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"Feeling what Happens": Full Correspondence and the Placebo Effect

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This paper proposes a theory whereby the physiological changes induced by placebos are accompanied by corresponding changes in the patient's mental state. I begin by defining the placebo problem, and review the three leading theoretical approaches for solving it — meaning theory, expectancy theory, and conditioning theory — before discussing the significant theoretical issue posed by a classic case of placebo immunosuppression in rats. The theory of full correspondence is then introduced as a way of explaining the nature of the placebo effect and of resolving the conflict between "meaning-oriented" and "mechanism-oriented" approaches to the phenomenon. After proposing how to test the theory experimentally and examining existing evidence for it, I consider its ability to integrate the dominant theoretical perspectives of the placebo effect within a framework centered on the patient's subjective experience, the one variable overlooked on both sides of the meaning/mechanism divide.

Keywords: placebo effect, full correspondence, consciousness

All instances of the placebo effect seem to share the following feature: our ability to influence our bodies in ways that go beyond what is usually deemed possible. That we are capable of controlling our bodies, such as when we pour a glass of water, type an email, or hug a child, is not in itself unusual. What is unusual about the placebo effect, however, is our ability to influence bodily functions over which we do not normally have control, such as the neuronal activity of pain, the quantity of white blood cells in the immune system, or the brain chemistry of Parkinson's disease. The problem, then, is to explain how we exercise some measure of control over these apparently involuntary functions.

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Placebo theorists have been attempting to solve this problem for some time. They have generally come down on one side or the other of the mind–body divide: on the mind side, "meaning-oriented" researchers have focused on the social and psychological aspects of the placebo effect, while on the body side, "mechanism-oriented" researchers have concentrated on the placebo's physiological features (Harrington, 1997). To borrow a simile from the great German physiologist, Ewald Hering (1834–1918), these orientations are like two teams of engineers digging from opposite sides of a mountain and trying to meet at some point in-between (Turner, 1994). There is a general belief, moreover, that the joining of these two tunnels would enable us to solve the mystery of the placebo effect. That is to say, any satisfactory solution to the placebo problem, as defined above, would have to satisfy the additional requirement of overcoming the epistemological barriers that separate these diametrically opposed schools of thought.

This paper proposes to fulfill both these requirements in a theory based on the following supposition: feelings accompany placebo effects in the same way that feelings such as embarrassment, hunger, or sexual arousal also exist alongside their corresponding physiological effects. In other words, I shall argue that the nature of the placebo effect is easily explained if we recognize the possibility that the physiological changes induced by placebos are accompanied by corresponding subjective experiences. That there should be a specific brain state for each of our mental states is virtually a universally accepted assumption among brain/mind theorists. Indeed, with each new advancement in brain research, we expect to find "ever finer correspondences between brain states and mental states, between brain and mind" (Damasio, 2002, p. 8). What I am proposing is the extension of this correspondence to mental functions whose existence we have yet to consider, namely, those associated with the neuronal activity of placebo effects.

Other theorists (Benedetti, 2009; Kirsch, 1997) have recognized a correspondence between the mind and body in placebo effects, but not to the extent considered here.[1] For example, Kirsch (1997) distinguished between two types of physiological responses to placebos, which I will hitherto call type I and type II

[1]There is one exception, however. In 1869, the Belgian philosopher, mathematician, and psychologist Joseph Delboeuf (1831–1896) proposed a similar idea to explain the case of Louise Lateau, a famous Belgian stigmatic. In April of 1868, still weak after recovering from a near fatal illness, this 18-year-old woman began bleeding from her left side, feet, hands, and forehead over a series of Fridays shortly after Easter. During these bouts of stigmata, Lateau was actively engaged in imagining the final moments of the passion of Christ. Given the close match between her bodily lesions and the contents of her overexcited imagination, Delboeuf (1869/1993) ventured the following hypothesis: "In certain exceptional and morbid cases, could not the felt sensation be joined by the corresponding organic modification [. . .]?" (p. 400). Delboeuf would go on to develop similar ideas, but in a slightly different direction, when he took up the study of hypnosis some 15 years later. It is only after I had hit upon the theory of full correspondence that I realized Delboeuf had already proposed a similar theory in 1869.

physiological placebo effects. Type I physiological placebo effects are assumed to come in mind–body pairs: the subjective experience being in close correspondence with its physiological counterpart. Examples include the psychological and physiological effects of placebo coffee and placebo tranquilizers. The physiological responses of type II placebo effects, on the other hand, "are not part of the physiological substrates of subjective experience" (p. 179); they have no counterparts in the mind. Kirsch points to the influence of placebos on cancer, skin conditions, and the immune system as examples of this more mysterious type of placebo effect. In sum, one could say Kirsch subscribes to a *partial* correspondence between mental and physiological events in the placebo effect, whereas I am proposing a *full* correspondence between the two.

If the idea of full correspondence has not been seriously considered until now (aside from Delboeuf's [1869/1993] and Kirsch's [1997] considerations), it is because we have paid insufficient attention to the feelings associated with the placebo effect. The reason for this oversight, as I shall later discuss, is tied to a deep-seated reluctance — similar to the skepticism of many researchers and theorists (e.g., Hróbjartsson and Gøtzsche, 2001; Kienle and Kiene, 1997) regarding the reality of the placebo effect — in recognizing consciousness as an acceptable object of scientific investigation. To many, consciousness and the placebo effect seem less real than the material objects that lie at the basis of our scientific understanding of the natural world. But to deny the existence of the placebo effect is to deny a well-documented natural phenomenon (e.g., Benedetti, 2009; Harrington, 1997; Moerman, 2002b), and to ignore consciousness in the study of that phenomenon is to ignore a vital clue in understanding it.

This paper will describe the theory of full correspondence in some detail, present evidence supporting it, and discuss its capacity to integrate existing theories within a single theoretical framework. My first step will be to situate the theory of full correspondence within the field of placebo research by reviewing its dominant theories — meaning theory, expectancy theory, and conditioning theory. This brief review is modeled on Anne Harrington's (1997) classic review of the placebo literature, which first introduced me to the epistemological tension described above and set the context for the problem addressed herein.

