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Perspective



# Placebo Effects: From the Neurobiological Paradigm to Translational Implications

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Today we are witnessing a new science of placebo, a complex discipline that encompasses several experimental approaches and translational implications. Modern neurobiological tools have been used to answer important questions in placebo research, such as the top-down modulation of sensory and motor systems as well as the influence of cognition, emotions, and learning on symptoms, diseases, and responses to treatments. What we have learned is that there is not one single placebo effect, but many. This review highlights the translational implications of this new knowledge, ranging from clinical trial design to medical practice to social and ethical issues.

## Introduction

A placebo is an inert treatment with no specific therapeutic properties, whereas the placebo effect is the response to the inert treatment. Although this is the most common definition, it is not completely correct, for placebos are made of many things, such as words, rituals, symbols, and meanings. Thus, a placebo is not the inert treatment alone, but rather its administration within a set of sensory and social stimuli that tell the patient that a beneficial therapy is being given. Indeed, a placebo is the whole ritual of the therapeutic act.

When a placebo is administered to a patient, observed clinical improvements can be due to several factors. Spontaneous remission can occur, with the improvement misinterpreted as an effect of the placebo itself, even though it would have occurred anyway. Methodological biases can also make the experimenter believe that an amelioration is taking place when the supposed benefit is actually attributable to the patient's biased report and/or the experimenter's biased measurement, a typical situation in the assessment of subjective symptoms. Finally, therapeutic benefit can be due to the patient's positive expectations, which in turn may reduce anxiety and/or activate reward mechanisms. All of these factors may contribute to the amelioration of a symptom. Therefore, in order to assess the efficacy of a therapy, it is necessary to compare the effects of a real treatment with the effects of a placebo, and the observed improvement can be due to spontaneous remission and/or methodological biases and/or the patient's expectations (Benedetti, 2013a, 2014b).

The still persisting confusion and misconception within the scientific community about the word placebo come from the different meaning that this word has for the clinical trialist and the neuroscientist. In fact, the former is mainly interested in comparing a therapy with a placebo and to establish whether the therapy is superior to the placebo. Although today most clinicians know and value the placebo effect, usually they are not interested in understanding whether the placebo-treated patients improve because of a spontaneous remission, a bias, or psychobiological factors. Conversely, the neuroscientist wants to isolate the psychobiological component from the spontaneous fluctuations of the symptom, the patient's biased reports, and the experimenter's biased measurements. In this sense, the neuroscientist uses the placebo to probe brain functions ranging from endogenous pain modulation to anxiety mechanisms and from Pavlovian conditioning to social learning. Therefore, when the neuroscientist talks about placebos and placebo effects, he means the psychobiological component of the clinical improvement, that is, all those psychological factors that contribute to change the time course of a symptom or ailment.

In the recent history of the placebo effect, and in general of placebo research, one of the main objectives has been its control within the setting of clinical trials. The reduction of the placebo effect in a clinical trial is considered today a priority in clinical research so as to better evidence the specific effect of the treatment. Many new designs have been devised in different medical conditions, such as depression (Fava et al., 2003), and different placebo components have been described within the setting of a clinical trial (Kaptchuk et al., 2008). Therefore, the methodological aspect of placebo research is an important element in the design of clinical trials, both in the past (Kaptchuk, 1998) and in more recent times (Enck et al., 2011, 2013).

Today we are witnessing a resurgence of placebo research that is mainly aimed at using a neurobiological approach (Benedetti, 2013a, 2014b). In fact, in contrast to several decades ago, when placebo research was mainly based on a psychological approach, today we utilize tools ranging from pharmacology to brain imaging and from genetics to animal models to explore what is going on in the patient's brain when he expects a therapeutic benefit. In this sense, we are witnessing the emergence of a new science of placebo that encompasses complex issues in the neurobiological domain as well as translational implications, particularly for the clinical trials setting but also for medical practice and society. In this article, I will review all these aspects, in order to give an idea of the complexity of the topic and provide some recommendations for how clinical trial designs can address the challenges of placebo responses.

