Consensus in Placebo Studies

lessons from the philosophy of science

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ABSTRACT In the relatively nascent field of placebo studies, empirical studies have burgeoned. Yet debate about how to define the terms *placebo* and "placebo effect" has not abated. A number of prominent scholars (drawn from medical practice, as well as philosophy, psychology, and anthropology) continue to propose and defend different conceptual models for these terms, and the perception that conceptual debate persists is often given as one justification for new definitions. Paradoxically—in spite of this lively debate—this article finds considerable underlying agreement about definitional matters within placebo studies. Drawing on key insights from philosophy of science, and by exploring the nature of scientific consensus and normal scientific research, this paper argues that well-developed placebo concepts form the basis for a placebo paradigm and that conceptual disagreement is overstated.

A COMMON OBSERVATION IN PLACEBO studies is that definitional disagreement is rife. Philosopher and historian of science Robin Nunn (2009a) recently

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argued that "Nobody who came and saw the placebo has conquered its definition" (1015). Nunn (2009b) insists that "the placebo construct conceals more than it clarifies," and that we need to prepare for "*a post-placebo paradigm*" (51). Pronouncements that disagreement is endemic are often the prologue for new definitions of *placebo* and "placebo effect": for example, in the opening of a recent philosophical paper on the issue, Jeremy Howick (2017) observed that debates about placebos "rage," and that "there is currently no widely accepted definition of the 'placebo'" (1). It is a judgment that echoes a claim by Franklin Miller, Luana Colloca, and Ted Kaptchuk who, writing in this journal in 2009, noted that "There is no standard definition of 'the placebo effect,'" and that "a variety of negative and muddled characterizations of the placebo effect, which are at best are half-truths" (2, 8). The anthropologist Daniel Moerman and medical researcher Wayne Jonas argue that the placebo effect concept has been expanded so broadly that it now includes "just about every conceivable sort of beneficial biological, social, or human interaction that doesn't involve some drug well-known to the pharmacopoeia" (Moerman and Jonas 2002, 417).

Undoubtedly, the meanings of the terms *placebo* and "placebo effect" have changed over time (De Craen et al. 1999); however, intense theoretical debate about the correct usage of these terms only emerged in the postwar era, after the publication of Henry Beecher's 1955 paper "The Powerful Placebo." While this present paper does not intend to provide an in-depth or exhaustive evaluative review of different conceptual models of these terms, it is worth reflecting on the variety of definitions that have been proposed.[1]

At first glance, conceptual disagreement in placebo studies reveals a thicket of impenetrable choice between different definitions and approaches. Placebos are sometimes defined as "dummy pills" or "fake treatments" used to determine the efficacy of interventions in clinical trials, whereas placebo effects are often defined as measurable therapeutic effects attributable to psychobiological mechanisms arising in practitioner-patient interactions (Blease, Bishop, and Kaptchuk 2017; Kaptchuk and Miller, 2015). Others agree that placebos are methodological tools but argue that they can only be defined relative to the particular treatment under scrutiny (Grünbaum 1986; Howick 2017). For example, Grünbaum (1986) proposes that in clinical trials we can differentiate between the "characteristic" and "incidental" features of treatments, and placebos are those interventions that have no characteristic treatment effects for a given condition (33). Placebo effects, in this view, are considered to be the effects of incidental features of any given treatment. Still other scholars take a very different perspective, arguing that we should completely reconceive placebo effects. For example, Howard Brody (1980) and Daniel Moerman and Wayne Jonas (2002) argue that placebo effects are better understood as a form of therapeutic "meaning response" that arise when patients

[1]The terms *nocebo* and "nocebo effect" are also subject to (less heated) debate.

are administered treatments (regardless of whether these treatments are "verum" or "placebo" interventions). Finally, some placebo researchers advocate abandoning the terms *placebo* and "placebo effect" altogether, as being too muddled to be useful to clinical researchers or scientists (Nunn 2009a, 2009b; Turner 2012).

The provenance of the paper is descriptive; the goal is not to evaluate these different conceptualizations directly. Rather, the primary aim is to investigate the frequently made assertion that significant disagreement in placebo research is "rife" (Howick 2017)—a claim that I conclude is overstated. Curiously, despite widespread allusion to definitional disarray in placebo literature, there has been scant reflection till now on how these key terms are (in fact) used by placebo scientists. Drawing on important, longstanding insights from post-Kuhnian philosophy of science, I argue that if conceptual discord were as pervasive and diffuse as many placebo scholars assert, scientific advancement would be impossible. On the contrary, I demonstrate in this paper that a well-established "placebo paradigm" is in operation within the field.

