The Neural Bases of Placebo Effects in Pain

Tor D. Wager

Columbia University

ABSTRACT—*Placebo effects are beneficial effects of treatment caused not by the biological action of the treatment but by one's response to the treatment process itself. One possible mechanism of placebo treatments is that they create positive expectations, which change one's appraisal of the situation and may thereby shape sensory and emotional processing. Recent brain-imaging evidence suggests that placebo-induced expectations of analgesia increase activity in the prefrontal cortex in anticipation of pain and decrease the brain's response to painful stimulation. These findings suggest that placebo treatments can alter experience, not just alter what participants are willing to report about pain. To the extent that they involve neural systems mediating expectancy and appraisal, placebo effects in pain may share common circuitry with placebo effects in depression, Parkinson's disease, and other disorders.*

KEYWORDS—*placebo; pain; expectancy; appraisal; fMRI*

> If thou art pained by any external thing, it is not this that disturbs thee, but thy own judgment about it. And it is in thy power to wipe out this judgment now.
>
> —Marcus Aurelius Antoninus (2001, p. 44)

Belief in the healing power of positive expectations has existed since the beginning of recorded history. The power of expectation to make people feel better has been exploited by physicians and charlatans—sometimes to promote healing and other times for less altruistic reasons. The healing potential of expectations has formally been recognized in scientific literature as the *placebo effect,* a term that generally refers to beneficial effects of a treatment that cannot be ascribed to the physical action of the treatment itself. A patient in pain, for example, may report feeling less pain after an injection of saline (i.e., a placebo injection), if the patient believes that a painkiller was administered. Placebo effects have been reported in a cornucopia of ailments, including pain, depression, Parkinson's disease, alcoholism, irritable bowel syndrome, panic and anxiety disorders, and high blood pressure, and have been reported after sham surgeries for heart disease and arthritic knee pain. Recognition in the medical community of placebos' healing potential has led to the standard practice since the 1940s of using placebo control groups in clinical trials.

In spite of the volume and breadth of research involving placebos, most studies have focused on testing drug effects against a placebo baseline, not on testing whether placebo treatments themselves are effective. For example, suppose investigators test depressed patients over a 3-month period of treatment and find a 30% recovery rate in the placebo group. Many patients will spontaneously recover during this time, even with no treatment; thus, the 30% "placebo response rate" could be due either to placebo treatment or simply to the natural course of depression. Testing for placebo effects directly requires an additional no-treatment control group. Because such a group is not often included in clinical studies, we still understand very little about the scope of disorders that may respond to placebo treatments and the psychological mechanisms that underlie the placebo response.

This relative lack of knowledge has led some researchers to suggest that placebo treatment engages no active beneficial psychophysiological processes; rather, they suggest, placebo effects are simply statistical artifacts such as regression to the mean and spontaneous recovery or demand characteristics, the tendency to comply with experimenters' expectations (Hrobjartsson & Gotzsche, 2004). However, recent evidence using no-treatment controls has demonstrated that active placebo effects exist for at least some diseases. In pain, depression, and Parkinson's disease, placebo effects have been demonstrated both in behavioral outcomes and in disease-specific brain activity.

In this paper, I discuss placebo effects on pain, focusing on two questions related to the effects of verbal suggestions (i.e., the suggestion that you have been given a painkiller, in the earlier example). First, what aspects of the continuum from sensing a noxious stimulus to feeling and reporting pain are affected by this kind of placebo treatment: sensation, subjective pain experience, or demand characteristics? Drawing on evidence from behavioral

Please address correspondence to Tor D. Wager, Department of Psychology, Columbia University, 1190 Amsterdam Ave., New York, NY 10027; e-mail: tor@psych.columbia.edu.

and brain-imaging studies, I suggest that placebo treatment may most strongly impact the subjective experience of pain. I then turn to the issue of what psychological and brain mechanisms are engaged by placebo treatment. My view is that placebo treatment primarily affects expectancy and appraisal, two related processes crucial in determining subjective pain experience.

EFFECTS OF PLACEBO ON PAIN

Placebo treatments may affect several aspects of the pain sensation–experience–reporting continuum: sensory transmission and processing, appraisal and the generation of subjective pain, and the pain-reporting process (Fig. 1A). The issue of which aspects are affected is at the heart of the debate over whether placebo treatments have "real" effects.

