Mindsets Matter: A New Framework for Harnessing the Placebo Effect in Modern Medicine

Sean R. Zion[1], **Alia J. Crum**
Stanford University, Stanford, CA, United States
[1]Corresponding author: e-mail address: szion@stanford.edu

Contents

Abstract

The clinical utility of the placebo effect has long hinged on physicians deceptively administering an objective placebo treatment to their patients. However, the power of the placebo does not reside in the sham treatment itself; rather, it comes from the psychosocial forces that surround the patient and the treatment. To this end, we propose a new framework for understanding and leveraging the placebo effect in clinical care. In outlining this framework, we first present the placebo effect as a neurobiological effect that is evoked by psychological processes. Next, we argue that along with implicit learning and expectation formation, mindsets are a key psychological process involved in the placebo effect. Finally, we illustrate the critical role of the social environment and treatment context in shaping these psychological processes. In doing so, we offer a guide for how the placebo effect can be understood, harnessed, and leveraged in the practice of modern medicine.

International Review of Neurobiology
ISSN 0074-7742
https://doi.org/10.1016/bs.irn.2018.02.002

1. INTRODUCTION

Henry Beecher, a World War II army medic, is credited with bringing about the modern study of the placebo effect. Upon exhausting his supply of morphine, Beecher continued treating his wounded patients with saline solution while reassuring them of the pain-relieving power of the infusion. His observation that patients tended to improve with the sham treatment and comforting words led to the publication of "The Powerful Placebo," which reported on the magnitude of the placebo effect across 15 clinical trials. Beecher's analysis revealed that over 35% of patients experienced therapeutic benefit from placebo treatments (Beecher, 1955). His finding intrigued a generation of scientists and laid the groundwork for decades of subsequent research on the placebo effect.

Since Beecher's time, the placebo effect has taken on new meaning depending on the context in which it is studied. In randomized, double-blind clinical drug trials, new drugs and treatments are compared to a placebo control. This gold standard for pharmaceutical research and development enables researchers to quantify the efficacy of the treatment as it compares to the effect of the placebo. The ultimate goal of these trials is to demonstrate the benefit of the active treatment beyond that of the placebo, and consequently, much of clinical research aims to subtract out or do away with the placebo effect (Crum, Leibowitz, & Verghese, 2017). Even when a significant difference between the active treatment and the placebo is found, any effect of the placebo is later usually forgotten. Despite the fact that the placebo effect yields clinically significant benefits in clinical trials for well over half of all medical conditions—including pain, depression, Parkinson's disease, anxiety disorders, cardiovascular disorders, and immunological diseases (de la Fuente-Fernandez & Stoessl, 2002; Goebel, Meykadeh, Kou, Schedlowski, & Hengge, 2008; Levine, Gordon, Smith, & Fields, 1981; Petrovic et al., 2005; Pollo, Vighetti, Rainero, & Benedetti, 2003; Shetty, Friedman, Kieburtz, Marshall, & Oakes, 1999; Walsh, Seidman, Sysko, & Gould, 2002)—the symbolic effect of randomized placebo-controlled trials is that placebos are seen either as an adversary that competes with the drug of interest or as an irrelevant variable to be discounted.

However, a handful of researchers have explored the placebo effect in its own right. Inspired to understand the strength of and mechanisms behind

the placebo effect, psychologists and neurobiologists have designed studies to investigate how a placebo alone can produce measurable benefit. These studies consider the placebo as the *primary variable of interest*, not merely as a control. Laboratory experiments have demonstrated the ability to evoke placebo responses through classical conditioning paradigms and through the manipulation of expectations (Montgomery & Kirsch, 1997). These paradigms reveal that placebo administration drives changes in both endogenous opioid and nonopioid neurotransmitter systems and modulates metabolic activity in many regions of the brain (Amanzio & Benedetti, 1999; Benedetti, 2008; Levine & Gordon, 1984).

While both clinical trials and direct placebo research have made great strides in illuminating the power and mechanisms of placebo effects, relatively little research has been devoted to understanding how placebo effects may be leveraged in clinical practice without the deceptive administration of an actual placebo treatment. In an effort to make progress in the clinical applications of the placebo effect, we offer a new framework for understanding the nature and clinical utility of this effect in the practice of medicine. This framework builds upon the wealth of existing clinical, neurobiological, and psychological research on the placebo effect and extends it by explaining how the components underlying placebo effects operate in clinical practice, without an objective placebo. We argue that the placebo effect is: (1) an integral component of the overall treatment effect in medicine, (2) a neurobiological effect that is evoked by specific psychological processes, which are shaped by social and environmental factors, and (3) a variable that can be harnessed, personalized, and maximized in the practice of medicine without the use of inert placebo pills or sham treatments. Through this conceptualization of the placebo effect, we can see that the placebo effect is neither a nuisance nor a mystery. It is a real and powerful effect that can be utilized in the practice of medicine by understanding and leveraging the psychosocial forces that surround a medical treatment.

In the sections that follow, we review the components of the treatment effect and explore how the effects of the drug and the placebo can be disentangled. We then describe the psychological processes that drive the neurobiological mechanisms that underlie the placebo effect. Finally, we discuss the social and contextual factors that inform and shape these psychological processes, offering a roadmap for how they can be harnessed in the practice of medicine.

2. THE TREATMENT EFFECT: DRUG PLUS PLACEBO EFFECTS

The drug effect and the placebo effect have long been considered separate and often competing entities, as evidenced by the placebo's aforementioned role in randomized control trials. What are these two effects and how can they be disentangled? The drug effect is the quantifiable change in disease processes that result from the pharmacological or physical properties of an active treatment—often a medication. These medications evoke clinical change by either: (a) simulating or stimulating normal biological processes that occur in the body or inhibiting processes that contribute to disease, or (b) blocking critical processes in microorganisms inhabiting the body. But these mechanisms are responsible for only part of a treatment's total effect. Placebo effects also occur as an inherent part of all active medical treatments, and the effect of the drug and the effect of the placebo work together to produce the total treatment effect (Fig. 1). From the patient's perspective, the components that contribute to the treatment effect are not particularly relevant—improvement from the drug or improvement from the psychosocial factors that drive the placebo effect is improvement nonetheless. However, for the health care practitioner, it is incredibly important to understand the components that drive the placebo effect and how they might interact with the drug effect.

The placebo effect can be considered in terms of its biological, psychological, and social/contextual components (Table 1). Driven by neurobiological

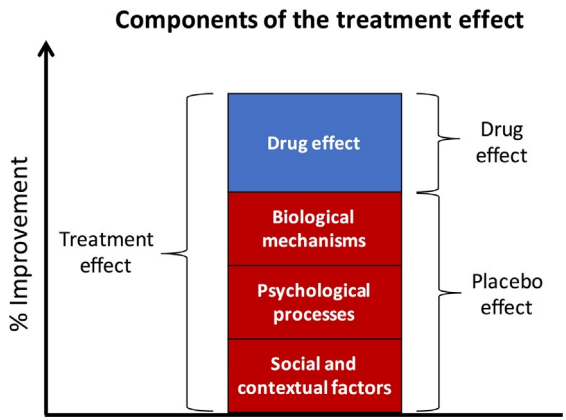

Fig. 1 The drug effect and the placebo effect contribute to the total effect of treatment. These components drive the total improvement a patient experiences from a medical treatment.

