The placebo effect as a personality driven phenomenon

Shalom Omondi

Abstract

The placebo and nocebo effect have been considered a curious clinical phenomenon in research. It explores how medicine and other drugs work both physically and emotionally by using a counterfeit in order to tell the effects of the drug in question. In recent years scientists have tried exploring the different concepts that make it work and are unique. But despite the successes of its mechanisms, the implications of its effects are still unclear. In past years scientists have investigated methods to personalize it.This paper goes over the influence that placebo has on different personality traits in relation to the Big Five personalities. This paper synthesizes evidence to argue that specific Big Five personality traits—notably lower neuroticism and higher agreeableness and openness—act as significant modulators of placebo responsiveness. By examining psychometric, clinical, and neuroimaging research, we posit that these inherent individual differences offer a crucial, yet underutilized, pathway for personalizing therapeutic strategies and enhancing treatment efficacy. In terms of neuroticism studies, further reveal that placebo responders exhibit activity in brain regions that are associated with cognitive control. Such findings suggest that personality traits are modulated and established in neural circuits. Clinically understanding suggests that by incorporating the psychometric view clinicians will be better equipped to enhance therapeutic responsiveness and harness placebo mechanisms in practice. Ultimately, the whole process identifies the benefits of factoring in placebos as a way to personalize and improve treatment.

Background

The placebo and nocebo effects are phenomena that emphasize the complicated interplay between personality and neuroscience, highlighting the role of psychological and physiological factors that shape a medical outcome. The placebo effect refers to positive health outcomes that are a result from an inert or an inactive treatment, while the nocebo effect refers to a negative or adverse reaction to an inert substance, stemming from negative expectations or beliefs. While these effects have been utilized in medical practice for years, researchers still have not managed to fully understand the physiological mechanisms underlying health and disease (Frisaldi et al., 2020).

Historically, placebos were used by physicians as a comfort mechanism to offer hope to patients especially when no effective treatment was around. The word placebo derived from the Latin vocabulary means “I shall please” which reflects its role in the belief of the patients in the treatment. It has since been seen as an influential tool in the medical field. Over time placebos became a valuable part in clinical trials, where it plays a critical role. It differentiates the role between the therapeutic effects of a drug and the added psychological factors that follow;In other words it shows if the improvement is due to the mind or rather just the medicine itself.

In contrast, the nocebo effect was seen as the opposite negative counterpart to the placebo effect. The nocebo as its name implies is the expectation to produce harm, even when there is treatment provided. The nocebo is generally known for causing a range of harm that is generated by biological and behavioral mechanisms. These outcomes are often triggered by a patient’s belief in the likelihood of distress, therefore making it harder to understand the results of medical tests because it can cause people in the study to experience side effects even when the real drug is not provided. Which can cause confusion as to whether there is an error in the treatment or if the side effects stem from people worrying about the drug having a negative effect on them (Colloca et al., 2011).

Over time, placebos have become significant to clinical trials, as a control treatment to help research differentiate the effects of an active treatment from the psychological influence that could affect health outcomes(Munnangi et al., 2023). The placebo effect is mainly divided into two subcategories: pure and placebo elements. The pure placebo is the most basic form, it involves passive substances such as saline injections or sugar-filled capsules that have no therapeutic effects and the second category is the placebo elements that may have a psychological effect surrounding the treatment process.The use of placebo and nocebo effects have been deemed unethical in certain clinical trials and medical practices. Some people raise ethical concerns because they argue that it is inhumane to deny patients in the control group beneficial treatments that are already available. Others raise concerns regarding the relevance of the placebo in clinical trials. Similarly so does the nocebo effect, particularly concerning the risk of harm caused by negative expectations.(Grünbaum, 1991).

Understanding the psychological process behind placebo and nocebo effects is critical to improving treatment outcomes and designing more effective clinical trials. Individuals' personality traits have become significant predictors of how people respond to treatment. In particular The Big five personality traits have been shown to influence the responses to both placebo and nocebo effects. For example, individuals in high neuroticism are more likely to experience nocebo effects due to increased anxiety and negative expectations while participants in high agreeableness may be more likely to respond to placebos positively due to their trust in professionals and treatment protocols.(Kern., et al 20).

