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A Glimpse of Placebo and Nocebo Effects or Cain and Abel Story

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Editorial

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The placebo is the famous term in randomized placebo-controlled trials (RCT) and has an important role in any clinical setting and processes of evaluation, diagnosis, and intervention. Typically, placebo refers to the nonspecific effect of interventions, when they are beneficial and we try to maximize its effects when treating patients, but in RCTs, researchers would like to minimize the placebo effects to observe and estimate the real effect of interventions such as drugs or other kinds of treatments (Benedetti, 1996; Aslaksen & Lyby, 2015). The word "placebo" is derived from the Latin verb "placere" (pleasing) or "I shall please"; it is used to indicate sham treatments or inert substances such as sugar pills. The placebo effect is a psychological and/or physiological response that follows administration of inert substances or treatments (Flaten & Al'Absi, 2013). For example, an inactive medication administered together with information that it is an analgesic medication has been found to decrease pain and pain-related physiological reactions (Benedetti, 1996). On the other hand, the negative arm of placebo so called nocebo effect appears with unpredictable, adverse events and worsening of symptoms (Weimer, Enck, Dodd, & Colloca, 2020). The term nocebo (I shall harm) was introduced in contrast to "placebo" to discern the positive from the harmful effects of placebos, when an inert substance is given within a negative context, inducing negative expectations about the outcome. The nocebo effect is defined as increased pain or other symptoms after administration of an inactive treatment purported to increase pain or unpleasant symptoms (Vambheim & Flaten, 2017), or negative outcome following the application of an inert treatment that the recipient believes to be effective (Data-Franco & Berk, 2013).

Underpinnings of the placebo and nocebo

The underpinnings of placebo and nocebo as interesting phenomena are psychological and neurobiological. Psychological mechanisms include expectancies, different kinds of conditioning, learning models, memory, motivation, somatic focus,

reward, anxiety reduction, and meaning system (Chavarria et al., 2017; Nasiri-Dehsorkhi, Vaziri, Esmaillzadeh, & Adibi, 2023). Expectations not only play an important role in health consequences but also they are the main components of placebo and nocebo phenomena (Nasiri-Dehsorkhi, Vaziri, Esmaillzadeh, & Adibi, 2024). Because expectation facilitates the perception of a specific sensation and stimulus categories, this effect helps clarify why side effects often occur as a cluster of multiple symptoms. Patients do not always have fixed expectations from the treatment or any therapeutic situations; when a patient has negative expectations of his/her treatment consequences, it can reduce the effectiveness of the intervention or even cause side effects or adverse results. In such a situation, the term nocebo effect is used (Nasiri-Dehsorkhi et al., 2024). Actually, the placebo and nocebo responses are mediated by expectations, associative and social observational learning processes, patient's temperament and personality, societal factors, and the quality of the patient-physician interaction (Schedlowski, Enck, Rief, & Bingel, 2015). Research findings indicated that several factors were identified as main source of the nocebo effect. These include negative expectations, misattribution of symptoms, pervious learning, contextual components, social environment, verbal and non-verbal behaviors, observational learning, and the features of the treatment have also been proposed as important mechanisms. In figure 1, we can see the interactive factors that could provide placebo and nocebo responses (Petrie & Rief, 2019; Daniali & Flaten, 2019). The past three decades literature has shown advances in the understanding of neurobiological and neuropsychological mechanisms of these twin brothers, placebo and nocebo responses, in various medical conditions (Schedlowski et al., 2015).

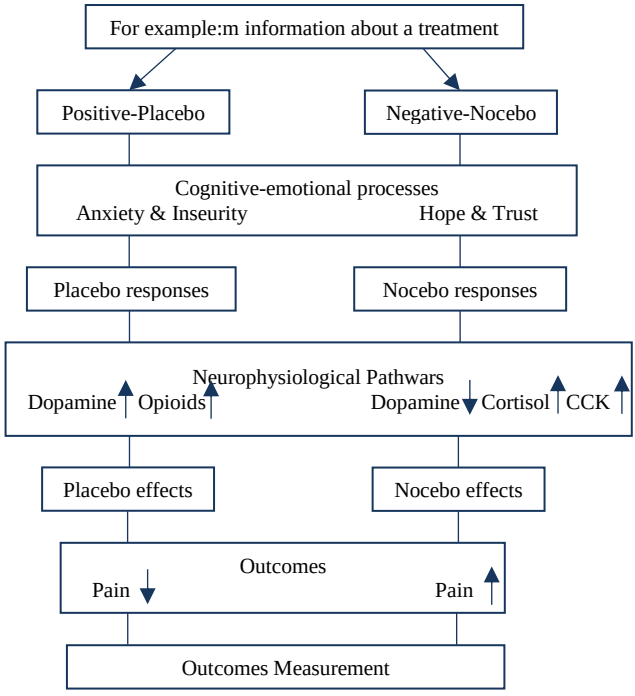

Figure 1. Descriptive map of psychological and neurobiological aspects of placebo and nocebo

For example, the frequency of the articles about placebo and nocebo effects in recent years is the best indication for this claim (Nasiri-Dehsorkhi, Vaziri, Esmaillzadeh, & Adibi-Sedeh, 2022).

