early hominids evolved in a number of ways. One of these was the care of the weak, the sick, the elderly and, more in general, the individual who needs help. For example, to survive in harsh conditions, it was crucial for our ancestors to obtain a daily nutritious diet of meat and other food. However, this daily provision was not guaranteed, because of the high variability of hunting success. Although the first altruistic exchanges were likely to occur among relatives, thus boosting kin selection, subsequently further food exchanges occurred with nonkin that were less lucky on that particular hunting day. According to the reciprocal altruism mechanism, these nonkin recipients eventually returned this favor (326).

There are many examples of early forms of compassion, such as a toothless skull dating back 1.7 million years that was found in the site of Dmanisi in the Eurasian Republic of Georgia, suggesting that companions might have helped him in finding soft plant food and hammering raw meat with stone tools (222). Similarly, Neanderthal men have been found to show signs of compassion towards their companions, dating back to about 60,000 years ago. For example, the analysis of undeveloped bone structure indicates that a man at Shanidar caves was a severe cripple from birth. His right upper limb was entirely useless and extensive bone scar tissue indicated that he was blind in his left eye. These extensive lesions suggest that he was apparently cared for by his companions until his death at age 40, which represents a very old age by Neanderthal standards (343).

Although in early hominids these altruistic acts were adopted by different members of the group, in the course of evolution a single member of the group assumed the role of the person who takes care of the sick, namely, the shaman. Prehistoric shamanism represents the first example of medical care, which is characterized by a good relationship between the sick and the shaman. The sick trusts the shaman and believes in his therapeutic capabilities; thus he refers to him for any psychological, spiritual, or physical discomfort. In this way, the shaman acquired a more and more central role and a higher social status in any social group across different cultures. While shamanistic procedures are mainly based on religious beliefs and the supernatural origin of diseases, several rational treatments emerged over the centuries. For example, a broken arm or leg was covered in river clay or mud and the cast allowed to dry hard in the sun, animal skin was used for bandages, and surgical procedures, such as skull trepanning, were carried out. The transition from shamans to modern doctors is recent and depended on the emergence of modern scientific methodology.

B. Four Different Steps Can Be Identified

The advantage to approach the doctor-patient relationship from an evolutionary perspective consists of considering this special interaction as a social/biological characteristic of mankind. It has evolved from grooming to social grooming, and hence to the emotional concern for the sick. Since some biological mechanisms of self-grooming and social grooming are partially understood, it is natural to broaden our biological knowledge to more complex forms of social interaction, such as the interaction between the healer and his patient. From a physiological and neuroscientific perspective, the whole process of the doctor-patient encounter can be subdivided into at least four steps (46) **(FIGURE 3)**.

The first is the step of "feeling sick," a crucial starting point that triggers the subsequent behavior. Physiology and neuroscience have a lot to say about feeling sick, for it involves sensory systems that convey different pieces of information related to peripheral organs and apparatuses, as well as brain regions that lead to conscious awareness. For example, the perception of a symptom such as pain is the product of bottom-up processes taking place in the peripheral and central nervous system and of top-down modulation from cognitive/evaluative and emotional/motivational brain areas. The second step is what makes a patient "seek relief," a kind of motivated behavior that is aimed at suppressing discomfort. This behavioral repertoire is not different from that aimed at suppressing hunger or thirst, and the brain reward mechanisms are crucial in this regard. These first two steps are the key elements that lead the patient to look for a healer/doctor who himself represents a powerful reward (46).

The third step is when the patient "meets the therapist," a special and unique social interaction in which the therapist represents the means to suppress discomfort. Here

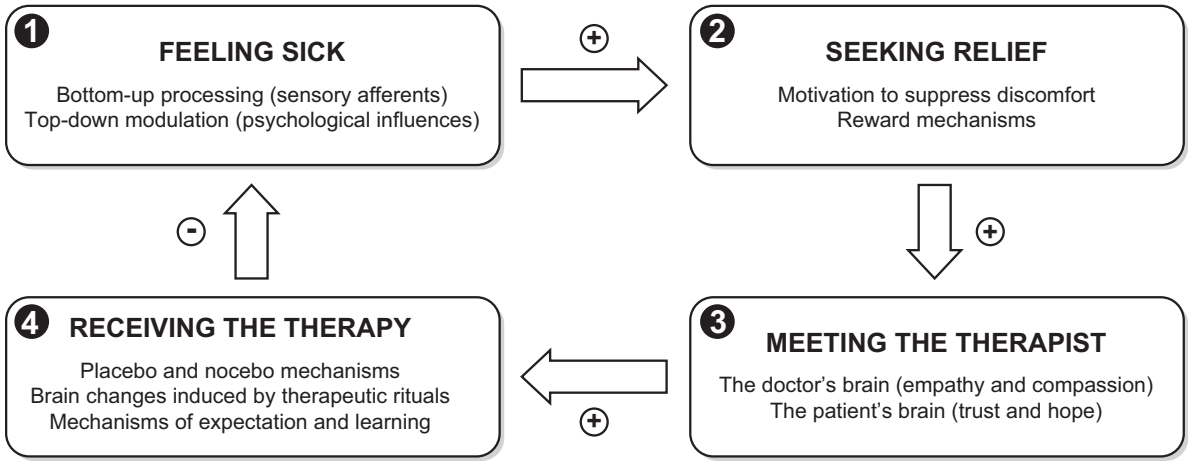

FIGURE 3. The four steps of the doctor-patient relationship. The interaction between the healer/therapist and his patient can be envisaged as a homeostatic system in which the variable to be controlled is represented by the feeling of sickness (symptoms). The very act of administering a treatment is a psychological and social event that is sometimes capable of inhibiting a symptom such as pain, even though the treatment is fake.

many intricate mechanisms are at work, such as trust and hope on the one hand and empathy and compassion on the other. Physiology and neuroscience are beginning to understand these complex functions both in the patient's brain, where expectations, beliefs, trust, and hope are key elements, and in the doctor's brain, in which empathic and compassionate behavior represents an essential factor. Finally, the fourth step is when the patient "receives the therapy," the final and perhaps the most important act of the doctor-patient interaction. The mere ritual of the therapeutic act may generate therapeutic responses through the patient's expectations and beliefs (placebo responses), which sometimes may be as powerful as those generated by real medical treatments. Today, these placebo responses can be approached from a biological perspective, whereby the biochemical, anatomical, and physiological link between expectation and therapeutic effect has been partially unraveled.

It can be seen in **FIGURE 3** that these four steps can be conceived as a homeostatic system in all respects. The feeling of sickness is the variable to be controlled. It tells a motivational system to seek relief. This is aimed at adopting the appropriate behavioral repertoire to eliminate the feeling of sickness. In a social group, such a behavioral repertoire is represented by the social contact with the healer, whose role is to administer a relieving treatment. It is crucial to understand that this system is always at work, regardless of whether the healer administers effective or ineffective therapies. Even if the therapy is totally ineffective, the patient's expectation of benefit (the placebo response) may be sufficient to inhibit discomfort. The real difference between shamans and modern doctors is that, whereas shamanic procedures are likely to lack specific effects completely, at least in most circumstances, modern doctors rely on effective procedures and medications with specific mechanisms of action. But this social-neural system is always there, as an ancestral system which is ready to come out, both with shamans and with modern doctors.

C. What Is the Link Between Placebo and Doctor-Patient Relationship?

If we look at **FIGURES 1 AND 3**, the link between placebo and doctor-patient interaction appears straightforward. The main element in the psychosocial context around the patient that leads to the placebo response is the doctor, and more in general the health professional. Indeed, any element in **FIGURE 1** is related to the figure of the doctor, who uses communication, words, and medical instruments and administers pills, injections, and medications (41, 67). Likewise, the behavioral repertoire that is adopted by the patient in **FIGURE 3** is aimed at looking for a doctor, who represents the means for relieving discomfort. Therefore, it is not surprising that a crucial element that triggers the placebo response comes from the very special social encounter between the patient and his doctor. In **FIGURE 3,** the crucial steps that need to be analyzed in depth are the third (meeting the therapist) and the fourth (receiving the therapy). It is here that a new physiology of the doctor-patient relationship and placebo does emerge. Meeting the doctor involves plenty of mechanisms in the patient's brain that are responsible for expectations, trust, and hope. Similarly, many mechanisms are at work in the doctor's brain, such as empathy and compassion. In turn, these lead to the final step of receiving the therapy which, regardless of its effectiveness or ineffectiveness, triggers placebo responses. The physiological underpinnings of the third and fourth steps of **FIGURE 3** are described in depth in the next sections.

III. NEUROPHYSIOLOGICAL MECHANISMS INVOLVED IN THE INTERACTION BETWEEN DOCTOR AND PATIENT

A. Exploring the Healer's and the Doctor's Brain

As the main components of the psychosocial context around the patient, the doctor's words, attitudes, and behaviors play a major role in the doctor-patient interaction and in the placebo responses. As briefly described above, altruism, empathy, and compassionate behavior emerged in mankind during the course of evolution, and the shaman assumed the role of caregiver. It is interesting to note that facial expressions are likely to have evolved for eliciting medical attention from others (345). A greater facial expression of pain in the presence of potential caregivers than in their absence is of primary importance, so that the presence of potential caregivers would prompt the release of suppression of pain facial expressions. This, in turn, triggers the caregiver's empathic and compassionate behavior. The social connection between the suffering patient, who expresses his discomfort, and the empathic doctor is at the very heart of the doctor-patient relationship. Empathy thus refers to an intersubjective process through which the cognitive and emotional experiences of another come to be shared, without losing sight of the original source of the experience (102). It is important to note that empathy is distinguished from compassion (32, 117, 161). Empathy is not necessarily linked to prosocial motivation, namely, the concern about the others' well being. In contrast, prosocial motivation is involved in compassion. In fact, compassion enables individuals to enter into and maintain relationships of caring and tends to motivate us to help people who are emotionally suffering. In the next sections, empathy and compassion will be treated separately, for different neural systems are involved in these behaviors.

1. *There are two different neural systems for empathy*

Experimental evidence suggests that there are at least two mechanisms of empathy: emotional contagion and cognitive perspective-taking (101). Whereas the former is thought to support our ability to empathize emotionally, i.e., to share the other person's emotional feelings ("I feel what you feel"), the latter involves complex cognitive components, whereby one infers the state of the other person ("I understand what you feel"), also known as theory of mind (266), or mentalizing (136), or mindreading (29).

Several studies suggest that understanding others on the basis of cognitive perspective taking and emotional contagion recruits different neural networks (161). **FIGURE 4** shows the two main systems that mediate empathic emotional ability on the one hand (light blue) and cognitive perspective taking on the other (blue). Whereas cognitive perspective taking activates the medial prefrontal regions, the superior temporal sulcus, the temporal pole, and the temporo-parietal junction (135, 283), empathizing with another person has been found to activate somatosensory and insular cortices as well as the anterior cingulate cortex (161). In a study by Singer et al. (296), the bilateral anterior insula and the rostral anterior cingulate cortex were acti-

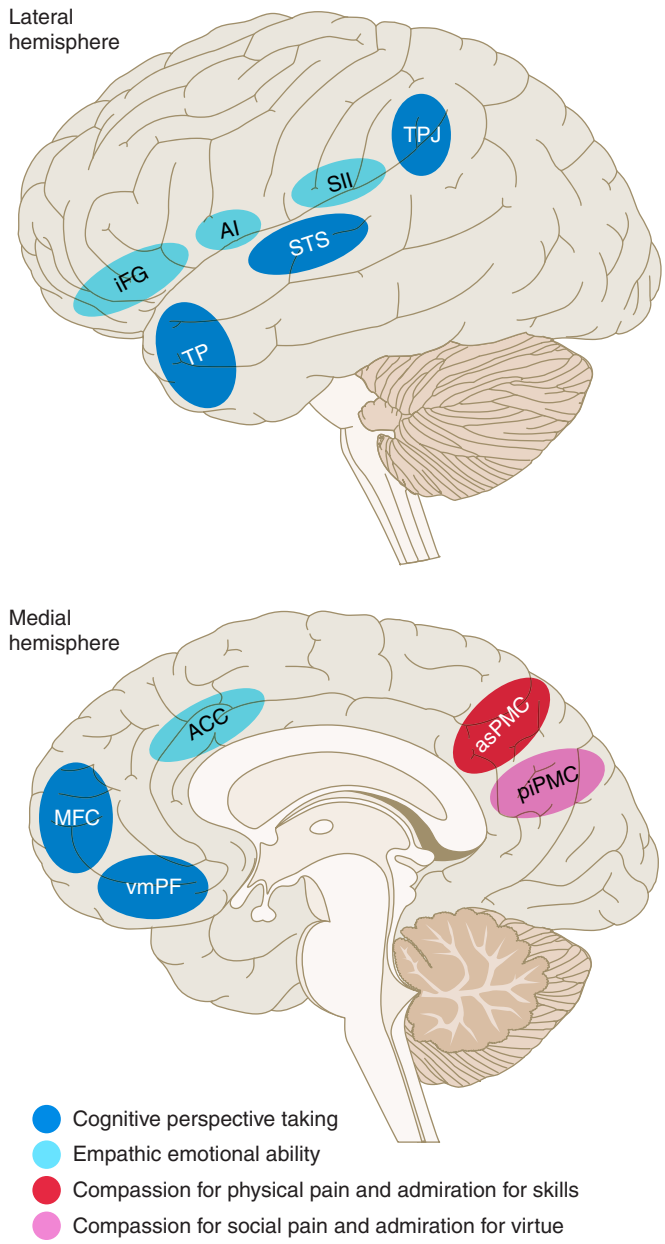

FIGURE 4. Brain regions that are involved in empathy, compassion, and admiration. During the doctor-patient relationship, several complex brain functions are involved, such as the doctor's empathic and compassionate behavior and the patient's admiration/trust towards the figure of the doctor. iFG, inferior frontal gyrus; AI, anterior insula; SII, secondary somatosensory area; TP, temporal pole; STS, superior temporal sulcus; TPJ, temporal parietal junction; MFC, medial frontal cortex; vmPF, ventromedial prefrontal cortex; ACC, anterior cingulate cortex; asPMC, anterosuperior posteromedial cortex; piPMC, posteroinferior posteromedial cortex.

vated when a female experienced pain herself as well as when she saw that her husband had experienced pain. The same group (297) showed that the empathic brain responses in the anterior insula and anterior cingulate cortex were not restricted to a beloved partner, but also occurred when an unknown but likable person was in pain, which has obvious implications for the doctor-patient interaction.

The involvement of other regions was demonstrated in subjects with lesions either in the ventromedial prefrontal cortex or in the inferior frontal gyrus. In fact, a remarkable behavioral and anatomic double dissociation between deficits in cognitive empathy (ventromedial prefrontal lesion) and emotional empathy (inferior frontal gyrus lesion) was found (291) **(FIGURE 4)**.

While pain is surely the modality that has been investigated in more detail, similar empathic responses have also been described in other modalities, like touch, taste, and disgust. For example, both observation of touch and first-hand experience of touch activate the secondary somatosensory cortex (182), and video clips showing people sampling pleasant and unpleasant tastes make observers experience the same tastes, along with activation in anterior insula cortex when both observing and experiencing disgust (174).

2. *Compassion for social and physical pain involves two discrete neural systems*

Compassion can be evoked by witnessing situations of personal loss and social deprivation (social pain), or by witnessing bodily injury (physical pain). Whereas the former pertains to social/psychological circumstances, the latter has to do with immediate physical circumstances (173). Compassion for social and physical pain has been found to engage two different neural circuits. The former is associated with strong activation in the inferior/posterior portion of the posteromedial cortices, whereas the latter produced a larger activation in the superior/anterior portion of the posteromedial cortices (173) **(FIGURE 4)**. These neural networks, one for the emotions related to someone else's psychological state and the other for the emotions related to someone else's physical state, are engaged by both compassion and admiration (see below).

