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# The sweetest pill to swallow: How patient neurobiology can be harnessed to maximise placebo effects

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## ABSTRACT

The burgeoning interest in placebo effects over the last 10–15 years has fallen into two main research areas: elucidation of the neurobiological mechanisms recruited following placebo administration, and investigations into the situations and contexts in which placebo effects are evoked. There has been little attention focused on bridging these two i.e. how to actively translate and apply these neurobiological mechanisms into daily clinical practice in a responsible way. This article addresses this gap, first through a narrative review of the last 15 years of neuroscience findings with special attention focussed on the elucidation of the neurotransmitters, pathways and mechanisms involved in placebo effects, and secondly, at how these psycho(neuro)biological effects could be harnessed in medical care.

## 1. INTRODUCTION

Placebos *are* a conundrum.

How can something which by definition is an inert treatment devoid of any pharmaceutical properties (*e.g.* a sugar pill, saline injection, or even words, rituals and meanings) produce a change in a patient?

The mention of the word ‘placebo’ is often immediately associated with placation and deception (Bensing and Verheul, 2010, de Craen et al., 1999 and Verheul et al., 2010). In spite of the bad press they receive, surveys carried out in the United States (Berger, 1999 and Sherman and Hickner, 2007), Denmark (Hrobjartsson and Norup, 2003) and Israel (Nitzan and Lichtenberg, 2004) reveal that placebos are being fairly widely administered in medical practice. In spite of the placebos’ dubious history, the neuroscientific investigations from the last 15 years (see Box 1 for search strategy and selection criteria) have shown that the placebo effect is in fact *a real biological phenomenon due to the psychosocial context of the patient and the therapy* (Finniss

et al., 2010 and Price et al., 2008). By their very definition placebo effects therefore bridge physiological processes with the interaction-rich environment in which they occur, and yet the practical potential in this overlap has not yet been tapped.

#### [Box 1]

In this article we would like to put forward how the knowledge gleaned from placebo effect research can provide valuable added benefits to daily medical situations when used in an open, ethical and responsible way.

After the initial title and abstract screening, the publications fell into categories: primary research papers, and reviews. Primary research papers were defined as those containing experimental evidence pertaining to placebo effect research. Reviews (including books) included summaries of findings from primary research papers. Other papers were also garnered via forward searching (citation index to see how often and by whom this paper had been cited) and backward searching (what publications did this author include that we may have missed) using the publications extracted from the database searches. Publications were included if they contained experimentally supported findings for neural substrates and neural mechanisms. Publications were excluded if they: included only historical and theoretical information (*i.e.* no experimental support); were for placebo-controlled trials for pharmaceutical testing; did not have a neuroscience-related content. This yielded around 200 publications and it is on the basis of these that this paper is written. The literature search itself was thus limited to the neuroscientific studies underlying placebo effects. These were then further supplemented with scientific studies from a wide variety of disciplines to illustrate examples and possibilities of clinical applications of placebo effects.

#### **1.1. Hidden in plain sight: open-hidden paradigm**

It is sobering to realise that until post-World War II, modern medicine was essentially the medicine of placebo effects (Kaptchuk, 1998, Raicek et al., 2012 and Shapiro and Shapiro, 1997). Placebo effects became more scientifically visible when Beecher (1955) reported that 35% of patients responded positively to placebo treatment. His choice to categorise placebo effects as something to be baselined – as opposed to investigating the occurrence of the effects themselves – resulted in the adoption of the randomised controlled trial (RCT), and later, the double-blind placebo-controlled clinical trial.

In recent years, meta-analyses of published data disrupted emerging theories when they implied that placebo effects were actually very small, and even non-existent (Hrobjartsson and Gøtzsche, 2001, Hrobjartsson and Gøtzsche, 2004a, Hrobjartsson and Gøtzsche, 2004b, Hrobjartsson and Gøtzsche, 2006, Hrobjartsson and Gøtzsche, 2007a and Hrobjartsson and Gøtzsche, 2007b). As a result of this, differences came to light between placebo effects observed during experimental conditions and those in clinical trials (Hrobjartsson and Gøtzsche, 2010, Vase et al., 2002 and Vase et al., 2009). In clinical trials, it is the new drug that is under scrutiny, and the placebo becomes a method of statistical differentiation; in experimental conditions designed for studying placebo effects, it is the placebo effect itself that is being investigated. It has now been established that placebo effects are larger under experimental conditions than clinical trials, and are especially present in placebo analgesia research (Hrobjartsson and Gøtzsche, 2010). The placebo effect is thus a real

psychobiological occurrence which does not denote natural history progression (spontaneous remissions), patient bias and regressions to mean. The latter are commonly found in the clinically executed placebo-controlled pharmaceutical trials. The quantitative magnitude of the placebo effect was revealed by Levine and co-workers during post-operative dental pain studies (Levine et al., 1981 and Levine and Gordon, 1984). Telling patients that a painkiller was being administered, whereas in fact a saline (placebo) solution was being given, was found to be as potent as a hidden intravenous 6–8 mg dose of morphine. For the patient, the sight and presence of a doctor openly injecting a painkiller was a potent analgesic in itself. These studies by Levine et al. introduced for the first time the open-hidden experimental design which has since been used widely in clinical (placebo) settings (Amanzio et al., 2001, Benedetti et al., 2003b and Colloca et al., 2004). In the most straightforward open set-up, an injection (e.g. a verum analgesic) is given in full view of the patient; in the hidden set-up, the treatment is administered via a computer-operated infusion pump, where the doctor is absent and the patient is unaware when the pharmacotherapy is being administered. If a drug is effective and the pharmacological action is the cause of the improvement, there should be no difference between the open and the hidden injections. The beauty of this open-hidden paradigm is that by eliminating extraneous surrounding components it provides a clean measure of the true pharmacological drug action under investigation. The difference between the two forms of administration (Fig. 1) comprises a black box of psychosocial-neurobiological constituents ('placebo effect components') inherent in eliciting placebo responses. There has recently been a call for creative experimental efforts to rigorously assess the clinical significance of placebo interventions and investigate these component elements that may contribute to the therapeutic benefit of placebo effects (Hróbjartsson et al., 2011).

