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The Placebo Phenomenon: A Narrow Focus on Psychological Models

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Abstract

The placebo effect is a complex phenomenon that can be described from neurobiological, psychosocial, and epistemological perspectives. Different leaders in the field have proposed multiple theories and models that attempt to describe both the nature and the mechanisms of action underlying placebo effects. This article focuses on the most relevant psychological models that have been suggested for characterizing the different mechanisms underlying the placebo effect. We outline how the dynamic psychoneurobiological aspects of the placebo phenomenon can be a potential reliable and useful tool in daily clinical practice for illness and symptom management within a wide variety of specialties and health-care practices.

> One of the most successful physicians I have ever known, has assured me, that he used more bread pills, drops of colored water, and powders of hickory ashes, than of all other medicines put together. It was certainly a pious fraud.
>
> —Thomas Jefferson (1807)

Clinicians and other health-care practitioners have known for hundreds of years that different procedures with unclear mechanisms of action or efficaciousness can still result in subjective improvement of clinical symptoms. Many scholars have attempted to define the placebo effect. This has resulted in the development of multiple frameworks and models that help explain and further explore placebo effects and responses. After providing some definitions and clarifications of terminology, this review will attempt to outline the different theories and models of the placebo phenomenon and describe their relevance in the field of medicine.

Definitions and Terminology

From a philosophical perspective, it is interesting to examine the origin of terms and their historical development. The term *placebo*, originating from the Latin root "placere" and

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translated as "to please," has had multiple connotations throughout history (Harrington 1997). *Placebo* can be defined as an inert substance (such as a saline injection or sugar pill) or a simulation of a medical therapy that is not directly known to cause an effect on a certain outcome (i.e. improvement of a disease state) (Miller, Colloca, and Kaptchuk 2009). On the other hand, "placebo effects" have been defined as the neurobiological changes that can result from patient, caregiver, or clinician's expectations, and "placebo responses" as the experimental or clinical observations resulting from spontaneous remission, regression to the mean, and natural symptom fluctuations of disease states (Colloca 2017; Colloca and Miller 2011a; Miller and Brody 2011).

Importantly, the placebo effect can be affected by more than just the administration of placebos. For example, administration of a placebo within a positive psychosocial context may engage the placebo effect, while administration of a placebo within a negative psychosocial context can cause an opposite, noxious effect, which is referred to as the "nocebo effect" (Blasini et al. 2017). Furthermore, these psychosocial contexts have been shown to influence patient outcomes without any administration of placebos or medical interventions, namely by shaping patient expectancies (Abe et al. 2011; Colloca and Benedetti 2005; Colloca et al. 2004; Di Blasi and Reilly 2005; Di Blasi et al. 2001). Herein, we will discuss some of the most relevant models of expectancy formation in the context of placebo and nocebo as well as the clinical relevance and usefulness of these factors.

The Conditioning Response Theory

The occurrence of the placebo phenomenon resulting from conditioned responses has been investigated by many (for a review, see Colloca 2014). In 1962, a pioneering study by Richard Herrnstein demonstrated the possibility of eliciting conditioned placebo responses with the use of scopolamine in rats. In the study, saline injections were temporally introduced in periods during which scopolamine had been previously injected; the saline injections mimicked the behavioral suppression observed with scopolamine administration. In accordance with earlier work conducted by Ivan Pavlov (1927), in which animals had been conditioned to experience the effects of morphine, Herrnstein (1962) states that "this placebo effect is based on the animal's experience … in conformity with the traditional paradigm of simple Pavlovian conditioning," and that "there appears to be no reason to suppose that the placebo effect in human patients differs in any way … other than in degree of complexity" (100).

Wickramasekera (1980) also described the placebo phenomenon as a conditioned response. Wickramasekera states that it is possible to train the body to elicit a placebo response by initially using active ingredients (unconditioned stimulus) paired with a placebo (conditioned stimulus) to cause a conditioned response. Once the body has associated the placebo with the response, then it would be possible to reduce or withdraw the active ingredient and only keep the placebo. Through association with active ingredients (unconditioned stimulus), the ritual of giving a placebo (the administrator, the environment, the method of administration) can become a conditioned stimulus that causes alleviation of pain and other symptoms. Thus, a conditioned response now becomes a placebo response that could be able to influence health outcomes. However, it is important to note that classical conditioning is not the only type of conditioning that can influence placebo effects. Operant conditioning, also known as instrumental conditioning, modifies behavior by means of associations of stimuli and consequences (either positive or negative reinforcement), rather than by pairing a stimulus with another stimulus as in the case of classical conditioning. Other researchers have observed behaviorally conditioned placebo responses related to immunosuppression in systemic lupus erythematosus and analgesia to nociceptive stimuli through reinforcement paradigms (Ader and Cohen 1982; Colloca and Benedetti 2006; Finniss and Benedetti 2005; Voudouris, Peck, and Coleman 1990).

