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The Placebo Response

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Glossary

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Analgesia – Significant lessening or complete termination of pain sensation.

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Nociception – Pain sensation.

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Placebo – An administered treatment that on its own has no known beneficial effect on a given condition.

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Placebo effects – Observed improvements in outcome measures attributed to the influence of the placebo treatment.

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Placebo response – The set of endogenous processes whereby conscious expectancies and conditioning recruit brain and body mechanisms to elicit beneficial effects on symptomatology and processing.

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Introduction

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The history of placebo effects over the last century has been a turbulent one. They have been variously dismissed as artifacts and embraced as compelling evidence of the healing power of the mind. In either case, the rigorous scientific study of placebo provides a unique window into the relationship between the mind, brain, and body. Such research is beginning to reveal the potential power of, and the limits on, how the brain affects the physiological and psychological manifestations of health and disease. In some cases, positive outcomes have been demonstrated to result from conscious expectations of therapeutic benefit. But some of the most potent placebo responses have been elicited by learning that may be outside of conscious awareness and at least partially impenetrable to volition and conscious thought. These studies, and more broadly the kinds of evidence that have and have not demonstrated the power of placebos, are the subject of this article.

A placebo treatment is one that is expected to have no direct physical or pharmacological benefit – for example, a starch capsule given for anxiety or pain, or a surgery where the critical surgical procedure is not performed. For this reason, placebos are routinely used as comparison conditions in clinical studies, against which to evaluate the effects of investigational treatments. However, placebo treatments have also frequently been used to actually treat a variety of ailments; they have had a place in the healer's repertoire for thousands of years, and are used as clinical treatments by physicians in industrialized countries today with surprising frequency.

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To the degree that placebo treatments are healing agents, their power lies in the psychobiological context surrounding treatment, resulting in an active response in the brain and body of the patient. This endogenous response is referred to as a placebo response, or meaning response. In many cases, the psychological meaning of the treatment induces shifts in cognition, emotion, and corresponding brain and nervous system activity that produce a palliative effect. In other cases, placebo responses result from associations learned in the brain through a process known as conditioning. In this process, associations between the elements of the treatment context (the shape of a hypodermic needle, or the color of a pill) and helpful neurobiological responses are formed in the brain. These associations may be learned and activated outside of the patient's consciousness. Thus, although a placebo treatment is itself inert, the placebo response on the part of a patient may have real healing benefits. What is typically measured in a study, however, are placebo effects – observed improvements in signs or symptoms attributed to the influence of the placebo treatment. Although the two terms are often used interchangeably, for the purpose of this article we distinguish between the placebo effect, an observed effect on specific outcome measures (e.g., the difference between a placebo-treated group and an untreated group in a study), and the placebo

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response, which is a set of endogenous processes (brain and body mechanisms) recruited by placebo-induced expectations and conditioning. By this definition, placebo effects are directly observed in studies, and placebo responses are psychophysiological processes whose nature must be inferred by observing placebo effects. A placebo effect may thus provide evidence for an underlying placebo response, though the strength of that evidence depends on the nature of the comparison performed in the study and range of alternative explanations. (We note that many scholars use the term ‘placebo response’ to refer to any improvement on a placebo treatment, which is not the sense in which we use the term here.)

p0020 The potential clinical significance of the placebo response has led to the standard use of placebo groups in clinical trials for therapeutic drugs and procedures. Clinical trials are experimental studies performed to test the therapeutic efficacy of medicines, surgical procedures, and other interventional procedures. The use of placebos has proven invaluable in providing a baseline against which to assess interventions; however, clinical trials are not typically designed to test the therapeutic effects of placebo treatments themselves. Thus, for reasons described below, they provide little evidence either for or against the existence of placebo responses as defined above.

p0025 In an influential paper published in 1955 entitled ‘The powerful placebo,’ Henry K. Beecher analyzed a series of placebo-controlled clinical trials in order to examine the efficacy of the placebo itself. Stemming from this first effort, another class of experimental studies is designed to specifically assess the therapeutic effects of placebo treatment and patients’ expectancies, and these studies provide the most direct evidence for active psychobiological placebo responses. These studies offer scientists a unique opportunity to investigate interactions between the brain and body. Behavioral, pharmacological, physiological, and most recently neuroimaging methodologies have allowed us to begin to understand the mechanisms by which placebos exert their effects. This, in turn, offers scientists a window into understanding how the brain exerts control over behavior, emotional experience, and physiological processes in the body. This overview is devoted to a critical review of these studies.

False Placebo Effects

Placebo effects have been the center of heated debates among researchers that have persisted in different forms throughout the past century. The central debate revolves around the issue of whether active, psychobiological placebo responses exist, and whether they affect health and disease processes in meaningful ways. Two alternative explanations for observed placebo effects have been offered: First, placebo effects in some studies may be statistical artifacts; and second, placebo effects in many studies may reflect changes in subjective reporting processes only, and not in meaningful disease processes.

The argument that the so-called ‘placebo effects’ are statistical artifacts applies primarily to clinical trials that are not designed to test the efficacy of placebo treatments, and are thus not carefully designed to avoid such artifacts. The argument that observed placebo effects are subjective reporting biases applies to clinical trials and experimental studies of placebo alike. In this section, we outline each argument, and in the following section, we evaluate the experimental evidence on reporting biases in various disease processes.

