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The Neural Bases of Placebo Effects in Anticipation and Pain

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Numerous studies of experimental and clinical pain show that placebo treatments reduce reported pain and that expectancies play a key role in their effectiveness. However, very little is known about the neurobiological mechanisms of either placebo analgesia or the generation of expectancy that enables it. To address this issue, I used functional magnetic resonance imaging to quantify placebo-induced changes in pain-processing brain regions during the experience of pain. Results show placebo-induced decreases in contralateral thalamus, anterior insula, and anterior cingulate, and increases in prefrontal brain regions that may maintain expectations for pain relief. These findings are discussed in light of several proposed neuropsychological mechanisms of placebo analgesia: altered appraisal of threat, diversion of attention, and activation of descending opioid systems for spinal control. These results suggest that placebo treatment alters the appraisal process, reducing the subjective distress caused by pain.

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Since time immemorial, physicians have prescribed just about any remedy imaginable for the various ailments that plague our species. These treatments included viper's flesh, fox lung, powdered gems, powdered Egyptian mummy (real or fake), mandrake, bleeding, magnetic therapy, and others—nearly 5000 medicines in all, not counting medical procedures.¹ The one thing these remedies have in common is that they are likely to have no direct effect on the disease for which they were prescribed—in fact, many of these treatments are dangerous or deadly in their own right.

Why did belief in these remedies persist for so long? Although the sociological reasons for belief in sham treatments should not be underestimated, perhaps there was a practical reason that these treatments are so persistent. Perhaps belief in a cure itself has a salubrious effect. Galen, for example, noted, "He cures most successfully in whom the people have the most confidence." This idea has been so persistent that healing effects attributed to patients' internal processes (whether mediated by belief or endogenous conditioned responses) have been incorporated into the medical canon and given a name: *placebo effects*. Placebo groups in double-blind

trials were introduced in the early 1900s and are now included in every major clinical trial.

What Can Be Healed With a Placebo?

Believing in a cure can do three things. It can promote positive expectations, decrease anxiety and stress, and increase motivation to live and to engage in healing behavior. But what processes and systems in the human body are affected by placebo treatments? The question is the subject of current debate. Hrobjartsson and Gotzsche^{2,3} conducted an influential meta-analysis of clinical trials comparing placebo groups and no-treatment control groups. They concluded that across 46 clinical conditions (including pain, Parkinson's disease, obesity, skin conditions, and many others), there is a significant placebo effect on average for graded benefits reported on continuous scales but not binary outcomes. In analyses within disease types, significant placebo effects were found only on pain. The authors attributed the statistically significant placebo effects in the meta-analysis to study selection bias and bias in participants' reports only (rather than to participants' actual experiences), concluding that there is no "real" placebo effect on objective health outcomes or subjective experience.

Although publication biases, reporting biases, and other

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statistical artifacts often are mistaken for active placebo effects,⁴ the broad claims of Hrobjartsson and Gotzsche's meta-analysis elicited several published criticisms.^{5,6} One issue with the study is the diverse nature of the medical conditions included, which the authors collapse across in their overall analyses. Within categories of disorders, only for pain were a substantial number of trials (44 trials with nearly 3000 participants). Hypertension, with 10 trials in the expanded second meta-analysis,³ was the next largest category. In addition, the clinical trials reviewed were not designed to assess placebo effects, and so they neither explicitly manipulated belief in the treatments tested nor attempted to avoid unblinding of the treatment assignment caused, for example, by differences in side-effects. A meta-analysis comparing studies that explicitly evaluated placebo with standard double-blind trials found that the former studies showed a significantly larger effect size ($d = 0.95$) than the latter ($d = 0.15$).⁷

Examination of individual studies designed to assess the placebo effect, most of them experimental, also provide ample evidence for placebo effects. Three domains that seem particularly susceptible to placebo effects are pain, depression, and Parkinson's disease, although placebo effects may be reliable in other domains that have been less extensively tested as well (eg, irritable bowel syndrome, anxiety, and others⁸⁻¹¹). For example, in a recent study Benedetti and coworkers¹² found that placebo stimulation of the subthalamic nucleus in patients with Parkinson's disease decreased both neuronal firing rates in the subthalamic nucleus and arm rigidity. Kirsch,¹³ in a meta-analysis of clinical studies of depression, compared placebo arms with normative data on no-treatment controls (few clinical trials have both placebo and no-treatment arms) and found evidence for substantial benefits of placebo treatment. Benedetti and coworkers,¹⁴ studying experimental pain, found substantial placebo-induced decreases in reported pain that were both specific to the body part that was treated with a placebo cream and reversed by the opioid antagonist naloxone. After a conditioning procedure in which placebo is paired with an active drug, placebos can induce immunosuppressive responses in animals and humans^{15,16} and changes in growth hormone and cortisol.¹⁷ These representative examples demonstrate reliable placebo effects on reported pain, and on both subjective and disease-specific objective outcome measures in several other domains.

