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DOES PERSONALITY PLAY A RELEVANT ROLE IN THE PLACEBO EFFECT?

Nenad Jakšić, Branka Aukst-Margetić & Miro Jakovljević

Department of Psychiatry, University Hospital Centre Zagreb, Croatia

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SUMMARY

Subjective factors influencing placebo response have been a focus of numerous theoretical conceptualizations and empirical research. One such factor, individual's personality, has been linked to different clinical conditions, their expressions and treatment outcomes. Thus, there is little surprise many researchers have tried to identify placebo-prone personality over the years. Because of certain methodological and conceptual issues of the earlier studies, these efforts have not been very fruitful. However, recent scientific endeavours, facilitated by improved experimental designs and neuroimaging technology, have 'reignited the old fires'. It is now suggested that studies exploring the placebo-related personality traits, such as optimism/pessimism, neuroticism, and novelty seeking, need to take into account situational variables (e.g., positive or negative expectations, patient-clinician relationship) and relevant underlying neurobiological mechanisms (e.g., endogenous opioid and dopaminergic systems). Even though many questions still remain to be answered, such as the identification of different situational variables interacting with personality traits, exploration and better understanding of placebo-related personality would facilitate the use of placebo in clinical practice and improve the methodology of clinical trials.

Key words: *placebo – personality - situation-personality interaction – optimism - endogenous opioids - dopamine*

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Introducing Placebo and Personality

Scientific interest for the placebo effect has been renewed in recent years, especially investigations of various mediating and moderating mechanisms. The two leading explanatory models refer to the phenomena of expectation and conditioning (Price et al. 2008), but there are other possible mechanisms, such as empathy and social learning, emotion and motivation, transference, 'meaning effects', spirituality and the healing ritual (Vallance 2006, Meissner et al. 2011a), as well as underlying neurobiological processes (Oken 2008, Meissner et al. 2011b). Because of the large variation in the size of the placebo response (Watson et al. 2012) and recent interest in different subjective factors influencing this phenomenon, it seems likely that some personality traits might have a moderating role in placebo responding and also be associated with the relevant neurobiological processes.

Personality is conceptualized as dimensions of individual differences in tendencies to show consistent patterns of thoughts, feelings, and actions across developmental periods and contexts (McCrae & Costa 2003). It exibits a strong genetic basis (Krueger & Johnson 2008, Svrakic & Cloninger 2010), as well as substantial physiological and neurobiological underpinnings (Zuckerman 2005, Celikel 2011, Ozura et al. 2012). Personality traits have been associated with vulnerability/ resiliency to certain somatic (Smith & MacKenzie 2006) and various psychiatric disturbances (Andersen & Bienvenu 2011, Aukst Margetic et al. 2012, Jaksic et al. 2012). More importantly, personality may be useful in tailoring treatment (Zinbarg et al. 2008), predicting adherence to therapy (Akerblad et al. 2008, Aukst Margetic et al. 2011), and overall treatment response (Quilty et al. 2008, Kampman & Poutanen 2011). Additionally, individuals with mostly negative attitudes ('pharmacophobics') and those with mostly positive attitudes ('pharmacophilics') towards pharmacotherapy exhibit differences with regard to some personality traits (Hong et al. 2010, Emilsson et al. 2011), although this is not a uniform finding (Sibitz et al. 2005). Considering this robustness and relevance of personality in different clinical and therapeutic contexts, it is little wonder the search for a specific placebo-prone personality has received considerable empirical attention.

Early Investigations of Placebo-Prone Personality

The idea that people with specific personal characteristics are more prone to placebo response seems intuitive and also easy to investigate. The earlier wave of placebo research suggested that placebo responders were individuals with certain personality characteristics: anxious, emotionally labile, suggestible, dependent on others, and church-going (Jospe 1978). However, most of these studies failed to produce strong or consistent findings (Shapiro & Morris 1978, Brody 1980, Lasagna 1986, Turner et al. 1994, Harrington 1999, Bootzin & Caspi 2002, Moerman 2002). For example, the association between placebo effects and various individual differences, such as submissiveness, sugestibility, introversion, extraversion, sociability, and intelligence, have often been found to be unreliable (Vallance 2006). As Brody (1980) has stated, 'in more

cases than not, an individual who responds to placebo in one set of circumstances will fail to respond in other circumstances'. This notion is also backed-up by studies showing that the elimination of 'placebo reactors' before the start of antidepressant trials does not result in the reduction of placebo response rate or increase of drug-placebo difference (Lee et al. 2004). Thus, most researchers have long claimed that there is no such thing as a placebo-responding personality, that is, placebo response cannot be predicted from dispositional variables.

