Brain and psychological mechanisms of the placebo effect: An affective appraisal account

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Running Head: MECHANISMS OF CLINICAL PLACEBO

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Abstract

Placebos are sham medical treatments. Nonetheless, they can have substantial effects on clinical outcomes. These depend on a person’s psychological and brain responses to the treatment context, and particularly on appraisals of future wellbeing. Appraisals can directly impact symptoms and physiology. They can also shape associative learning processes by guiding what is learned from experience. The brain networks engaged by placebo treatment share a striking similarity with a core system involved in self-generated emotion, self-evaluation, thinking about the future, social cognition, and expectation and valuation of reward and punishment. Thus, from a neurological standpoint, placebo treatments initiate a re-conceptualization of the self in context, altering the meaning and personal significance of symptoms, with consequences for decision-making and physiology.

Keywords: expectation, default mode, appraisal, pain, depression, Parkinson’s
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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 and powders of hickory ashes than of all other medicines put together…” ~ Thomas Jefferson, 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 non-human primates, and results from an open-label human trial were positive. Buoyed by these findings, the researchers conducted a large, multi-site, double-blind randomized trial comparing the treatment to a sham surgery.

The patients injected with the treatment showed marked, sustained improvement over two years. Surprisingly, however, the sham surgery patients improved at the same rate, over the same time period (Figure 1). Thus, the trial failed, signaling a potential finale to a decade-long program of ground-breaking research, and the sale of the company that funded it. On the other hand, it provides a remarkable demonstration of placebo-related improvements in a neurodegenerative disorder 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 (Kaptchuk et al 2010, Kaptchuk et al 2008), 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 placebo (Figure 2). In addition, placebo effects contribute to the effectiveness of many medical 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 confounds (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 aid healing? Their therapeutic potential lies 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 patients’ appraisals of the treatment context and how it will affect them, including expectations for recovery; patients’ learned associations with the treatment ritual and associated cues, such as pill-taking; and patients’ relationships with care providers (Colloca & Miller, Finniss et al, Price et al 2008). Placebo effects provide a window into how psychosocial processes impact health and disease.

Here, we review placebo effects on clinical outcomes and explore the behavioral and brain mechanisms that give rise to them. We argue that placebo effects are created largely by psychological appraisals, which depend on cognitive beliefs and influence non-cognitive learning processes to create durable, expectancy-independent placebo. Placebo treatments across disorders engage a brain system that mediates multiple varieties of cognitive appraisal, including self-generated emotions,
expectations, value-based decisions, self-evaluations, and beliefs about others. This system also overlaps with the “default network,” a brain system active at rest, involved in spontaneous thought and feeling (Gusnard & Raichle, Raichle et al), and implicated in multiple mood disorders (Etkin & Wager 2007, Kaiser et al 2015). This co-localization provides a neurological connection between placebo effects and emotional appraisal, on one hand, and mood and pain disorders on the other.

PLACEBO RESPONSES AND PLACEBO EFFECTS IN CLINICAL CONTEXTS

Over 3,000 published papers have studied the placebo effect (Weimer et al 2015) across a variety of clinical conditions, including Parkinson’s disease, depression, anxiety, sleep disorders, schizophrenia, appetite, obesity, skin conditions, gastrointestinal disorders, neuroendocrine responses, autonomic physiology, immune responses, and cognitive performance. We focus here on several perennial questions about placebo effects in clinical settings, including recent analyses comparing the magnitude of placebo effects across patient populations and types of placebo treatment.

Do placebos have meaningful effects on clinical outcomes?

Placebo responses can be as large as responses to contemporary pharmacological treatments, especially for chronic pain (Tuttle et al 2015) and depression (Fournier et al 2010, Kirsch et al 2008). But not all of the improvements observed are actually caused by the placebo. Patients may enroll in trials when fluctuating symptoms are at their worst, and improve due to regression to the mean or spontaneous recovery (see, e.g., (Wager & Fields 2013)). 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 identify placebo effects—effects caused by mind-brain responses to the placebo specifically.

