Meaning and Affect in Placebo Effect

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Abstract:

This paper presents and defends an integrated view of the placebo effect, termed "affective-meaning-making" model, which draws from theoretical reflection, clinical outcomes and neurophysiological findings. We consider the theoretical limitations of those proposals associated with the 'meaning view' on the placebo effect which (i) leave the general aspects of meaning unspecified, (ii) fail to fully analyse the role of emotions and affect, and (iii) establish no clear connection between the theoretical, physiological and psychological aspects of the effect. We point out that a promising way to overcome these limitations is given by grounding the placebo effect on Peirce's theory of meaning, in which the role of the meaning constitution and change is placed in logical and objective structures. We also show the connection between our theoretical proposal and the appraisal theory, and integrate it with emotion regulation.

Keywords: placebo effect, meaning, Peirce, medical epistemology, affect, emotion regulation.

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1. **Introduction**

Despite an increasing number of neurophysiological studies on the placebo effect (PE), its *integrated* theoretical, neurobiological and neuropharmacological analysis remains scarcely developed (Colloca and Miller, 2011a). As is well known, the concept of placebo and its effects are of common use in contemporary clinical practice and research. However, unambiguous, consistent and unproblematic definitions of these two concepts can hardly be found in the literature. Placebos have been labelled as "nonspecific" or "inert" substances, but such definitions can be misleading, as pointed out by Brody (2000), Howick (2011), Miller and Brody (2011) and Howick (2017). Sometimes, placebos are conceived and distinguished as "impure", but this expression has been criticized by Louhiala, Hemilä, Puustinen (2015) and Louhiala and Puustinen (2017). In addition, beliefs associated with PE are often regarded – and we believe without enough warrant – as simple self-fulfilling prophecies (on this line of criticism, see Chiffi and Zanotti, 2017). In the present paper, we do not aim at formulating a new definition (or explication) of PE. We offer a contribution towards the building of a theory of PE, which takes into account its epistemology and pragmatic meaning, and in such a way that it is sensitive to the recent findings in neurophysiological research.

A classical definition of placebo is provided by Grünbaum (1986). He defines a treatment process as a placebo not by its non-specific effects but in virtue of its therapeutic effects, which are due to incidental and not to the characteristic components of a therapeutic theory. However, Grünbaum's definition fails to connect PE with psychological and neurophysiological mechanisms. It is relative to a specific theory but not relativized to specific classes of patients, and thus fails to handle a series of issues such as nocebo, side-effects, placebo addiction, withdrawal symptoms and so forth (see, for instance, Lundh, 1987). A brilliant attempt to amend Grünbaum's definition has been recently proposed by Howick (2017).

In what follows, we will rely on a different tradition, in which PE is connected with the *meaning impact* of the patient's cognitive and affective evaluations of a clinical encounter (Brody, 2000; Moerman, 2002). This meaning-making approach to placebo seems to be particularly adequate in order to accommodate neurophysiological findings about the central nervous system (CNS) associated with PE with an integrated theoretical view over the full spectrum of placebo-related phenomena. Yet the meaning approach also faces some difficulties, which our analytical discussion is intended to address by means of the proposed theoretical integration. In particular, we argue that the problems related to the definition of PE also have an impact on both the neuropsychological and the theoretical discussion around these notions. The main mechanisms have been the following three: (i) *classical conditioning*, in which a natural stimulus is repeatedly associated to an unconditioned stimulus, a process that can occur both consciously and unconsciously; (ii) *expectation* (which is always conscious), related to the beliefs and goals of an agent, and (iii) an *affect theory*, in which the key role is played by the appraisals as those cognitive evaluations of problematic situations that can integrate different kinds of information usually required for the conceptualization of personal meanings and expected values (Goli, Rafieian, Atarodi, 2016; Ashar, Chang, Wager, 2017). We argue that the first two mechanisms, i.e. conditioning and expectation, are insufficient explanations that do not generalize well into a comprehensive theory about placebo and its many facets.