The aim of this review is to establish the current understanding of placebo and nocebo effects especially in individual differences relation to personality traits and the influence that placebos and nocebos have on them. Additionally, the review will focus on understanding the neuroscience behind the effects, exploring how neural pathways contribute to the understanding behind psychological analytics

To further understand the effect of placebos in our brian system, the following articles were reviewed with a focus on the psychometric view. This perspective reviews the interplay between psychological factors such as expectations, beliefs and personality traits and the psychological outcomes that are associated based on the placebo interventions. In order to recognize how traits that belong to the big five can regulate the effectiveness of placebo; researchers examine outside connections that affect the results based on individual differences which can allow room to make personalized medicine, where the treatment can be used to maximize therapeutic outcomes based on a person’s psychological profile.

Psychometric view

In 2014, researchers evaluated predictors of placebo responses (PR) (Horing et al., 2014). This article’s objective was to gain more insight on the effects prediction of placebo responses. It examined more information and identified factors that predict who responds to which placebo treatments. Independent studies were reviewed to assess the priors of PRs with 20 studies evaluated, and many focused on pain as a dependent variable. Psychological factors included optimism, self-efficacy, locus of control, and goal seeking behavior, suggesting that these emotional and cognitive factors are related to determining who responds to placebo treatments. Biological factors included; sex and dopamine availability. The study examined stable traits, this considers PR to fluctuate depending on the situation, rather than it being a stable fixed trait. Situational factors and interactional factors such as personality traits interacting with situational factors.

The results found that psychological traits like optimism and self efficacy were stronger predictors of PRs than traditional personality traits, suggesting that PR is a dynamic influenced by both internal and external factors. The study addressed the evolving nature of PR over time, dependent on the internal and external factors. The study also examined the evolving nature of PR overtime influenced by disposition and situational factors, and concluded that both psychological and biological mechanics play a role in determining PR.

The second paper by Horing examined how different personality traits influence placebo and nocebo responses in healthy adults. The researchers main goal was to determine whether people's personality characteristics had an effect in determining whether or not the placebo would work and to what extent in regards to the Big five personality traits. The research was a quasi experimental design with a control and uncontrolled group. The general criteria included healthy participants that were eighteen years or older and the experiment was designed to assess their responses to both placebo and nocebo conditions. The results were as follows: Optimism was the most frequently investigated personality trait and it had a positive association with the placebo response. Extraversion and agreeableness also had a positive correlation in regards to placebo responders, moreover they found out that higher anxiety was related to an increase of the nocebo effect.(Horing et al., 2014)

Finally, a reviewed article by Kern and colleagues analyzed how personality traits influence placebo and nocebo responses in a controlled and uncontrolled experiment. The review included studies involving healthy individuals aged 18 or older. As a review, the studies varied depending on the personality trait examined. Overall, the results found that there was a higher reaction in placebo responders. Higher levels of agreeableness was associated with placebo responders. Another study presented the same result but only for an augmented communication group. Neuroticism showed that it was positively correlated with placebo responders and was also related to increased psychological placebo responders. The studies also found that conscientiousness had a negative correlation with physical activity and another study discovered that it had a negative effect on the nocebo response.(Kern, 2020)

In essence, the work of Kern and colleagues illuminates the crucial influence of psychological traits and personality structures in shaping both placebo and nocebo responses. The psychometric perspective, by focusing on these individual differences, provides a robust framework for understanding the variability often seen in placebo effectiveness. This view compellingly argues that such responses are not arbitrary or purely situational, but are significantly molded by stable personality characteristics interacting within specific therapeutic contexts. This understanding is far from academic; it has profound implications for the advancement of medicine. If personality consistently modulates how individuals experience treatment effects, then the clinical challenge and opportunity lie in translating these

psychometric insights into strategies that can optimize therapeutic outcomes and minimize adverse nocebo effects in everyday patient care and in the rigorous environment of clinical trials.