Table 1 The Components of the Placebo Effect: Neurobiological Mechanisms (The Body's Healing Properties and Neurophysiology), Psychological Processes (Implicit Learning, Expectations, and Mindsets), and Social/Contextual Factors (Social Environment and Treatment Context)

Components of the Placebo Effect	
Biological mechanisms	
Body's healing properties	Biological properties of the body that facilitate healing, including homeostatic mechanisms, immune, and inflammatory responses. These contribute to the natural history of a disease, but can also be targets of placebo effects
Neurophysiology	Dopamine, endogenous opioids, and endocannabinoids are three of the major neurotransmitter systems implicated in moderating the placebo effect
Psychological processes	
Implicit learning	The nonconscious acquisition of knowledge. Classical conditioning, a form of implicit learning, is implicated in certain instances of the placebo effect
Expectations	A belief about the future based on a prediction of what is most likely to happen. Expectations underlie certain instances of the placebo effect and drive neurobiological mechanisms
Mindsets	A lens or frame of mind that orients an individual to a particular set of beliefs, associations, and expectations, and functions to guide attentional and motivational processes
Social and contextual factors	
Development and culture	Our caregivers and social environment influence the psychological processes that underlie the placebo effect. These processes are continuously shaped throughout life by the ideas, institutions, and interactions that constitute the culture in which we live
Patient-provider relationship	The patient–provider relationship shapes the mindsets a patient holds about health, illness, and treatments, and affects the quality of care a patient receives. This relationship is influenced by the warmth and competence of the provider and is further shaped by characteristics like empathy and trust

Continued

Table 1 The Components of the Placebo Effect: Neurobiological Mechanisms (The Body's Healing Properties and Neurophysiology), Psychological Processes (Implicit Learning, Expectations, and Mindsets), and Social/Contextual Factors (Social Environment and Treatment Context)—cont'd

Components of the Placebo Effect	
Observational learning and social influence	Learning through direct observation of others undergoing treatment (i.e., other patients) as well as interactions with individuals who yield influence over the patient (i.e., physicians and nurses) both may powerfully drive placebo effects
Treatment characteristics	The specific characteristics of the treatment that is provided to the patient. This includes factors like the shape, color, and branding of the treatment, the method of administration, and the physical environment in which the treatment is administered

mechanisms, the placebo effect recruits the involvement of disease-specific biological and neurotransmitter systems, such as components of the immune system and the endogenous opioid system. These biological mechanisms are evoked and modulated by conscious and nonconscious psychological processes, including implicit learning, expectations, and mindsets. Psychological processes, in turn, are shaped by the social environment and treatment context. As such, a social or environmental factor—like a knowledgeable and understanding physician who the patient trusts—can shape a patient's mindset about a disease or treatment, which can in turn evoke a biological change and subsequent healing response. In the remaining sections, we unpack these biological, psychological, and social elements underlying placebo effects that form the foundation of the treatment effect for all drugs and therapies.

3. PSYCHOLOGICAL PROCESSES ACTIVATE NEUROBIOLOGICAL MECHANISMS

Placebo effects are marked by neurobiological underpinnings (Wager & Atlas, 2015), which are activated by psychological processes. Two such processes have received the majority of research in this domain: nonconscious implicit learning, such as classical conditioning, and conscious expectations (Finniss, Kaptchuk, Miller, & Benedetti, 2010; Price et al., 1999). These mechanisms are neither mutually exclusive nor the only two mechanisms through which the placebo effect is thought to operate

(Stewart-Williams & Podd, 2004). Other mechanisms, like our mindsets, also play an important role in the placebo effect, but have received less attention. In the next sections, we review the existing literature on the role of implicit learning, expectations, and mindsets as they relate to the placebo effect in patients undergoing medical treatment. In particular, we review how these psychological elements trigger the neurobiological processes that lead to the measurable changes we refer to collectively as the placebo effect.

3.1 Implicit Learning

Implicit learning is a process by which information is learned outside of conscious awareness (Frensch & Rünger, 2003). It is a process of detecting associations within an environment and storing this information in the form of abstract representations (Seger, 1994). Classical conditioning, a form of implicit learning, underlies certain instances of the placebo effect. Early evidence for the role of implicit learning in the placebo effect came from animal studies (Ader & Cohen, 1982, 1993), versions of which were later replicated in humans (Goebel et al., 2002). Many of these studies repeatedly paired a neutral stimulus—the placebic vehicle (i.e., syringe or capsule)—with an unconditioned stimulus (i.e., the drug inside the syringe or capsule). Other experimental techniques in humans have also been used to tease apart the mechanism of conditioned placebo responses. For example, the use of "surreptitious reduction" paradigms in which a placebo treatment is paired with the hidden reduction of a painful stimulus also provides evidence for conditioned responses in studies of placebo analgesia (Voudouris, Peck, & Coleman, 1989, 1990).

Through similar processes, symbols and rituals within the medical context become associated with healing. Being directed to the exam room, having temperature, blood pressure, and heart rate measurements taken, and waiting patiently for the physician may all serve as situational cues that become implicitly associated with healing. Over time, these contextual cues are repeatedly paired with active medical treatments. Eventually, exposure to these cues alone may evoke conditioned responses in patients. Outside of the doctor's office, positive or negative experiences with active treatments may lead to associative links between treatment characteristics and outcomes. A child given bright pink, bubble-gum flavored liquid penicillin each time he or she has a bacterial infection will come to associate the perceptual characteristics of this medication with the subsequent healing response. Indeed, multiple sclerosis patients who received cyclophosphamide

(an immune suppressant) paired with a flavored syrup later displayed drug-consistent immune responses to the flavored syrup alone (Giang et al., 1996).

How does the nonconscious formation of associative links between healing symbols and treatment outcomes evoke quantifiable biological changes in the patient? Implicit learning recruits disease-related processes in the body to change objective biological markers. This has been demonstrated in studies of conditioned immune and allergic responses in both humans and animals. For example, conditioning rats with cyclosporine A, an immunosuppressive drug, resulted in sympathetic nervous system-mediated immune suppression even when the drug was absent (Exton et al., 2002). In humans, pairing the same immunosuppressant drug, cyclosporine A, with a flavored beverage reduced lymphocyte cell count, cytokine release, and expression of mRNA when the flavored beverage was later given on its own (Goebel et al., 2002). Side effects of active treatments also appear to be conditioned alongside the intended treatment effects. In a study by Benedetti and colleagues, subjects were given a powerful opioid analgesic medication that was subsequently replaced with a placebo treatment as part of a conditioning paradigm. Subjects not only experienced the main effects of the opioid when given the placebo, but they also exhibited respiratory depression, a common side effect of opioids (Benedetti, Amanzio, Baldi, Casadio, & Maggi, 1999).