Motivating a Kuhnian Analysis of Placebo Studies

Nunn's (2009b) very recommendation that we move towards a "post-placebo paradigm" (51), and Miller and colleagues' (2009) contention that "scientific research on the placebo effect has taken the shape of 'normal science' without guidance of any systematic theoretical paradigm" (15) draw on the language of the historian and philosopher of science Thomas Kuhn (1962). Kuhn had distinctive ideas about the structure of mature scientific research, including what he perceived to be the importance of theoretical agreement as a necessary antecedent for "normal science." If placebo studies can be described as a mature scientific paradigm, then on Kuhn's model we would expect to find consensus about definitions for *placebo* and "placebo effect."

However, deployment of Kuhn's terminology to assess the scientific status of placebo research invites three further questions. Does research in the field of placebo studies warrant the label "scientific paradigm"? What is meant by "paradigm" and "normal science"? And why adopt these philosophical terms of art, anyway? I address these questions in reverse order.

To begin with, then, why be committed to employing Kuhn's terms as a benchmark for evaluating placebo studies? There are two important considerations here. First, and as we have seen, on the occasions when placebo scholars have reflected on conceptual disagreement they often lapse into Kuhn's philosophical terminology. Therefore, resolving differences in opinion about the status of placebo studies as a (purportedly) paradigm-driven science suggests one justification for the adoption (and clarification of) Kuhn's terminology.

Second is the question about whether this is worth doing. Placebo scholars are not alone in exercising Kuhn's terminology—indeed, the term *paradigm* is ubiq-

uitous in scientific discourse. The casual ubiquity of certain philosophical jargon, however, may not be a good argument for its further proliferation. For a start, we might query whether someone writing that "we need to move to a post-placebo paradigm" needs to be read as invoking Kuhn. On the other hand, it might be argued that when someone writes of something achieving the status of "normal science," then it is safe to assume that they are, indeed, reliably appealing to Kuhn's terminology. To muddy the waters further, many scholars (across the humanities and sciences) invoke amalgams of the post-Popper philosophers-historians of science (such as Kuhn, Lakatos, Feyerabend, and Hacking), seemingly without wishing to commit themselves to working, strictly, within the framework of one or the other. A related consideration is the question about whether Kuhn's terminology is robust enough to be used as the scaffolding to evaluate placebo studies, in the first place. In short: is it reasonable to rely on Kuhn's claims about the nature of science as a framework for appraising placebo studies?

In this paper, I argue that these problems are resolvable, since we can endorse key aspects of Kuhn's philosophy of science without slavishly aligning ourselves with every aspect of his controversial body of work and with the ordeal of exegesis. Notwithstanding criticisms of his body of work, prominent aspects of Kuhn's early philosophy of science have bestowed an enduring legacy on contemporary views about the nature of science. Post-Kuhn, philosophers of science have been compelled to pay close attention in their analysis of scientific research to how scientists *in fact* think, behave, and work (rather than merely to stipulate, from the armchair, how science *ought* to work). So influential are these insights that today we might deem them truisms. They include Kuhn's observations that: (1) mature scientific research is fundamentally social in structure; (2) that comparatively "settled" theoretical and methodological commitments are a precondition for the emergence of scientific "paradigms" and "normal" scientific research to begin (terms of art that we will shortly unpack); and (3) that explicit theoretical beliefs as well as tacit scientific knowledge guide the articulation of, and progress in, normal scientific research. Therefore, in assessing placebo studies this paper will be restricted to a cautious, critical appraisal of those enduring features of Kuhn's work that may be said to afford us a reliable and practical yardstick for appraising the status of science.

Kuhnian Paradigms and Normal Science

In order to investigate the seriousness of conceptual disagreement in placebo studies, we need to take a brief detour to unpack Kuhn's terms of art. The term *paradigm* was famously (many philosophers would argue, infamously) bequeathed to science (and subsequently to broader, everyday usage) by Thomas Kuhn in his second and seminal book *The Structure of Scientific Revolutions* (*SSR*), first published in 1962. *SSR* opens with the decisive assertion that "History, if viewed

as a repository for more than anecdote and chronology could produce a decisive transformation in the image of science by which we are now possessed" (1). Kuhn's revolutionary idea was that we must examine science in vivo if we want to better understand the nature of scientific judgment, decision-making, and progress. In *SSR,* Kuhn mined case studies from the history of physics and chemistry to produce a new account of scientific theories and of theorizing—both of which, he proposed, were structured by "paradigms."

