Progress in Neuropsychopharmacology & Biological Psychiatry xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Progress in Neuropsychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Role of placebo effects in pain and neuropsychiatric disorders

Annabelle M. Belcher[a], Sergi Ferré[b], Pedro E. Martinez[c], Luana Colloca[a,d,e,f,*]

[a] Department of Psychiatry, School of Medicine, University of Maryland, Baltimore, USA
[b] National Institute on Drug Abuse, National Institutes of Health, Bethesda, USA
[c] National Institute of Mental Health, National Institutes of Health, Bethesda, USA
[d] Department of Pain and Translational Symptom Science, School of Nursing, University of Maryland, Baltimore, USA
[e] Department of Anesthesiology and Psychiatry, School of Medicine, University of Maryland, Baltimore, USA
[f] Center to Advance Chronic Pain Research, University of Maryland, Baltimore, USA

ARTICLE INFO

Keywords:
Nocebo effect
Pharmacological and context-dependent conditioning
Verbal suggestion
Expectancy
Social observational

ABSTRACT

The placebo (and the nocebo) effect is a powerful determinant of health outcomes in clinical disease treatment and management. Efforts to completely eradicate placebo effects have shifted dynamically, as increasingly more researchers are tuned to the potentially beneficial effects of incorporating those uncontrollable placebo effects into clinical therapeutic strategies. In this review, we highlight the major findings from placebo research, elucidating the main neurobiological systems and candidate determinants of the placebo phenomenon, and illustrate a perspective that can effectively frame future research on the topic. Finally, we issue a call for increased research on the efficacy of therapeutic strategies that incorporate placebo "tools," and argue that clinical trials of the placebo response in neuropsychiatric diseases and disorders has important and far-reaching translational and clinical relevance.

1. Introduction

> "*Placebos have doubtless been used for centuries by wise physicians as well as by quacks, but it is only recently that recognition of an enquiring kind has been given the clinical circumstance where the use of this tool is essential…*".

-Henry K. Beecher, 1955.

Thus begins a pioneering discussion from a medical practitioner's perspective in an article in JAMA entitled "The Powerful Placebo." Over sixty years later, Beecher's assessment of the practical utility of the placebo pill still holds true. Once largely constrained to studies of placebo analgesia, the placebo's therapeutic efficacy is being increasingly demonstrated across a broader range of illnesses and conditions including psoriasis (Ader et al., 2010), Parkinson's Disease (Colloca et al., 2004), migraine headaches (Kam-Hansen et al., 2014), allergic rhinitis (Schaefer et al., 2016), irritable bowel syndrome (Kaptchuk et al., 2010), sleep disorders (Perlis et al., 2015) and attention-deficit-hyperactivity disorder (Sandler and Bodfish, 2008) among many other conditions (for a review, see Benedetti, 2014). Complementary fields including neuroimaging and pharmacology have elucidated the principal neural mechanisms and neurotransmitter systems key to the expression of a placebo response. The growing evidence that placebo effects have neurobiological bases and anecdotal observations that placebo effects modulate clinical outcomes, substantiate placebo's rightful place in pharmaceutical cabinets. A large number of doctors already use placebos in daily clinical practice (a recent study found that number to be as large as 50%; Tilburt et al., 2008) suggesting that their utility is widely appreciated in current clinical practice. With induction- and context-dependent effects that often mimic treatment with the prescribed physiologically active compounds and with fewer side effects than encountered with pharmacological interventions, the argument for incorporating placebo into common clinical practice is a strong one.

The purpose of the current review is twofold: (1) to synthesize the literature regarding the known neurobiology of the placebo effect, with sharp focus on learning and memory mechanisms that form the placebo response, and (2) to focus on the placebo effect in medicine to argue for its incorporation as a tool for treating the most vexing neuropsychiatric diseases and pain disorders, including substance use disorders.

