When the Map is the territory: Peirce, James, and the Ontology of Placebos

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1. Peirce and James's on reality and subjective representations

Today Charles Sanders Peirce and William James are recognized as the two founding fathers of that philosophical tradition that goes under the name of American Classical Pragmatism. Peirce and James, however, were not just "professional philosophers" in the purely academic sense of the term. Rather, they were also "men of science" who developed their system of thought in close relation with the scientific issues of their own time. What follows is a modest attempt to pursue a similar interdisciplinary attitude, looking for possible connections between Peirce and James's intellectual legacy and contemporary scientific issues. Using the image of map-territory relation, in this talk I will explore how the confrontation between Peirce and James's different ideas on the belief-realty relation may be useful to articulate a crucial dilemma in contemporary biomedicine, namely, how we ought to think about subjective responses to therapy within the framework of evidence-based medicine (EBM). In particular, I will argue that current empirical discoveries on "placebo effects" locally vindicate James's claim that in many cases the "map is the territory", but that such discoveries ought to be placed within a broader epistemic and theoretical framework, one that may find in Peirce's theory of semiotics a new and important conceptual resources.

In order to accomplish this task, in this first section I will confront Peirce and James's two distinct accounts of how our subjective representations may affect reality. Let us begin, then, by looking at how Peirce and James would have answered to the following general question: In which sense our beliefs and expectations are a necessary precondition for the occurrence of certain real phenomena? As for Peirce, the answer is to be found within his realist theory of scientific inquiry. According to Peirce, science can be characterized as a peculiar method for fixing beliefs. In turn, following Alexander Bain's theory of belief, beliefs are defined in terms of "dispositions to act", or "habits of action". Notoriously, in *The Fixation of Belief* Peirce identifies four general methods for fixing belief: the methods of tenacity, the method of authority, the method of a priori, and the method of science. Among the four, the method of science is the only which allows for an impartial distinction between right and wrong beliefs: "To satisfy our doubts –writes Peirce– it is necessary that a method should be found by which our beliefs may be determined by nothing human, but by some external permanency – by something upon which our thinking has no effect" (CP 5.370-376, 1877). By relying on this impersonal and "external permanency", the method of science allows to resolve controversies among different and contrasting beliefs.

Peirce further elaborates on this idea in *How to Make Our Ideas Clear*, where he applies his pragmatic maxim to the concept of "The Real", achieving the following conclusion: "we may define the real as that whose characters are independent of what anybody may think them to be… The opinion which is fated to be ultimately agreed to by all who investigate, is what we mean by the truth, and the object represented in this opinion is the real. That is the way I would explain reality" (CP 5.405-408, 1878). According to Peirce, scientific inquiry is, in the long run, a fallible and auto-corrective process. Crucial to this self-corrective capacity are "an indefinite community of

investigators" who could pursue inquiry indefinitely, and the idea of an external reality that "is as it is, irrespectively of what any mind or any definite collection of minds may represent it to be (CP 5.565-566, 1902). Despite the changes that Peirce imparted to his doctrine of realism (Fisch 1981; Boler 1963; Mayorga 2011), the idea that science is a communitarian endeavor requiring this notion of reality remained remarkably stable along the years (CP 8.12, 1871; EP 2.457-458, 1911).

On Peirce's view, though our beliefs, expectations and faithful attitudes do have a bearing on the world and external real phenomena, they do so only insofar as they influence our conduct. This is what Peirce explains to James in a letter when, upon thanking him for the dedication in *The Will to Believe*, he writes: "Faith, in the sense that one will adhere consistently to a given line of conduct, is highly necessary in affairs. But if it means you are not going to be alert for indication that the moment has come to change your tactics, I think it is ruinous in practice" (Perry 1935, 2:222). For Peirce, it is precisely because (scientific) evidence does not depend on our prior faith in its coming or not that we may expect that, given enough time and resources, inquiry will eventually converge toward a shared opinion and that "truth, crushed to earth, shall rise again".