All science, Kuhn proposed, starts off with a pre-paradigm period when scientists (acting more like philosophers) debate, jostle, and argue about how best to understand some aspect of the world; "Effective research," he observed, "scarcely begins before a scientific community thinks it has acquired firm answers to questions like the following: What are the fundamental entities of which the universe is composed? . . . What techniques can legitimately be asked about such entities and what techniques employed in seeking solutions?" (4–5). According to Kuhn, the route to what he dubbed "normal science" is arduous. During this period of "pre-paradigm flux," he claimed that scientists are compelled to defend every aspect of their theories, including how to define terms and agreed methods for researching the disputed domain; locked in endless theoretical discussion, individuals are unable get on with the nitty-gritty—the "fact-gathering activity"—of scientific research (13).

Once such questions are settled, however, Kuhn claimed that scientists can get down to "normal science," which he characterized as a quintessentially social enterprise, comprising a community of like-minded thinkers: "Normal science is predicated on the assumption that *the scientific community* knows what the world is like" (5, emphasis added). This like-mindedness, Kuhn argued, is a result of a common, specialist background education: as a result, individuals who have undergone training in a field are "relatively unanimous" in their professional judgments and are thereby ready to work within a shared scientific paradigm (177). Kuhn claimed that a community of scientists working within a particular paradigm embraced not just explicit beliefs, including law-like statements about the domain of research, they also share implicit beliefs or tacit knowledge about how to pursue further scientific enquiries ("puzzles") and knowledge of what counts as a scientific problem (and "puzzle solution") within the paradigm. In Kuhn's account, then, scientific research is characterized by consensus and by complacency, which both constrains research and facilitates it. By assuming the correctness of fundamental theoretical questions, and by a process of reflective and practical training in the symbolic laws and specialized techniques of the paradigm, scientists are freed up to get on with the puzzle-solving that characterizes research. In this way, paradigms are "objects" for further articulation under their own directives (23): they are open-ended and suggestive of further research; and they are also the standard by which the quality of a proposed puzzle-solution can be measured.

Kuhn uses the example of Newtonian mechanics to illustrate paradigm-led science. Once Newton's *Principia Mathematica* became widely recognized as an important work, Newton's laws formed a model for undertaking problems in physics and mathematical mechanics. According to Kuhn, the paradigm is comprised of both "symbolic generalizations" or explicit scientific laws, such as $f = ma$, and also tacitly held metaphysical claims about the nature of reality, for example: "Forces, such as gravity exist." Newton's *Prinicipia* also acted as guiding exemplar for how scientists might model their work and interpret experimental results. Scientists who work within a Newtonian paradigm share propositional knowledge about scientific laws as well as know-how—learned skills in applying these laws to new scenarios. For Kuhn, this learned knowledge encompasses the tacit understanding that Newton's laws are elegant, simple equations, and that Newton's laws are to be interpreted as idealized models (since, for example, frictionless planes are not found in nature). In the case of Newtonian physics, puzzle-solving involved tasks such as investigating how Newton's laws accounted for the movement of the planets and figuring out how Newtonian mechanics might be extended to liquids. Kuhn also argues that scientists may be inarticulate about fundamental theoretical components of their research: "Though many scientists talk easily and well about the particular individual hypotheses that underlie a concrete piece of research, they are little better than laymen at characterizing the established bases of their field, its legitimate problems and methods" (44).

Kuhn's Legacy

Kuhn's views on scientific paradigms, and the structure of scientific progress, have been heavily criticized. Many of these criticisms take us well beyond our present interest (for example, the accusation that Kuhn defended epistemic relativism in his account of "incommensurability" between paradigms); other criticisms are more relevant to our present concern (Musgrave 1970). For example, Kuhn's use of the term *paradigm* has been criticized as too vague. In a well-known critique of the era, Margaret Masterman (1970) identified 21 different uses for the term in the first edition of the book; as a result of such criticism, Kuhn sharpened up and elaborated on what he meant by the term in the second edition. Notwithstanding these criticisms, the fuzziness of the term has also been considered an important strength by philosophers, sociologists, and (latterly) cognitive scientists, who have argued that the plurality of features that Kuhn attributes to paradigms—including metaphysical beliefs, symbolic generalizations, values, and heuristics—reflect the myriad functions of normal science (setting scientific puzzles, perceiving puzzles, identifying standards for judging puzzle solutions) (Bird 2005, 2012; Chen, Andersen, and Barker 1998; Dunbar 1999). In short, there are good reasons to broadly defend (and utilize) Kuhn's notion of science as a social activity involving inculcation into a paradigm that is structured around puzzle-solving activities ("normal science").