Meaning Theory

Building on the work of scholars sensitive to the role of culture and meaning in the placebo effect (Brody, 1997; Hahn, 1985, 1995; Kleinman, 1986, 1998), Daniel Moerman's (2002a, 2002b) "meaning response" theory, recently revised and expanded by Barrett et al. (2006) and Kradin (2004), draws on a rich history of studies revealing the symbolic and cultural factors involved in the placebo effect. Such studies have shown, for example, that two placebo tablets work better than one (Rickels, Hesbacher, Weise, Gray, and Feldman, 1970), that

capsules work better than tablets (Hussain and Ahad, 1970), injections better than pills (de Craen, Tijssen, de Gens, and Kleijnen, 2000), branded better than unbranded pills (Branthwaite and Cooper, 1981), and expensive better than inexpensive pills (Waber, Shiv, Carmon, and Ariely, 2008). In such pairs, Moerman (2002a, 2002b) noted, the former "means" more than the latter. Meaning theorists have drawn similar conclusions from studies showing how warm colors (pink, orange, and red) are consistently associated with stimulants and cool colors (green and blue) with sedatives and depressants (de Craen, Roos, Leonard de Vries, and Kleijen, 1996), how Chinese Americans born in unlucky years according to Chinese astrology tend to die younger than cohorts born under luckier stars (Phillips, Ruth, and Wagner, 1993), and how a warm, enthusiastic, and caring bedside manner increases the overall effectiveness of treatments and placebos (Di Blasi, Harkness, Ernst, Georgiou, and Kleijnen, 2001).

What these and countless other studies show is that our biology is deeply affected not only by the material basis of life, but also by the broader social world. As Barrett et al. (2006) wrote with respect to coffee drinking in particular, and "health-related behaviors" in general, we are "embedded within sociocultural networks of meaning. Conscious and subconscious 'meanings' combine with personal experiences — physiological and psychological — to form mind–body response patterns" (p. 189). For similar reasons, Moerman (2002a, 2002b) sees the placebo effect as a special case of a larger biosocial phenomenon he calls the "meaning response."

But meaning cannot tell the whole placebo story. We need to explain how "sociocultural networks of meaning" translate into physiological effects, how meaning moves from society to the body. One way of doing so is through the study and manipulation of expectations.

Expectancy Theory

Expectancy theorists take a more psychological approach to the placebo effect. They do not dispute the ideas advanced by meaning theorists, but they consider sociocultural factors to be a step removed from the psychological processes that produce the phenomenon, and the most important of these processes, they argue, is expectation. On this view, the placebo effect occurs when a patient is led to believe the treatment will have the desired effect. A classic example is an experiment using "trivaricane," a name invented by Montgomery and Kirsch (1996) for a placebo anesthetic cream they used to lessen the pain of unpleasant electrical stimulation. While the electric shocks were administered to both index fingers of their undergraduate participants, the placebo cream was applied to only one of the fingers. To enhance the placebo's effect, the researchers wore white lab coats, drew the cream from a bottle labeled "Trivaricane: Approved for research purposes only," and applied it wearing surgical

gloves "to avoid overexposure" (p. 175). The expectations created by this trivaricane-charged context produced a significant anesthetic effect, and because this effect was limited to the finger on which the cream was applied, appeals to general pain-relieving processes such as endorphin release or anxiety reduction were effectively ruled out.[2] Similar studies of placebo alcohol (Hull and Bond, 1986), placebo (decaffeinated) coffee (Flaten, Aasli, and Blumenthal, 2003; Kirsch and Weixel, 1988), anti-depressants (Kirsch and Sapirstein, 1999), and sedatives (Jensen and Karoly, 1991) have also provided strong support for expectancy theory.

Conditioning Theory

The classical conditioning theory of the placebo effect has a lot of experimental support too, with studies demonstrating behaviorally conditioned effects ranging from the reduction of pain, depression, and anxiety to the production of antibodies, insulin, and dopamine (Benedetti, 2009). Unlike the psychosocial orientation of meaning and expectancy theories, conditioning theory interprets the placebo effect as a type of associative learning. According to the conditioning account, for example, placebo aspirin works by inducing the pain relief previously associated with aspirin pills. In the language of classical conditioning, an aspirin pill is an unconditioned stimulus that produces the unconditioned response of pain relief. As the stimuli associated with aspirin pills, such as their taste, shape, and color, are repeatedly paired with the unconditioned stimulus, they become conditioned stimuli capable of triggering conditioned responses similar to the unconditioned response produced by the pills' pharmacological agent. In short, all the stimuli that had previously been associated with a medical treatment have the potential of eliciting that treatment's physiological effects when a placebo is substituted in its place (Ader, 1997).

The conditioning approach does not deny a role for meaning and expectation in many placebo effects, but it often sees this role as secondary to the primary one of conditioning because, as we shall see below, some conditioned placebo effects seem to occur in the absence of any conscious cognition. Meaning and expectancy theorists naturally take the opposite view, subsuming conditioning within their own explanatory frameworks whenever possible. For example, Kirsch (2004) believes "expectancy theory includes conditioning as a process by which expectancies are formed" (p. 341). Under certain conditions, moreover, the placebo effect will correspond to a subject's expectations even when conditioning predicts the opposite outcome (Kirsch, Lynn, and Miller, 2004; Montgomery

[2]Some of the subjects could have inferred that the anesthesia would extend to the other index finger because the cream had been absorbed into the bloodstream. None of the subjects seemed to have formed this expectation, however, since the effect was limited to the finger upon which the placebo cream was applied.

and Kirsch, 1997). And while acknowledging the apparent absence of expectancies in Benedetti, Amanzio, Baldi, Casadio, and Maggi (1999), discussed below, Kirsch (2004) nonetheless maintains that "conditioned placebo effects without expectancies are rare" (p. 342). Yet much turns on these rare cases, the most famous of which was a chance discovery by Robert Ader in 1974 of a conditioned immune system response in rats.