William James, on the other hand, developed a partially divergent analysis. Having in mind the problems of men's ordinary life rather than those of scientific inquiry, James entertained a life-long belief in the transformative power of our will and faith. As a young man who recovered from severe depression, James wrote at the end of his essay entitled *Is Life Worth Living?* that "Believe that life is worth living, and your belief will help create the fact" (James 1897, p. 503; Miller 2005: 274). According to James, "Faith means belief in something concerning which doubt is still theoretically possible; and as the test of belief willingness to act, one may say that faith is the readiness to act in a cause the prosperous issue of which is not certified in advance" (James 1897, p. 524). On James's view, "faith" is not an alternative to evidence or experience as a motive to action. Rather, as noted also by Miller (2005: 274), for James "faith consists of a form of belief under circumstances in which we lack adequate evidence to validate the truth of what we believe". Though James's primary focus in *The Will to Believe* is on religious faith may, his account applies as well to more real-life situations. In particular, James nurtured a life-long interest for those cases in which "faith creates its own verification" (James 1897: 529), or in which "belief help create the fact" (James 1897: 503); a remarkable example is the 'leap of faith':

> Often enough our faith in an uncertified result *is the only thing that makes the result come true.* Suppose, for instance, that you are climbing a mountain, and have worked yourself into a position from which the only escape is a terrible leap. Have faith that you can successfully make it, and your feet are nerved to its accomplishment. But mistrust yourself…and your feet will hesitate so long that, at last…you roll into the abyss. In such a case (and it belongs to an enormous class), the part of wisdom as well as courage is to *believe what is in line of your needs*, for only by such belief is the need fulfilled (James 1987: 500 original emphasis).

In the 'leap of faith' example we have no prior evidence that our leap would succeed or not, but our "trust" is a functional element in determining the final outcome. Two claims are here at stake. The first is epistemological: there are cases in which adequate evidence to decide between two options is lacking; hence in these cases we are legitimate in adopting a "believing attitude". The second claim, instead, is ontological: there are cases in which a fact cannot come at all unless a preliminary faith exists in its coming, and where "faith in a fact helps create the fact" (James 1897: 500). In other words, there are cases in which the coming into being of empirical phenomena depends on our prior faith, or trust, or hope, in their coming.

To sum up, Peirce and James elaborated two diverse views on how we ought to conceptualize the import that our expectations may have on reality. According to Peirce, scientific inquiry ought to be grounded in the belief that reality is independent from our subjective representations. Borrowing a phrase from scientist and philosopher Alfred Korzybski, Peirce's position can be nicely captured in the motto "The map is not the territory". Just like map stands for territories, our scientific representations (models, theories, opinions, expectations, etc.) stand for some phenomenic counterparts in the real world. Nonetheless, the world is what it is quite independently from our ways of representing it, just like a territory is what it is regardlessly of its being represented in a map. On the other hand, James elaborated a different view from Peirce, namely, that there is a subclass of cases in which our beliefs and expectations do operate as the precondition for the coming into being of new physical phenomena.

Though Peirce and James had two different aims in mind, it does not follow that their perspectives are incommensurable or incompatible. As I will show in the next sections, one of the key-questions in contemporary biomedicine, in fact, is precisely how we ought to integrate subjective ways of coping with medical treatment within the broader endeavor of pursuing an objective, evidence-based program of clinical research.

2. When the Map is the Territory: Placebo Effect in Clinical Research & Practice

In order to understand how Peirce and James's ideas may have an import for theoretical medicine, it is necessary to introduce what Evidence-based medicine (EBM) is; what the scientific evidence about placebo effects is now revealing to us; and why semiotics is increasingly perceived as a viable heuristic framework to conceptualize such effects. In the following three sections I shall consider each in turn.

2.1 Evidence-Based Medicine: the paradigm of double blind placebo-controlled randomized trials

Evidence-based medicine, or science-bases medicine, is a current growing trend in biomedicine according to which clinical decision-making has to be informed by the best quality of evidence (Howick 2011). According to EBM, not every method of assessing the effectiveness of a medical intervention (drug, surgical procedure, etc.) is equally reliable. Generally, the single judgment of a single expert is a source of evidence less reliable than a large observational study in with thousands of patients are enrolled and tens of professionals work coordinated by a unique protocol. In turn, large observational studies yield a lower quality of evidence in compares to randomized trials. By "best quality of evidence", then, it is usually meant by EBM proponents evidence gathered through large double-blind placebo controlled clinical trials (RCTs henceforth) or, even better, by systematic meta-reviews integrating the results of several high-quality RCTs.

