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Role of Placebo Effects in Pain and Neuropsychiatric Disorders

Annabelle M. Belcher[1], **Sergi Ferré**[2], **Pedro E. Martinez**[3], and **Luana Colloca**[4,5,6]

[1]Department of Psychiatry, School of Medicine, University of Maryland, Baltimore, USA

[2]National Institute on Drug Abuse, National Institutes of Health, Bethesda, USA

[3]National Institute of Mental Health, National Institutes of Health, Bethesda, USA

[4]Department of Pain and Translational Symptom Science, School of Nursing, University of Maryland, Baltimore, USA

[5]Departments of Anesthesiology and Psychiatry, School of Medicine, University of Maryland, Baltimore, University of Maryland, Baltimore, USA

[6]Center to Advance Chronic Pain Research, University of Maryland, Baltimore, USA

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.

Keywords

Nocebo Effect; Pharmacological and Context-Dependent Conditioning; Verbal suggestion; Expectancy; Social Observational

Correspondence to: Luana Colloca, MD, PhD, 655 W. Lombard Street Suite 729, 21201 Baltimore, MD; Phone: +1 410-706-8244; Fax: +1 410-706-5427; colloca@son.umaryland.edu.

1.0 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-Hensen 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%; Tibert 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.

2.0 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 in clinical practice long before being objectively studied, the first placebo-controlled clinical trial was likely conducted by John Haygarth in 1801 (de Crae 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, 2011; 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 Stöhler, 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 disorders, a therapeutic treatment target in major depression (Kube et al., 2017).

In general, expectations leading to placebo effects can be formed from information learned from the environment, via personal experiences and from anticipation of benefit. External inputs are dynamically connected with individual beliefs and internal states, leading to the formation of a placebo response (Colloca and Miller, 2011b). But learned expectations can also be produced via social observation, discussed in this next section.

2.1.3 Social observational learning—The third component in the triad of learning-induced health effects involves cues derived from social observational learning. Beyond direct first-hand experience, people can learn by observing others; by extension, placebo effects can be formed by means of observational learning in a social context without any deliberate reinforcement. Colloca and Benedetti (2009) investigated the role of observational social learning in placebo analgesia in healthy subjects who learned by observing the experience of a demonstrator who simulated an analgesic benefit. Substantial placebo analgesic effects were found following observation of the demonstrator, suggesting that the information drawn from observation of another person may establish a self-projection into the future outcome. These effects exhibited no extinction over the entire experimental session, indicating implicit acquisition and retention of behavioral output. The magnitude of observationally induced placebo effects was similar to those induced by directly experiencing the benefit through a conditioning procedure in which subjects underwent first-hand experience of benefit. Interestingly, the more pronounced observationally induced placebo effects were found in those subjects who presented higher empathy scores. This suggests a link between the ability to modify behaviors following mere observation, the formation of placebo analgesia effects and empathy. These observations emphasize that social interactions are potential cues to induce expectations of benefit and might activate specific brain–body mechanisms. Pursuant to this study, other reports have emerged suggesting strong social observational learning processes in the formation of placebo effects. Subjective experience of side effects from an inhaled substance was significantly different between subjects who observed a confederate react, or not react, to side effect symptoms (headache, itchy skin, etc.; Mazzoni et al., 2010); findings which corroborate the involvement of social cues in the placebo response. Social contagion has been reported also in the context of high altitude headache in which seeing the side effect in one single person caused a pandemic of the side effect in a group (Benedetti et al., 2014). In accord with this,

scores on personality trait assessments of empathy correlate positively with the potential to learn from these social observational cues (Colloca and Benedetti, 2009).

Recently, other studies have extended this line of research, demonstrating observationally induced placebo effects of viewing a video of a demonstrator reporting less pain (Hunter et al., 2014), and observationally induced nocebo effects, observing a treatment leading to hyperalgesia in a demonstrator (Vögtle et al., 2013). Sex effects have been reported (Swider and Babel, 2013), opening up new avenues to understand the potential impact of socially induced placebo/nocebo effects in real-world clinical settings (for a review, see Schenk et al., 2017).