Meaning versus Mechanism: Interpreting a Placebo Effect in Rats

Ader (1974) had initially set out to determine whether rats could be made to avoid saccharin-flavored water by inducing an association between the taste of saccharin and the experience of nausea. He began by giving groups of rats 1, 5, or 10 ml of water containing 0.1% saccharin, followed 30 minutes later by the injection of a nausea-inducing drug called cyclophosphamide, which also happens to be a powerful immunosuppressor. Control groups received the saccharin solution without cyclophosphamide. The rats were offered the same saccharin solution every three days and, as expected, the degree to which they avoided the flavored drink was found to vary with the quantity of saccharin consumed on the day of conditioning. Near the end of the experiment, Ader noticed something unexpected: several rats in the cyclophosphamide groups began dying, despite having received doses well below toxic levels. Moreover, as a general rule, the first rats to die received the largest volume of saccharin water in the initial pairing, the next rats to die, the second largest, and so on and so forth. Ader thus hypothesized that the rats had been conditioned to suppress their immune systems whenever they drank saccharin-flavored water, thereby leaving them vulnerable to pathogens in their environment. To test this hypothesis, he and a colleague subjected rats to a similar procedure in a subsequent study (Ader and Cohen, 1975), except this time they also injected the rats with sheep's blood and measured the quantity of antibodies produced by their immune systems. The results were as they had predicted. After a single pairing with cyclophosphamide, the saccharin alone acted as an immunosuppressor. These rats had been conditioned to respond to saccharin as if it were cyclophosphamide, just as Pavlov had conditioned his dogs to salivate at the sound of a bell after associating that sound with the arrival of food.

This experiment therefore showed that the placebo effect can be the result of processes that appear to be entirely mechanical, and because the effect was so clearly automatic and quantitative, it also suggested the possibility of explaining the fundamental mechanism of the placebo effect without recourse to expectancy, meaning, or any other cognitively based theories.[3] To reconcile these theories with conditioning, we might be tempted to apply expectancy

[3]As Harrington (1997) put it, "[t]he fact that [Ader] had achieved [a physiological placebo effect] in rats rather than in humans [. . .], undermined the frequent assumption that placebo effects were the product of peculiarly human interpersonal processes and unconscious wishes" (p. 6).

theory to Ader and Cohen's rats. After all, rats are surely capable of cognitions as commonplace as expectation. There are reasons to believe Ader and Cohen's experiment would not support expectancy theory, however, even if it were carried out with human beings. Stewart–Williams and Podd (2004) provided an elegant argument to this effect in their review of the expectancy-versus-conditioning debate over the mechanism of the placebo effect. They illustrated their argument with a personal example by M.E.P. Seligman, who, having caught the flu several hours after eating a meal with Béarnaise sauce, was later surprised to discover that the mere thought of tasting his favorite sauce produced strong feelings of nausea. If Seligman was surprised by his discovery, it is because the nausea came upon him unexpectedly, which is not what expectancy theory predicts. By analogy, it seems likely most conditioned taste aversion experiments operate in the same mechanical way and are largely oblivious to what the subject's expectations, hopes, or beliefs may be. Moreover, although the broader question of whether conditioning can occur in the absence of awareness is "long-standing and vexed," Ader and Cohen's experiment, along with other similar findings (e.g., Benedetti et al., 1999), seem to provide "persuasive evidence that conditioning in humans is not always cognitively mediated" (Stewart–Williams and Podd, 2004, pp. 332–333). Speaking specifically to this point, Benedetti (2009) added "there is experimental evidence in humans that *unconscious conditioned placebo responses* [emphasis added] are present in the immune and endocrine system (chapter 6) and in the cardiovascular and respiratory system (chapter 7)" (p. 45).

Unsurprisingly, Moerman (2002b) is uncomfortable with the Ader and Cohen (1975) study. He sees it, along with other conditioning experiments (for example, Benedetti et al., 1999, discussed below), as illustrating some of the limitations of his meaning response theory. When Pavlov's dogs learned to salivate at the sound of a bell that had previously been associated with food, Moerman (2002b) assumes "that the dogs didn't 'know' that the bell 'meant' food, that is, that their reactions were not cognitive ones involving understanding or meaning" (p. 124). Moerman is thus forced to concede instances of the placebo effect in animals, and possibly humans, that culturally oriented approaches seem powerless to explain.

The Theory of Full Correspondence

We are thus faced with two fundamentally different theoretical approaches to the placebo effect: one that explains the phenomenon in terms of meaning and expectations, and the other that explains it in terms of conditioning. My task will be to subsume these two approaches under a more general one. As I shall now argue, this more general approach to the placebo effect consists of a comprehensive correspondence between the subjects' mental states, on the one hand, and their physiological states, on the other.

With respect to Ader and Cohen's (1975) rats, the two main theoretical approaches to the placebo effect are easily reconcilable if we accept the following proposition: each time the rats drank the saccharin water after the initial pairing, the taste triggered the *memory* of how they felt the first time they tasted the sugary solution. In other words, on re-tasting the saccharin, the rats were reproducing not only the physiological effects of the cyclophosphamide, but the corresponding *psychological* effects as well. The initial injection of the toxin made the rats feel sick, and sick in a particular way, and that particular feeling was recalled each time they tasted the artificial sweetener. The more saccharin they tasted in the initial pairing, moreover, the stronger the subsequent association between the taste of the saccharin, on the one hand, and the biological *and* psychological effects of the cyclophosphamide, on the other. Thus, if the theory of full correspondence is true and the rats were remembering the feeling produced by the cyclophosphamide, "meaning oriented" and "mechanism oriented" approaches to the placebo effect can now meet on the common epistemological (and ontological) ground obtained by "*the feeling of what happens*" when the placebo effect occurs.

