



Editorial

Expectations and anxiety as mediators of placebo effects in pain

In this issue of *Pain*, Vase et al. provide evidence for some of the largest placebo effects yet reported in an experimental study. Testing patients with irritable bowel syndrome (IBS), they compared the effects of natural history (N), lidocaine (L) and placebo (P), administered on separate days, on pain induced by a rectal balloon. They found that with P, pain ratings were (surprisingly!) as low as with L, and both were substantially lower than N. To investigate psychological mediators, they measured expectations about pain, anxiety, and desire for pain relief, and found that decreases in expectation and anxiety ratings predicted decreases in pain during P and L. To investigate neurochemical mechanisms, they administered the opioid antagonist naloxone before P/L in some participants, and found no effects on either pain, drug, or placebo responses. In addition, they collected measures during early and late phases of the 40-min session, and found placebo effects that increase with time.

The most direct interpretation of Vase et al.'s results is that there is a causal link between expectation and pain perception that is not mediated by endogenous opioids (at least in hyperalgesic IBS patients). But this interpretation, however, tempting, engages several deep, perennial issues: What is the relationship between placebo-induced changes in reported pain, as Vase et al. and others have demonstrated, and placebo-induced changes in pain experience? What is the relationship between expectation, anxiety, and pain perception? Is there a causal link? and how strong is the evidence that the placebo effects are opioid insensitive?

The role of expectations. The issue of how expectations and anxiety affect pain can be broken down into two parts: (1) are expectations and anxiety affecting pain experience or simply ratings of pain? and (2) are they *causing* reductions in pain, or is the apparent correlation caused by a third variable? If placebo reductions in ratings of expectations about pain ('how much pain do you think you will feel?') are correlated with subsequent placebo reductions in pain experiences, one way they could do so is to alter pain experience. However, there are other alternatives, as shown in Fig. 1.

First, demand characteristics—the tendency for a subject to report an effect that they believe the experimenter expects

or desires them to report (e.g. reduced pain), may affect ratings of both expectation and pain, independent of any changes in pain experience. Demand characteristics may take several forms; for instance, judging what level of pain to report is a decision process, and judgments about experience in a variety of settings are themselves highly susceptible to expectations and context effects (e.g. Ericsson and Simon, 1980). In machine learning and Bayesian statistics, decisions are made by combining prior expectations with current information. Thus, *judgments about pain* may reflect an integration of *expectations* about pain (the prior information), which may be influenced by placebo treatment, and *pain experience* (new information coming in), which may not. This possibility provides the basis for a direct causal link between expectations and pain reporting (#1 in Fig. 1).

Alternatively, the correlation between expectation and subsequent pain ratings need not be causal at all. Stable individual differences in demand characteristics may be third variables that affect both ratings, causing apparent correlation (#2 in Fig. 1). These individual differences may be putatively stable personality traits like suggestibility (e.g. De Pascalis et al., 2002) or history of effective analgesic treatment, but they may also be situational factors relating to how convincing an individual finds the placebo treatment administered in a particular experimental context.

Finally, the process of reporting expectations and anxiety may itself affect judgment in a variety of ways. For example, an on-paper statement that one expects little pain and is not anxious may be regarded as a sort of social contract (#3 in Fig. 1), a commitment that participants are hesitant to reverse. A fundamental theme in the symphony of modern psychological research has been the study of consistency between actions and attitudes (Brownstein, 2003; Festinger, 1964). If people are asked to endorse a view (an action) without a convincing external justification for why they did it, they tend to revise their attitudes to be consistent with their actions. Thus, the reporting of expectations may establish a norm which shapes subsequent attitudes towards pain, and subsequent departures from this norm may cause psychological discomfort (Elliot and Devine, 1994).

The potential for demand characteristics does not preclude placebo effects on pain experience as well;

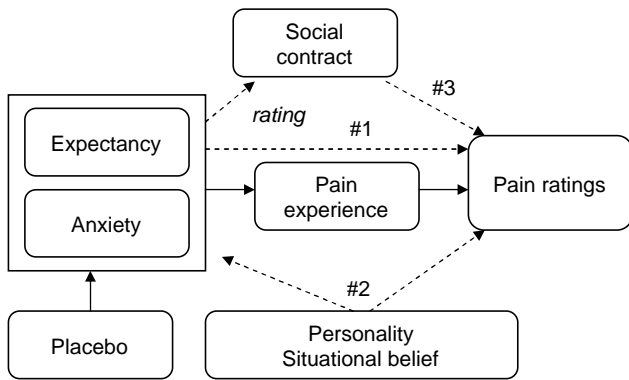


Fig. 1. Potential pathways by which placebo treatment may lead to changes in reported pain. The most straightforward route is by altering pain experience (solid arrows), perhaps mediated by placebo effects on expectations of pain and anxiety. However, other pathways bypass pain experience and directly affect pain reporting (dashed arrows). Identifying additional measures of pain experience and sources of non-experiential bias may allow us to disentangle which pathways are affected by expectations.

there may be an experiential component and a demand characteristic component. Measuring psychological variables and examining their relationships with pain processing, as Vase et al. have done, is a critical step towards understanding how mechanisms at the psychological and physical levels of description interact to affect reported pain. Parsing effects on experience from the effects on judgment process itself is a key next step. One way to do this is by measuring physiological variables related to pain experience. If pain reports under placebo are veridical measures of pain experience, then expectation ought to influence physiological markers of autonomic arousal and representations of pain in the central nervous system. Explicit estimation of biases in judgments are another way help parse out individual differences in non-experiential factors.

The complex effects of opioids. Vase et al. found no effects of naloxone on pain, either with or without placebo/drug treatment, or psychological ratings. There are several alternative explanations for the discrepancy between this study and previous ones. IBS patients have much prior experience with analgesic drugs, ample opportunity to develop opioid-independent conditioned analgesic responses, and perhaps other factors (e.g. high anxiety about pain) that make them different from most experimental participants. Alternatively, the dose of naloxone may have been insufficient to affect pain. Naloxone can produce both hyperalgesia and analgesia, depending on the dose (e.g. Levine, Gordon, and Fields, 1979). Sometimes it may act on pain-processing independent of placebo

(e.g. Gracely et al., 1983), and in other cases it may reverse placebo effects without producing hyperalgesia (e.g. Amanzio and Benedetti, 1999). Revealing the true pattern of naloxone–placebo interactions in this case relies on interpreting both positive and null effects. Thus, to infer that there is no clinically meaningful effect of naloxone, statistical power and the use of within-study positive controls are essential.

A drug for all seasons. Overall, Vase et al.'s placebo study exemplifies an extremely important approach for understanding not just regulation of pain, but the broader question of how drugs prescribed for various health problems interact with internal self-regulatory mechanisms and context (e.g. Volkow, 2004). The approach is to measure not only outcomes of drug (or placebo) manipulations, but potential mediators at both the psychological and biological levels. We may find that the critical factors in opioid–pain interactions, and indeed many areas of neuroscientific inquiry central to human health, are most easily characterized at the psychological level.

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