Placebo Effects on Sensory Input

Ascending pain signals travel through the spinal cord to reach the thalamus and then the sensory-processing regions of the cerebral cortex (S1 and S2; Fig. 1B). I refer to these regions as the *sensory pain network*, as they appear to be specifically activated by physical pain and touch, but not by cognitive operations or negative emotions. Neurons both in the spinal cord and in the sensory network project to another set of regions, including the anterior insula, anterior cingulate cortex (ACC), and mediodorsal thalamus. These regions constitute the *affective pain network*, as they are closely linked to the subjective feeling of pain (Craig, Chen, Bandy, & Reiman, 2000).

Changes in the sensory network or in the spinal cord itself would provide the strongest evidence for placebo effects on pain. According to the "gate control" theory (Melzack & Wall, 1965), the brain can block pain by engaging opioid neurons in and near the midbrain periaqueductal gray (PAG; Fig 1B), which then inhibit pain in the spinal cord. This is a standard explanation in medical textbooks for how placebos work.

Do placebos block pain in the spinal cord? This question has been difficult to test directly. However, indirect evidence indicates that placebo analgesia can be blocked by the opioid antagonist naloxone (Amanzio & Benedetti, 1999), suggesting that

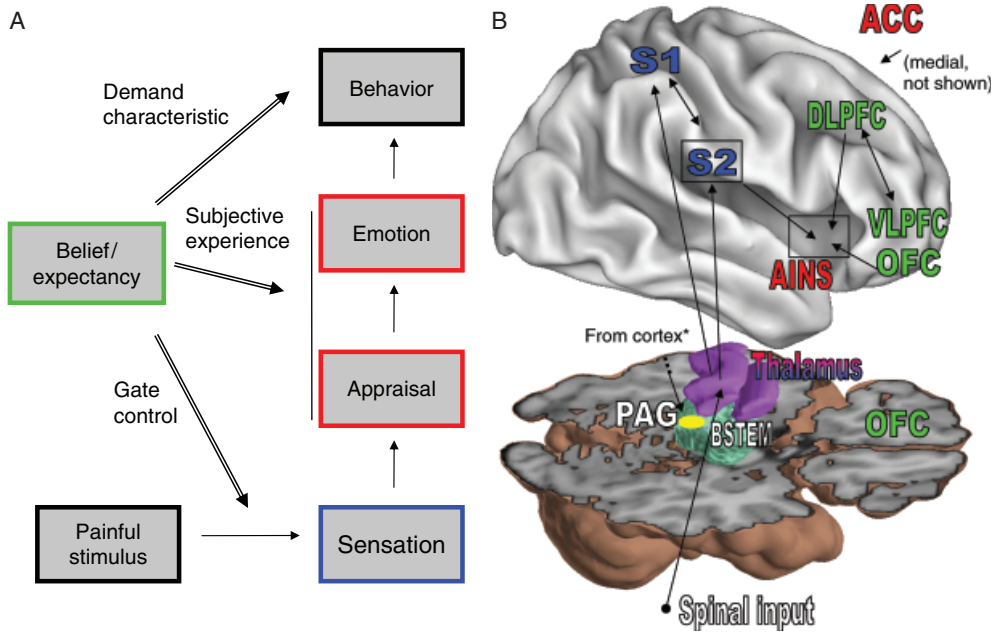

Fig. 1. (A) Routes by which expectancy, created by placebo treatments, may lead to changes in pain processing and (B) some important brain regions in the pain pathway. Pain begins when sensory signals from the spinal cord reach the brain via the thalamus and are sent to the primary (S1) and secondary somatosensory cortex (S2). These areas may be most important for the sensory aspects of pain, though the total pain experience may emerge from interactions among these and other regions, described below. From there, signals are sent to the anterior insula (AINS) and anterior cingulate (ACC), which are involved (along with regions in the limbic system) in the subjective experience and emotional quality of pain. These signals undergo an appraisal process, in which potential harm is assessed and corresponding emotions and behaviors are generated to tolerate, escape, or remove the source of pain. The appraisal and emotional components are central to what it means to ''feel pain.'' Appraisals are generated through interactions among the orbitofrontal cortex (OFC), AINS, ACC, and other regions, and they may be maintained in the dorsolateral prefrontal cortex (DLPFC). Expectancies, in the generation of which the DLPFC, OFC, and ventrolateral prefrontal cortex (VLPFC) may play a role, may inhibit spinal input, alter the experience of pain directly, or affect behaviors and pain reporting directly. The periaqueductal gray (PAG), in the brainstem (BSTEM), can block ascending spinal signals if activated, and it receives input from many regions mentioned above, including the OFC, ACC, DLPFC, VLPFC, and amygdala. However, the PAG also modulates activity throughout the emotional and cognitive networks of the brain.

placebo treatment requires opioid systems in the PAG. Recent brain-imaging studies found that placebo treatment increased activity in the midbrain region surrounding the PAG (Wager et al., 2004) and in prefrontal regions that correlate with increases around the PAG (Petrovic, Kalso, Petersson, & Ingvar, 2002; Wager et al., 2004).