As mentioned before, theorists already widely assume that for each mental state there exists a corresponding state of the brain. The theory of full correspondence extends this assumption to mental states whose existences have been hitherto overlooked and whose neurological correlates include, but are not limited to, all type II physiological placebo effects. Full correspondence thus views the nature of the placebo effect not so much in the mechanisms by which it is produced, as in the correspondence between the subject's mental and physical states *when* it is produced, regardless of the mechanism at work. The cues that trigger the placebo effect need not even be conscious, as demonstrated by Jensen et al. (2012); but at the moment the placebo effect occurs, full correspondence predicts that the observed physiological modification (or an earlier physiological trigger that led to this modification)[4] will be accompanied by a matching psychological modification. Returning to the problem with which I began my inquiry, the secret, then, to voluntarily producing the placebo effect lies in provoking, by whatever means, the psychological experience that corresponds to the physiological condition we wish to obtain.

In using the term correspondence, I do not mean to imply a dualistic relationship between the mind and body such that mental events are somehow *causing* physiological events. As stated in my introduction, I am merely making use of the basic identity thesis by which any mental state is assumed to have a corresponding bodily or brain state. This is essentially the same identity

[4]There need not be a one-to-one correspondence between the observed physiological effect and the patient's subjective experience, inasmuch as the target effect could arise anywhere along a chain of physiological events, the first of which having been triggered by a corresponding event in the mind. Dr. Ben Whatley brought the possibility of such upstream correspondence to my attention.

assumption in Kirsch (1985), Hyland (1985), Kirsch and Hyland (1987), and Hyland and Kirsch (1988) that served as the metatheoretical foundation for all of Kirsch's later work on response expectancies. In keeping with virtually all monist philosophies, Kirsch and Hyland assumed that for every mental state there is a corresponding brain state with which that mental state is associated. They also assumed that the "relation between a mental event and its physiological substrate is better described as an identity relation than as a relation of cause and effect" (Kirsch and Hyland, 1987, p. 421). Mental states do not *cause* physiological states, in other words, mental states *are* physiological states (and vice versa for the physiological correlates of mental states). A feeling of embarrassment does not cause the physiological activity with which it is associated; rather, the psychological experience of embarrassment and the physiological counterpart of this experience are two ways of describing the same event. We can speak of causal connections between mental states or causal connections between physiological states — based on the similar but independently conceived notions of causal isomorphism (Kirsch, 1985) and complementarity (Hyland, 1985) — but not of causal connections between these two categories of phenomena, at least not without invoking dualism and violating the law of conservation of energy (Kirsch, 1985). This view still allows for directionality between mental and physiological states, however. When alcohol is introduced into the nervous system, the cause of inebriation is clearly physiological; likewise, when someone chooses to have a drink, that choice can have any number of psychological causes behind it. The identity assumption adopted here presupposes that such brain/mind processes represent two sides of the same coin, regardless from which side they are initiated.

As I have already mentioned, Kirsch (1997) was not ready to extend this identity assumption to all placebo phenomena. To Kirsch et al. (2004), for example, it seems "highly unlikely that [Ader's] rats could expect immunosuppression or even have any representation of the phenomenon" (p. 385). This is a perfectly reasonable statement. Rats have no conception of the immune system, let alone the possibility of suppressing it with drugs, so it seems ridiculous to think they could have had any expectations regarding it. From the perspective of full correspondence, however, expectancy theory could still apply *if* the rats were led to expect, not the idea of a complex physiological phenomenon, but rather the feeling that corresponds to it. Unlike higher forms of consciousness, feelings are chiefly generated in the brain stem and thalamus rather than the more evolutionarily recent cerebral cortex; it is therefore reasonable to suppose that feelings are not restricted to humans or even to mammals (Damasio and Carvalho, 2013). Expectancy theory could thus broaden its range of application if it extended its investigations to feelings.

Of all our conscious experiences, feelings are the most likely correlates of type II physiological placebo effects. As defined by Damasio and Carvalho (2013),

"[f]eelings are mental experiences of body states" (p. 143). They include hunger, thirst, fear, and many varieties of pain and pleasure. As mental correlates of the body's physiological state they assist the organism in maintaining its internal homeostatic equilibrium. Because they are generated in the evolutionarily older regions of the brain, feelings are believed to represent the earliest forms of conscious experience (Damasio and Carvalho, 2013). If the bodily states of type II physiological placebo effects are also accompanied by feelings, it is possible that the ability to produce placebo effects is not a relatively recent evolutionary adaptation, as some have suggested (Bendesky and Sonabend, 2005; Humphrey, 2002; Trimmer, Marshall, Fromhage, McNamara, and Houston, 2013), but a rather ancient one. I first encountered this counterintuitive idea in Delboeuf's (1887) reflections on the origin of the curative powers of hypnosis, which are similar in many respects to those of placebos (Kirsch, 1999). Like Damasio and Carvalho (2013), Delboeuf believed that the conscious experiences of early organisms were restricted to the feelings associated with their internal bodily states. Over the course of evolution, Delboeuf went on to speculate, the regulation of these internal states became increasingly automated, allowing some organisms to concentrate their attention on the sensations produced by their developing sense organs and, eventually, on the thoughts generated by their evolving cognitive processes. Only, the ability to influence the processes that govern the internal bodily states was never lost, so that when the hypnotic subject heals himself, he is "reclaiming possession of a power he had ceased to exercise, but not abdicated" (Delboeuf, 1887, p. 812). On this view, many of the feelings associated with placebo effects would constitute a primordial record of our psychological past, comprising a wide range of psychological experiences, in sync with their corresponding physiological states, that have been pushed to the back of, but not expunged from, our modern cortex-dominated minds.

We may safely assume Ader's rats experienced the feeling of nausea; after all, it was for its nausea-inducing quality that Ader originally used cyclophosphamide. However, it is a different matter to assume that the rats experienced the psychological correlate of the immunosuppression produced by the drug. We do not know if they experienced it because we cannot ask them how they felt. But though we may not be able to test full correspondence on animals, we *can* test it on humans. And if the predicted consequences of full correspondence are not borne out by the empirical evidence in human subjects, then it is wrong. It does not matter whether one believes rats have psychological experiences or not, or even whether one thinks the theory of full correspondence is plausible or not. What matters is whether the novel results predicted by the theory are in fact observed or not.