While social observational learning can be gleaned from subtle, indirect cues obtained from the clinical environment, the interpersonal interaction appears to complement this mechanism. Among these cues are the prosocial behaviors and supportive environment that are (hopefully) encountered in the clinical experience—factors that have proven to be soluble determinants in treatment outcomes. In a clear design aimed to investigate the effects of patient-provider interactions, patients with Irritable Bowel Syndrome enrolled in a run-in phase of a randomized trial comparing *verum* and sham acupuncture reported greater symptom relief when they received an augmented sham acupuncture intervention arm consisting of a longer and more empathetic initial conversation with the practitioner (as compared to a more business-like sham intervention whereby communication between practitioner and patient was reduced to a minimum; Kaptchuk et al., 2008).

2.2 Neurobiological underpinnings of the placebo and nocebo effect

Studies of the neurobiological components underlying the placebo response have revealed distinct brain circuitries and pathways in the manifestation of the placebo effect. Brain activation during an analgesia placebo response involves pain-processing areas including the amygdala, anterior cingulate cortex (ACC), and prefrontal cortex (PFC) with subsequent descending inhibitory noxious control down to the level of the spinal cord (Eippert et al., 2009). Similarly, Wager et al. (2004) reported placebo-associated reductions in the activity of the rostral ACC, insular cortex and thalamus, reductions that correlated with the subjectively rated pain relief afforded by the placebo administration. Expounded upon in the following section (3.0), randomized controlled trial studies with patients have further elucidated the “placebo/nocebo processing” areas of the brain. In different patient populations, the striatum (Keitel et al., 2013; Frisaldi et al., 2014), PFC, subgenual cingulate, parahippocampus, and thalamus (Mayberg et al., 2002; reviewed in Enck et al., 2013) and peripheral release of cytokines (Goebel et al., 2008) have all been implicated in the placebo/nocebo response.

The key neurotransmitters identified in the expression of a placebo analgesic response include the opioid (with particular relevance for the μ-opioid receptor), cannabinoid and dopaminergic systems. In the late 70s, Howard Fields’ group was the first to report that the endogenous opioid system played an inextricable role in the formation of placebo effects, by showing that placebo expression could be entirely blocked by naloxone, an opioid inverse agonist that dose-dependently blocks opioid receptor function (Levine et al., 1978). In a now-classic paper, Amanzio and Benedetti (1999) parsed the relative contributions of

expectancy and conditioning to the placebo response, showing that placebo effects mediated by expectation and opioid conditioning were completely blocked by naloxone administration, but not when a non-steroidal anti-inflammatory drug with no effect on the opioid system (ketorolac) was used as the pre-conditioning agent. Evidence for dopamine system involvement in the placebo response first derived from findings that nucleus accumbens dopamine was associated with subjective expectations of improvement (de la Fuente-Fernandez, 2001). Using positron emission tomography in a study designed to simultaneously examine the relative contributio ns of these two main neurotransmitter systems implicated in the placebo response, Scott et al. (2008) reported placebo-induced opioid activation in the anterior cingulate, orbitofrontal and insular cortices, nucleus accumbens, amygdala, and periaqueductal gray matter, and dopaminergic activation in the ventral basal ganglia, including the nucleus accumbens. Interestingly, this group found the opposite—decreased opioid and dopaminergic neurotransmission—in the expression of a nocebo response, suggesting that dopamine-innervated brain areas underlying reward and motivated behavior reinforce the placebo and nocebo response (Zubieta and Stohler, 2009). Interestingly, a recent study using an animal model of conditioned placebo preference indicated that cue preference by reward learning depends on the dopamine system (the dopamine antagonist haloperidol blocked the place preference effect) whilst conditioned placebo analgesic effects are related to the dopamine and opioid systems (haloperidol and naloxone blocked the placebo analgesia, Lee et al., 2015). Future research on the interaction between opioids and dopamine systems (Moereno et al., 2017) is critical to advance knowledge on the formation of animal and human placebo effects.

