

## Placebo Effects

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A *placebo* is a treatment that is expected to have no inherent pharmacological or physical benefit—for instance, a starch capsule given for anxiety or pain, or sham surgery in which the critical surgical procedure is not performed. Placebos are often used for comparison in clinical studies, as a baseline against which to evaluate the efficacy of investigational clinical treatments. However, placebo treatments often elicit observable improvements in signs or symptoms on their own—these are *placebo effects*. For this reason, placebos have been used as healing agents for a variety of ailments; they have had a place in the healer's repertoire for thousands of years, and they are still used as a viable treatment option by physicians in industrialized countries with surprising frequency.

Psychologists and neuroscientists today are most interested in the *placebo response*, the brain and body response to the psychosocial (and perhaps neurobiological) context surrounding treatment. The study of the placebo response reveals active processes that provide a powerful window into brain-body interactions and the brain substrates of human behavior.

Studies of drug treatments for various disorders have investigated the effects of *exogenous* regulation of neural and psychological end-points, such as reported emotion, behavioral responses, and disease-specific brain activity. The brain however, comprises interlocking feedback mechanisms that provide powerful *endogenous* control of neural and psychological processes. These endogenous processes regulate perceptual, affective, and cognitive processes based on the evaluation of situational context. Contextual information leading to placebo responses arises from either conscious expectancies about anticipated effects of treatment, or from prior learning in the form of conditioning with active treatments. In some cases, these two sources of placebo responses can be complementary, while in other cases, they may be mutually exclusive in their influence on observed placebo effects. The context surrounding placebo administration may lead individuals to expect improvement, and positive outcomes would compose the placebo effect. Alternatively, contextual information can lead individuals

to expect worsening of symptoms; changes in the negative direction are observed as part of the *nocebo effect*. There is some evidence that the two involve separate mechanisms, although the placebo response has been much more thoroughly studied.

A literature on experimental manipulations of placebo treatments has produced substantial evidence that placebo effects result, in many cases, from active brain responses to context, rather than statistical artifacts and reporting biases. Neuroimaging and related techniques have allowed us to begin to understand the brain mechanisms by which placebos exert their effects.

### PLACEBO TREATMENTS IN EXPERIMENTAL RESEARCH VERSUS CLINICAL STUDIES

The potential significance of the placebo response has led to the standard use of placebo groups in clinical trials examining the efficacy of medicine or other specific treatments on clinical conditions. Patients are assigned to receive either active treatment or placebo, and comparisons between groups are performed to test whether the active treatment elicits greater improvement than placebo. Two critical assumptions underlie the rationale behind the placebo-controlled clinical trial. First, it is assumed that psychological and nonspecific effects, such as natural course of disease, effects of being in a healing environment, and patient expectation and motivation to heal, have equal effects on outcomes in active treatment and placebo groups. Second, it is assumed that nonspecific effects and treatment effects combine additively, so that subtracting outcomes for the placebo group from the treatment group will reveal the specific effects of the drug or procedure. Although these assumptions may not always hold, the placebo-controlled randomized clinical trial is perhaps the best tool for medical practitioners and pharmaceutical companies to determine treatment efficacy.

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Psychologists and neuroscientists are interested, however, in whether and how the psychological components of treatment—expectancies, appraisals, learning, context effects, and the relationship between patient and practitioner—can directly affect the bodily state: What are the effects of the treatment context, and how do they affect physiology? These questions can be answered by studying the placebo response. In the clinical context, this can be achieved through a three-arm version of the clinical trial; in addition to the active treatment and placebo groups, a subset of patients is assigned to a “natural history” comparison group that receives no treatment.<sup>1</sup> Comparisons between this no-treatment group and the placebo group allow researchers to avoid many potential statistical artifacts, some of which are described later in this chapter, to assess the placebo response—the active effects of psychological state.

While contrasts between the placebo and natural history arms of clinical trials allow researchers to examine the breadth of placebo effects, laboratory research on placebo allows researchers to examine the placebo response. Experimental investigations assess the psychological components of the placebo response, and the mechanisms by which these factors modulate physiological endpoints. Through mechanistic approaches to the study of the placebo response, researchers may gain insights into fundamental processes underlying mind-body interactions. These processes link placebo to many other psychological domains, as the central mechanisms supporting placebo responses involve many key concepts in psychology, including cognitive processes, such as appraisals, expectancies, learning, context effects, and valuation. Interpersonal processes also play a critical role in the placebo response; the patient-practitioner relationship may cultivate feelings of trust and “being cared for,” which may not only influence patient expectancies, but may also directly contribute to the development of the placebo response (Barrett et al., 2006; Hall, Dugan, Zheng, & Mishra, 2001). Studying the placebo response offers the opportunity to increase our understanding of how these social and cognitive processes may interact with the endogenous regulatory mechanisms to control the body’s physiological state.

Laboratory placebo research generally examines conditions whose onset can be controlled by experimenters, since there is no prior disease state on which to measure effects in healthy volunteers. In laboratory experiments on placebo

effects on pain, anxiety, or Parkinson’s disease, experimenters can compare performance (pain response, affective ratings, motor performance) in a control condition to a condition in which placebo treatment was administered in the form of a sham medication or procedure. Improvements (decreased pain, decreased negative emotion, increased motor performance) with the placebo treatment indicate positive effects of placebo. For this reason and others, pain is a particularly well-studied domain in placebo research, as the intensity of noxious stimulation can be experimentally controlled. Placebo effects in pain are typically measured as decreases in pain ratings (or, alternatively, pain-induced physiological activity) under placebo relative to a nonplacebo control condition.

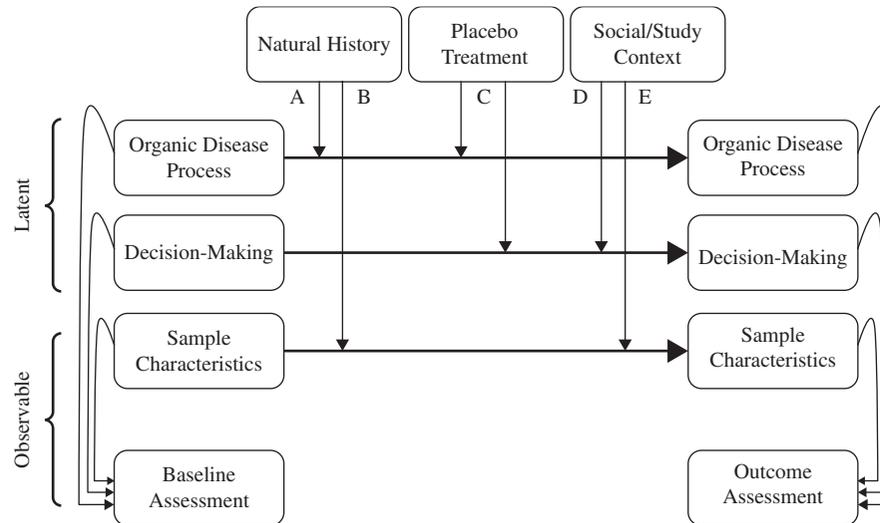
### ALL PLACEBO EFFECTS ARE NOT EQUAL: ACTIVE PLACEBO RESPONSES VERSUS STATISTICAL ARTIFACTS

Many factors may influence the reporting process to resemble placebo effects on subjective outcome measures without a concomitant *active placebo response*. Active placebo responses are those processes that interact with and affect the normal processing underlying a disease or condition. True placebo effects—those that have direct impact on the course of disease—necessarily involve active placebo responses, and placebo researchers must differentiate between active placebo responses and other psychological factors that influence subjective outcome measures (Wager & Nitschke, 2005). This is not to say that subjective outcomes without a physiological basis are not desirable in and of themselves; patient quality of life is of the utmost importance in the clinic, and any treatment that eliminates suffering arguably offers great benefit to the patient, no matter whether it affects disease physiology. Nonetheless, in the interest of using the placebo response as a window into mind-body interactions, we are most interested in the breadth and extent of active placebo responses.

#### Statistical Artifacts

It is essential to account for the natural course of a disease in clinical studies of placebo, as numerous factors may lead to observations of clinical improvement, yet have nothing to do with actual placebo administration (and are thus not part of an active placebo response). These factors include natural symptom fluctuation, regression to the mean, spontaneous remission, and participant sampling bias; Figure 63.1 illustrates the contribution of such factors to apparent disease progression. All these factors can

<sup>1</sup>Denying patients treatment for conditions when accepted treatments do indeed exist may be viewed as unethical, so this no-treatment control group can be achieved by assigning participants with non-life-threatening conditions to waiting lists, so that they ultimately do receive treatment.



**Figure 63.1** Factors that contribute to observed placebo effects in clinical trials.

*Note:* Improvement from baseline to outcome assessment is the measure of recovery or healing. These measures are observable outcomes based on some observable factors, such as the sample characteristics, and unobservable factors that include organic disease progression and decision-making processes about how to report signs and symptoms. Improvement in the average of the study sample may be influenced by factors that include effects of natural history, study context, and psychobiological responses to placebo. (A) Effects of time on organic disease: Natural history. (B) Effects of time or perceived disease severity over time on sample characteristics: Sampling bias. (C) Effects of placebo treatment on organic disease and decision-making processes: Active psychobiological placebo responses. (D) Effects of being in the study on decision making: Hawthorne effects and demand characteristics. (E) Effects of social factors (being cared for, implicit social contracts) on continued participation: Sampling bias. Experimental studies of placebo treatment compared with no-treatment controls can isolate active psychobiological placebo responses (C).

be adequately accounted for in clinical trials by comparing the placebo group to a natural history control group, assuming effective randomization and other standard statistical assumptions.

**Natural History: Spontaneous Remission and Natural Symptom Fluctuation**

Without treatment, outcomes (e.g., signs and symptoms) in all diseases follow a time course, referred to as a natural history. In many conditions, remission is part of the natural course of the illness, and with enough time, healing is likely to occur on its own. Patients are likely to eventually recover from many psychiatric illnesses, sleep disorders, and other conditions that may otherwise cause patients to seek treatment. In some other conditions, patients tend to get progressively worse. Even for conditions in which spontaneous remission is rare—such as chronic pain, Parkinson’s disease, and irritable bowel syndrome—signs and symptoms fluctuate over time. The constant variation in symptomatology within an individual could easily lead to apparent improvement with a treatment if patients are enrolled when their symptoms are particularly intense or the study terminates during a relatively symptom-free period.

**Regression to the Mean**

It is well known that if repeated measurements are made of a variable (e.g., severity of a symptom) that is measured with error or fluctuates around a mean, extreme values tend to be

closer to the mean with each successive measurement. Thus, a subgroup of patients will appear to improve over time in virtually any study, even if there is no actual improvement. What is decreasing in these improved patients is not the underlying symptom, but the value of the measurement error. If patients tend to enroll in a study when their symptoms are relatively severe, the entire group may appear to improve, whether treated with a drug, placebo, or nothing at all. In many cases, patients are likely to seek treatment at extreme points in the course of illness, leading to a high likelihood that symptoms will have diminished by the time a second measurement is made, simply due to the natural course of disease. This phenomenon was demonstrated in a study that compared chronic pain patients who had sought treatment to a matched group who had not sought treatment (Whitney & Von Korff, 1992). The former group reported more pain at initial assessment than the latter group; both groups’ reported pain levels approached the mean at a 1-year follow-up, with the group that sought treatment demonstrating steeper reductions in reported pain, demonstrating that self-selection can influence regression to the mean in a way that would affect observed treatment results.

