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Brain Mechanisms of the Placebo Effect: An Affective Appraisal Account

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Abstract

Placebos are sham medical treatments. Nonetheless, they can have substantial effects on clinical outcomes. Placebos depend on a person's psychological and brain responses to the treatment context, which influence appraisals of future well-being. Appraisals are flexible cognitive evaluations of the personal meaning of events and situations that can directly impact symptoms and physiology. They also shape associative learning processes by guiding what is learned from experience. Appraisals are supported by a core network of brain regions associated with the default mode network involved in self-generated emotion, self-evaluation, thinking about the future, social cognition, and valuation of rewards and punishment. Placebo treatments for acute pain and a range of clinical conditions engage this same network of regions, suggesting that placebos affect behavior and physiology by changing how a person evaluates their future well-being and the personal significance of their symptoms.

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INTRODUCTION

“One of the most successful physicians I have ever known, has assured me that he used more bread pills, drops of colored water, & powders of hickory ashes, than of all other medicines put together.” —Thomas Jefferson, Letter to Caspar Wistar, 1807

In a recent clinical trial for Parkinson’s disease, physicians surgically injected a viral vector designed to enhance dopaminergic function directly into patients’ brains (Olanow et al. 2015). Similar treatments had worked in nonhuman primates, and results from an open-label trial in patients were promising. Buoyed by these findings, the researchers conducted a large, multisite, double-blind randomized trial comparing the novel treatment to a sham surgery.

The patients injected with the treatment showed marked, sustained improvement over 2 years, as the researchers hoped. Yet, surprisingly, patients who underwent the sham surgery improved at the same rate over the same time period—and these gains were maintained for at least 2 years (**Figure 1**). Thus, the trial failed, signaling a potential finale to a decade-long program of groundbreaking research and triggering the sale of the company that funded it. However, it provided a remarkable demonstration of placebo-related improvements in a neurodegenerative disorder typically characterized by progressive decline.

This trial is not an isolated phenomenon. Clinically meaningful placebo effects have been observed in depression (Cuijpers et al. 2012, Khan et al. 2012), chronic pain (Hróbjartsson & Gøtzsche 2010, Madsen et al. 2009), irritable bowel syndrome (IBS) (Kaptchuk et al. 2008, 2010), and other conditions (Hróbjartsson & Gøtzsche 2010). In each case, patients given placebos fare substantially better than those in no-treatment conditions (natural history), demonstrating causal effects of placebos (**Figure 2**). Placebo effects also contribute to the effectiveness of many active treatments. For instance, the analgesic effects of several commonly used painkillers are markedly reduced when patients do not know they are receiving them (Atlas et al. 2012, Benedetti et al. 2003a, Colloca et al. 2004), and patients who adhere to medication for heart disease live longer—even if the medication is a placebo and even when controlling for a number of potential confounding variables (Pressman et al. 2012).

Placebos are by definition inert. They are sham medical treatments—drugs, devices, or other treatments with no inherent potency. How, then, can they heal? Their therapeutic potential lies

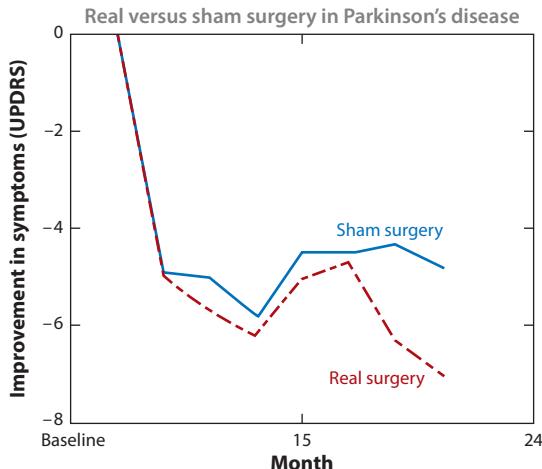


Figure 1

The placebo response. Sham brain surgery led to improvements in Parkinson's symptoms that were as large as active treatment (verum surgery) up to 2 years later (Olanow et al. 2015). Symptoms were measured with Unified Parkinson's Disease Rating Scale (UPDRS) motor off scores.

in the patient's brain and is driven by the patient's responses to the psychosocial context in which the placebo treatment is delivered (Benedetti 2014, Büchel et al. 2014, Wager & Atlas 2015). Key elements of the treatment context include the patient's relationships with care providers and other cues and rituals, such as visiting a doctor's office or taking a pill; these influence patients' appraisals about how a treatment will affect them, including expectations for recovery (Colloca & Miller 2011, Finniss et al. 2010, Frank & Frank 1993, Price et al. 2008). Placebo effects thus offer a window into how psychosocial processes impact health and disease.

Here, we review placebo effects on clinical outcomes and explore their behavioral and brain mechanisms. We argue that placebo effects are created largely by psychological appraisals. Appraisals depend on cognitive beliefs and also influence precognitive learning processes to create placebo effects that do not depend on cognitive beliefs or expectations. We present meta-analytic findings showing that placebo treatments engage a brain system that mediates multiple varieties of appraisals, including self-generated emotions, expectations, valuation, self-evaluations, and beliefs about others. This system overlaps with the default network, a brain system that is involved in spontaneous thought and feeling (Gusnard & Raichle 2001, Raichle et al. 2001) and is implicated in multiple mood disorders (Etkin & Wager 2007, Kaiser et al. 2015). This colocalization provides a neurobiological connection among placebo effects, emotional appraisal, and mood and pain disorders.

PLACEBO RESPONSES AND PLACEBO EFFECTS IN CLINICAL CONTEXTS

Do Placebos Have Meaningful Effects on Clinical Outcomes?

The response to placebo treatment is often as large as the response to pharmacological treatment, especially for chronic pain (Tuttle et al. 2015) and depression (Fournier et al. 2010, Kirsch et al. 2008). However, only some of the observed response is caused by the placebo treatment. Patients often enroll in trials when fluctuating symptoms are at their worst and then improve due to

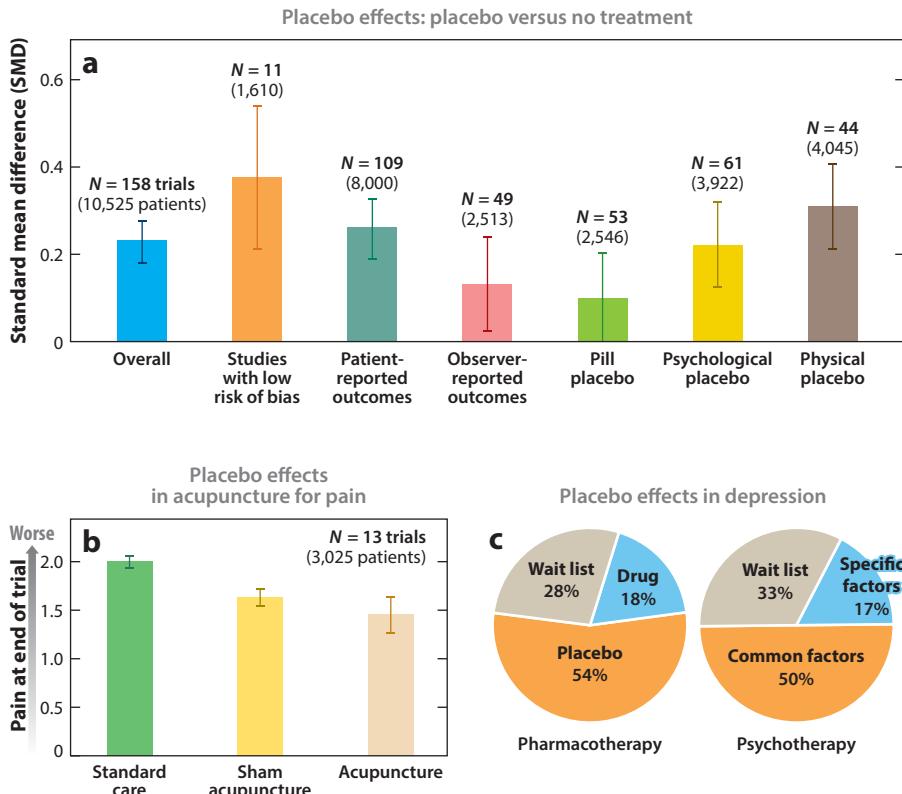


Figure 2

The placebo effect. (a) Meta-analysis of clinical trials comparing placebo treatments to treatment as usual or no treatment (Hróbjartsson & Gøtzsche 2010). Numbers of trials and patients are shown. Psychological placebos include, for example, nondirective, supportive conversations. Physical placebos include, for example, sham acupuncture and sham surgery. (b) The placebo effect accounts for most of the response to acupuncture in the treatment of clinical pain conditions; standardized pain scores at the end of treatment are shown from the Madsen et al. (2009) meta-analysis. (c) Estimated effect sizes for placebo (Khan et al. 2012) and common factors (Cuijpers et al. 2012) in the treatment of depression. Common factors are closely conceptually related to placebo effects. They include patient expectations, the patient-provider relationship, and other factors common to almost all psychotherapies.