Theoretical views on PE have indeed commonly taken into account solely the role of conditioning and expectation, while a theoretical reflection on the relation between the affect theory and PE has remained largely unexplored. We fill this gap by developing a new theoretical framework for the analysis of PE, comprehensive enough to integrate the main features of the affect theory with recent advances in the science of emotion regulation (see Gross, 2014).[1] We also develop an extended meaning model, which we will shape in terms of Charles S. Peirce's

[1] We hope that our view on PE may turn out to be relevant also for clinical practice, where it seems there is still much to be discovered about such phenomenon (Brody and Miller, 2011).

pragmatistic theory of meaning. Our integrated theoretical view, which we term *affective-meaning-making* model of PE, may provide some guidance in orienting the philosophical discussion and connecting it with the theory of affect and cognition.

The paper is composed of five parts. Section 2 introduces the meaning model of PE and some of its variants. Section 3 explains the key elements of Peirce's theory of meaning, signs and communication, and portrays that theory as the meaning model for placebo-related encounters. In order to connect the affective and the meaning-theoretic approaches to PE from a theoretical and neuroscientific perspective, Section 4 explores the possibility to integrate the affect theory with emotion regulation, Section 5 concludes with final reflections of the authors.

2. The meaning model of placebo effect

One of the most relevant theoretical approaches to placebo effect is the meaning model (Brody and Brody, 2000). According to this model, PE is renamed as 'placebo response'. The word "effect" echoes biomedical causality relation that need not be invoked by the word 'response'.[2] In the meaning model,

> "the placebo response seems to be the body's reaction to some healing signal in the environment, which acts through the mind. [...] For something to be a symbol, the receiving person has to be in a certain state of mind, and to have had a certain history. [...] We usually call something a symbol when it stands for or invokes something much more powerful or vast than the thing itself". (Brody and Brody, 2000, 7).

According to this model, PE is assumed the reaction of the body to a signal that belongs to the environment. The environment has some healing property that affects our minds and is acting through them. Therefore, PE is viewed as a meaning relation; a semiotic interaction between the

[2] On the relation between causality and clinical practice, see (Boniolo and Campaner, 2017).

mind and the body in a healing environment,[3] which is capable of orienting a patient's construction of meanings in a positive direction. As a result, patients may change their *thinking* and *feeling* about their illness or condition. It has furthermore been pointed out that

"something has *symbolic significance* for us when it makes us think or feel differently – because we interpret the symbol as representing something bigger than, or beyond its mere physical characteristics". (Brody and Brody, 2000, 9).

It is worth noting, however, that according to Brody PE is compatible with the standard biomedical model of care: clinical procedures (whether pharmaceutical ones such as injections, capsules, pills, etc.) could have *both* a direct effect on the body – as recognized by the biomedical model – but also a symbolic impact producing what is termed a "placebo response" (Brody and Brody, 2000; Giaretta, 2013). Brody has identified three main factors contributing to this change in the meaning of illness:

"[T]he placebo response is most likely to occur when the meaning of the illness experience is altered in a positive direction. A positive change in meaning occurs when one or more of 3 things happens: The patient feels listened to and receives a satisfactory, coherent explanation of his illness; the patient feels care and concern from those around him; and the patient feels an enhanced sense of mastery and control over his symptoms". (Brody, 2000, 650; see also Brody, 1980).

What is particularly relevant for us is Brody's idea that the change in the patient's belief state, which is due to PE, must be accompanied by observable psychological and neurophysiological phenomena (Brody, 1985). In fact, Brody does take into consideration the role of expectancy and classical conditioning, but he admits that "we have virtually no data directly linking any

[3] However, this may be problematic since PE needs not be associated with a healing function or healing environment.

understanding of meaning and symbolic significance with chemistry" (Brody and Brody, 2000, p. 108). This is no longer completely true, but we agree that an integrative perspective between symbolic significance and CNS is vital. Explaining the change of meaning also in terms of brain mechanisms is something that consolidates theoretical, clinical and neuropsychological research on PE. Moreover, we show below how Brody's semiotic view may be refined by a closer exposition of Peirce's pragmatic theory of meaning and signs.