In the practice of medicine, some benefit is derived from years of associating positive outcomes with white coats, pills, and exam rooms. While this may paint a picture of a patient mindlessly linking stimuli and response (Wickramasekera, 1980), implicit learning processes often induce positive responses by reinforcing patient expectations (Rescorla, 1988), as most conditioning paradigms in humans inherently manipulate expectations to some degree (Benedetti, Pollo, et al., 2003; Montgomery & Kirsch, 1997). Indeed, implicit learning is not required for placebo effects. Thus, while implicit learning may work directly, it may also operate by influencing our conscious expectations.

3.2 Expectancy

Expectations are beliefs about the nature and likelihood of future states. The expectation of a specific outcome can elicit cognitive, emotional, and behavioral changes that increase the likelihood of that event occurring (Kirsch, 1985; Montgomery & Kirsch, 1997). Expectations have been shown to be one mechanism driving many instances of the placebo effect.

Studies employing an open/hidden experimental design allow researchers to disentangle the contribution of expectations from drug effects. In this paradigm, a physician administers a drug either in full view of the patient (open condition) or hidden from the patient (hidden condition). Open administration mimics the conditions of routine medical practice, while hidden administration removes the external factors that contribute to the formation of expectations. The difference between these two conditions reflects the impact of the patients' psychological processes, like expectations, that can elicit real and quantifiable effects. Critically, this paradigm allows the role of expectations to be quantified without actually administering a placebo treatment. Studies employing open/hidden designs have found that medical treatments given covertly are less effective than those given openly, highlighting the contribution of expectations to the efficacy of treatments (Colloca, Lopiano, Lanotte, & Benedetti, 2004). This has been observed in numerous clinical conditions, including pain, anxiety, and Parkinson's disease (Benedetti, Maggi, et al., 2003; Levine & Gordon, 1984; Pollo et al., 2002).

Placebo analgesia has also been used as a paradigm to demonstrate the effect of positive or negative expectations on treatment efficacy (Price, Finniss, & Benedetti, 2008; Price et al., 1999). Compared to a no-expectation condition, patients who expected the potent analgesic remifentanil to work well experienced twice the analgesic effect, while those who held negative expectations experienced no analgesia (Bingel et al., 2011). These subjective effects corresponded with significant changes in the endogenous pain modulatory system. Imaging data from various clinical populations further demonstrate the mechanisms by which expectations evoke neurobiological responses in patients. In a study of patients with irritable bowel syndrome, verbal suggestions of pain relief produced clinically significant placebo effects. This placebo analgesia corresponded with reduced activity in the thalamus, somatosensory cortices, insula, and anterior cingulate and increased activity was noted in the rostral portion of the anterior cingulate, the amygdala, and the periaqueductal gray (Price et al., 2008). Furthermore, in a revealing study employing an open/hidden paradigm to quantify the magnitude of expectations on postsurgical dental pain, injecting saline in full view of the patient reduced pain at a magnitude equal to 6–8 mg of morphine (Levine & Gordon, 1984; Levine, Gordon, Bornstein, & Fields, 1979). In other words, when patients were not aware they were receiving treatment, and thus did not expect to receive benefit, it was as if they had been given 6–8 mg *less* morphine than they actually had.

The effect of expectation on pain is powerful, and it is therefore critical for physicians to be aware of how they are inducing and shaping patient expectations. Physicians may even have the ability to shape expectations and evoke placebo effects in patients who have formed maladaptive or harmful associative links between certain treatments and poor outcomes. For example, a 2003 study demonstrated that manipulating expectations was effective in overriding negative responses to pharmacological preconditioning in a placebo analgesia paradigm (Benedetti, Pollo, et al., 2003). However, in the clinical context, expectations are not always induced intentionally or explicitly. They are shaped by patients' mindsets, the social environment, and the treatment context in which a medical intervention occurs.

3.3 Mindsets

Mindsets are lenses or frames of mind that orient individuals to particular sets of associations and expectations (Crum, Salovey, & Achor, 2013). Mindsets help individuals make sense of complex information by offering them simple schematics about themselves and objects in their world. For patients, mindsets provide a scaffolding for understanding the broad nature of illnesses and treatments. While expectations and mindsets are intimately connected, they are not the same thing. Expectations are specific beliefs about future events. Mindsets are a more general psychological construal that orient an individual to a number of mindset-consistent expectations. For example, the mindset that "cancer is a catastrophe" may be associated with a number of different expectations such as "the treatment will be painful and keep me from the things I enjoy" or "I will not be able to cope with this" that are beyond the more specific expectations of believing a treatment will or will not work. Thus, understanding broader mindsets is also important for understanding the impact of illnesses and treatments.

Mindsets guide patients' attentional and motivational processes and affect both subjective and objective measures of health and well-being (Crum & Zuckerman, 2007). This has been documented in studies of stress, diet, and exercise, in which mindsets were found to affect both psychological states and markers of physical health, including blood pressure, weight loss, cortisol response, and hormone secretion (Crum, Corbin, Brownell, & Salovey, 2011; Crum & Langer, 2007; Crum et al., 2013). Research is beginning to shed light on mindsets about health and disease and their subsequent impact on patients, providers, and the health care system (Crum et al., 2017).

Mindsets can be intentionally and adaptively changed through targeted interventions. These interventions bridge the gap between traditional psychosocial interventions that primarily focus on improving subjective measures of well-being and medical interventions that are often evaluated exclusively in terms of their impact on physiological measures of health. For example, when exposed to information about the positive aspects of stress—that it can enhance immune function and boost cognitive performance—individuals with high stress finance jobs adopted a "stress is enhancing" mindset that shaped subsequent work performance (Crum et al., 2013). Similarly, hotel employees who were taught that their work provides a sufficient amount of daily physical activity, showed improvement on vital measures of health, without evidence of a corresponding behavior change (Crum & Langer, 2007). This research has also demonstrated that effective interventions can be short, simple, and inexpensive. So while patients may come to health care with their own preexisting mindsets, the malleability of mindsets suggests that physicians can intentionally shape their patients' mindsets. Helping a patient develop the mindset that their disease is manageable (as opposed to a catastrophe), for instance, may impact patient expectations about the course of their illness, the nature and occurrence of symptoms, and the efficacy of treatments. Rather than simply shaping expectations (e.g., this drug will work), physicians may be able to help their patients form more adaptive mindsets that elicit multiple downstream effects.