regression to the mean or spontaneous recovery (see, e.g., Wager & Fields 2013). Similarly, patients with the worst outcomes on placebo may drop out of studies, creating sampling biases that increase the apparent placebo response. Thus, it is crucial to distinguish the placebo effect—the mind-brain response to the placebo specifically—from the placebo response, or the overall response to placebo treatment.

Placebo effects in clinical disorders can be estimated in at least four ways. One common approach is to compare placebo treatment to no-treatment (natural history) or treatment-as-usual control groups in randomized clinical trials. Hróbjartsson and Gøtzsche have conducted several influential meta-analyses of such trials (most recently, Hróbjartsson & Gøtzsche 2010). Collapsing across all disorders and placebo treatment modalities, they found small but significant placebo effects [Standardized Mean Difference (SMD) = −0.23, 95% confidence interval (CI) (−0.28

-0.17], with stronger effect sizes in trials of high methodological quality [SMD = -0.38 , 95% CI (-0.55 – -0.22)] (Figure 2a). Other studies have provided more focused examinations of placebo effects in specific clinical contexts.

Focusing on pain, a meta-analysis including over 3,000 patients found comparable therapeutic effects of acupuncture and sham acupuncture, both of which provided substantially more relief than standard care based on physical therapy or medication regimes (Madsen et al. 2009) (Figure 2b). Focusing on depression, Khan et al. (2012) conducted a meta-analysis of trials with placebo, drug, and wait-list conditions (Figure 2c, left). They decomposed the overall drug response into active drug effects (18% of the total effect), placebo effects (54%), and improvement in wait-list conditions (28%). Highly similar results were reported by Cuijpers et al. (2012) in a meta-analysis that decomposed the effects of psychotherapy treatments for depression into nontreatment factors (i.e., wait list, 33%); treatment-specific factors, such as mindfulness or cognitive restructuring (17%); and common factors, such as patient expectations and the patient-therapist relationship, which are conceptually closely related to placebo effects (50%) (Figure 2c, right) (Wampold et al. 2015). Focusing on anxiety disorders, Bandelow et al. (2015) conducted a meta-analysis of clinical trials, including 234 studies with over 37,000 patients. They found treatment effect sizes of $d = 1.29$ for placebo pills, $d = 0.83$ for psychological placebos, and $d = 0.20$ for wait-list controls, demonstrating substantial placebo effects.

A second approach to estimating placebo effects is to compare open drug treatment with hidden drug treatment—when patients are aware versus unaware that they are receiving a drug. These studies have demonstrated substantial placebo effects on experimental pain (Atlas et al. 2012), postoperative pain, and Parkinson’s disease (Colloca et al. 2004), with awareness of drug administration treatment accounting for half or more of drug effects.

A third approach to estimating placebo effects is to compare outcomes across clinical trials in which patients had different probabilities of receiving active treatment or placebo. Increased probability of receiving active treatment enhances patient expectations of improvement (Rutherford 2016). Schizophrenia patients had twice as large a response to the same medication when administered in a comparator trial (comparing two or more active drugs without a placebo arm) relative to when administered in a placebo-controlled trial (Rutherford et al. 2014, Woods et al. 2005). Similarly, among depressed patients, both drugs and placebos achieved an approximately 10% higher response rate in comparator trials relative to placebo-controlled trials (Papakostas & Fava 2009, Sinyor et al. 2010, Snead et al. 2008). Similar results are observed for several anxiety disorders (Rutherford et al. 2015), highlighting the importance of treatment context.

A fourth approach to estimating placebo effects is to compare different types of placebo treatments (Figure 2a). In a systematic review of migraine prophylaxis, Meissner et al. (2013) found a modest (26%) response rates to sham pills, injections, and herbs; a larger response rate to sham acupuncture (38%); and an even larger response rate to sham surgery (58%). A similar pattern of increased response to more invasive placebo treatments was found in a meta-analysis of 149 trials of osteoarthritis pain (Bannuru et al. 2015) and in a meta-analysis of 11 trials of Parkinson’s disease (Goetz et al. 2008), although one meta-analysis did not find differences among different placebo modalities (Fässler et al. 2015). Thus, the modality of the placebo treatment contributes to the placebo effect, likely due to patients’ appraisals of a modality’s potency.

Placebo effects can last for months to years. For example, in clinical trials for neuropathic pain, Parkinson’s disease, and depression, the placebo response appears to grow over the course of the trial and is reliably observed for months or even years after initiating placebo treatment (Khan et al. 2008, Marks et al. 2010, Olanow et al. 2015, Quessy & Rowbotham 2008, Tuttle et al. 2015). A better understanding of when placebo effects are sustained vs. when they naturally extinguish may help shed light on placebo mechanisms.

How Reliable Is the Placebo Effect?

How reliably will a person respond to identical administrations of a placebo treatment? And will a person's response to one placebo treatment correlate with his or her response to a different placebo treatment?

In one of the most rigorous investigations of placebo reliability, Whalley et al. (2008) found that the analgesic responses to a placebo cream had moderately high test-retest reliability at one week, $r = 0.60\text{--}0.77$, agreeing with an estimate of $r = 0.55$ from a similarly designed experiment (Morton et al. 2009). This suggests that responses to the same placebo treatment are reliable over time. Yet, Whalley et al. (2008) also found that responses to one placebo cream were uncorrelated with responses to another placebo cream that was differently labeled but otherwise identical, $r(69) = 0.10, p < 0.41$. This pattern of reliable responding to identical placebo treatments but unreliable responding to different placebo treatments is supported by other previous studies (Kessner et al. 2013, 2014). For example, Kong et al. (2013) reported that participants had uncorrelated analgesic responses to sham acupuncture and pill placebo treatments.

Little evidence indicates that placebos elicit reliable responses in clinical contexts. One study did find that responses to an oral and intravenous antidepressant placebo treatment were correlated, $r = 0.35; p = 0.04$, and that response to the oral placebo also predicted later response to an active medication (Peciña et al. 2015). However, findings from other studies point to low reliability across contexts. Liberman (1967) found that placebo responses were uncorrelated across three types of pain, including experimental pain and the pain of childbirth. Müller et al. (2016) found that placebo analgesia in experimental pain was uncorrelated with responses to a placebo treatment for chronic pain. Similarly, meta-analyses of clinical trials for depression have found that patients' gains during the placebo lead-in phase are not related to their placebo responses during the active phase (Posternak et al. 2002).

One interpretation of these findings is that placebo effects depend strongly on individuals' appraisals of the treatment context. Thus, they can be reliable when the treatment context (and corresponding appraisals) are held constant, but they can change dramatically with even relatively minor changes in the treatment context (Koban et al. 2013) such as changing the name of a cream (Whalley et al. 2008).

Which Disorders Respond Most to Placebo Treatments?