[FIGURE 1]

### **1.2. Interaction-enhanced pharmacology**

In a clinical setting, a drug is most commonly administered in full-view of the patient, with their knowledge that it is being given. The open-hidden experimental set-up showed how the very act of administration triggers the placebo response component, in analgesia, Parkinson's disease, anxiety and depression (Colloca et al., 2004). This means that it could feasibly be an ever-present part of the total therapeutic effect in which overall outcome is greater than that produced purely by the chemical component(s). In daily clinical practice this means that the therapeutic effect produced by many treatments is inseparable from the context in which it is given and the doctor (practitioner or medical personnel) giving it. The fact that placebo effects exist *in addition to* the pharmacological action of the drug (Fig. 1) would seem to make them amenable to being used more often than they currently are. We have termed this 'interaction-enhanced pharmacology'. There is no unethical misleading or deception of patients since no fake drugs or other placebo substance need to be administered. Instead there is a harnessing of constituents, both in the doctor as well as in the patient through their mutual interaction to elicit the patient's innate capabilities, and thus enhance the effects of existing medical therapies.

## **2. THE PATIENT AS CENTRAL FACTOR**

When a patient steps into the doctor's office, neurobiological processes are triggered in reaction to psychosocial components before any pharmacotherapy has even been administered. Although a complex intertwining of these factors is actually present, various components have been established from placebo effect research that are involved in this interaction-enhanced pharmacology. These include:

### Treatment context

- Patient–doctor (patient–practitioner) interaction.
- Choice of intervention method used.

### Psychological processes

- Expectancy.
- Conditioning and reinforced expectancies.

### Neurophysiological mechanisms

- Opioidergic pathways.
- Dopaminergic pathways.
- Cannabinoidergic pathways.

## **2.1. Treatment context**

### *2.1.1. Patient–practitioner interaction*

In the whole psychosocial context surrounding medical treatment, the most powerful contributing factor is probably the patient–doctor interaction (Barrett et al., 2007, Brody, 2009 and Di Blasi et al., 2001). This interaction lies at the heart of medicine (de Haes and Bensing, 2009), is present in almost every step of medical care, and is known to play an important role in the outcome of illness (Bass et al., 1986, Greenfield et al., 1985, Starfield et al., 1981, Stewart et al., 1979 and Stewart, 1995). Patient–practitioner communication has to address the patient's 'double need' (Bensing et al., 1996 and Engel, 1988): to know and understand, and to feel known and understood. Doctor–patient communication has been shown to play an important role in fulfilling both these needs (Bensing and Dronkers, 1992). Affective communication is targeted at establishing a good therapeutic relationship between the practitioner and the patient (Bensing et al., 1996), and there have been many qualitative and observational studies around the characteristics necessary for a 'good doctor' e.g. warmth, eye contact, active listening, empathy, thoughtful silences, and leaving room for the patient to tell their story (Epstein and Street, 2007, Roter and Hall, 2006, Roter et al., 2006 and Stewart, 1995). An overview of the literature shows that 'although there is much inconsistency regarding emotional and cognitive care, one relatively consistent finding is that physicians who adopt a warm, friendly, and reassuring manner are more effective than those who keep consultations formal

and do not offer reassurance.’ (Di Blasi et al., 2001). By employing such communication techniques the patient feels cared for (Bensing et al., 1996, Epstein and Street, 2007 and Neumann et al., 2010).

The notion of the doctor as the drug (Balint, 1957) and the doctor as a walking placebo (Brody, 1997) have been known for some time, yet this ‘factor X’ (White, 1988) has been extensively demonstrated by Kaptchuk and co-workers. Embedded within the placebo arm of an intervention study on the effects of acupuncture on irritable bowel syndrome (IBS) symptoms was a trial that examined the effects of three different versions of patient–doctor interaction on the effectiveness of placebo acupuncture (Kelley et al., 2009). The group with an augmented patient–practitioner relationship reported symptom improvement on a magnitude as great as any medication approved for IBS by the American Food and Drug Administration (FDA) (Kaptchuk et al., 2009). Very recently, this same group has used fMRI to investigate the neural activity in the *doctor* whilst the patient was experiencing pain (Jensen et al., 2013). The doctor's ability to take the patient's perspective showed increased brain activations in areas associated with empathy, expectations and reward processing. We shall see later in this section (and also in Section 2.3) that expectations and reward processing are paramount for eliciting placebo responses in the patient.

It would thus seem that it is the quality of the patient-practitioner interaction that accounts for a sizeable chunk of the effect seen in placebo responses (Di Blasi et al., 2001), and as such this is a component in interaction-enhanced pharmacology worthy of making more use of.

### 2.1.2. Choice of intervention

The *method* with which an intervention is delivered is also influential. Different placebos have been found to modulate different effects. For example, placebo pills are better for sleep, and sham needles are better for pain ( Barrett et al., 2007 and Kaptchuk et al., 2000). When pills are used as a placebo intervention, the shape (Buckalew and Ross, 1981), colour (de Craen et al., 1996), recognised brand-name (Branthwaite and Cooper, 1981), and financial cost ( Geuter et al., 2013 and Waber et al., 2008) of pills can in themselves lead to clinical improvements as well as to the patient becoming pharmacologically conditioned. The differences between a placebo pill and a placebo sham device have also been investigated (Kaptchuk et al., 2006) with sham acupuncture patients exhibiting a significant reduction in pain compared to the placebo pill group. Even the act of taking part in a clinical trial can result in improvement (the Hawthorne effect) because of the examinations the person undergoes, the attention they receive from medical personnel and the expectancies triggered by taking part in a new therapy program (Last, 1983).

Surgery is perhaps the most powerful delivery method of all in terms of provoking a strong placebo effect (Benedetti et al., 2004a, de la Fuente-Fernández et al., 2001, de la Fuente-Fernandez et al., 2004 and Wager et al., 2004). Historically there have been well-cited examples of sham surgery to perform artery ligation (Cobb et al., 1959 and Dimond et al., 1958) for angina pectoris, laser myocardial revascularisation for people with coronary heart disease (Rana et al., 2005), sham arthroscopic surgery

for osteoarthritis of the knee (Moseley et al., 2002) and intra-articular injections of saline solution for knee pain (Rosseland et al., 2004).

The most striking experiment in the Parkinson's neuro-placebo genre concerned the transplantation of human fetal mesencephalic (Freed et al., 2001, Husten, 1999 and McRae et al., 2004) and nigrostriatal (Olanow et al., 2003) cells. Patients who thought they had undergone the active treatment (irrespective of whether they had received an actual transplant or had the sham surgery) showed significant improvements in perceived physical function and perceived social support. In those patients who continued to believe that they had received active treatment, this benefit was sustained for the 12 month duration of the study. Blinded medical evaluators detected significant improvements in all domains of motor function and activities of daily living in the patients who thought they had received active treatment.

## **2.2. Psychological processes**

From a psychological point of view, two principal mechanisms are well supported that contribute to the production of placebo effects. The first mechanism involves expectancy and the second involves classical conditioning.

