

The placebo effect

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ABSTRACT

The placebo effect is a suggestion-based effect of a pharmacologically inert drug. Placebos have been in use since antiquity and its treatment power originate from the patient's positive expectations about effect of the substance. Development of the placebo effect may be the result of either previous experiences which form conditioning mechanism or manipulations which form expectation mechanism. Placebos don't produce solely beneficial results, but like other therapeutic agents they are also associated with adverse effects. The nocebo response is used to define these adverse effects and defined as a negative changes in symptoms and signs as a result of receiving inert substance or treatment. Both placebo and nocebo effects most likely have similar physiological mechanisms. The underlying neurological mechanism responsible for the development of the placebo effect is a well-studied topic. Changes in neurochemical pathways during the development of the placebo and nocebo responses have been documented by several studies. Psychoneuroimmunology is new field of scientific study and the evolution of placebo response through the psychoneuroimmunological pathways are under investigation.

Keywords: Placebo, psychoneuroimmunology, nocebo.

The term placebo has been used since 1811 to describe a medicine given more to please than to benefit the patient. The placebo effect was first described in a study by Beecher in 1955.^[1] According to Beecher, approximately 35% of patients with various conditions can be treated with placebo. Also according to the Cambridge dictionary the current definition of the placebo effect is; a substance given to someone who is told that it is a particular medicine, either to make the patient feel as if they are getting better or to evaluate the effect of the particular medicine.^[2] Furthermore, randomized clinical trials, ideally double-blinded studies with a placebo control, have become the gold standard for clinical research, because they give the researchers the chance to discriminate specific effects of an intervention from those due to variation in the natural course of disease and from placebo effects.^[3]

A placebo is an inactive substance used instead of an real drug.^[4] It may be a drug or an intervention designed to simulate therapy. Despite placebo has no pharmacologic effect, it operates through some physiological mechanisms. It has been proven that placebos activate the same biochemical pathways that are activated by active drugs.

As an example, placebo analgesia can activate endocannabinoid tract and endogenous opioid pathways.^[5] That's why placebo should not be considered as a "no-treatment" condition; in fact, it is a sham intervention to simulate therapy without administering an active substance.

The placebo response is the change in symptoms or signs as a result of receiving the placebo substance or treatment^[4] and the literal translation of placebo from Latin to English is

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“I will please...I will be pleasant”.^[6] Not only do placebos produce beneficial results, but like other therapeutic agents they are also associated with adverse effects. These adverse effects are explained by the nocebo response, which is defined as a negative change in symptoms or signs as a result of receiving the placebo substance or treatment.^[4] The Latin to English translation of the nocebo effect is “I will harm”.^[7] The nocebo responses are often disease and active treatment specific adverse effects. The most common nocebo effects are being drowsiness and headache.^[1] In a study, researchers gave placebo opioids to participants who had recently taken genuine opioids. They found that the placebo drug, despite having no active ingredients, elicited respiratory depression which is a well-documented side effect of opioids.^[8]

HOW DOES THE PLACEBO EFFECT WORK?

There are two theories which are the explanation of the placebo effect has been conventionally thought to be based on: the expectation effect (Mentalistic Theory) and the conditioning effect (Pavlovian Theory). Conditioning effect and expectation effect are likely to be related but in somehow, they are separated mechanisms.

THE EXPECTATION EFFECT

Placebo effect operates by the patient's beliefs about the drug, treatment, or doctor. When the patient expects the drug to work, cortisol levels decrease and so the patient becomes less anxious and then recategorizes the symptoms.^[9,10] For instance, a “sharp pain” might recategorized as an “uncomfortable tingling”. On the other hand, if the patient expects the drug not to work, or expects to experience side effects, the placebo may result in negative outcomes this time. As explained earlier, in this situation the substance is defined as a nocebo.^[7]

THE CONDITIONING EFFECT

The conditioning effect was firstly described by Pavlov through the salivatory responses of the dogs to the repetitive stimuli. He found that the past experience had an effect on future

response. Many studies have revealed that the similar Pavlovian effect could come into play in the mechanism of placebo effect.^[11]

In a study, people who were given an active drug that previously raised a certain hormone level actually produced a similar, but smaller, hormone response when they were given a placebo later. On the other hand, those who didn't take the real drug before had no alteration on the hormonal level or activity when they received the placebo, despite being told that they would. This separates the effect of researcher's manipulations from the effects of learned experience of having positive effect of the drug in the past. The conditioning effect is a type of learned response after personal experience.^[10]

In a study on the effect of analgesics on Alzheimer's patients, researchers found that people with Alzheimer's disease experienced less pain relief from medicines and required higher doses. They hypothesized that lack of the conditioning effect in patients with Alzheimer's due to short-time memory loss about the effect of medicines could be responsible for this outcome. This also suggests that past experiences play a role in the conditioning aspect of the placebo effect.^[12]

THE PLACEBO EFFECT AND THE BRAIN

In the neural activity of the people who under placebo analgesia, neuro-imaging studies have found measurable changes. Areas found to be mostly affected include the brain stem, nucleus accumbens, spinal cord and amygdala. Neurochemical pathways found to be most linked with placebo responses are the dopaminergic and opioid-receptor pathways. Strong placebo response increases dopamine and opioid receptor activity resulting in stimulation of the reward and motivation systems of the brain. Conversely, it have been found that dopamine and opioid receptor activity reduced by the nocebos.

