The Neural Bases of Placebo Effects in Pain

**Introduction**

Placebo effects have a rich and controversial history and have been the focus of intrigue and heated debate throughout the past century. Their role in the healing professions is so significant that several researchers have written, “The history of medicine [is the] history of the placebo effect” (de la Fuente-Fernandez, Schulzer, and Stoessl 2004; Kradin 2004; A. K. Shapiro and Morris 1978). Some have argued that medical practitioners should be encouraged and even trained to take advantage of the healing power of placebos in their practices, while others have argued that clinical placebo administration is deceptive and unethical. Even the existence of placebo effects has been challenged; opponents have asserted that placebo administration is akin to quackery and that placebo responders are malingerers without real diseases. By contrast, the strongest proponents of placebo research have asserted that understanding the mechanisms of the placebo response will give us more insight into “self-healing competencies” (Hall, Dugan, Zheng, and Mishra 2001).

This controversy stems from several sources. First, early researchers did not—and could not, using the tools available at the time—investigate the neurobiological mechanisms of placebo effects. The lack
of plausible mechanisms made it difficult to agree on what counts as a placebo effect and to systematically consider different sources of placebo responses in different disease states and outcome measures. Second, many clinical studies were not designed to assess the strength and causes of placebo effects, and so placebo effects in many of these studies are confounded with statistical biases and potential artifacts related to study sampling and the natural course of disease. Finally, findings of placebo effects in many studies are based purely on self-reported improvements, which, skeptics are quick to point out, might be caused by cognitive and social biases unrelated to the clinical course of disease.

In recent years, a resurgence of experimental research designed specifically to study the effects of placebo treatments has shed considerable light on the potential mechanisms of placebo responses, providing a new look at whether, and under what conditions, thought patterns such as expectation, motivation, and belief affect health. These studies have used pharmacological manipulations and new techniques for recording activity in the functioning human brain, including event-related electrical potentials (ERPs), magnetic potentials using magnetoencephalography (MEG), intra-cranial electrical recording in humans, functional magnetic resonance imaging (fMRI), and positron emission tomography (PET). Together, these techniques are beginning to piece together the electrical and neurochemical pathways in the brain that can, under certain circumstances, shape perceptual, emotional, and physiological aspects of pain and other disorders.

The emerging picture painted by these techniques is that placebo treatments work by eliciting a combination of positive expectations and specific learning in the brain circuitry, which connects the frontal cortex with lower-level brain stem centers that regulate physiological responses in the body. Neurochemically, opioids and dopamine are two chemical messenger systems that have been implicated in these recent studies. Both neurochemical systems appear to be principal players in positive emotion and motivation. Thus, the effects of placebo treatments may share much in common with the widely-studied effects of emotion and stress on health. This emerging view is corroborated by the fact that the three clinical domains in which evidence of placebo effects is most convincing—pain, Parkinson’s disease, and depression—all appear to share common neurocircuitry in the emotional and motivational centers of the brain.
Placebo treatments, placebo effects, and placebo responses

A placebo treatment is one that is expected to have no direct physical or pharmacological benefit—for example, a starch capsule given for anxiety or pain, or a surgery where the critical surgical procedure is not performed. For this reason, placebos are routinely used as control or baseline conditions in clinical studies. The effects of therapeutic treatments are compared with placebo treatment, controlling for “nonspecific” aspects of the treatment, including effects of participating in the study and other effects discussed below. However, placebo treatments have also frequently been used to actually treat a variety of ailments; they have had a place in the healer’s repertoire for thousands of years (A. K. Shapiro and E. Shapiro 1999) and are used as clinical treatments by physicians in industrialized countries today with surprising frequency (Sherman and Hickner 2008).

The mere fact that a patient improves on a clinical outcome measure after a placebo treatment does not prove the power of the placebo; this complexity is one important source of the controversy mentioned earlier. After all, the patient might have improved spontaneously or due to some factor (perhaps a change of diet or exercise) other than the placebo treatment itself. For example, a patient might report reduced knee pain after a sham surgery (Moseley, Wray, Kuykendall, Willis, and Landon 1996), but this does not definitively prove that the placebo surgery was responsible for the reduction. The patient may have been on the mend anyway. What one would like to know is whether the placebo caused the reduction in pain. For that, one would have to know what would have happened had the same patient not received the placebo treatment.

While one can never know what would have happened in any particular instance if things had been done differently, researchers have developed some ways of probing the fundamentally unobservable difference between two different courses of action. Patients are assigned to different treatments—in our knee example, placebo treatment and no treatment—at random. If assignment is random and the sample is large enough, the researcher might reasonably assume that the two groups are the same in all other ways besides the type of treatment given. By comparing the placebo group with the no-treatment (or natural history) group, one can assess the effect of placebo treatment and control for factors associated with the natural course of disease.
Improvements observed in the placebo group above and beyond those observed in the no-treatment group are referred to as placebo effects. Thus, not all improvements on placebo treatments count as placebo effects. To unequivocally demonstrate a placebo effect, one must perform a controlled study comparing a placebo treatment to a natural history control group.

