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Placebo Response Correlates With Hypnotic Suggestibility

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Placebo response shares phenomenology and likely overlaps with substrates of cognition and personality. However, inconsistent findings abound regarding the potential link between suggestibility and responding to placebos. Here we directly probe whether suggestibility of the hypnotic type influences placebo response. Fifty healthy undergraduates underwent a standard measure of hypnotic suggestibility—the Harvard Group Scale of Hypnotic Susceptibility. These participants later ingested a placebo capsule in one of two similar conditions: (a) relaxation, wherein we identified the capsule as a strong dose of an herbal sedative, or (b) control, wherein we identified the capsule as inert. We indexed placebo response via changes in heart rate, blood pressure, and self-report measures of relaxation and drowsiness. We hypothesized that placebo response and hypnotic suggestibility would correlate positively in the relaxation condition. Hypnotic suggestibility correlated with subjective but not physiological response to ingesting the placebo sedative capsule. Here we report preliminary findings demonstrating a correlation between hypnotic suggestibility and subjective placebo response.

Keywords: placebo, suggestibility, hypnosis, mind–body medicine, self-regulation

Identifying good placebo responders, although controversial (Raz, 2007a), holds important implications for clinical science. Whereas many practitioners develop an intuitive feel for patients who may benefit from placebos (Raz, Harris, de Jong, & Braude, 2009), researchers have scarcely documented reliable cognitive and personality parameters that correlate with placebo response. Response expectancies—expectations concerning the occurrence of nonvolitional responses—play an important role in shaping placebo as well as hypnosis outcomes (Benham, Woody, Wilson, & Nash, 2006; Kirsch, 2001; Kirsch et al., 2014; Pollo et al., 2001; cf. Lifshitz, Howells, & Raz, 2012). Because expectation and suggestion converge at the crux of both hypnotic and placebo phenomena, researchers have posited a link between these varieties of mind–body regulation. In highly hypnotically suggestible individuals, a few brief words of suggestion can generate profound changes in perceptual, cognitive, neural, and bodily processes (Raz, 2007b). Thus, hypnotic suggestibility may be associated with placebo response. The present study directly tests this hypothesis.

Hypnosis offers a potent experimental tool for teasing apart the influence of suggestion from other behavioral parameters (Oakley & Halligan, 2013). Hypnotic suggestibility refers to the extent to which individuals respond to

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suggestions for alterations in their experience following a hypnotic induction procedure. This trait is highly stable and has excellent psychometric properties (Piccione, Hilgard, & Zimbardo, 1989). However, suggestion-based phenomena typically follow even in the absence of a formal hypnotic induction procedure (McGeown et al., 2012), and responses to hypnotic suggestions correlate strongly with responses to the same suggestions outside of hypnosis (Kirsch & Braffman, 2001). The ability of highly hypnotically suggestible individuals to transform suggestion and expectation into tangible mind–body regulation, therefore, appears to extend beyond the specific context of hypnosis (Raz, 2007b). Similar to placebo effects, moreover, hypnotic responses are typically experienced as occurring automatically or involuntarily (Kirsch & Lynn, 1997; Lynn, 1997). Thus, hypnotic suggestibility and placebo response may converge onto a common substrate of human behavior.

Whereas historically scholars viewed placebo effects as a manifestation of suggestibility (Honigfeld, 1964; Shapiro, 1964a, 1964b), studies exploring the relationship between hypnotic suggestibility and placebo response intimate that this correlation, if it exists, is modest at best (Baker & Kirsch, 1993; Barber, 1960; Evans, 1967; Kirsch, 1997; McGlashen, Evans, & Orne, 1969; Silber, 1967; Spanos, Perlini, & Robertson, 1989; Spanos, Stenstrom, & Johnston, 1988; Van Dyck & Hoogduin, 1990). Although hypnotic suggestibility represents a steady long-term trait with high test–retest reliability (Piccione et al., 1989), a recent study indicates that placebo response may be considerably less stable within the individual (Whalley, Hyland, & Kirsch, 2008). Nonetheless, the effectiveness of placebos depends on multiple situational and motivational factors (Honigfeld, 1964; Shapiro, 1964b). Thus, the link between personality factors and placebo response may vary depending on specific experimental parameters, contexts, and settings.

