

The Placebo Puzzle: Putting Together the Pieces

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This article outlines and assesses the main theories of the placebo effect and suggests how they might sit together in a larger model of placebo etiology. Among the approaches considered are expectancy theory, emotional change theory, classical conditioning, and the biological approach. Although these are sometimes assumed to be competing models, in many cases they shed light on different parts of the placebo puzzle. Expectancies are the core of most placebo effects in human beings. The effects of expectancies are sometimes unmediated but in other cases are mediated by changes in emotional state, immune system function, perception, or behavior. Although expectancies are implicated in most placebo effects, a small number of placebo effects may be solely attributable to nonconscious contingency learning.

Key words: placebo effect, expectancy, classical conditioning, anxiety, immune system, endogenous opioids

Physicians have long noted a peculiar phenomenon now widely known as *the placebo effect*. In the archetypal instance, a patient is prescribed an agent, unaware that it is merely a placebo (the classic example is a sugar pill), and despite the pharmacological irrelevance of this agent to the patient's condition, the patient then makes a genuine recovery. More generally, a placebo effect is any genuine psychological or physiological response to an inert or irrelevant substance or procedure. Interest in this phenomenon is not confined to medical practitioners. For the philosopher, it raises issues concerning the relationship of mind and body; for the skeptic, it provides a naturalistic explanation for the apparent efficacy of faith healings and so-called alternative medicines; and for the health psychologist, it showcases many of the psychological and behavioral variables that are the subject matter of this field.

Placebo effects have traditionally been attributed to the recipient's belief in the efficacy of a substance or procedure. There are, however, various other approaches to the problem.¹ Unfortunately, the number and plausibility of these approaches creates confusion for anyone wishing to think clearly about the mechanisms underlying the effect. This confusion is heightened by the fact that there is empirical support for each, which indicates that it is not a simple matter of choosing the correct approach and discarding the incorrect ones. Some theoretical integration and conceptual reorganization is required. This is the goal of the present article. Whenever possible, an inclusive approach is taken, guided by the assumption that the various theoretical approaches to the placebo effect each shed some light on the phenomenon and that a full account must synthesize the insights of each.

The article begins with discussion of the theory that the placebo effect is a myth, for if this is correct then any further discussion is unnecessary. However, although skeptics have raised various im-

portant issues regarding admissible evidence for the placebo effect, the best evidence favors the view that the placebo effect is a genuine phenomenon. After this conclusion is established, the next section deals with two of the main approaches to the placebo effect, expectancy theory and classical conditioning. The relationship of these approaches is often misconstrued. Typically, they are pitted against one another, but in fact they are compatible (although note that they are neither two separate but interacting processes nor two different ways of construing the same phenomenon). The subsequent section looks at the issue of how expectancies produce placebo effects. To account for the full range of expectancy-related placebo effects, it is necessary for one to combine the expectancy approach with several other theoretical accounts, including such theories as that placebo effects are a product of emotional change (e.g., anxiety reduction), schematic processing, or change in behavior. Finally, the place of biological approaches in a complete model of the placebo effect is considered. This inevitably raises the issue of the relationship of subjective to objective phenomena.

Before going any further, I think it is important to consider some of the major claims that have been made about the placebo effect. Any complete account of this phenomenon must be able to explain (or explain away) these characteristics. (a) An adequate theory must account for the full range of placebo effects, which includes not only subjective effects but also objectively measurable physiological effects. (b) The theory should account not only for desirable placebo effects but also for undesirable effects. Furthermore, it must account for the clinical observation that placebos can simultaneously produce both desirable and undesirable symptoms. For example, placebos can improve health but also produce placebo side effects (Shapiro, Chassan, Morris, & Frick, 1974). (c) In addition to side effects, placebos mimic other characteristics of the

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¹ The discussion here is limited to proximal causes of the placebo effect. For speculative accounts of the ultimate evolutionary origins of the phenomenon, see Humphrey (2002) and Evans (2003).

active agents they are believed to be. For instance, placebos mimic the dose-response relationship of active agents (e.g., two placebo pills work better than one, and a large capsule better than a smaller one; Buckalew & Ross, 1981; de Craen et al., 1999). (d) Placebo injections produce stronger effects than do placebo capsules and pills (de Craen et al., 1999; Kapitshuk, Goldman, Stone, & Stason, 2000). (e) Stronger placebo effects are found with self-report than with objective measures (Hróbjartsson & Gøtzsche, 2001; Nash & Zimring, 1969). (f) Active placebos (substances or procedures designed to treat one condition but used as placebos for another) appear to amplify the magnitude of placebo effects, producing stronger effects than inactive placebos (Thomson, 1982). (g) Placebo effects are found both in healthy and in ill people. Indeed, some of the best-established placebo effects have involved healthy participants in nonclinical, experimental settings. These include studies using placebo analgesics, placebo stimulants and tranquilizers, and placebo alcohol (Kirsch, 1997). (h) Placebo effects, including placebo analgesia, may be global or localized. In one study (Montgomery & Kirsch, 1996), a placebo anesthetic was applied to one index finger of each participant, and then the same level of pain stimulation was applied to both index fingers. Placebo analgesia was localized to the finger on which the placebo had been applied. At least one research group has replicated this result (Benedetti, Arduino, & Amanzio, 1999).

Explaining Away the Placebo Effect: The Placebo as a Myth

Before investigating any theories of the placebo effect, one must first address the possibility that there are no placebo effects and that the findings presented above are a product of methodological or interpretational errors. A number of arguments have aimed to establish this conclusion. One of the strongest begins with the observation that people often fail to distinguish between placebo effects and placebo responses. A placebo response is any change that occurs after the administration of a placebo (Kirsch & Sapirstein, 1999). This change may be due to many factors, including natural fluctuations in symptoms, spontaneous remission, or regression to the mean (McDonald, Mazzuca, & McCabe, 1983). A placebo effect is the portion of the placebo response, if any, that is attributable to the placebo; that is, it would not have occurred if the placebo had not been administered. The difficulty that arises when placebo responses are not distinguished from placebo effects is that genuine changes in the placebo group may be mistakenly attributed to the administration of a placebo. Claims of placebo efficacy are commonly based on clinical trials in which, following the administration of the placebo, an improvement is shown in the placebo control group. However, few clinical trials include a no-placebo control group, and unless the change in the placebo group can be compared with the change in a no-placebo control group, it is impossible to determine what proportion of the placebo response is a genuine placebo effect. In fact, critics point out that there may be no placebo effect at all. Later, I consider a meta-analysis of clinical trials that did use appropriate control conditions and supposedly confirmed this speculation.