It is evident that, in the meaning model, the notion of meaning is used not only in its semantic dimension, but also encompasses pragmatic and affective features. Some authors have suggested reframing what is usually called "placebo effect" not just as a "placebo response" but as a particular type of a "meaning response" (Morman and Jonas, 2002; Moerman, 2002). The meaning response is the result of the exposure to signs inducing some physiological or psychological effects relevant for the personal interpretation of the meaning of illness. This redefinition of PE in terms of the meaning response has recently been considered as "arguably the most important conceptual development in the area of placebo research" (Walach, 2015, 111).

Even though we do agree on the fundamental role of meaning in placebo research, we also think that this refined model deserves a deeper conceptual integration. First, we prefer not to change the terminology since it is unlikely that the ordinary usage of the term "placebo effect" would be radically changed in biomedical research. Second, Morman and Jonas (2002, 471) have stated in a peremptory way that "the one thing of which we can absolutely be certain is that placebos *do not* cause placebo effects. Placebos are inert and don't cause anything". Yet this statement depends on the assumption that placebos are inert and this, as we have seen, is not always true. In addition, Moerman's approach has been criticised since: (i) the "meaning response" is a broad term and can well be associated to phenomena that are different from PE; (ii) it does not explain cases in which conditioning is independent of perceived meanings, a problem that is not present, as we have seen, in Brody's theory; (iii) responses in meaning can be

positive or negative, while PE refers to positive and beneficial effects[4] (see Miller, Colloca, Kaptchuk, 2009). We maintain that the meaning perspective communicates crucial elements about PE, as soon as the notion of meaning is clarified and connected to psychological and neurophysiological findings. Using Brody's expression, we have to understand the meaning of PE also by means of our "internal pharmacy".

According to the meaning model, PE is a successful implementation of the intention to evoke a suitable process that comes from the understanding and evaluation of a system of significant signs that convey information from different sources and in which "emotion and cognition shape the interpretation of the signs, producing positive and negative impacts on health and perception" (Colloca and Miller, 2011b, 1924). Such an account may explain the relevance of a good doctor-patient communication and the presence of a positive clinical context with familiar rituals that can enhance PE (Benedetti, 2009).[5] These features may well allow patients to find significance in the signs present at clinical encounters. But the presence of similar rituals (which is nonetheless important) does not suffice to erect the backbone for the theoretical explanation of what happens in placebo as a meaning response. Appeal to rituals provides only the anthropological side of the explanation and, as such, remains an insufficient bedrock of a comprehensive theory. A more general (pragmatic and semiotic) explanation as the basis for the meaning model is therefore particularly welcome. Indeed, the theory of signs and communication of Peirce has been proposed as the theory of PE (Miller and Colloca, 2010; Colloca and Miller, 2011a; Walach, 2011). In what follows, we look into the details of those key

[4] Miller, Colloca, Kaptchuk (2009) have suggested to provide an interpretation of PE in terms of *interpersonal healing* which is associated with the view of medicine as an art of providing care for illness. It is related to the power of the doctor to make the patient feel better and the patient to have faith in the doctor in order to make themselves feel better. According to Miller (2005), this mutual faith between doctor and patient can be interpreted according to William James' concept of faith, i.e. "faith consists of a form of belief under circumstances in which we lack adequate evidence to validate of what we belief" (James, 1897, 527). Our approach which is based on Peirce's theory is quite different from Jamesian "will-to-believe" attitudes.

[5] Clinical rituals are also relevant in nursing. However, the role of PE in association with clinical rituals in nursing has not been extensively investigated (Zanotti and Chiffi, 2017).

elements in which way it may be so. The components of that theory such as meaning, actions, habits, interpretant, object and emotion turn out to be particularly relevant in erecting a comprehensive meaning model for PE. This model is not only consistent with but also reinforced by current neuropsychological research on CNS involved in the creation of cognitive and affective parts of PE. We believe that such integrated approach between theoretical and neurophysiological aspects of PE can now shed light on this complex and multifaceted phenomenon. In the next section, we will explore under a new light Peirce's pragmaticism as a theoretical foundation for PE.