Other critics, including historians, have argued that Kuhn's depiction of the emergence of new paradigms is too tidy. Some commentators have pointed out that not every conceptual disagreement in science needs to be fully settled in order for "normal" scientific research to begin in earnest; instead, core concepts such as symbolic generalizations (formalized statements that cover core definitions and laws) and methodologies need to be relatively fixed for normal science to take place (Bird 2014; Toulmin 1970).

Cultural Scaffolding and Placebo Research

With this revised Kuhnian framework in mind, and embracing the role of "philosophical anthropologists" within the field, we are ready to investigate how the terms *placebo* and "placebo effect" are in fact used by scientists. Recall that Kuhn argued that normal science, in essence, is a social enterprise. More recently, building on Kuhn's insights, the philosopher Robert McCauley (2011) has claimed that special cultural scaffolding needs to be in place for scientific reasoning and related activities to occur. McCauley argues that "Scientists get around some of their cognitive limitations by exploiting a vast array of tools (such as literacy and mathematical description) and cultural arrangements (such as journals, professional associations, and the division of labor") (67). He proposes that these kinds of cultural and institutional arrangements are not strictly necessary for scientific enquiry to occur; however, they do allow scientific research to proceed at a pace and proficiency unrivalled by that of individuals or smaller groups of scientists who work in relative isolation:

> The institution of science . . . is the collective product of an international community of inquirers for whom prestige, fame, and wealth turn, in no small part, on their seizing opportunities to criticize and correct each other's work. Such communal features of the scientific enterprise establish and sustain norms that govern scientific practice. (67)

Are cultural markers, of the kind that signify mature scientific enquiry, found in placebo studies? With our anthropologist hat on, I argue, we can grant that the answer is affirmative. Today, numerous formal national and international research networks exist in placebo studies. The trend from individual and small group–led research towards larger, nationally funded research collectives has arisen in the last two to three decades (see Harrington 1999). A number of research labs devoted to placebo studies have emerged; these research centers predominantly attract scientists from a range of biomedical and social science backgrounds but continue to engage with philosophers and bioethicists. Labs such as these have overseen the rapid pace of research publications in placebo studies: in the last two decades the number of scholarly articles published on placebo and nocebo effects has increased a tenfold from around 300 to over 3,400 papers (Enck, Klosterhalfen, and

Weimer 2016). These research outputs range across top-tier medical, scientific, and philosophical journals.[2]

Formal meetings and conferences have also grown in number in the last 10 years, in particular across Europe and North America. This has culminated very recently (in 2014) in the establishment of the first formal academic research association in the field (the "Society for Interdisciplinary Placebo Studies" or SIPS) and a curated database of academic articles in placebo studies (the *Journal for Interdisciplinary Placebo Studies*). The drive to marshal research meetings and organize opportunities for collaborative research further reflects the intensity of scholarship in placebo studies.

On the face of it, the array of cultural arrangements in place in placebo studies might be said to indicate the relatively recent emergence of normal scientific research. Notably, on a Kuhnian perspective—if normal science is occurring—we would also expect scientists to be "relatively unanimous" in their professional judgments (Kuhn 1962, 177). In short, we might expect to discern relative agreement about how to define fundamental placebo concepts, and perhaps even a degree of complacency about how to use these terms, as well as shared beliefs about the sorts of methodologies and tools that should be adopted to advance research.

However, it should be noted that the recent formation of SIPS also provides some indication of the newness of placebo studies as an academic subfield. SIPS embraces an unusually wide range of disciplines and academic scholars for an academic society, encompassing anthropology, biology, cognitive science, clinical research, genetics, psychology, psychotherapy, medicine, neuroscience, philosophy of science, and health-care ethics, as well as related subfields. How should we think about the existence of this breadth of research in placebo studies? As we have seen, Kuhn argued that effective scientific research could not get off the ground before the answers to fundamental conceptual and methodological questions were fully settled—that when locked in continuous debate, scientists behave more like philosophers during periods of pre-paradigm (or indeed, inter-paradigm) flux, in which they are compelled to defend every aspect of their preferred theories. At first glance, the multidisciplinary scope of placebo studies may be construed as indicative of disagreement in the field, and the failure to establish an overarching paradigm. Alternatively, the presence of a number of disciplines might be understood as indicative of a single overarching paradigm that ranges across different levels of enquiry. This is a question we will now address.

[2]While there is no specific academic journal devoted to publishing original research in placebo studies, a number of scientific journals list "placebo studies" in the "aims and scope" of their call for submissions.

