Why is pain experienced differently in war? Understanding the placebo effect in civilian life and its consequences.

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Abstract

The placebo effect is a phenomenon that occurs when patients experience therapeutic benefits from treatments without any active medication. By examining the neural systems that underlie placebo responses – particularly the roles of expectation, classical conditioning, and placebo-induced activation in specific brain regions, it becomes evident that placebo effects can influence disease-relevant neurobiological systems. This paper explores the mechanisms of the placebo effect and the therapeutic potential of placebos across various conditions including pain, Parkinson's disease, Alzheimer's disease, anxiety/depression, and schizophrenia. We also investigate the significance of placebo responses in psychiatric conditions and their overlap with predictive coding processes. Research suggests that placebo effects could enhance clinical practices by personalizing treatments and creating psychological contexts that reduce reliance on active medication. Our findings emphasize how important it is to understand how brain systems and neurochemical mediators (e.g., dopamine) interact to mediate placebo responses. This paper underlines the need for further research into placebo mechanisms to optimize their clinical application. By harnessing the potential of the placebo effect, we can develop cost-effective and patient-centered approaches to improve outcomes in both neurological and psychiatric diseases.

Introduction

Why is pain experienced differently in war versus civilian life? Henry Beecher, a physician and anesthesiologist, pondered this question after his experiences as a medic during World War II. Consider a soldier injured by a gunshot on the battlefield and a civilian wounded in a similar manner. The soldier may feel a sense of heroism, respect, and duty, while the civilian often experiences shock and distress. This difference illustrates the complex interplay between psychological factors and the perception of pain due to the placebo effect, a phenomenon in which patients experience an improvement in their condition despite the absence of active medication. Beecher initially observed the placebo effect when supplies of morphine on the battlefield dwindled. After substituting morphine with a saline solution unbeknownst to the soldiers, he found that the soldiers reported significant pain relief.

Furthermore, after the war, he noted that the amount of painkillers he prescribed to civilians was significantly higher than that administered to soldiers on the battlefield (Beecher, 1946). The placebo effect—derived from the Latin word "placebo" meaning "I shall please"—was initially used to refer to an inactive treatment that confers therapeutic value by placating a patient's concerns (Bernstein & Brown, 2017). Over time, the term has come to signify the real clinical improvements that follow the administration of an inert treatment shaped by patients'

expectations, beliefs, anticipation, and other psychological responses to the environmental and psychosocial context surrounding the experience (Benedetti et al., 2011)

It is important to distinguish between placebo responses and placebo effects. Placebo responses encompass any beneficial outcome in response to an inactive treatment and thus can include factors such as spontaneous remission and biased outcomes (e.g., subjective measures). Clinical trials implement controls for placebo responses by comparing active and inert treatments and using rigorous study designs (Kaptchuk, 1998). In contrast, placebo effects are clinical improvements arising from psychological factors attributable to the treatment context including medical treatment cues (e.g., a doctor's coat, pills, and words of encouragement and support) (Beecher, 1955), as these factors … informational context of medical care impact results—expectations and learning behaviors such as conditioning (Geuter et al., 2017). Two important technological advancements have enhanced our understanding of the placebo effect as a medical treatment. First, progress in modern neuroimaging provided evidence that placebo treatments may engage similar brain regions related to the endogenous disease systems for a particular condition. Compelling evidence shows that successful placebos share common biological pathways and activate the same receptor sites as the active pharmacological treatments (Benedetti et al., 2011). This evidence comes from studies in pain management, Parkinson's disease, and psychiatric disorders such as depression and anxiety (Bernstein & Brown, 2017)A better understanding of the neurobiology of the placebo effect can represent productive models to define brain pathways leading to the resolution of core symptoms in the absence of pharmacological treatment.

