Open-Label Placebo: Reflections on a Research Agenda

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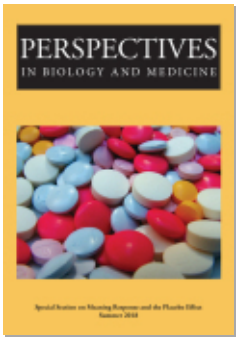

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Open-Label Placebo

reflections on a research agenda

Ted J. Kaptchuk

ABSTRACT Open-label placebos (OLP)—placebo pills honestly prescribed—have challenged the notion that placebos require either deception or concealment to evoke salubrious benefits. This essay describes how the author arrived at the counter-intuitive OLP hypothesis, discusses evidence for OLP effectiveness, and examines mechanistic explanations for OLP. Current dominant theories such as expectation and conditioning are found to be insufficient or inaccurate. The author proposes that emerging concepts of prediction and error processing (PEP), Bayesian brain, and embodied cognition are more appropriate models for understanding OLP. As a neural processing model, PEP argues that sensory predictions are embedded in and inseparable from perceptions; PEP circumvents mind-body dualism. The author discusses how OLP, mostly non-consciously, might perturb aberrant symptom amplifications and central sensitization resulting in perceptions of improvement in symptoms. Placebo effects are neurologically encoded predictions, less what patients think and more what they enact and perform.

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UNTIL RECENTLY, THE MEDICAL COMMUNITY assumed that placebos required either concealment in randomized controlled trials (RCTs) or deception in clinical practice to elicit placebo effects. Henry Beecher (1955) emphasized this orthodoxy, when he stated that placebo pills only work "as long as it is not detected as a placebo by the subject or the observer" and therefore, patients "believe it [is a drug] and consequently the expected results occurs" (1602, 1605). The time was ripe for such ideas: Norman Vincent Peale's *The Power of Positive Thinking* (1952) was already in its fourth year on the bestseller list when Beecher published his landmark paper. As time went on, the use of placebo pills became trapped in an ethical double-bind purgatory: placebos only work with concealment or deception, but post-1960s ethics required transparency and honesty. Placebo pills could still be an experimental foil in RCTs with proper informed consent, but in clinical practice placebos were effectively quarantined from medicine; deception was incompatible with respect for person. Importantly, this essay proposes that emerging models of prediction processing, Bayesian brain, and embodied cognition are more accurate theories for understanding OLP, and possibly placebo effects in general.

Like everyone else, I accepted Beecher's self-evident truths for a long time. In collaboration with my colleagues, most of my career in placebo research sought to determine the veracity of placebo effects in clinical practice, quantify these effects and their scope of action, separate these effects into component parts, study their interactions with pharmaceuticals, elucidate underlying neurobiology, examine historical issues, and ponder theoretical and bioethical issues (see citations under Kaptchuk). When studies involved human subjects, I thought I had to use masked RCT designs or even deception. Deeply uncomfortable with deception and, secondarily, with Beecher's untested knowledge claims, I decided to investigate OLP with the aim of moving placebo treatment towards legitimate ethical standards. The OLP agenda is in its infancy, and where it will lead is unclear. Early small trials often fail replication. Nonetheless, I undertake this essay to foster debate and to highlight OLP's disruptive potential for new theoretical and clinical insights.

ARRIVING AT THE OLP HYPOTHESIS

For me, the most significant inspiration to investigate OLP came from interviews performed by anthropologists as part of a qualitative study that was embedded in a RCT investigating components of the placebo response in irritable bowel syndrome (IBS) patients treated with placebo acupuncture under blind conditions (Kaptchuk et al. 2008, 2009). As I read the transcripts of the interviews, participants consistently expressed feelings and thoughts that differed dramatically from Beecher's orthodox view and what had been sanctioned in the subsequent placebo literature. Five unambiguous, consistent, and unexpected themes emerged in the interviews.

First, patients denied having positive expectations. A typical patient remark was: "I can't say I'm expecting that much, but I think if something did happen, it'd be a pleasant surprise. . . . It is worth a shot because otherwise, if nothing else, I'm no worse off than I am today, you know. . . . I haven't anything to lose." (All quotes from this study are from Kaptchuk et al. 2009.) Second, patients spontaneously spoke of "hope" as their motivation. When the interviewer asked one patient, "And what do you expect to get from the treatments?" her response was representative: "Hey, you know if, maybe there's some treatment that can help me. But I have no idea. I'm just hopeful." Third, patients linked hope with despair. A common refrain was: "You get to a point where you're so desperate, you'll try anything. If people told me if I [should] wear pink every day, I would do it. I really would try anything. . . . Um. If it doesn't work, well, I tried, so I didn't really lose." Fourth, patients worried about being treated with placebos. Placebos preoccupied their thoughts and they consistently tried to guess whether they were on real or placebo interventions. A characteristic remark was: "Mmm . . . you know . . . I don't know if the placebo acupuncture is just in different spots. . . . I have absolutely no idea if . . . it [is] just less effective location, than not, I don't know if it's real or placebo." Finally, patients worried that improvement was "all in their head." Typical of their remarks was: "Maybe I'm making the whole thing up?"