Placebo Effects as Statistical Artifacts

In a typical clinical trial, patients are randomly assigned to treatment either with a therapeutic intervention (e.g., a study drug) or a placebo, and outcomes are assessed under ‘double-blind’ conditions: neither the patient nor the assessor knows which treatment a person is taking. There are many variants on this procedure, but the vast majority of trials share this element in common. Comparisons between the treatment and placebo groups are performed in order to estimate the active effects attributable to the treatment (treatment efficacy). Two assumptions are made in this comparison: First, that all nonspecific effects of being in the study (natural outcome improvement or worsening over time, effects of patient expectation and motivation, health care setting effects, etc.) are common to both treatment and placebo groups, and second, that nonspecific effects and drug effects combine additively, so that a simple subtraction between the two will yield the active

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treatment effects. The critical question for placebo research is what those ‘nonspecific’ effects are, and how much of them can be attributed to causal effects of the placebo treatment itself (i.e., the placebo response). Put in concrete terms, placebo groups in studies of depression typically improve about 7–8 points on the Hamilton depression inventory (a clinical measure with a range from 0 to 54 points, with 24 or above indicating severe depression); but it would be an error to attribute all of this effect to the placebo response, because other factors also contribute to ‘nonspecific’ improvement in placebo groups. Some of these are (1) spontaneous remission, (2) natural symptom fluctuation, (3) regression to the mean, and (4) participant sampling bias.

than anything having to do with placebo administration. It is tempting in many contexts to look at subgroups of individuals on the basis of their initial disease state – that is, the most depressed patients – and follow them over time. But this is problematic due to regression to the mean: If one were to follow the most severe patients in the placebo group in almost any disease state, they would be seen to improve over time.

These first three factors demonstrate the importance of including a natural history (non-treatment) control group in clinical trials for assessing placebo effects. If a no-treatment group is included, then a comparison between the placebo-treated and the no-treatment group can be used to assess the effects of the placebo *per se*. Unfortunately, very few clinical trials include such groups, because the placebo effect itself is not of primary interest in these studies.

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s0020 **Natural history: spontaneous remission and natural symptom fluctuation**

p0045 Every disease has a natural history, a time-course that the disease state would follow without any intervention. Many disease states are time-limited, and patients experience spontaneous remission – most depressed patients, for example, eventually recover, as do those with anxiety disorders, sleep disorders, and many other conditions. Improvement in a placebo group in a clinical trial could therefore be due to spontaneous remission. Other diseases – such as hypertension, pain syndromes, Parkinson’s disease, irritable bowel syndrome, and many others – do not have high spontaneous remission rates, but the signs and symptoms fluctuate over time. A study may end while a patient is relatively symptom-free, which would look like healing attributable to placebo, but may in fact be a transient improvement after which symptoms may reappear.

Participant sampling bias

Participant sampling bias comes about as a result of the fact that participants who experience beneficial results from a treatment are more likely to continue in the study and adhere to treatment regimens than those who experience either no effect or adverse effects. Thus, the participants who complete clinical trials in placebo groups (as well as active treatment groups) are more likely to be those who improve over the course of the study. The result is that participants may appear to improve over the course of the study, but this apparent improvement actually reflects changes in the sample over time.

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s0025 **Regression to the mean**

p0050 Regression to the mean refers to the observation that when measurements are repeated, subsequent measurements are likely to be closer to the mean than the initial ones. This phenomenon is especially applicable to clinical improvements in placebo groups. If a patient seeks treatment and is enrolled in the study when his or her disease is worse than average, the patient’s state is likely to improve by the time the disease is next measured due to the natural course of the condition, rather

Placebo Effects as Reporting Biases

Another important source of potential error has to do largely with the important subjective aspects of many conditions in which the placebo effect is studied. In pain, depression, and nearly every illness, an essential component of the illness is the subjective experience of the condition.

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In some domains, there are clear objective measures of current state, such as motor performance or outwardly observable physical symptoms, but in many important clinical states objective measures are not available. For example, because pain is a subjective experience, clinical and experimental measures of pain are based on patients’ reports.

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Physiological measures based on skin conductance, heart function, and pupillary response can be measured, but they are indirectly related to pain; thus, while they may be more precisely measured in some cases, they cannot be assumed to accurately reflect the pain experience.

p0075 The problem with self-report-based measures is that they might be influenced by a number of factors that are not central to the disease process being studied. Thus, demonstrating placebo effects in subjective outcomes may say little about the power of placebo treatments to effect meaningful changes in disease progression. For example, a treatment that improves subjective well-being in cancer patients may be beneficial for this reason alone, but its viability as a specific treatment for cancer must certainly rest on its effects on the growth of the cancer. A few of the factors that create biases in subjective outcome assessment are described below. Ruling out reporting biases as causes of observed placebo effects is difficult in many cases; we address relevant evidence in the following sections.

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p0080 Demand characteristics refer to changes in patients' reports and behavior on the basis of their perception of how they are expected to behave. Often, these expectations are communicated by inadvertent cues from the investigator: Even a very subtle nod or widening of the eyes from a physician may communicate agreement or surprise on the physician's part. Such influences can be avoided by keeping experimenters and physicians blind to condition, when possible. In one interesting study, for example, physicians' expectations about a drug's effectiveness were shown to affect how effective patients thought it was in relieving pain. Other types of cues about expectations might result from the study procedures themselves or the way questions are worded. The question "How much did your pain decrease?" implies that it should have decreased to some degree.

p0085 Being observed often causes changes in behavior. Such changes are classically referred to as Hawthorne effects, after a landmark study that showed workers' performance improved dramatically once they were under observation in the

study. Hawthorne effects generally result from social influences that affect participants' reports and behavior. Male experimental participants, for example, will tolerate higher levels of painful stimulation when an experimenter is watching them.

Demand characteristics and reporting biases cover a range of different psychological effects, including Hawthorne effects in some cases, social compliance effects (in which patients say what they feel should be said), self-presentation biases (individuals often say what makes them look better in the eyes of others), and self-consistency biases (consistency with past behavior, to avoid admission that past behavior was in some way incorrect).