Could an improved understanding of the placebo effect help in developing more effective and personalized medical treatments? This question would be beneficial to all researchers. Right now, we cannot fully personalize medical treatment as individual differences will lend to differences in experience, values, and knowledge. However, by understanding how context is extremely important towards conditions, we can personalize not only a placebo but also actual active medical treatment, towards the individual. By knowing which brain regions are responsible for and are affected by the placebo effect, we can design more effective and personalized medical treatments.

The focus of this paper is to better characterize the placebo effect in pain reduction, psychiatric conditions, and neurological diseases such as Parkinson's Disease and Alzheimer's Disease. We will first describe the mechanisms of the placebo effect and then review evidence of the effectiveness of placebo effects across various conditions. Finally, we will conclude with an exploration of the brain systems involved in the placebo effect.

Materials and Methods

Electronic databases PubMed, Web of Science, and Scopus were utilized to conduct a literature search using keywords and MeSH terms 'placebo effect' or 'placebo response' and cross-referenced relevant publications.

Results

We found that there was evidence of a “placebo response” in treatments for Parkinson’s disease, pain, Alzheimer’s disease, and psychiatric conditions.

Parkinson’s Disease

The placebo effect in Parkinson’s disease (PD) has been attributed to dopamine release in the striatum (De La Fuente-Fernandez & Stoessl, 2002), a biochemical pathway that is consistent with the effects of most treatments for PD. In the early stages of the disease, dopamine agonists (pramipexole and ropinirole) – drugs that mimic the effect of dopamine by binding to and activating dopamine receptors---are commonly used. Monoamine oxidase inhibitors prevent the breakdown of dopamine, allowing more dopamine to be used for longer periods of time. These medications are more effective than placebos in providing mild symptomatic relief and can be used as monotherapy or adjunct therapy. Levodopa is the gold standard treatment for Parkinson’s disease is a chemical endogenous to the human brain that acts as a chemical precursor to dopamine. There is evidence that inhaled levodopa is a rescue medication that can be used when oral medications stop working during the day during “off” periods is more effective than a placebo for managing these fluctuations in symptoms. Another line of research suggests that the belief of improvement due to placebo increases activity in the ventromedial prefrontal cortex, a region known to modulate dopamine release in the striatum. However, the authors did not identify which factors are controlled in dopamine release in placebo groups.

In addition to placebo effects based on expectation, placebo responses to Parkinson’s treatments can also be seen in the duration of drug effects. In one study, the mean duration of the Parkinson’s drug named apomorphine, the only drug with an efficacy equivalent to levodopa had a mean duration of response (Carbone et al., 2019) around 90 min whereas the mean duration of the placebo effect lasted only 30 min, suggesting placebo responses are active in the early phases of symptom improvement.

Pain

Placebo analgesia is a well-studied phenomenon in which individuals experience relief from pain in response to a placebo. There are two important technological advancements that have improved our understanding of placebo analgesia. Using modern neuroimaging techniques that allow in vivo measurements of brain activity during pain experiments, several studies have found that placebo treatments modulate pain-related activity within specific circuits. One such study found that placebo-induced activation of the magnitude of opioid neurotransmission in several brain regions was correlated with lower pain intensity ratings of the endogenous opioid-mediated neurotransmitter system in the pregenual and subgenual anterior cingulate, insular cortex and the nucleus accumbens is significant in placebo analgesia (Zubieta et al., 2005). In another PET study, placebo analgesia was associated with changes in activity in the periaqueductal gray and the rostral ventromedial medulla, suggesting that the expectation of pain reduction can influence pain perception by modulating brain activity at the level of the brainstem (Grahl et al., 2018). Placebo analgesia also involves the modulation of pain perception in the central nervous system, with medial and prefrontal cortical areas exerting descending modulation on specific subcortical structures and brainstem nuclei to influence autonomic and cardiovascular function. The ventromedial region of the prefrontal cortex, in particular, has been implicated in mediating the motivational and reward-related components of

pain and placebo analgesia. In one study, the functional connectivity of the left medial prefrontal cortex and bilateral insula predicted participant post-treatment group outcomes in a study comparing topical analgesics to no-drug patches (Hashmi et al., 2012)

There are also studies using imaging techniques that have shown increased activity in brain regions that are involved in pain modulation such as the dorsolateral prefrontal cortex, rostral anterior cingulate cortex, and the periaqueductal gray in response to placebo treatment (Frisaldi et al., 2020).