To the degree that placebo treatments are healing agents, their power lies in the psychobiological context surrounding treatment (Moerman and Jonas 2002), resulting in an active response in the brain and body of the patient. Placebo treatments, by definition, are sensory cues (visual stimuli, sounds, touch, taste, odors, or combinations of these) that impact the brain but do not specifically affect health-related outcomes (e.g., reported pain, activity in relevant brain areas, clinical symptomatology) by more direct means. Thus, for a placebo to have an actual effect, it must induce some active response in the brain that causes a therapeutic change in behavior, experience, or physiology that in turn influences the outcome. We refer to the active process of perceiving and interpreting these sensory cues as a placebo response.

Do placebo effects exist?

The ultimate question with regard to placebo, put forth by Wilkins (Wilkins 1985), is “Which activities, delivered by which therapists in which settings, to which patients receiving which placebos, cause improvement for which complaints?”

On the one hand, placebo effects appear to be endemic across a wide variety of disease conditions and placebo treatments. Improvements after placebo treatments have been reported in a wide variety of disorders, ranging from pain to hypertension to mortality. However, as we argue above, improvements on placebo treatment do not necessarily entail active placebo responses. Without a placebo response, there can be no placebo effects—that is, no causal effects of placebo treatment. Kienle and Kiene (1997) reviewed evidence for clinical placebo effects and found that in many cases effects attributed to placebo treatment could be explained in other ways (as a byproduct of missing or improper experimental controls, sampling bias, and other factors). In fact, they identified twenty-one different kinds of methodological issues with these studies that could lead to apparent placebo effects.
More recently, Hrobjartsson and Gotzsche (2001, 2004) have taken a stronger stance. They conducted two meta-analyses of clinical placebo effects across a range of conditions, including pain, obesity, asthma, hypertension, insomnia, anxiety, and others. While a key component of Kienle and Kiene’s criticism of reported placebo effects was the lack of adequate controls in studies that purported to show placebo effects, Hrobjartsson and Gotszche took care to identify clinical studies that contained no-treatment control groups against which to evaluate the effects of placebo treatment.

In the first study, they examined evidence for placebo effects in 114 studies. The main analyses grouped different disorders together (which has subsequently been criticized (I. Kirsch and Scoboria 2001)). They examined both binary outcomes, such as the number of smokers vs. nonsmokers in placebo and no-treatment groups, and continuous outcomes, such as the number of cigarettes smoked. Overall, binary outcomes across the 114 trials showed no overall benefit of placebo, though continuous outcomes showed a significant benefit with placebo. Though the authors were more interested in binary outcomes, perhaps because binary classifications are often used to categorize patient groups and quantify recovery, continuous outcomes provide a more sensitive measure because most health-related outcomes follow continuous distributions.

For example, individuals have a range of blood pressure levels on a continuous scale, and there is no magic cutoff point at which the risk of heart attack or stroke suddenly jumps up; however, for clinical purposes, individuals are classified as having high blood pressure if their blood pressure exceeds a fixed cutoff value. Thus, a world-class sprinter with blood pressure on the low end of normal and an overweight lawyer with blood pressure just under the cutoff would both be classified as “normal,” though the actual blood pressure values certainly contain information about health risks.

Although the authors of these meta-analyses focused on the lack of placebo effects in binary outcomes, it is interesting to note that placebo effect sizes in several areas were relatively large, though they did not reach statistical significance. These effect sizes are shown in Table 1. As the table shows, the most widely studied condition was physical pain, with 1,602 patients in twenty-seven separate studies. Pain shows a large and significant effect size, with a Cohen’s d value (the mean placebo effect divided by its standard deviation) of 0.27.
Although the effect sizes in every other condition besides insomnia and anxiety were actually larger than that for pain, pain was found to be the only condition in which placebos were systematically found to have therapeutic effects. The authors focused on the subjective nature of the pain reporting process and suggested that placebo effects were artifacts of demand characteristics and reporting biases rather than powerful therapeutic phenomena.

Table 1. Meta-analysis results

<table>
<thead>
<tr>
<th>Disorder</th>
<th>N</th>
<th>Studies</th>
<th>Cohen's d</th>
<th>Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>1602</td>
<td>27</td>
<td>0.27</td>
<td>(0.40 to 0.15)</td>
</tr>
<tr>
<td>Obesity</td>
<td>128</td>
<td>5</td>
<td>0.40</td>
<td>(0.92 to 0.12)</td>
</tr>
<tr>
<td>Asthma</td>
<td>81</td>
<td>3</td>
<td>0.34</td>
<td>(0.83 to 0.14)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>129</td>
<td>7</td>
<td>0.32</td>
<td>(0.78 to 0.13)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>100</td>
<td>5</td>
<td>0.26</td>
<td>(0.66 to 0.13)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>257</td>
<td>6</td>
<td>0.06</td>
<td>(0.31 to 0.18)</td>
</tr>
</tbody>
</table>

Note: Adapted from Hrobjartsson and Gotzsche 2001

Another interesting finding from the meta-analysis is that there was evidence for significant heterogeneity across the studies, indicating that placebo effects may have been prominent in some studies and not others. Part of this heterogeneity surely relates to the many illnesses that were lumped together in the analyses. Another part relates perhaps to factors that are harder to quantify and are not described in research reports, such as the caring qualities and presence of the human research staff.