**Participant Sampling Bias**

Another important potential source of artifact in clinical trials comes about because participants who experience beneficial effects over the course of the study are more

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likely to adhere to treatment regimens and remain enrolled in the study than participants who experience no change. Attrition rates will be higher among those receiving no benefit from treatment, and an observed improvement with treatment will actually reflect changes in the sample over time (Turk & Rudy, 1990).

Comparisons between placebo and nontreatment control groups allow researchers to control for these various artifacts and assess the efficacy of placebo administration on a given condition. To our knowledge, the efficacy of placebo treatment has been examined with comparisons between placebo and nontreatment controls in Major Depressive Disorder, heart disease/hypertension, chronic pain, nausea, erectile dysfunction, and obesity.

#### Placebo Effects on Decision Making

Experimental research allows researchers to differentiate between active placebo responses and placebo effects on decision making that involve no changes in the underlying physiology of the disease or condition. A recent meta-analysis of clinical trials that compared placebo and no-treatment control groups found no significant benefit of placebo administration across clinical conditions, and only found significant placebo improvement in the context of placebos for pain (Hrobjartsson & Gotzsche, 2001, 2004). The authors argued that the observed placebo effects may be an artifact of reporting bias, since pain was always measured by self-report. Placebo administration may have caused changes in participant decision making, but may have had no effect on disease processes. This study has been criticized on at least two counts. First, its conclusions are based on clinical trials that were not intended to examine placebo effects, and so strong placebo expectancies may not have been formed in many cases (Wickramasekera, 2001). Second, their main analyses averaged across many different disease processes—obesity, hypertension, pain, and marital dysfunction trials were all considered together—and there may have been too few studies within particular disorders to achieve adequate power (Kirsch & Scoboria, 2001).

Those criticisms notwithstanding, the issue of whether changes in reported experience are purely subjective is an important one. Placebo effects may reflect subjective responses in two senses. First, they may be caused by brain processes that modulate subjective experiences of emotion, pain, and suffering. Such subjective effects are clinically relevant: A treatment that affects pain and quality of life is important whether it affects an organic disease process or simply the patient's ability to cope with it. Alternatively, subjective responses may be caused by biases in the cognitive decision-making processes involved in making reports

to an experimenter or physician. In this case, the placebo does not change the organic disease and subjective suffering, but may affect decisions about how to describe the painful experiences.

In many disorders, subjective assessment is a critical component; pain is a subjective phenomenon, and there is no better way to measure pain than to ask the patient. Nonsubjective measures that are responsive to pain, such as pupillometry and skin conductance, are indirectly related to pain experience, and can be affected by other factors without a change in perceived pain. Thus, while these measures are of interest partly because they are not subject to cognitive reporting biases, they cannot entirely replace self-report as an index of the pain experience.

The problem with relying solely on self-report based measures when studying the placebo response is that they can be influenced by factors that have little to do with the disease process being studied; placebo effects may be observed with self-report measures, yet the course of disease may remain unaffected. We review sources of reporting bias and then present evidence from carefully controlled experimental placebo research demonstrating that, despite these sources of *potential* error, active placebo responses do indeed exist in many clinical and psychological domains.

#### Hawthorne Effects

Participants often change their behavior as a result of being observed in the study environment. This phenomenon is referred to as the Hawthorne effect, after a series of landmark studies at the Hawthorne Works of the Western Electric Company (Roethlisberger & Dickson, 1939). These studies were designed to assess how several variables—break length, work-week duration, and company subsidation of meals and beverages—affected productivity. Irrespective of these manipulations, productivity increased relative to preexperiment levels. Researchers concluded that this increased productivity resulted from the attention and special privileges that study participants received. Hawthorne effects are particularly relevant in the consideration of natural history control groups in clinical trials; to avoid Hawthorne effects, control participants should receive the same amount of attention as placebo and treatment groups.

#### Demand Characteristics

Demand characteristics refer to changes in participants' behavior due to expectations about how they are expected to behave or what they are expected to report. In response to hypotheses about study aims, patients may exhibit social compliance effects—patients may say what they feel *should* be said (Kelman, 1958). The question, "How

much did your pain decrease?” implies that participants should have felt less pain, and they may feel pressure to report decreases despite no actual perceived changes. In the case of self-presentation biases, individuals often say what makes them look better in the eyes of others (Arkin, Gabrenya, Appelman, & Cochran, 1979); this is especially relevant if the experimenter is seen as an authority figure or relevant social figure. Finally, self-consistency biases may cause individuals to respond in ways that are consistent with past behavior or with views of the self (Wells & Sweeney, 1986).

Early research on placebo effects took advantage of then-current stage models of perception and decision making, and tested for effects of placebo treatments on measures derived from signal detection theory (SDT; Swets, Tanner, & Birdsall, 1961). The SDT characterization relied on the notion that sensory processes register a mixture of a true signal (such as a change in the strength of noxious input) and noise. The output of sensory processes is passed to a decision maker, which chooses a response (“signal present” or “signal absent”) based on the perceived sensation. Thus, the likelihood of a particular decision depends not only on the perceived signal strength, but also on the relative costs of false positive decisions and missed true signals. Studies of placebo effects asked participants to provide ratings of pain with and without placebo treatment. In a classic study, the SDT measure of discriminability assessed whether participants showed a reduced tendency to rate slightly more intense stimuli with higher pain ratings (to discriminate temperatures) with placebo (Clark, 1969). The SDT measure of response bias assessed whether they rated a given stimulus as less painful with the placebo. The study found that placebo affected response bias but not discriminability, whereas an opiate drug affected both.

Though this was an important finding, the issue is complex because pain is not a two-stage sensory-decision process. The ability to discriminate stimulus intensities and the experience of pain are not the same thing; a complex network of brain circuits creates the pain experience from a combination of sensory input and internal processes, and different sensory receptors at the peripheral level may even carry different information about sensory and nociceptive (pain-related) aspects of the stimulus (Price & Dubner, 1977; Price, Greenspan, & Dubner, 2003). Thus, what is at stake in placebo research is not stimulus discriminability, but the intensity of the feeling of pain, which is likely to be captured by the response bias SDT measure.

The placebo effects on response bias observed by Clark et al. could be caused by either changes in decision-making processes—the standard interpretation in SDT—or by widespread decreases in pain processing in the brain or spinal cord, with very different implications in each alternative.

The direct measurement of brain responses to noxious stimulation can help disentangle these alternatives. Placebo shifts in reporting bias would presumably affect the pain reporting process without affecting pain processing—under placebo, neural activity would increase in decision-making circuitry (dorsolateral prefrontal cortex [DLPFC] and orbitofrontal cortex [OFC], primarily) facilitating changes in evaluative report criteria, but pain-processing activity would remain unaffected. Alternatively, finding decreases in nociceptive processing in brain regions related to pain would suggest that the second alternative is more likely to be true. We review evidence on brain placebo effects later.

In considering the various artifacts previously described, it becomes clear that experimental research manipulating placebo treatments plays a key role in testing for active placebo responses. Sound experimental designs can eliminate issues of sampling bias and regression to the mean that can plague clinical trials. In addition, sensitivity to detect active placebo responses can be enhanced by considering and minimizing cognitive biases in self-report, either by using implicit behavioral measures or physiological outcome measures that are relatively nonsusceptible to reporting biases.

### Active Placebo Responses

Physiological outcome measures, including neuroimaging and electrophysiological measures of central and peripheral nervous system activity as well as peripheral outcome measures such as hormone secretion, provide powerful evidence for the existence of placebo responses beyond reporting biases. In the remainder of this chapter, we review evidence for the existence of active placebo responses in a variety of domains. We specifically examine placebo analgesia as a model system, and consider candidate central and proximal mechanisms of the placebo response.

#### *Central Nervous System Processes in Placebo*

Neuroimaging and electrophysiological methodologies provide evidence of active placebo responses in domains in which physical outcome measures may not exist or may map indirectly to stimulus processing. These methodologies—functional magnetic resonance imaging (fMRI), positron emission tomography (PET), electroencephalography (EEG), magnetoencephalography (MEG) and single-unit recording—reveal not only changes in brain-related outcomes (decreases in pain-related neural activity under placebo analgesia), but also underlying mechanisms subserving the placebo response, allowing for insights into how these mind-body interactions unfold.

Placebo responses have now been systematically studied using neuroimaging and electrophysiology techniques across several conditions and diseases, including

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Parkinson's disease (Benedetti et al., 2004; de la Fuente-Fernandez et al., 2002), Major Depressive Disorder (Mayberg et al., 2002), irritable bowel syndrome (Lieberman et al., 2004; Vase, Robinson, Verne, & Price, 2005), anxiety (Petrovic et al., 2005), drug reinforcement (Volkow et al., 2003), and pain (Bingel, Lorenz, Schoell, Weiller, & Buchel, 2006; Kong et al., 2006; Lieberman et al., 2004; Price, Craggs, Verne, Perlstein, & Robinson, 2007; Wager, Matre, & Casey, 2006; Wager, Rilling, et al., 2004; Wager, Scott, & Zubieta, 2007; Watson, El-Deredy, Vogt, & Jones, 2007; Zubieta, Yau, Scott, & Stohler, 2006). Results from these studies can be combined with knowledge of the neural bases of basic cognitive processes that may be involved in the placebo response to gain synergistic insight into the mechanisms supporting placebo responses.

A central thesis of this chapter is that common effects of placebo treatment on the brain suggest the involvement of common central brain mechanisms across disorders. Other brain processes and outcomes, however, appear to be disease-specific, and we examine evidence for these domain-specific proximal mechanisms as well. In the following sections, we use pain as a model system to discuss the brain mechanisms supporting active placebo responses and use observed commonalities to compare placebo responses in pain with those in other domains.

### PLACEBO ANALGESIA: PAIN AS A MODEL SYSTEM

In the laboratory context, the majority of studies of placebo have been conducted in the realm of pain. Pain is a unique domain with sensory, affective, and evaluative components, and one that has great significance for an organism's well-being. Pain is an interoceptive modality, yet can be quantitatively manipulated in the laboratory. Furthermore, the network of regions involved in the pain experience, known as the "pain matrix," has been well characterized in human and animal studies (for a detailed review, see Chapter 33, this Volume). Finally, pain is known to have a strong expectancy component, and may arguably be considered more open to influence of the central nervous system than many disease processes.

Placebo analgesia occurs when (a) an individual is experiencing pain, either due to natural ongoing sources or controlled noxious stimulation (heat, cold, pressure, shock, ischemia, or other painful stimulation); (b) the individual receives placebo treatment, in the form of a cream, inert medication, or other sham procedure, often with accompanying instructions that treatment will relieve pain; (c) pain with placebo is compared with a nonplacebo control condition, and pain reports decrease under placebo.