### *2.2.1. Expectancies*

In general terms, expectation is a cognitively driven process that prepares the body and mind to anticipate an event in order to be better able to cope with it. In healthcare terms, expectation can encompass an inherent sense of hope, anticipation, and the desire for relief around what will happen as a result of treatment (Crow et al., 1999, Kirsch, 1985, Kirsch, 2004 and Stewart-Williams and Podd, 2004), but it can also involve negative anticipation in the form of anxiety, fear or repulsion. In this case, this is termed 'nocebo effect' and is discussed later (Section 2.4).

Enhancing patients' expectations has been shown to significantly influence health outcomes (Crow et al., 1999 and Di Blasi et al., 2001). Something as simple as the words used to instruct the patient can have very clear repercussions on the patient's expectations (Kirsch, 1985). For example, the use of positive expectation ('This is a powerful painkiller') leads to analgesia (Amanzio and Benedetti, 1999, Benedetti et al., 1999, Price et al., 1999 and Vase et al., 2003). The clarity of instructions is also important because subtle changes in information given via the words used can influence the magnitude of the placebo effect. 'You may receive an active or a placebo agent' (Verne et al., 2003) produces smaller placebo responses than 'The agent you have been given is known to significantly reduce pain in some patients' (Vase et al., 2003).

### *2.2.2. Conditioning and reinforced expectancies*

The use of Pavlovian conditioning is a powerful means for inducing physiological changes. Verbal, conditioned and observational cues can create strong expectancies that influence the placebo response. Reported examples of pairing a conditioning stimulus with an associated health outcome are:

- A flavoured drink being associated with the immunosuppression of cyclosporine A (Goebel et al., 2002 and Goebel et al., 2005).
- Relief from allergic rhinitis (also via a flavoured drink; Goebel et al., 2009).
- Conditioned hypoglycaemia (via injection of insulin in shock therapy; Lichko, 1959 and Stockhorst et al., 1999).
- Conditioned growth hormone increase (associated stimulus here was the injection used to administer the hormone; Benedetti et al., 2003a).

This means that patients' previous experiences can not only shape their conscious expectations, but can also lead to conditioned responses. An interesting practical application of how a conditioned response can be re-conditioned has been investigated in cancer chemotherapy. Here anticipatory nausea and vomiting are unpleasant side effects frequently experienced as a result of chemotherapy, with the prevalence ranging from 10–63% (Stockhorst et al., 2000). Even with anti-emetic treatments it can reach 59% (Tyc et al., 1997). This is believed to be a conditioned nocebo effect (see also Section 2.4) (Andrykowski and Otis, 1990, Bernstein, 1991, Jacobsen et al., 1993, Nesse et al., 1980 and Stockhorst et al., 1998). The conditioning arises from a pairing of contextual stimuli (e.g. an odour present in the clinical environment; Nesse et al., 1980) with the resultant nausea and vomiting from the chemotherapy. However, there is evidence to suggest that this nocebo response is a learning phenomenon mediated by conditioning mechanisms, and as such that this conditioning can be relearned and reconditioned through a technique called overshadowing (Stockhorst et al., 1998). Following such a reconditioning training, patients showed no anticipatory nausea to the chemotherapy in contrast to 25% of the control subjects who did not undergo the overshadowing conditioning, and suffered from anticipatory nausea (Klosterhalfen et al., 2005, Stockhorst et al., 1998, Stockhorst et al., 2006 and Stockhorst et al., 2007). This kind of conditioning, based on psychosocial context components can thus be a very useful tool from a therapeutic perspective.

When a placebo is given as a drug substitute for the first time, the placebo response elicited may be present and it may be small. However, it is known that placebos are more effective when given as the drug-substitute once the original drug has been effectively experienced than when administered for the first time in the absence of a drug (Batterman, 1966, Batterman and Lower, 1968, Laska and Sunshine, 1973 and Sunshine et al., 1964). If a placebo is given after two previously effective experiences with an analgesic, the placebo analgesic response is much greater (Amanzio and Benedetti, 1999), the magnitude of the placebo response being dependent on the previous analgesic experience(s) (Colloca and Benedetti, 2006). This preconditioning has also been responsible for inducing robust placebo responses in Parkinson's patients (Benedetti et al., 2004a, Benedetti et al., 2009, de la Fuente-Fernández et al., 2001 and Strafella et al., 2006).

These conditioning and reinforced expectancies have also been applied within the sports' medicine environment (Benedetti et al., 2007b). An increase in quadriceps muscle performance and decreased muscle fatigue was achieved by a pre-

conditioning coupling of a 'high caffeine dose' (really a placebo) with reducing the weight actually lifted (Pollo et al., 2008). In this way the coupling of the 'caffeine' with the experience of being able to lift a heavier weight, can push muscular performance further.

Pharmacological conditioning is an effect that can occur whenever patients take pills which elicit desirable (and sometimes undesirable) effects. The shape, size, colour and taste of a pill can become associated with improvement very easily. A drug is not the only paired-stimulus that can occur. There are many other stimuli associated with hospitals (sights, sounds, smells), the equipment used, the diagnostic techniques employed, and the medical personnel themselves.

### **2.3. Neurophysiological mechanisms**

Three main neurotransmitters have been linked, so far, to the psychoneurophysiological mechanisms involved in the generation of placebo effects: opioids, dopamine and cannabinoids. Opioid-mediated pathways are employed in expectancy and conditioning; dopamine-mediated mechanisms in reward, motivation and expectancy of the reward. The most fruitful neurobiological models for studying placebo response have emerged from pain and Parkinson's disease. In pain modulation, the neural networks involved are the opioid–cholecystokinin–dopamine systems (Fig. 2a), with the role of cannabinoid (CB1) receptors in nonopioid-mediated placebo analgesia recently established (Benedetti et al., 2011); in Parkinson's disease it is part of the basal ganglia circuitry that produces the placebo response (Fig. 2b). In addition to opioids, dopamine and cannabinoids, investigations into the possible involvement of serotonergic pathways (Benedetti et al., 2005, Leuchter et al., 2002 and Mayberg et al., 2002) have been stimulated by placebo responses in antidepressant trials (Andrews, 2001, Khan et al., 2000 and Walsh et al., 2002) plus two meta-analyses (Brunoni et al., 2009 and Rief et al., 2009). Oxytocin (OXY) and nitric oxide (NO) have both been postulated as possible mediators of the placebo response, (OXY: Breton et al., 2008, Enck and Klosterhalfen, 2009 and Yang et al., 2007; NO: Fricchione and Stefano, 2005 and Stefano et al., 2001) but as yet little has been elucidated. The state-of-the-art knowledge is thus far that opioid-, dopamine-, and cannabinoid-mediated pathways are recruited in the production of placebo effects. Opioid- and cannabinoid-mediated pathways are employed in expectancy and conditioning (Benedetti et al., 2011, Colloca and Benedetti, 2005, de la Fuente-Fernández et al., 2001, Finniss and Benedetti, 2005, Geuter et al., 2013, Levine et al., 1978, Mayberg et al., 2002, Petrovic et al., 2002, Price et al., 2008, Volkow et al., 2003 and Zubieta et al., 2005) while dopamine-mediated mechanisms are employed in reward, motivation and expectancy of the reward (Benedetti et al., 2004a, Benedetti et al., 2009, de la Fuente-Fernandez and Stoessl, 2002 and Scott et al., 2008).