Response bias

Many experiments have demonstrated that decisions about the presence or absence and intensity of a stimulus (such as a disease symptom) are not a function of a stimulus alone, but of prior beliefs and the relative benefits and costs of the decision. This approach is the basis of signal detection theory (SDT). Consider the following simplified scenario. A patient is given a medication and is asked to judge whether the drug relieved pain. In simplified form, the patient truly feels different or she does not, and she may choose to respond "Yes, the drug helped" or "No, it did not help". A 'yes' response might be true pain relief or a false affirmative (an error). A 'no' response might reflect a true lack of pain relief or a false negative (another kind of error). The answer that the patient reports depends partly on the how well the patient can discriminate true from null effects, and partly on the relative costs and benefits of making the two kinds of error. The SDT framework acknowledges that a cost-benefit analysis influences patients' decisions on what to report, and provides a way of estimating both the discriminability of true versus null effects and the patient's response bias towards responding either 'yes' or 'no.'

SDT analysis has been employed since the late 1960s in order to investigate whether placebo administration alters sensitivity to pain (measured by the ability to discriminate between different levels of noxious stimulation), response bias, or both. These studies suggest that the placebo effect is actually a change in response bias alone, without any change in sensitivity. A complicating factor is

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that a change in ‘response bias’ after placebo treatment amounts to subjects reporting that noxious stimulation simply feels less painful after the treatment, even if they are no less accurate at discriminating different levels of intensity. These studies cannot provide evidence on whether those reports of feeling less pain occur because of changes in pain processing in the brain and spinal cord, or simply because of a cost–benefit analysis involved in the reporting decision. One way of disentangling these alternatives lies in the direct measurement of brain responses to painful stimuli, and we return to this alternative below.

studies have found placebo effects in immune function, cortisol levels, and growth hormone levels. In Parkinson’s disease, placebo effects have been reported in disease-relevant neural and neurochemical activity and in clinical signs of disease severity. In major depressive disorder, treatment with placebo induces changes in brain activity that mimic treatment with an active drug. Finally, in asthma, placebo effects have been reported in clinical measures of airway responsiveness. It is possible that placebo effects exist in other physiological processes; more research remains to be done to demonstrate the causal effects of placebo treatment in these and other areas.

Active Placebo Outcomes

Placebo Effects in Pain Physiology

It is clear that placebo treatments may influence subjective reports and observable conditions without affecting any underlying disease process. That is not to say that placebo effects on some outcomes, such as reported relief from pain or improvement in reported quality of life, are not valuable in their own right. In many cases, these outcomes are central to the comfort and happiness of patients, and to their ability to work productively and maintain positive social relationships. Nonetheless, it is valuable to review evidence for placebo effects on measurable biological processes in the brain and body. These are most often likely to be essential elements of a clinically meaningful placebo response in disease progression.

While placebo effects have been demonstrated in a wide range of domains, the majority of laboratory studies demonstrating causal effects of placebo treatment have been conducted in the context of pain. Pain is a common and debilitating condition with great biological significance for all organisms. Though it typically has a peripheral, physiological origin and physiological consequences in the body, pain is a subjective experience thought to be determined by an interplay between sensory, affective, and emotional brain systems. Because pain can be manipulated experimentally, and because much is known about the neural and physiological correlates of human and animal nociceptive processing, pain is uniquely suited for experimental investigations of the placebo response at multiple levels, from the involvement of specific endorphins and neurotransmitters, to the contributions of different brain regions, to the motivational significance of placebo effects for an individual.

In this section, we review some of the evidence for placebo effects on physiological outcomes, focusing on physical pain – one of the best-studied outcomes experimentally – as a model system. In brief, placebo effects have been reported on physiological indices of nociceptive (pain-related) processing, including measures of brain activity and neurochemical responses to painful stimuli, and placebo analgesic treatments have been shown to interact with active pain-relieving drugs. In clinical studies, there is a growing body of literature demonstrating placebo effects on reported clinical pain (a clinically meaningful outcome) in pain disorders such as irritable bowel syndrome.

Because of the clinical significance of pain experience, the vast majority of placebo studies to date have demonstrated effects on subjective experiences of analgesia or pain relief. The classic example of placebo analgesia is when a person is (1) experiencing pain, which may be ongoing or caused by noxious (normally painful) stimulation in a laboratory study; (2) the person is given a placebo treatment, often with information indicating that the treatment will diminish pain; and (3) pain under the placebo treatment is compared with pain in an otherwise comparable no-treatment

In other domains, particularly when conditioning is involved and sensory or internal cues become associated with active treatment, experimental

condition, either in the same or different individuals, and pain reports decrease reliably with the placebo. However, in spite of the predominant (and clinically appropriate) use of reported pain as a primary outcome, several lines of research demonstrate placebo effects in objective physiological outcomes.

p0130 Early studies of placebo analgesia, in the late 1960s, suggested that placebo treatment affected pain reports, but not the ability to discriminate stimuli of different temperatures from one another. This research was done in the tradition of then-recently developed SDT, which provided a method to separately measure an observer's ability to discriminate stimuli of two or more categories and the so-called 'response bias' in reporting on the basis of costs and benefits of making different types of errors. Because placebo effects were found in 'response bias,' but not discrimination ability, it was concluded that placebo treatments may amount to nothing more than an increase in the decision criterion for reporting a given stimulus as painful.