Here is one such prediction. Full correspondence predicts similar subjective experiences when the same placebo-induced type II physiological effects are observed across patients. Suppose after receiving a placebo, 55% of the recipients

show a physically detectable placebo effect while the other 45% do not. The full correspondence model predicts that the 55% who responded to the placebo will report a psychological experience associated with the effect, while the 45% who did not respond to the placebo will report no such experience. Finding evidence along these lines in the literature is difficult, however, because researchers rarely report how their subjects feel when investigating type II physiological placebo effects.

And here we touch upon a profoundly important historical and philosophical issue. The reason placebo theorists rarely report how their subjects feel is because they rarely consider the possibility that introspective experience could be relevant to understanding type II physiological placebo effects. The reason, in turn, for this blind spot regarding conscious experience has been ongoing for centuries: over the course of our scientific training and professional careers, we have been led to internalize, in true Kuhnian fashion, the notion that the study of conscious experience is somehow not a legitimate scientific pursuit. In discussions with some of my colleagues, for instance, I have been told that full correspondence fails because there is something "unscientific" about it. They are correct; it is not, technically speaking, a scientific theory. But this is only true, not because of a limitation in the theory, but because of a limitation in our criteria for what counts as a scientific theory. According to the received view, consciousness is a phenomenon to be explained away, rather than a source of evidence for explaining phenomena. Consciousness is supposed to be the *explanandum*, not part of the *explanans*. But if the full correspondence interpretation is correct, the placebo effect will remain impossible to understand so long as consciousness is not part of the explanation.

In *The Feeling of What Happens*, from which I borrowed the opening title for this paper, the renowned neurologist and clinician, Antonio Damasio, wrote how "[s]tudying consciousness was simply not the thing to do before you made tenure, and even after you did it was looked upon with suspicion. Only in recent years has consciousness become a somewhat safer topic of scientific inquiry" (1999, p. 7).[5] Some ten years later, it has fortunately become a somewhat safer topic for placebo theorists as well. Kaptchuk et al. (2009), for example, recently carried out a qualitative investigation of the subjective experiences of

[5]The turning point in the legitimization of the study of consciousness is marked by two important publications, both in 1994: *The Astonishing Hypothesis: The Scientific Search for the Soul,* by Francis Crick, Nobel laureate and co-discoverer of the DNA molecule; and the first volume of the *Journal of Consciousness Studies*. The first issue of the journal began with an interview with Crick and included articles by several eminent scholars interested in the study of consciousness. Although the topics ranged from the binding problem and quantum theories of mind to machine consciousness and mystical experiences, the articles shared the same underlying assumption: conventional approaches having failed to solve deep long-standing problems in consciousness, the time had come to take consciousness more seriously and to propose methods of inquiry better suited to understanding it.

patients undergoing placebo acupuncture for irritable bowel syndrome. As far as this research team knew, this is the first time anyone had analyzed the experiences of placebo patients in a randomized control trial. Indeed, given the existence of multiple competing theories of the placebo effect, they noted how peculiar it was that "none has been informed by actual interviews of patients undergoing placebo treatment" (p. 382). As a further sign of the times, another recent placebo study of irritable bowel syndrome patients pointed to the same lacuna, adding that to the authors' knowledge, theirs was "the first study to directly compare patients' experience of a placebo treatment versus an active treatment" (Vase, Nørskov, Petersen, and Price, 2011, p. 1917).

The results of the latter study, which included administering rectal placebo during a painful rectal balloon distention procedure, were consistent with those predicted by full correspondence: they showed placebo responders "actively engaging in generating a mindset for pain reduction," which, once established during the first 20 minutes following administration of placebo, maintained itself with less deliberate mental effort during the next 20 minutes (Vase et al., 2011, p. 1919). It seems once the placebo recipient settles into a state of pain reduction, it becomes easier, almost effortless for some, to prolong that state of mind. This is one example, incidentally, of the kind of fruitful research results one would expect to find under a full correspondence paradigm. The subjective measures of pain reduction in this study are corroborated, moreover, by objective measures of pain reduction in a previous fMRI study of irritable bowel syndrome using a similar design. Price, Craggs, Verne, Perlstein, and Robinson (2007) found reduced activity in the pain-related areas of the brain in irritable bowel syndrome patients who received rectal placebo during the rectal distention procedure. A stronger test of full correspondence would of course combine the above two studies into one, so that the subjective experience of placebo recipients could be directly compared by fMRI.

Ideally, what we need to assess in the theory of full correspondence are studies that compare the subjective experiences of patients who respond to type II placebos in a physiologically measurable way with those who do not. It so happens this is precisely the kind of study undertaken by Benedetti et al. (2004) in a surgical experiment involving Parkinson patients. The object of the experiment was not to test the theory of full correspondence, of course, but rather to see whether placebo medication for Parkinson patients could influence the activity of the brain and produce clinical improvement. But, as we shall see, Benedetti et al. included a condition that makes it possible to test full correspondence: they asked the placebo recipients how they felt.

A group of 11 Parkinson patients were administered three injections of apomorphine, a potent antiparkinsonian drug, in the days leading up to surgery. The surgical procedure consisted of inserting electrodes into the subthalamic nucleus, a region of the brain important in the treatment of Parkinson's disease,

