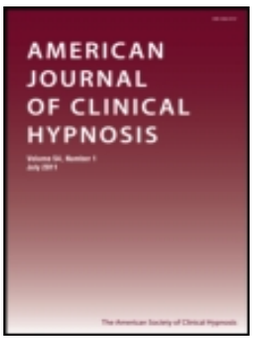

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Placebo and Nocebo Effects: A Complex Interplay Between Psychological Factors and Neurochemical Networks

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Placebo and nocebo effects have recently emerged as an interesting model to understand some of the intricate underpinnings of the mind–body interaction. A variety of psychological mechanisms, such as expectation, conditioning, anxiety modulation, and reward, have been identified, and a number of neurochemical networks have been characterized across different conditions, such as pain and motor disorders. What has emerged from the recent insights into the neurobiology of placebo and nocebo effects is that the psychosocial context around the patient and the therapy, which represents the ritual of the therapeutic act, may change the biochemistry and the neuronal circuitry of the patient's brain. Furthermore, the mechanisms activated by placebos and nocebos have been found to be the same as those activated by drugs, which suggests a cognitive/affective interference with drug action. Overall, these findings highlight the important role of therapeutic rituals in the overall therapeutic outcome, including hypnosis, which may have profound implications both in routine medical practice and in the clinical trials setting.

Keywords: anxiety, cholecystokinin, conditioning, dopamine, endocannabinoids, expectation, nocebo, opioid system, placebo, reward

Defining Placebo and Nocebo Effects

In recent years, the placebo effect has evolved from a nuisance in the setting of clinical trials to a topic worthy of scientific inquiry as analyzed in terms of specific brain regions and biochemical pathways. Starting from the early biological investigations of the placebo effect, in the 1960s in animals (Herrnstein, 1962) and in the late 1970s in humans (Levine, Gordon, & Fields, 1978), today placebo research is a complex field of investigation that ranges from psychology to psychophysiology, from pharmacology to neurophysiology, and from cellular/molecular analysis to modern neuroimaging techniques. A classical definition of placebo effect involves a change in the body–mind unit that occurs as a result of the symbolic significance that one attributes to an event or an object in the healing environment (Brody & Brody, 2011). Therefore, whereas in

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the clinical trial setting the conceptualization of placebo focuses on distal and external factors, such as inert treatments (e.g., sham surgery) and inert substances (e.g., saline solutions or water), in the context of psychology, the concept of placebo focuses on proximal and internal factors, namely a set of psychosocial stimuli surrounding the patient and the therapy (Moerman, 2002; Moerman & Jonas, 2002; Price, Finniss, & Benedetti, 2008). In this sense, when a treatment is given to a patient, be it sham or real, it is not administered in a vacuum but within a complex set of psychological states that vary from patient to patient and may be as important as the specific effect of a drug. This context includes the physical properties of the medication (color, shape, taste, smell), the characteristics of the healthcare setting (hospital or home, room layout), the sight of health professionals (words, attitudes, behaviors) and medical instruments, and the interaction between patient and doctors (Balint, 1955; Di Blasi, Harkness, Ernst, Georgiou, & Kleijnen, 2001).

The nocebo effect is opposite to the placebo effect, for it involves the pathogenic consequences of placebo administration within a negative psychosocial context (Amanzio, Corazzini, Vase, & Benedetti, 2009; Rief et al., 2009). For example, unwanted effects and side effects may occur as the result of negative expectations about some treatments (Amanzio et al., 2009; Barsky, Saintfort, Rogers, & Borus, 2002; Flaten, Simonsen, & Olsen, 1999; Mora, Nestoriuc, & Rief, 2011; Rief et al., 2009). Knowledge about the mechanisms of the nocebo response still lags behind the more detailed understanding of the placebo counterpart, mainly due to ethical limitations. Indeed, inducing negative expectations is an anxiogenic procedure (Benedetti, Lanotte, Lopiano, & Colloca, 2007; Colloca & Benedetti, 2007).