A subsequent meta-analysis (Meissner, Distel, and Mitzdorf 2007) analyzed many of the same studies and came to somewhat different conclusions. They first collected a group of thirty-four placebo-controlled clinical studies culled from the huge clinical trial literature. Studies of clinical conditions that were stable over time were selected, whether or not they included no-treatment control groups. An exploratory analysis identified two kinds of clinical outcomes: physical and biochemical. Physical outcomes, such as hypertension and airway responsiveness in asthma, showed evidence for improvement with pla-
cebo treatment during the course of the study, suggesting that placebo effects may exist in these outcome measures. Biochemical outcomes, including measures related to heart failure, infection, cholesterol, and rheumatoid arthritis, showed virtually no evidence for improvement on placebo treatment.

These groupings were applied to a second set of studies identified because they included no-treatment control groups, and thus the effects of placebo treatment itself could be more directly addressed. Analysis of this second data set confirmed that placebo effects in physical outcomes, but not biochemical outcomes, could be reliably identified. These results point out two important aspects of placebo responses: First, in contrast to the assertions of Hrobjartsson and Gotzsche, this meta-analysis of adequately controlled clinical trials does indeed offer evidence of systematic placebo effects in nonsubjective outcomes. Second, this study points to the necessity of investigating the mechanisms of placebo responses to get a better handle on why placebo effects are more consistently seen in physical, but not biochemical, outcomes.

Although Hrobjartsson and Gotzsche were right to be skeptical of the range of effects that have been called placebo effects, neither of these clinical meta-analyses include experimental studies designed specifically to address placebo effects and their mechanisms. Experimental studies involve control conditions that rule out virtually all the problematic artifacts discussed by Kienle and Kiene (1997) and typically involve stronger manipulation of expectancies than the typical double-blind conditions in clinical trials, in which patients are told that they may receive either active treatment or placebo. Patients taking part in clinical trials may guess at which treatment they received, and they may thus develop idiosyncratic expectations. Some patients receiving placebo believe they’re receiving an active drug, but many are likely to believe they’re receiving the placebo treatment, weakening the placebo response.

For this reason, studies that manipulate expectations experimentally (telling all participants that a placebo is an effective treatment and comparing this to a control substance that is said to have no effect) produce stronger placebo effects than double-blind clinical trials (Vase, Riley, and Price 2002). Likewise, improvement in depression is stronger in drug comparison studies, in which patients know they will get an active drug, than in double-blind studies (Ruther-
ford, Sneed, and Roose submitted). Thus, double-blind studies provide relatively weak expectancies of improvement and thus relatively weak placebo responses.

Controlled experimental studies have found evidence for placebo effects (and thus evidence for active placebo responses) in a wide variety of conditions, including reported pain (Benedetti 2007; Benedetti and Amanzio 1997; De Pascalis, Chiaradia, and Carotenuto 2002; Harrington 1999; Liberman 1964; Montgomery and Kirsch 1997; Price et al. 1999; Vase, Robinson, Verne, and Price 2005; N. J. Voudouris, Peck, and Coleman 1985; Wager, Matre, and Casey 2006; Wager et al. 2004; Wager, Scott, and Zubieta 2007), asthma (Kemeny et al. 2007), cortisol release (Benedetti, Amanzio, Vighetti, and Asteggiano 2006; Benedetti et al. 2003; Johansen, Brox, and Flaten 2003), depression (Mayberg et al. 2002), Parkinson’s disease (Benedetti et al. 2004; Colloca, Lopiano, Lanotte, and Benedetti 2004; de la Fuente-Fernandez et al. 2001; Pollo et al. 2002), conditioned immunosuppression (Goebel et al. 2002), allergic rhinitis (Goebel, Meykadeh, Kou, Schedlowski, and Hengge in press.), negative emotion (Petrovic et al. 2005), insomnia (Storms and Nisbett 1970), respiratory function (Benedetti et al. 1998; Benedetti, Amanzio, Baldi, Casadio, and Maggi 1999) and cardiovascular function (Lanotte et al. 2005; Pollo, Vighetti, Rainero, and Benedetti 2003).

As with the clinical studies, the most commonly reported effect is in pain, and pain has been most intensively studied. Pain is in many ways an ideal model system for studying placebo effects because it is clinically relevant, but it can also be applied experimentally and studied quantitatively in the laboratory. In addition, much is known about the neurobiology of pain that can provide insight into the mechanisms by which it works, in particular the brain-body pathways that participate in the creation of the pain experience and its effects on the body. This in turn allows us to use pain as a model system in which to investigate the mechanisms by which placebo responses modulate perception and physiology.