Clinical placebo effects have been estimated in several ways. The main approach is to compare placebo conditions to no-treatment or ‘natural history’ controls (Figure 2). Hróbjartsson and Gøtzsche have estimated placebo effects in the relatively small subset of trials that included no-treatment controls (Hrobjartsson & Gotzsche 2010). Collapsing across disorders, they found small but significant effects (Standardized Mean Difference [SMD] = -0.23), although effects were approximately twice as large in trials of high methodological quality (SMD = -0.38)(Figure 2a).

Focusing on pain, a meta-analysis including over 3,000 patients found substantial and comparable effects of both 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. (Khan et al 2012) analyzed trials with placebo, drug, and waitlist conditions (Figure 2c, left). They decomposed the overall drug response into several different components: Active drug effects (18% of the total effect), placebo effects (54%), and spontaneous improvement in wait-list conditions (28%). Cuijpers et. al. (Cuijpers et al 2012) reported similar effect sizes in a meta-analysis of psychotherapy treatments for depression (Figure 2c, right). In a meta-analysis of anxiety disorders including 234 studies and over 37,000 patients, Bandelow (Bandelow et al 2015) 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, also demonstrating substantial placebo benefits over no treatment.
A second approach to estimating placebo effects is to compare open drug treatment with hidden drug treatment—when patients are aware vs. unaware that they are receiving a drug. Such studies have shown placebo effects on experimental pain (Atlas et al. 2012) and several clinical conditions (Colloca et al. 2004), such that awareness of receiving the treatment can account for half or more of the treatment effects.

A third approach is to compare outcomes in trials where patients had a higher vs. lower probability of receiving an active treatment. Schizophrenia patients had twice as large a response to the same medications in comparator trials (comparing two or more active drugs, with no placebo arm) relative to placebo-controlled trials (Rutherford et al. 2014, Woods et al. 2005). Among depressed patients, both drugs and placebos achieve ~10% higher response rate in comparator trials relative to placebo-controlled trials (Papakostas & Fava 2009, Sinyor et al. 2010, Sneed et al. 2008), and similar results are observed for several anxiety disorders (Rutherford et al. 2015). This effect is likely mediated by patient expectations of improvement, which have been found to mediate the effect of active treatment likelihood on outcomes (Rutherford In press).

A fourth approach is to compare different types of placebo treatments. In a systematic review of migraine prophylaxis, Meissner et al. (Meissner et al. 2013) found modest (26%) response rates to sham pills, injections, and herbs, but larger responses to sham acupuncture (38%), and even larger responses 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 Parkinson’s
disease (Goetz et al 2008). These findings suggest that patient appraisals of the potency of the placebo modality contribute to the placebo effect.

The placebo responses reviewed above can last for months to years, in some cases. In clinical trials for neuropathic pain, Parkinson’s disease, and depression, the placebo response appears to grow over 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).

**How reliable is the placebo effect?**

In one of the most rigorous investigations of placebo reliability, Whalley et al. found that the analgesic responses to a placebo cream had moderately high test-retest reliability at one week, \( r = .60 \) to \( .77 \) (Whalley, Hyland, & Kirsch, 2008), similar to an estimate of \( r = .55 \) from a similarly designed experiment (Morton, Watson, El-Deredy, & Jones, 2009), and suggesting reliability of placebo response. Yet, Whalley et al. also found that responses to one placebo cream were uncorrelated with responses to another placebo cream that was differently labeled but otherwise identical, \( r(69) = .10, p < .41 \). Other studies have found that reliability depends on context. Subjects’ placebo responses can be correlated across contexts that are similar (Kessner et al 2014, Kessner et al 2013), but uncorrelated across contexts that differ (i.e., sham acupuncture vs. pill placebo) (Kong et al 2013).

There is little evidence on placebo reliability in clinical contexts. Peciña et al. found 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, in a classic study, Liberman (Liberman 1967) found that placebo responses were uncorrelated across three types of pain, including experimental pain and the pain of childbirth. Müller et al. also found that placebo analgesia in experimental pain was uncorrelated with responses to a placebo treatment for chronic pain (Müller et al., 2016). 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, Zimmerman, Keitner, & Miller, 2002).