If placebo treatment engages opioid systems that block pain in the spinal cord, one might expect decreased pain responses in both sensory and affective pain networks. However, in our recent work (Wager et al., 2004), we found evidence that S2 activity actually increased with administration of a placebo. Real opiate analgesics also increase activity in S2, however, suggesting that the relationship between pain and activation may be more complex. Future studies are needed to test specifically for drug and placebo effects on the sensory network and the spinal cord.

Placebo Effects on Central Pain

If placebos reduce pain but not sensory pain inputs, why do opioid antagonists block placebo effects? An alternative explanation is that both opioids and placebos directly affect the brain processes that give rise to pain appraisal and experience. The PAG sends output not only to the spinal cord, but also directly to the affective pain network. Activity in this network increases with subjective pain, but also in response to a range of personally significant aversive events, such as losing in a game, experiencing negative emotions, or seeing someone else in pain. These situations involve negative appraisals that have personal significance (Lazarus, 1991). That subjective pain is much more than sensory experience is demonstrated by a number of phenomena—including wound-site-specific battlefield analgesia, phantom pain, neuropathic pain, stroke, and pain after removal of sensory nerves that carry pain-related signals (Melzack & Wall, 1965). Thus, it is likely that subjective pain is produced or heavily influenced by appraisals of valence (how bad does it feel?) represented at least partly within this network, and that placebo treatments most strongly influence the appraisal process (Fig. 1A). In our experiments, we found that placebo treatment decreased pain-evoked activity in the affective pain network, consistent with this hypothesis (Wager et al., 2004).

PLACEBO EFFECTS ON PAIN REPORTING ONLY

A final alternative explanation for placebo effects is that espoused by skeptics: that placebo treatment affects only demand characteristics (Hrobjartsson & Gotzsche, 2004; Fig. 1A). Finding changes in brain activity in pain-processing regions and during pain experience argues against this view (Lieberman et al., 2004; Petrovic et al., 2002; Wager et al., 2004). More studies with quantitative, non-self-report-based outcome measures, such as measures of brain activity and peripheral physiology, are needed to replicate and extend these findings.

PROCESSES ENGAGED BY PLACEBO TREATMENT

The evidence reviewed above suggests that placebo treatment engages active brain processes that dampen pain. The treatment may be nothing more than a verbal suggestion; so how do mere suggestions come to alter how the brain processes pain? Here I suggest that placebo treatment provides a context that shapes appraisal both of cues that signal upcoming pain and of pain itself, and thereby creates positive expectancies in the face of imminent pain (Kirsch, 1985).

According to this view, expectancies are moment-by-moment predictions of the nature and emotional value of upcoming events. They are created when cues that signal imminent pain are perceived. Expectancies are based on situational context, which includes prior experience with pain and drugs and beliefs about medical treatment (Kirsch, 1985). The information carried in expectancies may be integrated with incoming sensory input to shape subjective pain and emotion. For this integration to occur, expectancies must be maintained in the brain until the predicted sensory events occur.

Theories of context-based regulation of attention and memory provide some idea of how this process may work (Miller & Cohen, 2001). Research on attention has shown that expectancies about the nature and relevance of stimuli can shape perceptual processing, even enhancing neural representations of expected features before they appear. Placebo-induced expectancies may shape the perception and appraisal of somatosensory stimuli much in the same way that expectancy shapes visual, auditory, and tactile perceptions, in this case by reducing the feeling of pain. One factor that differentiates expectancies about pain from other sensory expectancies, however, is their affective component. Thus, placebo treatment may influence cognitive expectancies about whether stimuli are worthy of attention or affective expectancies about personal harm.