With regards to pain, however, two critical issues remain largely unaddressed. One is how much of the pain effect is caused simply by cognitive bias in reporting or memory for pain rather than pain experience. A second is understanding the mechanisms whereby placebo treatment affects pain. Can studies of placebo effects on reported pain be dismissed as response bias? The naloxone-reversibility of placebo effects provides a partial answer, but opioids do not act only on the pain system; they are involved in non-pain-related emotional processes in the cortex as well.¹⁸ In a recent study,¹⁹ my colleagues and I investigated changes in brain activity during pain using functional magnetic resonance imaging (fMRI) and asked whether placebo treatment could reduce pain-induced activity in the network of brain regions that pro-

cesses pain. As I describe here, our results provide evidence for placebo-induced decreases in pain processing and suggest that response and study selection bias alone are insufficient to account for placebo effects in experimental pain. We also examined placebo-induced increases in brain activity during the anticipation of pain. Such activations could be related to generation and maintenance of expectancy, which are potential mechanisms for the action of placebo treatment. Our results suggest links between placebo analgesia, appraisal processes, and control of attention.

In the remainder of this article, I first provide some theoretical context on pain processing in the brain and then describe the results of some initial studies of placebo effects on pain processing. Finally, I consider appraisal and controlled attention as potential psychobiological mechanisms of placebo analgesia.

The Pain Matrix: Brief Review and Meta-Analytic Synthesis

Neuroimaging studies, including positron emission tomography (PET) and fMRI studies of healthy volunteers, have consistently identified a number of cortical and subcortical regions that respond to painful stimulation when compared with resting control conditions.^{20,21-23} To summarize consistently-reported pain regions, my colleagues and I performed a meta-analysis of activation peaks reported in 24 neuroimaging studies, published between 1997 and 2003, of experimental pain in healthy volunteers. The meta-analysis quantitatively evaluates which regions are consistently responsive to pain across studies, and it is accomplished by locating regions of the brain in which the density of reported peaks exceeds what would be expected by chance if those peaks were distributed randomly throughout gray matter.^{24,25} The set of significant regions, shown in Figure 1, have been referred to as the "pain matrix."²⁶ Along with specific brainstem nuclei and other subcortical regions not easily identifiable with neuroimaging, these regions comprise the core neural pathways for sensory, affective, and evaluative components of pain. Note, however, that some pain-responsive regions—such as dorsolateral prefrontal cortex (DLPFC)—activate a wide stretch of cortex in many pain studies and thus their peaks are not tightly grouped enough to appear in the meta-analysis.

One challenge in studying these regions is that little is known about which regions are involved in which components of the pain experience. Many of these same gross anatomical regions are activated by nonpainful cognitive and emotional demands, making it unclear whether activations represent pain-specific processes or the attentional and behavioral responses elicited by pain. In addition, pain itself activates antinociceptive endogenous opioid systems,²⁷ which may be part of an unconscious brain process or the result of spontaneous strategic regulation of pain.²⁸ A major center for opioidergic neurons is the periaqueductal gray (PAG) in the midbrain, which projects upward to cortical