It is interesting to note that compassionate concern towards a suffering person is related to the motivation to help and, accordingly, a positive intrinsic reward feeling may occur as a result of experiencing compassion for others (303). Indeed, Kim et al. (185) found that compassionate attitude activated a neural network in the midbrain/ventral striatum/septal network region, a key region involved in prosocial/social approach motivation and reward mechanisms. These findings emphasize the differences between empathic behavior, which does not necessarily involve motivational systems, and compassionate behavior, whereby the motivation to alleviate others' suffering represents the central element.

3. *Doctors can habituate to others' suffering*

There is some experimental evidence that habituation to others' suffering occurs in clinical practice. This may have evolved as a mechanism of self-control that is aimed at reducing negative emotions while doctors watch the suffering of their patients. This may be particularly true for those health professionals involved in invasive and painful procedures. Indeed, Cheng et al. (83) conducted a functional magnetic resonance imaging study, in which they compared physicians who practice acupuncture with naive participants (controls) while observing the insertion of needles into the mouth area, the hands, and the feet. The anterior insula, somatosensory cortex, periaqueductal gray, and anterior cingulate cortex were significantly activated in the control group, whereas the group of acupuncturist physicians did not show significant changes. The latter showed activation of the medial and superior prefrontal cortices and the temporoparietal junction, which are known to be involved in emotion regulation. The difference in brain activation between the two groups of naive and expert subjects is likely to reflect top-down processes related to past experience and practice with acupuncture.

B. Different Sensory Systems Are at Work During the Doctor-Patient Interaction

Needless to say, the auditory/language systems play a critical role in the doctor-patient relationship, for verbal communication represents one of the most important social interactions between therapists and their patients. The doctor's words and sentences may have a profound impact on the patient's psychological state. For example, some subtle differences in verbal communication may produce different effects. There is compelling evidence that different sentences such as "This painkiller may work" or "Rest assured, this painkiller does work" may lead to different therapeutic outcomes (41, 44). Besides this powerful verbal communication, there are a number of sensory inputs that represent the basis of nonverbal communication, most notably vision and touch.

1. *Visual stimuli are crucial in nonverbal communication*

Facial expressions represent an excellent source of information and play a fundamental role in signaling social intentions from which people infer meaning (134). Several brain regions are involved in detecting subtle differences in facial expressions, and these regions make up a complex network which is specifically aimed at processing facial emotions, whereas facial identity is processed by a different network (319). The specialness of face processing is shown by the

fact that even a split-second glimpse of a person's face tells us his/her identity, sex, mood, age, race, and direction of attention (324). In human brain imaging studies, a number of works support the idea that the lateral side of the right mid-fusiform gyrus, the "fusiform face area" or FFA, is activated robustly and specifically by faces (177, 324). It should be noted, however, that the fusiform face area does not respond only to face stimuli but also to non-face object, albeit less robustly. The information that is gained from faces is fundamental for social interaction, including the doctor-patient encounter, and some more details will be presented in section III*C1*.

Eye contact, i.e., the mutual eye gaze that connects people together, represents another important aspect of social interaction and solicits attention and interest of the interacting persons (290). Differently from other animals, whereby eye contact may represent a potential threat (118), in humans mutual eye gaze triggers attention and interest. At least five regions have been found to be activated more by direct gaze than by averted gaze: the fusiform gyrus (or fusiform face area), the anterior part of the right superior temporal sulcus, the posterior part of right superior temporal sulcus, the medial prefrontal cortex and orbitofrontal cortex, and the amygdala (290). These regions may be activated by direct gaze through different mechanisms, such as the activation of the arousal system (179), the activation of a communicative intention detector (135), and the activation of a subcortical face detection pathway (290).

Gestures and postures represent another important aspect of social interactions. The perceived behavior of others affects one's own behavior unconsciously. For example, people are likely to rub their face if their conversation partner does so (81). When observing the gestures of others, one can infer his intentions and, accordingly, adapt his own behavior. Mirror neurons are at the very heart of this social behavior and play a critical role whenever the behavior of others is observed (279).

Nonverbal communication, as briefly described here from facial expressions to eye contact and from the observation of others' gestures to guessing the others' intentions, is critical in any social encounter, including the special situation of the doctor-patient interaction. Nonverbal messages and intentions can be communicated either consciously or unconsciously to others, and indeed gestural communication may have represented a primitive form of language, as suggested by some (278).

2. *Emotionally meaningful tactile stimuli can make pain more bearable*

Touch may convey strong emotional information in many circumstances. For example, in section II*A* we have seen that social grooming is an important mediator of social relationships in nonhuman primates. The very act of grooming, scratching, rubbing, and licking another member of the same social group is a complex concertation of neural events that take place in both cortical and subcortical areas. In humans, a powerful emotional tactile stimulus is represented by hand-holding, which can be considered a nonverbal supportive social behavior in all respects. A study investigating the biological effects of hand-holding was performed on married women who were subjected to the threat of electric shock in three different conditions: while holding their husband's hand, while holding the hand of an anonymous male experimenter, or holding no hand at all (87). Holding the spouse's hand produced a decrease in unpleasantness ratings compared with no hand-holding, whilst holding the stranger's hand did not decrease unpleasantness. Functional magnetic resonance imaging showed reduced activation in right dorsolateral prefrontal cortex, left caudate-nucleus accumbens, and superior colliculus when the women held their husband's hand. All these areas are related to emotional and behavioral threat responses. A more limited reduction of activation occurred when they held the hand of a stranger, e.g., in the ventral anterior cingulate cortex, posterior cingulated and right postcentral gyrus. It is interesting to note that these effects of spousal hand-holding were related to marital quality: the higher the marital quality, the lesser the activation in the right anterior insula, superior frontal gyrus, and hypothalamus during spouse hand-holding, but not during stranger hand-holding.

C. Exploring the Patient's Brain

On the basis of the healer's/doctor's words, attitudes, and behaviors, several cognitive and emotional mechanisms are activated in the brain of the sick, such as those involved in complex functions like trust and hope. These, in turn, lead to expectations and beliefs, which represent some of the principal elements involved in the placebo responses, which will be treated starting from section IV.

1. *Trustworthiness decisions involve the amygdala and oxytocin*

Trust can be conceptualized as a set of beliefs that the therapist will behave in a certain way (316). Patients usually base their trust on the therapist's competence, compassion, confidentiality, reliability, and communication (254). Patients' trust in their physicians has always been considered as an important element that per se may have beneficial effects on the overall health status. This may occur through a better adherence to treatments as well as the reinforcement of clinical relationship and patient satisfaction (254).

Deciding if an unfamiliar person is trustworthy represents one of the most important decisions in everyday life. Either a good or a bad interaction very much depends on this decision. One hundred milliseconds of exposure to a neutral

face is sufficient for this complex task (346). This very short period of time shows that face exploration is not necessary for trustworthiness judgments, for a time lag of 100 ms is not sufficient for exploratory saccadic eye movements (319).

Patients with amygdala damage show an impairment in recognizing emotional facial expressions (8, 9, 78, 352). In particular, patients with bilateral amygdala lesion show a bias to perceive untrustworthy faces as trustworthy (8). A dissociation between processing of face evaluation and facial identity has been found. There are prosopagnosic patients who can recognize emotional expressions but not identity (68, 95, 108, 321). Likewise, there is some evidence that individuals with developmental prosopagnosia can make normal trustworthiness judgments but show impaired perception of face identity (319).

Besides these lesion studies, there is accumulating evidence on the role of the amygdala in trustworthiness judgements that comes from imaging studies. For example, in one study, subjects were asked to make either explicit or implicit trustworthiness judgments of unfamiliar faces. It was found that, regardless of the task, the amygdala activity increased in relation to subjective untrustworthiness, whereas the right superior temporal sulcus activity increased only during explicit trustworthiness judgments. Thus the automatic engagement of the amygdala and the intentional engagement of the superior temporal sulcus are dissociated (348). In a different study, it was found that the amygdala response to faces increased as the untrustworthiness of the faces increased (121), thus supporting the notion that the amygdala automatically categorizes faces according to perceived untrustworthiness.

Trust behavior has been found to undergo hormonal modulation by oxytocin. This hormone is known to have prosocial effects in humans, like the modulation of social interaction behavior and social cognition (31, 163) and the influence on a person's ability to infer another's mental state (107). In addition, couples receiving intranasal oxytocin prior to a videotaped "conflict discussion" show an increase in positive communication behaviors (105). Oxytocin has also been found to strengthen the anxiolytic effect of the presence of a friend during public speaking (162). Genetic variants of the serotonin transporter (5-HTT SLC6A4 polymorphism) and the oxytocin receptor (OXTR rs53576 polymorphism) have been studied in different populations. For example, mothers with these two polymorphisms present lower levels of sensitive responsiveness to their children (26).

One of the prosocial behaviors that is affected by oxytocin is trustworthy behavior. An increase in plasma oxytocin was found in subjects who participated in a trust game whereby cooperative behavior can benefit both parties (353). In a different study, it was found that in a trust game the intranasal administration of oxytocin was associated with a larger amount of money given by an investor to a trustee (197). Interestingly, oxytocin receptors are abundant in the amygdala (171). The neural circuitry of trustworthy behavior was studied by combining the intranasal administration of oxytocin with functional magnetic resonance imaging (35). The investigators found that oxytocin induced no change in trusting behavior after the subjects learned that their trust had been breached several times, while the control subjects who had not received oxytocin decreased their trust. This difference in trust adaptation was associated with a reduced activation in the amygdala, the midbrain regions, and the dorsal striatum in subjects receiving oxytocin.

Taken together, the findings on the amygdala and oxytocin reveal a specific neuronal circuitry that is involved in trustworthy behavior **(FIGURE 5)**. Oxytocin receptors are abundant in the amygdala; thus they can modulate its activity. The higher the activity in the amygdala is, the higher an emotion of untrustworthiness is generated. Oxytocin acts on its own receptors in the amygdala by reducing neural activity, thereby restoring an emotion of trustworthiness.

2. Admiration for virtue and for skills engages two separate neural systems

Admiration differs from trust, yet these two emotional elements are related to each other: if one admires a person, he is likely to trust him. Admiration may represent a very im-

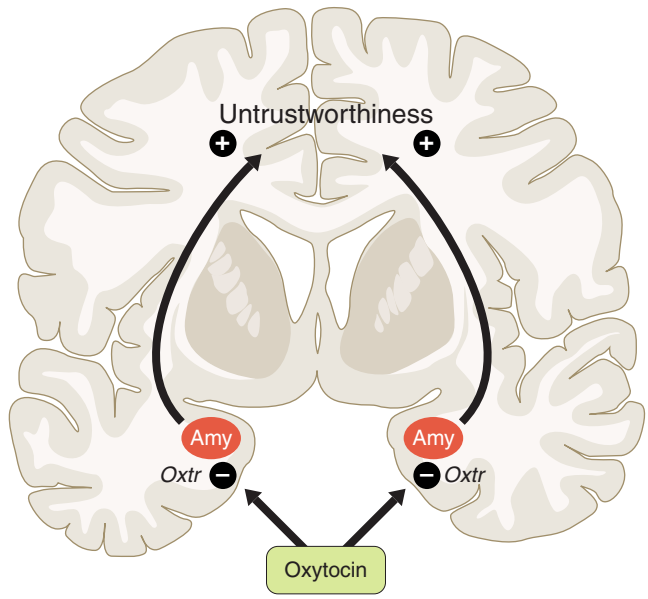

FIGURE 5. One of the key elements during the doctor-patient relationship is represented by the patient's trust. The amygdala (Amy) is responsible for untrustworthiness: the higher the amygdala activity, the more untrustworthy the judgments about a person. Oxytocin increases trust by binding to its own receptors (Oxtr) on the amygdala and by inhibiting its activity.

portant aspect of the therapist-patient encounter, for it can be elicited either by observing virtuous behavior towards the suffering of others or by displays of virtuosic skill. In the first case, admiration has to do with social/psychological circumstances, i.e., virtue, whereas in the second case it is related to physical circumstances, i.e., skillful abilities (173).

As for compassion, admiration was found to engage the posteromedial cortices, i.e., the posterior cingulate cortex, the retrosplenial area, and the precuneus. However, whereas admiration for virtue induced activation in the inferior/posterior portion of the posteromedial cortices, admiration for skills produced a larger activation in the superior/anterior portion of the posteromedial cortices (173) **(FIGURE 4)**.

3. *Hope and hopelessness may be related to serotonergic and noradrenergic mechanisms*

Hope can be defined as a positive motivational state that is based on a sense of successful goal-directed energy and planning to meet goals (301, 302). A key element of hope, although not the only one, seems to be the current unsatisfactory conditions of life, which may involve deprivation, damage, or threat (205). Motivation is central to hope, and actually it interacts with goal-directed behavior. High-hope individuals are capable of using alternative pathways if an impediment of any sort occurs in the planned behavior so that the same goal can be reached in a different way (301).

Some studies indicate that hope has beneficial effects on health, for example, better coping with arthritis (301), burn injuries (28), fibromyalgia (10, 313), and pain (75, 300, 301). In contrast, hopelessness and pessimism have been found to be associated with illness and mortality (120, 255, 284, 306). However, since hopelessness is often associated with depression, some negative effects can sometimes be attributed to the depressive symptoms and not to hopelessness itself.

It is not easy to approach hope and hopelessness from a neurophysiological perspective. For example, hopelessness and helplessness are often considered together. However, whereas hopelessness can be considered as a negative expectation with respect to the future, helplessness can be viewed as unrealistically low concepts of the own capabilities (e.g., see Ref. 165). In 1967 it was reported that dogs undergoing electric shocks not contingent on their behavior showed a subsequent difficulty to escape and avoid the shocks (251). This occurred because the dogs learned that the shocks were independent of any responses. This phenomenon, which was called "learned helplessness," has been used as an animal model of depression, despite a reformulation in more cognitive terms by Abramson et al. (1, 2), in which hopelessness was considered as a subset of helplessness.

Serotonin has been found to be involved in learned helplessness. For example, in some studies, after the presentation of uncontrollable shocks, rats could be separated into two different groups. Whereas one group did not learn to escape a controllable shock after previous exposure to uncontrollable shocks (learned helpless rats), another group learned an adequate response (nonlearned helpless rats). The learned helpless rats showed an upregulation of serotonin receptors in some regions of the brain, such as the cortex, hippocampus, septum, and hypothalamus, whereas a downregulation was observed in the hypothalamus. Changes in presynaptic activity at serotonergic synapses caused by uncontrollable shocks have also been described in the hippocampus and hypothalamus of learned helpless rats (20, 113, 114).

Interestingly, a negative correlation between prefrontal binding to serotonin 5-HT_{2A} receptors and levels of hopelessness was found in attempted suicide, according to the rule: the lower the binding to serotonin receptors, the higher the degree of hopelessness (325). An activation of the hypothalamus-pituitary-adrenal axis has also been found in a number of studies that used inescapable shocks as a model (165), and indeed, adverse experiences might lead to stress sensitivity. This, in turn, would lead to excessive norepinephrine release and its subsequent depletion, with the consequent hopelessness (228).

4. *Attributing a positive meaning to pain coactivates opioid and cannabinoid systems*

Empathic and compassionate behavior is not always included in the doctor's background and armamentarium, and bad communication is sometimes the rule in routine medical practice. The doctor's words and behavior may induce negative expectations in the patient and may lead to clinical worsening. One good example is represented by the way of communicating negative diagnoses, a task that requires good empathic and compassionate abilities. The impact of a negative diagnosis on the patient's brain and body can be substantial and can induce real worsening, e.g., pain increase. Anxiety plays a key role in these situations, and a bad interaction may indeed increase the patient's negative emotions. In this regard, the mechanisms underlying anxiety- and nocebo-induced hyperalgesia have been investigated in some detail and will be described in section V*A5*.