Reduced activation of anxiety-related areas can be observed during placebo response in brain imaging studies.^[13] In one functional magnetic resonance imaging (fMRI) study, it was shown that placebo treatments can modulate the activity of emotion related areas.^[14] On the first day

of the experiment, before the presentation of pictures that induced unpleasantness, either the benzodiazepine, midazolam, or the benzodiazepine receptor antagonist, flumazenil were given to the subjects. As expected, midazolam reduced the perception of unpleasantness and flumazenil reversed this effect. Therefore, the expectation effect of the placebo response was adjusted on the first day of the experiment. On the second day, the researchers told the subjects that either the same anti-anxiety drug or the anxiolytic blocker as the previous day would be given to them. But this time, placebo was given instead of the active drug. A significant placebo response of reduced unpleasantness was found when the patients thought that they had been treated with the anxiolytic drug, whereas no response consisted if they thought they had received the anxiolytic blocker. In the subjects that placebo response occurred, fMRI showed change in the regional blood flow of the anterior cingulate cortex and the lateral orbito-frontal cortex, which are also the regions found to be involved also in placebo analgesia.^[15,16]

The best evidence about effect of anxiety in mechanism of placebo responses is shown in nocebo response studies. To stimulate the nocebo effect, an inert substance is administered to the patients who are manipulated by researchers with negative verbal suggestions of clinical worsening, for example, pain increase. Expectations of a negative outcome, such as increased pain, activated several regions of the brain, such as the prefrontal cortex, anterior cingulate cortex, the insula, and hippocampus subsequently resulting in the exacerbation of pain.^[17,18]

Placebo also targets the brain areas that are activated and play a crucial role in mechanism of antidepressant drugs. This operation may be responsible for the 50-75% placebo response rates in antidepressant trials.^[18]

FUTURE DIRECTIONS IN PLACEBO EFFECT: PSYCHONEUROIMMUNOLOGY

Psychoneuroimmunology is a relatively new field of scientific study which investigates the direct effect of brain activity on the immune

system. Like a dog conditioned to salivate at the sound of a bell, a mouse can also be conditioned to restrain their immune system with a specific stimulus.^[19] It is currently being studied whether expectations of improvement in health could have an impact on the individual's immunity.

Learned placebo effect operates by modulating immune functions by mutual communication between central nervous system (CNS) and peripheral immune system.^[20] Ader et al.^[21] declare the basic model which assumes that there are three important steps in the formation of a conditioned immune response. First, the unconditioned stimuli (US) (e.g. an immunomodulatory drug) must be either directly sensed by the CNS or indirectly recognized via changes in the immune response. Second, the CNS associates signals caused by the US and the sensory information provided by the conditioned stimuli (CS) (generally a taste or odor). Third, in the evocation phase, the re-exposure to the CS must activate those brain areas which recognized the CS/US association, and subsequently the efferent pathways that modulate immune response become activated.^[22-24]

Experimental evidence in animals and humans showed that humoral and cellular immune functions can be affected by behavioral conditioning processes.^[13] The potential therapeutic relevance of learned immune responses has been mostly documented in experimental models for chronic inflammatory autoimmune diseases, or organ transplantation where a learned immunosuppression decreased disease exacerbation and mortality.^[20,25-27] Cyclosporine is a commonly used immunosuppressive drug for the prevention of graft against host disease (GVHD) in organ transplant patients. It is demonstrated by the experimental evidences in rodents and humans that immune cell functions can be modulated through behavioral conditioning.^[21,28,29] Association between immunosuppressive drug cyclosporine and gustatory stimulus (CS) is a well-established conditioning paradigm in humans. Re-exposition to the CS resulted in the impaired Th1 cytokine production and decreased T cell proliferation which are the immunopharmacological effects of cyclosporine A.^[21,30]

Conclusion

The placebo effect has been known and studied for many years. The placebo effect has been shown to be beneficial in many different diseases and different situations. Sometimes placebo can make patients feel better, or in the case of nocebo effect it may result in negative outcomes. Placebo and nocebo effects probably have similar physiological mechanisms. Experiments have shown that via these physiological mechanisms the immune functions can be regulated by behavioral conditioning processes. In light of this information, further research is needed about the use of the placebo and nocebo effect in psychoneuroimmunology.