Reading these transcripts shattered my placebo complacency. I realized patients did not endorse positive expectations, but rather spoke of something they called "hope." The interviews showed that patients were confused and worried by placebos, and that concealment did not fool them into thinking they were receiving real treatment. I began to wonder if it would be possible to reframe this hope, despair, and apprehension and honestly discuss and prescribe placebos instead. Would the anxiety be any worse? Was communication of positive and potentially deceptive, expectation really necessary? If people denied positive expectations, maybe the mechanisms of placebo effects were really more nonconscious, sensory-motor, and embodied than everyone assumed. In retrospect, I realize that I was perilously hasty in contemplating a decisive change in my research commitments based on a single qualitative study. Luckily, several subsequent qualitative reports replicated our original qualitative study (Eaves, Nichter, and Ritenbajugh 2014; Eaves et al. 2015; Hsu et al. 2014, Sherman et al. 2010). Additional other evidence, described below, supported my decision to undertake OLP.

Early Hints of OLP

Between 1965 and 1967, Park and Covi performed a series of three observational studies attempting to understand whether the generalizability and validity of research would be threatened by the new research methodologies being developed

in the early 1960s, such as informed consent about placebos, randomization and the research objective of a study (Park and Covi 1965; Park, Covi, and Uhlenhuth 1967; Park et al. 1966). (See Miller 2014 for background on these experiments.) The experiments were undertaken to "explore . . . the possibility of breaking with the traditional taboo of informing patients of the research nature of treatment" (Park, Covi, and Uhlenhuth 1967, 352). In their first publication, they examined placebo disclosure (Park and Covi 1965). After baseline measurements, 15 "neurotics" received an intake session of psychological counseling plus placebo pills, and after one week, the 14 completers showed clear and even dramatic improvement. The authors concluded: "patients can be willing to take placebo and can improve despite disclosure of the inert content of the pills." The trial was not testing whether placebos could be administered honestly as a therapeutic modality; furthermore, Park and Covi did not explore or discuss any clinical implications of OLP, probably because deceptive placebo was still considered ethical practice (Kaptchuk 1998; Rothman 1991). Despite the lack of controls and co-interventions, their study was an important precursor to OLP and, after our qualitative study, it reinforced my ruminations on OLP.

In 2005, I was part of a small qualitative study that sought to explore expectations in placebo-controlled RCTs (Stone et al. 2005). This study drew on a convenience sample of participants from four trials testing: (1) a collagen preparation for rheumatoid arthritis; (2) risedronate for bone loss in lupus; (3) abetimus sodium to treat kidney function in lupus; and (4) remacemide for Parkinson's disease. When asked about their expectations upon entering the study, most participants spontaneously endorsed hope. All participants spoke about how their previous experience with medicine led them to expect failure, and most ruminated that they feared being a "placebo responder." Even though I was a co-investigator in this small study, I originally thought it was too small and strange to have any practical implications. However, after our qualitative study, I started to take this study more seriously. To the best of my knowledge, this study encompassed the first set of retrospective interviews concerning placebos and expectation, and the qualitative study described earlier was the first randomized prospective study to explore patients' experiences concerning placebos in a RCT. How did we ignore patients' perspectives for so long?

The erosion of my confidence in dominant placebo theories was also seriously influenced by extensive reading. A critical paper was Frenkel's (2008) essay applying Merleau-Ponty's (1945) ideas of embodied cognition to understanding placebo effects. Frenkel argued that "the body understands and is capable of responding to meaning without . . . conceptual or linguistic content specified" (58). Other books on "embodied mind" supported this argument (Lakoff and Johnson 1999; Varela, Thompson, and Rosch 1991). A philosophic essay by Tamar Gendler (2008) had an even more important influence. She argued that sensorimotor and behavioral repertoires can "activate . . . an associative chain . . .

regardless of the [mental] attitude that one bears . . . including no attitude at all" (650). Significantly for OLP, she maintained that what she called a "mismatch" or "discordant" situation between propositional/cognitive knowledge on the one hand and motor routines and affective responses on the other could be resolved in favor of motor/affective input. She described these effects as "associative, automatic and arational [sic]," "insensitive to reality," and not involving an endorsement or acceptance of a proposition. (641).

Around this time, reports began appearing in top-tier journals on nonconscious processes affecting perceptions, emotions, and cognition. For example, in 1987, *Science* began what became a series of publications, commencing with Kihlstrom's "The Cognitive Unconscious" (1987), and continuing with experimental studies on nonconscious bias, embodiment, unconscious motivation, and nonconscious influences on perceptions (Bechara et al. 1997; Niedenthal 2007; Pessiglione et al. 2007; Williams and Bargh 2008). Such reading led me to resonate with the emerging and now current consensus shared by many cognitive scientists that the cognitive unconscious "is increasingly looking like the engine room of cognition, and the explicit mind like a fragile superstructure" (Frankish 2016, ix).

Ethical frustration further motivated my decision to undertake OLP. For a number of years, I struggled with how to make placebo research directly relevant to medical practice. The negative ethical baggage surrounding placebos made clinic applications improbable. There were occasional calls in the literature to try OLP (Brown 1994). But would it work? Ultimately, desperation to find an ethical clinical direction for my work fed my decision to risk scarce resources to investigate what most of my colleagues considered ridiculous.