Indeed, the lack of plausible identifiable mechanisms for placebo responses may be at the root of the controversy surrounding their existence. Understanding the mechanisms of placebo responses across various disorders and in placebo analgesia as a model system can provide some guiding principles that shed light on the complex question of “Which activities . . . in which settings . . . to which patients . . .
cause improvement for which complaints.” Brain imaging and related studies are beginning to address the question of which brain systems participate in placebo analgesia (Benedetti et al. 1998; Benedetti, Amanzio, and Maggi 1995; Benedetti et al. 2006; Benedetti, Lanotte, Lopiano, and Colloca 2007; Bingel, Lorenz, Schoell, Weiller, and Buchel 2006; Petrovic, Kalso, Petersson, and Ingvar 2002; Price, Craggs, Verne, Perlstein, and Robinson 2007; Scott et al. 2007, 2008; Wager et al. 2006; Wager et al. 2004; Wager et al. 2007; Zubieta et al. 2005; Zubieta, Yau, Scott, and Stohler 2006). We turn in the following sections to a more detailed investigation of laboratory placebo analgesia studies and some of these new findings.

**The laboratory placebo experiment**

In a paradigmatic placebo analgesia experiment in the laboratory, participants are placed in a context in which they will receive aversive stimulation (thermal pain, shock, etc.). Participants are given information suggesting that an external agent, such as an injection or an ointment, is a powerful analgesic that will reduce pain. The agent, however, is a pharmacologically inert substance such as saline or starch. Noxious stimulation is presented, and responses to stimulation with placebo are compared with responses to stimulation without placebo. This experimental design allows researchers to examine a variety of variables as indices of pain, including subjective ratings, physiological responses, and pain-related activity in brain regions known to be associated with pain processing. Changes in these pain-related dependent variables in the placebo condition may be attributed to the placebo response.

The same approach can be used to investigate the role of the placebo response in anxiety (placebo anxiolytics paired with aversive images (Petrovic et al. 2005), motor performance in Parkinson’s disease (sham stimulation of subthalamic nucleus paired with motor performance (Benedetti et al. 2003; Pollo et al. 2002) or any other relevant biopsychological process that may be elicited and measured in the laboratory.

Through careful manipulations, researchers are able to examine the specific contributions of various factors to the placebo response. Such studies include investigations of the role of the medical context on placebo; researchers have investigated pill characteristics (Blackwell, Bloomfield, and Buncher 1972), effects of branding (Branthwaite and
Cooper 1981), and method of delivery (Levine and Gordon 1984), among other detailed aspects of the medical context (see Barrett et al. 2006 for a review). The role of psychological processes has also been investigated through laboratory experiments. For example, many experimental studies have sought to elucidate the contributions of conscious expectancies and conditioning to the development of placebo responses and to understand whether the two processes act independently or in parallel (Benedetti et al. 2003; I. Kirsch 1985; I. Kirsch 2004; Montgomery and Kirsch 1997; Stewart-Williams and Podd 2004; N. J. Voudouris et al. 1985; N. J. Voudouris, Peck, and Coleman 1989; N. J. Voudouris, Peck, and Coleman 1990).

Many studies have used laboratory experiments to investigate the role of patient characteristics on the placebo effect; for a long time, researchers sought to identify factors that would identify “placebo responders”. This effort stemmed from the observation that in nearly every study of the placebo effect, a subgroup of individuals did not respond to placebo manipulations; it was thought that factors could be identified that would determine whether or not an individual would be susceptible to placebo manipulations. Personality traits such as suggestibility were investigated, but no significant relationship was ever convincingly demonstrated. For example, Liberman (1964) wrote, “Placebo reactivity should be viewed as a potential tendency that can become manifest in the right circumstances in anyone rather than as an attribute possessed by some but not by others.”

Perhaps most important, laboratory investigations allow researchers to examine the endogenous mechanisms responsible for the placebo effect. Research in both animals and humans has identified neurochemical factors and nervous system pathways subserving endogenous regulation of psychological and physiological endpoints. Researchers have the opportunity to differentiate between mechanisms contributing to placebo effects across domains and domain-specific mechanisms. Understanding these mechanisms can promote scientific understanding of endogenous control processes and mind-body connections as well as shed light on potential targets for clinical intervention.

We have adopted this approach in order to study placebo effects on pain by using neuroimaging methods to examine placebo responses during noxious thermal stimulation. Placebo-elicited reductions in reported pain correlate with decreases in important pain-related brain
activity (evidenced through both fMRI and ERPs) and relate inversely to opioid binding (evidenced with PET neurochemical imaging). This provides strong evidence that placebo effects are indeed active psychobiological processes and not simply reporting biases. We will now review this research to offer evidence of the mechanisms by which placebo responses modulate the pain experience.