#### **[FIGURE 2]**

##### *2.3.1. Expectancy: opioidergic pathways*

The initial link between opioid involvement and expectancy was established with pharmacological studies. These showed that expectancy triggered the activation of opioid-mediated analgesic pathways (Gracely et al., 1983 and Grevert et al., 1983)

and that these could be blocked by the opioid antagonist, naloxone (Gracely et al., 1983, Grevert et al., 1983, Levine and Gordon, 1984 and Levine et al., 1978). The advent of neuroimaging (functional magnetic resonance imaging, fMRI, and positron emission tomography, PET) led to the establishment of the cerebral areas involved in placebo analgesia (Bingel et al., 2006, Bingel et al., 2011, Kong et al., 2006, Petrovic et al., 2002, Petrovic et al., 2005, Raz et al., 2005, Scott et al., 2008, Wager et al., 2004, Zubieta et al., 2005 and Zubieta et al., 2006), summarised in Table 1 and Figs. 2a and 2b. fMRI and PET research yielded the important discoveries that placebo-induced expectation of analgesia triggers the release of the patient's own endogenous opioids (Bingel et al., 2006, Kong et al., 2006, Petrovic et al., 2002, Petrovic et al., 2005, Raz et al., 2005, Scott et al., 2008, Wager et al., 2004, Zubieta et al., 2005 and Zubieta et al., 2006), and that this recruits the same opioid-mediated pathway triggered by pharmaceutical analgesics (Petrovic et al., 2002).

#### [TABLE 1]

##### 2.3.2. *Motivation and reward: dopaminergic pathways*

When *motivation or reward* is involved, a dopaminergic pathway is recruited. Dopamine's (DA) involvement in reward and expectation of reward has been known since Garris et al. (1999) published their intracranial self-stimulation study. This provided evidence that expectation of rewards alone will elicit DA release in the nucleus accumbens (NAC), and dopamine has now an established role in reward and expectation mechanisms in general (Kelley and Berridge, 2002 and Tobler et al., 2005).

Since reduced pain, for example, can be perceived as a reward, placebos promising an expected reward of pain relief have been demonstrated to first release dopamine in the NAC which then subsequently trigger the activation of the downstream adaptive (e.g., opioid) responses to elicit an analgesic response (Scott et al., 2008). This NAC *dopamine release* positively correlates with the magnitude of *endogenous opioid release* in the NAC, ventral putamen, amygdala, aINS, posterior insula (pINS), and rACC. The magnitude of DA activation in the NAC correlates positively with the individual's expectations of analgesia and the magnitude of analgesia experiences.

Much valuable information concerning DA involvement in placebo processes has come from the study of patients with Parkinson's disease (PD), in which placebo effects are known to be common (Goetz et al., 2000 and Shetty et al., 1999). Since the first PD symptoms arise only when approximately 80% of the dopamine (DA) activity has been lost (Morrish et al., 1996) it was not known if the effects observed could be mediated by a nigrostriatal system in which there is pathological degeneration. Elegant research carried out using PET (de la Fuente-Fernández et al., 2001 and de la Fuente-Fernández et al., 2002), repetitive transcranial magnetic stimulation (rTMS) (Strafella et al., 2006), and single neuron studies (Benedetti et al., 2004a and Benedetti et al., 2009) has established that this same (damaged) basal ganglia circuitry STN-SNr-VA/VLa is necessary for the generation of placebo effects (STN, subthalamic nucleus; SNr, substantia nigra pars reticulata; VA, ventral anterior thalamus; VLa, ventral lateral thalamus).

The reward of increased movement, using the Parkinson's disease model, also elicits a dopaminergic pathway. PET measurements demonstrated a >200% increase in

extracellular dopamine concentration released into the striatum when a PD patient believed a placebo to be the DA agonist apomorphine (a powerful anti-Parkinsonian agent) (de la Fuente-Fernández et al., 2001). This was comparable to the response to the DA agonist amphetamine which results in release of endogenous DA in healthy subjects. In this study, all PD patients exhibited an increased DA release in the ventral striatum (NAC), but only those who showed improved motor activity showed larger amounts of DA in the dorsal (motor) striatum (nucleus caudatus and putamen) (Fig. 2a). These findings were confirmed in another PET study of PD patients undergoing sham (fake) repetitive transcranial magnetic stimulation (rTMS) (Strafella et al., 2006). Placebo-induced changes in NAC activity did not differ significantly between PD patients who experienced increased movement and those who did not (de la Fuente-Fernández et al., 2001).

Studies at the level of single neurons (using an implanted deep brain stimulation, DBS, electrode) have shown a decrease in neuronal firing in the substantia nigra pars reticulata (SNr) and increases in ventral anterior thalamus (VA) and ventral lateral thalamus (VL) activity (Fig. 1a) (Benedetti et al., 2009). Placebo non-responders showed either no changes in this circuit or only partial changes in the STN confirming that the whole STN-SNr-VA/VL is necessary for a clinical (behavioural) benefit to be seen. For example, recording of single neuron activity showed changes in neural firing correlated closely with clinical (e.g. wrist rigidity) and subjective improvement (“I feel better”) (Benedetti et al., 2004a), but no firing change occurred when there was no clinical placebo response. It appears the expectation of the reward of movement is sufficient to trigger DA release in the NAC (ventral striatum) in PD patients, but that the tangible motor differences lie in the magnitude of activation of the dorsal striatum (Benedetti et al., 2009 and de la Fuente-Fernández et al., 2002).

