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THE PLACEBO EFFECT: FROM CONCEPTS TO GENES

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Abstract—Despite its initial treatment as a nuisance variable, the placebo effect is now recognized as a powerful determinant of health across many different diseases and encounters. This is in light of some remarkable findings ranging from demonstrations that the placebo effect significantly modulates the response to active treatments in conditions such as pain, anxiety, Parkinson's disease, and some surgical procedures. Here, we review pioneering studies and recent advances in behavioral, neurobiological, and genetic influences on the placebo effect. Consistent with recent conceptualizations, the placebo effect is presented as the product of a general expectancy learning mechanism in which verbal, conditioned, and social cues are centrally integrated to change behaviors and outcomes. Examples of the integration of verbal and conditioned cues, such as instructed reversal of placebo effects are also incorporated into this model. We discuss neuroimaging studies that have identified key brain regions and modulatory mechanisms underlying placebo effects using well-established behavioral paradigms. Finally, we present a synthesis of recent genetics studies on the placebo effect, highlighting a promising link between genetic variants in the dopamine, opioid, serotonin, and endocannabinoid pathways and placebo responsiveness. Greater understanding of the behavioral, neurobiological, and genetic influences on the placebo effect is critical for evaluating medical interventions and may allow health professionals to tailor and personalize interventions in order to maximize treatment outcomes in clinical settings.

Key words: learning, expectancy, conditioning, modeling, pain.

Contents

INTRODUCTION

The placebo effect is a fascinating and important psychobiological phenomenon whereby treatment cues trigger improvement. While traditionally viewed as a nuisance variable to be controlled for, the past three decades have seen a surge in interest in the placebo effect in light of some remarkable clinical and laboratory

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Abbreviations: ACC, anterior cingulate cortex; *BDNF*, brain-derived neurotrophic factor; CCK, cholecystokinin; *COMT*, catechol-O-methyltransferase; *DBH*, dopamine beta-hydroxylase; DLPFC, dorsolateral prefrontal cortex; *DRD3*, dopamine receptor D3; FA, fractional anisotrophy; *FAAH*, fatty acid amide hydrolase; fMRI, functional magnetic resonance imaging; GMD, gray matter density; *HTR2*, 5-hydroxytryptamine (serotonin) receptor 2A; IBS, irritable bowel syndrome; MAF, Minor Allele Frequency; *MAO-A*, monoamine oxidase A; *NR3C1*, nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor); *OPRM1*, μ-opioid receptor gene; PAG, periaqueductal gray; PET, positron emission tomography; rACC, rostral ACC; RCTs, randomized clinical trials; S1/S2, somatosensory cortices; *SLC6A4*, solute carrier family 6 (neurotransmitter transporter), member 4; SNP, single-nucleotide polymorphism; TMS, transcranial magnetic stimulation; *TPH2*, tryptophan hydroxylase 2.

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discoveries that have demonstrated its potential power to improve patient outcomes. Furthermore, recent advances in neuroimaging and genetics have allowed researchers to begin to understand the brain mechanisms underlying the placebo effect as well as to explore its genetic bases. In this review, we highlight some historical and pioneering studies on the placebo effect, present a recently developed conceptual framework for understanding the placebo effect in which verbal, contextual, and social cues elicit expectancies that drive the placebo effect via learning, outline behavioral studies that demonstrate how distinct forms of learning shape the placebo effect, and review what is currently known about neurobiological and genetic bases of the placebo effect. The possibility that genetic variations could be used to predict individual placebo and nocebo responses is particularly exciting as it suggests a way that future placebo interventions could be individually targeted to patients to maximize their benefits.