Reconsidering the Role of Personality

However, several recent research endeavours have questioned those long standing convictions (Geers et al. 2005, 2007, Kelley et al. 2009, Schweinhardt et al. 2009, Owens & Menard 2011). In addition to common methodological problems, such as small sample sizes, the use of healthy volunteers rather than patients, and use of unreliable and invalid self-report personality scales (Vallance 2006, Geers et al. 2007), earlier placebo studies were not adequately prepared to examine individual differences in placebo responding. The most important flaw was the lack of a no-placebo control condition by which to assess the placebo effect, so the symptom reduction observed in placebo groups could be also explained by spontaneous remission or statistical regression artifact (Keinle & Keine 1997, Caspi & Bootzin 2002, Geers et al. 2005, Price et al. 2008). Furthermore, majority of such earlier studies included participants who were told that they will receive either the active or placebo treatment (a conditional expectation). On the other hand, studies that aim to examine the placebo effect itself, use participants who are usually not aware of the placebo group (a deceptive-placebo expectation). Consequently, participants in a conditional expectation group will be less prone to generating placebo responses (Vase et al. 2002, Geers et al. 2005), which reduces chances of identifying relevant personality variables.

Two major conceptual issues have also plagued the early placebo-reactor studies. First, it seems that only some specific personality traits, such as those that influence person's expectations regarding treatment and those with a relevant neurobiological basis, will be associated with placebo effects. Two such personality traits that have been promoted by researchers are optimism/pessimism (Geers et al. 2005, 2007, Hyland et al. 2007, Morton et al. 2009) and traits with placebo-related neurobiological underpinnings (Schweinhardt et al. 2009, Pecina et al. 2012). Second, the nature of the link between personality and placebo responding is currently being revisited. Some believe that this association is more complex than previously thought; both the strength and direction of this relation may change depending on various situational conditions. This would be in line with the social-cognitive perspective on personality where dispositional variables and situational factors interact to produce different reactions (Mischel 2004, Mischel & Shoda 2008, Wagerman & Funder 2009). Indeed, the social-cognitive perspective is intended to improve upon the more popular trait personality approach for behavioral prediction (e.g., placebo response), because it provides a way to take situational factors, as uniquely processed by the individual, into account.

The Interaction between Personality and Situation in Placebo Responding

The currently most popular such model emphasizes that the search for a placebo personality factor must be combined with the measurement of situational expectancy. Expectancy is widely considered the central mechanism of placebo phenomena (Price et al. 2008, Tracey 2010), with variability in expectations influencing the variability of the response (Vase et al. 2005, Flaten et al. 2006). The most promising personality trait, interacting with the mechanism of expectancy, is optimism or pessimism, defined as a generalized and relatively stable expectancy for positive or negative future outcomes (Solberg Nes & Segerstrom 2006). A considerable amount of research indicates that optimism is related to the flexible use of adaptive mental and behavioral coping strategies when faced with stressful life situations (Solberg Nes & Segerstrom 2006). More importantly, optimists tend to exhibit attentional bias for positive information (Isaacowitz 2005) and are more likely that pessimists to cognitively elaborate on, and be persuaded by, a positively framed message (Geers et al. 2003). Therefore, optimism/pessimism might serve as a moderator of placebo responding, by influencing the strength and/or the direction of the relation between expectancy and specific placebo effects. Geers and colleagues were the first to test this proposed interaction (Geers et al. 2005). This study included both optimists and pessimists who were randomly allocated to one of three experimental conditions. In the deceptive expectation group, participants were given a placebo treatment that was said to make them feel unpleasant symptoms. In the conditional expectation group participants were informed that they would receive either a treatment that produced unpleasant symptoms or a placebo treatment. A no-placebo control group was also present. In line with the initial interactionist hypothesis, pessimists were more likely than optimists to follow a negative placebo (nocebo) expectation when given a deceptive expectation but not when given a conditional expectation. In a similar study, participants were given an expectation for positive placebo symptoms – improved sleep quality (Geers et al. 2007). Results showed that optimistic individuals exhibited more benefits from placebo sleep therapy than pessimistic individuals in the placebo-expectation condition, but not in the other two conditions, confirming that dispositional optimism/pessimism and situational factors (such as the valence of the anticipated symptoms) interact to determine the effectiveness of a