This study (Benedetti et al., 2009) indicates the combination of several placebo-genic components in interaction-enhanced pharmacology. Following surgery (powerful placebo effect) to implant the DBS electrode, a placebo believed to be apomorphine (positive expectation; reward of increased movement since apomorphine is an effective anti-Parkinson drug) was administered. The outcomes are that patients reported an increased feeling of well-being, and muscle rigidity at the wrist was reduced. This latter was independently assessed by a neurologist blinded to the experiment using the Unified Parkinson's Disease Rating Scale (UPDRS). The effects lasted for 30–45 min due to ethical constraints limiting the intraoperative measurements (Benedetti et al., 2009).

### 2.3.3. Cannabinoidergic pathways

It has been known since Gracely et al. (1983) and Grevert et al. (1983) early work with opioid receptor antagonist challenges, that a time-dependant, non-opioid component could be present in placebo analgesia. The fact that it was not naloxone (an opioid antagonist) reversible, suggested mediation via a nonopioidergic pathway. This nonopioid pathway was further reinforced in experiments with nonsteroidal anti-inflammatory drugs (NSAIDs) (Amanzio and Benedetti, 1999): when conditioning took place with NSAID ketorolac, naloxone did not abolish the analgesic effect. With increasing evidence that NSAIDs interact with endocannabinoids (Fowler, 2007 and Shimizu, 2009) and cyclooxygenase-2 (Rouzer

and Marnett, 2008), the endocannabinoids became a pathway of interest for their possible role in the placebo analgesic effects of NSAIDs. Recently, Benedetti and co-workers have established the role of cannabinoid (CB1) receptors in this nonopioid placebo analgesia (Benedetti et al., 2011). Using rimonabant as the CB1 receptor antagonist, nonopioid analgesic responses were blocked, but rimonabant was ineffective on opioid placebo responses. These findings show the involvement of the CB1 receptors, but the actual site of action in the brain has not yet been elucidated.

#### **2.4. Reduction of counteracting effects for interaction-enhanced pharmacology**

Any intervention that is non-verum and yet has positive effects, is called placebo, but any intervention that is non-verum and yet has negative effects, is called nocebo. Just as positive expectancies play a role for maximising the use of placebo effect mechanisms, negative expectancies in the form of fears and anxieties can produce so-called 'nocebo' effects. For example, in analgesia studies the administration of a nocebo results in an increase in pain (hyperalgesia).

It has been found that when a patient openly sees the analgesic infusion of morphine or diazepam being interrupted, relapse of pain occurs faster and pain intensity is greater than when the infusion is discontinued covertly (Benedetti et al., 2003a, Benedetti et al., 2007a and Colloca et al., 2004). In anxiety studies on patients with high anxiety levels following surgery, the anxiolytic diazepam was administered both openly and hidden (Amanzio et al., 2001 and Benedetti et al., 2003b). In the open group there was a definite decrease in anxiety; in the hidden group diazepam was totally ineffective. Interruption of treatment was also tested: in the open condition anxiety increased significantly, whereas in the hidden condition it did not change. This open-hidden design methodology has also been carried out with Parkinson's disease (Benedetti et al., 2004b and Lanotte et al., 2005) and addiction studies (Volkow et al., 2003).

The neural pathways involved in negative expectation have been elucidated via the placebo pain model. In analgesia studies, negative words and negative expectations trigger blocking of the opioid-mediated expectancy (Benedetti, 1996, Benedetti, 1997 and Benedetti et al., 1995) via cholecystokinin (CCK). It is specifically anticipatory anxiety ('anxiety which turns to pain') rather than generalised anxiety that is involved in the CCK component of hyperalgesia (Fig. 3). Whereas verbal suggestions of pain decrease activate endogenous opioids (Amanzio and Benedetti, 1999 and Zubieta et al., 2005) suggestions of pain increase activate CCK (Benedetti et al., 2006b). This negative expectation could also be invoked when the patient distrusts the medical personnel or methods involved (Barsky et al., 2002 and Flaten et al., 1991). In the arena of sports' medicine, where placebos can increase physical performance (Section 2.2.2), the use of negative suggestions coupled to a sham electrical stimulation have been shown to adversely affect physical performance (Pollo et al., 2012). The impact of negative words and expectations has also been investigated in Parkinson's disease. Here, patients with DBS electrode implants were told that the stimulator had been turned off, so as to induce negative expectations of motor worsening (Benedetti et al., 2003a). Motor performance worsened even though the stimulation was on (Benedetti et al., 2003a, Mercado et al., 2006 and Pollo et al., 2002). We have seen how opioid and dopamine release in the nucleus accumbens (NAC) have been found to be a direct measure of placebo response: high placebo

responders show a greater increase in NAC opioid activity; likewise, in nocebo responders the NAC showed a deactivation in opioid release (Zubieta et al., 2005 and Zubieta et al., 2006).

**[FIGURE 3]**

Bingel et al. (2011) have shown, using fMRI, that positive expectancy doubled the analgesic benefit of opioid remifentanyl whereas negative expectancy abolished its analgesic effects. In addition to the endogenous pain modulatory system (comprising the somatosensory cortex, cingulate cortex, insula, thalamus, and PAG), different brain pathways were activated with the differing expectancies: positive expectation showed enhanced activation in the anterior cingulate cortex and striatum, whereas negative expectations resulted in increased neural activity in the hippocampus, midcingulate cortex, and medial prefrontal cortex. Very recently, it has also been demonstrated that both nocebo and placebo mechanisms can be elicited by non-conscious triggers which operate outside conscious awareness (Jensen et al., 2012). In working with patients to maximise enhancing factors, it is important to be able to minimise the counter-productive effects, such as use of positive expectancy-promoting vocabulary and soothing anticipatory anxiety. In this way, the practitioner can side-step the blocking of the opioid-mediated expectancy pathways, to be able to fully employ the positive expectancy, motivation and reward neurobiology. There is data showing that the announcement of painful interventions increases pain intensity (Lang et al., 2005), thus explaining too much to a patient may have detrimental effects by inducing anxious expectations. In general, making the patient aware in a positive manner of what is going on, why a certain procedure is being carried out and what positive results can be expected are all important factors in maximising the therapeutic outcome (Wells and Kaptchuk, 2012).

An important caveat here is that a functioning prefrontal cortex (PFC) is essential for expectancy in order to be able to initiate cognitive, top-down regulation. In placebo analgesia studies, Alzheimer's patients, in whom there is degeneration and disconnection of prefrontal lobes from the rest of the brain, show no placebo analgesic response (Benedetti, 2010 and Benedetti et al., 2006a). This was confirmed by temporarily disrupting the functioning of the DLPFC using rTMS in healthy subjects (Krummenacher et al., 2010). This interruption of the neural circuits blocked the placebo-induced analgesic effect completely. This implies that for interaction-enhanced pharmacology to be successful in clinical practice a functioning prefrontal cortex is necessary, otherwise the expectancy-driven mechanisms are unlikely to function.