HISTORICAL AND PIONEERING STUDIES ON THE PLACEBO EFFECT

Many researchers have proposed that the history of prescientific medicine is in fact the history of the placebo effect (Wolf, 1950; Moerman, 1997; Shapiro and Shapiro, 1997). However, it was not until placebos began to be used as controls in clinical trials that they became a mainstay of modern medicine. One of the first documented uses of placebos as controls was a trial conducted by Benjamin Franklin and Antoine Lavoisier who were commissioned by Louis XVI in 1784 to test Franz Mesmer's claim to have uncovered ''animal magnetism'' – a supposed invisible force that Mesmer believed contained healing properties (Kaptchuk, 2009). Franklin and Lavoisier exposed patients to supposedly ''mesmerized'' objects or untreated objects (i.e. placebos) without telling the patients which ones they were being exposed to. They found that patients' responses to the objects were entirely unrelated to whether or not the object had been mesmerized and concluded that animal magnetism had no scientific basis.

While the advent of the double-blind placebo-controlled trial was undoubtedly a critical step in the advance of scientific medicine, an unfortunate side effect was that it meant that despite being commonly used in clinical trials, the placebo effect was relegated to being considered only a nuisance variable to be controlled for. It was not until the mid-1900's that interest in the placebo effect as an interesting phenomenon in its own right emerged. Probably the most influential piece of research to this end was a meta-analysis by Beecher (1955). Here, Beecher combined the data from the placebo groups of 15 studies on different conditions including pain, seasickness, cough, and anxiety, and calculated that on average, placebos led to a 35% improvement in symptoms – leading him to argue that the placebo effect was powerful and worthy of study. Despite Beecher's methodology later being criticized (Kienle and Kiene, 1997), his research sparked great interest in the placebo effect's potential power to heal. There are now over 5000 research articles in the PubMed database that make specific reference to the placebo effect, which include demonstrations of placebo effects for pain, depression, anxiety, insomnia, immunosuppression, Attention Deficit Hyperactivity Disorder (ADHD), and even Parkinson's disease, to name a few (Colloca et al., 2013; Benedetti, 2014). In this section, we highlight some of the most important pioneering studies on the placebo effect conducted to date, which demonstrate the broad range of effects that placebo interventions can induce and their clinical relevance. These include evidence that placebo effects modulate active treatment outcomes, placebo surgery can be just as effective as real surgery, placebo effects may occur even without deception, and placebo effects are not always beneficial.

Placebo effects for active treatments

One of the most pivotal findings for demonstrating the clinical relevance of the placebo effect were the studies demonstrating that it contributes to the responses to active treatments, not just inert ones. Wolf (1950) was one of the first to report this. He showed that the effect of emetic treatments could be moderated by the instructions accompanying them. In a patient suffering from nausea, Wolf administered the emetic ipecac but told the patient it was an anti-emetic. Remarkably the patient's nausea was alleviated, both in terms of subjective and objective indices. More systematic analysis of these effects followed. Notably, Levine and colleagues (1981, 1984) compared open administration of placebos (i.e. administration in the presence of a nurse) with hidden administration of placebos and analgesics (i.e. via an automated intravenous pump) for pain relief post-dental surgery. They found that the open administration of placebo produced equivalent pain relief to hidden administration of 6–8 mg of morphine and claimed that a substantial component of treatment responses to open treatments could be attributed to the placebo effect. Perhaps the clearest demonstration of placebo effects modulating active treatment effects, however, was provided by Benedetti et al. (2003a). Benedetti and colleagues directly compared the effect of open versus hidden administration of active treatments across four different conditions, namely morphine for postoperative pain, diazepam for anxiety, subthalamic stimulation for Parkinson's disease, and beta-blockers for cardiovascular function. Across each of these treatments, they found that open treatment led to significantly larger improvement than the same hidden dose. This showed unambiguous evidence that the placebo effect was not confined to inert agents and that many active treatments involve a placebo component that substantially contributes to the overall treatment response, demonstrating the importance of considering the placebo effect in any treatment setting.

Placebo surgery

Another important discovery was that placebo effects also exist for surgery. In one of the first such studies, Cobb et al. (1959) compared internal mammary artery ligation with placebo surgery for angina. The ligation of the mammary artery was believed to reduce angina by facilitating