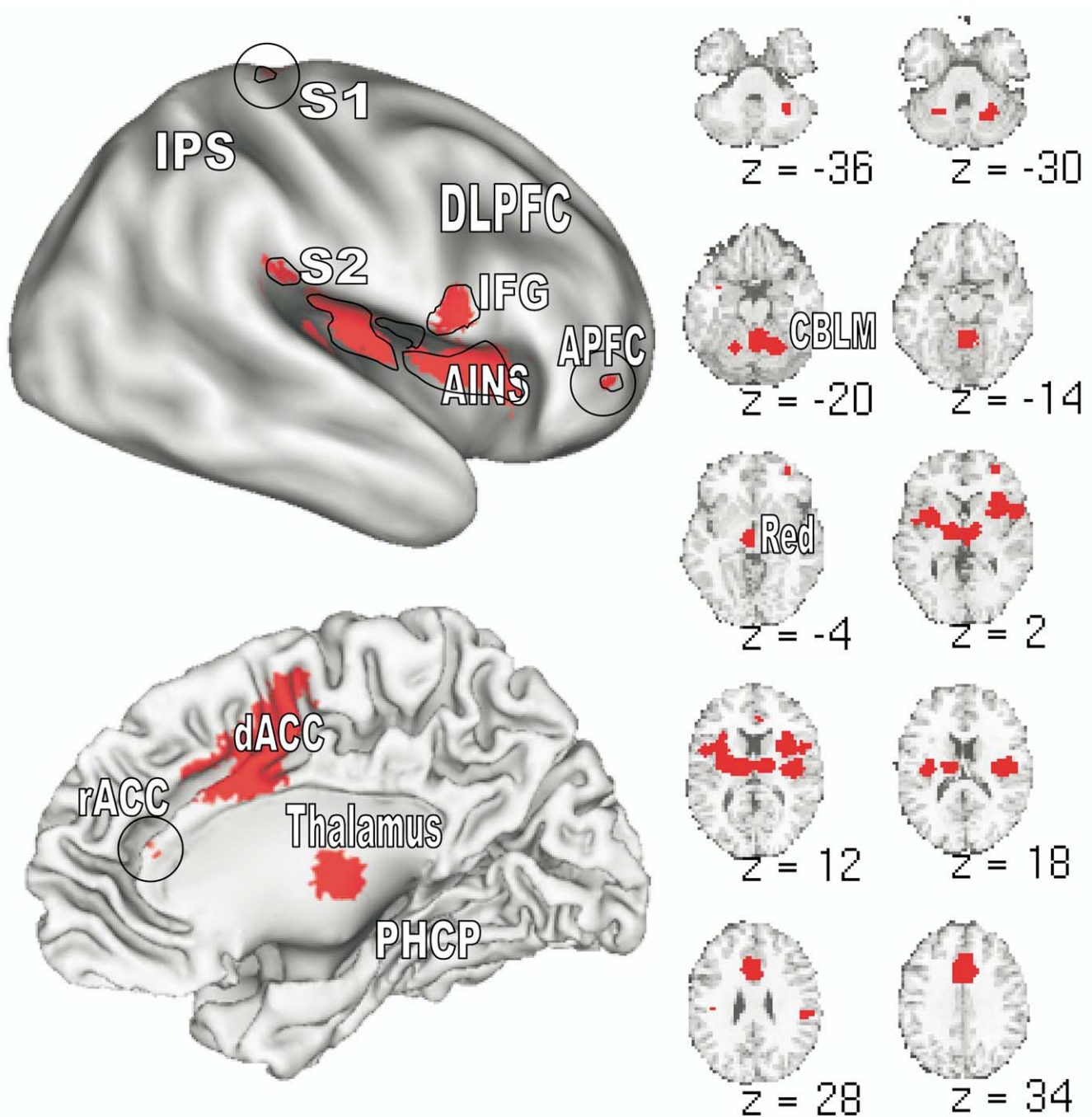


Figure 1 Significant regions from a meta-analysis of fMRI and PET studies of pain. Shaded blobs indicate consistent findings across studies. Top left: inflated cortical surface of the right hemisphere. Bottom left: medial surface. Right: Representative axial slices, with Montreal Neurologic Institute z-coordinates listed below slices. IPS, intraparietal sulcus; DLPFC, dorsolateral prefrontal cortex; IFG, inferior frontal gyrus; AINS, anterior insula; APFC, anterior prefrontal cortex; rACC and dACC, rostral and dorsal anterior cingulate cortex; PHCP, parahippocampal cortex; CBLM, cerebellum; Red, red nucleus/rostral midbrain. (Color version of figure is available online.)

sites of opioid release²⁷ and other mesolimbic areas, such as the ventral striatum and amygdala, and downward to the serotonergic nucleus raphe magnus and noradrenergic parabrachial nucleus of the pons, both of which exert inhibitory influences on spinal pain transmission.²⁹

According to current knowledge, pain-processing regions can be tentatively separated into several functional

networks. Nociceptive transmission fibers ascending in the anterolateral system of the spinal cord synapse in the ventral posterior thalamus and project to S1 and S2 somatosensory cortices, which presumably subserve the primary sensory response to painful stimulation. S1 and S2 are relatively specifically activated by pain and nonpainful touch and vibration and are seldom activated by nonpain

cognitive and emotional tasks. Activation is predominantly contralateral but very frequently bilateral; this may depend on the subregion within S1 and S2.³⁰ These regions comprise the sensory network. The anterior insula responds preferentially to pain and other stimuli that have an aversive impact on the self,³¹ and it has been suggested that this region is central to the subjective experience of pain. It is anatomically interconnected with other paralimbic pain-responsive structures, including the ventral striatum, rostral part of the dorsal anterior cingulate cortex, dorsomedial nucleus of the thalamus, and caudate nucleus. These regions form the core of the affective/motivational network. Pain also activates cortical structures consistently activated by demands on executive working memory, which involves the maintenance and manipulation of information held in short-term memory stores. These regions include the DLPFC, anterior prefrontal cortex, inferior frontal gyrus, and dorsal anterior cingulate, and they comprise the cognitive/evaluative network. It has been suggested that DLPFC, in particular, plays a role in the strategic regulation of pain.³²