The Placebo Paradigm: The Emergence of Normal Science

Do we observe anything like paradigm-led science within placebo studies? Recall that the Kuhnian perspective is a thoroughgoing naturalized philosophical approach: in other words, it unreservedly helps itself to the tools of science to address philosophical questions. Therefore, a painstakingly comprehensive investigation of conceptual consensus (and disagreement) might legitimately embark on a systematic review of placebo studies literature to extract and synthesize the explicit and implicit working assumptions and key concepts across published placebo research. In appraising the state of "placebo science," this paper limits itself to the more modest undertaking of a concise narrative review. By drawing on high-profile, high-impact review articles, including a very recent consensus report coauthored by a group of 29 placebo experts at the first SIPS conference (Evers et al. 2018), as well as on the large body of empirical research, we will be well placed to determine whether a placebo paradigm (or paradigms) exist. In order to answer that question, we need to consider the various components that might be said to comprise a scientific placebo paradigm.

Metaphysical Beliefs and Tacit Assumptions

What does the empirical literature show? Consider, first, the idea of (often tacitly) shared metaphysical assumptions about the field. There appears to be an acknowledged differentiation in placebo studies between placebos as the name of methodological controls used in randomized clinical trials and placebos as the name for sham interventions that act as props for the purpose of eliciting placebo effects either in clinical or basic research contexts. In this second category, placebos may be used deceptively or openly and together with other cues for the purpose of eliciting beneficial placebo effects in patients, for a particular condition, or for understanding these effects from neurobiological and psychological perspectives.

In the context of the use of placebos in clinical trials, we find that they are often described as "sham" treatments employed wholly for methodological purposes: "placebos are designed to look—and ideally taste, smell, and feel—like the drug that is being tested so that participants do not know which they are receiving" (Blease, Bishop, and Kaptchuk 2017; see also Finniss et al. 2010; Howick 2017). There is also a fundamental, often explicitly stated belief among placebo scholars that placebos used in clinical trials should mimic every aspect of the treatment under scrutiny other than the hypothesized remedial component(s).

When it comes to the second nuanced and distinctive use—placebos in clinical care and basic research—scientists adhere to the underlying metaphysical assumption that placebo effects constitute "a genuine psychobiological event" and that empirical research into the placebo effect is aimed at identifying the mechanisms that give rise to these effects (Benedetti 2014; Finniss et al. 2010; Kaptchuk

and Miller 2015). Other tacitly held assumptions—which are often explicitly articulated by placebo researchers—include the claim that placebos as dummy treatments (when used either in clinical or experimental contexts) are not necessary (nor even sufficient) to elicit the placebo effect proper (Evers et al. 2018; Kaptchuk et al. 2010). This in turn necessitates the nuanced distinction between "placebo responses" and "placebo effects": "placebo responses" are typically considered to be responses that arise after the administration of placebos and include any of the following: spontaneous remission, regression to the mean, Hawthorne effects, and reporting bias among patients (Benedetti 2014; Evers et al. 2018; Kaptchuk and Miller 2015). Therefore, there appears to be general consensus among empirical researchers that placebo responses may (or may not) include the "placebo effect" as a genuine psychobiological effect (Evers et al. 2018; Miller, Colloca, and Kaptchuk 2009).

Symbolic Generalizations

What about Kuhn's notion of symbolic generalizations and explicit laws: do we find anything resembling these components of paradigms within empirically oriented placebo research? There appears to be pervasive consensus that important mechanisms giving rise to the placebo effect are "expectancy responses" and "classical (Pavlovian) conditioning" (Benedetti 2014; Colloca and Miller 2011; Evers et al. 2018). In the special sciences (biology, psychology, economics), philosophers of science often refer to stable explanations that vary under different antecedent conditions as "ceteris parabis laws," or laws that hold "all things being equal." Psychological-level explanations—such as expectancy responses and classical conditioning—are noncontroversial examples of special science laws.

The mechanism of "response expectancy" is the patient's expectation that a treatment will be effective for their symptoms (Kirsch 1997). Classical conditioning refers to the repeated associations between a neutral stimulus and an active medication (an "unconditioned stimulus") that can result in the neutral stimulus eliciting beneficial effects that are characteristic of the active medication (Benedetti 2014; Colloca and Miller 2011; Finniss et al. 2010). Placebo effects as a psychobiological event, or process, are understood by empirical researchers to be elicited by factors in the clinical environment (Finniss et al. 2010).

Puzzle-Solving

In a Kuhnian framework, symbolic or law-like generalizations function as a standard for defining and evaluating "puzzle-solving" activities within a paradigm. We can locate several important puzzle-solving activities within the field of placebo studies.

