



First published online as a Review
in Advance on June 5, 2007

A Comprehensive Review of the Placebo Effect: Recent Advances and Current Thought

Donald D. Price,¹ Damien G. Finniss,²
and Fabrizio Benedetti³

¹Division of Neuroscience, Oral and Maxillofacial Surgery, University of Florida, Gainesville, Florida 32610-0416, ²University of Sydney Pain Management and Research Center, Royal North Shore Hospital, Sydney, Australia, ³Department of Neuroscience, University of Turin Medical School, and National Institute of Neuroscience, Turin 10125 Italy; email: dprice@dental.ufl.edu, placebo@bigpond.net.au, fabrizio.benedetti@unito.it

Annu. Rev. Psychol. 2008. 59:2.1–2.26

The *Annual Review of Psychology* is online at
<http://psych.annualreviews.org>

This article's doi:
10.1146/annurev.psych.59.113006.095941

Copyright © 2008 by Annual Reviews.
All rights reserved

0066-4308/08/0203-0001\$20.00

Key Words

natural history, emotions, analgesia, biological models

Abstract

Our understanding and conceptualization of the placebo effect has shifted in emphasis from a focus on the inert content of a physical placebo agent to the overall simulation of a therapeutic intervention. Research has identified many types of placebo responses driven by different mechanisms depending on the particular context wherein the placebo is given. Some placebo responses, such as analgesia, are initiated and maintained by expectations of symptom change and changes in motivation/emotions. Placebo factors have neurobiological underpinnings and actual effects on the brain and body. They are not just response biases. Other placebo responses result from less conscious processes, such as classical conditioning in the case of immune, hormonal, and respiratory functions. The demonstration of the involvement of placebo mechanisms in clinical trials and routine clinical practice has highlighted interesting considerations for clinical trial design and opened up opportunities for ethical enhancement of these mechanisms in clinical practice.

Contents

INTRODUCTION.....	2.2	Placebo-Related Increases and Decreases in Brain Activity.....	2.12
HISTORICAL AND CONCEPTUAL BACKGROUND.....	2.2	Future Directions in Relating Brain Activity to Psychological Variables Associated with Placebo.....	2.13
ENVIRONMENTAL AND PSYCHOSOCIAL DETERMINANTS OF THE PLACEBO EFFECT.....	2.4	EVIDENCE FOR OPIOID AND NONOPIOID MECHANISMS IN PLACEBO ANALGESIA.....	2.14
Contextual Factors that Influence Placebo Effects.....	2.4	Opioid Mechanisms.....	2.14
Factors that Influence the Magnitude of Placebo Analgesia.....	2.5	Nonopioid Agents and Mechanisms in Placebo Analgesia.....	2.15
PLACEBO EFFECTS CAUSED BY COGNITIVE AND EMOTIONAL CHANGES.....	2.6	MECHANISMS OTHER THAN EXPECTATION AND CONDITIONS OTHER THAN PAIN.....	2.15
Expectancy.....	2.7	Evidence for Classical Conditioning Mechanisms.....	2.15
Expectancy and Memory.....	2.7	Placebo Responses in the Immune and Endocrine System.....	2.16
Are Placebo Effects Related to a Desire-Expectation Emotion Model?.....	2.7	Other Biological Models of Placebo.....	2.17
Somatic Focus Moderates Effects of Goals and Expectancy.....	2.11	IMPLICATIONS FOR CLINICAL TRIALS AND CLINICAL PRACTICE.....	2.18
NEUROBIOLOGY OF THE DESIRE-EXPECTATION MODEL.....	2.12	CONCLUSIONS.....	2.20
The Functional Role of			

Placebo effect: the average placebo response in a group of individuals

Analgesia: a reduction in the magnitude of pain on the sensory or affective dimension or on both dimensions, depending on what is measured

INTRODUCTION

The placebo effect has been a topic of interest in scientific and clinical communities for many years, and our knowledge of the mechanisms of the placebo effect has advanced considerably within the past decade. A significant proportion of the research has occurred in the fields of pain and analgesia, and the placebo analgesic response appears to be the best-understood model of placebo mechanisms. Placebo mechanisms in other clinical conditions and populations have only recently begun to be identified. This article reviews and synthesizes current knowledge on placebo

mechanisms and identifies potential implications for clinical practice. Although emphasis is placed on placebo analgesia, the commonality of factors and mechanisms of other placebo phenomena are also discussed along with possible differences.

HISTORICAL AND CONCEPTUAL BACKGROUND

The placebo effect has been a phenomenon of significant interest and debate in medicine. Although the use of the word “placebo” dates back several centuries in the medical literature, the placebo effect has only recently

gained the attention and interest of many researchers and clinicians. The author of what is believed to be the first placebo controlled trial (conducted in 1799) stated, “[A]n important lesson in physic is here to be learnt, the wonderful and powerful influence of the passions of the mind upon the state and disorder of the body” (de Craen et al. 1999). Some 200 years later, advances in research design and technology have allowed scientists to identify some of the neurobiological and psychological mechanisms of the placebo effect and to further explore the complexities of the mind-brain-body interaction.

Placebos have typically been identified as inert agents or procedures aimed at pleasing the patient rather than exerting a specific effect. However, this conceptualization presents us with a paradox: If a placebo is inert, it can’t cause an effect, as something that is inert has no inherent properties that allow it to cause an effect. This paradox is highlighted in the many attempts to define placebos and the placebo effect, resulting in a degree of confusion and debate. More recently, our conceptualization of placebos and the placebo effect has changed, clarifying some of the issues relating to definitions and the paradox of how an inert substance or procedure can be believed to cause an effect.

Researchers who study the placebo effect are examining the psychosocial context surrounding the patient and the effect that this context has on the patient’s experience, brain, and body (Colloca & Benedetti 2005). The focus has shifted from the “inert” content of the placebo agent (e.g., starch capsules) to the concept of a simulation of an active therapy within a psychosocial context. This capacity of simulation empowers the influence of placebo. The placebo response may be driven by many different environmental factors involved in the context of a patient, factors that influence patients’ expectations, desires, and emotions. To the extent that it differs from

the untreated natural history condition, the response seen in a given individual following administration of a placebo is the placebo response. The responses of a population to placebo administration, such as in a clinical trial, represent the group effect or placebo effect.

Historically, one of the problems of analyzing placebo effects has been the misinterpretation of other phenomena as placebo effects. This results in confusion and misunderstanding about placebo phenomena and mechanisms. Therefore, it is important to note that the true placebo effect (a real psychobiological response) is seen in carefully designed experiments and in clinical populations where the responses to administration of a placebo are compared with a natural history group or untreated baseline condition. This is particularly important in studies of pain, where many painful conditions exhibit varied temporal patterns of intensity, and a reduction in pain following administration of a placebo may be either a placebo effect or something that would have happened regardless of the intervention. Another example is regression to the mean, a statistical phenomenon that assumes that in a given population, extremes in reported pain intensity will change over time toward the average of that population. In the case of pain, this phenomenon asserts that individuals tend to experience a higher level of pain intensity on initial assessment and lower pain intensity at subsequent assessments. If in this case a group of patients were given placebos, one could not be sure that the changes in reported pain scores were a placebo effect or a statistical phenomenon. Both these cases highlight the possible misinterpretation of other phenomena as placebo effects and the importance of a natural history group or baseline condition when assessing true placebo effects. In the case of clinical trials, it is particularly important to be able to differentiate the effect of a placebo from the changes due to the natural history of a particular condition.

Placebo response:

the change in a symptom or condition of an individual that occurs as a result of placebo (natural history minus placebo condition)

Expectation (in relation to placebo literature):

expected magnitude of symptom or condition or perceived likelihood of an outcome

Desire:

the experience of wanting to avoid something (avoidance goal) or wanting to obtain a pleasant or happy outcome (approach goal)

Natural history:

the magnitude of a symptom or condition that occurs over a specified amount of time in the absence of treatment

Regression to the mean:

individuals with extreme scores on any measure at one point probably will have less extreme scores, for purely statistical reasons, the next time they are tested

Open-hidden paradigm: a paradigm wherein a patient either fully views a treatment or receives it in a “hidden” manner, without cues

ENVIRONMENTAL AND PSYCHOSOCIAL DETERMINANTS OF THE PLACEBO EFFECT

Contextual Factors that Influence Placebo Effects

Environmental and psychosocial determinants of placebo responses/effects include conditioning, verbal suggestions, and behaviors manifested by healthcare providers. These factors are likely to vary greatly across clinical and research contexts and consequently generate considerable variability in the placebo effect itself. This variability is evident among placebo effect sizes for studies of pain treatments. Three meta-analyses have shown that although placebo effect sizes are small on average in studies that use placebo treatments only as a control condition (Cohen's d or pooled standardized mean difference = 0.15–0.27), there is considerable variability in placebo effect sizes (Hrobjartsson & Goetsche 2001, 2004; Vase et al. 2002). Thus, in the meta-analysis by Vase et al. (2002), the mean Cohen's d was only 0.15, but placebo effect sizes ranged from -0.95 to $+0.57$. Placebo analgesic effect sizes, although controversial, are larger in studies that use placebo treatments to analyze the mechanism of placebo analgesia (0.51 and 0.95 according to Hrobjartsson & Goetsche 2006 and Vase et al. 2002, respectively), but again considerable variability exists across studies (Vase et al. 2002). As a working hypothesis, it is reasonable to propose that factors that promote placebo effects are more likely to be limited in clinical trials and to be enhanced in studies that are about placebo mechanisms.

Meta-analyses are limited in providing understanding of the factors that contribute to placebo analgesia because they do not systematically vary factors that affect its magnitude. Mechanism studies have the potential to provide greater insight into sources of variability of placebo effects because they can provide experimental control of some of the relevant

factors. Most importantly, such studies can even be designed using human pain patients in the contexts of actual clinical treatments. Thus, the contribution of placebo analgesia to the effectiveness of analgesic drugs has been tested in clinical postoperative settings using hidden and open injections of traditional painkillers such as buprenorphine (Amanzio et al. 2001, Benedetti et al. 2003, Levine & Gordon 1984). The open-hidden paradigm represents a novel way of studying placebo mechanisms and the specific effects of a treatment, such as a drug. In this paradigm, the patient can receive a treatment in the standard clinical “open” manner, where the treatment is given by the clinician and in full view of the patient. Alternatively, the treatment can be received in a “hidden” manner, by means of a computer-programmed drug infusion pump, where the clinician is not present and the patient is unaware that the treatment is being administered (Levine & Gordon 1984). Several analgesia studies have used the open-hidden paradigm, demonstrating that open administration of a drug is significantly more effective than hidden administration (Amanzio et al. 2001, Benedetti et al. 2003, Colloca et al. 2004, Levine & Gordon 1984). In one study wherein medication was administered openly by a doctor who gave verbal suggestions for pain relief, pain reduction was greater than when the medication was administered by a hidden machine (Amanzio et al. 2001), as shown in **Figure 1**. In another open-hidden paradigm study, patients needed less medication to reach postoperative analgesia in comparison to hidden administration (Amanzio et al. 2001, Colloca et al. 2004). The difference in medication needed for analgesia between open and hidden injections directly reflects the placebo analgesic effect.