2.3 Genetic variants associated with placebo effects

Recently, genetic variants have been found to be associated with certain placebo effects in the context of pain (the best-documented area of research) and anxiety disorders and depression (for a review see, Colagiuri et al., 2015b). In a landmark study, Furmark et al. (2008) found evidence of a link between genetically controlled serotonergic modulation of amygdala activity and placebo-induced anxiety relief, and further demonstrating that a serotonin precursor (tryptophan hydroxylase-2 gene promoter, *TPH2*; rs4570625) polymorphism was a significant predictor of clinical placebo response. Additionally, genetic polymorphisms modulating monoaminergic tone (monoamine oxidase-A [*MAO-A*; rs6323; rs6609257; and rs2235186] and catechol-o-methyl-transferase [*COMT*; rs4680] (an enzyme important for prefrontal catecholaminergic degradation) have been related to the degree of placebo responsiveness in major depressive disorder as well as in Irritable Bowel Syndrome (Leuchter et al., 2009; Hall et al., 2012).

The functional rs1799971 polymorphism in the μ-opioid receptor gene (*OPRM1*) has been associated with neural and objective placebo analgesia along with placebo-mediated activation of dopamine neurotransmission in the nucleus accumbens using positron emission tomography (PET) and selective radio tracers to label μ-opioid and dopamine receptors (D_2/D_3; Peciña et al., 2015). The investigation of the role of genetic variations within the opioid system in pain and placebo-induced reduction of pain demonstrated that relative to G-allele carriers, AA homozygotes exhibited an increase in μ-opioid receptor availability in brain areas associated with pain and mood. Moreover, AA homozygotes presented less

dopamine release in the NAc after pain induction. The administration of an intravenous placebo treatment prompted individuals with G alleles to show worse mood, lower μ-opioid activation in the anterior insula (aINS), the amygdala (AMY), the NAc, the thalamus (THA), and the brainstem, and lower dopamine receptor activation levels ($D_{2/3}$) with higher NEO-Neuroticism personality scores observed in the G allele carriers.

A functional variant in the fatty acid amide hydrolase (*FAAH,* which metabolizes the endogenous cannabinoid anandamide) gene has been also involved in the regulation of pain modulation and placebo analgesia. Homozygous for the common Pro129/Pro129 *FAAH* genotype showed larger placebo analgesia and affective state (Peciña et al., 2014). The opioid and the cannabinoid systems in the context of placebo analgesia appear to act together in pain relief with endocannabinoids mediating placebo analgesia (Benedetti et al., 2011).

The bulk of evidence concerning the neurobiological correlates of the placebo/nocebo response derives from experimental laboratory studies. The fact that placebo effects may differ in patient populations begs a revisit to the areas that underlie the placebo/nocebo response. In the following section we discuss this discrepancy, and review placebo effects in randomized controlled trials (RCTs) of neuropsychiatric disorders.

3.0 Placebo effects in randomized controlled trials

Widely used by clinicians in daily practice and effectively elicited in laboratory experimental contexts, it is not denied that the placebo effect exists. Yet clear evidence for a strong placebo response has eluded researchers conducting clinical trials. In one of the first meta-analyses conducted aiming to uncover placebo effect sizes, the Danish Cochrane Center published a report about 15 years ago with the challenging title, “Is the placebo powerless?” (Hróbjartsson and Gøtzsche, 2001). Reviewing 130 articles reporting on placebo effects in a variety of conditions (pain, depression, nausea, insomnia, smoking, hypertension, anxiety, asthma, obesity), although the authors found consistent placebo effects, effect sizes were shown to be minor in comparison to the standards of effective medical treatment, as defined by clinical experience and/or regulatory authorities (FDA, EMA; Weimer et al., 2015). A subsequent follow- up meta-analysis revealed similar results (Hróbjartsson and Gøtzsche, 2004), lending weight to notions that placebo effects may be reflective of other, independent factors such as regression to the mean or spontaneous recovery. Others have argued for subtler reasons to explain why placebo effects in RCTs appear less effective than in experimental settings (Vase et al., 2002), including the fact that in many experiments, placebo effects are enforced verbally, are performed unblinded for the investigator, and do not control for “spontaneous variation of symptoms” (habituation, sensitization)—thereby confounding response biases with placebo effects (Horing, 2014). With the largest proportion of studies of the placebo effects constrained to pain and depression clinical trials, whether, and to what degree this holds for placebo effects in other neuropsychiatry arenas is unclear. Weimer and colleagues have recently published a qualitative review of the mediators and moderators of placebo effects in neuropsychiatric clinical trials. Among the several patient- and design-based factors assessed (e.g., individual variables versus study design variables), we found two variables that predicted a high