2. The placebo and nocebo effect

Derived from the Latin root *placere* ("to please"), the term *placebo* refers to the positive cognitive modulation of behaviors and outcomes (Colloca et al., 2013a, 2013b) related to medical treatment (its antithesis, nocebo, refers to negative cognitive modulation). Implemented

* Corresponding author at: 655 W. Lombard Street Suite 729, 21201 Baltimore, MD, USA.
E-mail address: colloca@son.umaryland.edu (L. Colloca).

http://dx.doi.org/10.1016/j.pnpbp.2017.06.003
Received 1 March 2017; Received in revised form 1 June 2017; Accepted 3 June 2017
0278-5846/ © 2017 Published by Elsevier Inc.

in clinical practice long before being objectively studied, the first placebo-controlled clinical trial was likely conducted by John Haygarth in 1801 (de Craen et al., 1999) when he demonstrated that a tool invented to treat pain and other ailments was nothing more than an expensive sham.

At its core, the placebo effect is driven entirely by processes that lie outside of a controllable, physiologically active intervention (usually the focus of empirical study and manipulation); thus, it has a long and checkered history as a nuisance variable with which to be contended in medicine. More recent investigations into the mechanisms and conditions under which placebo effects are robustly elicited have yielded a greater appreciation of its therapeutic potential, and increasingly more research has turned its focus to study ways in which to harness that potential (Colloca et al., 2016). Important to this understanding is an appreciation of how the placebo/nocebo response is formed. Traditionally, placebo effects have been attributed to two mechanisms: expectancies (e.g., a doctor's suggestion that a pill will work to ameliorate symptoms can enhance patient expectations about treatment efficacy), and Pavlovian conditioning (e.g., the medical context [a doctor's presence and the smell of a treatment / environment] in which a medication is supplied begins to take on properties of the medicinal benefits, and thus affords relief). But this simple dichotomy does not cover the full range of ways in which a placebo response can be induced, nor does it provide a theoretical framework for testing ideas of the placebo effect. We have previously illustrated a learning perspective in which to couch our understanding of how placebo effects are formed (Colloca and Miller, 2011a, 2011b; Colloca, 2014).

2.1. How placebo/nocebo effects are formed

Despite its historical presence in clinical practice and its long use as a positive control in clinical trials, empirical research on the underlying neurobiology of the placebo effect is in its early stages. Born in the late 70s with Levine's seminal finding that placebo analgesia expression is dependent on opioid receptor function (Levine et al., 1978; Zubieta and Stohler, 2009), the pace and breadth of knowledge acquired from these studies has been delivered at an impressive rate. Emerging from this relatively recent data is the notion that several neurobiological substrates and multiple systems are independently involved in the expression of a placebo response. An unresolved issue is how to square these multiple mechanisms with the expression of an isomorphic placebo effect. The bulk of this evidence is derived from studies of placebo analgesia, and suggests that placebo and nocebo effects can be elicited via three conduits: by conditioning, by verbal instruction, and via social observation and interactions (Colloca et al., 2013a, 2013b), indicating that a learning perspective provides a strong framework to approach the study of the placebo effect.

2.1.1. Learning via conditioning

Classical conditioning, the phenomenon whereby any external agent can, by coinciding in time with an ordinary reflex, becomes the conditioned signal for the formation of a new conditioned reflex (Pavlov, 1927), has served as the predominant framework for understanding the formation of placebo (and nocebo) effects. Similar to the conditioned stimulus of ringing a bell, visual, tactile, and gustatory stimuli associated with the efficacy of a medication can become conditioned stimuli via repeated associations with the unconditioned stimuli of an active medication (Colloca, 2014).