**Sensory components of pain**

Before we discuss our current understanding of the neurobiological mechanisms involved in placebo analgesia and what this can offer us in the way of understanding mind-body connections and endogenous regulation of physiological endpoints, it is important to review the basic physiological architecture underlying pain processing. In the case of pain induced by noxious stimulation, information about this stimulation is first registered by specialized nociceptors below the skin’s surface. Even at this level, it is clear that pain is a psychological construct since pain can occur without nociceptor stimulation, and nociceptors stimulation can occur without eliciting pain.

There are two types of primary afferent nociceptors (PANs) that are specialized to transmit information about pain: A and C fibers. These fibers are differentiated by diameter and amount of myelination, which allows them to transmit information about different sorts of pain, with sharp pain information relayed primarily by the larger myelinated A fibers and dull pain transmitted by the slower unmyelinated C-fibers. PANs synapse with neurons in the laminae of the spinal cord’s dorsal horn, which then cross to the anterolateral quadrant and form three ascending pathways: the spinothalamic tract, the spinoreticular tract, and the spinomesencephalic tract. Pain signals ascend to cortex via thalamus and brain stem relay centers, including the periaqueductal gray (PAG), rostral ventral medulla (RVM), and nucleus cuneiformis (NCF) (Tracey and Mantyh 2007). Sensory components of pain (intensity and location) are processed initially by primary and secondary somatosensory cortices (SI and SII, respectively). From here, pain signals are distributed further to higher cortical processing areas, such as anterior insula, dorsal and rostral anterior cingulate cortex (ACC), and orbitofrontal cortex (OFC); these regions are thought to play an important role in the affective components of pain (Price 2000).

Thus far, we have reviewed the mechanisms involved in trans-
mitting nociceptive information from peripheral sensation to cortical representation. As a result of research on the ascending pathways, researchers historically viewed pain as a sensory modality, with the main goal of pain to signal potential damage; the brain perceives and responds to nociceptive signals carried by the ascending pathways, the spinal cord is involved only as a relay station, and pain modulation is entirely peripheral.

**Pain modulation pathways**

Today, we know that the brain constructs pain only partly based on nociceptive input; pain has been found to exist in cases where nociceptive input is impossible, such as phantom pain (Oakley, Whitman, and Halligan 2002) and deafferentation (Hosobuchi 1986), and pain can also occur with light touch or spontaneously. Thus, the brain makes critical decisions about how extensively to process nociceptive input. The brain is not solely responsible for modulatory influences on the transmission of nociceptive information since there are feedback loops at multiple levels of the neuraxis. There are also many cognitive and physiological influences that determine the direction of pain in response to noxious stimulation, which may be mediated by feedback between structures at any level of the pain pathways. Decreased pain sensation may occur due to positive expectancies (Keltner et al. 2006; Koyama, McHaffie, Laurienti, and Coghill 2005), competition for attention (Bantick et al. 2002; Valet et al. 2004), and sympathetic arousal (Drummond, Finch, Skipworth, and Blockey 2001); sensitization may occur as a result of anxiety (Arntz and de Jong 1993; Arntz, Dreessen, and De Jong 1994), central sensitization (Iannetti et al. 2005), or inflammation (Wieseler-Frank, Maier, and Watkins 2005).

In 1965, Melzack and Wall put forth their influential gate control theory (Melzack and Wall 1965), which was the first significant step in research aiming to understand the mechanisms behind descending modulation of pain information. They hypothesized that central control mechanisms interact with afferent information at the level of the spinal cord in order to block nociceptive signals from reaching the thalamus and central nervous system. Subsequent research on the specifics of such modulation has brought us to our current understanding of pain as a CNS phenomenon; in order to understand pain, the brain, responsible for decisions and understanding of con-
text and a powerful source of descending modulation of spinal transmission, cannot be ignored.

We now know that this “gate control” may be achieved through descending endogenous opioids. Endogenous opioids were first implicated in placebo analgesia when the opioid antagonist naloxone, an agent that specifically binds to \(-\) opioid receptors, was shown to reverse behavioral placebo effects (Levine, Gordon, and Fields 1978). These results have been replicated (Benedetti, Arduino, and Amanzio 1999; Grevert, Albert, and Goldstein 1983; Levine and Gordon 1984; Levine, Gordon, and Fields 1979), although studies also support nonopioid mechanisms of placebo (Amanzio and Benedetti 1999; Gracely, Dubner, Wolskee, and Deeter 1983; Scott et al. 2007, 2008).

The release of these peptides is critically controlled by the periaqueductal gray (PAG) and rostral ventromedial medulla (RVM), and opioids have been shown to have an inhibitory effect on PAN synapses at the level of the spinal cord’s dorsal horn (Fields 2004).

Naloxone is also capable of reversing the analgesic effects of direct stimulation of the PAG (Morgan, Gold, Liebeskind, and Stein 1991). Since the PAG is a major center for opioids with the ability to provide both descending modulation of nociception as well as modulation of frontal and limbic circuitry, it is likely to serve a key role in the modulation of pain under placebo. This provides a promising mechanism by which context-dependent regulation of pain may occur, with reciprocal connections between important pain-processing and decision-making areas of cortex and the PAG.

