Demystifying the Placebo Effect

Prospectus
Phoebe Friesen

Introduction.
For a brief moment during the second half of the twentieth century, academics and scientists took great interest in the placebo effect, and several rich theoretical and empirical accounts of the phenomenon were produced. However, the topic quickly fell out of favour and has been largely neglected until a recent resurgence of research into the placebo effect in the last twenty or so years. This resurgence stems from two distinct fields of research, one concerned with understanding alternative medicine, and the other intent on investigating the neuroscientific basis of the connection between cognition and pain relief.

My dissertation project seeks to explore each of these bodies of literature, and develop an account of the placebo effect that engages both historical and theoretical conceptions of the phenomenon as well as current empirical research. Additionally, I hope to demonstrate the way in which an account of the placebo effect can shed light on issues within philosophy of mind, philosophy of medicine, and bioethics.

The placebo effect is an illuminating and fascinating phenomenon that philosophers have paid little attention to, and is worthy of further consideration. It is both theoretically rich and widely applicable to real world issues. A brief description of what I hope to cover within the five chapters of my dissertation follows.

Chapter 1.
Background: Evidence and Existing Accounts

The first chapter will be largely based on my second qualifying paper which sought to critically examine several accounts of the placebo effect that have been put forward, alongside new empirical evidence of the phenomenon.
The first section of the chapter briefly describes the two most prominent roles the placebo has played in the past, as a control in research and as a deceptive tool in practice. Most famously, the placebo has been considered a crucial component of the randomized double-blind placebo-controlled trial, the gold standard of evidence-based medicine. In this research setting, the placebo is known for its lack of effect, and is used as a comparison with an active treatment arm in hopes of demonstrating the efficacy of the treatment being investigated. In practice, however, placebos are meant to play the opposite role, prescribed precisely for their effect on patients, and often thought of as deceptive tools meant to ameliorate symptoms.

The second section describes what we have learned about the placebo effect in the past few decades, and suggests that despite the popularity of these two conceptions of the placebo, there may be space for a much larger role for the phenomenon to play. Several diverse examples of placebo effects are offered and descriptions of the two most important mechanisms thought to be involved in producing the phenomenon, expectations and conditioning, are given.

The third section offers critical evaluations of several accounts of the placebo effect that have been put forward, arguing that they are unable to account for this new evidence that points to the variability and potency of the placebo effect. The accounts considered include thinking of the placebo as merely the outcome measure of the placebo arm in a trial, as an inert treatment [1], as non-specific (non-specificity in terms of mechanisms, effects, and treatments are each considered) [1], as psychological [2], and as incidental [3]. Each account is demonstrated to be theoretically inconsistent or incapable of accounting for the diverse instantiations of the phenomenon.

The final section of the chapter takes inspiration from two available conceptions of the placebo effect in the literature, one that labels the phenomenon ‘contextual healing’ and another that calls it a ‘meaning response’. Aspects of these conceptions are then highlighted in order to develop criteria that I argue must be present in any account that seeks to fully capture the complexity and the potential of the placebo effect. These criteria include the ability to account for how placebo responses can occur consciously or unconsciously, the variability in terms of forms of placebo treatments and effects, as well as individual differences in placebo responses.
Chapter 2.
An Account of the Placebo Effect: Conditioned, Cognitive, and Network Placebo Responses

The second chapter aims towards developing such an account in detail. I begin by laying out three primary goals that I argue an account of the placebo effect ought to strive towards: demarcating placebo phenomena, highlighting explanatorily relevant features of the placebo effect, and providing promising avenues of direction for future research. I briefly return to two of the accounts discussed in the previous chapter in order to illustrate how placing too much weight on the goal of demarcation can lead to an account lacking in explanatory relevance, which inevitably fails to guide research towards fruitful investigations. Rather than seeking to develop one cohesive account of placebo phenomenon, I suggest that we should be responsive to causal processes underlying placebo effects, which point towards an account of the placebo effect which encompasses three types of responses: conditioned placebo responses, cognitive placebo responses, and network placebo responses. The bulk of the chapter is spent describing each of these types of placebo responses by way of their primary mechanisms, central features, and through the use of prototypical examples.