placebo/nocebo. These findings are further supported by a study that demonstrated a link between trait optimism and expectancies of positive well-being after the placebo treatment (Hyland et al. 2007), suggesting that optimism will be associated with placebo outcomes in contexts where positive expectancy is the relevant placebo mechanism.

Another example of the situation-personality interaction has been demonstrated for the personality trait of Extraversion, as well as Agreeableness to a lesser extent (Kelley et al. 2009). Extraversion is closely aligned with the temperament of positive emotionality/affect, referring to people who are described as sociable, talkative, energetic and assertive, while agreeableness manifests itself in individual characteristics that are perceived as kind, sympathetic, and cooperative (John & Srivastava 1999). Kelley et al. (2009) examined the relationships between personality of patients with irritable bowel syndrome and response to placebo acupuncture, in different therapeutic settings: warm emphatic interaction, neutral interaction or waitlist control. Several personality dimensions were signifycantly associated with placebo response, but extraversion was the only independent predictor, and this was true for the warm emphatic therapeutic setting. The authors suggested that extraverted and agreeable patients responded in a better way to the efforts of emphatic clinicians, thus further facilitating the warm therapeutic relationship. At the psychological level, this caring interaction could have reduced anxiety and increased positive expectancies. Conversely, when placebo effects are a consequence of medication with a minimal or neutral patient-clinician interaction, then these personality traits will not have such a relevant moderating role.

Placebo and Personality from a Neurobiological Perspective

Endogeous opioid system and dopamine system play an important role in placebo analgesia (Oken 2008). Regulation of the opioid system is controlled partly by inputs from the dopamine system, while D2 activation can also induce analgesia without activating the opioid system. The release of the endogenous opioids (Zubieta et al. 2005) and dopamine (Scott et al. 2008) during placebo analgesia has been shown to occur in several brain regions, including the ventral striatum, which is part of the mesolimbic reward system. Based on the reward theory, dopamine is critical in associating environmental stimuli to the anticipation of a reward (Oken 2008). Indeed, it has been shown that dopamine in the ventral striatum is not only released during the actual experience of placebo analgesia, but also during the anticipation of placebo-induced pain relief (Scott et al. 2007). This is in line with the notion that placebo represents a form of reward responding based on positive expectation of clinical benefit (de la Fuente-Fernandez et al. 2001). Additionally, certain personality traits linked to dopaminergic neurotransmission are associated with reward sensitivity (Yacubian et al. 2007).

Schweinhardt et al. (2009) were the first to examine the role of dopamine-related personality traits. For example, Novelty Seeking represents the individual‘s tendency to exploratory activity in response to novelty, impulsive decision making, and extravagant approach to cues of reward (Cloninger et al. 1993). This trait has been previously linked to variations in dopaminergic activity (Laine et al. 2001, Suhara et al. 2001). Schweinhardt et al. (2009) showed that dopamine-related traits accounted for 30% of the variance in the placebo analgesic response. In addition, these traits were related to brain gray matter, in particular in the ventral striatum. It was suggested that dopamine contributes to opioid-mediated analgesia by increasing motivation and expectations of clinical benefit. As the authors have stated, 'ventral striatum anatomy and function might be considered endophenotypes of dopamine-related personality traits that indicate susceptibility to placebo analgesia'.