How do mindsets and expectations relate to one another in the clinical context? A patient in pain, for instance, may have the specific expectation that a treatment will relieve their discomfort. However, this expectation may hinge on the broader mindset that their illness is manageable. These mindsets and the expectations they influence activate distinct brain regions associated with pain, anxiety, and reward (Benedetti, Carlino, & Pollo, 2011; Bingel et al., 2011; Zubieta & Stohler, 2009). They also affect the function of the peripheral nervous system and its downstream target organs and modulate the activity of the immune and endocrine systems (Crum et al., 2011; Pollo et al., 2003). While specific expectations facilitate placebo effects in experimental paradigms, mindsets may be particularly relevant in the practice of medicine, where individual expectations do not exist in isolation from one another.

Patients often enter the medical context with preexisting mindsets about health, disease, and treatments. When a physician shares information about disease and treatment with a patient, it is interpreted through the lens of the patient's mindsets, influencing his or her subsequent expectations.

The interactions that occur in the clinical context and the experience a patient has with his or her illness and treatment then shape existing mindsets, reinforcing or altering them. For example, a patient who has the mindset that their body is capable may preferentially attend to signals that their body is handling an illness well (Zion, Dweck, & Crum, 2018). They may expect their body to be able to manage an illness and the side effects of treatment. Critically, these expectations can often be self-fulfilling and an understanding and compassionate physician can help reinforce these adaptive mindsets (Howe, Goyer, & Crum, 2017).

4. SOCIAL AND CONTEXTUAL FACTORS INFORM PSYCHOLOGICAL PROCESSES

In Sections 2 and 3, the patient's internal psychological characteristics that contribute the placebo effect were discussed. Of course, these processes like implicit learning, conscious expectations, and mindsets do not exist in a vacuum; they are critically informed by the environment. Here, we break down the components of the social context and the treatment context that influence patient mindsets and contribute to the placebo effect in the practice of medicine (Fig. 2). First, we review some of the developmental and cultural factors that shape psychological processes outside the doctor's office. Next, we move into the social and contextual factors that influence psychological processes within the clinical context, including the patient–provider

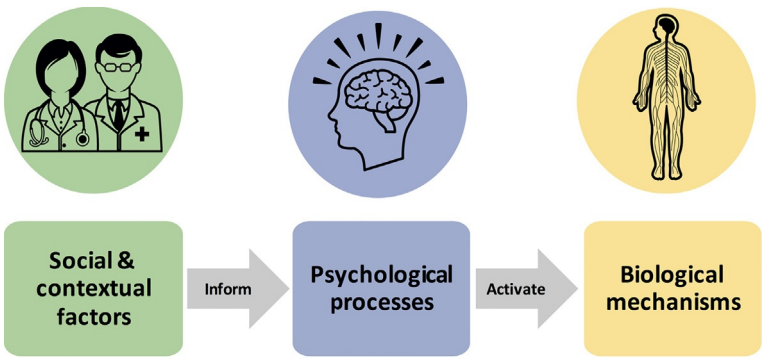

Fig. 2 The relationship between the components of the placebo effect. Social and contextual factors inform psychological processes, which in turn activate biological mechanisms.

relationship and social and observational learning. Finally, we review how the components of the treatment context—the characteristics of treatments and the physical environment—affect our psychological processes.

4.1 Developmental and Cultural Factors

The psychological processes that drive placebo effects may be set into motion long before a patient sets foot into a doctor's office. As children, our mindsets are shaped, in part, by our caregivers and our social environment (Gunderson et al., 2013; Mueller & Dweck, 1998). Mindsets can also be shaped less explicitly during these sensitive developmental periods through social influence and modeling (Bandura, 1977). Mindsets about health and illness may also develop early on from experiences with illness, visits to the pediatrician, and from observing family members and peers. As adults, these health mindsets are continually shaped through our interactions with the health care system and our positive and negative experiences with disease and treatment.

With age, our experiences shape our mindsets within cultural frameworks of norms and customs. Our mindsets are influenced by the culture in which we were raised, our social networks, religious customs, and the media (Markus & Kitayama, 2010). Culture, for instance, influences how pain is experienced. Individuals of Italian ancestry may focus on the immediacy of the pain and how it affects their current situation. American Jews and Protestants, conversely, tend to be more future oriented when experiencing pain, attending to the potential long-term implications of the experience (Zborowski, 1952). When managing one's health, individuals from western cultures in which individual agency and responsibility are often highly valued favor health promotion over illness prevention. Patients from East Asian cultures tend to take the opposite approach, favoring prevention over promotion and endorsing motivation for avoiding negative outcomes (Elliot, Chirkov, Kim, & Sheldon, 2001; Lockwood, Marshall, & Sadler, 2005).

The information we encounter can also have a particularly potent impact on our mindsets. For instance, the highly publicized claim citing a link between the MMR vaccination and autism—a link that has been thoroughly discredited by every major scientific organization—may have affected some patients' mindsets about the nature of vaccines (Godlee, Smith, & Marcovitch, 2011). Indeed, analyses years after the incident found that parents struggled to understand the true nature of the controversy or know

which sources of information to trust (Hilton, Petticrew, & Hunt, 2007). This trust is important. We place our trust in figures of authority like physicians and base this trust on their degree of competence, compassion, reliability, and how they communicate information (Pearson & Raeke, 2000). We assign value to their claims, allowing these figures to shape mindsets in important ways—for better or for worse.

4.2 The Patient–Provider Relationship—Communication, Warmth, and Competence

The relationship between patient and provider is a critical factor in the quality of care a patient receives, but can also influence the beliefs, expectations, and mindsets patients have about health and disease. The patient–provider relationship shapes the way important medical information is communicated and this influences the mindsets a patient holds about health, illness, and treatments. The patient–provider relationship can also affect physiological health outcomes, both by motivating behavior and through its impact on the patient's internal psychological processes. The patient–provider relationship shapes the patient's internal psychological processes by both direct communication and the nonverbal cues that convey competence and warmth.

How information is framed and communicated can be a particularly strong influence on patients' mindsets. Imagine an emergency room physician meets with an incoming trauma patient. Telling the patient, "I am going to administer a dose of morphine, a safe but powerful pain killer that will alleviate your pain" activates a series of related beliefs and expectations that enhance the subjective and objective efficacy of that treatment. These verbal suggestions shift attention and motivation and affect brain regions associated with pain relief and reward (Benedetti, Amanzio, Vighetti, & Asteggiano, 2006). If the same doctor were to instead tell their patient that the morphine they were giving them was an addictive opioid that could cause severe side effects like respiratory depression, a very different network of beliefs would be activated (Kast & Loesch, 1961). Furthermore, positive interactions in which a diagnosis is clearly made and agreed upon by both the patient and the practitioner can speed recovery from illness (Bass et al., 1986). This effect also occurs in the opposite direction—patients of physicians who communicate poorly have a 19% higher risk of not adhering to medical advice and treatment regimens (Haskard-Zolnierek & DiMatteo, 2009).