First, an extensive body of research focuses on the therapeutic significance of the placebo effect for a range of conditions and symptoms. On this agendum, a key underlying assumption is that placebo effects are not likely to be curative for

a range of diseases: "there is no evidence that placebos can shrink tumors . . . placebo effects do not alter the pathophysiology of diseases" (Kaptchuk and Miller 2015, 8). Rather, an emergent claim is that placebo effects may be remedial for certain subjectively experienced symptoms and conditions including pain, depression, anxiety, fatigue (Finniss et al. 2010; Kaptchuk and Miller 2015). Research is aimed at determining the size of placebo effects for a range of symptoms and conditions (for example, for pain, depression, irritable bowel syndrome, nausea) and comparing these effects with common medications for these conditions (Chvetzoff and Tannock 2003; Temple and Ellenberg 2000). To date, research pursuing this empirical agendum demonstrates that the magnitude of placebo effects is often comparable to many common classes of drugs in randomized trials, including analgesics, anxiolytics, and antidepressants (Kirsch et al. 2008; Temple and Ellenberg 2000).

A second puzzle-solving activity aims to better understand the factors that influence the size of placebo effects: this includes conditions under which placebo effects may be augmented in clinical contexts. Again, the underlying, guiding theoretical assumptions are that placebo effects are mediated by patient expectations, as well as by classical conditioning, and that these mechanisms may be elicited by contextual factors in the clinical environment, including practitioner socioemotional communication style and features of treatment paraphernalia. The aim is to discover which factors in the clinical encounter might influence expectations (and conditioning effects) and thereby harness placebo effects for the benefit of patients (Kaptchuk and Miller 2015; see also Finniss et al. 2010; Price et al. 2008). Researchers have investigated the relevance of treatment labeling, including whether the overt delivery of care (as opposed to, for example, administration of verum treatments via covert injections) influences the size of placebo effects (Colloca et al. 2004; Kam-Hansen et al. 2014).

Further experimental studies within this sphere of puzzle-solving are designed to deconstruct and deepen understanding of the relevant placebogenic factors in the practitioner-patient relationship; studies on expectancy responses show that verbal suggestions can manipulate patients' expectations, thereby mediating the size of placebo effects; while other studies have identified practitioner competence, warmth, empathic listening, and a confident bedside manner (among other factors) as relevant to augmenting the size of the placebo effects (Amanzio and Benedetti 1999; Howe, Gover, and Crum 2017; Kaptchuk et al. 2010; Price et al. 1999; Vase et al. 2003). Extending this research, placebo scholars have also begun to examine the necessity of deception in eliciting placebo effects. Various experimental set-ups have been designed to test the effectiveness of "open-label placebos" for particular conditions and symptoms. In these experiments, "placebo pills" are described as "inactive substances" which, when administered by a practitioner in an open, reassuring, and optimistic manner, will elicit placebo effects which may be remedial for certain conditions (Carvalho et al. 2016; Kaptchuk et

al. 2010). In all of these studies, the prescription of placebos is accompanied by a set of verbal instructions that describe the "power" of the placebo effect and how placebo effects work (Charlesworth et al. 2017).

A third kind of puzzle-solving is aimed at establishing the neurobiological pathways that give rise to placebo effects. The explicit theoretical assumption behind this research is that placebo effects are scientifically traceable, since they activate "specific, quantifiable, and relevant areas of the brain" (Kaptchuk and Miller 2015, 8). To date, this research has focused on the functional neuroanatomy of placebo analgesia—for example, by using PET and functional fMRI (Benedetti et al. 2005; Wager et al. 2004)—and it has assessed the role of opioid and non-opioid pathways, as well as the reversal of placebo effects by the opioid antagonist naxolene. Additional studies have investigated the involvement of certain neurotransmitters, such as endorphins, dopamine, and cholecystokinin, in eliciting placebo analgesia (Benedetti and Amanzio 1997; Finniss and Benedetti 2005). Additional research aims to understand the role of nonconscious cues in activating placebo effects (Jensen et al. 2012). Finally, other puzzle-solving activities include exploring whether some individuals are more likely to be placebo responders. So far, this research is specifically aimed at investigating the "placebome"—the genetic signatures that give rise to the myriad physiological pathways that give rise to placebo effects (Hall, Loscalzo, and Kaptchuk 2015).[3]

This brief review shows that particular disciplines (and subdisciplines) have overseen the emergence of a distinctive body of normal scientific research in placebo studies. The momentum behind much of this puzzle-solving activity has been driven by social, behavioral, and experimental psychology and cognitive neuroscience. Insofar as we can identify the emergence of Kuhnian "normal" science in placebo studies, it is at the nexus of these sciences.