What we have learned over the past years is that there is not a single placebo or nocebo effect but many, and each one can be triggered by a variety of psychological mechanisms, such as conditioning, expectation, anxiety modulation, and reward, which can in turn be modulated by other factors, such as desire, motivation, and memory. However, not all improvements observed after a sham treatment are attributable to real psychobiological phenomena. Confounding factors, such as spontaneous remission, patient's or experimenter's biases, regression to the mean, or the effect of unidentified co-interventions may also be involved, and in placebo research, these must be eliminated through the appropriate experimental approach. Considerable progress has also been made in our understanding of the neurobiological underpinnings of placebo and nocebo effects, particularly in conditions such as pain and Parkinson's disease (Carlino, Frisaldi, & Benedetti, 2014; Frisaldi, Carlino, Lanotte, Lopiano, & Benedetti, 2014). Other medical conditions, such as anxiety, hormone secretion, and immune responses, are less understood, but some of their neurobiological mechanisms have been identified as well (Benedetti, 2014).

In this article we will give a concise updated overview of all the mechanisms that may contribute to a given placebo or nocebo effect.

The Psychological Approach

Different explanatory mechanisms have been proposed to describe both placebo and nocebo effects. These mechanisms need not be mutually exclusive, and they can actually be at work simultaneously. The first explanation centers on expectation, generated as the product of cognitive engagement involving the subjectively experienced likelihood of a future effect, often induced by verbal suggestions (Kirsch, Wickless, & Moffitt, 1999; Price et al., 2008). Indeed, during a medical treatment, the patient has different expectations about the therapeutic outcome. The patient anticipates possible positive or negative effects of the therapy using different cues from the environment (e.g., the place where the treatment is administered), the emotional arousal (e.g., the potential benefit of the therapy), and the interaction with care providers (e.g., the verbal suggestions of improvement). This anticipatory process, in turn, triggers internal changes, resulting in such experiences as placebo analgesia, in which the mere belief that one is receiving an effective analgesic treatment can reduce pain (Amanzio & Benedetti, 1999; Benedetti, Arduino, & Amanzio, 1999; Wager et al., 2004). The same holds true for nocebo hyperalgesia, but in the opposite direction (Benedetti et al., 2007; Pollo, Carlino, & Benedetti, 2011).

Different levels of expectations are capable of inducing different levels of placebo responses. Price et al. (1999) showed that the same placebo cream applied onto three adjacent skin areas induces a progressively stronger analgesia according to the strength of the accompanying words (strong analgesic, weak analgesic, and control agent). This is true also in the clinical setting, where changing the symbolic meaning of a basal physiological infusion in postoperative patients resulted in different intakes of additional painkillers (Pollo et al., 2001). In a more recent study, Parkinson patients who were told that they had a specific probability (25%, 50%, 75%, or 100%) of receiving active medication, when in fact they always received a placebo, showed different degrees of dopamine activation. Only when patients were informed that they had a 75% probability of receiving active medication did a significant dopamine release occur, suggesting a tight relationship between the strength of expectation of improvement and the clinical outcome (Lidstone et al., 2010).

Expectations are unlikely to work alone, as they can be modulated by other factors, such as desire, self-efficacy, and reinforcing feedback (Price et al., 2008). Desire is represented by the experiential feeling of wanting a future event to happen or the opposite feeling of wanting to avoid a future situation. Self-efficacy is the personal belief to be capable of managing an adverse event, performing the right actions to induce positive changes. Self-reinforcing, often called "somatic-focus," is a cognitive process where a subject waits for any sign of improvement during a therapy and takes these signs as positive evidence that the treatment is successful, meanwhile discarding the opposite negative evidences. These cognitive processes are likely to work together with emotional states, like anxiety. A study with patients suffering from irritable bowel syndrome

showed that decreased anxiety levels correlated with pain relief perception when patients received a placebo treatment (Vase, Robinson, Verne, & Price, 2005).