3. Charles Sanders Peirce's pragmaticism as the theory of the placebo effect

"The life we lead is a life of signs", declared Peirce in his 1905 *Adirondack Lecture* (MS 1334).[6] What he means is that how we behave and how we shape our own conduct comes not from our actions but from our "resolutions to act". We seek not for certain actions but for general resolutions to act in certain ways in specific kinds of circumstances. Our resolutions are "signs of action", as they must have sufficient generality and applicability. Peirce talks about "habits" as such generalized resolutions to act (Pietarinen, 2005). They refer not to any individual action as the result of any individual choice, but to "generalizing tendencies" to act in particular situations.

The essence of Peirce's theory of meaning, which he in 1905 termed "pragmaticism", is that the meaning of signs comes from what conceivable consequences they have upon our conduct (Pietarinen, 2003). Pragmaticism has recently been reintroduced as a promising revisionary methodology across human, social and behavioural sciences, as it has a capability of reinterpreting fundamental concepts of those disciplines under a new light (see e.g. Kilpinen,

[6] Peirce's works are cited in the text parenthetically, in the ways that have become standard among Peirce's scholars. See the section "Abbreviations for the works of C. S. Peirce".

2009; Pietarinen, 2013). Here we apply this theory to PE. If our application succeeds, we would have at our disposal a novel theory that sustains the effect in which the notions of meaning, action and habit are all explainable and interconnected.

Pragmaticism states that general rules of action, or habits, are generalizing tendencies that lead us to action in conceivable situations, which can be described in general terms. It is a method to "put questions to our minds"; to interrogate ourselves and to assign meanings (in our thought) to signs in terms of those conceivable consequences that may follow from them. These questions are experiments on various ways of finding solutions in our thought regarding problems associated to meaning attribution. In the assessment of PE, what is often needed are the suggestions that can trigger the permission to find solutions in our thoughts. Following this perspective, and assuming thoughts to be connected with processes in the brain, solutions in those thoughts would also be (at least partially) solutions of the brain.

For this method to work, we need not articulate in exact terms what the nature of these suggestions is. They may come from an authority or other institutionalized contexts and can be appropriately expressed by such diverse phenomena as locutionary and perlocutionary acts, gestures, haptic forms of communication, as indeed any element of communication that bears significance to the situation in inducing what Peirce termed "a habit-change potential".

Peirce moreover emphasizes that there is a close alliance between pragmaticism and logic. "The true intellectual meaning of the concept" is "always pragmatic".[7] Pragmatic meaning refers to the processes by which we perceive signs having intellectual value. Signs can retain that value even when other contingent and indexical elements have been removed. It is what could be expressed as the true description of the "habit of behaviour" (or "a rule of behaviour"), which may be conceived as both *concrete* and *general*. The description is *concrete* in the sense that it defines

[7] Notes on Strong, *Why the Mind has a Body?* (L 427, July 25, 1904, unpublished, cf. MS 1463). In his notes on C. A. Strong's book and letter drafts intended to be sent to the author, Peirce emphasized that "pragmatism is a purely logical doctrine".

pragmaticism as the theory "that the real meaning, – the intellectual import and value – of anything lies in the manner of its regulation of motor reflexes" (MS 1338, cf. Monist, April 1905). The theory thus states that there is a connection, at the level of meanings, between signs and a modification of both physiology and conduct. The description is also *general* in that it takes the theory to assign meanings to signs and assertions that can "mean no more than they can possibly come to" (L 321, Charles Sanders Peirce to Howes Norris, Jr., June 4, 1912).

The definition of pragmaticism thus is, in fact, also about the limits of meaning which is given by possible conducts and habits of behaviour associated with the signs: "the only real significance of a general term lies in the general behaviour which it implies" (*ibid.*). In this sense, the theory concerns the process or activity which the "habit or manner of conduct" is intended to capture.

The key term here is "*the* ***conceivable*** *practical consequences* (i.e. consequences for rational conduct)". The consequences that signs have must be conceivable, in which case they "*completely exhaust the* INTELLECTUAL *meaning of any concept*" (MS 838, Essay of Reasoning, late, 1913?, boldface, emphasis and capitalization in the original). The signs that have intellectual (cognitive) purport are symbols, and their meaning consists not in our conduct as such but in "our *concept* of what our conduct *would* be upon *conceivable* occasions" (*ibid.*). Peirce further states that his theory of pragmaticism gives "a rule for defining [the reality of] mental characters by their outward manifestations" (*ibid.*). Its theoretical core is that there are "real possibilities" in conceivable situations that "can become actual" (MS 288; here "real" is taken in the sense of Peirce's "extreme scholastic realism"). To this core Peirce adds the qualification "no matter how improbable they may be" (EP 1: 131), namely such good habits and strategies function also on very low or zero probability scenarios.