Summary of the Conceptual Consensus

To review, in the placebo paradigm, "placebo effects" are understood to be positive health changes that occur as a result of specific psychobiological mechanisms (such as expectancy responses and classical conditioning); the placebo paradigm clearly differentiates placebo effects from those beneficial effects that may result from other psychological mechanisms, such as the use of psychological treatments).[4] These psychobiological mechanisms are elicited, in turn, by a range

[3]Beyond these forms of puzzle-solving, theoretical elucidation of symbolic generalizations is also ongoing. Debate about whether "expectancy responses" and classical conditioning amount to competing models of the psychobiological pathways of placebo effects, or whether classical conditioning can be better described as a form of expectancy response, is one example of the scope for theoretical refinement within normal science (Stewart-Williams and Podd 2004).

[4]It should be noted that the extent to which different psychological treatments rely on placebo effects is the subject of ongoing controversy; for example, it has been argued that these interventions do not work according to the face-value explanations proposed by psychotherapists (see Blease, Lilienfeld, and Kelley 2016; Blease, Trachsel, and Grosse Holtforth 2016; Gaab et al. 2016; Wampold and Imel 2015).

of cues in the context of the practitioner-patient encounter. In this way, expectancy responses, conditioning responses, and "contextual models" form a unified, overarching conceptualization of placebo effects (Di Blasi et al. 2001).

Within the placebo paradigm, the term *placebo* is nuanced and has two distinctive meanings. In RCT research contexts, placebos are conceived as epistemological tools: they refer to interventions employed to test the effectiveness of a treatment. As we have seen, clinical researchers contend that placebos in RCTs should mimic the verum treatment in every respect excluding the hypothesized active ingredient. Placebos in this context are therefore understood to be moving categories—their modality, as well as such features as how they look and taste (even their side effects), should mimic and therefore be wholly dependent on the features of the verum treatment under investigation.

The second use of the term *placebo,* in both clinical and basic research contexts, is different. From the standpoint of the placebo paradigm, *placebo* typically refers to a specific kind of intervention—often, sugar pills (usually microcrystalline cellulose pills)—which, alongside other cues in the clinical encounter, is administered with the aim of eliciting placebo effects in order to alleviate patient symptoms or investigate these remedial effects among patients.

The Placebo Paradox: Why Does Disagreement Persist?

If, as this paper has argued, there is evidence of conceptual consensus in the field of scientific placebo research, why do disagreements persist? Surely, if placebo concepts were fully settled, such disputes would never arise? We might conclude that Howick (and other discussants) are wrong that "there is no currently accepted definition of 'placebo'" (Howick 2017, 1); yet we might also concede there is something correct in their assertion that debate continues. The "placebo paradox" is the perception of widespread disagreement, in spite of background scientific consensus. I submit three explanations as to why conceptual disputes persist and why extensive agreement is so well hidden.

The first reason disagreement may persist, and why such disagreements are often orthogonal to the underlying conceptual agreement in placebo science, is the legacy of meaning change when it comes to these terms. We can identify both diachronic and synchronic shifts in terminology. Diachronically (or historically speaking) the terms *placebo* and "placebo effect" have undergone semantic evolution (De Craen et al. 1999). These semantic changes have been masked by nominal (if not conceptual) continuity. To illustrate this, consider the term *atom*. In the Ancient Greek natural philosophies of Leucippus and Democratus, the term meant something very different from its namesake in today's modern, scientific atomic theory. Similarly, in their history of the placebo concept De Craen and colleagues (1999) trace its semantic evolution, reporting that the first

documented medical use of the term dates from the late 18th century, when *placebo* was defined in the 1795 *New Medical Dictionary* as "a commonplace method or medicine" (511). This meaning shifted in the early 20th century, when placebos were understood to be a "necessary deception"—a noncontroversial tool in the doctor's treatment bag—that brought comfort to patients of low intelligence but had "no impact on pathophysiology" (511). In this way (and with subsequent subtle changes) *placebo* has undergone conceptual evolution up to the point where a placebo paradigm has now emerged.

In addition to historical shifts in terminology, placebo concepts are subject to synchronic semantic distinctions: in other words, the meaning of the term *placebo* differs subtly depending on the research context in which it is used (whether as a tool in RCTs or as the subject of investigation in clinical encounters). These subtle nuances mean that the terminology is more vulnerable to semantic confusion and may elude articulation. Confusion, moreover, is more likely to arise the further removed researchers (and indeed, other nonscientists) are from the activities of normal scientific placebo research.