and recording the neuronal activity before and after administration of placebo apomorphine. When the patients received their placebo injection, they were told it was the same apomorphine as the days before and that a feeling of well-being would follow. The effect of the placebo injection was measured in three ways: (1) degree of arm rigidity, (2) level of subthalamic nucleus neuronal activity, and (3) type of subjective experience. This experiment is unusual in that physiological measures are rarely paired with subjective measures when investigating placebo effects, especially type II physiological placebo effects. Indeed, one of the reasons Benedetti et al. (2004) included this subjective measure was to challenge the frequent objection that when patients report feeling better after placebo administration, such reports correspond to the patient's biases, "such as the patient's desire to please the investigator," rather than to objective physiological changes (Benedetti, 2009, p. 38). It is worth noting that the experimenters took great care not to influence their patients' introspective reports, so that the neurologist who recorded them had no knowledge of the patients' performance on the muscular and neuronal evaluations. The experimenters found that the six placebo recipients who displayed the physiological effects of apomorphine, namely decreased arm rigidity and reduced subthalamic nucleus activity, *were the same six to report feelings of well-being*, whereas the five non-responders neither displayed these physiological effects nor reported experiencing them. For example, the placebo responders reported such things as, "I'm falling asleep, like after apomorphine," "I feel like after the usual therapy," or "I feel much better," whereas the non-responders' reports were completely negative, such as, "I don't feel any effect," "It doesn't work," or "I feel no change" (p. 587). In other words, just as full correspondence leads us to expect, not only did the placebo responders reproduce the physiological effects of the drug, they also shared subjective experiences that roughly corresponded to those effects, while the non-responders neither reproduced nor felt these effects. Of course, full correspondence does not replace the conditioning model of the placebo effect; rather, it integrates the conditioning model with other models of the placebo effect by positing a common feature, namely, the patient's subjective experience. Also, with respect to my suggestion that feelings are the most likely subjective correlates of type II physiological placebo effects, it is interesting to note that the main targets of apomorphine in this experiment were the striatum and the subthalamic nucleus, both of which are common to all vertebrates and, therefore, extremely old from the point of view of evolution.

Case Study: Conditioning with or without Conscious Cognition

Let us apply full correspondence to a placebo study by Benedetti et al. (1999) that is widely believed to have occurred in the absence of conscious cognition (Benedetti, 2009; Kirsch, 2004; Moerman, 2002b; Stewart–Williams and Podd,

2004). In this conditioning study, surgical patients were given open injections of buprenorphine on the two days following their operation and a placebo injection on the third; thus, a conditioning paradigm very similar to the one Benedetti et al. (2004) would employ five years later, except this time the medication was administered after rather than before surgery.

Buprenorphine is a powerful semi-synthetic narcotic that can depress respiratory volume by 15% to 20% when taken in clinical doses (in this case 0.2 mg). It is important to note that respiratory depression is a typical side effect of narcotics and usually goes unnoticed by patients. When the placebo was administered, the patients were told it was the same drug they had received on the previous two days. As predicted, the experimenters found that both the buprenorphine and the placebo produced a significant drop in respiration. "Interestingly," Benedetti (2009) later wrote, "the patients themselves did not expect any effect and did not notice any decrease in ventilation, which suggests this effect is an *unconscious conditioning mechanism* [emphasis added] whereby the act of giving the drug was the conditioned stimulus" (p. 184). In addition to expectancy theory, these results seem to rule out meaning theory too, as Moerman (2002b) wrote regarding the experiment: "The treatments clearly had meaning ('narcotics are powerful painkillers'), but they did not have the meaning 'narcotics repress respiration,' even though that's true" (p. 124).

Full correspondence invites a different interpretation, one in which expectancy theory and the meaning response are not so easily dismissed. Supposing the theory of full correspondence is true, then the placebo reproduced not only the physiological effects of buprenorphine in placebo responders, but the psychological effects as well. This is hardly a controversial assumption given that Benedetti et al. (2004) found a firm match between the psychological effects of apomorphine and their corresponding physiological effects in the Parkinson study described above. It is therefore possible that the placebo injection led patients to expect they would feel the sensations associated with buprenorphine, which had the *meaning*: "buprenorphine is a powerful painkiller *and* produces a peculiar feeling," which in turn provoked the physiological and psychological effects of buprenorphine, and thereby the side effect of respiratory depression. In other words, that the placebo responders did not notice the effect the injections had on their respiration does not rule out the possibility that this placebo-induced side effect was mediated by expectation or the meaning response. After all, should we really be surprised, if, after manipulating expectations, a placebo aspirin produced an anti-inflammatory response in someone who knows nothing of its anti-inflammatory properties? If the subjective effects of aspirin are reproduced, full correspondence predicts that the physiological effects will be reproduced as well, including reduced inflammation. Under a full correspondence paradigm, expectation and meaning are therefore still theoretically possible in the Benedetti et al. (1999) study because what patients are expect-

ing and what buprenorphine means to them is that they will *feel* a certain way, and that feeling comes with its own physiological concomitants regardless of whether the patients are aware of them or not. But even if expectation and meaning played no part in the study, this would not imply that the placebo-induced physiological effects had no corresponding effects in the mind. Again, based on the results of Benedetti et al. (2004), it would be surprising if the physiological effects of buprenorphine were not accompanied by their psychological counterparts (they accompanied apomorphine, why not buprenorphine). Full correspondence does not guarantee expectation or meaning played a part in Benedetti et al. (1999), but it does suggest that theorists need not assume, as every one has, that this placebo experiment occurred in the absence of a mental experience, cognitive or otherwise.

Conclusion: A Meta-theoretical Framework

Full correspondence provides the conceptual means with which to resolve the conflict between meaning-oriented and mechanism-oriented approaches. The main source of the conflict is that certain placebo phenomena, such as conditioned immunosuppression in rats, are apparently so completely governed by mechanical processes that consciousness seems absent from the causal core of the placebo effect. And if consciousness is absent, so are expectation, meaning, and culture. I have argued, however, that placebo effects could occur through conditioning and yet also be *felt*, as was the case with the effects of placebo apomorphine in patients suffering from Parkinson's disease (Benedetti et al., 2004). Hence, if the type II physiological placebo effects produced by other conditioning experiments are similarly accompanied by corresponding mental experiences, then the epistemological gap between meaning and mechanism is effectively closed. According to the theory of full correspondence, in other words, the common denominator on both sides of the meaning–mechanism divide is the mental experience that accompanies all placebo effects.