Conditioned Placebo Responses
Conditioned placebo responses are deeply engrained responses that operate through classical conditioning involving central nervous system-centered systems, primarily impacting immune and endocrine functions. These conditioned responses have been observed across many species and are likely to have evolved long ago [4]. They occur through the pairing of a neutral stimulus with an unconditioned stimulus that reliably produces a response. After repeated pairings, the neutral stimulus becomes a conditioned stimulus and is able to reliably produced the response on its own. For example, pairing the taste of anise-flavored syrup with cyclophosphamide infusions, which decrease blood leukocyte (white blood cell) numbers, will lead to a decrease in one’s white blood cell count after exposure to only anise-flavored syrup [5]. While many conditioned placebo responses are evaluated through objective measures and may occur without any awareness of the individual, there is evidence that subjective experiences such as pain can also be impacted by unconscious classical conditioning [6].
**Cognitive Placebo Responses**

Cognitive placebo responses are likely to have developed much later than conditioned responses, and are mediated by expectations and beliefs. These placebo responses impact many types of pain as well as particular symptoms such as inflammation, asthmatic reactions, as well as tremors, rigidity, and bradykinesia (slowness of movements) in Parkinson’s patients [7-9]. In experiments investigating cognitive placebo responses, participants are led to expect that they will feel pain or symptom relief, despite being given a placebo treatment, or are led to expect greater pain or symptom worsening, despite being given an active treatment. Many powerful effects have been observed, with one experiment indicating that “telling a patient that a painkiller is being injected (actually a saline solution) is as potent as 6–8 mg of morphine” [10].

**Network Placebo Responses**

A third type of placebo response that has received much less attention in both theoretical and empirical research can be thought of as a network placebo response. This type of placebo response occurs in conditions that are constituted by both psychological and somatic symptoms, such as depression, panic disorder, irritable bowel syndrome, and chronic fatigue syndrome. Relying on work from Denny Borsoom and colleagues, I suggest that conditions like this ought to be reconceived as complex symptom networks, consisting of both psychological and somatic symptoms that causally impact each other, rather than seen through the lens of a latent variable model, where one unknown cause lead to many distinct symptoms [11]. Interestingly, each of these conditions has been linked to both anxiety and the immune system, suggesting that a combination of conditioned and cognitive placebo responses may be at play. While it’s possible that this third type of placebo response may eventually be collapsed into the two types of placebo responses described above (or vice versa), I argue that for now it is explanatorily useful to consider it as a distinct kind of response.

The next sections briefly considers the goals of an account of the placebo effect that the chapter started with, and makes the case that conceiving of the placebo effect as consisting of conditioned, cognitive, and network placebo responses helps contribute to the goals of demarcation, explanation, and providing directions for future research.
A final section of the second chapter (not include because of word count restrictions) will consider several topics related to the placebo effect and discuss how my proposed account might illuminate them. These topics include clinician empathy, placebo by proxy, alternative medicine, and positive psychology.

Chapter 3.  
Philosophical Implications: Modeling the Mind

The third chapter of my dissertation project will consider some of the philosophical implications of the account of the placebo effect developed within the second chapter. Three topics within philosophy of mind will be explored: the perception / cognition divide, Bayesian models of minimizing prediction error, and embodied cognition. This is currently the least developed chapter, so please consider the following to be preliminary.

The Perception / Cognition Divide
A debate within philosophy of mind has arisen regarding the boundaries of cognition and perception. A number of empirical articles have appeared in recent years that claim to provide evidence for top-down effects of cognition on perception, threatening the divide between the two domains [12, 13]. In response, some philosophers have criticized these claims, suggesting that the evidence could support many possible hypotheses, only one of which involves top-down effects of cognition on perception [14].

The second kind of placebo response described above, the cognitive placebo response, may intersect with this debate in interesting ways. There is clear evidence that cognitive processes like beliefs and expectations directly impact experiences of pain. The question, then, is whether pain should be considered to be a perceptual process, in which case cognitive placebo responses provide evidence for a top-down effect that threatens the divide between perception and cognition, or whether pain should be seen as a sensation, which may share some core features with perception but not all. This second option would suggest that the divide between perception
and cognition still remains intact. I will argue for this latter position, based on goal-directed differences between perception and sensations.