### **3. EXTENDING INTERACTION-ENHANCED PHARMACOLOGY**

Interaction-enhanced pharmacology employs the patient-practitioner interaction to stimulate positive expectations and to diminish anxious expectations of adverse effects or treatment failure, using communication strategies as described in Section 2.1.1. It employs the patient's own neuropsychological system to enhance the efficacy of existing (drug) therapies. By moving the emphasis towards utilising the patient's own inherent capabilities, this rationale could also be extended within clinical practice to:

- minimising side effects in treatments and therapies
- facilitating symptom relief

### 3.1. Minimising side effects

In medical terms, a side effect is defined as a secondary and usually adverse effect arising from a drug or treatment. One of the strengths of placebo effects is that they do seem to mimic the pharmacological pathways and effects that the drugs themselves elicit—and yet a placebo substance is by definition pharmacologically inert and contains no harmful substances.

In placebo analgesia studies, the placebo triggers the production of the patient's own endogenous opioids using opioid-mediated pathways and brain regions just like the verum analgesic to produce pain relief (Bingel et al., 2006, Bingel et al., 2011, Kong et al., 2006, Petrovic et al., 2002, Petrovic et al., 2005, Raz et al., 2005, Scott et al., 2008, Wager et al., 2004, Zubieta et al., 2005 and Zubieta et al., 2006). In Parkinson's disease, expectation and the reward of increased movement elicit dopamine release using the same nigrostriatal pathway as a potent anti-Parkinson and dopamine agonist apomorphine (Benedetti et al., 2009, de la Fuente-Fernández et al., 2001, Scott et al., 2008 and Strafella et al., 2006). The use of Pavlovian conditioning to produce physiological changes in the 'conditioned' immune system responses investigated by Goebel et al., 2002 and Goebel et al., 2005, showed that the effects of the conditioned stimulus were the same as those of the specific effects of immunosuppressant cyclosporine A, i.e. decrease in interleukin-2 (IL-2), interferon- $\gamma$  (IFN- $\gamma$ ) and suppression of lymphocytes (T-cell function). In another clinical study by these same researchers (Goebel et al., 2009), a flavoured drink used as a conditioned stimulus resulted in the same reduction in basophil activation, histamine skin prick test and subjective symptom scores as the histamine (H1) receptor antagonist desloratadine in patients allergic to house-dust mites. It would appear therefore that use of placebo treatments would make drug-like effects possible, but without the drugs—and therefore without the side effects. However, just as placebos can mimic verum interventions they can also mimic their adverse effects. For example, patients in the placebo arm of clinical trials showed similar (adverse) side effects to the drug under investigation (Kaptchuk et al., 2006 and Amanzio et al., 2009). In Kaptchuk's 2006 study, even 'side effects' for sham acupuncture were observed.

In theory, the ideal way to use placebo effects would be to utilise the interaction-enhanced pharmacology concept whereby the placebo mechanistic aspects are fully utilised, and yet tell the patient that they were getting a placebo (pill) in order to avoid any side effects due to their belief that they had been prescribed a verum pill. One of the greatest obstacles to the use of placebos in clinical practice has been the belief that for placebos to be effective they must be administered deceptively. Kaptchuk et al. (2010) have recently reported the successful 'open-label' (no deception) administration of placebos for IBS, where patients were told that they

would receive a placebo. The symptom relief patients reported was as large as that produced by commonly prescribed medication (alosetron) for IBS.

Since placebo's drug-mimicking properties trigger the patient's own 'internal pharmacy' this application could theoretically be useful whenever a drug has particularly noxious or unpleasant side effects (Ader et al., 2010, Greenberg and Roth, 1966, Kirsch et al., 2008, Olness and Ader, 1992 and Sandler et al., 2010). Whether or not the amount of verum medication can realistically be reduced by adding a placebo pill of the same appearance remains to be seen. However, extreme caution must be taken so as not to withhold a pharmacological therapy from a patient and thus endanger their health. It is preferable to utilise the interaction-enhanced pharmacology concept proposed here to *enhance* the effectiveness of the drug therapy.

### **3.2. Facilitating symptom relief**

Since placebo and placebo effects are often linked to more psychosomatic ailments, it is not surprising that symptoms such as migraine (Bendtsen et al., 2003, Clayton et al., 2005, de Craen et al., 2000, Diener, 1999, Ferrari et al., 2001, Henry et al., 1995, Macedo et al., 2006 and Tfelt-Hansen et al., 1995), insomnia (Fratello et al., 2005, McCall et al., 2003 and Walsh et al., 2000), irritable bowel syndrome (Kaptchuk et al., 2009, Kelley et al., 2009, Vase et al., 2003, Vase et al., 2005 and Verne et al., 2003), gastric disturbances (Bernstein, 2006, Enck and Klosterhalfen, 2005 and Musial et al., 2007) and genitourinary disorders (Bradford and Meston, 2007, Fink et al., 2002, McConnell et al., 1998, Mondaini et al., 2007, Moyad, 2002, Nickel, 1998 and van Leeuwen et al., 2006) have been found to respond well to placebos. Most of the above disorders manifest themselves as painful conditions, and as we have seen, the mode of action of placebo – in addition to its effectiveness – in pain relief has been well established.

In the area of cancer, it seems that placebos can induce symptom reduction but not prevent cancer progression (Chvetzoff and Tannock, 2003). However, the importance of symptom reduction in cancer patients is not to be underestimated as cancer is increasingly being seen as a chronic illness rather than a quick and deadly disease. Much research is directed towards cancer prevention, diagnosis and cure, but there is a large chasm as far as living with cancer is concerned. In a very different non-pharmacological experimental approach, the effect of expectancy in chemotherapy-related nausea has been investigated using acupressure wrist bands (Roscoe et al., 2010). These had been found previously (Roscoe et al., 2003) to be effective in reducing nausea in subjects who expected them to be effective. (Patients who received the wrist bands and did not expect them to be effective experienced no difference in nausea). The patients' expectations were enhanced regarding the efficacy of the wrist bands by increasing the information available about the bands. Reduced nausea was experienced by patients who had high levels of expected nausea.