Emerging Evidence for OLP

The first OLP RCT randomly assigned 80 irritable bowel syndrome (IBS) patients to either honestly prescribed OLP plus treatment as usual (TAU) or TAU alone (Kaptchuk et al. 2010). TAU alone controlled for the patient-clinician relationship (which were identical in both arms), time, spontaneous improvement, and regression to the mean. When people called our telephone line for information, they were clearly told that the intervention was "honestly described placebo pills." Our physicians and nurse practitioners were very busy with their paying jobs, and the orientation took about 10 minutes (excluding time for clinical assessment and reviewing informed consent). The discussion was natural—not formally scripted—and had the feel of a regular back-and-forth clinical interaction. In the original publication, I was still shocked and confused about the results and not sure how to describe a research agenda in infancy and still inchoate. In writing the original report, I used only words and ideas that would be comfortable for the medical community. I think this confusion caused imprecise statements of what and why we exactly did in this study and the studies described later. Below

I reframe the original wording and describe, to the best of my knowledge and experience, what actually happened and continues to happen in most OLP studies. Obviously, as new evidence evolves, the orientation would need modification. In the original OLP study, the orientation applied what I had learned from our qualitative study, my readings, and my gastroenterologist colleagues and included four key points:

1. *Remove the stigma of placebo effects.* We informed patients that IBS patients often have powerful placebo responses in double-blind RCTs for their condition. We stated that the hypothesis of the study was testing whether placebo effects still occurred if patients were informed about placebo treatment and we wanted to find out. We emphasized the truth and we explained that we did not know if OLP would work. Not infrequently, there was laughter and skepticism in these discussions.
2. *The automatic nature of placebo responses.* Patients were told their only responsibility was taking the pills. The presentation never suggested "positive thinking" was necessary or that the onus of responding was their mind. We touched on what is known about placebo: we mentioned specific neurotransmitters and brain regions or Pavlov's dogs, bells, and saliva, and we talked about brain-gut connections that happen automatically. We said this was how concealed placebo worked, and we indicated that if OLP worked, it probably had similar mechanisms.
3. *No requirement to believe.* We made it clear that participants didn't have to believe in the treatment for it to work. We made room for them to express their skepticism; it was obvious that most of our patients thought that knowingly taking placebos was ludicrous, and clinicians often shared their own incredulity. We talked about an attitude of "let what happens happen" (Ballou et al. 2017).
4. *Taking pills is critical.* Based on the literature from RCTs (Horwitz and Horwitz 1993) and theories of embodiment, we emphasized the importance of taking one pill twice daily. Patients were told that if they were going to feel any benefit, it might happen gradually or it could happen quickly.

At three weeks, the results were startling: 60% of OLP patients obtained "adequate relief" on a standardized questionnaire, compared to 35% for no treatment ($p = .002$). Other validated measures reported similar benefits. The outcomes were clinically meaningful. Like many of the later OLP publications, the impact of the study was amplified by extensive media attention.

Other Clinical OLP Trials

Subsequent OLP trials generally followed a similar model to the IBS study while each adopted unique refinements. The second study was performed on patients with chronic low back pain ($n = 97$) (Carvalho et al. 2016). An exploratory

extension that allowed patients on TAU to elect OLP at the end of main study was added. At the end of three weeks, the outcomes were similar to the IBS study: pain in OLP was reduced 28% compared to 9% in TAU alone ($p < .001$). At the beginning of the trial, patients were asked not to make any changes in their medication regime but to continue taking medication as needed. Sixty-four percent of participants reported decreasing their medication on OLP (Carvalho, Kirsch, and Kaptchuk 2017). During the three-week exploratory extension, patients switched from TAU to OLP had similar improvements strengthening the results of the main study.

A third study randomized patients with cancer-related fatigue ($n = 74$) for 21 days to either OLP + TAU or TAU alone (Hoenemeyer et al. 2018). After three weeks, patients on OLP reported a 29% improvement in fatigue severity ($p = 0.008$), and 39% improvement in fatigue-disrupted quality of life ($p = 0.002$). As an exploratory study, after three weeks, patients in TAU were allowed to take OLP for three weeks, and those on OLP were followed after they discontinued OLP. Patients who switched to OLP had similar improvements (an internal replication of the main study); remarkably, those who discontinued their OLP retained their improvement. (My own informal following of patients who discontinued OLP has not observed this persistence. Obviously, further investigation is needed here.)

A fourth, smaller two-week RCT built on an earlier pilot study. Originally Schaefer and colleagues (2016) randomized participants with allergic rhinitis ($n = 25$) to either OLP or TAU. They found significant OLP effects. Later, in a more elaborate larger 2x2 RCT ($n = 45$), they tested both OLP versus TAU and, at the same time, OLP and TAU with "positive expectation" versus OLP and TAU with no information about placebo effects and how to think about OLP (Schaefer, Sahin, and Berstecher 2018). Participants on OLP compared to TAU showed significant improvement ($p = 0.02$) and, in contrast, there was no interaction between the factors of expectancy, time, and placebo ($p = 0.89$) or expectancy and placebo ($p = 0.24$). Positive expectancy and information had no impact on the primary outcome but did improve secondary global outcome.

One experiment that included OLP was significantly different from the others described. It involved a complex within-subject randomized experiment, where patients served as their own control during multiple acute episodic migraine attacks ($n = 459$ documented attacks in 66 patients) (Kam-Hansen et al. 2014). Pills were labeled in different ways during each attack. A nested comparison of OLP versus no-treatment control (involving 132 baseline observations in 66 patients) found that, in two hours, OLP reduced pain by 15% compared to 15% worsening in no-treatment (just waiting). The total mean difference between conditions was 30% ($p = 0.001$). This experiment involved no orientation for OLP, just a label on the envelope saying "placebo." Like the allergic rhinitis trial just described above, this migraine experiment suggests that OLP might work even without any

explanation and can involve embodiment alone. Nonetheless, informed consent and respect for persons in clinical practice necessarily requires orientation and explanation.