The first powerful support for the existence of an active placebo response came in the late 1970s, when Levine and colleagues showed that placebo analgesia was reversed with administration of naloxone, a  $\mu$ -opioid receptor antagonist (Levine, Gordon, Jones, & Fields, 1978). This suggested that endogenous opioids were involved in the placebo response. The known effects of opiates on pain in both humans and animals led to the conclusion that placebo painkillers may be engaging the brain's natural pain-control mechanisms. Since this initial insight, researchers have explored placebo responses in pain using a variety of methodological approaches. Contemporary neuroimaging and electrophysiological techniques offer powerful tools for investigating the brain processes affected by placebo treatments and the brain mechanisms responsible for the placebo response. Researchers now can examine placebo-induced changes in brain regions known to be involved in pain processing. This provides support for the existence of active psychobiological mechanisms underlying placebo analgesia, and offers insights into the mechanisms by which the placebo response may modulate physiological endpoints.

### Pain-Related Processes Affected by Placebo Treatments

Earlier, we described potential sources of reporting bias and noted that these concerns are particularly valid in consideration of placebo effects on pain, since pain is a subjective phenomenon. We and others have used neuroimaging techniques to provide nonsubjective evidence for placebo effects on pain, and to begin an investigation of their underlying mechanisms. This approach allows us to examine differences in physiological correlates of pain processing under placebo.

In an initial study, we induced expectations of analgesia in participants using an inert cream that participants were told would have an analgesic effect (Wager, Rilling, et al., 2004). A series of thermal stimuli were delivered, and participants rated the intensity of their pain experience several seconds after the termination of each stimulus. Identical stimulation sequences were delivered on placebo- and control-treated skin regions for each participant (with locations and testing order counterbalanced). Compared with the control condition, the placebo treatment decreased the reported painfulness of both shock and heat stimulation, which replicated the placebo effect on reported pain shown in many experimental studies (Benedetti et al., 1998; Montgomery & Kirsch, 1997; Price et al., 1999; Voudouris, Peck, & Coleman, 1985). Concurrent fMRI showed decreased responsiveness to noxious stimulation in the placebo condition in rostral anterior cingulate cortex

(rACC), anterior insula (aINS), and thalamus, regions of the pain matrix thought to be critical for the affective experience of pain. Furthermore, the magnitude of these decreases correlated with placebo effects in reported pain. These data are consistent with the idea that placebo treatment *directly* affects the pain experience, and suggest that the affective component of pain might be particularly important. Subsequent studies have shown differences in the brain's response to noxious stimulation under placebo (Kong et al., 2006; Price et al., 2007)—though only Price et al. reported decreases in pain-processing regions—supporting the notion that placebo effects on nociceptive processing are indeed *active* processes, and that placebo effects on reported pain reflect real changes in pain processing, rather than simple reporting biases.

This approach also allows us to examine the temporal patterns of neural activity in response to pain. If the placebo effect is due entirely to reporting bias, then activity during pain under placebo should be the same as activity during pain in control conditions; differences might be largest later on, during the pain-reporting process. Examining the time course of placebo-related effects during thermal pain suggested that the decreased activity under placebo occurred both early and late in the pain period. Placebo decreases in rACC pain activity, which were correlated with reported placebo effects, were found in the early heat period. However, the largest main effects of placebo (control placebo) appeared in the contralateral insula and thalamus only in the late phase of stimulation. One explanation is that placebo effects may require a period of pain to develop or be strongest when pain is intense; alternatively, placebo responses may be most evident during residual pain after noxious stimulation has ended. A third interpretation is that the placebo reductions during late stimulation could reflect altered evaluation of pain rather than alterations in early sensory/perceptual nociceptive processes.

To test for placebo effects on early sensory/perceptual processing, we conducted a study using laser pain-evoked event-related potentials (Wager et al., 2006) that allowed us to examine activity at a higher temporal resolution than fMRI or PET. Laser-evoked potentials (LEPs) are a reliable marker of pain processing (Bromm & Treede, 1984) and arise from nociceptive processes that occur before most decision processes begin. Thus, the cognitive biases that some have argued may influence reported placebo effects are unlikely to affect LEPs. We focused on the N2/P2 complex (200 to 300 ms; Lorenz & Garcia-Larrea, 2003), which arises from the activation of A $\delta$  fibers and is sometimes followed by a later component thought to arise from C-fiber activation (Bromm & Treede, 1984). The P2 increases as a function of laser intensity and reported pain (Iannetti et al., 2004), and its likely source is the ACC

(Garcia-Larrea, Frot, & Valeriani, 2003; Lenz et al., 1998), a region important for both attention and pain that has been shown to be modulated by placebo in pain and emotion. P2 amplitude was indeed reduced under placebo, supporting placebo effects on early nociceptive processing. Consistent with these results, expectations of analgesia have been shown to directly modulate spinal nociceptive reflexes (Goffaux, Redmond, Rainville, & Marchand, 2007), providing direct evidence for placebo effects on even the earliest levels of nociceptive processing.

### Mechanisms of Placebo Analgesia

The studies reviewed in the previous section demonstrate the existence of psychobiological placebo effects on pain processing in the central nervous system. We now turn to consideration of the mechanisms by which these effects take place. Placebo treatments may affect several aspects of the continuum from sensation to experience to reporting that comprises pain processing: sensory transmission and processing, appraisal, and the generation of subjective pain, and the pain reporting process (see Figure 63.2).

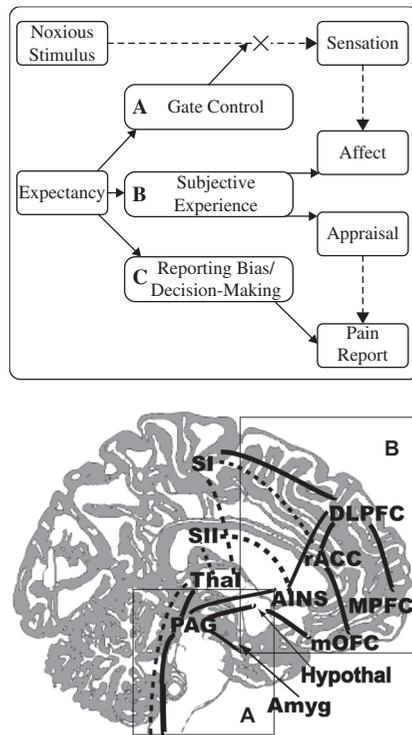
The issue of which aspects are affected has been at the heart of the debate over whether placebo treatments activate physiological pain-control systems and have clinically meaningful effects. We examine the levels of the nervous system at which the placebo response can be mediated, the role of specific neurotransmitters, and central mechanisms that give rise to placebo responses in pain and other conditions; this evidence is summarized in Table 63.1. We adopt the perspective that these mechanisms may not be mutually exclusive. Finally, we examine current knowledge about central nervous system placebo responses in other domains, and placebo effects on physiological outcome measures.

#### *Sensory Transmission and Processing: Spinal Inhibition*

An important mechanism by which placebo analgesia could take place was initially put forth in Melzack and Wall's gate control theory (Melzack & Wall, 1965). This theory posits that central control mechanisms interact with afferent information to prevent nociceptive signals from reaching the central nervous system, leading to decreases in cortical nociceptive processing. It is difficult to convincingly demonstrate inhibition of signals in the human spinal cord; the reductions in P2 amplitude previously discussed are expected if nociceptive afferents are inhibited, but they could also be caused by interactions within the brain.

One approach is to test for placebo-based modulation of nociceptive effects that have been shown to be spinally mediated in animal literature. Two such effects are secondary

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**Figure 63.2** Mechanisms of placebo analgesia.

*Note:* There are several routes by which placebo manipulations may lead to decreases in reported pain (refer also to Table 63.1). Dashed lines in both figures represent normal stages and pathways of pain processing. Pain begins when sensory signals from the spinal cord reach the brain via the thalamus and are sent to the primary (SI) and secondary somatosensory cortex (S2). From there, signals are sent to the anterior insula (AINS) and anterior cingulate (ACC), which are involved (along with regions in the limbic system) in the subjective experience and emotional quality of pain. (A) According to the gate control theory (Melzack & Wall, 1965), inhibition of spinal nociceptive input is possible through endogenous opioid release by the periaqueductal gray (PAG), which receives direct projections from dorsolateral prefrontal cortex (DLPFC), as well as orbitofrontal cortex (OFC), ACC, and amygdala. (B) A second alternative is that placebo responses are a result of changes in affective appraisals and the generation of subjective pain. Appraisals are generated through interactions among the OFC, AINS, ACC, and other regions, and may be maintained in the DLPFC. (C) Changes in decision making without a concomitant effect on pain perception are likely to involve increases in DLPFC activity and decreases in reported pain without modulating pain processing.

hyperalgesia—the tendency for skin around the site of painful stimulation to become sensitized—and the suppression of spinal nociceptive reflexes by painful stimulation of another body part. Matre, Casey, and Knardahl (2006) examined placebo effects on secondary hyperalgesia in humans by heating the skin at 46°C for five minutes. Expectation of pain relief reduced the size of the secondary hyperalgesic area, compared with a control condition in which pain relief was not expected. Sensitization of the skin area surrounding the stimulation site is thought to result from sensitization in the spinal dorsal horn. These results therefore implicate a spinal mechanism in the placebo

effect. Reported pain was still the primary outcome measure in this study, leaving open the possibility that central processes as well as spinal ones may play a role in secondary hyperalgesia in humans.

Goffaux et al. (Goffaux et al., 2007) took a complementary approach by measuring spinal reflexes. They examined a leg muscle contraction reflex called R3 that is triggered by stimulation of the sural nerve, which runs along the outside of the ankle. The reflex is mediated by spinal circuits that operate at very short latency, with measurable onset in EMG at ~50 ms and a peak at ~90 ms (Dowman, 2001). Both this reflex and EEG measures of early negative (N100/150) and positive evoked cerebral potentials are dampened by painful stimulation of another limb, for example, by immersing the arm in cold water. The interaction across body parts is thought to be mediated by central pain-control circuits in the brain stem, and is termed the diffuse noxious inhibitory control (DNIC) effect (Le Bars, Dickenson, & Besson, 1979). The DNIC effect can be produced in anesthetized animals, so it is thought to be a reflexive anti-nociceptive response to noxious stimulation that involves inhibition at the spinal level. Goffaux et al. manipulated expectations about the effects of cold-water immersion: One group was told that it would reduce pain, and another that it would increase pain. Interestingly, they found that expectancy modulated the strength of the DNIC effect. Expectations for pain relief decreased the amplitude of the R3 reflex and P260 evoked potentials relative to expectations for increased pain during the cold-water immersion, but did not affect very early cortical potentials.

These findings suggest that expectancy can modulate activity at the level of the spinal cord, but that some components of cortical processing are more affected than others. If the expectancy manipulation inhibited nociceptive transmission, the R3 reflex and all cortical evoked potentials ought to have been affected. Whereas expectancy effects in early small components may be difficult to detect, it is notable that, similar to the study of Wager et al. (2006), the P260 potential showed the largest effect. This potential is thought to be localized to the anterior cingulate cortex and may overlap with the P3a or P3b potential (Dowman, 2001; Garcia-Larrea, Peyron, Laurent, & Mauguiere, 1997), and it appears to be sensitive to cognitive expectations even under conditions when pain reports are not (Dowman, 2001). These effects may reflect attentional orienting or evaluative aspects of nociceptive processing. The idea that expectancy effects influence attention-related processes does not preclude spinal inhibition, as suggested by effects on the R3 reflex. Indeed, attention has been shown to influence activity in the spinal dorsal horn in direct recordings in monkeys (Bushnell, Duncan, Dubner, & He, 1984).