Clinical studies suggest substantial placebo responses in many disorders. These include multiple pain conditions (Tuttle et al. 2015, Vase et al. 2002), such as osteoarthritis (Bannuru et al. 2015, Moseley et al. 2002), migraine (Kam-Hansen et al. 2014, Meissner et al. 2013), IBS (Kaptchuk et al. 2010, Vase et al. 2005), and labor pain (Liberman 1967). Substantial placebo responses are also observed in depression (Cuijpers et al. 2012, Fournier et al. 2010, Kirsch et al. 2008), anxiety (Bandelow et al. 2015), Parkinson's disease (Goetz et al. 2008), schizophrenia (Rutherford et al. 2014), asthma (Wechsler et al. 2011), urological conditions (Sorokin et al. 2015), menopausal hot flashes (Freeman et al. 2015), and other conditions.

Estimating relative effect sizes across disorders is challenging. One meta-analytic comparison of responses to placebo pills across six patient groups found the largest placebo effects in generalized anxiety disorder and panic disorder and the smallest effects in psychosis and obsessive-compulsive disorder (Khan et al. 2005) (**Figure 3a**). Effects on depression and posttraumatic stress disorder were in between.

In a comparison of sham surgical interventions across disorders, Jonas et al. (2015) found moderately large placebo responses in pain, gastroesophageal reflux disease, and other conditions

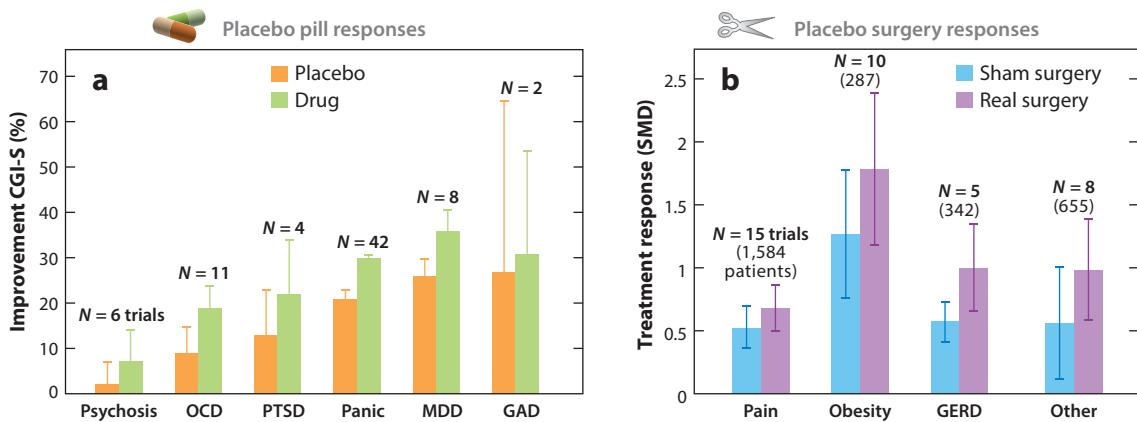


Figure 3

Placebo responses across disorders. (a) Pill placebo responses in different psychiatric disorders (Khan et al. 2005). (b) Sham surgery responses across different conditions (Jonas et al. 2015). The number of trials and patients (if available) in each condition is shown. Abbreviations: CGI-S, Clinical Global Impressions of Severity Scale; GAD, generalized anxiety disorder; GERD, gastroesophageal reflux disease; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; PTSD, posttraumatic stress disorder; SMD, standardized mean difference.

($SMD \approx 0.5$) (Figure 3b). For pain, the effects of sham surgery were nearly as large as real surgery, and were statistically indistinguishable. Because sham surgery studies typically do not include no-treatment control groups, the observed response includes factors not due to the sham surgery specifically, such as regression to the mean.

Although placebo treatments can affect physiological outcomes, such as hormone production or urinary flow rate (Meissner 2011, Meissner et al. 2007, Sorokin et al. 2015, Wager & Atlas 2015), they are largest for psychological outcomes (Figure 2a) (Hróbjartsson & Gøtzsche 2010). For example, one study found that a placebo treatment for asthma improved subjective symptom severity but did not improve forced expiratory volume, an objective measure of lung function (Wechsler et al. 2011). This suggests that there is a larger potential for placebo effects on outcomes that are more closely linked to patients' emotional and motivational states.

MECHANISMS OF PLACEBO EFFECTS

Theories of placebo mechanisms during the past several decades have focused primarily on expectations and learning (Kirsch 1985, Stewart-Williams & Podd 2004). Recent work has elaborated our understanding of how each class of processes works at both behavioral and brain levels of analysis (Benedetti 2014, Büchel et al. 2014, Enck et al. 2008, Price et al. 2008, Wager & Atlas 2015). Though the terms expectations and learning are used across many disciplines, they often have domain-specific meanings, which can lead to confusion. Here, we recast theories of expectation and learning in a somewhat broader context, focusing on interactions between precognitive associations, which refer to learned associations that can operate without cognitive awareness or intervention, and appraisals, which refer to interpretations of the meaning of events in a given context. These two broad classes of mechanisms interact with one another to create and maintain placebo effects. In this paper, we differentiate appraisals from precognitive associations and outline their critical role in the mechanisms underlying placebo effects. A key aspect of our argument is that the appraisal system is supported by the coordinated functioning of multiple brain systems

involved in emotion and cognition, converging in the ventromedial prefrontal cortex (vmPFC) and other regions in the so-called default mode network.

Appraisal and Precognitive Association: Separable but Interacting Mechanisms

Placebo effects are supported by two distinct but interacting processes: precognitive associations and appraisals.

Precognitive associations. Precognitive associations are responses to stimuli that are automatic in the sense that they can occur without cognitive effort and are largely invariant to cognitive context and goals. These associations are learned based on experience and are mediated by plasticity in stimulus- and response-specific neural pathways that are distributed throughout the nervous system. For example, in classical conditioning paradigms, *Aplysia* and *Drosophila* exhibit single-trial learning in response to aversive events (shocks), which manifests in the strengthening of specific neural pathways associated with defensive responses (Carew et al. 1983). Anencephalic animals and humans deprived of a forebrain and cortex can also learn to generate complex affective behavior (Berntson & Micco 1976) and autonomic responses via classical conditioning to shocks (Berntson et al. 1983). Likewise, the isolated spinal cord can learn complex motor responses, including learning to anticipate and avoid shocks (Grau 2014).

Precognitive associations with drug and context cues are likely to underlie some forms of placebo effects. Placebo effects are readily obtainable in rodents (Guo et al. 2011, Herrnstein 1962, Woods & Ramsay 2000) and humans by pharmacological conditioning, which involves repeated pairing of drugs with drug cues, usually over several days, and then testing by delivering the cues alone. Such procedures can produce effects on hormonal and immune responses (Goebel et al. 2002, Schedlowski & Pacheco-Lopez 2010), which after conditioning appear to be insensitive to verbal instructions about the treatment and, thus, presumably to patients' beliefs (Benedetti et al. 2003b, Wendt et al. 2013). Similarly, placebo analgesic responses become stronger and more durable with longer conditioning (Carlino et al. 2014, Colloca et al. 2010, Colloca et al. 2008a). After several days of training, responses can persist even after subjects are explicitly told that the treatment is inert (Schafer et al. 2015), suggesting a shift from being driven by beliefs to being driven by more stable precognitive associations.

Appraisals. Appraisals are cognitive evaluations of events and situations (Smith & Ellsworth 1985). This simple definition belies complexity: Situations are integrated mental representations of multiple kinds of information, including precognitive associations, long-term memories, expectations, goals, representations of others' mental states, and interoception of internal bodily states (Roy et al. 2012). Appraisals are not simple perceptions but rather constructed interpretations of events (Wilson-Mendenhall et al. 2011). Whereas precognitive associations are reactive responses to events, appraisals are conceptual acts (Barrett 2014). The appraisals that generate emotions are those with personal meaning—they matter to the self and one's future well-being. This sense of personal meaning is thought to be central in generating both emotions (Barrett 2012, Ellsworth & Scherer 2003, Lazarus & Folkman 1984, Ortony et al. 1988, Scherer 2001) and placebo responses (Moerman & Jonas 2002).