Whereas anxiety is linked to the anticipation of a negative event, expecting a positive event may involve the activation of the reward system. Through the activation of the mesolimbic and mesocortical dopaminergic reward pathways, the reward system fulfills its natural task of providing pleasurable feelings in response to life-sustaining functions, such as eating, drinking, or having sex, to encourage the repetition of those functions. Placebos have reward properties as well, since the expected clinical benefit is itself a form of reward (Lidstone & Stoessl, 2007).

Learning is another mechanism that plays a crucial role in placebo responsiveness. There is compelling experimental evidence that patients can learn, based on previous experiences, that a certain pill or a certain treatment is associated to a specific therapeutic outcome (Colloca & Miller, 2011). This mechanism can involve classical conditioning, a process whereby the repeated association of an unconditioned response (e.g., salivation after food presentation) with a conditioned stimulus (e.g., the ringing bell accompanying the food), which usually would not have an effect, will lead to a conditioned response (e.g., salivation after the ringing bell without the food presence). This mechanism occurs in the clinical context as well, where different contextual stimuli (e.g., the presence of a doctor, the shape and color of a pill) can be considered conditioned stimuli in all respects (Ader, 1997; Siegel, 2002; Wickramasekera, 1980). Classical conditioning seems to be the key mechanism, especially when unconscious physiological functions, such as endocrine secretion or immune responses, are involved. Indeed, it has been shown that after repeated administrations of sumatriptan, which stimulates growth hormone (GH), a placebo can mimic the effects of the drug, regardless of what the subjects expect (either decrease or increase of GH; Benedetti et al., 2003b). Therefore, cognitive factors, such as expectations, do not affect these unconscious physiological functions. Conditioned hormonal responses have been observed in humans for insulin and glucose (Stockhorst, Steingrüber, & Scherbaum, 2000) and for dexamethasone and cortisol as well (Sabbioni et al., 1997).

Similarly, behaviorally conditioned changes in peripheral immune functions have also been demonstrated in experimental animals, healthy subjects, and patients (Schedlowski & Pacheco-López, 2010; Vits et al., 2011). For example, in patients affected by multiple sclerosis, the repeated association of a flavored beverage with the immunosuppressive drug cyclophosphamide led to a decrease in peripheral leukocytes after the administration of the flavored drink alone (Giang et al., 1996). A similar paradigm was reproduced in healthy participants in whom conditioned immunosuppression, as assessed by lymphocyte proliferation, interleukin-2, and interferon-gamma, was observed after repeated association of a conditioned stimulus with cyclosporine A (Goebel et al., 2002).

Learning mechanisms through conditioning do not necessarily rely on the unconscious association between a conditioned and an unconditioned stimulus. According to more recent cognitive theories of classical conditioning, the mechanism can be based

on the cognitive information implicitly contained in the conditioned stimulus. In other words, the information contained in the conditioned stimulus would lead to the specific expectation that a given event will follow another event (Montgomery & Kirsch, 1996; Reiss, 1980; Rescorla, 1988; Voudouris, Peck, & Coleman, 1990).

The Biological Approach

Until the late 1970s, when Levine and colleagues (1978) first showed that the opiate antagonist naloxone was capable of reducing the placebo response in dental postoperative pain, the placebo effect was only considered as a nuisance that had to be taken into account to properly assess the effects of medicaments in clinical trials. But this and subsequent works in the 1980s and 1990s left little doubts that specific biochemical events were taking place after placebo administration. Among the relevant findings, placebo responders were found to have levels of β-endorphin in the cerebrospinal fluid that were more than double those of non-responders (Lipman et al., 1990), opioids released by a placebo procedure displayed the same side effects as exogenous opioids (Benedetti, Amanzio, Baldi, Casadio, & Maggi, 1999), and naloxone-sensitive cardiac effects could be observed during placebo-induced expectation of analgesia (Pollo, Vighetti, Rainero, & Benedetti, 2003). Indirect support also came from the placebo-potentiating role of the cholecystokinin (CCK) antagonist proglumide. In fact, the CCK system effects counteract those of opioids, delineating a picture where the placebo effect seems to be under the opposing influence of facilitating opioids and inhibiting CCK (Benedetti, Amanzio, & Maggi, 1995; Benedetti, Amanzio, & Thoen, 2011).