One interpretation of these reliability findings is that placebo effects depend strongly on individuals appraisals of the treatment context. Thus, they can be reliable when the treatment context is held constant, but change dramatically with even relatively minor changes in the setting (Koban et al 2013).

Which disorders respond most to placebo treatments?

Clinical studies suggest there are substantial placebo responses in the clinical treatment of variety of disorders. These include multiple varieties of pain (Tuttle et al 2015, Vase et al 2002), including 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). They also include depression (Cuijpers et al., 2012; Fournier et al., 2012; Kirsch et al., 2008), anxiety (Bandelow et al., 2015), Parkinson’s (Goetz et al 2008), schizophrenia (Rutherford et al 2014), asthma (Wechsler & Kelley 2011), and others.
Estimating the relative effect sizes across disorders is challenging, but several recent studies provide some direct comparisons. In a meta-analytic comparison of responses to placebo pills across six patient groups, Khan et al. (Khan et al 2005) found the largest placebo effects in generalized anxiety disorder (GAD) and panic disorder, and the smallest effects in psychosis and obsessive-compulsive disorder (OCD) (See Figure 3a). Effects on depression and post-traumatic stress disorder were in between.

In a comparison of sham surgical interventions across disorders, Jonas et al. (Jonas et al 2015) (Figure 3b) found moderately large placebo responses in pain, Gastroesophageal Reflux Disease (GERD), and other conditions (SMD \(\approx 0.5\)). For pain, these effects were nearly as large as real surgery, and not statistically distinguishable. However, to our knowledge, sham surgery studies have not also included no-treatment control groups, precluding estimates of placebo effects specifically.

Though placebo treatments can affect physiological outcomes (Meissner 2011, Wager & Atlas 2015), they appear to be largest for psychological outcomes (Hróbjartsson & Gøtzsche 2010, Wechsler et al 2011) and physical outcomes (e.g., blood pressure or forced expiratory volume) rather than biochemical outcomes (e.g., cholesterol) (Figure 2a) (Meissner et al 2007). One interpretation of these results is that there is a larger potential for placebo effects on outcomes more closely linked to patients’ emotional and motivational state.
MECHANISMS OF PLACEBO EFFECTS

Theories of placebo mechanisms over the past decades have primarily focused 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 these terms are familiar 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 *pre-cognitive associations*, which refer to learned associations that can operate without cognitive awareness or intervention, and *appraisals*—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 focus specifically on differentiating appraisals from pre-cognitive associations and outlining their critical role in understanding the mechanisms underlying placebo effects. A key aspect of our argument is demonstrating that the appraisal system is highly integrative, involving coordination of multiple brain systems involved in emotion and cognition that appear to converge in the ventromedial prefrontal cortex and other regions in the so-called ‘default mode network’.

*Appraisal and pre-cognitive association: Separable but interacting mechanisms*
Pre-cognitive associations

Pre-cognitive associations are responses to stimuli that are “automatic” in the sense that they can occur without cognitive intervention 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 and do not necessarily require higher level cortical processing. For example, in classical conditioning paradigms, aplysia and drosophila exhibit single-trial learning in response to aversive events (shocks) that manifests in the strengthening of specific neural pathways associated with defensive responses. Anencephalic animals and humans deprived of a forebrain and cortex can still 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).

Pre-cognitive 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). Most placebo analgesic responses are expectation-
dependent (Benedetti et al 2003b), though they become stronger and more durable with longer conditioning (Carlino et al 2014, Colloca et al 2010, Colloca et al 2008a). In addition, after several days of training, they can persist even in the absence of conscious beliefs and expectations (Schafer et al 2015), suggesting a shift from being driven by beliefs to more stable pre-cognitive 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 patterns of pre-cognitive associations, long-term memories, thoughts about the future, goals, and interoception of one’s internal bodily states (Roy et al 2012). They are not simple perceptions, but constructed interpretations of events (Wilson-Mendenhall et al 2011). Whereas pre-cognitive associations are reactive responses to events, appraisals are “conceptual acts” (Barrett 2014). The appraisals that generate emotions are those with personal meaning, implying that they are related, and close to, a representation of the self and one’s future wellbeing. 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 encompass expectations about future outcomes, assigning value to outcomes (another ‘act of meaning’), and inferring others’ mental states (Frith & Frith 2006).
Appraisals play a critical role in psychosocial interventions, symptom management, and placebo effects. For example, cognitive-based psychotherapies aim to explicitly alter patients’ appraisals through reframing and cognitive restructuring. Appraisals about the effectiveness of a treatment can impact overall treatment response. Pre-treatment expectations account for substantial variance in overall treatment outcome (Gaston et al. 1989, Joyce & Piper 1998, Sotsky et al. 1991), and may often be related to the perceived treatment credibility (Hardy et al. 1995, Kazdin & Krouse 1983) and competence of care providers (Frank & Frank 1993). Appraisals of the meaning and future impact of symptoms can strongly affect how one responds to symptoms.