placebo response: (1) low symptom severity at baseline, and (2) unbalanced group randomization (Weimer et al, 2015).

Randomized Controlled Trials (RCTs) using (principally) neuroimaging tools have contributed greatly to current understandings of the neurobiological mechanisms of the placebo and nocebo response, and a common theme is that of the involvement of distinct brain circuitries and pathways in the placebo response. For placebo analgesia, brain activation during a placebo response involves pain-processing areas including the amygdala, ACC, and PFC, with subsequent descending inhibitory noxious control (DINC) down to the level of the spinal cord (Eippert et al., 2009). For motor dysfunctions such as in Parkinson's Disease, activation of the striatal dopaminergic system (Keitel et al., 2013; Frisaldi et al., 2014) has been reported, for immune suppressive functions the control of the peripheral release of cytokines (Goebel et al., 2008), and for depression metabolic changes involving the PFC, subgenual cingulate, parahippocampus, and thalamus (Mayberg et al., 2002, discussed below). Many neural mechanisms in other diseases still wait for their exploration, especially in patients with psychiatric disorders that are difficult if not impossible to investigate with experimental models in healthy volunteers.

In the following sections, we review randomized controlled trial studies of brain mechanisms involved in placebo effects for three of the most common neuropsychiatric disorders: depression, disorders of anxiety, and substance use disorders.

3.1 Placebo effects in studies of neuropsychiatric disorders and disease

According to recent results from the National Survey on Drug Use and Health, in 2011 an estimated 19.6% of the adult U.S. population suffered a mental illness within the past year (SAMHSA, 2012). Three classes of mental health disorders (MHDs) are particularly common in the U.S.: depressive, anxiety, and substance use disorders (SUD), with lifetime prevalence rates of approximately 17%, 29% and 35%, respectively. These debilitating neuropsychiatric disorders represent the largest global burden of mental health, and unfortunately, are among the most difficult mental health ailments to treat, with variable therapeutic results from neuropharmacological and cognitive behavioral therapy interventions. As such, the pressing need for treatment alternatives for neuropsychiatric disorders cannot be understated.

There is little debate concerning strong placebo effects in short-term randomized controlled trials of anti-depressant treatment (Khan et al., 2000). With the first studies imaging the placebo response in the brain published only in the early 2000s (de la Fuente-Fernandez, 2001), investigators have continued the search for common neurobiological mechanisms underlying placebo effects in various medical conditions.

In 2002, Helen Mayberg's group published a seminal study investigating the placebo effect in clinical depression, and provided the first evidence of brain glucose utilization changes associated with the placebo response. In the study, patients with unipolar depression were enrolled in a 6-week double-blind treatment to receive either fluoxetine (a serotonin reuptake inhibitor) or placebo. Brain glucose metabolism (assessed with Positron Emission Tomography [PET]) and clinical assessments of depression were measured prior to and