Taken together these results are intriguing. They are mostly proof-of-concept and need replication and expansion. Because the OLP trials do not allow participants to be masked as to whether they have received open placebo, report bias may be a factor influencing the observed results. However, the consistency and magnitude of symptomatic relief across these several studies, involving a diverse set of medication conditions and implemented in different hospitals in the United States and Europe, suggest that a real therapeutic benefit may be produced by the OLP intervention. Luckily, more OLP studies are planned or underway.

MECHANISMS OF OLP

Scholars have already noted that it is likely that multiple distinct mechanisms and environmental cues are involved with placebo effects (Benedetti 2009; Enck, Benedetti, and Schedloweski 2008). Given its unique features, OLP may involve unique processes and need innovative theoretical foundations. Alternatively, OLP may elucidate an overlooked substrate of mechanisms that complement or challenge previous placebo theories that emphasize conscious beliefs. Time will tell. In this section, I critically examine both standard and novel theories of placebo effects in relationship to OLP.

Psychological Mechanisms

First, I'd like to make two global criticisms of common psychological theories of placebo. Most contemporary psychological models assume that placebo effects are caused by input from the environment that shapes cognitive or emotional states in the brain that in turn pour or trickle downwards to specific areas of the body. The model bypasses a critical question: How do environmental messages of healing—thoughts and feelings—get to their bodily targets without getting stuck in a "mini-me" representational map? In my perspective, these models assume a kind of tiny homunculus or Cartesian centralized control panel directing traffic. Current placebo theory lacks, at least from my perspective, a cogent explanation on how the hyphen in "mind-body" works: how the mind funnels into specific regions of the body to change symptom perception.

A second criticism concerns the evidence for theories about psychological mechanisms. Too often placebo research investigates how healthy volunteers respond to deceptive situations in laboratories over very short periods of time. These studies often involve experimentally induced symptoms such as painful stimuli. To be sure, these experiments have provided and will continue to provide important proof-of-concept data. Nonetheless, I think such experiments are mostly, if not totally, removed from the reality of patients experiencing symp-

toms. Chronic clinical symptoms generally involve complex pathophysiology interacting with psychological deregulation, are often connected with emotional and existential vulnerability (like cancer and cardiovascular disease), or are enmeshed with central sensitization (where the central nervous system is induced into a state of persistent high reactivity), or share aspects of functional somatic complaints, somatization, aberrant amplification of nociceptive signals, or medically unexplainable symptoms (Edwards et al. 2012; Hechler, Endres, and Thorwart 2016; Van den Bergh 2017a, 2017b; Woolf 2011). Symptoms rarely if ever resemble a noxious stimulus akin to a volunteer getting a jolt of pain.

Following are some comments concerning two specific psychological mechanisms: expectation and hope.

Expectation is the dominant theory of placebo, and it is commonly thought of as a propositional, conscious, conceptual, and probabilistic belief about the future (Wager and Atlas 2015). I have four main criticisms of expectation theories of placebo effects, especially in relationship to OLP. The first criticism is that expectation theory assumes previous positive experience. The qualitative data I described earlier raises serious doubt about the importance of positive previous experiences. Patients do not bring positive expectation about their condition into RCTs. Furthermore, OLP's fundamental message that "The pill is inert, like a sugar pill" or "Let's see what happens" cannot be called the provision of positive expectancies (Ballou et al. 2017). We were acutely aware that most of our trial participants were refractory patients who had a history of multiple failures or inadequate responses to previous interventions. We did not want to repeat the positive (and inaccurate) narrative they had heard many times before. Our honesty was critical. Furthermore, the allergic rhinitis and episodic migraine study described earlier suggest that "expectations" and even "cognitive information" are not necessary for OLP efficacy.

My second criticism is that expectation theory is too expansive. As Geers and Miller (2014) point out, expectation can often be deconstructed into various other, equally plausible psychological mechanisms, such as anxiety-reduction, positive affect, somatic recall, and interpretive frames that redirect attention, detection, weighing, and attribution. Similarly, Bubic and colleagues (2010) argued that besides expectation, "looking into the future" involves many other psychological mechanisms including preparation, anticipation, attention and prioritizing sensory processes. I suspect sharp boundaries between such future-oriented imaginative states rarely exist in the mental-emotional life of patients.

Third, clinical evidence is not consistent. Expectancy research in clinical populations often measures correlations between baseline expectation and outcomes. Such evidence is inconsistent. For example, one of the earliest clinical studies of correlations between baseline expectation and pain amelioration was performed with patients receiving intravenous drug infusions and nerve blocks. Physicians' expectations—but not patients'—showed a correlation (Galer, Schwart, and

Turner 1997). A follow-up experiment by the same team, investigating chronic pain spinal cord injury, found the reverse: only patients' expectancies correlated with outcomes (Turner 2002). Two large attempts to correlate baseline expectations with outcomes in acupuncture/placebo acupuncture RCTs provide another example. Linde and colleagues (2007) retrospectively combined four RCTs and found that baseline expectations correlated with improvement (n = 864). About 30% of patients were not naïve to acupuncture, but regression analyses showed no association with outcome. Later, Sherman and colleagues (2010) performed a prospective study of expectation and measured baseline expectations on patients naïve to acupuncture in three different ways (n = 477) to increase sensitivity. None of these measures were associated with increased response to either real or placebo acupuncture. Interestingly, the researchers measured expectations throughout the study and found that expectations constantly fluctuated, not unlike other studies that measured expectations multiple times (Eaves et al. 2015; Petersen et al. 2014).