In neurobiological terms, pain perception begins with attitudes and previous experiences (including placebo-induced beliefs) stored in long-term-memory systems distributed across the cortex and hippocampus. When presented with cues signaling upcoming pain, relevant memories are recalled and used to generate expectancies about how bad the pain will be. This appraisal is likely to involve the orbitofrontal cortex (OFC), which is critical for representing and updating the emotional value of cues. Expectancies are likely to be maintained during anticipation of pain in the prefrontal cortex, particularly the dorsolateral and ventrolateral prefrontal cortices (DLPFC and VLPFC, respectively)—the same areas important for maintaining context information in working memory and biasing sensory processing (Miller & Cohen, 2001).

Recent brain-imaging studies provide preliminary evidence supporting this model. In our studies and in other pain- and emotion-regulation studies (e.g., Lorenz, Minoshima, & Casey, 2003), DLPFC activation is associated with effective pain regulation. We found that, during the anticipation of pain, ACC,

OFC, and DLPFC activity was boosted by a placebo treatment. Participants with larger increases showed greater placebo-induced reductions in pain (Wager et al., 2004). Petrovic et al. (2002) also found that placebo treatment increased activation in the ACC and OFC, and Lieberman et al. (2004) found that activation of the right VLPFC and OFC correlated with pain relief in irritable bowel syndrome after placebo treatment.[1]

If expectations influence pain perception, then what is the difference between placebo-induced expectancy and simply expecting a less intense stimulus? Both reduce subjective pain. No studies have directly compared these two types of manipulations directly, but expectations about stimulus intensity also induce changes in pain processing in the insula that depend on the hippocampus (Ploghaus et al., 2001). In psychological terms, the difference is that placebo expectancies involve more pervasive changes in the context surrounding pain. In brain activity, the difference is that placebo expectancy increases prefrontal activation, whereas the evidence to date does not suggest that expecting less pain has the same effect.

An additional kind of expectancy effect comes from expectancy theory in motivation science (Vroom, 1964), which emphasizes motivational components of expectancy, including the expected costs and benefits of strategic effort. Perhaps placebo treatment increases the desire for pain relief or the perception of control over pain, which in turn encourages use of explicit pain-regulation strategies such as directed attention. Desire for pain relief does not appear to predict the magnitude of placebo effects (Vase, Robinson, Verne, & Price, 2003). However, feelings of efficacy in controlling pain do appear to increase pain tolerance. Whether changes in self-efficacy mediate placebo effects is not known, so this possibility remains open. What are most needed for understanding the relationship between placebo treatment and motivation are direct assessments of attention allocation, motivation, self-efficacy, and strategy use during placebo and no-placebo conditions.

By suggesting that expectancy and appraisal are processes that may underlie many kinds of placebo effects, I am not suggesting that placebo treatments produce the same outcomes across diseases. Placebo effects in depression (but not pain or Parkinson's disease) have been found in the subgenual cingulate, an area in which metabolic changes have been linked to depressive symptoms. Placebo treatment in Parkinson's disease produces decreased firing of subthalamic neurons and decreased muscle rigidity in human patients (Benedetti et al., 2004). Both the neural and behavioral signs affected by the placebo are specific markers of disease severity in Parkinson's and are not likely to be outcomes shared by other kinds of placebo effects. In addition, motivation and appraisal are probably not the only mechanisms for placebo effects; conditioning procedures may produce significant and meaningful effects through a variety of other mechanisms.

BENEFITS OF STUDYING PLACEBOS, AND UNANSWERED QUESTIONS

There are many reasons for studying placebo effects, including the possibilities of interleaving effective placebo treatments with real drugs and reducing the costs of clinical trials by controlling expectations more precisely. But perhaps the most compelling argument is that placebo research can help us understand the mechanisms by which therapeutic agents have their effects. Whether a drug works to relieve depression, for example, is the easy question. The more difficult question is why it works. What part of the drug's effect is due to simple pharmacological action, and what part is due to expectancy and drug-expectancy interactions? Understanding how internal regulatory processes interact with external treatments is a key issue in both basic and applied research, and it is central to understanding how the mind regulates the body's physiological state.

However, realizing this goal will require concerted work on a number of fronts. First, the question of what neuro-cognitive processes placebo treatments affect must be asked separately in each domain—depression, Parkinson's, hypertension, anxiety disorders, cognitive performance, and social interactions, to name some. Are there common effects of expectancy that act across domains, or is the term "placebo response" just a rubric for a collection of separate processes? Is the appraisal and regulation of pain a similar internal process to the appraisal and regulation of negative emotion? Second, what are the psychological mediators for placebo effects—changes in attention, self-efficacy, anxiety, attitudes? And what are the neural correlates of these? Can placebo effects be explained in terms of some more well-defined mechanism?

