

Hypnobo: Perspectives on Hypnosis and Placebo

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Abstract

Hypnosis and placebo share in phenomenology. While hypnosis-like phenomena have a documented history going back thousands of years, accounts of placebo effects span several centuries. With the rise of biological psychiatry and the “pharmacological revolution,” drug trials have taken a central place in clinical research. These clinical trials increasingly incorporate placebo-controlled conditions as part of their paradigms and may even involve an element of deception. In contrast, the therapeutic effects of hypnosis do not require deception. As researchers begin to identify genetic and neural correlates of hypnotizability, these findings may further elucidate placebo phenomena. Whereas identifying highly hypnotizable individuals may be of limited interest, identifying good placebo responders may revolutionize both basic research and clinical science, offer insights into transcultural psychiatry and elucidate individual differences.

Keywords: Hypnosis, placebo, expectation, clinical trials.

Placebo: Effects and responses

Hypnosis can be likened to a form of placebo (Kirsch, 1994). Whether inert pills or another form of sham treatment, placebo effects have a documented history going back several centuries (Moerman, 2002; Spiro, 1986). Only in the 1950s, however, did the medical establishment recognize that placebo treatments instigate important therapeutic changes (White, Tursky, & Schwartz, 1985). The use of placebo-controlled research, be it drugs and even some surgical procedures,

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often involves deception (Guess, 2002). Whereas hypnotic suggestions can produce therapeutic effects, they do not require deception in order to be effective. Thus, hypnosis can be construed as a nondeceptive placebo manipulation (Kirsch, 1994; Kirsch, 1999).

Placebo is a potent intervention; in ascending phylogeny, a larger role of cognition enhances the placebo effect (Kirsch, 2004). For example, studies of placebo in humans have triggered passionate dispute among pharmacologists, psychologists and psychiatrists when a meta-analysis of the results of 19 double-blind studies on psychiatric drugs controversially concluded that 75% of the effects supposedly caused by anti-depressant medications are in fact due to the placebo effect (Kirsch & Sapirstein, 1998). Although amply critiqued for its statistical approach and for analyzing studies that are very heterogeneous in subject selection criteria and the treatments employed (Klein, 1998), these placebo findings were supported by other studies (Greenberg, Bornstein, Greenberg, & Fisher, 1992; Greenberg, Bornstein, Zborowski, Fisher, & Greenberg, 1994; Greenberg & Fisher, 1989; Greenberg & Fisher, 1997) as well as by more recent reports showing even higher placebo effects (Kirsch, Moore, Scoboria, & Nicholls, 2002; Wagner & Khanna, 1986).

Pharmaceutical companies are well familiar with “the curse of the placebo effect” (Enserink, 1999). A chronic problem for psychopharmacology, the placebo effect plagues many drug trials, spoiling some and driving up the cost of others, as clinicians must increase their subject sample size to obtain statistically significant data. Regarded by drug developers as an occupational hazard that masks the effects of potentially useful compounds, some psychiatrists and clinical psychologists marvel at the power of the placebo effect, viewing it not as a problem but as a source of insight into mental health. Yet others challenge the scientific basis of much of the multi-billion dollar market for certain drugs arguing that many compounds, even those with good scientific pedigrees, may be little more than sophisticated placebos themselves (Kirsch, Moore, Scoboria, & Nicholls, 2002; Kirsch & Sapirstein, 1998; Raz, 2006). Either way, mainstream scientists agree that the topic of placebo has been neglected and that both academic and industry researchers have paid it too little attention (Enserink, 1999).

Typically, double-blind studies do not trick patients. Real drugs, unlike placebos, usually have real side effects (e.g., nausea and dizziness) and studies have shown that based on the presence of side effects most subjects can correctly identify whether they are receiving an active drug or placebo. This caveat in turn can yield greater results in the active ingredient group, not due to the substance itself, but because of the patient’s belief in its efficacy. Conversely, individuals in the placebo group may sense that they are not really receiving treatment and elicit diminished results. Ironically, therefore, whereas pharmaceutical companies try to market drugs as having few side effects, at least in the context of most drug trials, the more side effects the better the drug performs (Greenberg, Bornstein, Zborowski, Fisher, & Greenberg, 1994).

Since more placebos have been administered to research subjects than any single experimental drug, one might expect sufficient data regarding the effects of placebo. Unfortunately, that is not the case and there is a dearth of information regarding placebo effects. Moreover, some researchers do not seem to appreciate the difference between a placebo response and a placebo effect (Fisher, Lipman, Uhlenhuth, Rickels, & Park, 1965). The placebo response is the change that occurs following administration of a placebo. However, change might also occur without administration of a placebo and may be due to spontaneous remission, regression toward the mean, or other such factors. The placebo effect is the difference between the placebo response and the changes that occur without

the administration of a placebo (Kirsch, 1985; Kirsch, 1997).