Another example of inconsistent outcomes can be found in RCTs prospectively enhancing medications with expectations. For example, in order to study augmented expectations, Rutherford and colleagues (2017) randomized depression patients (n = 49) to an open-label anti-depressant (presumably having higher expectations) versus a double-blind anti-depressant. The open-label was superior to double-blind medication. Pollo and colleagues (2001) (n = 38) found similar results with post-surgical patients. In contrast, Bergmann and colleagues (1994) did a similar study using patients as their own control in a crossover RCT randomizing hospitalized patients with cancer pain to either drug or placebo (n = 49; total of 98 observations). Half the patients were treated as if they were in routine care and not told they were in an RCT and unknowingly received either medication or placebo. The other half were told they were in an RCT and would receive double-blind either a drug or placebo. The outcome was in the opposite direction: double-blind information increased medication effects, as well as placebo effects. (See section below on uncertainty and novelty for other examples of reduced expectations increasing placebo effects.) The largest RCT to prospectively investigate enhanced expectancy on medication and placebo (n = 601) produced another twist. Asthma patients were randomized to receive either an elaborate expectation enhancement that included scripted messages of the effectiveness of medication and computer presentations (including TV ads) or a neutral expectation (Wise et al. 2009). Here, positive expectations had no impact on medication outcomes, while placebo treatment with heightened expectation improved only subjective measures. Similar inconsistent results can be found in other studies. Whatever expectations may be, placebo researchers cannot advocate "expectations" with a big global brush: a more refined theory needs empirical demonstration on real patients. Placebo researchers who use expectation theory need to be more nuanced and explain who, when, and how.

My final criticism of expectation theory is that "nonconscious" and "multiple" expectations muddle the theory. The necessity of conscious awareness for placebo effects has been challenged. An elaborate series of well-designed behavioral and fMRI neuroimaging experiments demonstrated that subliminal healing cues can unconsciously activate placebo effects (Babel 2017; Jensen et al. 2012, 2014, 2015). In other words, one does not need to be aware of treatment to respond to placebo stimuli (Jensen 2018). In parallel, Ritter and colleagues (1999) showed that different expectations related to the same event can occur at the same time and be processed in different areas of the brain. More elaborate experiments with monkeys have shown similar results (Cisek and Kalaska 2005). This kind of data has yet to be incorporated into expectancy theories.

On a more positive note, despite these strong criticisms of expectation theory, I believe that expectancy is involved with many placebo effects, especially in acute experiments with healthy volunteers, in short-term procedural interventions for patients, and for new patient conditions where there is no history of failure. In these acute circumstances, especially in laboratory settings, it might be hard to separate expectation from suggestibility or gullibility. In fact, a recent large meta-analysis found medium to large effects with prospectively delivered verbal positive expectations in experimental and acute pain, and only small and clinically insignificant effects in chronic pain (Peerdeman et al. 2016). Such findings suggest that expectation models need refinement.

As described earlier, *hope* is a term that chronic patients self-describe as their deportment in RCTs. Currently, there is little discussion about hope in the placebo literature (for exceptions, see Kaptchuk et al. 2009; Spiro 1998). There is, however, an extensive social science literature on hope in chronic disease and oncology (Corbett, Foster, and Ong 2007; Good et al. 1990). The psychological literature has multiple theories and definitions of hope and debates continue as to whether it is a primarily emotion-based or cognitive-based category (Lopez, Snyder, and Pedroth 2003). I subscribe to social science theories where hope is a combination of opposites, balancing despair with an openness to a different future notion—a kind of "tragic optimism" (Averill and Sundarjan 2004; Eaves et al. 2016; Marcel 1962). As the anthropologist Mattingly (2010) explains: "paradoxically, hope is on intimate terms with despair. It asks for more than life promises. It is poised for despair" (3). Hope—like empathy, compassion, envy, and shame—is a complex construct that involves deep feelings, cognitive reflection on the past and present, prospection, and cultural rules of what is reasonable when one looks into the future.

I do not believe that hope is a magic bullet causing placebo effects any more than I believe expectation or anxiety reduction have this capacity. I consider hope, especially in chronic diseases, to be a posture that encourages and cognitively mimics neurological mechanisms of placebo to happen (see discussion below). Hope is a lifejacket against despair, a disposition that allows patients