The opioid antinociceptive system is certainly the best documented in different placebo studies, but it is not the only one implicated. Knowledge of other systems is scarce, but their existence emerges from the fact that in some situations, a placebo effect can still occur after blockade of opioid mechanisms by naloxone (Gracely, Dubner, Wolskee, & Deeter, 1983; Grevert, Albert, & Goldstein, 1983; Vase et al., 2005). It seems that different agents can bring about different placebo effects. For example, with a morphine conditioning and/or expectation-inducing protocol, Amanzio and Benedetti (1999) could, with naloxone, completely reverse placebo analgesia induced in experimental ischemic arm pain; with the use of ketorolac, a non-opioid analgesic, in the same protocol, however, only a partial blockade was observed. Recently, an important non-opioid component of placebo analgesia has been identified, and this is represented by the endocannabinoid system (Benedetti, Amanzio, Rosato, & Blanchard, 2011).

Along a different line of research, dopamine has also been suggested as a putative substance involved in placebo analgesia. The placebo response was first linked to this neurotransmitter after observations in Parkinson's disease, where it usually takes the form of motor improvement following the administration of an inert substance that the patient "believes" to be an effective antiparkinsonian drug. Here, it is mediated by

dopamine release in the *dorsal* striatum, a key structure in the motor circuit affected by the disease (de la Fuente-Fernández et al., 2001). However, it must be noted that dopamine is also released in the *ventral* striatum, notably in the nucleus accumbens, involved in the reward circuit. Contrary to the dorsal striatum, release in ventral striatum was not correlated with the experienced clinical benefit, leading the authors to suggest that this release might be related to the expectation of reward rather than to reward itself (de la Fuente-Fernández et al., 2002; de la Fuente-Fernández & Stoessl, 2002). As such, this dopamine mechanism might not be limited to effects in Parkinson's disease, but could be a generalized process underlying all placebo responses. For example, in a study combining placebo analgesia and a monetary reward task, it was demonstrated that the subjects with stronger nucleus accumbens synaptic activation (as measured by functional magnetic resonance imaging [fMRI]) during the monetary reward anticipation also showed more robust placebo responses and greater dopamine activity in the same nucleus (as measured with dopamine-agonist [^{11}C]raclopride positron emission tomography [PET]) (Scott et al., 2007). Moreover, in a subsequent PET study using the μ-opioid receptor-selective radiotracers [^{11}C] carfentanil and [^{11}C]raclopride, both opioid and dopamine neurotransmission were assessed with a pain placebo procedure. It was found that they were both coupled with the placebo response, with changes of activity induced in several brain regions associated with the opioid and dopamine networks (Scott et al., 2008; Figure 1).