When a strong psychological component is involved (e.g., pain or depression), placebo response rates are often high, making it more difficult to prove a drug's efficacy. In trials of antidepressants, about 65% of patients on a new drug commonly get better while 35% of the patients in the placebo group typically also improve. Frequently, the differences between the two groups are so small as not to be statistically significant. Poor patient selection is often the underlying factor. As a case in point, when companies started testing drugs for obsessive-compulsive disorders back in the mid-1980s, the placebo response rate was almost zero. A cumulative increase since that time created a new situation whereby some trials now fail because of a heightened rate of the placebo response. One possible cause is that as more and more studies are performed, competition for patients increases and clinicians loosen criteria, admitting people who are more likely to respond to a placebo. Because a high placebo response rate can make a drug seem less effective, the FDA now recommends that drug companies add a third "arm" to every trial – a group of patients that gets a drug whose effectiveness has been demonstrated in previous trials. If the trial does not prove the new drug's effectiveness, but also fails to find a difference between the placebo and the old drug, at least it counts as a "failed trial," rather than striking out on a drug that does not work.¹ In the context of this creative accounting of the regulatory review, a failed trial – unlike a negative outcome – is not scored against a drug. Thus, identifying good placebo responders (GPRs) is not only worthwhile in the context of research into the individual differences of attention and hypnotizability, but may provide information of great lucrative value for the pharmaceutical industry. For example, pharmaceutical giants may aspire to eliminate GPRs from their drug trials to facilitate heightened drug effects.

Substantive ethical considerations loom when scientists can potentially identify GPRs (e.g., within a pool of prospective subjects) and can thereby ensure the selection of a patient population that will best reflect the efficacy (or lack thereof) of a drug while minimizing (or maximizing) the placebo component. However, since hypnosis is a nondeceptive expectancy manipulation, and since prediction, anticipation, expectation, and suggestion tend to improve the placebo response, it may be reasonable to expect at least some positive correlation between highly hypnotizable individuals and GPRs. In highly hypnotizable persons, hypnotic procedures generate changes in the way these individuals experience themselves and the environment. However, the population that responds to suggestion and that which responds to hypnosis may not be disjoint sets (Barabasz, et al., 1999; Raz, Kirsch, Pollard, & Nitkin-Kaner, 2006). More specifically, placebo effects, just like hypnotic ones, relate to responses that are experienced as occurring automatically or involuntarily (Kirsch & Lynn, 1997; Lynn, 1997) and thus may converge onto a common substrate of human behavior. Indeed, the characteristics of highly hypnotizable individuals may well overlap with those of typical GPRs. Therefore, given evidence that the presence of a specific COMT polymorphism correlates with hypnotizability (Raz, 2005), it is likely that similar associations may tap at least some form of GPRs.

¹ The only standard for determining drug efficacy for "quality-of-life illnesses" is a placebo-controlled trial. A comparator (i.e., a "horse-race," or "drug A versus drug B") trial, not to be confused with placebo-controlled trial, typically boosts the drug effect. This is partly because when people know that they are being treated with either a more or less potent medicine, drug response tends to be more vigorous than when they know that they may be on either an actual drug or a placebo. Also, scientific experiments rarely control for variables known to influence drug response (e.g., expectation, suggestion, motivation, site location, and trial length) (Raz, 2006).

Previously, in order to screen for GPRs, most trials testing the effectiveness of psychotropic drugs began with a placebo washout phase. Hypothetically, this technique rids studies of placebo responders before randomization of subjects into drug and placebo groups. Whereas in theory this process lowers the level of response to placebo in the study and magnifies the superiority of the response to medication, analysis of 10 years of research literature demonstrates that, at least in antidepressant studies, the washout technique does not do what it set out to do. In other words, within placebo or drug groups neither measures of depression nor dropouts were affected by including a preliminary placebo washout in the design (Greenberg, Fisher, & Riter, 1995). In this regard, the prospect of identifying potential GPRs may revolutionize the field for both researchers and clinicians, not to mention industry. The science of hypnotizability may be key to this approach.