following the trial. As the group correctly posited, placebo responsive participants (i.e., those participant assigned to the placebo group and who showed clinical improvement) showed brain metabolism changes that overlapped considerably with those changes found in patients receiving fluoxetine who showed clinical improvement in depression. Specifically, placebo response was associated with regional metabolic increases involving the prefrontal, anterior cingulate, premotor, parietal, posterior insula, and posterior cingulate, and metabolic decreases involving the subgenual cingulate, parahippocampus and thalamus. Fluoxetine was further associated with subcortical and limbic changes in the brainstem, striatum, anterior insula and hippocampus, leading the authors to hypothesize a fluoxetine-conferred long-term treatment advantage (Mayberg et al., 2002). Although these findings further strengthen arguments for placebo-induced behavior and brain changes, an unfortunate caveat to this (and many clinical trial studies) is the omission of a no-treatment arm—a control which would allow for a more conclusive determination of placebo-related changes outside of spontaneous remission.

Given the plethora of evidence to suggest strong opioidergic involvement in the manifestation of the placebo response, as well as the known role of this neurotransmitter in the regulation of emotion, stress and social rewards (factors which are all relevant to depression), Peciña et al. (2015; again, using PET) explored μ-opioid receptor (MOR)-mediated neurotransmission as a potential candidate mechanism for the formation of placebo effects in major depression. As predicted, the authors found MOR activation to be associated with the placebo response in these patients, with higher baseline MOR binding in the nucleus accumbens associated with better response to antidepressant treatment. Furthermore, placebo response was associated with increased μ-opioid neurotransmission in a network of regions implicated in emotion, stress regulation, and the pathophysiology of major depression, namely, the subgenual anterior cingulate cortex, nucleus accumbens, midline thalamus, and amygdala.

A strong case has been made by many that placebo effects—if managed effectively—could open doors for non-pharmacological treatment alternatives. Brown (1994) issued a position paper calling for a 6-week placebo “front-line” treatment ahead of anti-depressant medication administration (Brown, 1994). The risks involved in the delay of routine accepted clinical treatment are not trivial, which makes the need for biomarkers of placebo responsiveness of paramount importance.

Indeed, manipulation of expectations and pharmacological conditioning in clinical trials is a promising strategy for developing knowledge relevant to promoting placebo effects in clinical practice. In a study of children with Attention Deficit Hyperactivity Disorder (ADHD), subjects received different combinations of stimulant drug (amphetamine) treatment and open-label “dose-extender” placebo pills. The subjects were then randomly assigned to 1 of 3 schedules of 8-week treatments: 1) 50% reduction of amphetamine dose by pairing drug with placebo; 2) 50% reduction of amphetamine without placebo substitution; or 3) full dose of amphetamine treatment. The group found that pairing a placebo pill with routine ADHD medication allowed subjects to be treated effectively with those conditioned placebo pills in the face of stimulant dose reduction—a treatment regimen with efficacy that rivaled that with sustained stimulant medication administration (Sandler

and Bodfish, 2008; Sandler et al., 2010). Based on a broad literature showing that placebo effects can be manifest in addiction contexts, there is strong justification for extending the ameliorative benefits of placebo effects to an addiction clinical treatment context.

3.2 Neurobiological substrates of Substance Use Disorder

Several decades of research have yielded considerable information regarding the neural, behavioral and genetic factors implicated in Substance Use Disorder (SUD). Interestingly, there is considerable overlap between these various factors and those implicated in the formation of placebo effects, further strengthening the argument for the incorporation of placebos into therapeutic strategies for the treatment of SUD as well as pain disorders (Colloca et al., 2016). Although an extensive review is outside the scope of this manuscript, the following sections briefly touch on several points of intersection, vis-à-vis those factors that are implicated in SUD.

