

Named Series: Brain Mechanisms of Placebo

## Placebo effects in the brain: Linking mental and physiological processes <sup>☆</sup>

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Received 8 April 2005; accepted 8 April 2005

The placebo effect presents something of a paradox in modern scientific research. On the one hand, the use of placebo treatments is firmly established in clinical trial methodology. On the other, an understanding of the mechanisms of placebo effects has been elusive. This may be partly because a variety of different effects have been lumped under the rubric of ‘placebo’: sampling biases, reporting biases or ‘demand characteristics,’ effects induced by the experimental context (the ‘Hawthorne effect’), regression to the mean, and spontaneous recovery, to name a few. However, in *none* of the effects listed above does placebo treatment have any direct psycho-physiological impact on the disease process—these ‘placebo effects’ do not cure, no symptoms are ameliorated. The prevalence of such effects has led some researchers to question whether all clinically observed placebo effects are simply the result of such biases (Hrobjartsson and Gotzsche, 2001).

Experimental research on placebo has been instrumental in ruling out these artifactual alternatives and redefining placebo effects in terms of active mechanisms (e.g., Price, 2000). Now, we are at the beginning of a new era in understanding how placebo treatments work and what effects they have. What’s different? Advances have been made in understanding the psychological mechanisms and consequences of appraisal and affect, and the once-separate fields of neuroscience, cognitive science, and emotion are increasingly integrated. New brain imaging techniques are beginning to provide objective, quantitative measures of brain activity related to psychological processes such as appraisal, affect, and

the subjective experience of pain. This is the approach taken by Lorenz et al. (2005) whose work appears in this issue. They used MEG and EEG to localize pain-evoked potentials in the cerebral cortex, and demonstrated that these potentials are influenced by expectations. Studies like this one have the potential to test placebo effects on different components of pain, including sensory processing, emotional experience, and judgments about pain. Lorenz et al. localize the expectancy-modulated pain potentials they observed to SII, one of the first cortical regions to receive nociceptive input, providing external validation that expectancy affects pain experience, not simply pain reporting.

In recent years, neurophysiological placebo research has created a renewed interest in placebo effects and a hope that they can provide new insight into mind–body interactions. Prior conditioning research with non-human animals has demonstrated that neutral stimuli can elicit a variety of conditioned ‘placebo effects,’ including immunosuppression (Ader and Cohen, 1982; Goebel et al., 2002; Herrnstein, 1962). Recent studies in humans have demonstrated that placebo treatments induce active psychobiological changes in several domains, including pain, Parkinson’s disease, and depression (Benedetti et al., 2004; Mayberg et al., 2002; Petrovic et al., 2002; Wager et al., 2004). The public is interested in placebo because the concept is empowering: it suggests that we can influence our health outcomes by changing our minds. Scientists are interested in placebo effects because they provide an entry point for studying the endogenous control processes that shape perception, affect, and motivation, and how these internal control processes interact with active treatments.

Recent technological advances make it possible, for the first time, to investigate the neural correlates of

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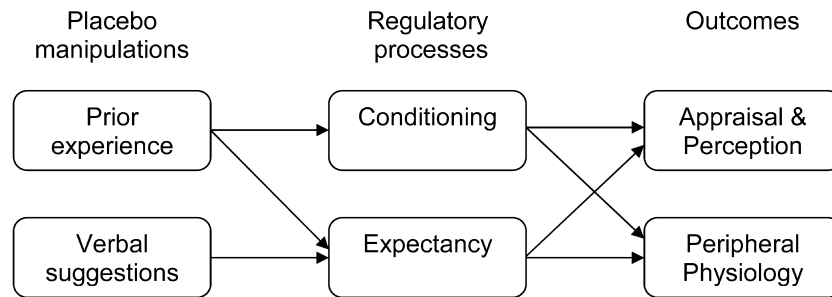


Fig. 1. Diagram showing relationships between placebo treatment, internal regulatory processes, and outcomes. A challenge in placebo research is identifying the internal processes that are engaged by treatment and their brain substrates. Conditioning and expectancy may act on common or unique brain pathways, and the relationship between them may vary across disease processes and treatments. Another challenge is in identifying placebo effects on specific outcomes within the brain and periphery.

subjective constructs like expectancy, pain, and emotion, and relate these measures to clinical outcomes in the brain and periphery.

Although the new research is promising, work on the physiology of placebo effects has just begun, and fundamental questions remain to be addressed. First, what regulatory processes are engaged by placebo treatments? Two major classes of processes have been proposed: conditioning and expectancy (Fig. 1). Different treatments may affect these processes differently. Verbal suggestions influence expectancy, but do not create conditioning. On the other hand, experience with active treatments may create conditioned associations between treatment context (e.g., an injection) and endogenous neurophysiological responses. Such conditioned responses may be unconscious and involuntary, engaging separate neural mechanisms from those involved in expectancy. However, conditioning procedures also create expectations that, in turn, may play a key role the conditioned response (Kirsch, 1985). We currently know very little about the brain processes and pathways involved in expectancy and how they interact with pathways crucial for conditioning. A second question is, what outcomes are influenced by placebo treatments? Candidates include emotional appraisals, attention, motivation, and peripheral physiology.

These two questions must be asked anew in each disease domain, as expectancy and conditioning may have different effects in different systems. As this work progresses, we may gain a better understanding of whether there is indeed a “placebo response” that engages common brain mechanisms in different domains, and how profoundly placebo can affect our mental and physical health. This first Named Series in *Brain, Behavior, and Immunity* is entitled “Brain Mechanisms of Placebo.”

The inaugural article in this Named Series is by Lorenz et al. (2005) in this issue. Forthcoming papers in the series will run in upcoming issues of the journal and will highlight new research being conducted to address the brain mechanisms of placebo.

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