Appraisals play a critical role in many kinds of active treatments. They stand at the center of many psychotherapies, which aim to explicitly alter patients' appraisals of clinically relevant events and stimuli through reframing, cognitive restructuring, or other techniques. For example, depressed patients' use of cognitive restructuring skills during psychotherapy sessions predict relapse rates one year posttreatment, controlling for a number of confounding variables (Strunk

et al. 2007). Pretreatment expectations of psychotherapy efficacy can also account for substantial variance in treatment outcomes (Gaston et al. 1989, Joyce & Piper 1998, Sotsky et al. 1991) and are often related to perceived treatment credibility (Hardy et al. 1995, Kazdin & Krouse 1983) and to the competence of care providers (Frank & Frank 1993). Relatedly, patient appraisals of perceived doctor empathy predict reduced severity and duration of cold symptoms and an increased immune response (Rakel et al. 2011).

Appraisals play a central role in placebo effects, especially those induced by verbal suggestion. Verbal suggestions alone have been shown to modulate adrenocorticotropic hormone and cortisol responses to ischemic pain (Benedetti et al. 2006), autonomic responses to painful events (Jepma & Wager 2015, Nakamura et al. 2012), and skin conductance during threat of shock (Meyer et al. 2015). Similarly, information about how other people had experienced painful stimuli robustly modulated pain-related autonomic responses (Koban & Wager 2016), although this information was never systematically reinforced. Finally, suggestions (in the form of package labeling) that a milkshake was “indulgent” resulted in reduced blood levels of the hunger-related hormone ghrelin, relative to a milkshake labeled as “sensible” (Crum et al. 2011). Together, these findings emphasize the role of the appraisal system in mediating placebo effects on multiple outcomes, including physiological responses.

Interactions between precognitive associations and appraisal. Appraisals and precognitive associations interact to create placebo effects. Placebo effects are typically small when they are induced solely by conditioning (Carlino et al. 2014, Montgomery & Kirsch 1997, Vase et al. 2002) or solely by verbal suggestions (Colloca et al. 2008b, de Jong et al. 1996). The largest placebo effects are induced when suggestions are reinforced via conditioned experience (Carlino et al. 2014, Colloca et al. 2008b, Schafer et al. 2015, Vase et al. 2002). This suggests that obtaining robust placebo effects requires repeated success experiences coupled with a cognitive attribution of benefit to the treatment. By governing attributions, appraisals guide precognitive associative learning processes, shaping what is learned from experience (for further discussion see Wager & Atlas 2015).

Brain Mechanisms Underlying Placebo Effects

Because there is “not one placebo effect but many” (Finniss et al. 2010, p. 687), placebo effects are not restricted to one brain system. Rather, multiple systems and mechanisms are involved, and understanding the principles by which appraisals and precognitive associations map onto brain systems is a challenge. The study of placebo effects can teach us something about these mappings, and conversely, understanding these mappings contributes to understanding the neurophysiology of placebo effects.

Placebo effects have been studied with functional magnetic resonance imaging (fMRI); electro- and magnetoencephalography (EEG and MEG); and positron emission tomography (PET)-based imaging of glucose, dopamine, and opioid activity. Most studies—approximately 50 to date—have focused on placebo analgesia, which has allowed quantitative meta-analyses of consistent placebo-induced analgesia findings across laboratories and paradigms (e.g., Amanzio et al. 2013, Atlas & Wager 2014). The placebo analgesia literature provides a foundation for insights into placebo effects in general and for comparing placebo-induced brain-activation patterns with those related to appraisal and other processes.

Pain-related processes reduced by placebo treatment. One question relates to the depth of placebo effects: Can placebo treatments influence symptoms in fundamental ways? As shown in **Figure 4**, placebo analgesics have been found to reduce pain-related activity in the cortex

Placebo-induced changes in brain function

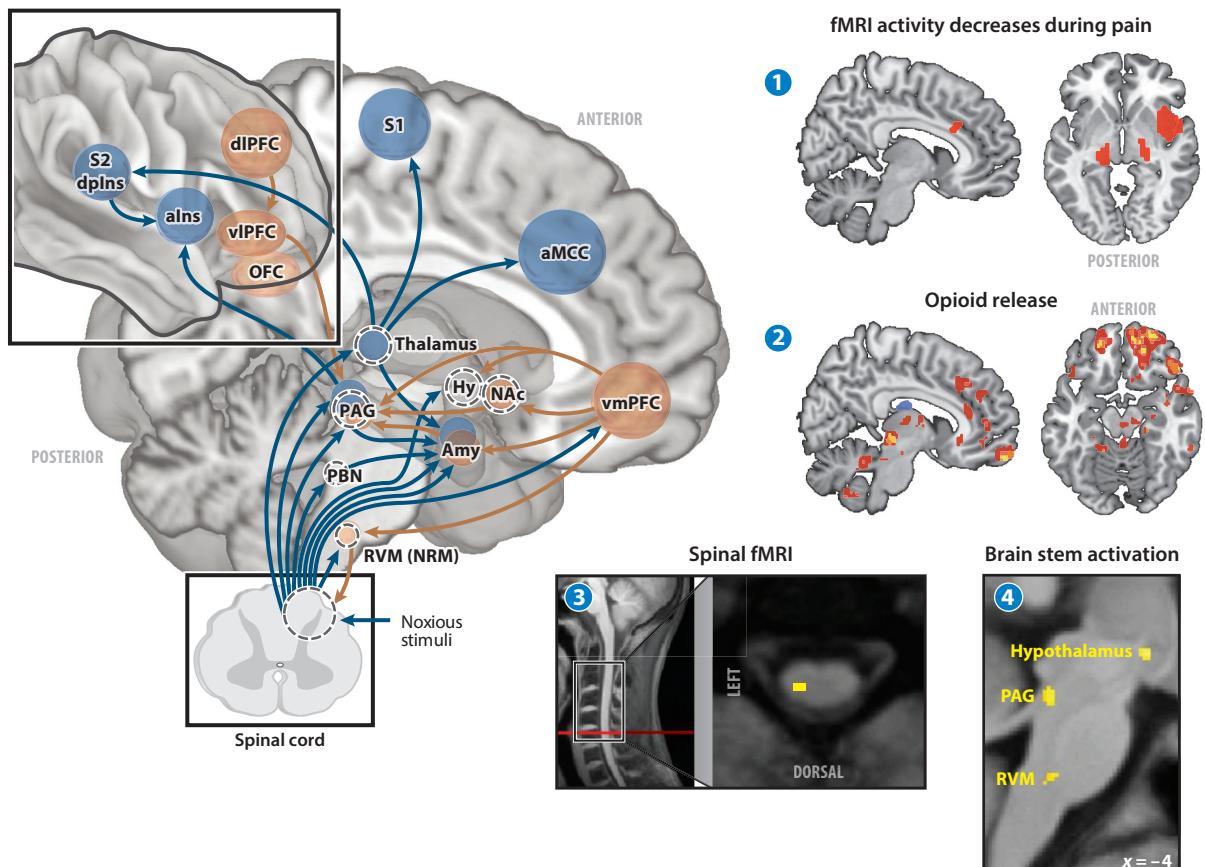


Figure 4

Brain mechanisms and pathways involved in placebo analgesia. Pathways involved in pain representation are shown in blue. Regions that modulate activity in pain-encoding circuits are shown in orange. Clockwise, from upper right: ① fMRI results showing brain regions in red that decrease during pain (Wager et al. 2004); ② regions with placebo-induced increases in μ -opioid activity (red and yellow; Wager et al. 2007); ③ pain-related spinal cord activity (yellow square) reduced by placebo treatment (Eippert et al. 2009b); and ④ brain stem regions activated by placebo treatment (Eippert et al. 2009a). Abbreviations: aIns, anterior insula; Amy, amygdala; aMCC, anterior midcingulate; dIPFC, dorsolateral prefrontal cortex; dPIns, dorsal posterior insula; fMRI, functional magnetic resonance imaging; Hy, hypothalamus; NAc, nucleus accumbens; OFC, orbitofrontal cortex; PAG, periaqueductal gray; PBN, parabrachial nucleus; RVM (NRM), rostral ventral medulla (nucleus raphe magnus); S1 and S2, primary and secondary somatosensory cortex; vIPFC, ventral lateral prefrontal cortex; vmPFC, ventromedial prefrontal cortex.