Conditioning has been studied in many different types of disorders, including Parkinson’s disease, hormone secretion, and immune responses (Ader 2003; Benedetti et al. 2003, 2004; de la Fuente-Fernandez et al. 2001; Giang et al. 1996; Goebel et al. 2002; Olness and Ader 1992). However, most of the research has focused on the placebo analgesic phenomenon (Colloca and Benedetti 2005; Finniss and Benedetti 2005). Studies have also suggested that conditioning and reinforcement produce more robust and longer-lasting placebo effects than verbal suggestions alone (Colloca and Benedetti 2006). In line with this concept, Colloca and colleagues (2016) described in a scoping review the potential for applying pharmacological conditioning through dose-extending placebos that can act as “booster[s] of the active agents” and can mimic the action of drugs through the engagement of placebo and endogenous modulatory mechanisms. Dose-extending placebos offer a potential treatment paradigm that could reduce pain and other symptoms while resulting in a limitation of side effects and costs as compared to continued administration of active drugs.

Evidently, conditioning plays an important role in evoking placebo effects. Since conditioning can be influenced by prior personal and medical experiences, learning, and environmental factors, some of these processes may not be consciously mediated. Moreover, some learning processes may occur independently of conditioning by means of vicarious observation, social learning, or verbal communication (Kirsch 1985, 1997, 2004). Given that placebo effects have been demonstrated to be influenced by verbal suggestions, conditioning processes, social observation, personality factors, and genetics, the underlying endogenous mechanisms mediating the processing of the vast amount of information within a clinical environment are far more integrated and complex than one single process alone (Bartels et al. 2014; Benedetti et al. 2003; Brody and Brody 2000; Colagiuri et al. 2015; Colloca and Benedetti 2006, 2009; Colloca and Grillon 2014; Corsi and Colloca 2017; Darragh et al. 2015; Hall, Loscalzo, and Kaptchuk 2015; Kirsch 2004; Klinger et al. 2017b; van Laarhoven et al. 2011; Vase et al. 2003; Vogtle, Barke, and Kroner-Herwig 2013; Wang et al. 2017). It has also been demonstrated that strong placebo analgesic effects can be achieved through conditioning, and that these effects are mediated by expectancies. In line with theories that support the role of learning in the cognitive processes involved in classical Pavlovian conditioning, expectancies and expectations can be reached through the conditioned learning that one event or stimulus will follow another event (Colloca and Benedetti 2016; Kirsch et al. 2004; Reiss 1980; Rescorla 1988).

The Expectancy Theory

Expectations and expectancies are interrelated entities but not synonymous to each other. Although the terms *expectancy* and *expectation* have been commonly interchanged, *expectation* refers to the measurable beliefs and constructs that are consciously verbalized by individuals, including patients and practitioners (Corsi and Colloca 2017), while *expectancy* has been defined as the subset of psychophysiologically driven predictions that can exist without an individual's full awareness (Colloca 2017; Laferton et al. 2017).

Both implicit and explicit learning mechanisms are able to elicit placebo effects. Implicit expectancies can be modified and constructed through the application of classical conditioning and associative learning paradigms, while explicit expectancies can be modeled through verbal suggestions and instructions (Bartels et al. 2014; Kirsch 2004; Martin-Pichora, Mankovsky-Arnold, and Katz 2011). In fact, research conducted by Schafer and colleagues (2015) has demonstrated that placebo effects can occur despite participants having been briefed on the nature of the sham intervention and having had further positive expectations violated in a paradigm that included both verbal suggestions and conditioning processes. This suggests that mechanisms driving subconscious behavioral and physiological processes might also play a role in shaping placebo effects.

