Placebo and Nocebo Effects: An Introduction to Psychological and Biological Mechanisms

Jian Kong and Fabrizio Benedetti

Contents

Abstract

Placebo and nocebo effects are essential components of medical practice and efficacy research, and can be regarded as a special case of context learning. A fundamental function of the central nervous system is to configure the way in which previous learned context becomes linked to corresponding responses. These responses could be either automatic procedures with little flexibility or highly adaptive procedures modified by associated contexts and consequences. Placebo and nocebo effects may represent a typical example of the combination of the two: conditioning effect, which is an inflexible, instinctual, and automatic response, and cognitive expectancy effect, which is a flexible adaptive response modified by prevailing conscious context. Given the fact that contextual learning originates in the brain, neuroimaging tools have been widely used to study

J. Kong (✉)
Psychiatry Department, Massachusetts General Hospital, Harvard Medical School, Building 120, 2nd street, Suite 101C, Charlestown, MA 02129, USA
e-mail: kongj@nmr.mgh.harvard.edu

F. Benedetti
Department of Neuroscience, University of Turin Medical School, National Institute of Neuroscience, Turin, Italy

F. Benedetti et al. (eds.), *Placebo*, Handbook of Experimental Pharmacology 225,
DOI 10.1007/978-3-662-44519-8_1

placebo and nocebo effects. In addition, pretest resting state fMRI may be a valuable biomarker to predict placebo responses.

Keywords
Placebo • Nocebo • Expectancy • Context learning • Consciousness • Unconsciousness • Resting state fMRI • Biomarker

1 Unconscious Conditioning and Conscious Cognitive Expectancy

A fundamental function of the central nervous system is to configure the way in which perceived information becomes linked to corresponding responses and meaningful experiences (Mesulam 1998; Lewis et al. 2009). These responses could be either automatic procedures with little flexibility or highly adaptive procedures modified by associated contexts and consequences.

The automatic process is fast and instinctual, but it restricts the range of events and tends to be inflexible. Inflexible bonds between incoming information and subsequent responses lead to instinctual and automatic behaviors that are resistant to change, even when faced by negative consequences. For instance, a study has shown that frogs whose optic nerve has been cut and allowed to fully regenerate after a 180° rotation of the eye can only snap at mud and moss on the ground when a fly was presented above the head (Mesulam 1998). Although human beings are less vulnerable to the emergence of such inflexible patterns, recent studies have shown that under certain circumstances, our actions can be initiated without conscious awareness of the goals to be attained or their motivating effect on our behavior (Custers and Aarts 2010). For instance, biased decisions may occur without conscious processing of contextual cues (Pessiglione et al. 2008). These findings imply that automatic instinctual processes still exist in human beings and influence our behavior.

The adaptive process, allowing for modifications and flexibility, exists only in advanced mammals. One of the most fundamental features of the human brain is that it does not passively analyze incoming information from the outside world; rather, it actively maintains ongoing representations and prior experiences, which can significantly sculpt neural responses to subsequent events (Mesulam 1998; Lewis et al. 2009).

Placebo and nocebo effects may represent a typical example of the combination of the two: conditioning effect, which is an inflexible, instinctual, and automatic response, and cognitive expectancy effect, which is a flexible adaptive response modified by prevailing conscious context. Taking our response to pain after placebo treatment as an example, the final effect may depend on both automatic conditioning responses and cognitive modulation based on previous knowledge and experience. The latter may modulate our pain experience during different states, including

anticipation, pain experience, and posttreatment evaluation (Kong et al. 2007; Amanzio et al. 2013).

Benedetti et al. (2003) systematically investigated the relationship between the conditioning and cognitive expectancy in both healthy and patient populations. They found that verbally induced expectations of analgesia or hyperalgesia (in healthy subjects) and motor improvement or impairment (in Parkinsonian patients) completely antagonized the effects of a conditioning procedure. In addition, they also measured the effects of opposite verbal suggestions (i.e., verbal cues that suggest an opposite physiological response) on hormonal secretion. Results showed that verbally induced expectations of an increase or decrease in the level of growth hormone (GH) and cortisol did not have any effect on the secretion of these hormones. However, when a preconditioning procedure was performed with sumatriptan, a 5-HT1B/1D agonist that stimulates GH and inhibits cortisol secretion, a significant increase in GH and decrease in cortisol plasma concentrations were found after placebo administration, despite the opposite verbal suggestions were given. These findings suggests that placebo responses are mediated by conditioning when unconscious physiological functions, such as hormonal secretion, are involved, whereas they are mediated by expectation when conscious physiological processes, such as pain and motor performance, come into play, even though a conditioning procedure is performed.