**Bayesian Models of Minimizing Prediction Error**

Another current wave within philosophy of mind revolves around Bayesian models of the mind that portray our brains as mechanisms attuned to making predictions about the world and minimizing potential errors while doing so [15-17]. Fundamental to these accounts is a picture of the brain as a hypothesis-generator, that is constrained both by top-down effects from higher levels that deal with more complex hypotheses as well as by bottom-up effects from lower levels that deal with basic processes like perception. In this section, I will explore where empirical evidence related to the placebo effect provides support for, or a challenge to, a Bayesian model of the mind.

At first glance, it may look as if such an account would be easy to reconcile with evidence regarding the placebo effect, given the crucial roles that top-down expectations and bottom-up conditioning play in producing the phenomenon. However, I will argue that the emphasis placed on integrated mental processes by Bayesian models of the mind is incompatible with empirical data on the placebo effect. The three types of responses described within my account each operate through distinct pathways and are unlikely to contribute to a unified hypothesis generator. While advocates of Bayesian models often celebrate how parsimonious their accounts are, I will argue that parsimony can lead us to miss out on valuable explanatory information, and so a Bayesian model of the mind is incompatible with placebo phenomena.

**Embodied and Embedded Cognition**

Two distinct but related models of the mind that many philosophers have recently come to embrace are those that fall under the terms embodied and embedded cognition. Embodied cognition points towards the way in which our minds are deeply impacted by the kinds of bodies we exist within, and how we depend heavily on our bodily features to cognize the way we do [18, 19]. Embedded cognition expands this observation to the wider world, and argues that the natural, social, and technical world we live in also constrains and constitutes much of our cognitive activity [20].
While there is more and more literature focusing on the importance of recognizing the way in which our minds are influenced by our bodies and the contexts we live in, there is a surprising lack of literature in philosophy concerned with how mental processes and the world around us impact our bodies. The wealth of evidence surrounding the placebo effect can help to fill in these gaps, and paint a more comprehensive picture of how feedback loops between the body and mind operate, as well as how the natural, social, and technical spaces we occupy influence how we heal as well as how we think. Network placebo responses may prove to be especially interesting in relation to embodied cognition given their complex interplay between the mental and physical, while conditioning placebo responses can help illuminate how not only our minds, but also our bodies, are fundamentally embedded.

Chapter 4. 
Implications for Research

While randomized controlled trials (RCTs) are often held up as the ‘gold standard’ of evidence-based medicine, several philosophers have criticized the place RCTs have been granted atop the evidence hierarchy. These critiques often focus on issues that arise in relation to the process of randomization, and tend to emphasize the importance (and sometimes the necessity) of involving other kinds of research in order to gain knowledge of what works within medicine. The account of the placebo effect presented in chapter two raises new worries for the RCT, both with regards to randomization and to controls, and this chapter aims to describe these worries and how we might ameliorate them.

It is generally recommended that researchers check for ‘baseline imbalances’, which occur if a factor that might impact participant outcomes (eg. sex, symptom severity) is not balanced across different conditions, since this would suggest that the intervention may not be all that contributes to a difference between groups [21]. Since baseline measures of participants’ expectations or previous experiences with a kind of intervention are rarely, if ever, collected, there is no way for researchers to determine if baseline imbalances might exist that could contribute to one group experiencing more placebo effects than another. This poses a serious risk for randomization.
The account of placebo effects laid out above raises even more worries with regards to their role as a control in RCTs. In an ideal experiment, the control group will receive exactly the same treatment as the active group, minus the intervention. However, if the expectations of participants can contribute to the efficacy of an intervention, researchers must ensure that the expectations in each condition are controlled for as well. Unfortunately, there are many interventions that produce distinct side effects and allow participants to immediately determine whether or not they have been randomized to the control group or not. This means the outcomes of participants in the active arm of an RCT may be attributable to either the intervention, a cognitive placebo response, or both. This interference can be prevented by using active placebo pills that mimic the side effects of a medication, but this is rarely done (when a meta-analysis was done of anti-depressant trials using active placebos, the difference between the active and control conditions entirely disappeared – see [22]).

This chapter will conclude with a discussion of several trial designs that have been proposed in order to steer clear of interference from placebo effect, including crossover designs, free choice paradigms, drug-disguising, early escape, and sequential parallel crossover design [22-26]. Several of these designs, however, were proposed with a narrow conception of the placebo effect in mind, as produced only through conditioning or through expectations, and are therefore unable to account for the diverse forms the placebo effect may take. Improvements to these designs are suggested, and recommendations for RCT designs that can avoid placebo interference are given.