Psychiatric Conditions

Meta-analytic evidence that indicates clinical outcomes in pain and subjective outcomes which are central in most psychiatric conditions, are significantly influenced by placebo effects. Most placebos are shown to have a prominent effect on the subjective components of a disease such as pain or distress which may in part explain the effectiveness of a placebo in psychiatric diseases with these features. There may be situations in psychiatric practice where it may be beneficial to rely on placebo effects within treatment. For instance, in a disease such as depression where cognitive distortions are linked to the symptoms of the disease, the benefits of any antidepressant treatment simply need to invoke a cognitive representation of the treatment itself (Wager & Atlas, 2015).

Given that treatments such as psychotherapy and physical exercise offer benefits without the risk of an active drug, an antidepressant's effect may be due to the placebo response rather than the actual active medication. Not only do, antidepressant medications only slightly outperform placebos (Moncrieff et al., 1996). In clinical trials exploring the factors that contribute to patient outcomes in antidepressant clinical trials, it has been observed that spontaneous remission accounts for 23.87% of the response, 50.97% arose from the expectation of treatment benefits, and only 25.16% for the drug effect (Kirsch and Sapirstein, 1998). Moreover, there is evidence that placebos in psychiatric treatment quantifiable biological changes that may be related to disease symptoms. For instance, in a functional brain imaging study using positron emission tomography, it was found that both placebo and the antidepressant fluoxetine induced metabolic increases in the ventral striatum and orbitofrontal cortex among responders after a week of treatment. As these metabolic changes occurred before the expected 8 weeks of treatment required before clinical improvement from antidepressants, this suggests that the initial increase in metabolism may be driven by the expectation and anticipation of the therapeutic effects, rather than the pharmacological action of the antidepressant drug itself (Mayberg et al., 2002). While placebo effects are pervasive in anxiety, and mild to moderate depression (Kirsch, 2019), the efficacy of the placebo is lower in other psychiatric disorders including obsessive-compulsive disorder and schizophrenia (Bernstein & Brown, 2017). Nonetheless, there is evidence that placebo effects have a profound impact on the treatment of psychosis (Hird et al., 2023) and hallucinations through the conceptual overlap between the placebo effect and predictive coding. Predictive coding is a computational process that explains how the brain uses prior beliefs to infer sensations. Putting this in the context of hallucinations, as argued by (Corlett et al., 2019), hallucinations can occur when prior beliefs exert an inordinate influence over perceptual inferences, creating percepts with co-corresponding stimuli.

This serves as a computational account of how the brain updates beliefs about the world, operating in a manner analogous to the placebo effect, where the placebo response relies on biased expectations that influence predictions. to make an inference about a sensation. As placebo responses rely on biased expectations that influence perception, hallucinations serve as overly precise predictions.

How do placebos change the brain?

In a meta-analysis of placebo analgesia, results indicated reliable reductions in activation during painful stimulation in regions associated with pain processing such as the anterior cingulate, thalamus, and insula, as well as reductions in brain regions implicated in emotion and value, namely, the amygdala and ventral striatum (Atlas & Wager, 2014). Research on placebo analgesia using functional brain imaging studies report reduced activity in brain areas associated with pain and negative emotions including the lateral and medial prefrontal cortex (see Wager and Atlas, 2015 for a review). Researchers suggest that placebo analgesia also engages prefrontal-subcortical motivational systems including a cortical-brainstem system that involves the dorsolateral, ventromedial prefrontal cortex, nucleus accumbens, periaqueductal gray (PAG), and rostroventral medulla (Wager & Atlas, 2015).