In this regard, the different meaning that is attributed to a symptom such as pain can be crucial in the global experience of pain. For example, clinicians have long known that cancer pain can be perceived as more unpleasant than postoperative pain (94, 127, 299), and this can be due to the different meanings of cancer on the one hand and of surgery on the other. Whereas the former often means death, the latter is associated with healing and recovery. Likewise, different religions attribute different meanings to pain and suffering, and this may lead to different pain experiences (164, 194, 342).

Only very recently were different attributions to pain investigated with a neurobiological approach, and this approach may have profound implications in medical practice, for example, within the context of negative diagnoses. In fact, how patients interpret their own pain experience can make a big difference. Benedetti et al. (66) changed the meaning of pain from negative to positive in healthy subjects through verbal suggestions. The subjects had to tolerate ischemic arm pain as long as possible. However, whereas one group was informed about the aversive nature of the task, as done in any pain study, a second group was told that the ischemia would be beneficial to the muscles, thus stressing the beneficial nature of the pain endurance task. In this latter group, pain tolerance was significantly higher compared with the first one, an effect that was partially blocked by the opioid antagonist naltrexone alone and by the cannabinoid antagonist rimonabant alone. However, the increased tolerance was antagonized completely by the combined administration of naltrexone and rimonabant, which suggests that a positive approach to pain reduces the global pain experience through the coactivation of the opioid and cannabinoid systems. These findings show that the way patients interpret their own symptoms may have a dramatic effect on their emotional experience.

IV. MECHANISM-BASED CLASSIFICATION OF PLACEBO RESPONSES

A. Mechanism-Based or Disease-Based Classification of Placebo Responses?

The final and perhaps the most important step in the doctor-patient interaction is represented by the very act of receiving a treatment **(FIGURE 3)**. The ritual of the therapeutic act and the effects that it may have on the therapeutic outcome is the element that has received great attention in the past few years. As described in section I, the psychosocial context and the therapeutic ritual surrounding the treatment and the patient **(FIGURE 1)** have been approached by using the placebo response as a model to understand the underlying physiological mechanisms. The doctor, and more in general the healer, is surely the key element in this therapeutic ritual, as we have seen in sections II and III.

What we have learned over the past years is that there is not a single mechanism of the placebo response, and actually there is not a single placebo response but many, so that different mechanisms are involved in different medical conditions and therapeutic interventions. One of the main problems in current placebo research is how these different mechanisms should be considered and classified. For example, placebo administration can induce either anxiety reduction or activation of reward mechanisms, depending on different circumstances. Likewise, different forms of learning can take part in placebo responsiveness in different conditions, ranging from classical conditioning to social learning. Therefore, a first approach to the classification of different placebo responses might be based on the mechanism that is involved.

On the other hand, today we do not know exactly when and in which conditions these mechanisms take place. For example, anxiety reduction might be important only in some medical conditions but not in others. Or, otherwise, learning might be a common mechanism across all medical conditions. Reasoning in this way, a second approach to the classification of different placebo responses, is a disease-based classification whereby the biological underpinnings are investigated in different conditions such as pain and Parkinson's disease.

Therefore, it is not clear whether we should differentiate the placebo responses on the basis of the mechanism or rather on the basis of the disease. This will be a future challenge in placebo research, that is, to understand where (in which disease), when (in which circumstance), and how (with which mechanisms) placebos work. Therefore, due to our limited understanding of the relationship between mechanisms and diseases, I will present both approaches. In this section IV, the general mechanisms that have been identified are described **(FIGURE 6)**, whereas in section V the placebo responses will described in different diseases.

B. Expectations of Therapeutic Benefit Play a Key Role in Many Conditions

Most of the studies aimed at identifying the underpinnings of the placebo effect have focused on expectations as the main mechanism, although today we do not know exactly if expectations are important in all medical conditions. Expectations of a future outcome are usually held by individuals about their own responses. Positive expectations lead to adopting a particular response, whereas negative expectations lead to its inhibition (187, 188). Expectations may also induce a decrease in self-defeating thoughts when expecting a positive outcome (308), and other factors may contribute such as motivation (269).

From both a psychological and a neuroscientific standpoint, expecting a future event may involve several brain mechanisms that aim to prepare the body to anticipate that event. For example, expecting a future positive outcome may lead to anxiety reduction and/or reward mechanisms activation, whereas expecting a negative outcome produces anticipatory anxiety, which is very important in anticipating a possible threat. Indeed, both subjective anxiety (122, 231, 327) and anxiety-related brain activity (256) have been found to be reduced after placebo administration.

Expectations may also induce changes through the activation of the reward circuit. These mechanisms are tradition-

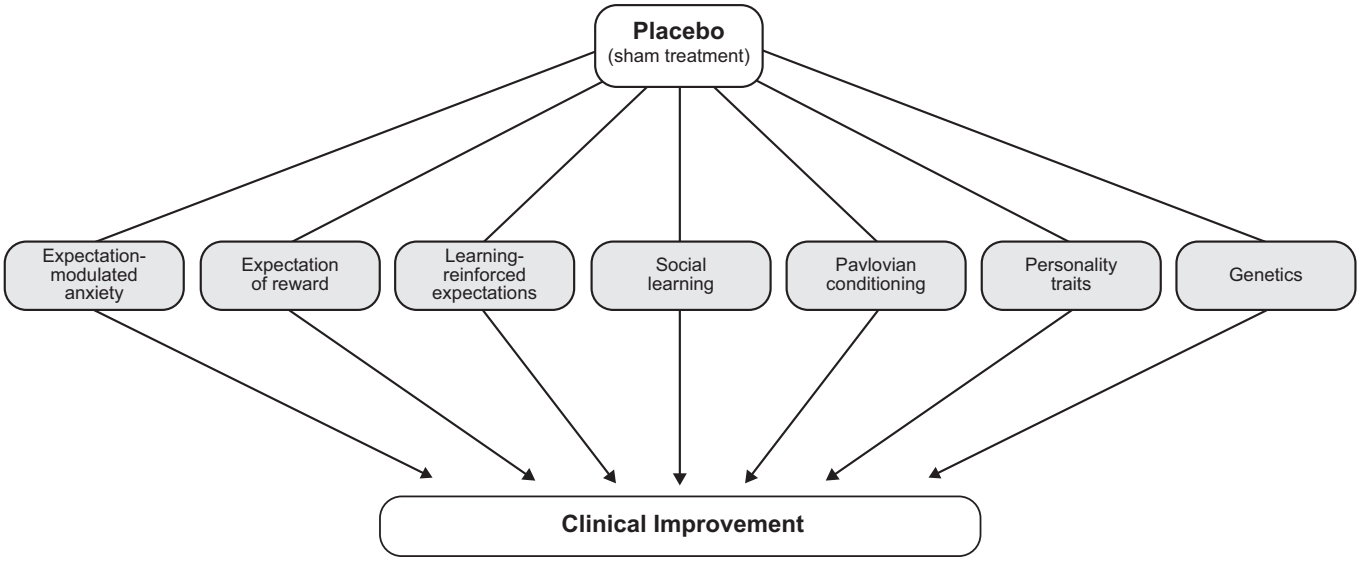

FIGURE 6. This figure includes only the psychobiological factors of **FIGURE 2**. It can be seen that several psychological and biological factors may be involved in the clinical improvement following administration of a placebo. Therefore, there is not a single placebo response but many, with different mechanisms across different medical conditions and therapeutic interventions.

ally studied by using natural rewards, like food, as well as monetary and drug rewards (176, 241). In the case of the placebo response, the reward is the therapeutic benefit itself and the consequent clinical improvement, which represent powerful rewards for the suffering patient. The nucleus accumbens plays a key role in reward mechanisms, and several studies found an increased activity of the nucleus accumbens and dopaminergic activity after placebo administration in Parkinson's disease (98, 99, 217), depression (229), and pain (287, 288). A detailed account will be given in the sections on pain, Parkinson's disease, and depression.

C. The Placebo Response Involves Learning Mechanisms

Patients can associate shape, color, and taste of a pill with symptom amelioration, such as pain decrease. Several other stimuli can be associated with clinical improvement, such as syringes, stethoscopes, white coats, hospitals, doctors, nurses, and so on. The mechanism that underlies this effect is classical conditioning, whereby a neutral stimulus, e.g., the color and shape of a pill, can become effective if repeatedly associated with an unconditioned stimulus, i.e., the drug inside the pill. Many placebo responses can be attributed to this associative learning, whereby the placebo is the neutral stimulus itself. In one of the first studies on the biology of the placebo effect (169), motor changes were observed in the rat after an injection of scopolamine, and the same changes occurred if an injection of saline solution (placebo) was performed after the injection of scopolamine.

In clinical practice, these sequence effects are common (16, 22, 33, 34, 204, 312), and they can also be exploited in clinical practice (106). Learning effects can be reproduced in the experimental setting as well. For example, Voudouris et al. (331, 332) associated a nonanesthetic cream (placebo) with the surreptitious reduction of the intensity of painful stimulation, so as to make the subjects believe that the cream was an effective anesthetic. These subjects, who had experienced a "true anesthesia/analgesia," became strong placebo responders, which suggests that conditioning is important. However, expectation was found to be crucial, because no placebo analgesic effect was found if the subjects were told that the cream was inert (243). This suggests that, during a conditioning procedure, conscious expectations of a future outcome play a major role.

Expectation and conditioning are not necessarily mutually exclusive, as they may represent two sides of the same coin (308). In other words, a conditioning procedure might lead to placebo responses through a mechanism of "reinforced expectations." Indeed, in the 1960s, a different interpretation of classical conditioning was put forward. According to this reinterpretation, conditioning does not depend merely on the pairing of conditioned and unconditioned stimuli, but on the cognitive information of the conditioned stimulus (276). Therefore, a conditioning procedure would lead to the expectation that a given event will follow another event (189, 275, 276).

Despite the reinterpretation of conditioning in cognitive terms, conditioned placebo responses in humans are not always cognitively mediated. For example, it has been suggested that unconscious conditioning is important in those placebo responses that involve unconscious physiological functions, whereas it is cognitively mediated when con-

scious processes come into play (65). Therefore, many placebo effects can be explained in the context of conditioning theories (3, 252, 295). In fact, a placebo is by definition a neutral stimulus with no therapeutic effects, in the same way as a conditioned stimulus is by definition neutral. Likewise, a placebo response is by definition elicited by a neutral stimulus, in the same way as a conditioned response is induced by a neutral stimulus.

Conditioning is not the only learning mechanism that may be involved in placebo phenomena. Social learning is another form of learning whereby people learn from one another by observation and imitation. As it will described in the section on pain, placebo effects can be elicited by social learning through the observation of others who respond to a painkiller (91).

D. Some Placebo Responses May Be Related to Personality Traits

A central issue in placebo research is whether individuals possess one or more specific characteristics, which can reliably identify them a priori as "placebo responders" or "placebo nonresponders," with important implications for both clinical trials design and personalized therapy optimization. Some studies have found that individual differences in suggestibility may contribute to the magnitude of placebo analgesia. In fact, the largest placebo responses were found in highly suggestible subjects who received suggestions presumed to elicit high expectations for drug efficacy (100). Pessimists have been found to be more prone than optimists to follow a negative placebo (nocebo) expectation, which suggests that the personality variable optimism-pessimism relates to placebo responding (139). In addition, individuals were tested on the basis of their level of optimism, and it was found that optimism was positively associated with better sleep quality after administration of a placebo sleeping treatment, thus suggesting that different degrees of optimism relate to placebo responding (140).

E. Different Genetic Variants Affect Placebo Responding

Recently, substantial placebo responses have been found for some genetic variants, for example in some psychiatric disorders (137, 274). In one study (137), patients with social anxiety disorder were genotyped with respect to the serotonin transporter-linked polymorphic region (5-HTTLPR) and the G-703T polymorphism in the tryptophan hydroxylase-2 (TPH2) gene promoter. With the use of functional neuroimaging, it was found that only those patients who were homozygous for the long allele of the 5-HTTLPR or the G variant of the TPH2 G-703T polymorphism showed robust placebo responses and reduced activity in the amygdala. Conversely, carriers of short or T alleles did not show placebo responses.

In another study in patients with major depressive disorder (209), polymorphisms in genes encoding the catabolic enzymes catechol-*O*-methyltransferase (COMT) and monoamine oxidase A were examined. Small placebo responses were found in those patients with monoamine oxidase A G/T polymorphisms (rs6323) coding for the highest activity form of the enzyme (G or G/G). Similarly, lower placebo responses were found in those patients with ValMet catechol-*O*-methyltransferase polymorphisms coding for a lower-activity form of the enzyme (2 Met alleles).

In a more recent study, the COMT functional val158met polymorphism was found to be associated with the placebo effect in irritable bowel syndrome. The strongest placebo response occurred in Met/Met homozygotes (154). Therefore, the role of genetic factors in placebo responding appears to be an important factor across a number of diseases, ranging from neuropsychiatric to gastrointestinal/psychosomatic disorders.

F. Other Possible Explanations Have Been Proposed

In addition to the classical psychological, neuroscientific, and biomedical approach, other perspectives of the placebo phenomenon have been proposed. For example, medical anthropologists have put forward the concept of embodiment. According to this view, our experiences are not only stored as conscious memories, but they are imprinted directly onto our body representation as well, with no conscious processes involved. Accordingly, placebo and nocebo effects would represent positive and negative effects of embodiment, respectively. This process does not need the involvement of conscious expectations (317). A body representation change can be achieved just by the complexity of the ritual of the therapeutic act. Crucial in the therapeutic ritual is the doctor-patient relationship, with empathy, attitudes, behaviors, as well as gesture and recitation all contributing to the positive treatment outcome (317).

V. DISEASE-BASED CLASSIFICATION OF PLACEBO RESPONSES

Differently from the previous section, the disease-based classification approaches the placebo effect by analyzing a single medical condition, such as pain and Parkinson's disease. Indeed, most of our knowledge on the physiological mechanisms of the placebo response comes from this approach. In many studies, however, placebos were administered without specifically investigating anxiety modulation or reward mechanisms or learning. Therefore, today we do not know exactly whether or not all these mechanisms take part in placebo responsiveness in a single condition such as pain. Despite these limitations, the disease-based approach has been the most productive in the past few years. One of

the most important future challenges of placebo research will be to understand in which medical conditions all the mechanisms listed in section IV and **FIGURE 6** are present. Today the most studied and understood conditions are certainly represented by pain, Parkinson's disease, and the immune and hormonal responses.

A. Placebo Analgesia Is the Most Studied and Understood Type of Placebo Response

1. *Expectation is the most important factor in placebo analgesia*

The reason why pain is the most studied condition is twofold. First, pain is a subjective experience that undergoes psychological and social modulation more than any other condition. The fine tuning of pain by many psychosocial factors makes pain an excellent model for investigating the placebo response. Second, modern placebo research has been influenced by the work by Beecher in the 1950s (36) who, as an army doctor during the Second World War, faced the problem of the lack of strong analgesics on the battlefield. Therefore, he treated his soldier patients with placebos many times and found that many subjects responded quite well very often. Despite several methodological flaws (44), Beecher's merit was to boost the interest of the scientific community in the placebo effect.

Today it is not clear why some individuals respond to placebos whereas some other individuals do not (see section VI*D*). It should be noted that a mean change in a placebo group might be seen in different situations, e.g., if all subjects in the placebo group show a moderate response or, otherwise, a small subset of subjects show a large response and others show no response at all. These variations are responsible for the large variability in placebo responses that is observed following placebo administration. For example, Levine et al. (211) found a percentage of 39%, Benedetti (40) of 26.9%, and Petrovic et al. (257) of 56%.