Importantly, PAG has been shown to be under prefrontal control. Frontal cortex activation correlates with reduced across-subjects [AU: plural OK here?] connectivity between PAG and thalamus (Lorenz, Minoshima, and Casey 2003; Valet et al. 2004). Stimulation of ventrolateral OFC blocks the analgesic effects of PAG stimulation (Zhang, Tang, Yuan, and Jia 1998). Finally, connectivity between rostral ACC and PAG increases under placebo (Bandler and Shipley 1994; Bingel et al. 2006). With the columns of the PAG organized to elicit coordinated behavior (inferior right for flight responses, superior right for fight responses, and left column for withdrawal) (Bandler and Shipley 1994), the PAG may be critical in allowing for frontal contextual information to influence drive state and physiology.
Placebo analgesia

With this background in mind, we can now begin to examine research on pain pathway regulation by placebo-induced cognitive expectancies. We used a placebo manipulation to induce expectations for pain relief during noxious thermal stimulation (Wager et al. 2004). A placebo cream was put on participants’ skin with the explanation that it was lidocaine and would have pain-relieving effects. This was compared to a control cream that participants were told would have no effect. Unbeknownst to participants, the two creams were actually identical. Participants reported a 22% decrease in pain with the placebo cream.

With fMRI, we can examine activity in the brain in order to determine where in the pain-processing stream placebos may have their effect activation during noxious stimulation is compared between placebo and control trials [AU: Are words missing here? Should this be two sentences with filled-in words? Please fix.]. Three potential mechanisms exist, which are not necessarily mutually exclusive. First, the placebo response may take place through spinal inhibition, as suggested by the gate control theory; in this case, we would expect to see widespread decreases of [AU: Is this what you mean?] noxious stimulation in pain-processing regions, since afferent nociceptive information would be prevented from reaching cortical levels of processing. This possibility [AU: OK?] is supported by work by Bushnell (Bushnell, Duncan, Dubner, and He 1984), Fields (Fields 2004), and Matre and colleagues (Matre, Casey, and Knardahl 2006).

Alternatively, the placebo response may induce changes in pain affect and central pain processing (Clark 1969; Rainville, Duncan, Price, Carrier et al. 1997), which would lead us to expect decreases in pain response in selected regions only. Finally, placebo treatments may induce changes in reporting bias but leave pain-evoked responses unaffected. This alternative would be manifest during functional imaging as changes in decision-making circuits during or after pain, at which point decisions are made retrospectively as to magnitude of pain during stimulation.

We examined pain processing both during noxious stimulation as well as during the anticipatory period preceding stimulation (Wager et al. 2004). We found that, relative to the control condition, placebo administration did indeed induce decreases in pain-process-
ing regions during painful stimulation. These decreases occurred both in regions associated with sensory-discriminative pain processing (thalamus) as well as in regions known to be responsible for processing the affective components of pain (anterior insula, ACC). These decreases have been replicated (Price, Craggs, Verne, Perlstein et al. 2007), although other research has failed to replicate decreases (Kong et al. 2006).

An important aspect of these results is that most of the observed placebo-induced decreases occurred late in the pain period. These delayed decreases could have resulted either from early inhibition of the pain response, as the gate control theory would suggest, or could have been an artifact of decision-making processes rather than actual pain inhibition. In order to examine fast, early effects of placebo, we conducted a second study in which we used laser-evoked pain (LEP) and ERPs (Wager et al. 2006). We found that placebo expectations decreased a medial frontal P2 component known to be sensitive to laser intensity and pain at 220 ms, too early to be affected by decision-making and report biases (Posner and Boies 1971). Early modulation of pain by expectancy has also been demonstrated in MEG (Lorenz et al. 2005) and electroencephalography (Watson, El-Deredy, Vogt, and Jones 2007). Even early decreases in pain processing such as these still do not conclusively prove that spinal inhibition has occurred, since placebo-induced decreases in attention to pain would also result in a reduction in P2 potentials. In fact, we found that P2 LEP placebo differences habituated over the course of the experiment while placebo effects on reported pain did not; this suggests that inhibition alone cannot fully explain observed placebo effects on reported pain.

Furthermore, if the gate control hypothesis were entirely responsible for changes in reported pain based on inhibition of ascending pain, then effects in the brain would be the same as decreasing the pain input by the same difference as changes in reported pain under placebo. Since we can quantify the relationship between P2 and laser intensity, we were able to actually examine this question and found that the extent of decrease in P2 amplitude was less than the difference that would be required in order to elicit the same difference in ratings based on applied pain. In other words, the difference in reported pain between placebo and control was greater than the difference in P2, suggesting that LEP reduction alone was not sufficient to account for reported placebo effects.