3.2.1 SUD and learning and memory processes—Like natural reinforcers such as food or sex, drugs (including opioids) act on multiple limbic, cortical and subcortical brain areas to modulate memories that surround the drug-taking experience—memories that further instantiate drug-seeking and -taking behaviors. Multiple studies have confirmed that the brain regions that participate in the anticipation, craving and seeking of drugs are the same regions that have an important role in the formation of several types of memory, including declarative, non-declarative and habit formation. These include brain regions such as the hippocampus, amygdala, dorsal striatum and prefrontal cortical areas (Torregrossa et al., 2011, Jasinska et al., 2014). Evidence for the strong role that learning and memory processes play in drug consumption behaviors derives from recent studies showing that disruption of the functional or structural plasticity processes involved in learning and memory formation during drug acquisition or retrieval disrupts drug-seeking behaviors (Malvaez et al., 2010 and Young et al., 2014). Barry Everitt and colleagues have made great strides towards furthering the argument for the conceptualization of addiction as an engagement of aberrant learning and memory processes (Everitt and Robbins, 2005). They have reframed this argument, proposing a theory that invokes a role for Pavlovian conditioning principles in the formation of addictive behaviors. In a virtual high-jacking of stimulus-response memory processes, repeated drug consumption leads to enhanced learning about the actions and environmental, drug-associated cues or conditioned stimuli (CSs) that predict opportunities for drug self-administration. Consequently, these CSs acquire an increasing role in controlling drug seeking behavior (Sjoerds et al., 2013). Similarly, placebo effects have been largely explored via conditioning paradigms and more recently conceptualized in terms of learned effects and contextual effects (Colloca and Miller, 2011; Colloca 2014; Wager and Atlas, 2015). Considering the Pavlovian conditioning principles involved in the placebo effect (see *2.1.1* above), there is strong rationale to believe that these same individuals who have been strongly conditioned to stimuli that predict drug use may also be highly placebo-responsive.

3.2.2 SUD and genetics—Converging evidence suggests that through interactions with environmental factors, genes determine susceptibility to developing SUD (Kendler et al., 2012). A rich literature has emerged in recent years promoting the use of endophenotypes

for the identification of SUD-associated genes (Gottesman and Gould, 2003), and many of these identified genetic factors have been found to either directly or indirectly moderate catecholaminergic, and particularly, dopaminergic transmission and function. These include those that code for polymorphisms of the dopamine D2 and D4 receptor genes, as well as polymorphisms of the dopamine transporter gene (LaHoste et al., 1996; Cornish et al., 2005; Volkow et al., 2006; Congdon et al., 2008; Wang et al., 2013; reviewed in Belcher et al., 2014 and). Of interest, strong associations have been drawn between the above described variations in the *COMT gene* (rs4680, VAL158MET polymorphism), and SUD (or its endophenotypes; Lohoff et al., 2008; Smith and Boettiger, 2012; Soeiro-De-Souza et al., 2013). The single nucleotide polymorphism in the human *OPRM1* gene (rs1799971) described above (see Section 2.3) for placebo analgesic responsiveness has long been a candidate SUD-associated gene, with associations made between the functional polymorphism A118G and alcohol and opioid dependence (Schwantes-An et al., 2016). Interestingly, this polymorphism, which is precisely the same that is relevant to placebo response (rs1799971), is very relevant for addiction treatment *response*, raising the distinct possibility that these gene-SUD associations (Anton et al., 2008; Ray and Hutchison, 2004; Lerman et al., 2004) may reflect genetically-conferred influences on placebo effects (Hall et al., 2012; Colagiuri et al., 2015b).

3.3. Harnessing placebo effects for the treatment of substance use disorder

As described above, the placebo effect is particularly interesting in the context of substance use disorder (SUD) for its high degree of overlap in the genes and brain substrates implicated in addiction, as well as for its clinical treatment implications. Several studies suggest that expectations play a role in differential drug consumption including nicotine (Juliano and Brandon, 2002; Kelemen and Kaighobadi, 2007), alcohol (Rohsenow and Marlatt, 1981; Hull and Bond, 1986), and marijuana (Metrik et al., 2009). In one of the earliest studies in line with this, Marlatt et al. (1973) showed that alcohol drinking patterns could be modulated in alcohol-dependent subjects, depending on what the subjects were led to believe concerning the alcohol content of the beverage: when expecting to sample a drink containing alcohol, alcohol-dependent subjects consumed almost twice as much of the beverage as those expecting to receive only non-alcoholic beverages. This strong top-down modulation of expectation provides girth for the hypothesis that placebo effects could be harnessed to help achieve better clinical outcomes for patients receiving treatment for SUD. But the process of effectively harnessing the potential therapeutic effects of expectations should be guided by an understanding of the neurobiological mechanisms that underscore expectation, an area in which Nora Volkow’s group has made great strides.