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REFERENCES

1. Beecher HK. The powerful placebo. *J Am Med Assoc* 1955;159:1602-6.
2. Cambridge Dictionary. Available at: <https://dictionary.cambridge.org/dictionary/english/placebo> [Accessed: August 01, 2019]
3. Turner JA, Deyo RA, Loeser JD, Von Korff M, Fordyce WE. The importance of placebo effects in pain treatment and research. *JAMA* 1994;271:1609-14.
4. Kwekkeboom KL. The placebo effect in symptom management. *Oncol Nurs Forum* 1997;24:1393-9.
5. Benedetti F, Amanzio M, Rosato R, Blanchard C. Nonopioid placebo analgesia is mediated by CB1 cannabinoid receptors. *Nat Med* 2011;17:1228-30.
6. Reid B. The nocebo effect: Placebo's evil twin. *Washington: Washington Post*; 2002. p. 201-3.
7. Data-Franco J, Berk M. The nocebo effect: a clinicians guide. *Aust N Z J Psychiatry* 2013;47:617-23.
8. Stewart-Williams S, Podd J. The placebo effect: dissolving the expectancy versus conditioning debate. *Psychol Bull* 2004;130:324-40.
9. Newman T. Placebos: The power of the placebo effect. Available at: <https://www.medicalnewstoday.com/articles/306437.php> [Accessed: August 02, 2019]
10. American Cancer Society. Placebo effect. Available at: <https://www.cancer.org/treatment/treatments-and-side-effects/clinical-trials/placebo-effect.html> [Accessed: August 02, 2019]
11. Haour F. Mechanisms of the placebo effect and of conditioning. *Neuroimmunomodulation* 2005;12:195-200.
12. Benedetti F, Arduino C, Costa S, Vighetti S, Tarenzi L, Rainero I, et al. Loss of expectation-related mechanisms in Alzheimer's disease makes analgesic therapies less effective. *Pain* 2006;121:133-44.
13. Benedetti F, Carlino E, Polo A. How placebos change the patient's brain. *Neuropsychopharmacology* 2011;36:339-54.
14. Benedetti F, Pollo A, Lopiano L, Lanotte M, Vighetti S, Rainero I. Conscious expectation and unconscious conditioning in analgesic, motor, and hormonal placebo/nocebo responses. *J Neurosci* 2003;23:4315-23.
15. Petrovic P, Dietrich T, Fransson P, Andersson J, Carlsson K, Ingvar M. Placebo in emotional processing-induced expectations of anxiety relief activate a generalized modulatory network. *Neuron* 2005;46:957-69.
16. Petrovic P, Kalso E, Petersson KM, Ingvar M. Placebo and opioid analgesia-- imaging a shared neuronal network. *Science* 2002;295:1737-40.
17. Wager TD, Rilling JK, Smith EE, Sokolik A, Casey KL, Davidson RJ, et al. Placebo-induced changes in FMRI in the anticipation and experience of pain. *Science* 2004;303:1162-7.
18. Colloca L, Sigauco M, Benedetti F. The role of learning in nocebo and placebo effects. *Pain* 2008;136:211-8.
19. Legg TJ, Newman T. Is the placebo effect is real? Available at: <https://www.medicalnewstoday.com/articles/306437> [Accessed: September, 2017]
20. Vits S, Schedlowski M. Learned placebo effects in the immune system. *Zeitschrift für Psychologie* 2014;222:148-53.
21. Ader R, Cohen N. Behaviorally conditioned immunosuppression and murine systemic lupus erythematosus. *Science* 1982;215:1534-6.
22. Goebel MU, Trebst AE, Steiner J, Xie YF, Exton MS, Frede S, et al. Behavioral conditioning of immunosuppression is possible in humans. *FASEB J* 2002;16:1869-73.
23. Hoenemeyer TW, Kaptchuk TJ, Mehta TS, Fontaine KR. Open-Label Placebo Treatment for Cancer-Related Fatigue: A Randomized-Controlled Clinical Trial. *Sci Rep* 2018;8:2784.
24. Vits S, Cesko E, Enck P, Hillen U, Schandendorf D, Schedlowski M. Behavioural conditioning as the mediator of placebo responses in the immune system. *Philos Trans R Soc Lond B Biol Sci* 2011;366:1799-807.
25. Klosterhalfen S, Klosterhalfen W. Conditioned cyclosporine effects but not conditioned taste aversion in immunized rats. *Behav Neurosci* 1990;104:716-24.
26. Bovbjerg DH. Conditioning, cancer, and immune regulation. *Brain Behav Immun* 2003;17:S58-61.

27. Exton MS, Schult M, Donath S, Strubel T, Nagel E, Westermann J, et al. Behavioral conditioning prolongs heart allograft survival in rats. *Transplant Proc* 1998;30:2033.
28. Goebel MU, Trebst AE, Steiner J, Xie YF, Exton MS, Frede S, et al. Behavioral conditioning of immunosuppression is possible in humans. *FASEB J* 2002;16:1869-73.
29. Albring A, Wendt L, Benson S, Witzke O, Kribben A, Engler H, et al. Placebo effects on the immune response in humans: the role of learning and expectation. *PLoS One* 2012;7:e49477.
30. Schedlowski M, Pacheco-López G. The learned immune response: Pavlov and beyond. *Brain Behav Immun* 2010;24:176-85.