to face illness and maintain a semblance of a life. Minimally, hope may resolve what Büchel and colleagues (2014) and Katja Wiech (2016) call the "paradox [or tension] of expectation." They ask, if expectancy is so powerful, why do clinicians not foster the most extreme expectancies? They argue that a modulation is necessary, because an inappropriately strong expectation might lead patients to disappointment and thereby disconfirm expectations. Alternatively, they argue, inordinately modest anticipation risks reducing the effects of expectations (Kirsch 2018). Fava and colleagues (2017) are even more emphatic, describing "violations of expectations" that "may precipitate a state that is worse than the initial one . . . [because] patients may interpret unfulfilled expectations about therapy as an indication that their condition is untreatable" (336; see also Rescorla and Wagner 1972; Rief et al. 2015). Examples of such enhanced expectations causing harm have been empirically demonstrated (Williamson, Thomas, and Stern 2004). I believe that hope's bi-directional nature—positive anticipation versus relentless sickness—resolves this paradox or potential harm. Hope automatically modulates and personalizes expectations. As a model, expectation relies on previous positive experience, while hope faces the unimpeachable experience of the present and maintains openness to new experience. Hope is the reality that patients know without any input from scientists or doctors: "the struggle to simultaneously maintain hopes high enough to embrace . . . any potential effects of the treatment, while at the same time avoiding hoping for too much and risking disappointment, if not despair" (Barnard 1995, 47). Hope is not a magic wand. Hope is not an idea, a proposition, or an expectation. Hope as a process connects with patience, forbearance, tolerance, humility, and honesty.

Uncertainty and Novelty

OLP patients are generally uncertain or skeptical about OLP's effects, and "some element of uncertainty is always present in hoping" (Pruyser 1963, 87). I suspect uncertainty can be a positive factor in placebo responses, especially OLP and certainly with "prediction processing," as I will describe below. The placebo literature ignores the presence of uncertainty and instead emphasizes its opposite: certainty, or strong positive expectancies. While several well-designed acute laboratory experiments have demonstrated that "certainty" produces better outcomes than "uncertainty"—for example, the well-known hidden-open administration of medication performed by Fabrizio Benedetti's team (Colloca et al. 2004; Pollo et al. 2001)—other well-designed studies have found contradictory evidence. Importantly, in a PET neuroimaging study, Lidstone and colleagues (2010) showed that Parkinson's patients responded better to placebo when they were uncertain whether the placebo was levodopa or a placebo, compared to when they were certain the placebo was levodopa. More dopamine was only released with the uncertainty. Lidstone concluded that the study "demonstrate[s] the importance of uncertainty and/or salience . . . over and above a patient's

prior treatment response in regulating placebo responses" (863). Bergmann and colleagues (1994), as mentioned earlier, showed similar behavioral effects in an RCT in cancer-related pain.

Interestingly, monkey models using electrophysiological recording of individual neurons have also shown the importance of uncertainty for gaining new information. Anticipatory licking responses, dopamine release, and electrophysiological responses of individual neurons demonstrated that only in the presence of uncertainty does the brain anticipate, seek out, and identify new data or reward (Fiorillo, Tobler, and Schultz 2003). Fiorillo argues that "subjective uncertainty indicates [when] an animal lacks accurate predictors [and needs to search] for a more accurate prediction" (1901). The role of uncertainty—if, when, and where it is helpful, neutral or an inhibitor of placebo effects—needs clarification.

Uncertainty is related to novelty. In fact, the hope literature clearly links "openness to novelty, possibility and surprise" (Barnard 1995, 47) with "a surrender, not only to reality-up-till-now, but also reality-from-now-on, including unknown novelties" (Pruyser 1962, 87). Supportive of this idea is the body of neuroimaging literature implicating novelty-seeking with dopamine release and various placebogenic mechanisms (Costa et al. 2014; Guitart-Masip et al. 2010).

Classical Conditioning

Classical conditioning, or "stimulation substitution," is a well-studied phenomenon that has been shown to operate in some placebo effects (Schedlowski et al. 2015). In my opinion, it is hard to believe that conditioning is a major factor in OLP patients with their frequent histories of medical failure. Furthermore, in OLP there is no formal conditioning process that takes place similar to placebo-conditioning "dose-extension" or "partial reinforcement" experiments (Ader et al. 2010; Goebel et al. 2008; Kirchof et al. 2018; Perlis et al. 2015; Sandler and Bodfish 2008; Sandler, Glesne, and Bodfish 2010). While conditioning seems absent in OLP, it remains to be seen whether conditioning dose-extension models and OLP can be additive, and to what extent the "orientation" process of OLP is itself an active component of dose-extension paradigms. I hypothesize that conditioning will be one of the two pillars of future honest placebo strategies. For situations in which powerful effective drugs that easily outperform placebo controls exist, placebo conditioning will be critical; for circumstances in which medications often fail to differentiate from placebo controls, OLP will be the way forward.

Patient-Clinician Relationship

Whatever the mechanisms, placebo treatment generally takes place within the context of patient-clinician engagement. The evidence for OLP generally includes a treatment-as-usual (TAU) or no-treatment control with identical supportive patient engagement until the last moment before randomization. This

suggests that supportive interaction alone is not sufficient for producing placebo effects in the context of such trials. Nonetheless, embodied nonverbal cues (vocal, facial, eye, speech, and bodily expressiveness; touch; sensitive proximity relations), evocative symbols (appearances, paraphernalia, healing space), and ritualized behaviors (attention, warmth, empathy, diagnostic procedures) that lead to trust and rapport may interact with OLP (Kaptchuk 2011; Knapp, Hall, and Horgan 2014). In a related issue, I suspect an uninterested physician could negate OLP benefits, and purchasing placebo pills independent of any patient-clinician relationship would reduce the effectiveness of OLP.