In a pivotal study, using a balanced placebo design, Volkow et al. (2003) investigated the effect of placebos in both cocaine abusers and non-drug abusing subjects. Using FDG-PET, they described the effects of methylphenidate on brain glucose metabolism in subjects who were informed they would: 1) receive the drug and indeed received the drug; 2) receive the drug but received placebo; 3) receive placebo but they received the drug; 4) receive placebo and indeed received placebo. They reported a significant effect of modulating expectations, as brain metabolic changes were about 50% greater when the subjects were informed about receiving drug, in comparison with the group of subjects who were informed about receiving

placebo. Surprisingly, methylphenidate induced smaller metabolism changes in the thalamic and cerebellar regions, thus indicating that expectations potentiated the pharmacological action of methylphenidate. In contrast, non-drug abusing subjects show different patterns of response. Healthy, non-drug using subjects presented brain glucose metabolism changes in regions such as the ventral gyrus (BA 25) and nucleus accumbens (NAc; Wang et al., 2006a; Volkow et al., 2006b). The different patterns of activation in cocaine and non-cocaine abusers show that the influences of expectations can dramatically change; yielding a clear demonstration that drug exposure that alters dopaminergic tone can fundamentally change expectation-related brain responses. The enhanced thalamic and cerebellar responses in cocaine abusers may be due to conditioned responses, whereas the changes in the striatum observed in the non-drug-abusing subjects may indicate the prevalence of novelty and reward mechanisms.

Spagnolo et al. (2015) recently reviewed the literature on placebo effects in SUD contexts, paying particular attention to the important salutatory (and if not managed correctly, detrimental) patient-provider relationship, determining that there is potentially very valuable use of positive expectations in this therapeutic context. Drug addiction has been characterized, at least in part, as a form of maladaptive learning (Kauer and Malenka, 2007; Robinson and Berridge, 2008). In a meta-analysis designed to investigate placebo effects in clinical trials for alcohol dependence, Litten et al. (2013) reported a negative relationship between placebo response and treatment effect sizes, suggesting that as in other disease arenas, addiction severity may be inversely correlated with placebo response. But to date, no study has attempted to use the placebo response as a treatment strategy in SUD.

As described in the preceding sections, converging evidence has yielded greater appreciation of the therapeutic potential of the placebo response. Increasingly more research has turned its focus to study ways in which to ethically harness that potential (Colloca et al., 2016), and various strategies have been offered in service of this goal. It is our view that these various strategies all incorporate learning principles, with differences in how the learning is acquired: via conditioning, verbal cues that guide expectation, or social observational cues that again, guide expectation. We submit that in addition to the clinical contextual cues that guide expectation (and thus, outcomes; meted out in Spagnolo et al., 2015), that the field of addiction treatment services would be benefitted greatly by clinical trials that incorporate aspects of these tools of the research on placebo effects.

One example of a "placebo tool" capitalizes on principles of Pavlovian condition, by pairing placebo pills and clinical contextual cues (conditioned stimuli) with a physiologically active treatment (unconditioned stimuli). Using this strategy in other treatment contexts, researchers have shown that medication dosages can be lowered without decreasing treatment efficacy. For example, Ader and colleagues demonstrated that placebos extend the effects of corticosteroids in psoriasis patients when given in accordance with a partial reinforcement paradigm (Ader et al., 2010). The frequency of disease relapse under this partial reinforcement paradigm was lower (26.7%) than in the control group (61.5%), outcomes that were clinically comparable to the reduction in symptoms induced by a full-dose regimen of topically applied corticosteroids (22.2%) (Ader et al., 2010). Similarly, Perlis and colleagues applied a reinforced therapeutic schedule to medically manage chronic