It is not just the way treatments are described that can influence patients' mindsets. When doctors intentionally or inadvertently assign meaning to conditions or symptoms, it can shape how the patient experiences them. Cancer pain, for example, is often perceived as more unpleasant than postoperative pain. While cancer pain carries with it associations of sickness and death, postsurgical pain is often associated with a recovery processes (Ferrell, Dean, Grant, & Coluzzi, 1995; Smith, Gracely, & Safer, 1998). By assigning positive or negative meaning to pain, medical providers are activating preexisting mindsets. This can influence pain tolerance and modulate endogenous opioid and cannabinoid systems in the brain (Zubieta & Stohler, 2009).

Although there is never one correct way to communicate with a patient or an ideal model of the patient–provider relationship, certain characteristics appear to be universally important. Indeed, decades of social psychological research suggest that two qualities are of paramount importance: warmth and competence. When a patient meets a physician, he or she rapidly assesses the benevolence of the physician's intentions (warmth) and their ability to carry out these intentions (competence) (Fiske, Cuddy, & Glick, 2007). Warmth denotes a physician's understanding of the patient as a whole person, with a life, values, and goals outside of the health care context, while competence denotes a physician's understanding of medicine (i.e., the disease, prognosis, and treatment). Patient assessments of physician warmth and competence shape patient expectations about treatment, impact mindsets about illness, and modulate the magnitude of the placebo effect. In a recent study, an allergic reaction was induced in participants via a histamine skin prick. A placebo cream was administered with either positive (i.e., this cream will reduce your symptoms) or negative (i.e., this cream will exacerbate your symptoms) expectations under different conditions of provider warmth and competence. Expectations had a larger impact on the efficacy of the placebo cream when it was administered by a warm and competent provider and negated the effects when administered by a cold and incompetent provider (Howe et al., 2017). The social context in which the treatment was administered—seen here as the interaction with a provider who varied in warmth and competence—moderated the impact of patients' expectations on their allergic response.

The strength and quality of the patient–provider relationship is further shaped by empathy and trust. Physicians signal their warmth through their empathy, or ability to understand a patient's unique situation. Empathy is expressed explicitly through verbal information and implicitly through

nonverbal cues like head and body position (Harrigan & Rosenthal, 1983). Displays of warmth and competence not only foster trusting patient–provider relationships, but they also help patients engage in adaptive psychological processes. For instance, physician empathy is significantly associated with reductions in patient anxiety and distress in addition to better clinical outcomes (Derksen, Bensing, & Lagro-Janssen, 2013). In a large retrospective study of over 20,000 diabetic patients, the patients of more empathetic physicians had significantly fewer metabolic complications (Del Canale et al., 2012). Practitioner characteristics such as empathy also affect biological markers of disease. In another study, patients who sought care for symptoms of the common cold were randomly assigned to either a standard interaction with a physician or an enhanced, empathetic interaction. Patients in the enhanced condition rated their physicians as more empathetic, reported lower severity of cold symptoms, and had a greater change in interleukin-8 (IL-8) and neutrophil counts 48 h after the interaction (Rakel et al., 2011).

4.3 Social Influence and Observational Learning

Medical treatments occur within a social environment that directly shapes their efficacy. Indeed, observational learning and social influence have long been suggested as potential mechanisms underlying certain placebo effects (Bootzin & Caspi, 2002). A patient who observes the behavior of another patient may modify their behaviors to more closely match those of the subject being observed (Zentall & Galef, 2013). Behavior modification, however, is not always needed to mediate the effect of observational learning on health outcomes. In an illuminating study, Colloca and Benedetti (2009) demonstrated that placebo effects can be experimentally induced through observational social learning (Colloca & Benedetti, 2009). In this study, participants who observed others undergoing an analgesic procedure experienced substantial placebo responses to the same paradigm. The placebo effect induced via social observation was comparable to those induced by conditioning and greater than those induced by verbal suggestion. The patient's degree of empathy was positively correlated with their placebo response, a finding that has implications for future research. The influence of social observation has important implications for certain integrative medical treatments and the design of novel interventions. For example, support groups or other forms of social interaction between patients may serve to encourage patients currently undergoing treatment, recruit some

of these learning mechanisms to improve treatment efficacy, and complement the verbal and nonverbal expectations induced by a health care provider.

In addition to observational learning, placebo effects can be modulated by explicit social influence. After consuming bottled water that was labeled as caffeinated, participants exhibited increased alertness, increased motor function, and decreased cognitive interference. These effects were largest for subjects who heard a confederate report positive effects from the faux caffeinated water, suggesting an important role of social influence. Furthermore, these socially influenced subjects were more likely to purchase the product and endorse its effects to others (Crum, Phillips, Goyer, Akinola, & Higgins, 2016). These findings suggest that patients may be influenced by others who express confidence in specific treatments. While this social influence may come directly from other patients, it may also come from the media and advertising, which tend to portray new and innovative treatments with compelling success stories.

4.4 Treatment Type and Characteristics

The physical environment in which the treatment takes place and the specific characteristics of the treatment itself can activate certain beliefs, expectations, and mindsets, thereby influencing treatment outcomes. Many patients, for instance, exhibit a substantial but transient rise in blood pressure when it is measured by a physician in a medical setting. This so-called white coat syndrome is thought to result from a physiological stress response evoked by the symbolic status and authority that is represented by the physician's traditional white coat (Manios et al., 2008). Indeed, studies have demonstrated that both representations of social influence and authority can shape a patient's psychological processes and subsequently affect clinical outcomes (Den Hond, Celis, Vandenhoven, O'brien, & Staessen, 2003). However, if this blood pressure reading is used as the basis for a diagnosis of hypertension, it may lead to over medicating of patients who are simply exhibiting a physiological response to the meaning of an environmental cue.

Perceptual characteristics of the treatment itself have also been found to play a role in shaping both psychological processes and treatment outcomes. Seemingly inconsequential features, such as the color of a medication can impact perceptions of medication quality and consequently affect the actual efficacy of that treatment. A 1996 study indicated that patients relate the color of a drug to its underlying mechanism and efficacy

(de Craen, Roos, Leonard de Vries, & Kleijnen, 1996). Shape and form also play a role according to a study in which patients perceived capsules to be stronger and more effective than tablets (Buckalew & Coffield, 1982).