TABLE 63.1 Mechanisms of placebo analgesia.

	Expected Central Nervous System Effects	Supporting Evidence
A) Gate control: Spinal inhibition of sensory transmission and processing	Widespread decreases in pain-processing regions Placebo-induced opioid release and PAG activation	Secondary hyperalgesia (Matre, Casey, & Knardahl, 2006) DNIC effects (Goffaux et al., 2007) PAG anticipatory increases (Wager, Rilling et al., 2004) PAG opioid release (Wager et al., 2007)
B) Subjective experience: Changes in appraisal and generation of subjective pain	Decreases in <i>select</i> pain-processing regions Increases in modulatory and affective regions	Reductions in pain-processing regions: insula, thalamus, ACC (Wager, Rilling et al., 2004; Price et al., 2007) OFC and rACC anticipatory increases (Wager, Rilling et al., 2004) Dopamine-opioid correlations (Scott et al., 2008) Reward-placebo correlations (Scott et al., 2007) Opioid binding and connectivity (Wager et al., 2007; Zubieta et al., 2005)
C) Reporting bias: Changes in decision making only	Changes in decision-making circuits during/after pain (pain processing decreases not expected)	Indirect evidence: Placebo modulated activity in pain matrix regions primarily during late pain period (Wager, Rilling et al., 2004) Indirect evidence: Insula is involved in decision making (Grinband, Hirsch, & Ferrara, 2006)

There is substantial evidence for centrally activated descending control systems in animals. In many (but not all) cases, these effects are mediated by endogenous opioids in the periaqueductal gray (PAG) and their projections to brain stem structures such as the rostral ventromedial medulla (RVM). The RVM, among other structures, contains neurons that exert powerful excitatory and inhibitory control (so-called On and Off cells) on spinal neurons (Fields, 2004). Thus, evidence implicating the PAG and opioids in placebo analgesia would provide further support for the spinal inhibition model.

The role of endogenous opioids in placebo analgesia is supported by studies using naloxone, an opioid antagonist that reverses placebo effects on reported pain in studies of expectancy-based placebo analgesia (Benedetti, Arduino, & Amanzio, 1999; Grevert, Albert, & Goldstein, 1983; Levine & Gordon, 1984; Levine, Gordon, & Fields, 1978; Petrovic, Kalso, Petersson, & Ingvar, 2002; Pollo, Vighetti, Rainero, & Benedetti, 2003). These results suggest that endogenous opioids indeed play a critical role in placebo analgesia.

Neuroimaging methodologies allow researchers to elaborate on the knowledge available from naloxone studies to better understand the role of endogenous opioids in the placebo response. In our early study of placebo analgesia using fMRI (Wager, Rilling et al., 2004), we observed increases in an area of the midbrain surrounding the PAG during anticipation of pain under placebo. This could be consistent with the gate control theory, in that placebo expectancy would increase opioid release by the PAG, and descending opioids would inhibit subsequent

pain at the level of the spinal cord's dorsal horn. Molecular imaging with PET provides an opportunity to understand where in the brain placebo changes opioid release. Radioactive tracers selective for  $\mu$ -opioid receptors (MORs) allow researchers to infer endogenous opioid activity, as tracer binding is inversely related to endogenous MOR opioid binding. Placebo did increase opioid binding in the PAG during noxious stimulation (Wager et al., 2007). Another important observation was that placebo administration resulted in *decreased* PAG opioid binding during pain anticipation, relative to the control condition, suggesting that the placebo response may reduce the threat normally associated with noxious stimulation. Importantly, PAG was not the only region to show increases in opioid binding with placebo; placebo administration resulted in increased opioid binding during pain in many other cortical regions, particularly in frontal and limbic regions (Wager et al., 2007; Zubieta et al., 2005). Furthermore, connectivity analyses revealed that placebo increased functional integration between PAG and these regions, among other functional networks (Wager et al., 2007). These results suggest that while PAG opioid release plays an important role in placebo analgesia, it may not only induce descending inhibition of nociception, as the gate control theory would suggest, but might also facilitate changes in brain networks that lead to reduced aversion to a given noxious stimulus, by virtue of PAG correlations with opioid release in central appraisal and valuation networks (including the OFC, NAC, amygdala, insula, medial thalamus, and rACC). We consider the role of central processing in the following section.

## 10 Placebo Effects

Placebo analgesia is not always opioid-mediated, since naloxone administration does not always reverse placebo effects on reported pain. In one study, hidden naloxone administration failed to reverse placebo effects on post-surgical pain (Gracely, Dubner, Wolskee, & Deeter, 1983). Placebo significantly decreased pain regardless of naloxone administration; naloxone increased pain across placebo and control conditions; and there was no interaction between the two. Similarly, a study of placebo analgesia in patients with irritable bowel syndrome (Vase et al., 2005) found large placebo effects that were not reversible by naloxone. There are several possible explanations, including that naloxone has different effects at different doses (Levine, Gordon, & Fields, 1979) and may affect placebo analgesia without overall effects on pain only at some doses, and that irritable bowel syndrome patients may be opioid-insensitive and have developed nonopioid pain-relief mechanisms through conditioning with medication.

An intriguing possibility is that placebo effects may be opioid-mediated when central expectancy is involved. An experiment by Amanzio and Benedetti (1999) suggested placebo analgesia created by verbal instructions (and thus mediated by conscious expectancies of pain relief) was reversible by naloxone. Conditioning responses to ketorolac, a nonopioid analgesic, by repeatedly injecting the drug produced placebo analgesia as well. After repeating the injection experience-drug effect pairing, injecting saline alone reduced pain. However, this type of placebo effect was completely naloxone-insensitive. Thus, placebo analgesia may involve both opioid and nonopioid mechanisms, and this may be determined by whether there is an expectancy component to the placebo response, as well as the specific neurochemical pathways involved in the learning process.

### Placebo Effects on Central Pain Processing

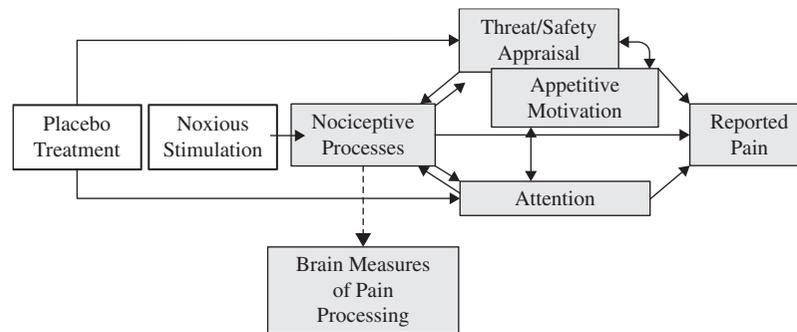
Though there is mounting evidence for the involvement of descending pain-control systems and endogenous opioids in placebo analgesia, there is also substantial evidence that spinal inhibition cannot provide a complete account. Wager et al. (2007) observed that placebo effects in reported pain were relatively large and persisted throughout the experimental session, whereas placebo effects in P2 amplitudes were smaller and decreased over time. We conducted a formal comparison of the actual P2 reduction versus the expected reduction if input-reduction were a complete account. The analysis revealed that reported pain effects were too large relative to P2 effects to be caused solely by input blockade, suggesting that there may be multiple sources of placebo effects on reported pain. Part of the effect may be due to spinal inhibition, and another part to changes in central pain processing and/or reporting bias.

In a classic study, Benedetti and colleagues showed that opioid-mediated placebo effects are involved with site-specific expectancies for analgesia (Benedetti, Arduino, et al., 1999). They induced specific expectations of analgesia on participants' hands or feet, and showed that naloxone reverses these specific analgesic effects. These results suggest that there is still a critical interaction with expectancy and the significance of pain that plays an important role in the ultimate pain experience. Opioid release may interact with frontal regions associated with the significance of the pain experience, rather than solely being responsible for a widespread descending inhibition.

Thus, the evidence on opioid involvement leaves ample room for central brain effects that do not involve the spinal cord. Whereas endogenous opioids are powerfully implicated in spinal inhibition, they are also known for several effects mediated largely or entirely within the brain, including their soporific and euphoric effects and their addictive potential. Opioids in DLPFC, nucleus accumbens (NAC), and insula are correlated with reported emotion during pain processing (Zubieta et al., 2006), and placebo treatments have been shown to reduce MOR binding (and thus likely increase opioid release) in brain structures implicated in the determination of affective value, including rACC, OFC, VMPFC, aINS, and NAC (Scott et al., 2007; Wager et al., 2007; Zubieta et al., 2005).

### *Appraisal and Subjective Pain—Changes in Pain Significance*

There are several possibilities for cognitive mechanisms that would lead to changes in pain significance with placebo administration. These processes require appraisals of the significance or meaning of treatment (Moerman & Jonas, 2002), which may lead to expectancies about positive treatment outcomes, decreases in attention to pain, and changes in pain-related affect (reduced anxiety/threat; increased appetitive processing). Geers, Helfer, Weiland, and Kosbab (2006) found that reported symptoms induced by placebo treatment were greater when attention was focused on the body. Placebo-induced anxiety reduction could also lead to reduction in pain processing (Turner, Deyo, Loeser, Von Korff, & Fordyce, 1994); this is supported by research demonstrating that decreases in reported anxiety correlate with decreases in pain under placebo and lidocaine (Vase et al., 2005). Changes in affect are supported by fMRI and opioid binding studies, in which placebo effects are localized to brain systems critical for affective appraisal, evaluation of the significance of stimuli for the self, and motivation; these results and their implications are discussed in more detail later. Figure 63.3 illustrates these processes and their potential respective contributions as mediators of the relationship between noxious stimulation and reported pain under placebo.



**Figure 63.3** Psychological mediators of the placebo response.

*Note:* The effect of placebo treatment on reported pain and brain measures of pain processing may be mediated by key psychological processes, including affective appraisals and executive attention. Placebo analgesia may come about through affect modulation, by reducing threat or anxiety appraisals, or by increasing appetitive motivation. Placebo analgesia may also result from decreased attention to noxious stimulation.

While more research needs to be done to directly assess the differential contributions of these brain mechanisms, such processes are likely to be similar to those involved in executive functions—basic cognitive processes coordinating the maintenance and manipulation of information. Information about context is known to require dorsolateral prefrontal cortex (DLPFC), which interacts with working memory—a system that maintains information in an active state in the brain—to maintain expectancies induced by placebo manipulations. Placebo instructions are likely to exert their effects by changing the cognitive context in which pain stimulation is perceived, and these altered appraisals of the situation give rise to changes in expectations about pain, harm, and pain relief. Thus, maintenance of placebo context is likely to be evident through increases in DLPFC activity, which ought to inhibit pain-processing regions of cortex; indeed, DLPFC increases during pain anticipation correlated with subsequent decreases during thermal stimulation in thalamus, insula, and rACC, and also correlated with PAG activity during anticipation (Wager, Rilling, et al., 2004). It is important to acknowledge, however, that such correlations do not conclusively determine whether the observed modulation of pain-processing regions was mediated by changes in attention, affect, or anxiety: All these require maintenance of the placebo context by DLPFC and would be expected to ultimately lead to decreases such as those observed. An approach that would allow researchers to differentiate between the contributions of these central processes would be to directly manipulate these variables to identify brain processes that mediate the relationship between DLPFC increases and subsequent pain matrix activity.