So, one danger is that genuine changes will be misattributed to the placebo. A second danger is that recipients and researchers will conclude that a genuine change has occurred when it has not (Kirsch, 1997). Placebo effects are generally measured with self-

report methods. This opens the door to a number of biases. First, people may not describe their own symptoms accurately or honestly. They may, for instance, exaggerate symptoms before treatment and minimize them afterward (Frank & Frank, 1991). In addition to misrepresentation, self-report data may be distorted by perceptual biases. In other words, there may be no change in the target variable, but the placebo recipient or other observers may falsely perceive that such a change has occurred.² The following example illustrates this point: If a prescribing physician or experimenter tells recipients to expect side effects, the recipients may notice symptoms that they would not have noticed otherwise but that would have occurred anyway (Ross & Olson, 1981). Perceptual biases may not only affect placebo recipients. False placebo effects may also be a product of observer bias. If placebo research is not conducted with double-blind research methodologies, there is the possibility that experimenters will "find" evidence of expected placebo effects even when such evidence is not really there. Finally, in addition to the possibility that taking a placebo creates perceptual bias, it may create a response bias (Morris & O'Neal, 1974). For example, a placebo analgesic may not alter the recipient's pain experience but just raise the criterion for labeling this experience painful (Clark, 1969).

The skeptics' arguments are persuasive and their criticisms pertinent. Between them, they can account for many of the alleged effects of placebos, including reports of subjective and objective effects and both desirable and undesirable effects. Some of the factors outlined, such as natural fluctuations and regression to the mean, are applicable only to clinical populations and to positive, health-related placebo effects and would not explain findings such as the dose-response relationship. However, other factors, such as the perceptual bias and response bias hypotheses, would also account for supposed placebo effects in healthy people. Furthermore, the perceptual bias hypothesis can account for apparent dose-response relationships and for simultaneous desirable and undesirable effects.

As plausible as the skeptics' arguments appear, the issue can of course be settled only by empirical research. Consider first the argument that apparent placebo effects are really due to factors such as spontaneous remission but that this has been overlooked because of the lack of no-placebo control groups in most clinical research. An influential recent meta-analysis (Hróbjartsson & Gøtzsche, 2001) attempted to address this issue. The researchers were able to locate 114 placebo-controlled clinical trials that also included no-treatment control groups. The studies were analyzed in terms of their outcome measures: continuous (e.g., gradations of fever) versus binary (e.g., dead or alive) data and subjective (self-report) versus objective data. The results of their meta-analysis came as a shock to many in the field. No statistically significant effects of placebos were found for either the binary or the objective data. The only significant placebo effects were found for studies using continuous, subjective data.

Hróbjartsson and Gøtzsche's (2001) meta-analysis was taken by many as a demonstration that the placebo effect is a myth. In fact, the results suggest at best that it is weaker than some have claimed

² It is not suggested that changes in the perception of an illness or symptom are unimportant or have no clinical relevance but only that they are not placebo effects.

and that it occurs in a narrower range of clinical conditions and circumstances. Even this conclusion may be unjustified, however, as the study had a number of difficulties that limit the generality of the conclusions that can be drawn from it (Ader, 2001; Brody & Weismantel, 2001; Greene et al., 2001; Kirsch & Scoboria, 2001). Most important, although the researchers were able to do a separate analysis for trials involving pain (and they found a significant effect), their other conclusions were based on combining studies involving a wide range of maladies. As a result, genuine placebo effects in a subset of these conditions may have been undetectable because they were pooled together with conditions in which there are no placebo effects. Also, as the authors themselves hinted, the placebo protocols and outcome measures were not sufficiently similar for a meaningful meta-analysis (Brody & Weismantel, 2001). In addition to these methodological limitations, the study was based solely on clinical data, and its findings need to be weighed against the well-controlled experimental research that consistently demonstrates placebo effects in humans and other animals (for reviews, see Benedetti & Amanzio, 1997; Kirsch, 1997).

Much of this experimental research also escapes the second category of problems, those associated with the use of self-report data. In many cases, subjective reports have been corroborated by objective measurements. For instance, changes in reported pain levels have been corroborated by indirect evidence suggesting that placebo analgesics sometimes increase the rate of activation of endorphin systems and other pain systems in the brain (Amanzio & Benedetti, 1999; Benedetti & Amanzio, 1997; Levine, Gordon, & Fields, 1978; see Biological Approaches section). Similarly, changes in reported arousal have been corroborated by objective measurements of physiological parameters such as blood pressure and heart rate (Frankenhaeuser, Jarpe, Svan, & Wrangsjö, 1963; Kirsch & Weixel, 1988). Further support for the view that apparent placebo effects are not due merely to self-report biases comes from the fact that placebo effects have been found in nonhuman animals, and research on these animals is of course not based on self-report data. The findings in question include a placebo response to amphetamines (Herrnstein, 1962) and placebo-induced immunosuppression (Ader & Cohen, 1975, 1982, 1991).

Overall, the evidence favors the view that the placebo effect is a genuine phenomenon and not merely a product of misattribution or misperception. Nonetheless, the criticisms made of the current placebo literature lead to several conclusions about what constitutes admissible evidence for the placebo effect. First, there must be a control group or no-treatment group or some other methodology that makes it possible to determine whether any changes are due to the administration of the placebo. Second, whenever possible, self-report measures should be accompanied by objective measurements such as physiological recordings, as objective measurements avoid the problem of demand characteristics, perceptual biases, and response biases. Finally, research into the placebo effect should be conducted with double-blind methodology to avoid the possibility of experimenter bias.

Expectancy and Conditioning

Accepting that placebos sometimes produce placebo effects, how can researchers account for this fact? The two main functional approaches to the placebo effect are expectancy theory and clas-

sical conditioning. These approaches provide a foundation for explanations of the placebo effect. As discussed below, however, the relationship between them is often misunderstood. (A detailed discussion of this issue can be found in Stewart-Williams & Podd, 2004.)

Expectancy Theory

Expectancy theory has become one of the most popular theories of the placebo effect. In this account, a hypothetical expectancy (e.g., "If I take drug X, I will experience effect Y") sets the stage for a placebo effect. Taking a placebo then produces a categorical expectancy (e.g., "I will experience effect Y"), and it is this belief that produces the placebo effect. People may acquire hypothetical expectancies in a number of ways. One is through direct personal experience. Other factors shaping expectancies include verbal information (suggestion), observational learning, and common factors in therapy (e.g., the quality of a therapeutic relationship, the normalization of symptoms, provider attention and care, and receiving a diagnosis). Personal experience appears to be more effective in shaping expectancies and placebo effects than manipulations such as verbal suggestion (Montgomery & Kirsch, 1997).