An important goal of placebo analgesia research is to identify factors that contribute to perceived efficacy of the therapeutic intervention. Factors associated with open injections and with suggestions that the agent is an effective analgesic may be especially useful in

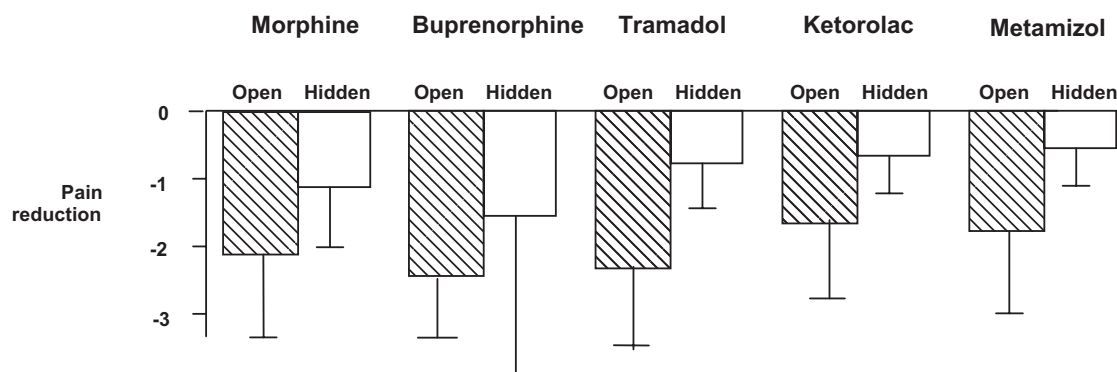


Figure 1

Comparison of analgesic effects of opioid (morphine, tramadol, buprenorphine) and nonopioid (ketorolac, metamizol) medications across hidden versus open intravenous injections in patients with postoperative pain. (Data are from Amanzio et al. 2001.)

clarifying how these factors either mediate or moderate placebo analgesia effects. A number of studies have now analyzed these factors.

Factors that Influence the Magnitude of Placebo Analgesia

The magnitude of placebo analgesia may range from no responses to large responses. It has long been known that there are placebo responders and nonresponders, although why this occurs is less clear. In placebo studies, differences between group averages are usually recorded rather than observations of individual responses to a placebo intervention. This point is very important because an identical mean change between a placebo group and a no-treatment group might be seen if all individuals in the placebo group exhibit a moderate response or, otherwise, a relatively small subset of individuals exhibit a large magnitude response and others show no response at all.

Beecher's widely cited study of clinical analgesic trials (Beecher 1955), from which he concluded that an average of 30% of patients respond to placebo treatments for pain, means little, if anything, because none of the studies he mentioned included no-treatment groups. However, more recent studies have tried to answer the same question. For example, Levine et al. (1979) found that 39% of

patients had an analgesic response to placebo treatment, and in a study of normal volunteers using ischemic arm pain, Benedetti (1996) found that 26.9% of the subjects responded to a placebo analgesic, as compared with a no-treatment control group. Another study involving cutaneous heating of the left hand found that 56% of subjects responded to the placebo treatment, as compared with the no-treatment controls (Petrovic et al. 2002).

Assessing the magnitude of the placebo analgesic effect is not an easy task, as the experimental conditions change across different studies. By measuring the average change in pain experienced by all the individuals who receive placebo and comparing this to the average change in the no-treatment group, several studies have found that the magnitude of the placebo analgesic effect is about 2 out of 10 units on a visual analogue scale (VAS) or numerical rating scale (NRS) (Amanzio et al. 2001; Benedetti et al. 1995, 1998; Gracely et al. 1983; Levine & Gordon 1984; Price 2001).

In studies where the known placebo responders in a group are separated for analysis, the average magnitude of analgesia found has been, not surprisingly, significantly greater. For example, Benedetti (1996), looking only at responders, found an average placebo analgesia magnitude of 5 units on the 10-unit

NRS. This is similar to results from a postoperative dental study that found a 3.3 cm (out of 10) lower mean post-treatment VAS score for placebo responders as compared with nonresponders (Levine et al. 1978).

Today it appears clear that the experimental manipulation used to induce placebo analgesia plays a fundamental role in the magnitude of the response. Among different manipulations that have been performed, both the type of verbal suggestions and the individual's previous experience have been found to be important.

Verbal suggestions that induce certain expectations of analgesia induce larger placebo responses than those inducing uncertain expectations. This point is illustrated by a study carried out in the clinical setting to investigate the differences between the double-blind and the deceptive paradigm (Pollo et al. 2001). Postoperative patients were treated with buprenorphine, on request, for three consecutive days, and with a basal infusion of saline solution. However, the symbolic meaning of this saline basal infusion varied in three different groups of patients. The first group was told nothing (natural history or no-treatment group), the second was told that the infusion could be either a potent analgesic or a placebo (classic double-blind administration), and the third group was told that the infusion was a potent painkiller (deceptive administration). The placebo effect of the saline basal infusion was measured by recording the doses of buprenorphine requested over the three-day treatment. It is important to stress once again that the double-blind group received uncertain verbal instructions ("It can be either a placebo or a painkiller. Thus we are not certain that the pain will subside"), whereas the deceptive administration group received certain instructions ("It is a painkiller. Thus pain will subside soon"). Compared with the natural history group, a 20.8% decrease in buprenorphine intake was found with the double-blind administration and an even greater 33.8% decrease was found in the group given deceptive administration

of the saline basal infusion. It is important to point out that the time-course of pain was the same in the three groups over the three-day period of treatment. Thus the same analgesic effect was obtained with different doses of buprenorphine. The above studies teach us that subtle differences in the verbal context of the patient may have a significant impact on the magnitude of the response.

Previous experience can also influence the magnitude of placebo analgesia. In one study, the intensity of painful stimulation was reduced surreptitiously after placebo administration to make the subjects believe that an analgesic treatment was effective (Colloca & Benedetti 2006). This procedure induced strong placebo responses after minutes, and these responses, albeit reduced, lasted from four to seven days. In a second group of subjects of the same study, the same procedure was repeated four to seven days after a totally ineffective analgesic treatment. The placebo responses were remarkably reduced compared with the first group. Thus, small and large placebo responses were obtained, depending on several factors, such as the previous positive or negative experience of an analgesic treatment and the time lag between the treatment and the placebo responses. These findings indicate that placebo analgesia is finely tuned by prior experience and these effects may last, albeit reduced, several days. These results emphasize that the placebo effect may represent a learning phenomenon involving several factors and may explain the large variability of the magnitude of placebo responses among studies.

PLACEBO EFFECTS CAUSED BY COGNITIVE AND EMOTIONAL CHANGES

Patients are likely to perceive environmental factors in different ways, and these differences are likely to contribute to the magnitude, duration, and qualities of placebo responses. Cognitive and emotional factors that have been proposed to contribute to placebo

effects include expected symptom intensity, desire for symptom change, changes in emotion, and distortions in memory.

Expectancy

Expectancy is the experienced likelihood of an outcome or an expected effect. For example, within the context of pain studies it can be measured by asking people about the level of pain they expect to experience. Montgomery and Kirsch conducted one of the first studies in which expected pain levels were manipulated and directly measured (Montgomery & Kirsch 1997). They used a design in which subjects were given cutaneous pain via iontophoretic stimuli. Once baseline stimuli were applied, subjects were secretly given stimuli with reduced intensities in the presence of an inert cream (i.e., conditioning trials). Then the stimulus strength was restored to its original baseline level and several stimuli were then used in placebo trials to test the effect of conditioning. Subjects rated expected pain levels just before placebo test trials and were divided into two groups. The first did not know about the stimulus manipulation, and prior conditioning markedly diminished their pain ratings during placebo trials. However, regression analyses showed that this effect was mediated by expected pain levels. Expectancy accounted for 49% of the variance in postmanipulation pain ratings. The second group was informed about the experimental design and learned that the cream was inert. There was no placebo analgesic effect in this second group. The regression analysis and difference in results across groups show that conscious expectation is necessary for placebo analgesia.

Price and colleagues further tested the extent to which expectations of pain relief can be graded and related to specific areas of the body (Price et al. 1999). Using a similar paradigm, they applied placebo creams and graded levels of heat stimulation on three adjacent areas of the subjects' forearm to give subjects expectations that cream A was a strong analgesic, cream B a weak analgesic, and cream C a con-

trol agent. Immediately after these conditioning trials, subjects rated their expected pain levels for the placebo test trials wherein the stimulus intensity was the same for all three areas. The conditioning trials led to graded levels of expected pain ($C > B > A$) for the three creams as well as graded magnitudes of actual pain ($C > B > A$) when tested during placebo test trials. Thus, magnitudes of placebo analgesia could be graded across three adjacent skin areas, demonstrating a high degree of somatotopic specificity for placebo analgesia. Expected pain levels accounted for 25% to 36% of the variance in postmanipulation pain ratings.

Expectancy and Memory

The memory of previous experiences is also likely to influence the experience of pain. Price et al. (1999) assessed the placebo effect based on both concurrent ratings of pain during the placebo condition and on retrospective ratings of pain that were obtained approximately two minutes after the stimuli were applied. The magnitude of placebo analgesic effects based on retrospective ratings was three to four times greater than the magnitude based on concurrent ratings. The main reason for this difference was that subjects remembered their baseline pain intensity as being much larger than it actually was. Similar to placebo analgesia effects assessed concurrently, the remembered placebo effects were strongly correlated with expected pain intensities ($R = 0.5-0.6$). Thus, placebo analgesia effects may be enhanced by distorted memories of pretreatment levels of pain. Furthermore, as remembered pain and expected pain are closely related, these psychological factors seem to interact. These findings were replicated by De Pascalis et al. (2002).

Are Placebo Effects Related to a Desire-Expectation Emotion Model?