RCTs are a particular kind of scientific experiment designed to avoid or mitigate confounding factors and biases that may distort the objective assessment of treatment effectiveness (Howick 2011). In a standard additive RCT design, research subjects are randomly divided in two arms. The "active" arm of the trial receives the treatment, while the other, the "control group", receives a 'placebo', i.e. a something that mimics the appearance of the active treatment but is believed to be pharmacologically (a sugar pill) and/or physiologically inert (sham acupuncture) for the condition under test. If neither the researchers nor the subjects know who belongs to the active arm and who to the control group, the trial is said to be "double-blinded". Finally, improvements in the two

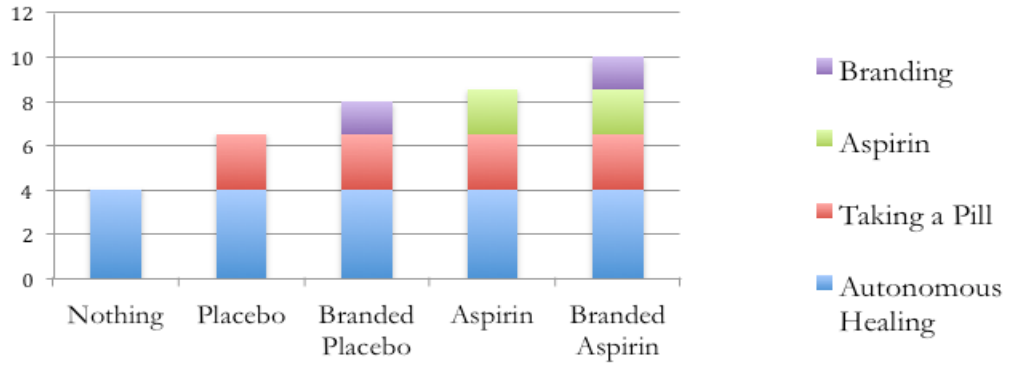
arms of the trials are measured and compared. If the active arm of the trial shows a statistically significant improvement (on a frequentist framework usually with p-value lower than 0.05) over the control group, then this *difference* is attributed to the specific action (effectiveness) of the treatment under test.

The current model of biomedicine requires that any new medical treatment be tested in RCTs before reaching the market. Arguably, the adoption of RCTs has been the single greatest advance in the history of medicine (Shapiro & Shapiro 1997). Before World War II, evidence about the effectiveness and efficacy of medical treatments was based on low quality sources such as observational studies, physicians' personal experience, authoritative sources, or anecdotal stories (Cochrane 1972). The result was that many treatments were ineffective, while other harmful and some even fatal. Retrospectively, the success of contemporary 20th biomedicine is the success of the RCT paradigm; that is, the success of an approach grounded on the principle that when it comes to assess treatments effectiveness what matters are not our "maps" –i.e. subjective perceptions, feelings, or expectations of scientists and research subjects–, but only "territories" –i.e. the specific effect of the treatment which is explainable in terms of molecular mechanisms and causal pathophysiological processes.

2.2 Placebo Effects in Clinical Research: reality and significance

In additive RCTs, treatment effectiveness is measured in terms of the differential improvement between the active and the control, or "placebo", group of the trial. Though this trial design aims at isolating the specific effect of the tested treatment, it does not say anything about other possible sources of improvement that could be measured in the two groups. For example, "placebo effects" are another well-known source of possible improvement. Consider the following example based on a real, large RCT performed by Braithwaite and Cooper (1981) on 815 women with headache who were told that "the study was on behalf of a well-known manufacturer of medicine, who was comparing the effectiveness of different brands of headache tablet currently on sale" (Moerman 2002).[1] Subjects were then randomized to four groups. Group A received a placebo pill generally labeled "analgesic tablet"; group B received the same placebo pill but with a label of a famous brand of analgesic tablets; group C received an active analgesic but unbranded placebo pill; group D received a branded analgesic pill; fig.1 shows the result of the trial.

[1] This example is taken from Moerman (2002), who adapted an original study done by Braithwaite and Cooper (1981). Specifically, the original study did not have a control group for natural disease or an "untreated group". As Moerman (2002: 19) explains, "we know that more often than not, headaches go away by themselves, although not usually within an hour. So […] I have added a "no treatment" column to the outcome (labeled "Nothing"), guessing that the average amount of improvement in such a group would be small but positive. And I have carried that across the whole figure, reasoning that the headache would be as likely to go away by themselves within an hour regardless of what medicine you might take".



This table shows two things. First, besides the active analgesic effect of the tablet, also "autonomous healing" had a measurable effect, as headache tends to disappear spontaneously after a couple of hours. Second, and more importantly, besides the active principle and autonomous healing *other* "non-specific effects" had a measurable impact on the trial outcome. These other factors were the act of "taking/receiving a pill" and the fact that the pill was "branded" or not. In other words, the simple fact of receiving a medical treatment, and knowing that such treatments is presumably effective given its branding, had the effect to enhance the analgesic effect of the active pill or of creating an analgesic effect on its own. The puzzling but rigorous conclusion is that placebos are more effective than nothing; branded placebos are more effective that generic ones; and the same phenomenon is true also in the case of active analgesics.