Previous studies examining the link between hypnotic suggestibility and placebo response focused on pain reduction (Baker & Kirsch, 1993; Frischholz, 2007; Hilgard & Hilgard, 1975; McGlashen et al., 1969). These studies reported either no correlation between placebo response and hypnotic suggestibility (Frischholz, 2007; Hilgard & Hilgard, 1975; McGlashen et al., 1969) or else a partial correlation between the two measures that proved statistically nonsignificant when controlling for expectancy (Baker & Kirsch, 1993). Here we investigate this relationship in the specific context of relaxation. Both placebo and hypnosis interventions can propel various forms of relaxation, including helping patients with insomnia (Serban, Padurariu, Ciobica, Cojocaru, & Lefter, 2013; Winkler & Rief, 2015) and modulating cardiovascular parameters such as blood pressure (Casiglia et al., 2012; Meissner, 2011). Whereas pain reduction paradigms require participants to override an automatic nociceptive reaction, our relaxation paradigm leverages the natural decrease in arousal associated with periods of quiet sitting. Similarly, the induction procedure of the Harvard Group Scale of Hypnotic Susceptibility, Form A (HGSHS:A; Shor & Orne, 1962) harnesses natural relaxation inclinations to facilitate response to suggestion. Because placebo response and hypnotic suggestion both invoke expectation to regulate mind and body, and because relaxation is common to many hypnotic procedures—including the standard procedures for measuring hypnotic suggestibility—we hypothesized that hypnotic suggestibility would correlate positively with subjective and autonomic response to a placebo sedative.

Method

Participants

Fifty healthy undergraduate students (35 females; age: 20 ± 3 years [mean ± *SD*], range: 18–39 years) were recruited from an undergraduate psychology course in which students were administered the HGSHS:A as part of the regular syllabus (Shor & Orne, 1962). At a later date, in a different location, with a different experimenter, and without mention of any link with the hypnotic suggestibility test, the 50 participants completed the placebo portion of the experiment. The placebo portion of the experiment took participants approximately 1 hr to complete, and participants received course credit in return for their participation. We asked participants to refrain from consuming caffeine or sedatives for 4 hr leading up to the placebo portion of the study (note, however, that the effects of some common sedatives last longer).

We excluded data from eight additional participants due to past sedative use ($n = 6$), sedative use at the time of testing ($n = 1$), and coffee consumption at the time of testing ($n = 1$).

Placebo Expectation Conditions

We randomized participants into one of two experimental conditions involving distinct expectation interventions. In both conditions, participants ingested a clear plastic capsule filled with inert blue microcrystalline powder. We provided different consent forms, audiovisual instructions, pill bottles, and written paragraphs to induce distinct expectations regarding the contents and effects of the pill. Specifically, in the control condition ($n = 28$), participants were told that they were in a no-treatment control group for the experiment and that they would ingest an inert pill that would likely have no effect. In the relaxation condition ($n = 22$), participants were told that the pill contained a strong dose (900 mg) of valerian, a common herbal sedative that makes most people feel sleepy and relaxed.

Measures

Immediately after ingesting the pill, participants rated how much they expected the pill to influence their mood, energy level, blood pressure, and heart rate. All self-report items employed an identical Likert scale (1 = *not at all* to 5 = *extremely*). We collected subjective and autonomic measures of relaxation at two time points: once immediately before they ingested the placebo pill and again 30 min after ingestion. Participants reported their subjective arousal/relaxation by rating their present state on the following indexes: tense, alert, talkative, irritable, jittery, cheerful, calm, relaxed, sluggish, tired, easygoing, and drowsy. Systolic and diastolic blood pressure as well as heart rate were recorded using a LifeSource UA-631V One-Touch Automatic Blood Pressure Monitor.