There is good experimental support for the expectancy account. For instance, it has been shown that expectancies predict placebo analgesia (Amanzio & Benedetti, 1999; Montgomery & Kirsch, 1997) and placebo-induced physiological arousal (Kirsch & Weixel, 1988). Expectancy theory also has a number of theoretical advantages. If the expectation of an effect helps to bring about that effect, then the theory can account for any effects for which a person can develop an expectation. Consequently, the theory can account for simultaneous positive and negative effects, placebo effects in healthy people, and localized placebo effects (Montgomery & Kirsch, 1996). Expectancy theory also offers an explanation for the greater efficacy of active placebos: The side effects produced by active placebos enhance people's expectancies and consequently enhance the placebo effect.

Despite these advantages, however, expectancy theory has a number of shortcomings. First, although expectancies are often associated with placebo effect magnitude (de Jong, van Baast, Arntz, & Merkelpach, 1996; Montgomery & Kirsch, 1997; Nash & Zimring, 1969; Price et al., 1999), this correlation is not always found (Spanos et al., 1993; Spanos, Perlini, & Robertson, 1989). Furthermore, cognitions other than expectancies may contribute to placebo effects. For instance, research suggests that people who experience placebo analgesia engage in more cognitive coping and less catastrophizing than nonresponders (Spanos et al., 1989). As well as contributing to genuine placebo effects, people's expectations may also increase the likelihood that they will perceive an effect when none has occurred. Finally, there is some ambiguity in the expectancy construct. Some maintain that expectancies should be defined as consciously accessible mental entities (Kirsch, Lynn, Vigorito, & Miller, in press), but others suggest that we should also allow unconscious expectancies (Hahn, 1997). There are a number of difficulties with the latter position. Expectancies are measured by self-report, which seems to imply the view that they are available to conscious scrutiny. If expectancies can be unconscious, then this is not what the expectancy research is measuring. Furthermore, the idea of unconscious expectancies is scientifically suspect, as it seems to make expectancy theory immune to falsi-

fication. Given these considerations, it is best assumed that expectancies are consciously accessible mental items. (For further discussion, see Stewart-Williams & Podd, 2004.)

Classical Conditioning

Another important approach to the placebo effect is based on classical conditioning research. According to traditional descriptions, classical (or Pavlovian) conditioning occurs when an organism is exposed to the repeated pairing of an unconditioned stimulus (US) and a conditioned stimulus (CS). The US is a stimulus that elicits an unlearned or unconditioned response (UR). Initially, the CS has no such effects. After sufficient CS-US pairing trials, however, the CS presented in the absence of the US elicits a response similar or related to the UR. This is known as a conditioned response (CR; Pavlov, 1927). Modern accounts of classical conditioning stress the information value of the CS, in terms of predicting the subsequent occurrence of the US (Kamin, 1968, 1969; Rescorla, 1968, 1988; Rescorla & Wagner, 1972). Conditioned learning does not depend only on the association of events. It generally occurs when there is a CS-US contingency, that is, when the CS is a reliable signal that the US will occur in the future (Wasserman & Miller, 1997). As a result of exposure to this contingency, subsequent exposure to the CS elicits a representation of the US (Domjan, 1993). The CR is a simple response to this representation, the evolutionary function of which is to prepare the organism for the upcoming presentation of the US (Siegel, 1984, 1989).

The classical conditioning account of the placebo effect has typically been framed in terms of the earlier model of conditioning. In this model, the active ingredient in a treatment is the US, and its pharmacological effects the UR. During a course of therapy, the active ingredient is paired with various stimuli, such as syringes, pill casings, or even the entire therapeutic setting. As a result of this pairing, these stimuli acquire the capacity to elicit a response similar to that produced by the active ingredients (Wickramasekera, 1985). In this framework, a placebo is a CS, and a placebo effect is a CR. Although this formulation is acceptable as far as it goes, the traditional account of classical conditioning on which it is based is outdated (Rescorla, 1988). In a more modern account, it might be added that conditioned placebo effects occur when an individual learns that certain stimuli reliably and uniquely predict the presentation of an active ingredient. The placebo effect is a response to this information.

The classical conditioning framework furnishes a number of testable predictions and suggests ways to maximize placebo effects. For example, on the basis of classical conditioning research, it would be predicted that the number of pairings of the CS and the US will determine the magnitude of the placebo effect and that therapists who routinely use active ingredients or powerful drugs will get stronger placebo effects than those who routinely use inert ingredients or weaker drugs (Wickramasekera, 1985). A further prediction is that placebo effects established through continuous reinforcement schedules will typically extinguish more rapidly than those established on intermittent schedules of reinforcement (Ader, 1997). Finally, Ader (1985) has suggested that an intermittent schedule (e.g., active drug 70% of the time, placebo 30% of the time) may be just as effective as a schedule of continuous reinforcement (i.e., active drug 100% of the time).

Conditioned learning may occur for any effects that an active agent can generate. Consequently, the classical conditioning framework can be applied to placebo effects in subjective or objective dimensions; desirable effects, undesirable effects, or the simultaneous occurrence of both; global or localized effects; and effects in both healthy and sick people. A stronger US produces a stronger CR, which fits with the fact that stronger effects are produced by placebo injections than by placebo pills and capsules. Similarly, a stronger CS produces a stronger CR, accounting for the dose-response relationship.

Relationship of Conditioning to Expectancy

On the one hand, classical conditioning is often pitted against expectancy theory as an explanation for the placebo effect, perhaps because it is assumed that conditioning is by definition a noncognitive form of learning. On the other hand, some theorists claim that the two approaches are compatible. This would be the case, for instance, if they were two ways of construing the same phenomenon (e.g., a physiological and a psychological perspective, or a third-person and a first-person perspective) or two distinct but interacting processes (in which case some placebo effects might be due to conditioning, some to expectancy, and some to a combination of the two). Both these approaches must be rejected, for both are based on a faulty initial assumption: that the two approaches are answers to the same question. However, unlike the expectancy approach, classical conditioning is not a theory. This is clear when it is considered that there are various different theories that aim to account for classically conditioned phenomena. Furthermore, whereas expectancy theory focuses on a psychological variable, classical conditioning is defined solely in terms of a certain relationship between stimulus inputs and subsequent outputs. More precisely, it occurs when exposure to a contingency between a CS and a US results in a change in the organism's behavior, physiology, or psychological state. This leaves open the question of the mediation of classically conditioned effects, that is, the mediation of the conditioned CS-CR link (Stewart-Williams & Podd, 2004).³

Some placebo effects fit the classical conditioning mold: Exposure to a CS-US contingency (input) shapes a placebo effect to the CS (output). In some cases, the learning underlying conditioned placebo effects appears to be nonconscious, in line with the common perception of conditioning. One research group, for instance, demonstrated that following conditioning with opioids, a placebo in the guise of an opioid drug could evoke respiratory depression for which the recipient had no expectation (Benedetti et al., 1998;

³ It might be argued that conditioning is by definition a nonconscious learning mechanism. However, common usage of the term is inconsistent with this view: Regardless of their position on the issue, it makes sense to most people to ask whether classical conditioning is mediated by conscious cognition. If conditioning were by definition a nonconscious process, this question would make no more sense than asking whether bachelors are married or unmarried.