p0135 However, another set of studies published in the late 1970s provided partial refutation of this conclusion by providing evidence that placebo treatments resulted in the release of brain opioids – endogenous (produced by the brain) neuropeptides known to play a key role in clinical pain relief. In these studies, the researchers gave participants a placebo treatment, which produced analgesia; but when they gave the same placebo treatment along with naloxone, a drug that blocks opioid receptors, the placebo analgesic effect was eliminated. These findings suggested that endogenous opioid release was a necessary component of at least one type of placebo analgesia (that elicited by verbal instructions and consequent expectancies of pain relief). Because opiate drugs are among the most widely used and best-known treatments for clinical pain and because opioids are involved in inhibition of pain-related neural signals at the earliest stages of processing in the spinal cord, the broader implication was that placebo treatment must have affected the brain physiology of pain.

p0140 These studies were replicated and extended in the late 1990s and early 2000s. Although naloxone can itself block pain or enhance pain depending on the dose and perhaps on the psychological conditions of the study, several studies demonstrated that naloxone could reverse placebo analgesia

without otherwise affecting reported pain, and that placebo analgesic effects were specific to the particular body site to which they were applied. This latter finding implied that placebo analgesia in these paradigms was not a general, 'global' response to the placebo treatment, but rather was mediated specifically by expectancies that pain would be reduced at a particular body site. Another important set of findings was that placebo effects could be driven by expectations or conditioning with an opiate drug, in which case they tended to be naloxone-reversible and thus implicate endogenous opioid release, or they could be created by conditioning with nonopiate analgesics, in which case they do not appear to be naloxone reversible, implicating nonopioid mechanisms.

While the inferences from these naloxone studies suggest that active endogenous opioid processes play an important role in the placebo response, these indirect inferences fail to fully resolve the question of whether pain processing itself is affected under placebo. Opioids could affect pain reports in nonspecific ways or offset the aversiveness of pain without affecting specific nociceptive processing. In order to resolve whether nociceptive processing is affected, changes in the brain processes underlying pain must be examined.

Neuroimaging methodologies, including positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), have allowed researchers to examine the brain's activity in response to pain and to identify a network of regions involved in the pain response, frequently referred to as the 'pain matrix.' The first study to use neuroimaging to examine the placebo response used PET to identify a common network between placebo analgesia and opioid analgesia. When compared to a condition in which participants received noxious stimulation without any analgesic administration, both placebo and opioid conditions revealed increased activity in rostral anterior cingulate (rACC) and the brainstem, two regions that are known to play important roles in pain modulation.

A second approach to the study of the placebo response assumes that if the placebo response truly decreases pain processing, this ought to be evident through decreased pain-related activity in these regions of the brain known to be responsive to

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pain. Thus, researchers can contrast the response to stimulation under placebo with stimulation in a nonplacebo control condition and look for differences in pain-related neural activity. The first study to use such an approach used fMRI, and did indeed find evidence of placebo-induced decreases in regions of the pain matrix that have been shown to be associated with the affective components of pain, including rACC and insula, as well as thalamus. Areas were also found that increased during anticipation, including the orbitofrontal cortex (OFC) and lateral prefrontal cortex (PFC), and, importantly, an area of midbrain surrounding the periaqueductal gray (PAG), a structure rich in endogenous opioids that is known to play an important role in pain modulation. Decreases in thalamus and insula, however, occurred late in the pain response, near the time when participants were asked to make ratings of the pain they had experienced; this therefore did not fully resolve whether the pain process itself had changed or whether the observed changes had been mediated by evaluation processes.

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Researchers followed this initial investigation with studies employing methodologies with improved temporal resolution, including electroencephalography (EEG) and magnetoencephalography (MEG). Just as research using PET and fMRI has identified specific regions involved in the pain experience, EEG research has identified specific temporal components that are known to be associated with pain. Thus, a similar approach can be employed in EEG and MEG research to examine whether the placebo response changes pain processing; researchers can look for placebo-induced decreases in the amplitude of evoked nociceptive event-related potential components. Importantly, the temporal resolution of these methodologies allows researchers to specifically examine pain-related components that follow nociceptive stimulation quickly enough to be unaffected by subsequent modulatory cognitive processes (such as poststimulus decision making). This approach is particularly suited to examine a long-standing hypothesis known as the gate control theory, which hypothesizes that descending mechanisms inhibit nociceptive input at the level of the spinal cord, thereby preventing nociceptive information from ascending to the cortex for processing.

Several studies have employed this approach, and all have offered support for at least some decrease of pain processing as part of the placebo response. One study examined the effect of cues on perceived pain, and found that invalid cues (those inducing expectations for lower or higher pain than applied stimulation) modulated activity in components associated with activity in secondary somatosensory cortex (SII) that occurred just 160 ms after pain stimulation. However, later components reflecting activity in posterior ACC varied with stimulus intensity, but were not affected by induced expectations and changes in perceived pain. A study that examined two of the major components of laser-evoked pain potentials, the P2 and N2, found that the amplitude of the P2 response was decreased with placebo treatment. Importantly, the P2 differences habituated over the course of the experiment, although placebo differences in reported pain persisted, suggesting that effects on early nociceptive processing and reported pain are dissociable. Furthermore, the extent of P2 decreases was less than that which would be expected if the gate control theory entirely explained changes in pain processing under placebo. These results suggest that while the placebo response does directly affect nociceptive processing, cognitive components are also important in the placebo response, as indicated by the large and persistent placebo effects on reported pain, relative to the smaller effects on P2 amplitude, which habituated over time.

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Since these initial findings, recent neuroimaging studies have added to our understanding of how the placebo response affects neural processing. Similar to the rationale behind the high temporal resolution studies reviewed above, one study sought to resolve whether placebo-induced decreases occurred early in the pain period. Rather than using a methodology with high temporal resolution, the authors used fMRI but acquired images only during nociceptive stimulation, and stopped the scanner during the pain rating periods. Decreases were observed in the right mid-insula, medial thalamus, and ACC during painful stimulation, again suggesting that the placebo response can indeed decrease nociceptive processing in the brain.