To determine subjective placebo response, we grouped the individual questionnaire items into two subscales. We performed this grouping post hoc because our expected construction of the dependent variable proved unreliable. We first used principal component analysis (with varimax rotation) to sort the questionnaire items into two groups based on their loadings. Namely, we classified each item (e.g., "alert") with the component on which it loaded the highest. The sign of the loading determined whether the item was reverse-scored. This process created two dependent variables. The first summed "calm," "relaxed," and "easygoing," as well as reverse-scored "tense," "irritable," and "jittery"; we labeled this dependent variable as Relaxation. The second summed "sluggish," "tired," and "drowsy," as well as reverse-scored "alert," "talkative," and "cheerful"; we labeled this dependent variable as Drowsiness. The internal consistency reliability for each of these measures was reasonable (Cronbach's alpha was .75 for Relaxation and .73 for Drowsiness). We then calculated differences for each individual from pre- to postingestion (post minus pre). These two dependent variables did not correlate, $r(48) = .023$, $p = .849$.

To determine physiological placebo response, we similarly calculated pre- to post-ingestion changes in measures of sedation (systolic blood pressure, diastolic blood pressure, and heart rate).

We explored the relationships between hypnotic suggestibility and (subjective and physiological) placebo response, as moderated by condition. We tested these relationships with linear regression, first with the main effects, then adding the interaction in the next step. Because these tests of interactions have low statistical power (Frazier, Tix, & Barron, 2004), we used an alpha value of .10 for those and .05 for the rest of the tests (cf. Milling, Kirsch, & Burgess, 2000). Within each condition, our next analysis tested for a correlation between hypnotic suggestibility and placebo response. With a sample size of 50, we could detect only fairly large effect sizes. For example, with an alpha of .05 and no family-wise Type I error correction, we had the power to detect linear correlations of .44 or higher 90% of the time.

As a manipulation check, we ensured that participants expected different effects from taking the pill depending on their condition. The expectation measure comprised 5-item Likert scales (1 = *not at all* to 5 = *extremely*) where participants rated how much they thought the pill would affect their mood, energy level, blood pressure, and heart rate. We averaged the responses to the expectation questions. The control condition had an average expectation score of 1.393 (bootstrapped 95% CI [1.237, 1.554]); the relaxation condition, 2.943 [2.716, 3.142].

The expectation scores thus differed between the groups, which demonstrated that the experimental intervention was successful. Beyond this difference, there was little variation in the expectation scores, so we did not analyze them further.

Results

Hypnotic suggestibility predicted drowsiness. Namely, people with higher suggestibility showed bigger increases in drowsiness after consuming the pill, regardless of whether they thought it was a relaxation or placebo pill (r = .292, 95% CI [.016, .528]; see Figure 1). Thus, there was a main effect of hypnotic suggestibility on drowsiness (see Table 1).

We also found that the relationship between suggestibility and relaxation differed based on condition (see Figure 2). In the relaxation condition, people who were more suggestible were more relaxed (r = .42, 95% CI [−.002, .715]); this relationship was weaker in the control condition (r = .007, 95% CI [−.367, .379]). See Table 1 for the interaction between suggestibility and condition.

Between conditions, there were no differences in terms of physiological placebo response or subjective placebo response (see Table 2 for means and Table 1 for statistics).

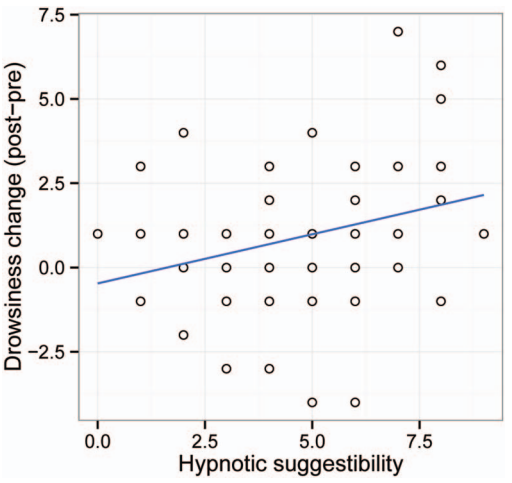

Figure 1. Correlation between subjective drowsiness change and hypnotic suggestibility. Each dot represents data from one participant. See the online article for the color version of this figure.