Neurobiological and Prediction-Processing Mechanisms of Placebo

Neurobiological research has provided legitimacy to the field of placebo effects. It is known that neurotransmitters (such as endorphins, cannabinoids, and dopamine) are involved, and that specific, quantifiable, and relevant areas of the brain are engaged. Genetic factors are emerging. For the sake of brevity, I refer the reader to the many excellent reviews on this subject (Enck, Benedetti, and Schledoweski 2008; Geuter, Koban, and Wager 2017; Hall, Loscalzo, and Kaptchuk 2015; Wager and Atlas 2015). Undoubtedly, some of these mechanisms may be involved with OLP; further research will tell.

Instead, I would like to draw attention to a particular area of investigation that shows promise: prediction and error processing (PEP), Bayesian brain, and embodied cognition models. PEP exists at the intersection of computational biology, cognitive science, and artificial intelligence. With the few exceptions that will be discussed below, the placebo literature has not engaged with PEP, but I believe that PEP could become a source for new directions in theory, research, and testable hypotheses. Furthermore, while the important neurological findings to date have been critical, they lack an integrative neural processing model that PEP proposes. My simple introduction below is no substitute for the many excellent reviews of the PEP model (Clark 2016; Firth 2007; Hohwy 2013: Shapiro 2011).

The basic idea of PEP is that perception is inseparable from prediction. Prior top-down likelihoods are neurologically and inextricably linked with bottom-up sensory information. The brain is neither passive and nor stimulus-driven. Rather the brain is constantly, mostly non-consciously, predicting incoming signals. According to Clark (2015), sensory information sent upwards to the brain is primarily information that deviates and does not match prior predictions: "The driving sensory signal is really just providing corrective feedback on the emerging top-down predictions" (7). The brain is interested in sensory bottom-up "errors," mismatches, or dissonances that can correct top-down predictions. It minimizes mismatch by either changing predictions or modifying sensory input. In this regard, it resembles "an efficient file compression program in a computer

[that] uses prediction to generate what is static or predictable and reserves valuable . . . processing capacity for what is not predicable" (Seligman et al. 2016, 10). The brain is

> a statistical organ that actively generates explanations from the stimuli it encounters—in terms of hypotheses that are tested against sensory evidence. . . . "Explanations," "hypotheses," and "belief" should in this context be understood not as consciously held mental states, but as neural encoded probability distributions (i.e. Bayesian beliefs, priors) that are tested against sensory evidence (posteriors). (Seth and Friston 2016, 1)

Thus, predictions are not endorsements of static rational propositions but happen on a "microscopic scale as millions of neurons talk to one another" (Barrett 2017, 59). Sensory data is also evaluated for "precision" (salience, or in statistical terms, inverse variance) of the signal. How much weight should be assigned to a signal? Is the signal important enough to override or shake the prediction? Going beyond traditional mind-body dualism, prediction is already encrypted at the very instant of perceived sensory information. Ultimately, there are no simplistic top-down and bottom-up interactions: sensory perceptions and prediction are bi-directional, or, to overstate the point, horizontal. Sensory data and bodily complaints including exteroception, interoception (visceral afferent), and proprioception (sense of position, motion and equilibrium) are "neurological occurrences." Conscious awareness certainly contributes, but it is not the final arbitrator. For PEP, there is no Cartesian homunculus or "representational bottleneck" in the brain of perceptions waiting to be updated from the periphery.

To date, PEP's most compelling evidence comes from research in visual and auditory processing. For example, the classic theory of visual processing, where sensory signals in the retina transduce light into neural firings that are sent upward to the visual cortex that constructs representations, has been discarded. When light touches the retina cells, predictions are already embedded in the retina. Only errors are forwarded to higher levels of the nervous system and refine predictions that will reformulate the predictions maintained in the retina. In the last two decades, considerable research in human and in salamander and rabbit retinal ganglion cells provides solid foundation for this PEP visual model (Berry et al. 1999; Hosoya, Baccus, and Meister 2005; Summerfield et al. 2006). Significant data in human auditory process has also produced consistent results, and artificial computer neural networks have provided important proof-of-concept (Chennu et al. 2013, 2016; Rao and Ballard 1999). In addition, anatomical models implicating aganular visceromotor cortices shaping interoception through predictions have been described (Barrett and Simmons 2015). Two everyday examples may help clarify the general idea of how PEP works: sticks in a forest infested by snakes are readily perceived as slithering serpents, and when bird watchers search for birds, they may see many things that resemble birds until they carefully develop a more refined view.

Direct evidence for PEP's involvement with placebo effects is still in the preliminary and pioneering stages. Small studies have demonstrated (at least in healthy normals) that "incoming sensory information is not analyzed *de novo* but interpreted based on prior information" (Koban et al. 2012; Wiech et al. 2014). Jung and colleagues (2017) found Bayesian modeling successfully predicted [placebo analgesia] in a simulated clinical situation (see also Anchisi and Zanon 2015; Grahl et al. 2018; Knill and Pouget 2004). Importantly, two leading placebo analgesia researchers have already written valuable review articles showing the compatibility of PEP and existing mechanistic evidence for placebo effects in acute pain in the context of experiments involving deception (Büchel et al. 2014, Wiech 2016; see also Ongaro and Kaptchuk 2018).