Potential Mechanisms for Brain Placebo Effects

If placebo treatment alters pain processing in the brain, we might expect it to do so in one or more of the following ways. One alternative is reporting bias—that placebo treatment affects only memory for pain or the pain-reporting process itself. If this is the case, we should see no changes during pain experience, except perhaps as they relate to memory formation. At the other end of the spectrum, placebo treatment may engage opioid systems in the PAG that block spinal pain afferents.³³ In this case, we should observe increased activation of the PAG with placebo treatment and decreased pain responses in all pain regions, including the sensory network. A third alternative is that placebo treatment changes the motivational and affective significance of pain; that is, it changes the feeling of pain as constructed in the brain by changing the behavioral significance of the painful stimulus. If this is the case, we should observe placebo effects predominantly in the affective/motivational network. Finally, by altering the personal significance of pain, placebo treatments may enable different strategies for reducing pain, such as deployment of attention away from the site of pain. Any of the last three mechanisms could be controlled through the cognitive/evaluative network, but the last one in particular, self-distraction, suggests that there may be changes in frontal and parietal regions that closely mirror the pattern of activation induced by cognitive attention deployment.

In our study, we used fMRI to study brain and reported placebo effects during the anticipation of pain, when cognitive and affective changes are engaged during expectancy of pain relief, and during the experience of pain.¹⁹ The design of each experiment was similar: In each, participants received a cue that signaled upcoming pain, followed a variable number of seconds later by a painful stimulus. In Experiment 1, the

stimulus was 6 painful shocks 1-s apart; in Experiment 2, it was a 20-s painful thermal stimulus. Stimuli were calibrated for each individual participant to be moderately painful. After a variable delay, participants rated the pain they experienced on that trial on a 10-point scale. In each experiment, participants' forearms were treated with 2 identical topical creams. Participants were told that one cream was a potent analgesic and provided with safety information about the drug. They were told that the other was an inert control cream. Participants were tested at the same stimulus intensity on placebo-treated and control-treated skin; in both studies, on average, stimuli were judged to be less painful with placebo treatment (eg, 22% decrease in pain, $P < 0.001$, Experiment 2), replicating experimental work on placebo effects in reported pain. In Experiment 2, we also calculated the test-retest reliability between placebo effects in an initial behavioral session and an fMRI session conducted weeks to months later, and we found that the magnitude of these effects was reasonably stable over time ($r = 0.62$, $P < 0.05$) and was predicted by the degree that participants expected the placebo to work ($r = 0.38$, $P < 0.05$).

Although these studies were designed to be similar in many ways, they also contained important differences. The right forearm was stimulated in Experiment 1, and the left forearm was stimulated in Experiment 2, to allow us to test whether brain effects were lateralized absolutely or relative to the side of stimulation. But perhaps most importantly, Experiment 1 involved a sample drawn from the population at large ($n = 23$), and the primary measure of interest was the correlation between placebo effects on reported pain and placebo effects (control–placebo) in the brain, across individuals. In Experiment 2, we established reported placebo effects in a random sample ($n = 50$), and then picked those who showed relatively large reported placebo effects ($n = 22$) for further study with fMRI. Thus, the main measure of interest in Experiment 2 was group effects of pain activity under control versus placebo treatment. By combining across experiments, we could tell whether pain activity was both reduced (or enhanced) by placebo treatment in a group of placebo responders, and whether these changes correlated with reported pain.

Effects of Placebo on the Pain Network

In the brain, we first isolated pain-responsive regions by comparing moderately painful stimuli to those that were perceptible but not painful (Experiment 1) or mildly painful (Experiment 2). Regions coded in this way have been referred to as “intensity coding” regions³⁴ and are assumed to be involved in the representation of the painful quality of the stimuli. This analysis identified all of the meta-analysis regions shown in Figure 1, with additional significant activation in the DLPFC, the orbitofrontal cortex (OFC), intraparietal sulcus, temporal–parietal junction, and visual cortex.

Comparing the magnitude of the brain response for control versus placebo treatment, we found that only a subset of