What is unclear is whether this system is consistent for the placebo effect in other neurological conditions, though it is likely there is some overlap. For instance, the ventromedial PFC, a key region for many conceptual processes, is implicated in representing the treatment context and generating predictions. Due to its combined roles of reward processing and pain, increased activity in the ventromedial prefrontal cortex (PFC) is important for placebo effects across various conditions (Petrovic et al., 2005). Activity in the ventromedial PFC has also been implicated in reward learning in Parkinson's disease (Schmidt et al., 2014).

Discussion

This paper delved into the mechanisms of the placebo effect which relies on expectation and context in order to provide therapeutic benefits in the absence of active medication. The research shows the placebo effect on various conditions, including findings on how placebo responses modulate pain, influence dopamine release in Parkinson's disease, and overlap with cognitive processes in psychiatric conditions. Overall, the findings underscore the potential of the placebo effect as a valuable tool in clinical practice.

The findings reveal the placebo effect can be effectively used in various conditions. In pain management, placebo analgesia is a well-documented phenomenon where individuals experience pain relief after receiving a placebo, despite the lack of active treatment. Neuroimaging studies indicate that placebo analgesia involves the activation of pain networks throughout brain regions. In Parkinson's disease, placebo effects are linked to dopamine release in the striatum, mirroring the biochemical effects of active treatments. Although, while there is a beneficial effect of placebo-induced dopamine release, active drugs like apomorphine demonstrate sustained efficacy. In Alzheimer's disease, the placebo effect appears to be less pronounced. Analysis of placebo groups suggests variability in cognitive decline measures which complicates detection of effective treatments, and this shows the challenges in isolating placebo effects in conditions. In contrast, placebo responses in anxiety and depression show

significant therapeutic effects, particularly in addressing distress and negative expectations. Studies suggest that cognitive representation rather than the active medication itself, drives these outcomes. However, the efficacy of placebos diminishes in more severe psychiatric conditions, such as schizophrenia and obsessive-compulsive disorder.

These findings are crucial for understanding the potential to transform patient care and clinical trial methodologies. Leveraging placebo effects could lead to more cost-effective and personalized treatments, potentially minimizing reliance on medication. In pain management, utilizing psychological cues and conditioning could enhance analgesia while reducing side effects.

For psychiatric conditions, the placebo effect's ability to invoke cognitive representations of relief suggests that the process of seeking psychiatric help may overlap with cognitive processes involved in the placebo effect., conditions such as anxiety and depression are associated with suffering and thus any treatment that leads to a reduction in suffering can be considered an effective treatment for the disorder. This perspective opens new paths of non-drug therapies, highlighting the effectiveness of non-drug approaches like psychotherapy. Even in psychiatric conditions where suffering is not the primary symptom, placebo effects can also be leveraged. For instance, in schizophrenia, exploring how cognitive expectations can influence treatment outcomes may provide insights into enhancing therapeutic strategies.

Despite its contributions, however, placebo treatments have clear limitations. First, the effectiveness of placebo responses depends on the specific condition, context, and individual characteristics, lending to variability that complicates the generalization of findings. Furthermore, reliance on self-reported outcomes and the subjective nature of placebo responses may introduce biases. Ethical concerns also arise when testing placebo effects on humans who are sick, particularly when withholding active treatment poses risks in conditions where effective treatments are already available. In addition, blinding or lying to participants about the treatment they are receiving also poses ethical dilemmas. Future research should then investigate how exactly consistent placebo experiments should be done because then it can benefit more and more people. Also, future research should investigate some of the interplay between placebo responses and individual differences, including genetics, personality, sex, and cultural influences, to close in on the complicated variability of the placebo effect. Further studies should also research the placebo effects in emerging areas, such as chronic illnesses, and explore technological applications like virtual reality to enhance therapeutic contexts. By addressing these questions, future research can deepen our understanding of placebo effects and their potential applications in clinical practice.

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