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Together, these studies provide evidence that the placebo response does indeed modulate pain

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processing, and begin to provide evidence of how this modulation may occur. Consideration of placebo responses in other domains allows us to consider candidate central and proximal mechanisms for these observed effects.

s0060 **Physiological placebo effects in other domains**

p0180 A controversial meta-analysis of clinical trials that compared placebo groups with no-treatment control groups found evidence of beneficial placebo effects only in subjective outcomes, particularly in studies of pain. The authors asserted that this was presumably a result of reporting biases and artifacts. The series of neuroimaging studies of placebo analgesia reviewed above clearly demonstrate that the placebo response does indeed influence physiological processing of nociceptive information. However, the subjective component of pain may play a critical factor in the etiology of the placebo response.

p0185 In order to determine the kind of effect the placebo response may have on outcomes without any subjective component, a meta-analysis was conducted that examined placebo effects in clinical trials of peripheral disease processes that used outcome measures assessing the state of peripheral organs, tissues, and body fluids was conducted. There was a significant positive effect of placebo administration on physical processes, such as blood pressure and forced expiratory volume (a clinical sign of asthma severity), but no consistent placebo effect was demonstrated in biochemical process measures, such as cortisol and cholesterol levels.

p0190 Thus, placebo effects appear to be strongest in physiological processes that can be directly controlled by the brain, and their effects on biochemical processes in the body are likely to be substantially weaker. However, these findings do not conclusively show that there are no effects on biochemical processes. First, some of the individual clinical trials included in the meta-analysis may indeed have shown support for placebo effects on biochemical processes, but there may have been significant heterogeneity among studies, causing the overall results of the analysis to be null. Second, a limitation of analyses of clinical trials is that they are not designed to study placebo effects, and expectancy effects in these studies may in some

cases be very weak. Laboratory studies use instructions and conditioning to elicit positive expectations (i.e., ‘This cream is known to be effective in relieving pain’ for the placebo, ‘This is a control cream with no known effect’ for the control), whereas in double-blind clinical trials, participants are told that they may receive either an active agent or an inert substance. Consistent with this notion, another meta-analysis has shown that laboratory studies of placebo mechanisms elicit stronger placebo effects than clinical studies in which placebo groups are used as a control.

Experimental investigations have demonstrated that placebo treatments can alter peripheral physiology across a variety of conditions. In asthma, placebo bronchodilator administration increases forced expiratory volume, a clinical measure of lung function. Preconditioning with active agents has been shown to elicit powerful placebo effects in the domains of growth hormone and cortisol secretion, as well as immunosuppression. Placebo analgesia not only affects pain-related physiology in the brain but has also been shown to reduce β -adrenergic activity in the heart. Experiments designed to investigate nocebo effects – whereby expectations for increased pain or negative outcomes lead to hypersensitivity or increased symptomatology – reveal that nocebo responses in pain involve hyperactivity of the hypothalamic–pituitary–adrenal axis, as evidenced by increased cortisol release and adrenocorticotropic hormone.

Mechanisms of Placebo Effects

The evidence reviewed above powerfully supports the existence of a placebo response, albeit one that varies in magnitude across outcome measures and disease processes, and with the strength of expectancy manipulations and use of conditioning procedures. However, a mechanistic understanding of the placebo response is critical to understanding how, in what outcomes, and under what conditions placebo responses occur. In summary, the placebo response can be divided to two mechanistic levels: central mechanisms and proximal mechanisms. Central mechanisms are those that may operate across domains (i.e., in pain, Parkinson’s disease, and depression), whereas proximal mechanisms

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tend to be domain-specific. We will again employ pain as a model system, since much is known about the central and peripheral pathways of pain processing.

s0070 **Central Mechanisms**

p0205 Central mechanisms are those involved in translating verbal instructions into positive expectancies and maintaining the activity corresponding to those expectancies in the brain. They are the mechanisms of generating and maintaining positive beliefs, which are likely to operate in similar ways across disorders. Conditioned placebo effects may involve additional, separate mechanisms. Studying placebo effects can thus provide a window into how these basic processes work, and how they shape mind–body interactions across a range of conditions.

s0075 **Expectancy versus conditioning: two routes**

p0210 An important theoretical debate about the central mechanisms subserving the placebo effect seeks to understand the psychological processes that give rise to the placebo response. Do conscious expectations mediate the placebo effect, or are changes in placebo due to classical conditioning? We will review the arguments of each perspective, noting that they are not mutually exclusive; both general expectancies and specific learning (conditioning) are likely to play important roles in placebo effects.

s0080 **Conditioning and the placebo effect**

p0215 Some researchers have argued that placebo effects are a result of conditioning. In the most common understanding of classical conditioning, an unconditioned stimulus (US) that normally elicits a certain response (the unconditioned response, or UCR) is paired with a neutral stimulus that elicits no response on its own. Over repeated pairings of the two stimuli, the previously neutral stimulus comes to elicit the same response as the US; the previously neutral stimulus is then referred to as a conditioned stimulus (CS), and the evoked response is 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).