In the last decades, several scientific studies have confirmed and extended these results, showing that placebo effects are ubiquitous across research settings. For example, taking again a fictional example of a trial in which an analgesic pill (such as aspirin) is tested, known "triggers" of placebo effects are: the form of the treatment (Johnson 1994; de Craen *et al.* 2000); its color (Hussain and Ahad 1970; Sallis and Buckalew 1984; de Craen *et al.* 1996); the clinicians' expectations (Gracely, *et al.* 1985; the words by which the pill is described (Flaten *et al.* 1999; Benedetti 2002); contextual factors (Di Blasi *et al.* 2001), and so on. All these factors may elicit positive placebo effects that may enhance the final magnitude of the analgesic effect of the pill. Collectively, all these studies support James's idea that sometimes there are cases in which "the map is the territory", and in which prior expectations and trust in the possibility of a future clinical improvement does in fact help to create this very fact.

Hence, Placebo effects are phenomena whose existence is established according to the same epistemological standards that certify the effectiveness of active principles in evidence-based drug approval. The next question is thus what placebo effects are, and how we should conceptualize them in order to harness their clinical potential. In the next section I will outline why recent trends in the biomedical research are increasingly pointing to Peirce's theory of signs as a useful heuristic model to meet this interrogative.

2.3 Placebo Effects in Clinical Practice: a Semiotic Outline

At the very beginning of his studies at the Harvard Medical School, William James observed "My first impressions are that there is much humbug therein, and that, with the exception of surgery, in which something positive is sometimes accomplished, a doctor does more by moral effects of his presence on the patient and family, than by anything else" (Perry 1935, 1: 216). More than a hundred years later, empirical research on placebo effects suggests that James's remark has some truth in it. Today, the physician-patient

interaction is a recognized as one of the main factors triggering positive placebo effects in healing processes (Adler 1973; Benedetti 2011). The therapeutic ritual alone may by itself generate "therapeutic responses (placebo responses) which sometimes may be as powerful as those generated by real medical treatments" (Benedetti 2011: xiv). It has been argued that most of the improvements reported in traditional, complementary and alternative medicine may be due to placebo effects alone generated in this way (Ernst and Pittler 1998; Humphrey 2002; Kaptchuk 2002; 2008).

Given this, one natural question for contemporary biomedicine is how we could intervene on those elements that are already present in a standard healing process (verbal communication, contextual clues, ritual procedures, etc.) as to enhance the benefits for the patients and minimize the negative ones –the so called 'nocebo effects'. How can we harness the placebo effects measured during clinical research as to mold them into a therapeutic aid within clinical practice? To answer this question one naturally needs a good model of what placebo effects are, and of how they can be triggered as to enhance healing processes in conjunction with autonomous self-healing processes and technological tools (drugs, procedures, surgery, etc.). Elaborating this model, in turn, requires an organic synthesis between what the empirical researches on placebo responses have so far revealed about their underlying mechanisms, and the theoretical framework within which such effects are currently conceptualized.

As for the empirical evidence on placebo effects, it comes from three distinct sources: RCTs specifically aimed at studying "placebo effects" (Hrobjartsson and Gotzche 2011); over 30 years of laboratory experiments that show how placebo interventions can elicit quantifiable changes in neurotransmitters, hormones and immune regulators (Benedetti 2009), and more recent studies with brain imaging techniques (Faria, Fredikson, and Furmark 2008). Collectively, these empirical researches have shed a considerable light on the psychological and neurophysiological mechanisms underlying placebo responses both in research and in clinical settings (Benedetti 2011; Pollo 2009; Finnis 2010). Neurophysiologists Fabrizio Benedetti, a leader in the field, summarizes the results of the last thirty years by saying: "the placebo effect is a real psychobiological phenomenon whereby the brain is actively involved and anticipates a clinical benefits…the brain may anticipate a clinical benefit through different mechanisms, such as expectation of a reward or expectation that reduces anxiety, as well as classical conditioning, and this may occur in different systems and apparatuses of the body" (Benedetti 2009: viii).