#### **4. CLINICAL IMPLICATIONS: HOW PATIENT NEUROBIOLOGY CAN BE HARNESSSED TO MAXIMISE PLACEBO EFFECTS**

This review has examined the neurobiological mechanisms underlying placebo effects and the different components capable of producing them. The concept of placebo is no longer simply confined to giving a fake pill to a difficult patient, but has grown to incorporate a broad range of psychosocial contexts that can be applied to medical care. This psychosocial context has its effect on patients every time clinicians interact with them, regardless of whether placebo or verum treatment is applied. In other words: placebo effects are inherent to every medical treatment and they have neurobiological implications that may affect patients' health and wellbeing. This evidence might thus be interpreted as an instigation (or even an ethical obligation) for doctors to use placebo effects for the benefit of the patient when providing care, and it even suggests that disregarding placebo effects might be sub-optimal care. In itself, this idea is not new. Many doctors have always employed, and still do employ, methods to attain placebo effects as a matter of course (Bensing and Verheul, 2010, de Craen et al., 1999, Roberts et al., 1993 and Tilburt et al., 2008), but they often do so without conscious effort. The neurobiological explanations for placebo effects can help to determine how to set off patients' neurobiology for maximising placebo effects. This review shows that probably the most potent method for doing so lies in the doctor–patient interaction (Bensing and Verheul, 2010, Di Blasi et al., 2001, Kaptchuk et al., 2009 and Van Dulmen and Bensing, 2001). Although more research is needed in this area, some directions can be outlined as to how the patients' neurobiological pathways might be activated by doctors' (or nurses') targeted communication, and in particular with reference to the opioidergic and the dopaminergic pathways.

Opioidergic activation is triggered by patients' expectations. The major components that are needed to attain positive expectations are that the practitioner has to state that positive effects of a treatment can be expected, in a clear and unambiguous way. Secondly the patient has to believe the message delivered, and for this, a good therapeutic relationship between practitioner and patient is important. There is ample evidence that a good relationship is significantly determined by a practitioner's affective communication style: warmth, eye contact, active listening, empathy, thoughtful silences, and leaving room for the patient to tell their story are of pivotal importance here (Epstein and Street, 2007, Roter and Hall, 2006 and Stewart, 1995). Perhaps unsurprisingly, the combination of enhancing expectation and communicating in a warm and empathic way seems to have the best effects in increasing patients' expectations (Verheul et al., 2010). Although dopaminergic activations are similarly triggered by expectations, these are foremostly generated in placebo effects when there is a reward aspect present (e.g. the reward of diminished pain). Several studies (Walter et al., 2005 for an overview) also show that cooperative social interaction activated the reward circuitry, whereas non-cooperative behaviour did not do so. This again points to practitioners' affective communication style as a way to harnessing placebo effects. It should be noted that studies *directly* assessing patients' neurobiology when trying to elicit placebo effects

in response to different kinds of practitioner communication are still missing and very much needed (Bensing and Verheul, 2010). Measuring the release of opioids and dopamine in patients whilst they are being exposed to different styles of doctor-patient communication (e.g. via video vignettes) seems a promising next step in this line of research.

## 5. CONCLUSION

Traditionally, the placebo effect has often been referred to in a derogatory, denigrating way as some sort of unwanted effect that would be better ignored than worthy of scientific investigation. In the light of modern day pharmacology it tends to be easily forgotten that recovery entails more than just pharmacological drug action. That the external trigger can be a pill, injection, surgery or the 'right' words or demeanour at the right time from a practitioner is a reminder that it is the patient, and not the doctor, who in the end is the real agent to recovery. The stimulus that the placebo provides, by raising expectancies embedded in a warm and empathic doctor-patient relationship, appears to stimulate the internal pharmacy that humans seem to possess. Over the last 15 years neuroscience has started to provide a scientifically satisfying method to investigate how, where and when these intriguing effects occur. So rather than writing them off as 'just the placebo effect', we need to fully appreciate how *much* that 'just' contains—and to start utilising and applying it in clinical practice. It is by being able to consciously tap into the neurobiology of the patient's own brain, and thus collaborating with their entire psychophysiological system, which could truly revolutionise modern medicine. It is this that could be the sweetest (placebo) pill we have yet to swallow.

## CONFLICT OF INTEREST

The authors have no conflicts of interest.

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## APPENDIX A.

Keywords, or combinations of keywords, used for the literature search were: placebo effect mechanism, placebo effect brain, placebo effect neuroscience, placebo effect neurobiology, placebo effect neurobiological mechanisms, placebo effect neural mechanisms, placebo effect neural correlates, placebo effect biological mechanisms, placebo effect biological models, placebo effect biochemical, placebo effect understanding, placebo effect review, placebo effect classical conditioning, placebo effect neurotransmitter, placebo effect dopamine, placebo effect dopamine pathway, placebo effect serotonin, placebo effect reward, placebo effect motivation, placebo effect non-specific, placebo effect expectation placebo response mechanism, placebo response brain, placebo response neuroscience, placebo response neurobiology, placebo response neurobiological mechanisms, placebo response neural mechanisms, placebo response neural correlates, placebo response biological mechanisms, placebo response biological

models, placebo response biochemical, placebo response understanding, placebo response review, placebo response classical conditioning, placebo effect neurotransmitter, placebo response dopamine, placebo response dopamine pathway, placebo response serotonin, placebo response reward, placebo response motivation, placebo response non-specific, placebo response expectation placebo effect pain, placebo effect analgesia, placebo effect Parkinsons, placebo effect depression, placebo effect Alzheimer, placebo effect dementia, placebo effect schizophrenia, placebo effect addiction, placebo effect sham surgery, placebo effect migraine, placebo effect deep brain stimulation placebo response pain, placebo response analgesia, placebo response Parkinsons, placebo response depression, placebo response Alzheimer, placebo response dementia, placebo response schizophrenia, placebo response addiction, placebo response sham surgery, placebo response migraine, placebo response deep brain stimulation

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## BOX, TABLES, FIGURES

Search strategy and selection criteria

In order to review the literature, an extensive systematic search was carried out of the English language-based electronic databases of PubMed (including MEDLINE), Web of Science, the Cochrane database and library, PsychLit, BIDS (Bath Information and Data Services), EMBASE and the Science Citation Index. Searching on 'placebo effects' alone yielded 119,774 hits from PubMed, and thus further refinement was necessary. Since there have been such rapid advances in the understanding of placebo mechanisms in recent years, the search was confined to results from 1995 to 2013, unless it later became obvious that there was an earlier seminal work that needed to be included. The keyword search terms used are listed in the [Appendix A](#). As the search started to identify data and information, the title and abstracts were quickly scanned to assess if the publication was indeed suitable.

Fig. 1. The part of the change attributable to the context in placebo effects.