Conditioning theory is correct to point out that many placebo effects can be explained through conditioned learning, but we should not necessarily assume that some conditioning procedures produce placebo effects in the absence of a felt experience. As pointed out in my discussion of Benedetti et al. (1999), the placebo responders could have felt the physiological effects of placebo buprenorphine even if these effects were not mediated by expectation, a meaning response, or some other higher cognitive process. In other cases, meaning theory and other anthropological approaches are correct in emphasizing the cultural factors that influence the placebo effect, but they could strengthen their case by attending to how the placebo effect is subjectively experienced. By interviewing placebo responders and determining the content of their mental life (or at least suitable proxies of that mental life, since interviews and questionnaires

can only provide analogues of first person experiences, not the experiences per se), as Kaptchuk et al. (2009) have done in their pioneering study, social theorists could establish more precisely how culture and meaning shape and give rise to certain placebo effects. Expectancy theory could similarly increase its explanatory power by exploiting the implications of full correspondence. Unlike culturally based theories, expectancy theory concentrates its attention not on the social causes of the placebo effect, but on one of its psychological causes. It is therefore closer to the source of the action, but it stops short of the placebo's final denouement. Expectancy theory has hitherto focused on the state of the subject's mind *before* the placebo effect occurs, rather than *while* it is occurring. It has been chiefly concerned with the final steps leading up to the effect, not the effect itself.

The theory of full correspondence neither replaces nor competes with the various existing approaches to the placebo effect; it is a meta-theory, designed to unify mechanically-oriented approaches and meaning-oriented approaches within the same epistemological and ontological framework. Nor does it establish the superiority of one approach over another. As there is not one but several ways of producing placebo effects, there are also several ways of describing how they are produced. In some cases expectation is the dominant cause, in others it is conditioning, and in still others it is meaning, hope, belief, or a combination thereof. Like so many specialized engineers, each approach is best suited for its particular area of expertise, its particular way of tunneling into Hering's metaphorical mountain. But they all meet at the same point: the place where the meaning and the mechanics of the placebo effect coincide with the feeling of what happens.

References

Ader, R. (1974). [Letter to the editor]: Behaviorally conditioned immunosuppression. *Psychosomatic Medicine, 36,* 183–184.

Ader, R. (1997). The role of conditioning in pharmacotherapy. In A. Harrington (Ed.), *The placebo effect: An interdisciplinary exploration* (pp. 138–165). Cambridge, Massachusetts: Harvard University Press.

Ader, R., and Cohen. N. (1975). Behaviorally conditioned immunosuppression. *Psychosomatic Medicine, 37,* 333–340.

Barrett, B., Muller D., Rakel D., Rabago D., Marchand, L., and Scheder, J.C. (2006). Placebo, meaning and health. *Perspectives in Biology and Medicine, 49,* 178–198.

Bendesky, A., and Sonabend, A.M. (2005). On Schleppfuss' path: The placebo response in human evolution. *Medical Hypotheses, 64*(2), 414–416.

Benedetti, F. (2009). *Placebo effects: Understanding the mechanisms in health and disease*. New York: Oxford University Press.

Benedetti, F., Amanzio, M., Baldi, S., Casadio, C., and Maggi, G. (1999). Inducing placebo respiratory depressant responses in humans via opioid receptors. *European Journal of Neuroscience, 11,* 625–631.

Benedetti, F., Colloca, L., Torre, E., Lanotte, M., Melcarne, A., Pesare, M., et al. (2004). Placebo-responsive Parkinson patients show decreased activity in single neurons of subthalamic nucleus. *Nature Neuroscience, 7,* 587–588.

Branthwaite, A., and Cooper, P. (1981). Analgesic effects of branding in treatment of headaches. *British Medical Journal, 282,* 1576–1578.
Brody, H. (1997). The doctor as therapeutic agent: A placebo effect research agenda. In A. Harrington (Ed.), *The placebo effect: An interdisciplinary exploration* (pp. 77–92). Cambridge, Massachusetts: Harvard University Press.
Crick, F. (1994). *The astonishing hypothesis: The scientific search for the soul.* New York: Maxwell Macmillan International.
Damasio, A. (1999). *The feeling of what happens. Body and emotion in the making of consciousness.* San Diego: Harvest Book.
Damasio, A. (2002). How the brain creates the mind. *Scientific American Special Edition, 12*(1), 4–9.
Damasio, A., and Carvalho, G.B. (2013). The nature of feelings: Evolutionary and neurobiological origins. *Nature Reviews Neuroscience, 14,* 143–152.
de Craen, A.J.M., Roos P.J., Leonard de Vries, A., and Kleijen, J. (1996). Effect of colour of drugs: Systematic review of perceived effect of drugs and of their effectiveness. *British Medical Journal, 313*(7072), 1624–1626.
de Craen, A.J.M., Tijssen, J.G.P., de Gens J., and Kleijnen, J. (2000). Placebo effect in the acute treatment of migraine: Subcutaneous placebos are better than oral placebos. *Journal of Neurology, 247,* 183–188.
Delboeuf, J. (1887). De l'origine des effets curatifs de l'hypnotisme. *Bulletins de l'Académie Royale des Sciences, des Lettres et des Beaux-Arts de Belgique,* 57th year, 3rd series, *13*, 773–812.
Delboeuf, J. (1993). Louise Lateau. In J. Carroy and F. Duyckaerts (Eds.), *Le Sommeil et les rêves, et autres textes* (pp. 387–400). Paris: Fayard. (Original work published in 1869)
Di Blasi, Z., Harkness, E., Ernst, E., Georgiou, A., and Kleijnen, J. (2001). Influence of context effects on health outcomes: A systematic review. *Lancet, 357*(9258), 757–762.
Flaten, M.A., Aasli, O., and Blumenthal, T.D. (2003). Expectations and placebo responses to caffeine-associated stimuli. *Psychopharmacology, 169,* 198–204.
Hahn, R.A. (1985). A sociocultural model of illness and healing. In L. White, B. Tursky, and G. E. Schwartz (Eds.), *Placebo: Clinical phenomena and new insights* (pp. 167–195). New York: Guilford Press.
Hahn, R.A. (1995). *Sickness and healing: An anthropological perspective*. New Haven: Yale University Press.
Harrington, A. (1997). Introduction. In A. Harrington (Ed.), *The placebo effect: An interdisciplinary exploration* (pp. 1–11). Cambridge, Massachusetts: Harvard University Press.
Hróbjartsson, A., and Gøtzsche, P.C. (2001). Is the placebo powerless? — An analysis of clinical trials comparing placebo with no treatment. *The New England Journal of Medicine, 344,* 1594–1602.
Hull, J.G., and Bond, C.F. (1986). Social and behavioral consequences of alcohol consumption and expectancy: A meta-analysis. *Psychology Bulletin, 99,* 347–360.
Humphrey, N. (2002). *The mind made flesh: Essays from the frontiers of psychology and evolution.* Oxford: Oxford University Press.
Hussain, M.Z., and Ahad, A. (1970). Tablet colour in anxiety states. *British Medical Journal, 3*(5720), 466.
Hyland, M.E. (1985). Do person variables exist in different ways? *American Psychologist, 40,* 1003–1010.
Hyland, M.E., and Kirsch, I. (1988). Methodological complementarity: With and without reductionism. *Journal of Mind and Behavior, 9,* 5–12.
Jensen, M.P., and Karoly, P. (1991). Motivation and expectancy factors in symptom perception: A laboratory study of the placebo effect. *Psychosomatic Medicine, 53,* 144–152.
Jensen, K.B., Kaptchuk, T.J., Kirsch, I., Raicek, J., Lindstrom, K.M., Berna, C., et al. (2012). Nonconscious activation of placebo and nocebo pain responses. *Proceedings of the National Academy of Sciences, 109*(39), 15959–15964.
Kaptchuk, T.J., Shaw, J., Kerr, C.E., Conboy, L.A., Kelley, J.M., Csordas, T. J., et al. (2009). "Maybe I made up the whole thing": Placebos and patients' experiences in a randomized controlled trial. *Culture, Medicine and Psychiatry, 33,* 382–411.
Kienle, G.S., and Kiene, H. (1997). The powerful placebo effect: Fact or fiction? *Journal of Clinical Epidemiology, 50*(12), 1311–1318.