Expectation seems to play a key role in placebo analgesia (188, 243, 269, 270). For example, Benedetti et al. (65) performed a pharmacological preconditioning for 2 days in a row with ketorolac, a nonopioid analgesic. On the third day, ketorolac was replaced with a placebo along with verbal suggestions of analgesia, and a powerful placebo analgesic response was observed. In a second group, the same procedure with ketorolac was carried out to see whether this placebo response was due to the pharmacological preconditioning itself. However, on the third day, the placebo was given along with verbal suggestions that the drug was a hyperalgesic agent. Not only were these instructions sufficient to block placebo analgesia completely, but they also produced hyperalgesia. This finding indicates that placebo analgesia depended on expectation of pain decrease, even though a preconditioning procedure was performed.

The decreased effectiveness of hidden treatments represents one of the best evidences of the crucial role of expectation. In this case, a painkiller is given covertly (unexpectedly) unbeknownst to the patient, and the outcome following the hidden (unexpected) administration is compared with that following an open (expected) administration. In postoperative pain following the extraction of the third molar (210, 213), it was found that a hidden injection of a 6–8 mg intravenous dose of morphine corresponds to an open injection of saline solution in full view of the patient (placebo). Thus a placebo is as powerful as 6–8 mg of morphine. This means that an open injection of morphine is more effective than a hidden injection because in the hidden administration condition there is no placebo component. A systematic study of the differences between open (expected) and hidden (unexpected) administrations of drugs has been performed for five widely used painkillers (morphine, buprenorphine, tramadol, ketorolac, metamizol) in the postoperative setting (19, 57, 62, 92). It was found that the analgesic dose needed to reduce the pain by 50% (AD_{50}) was much higher with hidden infusions than with open ones for all five painkillers, indicating that a hidden administration is less effective than an open one. In addition, it was found that pain ratings were much higher with a hidden injection than with an open one.

2. *Both endogenous opioids and endocannabinoids may take part in placebo analgesia*

The placebo effect represents today one of the most interesting models to understand the endogenous mechanisms of analgesia (42), and indeed, placebos have been found to activate different endogenous antinociceptive systems. The first study that was aimed at understanding the biological mechanisms of placebo analgesia used naloxone as an antagonist of the opioid receptors in patients with postoperative pain who had undergone the extraction of the third molar (212). The investigators found a disruption of placebo analgesia after naloxone administration, which indicates the involvement of endogenous opioids in the placebo analgesic effect. The involvement of the endogenous opioid network in the analgesic placebo response was then confirmed by a number of studies (148, 210, 220).

In a long series of experiments with rigorous experimental design, which were performed between 1995 and 1999, many mechanisms were clarified and the role of endogenous opioids in placebo analgesia was better explained **(FIGURE 7)**. With the use of experimental ischemic arm pain, it was definitely clarified that the effect following naloxone administration could be attributed to the blockade of placebo-induced opioid activation (40). In addition, the effects of a cholecystokinin (CCK) antagonist, proglumide, on placebo analgesia was tested on the basis of the anti-opioid action of CCK. It was found that proglumide potentiated placebo analgesia, which represents a novel and indirect way to test the opioid hypothesis (40, 51). More recent research has

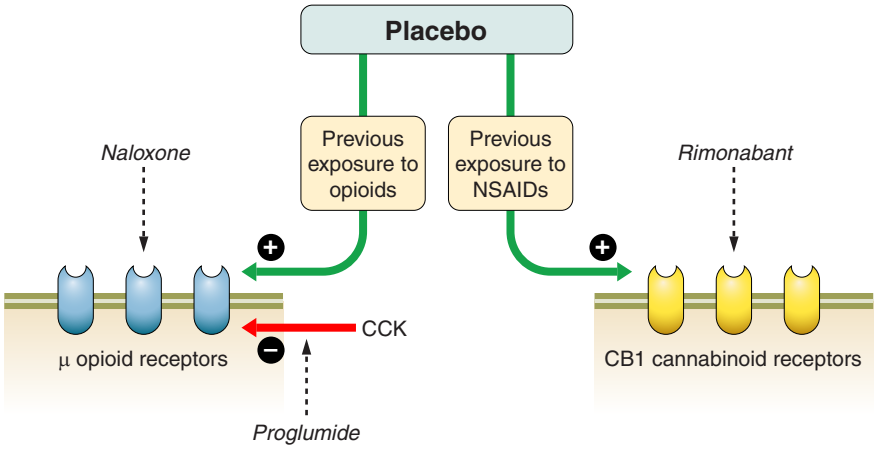

FIGURE 7. The mechanism of the placebo analgesic response depends on the previous exposure to different pharmacological agents, thus suggesting a memory for drug action. The previous exposure to opioids leads to opioid-mediated placebo responses, whereas the prior exposure to nonsteroid anti-inflammatory drugs (NSAIDs) leads to cannabinoid-mediated placebo responses. Cholecystokinin (CCK) antagonizes the opioid-mediated placebo responses. All these effects can be blocked by means of the appropriate antagonistic drugs, such as the opioid antagonist naloxone, the cannabinoid antagonist rimonabant, and the CCK antagonist proglumide.

shown that the activation of the CCK receptors by means of the agonist pentagastrin is capable of blocking the placebo analgesic response, thus emphasizing the role of CCK as an anti-opioid agent that may interfere with placebo responses (53).

On the basis that the placebo analgesic effect is not always mediated by endogenous opioids (147), Fields and Levine (128) suggested that different physical, psychological, and environmental situations could affect the endogenous opioid systems differently. In fact, Amanzio and Benedetti (16) showed that placebo analgesia is mediated by both expectation and conditioning, but whereas the former activates the opioid systems, the latter activates nonopioid systems. Indeed, the opioid antagonist naloxone can block those placebo responses that are induced by means of strong expectation cues. Similarly, if a placebo is given after repeated administrations of morphine (preconditioning procedure), the placebo response can be blocked by naloxone. Conversely, if the placebo response is induced by means of prior conditioning with a nonopioid drug, such as nonsteroid anti-inflammatory drugs (NSAIDs), it is naloxone insensitive (16).

On the basis of these findings, Benedetti and collaborators (52) induced opioid or nonopioid placebo analgesic responses and assessed the effects of the CB1 cannabinoid receptor antagonist rimonabant. Differently from naloxone, rimonabant had no effect on opioid-induced placebo analgesia following morphine preconditioning, whereas it completely blocked placebo analgesia following nonopioid preconditioning with the NSAID ketorolac. These findings indicate that those placebo analgesic responses that are elicited by NSAIDs conditioning are mediated by CB1 cannabinoid receptors **(FIGURE 7)**.

Since the involvement of the CB1 cannabinoid receptors in placebo analgesia is a very recent finding, little is known about their localization and activation. We only know that they are activated following a previous exposure to NSAIDs, which suggests that these drugs, besides the inhibition of cyclooxygenase and prostaglandin synthesis, activate an endocannabinoid pathway (52). In contrast, we know more details about the activation and localization of the placebo-activated opioid systems. For example, specific placebo analgesic responses can be obtained in different parts of the body (242, 270), and these responses are naloxone-reversible (55). If four noxious stimuli are applied to the hands and feet and a placebo cream is applied to one hand only, pain is reduced only on the hand where the placebo cream had been applied. This highly specific effect is blocked by naloxone, suggesting that the placebo-activated endogenous opioid systems have a precise and somatotopic organization (55).

In 2002, Petrovic et al. (257) found that both a placebo and the opioid agonist remifentanil affect the very same brain regions in the cerebral cortex and in the brain stem, which suggests that placebo-induced and opioid-induced analgesia share a common mechanism. A placebo induced the activation of the rostral anterior cingulate cortex and the orbitofrontal cortex, and there was a significant covariation in activity between the rostral anterior cingulate cortex and the lower pons/medulla, and a subsignificant covariation between the rostral anterior cingulate cortex and the periaqueductal gray, which suggests that the descending rostral anterior cingulate/periaqueductal gray/rostral ventromedial medulla pain-modulating circuit is involved in placebo analgesia. In 2005, Zubieta et al. (355) provided the first direct evidence of opioid-mediated placebo analgesia. With the use of in vivo receptor binding techniques with the ra-

diotracer carfentanil, a μ-opioid agonist, it was shown that a placebo procedure activates μ-opioid neurotransmission in the dorsolateral prefrontal cortex, the anterior cingulate cortex, the insula, and the nucleus accumbens. These findings were subsequently confirmed in a different study (335). By performing connectivity analysis with fMRI, Eippert et al. (115) found that a placebo treatment increases coupling between the periaqueductal gray and the rostral anterior cingulate cortex, and that this increased coupling is disrupted by naloxone.

Interestingly, all these opioid-mediated placebo responses have also been investigated in rodents, and similar mechanisms have been described (150, 247, 354). For example, Guo et al. (150) used the hot-plate test in an attempt to measure the reaction time of mice to a nociceptive stimulus (hot plate) after different types of pharmacological conditioning. This was performed by the combination of the conditioned cue stimulus with the unconditioned drug stimulus, either the opioid morphine or the nonopioid aspirin. If mice were conditioned with morphine, placebo analgesia was completely antagonized by naloxone, whereas if mice were conditioned with aspirin, placebo analgesia was naloxone-insensitive. In addition, placebo analgesia was found to be mediated specifically only by the μ-opioid receptors (354). Therefore, also in rodents, the mechanisms underlying placebo analgesia include both opioid and nonopioid components and may depend on the previous exposure to different pharmacological agents.

3. Imaging the brain after placebo administration

Neuroimaging has been fundamental in the understanding of placebo analgesia, and many brain imaging studies have been carried out to describe the functional neuroanatomy of the placebo analgesic effect (70, 115, 116, 158, 196, 218, 223, 224, 234, 257, 268, 288, 289, 320, 333–335, 355, 356). As described above, the first imaging study of placebo analgesia showed that a subset of brain regions are similarly affected by either a placebo or a μ-opioid agonist (257). These included the rostral anterior cingulate cortex, the orbitofrontal cortex, and the anterior insula, and there was a significant covariation in activity between the rostral anterior cingulate cortex and the lower pons/medulla, and a subsignificant covariation between the rostral anterior cingulate cortex and the periaqueductal gray, which suggests a descending pain-modulating circuit. This network may use endogenous opioids as neurotransmitters (115) and extends down to the spinal cord (116).

In a functional magnetic resonance imaging study of experimentally induced pain in healthy subjects, Wager et al. (334) found that placebo analgesia was related to neural activity decrease in pain-processing areas such as the thalamus, anterior insular cortex, and anterior cingulate cortex. Importantly, a correlation was present between the magnitudes of these decreases and the reductions in pain ratings. Not only did Wager et al. (334) image the time period of pain but also the time period of anticipation of pain, showing activations during the anticipatory phase in the orbitofrontal cortex, dorsolateral prefrontal cortex, rostral anterior cingulate cortex, and midbrain periaqueductal gray. It is interesting to note that the dorsolateral prefrontal cortex is associated with cognitive control, which is a crucial element in expectation (236), and the orbitofrontal cortex with evaluation and reward, which is consistent with a role in affective responses during the anticipation phase of pain (104).

Differently from most of the brain imaging studies, which were aimed at investigating placebo analgesia in the experimental setting, Price et al. (268) conducted a functional magnetic resonance imaging study in which brain activity of irritable bowel syndrome (IBS) patients was measured in response to rectal distension by a balloon barostat. A large placebo effect was produced by suggestions and accompanied by large reductions in neural activity in thalamus, primary and secondary somatosensory cortex, insula, and anterior cingulate cortex during the period of stimulation. It was also accompanied by increases in neural activity in the rostral anterior cingulate cortex, bilateral amygdala, and periaqueductal gray (269). This study shows that placebos act on the brain in a clinical relevant condition in the same way as they do in the experimental setting. Therefore, the involvement of key areas in placebo analgesia, such as the anterior cingulate cortex, is not limited to experimental noxious stimuli, but it also extends to clinical pain.

Lorenz et al. (223) used high temporal resolution techniques (magnetoencephalography) to discriminate whether expectations of analgesia exert their psychophysical effect during the early phase of cortical processing, namely, in the primary and secondary somatosensory areas, or during later cortical processing, such as in anterior cingulate cortex. These researchers found that the secondary somatosensory cortex was correlated to expectation-related subjective pain rating, while the anterior cingulate cortex was associated only with stimulus intensity and related attentional engagement. In other studies with laser evoked potentials (93, 337), early nociceptive components were found to be affected by placebos, thus indicating that later cognitive reappraisal and/or late bias-related neural activity cannot be responsible for this early modulation.

By using both positron emission tomography and functional magnetic resonance imaging, Scott et al. (288) tested the correlation between the responsiveness to placebo and that to monetary reward, and found that placebo responsiveness was related to the activation of dopamine in the nucleus accumbens, a region involved in reward mechanisms (172, 193, 285, 286) (see also section IV*B*). Monetary responses in the nucleus accumbens were assessed in the very same subjects by means of functional magnetic reso-

nance imaging, and a correlation was found between the placebo responses and the monetary responses. In fact, large nucleus accumbens responses to monetary rewards were associated with large nucleus accumbens responses to placebos. Therefore, placebo responsiveness may depend, at least in part, on the efficiency of the reward system. The same authors studied the endogenous opioid and the dopaminergic systems by using positron emission tomography with ^{11}C-labeled raclopride for the analysis of dopamine and [^{11}C]carfentanil for the study of opioids (289). The administration of a placebo induced the activation of opioid receptors in the anterior cingulate, orbitofrontal and insular cortices, nucleus accumbens, amygdala, and periaqueductal gray matter. Dopamine was activated in the nucleus accumbens. The perceived effectiveness of the placebo was associated with both dopamine and opioid activity. Interestingly, nocebo responses were associated with a deactivation of dopamine and opioid release.

Overall, these brain imaging data have been summarized by using a meta-analysis approach with the activation likelihood estimation method (17). Nine functional magnetic resonance studies and two positron emission tomography studies were selected for the analysis. During the expectation phase of analgesia, areas of activation were found in the left anterior cingulate, right precentral and lateral prefrontal cortex, and in the left periaqueductal gray (**FIGURE 8,** *top panel*). In the phase following pain stimulation, activations were found in the anterior cingulate and medial and lateral prefrontal cortices, in the left inferior parietal lobule and

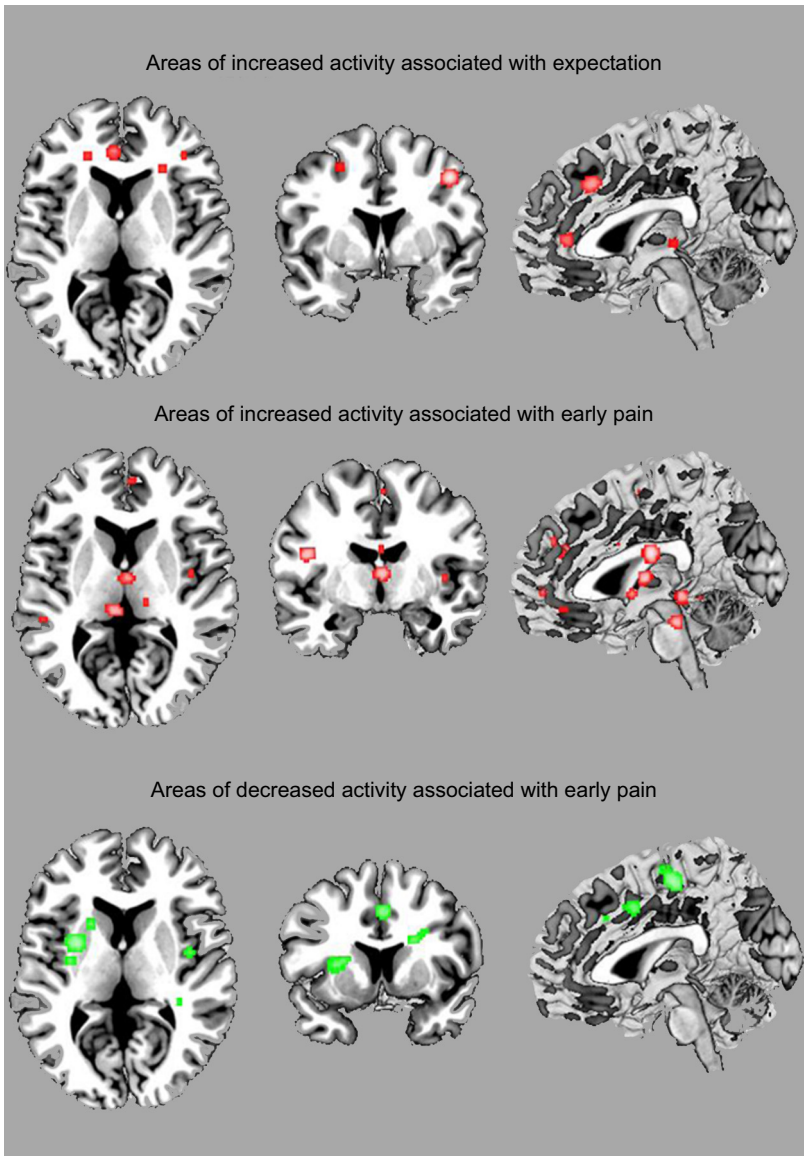

FIGURE 8. Activation likelihood estimation meta-analysis of different brain imaging studies of placebo analgesia in experimental pain. Red means activation areas, whereas green means deactivation areas. The sequence of events from placebo administration to inhibition of regions involved in pain processing can be subdivided into at least three stages: expectation of analgesia (*top panel*), activation in the early phase of pain stimulation (*middle panel*), and deactivation of some areas involved in pain processing (*bottom panel*).

postcentral gyrus, anterior insula, thalamus, hypothalamus, periaqueductal gray, and pons (**FIGURE 8,** *middle panel*). Conversely, deactivations were found in the left mid- and posterior cingulate cortex, superior temporal and precentral gyri, in the left anterior and right posterior insula, in the claustrum and putamen, and in the right thalamus and caudate body (**FIGURE 8,** *bottom panel*). These meta-analytic data summarize all brain imaging studies and give a global figure of the sequence of events following placebo administration **(FIGURE 8)**: after the activation of a pain modulatory network during the expectation phase (top) and the early pain phase (mid), several deactivations occur in different areas involved in pain processing (bottom).