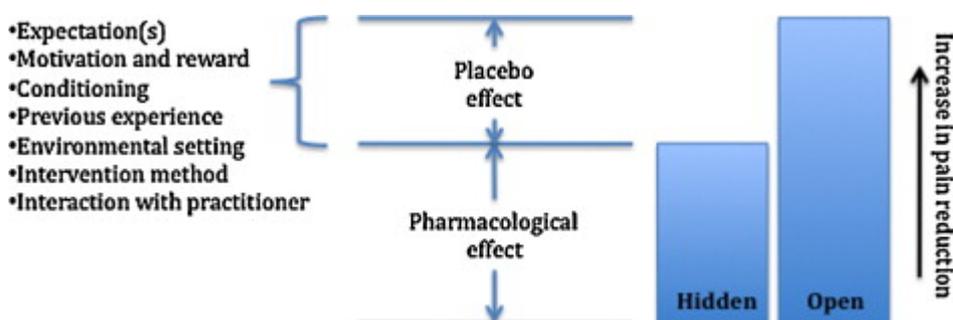
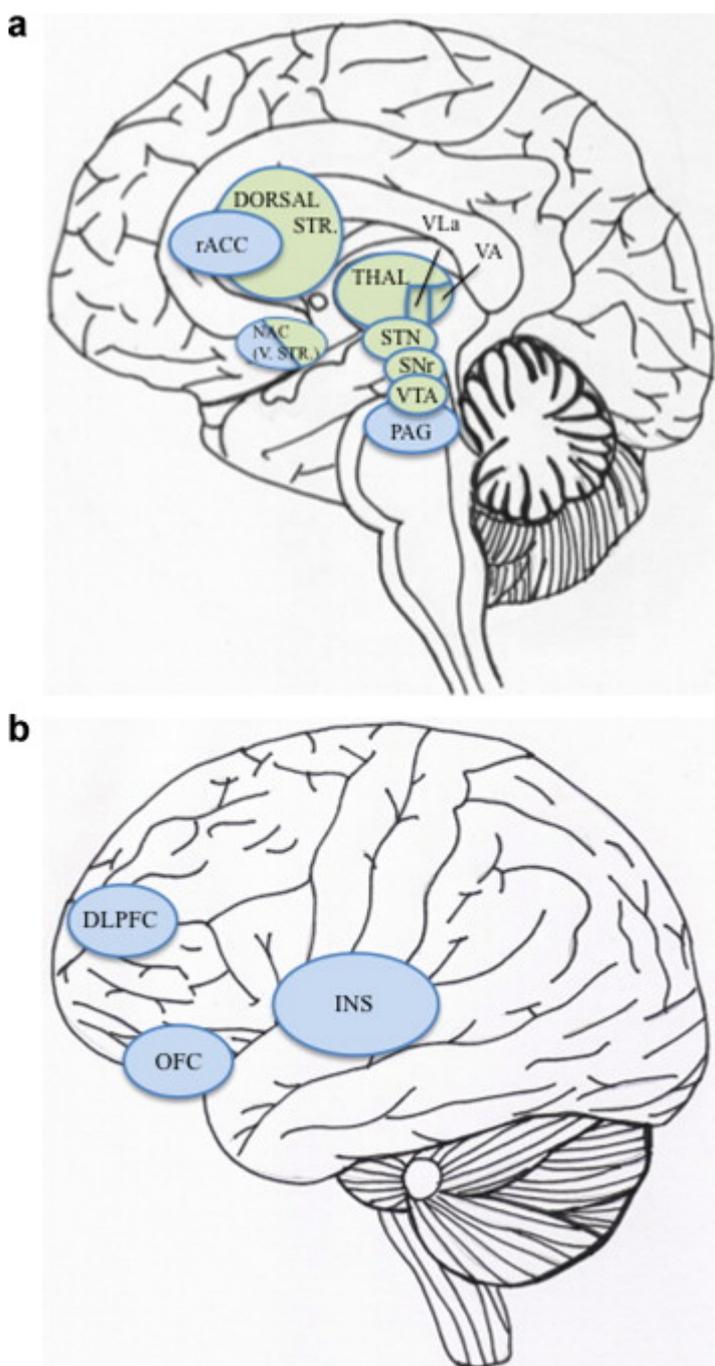


Fig. 2. (a) Mid-sagittal view of human brain, indicating brain regions active in placebo effects. Blue shaded areas are involved in opioid mechanisms, green shaded areas in dopamine. *Abbreviations:* rACC, rostral anterior cingulate cortex; dorsal str., dorsal striatum; NAC, nucleus accumbens; v.str., ventral striatum; thal, thalamus; VL<sub>a</sub>, ventrolateral thalamus; VA, ventral anterior thalamus; STN, subthalamic nucleus; SN<sub>r</sub>, substantia nigra pars reticulata; VTA, ventral tegmental area; PAG, periaqueductal grey (Source: Jayne Jubb) pathways. (b) Lateral view of human brain, indicating brain regions active in placebo effects. Blue shaded areas are involved in opioid. *Abbreviations:* DLPFC, dorsolateral prefrontal cortex; OFC, orbitofrontal cortex; INS, insula (Source: Jayne Jubb) mechanisms.



**Table 1**  
Brain areas involved in opioid-mediated placebo analgesia from fMRI and PET studies.

Brain area	Abbreviation	Function	References
Rostral anterior cingulate cortex	rACC	Cognitive and emotional integration	Bingel et al. (2006, 2011), Geuter et al. (2013), Kong et al. (2006), Petrovic et al. (2002), Raz et al. (2005), Scott et al. (2008), Wager et al. (2004), Zubieta et al. (2005)
Anterior insula	aINS	Representation and modulation of internal states, physical and emotional. Pain transmission	Bingel et al. (2011), Scott et al. (2008), Wager et al. (2004), Zubieta et al. (2005)
Nucleus accumbens	NAC	Reward and saliency	Scott et al. (2008), Zubieta et al. (2005)
Dorsolateral prefrontal cortex	DLPPFC	Pain at a fixed level requiring brain not to constantly update information	Bingel et al. (2011), Wager et al. (2004), Zubieta et al. (2005)
Orbitofrontal cortex	OFC	Constantly changing environment	Scott et al. (2008), Wager et al. (2004)
Thalamus	Thal	Pain transmission	Bingel et al. (2011), Scott et al. (2008), Wager et al. (2004)
Periaqueductal grey	PAG	Modulation of experience of pain	Bingel et al. (2006), Petrovic et al. (2002), Scott et al. (2008), Wager et al. (2004)

Fig. 3. The chain of pain in using verbal negative expectations.