(Wager et al. 2004) and spinal cord (Eippert et al. 2009b) and to activate the endogenous opioid system (Wager et al. 2007) and specific brain stem nuclei associated with pain control (Eippert et al. 2009a).

These examples are supported by a quantitative meta-analysis of published studies (Wager & Atlas 2015). Placebos can, under some circumstances, reduce pain-related brain responses in most or all of the cortical and subcortical targets of pain-related somatosensory input (**Figure 5, blue**). The most consistent reductions are in the anterior midcingulate, thalamus, and mid- and anterior insula. In a number of studies, these brain reductions correlate with the magnitude of reductions in pain (for a detailed review, see Wager & Atlas 2015). Reductions in sensorimotor

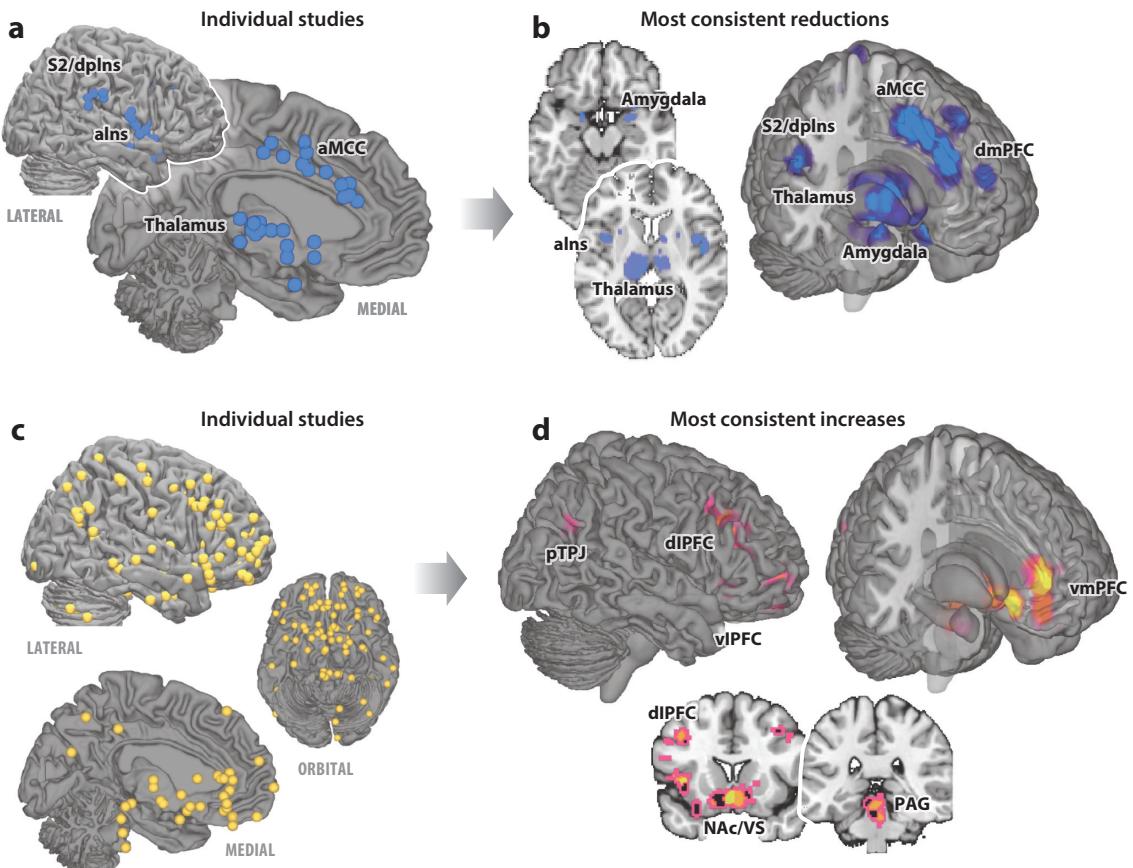


Figure 5

Consistent findings in neuroimaging studies of placebo analgesia. (a,c) Peak activation locations in studies of placebo analgesia. Each sphere is a finding from an activation map, with (a) blue spheres indicating decreases in pain-related activity (21 studies) and (c) yellow spheres indicating increases in pain- and anticipation-related activity (19 studies) (for details, see Wager & Atlas 2015). Locations from the same map within 12 mm were averaged into one sphere. (b,d) Consistent activations with at least three studies reporting effects within 10 mm. (b, blue) Consistent reductions during pain occur in the S1 and S2, thalamus, dACC, and aIns, which are associated with pain encoding. (d, yellow and pink) Consistent increases with placebo occur in the vmPFC, NAc/VS, PAG, dIPFC and vIPFC, and pTPJ. Abbreviations: aIns, anterior insula; aMCC, anterior midcingulate; dIPFC, dorsolateral prefrontal cortex; dmPFC, dorsomedial prefrontal cortex; dpIns, dorsal posterior insula; fMRI, functional magnetic resonance imaging; NAc, nucleus accumbens; OFC, orbitofrontal cortex; PAG, periaqueductal gray; PBN, parabrachial nucleus; pTPJ, posterior temporal-parietal junction; RVM (NRM), rostral ventral medulla (nucleus raphe magnus); S1 and S2, somatosensory regions 1 and 2; vIPFC, ventral lateral prefrontal cortex; vmPFC, ventromedial prefrontal cortex.

cortex and amygdala activity are less common, but they are consistent across a subset of studies. In parallel, EEG and MEG studies show placebo-induced reductions in cortical responses to painful laser stimuli at ~150–300 ms post-stimulus (Colloca et al. 2008b). These studies demonstrate that placebo treatments can affect multiple components of pain-related responses, sometimes at a deep (i.e., early sensory) level.

Brain generators of placebo analgesia. In addition to reductions in pain-related processes, placebo analgesia studies have also identified consistent increases in brain activity. The most

consistent placebo-related increases are shown in **Figure 5**; they include engagement of the dorsolateral and ventrolateral prefrontal cortex (dlPFC/vIPFC), vmPFC, medial orbitofrontal cortex (OFC), and mid-lateral OFC. Increases in activity in these areas are also correlated with the magnitude of reported analgesia (Wager & Atlas 2015). A number of studies have also reported increases in activity in the nucleus accumbens (NAc)/ventral striatum and periaqueductal gray (PAG)—two areas most closely associated with the opioid system—converging with molecular imaging studies that identified placebo-induced increases in opioid system activity (Scott et al. 2008, Wager et al. 2007). Many of these regions show anticipatory increases prior to pain, and these anticipatory increases are some of the strongest predictors of the strength of an individual's placebo analgesic response (Wager et al. 2011). The engagement of these regions in anticipation of pain suggests that their role in placebo analgesia may not be pain-specific but rather may be tied to broader appraisal and expectation processes.

Beyond pain: clinical placebo effects across disorders. Most studies of placebo mechanisms have studied placebo analgesia in experimentally induced pain in healthy subjects. A smaller literature has investigated the brain mechanisms of placebo effects on clinical disorders, most notably Parkinson's disease and depression. Results from these investigations converge with findings from the experimental placebo analgesia literature and also suggest the involvement of disorder-specific brain mechanisms.