Kirsch, I. (1985). Response expectancy as a determinant of experience and behavior. *American Psychologist, 40,* 1189–1202.
Kirsch, I. (1997). Specifying nonspecifics: Psychological mechanisms of placebo effects. In A. Harrington (Ed.), *The placebo effect: An interdisciplinary exploration* (pp. 166–186). Cambridge, Massachusetts: Harvard University Press.
Kirsch, I. (1999). Hypnosis and placebos: Response expectancy as a mediator of suggestion effects. *Anales de psicología, 15*(1), 99–110.
Kirsch, I. (2004). Conditioning, expectancy, and the placebo effect: Comment on Stewart–Williams and Podd. *Psychology Bulletin, 130,* 341–343.
Kirsch, I., and Hyland, M.E. (1987). How thoughts affect the body: A metatheoretical framework. *Journal of Mind and Behavior, 8,* 417–434.
Kirsch, I., Lynn, S.J., and Miller, R. (2004). The role of cognition in classical and operant conditioning. *Journal of Clinical Psychology, 60*(4), 369–392.
Kirsch, I., and Sapirstein, G. (1999). Listening to Prozac but hearing placebo: A meta-analysis of antidepressant medications. In I. Kirsch (Ed.), *How expectancies shape experience* (pp. 303–320). Washington, DC: APA.
Kirsch, I., and Weixel, L.J. (1988). Double-blind versus deceptive administration of a placebo. *Behavioral Neuroscience, 102*(2), 319–323.
Kleinman, A. (1986). *Social origins of distress and disease: Depression, neurasthenia, and pain in modern China.* New Haven: Yale University Press.
Kleinman, A. (1998). "Sociomatics": The contributions of anthropology to psychosomatic medicine. *Psychosomatic Medicine, 60,* 389–393.
Kradin, R. (2004). The placebo response: Its putative role as a functional salutogenic mechanism of the central nervous system. *Perspectives in Biology and Medicine, 47*(3), 328–338.
Moerman, D.E. (2002a). Explanatory mechanisms for placebo effects: Cultural influences and the meaning response. In H.A. Guess, A. Kleinman, J.W. Kusek, and L.W. Engel (Eds.), *The science of the placebo: Toward an interdisciplinary research agenda* (pp. 35–52). London: British Medical Journal Books.
Moerman, D.E. (2002b). *Meaning, medicine and the "placebo effect."* Cambridge: Cambridge University Press.
Montgomery, G., and Kirsch, I. (1996). Mechanisms of placebo pain reduction: An empirical investigation. *Psychological Science 7*(3), 174–176.
Montgomery, G., and Kirsch, I. (1997). Classical conditioning and the placebo effect. *Pain, 72,* 107–113.
Phillips, D.P., Ruth, T.E., and Wagner, L.M. (1993). Psychology and survival. *Lancet, 342*(8880), 1142–1145.
Price, D.D., Craggs, J., Verne, G.N., Perlstein, W.M., and Robinson, M.E., (2007). Placebo analgesia is accompanied by large reductions in pain-related brain activity in irritable bowel syndrome patients. *Pain, 127,* 63–72.
Rickels K., Hesbacher, P.T., Weise, C.C., Gray, B., and Feldman, H.S. (1970). Pill and improvement: A study of placebo response in psychoneurotic outpatients. *Psychopharmacologia, 16*(4), 318–328.
Stewart–Williams, S., and Podd, J. (2004). The placebo effect: Dissolving the expectancy versus conditioning debate. *Psychological Bulletin, 130,* 324–340.
Trimmer, P.C., Marshall, J.A.R., Fromhage, L., McNamara, J.M., and Houston, A.I. (2013). Understanding the placebo effect from an evolutionary perspective. *Evolution and Human Behavior, 34*(1), 8–15.
Turner, S.R. (1994). *In the mind's eye: Vision and the Helmholtz–Hering controversy*. Princeton: University of Princeton Press.
Vase, L., Nørskov, K. N., Petersen, G.L., and Price, D.D. (2011). Patients' direct experiences as central elements of placebo analgesia. *Philosophical Transactions of the Royal Society B, 366,* 1913–1921.
Waber, R.L., Shiv, B., Carmon, Z., and Ariely, D. (2008). Commercial features of placebo and therapeutic efficacy. *Journal of the American Medical Association, 299*(9), 1016–1017.