Cost may serve as a mediator between the social valuation of an object and the impact that object has on the individual. Numerous studies have found that beliefs about the characteristics of consumer goods—unrelated to their objective characteristics—shape how they are perceived (Lee, Frederick, & Ariely, 2006). Knowing the price of a bottle of wine, for instance, influences how pleasant that wine is perceived to be and affects blood oxygen levels in the medial orbitofrontal cortex, a region of the brain that is involved in expectation and reward (Kringelbach, 2005; Plassmann et al., 2008). Price has also been found to moderate the efficacy of treatments in clinical populations. In a double-blind study, patients with Parkinson's disease were randomized to receive an injection of saline that was described as either an inexpensive or an expensive "novel injectable dopamine agonist" (Espay et al., 2015). Patients responded to both placebo treatments, but those who received the expensive placebo exhibited greater benefit. If given an expensive treatment first, patients exhibited a twofold increase in motor function over the cheaper placebo. These changes in motor function were associated with corresponding changes in activation of the left putamen, a major target for dopaminergic projections that govern motor activation in Parkinson's disease.

Similar effects have been found in patients' strong preferences for brand name rather than generic drugs. Although generic drugs and their brand name counterparts contain the same type and dose of medication, patients perceive generic drugs to be less effective and experience more side effects when taking them. Generic drugs are also viewed as less trustworthy, less powerful, and many patients do not feel they are appropriate for serious medical conditions (Figueiras et al., 2010; Himmel et al., 2005). In a related study, university students were given placebos and told they would be taking a new beta-blocker (an antihypertensive medication) to reduce performance anxiety. Subjects were randomized to remain taking the original "medication" or to switch to either a different brand or a generic condition. Those who remained on the same placebo treatment exhibited a greater reduction in blood pressure and anxiety compared to those who changed treatments. The switch to a generic beta-blocker yielded the lowest efficacy and the greatest number of adverse events (Faasse, Cundy, Gamble, & Petrie, 2013).

5. DISCUSSION

In this chapter, we have argued that the power of the placebo effect is not separate from but a critical component of medical treatment. In other words, the total effect of any treatment is the combined effect of the pharmaceutical agent and the psychosocial components that make up the placebo effect. These components include the psychological processes and social/contextual factors that drive neurobiological changes and influence subjective and objective treatment outcomes. They can powerfully shape the impact of an active treatment and should not be discounted in the practice of medicine where they can be harnessed to improve patient care.

The power of the placebo to boost active treatments is not novel to many clinicians who witness its effects in their own patients on a daily basis. However, for decades, the notion of the placebo effect was synonymous with deceiving patients by prescribing an inert treatment, a practice that is at odds with the core principles of the profession. So how can the placebo effect be ethically harnessed in the practice of medicine? First, we encourage a wider dissemination of knowledge about the nature of the placebo effect as a psychological process with disease-specific neurobiological effects that are shaped by the social environment and treatment context. This process then can be harnessed to improve patient care and treatment outcomes in a relatively simple and cost-efficient way.

Second, we suggest being aware of each patient's individual psychological characteristics and tendencies, with a specific focus on their mindsets and expectations. How does each patient think about themselves and the world? Recognizing patients who may hold maladaptive mindsets and observing how these mindsets shape their expectations and subsequent health, disease, and treatment is one way to harness the power of the placebo effect in the clinical encounter. Taking an active role in understanding how and why patients have the mindsets they have about health and healing could allow physicians to nondeceptively leverage the same forces that underlie placebo effects in the clinical encounter.

Finally, we encourage physicians to recognize that how they interact with their patients shapes the social environment and treatment context, which in turn influences patient health outcomes. Does the patient trust that the provider has his or her best intentions in mind? Does the patient feel like he or she is understood as a whole person, not just as a body with

a disease? Does the provider exude characteristics of both warmth and competence? These variables are within the provider's control and can powerfully shape the ability to optimize treatment efficacy.

In understanding how the social environment and treatment context shape psychological processes, thereby affecting treatment outcomes, physicians today can harness the same power that Henry Beecher harnessed over 50 years ago—the power of the placebo phenomenon. This helps us move from a world in which the placebo effect is associated with deceptively administered sham treatments, to a world in which the placebo effect is recognized as the manifestation of the powerful social and psychological forces that scaffold all of medicine.

ACKNOWLEDGMENTS

We wish to acknowledge and thank the Stanford Mind & Body Lab, Kari Leibowitz, and Isaac Handley-Miner for their feedback and comments on the manuscript.

REFERENCES

Ader, R., & Cohen, N. (1982). Behaviorally conditioned immunosuppression and murine systemic lupus erythematosus. *Science*, *215*(4539), 1534–1536.

Ader, R., & Cohen, N. (1993). Psychoneuroimmunology: Conditioning and stress. *Annual Review of Psychology*, *44*, 53–85.

Amanzio, M., & Benedetti, F. (1999). Neuropharmacological dissection of placebo analgesia: Expectation-activated opioid systems versus conditioning-activated specific subsystems. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *19*(1), 484–494.

Bandura, A. (1977). *Social learning theory*. Englewood Cliffs, NJ: Prentice-Hall.

Bass, M. J., Buskc, C., Turner, L., Dickie, G., Pratt, G., & R.H. (1986). The physician's actions and the otucome of illnes in family practice. *The Journal of Family Practice*, *23*, 43–47.

Beecher, H. K. (1955). The powerful placebo. *JAMA*, *159*(17), 1602–1606.

Benedetti, F. (2008). Mechanisms of placebo and placebo-related effects across diseases and treatments. *Annual Review of Pharmacology and Toxicology*, *48*, 33–60.

Benedetti, F., Amanzio, M., Baldi, S., Casadio, C., & Maggi, G. (1999). Inducing placebo respiratory depressant responses in humans via opioid receptors. *European Journal of Neuroscience*, *11*(2), 625–631.

Benedetti, F., Amanzio, M., Vighetti, S., & Asteggiano, G. (2006). The biochemical and neuroendocrine bases of the hyperalgesic nocebo effect. *The Journal of Neuroscience*, *26*(46), 12014–12022.

Benedetti, F., Carlino, E., & Pollo, A. (2011). How placebos change the patient's brain. *Neuropsychopharmacology*, *36*(1), 339–354.

Benedetti, F., Maggi, G., Lopiano, L., Lanotte, M., Rainero, I., Vighetti, S., et al. (2003). Open versus hidden medical treatments: The patient's knowledge about a therapy affects the therapy outcome. *Prevention & Treatment*, *6*(1).

Benedetti, F., Pollo, A., Lopiano, L., Lanotte, M., Vighetti, S., & Rainero, I. (2003). Conscious expectation and unconscious conditioning in analgesia, motor, and hormonal placebo/nocebo responses. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *23*(10), 4315–4323.

Bingel, U., Wanigasekera, V., Wiech, K., Ni Mhuircheartaigh, R., Lee, M. C., Ploner, M., et al. (2011). The effect of treatment expectation on drug efficacy: Imaging the analgesic benefit of the opioid remifentanil. *Science Translational Medicine*, *3*(70), 70ra14.