Isolating the underlying mechanisms and systems that lead to the formation of placebo responses, however, is only half of the whole task. In fact, in order to complete the picture, and to be able to test and compare diverse protocols to exploit such effects in clinical settings, what is still missing is an account of the kinds of external stimuli that may trigger anticipatory responses. Albeit in the last years research and publications on placebo effects have intensified, substantial fragmentation among researches remains as to how placebo effects have to be properly conceptualized. To this date, no satisfactory and shared theory exists, and "scientific research on the placebo effect has taken shape of 'normal science' without guidance by any systematic theoretical paradigm" (Miller, Colloca and Kaptchuk 2009).

It is at this point that Peirce's theory of signs comes into the picture. According to Peirce, semiotic is "the doctrine of the essential nature and fundamental varieties of possible semiosis", or "sign-action" (EP 2:413, 1907). In contrast with the De Saussure, another pioneer of modern semiotics, Peirce thought that any process of semiosis involves at least three elements: (a) a sign, (b) an object and (c) an interpretant. (EP 2:411,1907). A minimal model of semiosis occurs when something (the sign or *representamen*) stands for something else (the object) to someone (the interpretant) under

certain respects. (CP 2.274; CP 2.228).[2] "A sign –write Peirce– or representamen, is something which stands to somebody for something in some respect of capacity. It addresses somebody … it creates in the mind of that person an equivalent sign … That sign I call the interpretant of the first sign. The sign stands for something, its object (CP 2.228). Peirce speculated that this triadic relation could account not only for human verbal and non-verbal communicatory practices, but also for most, if not all, other kinds of signifying relationship (MS 793:1). On Peirce's view, any process of information-exchange, signaling, coding, etc. is thus nothing but a special or more complicated form derived from this generative triadic relation.

According to Peircean semiotics, the sign mediates between an interpretant and an object. Peirce recognized three general ways in which an interpretant can pick out the reference to an object through a sign: icons, indexes and symbols. In the case of *icons*, a sign stands for its object in virtue of a similarity or likeness. So, a portrait is iconic because it is visually similar to the object portrayed. In the case of *indexes*, a sign stands for its object in virtue of a causal and physical connection. So, a weathercock stands for the direction of the wind in virtue of its being physically pointing in that direction. Finally, in the case of symbols, the sign stands for its object in virtue of a convention. So, the word "home" stands for any real home in virtue of a conventional association between its four letters and the class of objects in which there are all possible, existent and real homes.

As noted by Colloca and Miller (2011), each of these sign-object relations can be associated with factors that are known to produce placebo responses. For example, placebo responses elicited by the white coat of the physicians can be interpreted as the outcomes (interpretant) of an *iconic* information-decoding processes whereby a patient who previously observed the same kind of coat in a therapeutic environments leading relief (the *representamen*) comes to see the white coat as standing for that very sense of relief (the object). Likewise, placebo responses formed via classical Pavlovian conditioning can be interpreted in terms of the resulting interpretant of *indexical* information-decoding processes whereby a an conditioned stimulus (CS), say the ingestion of a pill, becomes associated with a unconditioned stimulus (US), say a decrease in the amount of the hormone cortisol. After conditioning occurs, the CS operates as an index of US able to trigger alone a conditioned response (CR). Finally, in the case of placebo responses formed by verbal messages, they can be seen as the interpretants of *symbolic* information-decoding processes whereby verbal formulas used by the physician or healer, such as "this is a powerful pain-killer", may elicit an analgesic effect on patients. In complex healing rituals, iconic, indexical and symbolic elements can be combined and present all at once, as in the case of physician wearing a white coat (iconic information) who touches a patient repeating a well-known procedure (indexical information) and use emphatic and reassuring verbal formulas (symbolic information). In conclusion, Peirce's icon-index-symbol trichotomy thus maps perfectly on processes that are known to be relevant for the formation of placebo responses. In this sense, Peirce's theory of signs seems to provide a promising conceptual framework to guide future research on placebo effects.

Conclusion

[2] It has to be noted, however, that this model is only a very simplified representation of Peirce's theory of signs. For a more comprehensive introduction to Peirce's theory of sign see Short (2007).

Biomedicine is one of the most cutting-edge, fascinating and rapidly moving fields of scientific inquiry, and a key driver of technological innovation and political change. Naturally, such transformative power is not deprived of complex normative, philosophical and epistemic issues. In this contribution, I have suggested that American Classical Pragmatism do indeed have something important to say about some of these topics. In particular, I have discusses how James's view on the role that beliefs and expectations may have in bringing about new real phenomena is now locally vindicated by a growing number of research that are trying to make sense of placebo effects, and of how Peirce's theory of sign may foster future research along this direction. On the one hand, James's reflections on the role of faith belief and trust, and on the irreducible subjectivity of our individual experience, may still provide a rich conceptual repertoire useful to conceptualize crucial differences between research contexts, in which evidence and objective epistemic gains are the things to value, from clinical settings where instead is the uniquely individual therapeutic outcome what matter the most. One the other hand, Peirce's theory of signs is today increasingly perceived as a promising heuristic framework to conceptualize how placebo responses can be triggered by meaningful or contextual stimuli. In conclusion, biomedical sciences, and especially researches on placebo effects, seem to provide an ideal and fertile ground to keep on applying and developing classical pragmatism to contemporary scientific questions.