Besides all this pharmacological approach, PET, fMRI, magneto-electroencephalography (MEG), and electroencephalography (EEG) have all been usefully employed to characterize the spatial and temporal domains of placebo analgesia (Colloca et al., 2008; Kong, Kaptchuk, Polich, Kirsch, & Gollub, 2007; Rainville & Duncan, 2006). Reduced pain-related brain activation during placebo analgesia has been repeatedly and independently reported in many studies, often with strict correlation with psychophysical pain measures, supporting the view that during placebo analgesia, what is altered is not the evaluation of an unchanged incoming pain information but rather a direct modulation of nociceptive afferent signals (Bingel, Lorenz, Schoell, Weiller, & Büchel, 2006; Kong et al., 2006; Koyama, McHaffie, Laurienti, & Coghill, 2005; Lieberman et al., 2004; Price, Craggs, Verne, Perlstein, & Robinson, 2007; Wager et al., 2004; Watson et al., 2009). Areas of the pain matrix showing decreased activation include thalamus, insula, rostral anterior cingulate cortex (rACC), primary somatosensory cortex, supramarginal gyrus, and left inferior parietal lobule. Scalp laser-evoked potentials (LEPs) amplitude was also found to be reduced during the placebo analgesic response, namely in the N2–P2 components, thought to be originated in the bilateral insula and in the cingulate gyrus (Colloca et al., 2008; Wager, Matre, & Casey, 2006; Watson, El-Deredy, Vogt, & Jones, 2007). Modulation of pain-related neural activity by placebo has been shown to extend down to the spinal cord level. Recently, an elegant study demonstrated the direct involvement of the spinal cord in placebo analgesia by showing with fMRI that the responses to painful heat stimulation

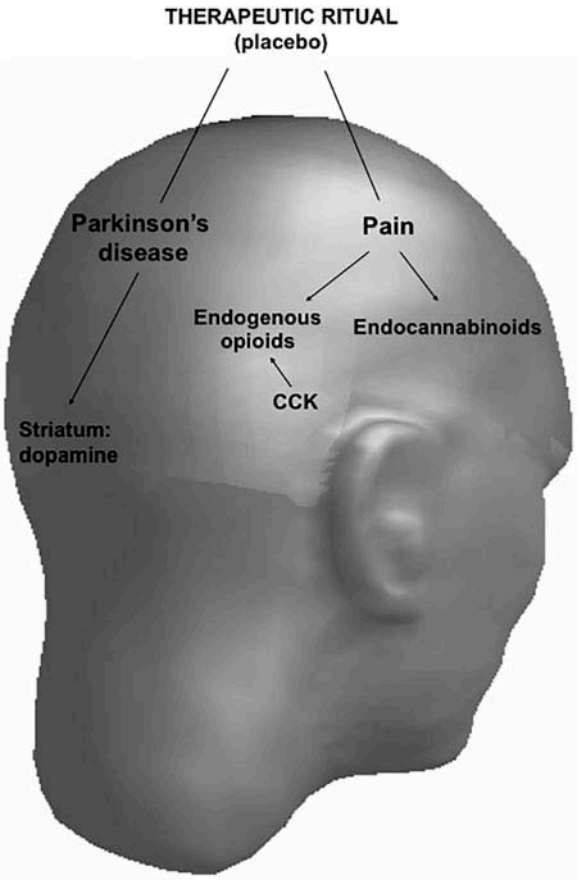

FIGURE 1 Neurobiological mechanisms of the placebo effect in the most studied conditions. In Parkinson's disease, placebos induce the release of dopamine in the striatum. In pain, placebos induce the activation of either endogenous opioids or endocannabinoids. CCK has an inhibitory effects on opioids, thus inhibiting placebo analgesia. CCK is also involved in nocebo hyperalgesia.

are reduced under placebo analgesia in the ipsilateral dorsal horn (Eippert, Finsterbusch, Bingel, & Buchel, 2009).

Data from imaging studies neatly converge with the neuropharmachological evidence described above to support the model of the recruitment of the descending pain inhibitory system to negatively modulate pain processing during the placebo response (Petrovic, Kalso, Petersson, & Ingvar, 2002; Wager, Scott, & Zubieta, 2007; Zubieta et al., 2005). Focusing strictly on the pain anticipatory phase, i.e., on the time lag between the display of a cue signaling the impending pain stimulus and the delivery of the stimulus, Wager and colleagues (2004) observed an increase in dorsolateral prefrontal cortex (DLPFC)

activity, negatively correlated with the signal reduction in the thalamus, ACC, and insula, and with reported pain intensity, but positively correlated with increase in a midbrain region containing the periaqueductal gray (PAG). Further support for a link between limbic areas and the PAG came from a connectivity analysis showing correlation between the activation of rACC and that of the PAG and bilateral amygdala (Bingel et al., 2006). In a recent study, the same authors also showed strict opioid specificity of this coupling, which was abolished by naloxone administration (Eippert et al., 2009).