From this core we can excavate a novel application of the theory of meaning in the context of PE. By giving a permission to change, the patient's present state of health[8] may undergo a modification because the patient is capable of perceiving those future changes in the light of *conceivable situations that are real, in the sense of being real possibilities that may become actual*. What matters within the realm of real possibilities is not what we expect to happen or what we would or could obtain in the light of the calculations of probabilities of an expected outcome of various interventions (Chiffi and Zanotti, 2016). Expectations do not give permission for habits of action that characterize the subject's present behaviour to be modified in the future. A real permission derives from the significance of signs that are involved in the engagement with the relevant conditions accompanying a placebo administration. The most powerful among such signs are *intellectual signs*, which are cognitive symbols such as concepts, thoughts and generalities that give rise to habits of behaviour. Intellectual signs are also the only types of signs that can contribute to the modification of habits.

Intellectual signs can, for example, be gained from institutionalized medical contexts as technical explanations on the presumed mechanisms of the effectiveness of the placebo treatment. These intellectual signs are typically needed to accompany standard clinical and therapeutic encounters. This occurs since it is only in terms of intellectual signs that it is possible to exercise one's critical thinking faculties, to exclude faith-based contexts and to begin reasoning about the meanings of intellectual signs and their role in the placebo treatment.

Systems of intellectual signs include language, communication, symbols, conceptual schemas and reasoning, and they are connected to the world by the mediation of human practices (Pietarinen, 2006). Meaning is the *reality and generality* of habits by which we act in the world. We can change the interpretations of our meanings by changing our practices. New practices may

[8] Eligible patients' conditions are typically characterized as, and modified by, relatively moderate psychological symptoms such as anxiety, depression or fear, or physiological conditions such as neuropathia or dermatitis, among a handful of others.

cause transformative changes in habits when a *real* connection obtains between the intellectual sign and its *possible* consequences. What is crucial is that this connection has *counterfactual force*. PEs are particularly instructive examples of such meaning relationships, as they exemplify counterfactual force exerted on subjects that are anxiously anticipating their future conditions. Just as a concept with no conceivable practical consequences would be pointless, a placebo effect without any symbols or personal interpretations of their meaning cease to be a real and meaningful notion.

If PE indeed is the manifestation of changes in the meaning relationships in this pragmaticist sense, it may open up some new perspectives on how that effect may be utilized or even reinforced in actual practices. For example, would it be possible to introduce a *second-order placebo effect* on the standard or first-order placebo effect? In the case of a positive answer, would it then be possible to reiterate such process in order to enhance the effect, even indefinitely so? Recent studies have registered an increase in the placebo's effect size (Tuttle et al., 2015). Such increments may be due to many reasons, but they could also be an indication that an increased awareness of and reflection on PE influences its very assessments.

Peirce pointed out that we have to investigate "practical conduct under all and every conceivable circumstance, supposing this conduct to be guided by reflexion carried out to an ultimate limit" (MS 1482, cf. CP 6.490). The future conduct is thus not only modified by habits but is guided by profound reflective analysis. In order to carry the reflection "to an ultimate limit", it would have to be iterated to produce repeated reflections on one's own reflections. This confirmatory process is known to reinforce PE.

Various properties of PE are, in fact, in perfect alignment with Peirce's theory. Knowing the meaning of PE also means that the subjects have formed a habit of acting in certain ways whenever they know the treatment to be a placebo or not. It does not suffice to think of meaning only at a conceptual and static level; it is necessary to induce a change in the habit of acting in certain ways when faced with relevant situations. PE appears to work best with open-

minded, inquisitive personalities engaged with the intellectual side of the meaning of signs. This is also the fullest grade of meaning in pragmaticism.[9] The fact of there being nothing peculiar in consciously taking placebo and it being effectual is just another manifestation of the kind of meaning that has a robust pragmatic dimension. Indeed, we submit that pragmaticism is currently the only theory of meaning that explains the effect in fully general terms.