In a pioneering essay, Kirsch (1985) suggested the *response expectancy theory*, based on the premise that a placebo causes an effect because the recipient expects an effect to occur. Response expectancy was defined by Kirsch as the "anticipation of automatic, subjective, and behavioral responses to particular situational cues," which can have considerable effects on the efficacy and effectiveness of antidepressants, psychotherapy, and hypnotizability (Kirsch 1997, 69). As described by Kirsch and others, expectancy influences the perceptions of what is to occur within a situation or experience (Bruner 1957). Generally, both expectations and expectancies can be shaped by a patient's previous experiences as a result of conditioning, learning, or observations that provide information about how likely an outcome is to occur.

A randomized study in post-thoracotomy patients receiving buprenorphine for pain investigated the effects of verbal suggestions on clinical acute pain (Pollo et al. 2001). One set of patients was not told about the analgesic properties of the medication, a second was told they were receiving powerful pain medication or placebo, and a third was informed that they were receiving a powerful analgesic. This study showed a significant decrease in pain medication use in the third group when compared to the other two groups, and this result suggested that verbal communication influences explicit expectations, and thus placebo and nocebo effects (Blasini et al. 2017; Colloca and Finniss 2012; Colloca and Miller 2011c; Klinger et al. 2017a; Miller and Colloca 2010; Pollo et al. 2001; Schwarz, Pfister, and Büchel 2016, 2018). Expectancies can also be modulated by a person's emotional appraisal of the situation (in other words, by fear, anxiety, or the prospect of reward). However, the placebo effect may be shaped in either a positive or negative way secondary to the patient's previous experiences or emotional factors, which may enhance or detract from the learned response (Colloca and Miller 2011d).

Recent focus on the influences of personality and psychological traits and factors in placebo responsiveness has also revealed that suggestibility, catastrophizing, anxiety sensitivity, rumination, and helplessness can trigger the occurrence of nocebo effects (Blasini et al. 2017; Corsi and Colloca 2017; Corsi et al. 2016; Schwarz, Pfister, and Büchel 2016; Vogtle, Barke, and Kroner-Herwig 2013). However, in a study conducted by Corsi and Colloca (2017), it was shown that psychological factors did not directly influence participants' expectations of pain. Thus, some of these mechanisms may work through unconscious processes influencing automatic behaviors and responses to stimuli, as also depicted in Kirsch's response-expectancy theory (Kirsch 1997).

Importantly, individual responsiveness to placebo and nocebo effects has been associated with candidate genes related to neurotransmitter and endogenous modulatory system pathways, such as the opioidergic, endocannabinoid, serotonergic, and dopaminergic systems (Blasini et al. 2017; Colagiuri et al. 2015; Hall, Loscalzo, and Kaptchuk 2015). Therefore, aspects of placebo and nocebo mechanisms, and potentially of the formation of expectancies, can be automatically mediated regardless of conscious expectations and cognitions. Unconscious conditioning process, such as placebo effects related to immune or endocrine system responses to perceived stress and pharmacological conditioning, have also been reported in the literature (Albring et al. 2014; Colloca and Miller 2011b; Colloca, Enck, and DeGrazia 2016; Wendt, Albring, and Schedlowski 2014). Although these concepts require further investigation, it is argued that implicit learning of complex contextual information can be acquired in an incidental manner without a person's full awareness and still induce implicit expectancies that boost placebo and nocebo effects (Rose, Haider, and Büchel 2005).

The Mindset Model

An emerging model is represented by the concept of patient mindsets and their roles in health outcomes and placebo effects (Zion and Crum 2018). Crum and Zuckerman (2017) have explored the role of patients' mindsets during clinical encounters or situations and how these mindsets can influence treatment effectiveness and health behaviors. Mindsets, which are views or frameworks that orient and direct individuals to develop associations or beliefs regarding situations or experiences, can be shaped by multiple factors, including societal norms, culture, religious doctrines, and social media. Mindsets help create a mental shortcut that simplify complex inputs to be integrated by neuropsychological processes and that help shape and orient decision-making and related behaviors. Thus, mindsets can strongly influence the effectiveness of treatments or interventions as well as the patient's behaviors within and outside the clinical environment. Mindsets in the context of expectations and expectancies can elicit biological changes related to immune, endocrine, and cardiovascular factors (Albring et al. 2012; Crum and Zuckerman 2017; Finniss et al. 2010; Howe, Goyer, and Crum 2017; Pollo et al. 2003). Two types of mindsets in particular have been described as having the most relevant influences within the patient-physician interaction: mindsets about the capacity to change, and mindsets about treatment efficacy (Crum and Zuckerman 2017).