Jensen and Karoly (2012) assessed whether a conditioning paradigm, using two similar, but not identical, facial cues during high and low pain, could induce placebo and nocebo responses with and without conscious awareness of the faces in two experiments in healthy subjects. The results showed significant placebo and nocebo effects using both clearly visible stimuli and nonconscious stimuli, indicating that even for conscious physiological processes, such as pain processing, the placebo and nocebo effects can operate without conscious awareness of the triggering cues. Interestingly, in this study, the data also showed that although the nocebo hyperalgesia effects evoked by both supraliminal and subliminal cues are comparable, placebo analgesia evoked by supraliminal cues is more robust than the placebo analgesia evoked by subliminal cues. We speculate that this may be associated with damage and risk avoidance of nocebo effect, which is important for survival. Thus, the unconscious, automatic response may have been more important for survival than the conscious, flexible responses, which may be a response that has developed during evolution.

Based on the results presented above, it seems that both placebo and nocebo effects involve unconscious, automatic conditioning and conscious cognitive modulation of expectation. The latter may be unique to human beings, and it can either enhance or eliminate the automatic conditioning effects depending on the specific context and outcome measurements. The resulting behavioral response is the combination of the two effects.

We believe that future studies should be focused on the following questions:

(1) What happens in the clinical setting? Is cognitive expectancy more important than unconscious conditioning, or vice versa? Both placebo and nocebo effects are clinical phenomena; the environment and context associated with each patient is

complex and unique; thus, we can imagine that there are multiple formulas/proportions of different components. (2) What are the mechanisms of placebo and nocebo effects in the clinical setting? How can different conditioning experiences, particularly different pharmacological conditioning experiences, shape various pathways to produce placebo and nocebo effects (Amanzio and Benedetti 1999)? Are there any common mechanisms for different disorders?

2 Brain Imaging Studies of Placebo and Nocebo Effects

Given the fact that cognitive modulation/contextual learning originates in the brain, investigators started applying neuroimaging tools to study placebo and nocebo effects about one decade ago. With the development of advanced imaging techniques such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and high-resolution EEG system, our understanding of placebo and nocebo effects has been greatly enhanced. Technical improvements in fMRI due to more powerful magnets, increasingly sophisticated imaging hardware, and in particular the development of new experimental paradigms and data analysis methods allow us to investigate neural events as dynamic processes within the brain and spinal cord. Both the spatial and temporal aspects of neural activity underlying placebo and nocebo effects can now be explored. Technical advances in PET imaging not only provide tools for investigating brain metabolism, blood flow changes, and other nonselective markers of neural activity, but also to investigate whole brain determinants of specific receptor-binding distributions in fully conscious humans. Such progress enables us to indirectly assess neurotransmitter changes associated with placebo analgesia. For instance, it allows us to indirectly measure the release of endogenous opioids in the brain.

Previous studies provide solid evidence that placebo treatment can significantly change outcome measurements. For instance, subjective pain intensity ratings have been shown to be reduced after placebo treatment in studies of placebo analgesia (Benedetti 2008; Benedetti et al. 2005; Kong et al. 2007). However, the mechanisms underlying these effects are far from apparent. A key question left unanswered concerns how and why the outcome measurements are reduced. Is it due to subjects' response bias or desire to please the experimenter, as suggested by some researchers (Hrobjartsson and Gotzsche 2001; Tedeschi et al. 1971; Cleophas 1995), or because biological changes happen after the placebo treatment, as for drug effects, or a combination of both?

Brain imaging tools hold the potential to resolve these questions. Using placebo treatment of pain as an example, previous studies suggest that brain regions including the thalamus, secondary somatosensory cortex (S2), insula, primary somatosensory cortex (S1), and anterior cingulate cortex (ACC) may be associated with the encoding of different pain intensity levels (Coghill et al. 1999; Bornhovd et al. 2002; Buchel et al. 2002; Alkire et al. 2004; Kong et al. 2006b, 2010a). Thus, we might reason that for post-placebo treatment, decreased brain activity in these regions indicates reduced incoming noxious information. In fact, under certain

circumstances, brain imaging studies have begun to attest this very notion (Wager et al. 2004). This is just one example of how placebo treatment might be conceptualized through neurobiology. We believe that in order to fully understand placebo and nocebo phenomena, all contributions to outcome measurement changes should be properly acknowledged and investigated (Kong et al. 2007; Amanzio et al. 2013).