Placebo effects induced by verbal suggestions are likely mediated via patients’ appraisals. Verbal suggestions alone have been shown to modulate adrenocorticotropic hormone (ACTH) 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). In another study, instructions about the social context—specifically, about how previous participants had perceived the stimuli—caused robust modulation of pain-related autonomic responses (Koban & Wager 2015). These instructions were never systematically reinforced, pointing to cognitive appraisal rather than associative learning as a mechanism. Finally, Crum et al. (2011) delivered suggestions, in the form of package labeling, that a milkshake was ‘indulgent.’ These suggestions reduced blood levels of the hunger-related hormone ghrelin, compared with a milkshake label describing the drink as
'sensible.' Together, these findings emphasize the flexible role of the appraisal system in mediating placebo effects on multiple outcomes, including physiological responses.

Interactions between pre-cognitive associations and appraisal

Appraisals also guide pre-cognitive associative learning processes, shaping how placebo effects develop over time. Placebo effects are typically small when they are induced solely by reinforcement (Carlino et al. 2014, Montgomery & Kirsch 1997, Vase et al. 2002) or 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 the attribution of benefit to the treatment (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), placebo effects are not likely to be mapped to one discrete brain system. Rather, there are multiple systems and mechanisms involved, and understanding the principles by which appraisals and pre-cognitive 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, allowing quantitative assessment of how they replicate across multiple laboratories and paradigms (e.g., (Amanzio et al 2013, Atlas & Wager 2014)). This literature provides a foundation for several theoretically important points about placebo effects, and provides a basis for comparing placebo-induced brain activation patterns with those related to appraisals and clinical outcomes.

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 3, placebo analgesics appear to be able to reduce pain-related activity in the cortex (Wager et al 2004) and spinal cord (Eippert et al 2009c), and activate the endogenous opioid system (Wager et al 2007) and specific brainstem nuclei associated with pain control (Eippert et al 2009a).

These examples are supported by a more systematic review of published studies. 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 (blue in Figure 3). The most consistent reductions are in the dorsal anterior cingulate (dACC), thalamus, and mid- and anterior insula. In a number of studies, these brain reductions correlate with the magnitude of reductions in pain (see (Wager & Atlas 2015) for a detailed review). Reductions in sensorimotor cortex and in the amygdala are less common, but are consistent across a subset of studies. In parallel, EEG and MEG
studies shown placebo-induced reductions in cortical responses to painful laser stimuli at ~150-300 msec post-stimulus (Colloca et al 2008b). These studies demonstrate that placebo treatments can have multiple effects on pain-related responses, sometimes at a ‘deep’ (i.e., early sensory) level—though the most effective type of treatment and responder remains an open question (Wager & Atlas 2015).

Brain generators of placebo analgesia

In addition to reductions in symptom-related processes, placebo analgesia studies have identified consistent increases in activity. The most consistent placebo-related increases are shown in Figure 5, and include engagement of the dorsal and ventral lateral prefrontal cortex (dIPFC/vIPFC), ventromedial prefrontal cortex (vmPFC) and medial OFC, and mid-lateral OFC. Increases in these areas are also correlated with the magnitude of reported analgesia (Wager & Atlas 2015). A number of studies have also reported increases in the nucleus accumbens/ventral striatum (nAC/VS) and periaqueductal gray (PAG)—two areas most closely associated with the opioid system—converging with molecular imaging studies identifying 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 some of the strongest predictors of the strength of an individual’s placebo analgesic response involve anticipatory increases (Wager et al 2011), suggesting that their role in placebo analgesia is not pain-specific but rather part of a broader change in appraisal.
Beyond pain: Clinical placebo effects across disorders

A small but growing literature has investigated the brain mechanisms of placebo effects on clinical disorders, especially Parkinson’s disease. Results from these investigations converge with those from the experimental placebo analgesia literature and point to the central role of the vmPFC and the VS in generating placebo effects.