In a study of 84 females working as room attendants, those who were told that their work satisfactorily met the general recommendations of an active lifestyle for promoting health significantly perceived having more exercise than before when compared to the control group, even when the actual health behaviors did not change at four weeks of intervention (Crum and Langer 2007). Furthermore, the exercise-informed group presented with decreased weight, body fat, waist-to-hip ratio, body mass index, and blood pressure when compared to the control group that was not informed of work-related activity as exercise. The authors concluded that these results highlight a potential placebo mechanism influencing health-related changes associated with exercise, and that the benefits of physical activity can be greater when individuals are aware of the benefits of these daily life integrated activities. Another study on adolescents suffering from type I diabetes mellitus showed that those who thought and believed their health could be improved and could change had lower levels of hemoglobin A_{1C} on average throughout one year (Mueller, Dweck, and Wright 2012). Moreover, investigations on the effects of mindsets on the stress response showed that shifting the negative perceptions of stress towards an “enhancing” mindset that focuses on the capacity of the physiological stress response to improve functioning and cognitive ability resulted in a more adaptive cortisol profile (lower cortisol for those with high cortisol reactivity, and higher for those with lower cortisol reactivity during stress) and in an increased inclination for receiving feedback after exposure to a stressful task (Crum, Salovey, and Achor 2013).

The potential for patient mindsets to influence physiological factors and important health behaviors through the promotion of growth-mindsets and individual capacities to change offers an opportunity to strongly impact patients’ clinical and health outcomes with a minimal degree of invasiveness. Future research may reveal an advantage of utilizing these strategies in clinical environments to shape placebo effects through a focus on malleable patient mindsets about their own perceptions of health and related behaviors, interventions, and treatments (Crum, Leibowitz, and Verghese 2017; Crum and Zuckerman 2017).

Computational Models

Recently, some reviews have suggested that expectancies and placebo effects that influence and modify a patient’s perception of pain also correspond to computational rules and models. It is well known that pain processing is divided into two different neurophysiological systems, one being the sensory-discriminative system, which processes nociceptive pain stimuli, and the second being the cognitive-affective system, which processes the psychological and affective features of pain. Recent neuroimaging studies that have investigated pain perception have shown that these two systems work together and are indeed integrated with high-level cognitive influences. Büchel and colleagues (2014) postulated that the ascending and descending pain systems represent a unique system based on the actions of predictive coding-meaning. Therefore, the brain is not a mere decoder of signals from nociceptive stimuli; rather, the brain graciously and actively makes inferences based on the interplay between prior experience and expectancies. Büchel and colleagues suggested that a Bayesian computational model based on a predictive coding framework may account for differences in the magnitude and precision of expectations that influence the strength of placebo effects in the context of pain systems.

Through predictive coding and computational modeling, Wiech (2016) further indicated that pain perception can be conceptualized as an *inferential process*, in which prior experiences or information are used to shape expectancies by creating a sort of "template" about future painful events, and thus provide information about how to interpret sensory inputs. Predictive coding postulates that people are more likely to interpret sensory information in accordance with their own expectations rather than with "competing interpretations" that violate such expectations. Thus, expectations can bias perception of pain through actions in brain regions that process somatosensory input and in regions involved with the interpretation of such sensory information. However, the effects of an expectation on pain perception are thought to be limited by how likely the expectation is considered "reality." If the expectation is too "far-fetched," then a modification of the expectation occurs—making pain perception modulation an active and dynamic process that is enabled and modified by learning processes and experiences. Future research in this direction can help advance precision medicine and predictability of individual placebo responsiveness.

Conclusion

Placebo and nocebo effects are complex phenomena that encompass psychological, biological, neuronal, and interpersonal aspects of human physiology and behavior. All the various frameworks discussed, describe concepts about how the placebo and nocebo effects work. These concepts often overlap to help create an integrative explanation that supports the highly flexible and dynamic nature of cognition and its ability to influence different placebo and nocebo effects and clinical outcomes. Given the high complexity of human behaviors and the highly integrative capacities of subconscious processes, there is likely no single mechanism being activated during the engagement of the placebo effect. Rather, many mechanisms underlie placebo and nocebo effects within different contexts and diseases.

Knowledge about placebo effects can favor physicians and health-care providers' becoming actively engaged in improving the clinical environment so as to optimize the context and potential cues that can condition patients to develop positive expectancies.

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