4. Learning plays a major role

Learning is central to placebo responsiveness (see sect. IVC), and the magnitude of placebo analgesia has been found to depend on the prior experience of analgesic effects (89). There is some experimental evidence suggesting that previous positive experience leads to reinforced expectations rather than to unconscious Pavlovian responses. For example, as already described in section IVC, in a classical experiment, Voudouris et al. (331, 332) showed the role of conditioning in the placebo effect, although Montgomery and Kirsch (243) emphasized that this effect is mediated by conscious expectations.

To support the mechanism of learning-induced reinforced expectations, Colloca and Benedetti (91) studied social observation learning, in which subjects underwent a placebo treatment after they had observed a demonstrator showing analgesic effect when painful stimuli were paired to a green light. Observing the beneficial effects in the demonstrator induced substantial placebo analgesic responses, and these were correlated positively with empathy scores. It is important to note that this social learning elicited placebo responses that were similar to those induced by directly experiencing the benefit through a conditioning procedure.

5. Nocebo hyperalgesia is mediated by cholecystokinin

Different nocebo effects are present in daily life and in routine clinical practice, although they are not always studied under strictly controlled conditions (61, 90). For example, negative diagnoses may lead to an amplification of pain intensity, and nocebo-related effects may occur when distrust towards health professionals are present. Unwanted effects and side effects may occur as the result of negative expectations (18, 30, 130, 244, 277), and these may reduce the efficacy of some treatments. For example, verbal suggestions can change the direction of nitrous oxide action from analgesia to hyperalgesia (110), and health warnings in western societies may have an important impact on the perceived symptoms of many individuals, such as mobile phone headache (248).

Compared with placebo analgesia, much less is known about nocebo hyperalgesia, mainly due to ethical limitations. In 1997, a trial in postoperative patients was run with the nonspecific cholecystokinin (CCK)-1/2 receptor antagonist proglumide (50). This CCK antagonist was found to antagonize nocebo hyperalgesia, even though it is not a specific painkiller, which suggests that CCK mediates the nocebo hyperalgesic response. This effect was not antagonized by naloxone. To overcome the ethical limitations in the clinical setting, a similar study was run by using experimental pain in healthy subjects as a model (54). The administration of a placebo, along with verbal suggestions of pain increase (nocebo), was found to induce both hyperalgesia and hyperactivity of the hypothalamic-pituitary-adrenal axis, with an increase of adrenocorticotropic hormone (ACTH) and cortisol blood concentrations. Both nocebo hyperalgesia and hypothalamic-pituitary-adrenal hyperactivity were blocked by the benzodiazepine diazepam, whereas the administration of the mixed CCK type-1/2 receptor antagonist proglumide antagonized nocebo hyperalgesia, but had no effect on ACTH and cortisol. This suggests a role for CCK in the hyperalgesic but not in the anxiety component of the nocebo effect. These data strongly suggest that a close relationship between anxiety and nocebo hyperalgesia exists and that proglumide does not influence anticipatory anxiety, but rather it interrupts a CCKergic link between anxiety and pain. A support to this view comes from a social-defeat model of anxiety in rats, in which CI-988, a selective CCK-2 receptor antagonist, prevents anxiety-induced hyperalgesia (21).

The discrepancy between anxiety-induced hyperalgesia and stress-induced analgesia may be only apparent (90). Whereas hyperalgesia may occur when the anticipatory anxiety is about the pain itself (54, 180, 198, 282), analgesia may occur when anxiety is about a stressor that shifts the attention from the pain (131, 314, 344). In anxiety-induced hyperalgesia, attention is directed toward the pain itself, and this leads to the activation of the CCKergic systems which, in turn, have a facilitatory effect on pain transmission. Conversely, in stress-induced analgesia, increased arousal stems from an environmental stressor so that attention is now diverted from the pain itself, and this leads to the activation of the endogenous opioid systems which, in turn, have an inhibitory effect on pain (314, 344).

Brain imaging techniques have been fundamental in the understanding of the neurobiology of negative expectations. Amplification of pain perception as well as of the activity of several brain regions, like the anterior cingulate cortex, the prefrontal cortex, and the insula, has been found during the anticipation of pain (84, 96, 170, 180, 198, 195, 199, 223, 258, 264, 265, 267, 282). For example, Keltner et al. (180) used two visual cues, each conditioned to one of two noxious thermal stimuli (high and low), and found that subjects reported higher pain when the noxious stimulus

was preceded by the high-intensity visual cue. In addition, significant differences in the ipsilateral caudal anterior cingulate cortex, the head of the caudate, cerebellum, and the contralateral nucleus cuneiformis were found for the two different visual cues. With all these studies taken together, it appears clear that expectation of either low or high painful stimuli has a strong influence on the perceived pain.

As already described in section V*A3*, nocebo effects have also been found to be associated with a decrease in dopamine and opioid activity in the nucleus accumbens, thus underscoring the possible role of the reward and motivational circuits in nocebo effects as well (289).

B. Characterizing the Placebo Response in Parkinson's Disease

1. Parkinson's disease is an excellent model to study expectation-induced placebo responses

Parkinson's disease is a disorder of movement, although sensory, cognitive, mood, sleep, autonomic disturbances may be present as well. The main motor symptoms are tremor, rigidity, and bradykinesia. Tremor is at rest and involves mainly the upper limbs, although other body parts may be subject to tremor, such as the chin. Rigidity involves all the muscles, with a global impairment of movements and gait. Bradykinesia means that movements slow down so that any action is performed very slowly and with difficulty.

By reviewing several studies, Shetty et al. (294) found that 12 of 36 studies reported a 9–59% improvement in motor symptoms following placebo treatment. Goetz et al. (145) found that 14% of the patients enrolled in a 6-mo clinical trial achieved a 50% improvement in motor function while on placebo treatment. All domains of Parkinsonism were subject to the placebo effect, but bradykinesia and rigidity were more susceptible than tremor, gait, or balance. Substantial improvements after placebo administration are also present in surgical treatments of Parkinson's disease, such as after sham intrastriatal transplantation (249, 338).

Expectation of clinical benefit has been found to play a key role. In Parkinson patients, a placebo is administered along with verbal suggestions of motor improvement. In one study (65, 262), patients who had undergone electrode implantation for deep brain stimulation were tested in a condition in which they expected good motor performance and in a condition in which they expected bad motor performance. By using a movement analyzer, the hand movement was found to be faster when the patients expected good rather than bad motor performance. These findings have been confirmed by Mercado et al. (235), particularly for bradykinesia.

The important role of expectations is further supported by a clinical trial of human fetal mesencephalic transplantation (233). Although the real transplant group and the sham surgery group did not differ on several outcome measures, the perceived assignment of treatment group produced significant differences. Those patients who believed they had received the real transplant showed better improvements, regardless of whether they had received placebo surgery or true fetal tissue implantations.

2. Placebo induces dopamine release in the striatum

Dopamine has a critical role in the modulation of the basal ganglia functioning (11, 151), and its depletion results in difficulties initiating movement (akinesia), slowness of movement (bradykinesia), rigidity, tremor at rest, and postural instability. The disruption of dopamine function in the neural pathway from the substantia nigra pars compacta to the striatum (putamen and caudate nucleus) represents the pathophysiological substrate of Parkinson's disease. The pharmacological treatment of Parkinson's disease is aimed at replacing the lost dopamine by either dopamine precursors or synthetic agonists acting at dopamine receptors.

In 2001, de la Fuente-Fernandez et al. (98, 99) conducted the first brain imaging study of the placebo effect by means of positron emission tomography. These researchers assessed the release of dopamine by using the radiotracer raclopride, which competes with endogenous dopamine for D2 and D3 receptors, and found a dopamine release in the striatum after placebo administration. This release corresponded to a change of ~200% in extracellular dopamine concentration, which corresponds to the response to amphetamine in subjects with an intact dopaminergic system. Those patients who reported clinical improvement showed the greatest release of dopamine in the motor striatum (putamen and dorsal caudate). This relationship was not present in the ventral striatum. In fact, all patients showed increased dopamine release in the ventral striatum, irrespective of whether they perceived any improvement.

Differently from the dorsal motor striatum, the ventral striatum (i.e., the nucleus accumbens) is involved in motivation and reward anticipation (172, 193, 285, 286). Therefore, de la Fuente-Fernandez et al. (98, 99) suggested that the activation of dopamine in the ventral striatum was associated with the patients' expectation of improvement, which certainly represents a form of reward, rather than to the improvement itself. In a more recent study (217), it was found that the strength of expectation can modulate dopamine release. In fact, a significant release of dopamine in the striatum was found only when the declared probability of receiving active medication was 75%, but not at other probabilities (25%, 50%, 100%), which underscore the importance of uncertainty and/or salience.

3. Characterizing the neuronal circuit through single-neuron recording

The subthalamic nucleus is the major target in the surgical therapy of Parkinson's disease. During the implantation of the electrodes for deep brain stimulation, there are at least two criteria of identification of the subthalamic nucleus: one is anatomical, and the other is electrophysiological. In fact, although this anatomical localization is quite precise, usually it is not sufficient for a correct placement of the electrodes; thus electrical activity microrecording is performed. According to the classic pathophysiological view of Parkinson's disease, the dopamine depletion in the striatum induces both hyperactivity (high firing rate) (72) and bursting activity (69, 214) of subthalamic nucleus neurons. This might be due to a lower activity of the external globus pallidus which sends inhibitory projections to the subthalamic nucleus. Therefore, the external globus pallidus hypoactivity would result in decreased inhibition upon the neurons of the subthalamic nucleus. The high-frequency therapeutic stimulation of the subthalamic nucleus would modify this abnormal activity (219), and this might be achieved through the stimulation of the inhibitory afferents from the external globus pallidus to the subthalamic nucleus or by a direct effect on membrane excitability of the subthalamic neurons or, otherwise, by an interference with oscillatory activities.

In 2004, Benedetti et al. (59) conducted the first study of the placebo effect at the single-neuron level by exploiting the intraoperative recording during electrode implantation. These researchers performed a double-blind study in which the activity from single neurons in the subthalamic nucleus before and after placebo administration was recorded to see whether neuronal changes were associated with the clinical placebo response. To make the placebo response stronger, the placebo was administered in the operating room after several preoperative administrations of the antiparkinsonian drug apomorphine (pharmacological preconditioning procedure).

The activity of neurons was recorded from one subthalamic nucleus before the placebo and used as a control. After the subcutaneous injection of saline solution (placebo), activity was recorded from neurons of the other subthalamic nucleus. Those patients who showed a decrease in arm rigidity and an improvement in subjective report of well-being also showed a substantial decrease in firing rate compared with the preplacebo subthalamic nucleus. Although the mean firing rate of neurons is a good approach to assess the activity of the subthalamic nucleus, bursting activity has also been described in Parkinson's disease (69, 214). Therefore, in the single-neuron analysis by Benedetti et al. (59), the bursting activity of the subthalamic nucleus neurons before and after placebo administration was also investigated. It was found that whereas the subthalamic nucleus neurons of the placebo responders shifted significantly from a pattern of bursting activity to a pattern of nonbursting discharge, the placebo nonresponders did not show any difference in the number of bursting neurons before and after placebo administration. There was a nice correlation between subjective reports of the patients, clinical responses, and neurophysiological responses. In fact, firing rate and bursting activity decreased in subthalamic nucleus neurons, and this decrease was correlated with the patients' subjective reports of well-being and the muscle rigidity reduction at the wrist.

In a subsequent study by the same group, the partial characterization of the neuronal circuit that is affected by placebo administration was performed (60). When a clinical placebo response was present, a decrease in firing rate in subthalamic nucleus neurons, a decrease in the substantia nigra pars reticulata, and an increase in the ventral anterior (VA) and anterior ventral lateral (VLa) thalamus could be observed **(FIGURE 9)**. Conversely, placebo nonresponders showed either no changes or partial changes in the subthalamic nucleus **(FIGURE 9)**. Thus the whole subthalamic-nigral-thalamic circuit appears to be important for a clinical placebo response to occur. However, it should be noted that other nuclei, such as the striatum and the internal globus pallidus (GPi), may be involved in these placebo responses. Therefore, a future challenge will be to determine which regions of the basal ganglia change their activity following a placebo treatment.

C. Immune and Hormonal Responses Are Powerfully Affected by Placebos

One needs not believe in the treatment and trust his doctor to respond to a placebo treatment or, in other words, cognitive factors are not necessarily involved. Immune and hormonal responses represent two good examples of unconscious placebo responses, whereby the underlying mechanism is likely to be, at least in most of the cases, classical Pavlovian conditioning. These conditioned placebo responses take place regardless of what the patient expects. Although immunologists and endocrinologists have long known the effects of behavioral conditioning, this can be reconceptualized in terms of placebo response (328).