Placebo treatments in Parkinson’s have demonstrated effects on three systems: a) the nigrostriatal dopaminergic pathway, projecting from the substantia nigra to the dorsal striatum, b) the mesolimbic dopaminergic pathway, projecting from the ventral tegmental area to the ventral striatum and vmPFC, and c) the subthalamic nucleus-thalamocortical pathway. In a landmark study using radiolabeled raclopride imaging, 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 those effects, but only for patients randomized to instructions that they had a 75% chance of receiving the drug (Lidstone 2010), suggesting a key role of appraisals in this response. Similarly, a recent fMRI study examined learning-related brain function in the mesolimbic dopamine pathway. Placebo medication enhanced reward (but not punishment) learning performance, and altered corresponding learning-related activity in the nAC/ventral striatum and vmPFC (Schmidt et al 2014).

Another paradigm for studying the placebo effect in Parkinson’s disease, involves sham stimulation of the subthalamic nucleus (STN), thought to be a central brain structure in Parkinson’s pathophysiology. 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: neuronal and clinical responses to placebo treatment increased linearly as a function of the number of drug conditioning trials prior to the placebo administration (Benedetti et al 2016).

A metabolic PET study in Parkinson’s identified a pattern of increased brain activity—including the vmPFC and striatum, among other regions—that correlated with improvement following double-blind sham surgery (Ko et al 2014). Activity in these regions: a) predicted symptom improvement after subsequent sham surgery; b), increased after surgery; c) decreased after patients were told the surgery was not real; and d) was not associated with changes in a levodopa treatment group, an experimental gene therapy group, or a natural history group. These findings suggest a specific role for this network in generating placebo effects.

Just as the dopamine system is implicated in placebo effects in multiple disorders, the opioid system likely plays an important role beyond pain as well, particularly in depression. 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 response (to the intravenous placebo) with clinical improvement, and parallel earlier findings that responses to placebo and medication are predicted by pre-treatment activity in fronto-striatal systems in depression (Benedetti et al 2005, Leuchter et al 2002) and chronic back pain (Hashmi et al 2012).
Together, these studies of clinical disorders converge with the experimental placebo analgesia literature in highlighting the involvement of striatal and medial prefrontal systems in the genesis of placebo responses, with a prominent role of dopaminergic—and perhaps opioidergic—pathways.

A brain system for affective appraisal

The ‘default-mode network’ links placebo with other forms of appraisal

The brain networks and neurochemical systems engaged by placebo treatments across disorders are also implicated in particular aspects of cognition and emotion beyond the placebo context. Most notably, the brain regions engaged during placebo analgesia (Figure 5) are encompassed by the ‘default mode’ network, which includes the dorsal and ventral medial prefrontal cortex (dmPFC and vmPFC), posterior cingulate (PCC), temporal-parietal junction (TPJ) and superior temporal sulcus (STS), among other regions (Figure 6). The ‘default mode network’ is typically de-activated during tasks that require attention to external stimuli and sensorimotor control (Raichle et al 2001) and is often associated with spontaneous thought (Mason et al 2007), autobiographical memory retrieval (Vincent et al 2006), and mental prospection (Buckner & Carroll 2007). Interestingly, this network is also activated above baseline in a number of other appraisal-related processes such as the generation of negative and positive emotion (Lindquist et al 2016, Lindquist et al 2012a, Wager et al 2015), assessing others’ mental states (Frith & Frith 2006), self-related processing (Gusnard et al 2001), and representing expected value (Hare et al 2008). These characteristics suggest that the
‘default mode’ network plays a fundamental role in affective appraisal, linking placebo effects with other forms of concept-driven cognition.