Benedetti, Amanzio, Baldi, Casadio, & Maggi, 1999).⁴ In other cases, however, placebo effects shaped by conditioning procedures are mediated by conscious expectancies. For example, in a series of experiments, Voudouris, Peck, and Coleman (1985, 1989, 1990) showed that a conditioning manipulation could enhance the placebo analgesic response to an inert cream. Later investigation suggested that this effect was mediated entirely by the change the manipulation produced in the participants' expectancies concerning the cream (Montgomery & Kirsch, 1997). This is not to deny that it was an instance of classical conditioning but rather to specify the mechanism of this conditioned placebo effect.

So, some placebo effects are examples of classical conditioning, and of these some are mediated by expectancies whereas others are not cognitively mediated. In addition, not all expectancy-mediated placebo effects are examples of classical conditioning. Some are shaped by verbal information rather than a CS-US contingency and therefore do not fit the input-output pattern that defines classical conditioning. Note that this is not to argue that some placebo effects are due to expectancy, others to conditioning, and others still to a combination of both. That would be to suppose that classical conditioning is a specific form of learning, inevitably distinct from processes of expectancy. This is not the case, however. As noted, conditioning is defined solely in terms of a particular relationship between stimulus inputs and behavioral, physiological, or psychological outputs, and in some cases expectancy learning mediates this relationship. In short, expectancy mediates some but not all placebo effects, and classical conditioning procedures are one of the various sources of learning that can lead to placebo effects.

How Do Expectancies Produce Placebo Effects?

Although not all placebo effects are mediated by conscious expectancies, expectancies appear to play a pivotal role in most placebo effects in humans. A key task facing expectancy theorists is to explain how expectancies can result in placebo effects. One suggestion comes from Kirsch's (1997) response expectancy theory, according to which "some of the effects of expectancy may be direct, rather than mediated" (p. 175). In clearing the ground for this view, Kirsch (1997) pointed out that some connections among variables must be unmediated, or else there would be an infinite regress of intervening variables. As such, there is no difficulty in the notion that expectations for subjective states can lead directly to those states. Although it is not clear that all subjective effects can be explained in this way, in some cases Kirsch's (1997) hypothesis has an intuitive plausibility. For instance, the expectation of anxiety is likely to be anxiety provoking, and the expectation of depression is likely to be depressing (Kirsch, 1985, 1997). As discussed later, however, there are other ways to explain subjective placebo effects.

In addition to subjective effects, Kirsch (1985) noted that expectancy theory can account for some objectively measurable effects of placebos without invoking mediating variables. The effects in question are autonomic responses directly connected with subjective states. These include blood pressure and heart rate, which are associated with subjective experiences of arousal and relaxation. Kirsch (1997) suggested that expectancy theory has more trouble accounting for other physiological effects, effects that are not intimately and immediately linked with subjective

states. If expectancies do produce such effects, it may be necessary to invoke mediating variables. A number of other cognitive theories of the placebo effect may be relevant in this connection. Although none has made the headway that expectancy theory has, there is reason to suppose that each may contribute to an expectancy-based model of the placebo effect. In the following sections, roles are found for emotional change, schematic processing, and behavior change in mediating between expectancies and subsequent placebo effects.

Emotional Change Theory

First, let us consider the theory that placebo effects are a product of emotional change. This is most commonly discussed in terms of anxiety reduction. The idea is this: When people take placebos that they think will lead to the amelioration of unpleasant symptoms or that enhance their sense of mastery and control over a disease, this is likely to promote a reduction in anxiety and stress, which in turn may lead to improvements in psychological and physical health (Brody & Brody, 2000; Lick & Bootzin, 1975; Lundh, 1987). Reduced levels of depression and demoralization may provide a further contribution (Frank & Frank, 1991). Emotional change theory is not limited to the explanation of desirable effects of placebos. If a placebo can have desirable effects by making one less anxious or depressed, it can presumably also have undesirable effects by making one more anxious or depressed.

Changes in emotional state may exert their influence via a number of channels. First, such changes can influence other subjective variables. For example, anxiety can exacerbate pain, and consequently a reduction in anxiety would be expected to reduce pain (Benedetti & Amanzio, 1997; Staats, Hekmat, & Staats, 1998). Second, emotional change theory is associated with a plausible mechanism through which emotional states may influence physical health and thereby account for some objectively measurable placebo effects. The growing field of psychoneuroimmunology investigates how mental states influence the immune system (Maier, Watkins, & Fleshner, 1994). Chronic anxiety, stress, and depression impair immune system function (Lundh, 2000). Consequently, lessening these emotional states may enhance the healing process.⁵ Various other factors may also contribute to placebo-induced improvements in physical health. For instance, decreased anxiety may lead to improved sleep patterns, or decreased depression to greater levels of activity; both of these factors may contribute to improved health.

⁴ It was noted earlier that most modern classical conditioning theorists view conditioning as a process in which the CS acquires the capacity to elicit a mental representation of the US. This representation is sometimes explicitly identified as an expectation. In this view, all conditioning would be mediated by expectancy. As noted, however, there are strong reasons to restrict the definition of expectancies to consciously accessible mental states. Under this definition, classical conditioning is sometimes but not always mediated by expectancies.

⁵ Sometimes the improved healing rates found in people taking placebos may be due to a release from negative placebo effects. In such cases, rather than contributing a new, positive influence to health, placebos may simply allow the natural healing process to take place uninhibited by negative placebo effects. This would account only for placebo effects in people with health problems.