In the case of the placebo effect, there are several routes by which conditioning may result in placebo effects. For example, a pharmacological agent (US) might be administered in the form of a pill (CS) to elicit the specific effects of the drug (UCR); subsequent administration of the pill without the active pharmacological ingredients might still elicit the same effects. Researchers have even suggested that the medical context itself can serve as the conditioned stimulus; thus, people may associate intrinsically neutral items such as syringes or even doctors with the changes associated with treatment, and placebo effects may result from conditioning to these contextual stimuli. Proponents of the classical conditioning model of placebo have argued that a lifetime of medical treatments serve as conditioning trials to pair the medical context (CS) with therapeutic effects (CR). Support for the classical conditioning model of placebo comes from research demonstrating that placebo effects are stronger after exposure to active drugs, that placebo analgesics are more effective when labeled with well-known brands, and from research that shows that some side effects of drugs that are unlikely to be consciously perceived or mimicked – such as respiratory depression following opiate treatment – may be reproduced by placebo treatments after conditioning. In addition, some placebo effects, such as increased cortisol and growth hormone after conditioning with an active drug, are not reversible by telling subjects that the medication is a placebo, suggesting that some learning has occurred that is not modifiable by conscious expectancies.

Brain Mechanisms of Conditioning

While conditioning has been studied for more than half a century, and we know much about the neural circuitry involved in fear conditioning, mechanistic research that would directly support a conditioning model of placebo is quite scarce. Primary support for a model in which conditioning recruits endogenous mechanisms comes from studies of conditioned immunosuppression. In a series of

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studies in rats, saccharin was paired with an immunosuppressive agent, and the rats that had been preconditioned exhibited decreased antibodies when given saccharin in a later test phase. A similar approach has been used to show evidence of conditioned immunosuppression in humans, measured by immune factor expression in mRNA and lymphocytes (white blood cells). These studies offer support for conditioning-based placebo effects on immune responses.

p0230 However, while this offers some insight into the role of conditioning in endogenous processes, little is known about brain mechanisms specific to conditioning-based placebo responses in humans, and mechanisms supporting conditioned immunosuppression are unlikely to generalize to other domains, such as pain. In one PET study mentioned earlier, researchers compared brain responses to painful stimulation under opioid-based analgesia with responses to placebo analgesia. Opioid administration always preceded the placebo analgesia condition, which may have induced a conditioning-based placebo effect. 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 promising, this and other studies 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.

s0090 **Expectancy and the placebo effect**

p0235 An alternative view to the conditioning-based placebo response proposes that conscious expectancies mediate the changes associated with placebo effects. In this view, the internal beliefs and expectations associated with the inert treatment are responsible for the endogenous regulation of processes in order to produce the requisite changes associated with placebo response; put simply, one experiences changes associated with placebo administration because one expects to.

p0240 Expectancies involve appraisals of the significance of a stimulus or event in the context of its anticipated outcome. For the most part, expectancies are conscious at the time when decisions are made, or, if they are not conscious (as may happen during rapid decision making), expectancies can be

brought into consciousness when attention is drawn to them. This is an important distinction from conditioning theories, which assume that organisms need not have conscious awareness of contingencies between stimuli in order for conditioning to occur. Thus, one way to define the distinction between expectancy effects and conditioned responses is that expectancy effects depend on the participant's state of mind, whereas conditioned responses do not. By this definition, expectancy-based effects can be altered by instructions to subjects, whereas conditioned effects cannot.

The power of expectancies has been illustrated in many areas of research, from basic perception to complex physiological processes. One way that researchers have learned about the influence of expectations on physiological processes is by comparing the effects of hidden and open drug administration. Positive expectancies (expectations for relief) are active when patients are aware that they are receiving a given drug, as is the case when drugs are administered in full view of the patient. When this is contrasted with conditions in which drugs are administered surreptitiously (e.g., when a drug is administered intravenously under the guise of saline administration), researchers generally find that the open administration has a greater beneficial effect. When the contextual cues surrounding treatment are the same in both open and hidden cases, a conditioning-based explanation for the effect is unlikely. A practical application of this research is evident in hospitals, where patients are allowed to self-administer analgesic agents such as morphine; it takes far less morphine to produce the same pain-relieving effect when patients control drug delivery and expect relief than when doctors administer the drug without patient expectations.

p0250 The same positive expectancies may therefore be the driving force behind the power of placebo. The expectancy model of placebo is supported by research demonstrating that placebo effects can occur with verbal instruction alone (i.e., without prior experience with a drug or active treatment). In addition, in some studies, placebo effects on pain that have been induced through a conditioning procedure have been reversed completely by revealing to the participants that the placebo treatment was a sham. Thus, the placebo effects in these studies

do not meet the criteria for conditioned responses (involving specific learning not modifiable by beliefs).

p0255 It is also worth noting that for conditioning to occur, the brain must be capable of learning an association (i.e., forming a pathway) between a CS and either the UCS or the UCR, and reactivation of that pathway must be able to elicit the UCR. Placebo responses do not always fit these criteria. For example, during the extinction phase of conditioning, a conditioned stimulus that is not reinforced will cease to elicit a conditioned response; however, placebo effects can remain far longer than extinction would permit. In other cases, an association formed over repeated experiences can be reversed immediately by a change in instructions, which is not consistent with models of conditioning.

s0095 **Brain Mechanisms of Expectancy**

p0260 Placebo instructions change 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. The brain mechanisms of such expectations 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 – systems for maintaining information in an active state in the brain – in order to maintain expectancies induced by placebo manipulations. Expectations about the value of upcoming stimuli are also critical to the pain process and are potentially highly involved in the placebo response across domains. 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. Brain representations of active contextual information and stimulus value may directly or indirectly influence more basic perceptual, behavioral, and somatic (peripheral)

processes through connections with other parts of the brain that represent percepts, motor actions, and somatic states.

By drawing on knowledge from brain mechanisms of cognitive control, researchers can define reasonable hypotheses about brain mechanisms supporting an expectancy-based placebo response. These can be tested by contrasting anticipatory activity in a placebo condition to anticipatory activity during a control condition, so that one can identify processes related to pain expectancy that are shaped by placebo treatment. This approach was used in an fMRI study of placebo analgesia, which 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 brain activity during thermal stimulation. Other studies have replicated and extended this result, showing that placebo treatments for negative emotion activate the same brain regions, and that endogenous opioids – neurochemicals linked to relaxation, euphoria, and pain relief – are released in these regions following placebo treatment.