Although expectancy seems to be an important psychological mediator of placebo effects,

IBS: irritable bowel syndrome

it is unlikely to operate alone. Desire, which is the experiential dimension of wanting something to happen or wanting to avoid something happening, is also likely to be involved in placebo phenomena. Desire and expectation also interact and underlie common human emotions, such as sadness, anxiety, and relief (Price & Barrell 2000; Price et al. 1985, 2001). In the context of analgesic studies, it is quite plausible that patients and subjects have some degree of desire to avoid, terminate, or reduce evoked or ongoing pain. On the other hand, some placebo effects involve appetitive or approach goals, such as positive moods or increased arousal. In the following discussion, we provide an account of how decreased desire may contribute to placebo analgesia and increased desire may contribute to placebo effects during appetitive goals. We then propose that the roles of goals, expectation, desire, and emotional feelings all can be accommodated within the same explanatory model.

To further understand how desire and expectation influence placebo analgesia, Verne et al. (2003) and Vase et al. (2003) conducted two similar studies. Patients with irritable bowel syndrome (IBS) were exposed to rectal distention by means of a balloon barostat, a type of visceral stimulation that simulates their clinical pain, and tested under the conditions of untreated natural history (baseline), rectal placebo, and rectal lidocaine. Pain was rated immediately after each stimulus within each condition. The first study was conducted as a double-blind crossover clinical trial in which patients were given an informed consent form that stated they “may receive an active pain reducing medication or an inert placebo agent” (Verne et al. 2003). In this study, there was a significant pain-relieving effect of rectal lidocaine as compared with rectal placebo ($p < 0.001$), and there was a significant pain-relieving effect of rectal placebo (pain in placebo < natural history). In a second similarly designed study, patients were told, “The agent you have just been given is known to significantly reduce pain in some patients” at the onset of each treatment con-

dition (rectal placebo, rectal lidocaine) (Vase et al. 2003). A much larger placebo analgesic effect (Cohen's $d = 2.0$) was found in the second study, and it did not significantly differ from that of rectal lidocaine. These two studies show that adding an overt suggestion for pain relief can increase placebo analgesia to a magnitude that matches that of an active agent. Comparison of the placebo effect sizes of the two studies is shown in **Figure 2**.

In both studies, patients were asked to rate their expected pain level and desire for pain relief right after the agent was administered. Data from the two studies were pooled in order to determine whether changes in desire/expectancy ratings predicted changes in pain ratings across natural history and placebo conditions (i.e., placebo responses) (Vase et al. 2004). The placebo effect (natural history pain intensity–rectal placebo pain intensity), change in expected pain (natural history pain expectation–rectal placebo pain expectation), and change in desire for pain relief (natural history desire–rectal placebo desire) were all calculated for each of 23 subjects. The changes in expectation and desire were entered into a hierarchical regression equation along with their interaction, and the placebo response served as the predicted variable (**Table 1**). First, desire change scores and expected pain change scores were entered into the model. This component accounted for 16% of the variance in placebo effects but this factor alone was not statistically significant (**Table 1**). Second, after statistically controlling for this component, a second component, change in desire X change in expectation, was entered into the regression equation, and it accounted for an additional 22% of the variance in the placebo effect. This second component was statistically significant (**Table 1**). The entire model accounted for 38% of the variance in the placebo effect (**Table 1**). This analysis suggests that both desire for pain relief and expected pain relief contribute to placebo analgesia, and a main factor is a multiplicative interaction between desire for pain reduction and expected pain intensity.

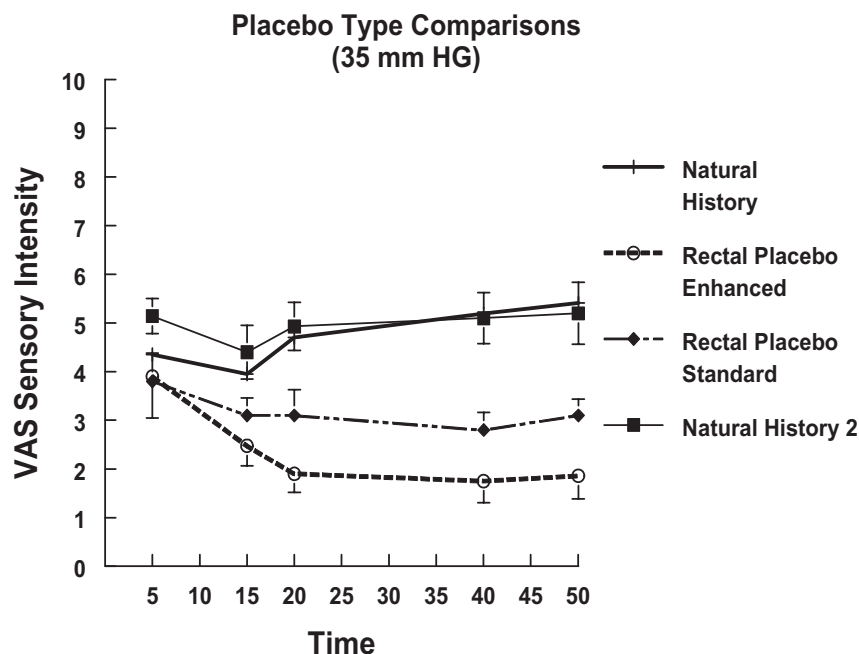


Figure 2

Comparisons of natural history, rectal placebo, and rectal lidocaine scores on a visual analogue scale (VAS) during a 50-minute session within a clinical trial design, where no suggestions for pain relief are given (*left*) and within a placebo design with verbal suggestions for pain relief (*right*). The X-axis refers to time in minutes. (Data are from Vase et al. 2003 and Verne et al. 2003.)

Table 1 The contribution of changes in expectancy and desire to rectal placebo analgesia

Model	R ² change	P
Δ Expectancy + Δ desire	0.16	0.17
Δ Expectancy X Δ desire	0.22	0.02
Total model	0.38	0.02

This interaction is consistent with Price and Barrell's desire-expectation model of emotions, which shows that ratings of negative and positive emotional feelings are predicted by multiplicative interactions between ratings of desire and expectation (Price et al. 1984, 1985, 2001; **Figure 3**). Desire to reduce pain would be considered an avoidance goal, according to the desire-expectation model, and these results suggest that analgesia would be related to a reduction in negative emotions, as illustrated in the top panel of **Figure 3**. This prediction was supported by significant reductions in anxiety ratings in the two experiments (Vase et al. 2003, Verne et al. 2003). It is further supported by a subsequent study showing that ratings of desire for pain reduc-

tion, expected pain, and anxiety all decreased over time as the placebo effect increased over time (Vase et al. 2005). All of these studies support the desire-expectation model.

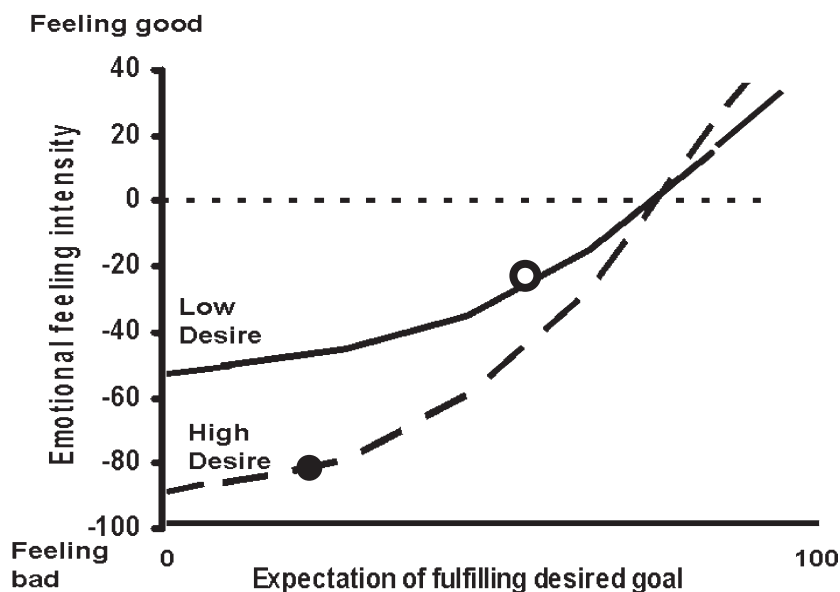
Interestingly, the desire-expectation model predicts that placebo responses in approach or appetitive goals would relate to increased levels of desire in the placebo condition, unlike avoidance goals (compare top and lower panels of **Figure 3**). The reason that this is so is that increased desire for a pleasant outcome is associated with increased positive emotional feelings throughout most of the range of expectation (**Figure 3**, lower panel). Support for this prediction was obtained in an experiment wherein participants were given placebo pills that were said to have a sedating effect (Jensen & Karoly 1991). The desire to feel such effects were manipulated by telling participants that individuals who react to the pills have either positive or more negative personality characteristics. The authors found greater placebo responses in subjects who were told that sedative effects were related to positive traits, and they had larger ratings of desire to experience sedation

than did the other participants who associated sedation with negative consequences.

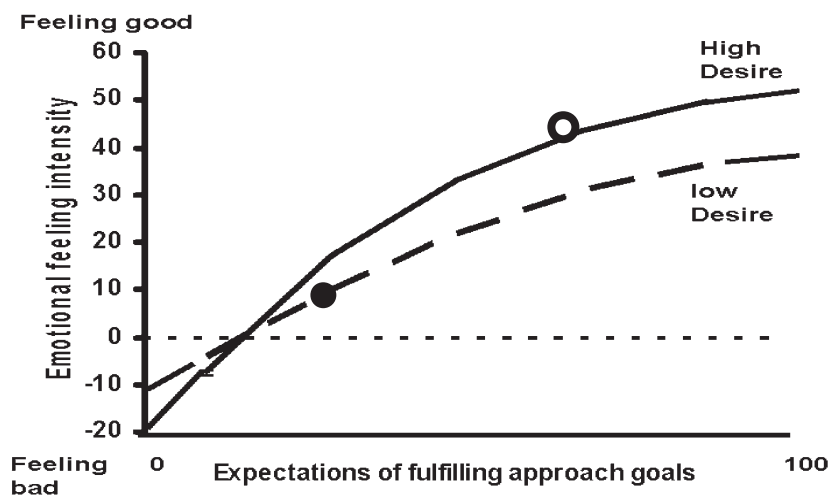
Based on several interrelated experiments, Geers et al. (2005) argue that the placebo effect is most likely to occur when individuals have a goal that can be fulfilled by confir-

mation of the placebo expectation, consistent with the model just described. Their results demonstrated a role for desire for an effect across a variety of symptom domains, including those related to positive (approach or appetitive) and negative (avoidance) goals. For