A line of research on Parkinson's disease has demonstrated placebo effects on three systems: (a) the mesolimbic dopaminergic pathway, which projects from the ventral tegmental area to the ventral striatum and vmPFC; (b) the nigrostriatal dopaminergic pathway, which projects from the substantia nigra to the dorsal striatum; and (c) the subthalamic nucleus-thalamocortical pathway associated with Parkinson's motor dysfunction. In a landmark early study using radiolabeled raclopride PET imaging, de la Fuente-Fernandez et al. (2001) found enhanced dopamine activity in the dorsal striatum after patients took a sham medication as compared to a control condition. A larger follow-up study replicated these effects, but only for patients randomized to receive (false) instructions that the placebo treatment was 75% likely to be an active drug (Lidstone 2010), which suggests a key role for appraisals in this response. Another metabolic PET study identified a pattern of increased brain metabolism in the vmPFC and striatum, among other regions, that both predicted and correlated with clinical improvement following double-blind sham surgery in Parkinson's patients (Ko et al. 2014). In addition, an fMRI study of learning-related brain function in the mesolimbic dopamine pathway found that placebo medication enhanced performance in a reward (but not punishment) learning task and altered learning-related activity in the NAc/ventral striatum and the vmPFC (Schmidt et al. 2014). Taken together, these studies demonstrate robust placebo responses in the mesolimbic and nigrostriatal dopaminergic pathways in Parkinson's patients.

Another paradigm for studying the placebo effect in Parkinson's disease has used sham stimulation of the subthalamic nucleus (STN), a brain structure implicated in the pathophysiology of Parkinson's motor dysfunction. Sham STN stimulation compared with no treatment resulted in improved motor function and reduced neural firing in the STN (Benedetti et al. 2004). In a follow-up study, this effect was shown to depend on prior learning: Both thalamic neuronal and clinical responses to placebo treatment increased as patients were administered a greater number of active drug conditioning trials prior to the placebo treatment (Benedetti et al. 2016).

In major depression, the placebo response has been well-documented (Fournier et al. 2010, Kirsch et al. 2008), and studies investigating its brain bases have implicated prefrontal and striatal regions as well as the opioid system. In an innovative study, Peciña et al. (2015) imaged μ -opioid activity in depressed patients during administration of an intravenous placebo antidepressant.

Placebo treatment increased μ -opioid neurotransmission in the vmPFC and NAc, among other regions. These increases predicted improvement in depressive symptoms following both a 1-week treatment with a pill placebo and a later 10-week trial of an antidepressant medication. These findings connect the acute placebo brain response (to the intravenous placebo), sustained clinical improvement to sham antidepressant pills, and the opioidergic system. They also converge with earlier findings linking pill placebo responses with increased activity in prefrontal and posterior cingulate cortices, as measured with fMRI (Mayberg 2002) and EEG (Leuchter et al. 2002).

A growing literature has investigated placebo responses in several chronic pain disorders. In IBS patients undergoing fMRI scanning during painful rectal distension, placebo treatments have been shown to reduce activity in multiple nociceptive areas and to increase activity in the midfrontal gyrus (MFG), the superior temporal lobe, and posteromedial cortex (Craggs et al. 2008, 2014; Lieberman et al. 2004). In patients with chronic knee osteoarthritis, altered functional connectivity between the right MFG, the perigenual ACC, and the posterior cingulate (PCC) and the rest of the brain predicted placebo treatment response in two independent cohorts (Tétreault et al. 2016). Similarly, mPFC–insula functional connectivity predicted placebo treatment response in a randomized controlled trial of patients with chronic back pain (Hashmi et al. 2012).

The brain bases of placebo effects have also been investigated in patients with substance use disorders. In active cocaine abusers undergoing raclopride PET imaging, methylphenidate and placebo administration lead to statistically indistinguishable levels of dopamine release in striatal regions, demonstrating a drug-mimicking effect of placebo on striatal dopaminergic systems (Volkow et al. 2011). Similarly, methylphenidate administered to cocaine abusers was also found to elicit a $\sim 50\%$ larger increase in thalamic and cerebellar brain metabolism and a $\sim 50\%$ increase in mood when subjects believed they were receiving the drug versus when they believed they were receiving a placebo (Volkow et al. 2003). Parallel findings have been observed in cigarette smokers, who reported significantly reduced craving and a significant correlation between insular activity and craving after smoking a cigarette that they believed contained nicotine, but no such changes when they were told that the cigarette did not contain nicotine (Gu et al. 2016). Belief that a cigarette did not contain nicotine, as compared with believing that it did, also strongly diminished brain responses in the striatum related to value and reward prediction errors during a learning task (Gu et al. 2015).

In summary, findings in clinical disorders converge with those from placebo analgesia in acute pain and point to disorder-specific placebo mechanisms. They highlight the involvement of medial prefrontal, posteromedial, and temporal cortex in the genesis of placebo responses, including a role for dopaminergic—and perhaps opioidergic—pathways. At the same time, these findings suggest that elements of the placebo response are localized in disorder-specific brain systems, such as the subthalamic nucleus for Parkinson’s disease.

A Brain System for Affective Appraisal

The brain regions engaged during placebo analgesia (**Figure 5**) are encompassed by the default mode network, which includes the dorsal medial prefrontal cortex (dmPFC) and vmPFC, PCC, temporal-parietal junction (TPJ), and superior temporal sulcus (STS), among other regions (**Figure 6**). The default mode network supports a broad category of processes related to affective appraisal. It is associated with spontaneous thought (Mason et al. 2007), autobiographical memory retrieval (Vincent et al. 2006), prospection (Buckner & Carroll 2007), generating negative and positive emotion (Lindquist et al. 2012, 2016; Wager et al. 2015), assessing others’ mental states (Frith & Frith 2006), self-related processing (Gusnard et al. 2001), representing expected value (Hare et al. 2008), and more. A central mechanism of placebo treatments is their engagement of