Chapter 5.
Implications for Clinical Practice

The final chapter of my dissertation will consider how the account of the placebo effect presented above pertains to clinical practice. I will make three distinct arguments concerning how medicine is impacted by these findings and how we ought to respond. The three arguments will relate to patient autonomy, the role of the clinician, and disparities in health care.
**Patient Autonomy**

The first argument is an optimistic one, suggesting that rather than continuing to think of placebos as inherently linked to deception, violations of autonomy, and paternalism, we ought to consider the many ways in which placebos can lead to an increase in individual agency. This suggestion connects easily with conditioned placebo responses, since individuals may create their own pairings, or rituals, in order to increase the efficacy of an intervention. The possibility of using placebo conditioning to reduce one’s dose of a medication in order to avoid side effects, while maintaining the same level of efficacy, is an exciting one [27]. Cognitive placebo responses are not so straightforward in relation to agency, since one must actually expect or believe that a particular intervention will work in order to bring the response about. This is the (literal!) embodiment of William James’ observation that some things simply cannot come about without one believing in them first [28]. This doesn’t seem impossible to attain however, and possibilities will be discussed. Finally, network placebo effects may be especially responsive to agent-driven placebos, given the success of open label placebo treatments with IBS, and in light of their links with anxiety and the immune system, both of which are responsive to conditioning.

**The Role of the Clinician**

The second argument suggests that if we take seriously the growing evidence regarding placebo effects, the physician’s role will need to be expanded. If not only the particular intervention, but the clinician’s tone of voice, the context of delivery of care, and an individual’s history and beliefs, all give shape to clinical outcomes (especially with regards to particular conditions), there is much more to potential for benefit, and also for harm, within the practice setting. This suggests that, at least within those domains of health care that relate to pain relief, psychosomatic conditions, and CNS-centered systems, possible placebo responses should be taken into account, and where possible, harnessed for their benefit. This suggests that the clinical goals of beneficence and non-maleficence include more than traditionally thought, including treating a patient with respect and compassion, as well as understanding both their expectations and history in relation to health care. An implication of this larger clinical role is that if an individual patient is accustomed to healing practices unlike those available in the clinical setting, these should be invited into/ incorporated into care as much as possible [29].
Disparities in Health Care

Finally, the third argument I hope to make suggests that as we continue to neglect the many ways in which the placebo effect impacts clinical outcomes, we may be unwittingly contributing to an increase in disparities in health. This argument connects what is known about the placebo effect to a large body of literature that suggests that minorities, poor English speakers, and people of low SES elicit less empathy in physicians, and have less trust in physicians than the average person [30-35]. This suggests that nocebo effects are more likely to occur and placebo effects are less likely to occur in those who already have the worst health outcomes overall, and that neglecting this powerful phenomenon may be an injustice in itself.

References.

Chapter 2: An Account of the Placebo Effect: Conditioned, Cognitive, and Network Placebo Responses

Introduction.

This chapter lays out my account of the placebo effect. I begin by introducing three primary goals that I argue an account of the placebo effect ought to strive towards: demarcation, explanation, and direction, along with a brief discussion of how these goals relate to accounts that have previously been proposed. Next, the bulk of the chapter is spent introducing the account, which divides the phenomenon into three types of placebo responses: conditioned placebo responses, cognitive placebo responses, and network placebo responses. Following this exposition, I briefly describe the ways in which this account is able to meet the three primary goals.