The literature on the placebo and nocebo effect is rich (see other related reviews for more details: Hrobjartsson and Gotzsche 2001; Hoffman et al. 2005; Kong et al. 2007; Finniss et al. 2010; Miller et al. 2009; Miller and Kaptchuk 2008; Barsky et al. 2002; Enck et al. 2008). In the next sections we will focus on several topics that may be helpful for understanding a complete picture of placebo treatment.

3 Reward System and Placebo Effect

Expectation is a critical component of all medical care and represents an important dimension of the "non-pharmacological component of pharmaceuticals" (Finniss et al. 2010; Benedetti 2008). In recent years, investigators have attempted to link positive expectancy to the reward system by reasoning that symptom reduction (decreased suffering) can be regarded as a special case of reward (de la Fuente-Fernandez et al. 2001, 2002; Scott et al. 2007, 2008; Leknes et al. 2011).

In an early study of placebo effects in patients with Parkinson's disease, investigators (de la Fuente-Fernandez et al. 2001, 2002) found that dopamine release increased in the ventral striatum (a key region in the reward system), suggesting the reward system association with expectations of improvement. In a subsequent study, Scott et al. (2007) found that dopamine release from the nucleus accumbens, observed during placebo administration, was related to its anticipated effects, perception-anticipation incongruity, and subsequent placebo effects. In a more recent morphometry study, Schweinhardt et al. (2009) found that dopamine-related traits can predict a substantial portion of the pain relief and individual gains from a sham treatment: the magnitude of placebo analgesia was correlated to gray matter density in the ventral striatum. In a more recent study, Yu and colleagues found that combining the resting state regional coherence at ventral striatum, Catechol-O-methyl transferase (COMT) and dopamine-related traits can be used to predict placebo response (Yu et al. 2014). The ventral striatum (nucleus accumbens) is also involved in placebo effects in anxiety (Petrovic et al. 2005), depression (Mayberg et al. 2002), psychotropic drug use (methylphenidate) (Volkow et al. 2003), and expectancy modulation of cue conditioning (Atlas et al. 2010). This involvement of the ventral striatum across multiple placebo conditions/modalities indicates that reward may represent a fundamental element of expectancy.

4 Endogenous Opioids and Placebo Analgesia

Placebo analgesia effect is one of the most robust and well-studied placebo effects. Although the dopamine reward system may play a role in placebo effects, most of the studies indicate the endogenous opioids and the pain descending modulatory network as the main mechanism in placebo analgesia (Zubieta et al. 2005; Scott et al. 2008; Wager et al. 2007; Eippert et al. 2009).

As the most studied pain modulatory mechanism for pain, the descending pain control system includes the periaqueductal gray (PAG), the rostral ventromedial medulla (RVM), frontal gyrus, anterior cingulate cortex, hypothalamus, and amygdala (Fields 2004; Kong et al. 2010b). PET studies have found significant μ-opioid binding potential changes after placebo treatment as compared with control condition (Zubieta et al. 2005; Scott et al. 2008; Wager et al. 2007), providing direct evidence of involvement of the endogenous opioid system.

In addition, fMRI studies (Wager et al. 2004; Price et al. 2007; Eippert et al. 2009) also found observable fMRI signal decreases in the brain's "pain matrix" as well as a decreased subjective pain experience, which provide direct evidence of the descending control system. Nevertheless, not all studies have found significant fMRI signal decrease in pain-related brain regions. In a previous study, Kong et al. (2006a) found significant fMRI signal increase in brain regions such as rostral ACC and anterior insula, but no significant fMRI signal decrease when comparing placebo treatment with controls, which suggest that other mechanisms such as emotion modulation may also be involved in placebo analgesia.

Despite some differences in previous studies, the results presented above may not be contradictory, as individual differences in detailed experimental paradigms may also underlie these differences. For instance, in our previous study (Kong et al. 2006a), the pain stimuli sequences after treatment were applied alternately between the placebo-treated side and untreated control side. Since opioid effects may be long lasting, as opioid activation can trigger naloxone insensitive analgesia that extends beyond the original opioid response (Atlas and Wager 2012), a method of applying stimuli on alternate sides (placebo and control) may not be sensitive to detect the opioid effects.

In addition, in three of the previous placebo analgesia studies (Wager et al. 2004; Price et al. 2007; Eippert et al. 2009) that reported an attenuation of brain activity in the pain matrix for reported analgesia, the authors used a relatively long duration of pain stimuli (20–30 s) as compared to the study by Kong et al. (2006a) that used pain stimuli lasting about 10 s. Their results confirm that the decreases in fMRI signal during the placebo condition (compared to the control condition) were mainly observed in a later phase of the pain stimulation. For example, Eippert et al. (2009) found a significant group-by-condition interaction during late pain (last 10 s), but not during early pain (first 10 s). Interestingly, they also found that naloxone could significantly reduce neural placebo effects, but only during late pain, not the early pain, implying that other mechanisms may be involved placebo analgesia. Indeed, a recent study shows that the endocannabinoid system could be involved under some circumstances (Benedetti et al. 2011).