Bootzin, R. R., & Caspi, O. (2002). Explanatory mechanisms for placebo effects: Cognition, personality and social learning. In H. A. Guess, A. Kleinman, J. W. Kusek, & L. W. Engel (Eds.), *The science of the placebo: Toward an interdisciplinary research agenda* (pp. 108–132). London: BMJ Books.

Buckalew, L. W., & Coffield, K. E. (1982). An investigation of drug expectancy as a function of capsule color and size and preparation form. *Journal of Clinical Psychopharmacology*, *2*(4), 245–248.

Colloca, L., & Benedetti, F. (2009). Placebo analgesia induced by social observational learning. *Pain*, *144*(1), 28–34.

Colloca, L., Lopiano, L., Lanotte, M., & Benedetti, F. (2004). Overt versus covert treatment for pain, anxiety, and Parkinson's disease. *The Lancet. Neurology*, *3*(11), 679–684.

Crum, A. J., Corbin, W. R., Brownell, K. D., & Salovey, P. (2011). Mind over milkshakes: Mindsets, not just nutrients, determine ghrelin response. *Health Psychology*, *30*(4), 424–429.

Crum, A. J., & Langer, E. J. (2007). Mind-set matters exercise and the placebo effect. *Psychological Science*, *18*(2), 165–171.

Crum, A. J., Leibowitz, K. A., & Verghese, A. (2017). Making mindset matter. *BMJ (Clinical Research Ed.)*, *674*, j674.

Crum, A. J., Phillips, D. J., Goyer, J. P., Akinola, M., & Higgins, E. T. (2016). Transforming water: Social influence moderates psychological, physiological, and functional response to a placebo product. *PLoS One*, *11*(11), 1–18.

Crum, A. J., Salovey, P., & Achor, S. (2013). Rethinking stress: The role of mindsets in determining the stress response. *Journal of Personality and Social Psychology*, *104*(4), 716–733.

Crum, A., & Zuckerman, B. (2007). Changing mindsets to enhance treatment effectiveness. *JAMA*, *317*(20), 2063–2064.

de Craen, A. J., Roos, P. J., Leonard de Vries, A., & Kleijnen, J. (1996). Effect of colour of drugs: Systematic review of perceived effect of drugs and of their effectiveness. *BMJ (Clinical Research Ed.)*, *313*(7072), 1624–1626.

de la Fuente-Fernandez, R., & Stoessl, A. J. (2002). The placebo effect in Parkinson's disease. *Trends in Neurosciences*, *25*(6), 302–306.

Del Canale, S., Louis, D. Z., Maio, V., Wang, X., Rossi, G., Hojat, M., et al. (2012). The relationship between physician empathy and disease complications. *Academic Medicine*, *87*(9), 1243–1249.

Den Hond, E., Celis, H., Vandenhoven, G., O'brien, E., & Staessen, J. A. (2003). Determinants of white-coat syndrome assessed by ambulatory blood pressure or self-measured home blood pressure. *Blood Pressure Monitoring*, *8*(1), 37–40.

Derksen, F., Bensing, J., & Lagro-Janssen, A. (2013). Effectiveness of empathy in general practice: A systematic review. *British Journal of General Practice*, *63*(606), 76–84.

Elliot, A. J., Chirkov, V. I., Kim, Y., & Sheldon, K. M. (2001). A cross-cultural analysis of avoidance (relative to approach) personal goals. *Psychological Science*, *12*(6), 505–510.

Espay, A. J., Norris, M. M., Eliassen, J. C., Dwivedi, A., Smith, M. S., Banks, C., et al. (2015). Placebo effect of medication cost in Parkinson disease a randomized double-blind study. *Neurology*, *84*(8), 794–802.

Exton, M. S., Gierse, C., Meier, B., Mosen, M., Xie, Y., Frede, S., et al. (2002). Behaviorally conditioned immunosuppression in the rat is regulated via noradrenaline and β-adrenoceptors. *Journal of Neuroimmunology*, *131*(1–2), 21–30.

Faasse, K., Cundy, T., Gamble, G., & Petrie, K. J. (2013). The effect of an apparent change to a branded or generic medication on drug effectiveness and side effects. *Psychosomatic Medicine*, *75*(1), 90–96.

Ferrell, B. R., Dean, G. E., Grant, M., & Coluzzi, P. (1995). An institutional commitment to pain management. *Journal of Clinical Oncology*, *13*(9), 2158–2165.
Figueiras, M. J., Cortes, M. A., Marcelino, D., Weinman, J., Joa, M., & Weinman, J. (2010). Lay views about medicines: The influence of the illness label for the use of generic versus brand. *Psychology and Health*, *25*(9), 1121–1128.
Finniss, D. G., Kaptchuk, T. J., Miller, F., & Benedetti, F. (2010). Placebo effects: Biological, clinical and ethical advances. *Lancet*, *375*(9715), 686–695.
Fiske, S. T., Cuddy, A. J. C., & Glick, P. (2007). Universal dimensions of social cognition: Warmth and competence. *Trends in Cognitive Sciences*, *11*(2), 77–83.
Frensch, P. A., & Rünger, D. (2003). Implicit learning. *Current Directions in Psychological Science*, *12*(1), 13–18.
Giang, D. W., Goodman, A. D., Schiffer, R. B., Mattson, D. H., Petrie, M., Cohen, N., et al. (1996). Conditioning of cyclophosphamide-induced leukopenia in humans. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *8*(2), 194–201.
Godlee, F., Smith, J., & Marcovitch, H. (2011). Wakefield's article linking MMR vaccine and autism was fraudulent. *BMJ (Clinical Research Ed.)*, *342*(7788), c7452.
Goebel, M. U., Meykadeh, N., Kou, W., Schedlowski, M., & Hengge, U. R. (2008). Behavioral conditioning of antihistamine effects in patients with allergic rhinitis. *Psychotherapy and Psychosomatics*, *77*(4), 227–234.
Goebel, M. U., Trebst, A. E., Steiner, J., Xie, Y. F., Exton, M. S., Frede, S., et al. (2002). Behavioral conditioning of immunosuppression is possible in humans. *Official Publication of the Federation of American Societies for Experimental Biology*, *16*(14), 1869–1873.
Gunderson, E. A., Gripshover, S. J., Romero, C., Dweck, C. S., Goldin-Meadow, S., & Levine, S. C. (2013). Parent praise to 1–3 year-olds predicts children's motivational frameworks 5 years later. *Child Development*, *84*(5), 1526–1541.
Harrigan, J. A., & Rosenthal, R. (1983). Physicians' head and body positions as determinants of perceived rapport. *Journal of Applied Social Psychology*, *13*(6), 496–509.
Haskard-Zolnierek, K. B., & DiMatteo, M. R. (2009). Physician communication and patient adherence to treatment: A meta-analysis. *Medical Care*, *47*(8), 826–834.
Hilton, S., Petticrew, M., & Hunt, K. (2007). Parents' champions vs. vested interests: Who do parents believe about MMR? A qualitative study. *BMC Public Health*, *7*(1), 42.
Himmel, W., Simmenroth-Nayda, A., Niebling, W., Ledig, T., Jansen, R. D.-D., Kochen, M. M., et al. (2005). What do primary care patients think about generic drugs? *International Journal of Clinical Pharmacology and Therapeutics*, *43*(10), 472–479.
Howe, L. C., Goyer, J. P., & Crum, A. J. (2017). Harnessing the placebo effect: Exploring the influence of physician characteristics on placebo response. *Health Psychology*, *36*(11), 1074–1082.
Kast, E. C. E., & Loesch, J. (1961). Influence of the doctor-patient relationship on drug action. *The Illinois Medical Journal*, *119*, 390–393.
Kirsch, I. (1985). Response expectancy as a determinant of experience and behavior. *American Psychologist*, *40*(11), 1189–1202.
Kringelbach, M. L. (2005). The human orbitofrontal cortex: Linking reward to hedonic experience. *Nature Reviews. Neuroscience*, *6*(9), 691–702.
Lee, L., Frederick, S., & Ariely, D. (2006). Try it, you'll like it: The influence of expectation, consumption, and revelation on preferences for beer. *Psychological Science*, *17*(12), 1054–1058.
Levine, J. D., & Gordon, N. C. (1984). Influence of the method of drug administration on analgesic response. *Nature*, *312*(5996), 755–756.
Levine, J. D., Gordon, N. C., Bornstein, J. C., & Fields, H. L. (1979). Role of pain in placebo analgesia. *Proceedings of the National Academy of Sciences of the United States of America*, *76*(7), 3528–3531.
Levine, J. D., Gordon, N. C., Smith, R., & Fields, H. L. (1981). Analgesic responses to morphine and placebo in individuals with postoperative pain. *Pain*, *10*(3), 379–389.