Effective placebo administration induces expectations for reduced symptomatology or diminished pain, which affects how the brain processes the condition or stimulus. The processes most likely to be altered are those that assign

value and meaning (for the self, or survival) to the stimulus. Orbitofrontal cortices and rACC have been shown to be highly involved in the process of valuation. Placebo administration has been shown to result in increased opioid binding in rACC and OFC during pain in placebo relative to control (Wager et al., 2007). Increases in rACC during pain anticipation under placebo correlated with placebo effects on reported pain, and placebo-induced decreases in rACC during pain correlated with anticipatory increases in DLPFC and PAG (Wager, Rilling, et al., 2004), supporting the possible connection between executive function, descending modulation, and placebo-induced changes in pain affect. Finally, Bingel and colleagues demonstrated that rACC activity covaried with PAG and amygdala activity during placebo, but not control, conditions (Bingel et al., 2006).

An emerging model is that the largest effects of placebo are found in brain regions at the interface between nociceptive afferents and cognitive contextual processes. These regions, which include midlateral OFC, rACC, medial thalamus, and anterior insula, are part of a broader network of structures thought to be a neuroanatomical substrate for the computation of abstract reward/punishment value—or, in other terms, appraisal of the significance of a stimulus or context for the well-being and survival of the organism. This extended appraisal network includes medial prefrontal cortex (MPFC), OFC, extended amygdala, nucleus accumbens, ventral striatum, medial thalamus, and the medial temporal lobes. All these regions have shown fMRI and opioid-binding changes during placebo analgesia. More research must be done to establish how this network functions in the appraisal process and what particular roles its individual regions play. At a broad level, however, these regions are connected both anatomically—via monosynaptic and largely bidirectional projections (Price, 2000)—and functionally, as evidenced by coactivation in studies of placebo and emotional responses (Kober et al., 2008).

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Expanding on the fact that placebo treatments may modulate valuation processes, some researchers have suggested that placebo analgesia may be thought of as a special case of reward processing; pain relief may be considered to be a positive outcome (Fields, 2004; Irizarry & Licinio, 2005). Scott and colleagues (Scott et al., 2007) used PET molecular imaging to examine the role of dopamine in placebo analgesia, using [<sup>11</sup>C]raclopride to label dopamine binding during placebo. The authors also examined correlations between the dopamine binding results and fMRI activation during a separate session. During the fMRI session, participants performed a monetary incentive delay (MID) task (Knutson, Fong, Adams, Varner, & Hommer, 2001), and analyses focused on activity during anticipated monetary reward in the nucleus accumbens, a region rich in dopaminergic neurons. Dopamine binding levels correlated with the anticipated effectiveness of the placebo, and the magnitude of the dopamine response to pain anticipation correlated with reported placebo analgesia during pain. Furthermore, high placebo responders were found to recruit nucleus accumbens to a greater extent during reward anticipation in the MID task, and nucleus accumbens activity during reward anticipation correlated with dopamine activity during placebo analgesia.

The role of dopamine in placebo analgesia is further supported by work showing that dopamine D2 receptor agonists produce analgesia (Lin, Wu, Chandra, & Tsay, 1981; Magnusson & Fisher, 2000; Morgan & Franklin, 1991). Scott et al. (Scott et al., 2008) used PET to image both opioid and dopamine receptor binding in the same individuals. Placebo induced both opioid and dopamine release (reduced binding) in the NAC, among other brain regions. Strikingly, endogenous dopamine increases in NAC were correlated with both opioid increases in NAC and reported placebo analgesia. Finally, pain processing and placebo treatments have been shown to involve components of the ventral striatum, a region rich in dopaminergic neurons that has been shown to be critical in reward processing and learning. Pain tolerance is correlated with drops in dopamine D2 receptor binding in the putamen (Hagelberg et al., 2002), and placebo analgesia induces increased MOR binding in the nucleus accumbens (Wager et al., 2007; Zubieta et al., 2005).

### *Mechanisms of the Nocebo Response*

As the nocebo response involves inducing expectations for worse symptomatology or pain, its mechanisms are considerably less understood than the placebo response due to ethical constraints. However, researchers have begun to examine the nocebo response by investigating neurochemical activity in paradigms that induce expectations for increased pain, and current knowledge suggests that placebo

and nocebo effects may involve similar brain mechanisms; they may involve opposite manipulations of the affective appraisal systems that evaluate the survival value of potential actions and outcomes. Scott et al. (2008) have reported that participants experiencing placebo and nocebo responses to a verbal suggestion of analgesia are at opposite ends (high and low, respectively) of a continuum of placebo-induced opioid and dopamine activity in the NAC, a key component of the brain's motivational circuitry.

There is also evidence that nocebo manipulations can affect HPA axis activity, and that they share some pharmacological similarity with placebo responses. Benedetti, Amanzio, and Maggi (1995) found that placebo responses were potentiated by proglumide, a cholecystokinin (CCK) antagonist. This was significant because CCK, in turn, blocks opioids; thus, the results suggested that proglumide disinhibited an endogenous opioid response to placebo. More recently, nocebo effects were shown to be reversed by proglumide, providing evidence for opposing effects of placebo and nocebo on the same neurochemical system. Benedetti and colleagues administered saline to postoperative patients with the instruction that it would increase pain for a short time (Benedetti, Amanzio, Casadio, Oliaro, & Maggi, 1997), which successfully induced increases in reported pain. These nocebo effects were reversed with administration of proglumide. These results were replicated in a later study, in which proglumide was found to reverse the nocebo effect in healthy subjects during ischemic arm pain (Benedetti, Amanzio, Vighetti, & Asteggiano, 2006).

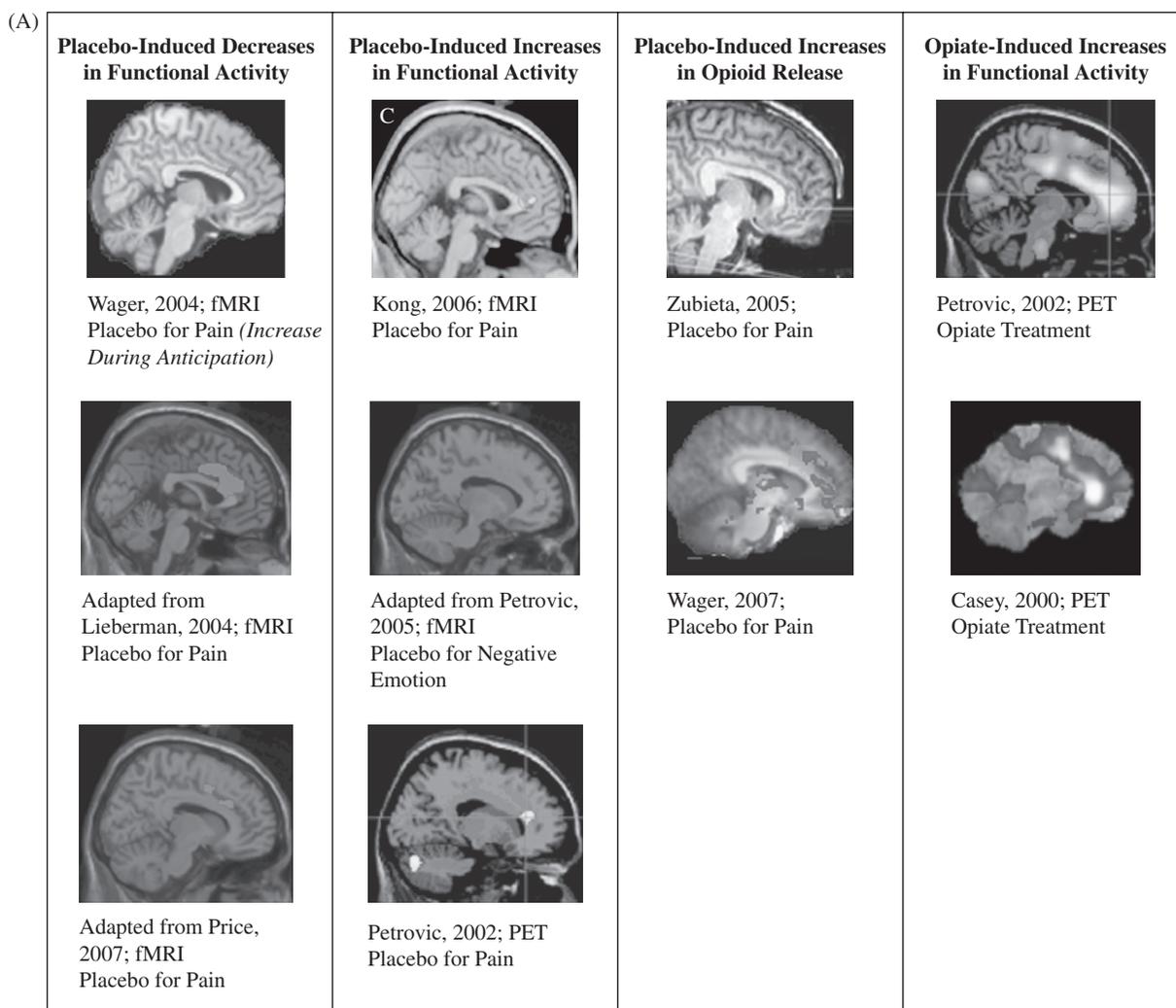
Interestingly, nocebo manipulations in this latter study also induced increases in cortisol and adrenocorticotropic hormone, indexes of the hypothalamic-pituitary-adrenal (HPA) axis. The antianxiety drug diazepam reversed both HPA effects and hyperalgesia, suggesting that increased anxiety (in a general sense of the word) underlies the nocebo response (Benedetti, Lanotte, Lopiano, & Colloca, 2007). Proglumide, by contrast, reversed only the hyperalgesia, suggesting that it works on neural circuits more specific to pain processing and evaluation, and further that it is the cortisol response to *threat* that was affected by the nocebo manipulation rather than the cortisol response to *pain*. This is because one treatment (proglumide) affected pain without affecting the cortisol nocebo response; thus, the cortisol nocebo response is unlikely to be caused by the pain itself. Interestingly, placebo treatment in this study did not reliably reduce HPA axis responses, suggesting that placebo and nocebo may be dissociable. It is unknown whether the difference between placebo and nocebo responses resulted from floor effects in the cortisol response to threat; if the subjects were not substantially threatened by the pain, there would be little threat-related cortisol response to be reduced by placebo treatment.

**CENTRAL VERSUS PROXIMAL MECHANISMS: PLACEBO RESPONSES ACROSS DOMAINS**

Having reviewed current knowledge of mechanisms supporting placebo analgesia in depth, we now turn to placebo responses across domains. We expect that many elements of the placebo response will be domain-specific; however, neuroimaging studies of the placebo response in different modalities and conditions reveal certain commonalities that may reflect general modulatory and appraisal processes. We refer to processes involved across domains as *central mechanisms*, and domain-specific central nervous system processes as *proximal mechanisms*.

