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Placebo Effect: The Stem of Seminal Studies with Active Treatment Neurobiological Mechanisms, And Implications for Parkinson's Disease with Deep Brain Stimulation

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ABSTRACT: Despite long standing controversies about the therapeutic validity of placebo due to its administration of inert substances, placebo emerges for its efficacy to amplify the therapeutic benefits of active medical interventions through patients' psychological beliefs and expectations. Advances in neuroimaging and utilization of hormonal agonists have elucidated underlying brain mechanisms and biochemical pathways such as the endogenous opioid systems. This research synthesizes pivotal studies on placebo effect, including Beecher's 1995 analysis; whereas, Hróbjartsson and Gøtzsche's 2001 meta analysis refuted its clinical significance. In-depth interaction in the assumption of additivity between placebo and active treatment as well as deep brain stimulation in Parkinson's Disease reveals the placebo's prominence in brain reward mechanisms. Moreover, placebo mechanisms induce significant neurotransmission in the endogenous opioid systems and several brain regions including periaqueductal gray. Further inquiries are necessitated for precision in examining the role of expectation, emotions, interactions with test administrators, as well as genetic levels.

KEYWORDS: Placebo effect, Therapeutic benefits, Psychological beliefs, Neuroimaging, Brain mechanisms, Endogenous opioid systems, Parkinson's Disease, Further inquiries

INTRODUCTION

Placebo Effect, a phenomenon where patients experience therapeutic improvements following the administration of a medical treatment with no effects, is shown to be beneficial due to the patients' psychological beliefs of its effectiveness. While placebos were originally regarded as inert substances such as sugar pills or saline injections provided to patients in order to pacify them where no treatments were available (Ader et al., 1997), the placebo effect has the potential to complement and amplify the effectiveness of medical interventions which have demonstrated specific treatment efficacy (Miller et al., 2009). Furthermore, the latest innovations in neuroimaging and genetics have substantially revealed brain mechanisms behind this effect (Colagiuri et al., 2015).

THE SEMINAL STUDIES OF PLACEBO EFFECT

One of the first documented studies related to placebo was an investigative placebo-controlled blind trial experiment of animal magnetism 1784 by Benjamin Franklin along with eight other scientists to test Mesmer's claim. One of the first experiments was to trick a young woman to believe an individual in an adjacent room directing animal magnetism towards him as she responded by falling into convulsions; another experiment enabled the individual to believe that the water drunk was magnetized while it really has no effect (Herr, 2005). Therefore, it is concluded that it was indeed the power of their own minds causing them to mitigate the symptoms (Herr, 2005; Ziesche, 2022).

The Powerful Placebo 1955 by Henry K. Beecher noted that placebos are found to be effective at the significant rate of 35.2% with the range of 2.2%. from 1,082 patients with severe conditions in 15 (Beecher, 1955; Chloé Pronovost-Morgan et al., 2023; Mehta & Gupta, 2024) One of the studies discussed in the paper is the study of adrenal cortex in psychoneurotic patients with anxiety requiring hospitalization by Cleghorn, Graham, and the other scientists (Cleghorn & Graham, 1950). In their study, the symptoms were based on the criteria of adrenal cortical activity: changes in circulating neutrophils, lymphocytes, eosinophils, the ratio of uric acid to creatinine, and potassium, sodium, 17-ketosteroids, and lipid determinations (Cleghorn & Graham, 1950). From their observations, it is shown that patients with higher levels of anxiety experience greater disturbances in adrenal cortical activities than those with minimized anxiety. Therefore, these results state that placebos have the potential to affect adrenals and drug action and also the effect positively correlates with the severity of the disease.

This further led to the study of randomized double-blind comparison of placebo and active treatment in the older patients with isolated systolic hypertension in Europe 1997. This study aims to lower the cardiovascular risks in strokes as hypertension occurs approximately 15 percent of those individuals aged above 60 (Staessen et al., 1997). After the 2 year follow-up period with two phases conduction: nitrendipine and enalapril, the result of this study shows the decline in sitting systolic and diastolic blood pressure in the placebo group by 13 and 2 mm Hg respectively from 2,297 participants, stating how inert pills can induce lowering effects on blood pressure (Staessen et al., 1997; Wilhelm et al., 2016).

However, Hrobjartsson and Gotzsche, through their literature analysis of the previous clinical trials comparing placebo with no treatment, proved otherwise. In their selection of studies, studies of only randomly assigned patients were included, excluding studies in which randomization was not concealed, group assignments were predictable, and if the participants' objectives in the experiments were of monetary value and their physiological health was optimal (Hróbjartsson & Gøtzsche, 2001). The data was extracted from the report of trials in pilot studies, contracted from the author if the information was not sufficient, as well as was noted the methodology of randomization, purpose of trial, and the certain types of placebos tested in the selected researches: pharmacologic (typically was a lactose tablet), physical (a procedure performed with the machine turned off), or psychological (attention placebo: neutral conversation between the participants and the treatment provider).