Placebo and Hypnotizability

Expectation plays a role in placebo phenomena and most researchers acknowledge the tangible effects of expectation in hypnosis. However, whether expectation is a critical determinant (Kirsch & Wickless, 1989; Kirsch, Wickless, & Moffitt, 1999) or yields a more nuanced influence on hypnotic effects (Benham, Bowers, Nash, & Muenchen, 1998) is a matter of continuing discussion (Raz, 2007). Although the placebo response has been traditionally considered a manifestation of suggestibility (Honigfeld, 1964; Shapiro, 1964a; Shapiro, 1964b), general consensus regarding the relationship between hypnotizability and GPRs proposes that this correlation, if it exists, is modest at best (Baker & Kirsch, 1993; Barber, 1960; Evans, 1967; Kirsch, 1997; McGlashan, Evans, & Orne, 1969; Silber, 1967; Spanos, Perlini, & Robertson, 1989; Spanos, Stenstrom, & Johnston, 1988; Van Dyck & Hoogduin, 1990). “A recent unpublished study reports that, at least in the context of experimental pain, placebo response can be unstable. These findings go counter to the idea of reliable personality predictors of the placebo effect and show that while context-specific trait predictions can occur, personality predictors will likely be inconsistent across contexts (Whalley, Hyland, & Kirsch, 2007).” Nonetheless, the effectiveness of placebo has long been known to depend upon multiple situational and motivational factors (Honigfeld, 1964; Shapiro, 1964b). As a case in point, early studies have identified placebo to be more effective in a clinical setting than in an experimental context (Beecher, 1959). Furthermore, as in the case of taxonomies for attention (Raz & Buhle, 2006), multiple placebo typologies abound where “hypnotizability” and “expectation” seem to subserve only some of its underlying phenomenology (Kirsch, 2004).

One early study reported that hypnotic analgesia and placebo response to experimental pain are discernable (McGlashan, Evans, & Orne, 1969). Whereas subsequent studies extended this difference, the main direction remained focused on a comparison of hypnotic analgesia to placebo in the specific context of pain. Pain, however, may not be the best domain to explore hypnosis as placebo – psychopathology, for example, may be far superior (Raz, 2006) – and the effect of suggestion, hypnotic and nonhypnotic, has been a major force in extending the notion of placebo to such parameters as anticipation and expectation (Spanos, Perlini, & Robertson, 1989). [Compare with recent independent and multidisciplinary accounts on this topic (Green, 2006; Price, 2006; Price, Fillingim, & Robinson, 2006; Sharav & Tal, 2006; Sharav & Tal, 2007)]. In this regard, hypnotizability may be of

²“Positive” or “negative” depends on context: when taking diphenhydramine as a sleeping agent and experiencing dry mouth and nose, those are side effects; when taking it as a decongestant, getting sleepy is the side effect (Moerman, 2002).

placebo value by generating positive expectancies (Van Dyck & Hoogduin, 1990).² Brain imaging data have recently illuminated at least some neural substrates related to such processes both within (Kosslyn, Thompson, Costantini-Ferrando, Alpert, & Spiegel, 2000) and outside of hypnosis (Wager, et al., 2004).

Consistent with differential changes following administration of a veridical antidepressant, neuroimaging of a placebo response identified regional metabolic increases involving the prefrontal, anterior cingulate cortex (ACC), premotor, parietal, posterior insula, and posterior cingulate, and metabolic decreases involving the subgenual cingulate, parahippocampus, and thalamus (Mayberg, et al., 2002). Expectation has been shown to influence brain function, not only in the modulation of acute and chronic pain, but also in other disorders involving both certain and uncertain expectations (Ploghaus, Becerra, Borras, & Borsook, 2003). Specifically, placebo analgesia induced a decrease in brain activity in pain-sensitive brain regions, including the thalamus, insula, and ACC, and associated with an activity increase during anticipation of pain in the prefrontal cortex, providing evidence that placebo alters the experience of pain (Price & Barrell, 2000; Wager, et al., 2004). Thus, regardless of the formal relationship between hypnotizability and GPRs, it may be helpful to apply hypnosis for its placebo value at least as a method of generating positive anticipations (Raz, 2004b).

Conclusion

“Hypnotizability alone is unlikely to predict generic GPR (Whalley et al., 2007). However, as researchers begin to unravel and merge onto the functional neuroanatomy of placebo (Mayberg, et al., 2002; Wager, et al., 2004), at least three avenues can further illuminate the substrates of placebo response. One is an experimental design informing all participants that half of them will be on placebo and the other half will get the active drug while in reality each half is subdivided into a placebo and a test group. Although entrenched in deceit, this methodology makes it possible to find out what a drug does when people think that they are not getting it. Two other variations can improve upon existing placebo paradigms: to create a situation whereby subjects report what group they think that they are in, and to compare drugs with “active placebos” – agents that mimic only the active drug’s side effects – instead of inert placebos. However, a clever trial design can at best reduce the placebo response, which may always remain an integral part of the effectiveness of most, if not all, drugs.

Ethical considerations aside, research into hypnotizability may further illuminate aspects of placebo phenomenology. Previous studies have established that attention is a strong regulator of cognition, emotion, thought and action (Raz, 2004a), and that attention and hypnosis overlap (Raz, 2004b). Furthermore, recent studies report that the genetics of attention informs the genetics of hypnosis (Raz, 2005; Raz & Buhle, 2006). It is easy to appreciate the relative merits of identifying individuals who may favorably respond to placebo interventions. My colleagues and I hope to provide converging data before long, drawing on neuroimaging, behavioral, and genetic assays to elucidate the characteristics of and interaction between hypnotizability and placebo response in contexts other than pain.

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