1. Many immune responses can be placebo conditioned

A long series of experiments performed in the 1970s and 1980s gave scientific evidence that immunological responses can be conditioned. Ader and Cohen (4) used a taste aversion conditioning paradigm in rats to pair a flavored drinking solution (saccharin) with the immunosuppressive drug cyclophosphamide. A subsequent immunization with sheep red blood cells was then performed. Reexposure to saccharin at the time of antigenic stimulation produced lower hemagglutinating antibodies 6 days after the injection of the sheep red blood cells, which indicates

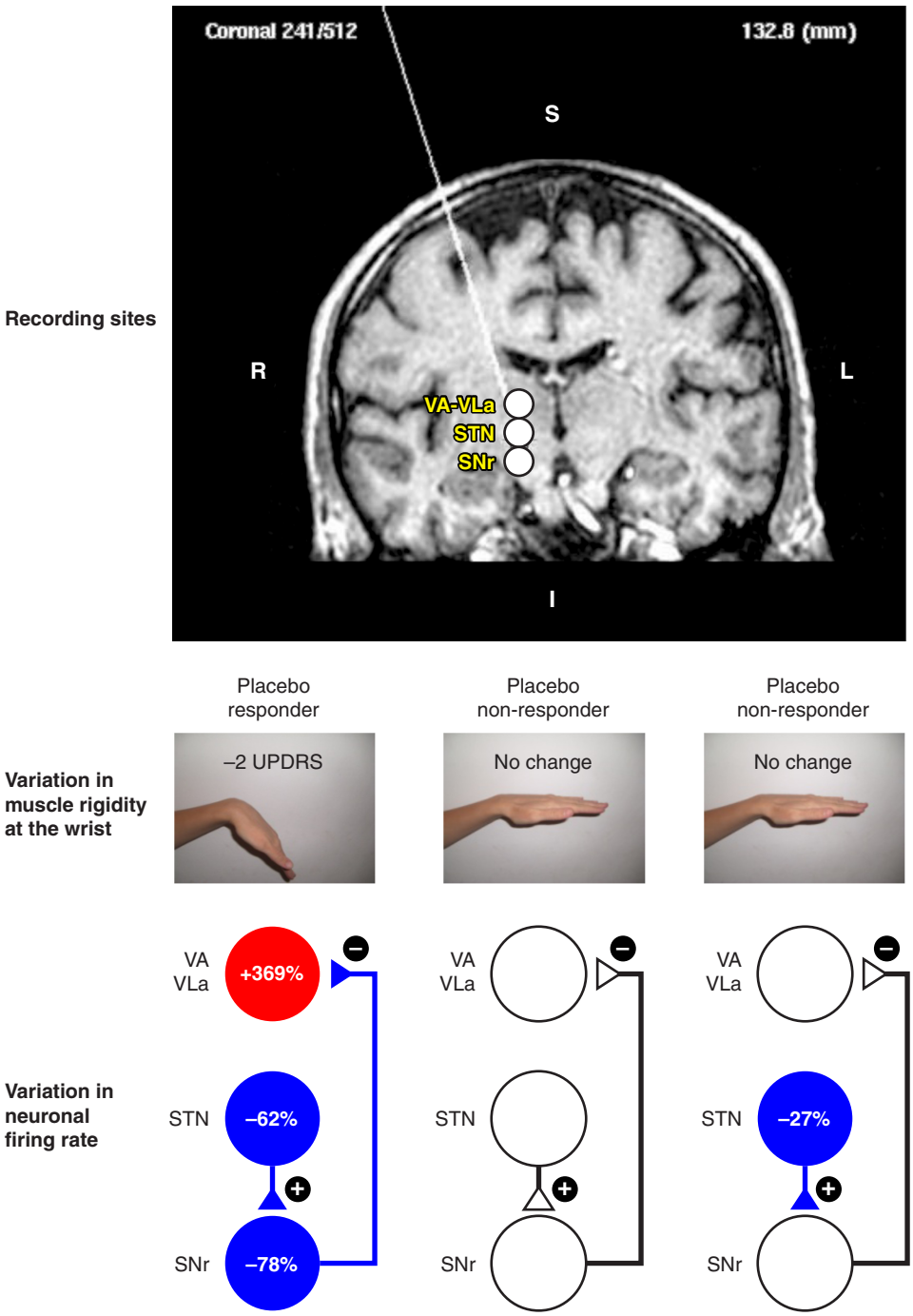

FIGURE 9. Neuronal changes in placebo responders and nonresponders in Parkinson's disease. *Top panel*: the intraoperative recording sites (VA, ventral anterior thalamus; VLa, anterior ventral lateral thalamus; STN, subthalamic nucleus; SNr, substantia nigra pars reticulata). *Bottom panel*: a placebo responder with a decrease of −2 on the UPDRS scale (Unified Parkinson's Disease Rating Scale), along with the neuronal activity changes, expressed as the percentage increase/decrease relative to baseline. The *bottom panel* also shows two placebo nonresponders. Whereas the first nonresponder shows no change in neuron activity, the second nonresponder shows a decrease in the STN which, however, is not enough to induce SNr and VA-VLa changes.

that saccharin can mimic the immunosuppressive effect of cyclophosphamide.

Behavioral conditioning has also been found in a graft-versus-host response, a phenomenon that is suppressed by low doses of cyclophosphamide (341). Whereas three low-dose injections of cyclophosphamide are capable of reducing the weight of lymph nodes following the injection of a cellular graft, a single low dose is less effective. However, if the single low dose of cyclophosphamide is paired to saccharin in rats that had previously been conditioned with saccharin, the single low dose is capable of inducing graft-

versus-host responses that are similar to those obtained with three doses.

With the use of an antigen as an unconditioned stimulus, a conditioned enhancement of antibody production is also possible. Skin tissue was grafted from C57BL/6J mice to CBA mice many times (146). Although the recipient mice were then reexposed to the grafting procedures but without receiving the allogenic tissue, there was nonetheless an increase in the number of cytotoxic lymphocyte precursor cells in response to the conditioned stimulus. Similarly, mice received repeated immunizations with keyhole limpet hemocyanin paired with a gustatory conditioned stimulus, and a classically conditioned enhancement of anti-keylole limpet hemocyanin antibodies was observed when the mice were reexposed to the gustatory stimulation along with a low-dose injection of keyhole limpet hemocyanin (6). An increase in IgG and IgM was subsequently found in animals reexposed to a conditioned stimulus previously paired with an antigen (13). Since these conditioned immune responses have been found to undergo extinction, associative processes are likely to be involved in the behavioral alteration of immune responses (74, 146).

Whereas these early studies were performed in animals, compelling evidence emerged that conditioned immune responses could be obtained in humans as well. Although some studies produced contrasting results (73, 138, 191, 221, 298), there is now general agreement that behavioral conditioning is possible in humans (252). For example, in a study by Goebel et al. (144), repeated associations between cyclosporine A and a flavored drink induced conditioned immunosuppression in healthy subjects, in which the flavored drink alone produced a suppression of the immune functions, as assessed by means 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 (**FIGURE 10,** *top panel*). The effects of the conditioned stimulus were the same as those of the specific effects of cyclosporine A. A subsequent study by the same group suggested that more than a single associative learning trial would be necessary to produce immune conditioned effects (142).

These conditioned immune responses may have a biological and clinical relevance. Ader and Cohen (5) paired a conditioned stimulus (a solution of saccharin) with an unconditioned stimulus (cyclophosphamide) in NZB/NZW hybrid mice, which represent a standard model for systemic lupus erythematosus in humans (307, 315). Cyclophosphamide can delay the development of a lethal glomerulonephritis at 8–14 mo of age (80, 245). Ader and Cohen (5) found that those mice that were conditioned by pairing saccharin and cyclophosphamide showed less severe glomerulonephritis, as assessed through proteinuria measurements, and longer

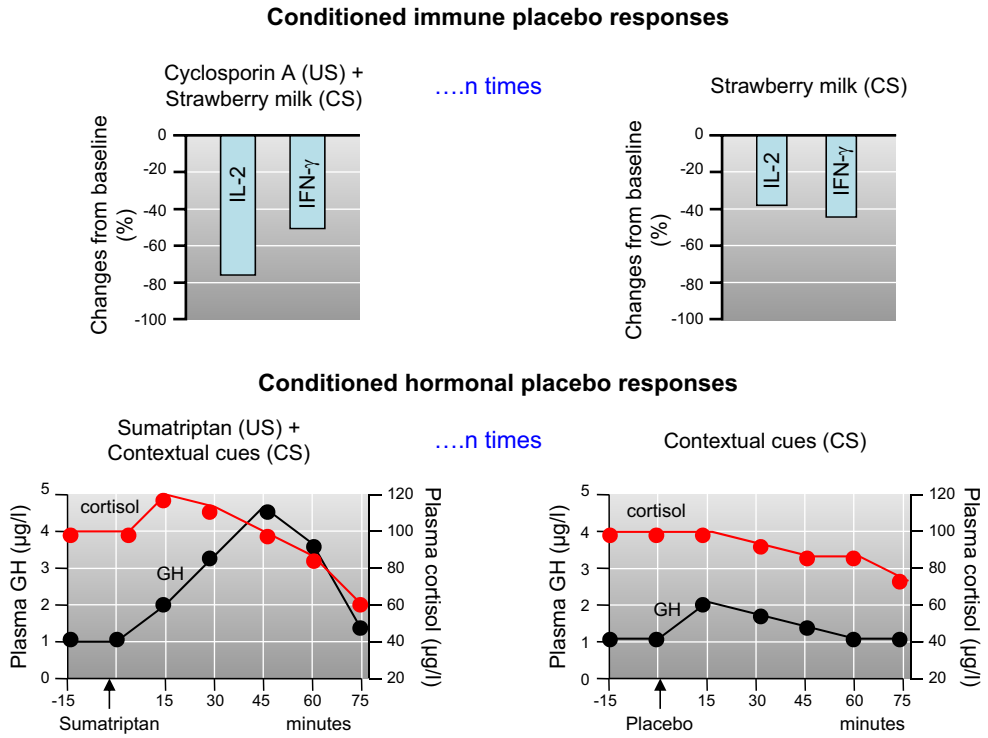

FIGURE 10. Conditioned immune and hormonal placebo responses. The association between the immunosuppressor cyclosporine A (US, unconditioned stimulus) and strawberry milk (CS, conditioned stimulus) for *n* times leads to conditioned immunosuppression of both interleukin 2 (IL-2) and interferon-γ (IFN-γ) when the CS alone is presented (*top panel*). Likewise, the association between the serotonin agonist sumatriptan and contextual cues for *n* times leads to conditioned growth hormone (GH) and cortisol responses when the contextual cues alone are presented (*bottom panel*).

survival times compared with nonconditioned mice. Similar results were obtained in a rodent model of arthritis (192, 226) as well as in transplantation models of graft reject (123, 149).

It is also interesting to remember a clinical case study of a child with lupus erythematosus (250). Taste and smell stimuli were paired with cytoxan, according to the animal conditioning paradigm. A clinically successful outcome was obtained in 1 year by using taste and smell stimuli alone on half the monthly chemotherapy sessions. Likewise, patients with multiple sclerosis received four monthly cyclophosphamide treatments paired with anise-flavored syrup, and after 6 mo of placebo paired with the drink, 8 out of 10 patients displayed decreased peripheral leukocyte counts, an effect that mimics that of cyclophosphamide (141). In another clinical study, Goebel et al. (143) used a behavioral conditioning procedure to analyze whether the effects of a histamine 1 (H1) receptor antagonist are inducible in house-dust mite allergy patients. In the association phase, these patients received a novel-tasting drink once daily, followed by a standard dose of the H1 receptor antagonist desloratadine for five consecutive days. When the patients were reexposed to the novel-tasting drink, the investigators found decreased basophil activation, as well as the skin prick test and subjective symptom scores similar to those of desloratadine. The possible positive effects of behavioral conditioning in the clinical setting have recently been supported by a study in psoriasis patients who were administered corticosteroid and placebo treatment alternately (7).

Some of the mechanisms underlying the brain-immune interaction and the pathways responsible for behavioral conditioning of immune responses have been partially elucidated. Lesions of the insular cortex in rats have been found to disrupt the acquisition of conditioned immunosuppression by taste aversion (272). Likewise, the lesion of the amygdala interferes with the acquisition of conditioned immunosuppressive responses but has no effect on the performance of preexisting conditioned responses (271). In addition, the insular cortex and the amygdala have been found to be involved in conditioned enhancement of antibody production when taste or smell stimuli are paired with antigenic stimulation (82, 273).

By using the association between saccharin as conditioned stimulus and cyclosporine A as unconditioned stimulus, it has also been found that the insular cortex is essential for acquiring and evoking these conditioned placebo responses. Conversely, the amygdala has been found to mediate the afferent signals at the time of acquisition. The ventromedial hypothalamic nucleus has been found to participate in the efferent signals to the immune system, which are necessary to elicit the behaviorally conditioned immune response (252, 253).

2. *Hormones can show robust placebo conditioned responses*

In the endocrine system, similar effects have been described. Insulin-induced hypoglycemia can be conditioned by pairing insulin with a conditioned stimulus in animals (14, 15). After repeated pairings between a conditioned stimulus and insulin, a significant decrease of blood glucose following the presentation of the conditioned stimulus alone occurs (350), and this conditioned effect undergoes extinction (351). This conditioned hypoglycemia was found to be mediated by the vagus nerve, as both vagotomy and pharmacological blockade with atropine abolished it (349).

As for immune responses, hypoglycemia can also be conditioned in humans (310, 311). The first human observation was performed in schizophrenic patients when insulin was replaced with a placebo in insulin shock therapy (216). Some contrasting results were obtained in subsequent studies, and this was likely to be due to the number of acquisition trials (124–126). In fact, a substantial change of blood glucose was found in 9 of 16 subjects after 4 acquisition trials, whereas only 2 of 16 subjects showed substantial changes after 2 acquisition trials. That conditioned hypoglycemia can be obtained in humans is further supported by other studies (310, 311).

The role of conditioning and expectation in the secretion of different hormones, such as growth hormone and cortisol, has been analyzed in another study (65). In a first condition, suggestions of growth hormone increase and cortisol decrease were given to healthy subjects. These verbal suggestions produced no effect. In a second condition, the serotonin 5-$HT_{1B/1D}$ receptor agonist sumatriptan, which stimulates growth hormone and inhibits cortisol secretion, was administered for two consecutive days and then replaced with a placebo on the third day. This time, an increase of growth hormone and a decrease of cortisol plasma concentrations were found after placebo administration (**FIGURE 10,** *bottom panel*). It is important to emphasize that these conditioned hormonal effects occurred irrespective of the verbal suggestions the subjects received. Even though the subjects expected a growth hormone decrease, the placebo mimicked the sumatriptan-induced growth hormone increase. Likewise, even though the subjects expected a cortisol increase, the placebo mimicked the sumatriptan-induced cortisol decrease. In this case, the conditioned stimulus is likely to be represented by the context around the treatment. These are the best examples of unconscious placebo effects that take place even if the patient's expectations go in the opposite direction. Recent experimental evidence suggests that unconscious placebo responses may occur in pain as well (175).

D. Investigating the Mechanisms in Other Less Known Conditions

1. *Imaging placebo responses in psychiatric disorders*

The placebo response rate in patients suffering from depression is very high. In a meta-analysis by Kirsch and Sapirstein (190), it was found that 75% of the response to the active drug is attributable to a placebo effect; thus the specific pharmacodynamic effect of the drug would account for only the 25%. A high correlation was also found between placebo response and drug response, which indicates that virtually all the variation in drug response size was due to the placebo component. There is now accumulating evidence of significant and increasing rates of placebo responses in antidepressant trials (23, 183, 336), although little is known on the cause of such an increase. Expectations about the therapeutic benefit may play an important role. For example, in a study with the antidepressant reboxetine, subjects were asked to self-rate their expectations of the effectiveness of the medication as follows: somewhat effective, very effective (200). The results showed that 90% of the patients who reported very positive expectations responded to the treatment, whereas only 33.3% of those who reported low expectations responded to the medication.

Little is known about the underlying mechanisms of these placebo responses in depressed patients. The main problem is represented by the fact that, unlike single-dose trials, such as in pain or Parkinson's disease, antidepressants require on average a minimum of 2–3 wk to see clinical effects. Therefore, the ethical and methodological approach to the study of the placebo response in depression is difficult. For example, the comparison between a placebo and a no-treatment group to rule out spontaneous remission requires that some patients are not treated for a long period of time. Therefore, although depression is an interesting model for placebo studies, it has not been investigated in detail thus far.

The first attempt to uncover some neural correlates of the placebo antidepressant response was performed by Leuchter et al. (208) by means of quantitative electroencephalography and cordance, a new analysis developed by the authors themselves. After 9 wk of placebo or fluoxetine or venlafaxine treatment, it was found that those patients who showed symptom reduction in the placebo group were characterized by an increase in prefrontal cordance, particularly in the right hemisphere. Conversely, those patients who responded to medication showed decreased cordance in prefrontal areas, thus suggesting that placebo treatment induces prefrontal changes that are distinct from those associated with antidepressant medication.