Although emotional change theory can account for desirable effects and undesirable effects, it cannot easily account for the simultaneous occurrence of both (Kirsch, 1985). This is because, according to this account, desirable and undesirable placebo effects are produced by opposite causes (e.g., high vs. low anxiety), which logic dictates cannot occur simultaneously. Another shortcoming is that none of the emotional changes suggested can account for placebo effects in normal, healthy individuals (Kirsch, 1997). Furthermore, because emotional change is a global mechanism, it cannot account for localized placebo effects, such as the localized placebo analgesia demonstrated by Montgomery and Kirsch (1996) and Benedetti, Arduino, and Amanzio (1999). Note, though, that even if emotional change cannot account for all placebo effects, there is research to suggest that it does play a role in some (see de Jong et al., 1996).

It may be possible to incorporate emotional change into an expectancy-based account of the placebo effect. The relevant emotional changes are presumably not direct responses to a placebo; instead, they may be responses to placebo-induced expectancies. For instance, the expectation that one will recover from an illness is likely to reduce anxiety about the illness. This emotional change may sometimes mediate the relationship between expectancies and placebo effects. As yet, this hypothesis has not been subjected to direct empirical test. Such a test would be a valuable contribution to the placebo literature.

Perceptual Change: The Schematic Processing Approach

Another suggestion concerning the etiology of the placebo effect is that it is a product of selective processing (Jensen & Karoly, 1985; Pennebaker & Skelton, 1981). This approach can be usefully framed in the language of schema theory. Taking a placebo activates a cognitive schema of the expected effects. Once this schema has been activated, people are more likely to (a) notice and recall any information or experience consistent with that schema, (b) interpret ambiguous information in a manner consistent with the schema, and (c) overlook mildly inconsistent information or dismiss it as invalid (Fiske & Taylor, 1991; Pennebaker & Lightner, 1980; Pennebaker & Skelton, 1981). Expecting relief from an illness, for example, people might notice small positive changes they would otherwise have overlooked and overlook small negative changes they would otherwise have noticed (Peck & Coleman, 1991).

In themselves, these changes in perception would not constitute placebo effects; they might simply lead a person to infer that an effect has occurred when it has not. For example, chronic pain patients taking placebo analgesics might "remember" having experienced less pain than they did prior to the placebo but actually have experienced as much as ever. This is the main problem with the original formulation of the selective processing approach. However, schematic processing may indirectly shape genuine subjective placebo effects. Various lines of research suggest that attending to internal experiences such as sensations and emotions can amplify these experiences (Franzoi, 1996). By attending to pain, for instance, a person might actually experience more pain. Similarly, in hypochondriasis, the conviction that one has a particular disease appears to amplify the experience of any supposed symptoms (Avia, 1999; Barsky, 1992). This suggests a route by which schema-mediated changes in perception and attention could

lead to genuine placebo effects, if only in subjective experience. Simply stated, placebos activate schemas, schemas direct attention, and self-directed attention intensifies that to which we attend.

The above examples of attentional amplification may create the impression that the proposed mechanism is applicable only to undesirable effects, such as the intensification of pain or undesirable somatic symptoms. However, the mechanism would apply to any subjective state for which a person has a schema, including desirable states such as positive mood. It may even account for placebo effects that involve the amelioration of a state, such as the reduction of pain. The reception of a placebo analgesic, for instance, might activate a schema of a pain-free state. The recipient's attention would then be diverted from any nonsevere pain and refocused on sensations that are indicative for the recipient of a pain-free state. As a result, the latter sensations may increase in intensity whereas the former are eclipsed. At this stage, there is little research pertaining to the possible role of schematic processing and attention in the placebo effect. If these variables are involved, however, they may help to explain how expectancies can bring about the expected subjective effects: The formation of a categorical expectancy can be interpreted as the activation of a schema of the expected effects of the placebo, and the effects of the expectancy may be a product of its influence on attention and the subsequent effects of attention on subjective state.

Behavioral Change

In addition to changes in perception and emotional state, placebos may promote changes in behavior, and these may in turn contribute to the production of placebo effects (Turner, Deyo, Loeser, Von Korff, & Fordyce, 1994). For instance, when people believe they are recovering from an illness, they are likely to feel happier and socialize more. This behavior may reduce loneliness and enhance social support, which could lead to improved immune system function and thus improved health. The behavior of other individuals in the patient's environment may also be relevant. If others believe a positive change in health status has occurred, they may act toward patients in ways that encourage them to be more active as opposed to acting in ways that may reinforce the sick role. Notice that these speculations apply only to health-related placebo effects, and as a result that this approach is somewhat limited in its explanatory power. Nonetheless, behavioral change may shed some light on the mechanisms through which expectancies bring about this subset of placebo effects. As such, it may be possible to bring behavioral change under the umbrella of an expectancy account. The changes in behavior that result in health-related placebo effects might follow from altered expectancies (e.g., the expectation of improved health) or from expectancy-induced changes in emotional state. In short, behavioral change may be one among several variables that mediates the connection between expectancies and placebo effects and takes its place alongside emotional change and schematic processing.

Biological Approaches

The major focus of the present article is the psychological factors involved in the placebo effect, not their biological correlates. Nevertheless, the correlates of a number of placebo effects have been uncovered, and it is important to put these into the

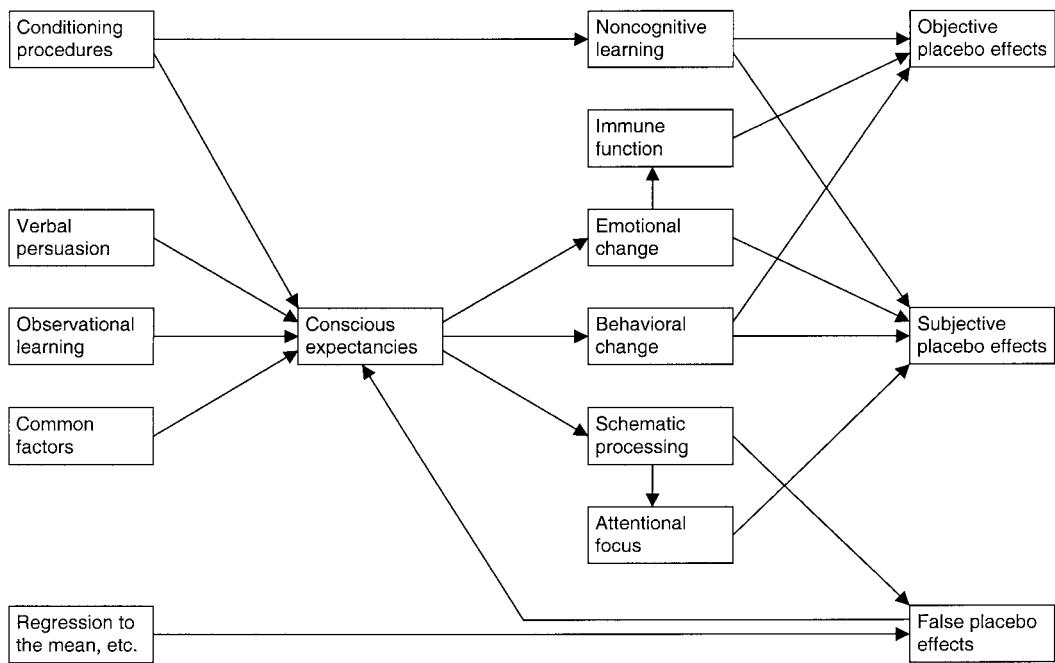


Figure 1. An integrative model of the placebo effect.