Another recent study (Pecina et al. 2012) showed that several personality traits predicted up to 25% of placebo analgesic responses and 27% of the Nucleus accumbens (NAc) m-opioid neurotransmission. Two traits from the Big Five Model of personality (Costa & McCrae 2003), namely Agreeableness and Neuroticism, were found to be relevant. Agreeableness serves as a facilitator of good therapeutic relationship and strong engagement in treatment efforts (Quilty et al. 2008), making these individuals potentially reliable placebo responders (Mackenbach 2005). Indeed, it was previously mentioned that agreeableness facilitates placebo acupuncture (Kelley et al. 2009). There are also suggestions that empathic responses (typical of agreeable individuals), at least those related to the observed pain (Danziger et al. 2009), and placebo analgesia share some common neurobiological mechanisms (Pecina et al. 2012). Neuroticism is widely defined as the tendency to experience negative affect, especially when threatened, frustrated, or facing loss. Individuals who score high on neuroticism are more likely than the average to experience such feelings as anxiety, anger, envy, guilt, and depressed mood (John & Srivastava 1999). Opposite to agreeableness, neuroticism was a negative predictor of placebo responding in this study, with its facet Angry Hostility exhibiting the strongest relation. This is in accordance with findings linking neuroticism and similar personality contructs (e.g., Harm Avoidance) to pain-related intensity and anxiety (Conrad et al. 2007, Coen et al. 2011, Knaster et al. 2012), as well as to the dopaminergic system (Lee et al. 2005, Barbato et al. 2012). Moreover, another recent study has linked harm avoidance with lower m-opioid drive in several brain regions that modulate negative emotions (Tuominen et al. 2012). Similarly, anger has been repeatedly associated with greater pain intensity and lower activity of the enodgenous opioid system (Bruehl et al. 2009, 2011, Burns et al. 2009). In this

study, angry hostility trait was negatively associated with the capacity of a placebo to activate m-opioid receptor mediated neurotransmission within the periaqueductal grey, anterior and posterior insula, orbitofrontal cortex, dorsal anterior cyngulate cortex, Nca, and amygdala (Pecina et al. 2012). Finally, Ego-Resiliency was another positive predictor of placebo response in this study. Individuals higher in this personality trait are better able to recover from negative emotional experiences and flexibly adapt to fluctuating demands of stressful experiences (Block 2002, Tugade & Fredrickson 2004). Resilience has been related to lower levels of ventral tegmental area dopamine neuron excitability (Krishnan et al. 2007) and enhanced brain reward functions (Vythilingam et al. 2009). The ability to activate endogenous m-opioid neurotransmission during a sustained painful stressor has been linked with decreased tonic synaptic dopamine (Zubieta et al. 2003), suggesting a way in which stress resiliency can lead to better placebo effectiveness.