AVOIDANCE GOAL



APPROACH GOAL



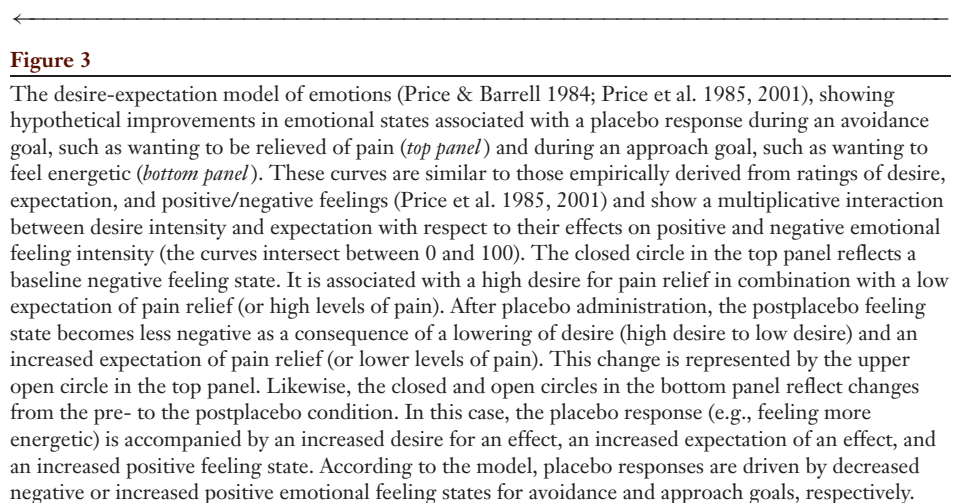
example, participants listened to a piece of music in one of their experiments. One group was given a suggestion that the music would improve mood, and another was not given any suggestion. Two additional groups also were either given this suggestion or no suggestion; in addition, they were either primed with a goal of independence or cooperation. Only the latter was compatible with the goal of improving mood. Placebo responses were calculated as differences in mood ratings across baseline and postplacebo conditions. The placebo effect was largest in the subjects given placebo suggestion coupled with the cooperation priming that was compatible with mood improvement. The remaining groups had low to negligible placebo effects. Taken together, these results show the importance of motivation (desire) across different types of placebo responses involving approach and avoidance goals.

Somatic Focus Moderates Effects of Goals and Expectancy

In addition to the roles of goals, desires, and expectations in placebo responding, there is evidence that the degree of somatic focus has a moderating influence on these psychological factors (Geers et al. 2006, Lundh 1987). In an experiment that induced expect-

tations of unpleasant symptoms, individuals who expected they were taking a drug but given placebo tablets reported more placebo symptoms when they closely focused on their symptoms (Geers et al. 2006). This type of interaction also has been proposed for approach goals. Thus, Lundh (1987) proposes a cognitive-emotional model of the placebo effect in which positive placebo suggestions for improvements in physical health lead individuals to attend selectively to signs of improvement. When they closely notice these signs, they are said to take them as evidence that the placebo treatment has been effective.

If somatic focus operates as a kind of feedback that supports factors underlying placebo responding, increasing the degree or frequency of somatic focusing could increase the magnitudes of placebo responses over time. This possibility is supported by observations showing that the growth of the placebo effect at least partly depends on the frequency of test stimuli. As discussed above, ratings of desire, expectation, and anxiety decrease over time along with the increase in placebo effect (Vase et al. 2005). As shown in **Figure 1**, it took about 20 minutes for the placebo effect to increase to its maximum level in conditions wherein stimuli were applied at seven times per 50 minutes (**Figure 1**) (Vase et al.



fMRI: functional magnetic resonance imaging

2003, Verne et al. 2003). This same pattern of increase was found in a subsequent experiment that applied seven stimuli in 10 minutes (Price et al. 2007). The placebo effect increased to its maximum level during the first three stimuli and over 3–4 minutes with this more rapid stimulus frequency. Taken together, the results of Geers et al. (2006) and Vase et al. (2005) support a model of placebo mechanism wherein goals, desire, expectation, and consequent emotional feelings code-terminate the placebo response. Somatic focus provides a self-confirming feedback that facilitates these factors over time, leading to more positive (or less negative) emotional feelings about prospects of avoiding aversive experiences or obtaining appetitive experiences (Figure 2).

If the desire-expectation model is accurate, then placebo phenomena occur within the context of emotional regulation and symptoms should be influenced by desire, expectation, and emotional feeling intensity regardless of whether these factors are evoked by placebo manipulations. A separate line of evidence for the role of expectancy in placebo analgesia includes studies that manipulate expectancy in nonplacebo contexts. Three studies found large reductions in pain from expectancy manipulations, and two of these studies found corresponding reductions in pain-related brain activity (Keltner et al. 2006, Koyama et al. 2005, Rainville et al. 2005). Desire and emotions also influence pain in nonplacebo contexts. Rainville et al. (2005) recently have shown that hypnotic inductions of changes in desire for relief as well as inductions of positive and negative emotional states modulate pain in directions they claim are consistent with the desire-expectation model.

Thus, to put it simply, placebo responses seem to relate to feeling good (or less bad) about prospects of relief (avoidance goal) or pleasure (approach goal) that are associated with treatments or medications. These feelings can be separately influenced by de-

sire and expectation or by the combination of both factors. An explanation at a more mechanistic level is needed. For example, do placebo-induced changes in expectations, desires, and emotions simply lead to subjective biases about symptoms/effects, or do they affect their biological causes?

NEUROBIOLOGY OF THE DESIRE-EXPECTATION MODEL

The Functional Role of Placebo-Related Increases and Decreases in Brain Activity

Several neurobiologists have found that placebo effects are accompanied by reductions in neural activity within brain areas known to process symptoms such as anxiety and pain. They also have found that these reductions are accompanied by increases in neural activity within brain areas known to be involved in emotional regulation (Fields 2004, Petrovic et al. 2005, Zubieta et al. 2001). They propose that placebo responses are generated as a function of reward and/or aversion and associated neural circuitry.

In two functional magnetic resonance imaging (fMRI) experiments published in a single study, Wager et al. (2004) found that placebo analgesia was related to decreased neural activity in pain processing areas of the brain. Pain-related neural activity was reduced within the thalamus, anterior insular cortex, and anterior cingulate cortex during the placebo condition as compared with the baseline condition. In addition, the magnitudes of these decreases were correlated with reductions in pain ratings.

Another important aspect of Wager et al.'s (2004) study was that they imaged not only the period of pain but also the period of anticipation of pain. They hypothesized increases in neural activity within brain areas involved in expectation. In support of their hypothesis, they found significant positive correlations ($r = 0.4$ – 0.7) between increases

in brain activity in the anticipatory period and decreases in pain and pain-related neural activity during stimulation within the placebo condition. The brain areas showing positive correlations during the anticipatory phase included the orbitofrontal cortex (OFC), dorso-lateral prefrontal cortex (DLPFC), rostral anterior cingulate cortex (rACC), and midbrain periaqueductal gray (PAG). The DLPFC has been consistently associated with the representation of and maintenance of information needed for cognitive control, consistent with a role in expectation (Miller & Cohen 2001). On the other hand, the OFC is associated with functioning in the evaluative and reward information relevant to allocation of control, consistent with a role in affective or motivational responses to anticipation of pain (Dias et al. 1996). Such a role is consistent with results showing that desire for relief is a factor in placebo analgesia.

A limitation of Wager et al.'s (2004) study is that most of the decreases in neural activity within pain-related areas occurred during the period that subjects rated pain, leaving open the possibility that placebo effects mainly reflected report biases. In a subsequent fMRI study, brain activity of IBS patients was measured in response to rectal distension by a balloon barostat (Price et al. 2007). As shown in **Figure 4** (see color insert), a large placebo effect was produced by suggestions and accompanied by large reductions in neural activity in known pain-related areas, such as thalamus, S-1, S-2, insula, and ACC, during the period of stimulation, thereby reflecting effects unlikely to result from report biases. It was also accompanied by increases in neural activity in the rostral ACC, bilateral amygdala, and PAG (unpublished observations), areas known to be involved in reward/aversion, emotions, and the classical descending pain modulatory pathway (Basbaum & Fields 1978). The latter includes a core rACC-amygdala-PAG-rostroventral medulla-spinal cord connection, wherein pain-related signals are inhibited in the dorsal horn of the spinal cord (Basbaum & Fields 1978, Mayer & Price

1976). This network contains endogenous opioids.

However, the involvement of brain areas involved in emotional regulation and hence in placebo responses is not restricted only to pain modulation. Petrovic et al. (2005) demonstrated a placebo effect related to the reduction of anxiety associated with viewing unpleasant pictures. Reductions in experienced unpleasantness were accompanied by increases in brain areas involved in reward/aversion and previously shown to be involved in placebo analgesia. These areas included those previously implicated in emotional modulation, such as the OFC, rACC, and amygdala. They also included areas involved in treatment expectation, such as ventrolateral prefrontal cortex and rACC.

Future Directions in Relating Brain Activity to Psychological Variables Associated with Placebo

Large placebo effects that accompany corresponding decreases in activity within symptom-related areas of the brain underscore both the psychological and biological reality of the placebo response and support current models of mind-brain interactions (Schwartz et al. 2005).

However, elucidating the relationships between cognitive and emotional factors to placebo responses is an enormous challenge, as is determining their neurobiological underpinnings. Psychological studies of placebo responses have included progressively more variables, such as expectancy, desire, somatic focus, and type of goal. Measures of these variables potentially can be incorporated into brain imaging and other types of neurobiological studies so that explicit mechanistic hypotheses about these factors can be tested at both a more refined psychological and neurobiological level. Such improvements should provide increasing potential for utilizing knowledge of these mechanisms in clinical research and practice.

CCK:
cholecystokinin

EVIDENCE FOR OPIOID AND NONOPIOID MECHANISMS IN PLACEBO ANALGESIA

Opioid Mechanisms

An important step in understanding the mechanisms of placebo-induced analgesia was made in the clinical setting when Levine et al. (1978) provided evidence that placebo analgesia is antagonized by naloxone, an opioid antagonist, which indicates mediation by endogenous opioid systems. Other studies subsequently further confirmed this hypothesis (Benedetti 1996, Grevert et al. 1983, Levine & Gordon 1984). These include studies described above that use verbal suggestion, conditioning, and open-hidden injections. For example, enhanced analgesia with open as compared to hidden injections was eliminated by naloxone (Amanzio et al. 2001). In addition, cholecystokinin (CCK) was found to inhibit placebo-induced analgesia, as CCK antagonists are capable of potentiating the placebo analgesic effect (Benedetti 1996, Benedetti et al. 1995). In fact, CCK is an antiopioid peptide that antagonizes endogenous opioid neuropeptides, so that its blockade results in the potentiation of opioid effects (Benedetti 1997).