The expectancy versus conditioning debate

It is difficult to resolve the relative contributions of expectancy and conditioning to placebo effects, because the two 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, in spite of 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. In a classic placebo study, expectancies of pain relief were manipulated by surreptitiously turning down the stimulus intensity during testing of a topical placebo solution. Placebo effects on pain developed over the course of this manipulation.

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However, some participants were informed that the intensity was being reduced during the placebo administration, while others were told that it was not; this latter group presumably attributed the reduction in pain to the placebo. Although the physical stimuli were identical for the two groups, including the putative CS (placebo application) and UCS (reduction in pain), placebo effects were about 7 times as large when the verbal instructions led participants to expect large reductions in pain attributable to the placebo.

p0275 Other studies have demonstrated that ‘conditioned’ placebo effects in pain and even basic fear conditioning in humans are reversible by changing the instructions to subjects, suggesting that expectations are mediating the effects rather than automatic, learned associations. However, some kinds of placebo effects are not reversible by changing the instructions. In another classic study, researchers repeatedly injected sumatriptan, a drug that induces cortisol and growth hormone release, thereby forming an association between the injection and the drug response. After this conditioning procedure, injecting saline alone elicited cortisol and hormonal increases, and these increases were not blocked by changing the verbal instructions.

p0280 A second way to discriminate between conditioning and expectancy is by measuring brain activity itself. The patterns of placebo-induced activity increases 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; in pain, these same expectancy- and appraisal-related regions have been shown to exhibit placebo-induced opioid release. 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, the area in the human brain where cellular learning underlying placebo effects may be taking place is still unknown.

Other central mechanisms

Opioid release in anticipation of pain under placebo correlates with dopamine release in the nucleus accumbens – a region known to be highly involved in reward processing. Similarly, the placebo response in Parkinson’s disease has been linked to increased dopamine release in this region. A promising new theory of placebo has thus suggested that placebo administration may actually be rewarding, and that it is this positive affective shift that results in decreased pain under placebo, and increased motor performance in Parkinson’s disease. Work demonstrating correlations between dopamine release under placebo with subsequent activity in a reward task shows that individual differences in reward response correlate with individual differences in placebo. Researchers have postulated that two activation systems that are mutually exclusive exist – a positive, approach system (behavioral activation system), and a negative, withdrawal system (behavioral inhibition system). Placebos may induce a shift from a withdrawal system to an approach system, and this may induce concomitant effects on pain, depression, Parkinson’s disease, and other conditions, which would be observed as placebo responses.

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Proximal Mechanisms

Proximal mechanisms refer to the pathways whereby central mechanisms interact with the actual processing of a stimulus or condition in order to elicit changes in domain-specific activity. Proximal mechanisms are therefore likely to be different for different disorders. We will specifically review proximal mechanisms for pain, depression, and Parkinson’s disease, as these placebo responses are the most well understood.

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Proximal placebo mechanisms in pain

A central question in the study of placebo analgesia has concerned the level (or levels) of the pain pathway at which the placebo response has its effect. The naloxone studies reviewed earlier illustrate the important role of endogenous opioids in the expectancy-based and opioid-conditioned placebo responses. Endogenous opioids facilitate modulation of both descending pain-control circuits and central processing of nociceptive information, illustrating

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their significance as one of the key mediators of the placebo response in pain.

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The gate control theory and its successors postulate that descending modulatory signals under placebo can cause inhibition of nociceptive processes in the spinal cord, before signals reach the brain. In animal work, a specific type of opioid receptor, the μ -opioid receptor (MOR), has been shown to inhibit nociceptive transmission at the level of the spinal cord's dorsal horn. The PAG, a region that has been repeatedly demonstrated to be involved in placebo analgesia, is rich in MORs and plays an important role in this descending modulation in animals. As mentioned earlier, an fMRI study that directly examined the placebo response found placebo increases in an area of the midbrain surrounding the PAG during anticipation of pain. This activity could be consistent with the gate control hypothesis, in that the placebo context would increase opioid release by the PAG, and descending opioids would inhibit subsequent pain at the level of the spinal cord's dorsal horn. Further support for the role of the PAG in the placebo response comes from PET studies showing that placebo treatment causes increased opioid release in PAG during pain. Spinal inhibitory mechanisms in humans are also supported by a study showing that placebo manipulations can reduce the area of skin that develops hyperalgesia with repeated thermal stimulation. Animal studies have shown that this hyperalgesia is due to spinal neuron sensitization; hence, placebo effects that decrease the area of hyperalgesia are considered as evidence of descending modulation at the level of the spinal cord.

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While these studies and others suggest that early modulation of ascending nociceptive signals may play a key role in placebo analgesia, it is important to recognize that this may not be the only factor responsible for observed placebo effects in pain. The EEG results reviewed earlier suggest that while early inhibition does indeed occur, it cannot entirely account for the magnitude of decreases in reported pain. Recent studies have taken a mechanistic approach to investigating the role of endogenous opioids in the placebo response, elaborating on the knowledge available from naloxone studies. These studies have shown where in the brain placebo changes opioid release,

strengthening the argument for placebo changes in central nervous system processing. In PET studies of placebo analgesia that measured MOR activity directly, PAG opioid activity both decreased in anticipation of pain under placebo and increased during painful heat, suggesting that placebo might diminish the threat associated with upcoming nociceptive stimulation and enhance opioid release induced by pain. These studies also demonstrated that placebo treatment increases μ -opioid system activation in the OFC, perigenual ACC, rACC, right anterior insula, left dorsolateral PFC, thalamus, amygdala, and the nucleus accumbens, suggesting that placebo treatments affect opioid responses in many regions critical for affective valuation. The rACC and insula regions corresponded to those that had been shown to decrease during pain in the aforementioned fMRI experiments, suggesting that these changes in pain responses may have been opioid-mediated. In one of these studies, placebo increased connectivity between PAG and rACC, as well as other distinct subsystems of correlated regions, suggesting that placebo treatment involves central opioid release that increases functional integration across regions. These effects could influence the central processing of pain above and beyond effects mediated by descending spinal control systems.