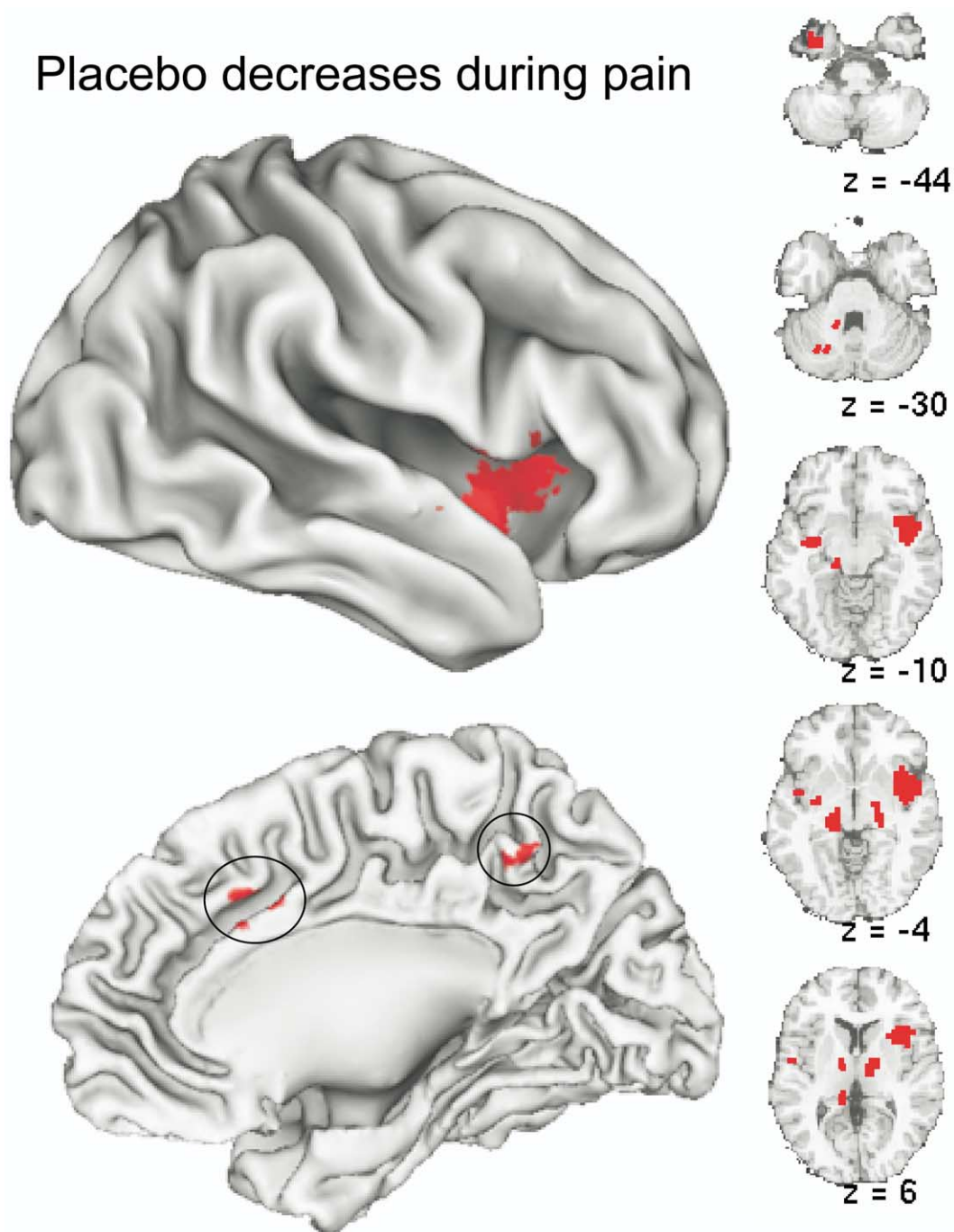


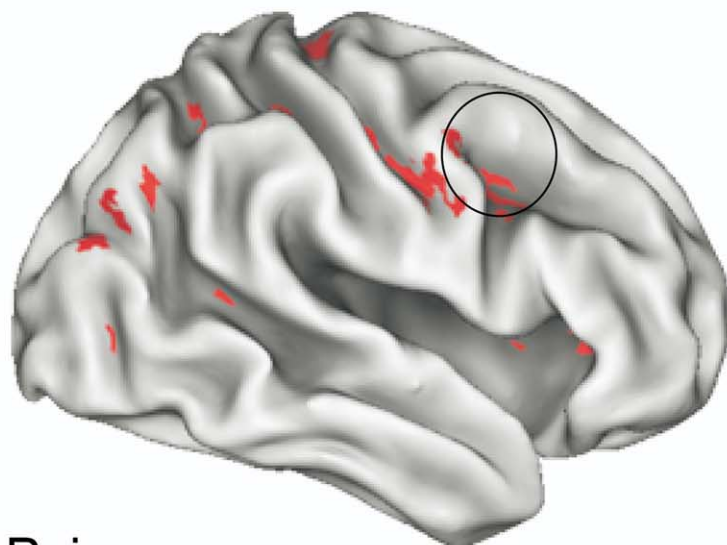
Figure 2 Regions showing significant decreases with placebo treatment during the late phase of painful heat stimulation (control–placebo, Experiment 2). Insula, thalamus, and cerebellum activations are in pain-responsive regions. The medial surface (bottom left) shows regions in which reported placebo effects are correlated with greater placebo-induced decreases in the early phase of heat. (Color version of figure is available online.)

regions showed evidence for decreased responses and that the remaining areas showed no decreases, even at low, uncorrected thresholds. Placebo-induced decreases were found in the contralateral anterior insula and dorsal thalamus, with some evidence for bilateral decreases, shown in Figure 2. These effects correlated with reported placebo effects in Experiment 1 and were found in the group in Experiment 2, as expected.