This brings us to the next point. Second, and with a note of caution, we can observe that much of the debate about definitional matters takes place outside the confines of normal science. Many (indeed, arguably the majority) of scholars who propose new definitions for the term "placebo effect" tend not to be empirical researchers who work squarely within the placebo puzzle-solving activities. Instead, they are philosophers, anthropologists, historians, and medical practitioners who work outside the placebo paradigm. It is at least conceivable that, working outside normal science, these scholars fail to perceive the significant agreement that exists within placebo studies. (As this paper has argued, conducting scientific placebo research requires allegiance to fundamental metaphysical beliefs, symbolic generalizations, and psychological laws.) In short, outside the empirical action, some disputants may be more likely to overstate disagreement and overestimate the relative stability of new definitions.

This point deserves further clarification, since it may be met with misgivings, particularly among those proponents of alternative conceptual frameworks who are not placebo scientists. The existence of scientific consensus, it might be claimed, does not thereby justify that consensus; other definitions (so the argument might run) should not be prejudicially delegitimized on the grounds that they are not located within the current placebo paradigm. Scientists, it might be claimed, are just oblivious to the deep problems with their terminology. These are fair points, but they are not the goal of this paper. Rather the present aim is to challenge the descriptive claim that there is scant agreement in the field of placebo studies about placebo concepts. Manifestly, as this paper has argued, conceptual agreement both exists and is pervasive.

Third, at least occasionally, we can expect conceptual disagreement to be perceived and even perpetuated by placebo scientists too. This may occur in spite

of their allegiance to a relatively fixed conceptual framework. As Kuhn (1962) observed, scientists are often prone to inarticulacy about fundamental theoretical components of their research. While normal science necessitates consciously held, reflective, and therefore explicit knowledge of symbolic generalizations, many core components of paradigms (such as Kuhn's metaphysical beliefs) are tacitly held assumptions. The upshot is that scientists working within a paradigm are not always the best expositors of their knowledge—even while they are adept at using it.[5]

Conclusion: Disagreement Is Exaggerated

Conceptual consensus in placebo studies is often disregarded by commentators. On the one hand, Nunn (2009b) argues that it is time for a new placebo paradigm, yet this claim implies that there is something like an established placebo paradigm that is in crisis or failing in some regard, and ripe for replacement by another scientific paradigm. There is no evidence that this is the case (nor does Nunn present us with any). Rather, as the foregoing Kuhnian exploration of placebo research shows, a successful program of normal scientific research has emerged in placebo studies. On the other hand, Miller, Colloca, and Kaptchuk (2009) argue that normal science has emerged in placebo studies, "without the guidance of any systematic theoretical paradigm" (15). This analysis puts the cart before the horse, as normal science is *dependent* on the guidance of theoretical agreement. Without such consensus, the puzzle-solving activities that occur in placebo studies would not be possible. In both cases, Nunn and Miller and colleagues appear to misapply Kuhn's terminology: the result is two conclusions at odds about the state of the field.

This paper reaches a different conclusion—namely, that a mature placebo paradigm is underway, and that conceptual matters are therefore largely (and necessarily) settled. Kuhn noted that not every conceptual dispute needs to be settled before normal science can begin, but that relative theoretical consensus must emerge for the business of empirical, scientific problem-solving to get underway. In light of our Kuhnian analysis of placebo studies, we can locate substantial explicit and implicit agreement over definitions of the terms *placebo* and "placebo effect."

However, the fact that there is widespread conceptual agreement in a field is not a reason to foreclose discussion about definitions. There may be legitimate reasons for raising such questions and embarking on a quest for conceptual re-

[5]This is a different point from Miller, Colloca, and Kaptchuk's (2009) claim that normal science has emerged in placebo studies "without the guidance of any systematic theoretical paradigm" (15). A theoretical substructure is necessary for placebo paradigm to emerge, but the nature of normal science means that scientists working within a paradigm (at least occasionally) may fail to articulate key concepts.

vision (Turner 2012). But this paper urges that future debate and commentary about definitional matters should acknowledge that conceptual agreement does exist, and that it forms the foundation of progressive, normal scientific research in placebo studies.

How might recognition of the placebo paradigm inform future debate about definitional matters in placebo studies? I suggest that discussion about conceptual matters could be more usefully focused on two key issues. First, there are practical concerns. Clear communication and understanding of placebo concepts (among scientists, clinical researchers, and the public) are important, so in this respect, it is conceivable that placebo concepts (especially as they are deployed in RCTs and clinical contexts) might yet be relabeled or renamed (Nunn 2009a, 2009b; Turner 2012). Second, it is entirely possible that conceptual change may arise from *within* the placebo paradigm as a result of future scientific advances. Such conceptual refinement is to be expected, as science bootstraps its way to progress. Notwithstanding these issues, it must be acknowledged that the conceptual agreement embedded within the placebo paradigm reflects the important scientific strides in the field, as well as widespread consensus about conceptual issues.

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