The reason why we take Peirce's pragmaticism rather than his semiotics (see e.g. Goli, 2016) as the grounding theory for placebo effects is that the former is his mature, fully general and logical theory of meaning. It explains meaning in terms of practical consequences that signs have and does so without appeals to psychological mechanisms such as conditioning or expectations (other two main ingredients for the explanation of PE). Peirce ruled out expectations from being habits precisely for their lack of generalizability; in contrast, the generalized forms of habits can be expressed using counterfactual reasoning. The logical system involved in PE is no longer merely dependent on particular rituals or cultures: it works independently of their specification. Such further conditions nonetheless enter the picture when PE is interpreted within the contexts of conditioning, expectation and affect (see below). Pragmaticism is a promising naturalistic theory of generalized placebo effects, taken as conceivable consequences that *could* or *would* lead to habit-changes, whatever the relevant conditions and procedures may be. With sufficient generality and experiential bearings, those effects attain the highest grade of meaning, which does not derive solely from contingent, mechanistic or anthropological explanations.

Last, the generalizability of PE leaves room for emotions and feelings. In fact, the role of emotions and feelings is importantly highlighted in Peirce's notion of the *interpretant*:[10]

[9] Kilpinen (2016, 199) has elaborated on the theme of habits as subject to conscious control and on the positive correlation between the rationalizability and habit-change: "For Peirce, habitual action is not outside the control of the acting subject's consciousness. The consciousness is present even in so radical sense that the habitual character of action is supposed to correlate positively with its logicality and rationality". We take this to hit the nerve of what is fundamentally essential in PE as well.

[10] Interpretant is in Peirce's semiotics the effect that the sign creates or determines: signs are triadic structures of signs (representations), their objects, and their interpretants, and objects determine the sign which represents the

"In all cases [the Interpretant] includes feelings; for there must, at least, be a sense of comprehending the meaning of the sign. If it includes more than mere feeling, it must evoke some kind of effort. It may include something besides, which, for the present, may be vaguely called 'thought'. I term these three kinds of interpretant the "emotional", the "energetic", and the "logical" interpretants". (EP 2. 409).

Emotional interpretants characterize the first stage of meaning – the position in which the creation of meaning relationships takes its beginnings. This initiation of meaning is followed by the actual effect, such as an action, conduct or permission to change. Peirce termed such interpretants *energetic*. Finally, at the third stage of the intellectual comprehension in its ultimate form, interpretants give rise to changes in the habit of action. These interpretants are *logical*. It is this last part that we take to accommodate the full meaning of placebo-induced treatments and procedures and is, thus, their ultimate effect.[11]

Since we also want our theoretical approach to be grounded on empirical research, the next section is devoted to the investigation of the neurophysiological aspects associated with meaning and emotion creation (and regulation) in placebo effect as well as to the connection between empirical research findings and the proposed philosophical framework.

4. Affective Features of Placebo Effect

PE shows some features of health improvement that go beyond the characteristic aspects of relevant treatments. But how can this be? One possibility is that the therapeutic potential of placebo resides also in the individual's CNS receiving both the placebo and the associated suggestions. What is then the role of the brain in producing or at least in enhancing PE?

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object through its interpretant. The interpretant is thus the representation of that sign's determination by its object. Naturally, there are many types of interpretants, which led Peirce to suggest elaborate classifications of them with respect to the classification of various categories of signs.

[11] One way of looking at this trichotomy of emotional, energetic and logical interpretants is in terms of perlocutionary effects in the theory of speech acts.

Neuroimaging studies have shown that placebos have the power to alter activity in the brain as well as in the spinal cord. The placebo affects the CNS, and neural systems produce PE (e.g. activates mechanisms, some of them unknown, which benefit the subject) especially when a positive clinical context is present and other relevant conditions are met. Thus, the question can be formulated in the following way: How does the placebo affect the brain to produce PE? An emerging theoretical perspective suggests that the power of placebo resides in its capacity to induce clinically relevant meanings.