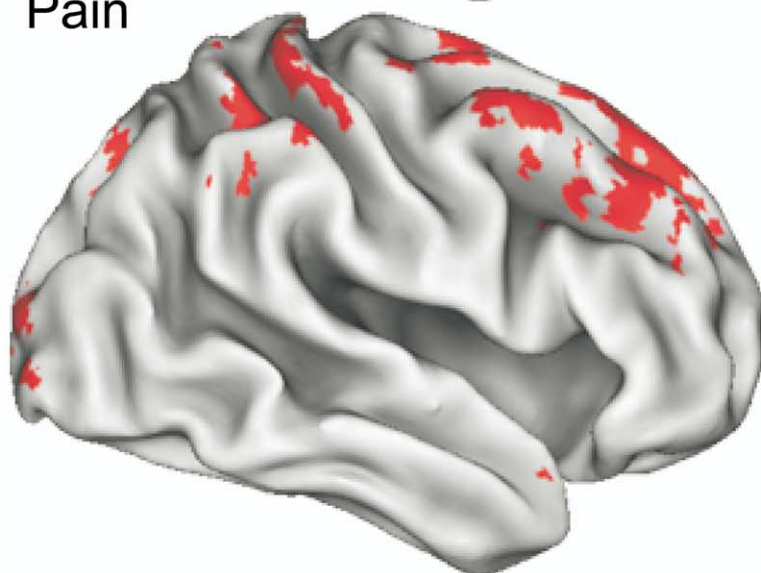
In Experiment 2, we were able to separate the pain re-

sponse into 3 phases during painful heat; placebo-induced decreases in this experiment were found only in the late phase, after stimulus offset and during recovery. The rostral anterior cingulate cortex also showed decreases (control–placebo) that correlated with placebo effects in reported pain in both experiments. In this case, only early heat-related activity was correlated with reported placebo effects. These effects are consistent with the idea that placebo treatment directly affects the affective component of pain. The strongest placebo

Anticipation



Pain



Anticipation

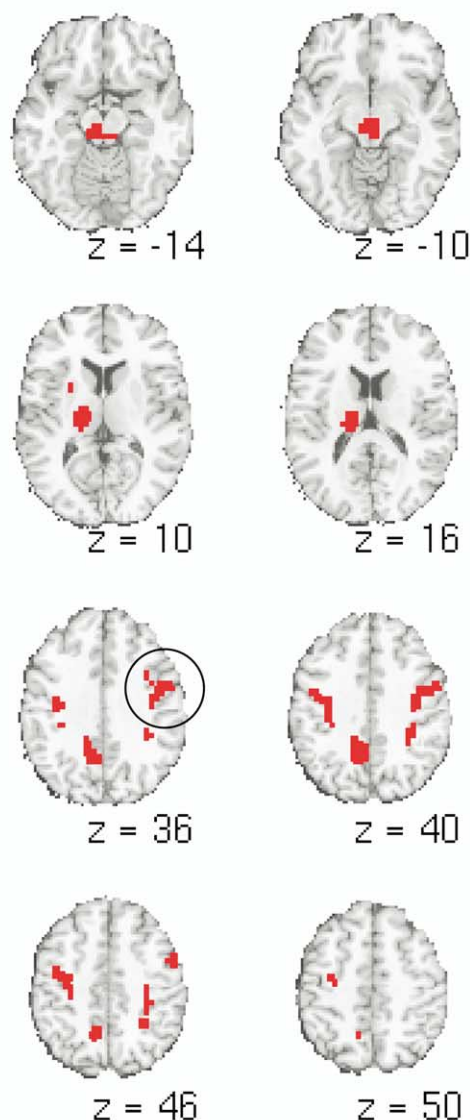


Figure 3 Placebo-induced increases (placebo–control) in anticipation of pain (top left and slices at right) and during pain (bottom left) in Experiment 2. (Color version of figure is available online.)

responders may show early decreases in anterior cingulate, with changes in insular cortex following during evaluation of and recovery from pain.

Placebo-Induced Activation of the Cognitive/Evaluative Network

During the anticipation of pain, we found placebo-induced increases in OFC (Experiment 1), DLPFC (Experiments 1 and 2; see Fig. 3), rostral medial PFC (anterior to pain regions), anterior PFC, and superior parietal cortex. In Experiment 1, DLPFC and OFC increases were correlated with increases in the reported placebo effect. As expected, in Experiment 2, increases were significant in the group of placebo responders. Frontal and parietal areas over-

lapped with, but were not limited to, pain-responsive regions. Increases in PAG during anticipation of pain were also found in both studies, and these increases were correlated with increases in OFC and DLPFC.