Thus, while there is support for early inhibition of nociceptive
signals based on the differences in P2 amplitude between placebo and control conditions, the magnitude of these differences is not large enough to entirely explain placebo effects on reported pain. This suggests that there may be important additional mediators of the relationship between placebo-based expectancies and reported pain, such as attention, appraisal, and other cognitive factors.

We also conducted a study using PET molecular imaging in order to examine neurochemical mechanisms of placebo (Wager et al. 2007). Opioids are known to relieve pain, so their involvement in placebo analgesia provides further evidence that placebos recruit powerful endogenous mechanisms to alter pain processing rather than simply affecting decision making and pain reports. Furthermore, in the fMRI experiment reviewed earlier, an area of the midbrain surrounding the PAG was found to be recruited during pain anticipation under placebo and was correlated with right dorsolateral prefrontal cortex (DLPFC). Studying the role of endogenous opioids in placebo analgesia may provide a basis for understanding the mechanisms by which the frontal cortex, known to be involved in higher-level processes such as executive function, expectancy, and evaluation, might modulate pain. We used PET in order to examine opioid binding in placebo during warmth and painful heat. \([^{11}\text{C}]\text{Carfentanil}\), a radioactive tracer, binds to opioid receptors, which allows us to infer opioid binding activity: \([^{11}\text{C}]\text{Carfentanil}\) binding is inversely related to opioid binding, since the two compete for receptor space.

Thus, if we see decreased tracer binding in a region during placebo relative to the control condition, we can infer that endogenous opioid binding has increased under placebo. In general, we assume there is a basic feedback loop between nociception and opioid release, where nociception recruits opioid release in order to inhibit subsequent nociception. Our results suggest that placebo leads to opioid potentiation; placebo modulated reported pain and led to increases in opioid binding during heat but not during nonpainful warmth. Placebo-heat interactions were observed in NRM, PAG, OFC, and rACC, among other pain-responsive regions of interest, and networks of these regions were found to be functionally integrated under placebo. These results help elucidate the critical role of endogenous opioids in the placebo response; opioid release in affective brain regions is potentiated during placebo.

In complementary work, researchers have examined the role of
dopamine, a neurotransmitter thought to be highly related to reward, prediction, and learning, in placebo analgesia. Since some have argued that analgesia may be a special case of reward processing—pain relief may be thought to be rewarding in and of itself (Fields 2004; Irizarry and Licinio 2005)—researchers have been interested in examining the contributions of dopamine systems to placebo analgesia. Recent studies have used PET molecular imaging with $^{11}$C]raclopride to label dopamine binding during placebo analgesia.

In one study (Scott et al. 2008), researchers directly investigated the connection between opioid and dopamine systems in placebo analgesia by using PET to image both dopamine and opioid receptor binding in the same individuals. Placebo induced increased opioid and dopamine release (reduced tracer binding) in the nucleus accumbens as well as other areas. Dopamine increases in the nucleus accumbens were correlated with opioid increases in the same region as well as with reported placebo analgesia. This provides evidence for the role of dopamine in placebo analgesia and suggests that there may be an important relationship between dopamine and opioid systems in the placebo response. The same group also examined the relationship between placebo analgesia, endogenous opioid release, and reward processing (Scott et al. 2007) and focused on the nucleus accumbens (NAcc), a dopamine-rich part of the basal ganglia’s ventral striatum. Dopamine binding in the NAcc during noxious stimulation correlated with anticipated effectiveness of the placebo, and the magnitude of dopamine binding during pain anticipation correlated with the magnitude of placebo effects on reported pain.

In a subsequent fMRI portion of the experiment, participants participated in a monetary reward task; high placebo responders were found to show greater NAcc activity during reward anticipation, and NAcc activity during reward anticipation was correlated with dopamine activity during placebo analgesia. These results provide evidence for a link between placebo analgesia and reward processing.

In conclusion, placebo treatments manipulate cognitive context in order to shape the pain experience. We have presented evidence for an early inhibition component, supported by early LEP effects on pain, and a larger central (limbic) component. Mechanisms of placebo analgesia involve frontal regulation of PAG and limbic system, mediated to a large extent by endogenous opioid release as well as dopamine subsytems.
Extending the findings to other domains

If placebo analgesia is a model system for placebo responses, then what are the principles of placebo responding that may be drawn? In both the fMRI and PET opioid binding studies, the regions that showed the greatest placebo responses were those known to be related to affect and value, such as the insula, rostral ACC, and OFC. For instance, a meta-analysis in our lab (Kober et al. in press) that examined 162 studies of emotion showed that the anterior insula was more consistently activated during various kinds of negative emotional experience than during positive experience. Thus, insula changes need not be specific for pain; they could indicate shifts in emotional experience. Dopamine and NAcc activity, also shown to be involved in placebo analgesia, are also thought to be central for a variety of affective or value-based processes, such as hedonic experiences (pleasure and pain) and the motivated pursuit of goals. In fact, both opioid and dopamine systems have been linked to positive shifts in hedonic processes and appetitive motivation.