Fields & Levine (1984) hypothesized that the placebo response may be subdivided into opioid and nonopioid components. In fact, they suggested that different physical, psychological, and environmental situations could affect the endogenous opioid systems differently. This problem was addressed by Amanzio & Benedetti (1999), who showed that both expectation and a conditioning procedure could result in placebo analgesia. The former is capable of activating opioid systems, whereas the latter activates specific subsystems. In fact, if the placebo response is induced by means of strong expectation cues, it can be blocked by the naloxone. Conversely, as described below, if the placebo response is induced by means of prior conditioning with a nonopioid drug, it is naloxone-insensitive.

Regional placebo analgesic responses can be obtained in different parts of the body (Montgomery & Kirsch 1996, Price et al. 1999), and these responses are naloxone-reversible (Benedetti et al. 1999b). If four noxious stimuli are applied to the hands and feet and a placebo cream is applied to one hand only, pain is reduced only on the hand where the placebo cream had been applied. This effect is blocked by naloxone, which suggests that the placebo-activated endogenous opioids have a somatotopic organization (Benedetti et al. 1999b). An additional study supporting the involvement of endogenous opioids in placebo analgesia was performed by Lipman et al. (1990) in chronic pain patients. It was found that those patients who responded to placebo showed higher concentrations of endorphins in the cerebrospinal fluid compared with those patients who did not respond.

A likely candidate for the mediation of placebo-induced analgesia is the opioid neuronal network described above (Fields & Basbaum 1999, Fields & Price 1997), and this hypothesis is supported by a brain imaging study that found similar regions in the cerebral cortex and in the brainstem affected by both a placebo and the rapidly acting opioid agonist remifentanyl. This suggests a related mechanism in placebo-induced and opioid-induced analgesia (Petrovic et al. 2002).

The direct demonstration of placebo-induced release of endogenous opioids has been obtained by using in vivo receptor binding with positron emission tomography by Zubieta et al. (2005). By using an experimental model of pain in healthy volunteers, these authors found an increase of μ -opioid receptor neurotransmission in different brain regions, such as the anterior cingulate cortex, the orbitofrontal cortex, the insula, and the nucleus accumbens.

As is described in detail below, placebo-activated endogenous opioids have also been shown to affect the respiratory centers (Benedetti et al. 1998, 1999a) and the

cardiovascular system (Pollo et al. 2003), thus indicating that they act not only on pain transmission but on other systems as well.

Nonopioid Agents and Mechanisms in Placebo Analgesia

Placebo analgesic responses have been found to be mediated by mechanisms other than opioids in other circumstances. For example, they have been found to be naloxone insensitive, thus nonopioid mediated, if the subjects were previously exposed to a nonopioid drug, such as ketorolac (Amanzio & Benedetti 1999). When ketorolac was administered for two days in a row and then replaced with a placebo on the third day, the placebo analgesic response was not reversed with naloxone. This suggests that specific pharmacological mechanisms are involved in a learned placebo response, depending on the previous exposure to opioid or nonopioid substances. Another example of placebo analgesia that is nonopioid-mediated has been studied in IBS patients who exhibit strong placebo responses. Placebo effects in these patients were found to be naloxone-insensitive, suggesting mediation by nonopioid mechanisms (Vase et al. 2005).

Although other neurochemical mechanisms have not yet been identified, it is worth noting that the possible involvement of some neurotransmitters has been found in some conditions. For instance, by using the analgesic drug sumatriptan, a serotonin agonist of the 5-HT_{1B/1D} receptors that stimulates growth hormone (GH) and inhibits cortisol secretion, it was shown that a conditioning procedure is capable of producing hormonal placebo responses. In fact, if a placebo is given after repeated administrations of sumatriptan, a placebo GH increase and a placebo cortisol decrease can be found (Benedetti et al. 2003b). Interestingly, verbally induced expectations of increase/decrease of GH and cortisol did not have any effect on the secretion of these hormones. Therefore, whereas hormone secretion is not affected by expecta-

tations, it is affected by a conditioning procedure. Although we do not know whether these placebo responses are really mediated by serotonin, a pharmacological preconditioning appears to affect serotonin-dependent hormone secretion. These new findings may help in the investigation of nonopioid mechanisms in placebo analgesia.

The verbal instructions that induce expectations may have either a hopeful and trust-inducing meaning, eliciting a placebo effect, or a fearful and stressful meaning, inducing a nocebo effect (Benedetti & Amanzio 1997; Hahn 1985, 1997; Moerman 2002). In a study performed using postoperative patients (Benedetti et al. 1997) and healthy volunteers (Benedetti et al. 2006), negative expectations were induced by administering an inert substance along with the suggestion that pain was going to increase. In fact, pain increased and this increase was prevented by the CCK antagonist proglumide. This indicates that expectation-induced hyperalgesia of these patients was mediated, at least in part, by CCK. The effects of proglumide were not antagonized by naloxone (Benedetti et al. 1997), which suggests that endogenous opioids were not involved. Since CCK plays a role in anxiety and negative expectations themselves are anxiogenic, these results suggest that proglumide acts on a CCK-dependent link between anxiety and pain (Benedetti et al. 2006). Although this study analyzed nocebo hyperalgesia and not placebo analgesia, it shows that CCK-ergic systems may be activated by negative verbal suggestions that induce negative expectations.

MECHANISMS OTHER THAN EXPECTATION AND CONDITIONS OTHER THAN PAIN

Evidence for Classical Conditioning Mechanisms

Some of the placebo analgesia studies discussed so far suggest that conditioning can

have a role in at least some placebo responses, although in most cases the proximate psychological mediators seem to be expectations, motivations, and emotions. These findings do not negate conditioning as a factor, only a classical Pavlovian model that doesn't require conscious expectations. Classical conditioning seems to play a key role for phenomena other than pain.

In classical conditioning, repeated associations between a neutral stimulus (conditioned stimulus, or CS), for example a syringe or a pill, and an unconditioned stimulus (US), for instance the active drug inside the syringe or pill, lead to a conditioned response (CR), whereby the CS alone induces a physiological response that is similar in all respects to that of the US. This mechanism emphasizes once again that there is not just a single placebo effect; rather, there are many, with different mechanisms taking place in different conditions on the one hand and in different systems and apparatuses on the other. Two of the best examples of placebo responses as conditioned responses come from the immune and endocrine system.

Placebo Responses in the Immune and Endocrine System

McKenzie (1896) reported an interesting observation relevant to the understanding of the placebo effect in the immune system. In this study, it was shown that some people who are allergic to flowers show an allergic reaction when presented with something that superficially looks like a flower, but contains no pollen (i.e., an artificial flower). Ader & Cohen (1982) provided experimental evidence that immunological placebo responses can be obtained by pairing a solution of sodium saccharin (CS) with the immunosuppressive drug cyclophosphamide (US). In fact, mice treated in this way show conditioned immunosuppression, that is, immune responses to sodium saccharin alone. Ader et al. (1993) also showed that a conditioned enhancement of antibody production is possible using an antigen as un-

conditioned stimulus of the immune system. In this case, mice were given repeated immunizations with keyhole limpet hemocyanin (KLH) paired with a gustatory conditioned stimulus. A classically conditioned enhancement of anti-KLH antibodies was observed when the mice were re-exposed to the gustatory stimulation alone.

These studies in animals have been repeated in humans. Olness & Ader (1992) presented a clinical case study of a child with lupus erythematosus. The child received cyclophosphamide paired with taste and smell stimuli, according to the conditioning procedure used in animals. During the course of twelve months, a clinically successful outcome was obtained by using taste and smell stimuli alone on half the monthly chemotherapy sessions. In another study, multiple sclerosis patients received four intravenous treatments with cyclophosphamide (US) paired with anise-flavored syrup (CS) (Giang et al. 1996). Eight out of ten patients displayed decreased peripheral leukocyte counts following the syrup alone, an effect that mimics that of cyclophosphamide. Recently, these findings have been confirmed in humans (Goebel et al. 2002). In fact, repeated associations between cyclosporin A (US) and a flavored drink (CS) induced conditioned immunosuppression, in which the flavored drink alone produced a suppression of the immune functions, as assessed by means of interleukin-2 and interferon-gamma messenger ribonucleic acid expression, in vitro release of interleukin-2 and interferon-gamma, as well as lymphocyte proliferation.

Some hormonal placebo responses, similar to the conditioning-induced immunological responses, have been described. As noted in the previous section on nonopioid mechanisms, by using an analgesic drug—the serotonin agonist sumatriptan, which stimulates GH and inhibits cortisol secretion—it was shown that a conditioning procedure is capable of producing placebo secretive responses of hormones (Benedetti et al. 2003). In fact, if a placebo is given after repeated

administrations of sumatriptan, a placebo GH increase and a placebo cortisol decrease can be found. Interestingly, verbally induced expectations of increase/decrease of GH and cortisol did not have any effect on the secretion of these hormones, indicating that hormone secretion is not affected by verbal suggestions and expectations, but rather by a form of conditioning that does not require conscious expectations.

All these findings in the immune and endocrine system suggest that a CS may acquire all the properties and characteristics of a placebo. These findings also have important clinical implications, as the pharmacotherapeutic doses in different diseases can be reduced by pairing chemotherapies with a number of conditioned stimuli.

Other Biological Models of Placebo

Besides these conditioning studies in the immune and endocrine systems, which clearly show the involvement of systems and mechanisms other than pain transmission in the placebo effect, a number of studies exist in which some biological responses to placebo administration have been described in detail. These studies are now emerging as interesting models to better understand the placebo effect across different diseases. These models, which are described below, are the respiratory and cardiovascular system, Parkinson's disease, and depression.

Respiratory and cardiovascular placebo responses. Placebo-activated endogenous opioids have been shown to produce a typical side effect of opioids, that is, respiratory depression (Benedetti et al. 1998, 1999a). After postoperative patients receive repeated administrations of analgesic doses of buprenorphine, which induces a mild reduction of ventilation, a placebo is capable of mimicking the same respiratory depressant response. Remarkably, this respiratory placebo response is totally blocked by naloxone, indicating that it is mediated by en-

dogenous opioids. The involvement of other systems in the action of placebo-activated endogenous opioids is further supported by a study in which the sympathetic control of the heart was analyzed during placebo analgesia (Pollo et al. 2003). In a pharmacological study in healthy volunteers, it was found that placebo analgesia in experimental ischemic arm pain was accompanied by a reduction of heart rate. Both the placebo analgesic effect and the concomitant heart rate decrease were reversed by the opioid antagonist naloxone, whereas the β -blocker propranolol antagonized the placebo heart rate reduction but not placebo analgesia. There are at least two possible mechanisms through which the heart is affected during placebo analgesia. It might be a consequence of pain reduction itself or, otherwise, the placebo-activated endogenous opioids might inhibit the cardiovascular system directly. Further research is necessary to differentiate between these two mechanisms.