The prefrontal regions seem to play a key role in placebo analgesia. In Alzheimer patients, loss of placebo responses on one hand and reduction of connectivity between the prefrontal lobes and the rest of the brain on the other progress in parallel (Benedetti et al., 2006). In addition, transitory inhibition of excitability in the prefrontal cortex, as can be obtained by repetitive transcranial magnetic stimulation, has also been shown to be equally effective in producing abolition of placebo analgesia (Krummenacher, Candia, Folkers, Schedlowski, & Schönbächler, 2010).

As for the placebo counterpart, most knowledge about nocebo effects comes from the field of pain and analgesia. However, to design experiments aimed at gathering information on the negative outcome of sham treatments is not an easy task, all the more so when pain is involved. Ethical limitations forbid inflicting deliberate harm, and many studies are carried out on healthy volunteers (rather than patients), in whom only expectations about incoming pain are negatively modulated, without actual administration of any drug. In this context, it is not surprising that our knowledge on nocebo hyperalgesia still lags behind the more detailed understanding of placebo analgesia (Benedetti et al., 2007; Colloca & Benedetti, 2007). An early study showed that nocebo pain responses induced in post-operative patients by negative expectation regarding a saline infusion could be prevented by the CCK antagonist proglumide, a nonspecific CCK-1 and CCK-2 antagonist, in a dose-dependent manner. This blockade was not mediated by endogenous opioids, as it was unaffected by naloxone (Benedetti, Amanzio, Casadio, Oliaro, & Maggi, 1997). As the expectation of pain increase is a highly anxiogenic process, and both anxiety and anxiety-induced hyperalgesia have been shown to be enhanced by CCK and attenuated by CCK antagonists in animal models (Andre et al., 2005; Hebb, Poulin, Roach, Zacharko, & Drolet, 2005; Lydiard, 1994), it is also rational to assume that anxiolytic drugs can interfere with nocebo hyperalgesia. In a study on healthy volunteers employing a protocol of experimental ischemic arm pain, it has been shown that nocebo hyperalgesia can indeed be regarded as a stress response as it is accompanied by increased levels of adrenocorticotropic hormone (ACTH) and cortisol, which indicates hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis. After administration of a benzodiazepine anxiolytic drug (diazepam), both HPA hyperactivity and nocebo hyperalgesia were blocked. When proglumide was given together with nocebo suggestions, only hyperalgesia was completely prevented. There was no effect on the HPA axis (Benedetti, Amanzio, Vighetti, & Asteggiano, 2006). This suggests that CCK does not act on the general process of nocebo-induced anxiety but, rather,

specifically on nocebo/anxiety-induced hyperalgesia. Put differently, nocebo suggestions induce anxiety, which in turn separately induces both HPA and pain enhancement. While diazepam acts on anxiety, thus blocking both effects, proglumide acts only on the pain pathway, downstream of the nocebo-induced anxiety.