Table 1
Regression Tables for Relationships Between Hypnotic Suggestibility and Placebo Response, as Moderated by Condition

Measure/effect	b^*	t	p
Heart rate			
Condition	.040	.138	.891
Hypnotic suggestibility	.072	.490	.626
Interaction	−.310	−1.003	.321
Systolic blood pressure			
Condition	−.046	−.158	.875
Hypnotic suggestibility	.032	.221	.826
Interaction	−.381	−1.239	.222
Diastolic blood pressure			
Condition	.006	.019	.985
Hypnotic suggestibility	.186	1.294	.202
Interaction	.139	.454	.652
Relaxation			
Condition	−.244	−.852	.398
Hypnotic suggestibility	.182	1.269	.211
Interaction	.526	1.773	.083
Drowsiness			
Condition	.022	.079	.937
Hypnotic suggestibility	.290	2.075	.044
Interaction	.411	1.400	.168

Note. b^* refers to the standardized regression coefficient. Only subjective placebo response showed effects. The residual "degrees of freedom" for each full model was 46. We tested the main effects in the first step followed by the interaction in the second step.

Discussion

We observed correlations between hypnotic suggestibility and subjective response to a placebo sedative. Our results partially support our original hypothesis: hypnotic suggestibility correlated with subjective—but not physiological—indices of placebo response. The present findings reflect one of the few empirical demonstrations of a stable individual trait correlating with responsiveness to placebo (cf. dispositional optimism by Geers, Wellman, Fowler, Helfer, & France, 2010).

Our results differ from previous findings probing the relationship between placebo response and hypnotic suggestibility. Using a pain paradigm, an early study reported an absence of correlation between hypnotic suggestibility and placebo response (McGlashen et al., 1969). Retrospective examination of these original data revealed that hypnotic analgesia reduced pain far more effectively than placebo and that placebo response among highly suggestible indi-

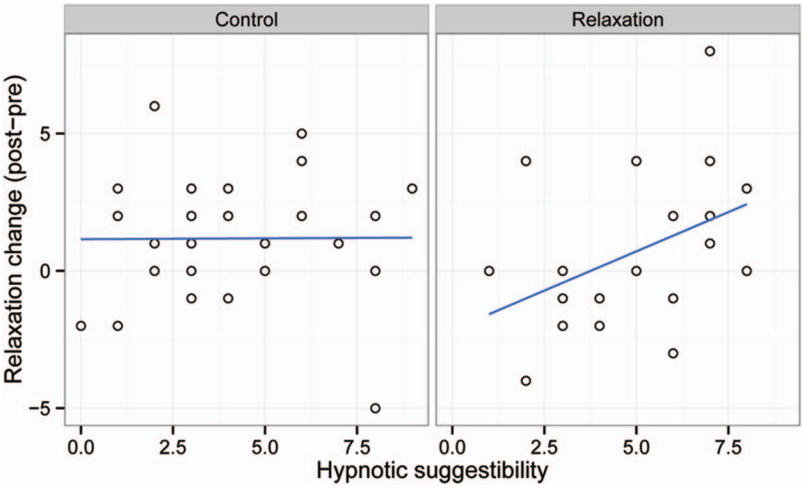

Figure 2. Correlations between subjective relaxation change and hypnotic suggestibility scores. Each dot represents data from one participant. See the online article for the color version of this figure.

viduals was negligible or even negative (Frischholz, 2007; Hilgard & Hilgard, 1975). An independent group later replicated these findings, reporting that hypnotic analgesia relieved pain more effectively than placebo and that hypnotic suggestibility only marginally correlated with pain reduction (Baker & Kirsch, 1993). The discrepancy between earlier findings and the present results may derive from the difference in contexts. Further studies investigating the connection between hypnotic suggestibility and placebo response in both relaxation and analgesia paradigms would serve to determine the reliability and generalizability of our findings.