Parkinson's disease. Recently, Parkinson's disease has emerged as an interesting model to understand the neurobiological mechanisms of the placebo response. In this model, patients are given an inert substance (placebo) and are told that it is an anti-Parkinsonian drug that produces an improvement in motor performance. It has been shown that Parkinsonian patients respond to placebos quite well (Goetz et al. 2000, Shetty et al. 1999), and a study that used positron emission tomography to assess endogenous dopamine release shows that placebo-induced expectation of motor improvement activates dopamine in the striatum of Parkinsonian patients (de la Fuente-Fernandez et al. 2001). In addition, Pollo et al. (2002) showed that different and opposite expectations of bad and good motor performance modulate the therapeutic effect of subthalamic nucleus stimulation in Parkinsonian patients who had undergone chronic implantation of electrodes for deep brain stimulation. For example, in an analysis of the effect of

subthalamic stimulation on the velocity of movement of the right hand, the hand movement was found to be faster when the patients expected a good motor performance (Pollo et al. 2002). The expectation of good performance was induced through a placebo-like procedure, thus indicating that placebo-induced expectations have an influence on the outcome of the treatment. All these effects occurred within minutes, which suggests that expectations induce neural changes very quickly.

The ability to study Parkinsonian patients who are implanted with electrodes for deep brain stimulation has been exploited recently to record from single neurons after placebo administration (Benedetti et al. 2004). In this study, the activity from single neurons in the subthalamic nucleus was recorded before and after placebo administration to see whether neuronal changes were linked to the clinical placebo response. The placebo consisted of a saline solution that was given to patients along with the suggestion that it was an anti-Parkinsonian drug. It was found that the placebo responders showed a significant decrease of neuronal discharge and the disappearance of bursting activity of subthalamic neurons, whereas the placebo nonresponders did not exhibit these changes. These findings in Parkinson's disease patients offer opportunities to administer an exciting and innovative approach with the possibility of recording from single neurons in awake patients during the placebo response.

Depression. The neural mechanisms of placebo treatments have also been studied in depression. However, these studies need further research and confirmation since, due to ethical constraints, they did not include appropriate control groups. Depressed patients who received a placebo treatment showed both electrical and metabolic changes in the brain. In one study, placebos induced electroencephalographic changes in the prefrontal cortex of patients with major depression, particularly in the right hemisphere (Leuchter et al. 2002). It has been suggested

that this finding of brain functional changes during placebo treatment can be used to identify the subjects who are likely to be placebo responders. In particular, Leuchter et al. (2004) found that placebo responders had lower pretreatment frontocentral coherence (a measure of electroencephalogram activity) in comparison with all other subjects. Placebo responders also had faster cognitive processing time, as assessed by neuropsychological testing, and lower reporting of late insomnia. Based on these data, the authors suggest a combination of clinical, neurophysiological, and cognitive assessments for identifying depressed subjects who are likely to be placebo responders.

In another study, changes in brain glucose metabolism were measured by using positron emission tomography in subjects with unipolar depression (Mayberg et al. 2002). Placebo treatments were associated with metabolic increases in the prefrontal, anterior cingulate, premotor, parietal, posterior insula, and posterior cingulate cortex, and metabolic decreases in the subgenual cingulate cortex, para-hippocampus, and thalamus. Interestingly, these regions also were affected by the selective serotonin reuptake inhibitor fluoxetine, a result that suggests a possible role for serotonin in placebo-induced antidepressant effects (see Benedetti et al. 2005 for a review).

IMPLICATIONS FOR CLINICAL TRIALS AND CLINICAL PRACTICE

Recent advances in our understanding of placebo responses have raised some implications for clinical trials and clinical practice. Some of these implications center on the ethical enhancement of factors that drive placebo mechanisms during administration of an active therapy. It is important to note that the clinical implications for placebo use involve exploitation of placebo factors and mechanisms when there is an active treatment being administered, not the deliberate use of a placebo when there is an active treatment

available, which is unethical. The research on the placebo effect has highlighted the involvement of several factors in placebo responses, and studies of placebo mechanisms have started to identify the ways in which these factors drive responses. Despite increases in the number of studies of placebo mechanisms, there has been limited investigation of the harnessing of these mechanisms to improve clinical trials and clinical practice.

A recent study illustrates the long-term clinical benefits of placebo factors when patients believe they have been given active treatments. In a double-blind study of human fetal mesencephalic transplantation (an experimental treatment for Parkinson's disease), investigators studied the effect of this treatment compared with a placebo treatment for twelve months, using a standard randomized controlled trial design (McRae et al. 2004). They also assessed the patient's perceived assignment to either the active (fetal tissue implant) or placebo treatment (sham surgery). There were no differences between the transplant and sham surgery groups on several physical and quality-of-life measures made by both medical staff and patients. Instead, the perceived assignment of treatment group had a beneficial impact on the overall outcome, and this difference was present at least twelve months after surgery. Patients who believed they received transplanted tissue had significant improvements in both psychological (quality of life) and physiological (motor function) outcomes, regardless of whether they received sham surgery or fetal tissue implantations. This study is unusual in providing evidence that the placebo effect can last a long time, quite possibly due to the elaborate and invasive nature of the placebo treatment.

In two similar studies (Bausell et al. 2005, Linde et al. 2007), real acupuncture was compared with sham acupuncture for different painful conditions, such as migraine, tension-type headache, chronic low back pain, and osteoarthritis. These studies examined the effects of patients' expectations on the therapeutic outcome, regardless of the group to

which the patient belonged. To do this, patients were asked either which group they believed they belonged to (either placebo or real treatment) (Bausell et al. 2005) or whether they considered acupuncture to be an effective therapy in general and what they personally expected from the treatment (Linde et al. 2007). These studies found that patients who believed they belonged to the real treatment group experienced larger clinical improvement than those patients who believed they belonged to the placebo group (Bausell et al. 2005). Likewise, patients with higher expectations about acupuncture treatment experienced larger clinical benefits than did patients with lower expectations, regardless of their allocation to real or sham acupuncture (Linde et al. 2007). Thus, it did not really matter whether the patients actually received the real or the sham procedure. What mattered was whether they believed in acupuncture and expected a benefit from it.

We think that these studies represent a good example of how clinical trials should be viewed from a theoretical perspective and how they should be conducted from a practical viewpoint. They underscore the necessity to consider clinical trials from a different perspective, in order to make their interpretation more reliable. Some confusing outcomes of clinical trials could be clarified by the simple questions, "What do you expect from this treatment?", or "Which group do you believe you are assigned to?"

These studies also illustrate how incorporation of placebo-related measures can improve clinical trials. Assessing variables that contribute to the placebo effect, such as perceived group assignment, expected changes, and desire for clinical benefits, could provide a means of assessing the contribution of placebo even when there is no natural history condition. Recall that factors such as these account for large amounts of variance in placebo responses. A secondary benefit would be a means of assessing the extent to which double-blind conditions are maintained. Enhancing and maintaining the placebo component of a

proven therapy could occur because of several psychosocial factors and suggestions that are ethically permissible (e.g., “The agent you have just been given is known to significantly reduce pain in some patients”).

Further implications of the role of placebo mechanisms on the outcome of an active therapy are seen with the differences between a standard administration of a treatment and a hidden administration, a paradigm described earlier. This difference in effect has been demonstrated not only for pain (**Figure 1**) but also for other conditions such as Parkinson’s disease. In the case of Parkinson’s disease, deep brain stimulation of the subthalamic nucleus has been shown to be less effective (by means of autonomic and motor responses) when administered covertly rather than in a standard clinical (open) manner (Colloca et al. 2004). Similar to analgesia studies, this study shows that the overall effect of a treatment such as administration of an active agent is a combination of the pharmacological properties of the drug and the placebo mechanisms that are driven by the psychosocial context surrounding the drug administration. The larger the difference between the two administrations, the more significant the placebo mechanisms are in the overall effect. On the other hand, a smaller difference between the administrations indicates that the pharmacological properties of the drug are playing a more significant role rather than placebo mechanisms. The factors involved in this difference are those that mediate placebo effects, as the difference in the administrations represents the psychosocial context of the treatment.

The open-hidden paradigm underscores the importance of placebo mechanisms, particularly expectations, on the outcome of a given treatment. In doing so, it demonstrates that the therapeutic interaction between a clinician and a patient can play a significant role in the outcome of a therapy. It also presents researchers with a different paradigm to study the overall effect of a drug, where one can establish the pharmacological and placebo

components of a drug without actually administering a placebo. The paradigm also highlights the potentially negative impact of a loss of placebo mechanisms on the outcome of a therapy and highlights the clinical importance of assessment of these factors prior to therapy in some instances. One such instance is analgesic therapy for patients with Alzheimer’s disease. In this condition, there is a disruption of expectation mechanisms due to cognitive impairment.

In a recent study, one of us assessed overt and covert administration of a local anesthetic following venipuncture in Alzheimer’s disease sufferers (Benedetti et al. 2006). In this experiment, the placebo component, represented by the differences in response to open and hidden local anesthetic administration, was correlated with both cognitive status and functional connectivity between different brain regions. Interestingly, patients with reduced frontal assessment battery scores showed a decreased placebo component to the therapy. Similar disruption of the placebo component was seen with reduced connectivity between the prefrontal lobes and the rest of the brain. Of clinical importance is the fact that the reductions in the placebo component had an effect on treatment efficacy, with those patients with greater losses of placebo mechanisms requiring larger doses of the drug to produce adequate analgesia. This study further highlights the importance of expectancy-related (placebo) mechanisms in the overall therapeutic outcome and the need for consideration of these mechanisms when prescribing an analgesic regime to patients with cognitive impairment (Benedetti et al. 2006).