## Recent Insights into the Neurobiological Mechanisms

Taking a neuroscientific perspective to the study of the placebo response, isolating the psychobiological component from

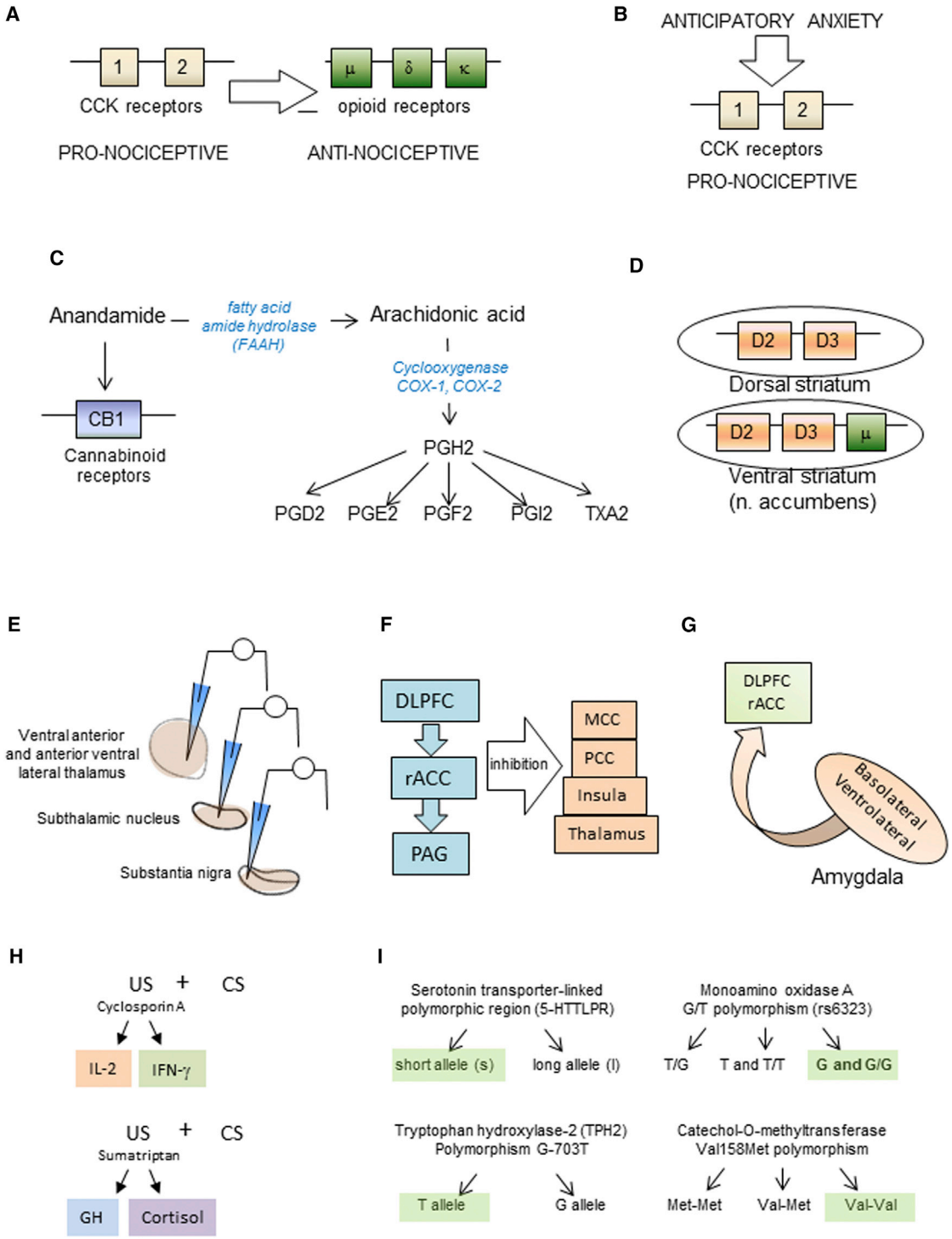


**Figure 1. Principal Neurobiological Mechanisms of the Placebo Response that Have Been Identified across a Variety of Conditions**

(A) The antinociceptive opioid system is activated in placebo analgesia in some circumstances, and the μ opiod receptors play a crucial role. The pronociceptive cholecystokinin (CCK) system antagonizes the opioid system, thus blocking placebo analgesia.

(B) The pronociceptive CCK system is activated by anticipatory anxiety in nocebo hyperalgesia, with some evidence that the CCK-2 receptors are more important.

(C) Different lipidic mediators have been identified in placebo analgesia and nocebo hyperalgesia. Whereas placebos activate the CB1 cannabinoid receptors and inhibit prostaglandins (PG) synthesis in some circumstances, nocebos increase PG synthesis. In addition, different genetic variants of FAAH affect the magnitude of placebo analgesia.

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