In addition, one cue-expectancy study (Atlas et al. 2010) found that similar to placebo analgesia and nocebo hyperalgesia, significant fMRI signal decreases in pain-related brain regions and significant decreases in subjective pain intensity ratings were observed when subjects expected a low intensity pain as compared with control conditions. The rapid shifts of different predictive cues require any modulatory mechanism to be transient and reversible, due to the long-lasting effects of opioids in the brain; it is unlikely that endogenous opioid mechanisms are involved in cue modulation effects (Atlas and Wager 2012).

In summary, it appears that multiple brain mechanisms are involved in placebo analgesia, and that both subjective pain intensity rating reduction and fMRI signal reduction in pain-related brain region may happen without the involvement of endogenous opioids (Tracey 2010; Benedetti et al. 2011). Future research should focus on how to dissociate these different pain modulation mechanisms.

5 Do Placebo and Nocebo Share the Same Network?

A significant proportion of clinical improvement following different therapies, especially for subjective symptom outcomes, is directly attributable to placebo effects (Kaptchuk 2002), whereas a significant proportion of adverse events to medications is represented by nocebo effects (Amanzio et al. 2009; Barsky et al. 2002). Therefore, understanding similarities and differences in the mechanisms of placebo and nocebo effects represents an important challenge for future research.

Benedetti et al. (1997) found that nocebo hyperalgesia is mediated by cholecystokinin. In a brain imaging study, Kong et al. (2008) found that nocebo hyperalgesia may be predominantly produced through an affective-cognitive pain pathway (medial pain system), and the hippocampus may play an important role in this process. In a subsequent study that investigated the influence of expectancy on the analgesic effect of remifentanil, Bingel et al. (2011) also found that the positive expectancy effects were associated with activity in the endogenous pain modulatory system, and the negative expectancy effects with activity in the hippocampus, suggesting different mechanisms underlying placebo and nocebo effects. In a PET study, Scott et al. (2008) found an overlapping network including the anterior cingulate, orbitofrontal and insular cortex, nucleus accumbens, and amygdale, suggesting a similar mechanism of placebo analgesia and nocebo hyperalgesia. Future studies that directly compare the placebo and nocebo effects using the same cohort of subjects will help provide a general model of how different expectancies can modulate brain responses.

6 Additive Effect of Placebo and Real Treatment

Evidence-based medicine relies on the placebo-controlled randomized clinical trial (RCT) to distinguish the effects of an active (verum/genuine) pharmacological agent or procedure from the effects of a mimicking placebo treatment. Both for biomedicine and for complementary and alternative medicine (CAM), detecting this difference has become a challenge, especially for subjective outcomes.

The prevailing model for understanding verum-placebo differences has been the "additive model" (Kirsch 2000). This model presupposes that the placebo effect in the treatment and placebo arms of an RCT are of equivalent magnitude and that one can simply subtract the magnitude of the placebo response from the medication response to determine the presence (or absence) of verum effects. The possibility that under different conditions the pharmacological and placebo effects could act differentially in the two arms of a RCT is rejected a priori (Kleijnen et al. 1994; Kirsch 1999). Alternatively, it is possible that drug and placebo effects interact (Kirsch 1999). The possibility that placebo-induced expectancies might modify the drug effect (i.e., the difference between the drug response and the placebo response) has received insufficient attention. Recently, brain imaging has started shedding new light on this field.

Kong et al. (2009b) investigated how expectancy can modulate acupuncture treatment effects using a conditioning-like expectancy manipulation paradigm. The results indicate that expectancy can significantly modulate the analgesic effect of acupuncture treatment in both subjective pain rating changes and fMRI signal changes. In addition, it was found that, although verum acupuncture and sham acupuncture induced subjective reports of analgesia of equal magnitudes, fMRI analysis showed that (1) verum acupuncture produced greater fMRI signal decreases in pain-related brain regions during the application of calibrated heat pain stimuli on the right arm and (2) high expectancy produced greater fMRI signal changes in emotion-related brain regions.