**Relationship with self-generated emotion**

Figure 6 shows regions that are prominently activated by a subset of emotion studies in which participants are asked to self-generate both negative and positive emotional responses by recalling or simulating (imagining) potential events and situations (based on data from (Lindquist et al 2012a)). Unlike the majority of emotion studies which examine brain responses elicited by affective stimuli, these activations occur in the absence of any external stimulation and are generated purely from participants’ thoughts and memories. Self-generated negative emotions are associated with activation in the vmPFC, dmPFC, 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’ (Mechias et al 2010), in which anxiety is generated by *knowledge* about associations between cues and shocks, without reinforcement. 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.

**Inferences about others**

A key aspect of appraisal 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 into late adolescence (Blakemore 2008) and are important for inferring the preferences of another individual (Mitchell et al 2006), the intensity of another's affective experience (Krishnan et al 2016, Morelli et al 2015), and also tracking conversations between multiple people (Wagner et al 2016). For example, when participants make judgments about how their friends rank on a particular trait dimension, the DMPFC becomes more active as the number of friends to rank increases, suggesting a role in integrating social information (Meyer et al 2012). A related type of social cognition, which selectively recruits the STS and TPJ, involves inferring others’ beliefs (Saxe & Kanwisher 2003) and predicting others’ intentions in competitive games (Carter et al 2012, Hampton et al 2008).

Self-concept: Self-focused cognition

While thinking about others preferentially engages the dmPFC, self-referential processing preferentially activates the vmPFC, particularly the pregenual cingulate and anterior medial PFC (Denny et al 2012). This includes tasks as simple as judging the degree to which words describe oneself (Kelley et al 2002), and 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). It 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).
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, these regions are also involved in spontaneous internally directed and autobiographical thought (Andrews-Hanna et al 2014), imagining potential future situations (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 subjective worth of an item or choice outcome. Value is typically operationalized as the amount of resources or effort that an agent might spend to obtain an outcome. At its heart, however, it is an appraisal of the gain or cost (economic, social, or physical) to 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 they are often considered part of a ‘reward system,’ value-related 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 expected reward (Tremblay & Schultz 1999) and punishment (Morrison & Salzman 2011), with separate populations of dopamine neurons related to each
(Matsumoto & Hikosaka 2009). They also code for relative value, rather than features of
the stimulus (Tremblay & Schultz 1999), and change rapidly with learning as reward
contingencies change (Kim & Hikosaka 2013). Accordingly, value representations in
vmPFC and ventral striatum 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 (Robinson & Berridge 2013). Activity markers in the
mesolimbic dopamine system, including ventral tegmental area, nAC, and OFC, tracked
this change. In converging evidence, lesions to the VMPFC-OFC do not appear to
impair basic value preferences (Izquierdo et al 2004), emotional responses (Rudebeck
& Murray 2013), or simple forms of value learning (Milad & Quirk 2002) (for 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 2013).

Correspondingly, human FMRI activity in this system appears to reflect a form of
expected affective value related to both reward pursuit (Chib et al 2009) and
punishment avoidance (Roy et al 2012). Value-related vmPFC activity is sensitive to
diverse forms of conceptual information, including personal goals (Hare et al 2008),
verbal suggestions about how others value items (Plassmann & Wager 2014), and
homeostatic motivational states (Gottfried et al 2003).

An integrated view of appraisal

These findings suggest that appraisals—which are crucial for most placebo
effects—are mediated by a distributed system adapted for representing schemas or ‘situations,’ including a representation of one’s goals and wellbeing in the context of events and stimuli (Figure 6). This appraisal system is highly integrative, involving coordination of brain systems involved in 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.