The OFC is associated in numerous studies with representation of primary rewards and particularly with updating the reward or punishment value of a cue.^{35–38} OFC and its connections with the amygdala appear to play a critical role in representing and updating the motivational significance of environmental cues.^{39–43} In our experiments, the cue that signaled upcoming pain at the start of the anticipation period may take on different motivational significance with placebo treatment.

DLPFC is thought to play an important role in working memory, a system for actively maintaining and manipulating currently relevant information in short-term memory.^{24,44,45} “Currently relevant” is shorthand for representing a whole

Distraction effects on pain regions

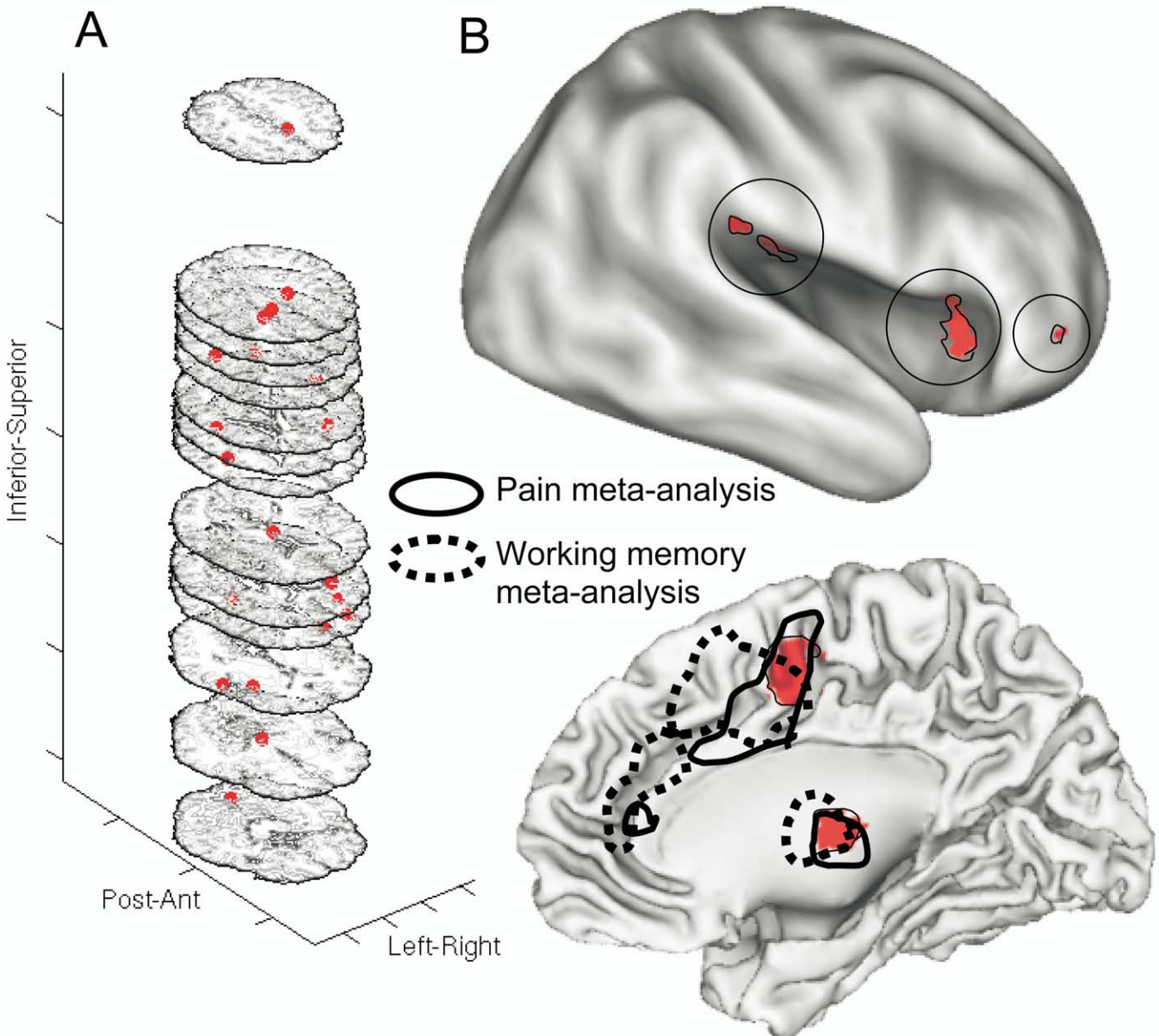


Figure 4 (A) Peak coordinates from four studies to date that have directly compared pain responses with and without a distracting secondary task. (B) Pain-responsive regions within 10 mm of a pain-reduction peak in at least one study. Pain-responsive regions were defined using the meta-analysis (Fig. 1). Pain reduction is defined by the contrast: [Pain without distraction – Control without distraction] – [Pain with distraction – Control with distraction]. Top panel: lateral surface of right hemisphere, as in Figure 1. Bottom panel: right medial surface, with outlines for pain-responsive regions from the meta-analysis (solid dark lines) and significant regions for executive working memory (dashed lines; from ref. 22). Pain and working memory activations are overlapping, but not identical, on the medial surface. Distraction-induced decreases in pain appear to lie in pain-responsive regions near the border of working memory-responsive regions. Areas showing increased activation with distraction are not shown. (Color version of figure is available online.)

situational context in a rapidly accessible form, including information about cues to avoid, stimulus-response contingencies that are likely to be used, and predictions about the future. Single cells in DLPFC fire selectively to task-relevant stimuli, when particular rules are appropriate, and when par-

ticular outcomes are anticipated.⁴⁶⁻⁴⁸ Activity in this region is thought to bias perceptual processing toward relevant information in all sensory modalities, enhancing representations of relevant percepts and suppressing representations of irrelevant ones. Thus, one way that placebo may decrease pain is

to make it, and the cues that predict it, less salient, thereby shifting processing resources away from the feeling of pain and onto other stimuli. DLPFC may be integral to (1) maintaining the expectation for pain relief, and using that expectation as a context for (2) directing attention away from pain.

Increases in the PAG suggest, at first glance, that opioidergic descending systems of the PAG may be activated by the warning cue under placebo treatment. Although this result is consistent with the gate control theory,³³ little is known about how frontal regions might activate opioid systems in anticipation of pain, whether they can be activated by transient cognitive activity at all, and why we found placebo effects in PAG only during anticipation and not during pain. Although most studies have focused on connections between the PAG and the brainstem and spinal cord, evidence exists that the PAG receives projections from insula, anterior cingulate, nucleus accumbens, amygdala, and frontal cortex.⁴⁹⁻⁵¹ With respect particularly to frontal control over PAG antinociceptive systems, a series of studies in anesthetized rats shows that microstimulation of ventrolateral OFC transiently attenuates nociceptive reflex responses and that this effect is blocked by lesions of the PAG.^{52,53}