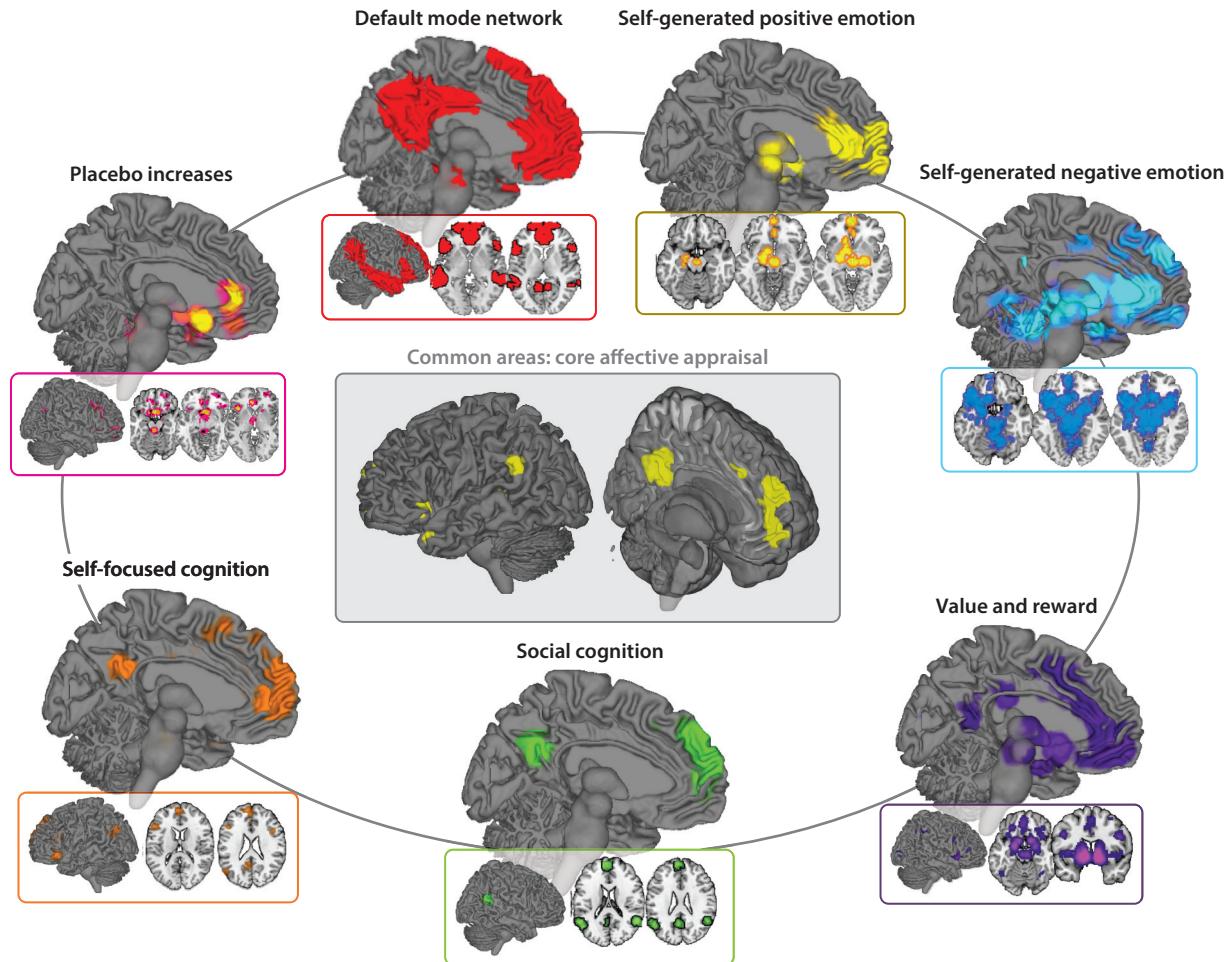


Figure 6

Appraisal-related processes converge in the default network. Meta-analyses converge on a core appraisal system. (*Clockwise from top*) The default mode system (red) is based on a parcellation of 1,000 resting-state connectivity scans (Yeo et al. 2011) (subcortical regions are not included in this map). Meta-analyses depicted along the perimeter show activity during recall and imagery techniques for self-generating positive (yellow; 21 study maps) or negative (blue; 56 study maps) emotional states (data from Linquist et al. 2012); (purple) value-related activity from 375 studies of “reward” and “value” from <http://Neurosynth.org> (Yarkoni et al. 2011); (green) social, other-focused cognition across 48 studies (Denny et al. 2012); (orange) self-focused cognition engaged by self-referential judgments across 48 studies (Denny et al. 2012).

appraisal processes in default mode network regions. Developing an integrative understanding of the role and function of the default network will be critical for advancing understanding of placebo brain mechanisms. In this section, we describe key appraisal-related functions of the default mode network and their relation to placebo effects.

Self-generated emotion. Key regions of the default mode network are prominently activated when participants are asked to self-generate both negative and positive emotional responses by recalling or simulating (imagining) events and situations (Figure 6; yellow and blue maps, data

from Lindquist et al. 2012). Unlike the majority of emotion studies that examine brain responses elicited by affective stimuli, these activations occur in the absence of any external stimulation and are generated purely by participants' thoughts. Self-generated negative emotions are associated with activation in the vmPFC, dmPFC, and PCC along with a wide swath of limbic regions, including the amygdala, insula, striatum, and PAG. The medial prefrontal activity overlaps with activity related to instructed fear, in which anxiety is generated by conceptual knowledge about associations between cues and shocks, without reinforcement (Mechias et al. 2010). Self-generated positive emotion consistently activates an overlapping, but more restricted, set of regions, including all the major elements of the mesolimbic dopamine system—the vmPFC, striatum, and ventral tegmental area. Placebo treatments likely elicit patients' memories of previous treatment experiences to influence clinical outcomes and placebo-induced brain responses (Kessner et al. 2013, 2014).

Inferences about others. Another key function of the default network is social cognition—in particular, the ability to infer the intentions, beliefs, and mental and affective states of others. This inferential process is known as mentalizing or theory-of-mind and reliably recruits a network of regions described as the social brain (Blakemore 2008) that include the dmPFC, PCC, STS, and TPJ (Amodio & Frith 2006, Frith & Frith 2006, Van Overwalle 2009)—all of which are included in the default mode network and overlap with systems implicated in emotional appraisal (Etkin et al. 2011). These regions mature in late adolescence (Blakemore 2008) and are important for inferring the preferences of another individual (Mitchell et al. 2006) or the intensity of another's affective experience (Krishnan et al. 2016, Morelli et al. 2015). They are preferentially engaged by observing social interactions (Wagner et al. 2016) and by processing social information. For example, when participants made judgments about how their friends ranked on a particular trait, activity in this network increased as participants were asked to rank a greater number of friends, suggesting a role in integrating increasing amounts of social information (Meyer et al. 2012).

One recent social cognition study manipulated whether participants felt understood or not understood after sharing personal experiences. Feeling understood versus not understood activated different components of the default mode network, including the dmPFC and the precuneus (Morelli et al. 2014). Feeling understood and cared for by a provider is thought to be a central component of the placebo effect (Colloca & Miller 2011, Frank & Frank 1993, Wager & Atlas 2015), and three clinical trials have found that patients randomized to more supportive versus less supportive physician interactions experience superior health outcomes in the cases of the common cold (Rakel et al. 2011), IBS (Kaptchuk et al. 2008), and chronic back pain (Fuentes et al. 2014).

Self-focused cognition and self-concept. Other-focused and self-focused cognition engages broadly overlapping brain systems (Buckner & Carroll 2007). However, whereas thinking about others preferentially engages the dmPFC, self-referential processing preferentially engages the vmPFC, particularly the pregenual cingulate and anterior medial prefrontal cortex (Denny et al. 2012). This includes tasks as simple as judging the degree to which words describe oneself (Kelley et al. 2002), and it extends to self-evaluations across a variety of domains, including preferences, personality, mental states, and physical attributes (Jenkins & Mitchell 2011, Kelley et al. 2002, Mitchell et al. 2006). Self-referential processing is also involved in judgments of others, but particularly to the degree that others are seen as similar to or close to oneself (Jenkins et al. 2008, Mitchell et al. 2006).

Self-focused cognition revolves around a concept of the self. Notions of what it means to have a self-concept are evolving, but one idea is that an implicit or explicit representation of the self serves as a reference point for valuing other concepts and relating them to one's goals and values.

Thus, default mode regions are also involved in autobiographical thought (Andrews-Hanna et al. 2014), imagining potential future situations the self may encounter (Buckner & Carroll 2007), and self-relevance biases in memory encoding (Kelley et al. 2002, Rogers et al. 1977)—all of which involve positioning the self in a context.

Value. Value is an abstract concept that describes the worth of an item or outcome. Value is typically operationalized as the amount of resources or effort that an agent would spend to obtain the outcome. At its heart, however, value is an appraisal of the gain or cost (economic, social, or physical) to current and future well-being, made in reference to the self and in consideration of one's goals. Studies have consistently observed that the vmPFC and NAc/ventral striatum are associated with subjective value (Bartra et al. 2013, Hare et al. 2008, Padoa-Schioppa 2011). These regions are among the cortical areas most richly innervated by both dopamine and opioids, which are key players in emotion, motivation, and hedonic pleasure (Berridge & Kringelbach 2008).

Though often considered in terms of reward, responses in these regions and in the dopamine system more generally show many hallmarks of encoding conceptual appraisals. Neurons in the vmPFC–lateral OFC group code for anticipated reward (Tremblay & Schultz 1999) and anticipated punishment (Morrison et al. 2011), with separate populations of dopamine neurons related to each (Matsumoto & Hikosaka 2009). They also code for relative value among rewarding options, rather than physical reward properties of a given stimulus (Tremblay & Schultz 1999), and they change rapidly with learning as reward contingencies change (Kim & Hikosaka 2013). Importantly, these value representations in vmPFC and ventral striatum are computed with respect to higher-order goal states and can instantly shift from repulsion to pleasure based on shifts in internal homeostatic states. In one study, rats initially repulsed by an intensely salty liquid were highly motivated to obtain the liquid when in a sodium-deprived state, without any additional learning. Activity markers in the mesolimbic dopamine system, including ventral tegmental area, NAc, and OFC, were associated with this change (Robinson & Berridge 2013).