Thus, placebo responses may exist (and be strongest) in outcomes that are most directly affected by this evaluation system of the brain. Indeed, placebo effects are also found in other disorders in which emotional evaluation and motivation play a role. One of the most prominent is Major Depressive Disorder (I. Kirsch 1998, 2000; I. Kirsch et al. 2008; Mayberg et al. 2002; Rutherford et al. submitted). For example, Rutherford found that patients assigned to a drug in a clinical trial respond more strongly in comparator trials, in which they are told they will get an active drug for certain, than in double-blind trials, in which they have only a 50% chance of receiving the drug. Mayberg and colleagues (Mayberg et al. 2002) showed that placebo antidepressants affect brain metabolic activity much in the same way as their active pharmacological counterparts, including important changes in subgenual ACC, a region consistently affected in depression and that is the target of deep brain stimulation for treatment-resistant patients.

A second disorder that is perhaps even better understood in terms of its neurobiological bases and the role of the placebo response therein is Parkinson’s disease, a movement disorder caused by degeneration of dopamine-producing neurons in the basal ganglia’s substantia nigra. Placebo responses in Parkinson’s disease have been shown to modu-
late striatal dopamine release (de la Fuente-Fernandez et al. 2001) and activity in the subthalamic nucleus, a stimulation site used in the treatment of Parkinson’s (Benedetti et al. 2004), and expectations for enhanced vs. poor motor performance can modulate the effects of subthalamic nucleus stimulation (Pollo et al. 2002). Dopamine itself is important in motivated behavior (Berridge and Robinson 1998; Schultz, Dayan, and Montague 1997; Smith and Berridge 2005), so it is quite reasonable to view these data in light of placebo responses entailing motivation and appraisal subsystems.

It is even possible to reconcile research that demonstrates placebo responses in physical outcome measures, such as the meta-analysis reviewed earlier (Meissner et al. 2007), with this affective account of placebo responses. Saying something is “physical” does not mean it cannot be susceptible to motivation. In asthma, for example, one measure that has commonly shown placebo effects is FEV-1, or forced expiratory volume (Kemeny et al. 2007; Leigh, MacQueen, Tougas, Hargreave, and Bienenstock 2003). FEV-1 may be influenced by brain stem centers that control respiration, and these brain stem centers are targets of projections from some of the same higher-level regions that showed placebo effects in pain—in particular, the PAG and ventromedial PFC. Thus, to say that placebo effects are related to evaluation and motivation does not imply that they cannot be “real” and have objectively measureable consequences in the body. The central systems most closely associated with appraisal control brain stem circuits that affect all the major organ systems.

In addition, motivation in this sense need not even be conscious. Psychology researchers have demonstrated a wealth of effects of unconsciously processed stimuli on perception and behavior (Bargh, Gollwitzer, Lee-Chai, Barndollar, and Trotschel 2001) (Winkielman, Berridge, and Wilbarger 2005), including potentiating physiological skin conductance responses to fear conditioning (Olsson and Phelps 2004). Fields (Fields 2004) has argued that the core limbic systems of the brain control spinal pain transmission in an adaptive way—decreasing pain under conditions in which it is essential to do so (fight, flight) and increasing it under others, depending on the environmental context.

Our proposal that placebo responses are mediated by changes in affective evaluation is not entirely unrelated to proposals that placebo involves “reward” (de la Fuente-Fernandez et al. 2004; Scott et al.
2007), mentioned in the preceding section. However, saying that reward plays a role in placebo seems a bit akin to saying that changes with placebo are the same as those involved in any manipulation of positive emotion—say, in receiving a bag of candy or finding a five-dollar bill on the ground. In fact, there is not substantial evidence that pain can be affected by these things. The alternative is something more subtle: That placebo changes appraisals of safety and threat depending on the perceived context and beliefs about the placebo treatment, and that these changes in appraisal are mediated by brain circuitry in the limbic system that affects emotion, motivation, and pain. Thus, to ask “Does placebo affect the body or just the brain” may be asking the wrong question. We may instead want to ask, “How does placebo affect the brain, and under what conditions are brain-peripheral pathways affected?”

Summary

Careful experimental manipulations have the power to provide strong evidence of active placebo responses, refuting assertions that placebo effects are nothing but reporting biases and statistical artifacts. Research using placebo analgesia as a model system suggests that placebo responses recruit powerful endogenous processes to modulate perception, and that such modulation may be mediated by changes in affective evaluation. This motivational account is not limited to placebo analgesia, for similar mechanisms have been demonstrated to be involved in placebo responses in Major Depressive Disorder and Parkinson’s disease. The cortical and subcortical regions involved in affect and evaluation are indeed able to modulate peripheral outcomes, providing candidate mechanisms that may support placebo responses across a range of disorders and clinical conditions. These placebo response mechanisms are presumably at work in active behavioral and pharmacological therapies as well. These mechanisms elucidated by experimental research on the placebo response thereby provide a powerful window into understanding how the brain is capable of modulating the body’s physiological state.
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