The vmPFC, in particular, appears to be a critical hub in the appraisal process (Roy et al 2012). It is anatomically and functionally connected to (a) portions of the VS 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) central to emotion and governance of physiological responses in the body. Indeed, multiple theories have proposed that the vmPFC-OFC system represents expected outcomes in the cognitive sense (Schoenbaum & Takahashi 2009)—an “abstract value signal” (Wallis 2007) involving “predictions about specific outcomes associated with stimuli, choices, and actions...based on current internal states” (Rudebeck & Murray 2014). Such representations are “model based,” (Daw et al 2011), in that they are based on a structured, internal model of stimulus-outcome and action-outcome contingencies (Doll et al 2012). In short, its activity reflects personally relevant forms of flexible, conceptual thought.
Parallel studies provide converging evidence that the VMPFC is critical for representing other forms of structured, conceptual relationships (Binder et al 2009, Constantinescu et al 2016, Doeller et al 2010). For example, it is centrally involved in semantics (Binder et al 2009), which involve structured, relational representations among concepts. Concepts are defined based on their similarity to others—for example, the meaning of “boxer” is represented in relation other concepts, like “fighting,” “martial arts,” “hockey,” and so forth. But conceptual meaning in this sense is also flexible and context-dependent, as “boxer” takes on an entirely different meaning in relation to “poodle,” “lab,” and “retriever.” Concepts close to the concept of ‘self’ are encoded more deeply than general semantic knowledge (Rogers et al 1977) and preferentially activate the vmPFC (Jenkins et al 2008, Kelley et al 2002, Mitchell et al 2006). Thus, one view on the appraisal system’s underlying function is to allow the mental construction of a conceptual space Constantinescu et al (2016), positioning one’s concept of self in relation to situations and events. This allows us to make projections about future events and alternative courses of action, and envision their impact on our wellbeing.

CONCLUSIONS AND FUTURE DIRECTIONS: HOW DO APPRAISALS HEAL?

In this review, we discuss evidence that placebo treatments can have meaningfully large effects on clinical outcomes across disorders—particularly those in which emotion and motivation play a central role. Understanding how these effects arise is very much an open challenge, but they appear to involve interactions between
appraisal and learning mechanisms, which can potentially compound over time to create long-lasting effects.

Multiple kinds of placebo effects, including those relevant for pain, Parkinson’s disease, depression, and anxiety engage the ‘default mode network’, and in particular a core set of regions including the vmPFC, NAc, PCC, and TPJ. These regions are involved in multiple kinds of emotion generation, social- and self-referential cognition, and value-based learning and decision-making, suggesting a common system involved in conceptual thought. Establishing such a flexible, relational system allows us to simulate potential outcomes and develop expectations about future events. It also allows us to relate those events to a representation of the ‘self’ and one’s goals and well-being.

But, how do these appraisal systems affect long-term clinical outcomes? Though we still have much to learn to answer this question, we offer here three ideas that may 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, how to exercise—which can have profound influences on health behaviors over time. Second, the appraisal system is important for determining which thoughts should be prioritized and which can be ignored. Dysregulation of this system is prominently related to depressive rumination, catastrophizing in disorders including depression and PTSD. And third, when imagined or perceived events are conceived of as very ‘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, that are relevant for both behavior and physical health.

One intriguing, speculative possibility for how this happens is that relationships between appraisal and learning create positive feedback loops, which lead to self-fulfilling prophecies. The pain literature reviewed here and elsewhere (Buchel et al 2014) shows that positive appraisals influence how symptoms are perceived, laying an empirical foundation for such feedback loops. The more positive one’s expectations, the less pain is perceived—and the less pain, the more positive expectations are reinforced. Over time, positive expectations become more automatic, transitioning from conceptual appraisal systems to circuits encoding learned, pre-cognitive value associations (Schafer et al., 2015). This is good news, if one’s initial appraisals are positive – but bad news if they are negative, miring patients in feedback cycles of self-reinforcing negative appraisals. This 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.
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Figure captions

Figure 1. **The placebo response.** Sham surgery led to improvements in Parkinson’s symptoms that were as large as active treatment over two years. Reproduced based on Olanow et al., 2015.

Figure 2. **The placebo effect.** A) Placebo effects across clinical conditions from Hróbjartsson & Gøtzsche, 2010. Numbers of trials and patients are shown. Psychological placebos include, e.g., nondirective, supportive conversations. Physical placebos include, e.g., sham acupuncture and sham surgery. B) The placebo effect in acupuncture accounts for most of the treatment response; data from Madsen et al., 2009. C) Estimated placebo effects in depression, drawn from meta-analyses of Khan et al., 2012 (left) and Cuijpers et al., 2012 (right). SMD = standardized mean difference.