Section 1.
The Goals of an Account of the Placebo Effect

A first step in developing an account of the placebo effect is to ask what the purpose of such an account might be. A minimal requirement that immediately comes to mind is one of demarcation. The term ‘placebo’ is notoriously slippery, and as we saw in the last chapter, it is best known for the conflicting roles it has played as a non-effective control in a research setting and as an effective deceptive tool in a clinical setting. So, at the very least, an account of the placebo effect ought to say what falls inside and outside the boundaries of placebo. Similarly, an ideal account of the placebo effect will not only provide tools for distinguishing between placebo effects and non-placebo effects, but will provide tools that are explanatorily relevant. By explanatorily relevant, I mean that the account should cohere with existing empirical data related to the phenomenon and should highlight aspects of that data that help to explain why, how, where, and when the placebo effect occurs. Finally, a successful account of the placebo effect ought to provide direction for future research. This goal is closely related to the second goal of
explanation, but is unique in that it is forward-looking towards the unknown, or not yet known, as opposed to backward-looking or present-looking towards what we already have learned. Keeping this goal in mind as distinct is likely to give shape to a slightly different account of the placebo effect than simply focusing on demarcation and explanation, as the goal of direction points towards potentially salient areas of investigation that are yet to be fully explored. This goal seems especially important for an account of the placebo effect because in-depth research into the nature of the phenomenon is in the early stages and much remains to be uncovered.

Taken together, the goals that this account of the placebo effect aspires towards are to demarcate the phenomenon, to highlight explanatorily relevant features of the placebo effect, and to provide promising avenues of direction for future research. It should be noted that each of these goals is intimately related to the other two, such that an account that is too wide or narrow and fails to adequately demarcate the phenomenon will struggle to pinpoint that which is explanatorily relevant, while that which fails to highlight the features of the placebo effect that are explanatorily relevant will be unlikely to guide future research in fruitful directions. Crucially, an account of the placebo effect ought to aim towards achieving each of these goals in balance, for focusing too much on only one can lead away from the others and detract from understanding of the phenomenon. If we briefly revisit the accounts of the placebo effect considered in the last chapter, we can see how an over-estimation of the importance of the goal of demarcation detracted from the goals of explanation and direction.

In taking inspiration from the role of the placebo as a control to be compared to ‘active’ interventions in research settings, several accounts have proposed to demarcate placebo effects from other effects based on the form of treatment administered. For example, Grünbaum’s account of placebo effects as produced by incidental treatment factors (those considered not necessary to the treatment) as opposed to characteristic treatment factors (those considered necessary to the treatment) draws the boundaries of the placebo effect within the form of treatment, and the way clinicians or communities understand treatments (3). While this account is successful in drawing a sharp line between what constitutes a placebo effect and what doesn’t, it contains very little information about what is explanatorily relevant to the phenomenon, or where researchers ought to look next. Shapiro’s account of the placebo effect as a ‘non-specific
effect’, which generates a kind of generic relief or anxiety through the experience of receiving medical care, highlights not the form of treatment, but the type of effect produced (4). This account also aims towards the goal of demarcation, by contrasting ‘non-specific’ placebo effects with the ‘specific effects’ that were thought to result from ‘active’ medical interventions. As we’ve seen, placebo effects can be very specific\(^1\), so in retrospect this account also failed to capture what’s explanatorily relevant about placebo effects.

Upon reflection, it becomes clear why these accounts and others, which focus on the form of placebo treatments and the effects of placebo treatments, missed out on explanatorily relevant information. The empirical research available today suggests that there is virtually a limitless number of things that might constitute the ‘treatment’ that initiates a placebo effect – a statement, a smell, a smile, a particular setting, etc – and there also a wide variety of forms that the placebo effect might take – pain relief, a reduction in Parkinson’s tremors, a boost in one’s immune functioning, asthmatic relief, etc. This suggests that drawing boundaries around that which contributes to a placebo response or the way in which a placebo response takes shape might prove to be a very difficult, if not impossible, task. Granted, a lot less was known about what constituted placebo effects at the time when Grünbaum and Shapiro were developing their accounts, and so focusing on the form of treatment or the kind of effects produced was an entirely reasonable thing to do; when one doesn’t have knowledge of the causal structure of a phenomenon, the best one can do is offer a description of when it seems to turn up\(^2\).

Fortunately, looking retrospectively at these accounts, among others, we can start to see where we might find better building blocks for an account of the placebo effect that can contribute to the goals of demarcation, explanation, and direction. Rather than focusing on the form a placebo treatment might take, or the kinds of effects it might produce, we could try looking towards the causal processes that constitute placebo phenomena – an approach that is very likely to be both

\(^1\) See Chapter 1, Section 3c2.
\(^2\) For example, the DSM (Diagnostic and Statistical Manual of Mental Disorders), now in its fifth edition, still takes an atheoretical position with regards to the cause of any of the mental disorders it includes within its taxonomy, a stance that reflects the lack of consensus concerning how we ought to understand the causal processes contributing to mental disorders (4).
explanatorily relevant and effective with regards to demarcation\textsuperscript{3}. This is what I hope to offer in the following section.