context of the present discussion. By far the most famous discovery related to the neurobiology of the placebo effect concerns the opioid antagonist naloxone, which, as noted earlier, sometimes blocks placebo analgesia (Benedetti & Amanzio, 1997; Fields & Levine, 1984; Levine et al., 1978). Similarly, blocking cholecystokinin, a neuropeptide that has antiopioid effects, leads to heightened placebo analgesia (Benedetti & Amanzio, 1997). The implication of these findings is that endogenous opioids (endorphins) are involved in some instances of placebo analgesia.⁶

The endorphin discovery is often presented as a theory of the placebo effect, in competition with psychological explanations such as expectancy theory. Kirsch (1985) argued, however, that rather than being another theory of the placebo effect, endorphin release is better construed as an example of a placebo effect, one set in motion by such factors as expectancies. Another reason to be wary of the idea that endorphin release is a theory of the placebo effect comes from consideration of the relationship of mind to brain. Although there are a variety of possible solutions to this age-old philosophical question, the dominant view among modern philosophers is that mind and brain activity are somehow one and the same thing (Dennett, 1991). From this perspective, it might be argued that endorphin release is not the cause of placebo analgesia; instead, endorphin activity *is* placebo analgesia, viewed from a biological rather than a psychological perspective. This would imply that the biological perspective is not an alternative theoretical account competing with psychological accounts of the placebo effect. It is an analysis of the same phenomenon from a different perspective.

Putting Together the Pieces

The preceding discussion has touched on some of the connections and consistencies among the different approaches to the

placebo effect. Figure 1 shows how these pieces might fit together. On the left of the figure are some of the main factors thought to be involved in the shaping of placebo effects. On the right are three placebo outcomes: subjective placebo effects, objectively measurable placebo effects, and false placebo effects.⁷ The figure depicts various possible paths from shaping factors to placebo outcomes. First, conditioning procedures may result in noncognitive learning or in the formation of consciously accessible expectancies. (In other words, classically conditioned placebo effects may or may not be mediated by conscious expectancies.) In contrast, variables

⁶ Other recent findings related to the neurobiology of the placebo effect include the discovery that the placebo effect in Parkinson's disease is mediated by an increased level of endogenous dopamine in the striatum (de la Fuente-Fernandez & Stoessl, 2002) and that dopamine mediates placebo-induced enhancement of motor performance (Benedetti, 2002).

⁷ If it is accepted that mind is equivalent to brain activity, the distinction between subjective and objective effects may seem somewhat problematic and arbitrary. After all, if subjective experiences are isomorphic with patterns of activity in the brain, then in principle direct objective measurements could be made of subjective experiences. In practice, though, the distinction is useful most of the time. The subjective category embraces all conscious bodily activity (i.e., some brain activity), whereas the objective category usually refers to nonconscious bodily activity outside the brain (e.g., heart beat, which although we may be conscious of it, is not itself a conscious experience). The distinction breaks down only when objective measurements are made of conscious bodily activity (e.g., through brain imaging), at which time we must recognize that the terms *subjective* and *objective* do not label two distinct ontological kinds but rather two different perspectives on the same thing. The objective perspective consists of brain activity viewed from the perspective of an outside observer, whereas the subjective perspective consists of brain activity viewed from the perspective of the acting brain itself.

such as verbal persuasion, observational learning, and common factors in therapy presumably shape only conscious expectancies. Other variables, such as regression to the mean, natural fluctuations in an illness, spontaneous remission, and perceptual biases, may result in false placebo effects.

Noncognitive learning may result in both subjective and objectively measurable placebo effects. In contrast, expectancies may directly produce subjective placebo effects (Kirsch, 1997), or the effects of expectancies may be mediated by emotional change, behavioral change, or schematic processing. Like noncognitive learning, behavioral change may lead to both subjective and objective placebo effects. Emotional change may lead directly to (other) subjective effects, and may indirectly result in objective placebo effects, via its influence on the functioning of the immune system. Schematic processing may lead directly to false placebo effects and may indirectly result in genuine subjective placebo effects through the amplification of subjective states that occurs when people focus their attention on these states. Figure 1 also suggests that false placebo effects may influence the recipient's expectancies about placebos, which in turn may increase the likelihood of genuine placebo effects in the future.

This model of the placebo effect provides a tidy framework for locating research efforts and a reminder that these approaches are not necessarily in competition. The placebo effect is a complex phenomenon and is likely to involve the interplay of a variety of factors. An understanding of these factors may be of assistance to health professionals. It may, for example, enable them to maximize therapeutic benefits without the use of stronger drugs or larger doses. However, some of the mechanisms involved in the placebo effect may be better accessed by means other than the use of placebos. For instance, if the reduction of anxiety and depression enhances physical health, psychotherapy may be superior to the use of placebos in producing this emotional change. Nonetheless, as this very example shows, research into the mechanisms underlying the placebo effect may be extremely valuable, as it can be expected to yield knowledge that will prove useful beyond the context of placebo use.

References

Ader, R. (1985). Conditioned immunopharmacological effects in animals: Implications for a conditioning model of pharmacotherapy. In L. White, B. Tursky, & G. E. Schwartz (Eds.), *Placebo: Theory, research, and mechanisms* (pp. 306–323). New York: Guilford Press.

Ader, R. (1997). The role of conditioning in pharmacotherapy. In A. Harrington (Ed.), *The placebo effect: An interdisciplinary exploration* (pp. 138–165). Cambridge, MA: Harvard University Press.

Ader, R. (2001). Much ado about nothing. *Advances in Mind-Body Medicine*, 17, 293–295.