Converging evidence comes from lesion studies. Lesions to the vmPFC-OFC do not appear to impair basic value preferences (Izquierdo et al. 2004), emotional responses (Rudebeck et al. 2013), or simple forms of value learning (Milad & Quirk 2002) (for a review, see Stalnaker et al. 2015), but instead disrupt the ability to make value-guided choices in the context of an animal's current goals and homeostatic states (Roy et al. 2012, Rudebeck & Murray 2014).

Correspondingly, human fMRI activity in this system appears to reflect a form of expected affective value related both to pursuit of reward (Chib et al. 2009) and to avoidance of punishment (Roy et al. 2012). Value-related vmPFC activity is sensitive to diverse forms of conceptual information, including personal goals (Hare et al. 2008), homeostatic motivational states (Gottfried et al. 2003), and verbal suggestions about how others value items (e.g., “this is expensive wine”) (Plassmann & Wager 2014), which are closely related to placebo effects. Perceptions of value are known to modulate the effectiveness of placebo treatments, with more expensive placebos exerting greater analgesic effects and recruiting increased medial prefrontal cortex activity relative to less expensive placebos (Geuter et al. 2013).

An integrated view of appraisal. These findings suggest that a range of appraisal processes—which are crucial for most placebo effects—engage a common core brain system (**Figure 6**). This appraisal system is adapted for representing schemas or situations, including representations of one's goals and well-being in the context of events and stimuli. This system is highly integrative, involving brain systems supporting memory, prospection, social cognition, emotion, interoception, and autonomic and neuroendocrine control. Brain networks important for each of these

domains are partly differentiable but involve points of convergence, particularly in the vmPFC, PCC, and inferior TPJ, all of which are part of the default mode network (**Figure 6**).

The vmPFC, in particular, may be a critical hub in the appraisal process (Roy et al. 2012). It is anatomically and functionally connected to (*a*) portions of the ventral striatum and lateral OFC that encode the value of rewarding and aversive events (Pauli et al. 2016, Price 1999, Wallis 2007), (*b*) portions of the hippocampus and parahippocampal cortex (Kahn et al. 2008) that participate in episodic and semantic memory (Binder et al. 2009), and (*c*) specific portions of the hypothalamus and PAG (Keay & Bandler 2001, Price 1999) that are central to emotion and the governance of physiological responses. Converging evidence also suggests that the vmPFC is critical for representing structured, conceptual relationships (Binder et al. 2009, Constantinescu et al. 2016, Doeller et al. 2010). For example, the vmPFC is centrally involved in semantics (Binder et al. 2009). Semantic meaning is flexible and context dependent, such that the meaning of “boxer” can shift depending on the context (i.e., “fighting” versus “poodle”). The vmPFC is also centrally involved in self-referential cognition (Denny et al. 2012, Jenkins et al. 2008, Kelley et al. 2002, Mitchell et al. 2006) and may encode “abstract value signals” (Wallis 2007, p. 46) involving “predictions about specific outcomes associated with stimuli, choices, and actions...based on current internal states” (Rudebeck & Murray 2014, p. 1143). Thus, one view of the appraisal system’s underlying function is that it allows the mental construction of a conceptual space (Constantinescu et al. 2016), positioning one’s concept of self in relation to valued situations and events. This enables projections about future events and alternative courses of action by imagining their impact on our overall well-being.

CONCLUSIONS AND FUTURE DIRECTIONS: HOW DO APPRAISALS HEAL?

Placebo treatments can have large and sustained effects on clinical outcomes in multiple disorders, particularly those in which emotion and motivation play a central role. Understanding how these effects arise and are maintained is an open challenge. We believe that interactions between associative learning systems and appraisals play a central role. Learning can occur in many neural circuits, but appraisal appears to be supported by a specialized system—a collection of midline cortical and temporoparietal regions associated with the so-called default mode network. This network is involved in emotion generation, social and self-referential cognition, and value-based learning and decision making, pointing to a common core function of flexible, conceptual, and affective thought. This system allows us to simulate potential outcomes and to develop expectations about future events. It also allows us to relate those events to a representation of the self, including our broader goals and overall well-being. This system is engaged by placebo treatments for pain, mood disorders, Parkinson’s disease, and other conditions. Taken together, these findings suggest that placebos work by engaging systems in the default mode network that govern how a person conceptualizes their future well-being and the personal significance of their symptoms.

Yet, it remains unclear how appraisals create sustained, long-term improvements in health. We offer here four ideas that address this question. First, conceptual representations in the vmPFC and associated appraisal system strongly influence goal-directed decision making—what to eat, when to sleep, whether to exercise—which can have profound influences on health over time. Second, the appraisal system is important for assigning affective value and significance to thoughts. Dysregulation of this system is prominently related to depressive rumination, catastrophizing, and posttraumatic stress disorder (Etkin & Wager 2007, Kaiser et al. 2015). Third, when imagined or perceived events are conceived of as close to the self, they create strong, organism-wide emotional responses. These responses directly influence physiological

processes, including changes in autonomic output and hormone release, which are relevant for both behavior and physical health and may directly influence disease pathophysiology.

Fourth, appraisals and associative learning systems may form positive feedback loops. The pain literature reviewed here and elsewhere (Büchel et al. 2014) shows that positive appraisals influence how symptoms are perceived. The more positive initial expectations are, the less pain is perceived—which then reinforces the initial expectation of low pain. Put simply, appraisals can become self-fulfilling prophecies, by virtue of their direct influences on mood, physiology, and behavior. In the context of positive feedback loops, over time positive appraisals may become more automatic and ingrained, transitioning from conceptual appraisal systems to circuits encoding learned, precognitive associations (Schafer et al. 2015). Positive feedback loops may be one reason that cognitive- and emotion-focused therapies work to change participants' conceptions of themselves and their situations, and a reason that placebo treatments—which are injections of ideas into the course of a treatment—can have long-lasting therapeutic effects.

SUMMARY POINTS

1. Placebo treatments can have large, clinically relevant therapeutic effects on pain, mood disorders, and Parkinson's disease.
2. Placebo effects are mediated by multiple mechanisms. Two main mechanisms are:
 - a. Precognitive associations—relatively stable, stimulus-response associations that can be learned by diverse brain circuits, and
 - b. Appraisals—cognitive evaluations of situations integrating multiple kinds of information in a cohesive, constructed conceptualization with personal meaning.
3. Appraisals are supported by a core brain system associated with the default mode network that includes the ventromedial prefrontal cortex. This system is instrumental in forming conceptual expectations and beliefs, self-generating emotion, representing knowledge about oneself and others, and integrating information into calculations of anticipated value. This appraisal system is reliably engaged by placebo treatments.

FUTURE ISSUES

1. Many studies have investigated the biological mechanisms underlying immediate, short-term placebo effects on health, physiology, and performance. What mechanisms underlie sustained, long-term placebo effects? Why don't placebo effects naturally extinguish?
2. How do placebo mechanisms relate across diverse disorders and outcomes?
3. How do the mechanisms of placebo treatments relate to the mechanisms of other psychosocial treatments (e.g., psychotherapy) that explicitly aim to initiate changes in patients' appraisals?
4. How do patient characteristics and treatment contexts interact to create appraisals supporting or obstructing treatment?

DISCLOSURE STATEMENT

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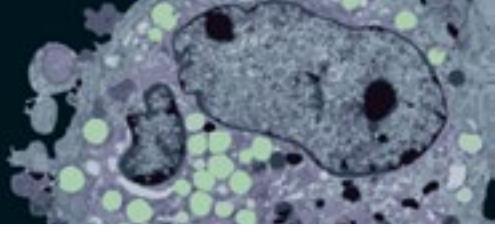
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