Figure 3. **The placebo response across disorders.** A) Pill placebo responses in different psychiatric disorders, from Khan et al. 2005. B) Sham surgery responses across different conditions, from Jonas et al., 2015. The number of trials and patients (if available) in each condition is shown. CGI-S = Clinical Global Impressions of Severity Scale. SMD = standardized mean difference.

Figure 4. **Brain mechanisms involved in placebo analgesia.** Brain 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 yellow. Clockwise, from upper right: 1) fMRI results showing brain regions that decrease during pain (Wager et al. 2004). 2) Regions with placebo-induced increases in μ-opioid activity (red/yellow; Wager et al. 2007); 3) Pain-related spinal cord activity reduced by placebo treatment (Kim & Hikosaka 2013). 4) Brainstem regions activated by placebo treatment (Eippert et al 2009b).

Figure 5. **Consistent findings in neuroimaging studies of placebo analgesia.** Left: peak activation locations in studies of placebo analgesia. Each sphere is a finding from an activation map, with blue spheres indicating decreases in pain-related activity (21 studies) and yellow spheres increases in pain- and anticipation-related activity (19 studies). Locations from the same map within 12 mm were averaged into one sphere. Right: Consistent activations, with at least 3 studies reporting effects within 10 mm. Consistent reductions during pain (blue) include somatosensory regions, thalamus, dorsal anterior cingulate (ACC), and anterior insula, which are associated with pain encoding. Consistent increases with placebo include the ventromedial prefrontal cortex (PFC), nucleus accumbens (NAc)/ventral striatum, periaqueductal gray (PAG), dorsolateral PFC, ventrolateral PFC, and posterior temporal-parietal junction (TPJ).

Figure 6. **Appraisal related processes converge in default network.** Meta-analyses converging on a core appraisal system. 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). Self-generated emotions involved using recall and imagery to generate positive (yellow, 21 study maps) or negative (blue, 56 study maps) emotional states; data from (Lindquist et al 2012b). Value-related activity (purple) from 375 studies of ‘reward’ and ‘value’ from Neurosynth.org (Yarkoni et al 2011). Social, other-focused cognition (green) from a meta-analysis of 48 studies (Denny et al 2012). Self-focused cognition (orange) from 48 studies of self-referential judgments (Denny et al 2012).
Real vs. sham surgery in Parkinson's

Improvement in Parkinson's symptoms

Baseline  Month 15  Month 24

-8  -6  -4  -2  0
### Placebo effects: Placebo vs. no treatment

- **Overall**: N = 158 (10,525)
- **Studies with low risk of bias**: N = 11 (1,610)
- **Patient reported outcomes**: N = 109 (8,000)
- **Observer reported outcomes**: N = 49 (2,513)
- **Pill placebo**: N = 61 (3,922)
- **Psychological placebo**: N = 44 (4,045)

### Placebo effects in acupuncture for pain

- **N = 13 trials (3,025 patients)**

### Placebo effects in depression

- **Common factors**: 50%
- **Specific factors**: 43%
- **Psychotherapy**: 17%
- **Pharmacotherapy**: 18%
Placebo responses across disorders

Pill placebo responses

Placebo surgery responses

% improvement CGI-S

N = 6
N = 11
N = 4
N = 42
N = 8
N = 2

Psychosis OCD PTSD MDD Panic GAD

Treatment response (SMD)

N = 10 (287)
N = 5 (342)
N = 8 (655)

Pain Obesity GERD Other

N = 15 (1,584)
Noxious stimuli RVM (NRM) PBN vmPFC dACC NAC S1 aINS S2 dpINS Thalamus PAG dlPFC vlPFC OFC AMY Hypothalamus

fMRI activity decreases during pain

Opioid release

Spinal fMRI

Brainstem activation

Left Dorsal
Individual studies

Most consistent reductions

Most consistent increases
Self-generated negative emotion

Common areas: Core affective appraisal

Placebo increases

Self-focused cognition

Social cognition

Value and reward

Self-generated positive emotion

Default mode network

Self-focused cognition