Using a conditioning-like expectancy manipulation model, Bingel et al. (2011) investigated how different expectancies can modulate the analgesic effect of a potent opioid, remifentanil, using fMRI. The effect of a fixed concentration of the μ-opioid agonist remifentanil on constant heat pain was assessed under three experimental conditions using a within-subject design: with no expectation of analgesia, with expectancy of a positive analgesic effect, and with negative expectancy of analgesia (i.e., expectation of hyperalgesia or exacerbation of pain). Results showed that positive treatment expectancy can significantly enhance the analgesic benefit of remifentanil; at the same time, negative treatment expectancy abolished remifentanil analgesia effect. Brain imaging results also showed that the positive expectancy effects were associated with activity in the endogenous pain modulatory system, and the negative expectancy effects with activity in the hippocampus.

In another study, Atlas et al. (2012) also investigated the influence of expectancy on remifentanil. Two experiments were performed, and in both experiments remifentanil (or placebo treatment) was administered to all subjects during

experimental thermal pain. Results showed that remifentanil and expectancy both reduced pain, but drug effects on pain reports and fMRI activity did not interact with expectancy. Regions associated with pain processing showed drug-induced modulation during both open (expected) and hidden (unexpected) administrations, with no differences in drug effects as a function of expectation. These findings suggest that remifentanil and placebo treatments both influence clinically relevant outcomes and operate without mutual interference.

In a more recent verbal suggestion balanced placebo study using a topical analgesic treatment (lidocaine), Schenk et al. (2014) investigated the interaction between lidocaine and expectancy with a clinical pain-related model (capsaicin pretreated skin) in healthy subjects. They found that active treatment can significantly reduce the pain rating as compared with placebo treatment, while the main expectancy effect (open administration compared with hidden administration) is not significant. However, unlike Atlas et al. (2012), they found a significant interaction between treatment and expectancy. In two lidocaine groups, open administration showed significantly greater pain rating reduction than hidden administration, but there was no significant difference between open and hidden administration of placebo treatment.

The inconsistent results may derive from different reasons: (1) different ways of manipulating expectancy, e.g., verbal suggestion vs. a more powerful conditioning-like procedure (Colloca et al. 2008; Wager et al. 2004; Kong et al. 2013b). (2) Different active treatment modalities (remifentanil, lidocaine, and acupuncture). Taken together, these results suggest that the effect of expectancy on treatment outcome may depend on the strength of the expectancy manipulation, the treatment modality, and the status of the participants (subjects vs. patients).

7 Predicting Placebo Responses

Given the high impact of the placebo response in medical practice and research, predicting placebo responses has always been an abstractive topic to placebo researchers. In recent years, investigators started applying imaging tools to predict placebo responses (Honey et al. 2008; Wager et al. 2011; Hashmi et al. 2012, 2014; Kong et al. 2013a; Yu et al. 2014). In a previous study, Wager et al. (2011) found that increased anticipatory activity in a frontoparietal network and decreases in a posterior insular/temporal network predicted placebo analgesia. During pain, decreases in limbic and paralimbic regions, not the pain-associated brain region, most strongly predicted placebo analgesia. These results indicate that enhancement of emotional appraisal circuits may be responsible for individual variation in placebo analgesia, rather than early suppression of nociceptive processing.

Ideally, a clinical applicable marker to predict placebo response should be a measurement applied before the treatment started. The pretest resting state functional connectivity has the potential to be used as a marker. In a previous study, Kong et al. (2013a, b) found that pretest resting state functional connectivity between the right frontoparietal network (as identified by independent component

analysis) and the rostral anterior cingulate cortex/medial prefrontal cortex was positively associated with conditioning cue effects indicated by pain rating changes. In another study (Yu et al. 2014), it was found that the regional homogeneity (ReHo), an index of local neural coherence, in the ventral striatum, was significantly associated with conditioning effects on pain rating changes evoked by placebo visual cue. It was also found that the number of Met alleles at the COMT polymorphism was linearly correlated to the suppression of pain. These findings demonstrate the potential of combining resting state connectivity and genetic information to predict placebo effect. In the same study, personality was also found to represent a possible predictor. In another recent study (Hashmi et al. 2014), it was found that the efficiency of information transfer within local networks calculated with graph-theoretic measures (local efficiency and clustering coefficients) significantly predicted conditioned analgesia in older patients with knee Osteoarthritis.

Taking together, resting state functional connectivity holds the potential to predict placebo response. Nevertheless, we have to interpret the above results with caution, and independent replication of these studies is needed before we can draw solid conclusions.

