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Review

The sweetest pill to swallow: How patient neurobiology can be harnessed to maximise placebo effects

Jayne Jubb, Jozien M. Bensing*

NIVEL (The Netherlands Institute for Health Services Research), Otterstraat 118–124, 3513 CR Utrecht, The Netherlands

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ABSTRACT

The burgeoning interest in placebo effects over the last 10–15 years has fallen into two main research areas: elucidation of the neurobiological mechanisms recruited following placebo administration, and investigations into the situations and contexts in which placebo effects are evoked. There has been little attention focused on bridging these two *i.e.* how to actively translate and apply these neurobiological mechanisms into daily clinical practice in a responsible way. This article addresses this gap, first through a narrative review of the last 15 years of neuroscience findings with special attention focussed on the elucidation of the neurotransmitters, pathways and mechanisms involved in placebo effects, and secondly, at how these psycho(neuro)biological effects could be harnessed in medical care.

Contents

Abbreviations: aINS, anterior insula; CB, cannabinoid; DA, dopamine; DLPFC, dorsolateral prefrontal cortex; dorsal str., dorsal striatum; INS, insula; NAC, nucleus accumbens; OFC, orbitofrontal cortex; PAG, periaqueductal grey; PET, positron emission tomography; pINS, posterior insula; rACC, rostral anterior cingulate cortex; SNr, substantia nigra pars reticulate; STN, subthalamic nucleus; Thal, thalamus; V. str., ventral striatum; VLa, ventrolateral thalamus; VA, ventral anterior thalamus; VTA, ventral tegmental area.

* Corresponding author. Tel.: +31 302729686; fax: +31 302729686.
E-mail addresses: j.jubb@nivel.nl (J. Jubb), j.bensing@nivel.nl, contact@jaynejubb.com (J.M. Bensing).

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1. Introduction

Placebos *are* a conundrum.

How can something which by definition is an inert treatment devoid of any pharmaceutical properties (*e.g.* a sugar pill, saline injection, or even words, rituals and meanings) produce a change in a patient?

The mention of the word 'placebo' is often immediately associated with placation and deception (Bensing and Verheul, 2010; de Craen et al., 1999; Verheul et al., 2010). In spite of the bad press they receive, surveys carried out in the United States (Berger, 1999; Sherman and Hickner, 2007), Denmark (Hrobjartsson and Norup, 2003) and Israel (Nitzan and Lichtenberg, 2004) reveal that placebos are being fairly widely administered in medical practice. In spite of the placebos' dubious history, the neuroscientific investigations from the last 15 years (see Box 1 for search strategy and selection criteria) have shown that the placebo effect is in fact *a real biological phenomenon due to the psychosocial context of the patient and the therapy* (Finniss et al., 2010; Price et al., 2008). By their very definition placebo effects therefore bridge physiological processes with the interaction-rich environment in which they occur, and yet the practical potential in this overlap has not yet been tapped.

In this article we would like to put forward how the knowledge gleaned from placebo effect research can provide valuable added benefits to daily medical situations when used in an open, ethical and responsible way.

Box 1
Search strategy and selection criteria
In order to review the literature, an extensive systematic search was carried out of the English language-based electronic databases of PubMed (including MEDLINE), Web of Science, the Cochrane database and library, PsychLit, BIDS (Bath Information and Data Services), EMBASE and the Science Citation Index. Searching on 'placebo effects' alone yielded 119,774 hits from PubMed, and thus further refinement was necessary. Since there have been such rapid advances in the understanding of placebo mechanisms in recent years, the search was confined to results from 1995 to 2013, unless it later became obvious that there was an earlier seminal work that needed to be included. The keyword search terms used are listed in the Appendix A. As the search started to identify data and information, the title and abstracts were quickly scanned to assess if the publication was indeed suitable.
After the initial title and abstract screening, the publications fell into categories: primary research papers, and reviews. Primary research papers were defined as those containing experimental evidence pertaining to placebo effect research. Reviews (including books) included summaries of findings from primary research papers. Other papers were also garnered via forward searching (citation index to see how often and by whom this paper had been cited) and backward searching (what publications did this author include that we may have missed) using the publications extracted from the database searches. Publications were included if they contained experimentally supported findings for neural substrates and neural mechanisms. Publications were excluded if they: included only historical and theoretical information (*i.e.* no experimental support); were for placebo-controlled trials for pharmaceutical testing; did not have a neuroscience-related content. This yielded around 200 publications and it is on the basis of these that this paper is written.
The literature search itself was thus limited to the neuroscientific studies underlying placebo effects. These were then further supplemented with scientific studies from a wide variety of disciplines to illustrate examples and possibilities of clinical applications of placebo effects.

1.1. Hidden in plain sight: open-hidden paradigm

It is sobering to realise that until post-World War II, modern medicine was essentially the medicine of placebo effects (Kaptchuk, 1998; Raicek et al., 2012; Shapiro and Shapiro, 1997). Placebo effects became more scientifically visible when Beecher (1955) reported that 35% of patients responded positively to placebo treatment. His choice to categorise placebo effects as something to be baselined – as opposed to investigating the occurrence of the effects themselves – resulted in the adoption of the randomised controlled trial (RCT), and later, the double-blind placebo-controlled clinical trial.

In recent years, meta-analyses of published data disrupted emerging theories when they implied that placebo effects were actually very small, and even non-existent (Hrobjartsson and Gøtzsche, 2001, 2004a, 2004b, 2006, 2007a, 2007b). As a result of this, differences came to light between placebo effects observed during experimental conditions and those in clinical trials (Hrobjartsson and Gøtzsche, 2010; Vase et al., 2002, 2009). In clinical trials, it is the new drug that is under scrutiny, and the placebo becomes a method of statistical differentiation; in experimental conditions designed for studying placebo effects, it is the placebo effect itself that is being investigated. It has now been established that placebo effects are larger under experimental conditions than clinical trials, and are especially present in placebo analgesia research (Hrobjartsson and Gøtzsche, 2010). The placebo effect is thus a real psychobiological occurrence which does not denote natural history progression (spontaneous remissions), patient bias and regressions to mean. The latter are commonly found in the clinically executed placebo-controlled pharmaceutical trials.

The quantitative magnitude of the placebo effect was revealed by Levine and co-workers during post-operative dental pain studies (Levine et al., 1981; Levine and Gordon, 1984). Telling patients that a painkiller was being administered, whereas in fact a saline (placebo) solution was being given, was found to be as potent as a hidden intravenous 6–8 mg dose of morphine. For the patient, the sight and presence of a doctor openly injecting a painkiller was a potent analgesic in itself.

These studies by Levine et al. introduced for the first time the open-hidden experimental design which has since been used widely in clinical (placebo) settings (Amanzio et al., 2001; Benedetti et al., 2003b; Colloca et al., 2004). In the most straightforward open set-up, an injection (e.g. a verum analgesic) is given in full view of the patient; in the hidden set-up, the treatment is administered via a computer-operated infusion pump, where the doctor is absent and the patient is unaware when the pharmacotherapy is being administered. If a drug is effective and the pharmacological action is the cause of the improvement, there should be no difference between the open and the hidden injections.