Due to their criteria mentioned above, only 114 trials were analyzed. Their results were investigated with 40 clinical conditions including but not limited to hypertension, asthma, hyperglycemia, hypercholesterolemia, Raynaud's disease, carpal tunnel syndrome, and the others (Hróbjartsson & Gøtzsche, 2001). Regarding the results relative to those with no treatments, the placebo effects do not have a significant impact on the binary outcomes; however, there are profound differences in the subjective outcomes in the observed trials (Vollert et al., 2020). From the result, this signifies the essence of the effect to the subjective area or emotions in the patients along the treatment.

ASSUMPTION OF ADDITIVITY

As studies of placebo analgesia, a diminution or elimination of pain after receiving placebo-induced treatment, flourished, questions whether combination of placebo and active treatment can increase the positive effect in the context of pain relief. In double-blind randomized placebo controlled trials or RCTs, the assumption of additivity states that the true effect of the treatment is determined by calculating the effect of the active treatment and subtracting the response in the placebo group (Tallarida, 2001; Adriani Nikolakopoulou et al., 2023). The three types of outcomes from the way placebo and active treatment interact are subadditivity, an instance when the combined therapeutic effect is less than the sum of the isolated effects of active treatment and placebo and superadditivity, the case when the combined effect exceeds the sum of individualized effects of active treatment and placebo which can lead to an overestimation of active treatment's efficacy in RCTs, or even a reverse reaction to the treatment (De La Fuente-Fernández et al., 2001; Rémy Boussageon et al., 2022).

In 2018, a 2 2 factorial design which manipulates the types of treatments (to compare effects of several independent variables) and instructions was employed in order to obtain four sets of data with the distinguished samples of participants: one sample which both receives and is told with active treatment, another one which both receives and is told with placebo treatment, and the other two which either receives placebo and is told to have active treatment or receives active treatment and is told to have placebo (Enck et al., 2011; Haerling (Adamson) & Prion, 2020). In the seven studies, four were found against additivity while the three remaining supported the assumption of additivity under certain conditions. Therefore, this suggests the complexity of the interaction between placebo and active treatment which depends on several factors such as mechanisms of active analgesic and the physical or psychological processes (Coleshill et al., 2018).

PARKINSON'S DISEASE

It is proven that the placebo effect is prominent in the brain reward mechanism as the release of brain dopamine and other neurotransmitters could be a common substrate for placebo effect in different medical conditions (Shetty et al., 1999; McGee et al., 2023). Moreover, placebos impact the role of dyskinesia in Parkinson's disease (Goetz et al., 2008). In a double-blind trial of pergolide in treating Parkinson's disease, profound improvement of the placebo group was discovered 16% after 4 weeks and 23% after 24 weeks (Diamond et al., 1985). On the other hand, in the pergolide-treated group, similar numbers have been seen: 17% after 4 weeks and 30% after 24 weeks (Diamond et al., 1985). Therefore, the differences between both groups are scarce in regards to the numbers.

In examining the distinguished effect based on the perception of costs in scientific placebo whether cheap or expensive of treating Parkinson's disease, 12 patients with mean age of 62.9 years and mean disease duration of 11 years were randomized and after each intervention, the patients were tested with the criteria of the Unified Parkinson's Disease Rating Scale motor subscale, the Purdue Pegboard Test, and a tapping task (Espay et al., 2015). As a result, both types improved motor functions; however, the expensive type was shown to have greater benefit. However, cheap placebo increased brain activation in the left lateral sensorimotor cortex and other regions (Espay et al., 2015). It is concluded that perception on cost can have an effect on placebo effect. Similar results

have also been shown in measuring treatment effect with neuroimaging after reducing costs (Anderson & Cohen, 2013) and examining task performance after levodopa treatment. (LeWitt & Kim, 2015).

DEEP BRAIN STIMULATION

The examination of placebo effects in transplanting human embryonic dopamine neurons into the brains of individuals with Parkinson's disease has shown the profound impacts and strengths in the perceived outcome. In the volunteer sample of 30 individuals, 12 received the implants while 18 received sham surgery and the outcomes were based on the time period of four, eight, and twelve months after the surgery. In the result, those who believed they had received the transplants gave better scores showing the strong value of place-controlled surgical trials (McRae et al., 2004; Nikoletta Bódi et al., 2009).