Psychological Mechanisms: Attention, Appraisal, and the Role of Expectations

The frontal activations we and others^{11,54} have observed with placebo treatment suggest that placebo is an active brain process with a substantial cognitive and evaluative component, not simply a reporting bias or passive adaptation. These results also provide parallels between placebo effects and other often-studied processes—namely, the appraisal of threat or benefit, control of attention, and maintenance of task contexts in working memory.

There are several alternatives for the psychological processes whereby expectancy can lead to reductions in pain processing. One is that placebo-induced changes in perceived significance and potential harm of a stimulus directly modify the brain regions (eg, anterior insula, mediodorsal thalamus) that give rise to the feeling of subjective distress. Altered appraisal of the significance of pain may also work by activating opioidergic systems that block pain at the spinal level, but more research must be done to test this possibility directly. Opioidergic activity in limbic regions themselves may be an important part of the subjective appraisal process.¹⁸

Another possible psychological mechanism for placebo effects is attention deployment. Diversion of attention has been shown to decrease both subjective pain and activity in sensory and affective pain networks⁵⁵⁻⁵⁸ and to increase activity around the PAG⁵⁹ (but see Petrovic et al⁵⁶). Placebo treatment may signal to the participant that it is okay to ignore pain and attend elsewhere. Again, the process starts with an altered evaluation of the significance of pain, but according to this explanation, attention is a critical mediator.

To provide a preliminary test of this view, we have aggregated across studies that have shown decreases in pain-responsive regions with a concurrent cognitive distractor task.^{*,56,58,60,61} The results are shown in Figure 4. On the left side of the figure (Fig. 4A), we have plotted each peak activation coordinate from these studies that lies within the regions identified in the pain meta-analysis (Fig. 1). On the surface renderings (Fig. 4B), we show right-hemisphere pain regions whose activity is diminished by a distracting task in at least one study (the sphere 10 mm around each peak distraction effect is marked.) As Figure 4 shows, distraction can diminish pain-responsive regions in anterior cingulate, anterior insula, peri-S2, and thalamus. Decreases in left rostral medial PFC⁶⁰ are not shown on the figure. These studies generally report increases in frontoparietal attention regions that are thought to subservise performance of the distractor task. Given the current information, it is plausible that placebo treatments work by facilitating attentional shifts away from the site of pain, but more carefully controlled studies of placebo and distractor tasks in the same participants will be required to test this hypothesis more directly.

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