CONCLUSIONS

Our understanding and conceptualization of the placebo effect has changed in recent times, shifting from a focus on the inert content of a physical placebo agent to the overall simulation of a therapeutic intervention. Research has allowed for the identification of not one but many placebo responses, each of which

may be driven by different psychological and neurobiological mechanisms depending on the particular context in which the placebo is given. We are still some way from understanding the relationships between the identified psychological variables and their neurobiological underpinnings, although a body of literature is emerging that identifies the roles of certain cognitive and emotional factors and various biochemical and neuroanatomical mechanisms in driving placebo responses. This literature also shows that placebos have

actual biological effects on the brain and body and are more than response biases. The demonstration of the involvement of placebo mechanisms in routine clinical practice and clinical trials has opened up opportunities to look at the ethical enhancement of these mechanisms in clinical practice. Further experimental and clinical research will hopefully provide for improved understanding of placebo mechanisms and the ability to harness them for the advancement of clinical practice.

SUMMARY POINTS

1. The concept of placebo response has shifted in emphasis from viewing it as caused by an inert physical agent to viewing it as the result of simulation of an active therapy.
2. Placebo effects can be produced by suggestions, past effects of active treatments, and cues that signal that an active medication or treatment has been given.
3. Proximate psychological mediators of placebo responses include expectations, desires, and emotions that target prospective symptom changes.
4. Psychological mediators are related to brain structures involved in reward/aversion and regulation of emotions.
5. Placebo analgesic effects require endogenous opioids in some circumstances (e.g., prior conditioning with opioids) and not in others (e.g., prior conditioning with nonopioid drugs).
6. Although desire, expectations, and emotions may be required for some placebo phenomena, such as pain, Parkinson's disease, depression, and mood changes, other placebo responses (immune, hormonal, and respiratory responses) result from less conscious processes such as classical conditioning.
7. Assessment of mediators of placebo responses, such as expected benefits and perceived group assignment, could improve clinical trials by providing a means of separately assessing the contributions of placebo factors and factors related to active treatment, as well as monitoring the extent of blinding within the trial.
8. Knowledge concerning mediators and mechanisms of placebo effects within active therapies could serve to enhance this component through ethical use of suggestions and optimum caregiver-patient interactions.

FUTURE ISSUES

1. There is a need to further characterize relationships between psychological mediators of placebo responses and their associated neural mechanisms.

2. Healthcare professionals need to be educated about the characteristics and underlying mechanisms of placebo so that they can optimize placebo components of therapy.
3. Powerful placebo effects reflect mind-brain-body relationships, and there is a need to philosophically resolve explanations of these relationships without resorting to eliminative materialism or forms of dualism that completely divide the mind from the body.

ACKNOWLEDGMENTS

Support for this research was provided by grant RO1 (AT001424) from the National Center for Complementary and Alternative Medicine to Dr. Michael Robinson. This work was also supported by grants from Istituto San Paolo di Torino and Regione Piemonte to Fabrizio Benedetti. We thank our many colleagues who participated in some of the research reviewed here. We thank Drs. Michael Robinson, Nicholas Verne, and Lene Vase for data and data analysis associated with **Table 1**.

LITERATURE CITED

- Ader R, Cohen N. 1982. Behaviorally conditioned immunosuppression and murine systemic lupus erythematosus. *Science* 215:1534–36
- Ader R, Kelly K, Moynihan JA, Grotta LJ, Cohen N. 1993. Conditioned enhancement of antibody production using an antigen as the unconditioned stimulus. *Brain Behav. Immun.* 7:334–43
- Amanzio M, Benedetti F. 1999. Neuropharmacological dissection of placebo analgesia: expectation-activated opioid systems versus conditioning-activated specific subsystems. *J. Neurosci.* 19:484–94
- Amanzio M, Pollo A, Maggi G, Benedetti F. 2001. Response variability to analgesics: a role for non-specific activation of endogenous opioids. *Pain* 90:205–15
- Basbaum AI, Fields HL. 1978. Endogenous pain control mechanisms: review and hypothesis. *Ann. Neurol.* 4(5):451–62
- Bausell RB, Lao L, Bergman S, Lee WL, Berman BM. 2005. Is acupuncture analgesia an expectancy effect? Preliminary evidence based on participants' perceived assignments in two placebo-controlled trials. *Eval. Health Prof.* 28:9–26
- Beecher HK. 1955. The powerful placebo. *JAMA* 159:1602–6
- Benedetti F. 1996. The opposite effects of the opiate antagonist naloxone and the cholecystokinin antagonist proglumide on placebo analgesia. *Pain* 64:535–43
- Benedetti F. 1997. Cholecystokinin type-A and type-B receptors and their modulation of opioid analgesia. *News Physiol. Sci.* 12:263–68
- Benedetti F, Amanzio M. 1997. The neurobiology of placebo analgesia: from endogenous opioids to cholecystokinin. *Prog. Neurobiol.* 52:109–25
- Benedetti F, Amanzio M, Baldi S, Casadio C, Cavallo A, et al. 1998. The specific effects of prior opioid exposure on placebo analgesia and placebo respiratory depression. *Pain* 75:313–19
- Benedetti F, Amanzio M, Baldi S, Casadio C, Maggi G. 1999a. Inducing placebo respiratory depressant responses in humans via opioid receptors. *Eur. J. Neurosci.* 11:625–31
- Benedetti F, Amanzio M, Casadio C, Oliaro A, Maggi G. 1997. Blockade of nocebo hyperalgesia by the cholecystokinin antagonist proglumide. *Pain* 70:431–36

- Benedetti F, Amanzio M, Maggi G. 1995. Potentiation of placebo analgesia by proglumide. *Lancet* 346:1231
- Benedetti F, Arduino C, Amanzio M. 1999b. Somatotopic activation of opioid systems by target-expectations of analgesia. *J. Neurosci.* 9:3639–48
- Benedetti F, Arduino C, Costa S, Vighetti S, Tarenzi L, et al. 2006. Loss of expectation-related mechanisms in Alzheimer's disease makes analgesic therapies less effective. *Pain* 121:133–44
- Benedetti F, Colloca L, Torre E, Lanotte M, Melcarne A, et al. 2004. Placebo-responsive Parkinson patients show decreased activity in single neurons of subthalamic nucleus. *Nat. Neurosci.* 7:587–88
- Benedetti F, Mayberg HS, Wager TD, Stohler CS, Zubieta JK. 2005. Neurobiological mechanisms of the placebo effect. *J. Neurosci.* 25:10390–402
- Benedetti F, Pollo A, Lopiano L, Lanotte M, Vighetti S, et al. 2003. Conscious expectation and unconscious conditioning in analgesic, motor and hormonal placebo/nocebo responses. *J. Neurosci.* 23:4315–23
- Colloca L, Benedetti F. 2005. Placebos and painkillers: Is mind as real as matter? *Nat. Rev. Neurosci.* 6(7):545–52
- Colloca L, Benedetti F. 2006. How prior experience shapes placebo analgesia. *Pain* 124:126–33
- Colloca L, Lopiano L, Lanotte M, Benedetti F. 2004. Overt versus covert treatment for pain, anxiety, and Parkinson's disease. *Lancet Neurol.* 3:679–84
- de Craen AJ, Kaptchuk TJ, Tijssen JG, Kleijnen J. 1999. Placebos and placebo effects in medicine: historical overview. *J.R. Soc. Med.* 92(10):511–15
- de la Fuente-Fernandez R, Ruth TJ, Sossi V, Schulzer M, Calne DB, et al. 2001. Expectation and dopamine release: mechanism of the placebo effect in Parkinson's disease. *Science* 293:1164–66
- De Pascalis V, Chiaradia C, Carotenuto E. 2002. The contribution of suggestibility and expectation to placebo analgesia phenomenon in an experimental settings. *Pain* 96:393–402
- Dias R, Robbins TW, Roberts AC. 1996. Dissociation in prefrontal cortex of affective and attentional shifts. *Nature* 380(6569):69–72
- Fields HL. 2004. State-dependent opioid control of pain. *Nat. Rev. Neurosci.* 5:565–75
- Fields HL, Basbaum AI. 1999. Central nervous system mechanisms of pain modulation. In *Textbook of Pain*, ed. PD Wall, R Melzack, pp. 309–29. Edinburgh, UK: Churchill Livingstone
- Fields HL, Levine JD. 1984. Placebo analgesia—a role for endorphins? *Trends Neurosci.* 7:271–73
- Fields HL, Price DD. 1997. Toward a neurobiology of placebo analgesia. In *The Placebo Effect: An Interdisciplinary Exploration*, ed. A Harrington, pp. 93–116. Cambridge, MA: Harvard Univ. Press
- Geers AL, Helfer SG, Weiland PE, Kosbab K. 2006. Expectations and placebo response: a laboratory investigation into the role of somatic focus. *J. Behav. Med.* 29(2):171–78
- Geers AL, Weiland PE, Kosbab K, Landry SJ, Helfer SG. 2005. Goal activation, expectations, and the placebo effect. *J. Personal. Soc. Psychol.* 89(2):143–59
- Giang DW, Goodman AD, Schiffer RB, Mattson DH, Petrie M, et al. 1996. Conditioning of cyclophosphamide-induced leukopenia in humans. *J. Neuropsychiatry Clin. Neurosci.* 8:194–201
- Goebel MU, Trebst AE, Steiner J, Xie YF, Exton MS, et al. 2002. Behavioral conditioning of immunosuppression is possible in humans. *FASEB J.* 16:1869–73
- Goetz CG, Leurgans S, Raman R, Stebbins GT. 2000. Objective changes in motor function during placebo treatment in PD. *Neurology* 54:710–14