As for placebo analgesia, neuroimaging techniques have also highlighted important contributions to our knowledge of nocebo hyperalgesia. Inducing negative expectations results in both amplified unpleasantness of innocuous thermal stimuli as assessed by psychophysical pain measures (verbal subject report) and increased fMRI responses in the ACC and in a region including the parietal operculum and posterior insula (Sawamoto et al., 2000). Together with the hippocampus and the prefrontal cortex, these are regions also involved in pain anticipation (Chua, Krams, Toni, Passingham, & Dolan, 1999; Hsieh, Stone-Elander, & Ingvar, 1999; Keltner et al., 2006; Koyama et al., 2005; Koyama, Tanaka, & Mikami, 1998; Lorenz et al., 2005; Ploghaus et al., 2001; Porro et al., 2002; Porro, Cettolo, Francescato, & Baraldi, 2003). In some cases, the same study has addressed both positive (placebo) and negative (nocebo) expectations with opposite modulation of pain-related brain areas (Keltner et al., 2006; Koyama et al., 2005; Lorenz et al., 2005). Kong et al. (2008) emphasized the effect of negative expectations about pain perception following sham acupuncture and compared fMRI responses following thermal stimuli of equal intensity delivered at control sites or at sites along the suggested course of an acupuncture meridian (nocebo). Increased pain reports for the nocebo sites paralleled increased activity in several areas of the medial pain matrix (including bilateral dorsal ACC, insula, left frontal and parietal operculum, orbitofrontal cortex, and hippocampus). Of particular interest is the involvement of the hippocampus, as its activity is also anxiety driven (Ploghaus et al., 2001).

From all these studies, it appears that the circuitry underlying nocebo hyperalgesia largely involves, with opposite modulation, the same areas engaged by placebo analgesia. The current model suggests that the DLPFC here too might exert active control on pain perception by modulating corticosubcortical and corticocortical pathways.

Implications for Clinical Practice and for Hypnosis

One of the most compelling evidences that expectation is a key element in the therapeutic outcome is represented by the hidden administration of therapies (Benedetti, Carlino, & Pollo, 2011; Colloca, Lopiano, Lanotte, & Benedetti, 2004). This means that a treatment is given without information, so that the patient is unaware that a treatment is being performed. Therefore, there are no expectations about any clinical improvement, and this leads to a reduced efficacy of the therapy. In terms of medical practice, this has profound implications because the information delivered by health professionals may make a big difference in the therapeutic outcome. This approach is quite difficult from a methodological point of view, and it is at the borderline between the experimental setting and

clinical practice. A doctor carries out the open administration, telling the patient (e.g., at the bedside) that the injection is a powerful analgesic and that the pain is going to subside in a few minutes. In contrast, a hidden injection of the same analgesic at the same dose is performed by an automatic infusion machine that starts the painkilling infusion without any doctor or nurse in the room; these patients are completely unaware that an analgesic therapy has been started. For example, the effectiveness of diazepam, one of the most frequently used benzodiazepines for treating anxiety, is reduced or completely abolished when diazepam is administered unbeknown to the patient (Benedetti et al., 2003a, 2011c; Colloca et al., 2004). The same effects are present in other conditions such as pain and Parkinson's disease (Benedetti et al., 2003a, 2011c; Colloca et al., 2004). For example, in postoperative pain following the extraction of the third molar (Levine & Gordon, 1984; Levine, Gordon, Smith, & Fields, 1981), a hidden intravenous injection of 6–8 mg of morphine corresponds to an open intravenous injection of saline solution in full view of the patient (placebo). In other words, telling the patient that a painkiller is being injected (with what is actually a saline solution) is as potent as 6–8 mg of morphine. This holds true for a variety of painkillers, such as morphine, buprenorphine, tramadol, ketorolac, and metamizole (Amanzio, Pollo, Maggi, & Benedetti, 2001; Benedetti et al., 2003a; Colloca et al., 2004).

Open and hidden administrations have been studied in combination with fMRI (Bingel et al., 2011). Expectation of remifentanil (told remifentanil, gets remifentanil) produces more pronounced analgesic effects compared to no-expectation (told saline, gets remifentanil). Moreover, expectation of interruption (told interruption, gets remifentanil), abolishes the overall analgesic effect. fMRI shows that the enhancement of analgesia in the positive expectation condition is associated with activity in the DLPFC and pregenual ACC, whereas negative expectation of interruption is associated with activity in the hippocampus.