References

Levine, J. D., Gordon, N. C. & Fields, H. L. 1978. The mechanisms of placebo analgesia. *Lancet* 2, 654 – 657.

Petrovic, P., Kalso, E., Petersson, K. M. & Ingvar, M. 2002. Placebo and opioid analgesia–imaging a shared neuronal network. *Science* 295, 1737 – 1740.

Benedetti, F., Arduino, C. & Amanzio, M. 1999 Somato- topic activation of opioid systems by target-directed expectations of analgesia. J. Neurosci. 19, 3639–3648.

Benedetti, F. 2009. *Placebo effects: Understanding the mechanisms in health and disease.* Oxford: Oxford Univ. Press.

Brody, H. 1997. The doctor as therapeutic agent: A placebo effect research agenda. In *The placebo effect: An interdisciplinary exploration,* ed. A. Harrington, 77–92. Cambridge: Harvard Univ. Press.

Colloca, L., et al. 2004. Overt treatment versus covert treatment for pain, anxiety, and Parkinson's disease. *Lancet Neurol* 3:679–84.

Finniss, D. G., et al. 2010. Placebo effects: biological, clinical, and ethical advances. *Lancet* 375:686–95.

Finniss, D. G., Kaptchuk, T. J., Miller, F. & Benedetti, F. 2010. Biological, clinical, and ethical advances of placebo effects. Lancet 375, 686 – 695.

Grunbaum,A. 1994. The placebo concept in medicine and psychiatry. In *Philosophical psychopathology,* ed. G. Graham and G. L. Stephens, 285–324. Cambridge: MIT Press.

Kandel, E. R., I. Kupferman, and S. Iversen. 2000. Learning and memory. In *Principles of neural science,* 4th ed., ed. E. Kandel, J. H. Schwartz, and T. M. Jessell, 1227–46. New York: McGraw-Hill.

Kaptchuk,T. J. 2000. *The web that has no weaver.* Chicago: Contemporary Books.

Kaptchuk,T. J. 2002.The placebo effect in alternative medicine: Can the performance of a healing ritual have clinical significance. *Ann Int Med* 136:817–25.

Kirsch, I. 1997. Specifying nonspecifics: Psychological mechanisms of placebo effects. In *The placebo effect:An interdisciplinary exploration,ed.A.Harrington,166–86.Cambridge:*