**Central Mechanisms**

Many neuroimaging studies of placebo reveal placebo-induced activation of rACC (Casey et al., 2000; Kong et al., 2006; Lieberman et al., 2004; Petrovic et al., 2005; Petrovic & Ingvar, 2002; Price et al., 2007; Wager, Rilling, et al., 2004; Wager et al., 2007) and lateral OFC (Lieberman et al., 2004; Petrovic et al., 2005; Wager, Rilling, et al., 2004; Wager et al., 2007), regions highly involved in affective appraisal and cognitive control; results from these studies are presented in Figure 63.4a and 63.4b. Thus, processes subserved by these regions are likely to serve as central mechanisms, supporting the etiology and maintenance of placebo responses across domains.



**Figure 63.4** Consistency of placebo results across studies.

*Note:* Neuroimaging studies of the placebo response and related processes reveal certain commonalities that provide synergistic insight into the mechanisms underlying the placebo response across domains. (A) Many studies reveal placebo-induced modulation of dorsal rostral anterior cingulate (rACC) a region involved in regulating affect and appraisal. (B) Numerous studies also reveal placebo increases in lateral orbitofrontal cortex (OFC), a region highly involved in cognitive control and evaluative processing.

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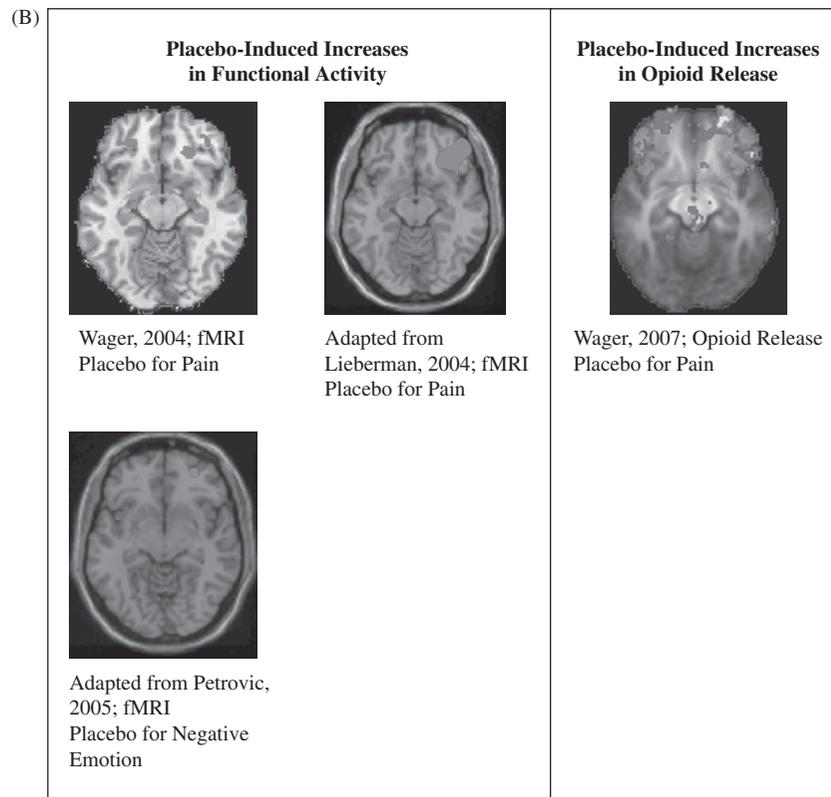


Figure 63.4 (Continued)

Placebo treatment was used to induce expectations of anxiety relief during the viewing of emotional images (Petrovic et al., 2005). Regions that exhibited increased activity under placebo during the viewing of unpleasant emotional pictures (rACC, lateral OFC) were the same that were shown to exhibit increased activity in anticipation of noxious stimulation under placebo analgesia (Wager, Rilling, et al., 2004). The specific instantiations of the placebo response, however, are modality-specific, creating differing downstream placebo effects; placebo during unpleasant picture viewing elicited decreased amygdala and extrastriate activity, while placebo during painful stimulation elicited decreased activity in rACC, aINS, and thalamus, areas responsible for pain processing. Thus, a common modulatory network may be active in maintaining positive expectancies and contextual knowledge, and may serve to downregulate whichever network of regions is responsible for producing the modality-specific appraisal of one's current state.

Lateral OFC and rACC are thus likely to influence placebo by regulating affect and appraisal. These regions are known to be an important part of a cognitive control network responsible for maintaining goals, rules, and expectations in both cognitive and affective domains. Figure 63.5 presents results from a meta-analysis of cognitive control studies, demonstrating an overlap in lateral OFC between

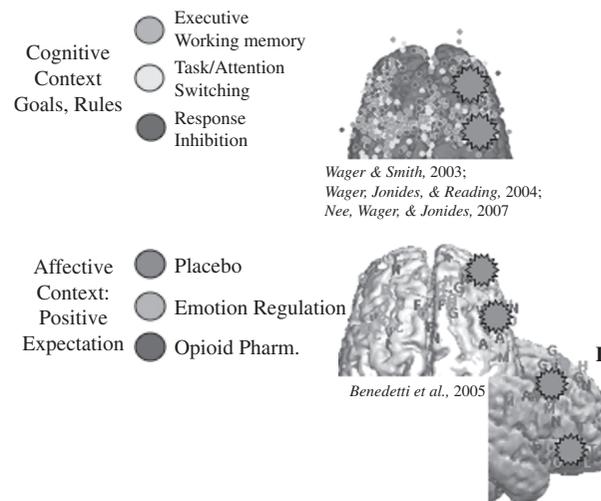


Figure 63.5 Prefrontal regulation of pain and affect.

Note: Meta-analyses of neuroimaging studies (Benedetti, Mayberg, Wager, Stohler, & Zubieta, 2005; Nee, Wager, & Jonides, 2007; Wager, Jonides, & Reading, 2004; Wager & Smith, 2003) that examined regulation of cognitive and affective context: Each point shows results from a study. Overlap between cognitive and affective regulation can be seen in dorsolateral prefrontal cortex (DLPFC) and lateral orbitofrontal cortex (OFC). These regions likely support central modulatory mechanisms of placebo, providing placebo-induced regulation of domain-specific processes.

studies that examined cognitive context (e.g., attention switching), and studies that examined affective context (e.g., placebo).

The prominence of placebo responses in central systems for affective appraisal establishes a link between placebo analgesia and manipulations of threat and safety appraisals in other paradigms, including threats to social status and physical safety. In addition to the important role of rACC and OFC across domains, appetitive motivational shifts (involving dopamine) in the ventral striatum/NAC have also been proposed as a common mechanism for placebo effects across disorders (de la Fuente-Fernandez, Schulzer, & Stoessl, 2004), and recent studies have found that placebo analgesia is predicted by fMRI responses to anticipated monetary reward (Scott et al., 2007) and dopamine activity (Scott et al., 2008) in the nucleus accumbens. Overall, these results are promising, and more study is needed to establish the role of central appraisal systems in placebo responses across different conditions.

### Proximal Mechanisms

Proximal mechanisms are the domain-specific central nervous system pathways subserving the placebo response. We briefly review current knowledge of these pathways in the domains of Parkinson's disease (PD), Major Depressive Disorder (MDD), and anxiety.

#### *Parkinson's Disease*

While the role of dopamine (DA) in placebo analgesia points to an appetitive motivational/appraisal account of placebo that may be relevant across domains, DA arguably plays a much more critical role in the placebo response in PD. PD is a debilitating movement disorder known to result from the degeneration of dopamine-producing neurons in the nigrostriatal pathway. Researchers have learned about the mechanisms of the PD-specific placebo response by examining placebo effects on motor performance, dopamine release, and single neuron activity in the substantia nigra. PET studies of dopamine D2 receptor activity have provided evidence that placebo treatments lead to dopamine release in the striatum (de la Fuente-Fernandez et al., 2001). Complementary evidence has been obtained from neurosurgical studies, in which researchers have examined placebo effects on activity in the subthalamic nucleus (STN), a stimulation site used in the treatment of Parkinson's, and have examined interactions between placebo expectancies and STN stimulation. Placebo administration directly affected STN activity in placebo responders (those who demonstrated placebo effects on muscle rigidity, a clinical sign of the disease), evidenced by decreased bursting and neuronal frequency discharge (Benedetti et al., 2004).

Researchers have also demonstrated differing effects of ventral STN stimulation on autonomic activity between hidden and open stimulation (Lanotte et al., 2005), and expectations for poor versus enhanced motor performance have been shown to modulate the effects of STN stimulation (Pollo et al., 2002). Finally, the placebo response in PD is thought to arise primarily through expectancies, as verbal instructions to induce expectations of improved motor performance were found to reverse the effects of conditioning trials in which STN stimulation was turned off, resulting in decreased motor performance (Benedetti et al., 2003).

#### *Major Depressive Disorder*

In MDD, placebo effects on the brain were examined by using PET imaging to measure baseline metabolic activity before, during, and after treatment with either placebo or fluoxetine, a common selective-serotonin reuptake inhibitor prescribed as an antidepressant (Mayberg et al., 2002). Many changes that were observed as part of successful treatment with the active drug were also observed in placebo responders, including metabolic decreases in subgenual ACC. This region has been shown to be consistently affected in depression and is a target of deep-brain stimulation in patients who do not otherwise respond to treatment. Other common sites of activity over the course of treatment with either fluoxetine or placebo included metabolic increases in prefrontal, parietal, and posterior cingulate cortex, and decreases in parahippocampus and thalamus. Importantly, these common results differ from patterns of brain activation over the course of other types of treatment, such as cognitive behavioral therapy and interpersonal psychotherapy (Brody et al., 2001; Goldapple et al., 2004), which tend to lead to metabolic decreases in prefrontal activity, rather than increases. These results suggest that both active drug and placebo treatments work in part by changing central systems involved in affective valuation and motivation. It is important to point out that this study was longitudinal, and due to ethical constraints about denying treatment to patients when successful treatments are known to exist, no natural history control group was included in these analyses. It is therefore possible that observed results in both conditions may include factors attributable to the natural course of MDD. Much more work remains to be done to unpack the brain mechanisms involved in both verum and placebo treatment for depression.

#### *Anxiety*

While studies of the placebo response in PD and MDD have generally examined effects in clinical populations, Petrovic and colleagues used emotional images and active anxiolytics to examine placebo effects on anxiety

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and emotion processing in healthy participants (Petrovic et al., 2005). On their first day in the laboratory, participants viewed and rated neutral and unpleasant images without treatment, then were given benzodiazepine, which decreased ratings of unpleasantness, followed by a benzodiazepine antagonist that reversed the effects of the anxiolytic. On the following visit, participants were scanned using fMRI while they were told they would undergo the same procedure. During this session, saline was administered in place of both the benzodiazepine and its antagonist, resulting in placebo and control conditions, respectively. As mentioned, this study revealed decreases in regions specific to emotion processing, and increases in regions that overlapped with modulatory regions that had been identified in studies of placebo analgesia (Petrovic et al., 2002; Wager, Rilling, et al., 2004). More specifically, placebo induced decreases in extrastriate activity and amygdala that correlated with reported placebo effects, and increases in OFC, rACC, and ventrolateral PFC activity (only rACC and vIPFC correlated with subjective placebo effects). Finally, treatment expectations on day 1 correlated with the extent of decreases in extrastriate cortex, increases in rACC, and placebo-induced activity in ventral striatum.