As mentioned in the introduction, Grünbaum's definition fails to appreciate some facets of PE, as it does not connect it with any psychological or neurophysiological mechanism. We want our perspective on placebo effect to be immune to this criticism. Neuropsychological aspects related to the meaning perspective have suggested that it is the "appraisal" (namely the implicit process by which we generate the meaning of a stimulus) that may be the key factor responsible for PE. In this vein, Ashar, Chang and Wagner (2017, 75) recently pointed out that: "*placebo effects are created largely by psychological appraisals. Appraisals depend on cognitive beliefs and also influence precognitive learning processes to create placebo effects that do not depend on cognitive beliefs or expectations*".

We maintain that the meaning approach to placebo becomes useful in understanding placebo effect as soon as it is connected to relevant neurophysiological mechanisms. As we have already pointed out, typical perspectives on placebo include classical conditioning and expectations as the main mechanisms of action (Stewart-Williams, Podd, 2004; Wager and Atlas, 2015). Especially the second mechanism is without any doubt related to meaning. Theories of expectation and learning have recently been recast in the larger context of appraisals and appraisal systems in the brain (Ashar et al., 2017). Appraisals are either spontaneous interpretations of a stimulus (Smith and Ellsworth, 1985) or conceptual acts (Barret, 2014). Appraisals are believed to generate emotions (Lazarus and Folkman, 1984) and, as we have seen, they may play a decisive role in PE. One case in point is psychotherapy, where pre-treatment expectations on its efficacy account for variance in the treatment outcomes (Joyce and Piper,

1998). Notably, when pre-cognitive associations (conditioning) and cognitive expectations (the two sides of appraisals) are both induced, larger PE can be observed (Carlino et al., 2014; Colloca et al., 2008; Schafer et al., 2015).

Appraisal systems arise in the brain as a distributed network involved in both cognitive and emotional meaning generation. Ashar et al. (2017) propose that this network overlaps with the one found to be affected by placebo. Although we can generally agree with the common appraisal and meaning perspective, we want to suggest some modifications to their proposal. Appraisal contributes to explaining the generation of positive ("this disease won't harm me") or negative ("this disease will harm me") attitudes but does not seem to make sense of changes in attitudes which are intuitively connected with the placebo (or nocebo) effects. If so, then appraisal cannot fully explain PE. Even though there is a partial overlap with areas *reduced* by PE and the brain network responsible for emotion generation (appraisal), this does not apply when considering areas *activated* by PE.

In our view, appraisals may thus only partially explain the story behind PE. To get a more complete picture, a further mechanism should be included, namely emotion regulation. With emotion regulation we mean a series of heterogeneous processes that alter one of the components of the emotional response (Gross, 1999). One of the mechanisms by which emotional components become altered is by changing the meaning of the emotional stimulus. This *meaning changing* or reappraisal (or, what would in Peirce's terms be the habit-change potential) has been widely shown to regulate emotions at a psychological, neural and bodily level (Beauchaine, 2001; Demaree, Robinson, Everhart, and Schmeichel, 2001; Grecucci et al., 2013 a,b; Grecucci and Job, 2015).

Let us consider the case of receiving the diagnosis of Parkinson disease. When someone appraises the event, this *meaning generation* produces unpleasant emotions:

Appraisal: "I have a Parkinson disease" —> unpleasant emotion generation

When a (dummy) treatment is administered, following our precognitive associations and cognitive expectations (appraisals), a *meaning changing* begins (emotion regulation through reappraisal, and maybe through other strategies):

Reappraisal: "I'm receiving a treatment to cure it" —> emotion regulation

Once emotion regulation takes place, all the psychological and physiological effects unfold over the body, by regulating affective, subjective, bodily and behavioural components (see Gross, 2014 for a comprehensive revision of the literature).