Harvard Univ. Press.
Miller, F. G., L. Colloca, and T. J. Kaptchuk. 2009. The placebo effect: Illness and interpersonal healing, *Perspect Biol Med* 52:518–39.
Moseley, J. B., et al. 2002. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. *N Engl J Med* 347:81–88.
Peirce, C. 1904. New elements. In *The essential Peirce,* vol. 2, ed. The Peirce Edition Project, 300–324. Bloomington: Indiana Univ. Press, 1998.
Peirce, C. 1940. Logic as semiotic: The theory of signs. In *Philosophical writings of Peirce,* ed. J. Buchler, 98–119. New York: Dover.
Siegel S. 2002. Explanatory mechanisms for placebo effects: Pavlovian conditioning. In *The science of the placebo: Toward an interdisciplinary research agenda,* ed. H. A. Guess, A. Kleinman, and J.W. Kusek, 133–57. London: BMJ Books.
T.L. Beauchamp & J.F. Childress. 2009. *Principles of Biomedical Ethics* 6th edn.
James, W. 1897. *The will to believe and other essays in popular philosophy*. New York: Longmans, Green. Repr. In *William James: Writings 1878-1899*. New York: Library of America, 1992.
Moerman, D. 2002. *Meaning, medicine and the 'placebo effect."* Cambridge: Cambridge Univ. Press.
Perry, R.B. 1935. *The thought and character of William James*. 2 vol. Boston: Little, Brown.
Harrington, A. 2002. "Seeing" the placebo effect: Historical legacies and present opportunities. In *The science of placebo*, ed. H.A. Guess, et al., 32-52- London: BMJ Books.
Kaptchuk, T. J. 2002. The placebo effect in alternative medicine: can the performance of a healing ritual have clinical significance? Ann. Intern. Med. 136, 817–825.
Walach, H. & Jonas, W. B. 2004. Placebo research: the evidence base for harnessing self-healing capacities. J. Altern. Complement Med. 10(Suppl. 1), S103–S112.
Miller, F. G., Colloca, L. & Kaptchuk, T. J. 2009. The placebo effect: illness and interpersonal healing. Perspect.
Kirsch, I. 2004. Conditioning, expectancy, and the pla- cebo effect: comment on Stewart-Williams and Podd (2004). Psychol Bull. 130, 341 – 343
Kaptchuk, T. J. et al. 2008. Components of placebo effect: randomised controlled trial in patients with irritable bowel syndrome. Br. Med. J. 336, 999 – 1003
Colloca, L. & Benedetti, F. 2009. Placebo analgesia induced by social observational learning. Pain 144, 28 – 34.
Colloca, L., Petrovic, P., Wager, T. D., Ingvar, M. & Benedetti, F. 2010. How the number of learning trials affects placebo and nocebo responses. Pain 151, 430 – 439.
Colloca, L. & Benedetti, F. 2006. How prior experience shapes placebo analgesia. Pain 124, 126 – 133.
Schultz, W. 2006. Behavioral theories and the neurophysiology of reward. Annu. Rev. Psychol. 57, 87 – 115.
Benedetti, F., Pollo, A., Lopiano, L., Lanotte, M., Vighetti, S. & Rainero, I. 2003. Conscious expectation and unconscious conditioning in analgesic, motor, and hormonal placebo/nocebo responses. J. Neurosci. 23, 4315 – 4323.
Colloca, L., Sigaudo, M. & Benedetti, F. 2008. The role of learning in nocebo and placebo effects. Pain 136, 211–218.
Hoffman, G. A., Harrington, A. & Fields, H. L. 2005. Pain and the placebo: what we have learned. Perspect. Biol. Med. 48, 248 – 265.
Harrington, A. 1997. The placebo effect: an interdisciplinary exploration (ed. A. Harrington), p. 5. Cambridge, MA: Harvard University Press.

Miller, F. G. & Colloca, L. 2010. Semiotics and the placebo. Perspect. Biol. Med. 53, 509 – 516.
Shapiro, A. K. & Shapiro, E. 1997. The powerful placebo: from ancient priest to modern physician. Baltimore, MD: Johns Hopkins University Press.
Hróbjartsson, A. & Gøtzsche, P. C. 2004 Placebo interventions for all clinical conditions. Cochrane Data- base Syst. Rev. CD003974. (doi:10.1002/14651858. CD003974.pub2)
Hróbjartsson, A. & Gøtzsche, P. C. 2004 Is the placebo powerless? Update of a systematic review with 52 new randomized trials comparing placebo with no treatment. J. Intern. Med. 256, 91–100. (doi:10.1111/j.1365-2796. 2004.01355.x)
4 Hróbjartsson, A. & Gøtzsche, P. C. 2010 Placebo interventions for all clinical conditions. Cochrane Data- base Syst. Rev. CD003974.
Williamson, M. J., Thomas, M. J. & Stern, R. M. 2004. The contribution of expectations to motion sickness symptoms and gastric activity. J. Psychosom. Res. 56, 721 – 726.
Vits, S., Cesko, E., Enck, P., Hillen, U., Schadendorf, D. & Schedlowski, M. 2011 Behavioural conditioning as the mediator of placebo responses in the immune system. Phil. Trans. R. Soc. B 366, 1799 – 1807.
Levine, J. D. & Gordon, N. C. 1984 Influence of the method of drug administration on analgesic response. Nature 312, 755–756.
Colloca, L. & Miller, F. G. 2011 How placebo responses are formed: a learning perspective. Phil. Trans. R. Soc. B 366, 1859 – 1869.
Colloca, L. & Miller, F. G. 2011 Harnessing the placebo effect: the need for translational research. Phil. Trans. R. Soc. B 366, 1922 – 1930.
Walach, H. 2011 Placebo controls: historical, methodological and general aspects. Phil. Trans. R. Soc. B 366, 1870 – 1878.
Kaptchuk, T. J. 2011 Placebo studies and ritual theory: a comparative analysis of Navajo, acupuncture and biomedical healing. Phil. Trans. R. Soc. B 366, 1849 – 1858.
Kaptchuk, T. J. et al. 2006 Sham device v inert pill: randomised controlled trial of two placebo treatments. BMJ 332, 391 – 397.
Jonas, W. B. 2011 Reframing placebo in research and practice. Phil. Trans. R. Soc. B 366, 1896–1904.
Brody, H. 2000. *The Placebo Response*. Harper Collins, New York.
Flaten MA, Simonsen T and Olsen H. 1999. Drug-related information generates placebo and nocebo responses that modify the drug response. *Psychosomatic Medicine*, 61, 250-55.
Allan LG and Siegel S. 2002. A signal detection theory analysis of the placebo effect. *Evaluation and Health Professions*, 25, 410-20.
Benedetti F. 2002. Ho the doctor's words affect the patient's brain. *Evaluation and the Health Professions*, 28, 5-6.
Branthwiate A and Cooper P. 1981. Analgesic effects of branding in treatment of headaches. *British Medical Journal*, 282. 1576-78.
Colloca L and Benedetti F. 2006. How prior experience shapes placebo analgesia. *Pain,* 124, 126-33.
Di Blasi Z, Harkness E, Ernst E, Georgiou A and Keijen J. 2001. Influence of context effect on health outcomes: a systematic review. *Lancet*, 357, 757-62.
Begay D.H., and N.C. Maryboy. 2000. The Whole Universe Is My Cathedral: A Contemporary Navajo Spiritual Synthesis. *Medical Anthropology Quaterly*, 14, 4, 498-520.