Proximal placebo mechanisms in major depressive disorder

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In depression, placebo effects on the brain have been examined by using PET imaging to measure baseline metabolic activity before, during, and after treatment with either placebo or an active medication. 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 anterior cingulate. 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 included increases in prefrontal, parietal, and posterior cingulate cortex. Importantly, these common results differ from patterns of brain activation over the course other types of treatment, such as cognitive behavioral therapy. This suggests that both active drug and placebo

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treatments work in part by changing central systems involved in affective valuation and motivation. Much more work remains to be done to unpack the brain mechanisms involved in both verum and placebo treatment for depression.

s0125 **Proximal placebo mechanisms in Parkinson's disease**

p0315 In Parkinson's disease, active placebo responses are likely to involve dopaminergic pathways. PET studies of dopamine D2 receptor activity have provided evidence that placebo treatments lead to dopamine release in the striatum. Complimentary evidence has been obtained from neurosurgical studies, in which placebo (sham) stimulation of the subthalamic nucleus – a stimulation site used in the treatment of Parkinson's – has been shown to affect both subthalamic nucleus activity (decreased bursting and neuronal frequency discharge) and muscle rigidity, which is a clinical sign of the disease. Recent evidence indicates that expectations of effective treatment affect dopamine levels and muscle activity in a dose-dependent fashion.

p0320 Whether dopaminergic mechanisms play a role in placebo effects in pain, depression, and other domains remains to be tested more thoroughly. It has been proposed that dopamine release underlies positive affective and motivational shifts that lead to improved outcomes across disorders. Whether outcomes can be influenced by changes in affective and motivational states may determine whether placebo treatments are effective; ongoing research is now being conducted to test this hypothesis.

s0130 **Summary**

p0325 While many factors can potentially lead to observed placebo effects without changing underlying processing, careful experimental manipulations provide evidence of active placebo responses in the domains of pain, Parkinson's disease, depression, asthma, and conditioned immunosuppression. There is clinical evidence for effects on other conditions, such as hypertension, anxiety, and heart function, but more experimental research is needed to assess whether placebo treatments can truly affect outcomes in these domains. Neuroimaging methodologies allow researchers to identify and

examine active central and proximal mechanisms supporting the placebo response. This, in turn, provides a powerful window into mind–body interactions.

See also: Psychoactive Drugs and Conscious Alteration (00064); Hypnosis and Suggestibility (00038).

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Biographical Sketch



Lauren Y Atlas began her doctoral work at Columbia University in September 2006. She completed her undergraduate education in 2003 at the University of Chicago, where she worked with John Cacioppo in the Social Neuroscience Laboratory. Her undergraduate thesis research examined cardiovascular differences between lonely and nonlonely participants during active and passive coping. After graduating, she worked as fMRI project coordinator in Stanford's Mood and Anxiety Disorders Laboratory under the direction of Ian Gotlib, where she was involved in projects investigating the neural bases of cognitive and affective processing in major depressive disorder, social anxiety disorder, and bipolar disorder. Her graduate work with Dr. Tor Wager at Columbia takes a mechanistic approach to the study of how expectancies modulate affective experience. Current projects use fMRI and psychophysiology methodologies to examine brain pathways mediating the relationship between applied nociceptive stimulation and subjective pain.



Dr. Tor D Wager received his PhD from the University of Michigan in cognitive psychology, with a focus in cognitive neuroscience, in 2003. He joined the faculty of Columbia University as an assistant professor of psychology in 2004. His primary research interest is in the neural and psychological bases of cognitive and affective control. His research quantifies behavioral performance and brain activity to investigate the neural mechanisms by which humans have flexible control over their behavior. This approach emphasizes the mutual constraints on interpretation afforded by studying behavior and functional anatomy at the same time. His main research interests along those lines are brain and psychological mechanisms underlying the cognitive control

of pain and affect; individual differences in selective attention, inhibition, task switching, and other executive processes; and the relationship between affective regulation and cognitive control. He is also interested in developing image analysis and statistical modeling methods that will improve our ability to use fMRI as a research tool in cognitive and affective neuroscience. Current projects along these lines include optimization of experimental design for fMRI experiments, meta-analysis of functional imaging data, nonlinear alternatives to hemodynamic response fitting, robust regression techniques in massively univariate linear models, and application of multivariate techniques.

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Non-Print Items

Abstract:

Placebos have been surrounded by controversy throughout the past century. In this article, we first review phenomena that may lead to 'false' placebo effects, or observed improvements that are attributed to placebo treatment, but do not involve any underlying change in the illness or condition being treated. We then review evidence supporting the existence of active placebo responses, or changes in brain processes that result in an improvement in the treated condition. We focus on neuroimaging evidence for placebo effects on pain, which is perhaps the best-studied area in placebo research to date, and examine candidate central and proximal mechanisms for placebo responses across and within domains.

Keywords: Analgesia; Conditioning; Demand characteristics; Depression; Expectancy; fMRI; Nocebo; Nociception; Opioids; Pain; Parkinson's disease; PET; Placebo; Signal detection theory

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