Bayesian brain models also may help explain an emerging finding in placebo studies. Baseline variability—measured baseline fluctuations—seems to be a predictor, at least for pain, of likelihood of response to placebo. For example, an analysis of 12 clinical trials for painful conditions found an increased likelihood of response in the placebo-treated group for participants with a higher standard deviation in the baseline seven-day diary (Farrar et al. 2014). These findings have been replicated in other studies (see Ballou et al. 2018). For PEP, such a situation of fluctuating and imprecise priors leaves more room for perception and acknowledgment of new "errors" or information; in situations where the priors are precise and salient, there is little room for new updated errors to correct predictions. Bayesian brain is especially crucial for making inferences under ambiguity where the priors are "noisy and ambiguous" and where a high degree of uncertainty exists (Tenenbaum et al. 2011, 1279; also see Gershman, Horvitz, and Tenenbaum 2015).

A Narrative OLP Hypothesis Based on Prediction and Error Processing

Imagine some chronic patients who are propelled forward by hope. They join an OLP RCT. They enter a novel healing situation and a new drama begins. The main plot is counter-intuitive, defying credulity. They hear a short orientation where the doctor discusses placebos in double-blind RCTs and states they are now testing whether placebos can work even if patients know they're taking placebo. Patients take the pills. Heightened vigilance, uncertainty, and salience arise. On the cognitive level, patients ask: "Is this for real?" "Am I nuts taking placebos for a condition that has bedeviled my life?" The same questions happen on the non-conscious neurological level. Attention and salience is directed at the symptoms. According to PEP, the brain strives to reduce uncertainty. Should the brain change the prediction (central sensitization or aberrant amplification of nociceptive signals) because of embodied pill-taking behavior in the context of medical intervention, or should it keep the old prediction of symptoms because

the procedure is irrational? PEP suggests that Gendler's (2008) notion, mentioned earlier, is operating: a "mismatch" or "discordant" situation between propositional/cognitive knowledge on the one hand and motor routines and affective responses on the other can be resolved in favor of motor/affective input. PEP suggests that non-rational and automatic processes can override the mind.

How can knowledge that something is fake work? A simple example illustrates that this may not be so far-fetched. We attend a performance of a Shakespeare tragedy, *Romeo and Juliet* for instance, knowing that it is not "real." Nevertheless, we enter into the drama and allow ourselves to be moved. Often we experience emotional and physical responses (fear, grief, lumpy throats, knotty stomachs, tears) similar to those we'd expect if we were witnessing the events directly. If the performance is evocative, we can feel this embodied response even after a dozen performances. Just disclosing the story by itself doesn't make the audience cry.

Going further, can simulated input—such as OLP—change concrete sensory processes? A heuristic example may be helpful here. Binocular rivalry vision mismatch (BRVM) is a relatively minor example of PEP theory that shares striking similarities, metaphorically if not neurologically, with OLP. BRVM uses a special experimental set-up, whereby each eye of a person is simultaneously shown a different visual stimulus—say, for example, Einstein's face and a tree. There is tremendous neurological "error" or dissonance. Instead of seeing some combination of both, a person sees either Einstein's face or the tree (Blake and Wilson 2011; Hohwy, Roepstorff, and Friston 2008; Lee, Blake, and Haeger 2005). PEP theorists see a Bayesian logic here. There is a highly unusual visual input with two possibilities: a combined tree-face image could account for the visual input, but there is a very low prior probability for such a tree-face combination existing in the real world; it is therefore predicted to be either tree or face. Prediction therefore overrides—without any conscious intention and awareness—the sensory input with its dissonance and creates a single image. OLP may involve a similar "error" or mismatch: medical situations (things might change) versus physically take dummy pills (things will not change). Which is real? I speculate that PEP processes correct the neurological, cognitive, and embodied mismatch/dissonance embedded in OLP and produces one of two consistent predictions: either the symptoms are better or the symptoms are not better. Any improvement is embodied and automatic, the performance of healing overrides conscious awareness.

Whether the narrative hypothesis I propose is even partly true needs empirical verification. As mentioned above, some preliminary evidence exists. The compelling research produced by Jensen and colleagues (2012, 2014, 2015) suggests that placebo effects can sometimes be entirely produced by nonconscious environmental cues (see also Babel et al. 2017). Furthermore, I would argue that the best evidence for placebo effects involving PEP might be the OLP RCTS themselves. If OLP placebo effects were primarily mental phenomena, I suspect

that when patients closely examine any positive response by eating salad in IBS or lifting heavier objects in cLBP, the improvement would disappear, as in the simple snake and bird examples I mentioned earlier. If OLP is real, one parsimonious explanation is an embodied neurological occurrence.

Does the PEP hypothesis only apply to OLP? Placebos effects—OLP, double blind, concealed, or those accompanying a drug—are not magic or positive thinking. It is possible that to some extent all types of placebo effects involve the embodied and nonconscious input that I propose is involved with OLP. Because experimentally we have generally looked at conscious awareness as the medium for most placebo effects, we have generally overlooked non-conscious possibilities of placebo activation. OLP suggests that this omission is outdated, and that PEP needs to be incorporated into placebo theory.

Conclusion

In this essay, I have presented evidence and speculation on OLP, developed an OLP hypothesis, and critically examined mechanistic models. I argue that the efficacy of OLP may derive from the effect of constantly searching neurological systems attending to sensory, motor, affective, and cognitive stimuli in the context of an embodied and imaginative ritual performance of healing. Placebo effects, especially those resulting from OLP, appear to be more a neurological occurrence than a conscious top-down mind-body event. Thus, placebo effects are primarily elicited by what you do, and only secondarily—or not at all—by what you think.

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