de Craen, A.J., P.J. Roos, A. Leonard de Vries, and J. Kleijnen. 1996. Effect of Colour of Drugs: Systematic Review of Perceived Effect of Drugs and of their Effectiveness. *British Medical Journal* 313, no 7072: 1624-6.
de Craen, A.J, J.G. Tijessen, J. de Gans, and J. Kleijnen. 2000. Placebo Effect in the Acute Treatment of Migraine: Subcutaneous Placebos are Better that Oral Placebos. *Journal of Neurology* 247, 3, 183-8.
Gracely, R.H., R. Dubner, W.R. Deeter, and P.J. Wolskee. 1985. Clinician's Expectations Influence Placebo Analgesia. *Lancet* 1, 8419: 43.
Hussain, M.Z. and A. Ahad. 1970. Tablet Colour in Axiety States. *British Medical Journal*, 3, 720: 466.
Johnson A.G. 1994. Surgery as a Placebo. *Lancet* 344, 8930: 1140-2.
Moerman, D.E. 2000. Cultural Variations in the Placebo Effect: Ulcers, Anxiety, and Blood Pressure. *Medical Anthropology Quaterly* 14, 1:1-22.
Morris, David B. 1997. Placebo, Pain, and Belief: A Biocultural Model. In *The Placebo Effect: An Interdisciplinary Exploration*. Ed. Anne Harrington, pp. 187-207. Cambridge, MA: Harvard University Press.
Muller, B.P. 1965. Personality of Placebo Reactors and Nonreactors. *Diseases of the Nervous System* 26: 58-61.
Sallis, R.E., and L.W. Buckalew. 1984. Relation of Capsule Color and Perceived Potency. *Perceptual and Motor Skills* 58, 3, 897-8.
Stewart, M.A. 1995. Effective Physician-Patient Communication and Health Outcomes: A Review. *CMAJ* 152, 9, 1423-33.
Wolff, B. Berthold, and Sarah Langley. 1968. Cultural Factors and the Response to Pain. *American Anthropologist* 70, 3, 494-501.
Zborowsky, Mark. 1952. Cultural Components in Responses to Pain. *Journal of Social* Issues, 8, 16-30.
Howick, J. 2011. The Philosophy of Evidence-Based Medicine. London: BMJ Books.
Cochrane, AL. 1972 Effectiveness and efficiency: random reflections on health services. London: Nuffield Provincial Hospital Trust.
Couto, JS. 1998. Evidence-based medicine: a Kuhnian perspective of a transvestite non-theory. Journal of Evaluation in Clinical Practice, 4(4), 267-75
Kuhn, TS. 1962. The Structure of Scientific Revolutions. The University of Chicago Press, Chicago.
Cartwright N, Goldfinch A, Howick J (eds). 2007. Evidence-based Policy: Where is our Theory of Evidence? Milan: Graduate Conference of the Graduate School in Social Sciences.
La Caze A. 2009. Evidence-based must be. Journal of Medicine and Philosophy, 34, 509-27.
Worrall J. 2002. What evidence in evidence-based medicine? Philosophy of Science, 69(suppl.), S316-S330.