Caveats

Our study lacked a no-treatment control condition. Ideally, participants in the no-treatment arm would undergo the same experimental procedure as the other participants but without ingesting a placebo capsule. This supplementary condition would permit a more fine-grained analysis to dissociate the placebo response (i.e., the total nonpharmacological effect associated with ingesting the placebo capsule) from the placebo effect (i.e., the placebo response minus nonspecific factors such as natural remission and regression to the mean; Raz, 2007a). Without this no-treatment condition, our paradigm cannot fully tease apart the specific contribution of top-down expectation-related changes. Another limitation is that we observed a subjective change but no physiological change. These results accord with prior evidence demonstrating a decoupling between self-reports and biological outcomes in response to placebo interventions (e.g., in the case of asthma, see Wechsler et al., 2011). On one hand, subjective scores may be more susceptible to demand characteristics associated with a desire to please the experimenters, especially when receiving compensation in the form of course credit. On the other hand, subjective alterations may be more meaningful than physiological changes in the treatment of certain conditions where the primary symptoms center on experiential distress (e.g., anxiety, depression, or chronic pain). Finally, our study had a relatively small sample size and thus limited statistical power. Given the above limitations, we offer the present findings as intriguing preliminary evidence warranting future investigation.

Conclusion

The present findings indicate that suggestibility of the hypnotic type correlates with placebo responding in a specific experimental context. Our study contributes to a controversial dialogue surrounding placebo effects in medicine.

Table 2
Mean Changes (Post Minus Pre) by Condition on Physiological and Subjective Measures in Raw Units

	Heart rate (beats per minute)	Systolic blood pressure (mm Hg)	Diastolic blood pressure (mm Hg)	Subjective relaxation	Subjective drowsiness
Control	−6.179 [−10.251, −2.855]	−3.643 [−6.358, −.928]	−2.571 [−4.607, −.321]	1.179 [.357, 1.929]	.786 [−.144, 1.714]
Relaxation	−5.682 [−8.136, −3.317]	−3.909 [−6.636, −1.182]	−2.273 [−4.727, .182]	.682 [−.409, 1.864]	1 [.227, 1.865]

Note. There were no differences between conditions. Square brackets show bootstrapped 95% CIs.

Identifying good placebo responders may help pharmaceutical companies inflate the outcomes of randomized control trials by excluding high responders from the placebo arm (Raz, 2007a). In the clinical domain, medical associations and practitioners hotly debate the value of placebo treatments. Placebos may serve as viable interventions in specific circumstances: for example, when interventions demonstrate strong placebo influences alongside substantial side effects or when no effective pharmacological treatments exist (Foddy, 2009). Survey data suggest that, regardless of official ordinance, clinicians routinely prescribe placebos, albeit typically in their "impure" incarnations (Fässler et al., 2010; Raz & Harris, 2015). "Impure" placebos refer to nondeceptive treatments lacking direct pharmacological efficacy—for example, vitamins and subtherapeutic doses—that leverage nonspecific effects inherent to the clinical context and doctor–patient bond: first and foremost, the powerful expectation that treatments will heal. Further investigation along these lines may help predict the patients who will likely respond more strongly to placebos, whether pure or impure, and may therefore serve to optimize clinical outcomes (Spiegel & Spiegel, 2004). Here we show that a stable personality trait—hypnotic suggestibility—correlates with placebo response in the specific context of relaxation. Future studies would need to explore whether and to what extent this link generalizes to a broader hypothetical trait of "good placebo responder" in other experimental and clinical contexts. Our preliminary findings lay the foundation for future efforts unraveling the influence that individual, cognitive, and personality traits wield over mind–body regulation.

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