Open Questions and Potential Practical Implications

Despite recent efforts to elucidate the role of personality in placebo responding, some questions still remain unanswered, in part providing suggestions for future research. First, which situational variables interact with personality to produce placebo or nocebo effects? It was demonstrated that optimists only manifest a placebo effect in the presence of positive expectations, which usually vary from one situation to another, but would other situational variables (e.g., treatment cost, form of medication, clinician's personality) also play a relevant role? Second, although several personality traits have been directly associated with placebo effects and its neurobiological mechanisms (endogenous opioid and dopamine systems), there is only few such studies and additional traits and biological mechanisms might be significant. For example, serotonin-related traits such as neuroticism (Canli 2008) and harm avoidance (Celikel 2011) might support the idea of some other nonopioid placebo mechanisms, such as the role of serotonin in placebo antidepressant (Price et al. 2008), anxiolytic (Furmark et al. 2008), and analgesic (Watson et al. 2012) responses. Also, the relevance of optimism in situation-personality interactionist studies could partially be explained by its dopaminergic underpinnings (Sharot et al. 2012). Given the complexity and heterogeneity of neurobiology of personality (Depue & Fu 2011), these studies migh also help shed some new light on different genes, neurochemicals and brain regions involved in the placebo phenomenon. Third, suggestibility has been perhaps the most popular personality characteristic proposed by early placebo researchers (Jospe 1978, Shapiro & Morris 1978). Some studies have demonstrated a contribution of suggestibility to placebo analgesia (De Pascalis et al. 2002), but others have not (van Laarhoven et al. 2011). As with most other traits, contradictory findings have been ascribed to the lack of consistent situational placebo variables. This is in line with some of the research focusing on a very related construct, hypnotizability, indicating that hypnotic suggestibility is not as trait-like and immutable as previously thought (Fassler et al. 2008). Future studies might want to combine self-report measures of trait suggestibility with different placebo contexts, as has been done with, for example, optimism/pessimism. Fourth, more prudent, perhaps, than individual studies that link one personality trait to placebo responding and its neurobiological mechanisms are multivariate studies of the links between multiple traits and multiple aspects of placebo. This would help clarify a common issue in personality research, whether certain traits are uniquely related to criterion variables or if the significant association can be explained by the trait's overlap with other related constructs. For example, several studies have indicated the independent role of trait optimism in predicting placebo effects (Geers et al. 2005, 2010, Morton et al. 2009), whereas others have failed to confirm this (Pecina et al. 2012). Fifth, future studies need to investigate the role of specific personality traits in various clinical conditions and populations, not only placebo analgesia, which would help us better understand the homogeneity of the placebo phenomenon. One could reason that traits strongly related to pain anxiety, such as harm avoidance (Knaster et al. 2012), might be a less significant predictor/moderator of, for example, placebo-induced motor improvement in Parkinson's disease. Sixth, we have already mentioned the positive association between sensation seeking personality traits and placebo response (Schweinhardt et al. 2009), but these same traits have also been implicated in poor psychiatric medication adherence (Liraud & Verdoux 2001, Akerblad et al. 2008, Aukst Margetic et al. 2011). This further complicates the search for reliable placebo responders, as some of them might not find it easy to adhere to proposed medication regimens, although there is also convergence between placebo response and treatment adherence with regard to some other personality traits (Axelsson et al. 2011, Emilsson et al. 2011). Additionally, negative ('pharmacophobic') attitudes towards standard pharmacological treatment, such as those regarding its 'unnaturalness' and adverse consequences, have been linked with high neuroticism (Emilsson et al. 2011) and low extraversion (Hong et al. 2010, Emilsson et al. 2011). It is interesting to note that these traits, as previously described, are also associated with low placebo response, suggesting that overall negative attitudes towards medication might have a moderating influence on the placebo effect. Future studies need to examine these potential relations, which could promote the idea of prescribing placebo interventions without deception in daily clinical practice (Colloca & Miller 2011), at least to 'pharmacophobic' patients.

Finally, investigation of the role of personality in placebo has some practical implications. Identifying relevant personality traits might help reduce response variability in clinical trials. More specifically, this would allow for the allocation of the same number of potential responders and non-responders in both the treatment and placebo group. Being aware of potential placebo responders in randomised control trials would permit researchers to differentiate between therapeutic and placebo responses in the treatment groups. Also, being able to assess relevant personality traits and related situational factors would help clinicians identify patients who have a good chance of responding to the placebo aspect of a therapeutic intervention.

Conclusions

There has long been an interest in subjective factors influencing placebo response. One such factor, individual's personality, has been linked to different clinical conditions and treatment outcomes, so there is little surprise researchers have tried to identify placebo-prone personality over the years. Due to methodological and conceptual issues of the early studies, these efforts have not been too fruitful. However, recent endeavours, facilitated by improved experimental designs and neuroimaging technology, have 'reignited the old fires'. It is now suggested that studies exploring the placebo-related personality traits, such as optimism/pessimism, neuroticism, and novelty seeking, need to take into account situational variables (e.g., positive or negative expectations, patient-clinician relationship) and relevant neurobiological mechanisms (e.g., endogenous opioid and dopaminergic systems). Even though many questions still remain to be answered, exploration and better understanding of placebo-related personality would facilitate the use of placebo in clinical practice and improve the methodology of clinical trials.

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Correspondence:

Nenad Jakšić, MP
Department of Psychiatry, University Hospital Center Zagreb
Kišpatićeva 12, 10 000 Zagreb, Croatia
E-mail: nenad_jaksic@yahoo.com