In a different study (229), changes in brain glucose metabolism were measured by means of positron emission tomography in unipolar depression patients who received either a placebo or fluoxetine for 6 wk, and common and unique responses were described. Both the placebo and fluoxetine group showed regional metabolic increases in the prefrontal, anterior cingulate, premotor, parietal, posterior insula, and posterior cingulate, and metabolic decreases in the subgenual, para-hippocampus and thalamus, with larger responses to fluoxetine compared with placebo. However, the responses to fluoxetine were associated with additional subcortical and limbic changes in the brain stem, striatum, anterior insula, and hippocampus. In contrast, there were no changes unique to placebo at 6 wk. Interestingly, there were unique ventral striatal (nucleus accumbens) changes in both placebo and fluoxetine responders at 1 wk of treatment, namely, well before therapeutic benefit, which suggests that they were related to expectation of the therapeutic benefit (63, 229). It should be remembered that the same involvement of the ventral striatum (nucleus accumbens) was found after placebo administration in Parkinson's disease (98, 99) and in pain (288), which emphasizes once again the important role of reward mechanisms in some placebo responses.

Anxiety is another psychiatric disorder that has been partially investigated. That expectations play an important role in anxiety is shown by the hidden administration of antianxiety drugs (see sect. VI*A* for the hidden paradigm). The efficacy of diazepam, one of the most used benzodiazepines for the treatment of anxiety, was assessed after overt and covert administration in postoperative patients with high anxiety scores (57, 62, 92). Whereas in the open group there was a clear-cut decrease in anxiety, in the hidden group diazepam was totally ineffective, which indicates that anxiety reduction after the open diazepam was a placebo response. The open-hidden interruption of a diazepam treatment has also been investigated (57, 62, 92). Whereas in the open condition anxiety increased significantly after 4 and 8 h, in the hidden condition it did not change, thus indicating that the anxiety relapse after the open interruption of diazepam could be attributed to the negative expectation of anxiety relapse (nocebo effect).

A few pieces of information are available on the mechanisms underlying the placebo effect in anxiety. For example, Petrovic et al. (256) found that placebo treatments can modulate emotional perception. In this study, before the presentation of unpleasant pictures, subjects were treated on the first day with either the benzodiazepine midazolam, which reduced the unpleasantness, or the benzodiazepine receptor antagonist flumazenil, which reversed this effect. Therefore, on the first day strong expectations of the treatment effect were induced. On the second day, the real medications were replaced with a placebo, but the subjects were told that they would be treated with the same pharmacological agents of the previous day. A powerful placebo response (unpleasantness reduction) was found when the sub-

jects thought they had been treated with the anxiolytic drug, whereas no response occurred if they thought they had received the anxiolytic blocker. These subjective changes were accompanied by functional magnetic resonance imaging changes in both the anterior cingulate cortex and lateral orbitofrontal cortex. It should be noted that these are the very same regions also involved in the analgesic placebo response (257, 334), which indicates that similar mechanisms might be involved in the placebo response of emotional stimuli and in placebo analgesia.

Since reward mechanisms may be involved in some types of placebo responses, it is not surprising to find placebo effects in addiction. The reinforcing effects of drugs of abuse, such as cocaine, result from a complex interaction between pharmacological effects, psychological factors, and conditioned responses (280). In drug abusers, the response to a drug is more pleasurable when subjects expect to receive the drug than when they do not (186). The effect of methylphenidate on brain glucose metabolism has been analyzed in cocaine abusers by adopting a balanced placebo design (330). In the first condition, cocaine abusers expected to receive the drug, and indeed received the drug. In the second condition, they expected to receive a placebo but actually received the drug. Therefore, whereas in the first case methylphenidate was expected, in the second case its administration was unexpected. The increases in metabolism were ~50% larger, particularly in the cerebellum and the thalamus, when methylphenidate was expected than when it was not. In contrast, methylphenidate induced larger increases in left lateral orbitofrontal cortex when it was unexpected than when it was expected. The self-reports of "high" were also 50% greater when methylphenidate was expected than when it was not. This study indicates that expectations enhance the drug effects. In a different study, the same investigators found that expectations about receiving methylphenidate activate the nucleus accumbens (329).

2. *Placebo-activated endogenous opioids may affect respiration and the heart*

Narcotics may induce several side effects, such as respiratory depression, nausea, constipation, and urinary retention. Placebos have been found to mimic narcotic-induced respiratory depression (48, 49). In a study in the postoperative setting, the opioid buprenorphine was given for three consecutive days, and both analgesia and respiratory depressant effects were measured (49). After every buprenorphine infusion, a mild reduction in ventilation was observed. Buprenorphine was replaced with a placebo on the fourth day, and this mimicked the respiratory depressant effect of buprenorphine. This placebo depressant response could be prevented by the opioid antagonist naloxone, which suggests the involvement of endogenous opioids at the level of the respiratory centers.

In the respiratory system, placebos have been found to reduce bronchial hyperreactivity in asthma (181, 225), and substantial improvements in asthmatic symptoms have been described following a placebo treatment (339). However, so far the physiological underpinnings are totally unknown. Likewise, cough is powerfully affected by placebo treatments (111, 112, 206), and a placebo conditioning procedure has been found to affect capsaicin-evoked urge-to-cough (207), but again the underlying biological mechanisms are not known.

As for the respiratory system, the data on the placebo effect in the cardiovascular system and circulatory diseases are scanty. In addition, some studies that claim powerful placebo effects in cardiovascular diseases suffer from methodological flaws that limit the interpretation of the results. There are only a few studies in the laboratory setting that may shed light on the biological underpinnings of the placebo response at the level of the heart. For example, it has long known that heart responses can be conditioned, and conditioned bradycardia has been found to involve the endogenous opioid systems (157, 166–168). To date, there is no study testing placebo-activated endogenous opioids on the heart. However, there is some indication that during placebo analgesia, the activation of the endogenous opioid systems may also affect the heart.

In fact, in a study by Pollo et al. (263), a placebo was given to subjects who underwent the induction of experimental pain, along with the suggestion of analgesia. Besides the assessment of the analgesic effect, both heart rate and heart rate variability were measured. In a first part of this study in the clinical setting, patients who were assessed for their autonomic functions were delivered noxious stimuli and a placebo was applied to the skin along with the verbal suggestions that it was a potent local anesthetic. These subjects showed consistent placebo analgesic responses that were accompanied by reduced heart rate. Because of ethical limitations in the clinical setting, in a second part of this study the same placebo effect was reproduced in the laboratory setting by using experimental ischemic arm pain. It was found that the opioid antagonist naloxone blocked both placebo analgesia and the concomitant reduced heart rate, whereas the β-blocker propranolol antagonized only the placebo heart rate reduction but not placebo analgesia. Conversely, muscarinic blockade with atropine did not produce any effect on both placebo responses, indicating no involvement of the parasympathetic system. A spectral analysis of heart rate variability was also performed, which allows the identification of the sympathetic and parasympathetic activity of the heart. It was found that the β-adrenergic low-frequency spectral component was reduced during placebo analgesia, which suggests a reduction of sympathetic activity during placebo analgesia. Importantly, this effect was reversed by naloxone, which suggests the involvement of endogenous opioids. The reduction of the

sympathetic control of the heart during the placebo analgesic response might be due to either a direct effect of the endogenous opioids on the heart or, otherwise, an indirect effect through the reduction of the pain itself.

All these placebo effects in the respiratory and cardiovascular system require confirmation and further investigation. Indeed, they represent an interesting model to understand the physiology of different placebo responses in conditions other than pain, neurological diseases, and psychiatric disorders. Therefore, a future challenge will be to investigate these systems in more detail, as has been done for pain and Parkinson's disease.

3. *Moving from the clinical setting to physical performance*

As occurs in the clinical setting, also in the world of sport placebos and nocebos can exert their influence on physical performance. All available data indicate athletes expectations as important elements of physical performance, in spite of the fact that very different experimental conditions have been investigated. These range from short anaerobic sprints to long aerobic endurance cycling, and many different outcome measures have been used, such as time, speed, and weightlifted.

For example, weightlifters receiving a placebo have been found to improve on average ~10% in different exercise tasks (24). Similarly, in a different study subjects received a placebo that they believed to be a steroid and performed significantly better, with average values around 4% (227). A similar measurable placebo effect of 3.8% was reported by Clark et al. (85) in a 40-km cycling time trial. Another study showed that it is possible to modulate the subject expectations, according a dose-response paradigm (39). Similar placebo effects were found in other studies (38, 132, 230, 232). Interestingly, if an athlete holds negative beliefs about the ergogenic aid just received, a nocebo effect may occur so that the following performance drops as well (37, 261). For example, in healthy subjects performing a leg extension exercise to total exhaustion, Pollo et al. (261) analyzed the contribution of expectation alone or the combination of conditioning and expectation to the nocebo effect. By evaluating the change of work performed and the rate of perceived exertion, the researchers found that it is possible to negatively modulate the physical performance in both cases.

An important point that might be relevant to training strategies is whether pharmacological or nonpharmacological conditioning is effective in shaping the placebo response in the sport context. In a simulation of sport competition, in which subjects had to compete with each other in a competition of pain endurance, Benedetti et al. (64) found that placebo administration on the day of competition induced longer pain tolerance compared with an untreated group. However, if a pharmacological preconditioning was performed with morphine in the training phase, the replacement of morphine with a placebo on the day of competition induced an increase of pain endurance and physical performance that was significantly larger than placebo without prior morphine preconditioning. This placebo response after morphine preconditioning could be prevented by the administration of the opioid antagonist naloxone, which suggests that this placebo response is opioid-mediated.

Similar findings were obtained with a nonpharmacological conditioning procedure (260), in which the effects of an ergogenic placebo on the quadriceps muscle were investigated. A placebo, which the subjects believed to be caffeine at high doses, was administered in two different sessions. In each of these sessions, the weight to be lifted with the quadriceps muscles was reduced unbeknownst to the subject, so as to make him believe that the "ergogenic agent" was really effective. After this conditioning sessions, the load was restored to the original weight, and muscle work and fatigue were assessed after placebo administration. A robust placebo effect occurred, which consisted of a significant increase in muscle work and decrease in muscle fatigue.

In many of the above-reported studies, in which athletes were asked to perform at their limit, placebo treatments apparently acted by pushing this limit forward. This suggests that placebos could affect a central governor of fatigue, which has been proposed as a brain center regulating exercise performance (155, 202, 246). Overall, by taking all these studies into consideration, the increase in performance following placebo administration may have practical applications, but it also raises important questions as to how these effects should be exploited in sport competitions.

VI. NEW EMERGING CONCEPTS FROM THE RECENT INSIGHTS INTO THE PHYSIOLOGY OF PLACEBOS

A. Drugs Without Therapeutic Rituals Are Less Effective

One of the most interesting concepts that is emerging from the recent physiological understanding of placebos and expectations is related to the reduced efficacy of drugs when administered covertly. In fact, if the placebo/expectation component of a treatment is eliminated by means of a hidden administration (unbeknownst to the patient), all the biological events described in the previous sections are absent as well.

As described throughout this article, in all studies that are aimed at identifying the placebo component of a therapy, a sham treatment (the placebo) that simulates the real treatment in all respects is usually administered to eliminate the

specific effects of the treatment itself. In recent years, a different method for the analysis of the placebo effect has been introduced, and this allows us to investigate the placebo response without the actual administration of any placebo. In fact, it is possible to eliminate the placebo psychobiological component and to maintain the specific effects of the treatment by administering the therapy unbeknownst to the patients so that no expectations are present about a positive therapeutic outcome. Then hidden therapies are compared with open ones **(FIGURE 11)**. This approach is interesting because open therapies are expected, whereas hidden therapies are unexpected. In this way, the use of the open-hidden (expected-unexpected) paradigm provides important information on the role of expectations in the therapeutic outcome (88).

In the 1980s and 1990s, analgesic drugs were administered by machines through hidden infusions (51, 147, 210, 213). In postoperative pain following the extraction of the third molar, Levine et al. (213) and Levine and Gordon (210) found that 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). Therefore, telling the patient that a painkiller is being injected (actually a placebo) is as powerful as 6–8 mg of morphine.

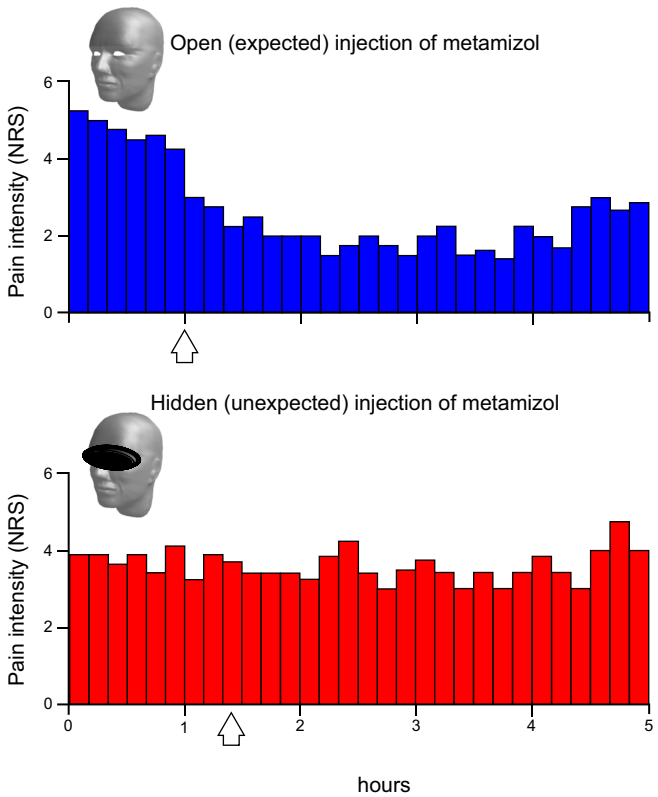

FIGURE 11. Comparison between an open and a hidden administration of metamizol in postoperative pain. Whereas the arrow in the *top panel* indicates the timing of metamizol administration by the doctor, the arrow in the *bottom panel* indicates metamizol administration (same dose and same infusion rate) by a computer unbeknownst to the patient. Note the analgesic effect following the open administration but no effect at all following the hidden administration. Therefore, the pain reduction in the *top panel* is not attributable to the pharmacodynamic effect of metamizol but merely to a psychological effect.

The differences between open and hidden injections of four widely used painkillers (buprenorphine, tramadol, ketorolac, metamizol) in the postoperative setting were analyzed by Amanzio et al. (19), who found that the analgesic dose needed to reduce the pain by 50% was higher with hidden administrations compared with open ones, which clearly shows how a hidden administration is less effective than an open one. Likewise, the same researchers showed that pain ratings in the postoperative setting were higher with a hidden analgesic infusion compared with an open one. Another study was carried out in postoperative patients with high scores of State-Trait Anxiety Inventory-State (STAI-S) after surgery (62). To reduce state anxiety, some of them were treated with open (expected) administrations of diazepam, whereas other patients were given hidden (unexpected) infusions of diazepam. The difference between the open and the hidden administration of diazepam was highly significant at 2 h after the injection, such that in the open group there was a clear-cut decrease of the STAI-S, whereas in the hidden group diazepam was totally ineffective.

This open-hidden approach has also been applied to nonpharmacological treatments such as deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease, with similar findings (58, 62, 203, 262).