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. There is some evidence that these two components operate independently from each other. Both remifentanil and expectations reduce pain, but drug effects on pain reports and brain activity, as assessed by fMRI, do not interact with expectations. Regions associated with pain processing show no differences in drug effects as a function of expectation in the open and hidden conditions. Instead, expectations modulate activity in frontal cortex, with a separable time course from drug effects (Atlas et al., 2012). Therefore, drugs and expectations both influence clinically relevant outcomes, yet they seem to operate without mutual interference.

All these studies emphasize how the knowledge about the treatment affects the therapeutic outcome. This may have profound implications in medical practice, whereby the doctor–patient interaction and communication may have a crucial role. Interestingly, a recent survey on a population of Italian patients found that the most important concern among patients about the doctor–patient relationship is represented by the information

given by doctors about the treatment, particularly the explanations about its efficacy, duration, utility, and risks (Giudetti & Pampallona, 2014). In light of this survey, it should be expected that all therapies delivered with no information would be less effective.

Placebo and hypnosis are deeply linked by their phenomenology since hypnosis can be regarded as a non-deceptive expectation manipulation, where hypnotic suggestions can produce therapeutic effects that do not require deception. In other words, hypnosis is a means of eliciting placebo effects without the use of placebos (Kirsch, 1994). The essence of this approach is to create with the patient a context in which any expectation for change will occur (Matthews, Lankton, & Lankton, 1993). A number of studies have compared placebo and hypnosis effects in different clinical settings. For example, in the treatment of headache, both hypnosis induction and placebo administration were found to produce a significant decrease in headache pain compared to a control condition (Spanos et al., 1993). Likewise, in a study designed to assess the placebo component in hypnosis, participants were asked to rate experimentally induced ischemic pain. Changes in pain threshold and tolerance were evaluated following the induction of hypnotic and placebo analgesia and compared to an initial baseline performance (McGlashan, Evans, & Orne, 1969). As summarized in Hilgard and Hilgard (1975), the results showed that those participants who were not susceptible to hypnosis reported similar pain reductions in both placebo and hypnosis conditions, whereas those participants who were highly susceptible to hypnosis reported far greater pain reductions after hypnotically suggested analgesia compared to placebo-induced analgesia. Interestingly, although it is possible to find specific characteristics that define a participant as highly susceptible to hypnosis, it is still difficult to find a personal characteristic that can define a good placebo responder (Frischholz, 2007). Indeed, some individuals can be classified as good "placebo responders" whereas others are not (Benedetti & Frisaldi, 2014), but a validated operational method for identifying these differences does not exist to date.

Recent imaging studies have indicated an important role of rACC and DLPFC in the hypnotic inductions, and these are crucial regions involved in placebo and nocebo responsiveness. McGeown, Mazzoni, Venneri, and Kirsch (2009) found that hypnotic inductions produce a unique pattern of brain activation in highly suggestible subjects that consists in decreased brain activity in the anterior part of the "default mode" network, a set of midline brain structures that includes the anterior cingulate, ventral, and dorsal medial prefrontal cortex; posterior cingulate; and precuneus (Fox & Raichle, 2007; Mason et al., 2007; Raichle et al., 2001). The default mode network refers to those areas of the brain that are activated when people are not engaged in any specific cognitive task but, rather, are letting their minds wander at rest. These findings support the hypothesis that highly suggestible people approach hypnosis as an active task in which attention is focused on the anticipated upcoming suggestions rather than a fundamental shift in the functioning of consciousness (Mazzoni, Venneri, McGeown, & Kirsch, 2013).

By translating all these considerations into routine medical practice, special attention should be paid to those psychological factors that either improve or worsen the

effectiveness of hypnosis, first and foremost the promotion of positive expectancies (Kirsch, 1994). Understanding placebo and nocebo effects in hypnotic treatments is certainly a challenge that will lead to a better knowledge of both clinical practice and the neurobiological underpinnings of hypnosis. Since one of the main purposes of hypnosis is to understand and gain control of emotions with beneficial effects for stress reduction, it would be interesting to explore the possible effects of the combined use of hypnosis and placebo treatments to boost their positive outcomes.

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