insomnia using 10 mg zolpidem pill with 50% active medication and 50% placebos for 12 weeks. The partial reinforcement group showed the same clinical benefit as the groups randomized to 10 mg or 5 mg or intermittent 10 mg nightly dosing (Perlis et al., 2015). Children with ADHD showed a therapeutic benefit when placebo pills were paired with a 50%-reduced dose of amphetamine (Sandler and Bodfish, 2008; Section 3.2). Thus, pairing a conditioned stimulus with corticosteroids, zolpidem or amphetamines produced placebo conditioned responses that allowed individuals to be treated effectively with lower doses of the active medication. Given the increase in clinically available drugs for the treatment of alcohol, stimulant and opioid dependence (including disulfiram, buprenorphine and methadone), it would not be difficult to imagine cleverly designed randomized controlled trials exploring pharmacological conditioning or verbal manipulation of expectation paradigms that incorporate placebo administration into the treatment protocol.

As with all studies incorporating placebo administration, the potential is great to move into ethically murky areas if the placebo administration protocol requires blind participant treatment assignation. A very interesting and relatively new area of research suggests that placebos can be efficacious, even under non-blind administration conditions (i.e., the patient is aware that s/he is taking a physiologically inert pill). This strategy for ethically harnessing placebo effects is known as "open-label placebo" administration. In the large majority of these studies, patients in research settings are given placebo pills in an honest and transparent manner, and are told something in accord with, "we know that placebos have powerful effects in double-blind trials and we want to test whether placebos work even if a patient knows they’re taking placebos." Several such experiments have yielded positive results on conditions such as irritable bowel syndrome (Kaptchuk et al., 2010), chronic low back pain (Carvalho et al., 2016), migraine headache (Kam-Hansen et al., 2014), allergic rhinitis (Schaefer et al., 2016) and depression (Kelley et al., 2012). Open-label placebo administration circumvents many of the ethical problems historically associated with traditional (deceptive) placebo use, including disrespect of patient autonomy, threats to a clinician’s integrity, and potential damage to societal trust in the medical profession (Colloca et al., 2016, Blease et al., 2016). Again, the incorporation of open-label placebo administration into existing addiction treatment services would inform greatly the potential for placebo effects as a treatment strategy for SUD. Further research is needed in SUD populations, with an aim to understand whether, and to what degree, placebo effects could achievably be used as a treatment strategy for addiction. Understanding the capacity for learning- induced placebo effects to impact outcomes in these patient populations could have very significant clinical and translational implications.

4.0 Conclusions

Placebo and nocebo effects have long been known to be strong modulators of clinical treatment outcomes. These effects are elicited via verbal, conditioned and social cues. Increasingly, the neurobiological systems important for the placebo effect are beginning to be understood. We argue that a learning framework for understanding placebo/nocebo effects provides strong heuristic value because it allows for a single unifying framework in which to explore questions regarding whether, and to what degree, the placebo effect can be managed, and further, the individual differences that determine placebo responsiveness. We

submit that the placebo effect, already shown to be effective for enhancing outcomes in a wide range of clinical treatment settings, can be further harnessed for the effective treatment of chronic diseases such as pain and neuropsychiatric disorders, including depression, anxiety disorders and substance use disorder. To achieve this goal will require more investigators to conduct careful large pragmatic clinical trials and laboratory research in chronic pain and neuropsychiatric disorders conditions that often overlap, of which to date, there is a dearth.

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Highlights

- Placebo and nocebo effects can be elicited by verbal, conditioned and social cues
- Placebo/nocebo expression strength is dependent on multiple neurobiological and genetic determinants, subject to individual differences
- As the placebo effect is increasingly understood, ways in which to harness that therapeutic potential to treat chronic pain and neuropsychiatric disorders is increasingly appreciated