### ETIOLOGY OF THE PLACEBO RESPONSE: EXPECTANCY VERSUS CONDITIONING

Given evidence that the placebo response does indeed involve active psychobiological mechanisms in multiple domains, the question arises of exactly how the response comes about. For about half a century, placebo researchers have focused on two possible sources: classical conditioning or conscious expectancies. Briefly, conditioning-based placebo responses result from the association between active treatment outcomes and the context or procedures surrounding treatment, regardless of the organism's awareness of the contingencies between stimuli. Expectancy-based placebo responses result from appraisals of anticipated treatment outcomes that inherently depend on the organism's beliefs about treatment. Thus, an important distinction is that only expectancy-based placebo effects can be altered by verbal instructions to participants. We assess how each factor may contribute to the development of the placebo response, and examine research directly comparing the two processes. We suggest that some placebo responses may be mediated entirely by expectancies; others may be primarily due to conditioning; and in other cases the two may not be mutually exclusive, as conditioning can serve to induce conscious expectations about placebo treatment outcomes.

### Conditioning-Based Placebo Responses

Many psychologists became interested in placebo research in the 1950s, with the publication of Beecher's *The Powerful Placebo* (Beecher, 1955). This coincided with psychology's shift toward behaviorist views of psychological phenomena. Consistent with the dominant trends, the placebo response was explained in terms of classical conditioning. In the original Pavlovian stimulus-substitution model of classical conditioning, organisms learn to pair a neutral stimulus (a stimulus that elicits no response on its own) with an unconditioned stimulus (UCS) that normally elicits an unconditioned response (UCR). With repeated pairings, the neutral stimulus comes to elicit the same response as the UCS; the neutral stimulus has become a conditioned stimulus (CS), and the evoked behavior is referred to as a conditioned response (CR). Conditioning can occur in aversive contexts (in fear conditioning, a light may be paired with a shock, to elicit freezing in response to the light) or appetitive contexts (as in Pavlov's classic experiments, food can be paired with a tone and animals eventually salivate in response to the tone).

A simple classical conditioning account of placebo would propose that a pharmacological agent serves as a UCS that elicits healing effects (UCR; Montgomery & Kirsch, 1997; Wickramasekera, 1980); when the agent is delivered in pill form, the pill becomes the CS, and later administration of the pill without the pharmacological agent will elicit the active effects of the drug as the CR. Proponents of the classical conditioning view of placebo have even suggested that over a lifetime of pairings, neutral stimuli related to the medical context—doctors' offices, the procedures surrounding medicine administration, medical devices, and doctors themselves—become associated with the results of treatment, and that placebo effects are the result of conditioning to these contextual stimuli.

Several findings offer support for a classical conditioning account of the placebo response. Benedetti and colleagues showed that placebo effects following active administration of an opiate analgesic included respiratory depression, a side effect of the active medication, although participants reported no awareness of this associated side effect (Benedetti, Amanzio, Baldi, Casadio, & Maggi, 1999). In another study, participants were pretreated with pharmacological agents that elicited increases or decreases in cortisol and growth hormone release (Benedetti et al., 2003). Placebos were subsequently administered alongside verbal suggestions that treatment would produce the opposite effect, but the directionality of the physical outcomes in these two domains was not reversed. These results suggest that some placebo responses involve learning that is not modifiable by conscious expectancies.

Primary mechanistic evidence that conditioning can serve to recruit endogenous disease-related processes comes from human and animal studies of conditioned immunosuppression and conditioned induction of anti-allergic effects. Immunosuppression refers to the reduction of immune system efficacy; this may be deliberately induced in medical procedures such as organ transplants to prevent the immune system from rejecting the foreign organ. Rats that receive cyclophosphamide, an immunosuppressive agent, alongside saccharin during conditioning exhibit decreased antibodies when saccharin solution is later presented on its own, relative to rats that were not conditioned and conditioned rats that were not exposed to saccharin at test (Ader & Cohen, 1975). A later study used  $\beta$ -adrenoceptor antagonists and 6-OHDA, a chemical that depletes noradrenaline, in a similar case of conditioned immunosuppression using the immunosuppressive drug cyclosporin A (CsA) and found that immunosuppressive effects in the spleen were mediated by the sympathetic nervous system (Exton et al., 2002). Finally, humans who received CsA paired with a unique beverage over repeated sessions demonstrated immunosuppression when they were exposed to the CS a week later, as indexed by lymphocyte proliferation, mRNA expression, and cytokine production and release (Goebel et al., 2002).

A similar approach was taken to induce conditioning of anti-allergic effects in humans (Goebel, Meykadeh, Kou, Schedlowski, & Hengge, 2008). A unique beverage was repeatedly paired with antihistamine in patients with allergic rhinitis. Participants who received the beverage alongside a placebo pill at test exhibited levels of basophil, a white blood cell that releases histamine, that were comparable to those who received the active medication, while participants who received water alongside placebo demonstrated no basophil inhibition. These data suggest that conditioning can indeed recruit powerful endogenous mechanisms related to immune functioning, and offer preliminary windows into central nervous system pathways that may be involved in the etiology of a conditioning-based placebo response. However, while this offers some insight into the role of conditioning in endogenous processes, it is unknown how mechanisms supporting conditioned immunosuppression may generalize to other domains, such as pain and Parkinson's disease. Furthermore, participant expectancies were not assessed in these studies, and it is possible that conscious expectancies about the novel beverage and its effects on immune function may have played an important role in the observed effects.

Little is known about brain mechanisms that would specifically support a classical conditioning account of placebo, although there have been decades of research on conditioning in animal models, and aversive conditioning

mechanisms have been studied in humans using fMRI (Phelps, Delgado, Nearing, & LeDoux, 2004; Phelps et al., 2001). Different conditioning mechanisms are responsible for effects in different systems, so despite the wealth of knowledge about the specific neural circuitry involved in the realm of aversive conditioning, it is difficult to generalize across domains or infer mechanisms in domains that have not been directly examined. In eyelid conditioning, an auditory stimulus (CS) is paired with an air puff (US) to the eye, and this gradually leads to the conditioned response of an eyeblink (CR) when the tone is presented. Although these two stimuli originate in different modalities and travel through separate pathways (CS via mossy fibers, US via climbing fibers), both pathways include synapses onto the purkinje cells in the cerebellar cortex (Kim & Thompson, 1997). In fear conditioning, an auditory stimulus (CS) is paired with a shock (US), creating a startle response (CR). Again, these stimuli are processed separately (CS travels from auditory thalamus, US from brain stem), but both share common synapses in the lateral amygdala (Rogan & LeDoux, 1995; Rogan, Staubli, & LeDoux, 1997). These examples suggest that for these specific types of conditioned learning to occur, US and CS pathways must share common nuclei; furthermore, conditioning recruits unique pathways depending on stimulus and response modalities. Thus, conditioning-based placebo mechanisms are likely to involve similar neural mechanisms in principle, but our knowledge of mechanisms specific to aversive conditioning are unlikely to generalize to positive conditioning-based placebo responses.

Though little was known about the brain mechanisms of conditioned immunosuppression for many years, recent studies have begun to investigate them. An important study by Pacheco-Lopez et al. (Pacheco-Lopez et al., 2005) used a rat model to assess the effects of lesions of the insula, amygdala, and ventromedial hypothalamus on conditioned immunosuppression and taste aversion. Insula lesions disrupted both aversion to the taste paired with the immunosuppressive drug (the CS) and several peripheral markers of immunosuppression, both before the conditioning procedure and afterward, during evocation by presenting the CS. Thus, the insula is implicated in both acquisition and retrieval of the memory that leads to immunosuppression. Amygdala lesions disrupted immunosuppression only before conditioning, implicating it in the learning process but not the expression of the learned response. Conversely, hypothalamic lesions disrupted expression but not acquisition of the immunosuppressive response.

The neural mechanisms for conditioned placebo responses in pain and other domains remain unknown, and more research is needed to disentangle pathways that subserve conditioned CS-US or CS-UR learning and

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conscious expectancies. In one fMRI study, researchers compared brain responses to painful stimulation under opioid-based analgesia with responses to placebo analgesia (Petrovic et al., 2002). Opioid administration always preceded the placebo analgesia condition, which may have induced a conditioning-based placebo response. Brain responses to each were compared with a pain control condition, and both were associated with increased activity in rACC, and increased rACC-brainstem connectivity. While this and other brain-based studies are promising, they have not directly compared conditioning processes with nonconditioning expectancy manipulations (verbal instructions only), and the nature of the conditioning-specific placebo response remains yet to be elucidated.

### Expectancy-Based Placebo Responses

A central question in cognitive neuroscience over the past 50 years concerns the processes affected by expectancies, which shape perception across virtually every sensory and affective domain. Expectancies involve appraisals of an event's significance in the context of its anticipated outcome; appraisal systems can affect brainstem and hypothalamus nuclei as part of coordinated behavioral and physiological responses that promote homeostasis. In the expectancy view of placebo, beliefs and expectations associated with treatment administration are responsible for recruitment of endogenous mechanisms to produce the requisite changes associated with the placebo response. Expectancy-based placebo effects are mediated by beliefs about upcoming experience, and do not necessitate prior exposure to an active treatment for the effect to occur.

An important distinction between expectancies and conditioning-based learning is that expectancies are generally conscious at the time when decisions are made (Stewart-Williams & Podd, 2004); if they are not conscious, they can be made conscious with directed attention (Kirsch, 2004; Kirsch & Lynn, 1999). Many conditioning theories posit that conditioning will occur regardless of the organism's awareness of the contingencies between stimuli. Thus, only expectancy effects depend on an individual's state of mind, which suggests that expectancy-based placebo effects can be altered by verbal instructions to participants, whereas conditioning-based placebo effects cannot. In the following section, we review several studies that have compared the respective contributions of expectancies and conditioning-based learning to the placebo response. In most cases, these studies suggest that expectancies provide a stronger account for observed placebo effects on reported pain.