Ader, R., & Cohen, N. (1975). Behaviorally conditioned immunosuppression. *Psychosomatic Medicine*, 37, 333–340.

Ader, R., & Cohen, N. (1982, March 19). Behaviorally conditioned immunosuppression and murine systemic lupus erythematosus. *Science*, 215, 1534–1536.

Ader, R., & Cohen, N. (1991). The influence of conditioning on immune responses. In R. Ader, D. L. Felten, & N. Cohen (Eds.), *Psychoneuroimmunology* (2nd ed., pp. 611–646). San Diego, CA: Academic Press.

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.

Avia, M. D. (1999). The development of illness beliefs. *Journal of Psychosomatic Research*, 47, 199–204.

Barsky, A. J. (1992). Amplification, somatization, and the somatoform disorders. *Psychosomatics*, 33, 28–34.

Benedetti, F. (2002). How the doctor's words affect the patient's brain. *Evaluation and the Health Professions*, 25, 369–386.

Benedetti, F., & Amanzio, M. (1997). The neurobiology of placebo analgesia: From endogenous opioids to cholecystokinin. *Progress in Neuropathology*, 52, 109–125.

Benedetti, F., Amanzio, M., Baldi, S., Casadio, C., Cavallo, A., Mancuso, M., et al. (1998). The specific effects of prior opioid exposure on placebo analgesia and placebo respiratory depression. *Pain*, 75, 313–319.

Benedetti, F., Amanzio, M., Baldi, S., Casadio, C., & Maggi, G. (1999). Inducing placebo respiratory depressant responses in humans via opioid receptors. *European Journal of Neuroscience*, 11, 625–631.

Benedetti, F., Arduino, C., & Amanzio, M. (1999). Somatotopic activation of opioid systems by target-directed expectations of analgesia. *Journal of Neuroscience*, 19, 3639–3648.

Brody, H., & Brody, D. (2000). Three perspectives on the placebo response: Expectancy, conditioning, and meaning. *Advances in Mind-Body Medicine*, 16, 216–232.

Brody, H., & Weismantel, D. (2001). A challenge to core beliefs. *Advances in Mind-Body Medicine*, 17, 296–298.

Buckalew, L. W., & Ross, S. (1981). Relationship of perceptual characteristics to efficacy of placebos. *Psychological Reports*, 49, 955–961.

Clark, W. C. (1969). Sensory decision theory analysis of placebo effect on the criterion for pain and thermal sensitivity (d'). *Journal of Abnormal Psychology*, 74, 363–371.

de Craen, A. J. M., Moerman, D. E., Heisterkamp, S. H., Tytgat, G. N. J., Tijssen, J. P. G., & Kleijnen, J. (1999). Placebo effect in the treatment of duodenal ulcer. *British Journal of Clinical Pharmacology*, 48, 853–860.

de Jong, P. J., van Baast, R., Arntz, A., & Merkelbach, H. (1996). The placebo effect in pain reduction: The influence of conditioning experiences and response expectancies. *International Journal of Behavioral Medicine*, 3, 14–29.

de la Fuente-Fernandez, R., & Stoessl, A. J. (2002). The biochemical bases for reward: Implications for the placebo effect. *Evaluation and the Health Professions*, 25, 387–398.

Dennett, D. C. (1991). *Consciousness explained*. New York: Little, Brown.

Domjan, M. (1993). *The principles of learning and behavior*. Pacific Grove, CA: Brooks/Cole.

Evans, D. (2003). *Placebo: The belief effect*. London: HarperCollins.

Fields, H. L., & Levine, J. D. (1984). Placebo analgesia: A role for endorphins? *Trends in Neurosciences*, 7, 271–273.

Fiske, S. T., & Taylor, S. E. (1991). *Social cognition* (2nd ed.). New York: McGraw-Hill.

Frank, J. D., & Frank, J. B. (1991). *Persuasion and healing: A comparative study of psychotherapy* (3rd ed.). Baltimore: Johns Hopkins University Press.

Frankenhaeuser, M., Jarpe, G., Svan, H., & Wrangsjö, B. (1963). Psychophysiological reactions to two different placebo treatments. *Scandinavian Journal of Psychology*, 4, 245–250.

Franzoi, S. L. (1996). *Social psychology*. Madison, WI: Brown & Benchmark.

Greene, P. J., Wayne, P. M., Kerr, C. E., Weiger, W. A., Jacobson, E., Goldman, P., & Kapchuk, T. J. (2001). The powerful placebo: Doubting the doubters. *Advances in Mind-Body Medicine*, 17, 298–307.

Hahn, R. A. (1997). The nocebo phenomenon: Scope and foundations. In A. Harrington (Ed.), *The placebo effect: An interdisciplinary exploration* (pp. 56–76). Cambridge, MA: Harvard University Press.

Herrnstein, R. J. (1962, November 9). Placebo effect in the rat. *Science*, 138, 677–678.

Hróbjartsson, A., & Gøtzsche, P. C. (2001). Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. *New England Journal of Medicine*, 344, 1594–1602.

Humphrey, N. K. (2002). Great expectations: The evolutionary psychology of faith-healing and the placebo effect. In C. von Hofsten & L. Backman (Eds.), *Psychology at the turn of the millennium: Vol. 2. Social, developmental, and clinical perspectives* (pp. 225–246). Florence, KY: Routledge.

Jensen, M. P., & Karoly, P. (1985). Control theory and multiple placebo effects. *International Journal of Psychiatry in Medicine*, 15, 137–147.

Kamin, L. J. (1968). "Attention-like" processes in classical conditioning. In M. R. Jones (Ed.), *Miami symposium on the prediction of behavior: Aversive stimulation* (pp. 9–31). Miami, FL: University of Miami Press.

Kamin, L. J. (1969). Predictability, surprise, attention, and conditioning. In B. A. Campbell & R. M. Church (Eds.), *Punishment and aversive behavior* (pp. 279–296). New York: Appleton-Century-Crofts.

Kaptchuk, T. J., Goldman, P., Stone, D. A., & Stason, W. B. (2000). Do medical devices have enhanced placebo effects? *Journal of Clinical Epidemiology*, 53, 786–792.

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

Kirsch, I. (1997). Specifying nonspecifics: Psychological mechanisms of placebo effects. In A. Harrington (Ed.), *The placebo effect: An interdisciplinary exploration* (pp. 166–186). Cambridge, MA: Harvard University Press.

Kirsch, I., Lynn, S. J., Vigorito, M., & Miller, R. R. (in press). The role of cognition in classical and operant conditioning. *Journal of Clinical Psychology*.