Clinical view

The interplay between personality traits and placebo/nocebo responses can be demonstrated through psychometric analysis and neuroimaging studies. The research has significantly increasing implications for clinical research and medical practice. As placebo response rates continue to rise in psychrometric and pain related disorders, understanding how individual differences shape these effects become vital to not only refine drug development but also to optimize therapeutic outcomes in real-world settings. Recent study suggests that psychological factors such as optimism, anxiety and expectations can reverently influence clinical trial outcomes and treatment efficacy. These findings present an opportunity to develop more personalized approaches to care that provide therapeutic benefits of expectancy and minimize adverse nocebo effects. This section explores how such findings can be utilized in a clinical setting and provide medical interventions.

Foundations of Placebo Effect in the Clinic

The first paper I looked at was a comprehensive review that outlines how placebo effects arise in clinical and experimental settings and combines insights from pain treatment, neurological disorders, surgery, clinical patient interactions and neurobiology. In relation to psychological personality factors traits like optimism, anxiety, absorption and suggestibility influence placebo/nocebo responses but relationships are inconsistent and context dependent. Elements like patient adherence and sense of control also contribute to outcomes possibly due to personality or mood variables.In addition elements like patient adherence and sense of control also contribute to outcomes. Physical attributes of treatment (e.g pill size and color) and symbolic factors(the brand) can alter the placebo efficacy. Clinical behaviour (warmth, enthusiasm) can strongly impact patient expectations and health outcomes as well.(Wager et al., 2015)

Placebo effects are scattered across conditions including plain Parkinson's disease, cognitive disease and surgery. These effects arise from expectation, conditioning and clinical interaction and are mediated by complex neurobiology. This review emphasizes that placebo effects reflect the complex interplay between psychology, personality and neurobiology. They are not merely artifacts of trials but genuine psychological responses.

Impact of Placebo Response Rates on Clinical Trial Outcomes

Although neurotransmitter pathways have traditionally been emphasized in understanding antidepressant and placebo responses, emerging research highlights the importance of psychological and personality-based factors in shaping clinical outcomes.

Next, a research article in regards to different levels of placebo response and clinical response based on depressive disorders. The objective of the study was to evaluate how diverse levels of placebo response antidepressant trials influence the drug response, the relative risk ratio and the number needed to treat(NNT) the depression across different levels. The study was designed as a meta analysis of 169 monotherapy and 35 adjunctive therapy in major depressive disorder (MDD) between the years January 1980 to March 2011. The statistical trend observed brain-based responsiveness. The monotherapy results showed that as placebo response increased, the efficacy of active drug (risk ratio) decreased. However both antidepressant rates improved with higher placebo baselines, making it harder to show whether the drug works better than the placebo. Similar trends were seen in the adjunctive therapy trials but the active drug response to (NNT) rose dramatically.(Papakostas, 2012)

Based on this study it can be interpreted that high placebo responses show weaker drug-placebo separation making it harder to declare the superiority statistically speaking. Even though active drug response increases with placebo, it does not grow enough to offset the rise in placebo effect. Therefore making the drug's relative benefit diminish and making NNT worse. Nevertheless it indicates that positive trial outcomes are more likely in settings where placebo response is controlled or lower. In regards to these implications Iovieno & Papakostas concluded that in clinical trials it is necessary to keep the placebo rates below 30%-40% in order to detect meaningful efficacy. In non-superiority trials with high placebo response they should be interpreted with caution because it might be seen as placebo noise rather than the drug failure.

Furthermore, the following paper looked at how placebo responses in antidepressant trials. The review proposed a model where placebo response is driven by interacting factors which includes expectancy, therapeutic settings, measurement bias and natural illness which shows that placebo responses can account for most of the observed improvement in subjects receiving medication.The model suggests that rising placebo rates can obscure true drug effects making it harder to distinguish clinical benefits from inert responses. In clinical trials expectancy and context can be harnessed to improve real world treatment outcomes but they may confound trial results.