Conclusions

In summary, both unconscious learning mechanisms and conscious expectancies can be involved in placebo and nocebo effects, particularly placebo analgesia and nocebo hyperalgesia. When expectancy is enhanced, it holds the potential to significantly enhance or overcome the real treatment effect. Appropriate application of the power of both learning and expectancy may provide new pathway to promote good therapeutic outcomes. In addition, brain imaging measurements may be applied as a potential marker to predict placebo responses, with profound implications for clinical trials.

References

Alkire MT, White NS, Hsieh R, Haier RJ (2004) Dissociable brain activation responses to 5-Hz electrical pain stimulation. Anesthesiology 100:939–946

Amanzio M, Benedetti F (1999) Neuropharmacological dissection of placebo analgesia: expectation-activated opioid systems versus conditioning-activated specific subsystems. J Neurosci 19(1):484–494

Amanzio M, Corazzini LL, Vase L, Benedetti F (2009) A systematic review of adverse events in placebo groups of anti-migraine clinical trials. Pain 146(3):261–269

Amanzio M, Benedetti F, Porro CA, Palermo S, Cauda F (2013) Activation likelihood estimation meta-analysis of brain correlates of placebo analgesia in human experimental pain. Hum Brain Mapp 34(3):738–752

Atlas LY, Wager TD (2012) How expectations shape pain. Neurosci Lett 520(2):140–148

Atlas LY, Bolger N, Lindquist MA, Wager TD (2010) Brain mediators of predictive cue effects on perceived pain. J Neurosci 30(39):12964–12977

Atlas LY, Whittington RA, Lindquist MA, Wielgosz J, Sonty N, Wager TD (2012) Dissociable influences of opiates and expectations on pain. J Neurosci 32(23):8053–8064

Barsky AJ, Saintfort R, Rogers MP, Borus JF (2002) Nonspecific medication side effects and the nocebo phenomenon. JAMA 287(5):622–627

Benedetti F (2008) Mechanisms of placebo and placebo-related effects across diseases and treatments. Annu Rev Pharmacol Toxicol 48:33–60

Benedetti F, Amanzio M, Casadio C, Oliaro A, Maggi G (1997) Blockade of nocebo hyperalgesia by the cholecystokinin antagonist proglumide. Pain 71(2):135–140

Benedetti F, Pollo A, Lopiano L, Lanotte M, Vighetti S, Rainero I (2003) Conscious expectation and unconscious conditioning in analgesic, motor, and hormonal placebo/nocebo responses. J Neurosci 23:4315–4323

Benedetti F, Mayberg HS, Wager TD, Stohler CS, Zubieta JK (2005) Neurobiological mechanisms of the placebo effect. J Neurosci 25(45):10390–10402

Benedetti F, Amanzio M, Rosato R, Blanchard C (2011) Non-opioid placebo analgesia is mediated by CB1 cannabinoid receptors. Nat Med 17:1228–1230

Bingel U, Wanigasekera V, Wiech K, Mhuircheartaigh RN, Lee MC, Ploner M et al (2011) The effect of treatment expectation on drug efficacy: imaging the analgesic benefit of the opioid remifentanil. Sci Transl Med 3(70):70ra14

Bornhovd K, Quante M, Glauche V, Bromm B, Weiller C, Buchel C (2002) Painful stimuli evoke different stimulus–response functions in the amygdala, prefrontal, insula and somatosensory cortex: a single-trial fMRI study. Brain 125:1326–1336

Buchel C, Bornhovd K, Quante M, Glauche V, Bromm B, Weiller C (2002) Dissociable neural responses related to pain intensity, stimulus intensity, and stimulus awareness within the anterior cingulate cortex: a parametric single-trial laser functional magnetic resonance imaging study. J Neurosci 22(3):970–976

Cleophas TJ (1995) The importance of placebo effects. JAMA 273:283

Coghill RC, Sang CN, Maisog JM, Iadorola MJ (1999) Pain intensity processing within the human brain: a bilateral, distributed mechanism. J Neurophysiol 82:1934–1943

Colloca L, Tinazzi M, Recchia S, Le Pera D, Fiaschi A, Benedetti F et al (2008) Learning potentiates neurophysiological and behavioral placebo analgesic responses. Pain 139(2):306–314

Custers R, Aarts H (2010) The unconscious will: how the pursuit of goals operates outside of conscious awareness. Science 329(5987):47–50

de la Fuente-Fernandez R, Schulzer M, Stoessl AJ (2002) The placebo effect in neurological disorders. Lancet Neurol 1:85–91

de la Fuente-Fernandez R, Ruth TJ, Sossi V, Schulzer M, Calne DB, Stoessl AJ (2001) Expectation and dopamine release: mechanism of the placebo effect in Parkinson's disease. Science 293:1164–1166