Lockwood, P., Marshall, T. C., & Sadler, P. (2005). Promoting success or preventing failure: Cultural differences in motivation by positive and negative role models. *Personality and Social Psychology Bulletin*, *31*(3), 379–392.

Manios, E. D., Koroboki, E. A., Tsivgoulis, G. K., Spengos, K. M., Spiliopoulou, I. K., Brodie, F. G., et al. (2008). Factors influencing white-coat effect. *American Journal of Hypertension*, *21*(2), 153–158.

Markus, H. R., & Kitayama, S. (2010). Cultures and selves. *Perspectives on Psychological Science*, *5*(4), 420–430.

Montgomery, G. H., & Kirsch, I. (1997). Classical conditioning and the placebo effect. *Pain*, *72*(1–2), 107–113.

Mueller, C. M., & Dweck, C. S. (1998). Praise for intelligence can undermine children's motivation and performance. *Journal of Personality and Social Psychology*, *75*(1), 33–52.

Pearson, S. D., & Raeke, L. H. (2000). Patients' trust in physicians: Many theories, few measures, and little data. *Journal of General Internal Medicine*, *15*(7), 509–513.

Petrovic, P., Dietrich, T., Fransson, P., Andersson, J., Carlsson, K., & Ingvar, M. (2005). Placebo in emotional processing-induced expectations of anxiety relief activate a generalized modulatory network. *Neuron*, *46*(6), 957–969.

Plassmann, H., O'Doherty, J., Shiv, B., Rangel, A., Doherty, J. O., Shiv, B., et al. (2008). Marketing actions can modulate neural representations of experienced pleasantness. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(3), 1050–1054.

Pollo, A., Torre, E., Lopiano, L., Rizzone, M., Lanotte, M., Cavanna, A., et al. (2002). Expectation modulates the response to subthalamic nucleus stimulation in Parkinsonian patients. *Neuroreport*, *13*(11), 1383–1386.

Pollo, A., Vighetti, S., Rainero, I., & Benedetti, F. (2003). Placebo analgesia and the heart. *Pain*, *102*, 125–133.

Price, D. D., Finniss, D. G., & Benedetti, F. (2008). A comprehensive review of the placebo effect: Recent advances and current thought. *Annual Review of Psychology*, *59*, 565–590.

Price, D. D., Milling, L. S., Kirsch, I., Duff, A., Montgomery, G. H., & Nicholls, S. S. (1999). An analysis of factors that contribute to the magnitude of placebo analgesia in an experimental paradigm. *Pain*, *83*(2), 147–156.

Rakel, D., Barrett, B., Zhang, Z., Hoeft, T., Chewning, B., Marchand, L., et al. (2011). Perception of empathy in the therapeutic encounter: Effects on the common cold. *Patient Education and Counseling*, *85*(3), 390–397.

Rescorla, R. A. (1988). Pavlovian conditioning: It's not what you think it is. *American Psychologist*, *43*(3), 151–160.

Seger, C. (1994). Implicit learning. *Psychological Bulletin*, *115*(2), 163–196.

Shetty, N., Friedman, J. H., Kieburtz, K., Marshall, F. J., & Oakes, D. (1999). The placebo response in Parkinson's disease. Parkinson Study Group. *Clinical Neuropharmacology*, *22*(4), 207–212.

Smith, W. B., Gracely, R. H., & Safer, M. A. (1998). The meaning of pain: Cancer patients' rating and recall of pain intensity and affect. *Pain*, *78*(2), 123–129.

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

Voudouris, N. J., Peck, C. L., & Coleman, G. (1989). Conditioned response models of placebo phenomena: Further support. *Pain*, *38*(1), 109–116.

Voudouris, N. J., Peck, C. L., & Coleman, G. (1990). The role of conditioning and verbal expectancy in the placebo response. *Pain*, *43*(1), 121–128.

Wager, T. D., & Atlas, L. Y. (2015). The neuroscience of placebo effects: Connecting context, learning and health. *Nature Reviews. Neuroscience*, *16*(7), 403–418.

Walsh, B. T., Seidman, S. N., Sysko, R., & Gould, M. (2002). Placebo response in studies of major depression: Variable, substantial, and growing. *JAMA*, *287*(14), 1840–1847.

Wickramasekera, I. (1980). A conditioned response model of the placebo effect: Predictions from the model. *Biofeedback and Self-Regulation*, *5*(1), 5–18.
Zborowski, M. (1952). Cultural components in responses to pain. *Journal of Social Issues*, *8*(4), 16–30.
Zentall, T. R., & Galef, B. G., Jr. (2013). *Social learning: Psychological and biological perspectives*. Psychology Press.
Zion, S. R., Dweck, C. S., & Crum, A. J. (2018). In sickness and in health: Validation of a health mindset scale in healthy and chronically ill populations. In *Presented at the Society for Personality and Social Psychology, Atlanta, GA*.
Zubieta, J. K., & Stohler, C. S. (2009). Neurobiological mechanisms of placebo responses. *Annals of the New York Academy of Sciences*, *1156*(734), 198–210.