In this research through systematic review Kern found out that optimism enhances placebo response while anxiety/neuroticism increases nocebo effects. While numerous studies, such as those by Kern, suggest optimism enhances placebo response and neuroticism increases nocebo effects, the landscape is complex. Notably, a 2023 meta-analysis by Kang et al. found no definitive association between broad personality traits and placebo magnitude,

challenging the notion of a simple 'placebo personality.' This discrepancy underscores the possibility that interactions between specific personality facets (rather than broad traits), contextual factors, and the type of intervention may be more critical than previously understood, demanding more nuanced research designs to dissect these complex relationships. The placebo response in antidepressant trials have increased over time and the rising placebo effect is making it more difficult to detect the actual efficacy of the medication in clinical trials. The study suggests prolonged factors such as longer study durations, larger sample sizes and increased participant expectations.(Kern, 2012)

The reviewed clinical trial research highlights the growing complexity of placebo responses in modern trials, especially in psychological conditions like depression. The increase of placebo response rates as shown in the Kern paper becomes a critical challenge in distinguishing drug efficacy from patient expectations. At the same time experimental findings reveal that placebo effects can be actively generated by factors that were established before the research such as verbal suggestions, prior treatments and patient clinician interactions. These outcomes suggest that placebo responsiveness is tied to stable individual differences, including personality traits. Recognizing and considering these effects is essential to improve the accuracy of clinical trials in order to develop more personalized, expectation-informed therapeutic strategies.(Kern, 2012)

Strategic Applications: Minimizing, Maximizing, and Personalizing Placebo Effects

Lastly I viewed a research paper by Enck and colleagues that explored how an improved understanding of placebo mechanisms enables three distinct applications across medicine and drug development. Minimizing placebo effects during clinical trials can be used to enhance the clarity of the drug efficacy, maximizing placebo effects can be used to improve patient outcomes and personalized placebo responses are mainly tailored to individual traits. To be able to minimize the placebo in order to notice the efficacy of the drug, the authors recommended trial design adaptations that use active placebos in order to maintain blinding, implemented run in phases to exclude high placebo responders, leveraged adaptive designs and enriched enrollment or withdrawal/run in trials in order to manage placebo effects. Finally monitor patient expectations, prior treatment history and ensure blinding integrity, while capturing natural disease progression.(Enck, 2013)

Once therapy is approved, in order to maximize clinical treatment there is a necessity to harness expectancy and conditioning to enhance real-world effectiveness. Encourage positive treatment narratives through planning patient education and structured care observations. Lastly tailor the treatment context by using visual cues and supportive information in order to activate beneficial placebo pathways. Through this approach, therapeutic outcomes are improved without increasing the risk of pharmacological load. During this process the authors suggest that

it is imperative to take into account variability based on genetics, personality traits and prior treatment experiences. By profiling these variabilities, interventions could be tailored and geared toward individuals predicted to benefit. The aim of this study is to suppress unwanted placebo treatment, amplify beneficial placebo attributes and align placebo mechanisms with individual traits essentially improving drug development accuracy and patient care efficacy.

Together the three papers revealed that placebo effects in medicine from clinical research to neurosciences merges critical insight of how personality traits play a central role in shaping placebo responses. The meta analysis paper by Iovieno & Papakostas illustrates how placebo response rates in antidepressant trials significantly affect clinical outcomes. But with relation to all these results it still begs the question why do some patients respond strongly to placebo than others? The variation suggests that the influence of personality specific psychological factors such as suggestibility, optimism or prior treatment experience impact the placebo responses.

The review by Enck et al. connects placebo to personality traits as it highlights traits like reward sensitivity, anxiety levels and coping stu;es can predict how strongly a person will respond to placebo intervention and coping styles can predict how strongly a person will respond to the placebo international and more importantly it suggests that responsiveness to placebo may be hardwired causing a stable dispositional characteristics making the medicine more personalised for the candidate rather than a confounding variable. Additionally the biologic insight implemented by Diedrich and Gotez show that the placebo effect activates core pathways that are linked to motivation, learning and expectation.

The findings emphasize that a placebo response is not by coincidence. It is formed and influenced by a person’s personality, psychological traits and neurobiological profile. Identifying these traits could enhance and improve both clinical trial design and patient care by accounting for placebo responders and by leveraging expectation to support healing. Future research may benefit from treating personality as not just a background variable but a valuable predictor of treatment responses.