Eippert F, Bingel U, Schoell ED, Yacubian J, Klinger R, Lorenz J et al (2009) Activation of the opioidergic descending pain control system underlies placebo analgesia. Neuron 63(4):533–543

Enck P, Benedetti F, Schedlowski M (2008) New insights into the placebo and nocebo responses. Neuron 59(2):195–206

Fields H (2004) State-dependent opioid control of pain. Nat Rev Neurosci 5(7):565–575

Finniss DG, Kaptchuk TJ, Miller F, Benedetti F (2010) Biological, clinical, and ethical advances of placebo effects. Lancet 375(9715):686–695

Hashmi JA, Baria AT, Baliki MN, Huang L, Schnitzer TJ, Apkarian AV (2012) Brain networks predicting placebo analgesia in a clinical trial for chronic back pain. Pain 153(12):2393–2402. doi:10.1016/j.pain.2012.08.008

Hashmi JA, Kong J, Spaeth R, Khan S, Kaptchuk TJ, Gollub RG (2014) Functional network architecture predicts psychologically mediated analgesia related to treatment in chronic knee pain patients. J Neurosci 34(11):3924–3936

Hoffman GA, Harrington A, Fields HL (2005) Pain and the placebo: what we have learned. Perspect Biol Med 48(2):248–265

Honey GD, Corlett PR, Absalom AR, Lee M, Pomarol-Clotet E, Murray GK et al (2008) Individual differences in psychotic effects of ketamine are predicted by brain function measured under placebo. J Neurosci 28(25):6295–6303. doi:10.1523/JNEUROSCI.0910-08.2008

Hrobjartsson A, Gotzsche PC (2001) Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. N Engl J Med 344(21):1594–1602

Jensen KB, Kaptchuk TJ, Kirsch I, Raicek J, Lindstrom KM, Berna C, Gollub RL, Ingvar M, Kong J (2012) Nonconscious activation of placebo and nocebo pain responses. Proc Natl Acad Sci USA 109(39):15959–15964

Kaptchuk TJ (2002) The placebo effect in alternative medicine: can the performance of a healing ritual have clinical significance? Ann Intern Med 136(11):817–825

Kirsch I (1999) How expectancies shape experience. American Psychological Association, Washington, DC

Kirsch I (2000) Are drug and placebo effects in depression additive? Biol Psychiatry 47(8):733–735

Kleijnen J, de Craen AJ, van Everdingen J, Krol L (1994) Placebo effect in double-blind clinical trials: a review of interactions with medications. Lancet 344(8933):1347–1349

Kong J, Gollub RL, Rosman IS, Webb JM, Vangel MG, Kirsch I et al (2006a) Brain activity associated with expectancy-enhanced placebo analgesia as measured by functional magnetic resonance imaging. J Neurosci 26(2):381–388

Kong J, White NS, Kwong KK, Vangel MG, Rosman IS, Gracely RH et al (2006b) Using fMRI to dissociate sensory encoding from cognitive evaluation of heat pain intensity. Hum Brain Mapp 27(8):715–721

Kong J, Kaptchuk TJ, Polich G, Kirsch I, Gollub RL (2007) Placebo analgesia: findings from brain imaging studies and emerging hypotheses. Rev Neurosci 18(3–4):173–190

Kong J, Gollub RL, Polich G, Kirsch I, Laviolette P, Vangel M et al (2008) A functional magnetic resonance imaging study on the neural mechanisms of hyperalgesic nocebo effect. J Neurosci 28(49):13354–13362

Kong J, Kaptachuk TJ, Polich G, Kirsch IV, Angel M, Zyloney C et al (2009a) Expectancy and treatment interactions: a dissociation between acupuncture analgesia and expectancy evoked placebo analgesia. Neuroimage 45:940–949, PMID: 19159691

Kong J, Kaptchuk TJ, Polich G, Kirsch I, Vangel M, Zyloney C et al (2009b) An fMRI study on the interaction and dissociation between expectation of pain relief and acupuncture treatment. Neuroimage 47(3):1066–1076, PMID: 19501656

Kong J, Loggia ML, Zyloney C, Tu P, Laviolette P, Gollub RL (2010a) Exploring the brain in pain: activations, deactivations and their relation. Pain 148:257–267, PMID: 20005043

Kong J, Tu PC, Zyloney C, Su TP (2010b) Intrinsic functional connectivity of the periaqueductal gray, a resting fMRI study. Behav Brain Res 211(2):215–219

Kong J, Jensen K, Loiotile R, Cheetham A, Wey HY, Tan T et al (2013a) Functional connectivity of frontoparietal network predicts cognitive modulation of pain. Pain 154(3):459–467