At a broader level, future research must lay the foundations for bridges between psychological and neurobiological descriptions of placebo and other regulatory processes. The stronger these bridges, the more we will have objective biological measures for processes such as expectation, emotion, and pain that were previously knowable only through self-report.

Recommended Reading

Harrington, A., ed. (1999). *The placebo effect*. Cambridge, MA: Harvard University Press.

Kirsch, I. (1985). Response expectancy as a determinant of experience and behavior. *American Psychologist*, *40*, 1189–1202.

Acknowledgments—Thanks to Ed Smith, Dagfinn Matre, Kevin Ochsner, Ralph Wager, Ethan Kross, and Hedy Kober for helpful comments, and to Bob Rose and the Mind Brain Body and Health initiative for their generous support.

[1]Importantly, brain increases in a placebo condition compared to a matched control are likely to reflect differences in the demand on retrieval, evaluation, and maintenance of context information. Thus, appraisals and expectancies are generated with or without a placebo, but the placebo treatment may increase demand on these processes, thus increasing activation.

REFERENCES

Amanzio, M., & Benedetti, F. (1999). Neuropharmacological dissection of placebo analgesia: Expectation-activated opioid systems versus conditioning-activated specific subsystems. *Journal of Neuroscience*, *19*, 484–494.

Antoninus, Marcus Aurelius (2001). *Meditations of Marcus Aurelius Antoninus* (G. Long, Trans.). Retrieved August 10, 2005 from http://www.netlibrary.com/Reader/

Benedetti, F., Colloca, L., Torre, E., Lanotte, M., Melcarne, A., Pesare, M., Bergamasco, B., & Lopiano, L. (2004). Placebo-responsive Parkinson patients show decreased activity in single neurons of subthalamic nucleus. *Nature Neuroscience*, *7*, 587–588.

Craig, A.D., Chen, K., Bandy, D., & Reiman, E.M. (2000). Thermosensory activation of insular cortex. *Nature Neuroscience*, *3*, 184–190.

Hrobjartsson, A., & Gotzsche, P.C. (2004). Is the placebo powerless? Update of a systematic review with 52 new randomized trials comparing placebo with no treatment. *Journal of Internal Medicine*, *256*, 91–100.

Kirsch, I. (1985). Response expectancy as a determinant of experience and behavior. *American Psychologist*, *40*, 1189–1202.

Lazarus, R.S. (1991). Cognition and motivation in emotion. *American Psychologist*, *46*, 352–367.

Lieberman, M.D., Jarcho, J.M., Berman, S., Naliboff, B.D., Suyenobu, B.Y., Mandelkern, M., & Mayer, E.A. (2004). The neural correlates of placebo effects: A disruption account. *Neuroimage*, *22*, 447–455.

Lorenz, J., Minoshima, S., & Casey, K.L. (2003). Keeping pain out of mind: The role of the dorsolateral prefrontal cortex in pain modulation. *Brain*, *126*, 1079–1091.

Melzack, R., & Wall, P.D. (1965). Pain mechanisms: a new theory. *Science*, *150*, 971–979.

Miller, E.K., & Cohen, J.D. (2001). An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience*, *24*, 167–202.

Petrovic, P., Kalso, E., Petersson, K.M., & Ingvar, M. (2002). Placebo and opioid analgesia—Imaging a shared neuronal network. *Science*, *295*, 1737–1740.

Ploghaus, A., Narain, C., Beckmann, C.F., Clare, S., Bantick, S., & Wise, R., et al. (2001). Exacerbation of pain by anxiety is associated with activity in a hippocampal network. *Journal of Neuroscience*, *21*, 9896–9903.

Vase, L., Robinson, M.E., Verne, G.N., & Price, D.D. (2003). The contributions of suggestion, desire, and expectation to placebo effects in irritable bowel syndrome patients: An empirical investigation. *Pain*, *105*, 17–25.

Vroom, V.H. (1964). *Work and motivation*. New York: Wiley.

Wager, T.D., Rilling, J.K., Smith, E.E., Sokolik, A., Casey, K.L., Davidson, R.J., Kosslyn, S.M., Rose, R.M., & Cohen, J.D. (2004). Placebo-induced changes in fMRI in the anticipation and experience of pain. *Science*, *303*, 1162–1167.