In a within patient trial design in comparing on and off drug, three conditions (off drug, placebo, and on drug) were implemented on patients (Schmidt et al., 2014). Subsequently, they underwent instrumental learning tasks whilst being scanned with fMRI (Pessiglione et al., 2008). Placebo effect mimics the effect of dopamine medication as well as enhanced value signals in the vmPFC (Schmidt et al., 2014).

The bilateral deep brain stimulation employed by the microelectrode-guided placements of electrodes in the subthalamic nuclei, the patients tested were 2 male and 8 female patients with the mean age of 61 years (Mercado et al., 2006). The mean dose of L-dopa and dopamine agonists was at 690 mg in the on/off stimulator, testing with the awareness of the patients as well as the stimulation. The Unified Parkinson's Disease Rating Scale (UPDRS) is a criteria based on the objective score of motor function and patient's assessment of activities in their daily lives (Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease, 2003). When the stimulator is off, those who are advised by the medical staff that it is on scored lower UPDRS scores (clinically better) than those aware that it is off as the mean was 30.6 and 34.5 respectively (Mercado et al., 2006; Dayal et al., 2017; Park et al., 2020). Moreover, the placebo-induced expectation affects neural changes rapidly with different verbal expressions about motor performance with the evidence of rapid hand movement (Radomska et al., 2022; Mameli et al., 2023). Patients remain highly satisfied with the procedure of STN-DBS with the improvement of non-motor symptoms after 24 months follow-up despite the return of PDQ-39 to base level (Dafsari et al., 2018; Lin et al., 2019).

NEUROBIOLOGICAL MECHANISMS BEHIND PLACEBO EFFECT

The research of neurobiology was initiated in 1978 as it was found that the placebo effect can be blocked by opioid antagonist naloxone, a type of medicine used to counteract opioid overdoses (Levine et al., 1978). Therefore, this reveals the significant role of endogenous opioid systems in placebo-induced analgesia and the role of expectation and conditioning in biochemical pathways (Levine et al., 1978; Benedetti et al., 1999).

In the studies involving PET scan and dopaminergic tracers in the Dopamine D2 and D3 receptors, significant neurotransmission in the endogenous opioid systems was observed in the pre- and subgenual rACC, anterior insula, medial thalamus, orbitofrontal cortex, amygdala, as well as periaqueductal gray (Seeman et al., 2006). This is observed in the regional differences in activation between high and low placebo responders where activation is only seen in only the high placebo responders (Zubieta & Stohler, 2009).

In the neuroimaging process, neuronal circuitry was examined. Since rostral anterior cingulate cortex and brainstem are involved in regulating opioid analgesia, increased activity in contralateral thalamus, the insula bilaterally and the caudal AAC can also be found in this part by utilizing positron emission tomography (Willoch et al., 2000; Petrovic, 2002). In the study of cerebral blood flow in comparison to the opioid analgesia responses, the involvement of placebo and opioid receptors and brainstem regions has revealed that placebos have the possibility of triggering the bodily opioid mechanisms which provide the sense of pain relief and the release of neurotransmitters such as dopamine and endorphin (Ortega et al., 2022; Kerr & Gregg, 2024).

In Petrovic's trials, μ-opioid receptor agonist remifentanil on regional cerebral blood flow synchronized with the effect of placebos. Placebo alters the mechanisms in midbrain periaqueductal gray, a gray matter around cerebral aqueduct involved with pain inhibition, opioid system, and emotional aspects of pain (Wilson-Poe et al., 2021; Tinoco et al., 2023; Lubejko et al., 2024). The parallel of pharmacological conditioning in injections of placebo can induce neuroendocrine responses which disrupts the secretion of hormones such as peripheral cortisol and oxytocin (Skvortsova et al., 2019; Meeuwis et al., 2019). Moreover, the immune system plays a role as a substrate for placebo effect (Pfaar et al., 2021; Tresker, 2022). According to one study by Kamenica, exposure to pro-drug with placebo described as antihistamine resulted in a diminished size of skin wheal responses after an allergen-induced exposure. (Wager & Atlas, 2015).

FUTURE DIRECTIONS

Measuring the role of expectation in placebo effect through psychometric instruments should be suggested to calculate both positive and negative expectations rather than solely utilizing questionnaires (Lindheimer et al., 2019). Effects from discrete emotions could be further researched in cognitive and physiological responses in order to understand the precise effects of placebo (Geers et al.,

2020). Future directions necessitate specified study designs which are capable of extricating the components among different cultures and healthcare systems.

Since interaction between the patients and medical practitioners have shown to induce a distinguished magnitude of effects on the patients, thus, there should be more inquiries whether personality traits or behaviors of the test administrators can possibly increase or decrease the effects (Zion & Crum, 2018). Specifically, further investigations into hormonal levels or even genetic levels could be conducted to understand more on it.

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