Research findings have demonstrated that a number of neural networks are engaged in the placebo effect. These include the opioid, endocannabinoid, cholecystokinin (CCK), and dopamine systems. Recent functional imaging findings have shown changes in the brain related to the placebo effect. These brain areas include the anterior cingulate cortex, thalamus, posterior insula, and the cortex of somatosensory areas. These findings indicated that the placebo effect had true neurobiological mechanisms, but we do not know its triggers yet.

Findings about the neurobiology of placebo analgesia confirm that healthy brain activity is the base of placebo responses. However, people with highly functioning brains are able to develop robust placebo responses. Individuals with serious brain dysfunctions show no or reduced placebo response. Therefore, not surprisingly, placebo mechanisms are based on healthy brain connectivity, as has been confirmed by recent studies (Petrie & Rief, 2019).

Some psychological components are well known to contribute to the placebo effect. One of them is expectation theory, for example, if the expectation is high that a drug or treatment will be effective, a patient is more likely to experience a placebo effect. Besides, interpersonal interaction, specifically in clinical settings, is another important element in this regard (Lembo, 2020). On the other hand, cultural aspects also play a role in the illness representation, and apply their role through emotional and cognitive aspects (Reichardt, et al., 2018).

Crucial role of positive expectations in placebo responses could improve our understanding of the neurobiology of expectations and could represent the important relation between the clinical psychology and neurobiology of placebo mechanisms. From the neurobiological aspect, dopaminergic system and the nucleus accumbens are both significantly engaged in the processing of reward and it has led to the formulation of the placebo-reward hypothesis: Expecting a positive treatment effect followed by structures of reward processing system (De la Fuente-Fernandez, Ruth, Sossi, Schulzer, Calne, & Stoessl, 2001). In contrast to the placebo response, neurophysiological correlates of the nocebo response seem to involve more with negative expectations and anxiety pathways. For example, studies on nocebo hyperalgesia indicated hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis and CCK, a peptide hormone of the gastrointestinal (GI) system that is involved in anxiety symptoms (Petrie & Rief, 2019; Benedetti, Lanotte, Lopiano, & Colloca, 2007).

Genes perspective to the placebo and nocebo responses

Recent studies on genomics have presented a detailed examination of pharmacogenetic effects on active or inert interventions. The main question of these studies was that "why some people respond to a placebo and others do not?". Multiple genes associated with the placebo response are related to neurotransmitter pathways. One such gene is catechol-O-methyltransferase (COMT), which encodes an enzyme that metabolizes catecholamines like dopamine and epinephrine. Research has shown that polymorphisms in this gene are related to a stronger placebo response (Hall et al., 2016). Interestingly, the same gene seems to be involved in the development of nocebo responses, as well (Petrie & Rief, 2019).

Diversity of the nocebo responses

The high rates of nocebo effects are related to medical treatments and can cause significant issues in adherence and persistence with medical therapy and decrease the

quality of life for many patients, and its consequence is increasing of medical cost (Kardas, Lewek, & Matyjaszczyk, 2013). Complaint of drug side effects is the main focus of literature in nocebo studies; over time, the use of the term nocebo has widened. The term nocebo is now used to refer to the adverse effects of active treatments that cannot be attributed to the pharmacological or other active ingredients of the therapy (Barsky, Saintfort, Rogers, & Borus, 2002). Nowadays, the term nocebo has been extended to describe reported adverse effects following exposure to benign new technology, environmental agents, or stimuli that the individual believes are likely to cause symptoms or have other negative health effects (Rief, Glaesmer, Baehr, Broadbent, Brahler, & Petrie, 2012). For example, electro-sensitivity is one of those conditions, complaining of symptoms after being exposed to weak electromagnetic fields, such as Wi-Fi or cell phone signals, even though double-blind studies do not support a link between such exposure and symptoms or physiological effects (Rubin, Hillert, Nieto-Hernandez, van Rongen, & Oftedal, 2011). A popular illustration of the nocebo effect is the gluten-free diets. Many individuals now believe that they are gluten sensitive and report symptoms such as abdominal discomfort and bloating, as well as headache, lethargy, and other symptoms, following ingestion of products containing gluten. The gluten-free food manufacturing industry has grown rapidly to accommodate the popularity of this new diet, but double-blind provocation trials with either placebo or gluten have failed to support this sensitivity in individuals without celiac disease; a more likely explanation for the reported symptoms is the anticipation of intolerance and a misattribution of normal symptoms (Lionetti et al., 2017).

As mentioned in the beginning of the article, the placebo effect plays a valuable role in making any treatment more effective, while nocebo effects not only can neutralize the treatment but also impose unwanted side effects on the patient. In RCTs, the researcher seeks to control the placebo and nocebo effects with precise methods, and this actually shows the perfection of that research. By defining these two incongruous brothers, the present article aims to encourage the research interest of those interested in the field of placebo and nocebo effects to conduct more studies in this regard and to take their mentality beyond the field of therapeutic interventions. On the other hand, knowing the effects of placebo tells us that we are capable of repairing and correcting ourselves, and we could be very careful with our words, writings, and thoughts after the word "I am…". We should remember that, our negative thoughts significantly impact our health and performance through nocebo response process. Some systematic studies indicated that characteristics and nonverbal behaviors of providers like experimenters/clinicians contribute to the elicitation and modulation of pain, placebo, and nocebo effects. Therefore, our knowledge about placebo and nocebo effects says that when we believe that something affects our health positively or negatively, our mindset is a critical factor in our overall health.

Conflict of Interests

Authors have no conflict of interests.

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