Some brain imaging studies give support to the notion that expectation may enhance the therapeutic responses. For example, as already described in section V*D1*, Volkow et al. (330) used a balanced placebo design to study the effects of methylphenidate on brain glucose metabolism. The balanced placebo design and the open-hidden protocol are similar, for in the former one group expects a placebo but actually it receives the drug, whereas a second group expects to receive the drug, and indeed receives the drug. Therefore, the first group (told placebo, but gets drug) is similar to a hidden administration, whereas the second group (told drug, gets drug) is the same as an open administration. By using this experimental approach, cocaine abusers were subdivided into four groups: *1*) told methylphenidate, gets methylphenidate; *2*) told methylphenidate, gets placebo; *3*) told placebo, gets methylphenidate; and *4*) told placebo, gets placebo. Brain glucose metabolism increased by ~50%, particularly in the cerebellum and the thalamus, when methylphenidate was expected than when it was not.

More recently, the powerful analgesic remifentanil was found to be modulated by expectations as well. Bingel et al. (71) found that expectation of remifentanil (told remifen-

tanil, gets remifentanil) produced more pronounced analgesic effects compared with no expectation (told saline, gets remifentanil). Moreover, during a hidden infusion of remifentanil, expectation of interruption (told interruption, gets remifentanil) abolished the analgesic effect of remifentanil. Functional magnetic resonance responses showed that the enhancement of analgesia in the positive expectation condition was associated with activity in the dorsolateral prefrontal cortex and pregenual anterior cingulate cortex, whereas negative expectation of interruption was associated with activity in the hippocampus.

B. Therapeutic Rituals and Drugs: Common Pathways?

A second interesting aspect that is emerging from the recent physiological understanding of the placebo response is related to the common biochemical pathways that are activated by social stimuli and therapeutic rituals on the one hand and by drugs on the other. Drugs such as narcotics, cannabis, and anti-Parkinson's agents bind to μ-opioid receptors, cannabinoid receptors, and dopamine receptors, respectively. Likewise, expectations of analgesia or expectations of motor improvement activate the very same receptorial pathways, with similar effects as those produced by the real pharmacological agents. This is particularly relevant from an evolutionary point of view to understand human biology, for the receptorial targets of some drugs are already present in the human brain (e.g., opioid and cannabinoid receptors). Therefore, it is plausible to suppose that both the human and the animal brains are endowed with endogenous systems that are very important for socially driven therapeutic effects, as occurs in the placebo response (46).

These common pathways shared by therapeutic rituals and drugs, with the consequent possible interference between social stimuli and pharmacological agents, are likely to have a profound meaning in medical practice. Drugs are not injected into a vacuum but into a complex living organism that has expectations and beliefs. For example, when a narcotic agent is administered, it binds to μ-opioid receptors, but the very same μ-opioid receptors are activated by the patient's expectations about the narcotic. Similarly, when an anti-Parkinson's dopaminergic agent is administered, it binds to D2/D3 dopamine receptors, but the very same dopamine receptors are activated by the patient's expectations about the anti-Parkinson's drug.

Today we do not know whether therapeutic rituals can indeed modify a receptor, so as to change the drug-receptor binding properties. Although this will be surely a major target for future research, this mechanism seems unlikely as far as we know today. The global effect of a drug derives from its specific pharmacodynamic action plus the psychological (placebo) effect coming from the very act of its administration. A recent study suggests that these two components operate independently from each other. Atlas et al. (25) conducted a study to directly examine the relationship between expectations and opioid analgesia. They administered the opioid agonist remifentanil to human subjects during experimental thermal pain and manipulated participants' knowledge of drug delivery using an open-hidden design. Both remifentanil and expectations reduced pain, but drug effects on pain reports and brain activity, as assessed by functional magnetic resonance imaging, did not interact with expectations. Regions associated with pain processing showed no differences in drug effects as a function of expectation in the open and hidden conditions. Instead, expectations modulated activity in frontal cortex, with a separable time course from drug effects.

Therefore, drugs and expectations both influence clinically relevant outcomes, yet they seem to operate without mutual interference. This suggests that, although pharmacological agents and therapeutic rituals use the same type of receptors, these receptorial pathways are independent from each other, being located in different areas of the brain.

C. No Prefrontal Control, No Placebo Response

A common finding across different neuroimaging studies is represented by the involvement of the prefrontal areas, like the dorsolateral prefrontal cortex, in the placebo response **(FIGURE 8)**. Since in Alzheimer's disease the frontal lobes are severely affected, with marked neuronal degeneration in the dorsolateral prefrontal cortex, the orbitofrontal cortex, and the anterior cingulate cortex (318), it is reasonable to expect a disruption of placebo responsiveness in these patients.

On the basis of these considerations, Benedetti et al. (56) studied Alzheimer's patients at the initial stage of the disease and after 1 year, to see whether the placebo component of the therapy was affected by the disease. The placebo component of the analgesic therapy was found to be correlated with both cognitive status and functional connectivity among different brain regions, according to the rule "the more impaired the prefrontal connectivity, the smaller the placebo response." In a more recent study, Stein et al. (305) used diffusion tensor magnetic resonance imaging to test the hypothesis of the role of white matter integrity in placebo responsiveness. The individual placebo analgesic effect was found to be correlated with white matter integrity indexed by fractional anisotropy, particularly in the right dorsolateral prefrontal cortex, left rostral anterior cingulate cortex, and the periaqueductal gray. Probabilistic tractography seeded in these regions showed that stronger placebo analgesic responses were associated with increased mean fractional anisotropy values within white matter tracts connecting the periaqueductal grey with the rostral anterior cingulate cortex and the dorsolateral prefrontal cortex. Therefore, both the study on Alzheimer's patients (56) and on white matter integrity in normal subjects (305) demonstrate the importance of prefrontal functioning and connectivity in the placebo response.

To support the crucial role of the prefrontal cortex in the occurrence of placebo responses, Krummenacher et al. (201) used repetitive transcranial magnetic stimulation (rTMS) to inactivate the prefrontal cortex during placebo analgesia. These investigators inactivated the left and right dorsolateral prefrontal cortex during a procedure inducing placebo analgesia and found that rTMS completely blocked the analgesic placebo response. Therefore, the inactivation of the prefrontal lobes has the same effects as those observed in prefrontal degeneration in Alzheimer's disease and reduced integrity of prefrontal white matter **(FIGURE 12)**. Thus a disruption of prefrontal control is associated with a loss of placebo response (45).

Two clinical implications emerge from these findings. First, to compensate for the disruption of placebo/expectation-related mechanisms, we need to consider a possible revision of some therapies in Alzheimer's patients. Second, we should consider the potential disruption of placebo mechanisms in all those conditions where the prefrontal regions are involved, as occurs in vascular and frontotemporal dementia as well as in any lesion of the prefrontal cortex.

D. Creating Placebo Responders and Nonresponders in the Lab

All the recent findings on the neurobiology of different placebo responses show that the placebo effect can be manipulated in a number of ways. Therefore, some of the mechanisms described in the previous sections can be exploited in clinical trials as well as in medical practice, although the objectives are certainly opposite in the two situations. In fact, whereas placebo responses need to be reduced in clinical trials, their increase is desirable in routine medical practice. With this in mind, today we are in a good position to consider the possibility to manipulate placebo responses in both directions to create either placebo responders or nonresponders in the laboratory. However, it is important to remember that the improvement that may take place in a patient who has received a placebo may depend on plenty of factors, such as spontaneous remission, regression to the mean, experimenter's and patient's biases, and the like. By keeping all these factors constant, the real placebo response, i.e., the real psychobiological phenomenon, can be manipulated and/or controlled in a number of ways.

For example, learning plays a critical role in placebo responsiveness so that subjects can be trained to respond or not. Indeed, placebo analgesia is more robust when preconditioning with analgesic treatments is performed. Colloca and Benedetti (89) used a paradigm in which the intensity of painful stimulation was reduced unbeknownst to the subjects, so as to make them believe that a treatment was effective. Powerful placebo responses were obtained after minutes, and these responses lasted up to 4–7 days. The same conditioning procedure was repeated in a second group of subjects 4–7 days after an ineffective analgesic treatment, and this produced a reduction in the magnitude of placebo responses. In this study, small, medium, and large placebo responses were elicited, which indicates that the magnitude of the responses can indeed be controlled by means of learning procedures. In a subsequent study, both behavioral and neurophysiological (laser evoked potentials) placebo responses were found to be affected by learning (93). In addition, social observational learning was found to produce placebo responses that were similar to those induced by directly experiencing the benefit through a conditioning procedure (91).

Whereas on the one hand placebo responses can be increased in the laboratory setting by means of a variety of learning

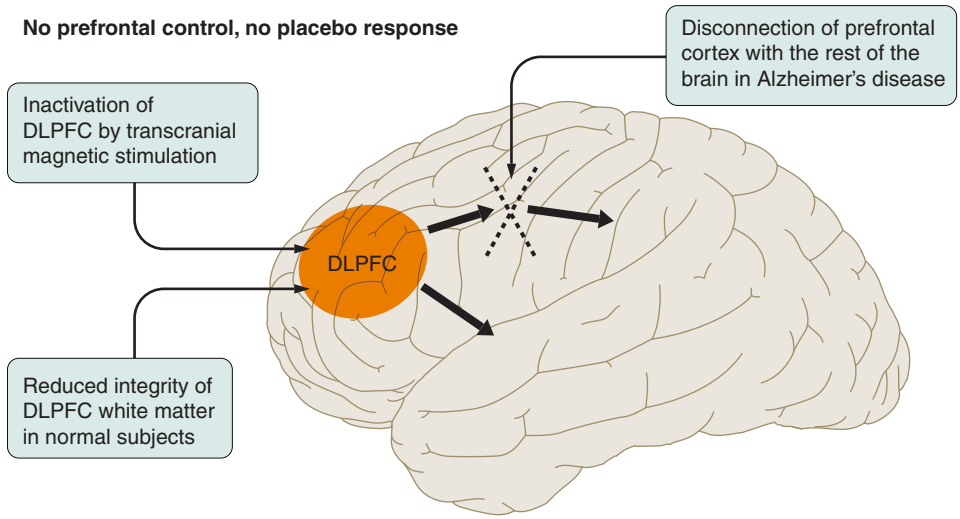

FIGURE 12. If there is no prefrontal control, there is no placebo response. There are at least three evidences for this assertion. First, placebo analgesic responses are reduced or completely absent in Alzheimer's patients with functional disconnection of the prefrontal lobes with the rest of the brain. Second, reduced integrity of the prefrontal white matter is related to reduced placebo analgesic responses. Third, the inactivation of the dorsolateral prefrontal cortex with transcranial magnetic stimulation leads to the blockade of placebo analgesia.

procedures, on the other hand they can be reduced, or even completely abolished, in a number of ways. The classical blockade of placebo analgesic responses has been obtained pharmacologically by means of opioid antagonists, like naloxone (16). Today we know that naloxone blocks a descending pain modulating system. By combining naloxone administration with functional magnetic resonance, Eippert et al. (115) found that naloxone reduced placebo responses as well as brain responses in pain-modulatory cortical structures, such as the dorsolateral prefrontal cortex and the rostral anterior cingulate cortex. These data from the naloxone studies clearly demonstrate that placebo analgesic responses can be inhibited through the pharmacological blockade of cortical and subcortical opioid neurotransmission in the experimental setting.

As described in the section VIC, repetitive transcranial magnetic stimulation (rTMS) has been used to inactivate the prefrontal cortex, and this inactivation leads to the disruption of the placebo analgesic response (201). All these studies on learning, pharmacological manipulation, and rTMS indicate that it is indeed possible to modulate placebo responsiveness in both directions (increase or decrease) through a variety of approaches. In addition to this kind of manipulation, another field that is emerging in placebo research is genetics, whereby some genotypes related to high or poor responsiveness to placebos have been identified in some medical conditions (see sect. IV*E*).

From both an ethical and methodological point of view, it is out of question that it is both desirable and advisable to increase placebo responses in clinical practice. Conversely, whether or not laboratory-created placebo nonresponders can be enrolled in a clinical trial remains an open question for at least two reasons. First, also the global response to the active treatment would be reduced and, second, the trial would not be representative of the general population. Therefore, although it is today possible to create placebo nonresponders in the laboratory, the practical application in clinical trials needs further research and discussion.

VII. UNRAVELING PLACEBO MECHANISMS: GOOD FOR SCIENCE, BAD FOR SOCIETY?

A. Placebo Is a Privileged Window Into Complex Brain Mechanisms

Today placebos and placebo responses represent an active field of neurobiological research, and their study can be viewed as a melting pot of concepts, ideas, and models for neuroscientific investigation, ranging from molecular and cellular to cognitive and social neuroscience. This is due to the involvement of many mechanisms across a number of conditions, systems, and interventions. As emphasized in the present review, different processes may contribute to placebo responsiveness in different conditions, such as anxiety modulation, reward mechanisms activation, and learning. The genetics of the placebo effect is only at the very beginning, yet some genetic variants have been found to respond to placebos compared with others. Today this experimental approach is paying dividends and bodes well for the future. In particular, as pointed out throughout this review, placebos can be considered within the context of the doctor-patient relationship, and in this way they contribute to the understanding of this complex and unique social interaction.

The impact of this new approach on the doctor-patient relationship is straightforward. Physicians, psychologists, and health professionals can better understand what kind of changes they can induce in their patients' brains. With this physiological and neuroscientific knowledge in their hands, health professionals "see" directly how their words, attitudes, and behaviors impact on the brains of their patients. This "direct vision" of the patient's brain will hopefully boost health professionals' empathic, humane, and compassionate behavior further. Teaching courses about the physiology of the doctor-patient interaction in the education of health professionals will lead to a better awareness of the potential power that the doctor's behavior may have on the patient's behavior and capacity of recovery from illness. Moreover, understanding the physiological underpinnings of the doctor-patient relationship will lead to better medical practice and clinical profession, as well as to better social/communication skills and health policy.

B. Placebo Is a Bad Justification for Bizarre Therapies

Unfortunately, a negative counterpart of placebo research does exist. The perception of a symptom and the course of a disease can be modulated by different factors, such as trusting a doctor and believing in a therapy. This raises a number of ethical concerns both in medical practice and in our society. Although ethicists have long known the issues related to placebo (77, 129, 237, 238), the recent neuroscientific insights into the mechanisms of the placebo response have boosted the ethical debate even further (47). In fact, today we know that the very ritual of the therapeutic act can change the physiology of the patient's brain; thus anybody who performs a therapeutic ritual can trigger these effects. If sugar pills and syringes with saline solutions may induce placebo effects when handled by doctors, so the same placebo effects can be triggered by quacks and shamans through eccentric rituals and bizarre concoctions.

There is a worrisome relationship between the growing bizarre healing practices and the neurobiological advances in placebo research. In fact, quacks often refer to the powerful placebo responses they can elicit, and to the real physiological effects that are produced (release of endorphins, activation of endo-

cannabinoids, and the like). These real physiological effects are taken by many quacks as a justification for odd, weird, and bizarre therapies. According to this dangerous point of view, any procedure that increases expectations and beliefs would be justified, for it does not matter where it comes from. What matters is that the physiological mechanisms of the placebo response are activated.

By unraveling the brain mechanisms of the placebo response, which per se may represent a human foible and a vulnerable trait of mankind, science risks to be exploited in the wrong way. Paradoxically, these physiological advances can turn into a regression of medicine to past times. Therefore, placebo research needs to be communicated to society in a different way so that the new physiology of placebo and the doctor-patient relationship faces the ethical problem of a good communication between science, ethics, and media. Some of the most important final questions that need to be solved are: What is the ethical limit to hand out placebos and to increase expectations? Can we accept every means available, whether a sugar pill or a bizarre concoction? And what about those patients who trust eccentric and bizarre rituals but not pills and injections? Should their opioid and cannabinoid systems be activated by means of a bizarre ritual? The future ethical debate promises to be exciting and stimulating, for we are dealing with particularly vulnerable aspects of human beings, namely, expectations, beliefs, and suggestibility.

ACKNOWLEDGMENTS

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GRANTS

This work was supported by grants from Regione Piemonte, Volkswagen Foundation, and NH-BEE Program.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author.

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