Early support for a classical conditioning interpretation of the placebo effect arose from studies with animals, with demonstrations that dogs, rats and mice display central behavioral (attenuations in lever-pressing and behavioral responses to pain) and peripheral (immunosuppressive and hormone) responses to learned drug-paired conditioned cues, even in the absence of the drug (Herrnstein, 1962; Ader and Cohen, 1975, 1982; Ader et al., 1993; Pacheco-Lopez et al., 2009; Guo et al., 2011; reviewed in Colloca, 2014). Ader and colleagues championed efforts to extend these proof-of-concept findings to humans, and in a series of studies, showed that a schedule of pharmacological reinforcement with immunosuppressors associated with placebos worked to maintain positive clinical outcomes in patients suffering from immune disorders (Olness and Ader, 1992; Giang et al., 1996). In a landmark study, Goebel et al. (2002) showed that placebo can suppress markers of immune function (mRNA expression and release of IL-2 and IFN-gamma as well as lymphocyte proliferation).

This phenomenon of placebo conditioning has been demonstrated in other contexts, most notably, in conditions of experimental pain. In a series of experiments, Benedetti's group showed that a placebo response could be elicited by pairing morphine with placebo, an effect that is dependent on the strength of the association paradigm that was used to create the conditioned response (Amanzio and Benedetti, 1999; Benedetti et al., 2003, 2007a, 2007b). This same group has explored the effects of conditioning using other drugs, including serotonin receptor agonists (sumatriptan, which works at 5-$HT_{1B/1D}$ receptors; Benedetti et al., 2003) and dopamine receptor agonists (apomorphine, a non-selective agonist; Benedetti et al., 2016).

Although the majority of conditioned placebo effects have been explored under continuous reinforcement paradigms (i.e., placebo is associated with the relevant outcome 100% of the time), partial reinforcement paradigms (learning paradigms in which a cue is paired with the relevant outcome on some, but not all trials; Bouton, 2007) also induce placebo and nocebo effects (Au Yeung et al., 2014; Colagiuri et al., 2015a). Relative to continuous reinforcement, partial reinforcement leads to weaker placebo/nocebo effects, but these effects are less susceptible to extinction. Interestingly, nocebo effects are more resistant to extinction, irrespective of reinforcement schedule (Colloca et al., 2008, 2010).

We have previously argued (Colloca and Miller, 2011b) that conditioning can be understood as a process generating expectations in humans and nonhuman animals. In the following section, we turn our focus to an understanding of verbally conferred and expectation-induced placebo effects.

2.1.2. Learning from verbal cues

Kirsch (1985, 1990), author of a general model of expectancy, posited that a placebo produces an effect because the recipient expects it. When placebo interventions do not have physical components with intrinsic pharmacological or physiological properties, it is assumed that these effects are due to the recipient's expectations. According to this view, Kirsch labeled beliefs that appear to mediate the placebo effects "response expectancies," defining them as "anticipation of the occurrence of non-volitional responses". Thus, for example, the expectation of symptom relief such as pain reduction following a placebo that is presented to the subject as a pain-relieving medication may produce an analgesic effect (Colloca and Miller, 2011b).

In a clinical psychology framework, expectations have been defined as future-directed cognitions that focus on the incidence or non-incidence of a specific event or experience (Kube et al., 2016). Based on the Rescorla-Wagner model (Rescorla, 1967), expectations are developed through learning processes (Cleeremans and McClelland, 1991; Colloca and Benedetti, 2009; Colloca and Miller, 2011a). Expectations contribute substantially to clinical outcomes in various medical conditions (Auer et al., 2016; Nestoriuc et al., 2016), and have been shown to be one of the major components contributing to placebo and nocebo responses in clinical trials (Rief et al., 2008; Rief et al., 2011; Schwarz et al., 2016), substantially enhancing the effects of drug-specific components (see Kube and Rief, 2016, for a review). With regard to antidepressant clinical trials, large placebo effects have been reported (Kirsch and Sapirstein, 1998; Kirsch et al., 2002; Kirsch et al., 2008; Rief et al., 2009), and they are assumed to be mainly based on expectation mechanisms (Shedden-Mora et al., 2011; Rutherford et al., 2016). Given the great impact of expectancies in clinical research, Rief et al. (2015) have discussed expectancies as core features of mental

Download English Version:

https://daneshyari.com/en/article/8950162

Download Persian Version:

https://daneshyari.com/article/8950162

Daneshyari.com