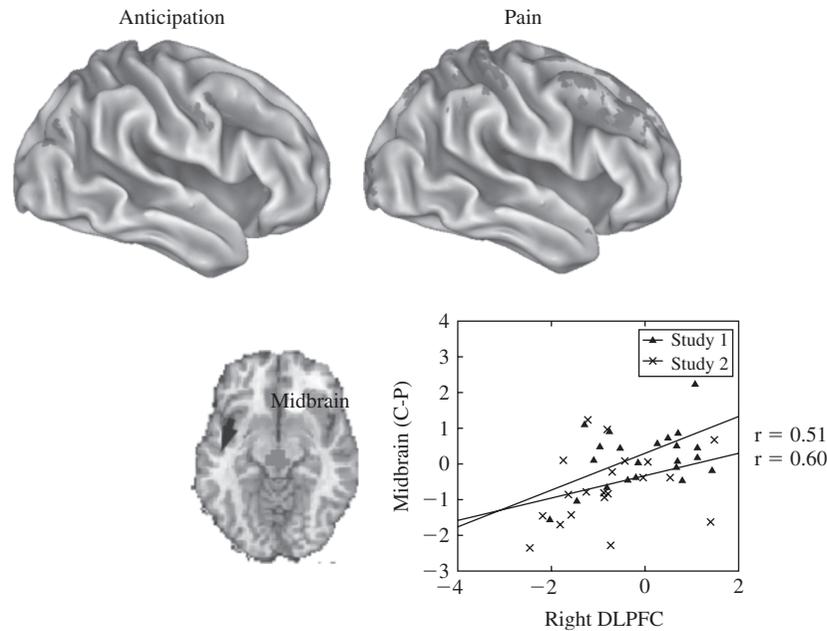
As expectancies modulate perception across many domains, we have much to draw from in positing potential brain mechanisms underlying expectancy-based placebo

effects. In many studies, expectancy mechanisms are probed by paradigms that employ novel stimuli that are predictive of different levels of stimulation. This allows researchers to examine the development of expectancies over time, as participants learn to predict stimulation based on cues. Conditioning explanations cannot account for behavior when participants have no prior experience with the predictive stimuli, or in paradigms that include contingency reversals. These paradigms allow researchers to investigate how these expectancies affect processing; and neuroimaging and electrophysiology methodologies can reveal brain mechanisms responsible for maintaining expectancies and supporting the relationship between expectancies and perceived experience. Expectancy manipulations have been shown to modulate stimulus processing in neuroimaging and electrophysiology studies of pain (Keltner et al., 2006; Koyama, McHaffie, Laurienti, & Coghill, 2005; Lorenz et al., 2005), emotion (Berpohl et al., 2006), taste (Nitschke et al., 2006; Sarinopoulos, Dixon, Short, Davidson, & Nitschke, 2006), and reward (Hampton, Adolphs, Tyszka, & O'Doherty, 2007; Spicer et al., 2007).

As described earlier, researchers can define reasonable hypotheses about brain mechanisms supporting an expectancy-based placebo response by drawing on knowledge from brain mechanisms of cognitive control. These can be tested by contrasting anticipatory activity in a placebo condition with anticipatory activity during a control condition, so that the researcher can identify processes related to pain expectancy that are shaped by placebo treatment. This approach was used in an fMRI study of placebo analgesia (Wager, Rilling, et al., 2004) that revealed increases in DLPFC, OFC, and rACC activity during anticipation of pain with placebo. These anticipatory increases correlated with placebo effects on reported pain, and anticipatory increases in DLPFC and OFC correlated with subsequent placebo-induced reductions in pain matrix activity during thermal stimulation. Importantly, anticipatory increases in DLPFC correlated with activity in an area of the midbrain surrounding the PAG (see Figure 63.6), offering support for the interaction between expectancies and opioid release. Other studies have replicated and extended this result, showing that placebo treatments for negative emotion activate the same brain regions (Petrovic et al., 2005), and that endogenous opioids—neurochemicals linked to relaxation, euphoria, and pain relief—are released in these regions following placebo treatment (Wager et al., 2007; Zubieta et al., 2005).

### Reconciling Expectancy and Conditioning Accounts of Placebo

It is difficult to resolve the relative contributions of expectancy and conditioning to placebo effects, because the two



**Figure 63.6** Placebo-induced activation of the cognitive/evaluative network.

*Note:* Contrasts between placebo and control conditions in an fMRI study of placebo analgesia (Wager, Rilling, et al., 2004) revealed increases in brain regions known to be involved in executive function and affective appraisal, including dorsolateral prefrontal cortex (DLPFC) and orbitofrontal cortex (OFC). Increases were observed both in anticipation of pain (top left) and during thermal stimulation (top right). Placebo-induced increases were also observed in an area of the midbrain surrounding the periaqueductal gray (PAG; bottom), and anticipatory activity in this region correlated with anticipatory increases in right posterior DLPFC (bottom right), offering support for the influence of expectancies on placebo-induced pain modulation.

are not always mutually exclusive; in some cases, conditioning procedures are likely to shape both learning and expectations. There are two ways to distinguish between learning and expectancy mechanisms: One relies on behavioral observations, and the other on measurement of the brain. Earlier, we suggested that conditioning results in learning that persists over time, despite expectancies; when a CS is presented without the UCS, extinction of the CR is relatively slow. Thus, effects that can be reversed in a single trial or affected by verbal instructions are not likely to be the result of conditioning, but rather expectancies. A second way to discriminate between conditioning and expectancy is by measuring brain activity. The patterns of activity increases and opioid release with placebo in OFC and rACC, and increases in DLPFC, suggest that general mechanisms of appraisal and expectancy are at work. Such effects have been found in pain and, though less well studied, depression. A difficulty, however, is that there is no way to ensure by looking at the brain that these responses are not the result of some conditioned association being activated. Another difficulty is that it is currently difficult or impossible to measure learned associations directly in the human brain; whereas synapse strength, gene expression, and other molecular markers of learning can be investigated in animal models, the techniques for probing them are invasive and cannot be used in humans—and, in addition, it is

still unknown where in the human brain cellular learning underlying placebo effects may be taking place.

Several experiments have attempted to directly compare expectancy-based and conditioning-based placebo effects in studies of placebo analgesia (Benedetti et al., 2003; de Jong, van Baast, Arntz, & Merkelbach, 1996; Montgomery & Kirsch, 1997; Voudouris et al., 1985; Voudouris, Peck, & Coleman, 1989, 1990), using variations of the same basic procedure. Verbal instructions to participants suggest that the placebo treatment is an effective analgesic drug. Some participants receive these instructions alone. Other participants are additionally exposed to an active treatment or procedure, which in most cases has involved the surreptitious reduction of painful stimulus intensity during treatment under the placebo condition. This serves as an unconditioned response (UR) or UCS with which the CS—cues associated with stimulation during placebo conditions—are associated. In some cases, a third group receives the conditioning procedure, but they are not verbally instructed that the placebo is an effective drug. The key comparisons are whether conditioning without verbal instructions reduces pain, and whether conditioning plus instructions is more effective than conditioning alone.

Voudouris and colleagues (1985, 1989, 1990) used this approach and reported that conditioning provided the stronger explanation for observed placebo effects,

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since conditioning plus instruction was much more effective than instruction alone. Conclusions drawn from these experiments were contested, as some argued that such studies do not compare expectancy and conditioning, but instead compare expectancies mediated by physical processes (conscious expectancies that come about as a result of the conditioning procedure) to expectancies mediated by verbal information alone (Stewart-Williams & Podd, 2004). Conscious expectancies may mediate learning in both conditions, and any observed differences may be due to the fact that physiological experiences induce stronger expectancies than verbal suggestion.

Results supporting an expectancy account of placebo analgesia were reported by de Jong and colleagues (1996), who used essentially the same experimental design, but added a group of participants who were exposed to conditioning trials with the critical addition that they were informed that noxious stimulation was being lowered during application of the cream. If the conditioning process were entirely responsible for observed placebo effects (if all that matters is the pairing of UCS and CS), then participant knowledge about the procedures would not counteract the efficacy of the conditioning manipulation on observed placebo effects; however, pain reports under placebo in this group did not differ from reported pain in the control condition. Furthermore, de Jong's group added measures for participants' conscious expectations of pain relief, which Voudouris and colleagues had not included in their original study, and found that these ratings predicted the magnitude of placebo effects. Later, Montgomery and Kirsch (1997) took a similar approach and demonstrated that although the magnitude of placebo effects seemed to offer support for a conditioning explanation of placebo, results were entirely mediated by participants' reported expectations of pain relief in the conditioning group. These studies both suggest that expectancy theory provided a better account for observed placebo effects than a conditioning explanation.

In a more expansive examination of the contributions of expectancy and conditioning to placebo effects, Benedetti and colleagues (2003) analyzed the contributions of the two potential sources to placebo effects in pain, Parkinson's disease (PD), and hormone secretion. In each modality, preconditioning with an active treatment (Keterolac for analgesia, turning off subthalamic nucleus stimulation for decreased motor performance in Parkinson's disease, and Sumatriptan for growth hormone increase and cortisol decrease) was followed by verbal instructions to induce opposing expectations in the respective groups (hyperalgesia, movement velocity increase in PD, and suggestions of GH decrease and cortisol increase). Consistent with de Jong and Montgomery and Kirsch's earlier findings, conscious expectations reversed the effects of conditioning in

pain, as well as PD. However, expectancies did not reverse the effects of preconditioning in hormonal secretion. The authors take this to suggest that placebo responses close to behavior (pain reports and motor symptoms) are mediated by expectancies, but that conditioning of some hormonal and peripheral responses can occur outside the regulation of conscious expectancies.

While the series of studies reviewed here suggest that classical conditioning and expectancies are competing explanations that must be pitted against one another to determine the true source of the placebo response, some have argued that it may not be necessary to view the two potential mechanisms as competing explanations. We framed our introduction to Pavlovian conditioning in a manner consistent with the early stimulus-substitution models of the phenomenon, which focused on contiguity, the notion that the paired presentation of stimuli is responsible for the acquisition of conditioned responses. However, computational accounts have suggested that conditioning can be explained as a *process* by which an organism learns the relationships between events, and that organisms learn to pair stimuli with subsequent *outcomes*, rather than responses (Rescorla, 1988a, 1988b). A response is generated only insofar as the stimulus provides useful information about an upcoming event, and behaviors that are performed during conditioning are performed in anticipation of the expected outcome. Some suggest that this anticipatory behavior is closely linked to expectancies. In cases in which the conditioning process allows for conscious understanding of the relationships involved, expectancies may be likely to mediate the process of learning stimulus-outcome relationships over the course of conditioning, providing a way to reconcile the two accounts.

### SUMMARY

The placebo response is not only clinically relevant, but also serves as a valuable window into the powerful interaction between basic psychological processes, such as expectancies and affective appraisals, and the bodily state. Although many factors can potentially lead to observed placebo effects without affecting underlying physiology, careful experimental manipulations and supporting neuroimaging investigations provide evidence of active psychobiological placebo responses. Nearly all the studies reviewed identify a subset of participants who do not respond to the placebo manipulation (report no difference between placebo and control conditions). Early placebo researchers believed there was a true population of placebo responders, and behavioral studies sought to identify trait-level personality factors that would differentiate the

placebo responder from the nonresponder. These attempts proved futile, and researchers adopted the view that anyone could demonstrate placebo reactivity under the correct circumstances (Lieberman, 1964). Neuroimaging analyses, such as those reviewed earlier, generally account for responder differences through correlations between brain activity and extent of reported placebo effects, or statistical comparisons between placebo responders and nonresponders. We have reviewed specific evidence of placebo effects on pain, Parkinson's disease, Major Depressive Disorder, and anxiety, and suggest that placebo responses in these domains may share common central mechanisms, including affective appraisal, cognitive control, and factors related to the etiology of the placebo response. Much more experimental research is needed to elaborate on our knowledge of factors contributing to individual differences in the development of the placebo response, proximal placebo mechanisms in domains other than those reviewed, and to build a more comprehensive account of central and proximal mechanisms of the placebo response.

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