Kong J, Spaeth R, Cook A, Kirsch I, Claggett B, Vangel M et al (2013b) Are all placebo effects equal? Placebo pills, sham acupuncture, cue conditioning and their association. PLoS ONE 8 (7):e67485. doi:10.1371/journal.pone.0067485

Leknes S, Lee M, Berna C, Andersson J, Tracey I (2011) Relief as a reward: hedonic and neural responses to safety from pain. PLoS ONE 6(4):e17870

Lewis CM, Baldassarre A, Committeri G, Romani GL, Corbetta M (2009) Learning sculpts the spontaneous activity of the resting human brain. Proc Natl Acad Sci USA 106(41):17558–17563

Mayberg HS, Silva JA, Brannan SK, Tekell JL, Mahurin RK, McGinnis S et al (2002) The functional neuroanatomy of the placebo effect. Am J Psychiatry 159(5):728–737

Mesulam MM (1998) From sensation to cognition. Brain 121:1013–1052

Miller FG, Kaptchuk TJ (2008) The power of context: reconceptualizing the placebo effect. J R Soc Med 101(5):222–225

Miller FG, Colloca L, Kaptchuk TJ (2009) The placebo effect: illness and interpersonal healing. Perspect Biol Med 52(4):518–539

Pessiglione M, Petrovic P, Daunizeau J, Palminteri S, Dolan RJ, Frith CD (2008) Subliminal instrumental conditioning demonstrated in the human brain. Neuron 59(4):561–567

Petrovic P, Dietrich T, Fransson P, Andersson J, Carlsson K, Ingvar M (2005) Placebo in emotional processing–induced expectations of anxiety relief activate a generalized modulatory network. Neuron 46(6):957–969

Price DD, Craggs J, Verne GN, Perlstein WM, Robinson ME (2007) Placebo analgesia is accompanied by large reductions in pain-related brain activity in irritable bowel syndrome patients. Pain 127(1–2):63–72

Schenk LA, Sprenger C, Geuter S, Buchel C (2014) Expectation requires treatment to boost pain relief: an fMRI study. Pain 155(1):150–157. doi:10.1016/j.pain.2013.09.024

Schweinhardt P, Seminowicz DA, Jaeger E, Duncan GH, Bushnell MC (2009) The anatomy of the mesolimbic reward system: a link between personality and the placebo analgesic response. J Neurosci 29(15):4882–4887. doi:10.1523/jneurosci.5634-08.2009

Scott DJ, Stohler CS, Egnatuk CM, Wang H, Koeppe RA, Zubieta JK (2007) Individual differences in reward responding explain placebo-induced expectations and effects. Neuron 55(2):325–336

Scott DJ, Stohler CS, Egnatuk CM, Wang H, Koeppe RA, Zubieta JK (2008) Placebo and nocebo effects are defined by opposite opioid and dopaminergic responses. Arch Gen Psychiatry 65 (2):220–231

Tedeschi JT, Schlenker BR, Bonoma TV (1971) Cognitive dissonance: private ratiocination or public spectacle? Am Psychol 26:685–695

Tracey I (2010) Getting the pain you expect: mechanisms of placebo, nocebo and reappraisal effects in humans. Nat Med 16(11):1277–1283

Volkow ND, Wang GJ, Ma Y, Fowler JS, Zhu W, Maynard L et al (2003) Expectation enhances the regional brain metabolic and the reinforcing effects of stimulants in cocaine abusers. J Neurosci 23(36):11461–11468

Wager TD, Rilling JK, Smith EE, Sokolik A, Casey KL, Davidson RJ et al (2004) Placebo-induced changes in FMRI in the anticipation and experience of pain. Science 303:1162–1167

Wager TD, Scott DJ, Zubieta JK (2007) Placebo effects on human mu-opioid activity during pain. Proc Natl Acad Sci USA 104(26):11056–11061

Wager TD, Atlas LY, Leotti LA, Rilling JK (2011) Predicting individual differences in placebo analgesia: contributions of brain activity during anticipation and pain experience. J Neurosci 31(2):439–452

Yu R, Gollub RL, Vangel M, Kaptchuk T, Smoller JW, Kong J (2014) Placebo analgesia and reward processing: integrating genetics, personality, and intrinsic brain activity. Hum Brain Mapp. doi:10.1002/hbm.22496

Zubieta JK, Bueller JA, Jackson LR, Scott DJ, Xu Y, Koeppe RA et al (2005) Placebo effects mediated by endogenous opioid activity on mu-opioid receptors. J Neurosci 25(34):7754–7762