



Journal of Neurotherapy: Investigations in Neuromodulation, Neurofeedback and Applied Neuroscience

Mechanism(s) of the Placebo Response and the Future of Neurofeedback Research

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Published online: 08 Sep 2008.

To cite this article: T. J. La Vaque PhD (2002) Mechanism(s) of the Placebo Response and the Future of Neurofeedback Research, *Journal of Neurotherapy: Investigations in Neuromodulation, Neurofeedback and Applied Neuroscience*, 6:1, 1-4, DOI: [10.1300/J184v06n01_01](https://doi.org/10.1300/J184v06n01_01)

To link to this article: http://dx.doi.org/10.1300/J184v06n01_01

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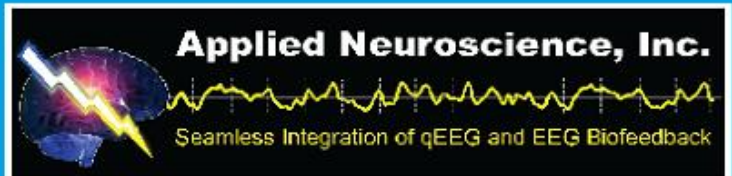
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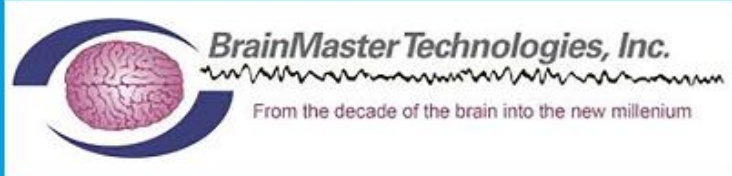
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EDITORIAL



Mechanism(s) of the Placebo Response and the Future of Neurofeedback Research

There may be a sea change occurring in scientific interest in the placebo response. Until just a few years ago the placebo controlled design was regarded as a useful control device that helped elevate clinical trials of drugs or procedures to a more “scientific” status. Indeed, the double-blind placebo controlled clinical trial has been regarded as the “gold standard” for proof of efficacy. If the placebo (or sham) treatment condition can be regarded as a therapeutically inert condition, it can be seen as a legitimate means of testing the “nonspecific” features of investigational interventions.

Recent studies have changed that, at least in the minds of some researchers. The National Institutes of Health (NIH) National Center for Complementary and Alternative Medicine (NCCAM) announced a plan to release an inter-institute sponsored Request for Applications (RFA) in September of 2001. The RFA’s are for The Placebo Effect in Clinical Practice and the Elucidation of the Underlying Mechanisms of the Placebo Effect. The goal of the Clinical Practice RFA is to stimulate

research investigations examining the patient-practitioner factors that promote a placebo response in order to “improve health and promote wellness.” The goal of the Underlying Mechanisms RFA is to encourage research examining the underlying biological mechanisms of the placebo response. The NIH plans to commit “\$4 to \$5 million dollars per year for the next few years” to the project. See <<http://grants.nih.gov/grants/guide/notice-files/NOT-AT-01-003.html>>.

The initiative stemmed from a trans-institute NIH workshop held in November of 2000 that generated a great deal of interest. Not too long ago, such a workshop would have been considered nearly heretical given the climate of “placebo orthodoxy” that permeates the health care regulatory and research agencies. In the past, there has been great interest in eliminating the placebo response as a source of unwanted variance and “noise” in clinical trials. By contrast, these recently announced initiatives are aimed at learning how to *potentiate* the placebo response for clinical application.

The placebo response was, at one time, about the only thing a physician could rely upon for clinical “efficacy” (Shapiro & Shapiro, 1997). The concept of the “placebo” emerged from early “blinded” demonstrations designed to debunk non-orthodox medical practices such as Mesmerism, animal magnetism, and homeopathy. The term “blinded” apparently derives from the early practice of blindfolding study participants, or hiding them in closets or under blankets, to keep them ignorant of the true test conditions (Kaptchuk, 1998). Experimental psychologists frequently employed the “blinded” condition in the early 1800’s. The goal was always to remove the element of fraud or suggestion from the experimental equation. The use of the “blinded” control as a test of efficacy was used only infrequently in Europe in the 1800’s and early 1900’s, and was typically reserved as a challenge to “unorthodox” medicine. As is well known, in the mid 1950’s medicine as a discipline began to internalize the “placebo control” as the means by which it aimed to become a scientific discipline, moving the laboratory method of “controls” to the clinical trials setting.

Now reports have raised tantalizing questions about the placebo control as an “inert” condition. Evidence that placebo analgesia relies upon endogenous opiate release has been accumulating (Amanzio & Benedetti, 1999; Benedetti et al., 1998; Levine, Gordon, & Fields, 1978). The role of classical conditioning in the physiology of the placebo response has been demonstrated in the immune system (Ader & Cohen, 1985, 1992). The relaxation response may trigger a generalized physiological state that mediates the ubiquitous beneficial effects associated with that in-

tervention (Critchley, Melmed, Featherstone, Mathias, & Dolan, 2001; Stefano, Fricchione, Slingsby, & Benson, 2001).

Most recently, a provocative report indicated that the placebo response associated with Parkinson's Disease (PD) is associated with specific dopamine release (de la Fuente-Fernández et al., 2001). The authors used positron emission tomography (PET) to estimate both pharmacologically and behaviorally induced dopamine release based upon [¹¹C]raclopride (RAC) isotope competition with dopamine for binding to dopamine D₂/D₃ receptors. In the presence of increased dopamine (endogenous or pharmacological) there would be evidence of less binding of the RAC isotope at the D₂/D₃ receptors. The study examined striatal system (caudate nucleus and putamen) RAC binding in six patients under two conditions: a double-blind placebo control (apomorphine vs. placebo) and an open study without placebo. The magnitude of the placebo response was "comparable to that of therapeutic doses of levodopa or apomorphine." There appeared to be a dose-dependent relationship between the estimated amount of dopamine release and the placebo benefit reported by the patients. The authors concluded that the "findings indicate that the placebo effect in PD is powerful and is mediated through activation of the damaged nigrostriatal dopamine system."

It is becoming clear that there is no single "placebo response." The restorative mechanism appears to depend upon the nature of the disease or disorder itself. Other studies have demonstrated the potent influence of behavioral therapies upon brain function in the treatment of obsessive-compulsive disorder. As in the PD study, the effects were equivalent to those obtained with pharmacological therapies (Schwartz, Stoessel, Baxter, Martin, & Phelps, 1996). Brain imaging studies have also implicated specific brain areas in the development of a biofeedback assisted relaxation response, and "suggest a functional neuroanatomy of how cognitive states are integrated with bodily responses" (Critchley et al., 2001).

Successful scientific inquiry often does not provide absolute answers. Successful scientific inquiry most usually refines and changes the questions we are able to ask. It appears that the placebo response question is coming full circle in modified form. As we understand the mechanisms of the placebo response, and improve our ability to manipulate and potentiate the effect, "the" placebo response is likely to become a sought after and desired therapeutic modality rather than a scientific orphan useful only as a foil to avoid bias or deception in research. In coming years, the very term "placebo effect" may cease to exist. Applied psychophysiology in general, and operant control of brain

activity in particular, appears to be ideally suited to the task of understanding and manipulating the mind-body domain. It will require a wedding between the technology of psychophysiology and the technology of traditional medicine. It can be an exciting venture.

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