At the neuronal level, placebo affects the brain by reducing activity in the cingulate cortex, the amygdala and the ventromedial prefrontal cortex. This network overlaps with unpleasant emotion generation network (amygdala for fear and cingulate for pain). In other words, what is now known about neuronal processes gives support to the hypothesis by which placebo alters emotions elicited by the clinical conditions that may worsen the physiological response to the illness itself ("I have been diagnosed with Parkinson disease"). More interestingly, PE increases neural activity in the dorsal and ventral parts of the prefrontal cortex, as well as portions of the ventromedial prefrontal cortex, nucleus accumbens and periacqueductal gray. That is, the administration of a placebo (together with other relevant conditions, such as suggestions) activates a psychological process in specific parts of the brain. This network of areas largely overlaps with the network engaged during emotion regulation tasks when participants use the strategy of reappraisal (Frank et al., 2014). Our hypothesis that placebo relies on emotion regulation processes is supported by neuroimaging evidence, which, in itself, is stronger than the evidence supporting the hypothesis of having only the involvement of appraisals. It is true that cycles of appraisals and reappraisals, as well as cycles of emotion generation and emotion regulation, take place continuously in a dynamic and circular fashion. Namely, PE and the fate of

the clinical condition under examination may be produced by dynamic cycles of these complementary processes.

In sum, one of the most surprising findings in placebo research is that the phenomenon emerges in the brain in the presence of specific external features that enhance it: when placebo is administered in an appropriate manner, the brain activity is altered as a consequence, despite the fact that no pharmacochemical factors contribute to the characteristic features of a therapy. The theories of *meaning generation* (precognitive association and appraisals) and *meaning changing* (emotion regulation through reappraisal) can explain how the brain produces PE. A specific circuit in the brain (largely based on prefrontal cortex areas) activates and produces a widespread regulatory effect over cognitive, behavioural, bodily and physiological components.

PE results in our view of the following changes in mental states:

A) *Meaning generation*:

1) By precognitive associations

2) By expectations

(both are included in the extension of the term 'appraisal')

B) *Meaning changing*:

3) By emotion regulation through reappraisal.

During the meaning generation and meaning change phases, PE may be enhanced by the heightened levels of significance patients attach to clinical rituals and to the contexts in which medical and sham medical procedures take place. The roots of this effect are not merely attributable to strictly cognitive changes, but also to neurophysiological changes in the areas of the brain associated with affective appraisal and emotion regulation including related bodily effects. Therefore, both the cognitive and affective components of meaning are essential for the

appropriate meaning generation and change in significance as envisaged in pragmaticism and in the theory of intellectual (cognitive) signs and communication. The considerable dynamics of meaning that pragmaticism allows need not assume ordinary notions of sense and reference, and for these reasons seem to propose a particularly appropriate apparatus to examine the theoretical roots of PE.

5. Conclusion

In the paper, we discussed and extended the 'meaning view' associated with PE. We considered theoretical limitations of those proposals that (i) leave the general aspects of meaning unspecified, (ii) fail to fully analyse the role of emotions and affect placebo-related theories of meaning, and finally (iii) establish no clear connection between the theoretical, physiological and psychological aspects of PE. We showed that a promising way to overcome these limitations is given by grounding PE on Peirce's theory of meaning, termed "pragmaticism", in which the role of the meaning constitution and change is placed in logical and objective structures. Issues such as changes in the habits of action, self-awareness of the placebo and emotions were shown to play a non-secondary role in the pragmatic evaluation of meaning. We also pointed out the connection between our theoretical proposal and the appraisal theory and integrated it with emotion regulation. Expectations and evaluations may affect decisions and singular behaviours, but only affective reappraisal has been shown to affect physiological responses at multiple levels of activity. In conclusion, we have defended an integrated *affective-meaning-making* view on PE that draws from theoretical reflection and pragmatist tradition in philosophy, clinical outcomes, as well as recent neurophysiological findings. New lines of research will explore how to empirically evaluate our model in order to be applied to clinical practice.

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Abbreviations for the Works of C. S. Peirce

- CP, followed by volume and paragraph number: Peirce (1931–1966).
- EP, followed by the number of volume and page number: Peirce (1998).
- MS, followed by manuscript number and, when available, page number: unpublished manuscripts in the Houghton Library, Harvard University. MS enumeration according to Robin in Peirce, C.S. (1967).
- L, followed by letter number and, when available, page number: unpublished manuscripts in the Houghton Library, Harvard University. L enumeration according to Robin in Peirce, C.S. (1967).

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