Kirsch, I., & Sapirstein, G. (1999). Listening to Prozac but hearing placebo: A meta-analysis of antidepressant medications. In I. Kirsch (Ed.), *How expectancies shape experience* (pp. 303–320). Washington, DC: American Psychological Association.

Kirsch, I., & Scoboria, A. (2001). Apples, oranges, and placebos: Heterogeneity in a meta-analysis of placebo effects. *Advances in Mind-Body Medicine*, 17, 307–309.

Kirsch, I., & Weixel, L. J. (1988). Double-blind versus deceptive administration of a placebo. *Behavioral Neuroscience*, 102, 319–323.

Levine, J. D., Gordon, N. C., & Fields, H. L. (1978). The mechanism of placebo analgesia. *Lancet*, 2, 654–657.

Lick, J., & Bootzin, R. (1975). Expectancy factors in the treatment of fear: Methodological and theoretical issues. *Psychological Bulletin*, 82, 917–931.

Lundh, L.-G. (1987). Placebo, belief, and health: A cognitive-emotional model. *Scandinavian Journal of Psychology*, 28, 128–143.

Lundh, L.-G. (2000). Suggestion, suggestibility, and the placebo effect. *Hypnosis International Monographs*, 4, 71–90.

Maier, S. F., Watkins, L. R., & Fleshner, M. (1994). Psychoneuroimmunology: The interface between behavior, brain, and immunity. *American Psychologist*, 49, 1004–1017.

McDonald, C. J., Mazzuca, S. A., & McCabe, G. P. J. (1983). How much of the placebo "effect" is really statistical regression? *Statistics in Medicine*, 2, 417–427.

Montgomery, G., & Kirsch, I. (1996). Mechanisms of placebo pain reduction: An empirical investigation. *Psychological Science*, 7, 174–176.

Montgomery, G. H., & Kirsch, I. (1997). Classical conditioning and the placebo effect. *Pain*, 72, 107–113.

Morris, L. A., & O'Neal, E. C. (1974). Drug-name familiarity and the placebo effect. *Journal of Clinical Psychology*, 30, 280–282.

Nash, M. M., & Zimring, F. M. (1969). Prediction of reaction to placebo. *Journal of Abnormal Psychology*, 74, 568–573.

Pavlov, I. P. (1927). *Conditioned reflexes*. London: Oxford University Press.

Peck, C., & Coleman, G. (1991). Implications of placebo theory for clinical research and practice in pain management. *Theoretical Medicine*, 12, 247–270.

Pennebaker, J. W., & Lightner, J. M. (1980). Competition of internal and external information in an exercise setting. *Journal of Personality and Social Psychology*, 39, 165–174.

Pennebaker, J. W., & Skelton, J. A. (1981). Selective monitoring of physical sensations. *Journal of Personality and Social Psychology*, 41, 213–223.

Price, D. D., Milling, L. S., Kirsch, I., Duff, A., Montgomery, G. H., & Nicholls, S. S. (1999). An analysis of factors that contribute to the magnitude of placebo analgesia in an experimental paradigm. *Pain*, 83, 147–156.

Rescorla, R. A. (1968). Probability of shock in the presence and absence of CS in fear conditioning. *Journal of Comparative and Physiological Psychology*, 66, 1–5.

Rescorla, R. A. (1988). Pavlovian conditioning: It's not what you think it is. *American Psychologist*, 43, 151–160.

Rescorla, R. A., & Wagner, A. R. (1972). A theory of Pavlovian conditioning: Variations in effectiveness of reinforcement and nonreinforcement. In A. H. Black & W. F. Prokasy (Eds.), *Conditioning II: Current research and theory* (pp. 64–99). New York: Appleton-Century-Crofts.

Ross, M., & Olson, J. M. (1981). An expectancy-attribution model of the effects of placebos. *Psychological Review*, 88, 408–437.

Shapiro, A. K., Chassan, J., Morris, L. A., & Frick, R. (1974). Placebo-induced side effects. *Journal of Operational Psychiatry*, 6, 43–46.

Siegel, S. (1984). Pavlovian conditioning and heroin overdose: Reports by overdose victims. *Bulletin of the Psychonomic Society*, 22, 428–430.

Siegel, S. (1989). Pharmacological conditioning and drug effects. In A. J. Goudie & M. W. Emmett-Oglesby (Eds.), *Psychoactive drugs: Tolerance and sensitization. Contemporary neuroscience* (pp. 115–180). Clifton, NJ: Humana.

Spanos, N. P., Liddy, S. J., Scott, H., Garrard, C., Sine, J., Tirabasso, A., & Hayward, A. (1993). Hypnotic suggestion and placebo for the treatment of chronic headache in a university volunteer sample. *Cognitive Therapy and Research*, 17, 191–205.

Spanos, N. P., Perlini, A. H., & Robertson, L. A. (1989). Hypnosis, suggestion, and placebo in the reduction of experimental pain. *Journal of Abnormal Psychology*, 98, 285–293.

Staats, P., Hekmat, H., & Staat, A. (1998). Suggestion/placebo effects on pain: Negative as well as positive. *Journal of Pain and Symptom Management*, 15, 235–243.

Stewart-Williams, S., & Podd, J. (2004). The placebo effect: Dissolving the expectancy versus conditioning debate. *Psychological Bulletin*, 130, 324–340.

Thomson, R. (1982). Side effects and placebo amplification. *British Journal of Psychiatry*, 140, 64–68.

Turner, J. A., Deyo, R. A., Loeser, J. D., Von Korff, M., & Fordyce, W. E. (1994). The importance of placebo effects in pain treatment and research. *Journal of the American Medical Association*, 271, 1609–1614.

Voudouris, N. J., Peck, C. L., & Coleman, G. (1985). Conditioned placebo responses. *Journal of Personality and Social Psychology*, 48, 47–53.

Voudouris, N. J., Peck, C. L., & Coleman, G. (1989). Conditioned response models of placebo phenomena: Further support. *Pain*, 38, 109–116.

Voudouris, N. J., Peck, C. L., & Coleman, G. (1990). The role of conditioning and verbal expectancy in the placebo response. *Pain*, 43, 121–128.

Wasserman, E. A., & Miller, R. R. (1997). What's elementary about associative learning? *Annual Review of Psychology*, 48, 573–607.

Wickramasekera, I. (1985). A conditioned response model of the placebo effect: Predictions from the model. In L. White, B. Tursky, & G. E. Schwartz (Eds.), *Placebo: Theory, research, and mechanisms* (pp. 255–287). New York: Guilford Press.