Neuroimaging & Placebos

To explore how psychological expectations influence outcomes in different contexts, some researchers have turned to neuroimaging techniques for more insight. Neuroimaging allows scientists to observe the change of activity in the brain in regards to placebo and nocebo responses, which helps identify individual traits that influence brain activity . Neuroimaging has become a rapidly growing field in science because it brings insight as to how placebo affects physiology, clinical pharmacology and other fields related to clinical trials.This section explores the relevance of underlying placebo responses and their significance in clinical research.

Diedrich and Gotez review the neurobiological mechanisms that support the placebo effect across three different neurological and psychiatric conditions: Parkinson's disease , pain syndromes and depression. It highlights how placebo responses (seen in at least half the patients) are driven by complex mechanisms that can interchange depending on the condition at hand. Neuroimaging studies like these reveal tangible physiological underpinnings, like increased striatal dopamine release in response to placebos. Crucially, this dopaminergic activation, central to reward and expectation, may be differentially engaged depending on personality. For instance, individuals higher in trait optimism or agreeableness—traits linked to positive expectations and trust in treatment—might exhibit more robust activation in these reward pathways when presented with a placebo, providing a potential neural mechanism for the observed personality-placebo correlations. Electrophysiological recording, revealed changes in the subthalamic nucleus activity during placebo exposure. The results showed that in Parkinson's disease up to 50% of the people, especially the ones at a critical stage or that are undergoing invasive procedures showed noticeable improvements. From this article we can infer that expectation of benefit triggers dopaminergic reward pathways.(Diedrich et al., 2008)

Other experiments have regarded the pain syndrome placebo effect –showing that endogenous opioids are released through activation of cortical regions and that the effect can be blocked by opioid antagonists. This is known as the analgesic placebo effect. The expectation was that openly administered analgesics produce significantly stronger effects that can convert administration which underlines the significance of patient awareness and expectancy. The depression aspect partially mimics SSRI- induced brain activation patterns. Conditions governed by higher-level cortical control tend to show larger placebo effects. While those without induced regulations are less responsive. Diedrich and Goetz came to a conclusion that across conditions, conscious expectation plays a critical role. Open treatment yields stronger responses than hidden ones as well as placebos are more robust in conditions with clear cortical involvement and less with those without (Colagiuri et al., 2011).

Conclusion

Converging evidence from psychometric assessments, clinical trial intricacies, and neuroimaging illuminates how stable individual differences—particularly traits like optimism, agreeableness, and neuroticism—are not just correlates but significant predictors of the mind's capacity to shape healing in response to placebos.

Moreover expanding research to include other clinical domains could help establish whether the psychometric properties are similar across all systems. Eventually, future studies should explore how combining in trial design and clinical decision making can improve therapeutic precision and enhance patient outcomes. Placebo responsiveness is not uniformly distributed across individuals but it is shaped by psychological profiles that can be assessed and

potentially leveraged in clinical practice. This recognition underscores the importance of integrating personality assessments into therapeutic strategies, allowing for more targeted, patient care. In relation to clinical practice, rising placebo and nocebo responses present both challenge and opportunity to enhance outcomes by incorporating psychological insight into treatment planning

Future research should investigate whether interventions targeting specific personality facets (e.g., cognitive restructuring for high neuroticism, or expectation-setting for highly agreeable individuals) can predictably modulate placebo/nocebo responses in controlled trials. While different traits such as optimism, self-efficacy and anxiety have shown consistent associations with the placebo effect, further research is needed to determine where the relationships are coincidental or situational. Experimental designs could clarify how trait stability interacts with expectation over time by tracking serotonin. Moreover expanding research to include other clinical domains could help establish whether the psychometric properties are similar across all systems. Eventually, future studies should explore how combining in trial design and clinical decision making can improve therapeutic precision and enhance patient outcomes. Placebo responsiveness is not uniformly distributed across individuals but it is shaped by psychological profiles that can be assessed and potentially leveraged in clinical practice. This recognition underscores the importance of integrating personality assessments into therapeutic strategies, allowing for more targeted, patient care. In relation to clinical practice, rising placebo and nocebo responses present both challenge and opportunity to enhance outcomes by incorporating psychological insight into treatment planning

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