- Gracely RH, Dubner R, Wolskee PJ, Deeter WR. 1983. Placebo and naloxone can alter post-surgical pain by separate mechanisms. *Nature* 306:264–65
- Grevert P, Albert LH, Goldstein A. 1983. Partial antagonism of placebo analgesia by naloxone. *Pain* 16:129–43
- Hahn RA. 1985. A sociocultural model of illness and healing. In *Placebo: Theory, Research, and Mechanisms*, ed. L White, B Tursky, GE Schwartz, pp. 167–95. New York: Guilford
- Hahn RA. 1997. The nocebo phenomenon: scope and foundations. In *The Placebo Effect: An Interdisciplinary Exploration*, ed. A Harrington, pp. 56–76. Cambridge, MA: Harvard Univ. Press
- Hrobjartsson A, Gøtzsche PC. 2001. Is the placebo effect powerless? An analysis of clinical trials comparing placebo with no-treatment. *N. Engl. J. Med.* 344:1594–602
- Hrobjartsson A, Gøtzsche PC. 2004. Is the placebo effect powerless? Update of a systematic review with 52 new randomized trials comparing placebo with no treatment. *J. Int. Med.* 256:91–100
- Hrobjartsson A, Gøtzsche PC. 2006. Unsubstantiated claims of large effects of placebo on pain: serious errors in meta-analysis of placebo analgesia mechanism studies. *J. Clin. Epidemiol.* 59:336–38
- Jensen MP, Karoly P. 1991. Motivation and expectancy factors in symptom perception: a laboratory study of the placebo effect. *Psychosomatic Med.* 53(2):144–52
- Keltner JR, Furst A, Fan C, Redfern R, Inglis R, et al. 2006. Isolating the modulatory effect of expectation on pain transmission: a functional magnetic resonance imaging study. *J. Neurosci.* 26(16):4437–43
- Koyama T, McHaffie JG, Laurienti PJ, Coghill RC. 2005. The subjective experience of pain: where expectations become reality. *Proc. Natl. Acad. Sci. USA* 102(36):12950–55
- Leuchter AF, Cook IA, Witte EA, Morgan M, Abrams M. 2002. Changes in brain function of depressed subjects during treatment with placebo. *Am. J. Psychiatry* 159:122–29
- Leuchter AF, Morgan M, Cook IA, Dunkin J, Abrams M, et al. 2004. Pretreatment neurophysiological and clinical characteristics of placebo responders in treatment trials for major depression. *Psychopharmacology* 177:15–22
- Levine JD, Gordon NC. 1984. Influence of the method of drug administration on analgesic response. *Nature* 312:755–56
- Levine JD, Gordon NC, Bornstein JC, Fields HL. 1979. Role of pain in placebo analgesia. *Proc. Natl. Acad. Sci. USA* 76:3528–31
- Levine JD, Gordon NC, Fields HL. 1978. The mechanisms of placebo analgesia. *Lancet* 2:654–57
- Linde K, Witt CM, Streng A, Weidenhammer W, Wagenpfeil S, et al. 2007. The impact of patient expectations on outcomes in four randomized controlled trials of acupuncture in patients with chronic pain. *Pain* 128(3):264–71
- Lipman JJ, Miller BE, Mays KS, Miller MN, North WC, et al. 1990. Peak B endorphin concentration in cerebrospinal fluid: reduced in chronic pain patients and increased during the placebo response. *Psychopharmacology* 102:112–16
- Lundh LG. 1987. Placebo, belief, and health. A cognitive-emotional model. *Scand. J. Psychol.* 28(2):128–43
- Mayberg HS, Silva AJ, Brannan SK, Tekell JL, Mahurin RK, et al. 2002. The functional neuroanatomy of the placebo effect. *Am. J. Psychiatry* 159:728–37
- Mayer DJ, Price DD. 1976. Central nervous mechanisms of analgesia. *Pain* 2:379–404
- McKenzie JN. 1896. The production of the so-called “rose-cold” by means of an artificial rose. *Am. J. Med. Sci.* 91:45

- McRae C, Cherin E, Yamazaki G, Diem G, Vo AH, et al. 2004. Effects of perceived treatment on quality of life and medical outcomes in a double-blind placebo surgery trial. *Arch. Gen. Psychiatry* 61:412–20
- Miller EK, Cohen JD. 2001. An integrative theory of prefrontal cortex function. *Annu. Rev. Neurosci.* 24:167–202
- Moerman DE. 2002. Meaningful dimensions of medical care. In *The Science of the Placebo: Toward an Interdisciplinary Research Agenda*, ed. HA Guess, A Kleinman, JW Kusek, LW Engel, pp. 77–107. London: BMJ Books
- Montgomery GH, Kirsch I. 1996. Mechanisms of placebo pain reduction: an empirical investigation. *Psychol. Sci.* 7:174–76
- Montgomery GH, Kirsch I. 1997. Classical conditioning and the placebo effect. *Pain* 72:107–13
- Olness K, Ader R. 1992. Conditioning as an adjunct in the pharmacotherapy of lupus erythematosus. *J. Dev. Behav. Pediatr.* 13:124–25
- Petrovic P, Dietrich T, Fransson P, Andersson J, Carlsson K. 2005. Placebo in emotional processing-induced expectations of anxiety relief activate a generalized modulatory network. *Neuron* 46(6):957–69
- Petrovic P, Kalso E, Petersson KM, Ingvar M. 2002. Placebo and opioid analgesia—imaging a shared neuronal network. *Science* 295:1737–40
- Pollo A, Amanzio M, Arslanian A, Casadio C, Maggi G, et al. 2001. Response expectancies in placebo analgesia and their clinical relevance. *Pain* 93:77–84
- Pollo A, Torre E, Lopiano L, Rizzone M, Lanotte M, et al. 2002. Expectation modulates the response to subthalamic nucleus stimulation in Parkinsonian patients. *NeuroReport* 13:1383–86
- Pollo A, Vighetti S, Rainero I, Benedetti F. 2003. Placebo analgesia and the heart. *Pain* 102:125–33
- Price DD. 2001. Assessing placebo effects without placebo groups: an untapped possibility? *Pain* 90:201–3
- Price DD, Barrell JE, Barrell JJ. 1985. A quantitative-experiential analysis of human emotions. *Motiv. Emot.* 9:19–38
- Price DD, Barrell JJ. 1984. Some general laws of human emotion: interrelationships between intensities of desire, expectation and emotional feeling. *J. Personal.* 52(4):389–409
- Price DD, Barrell JJ. 2000. Mechanisms of analgesia produced by hypnosis and placebo suggestions. *Prog. Brain Res.* 122:255–71
- Price DD, Craggs J, Verne GN, Perlstein WM, Robinson ME. 2007. Placebo analgesia is accompanied by large reductions in pain-related brain activity in irritable bowel syndrome patients. *Pain* 127:63–72
- Price DD, Milling LS, Kirsch I, Duff A, Montgomery GH, et al. 1999. An analysis of factors that contribute to the magnitude of placebo analgesia in an experimental paradigm. *Pain* 83:147–56
- Price DD, Riley J, Barrell JJ. 2001. Are lived choices based on emotional processes? *Cogn. Emot.* 15(3):365–79
- Rainville P, Bao QV, Chetrien P. 2005. Pain-related emotions modulate experimental pain perception and autonomic responses. *Pain* 118(3):306–18
- Schwartz JM, Stapp HP, Beauregard M. 2005. Quantum physics in neuroscience and psychology: a neurophysical model of mind-brain interaction. *Philos. Trans. R. Soc. London B Biol. Sci.* 360:1309–27
- Shetty N, Friedman JH, Kieburtz K, Marshall FJ, Oakes D. 1999. The placebo response in Parkinson's disease. Parkinson study group. *Clin. Neuropharmacol.* 22:207–12

- Vase L, Price DD, Verne GN, Robinson ME. 2004. The contribution of changes in expected pain levels and desire for pain relief to placebo analgesia. In *Psychological Modulation of Pain*. ed. DD Price, M Catherine Bushnell, pp 207–34. Seattle, WA: IASP Press
- Vase L, Riley JL III, Price DD. 2002. A comparison of placebo effects in clinical analgesic trials versus studies of placebo analgesia. *Pain* 99:443–52
- Vase L, Robinson ME, Verne GN, Price DD. 2003. The contributions of suggestion, expectancy and desire to placebo effect in irritable bowel syndrome patients. *Pain* 105:17–25
- Vase L, Robinson ME, Verne GN, Price DD. 2005. Increased placebo analgesia over time in irritable bowel syndrome (IBS) patients is associated with desire and expectation but not endogenous opioid mechanisms. *Pain* 115(3):338–47
- Verne GN, Robinson ME, Vase L, Price DD. 2003. Reversal of visceral and cutaneous hyperalgesia by local rectal anesthesia in irritable bowel syndrome (IBS) patients. *Pain* 105:223–30
- Wager T, Rilling JK, Smith EE, Sokolik A, Casey KL, et al. 2004. Placebo-induced changes in fMRI in the anticipation and experience of pain. *Science* 303(5661):1162–67
- Zubieta J, Smith YR, Bueller JA, Ketner B, Kilbourn MR, et al. 2001. Regional μ -opioid receptor regulation of sensory and affective dimensions of pain. *Science* 293:311–15
- Zubieta JK, Bueller JA, Jackson LR, Scott DJ, Xu Y, et al. 2005. Placebo effects mediated by endogenous opioid activity on μ -opioid receptors. *J. Neurosci.* 25:7754–62

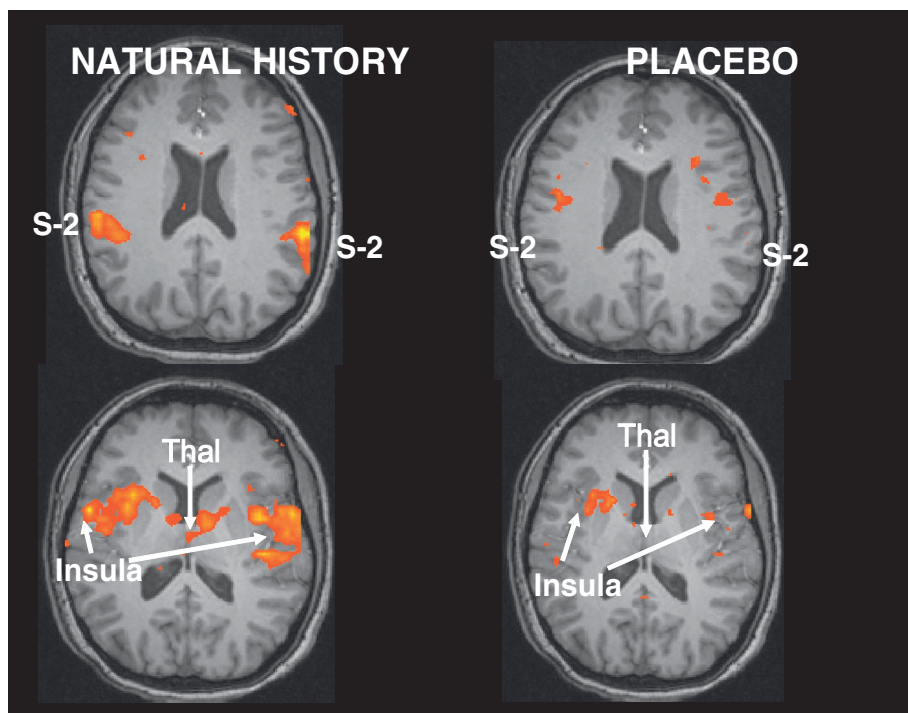


Figure 4

Brain regions showing large reductions in pain-related brain activity, as represented by red-yellow regions, during the placebo condition (*right horizontal brain slices*) compared with untreated natural history or baseline condition (*left horizontal brain slices*). The thalamus (Thal), second somatosensory area (S-2), and insular cortical regions (Insula) showed reduced activity. These functional magnetic resonance images are based on data from Price et al. 2007.