\textbf{Section 2.}  
\textbf{My Account: Conditioned, Cognitive, and Network Placebo Responses}

As described in the previous chapter, the last two decades have produced a wealth of data in terms of the kinds of mechanisms that underlie placebo effects. Evidence points towards two primary causal processes that constitute placebo responses: conditioning and expectancy (1, 5, 6). In constructing an account of the placebo effect that sees these causal processes as central, the first question to ask is whether there are in fact two distinct placebo effects, or if these processes might share enough features to be united under one account. While most accounts to date have sought to capture all placebo phenomena under one heading (with the exception of Fabrizio Benedetti, who has proposed a particularism with regards to placebo effects (7)), it appears to me that there are more differences than similarities between the causal processes of conditioning and expectancies. In light of this, and keeping in mind the three goals of demarcation, explanation, and direction, I propose that an account of the placebo effect should encompass three kinds of placebo responses that impact clinical outcomes (both positively and negatively), including both a \textit{conditioned placebo response} and a \textit{cognitive placebo response}, as well as a third kind of response called a \textit{network placebo response}.

While the first two of these responses, conditioned and cognitive placebo responses, fall fairly directly out of the mechanisms that underlie them, a description of network placebo responses has yet to be articulated in the literature. I will argue, however, that making space for this third form of placebo response in a taxonomy of placebo phenomena is worthwhile, in that it is likely

\textsuperscript{3} Irving Kirsch’s account of the placebo effect does aim towards the goals of explanation and demarcation by focusing on causal processes. He argues that “the placebo effect is that portion of the treatment effect that was produced psychologically, rather than through physical means” (4). As discussed in the previous chapter, however, his account of the placebo effect fails to capture placebo responses that are initiated through unconscious conditioning processes, and so is too limited in scope – see Chapter 1, Section 3d.
to contribute to the three goals of demarcation, explanation, and in particular, direction. In what follows, I will describe each type of response in detail, by way of their primary mechanisms, central features, and through the use of examples. I will discuss the responses primarily through discussion of placebo responses, as opposed to nocebo responses (the negative version of a placebo effect), but it should be kept in mind that what follows applies equally as well to conditioned, cognitive, and network nocebo responses.

2a. Conditioned Placebo Responses

Classic conditioning occurs in two phases. The first phase is called acquisition and includes pairing a neutral stimulus with an unconditioned stimulus that reliably produces a response, sometimes repeatedly. The second phase, evocation, occurs after the association has been acquired, and occurs once the neutral stimulus, which has now become a conditioned stimulus, is able to reliably produced the response on its own (8). This is the basic mechanism that underlies conditioned placebo responses, which can be thought of as unconscious processes of classical conditioning that impact clinical outcomes. Conditioned placebo responses primarily impact immune and endocrine (hormone) functioning (7). See Table 1 below for a depiction of the immune parameters that have been found to be impacted by conditioned placebo responses.

<table>
<thead>
<tr>
<th>Conditioned stimulus</th>
<th>Unconditioned stimulus</th>
<th>Conditioned response</th>
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<tbody>
<tr>
<td>Taste/odor</td>
<td>Immunosuppressant drugs</td>
<td>Antibody production</td>
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<td></td>
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<td>Lymphocyte proliferation</td>
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<td>Hypersensitivity</td>
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<td>NK-cell activity</td>
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<td></td>
<td></td>
<td>Cytokines</td>
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<tr>
<td>Taste/odor</td>
<td>Immunostimulating drugs/antigens</td>
<td>Skin hypersensitivity</td>
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<tr>
<td>Auditory/visual</td>
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<td>NK-cell activity</td>
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<td>Touch</td>
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<td>Neutrophil activity</td>
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Table 1. from (1)
Conditioned placebo responses appear to be deeply-engrained responses that evolved long ago. In 1982, Ader and Cohen demonstrated that the onset of autoimmune disease in lupus-prone mice could be delayed by using a conditioning procedure and an amount of immunosuppressive drug too insignificant to delay the onset on its own (9). Since then, conditioned placebo responses have been observed across many species (10-14). In a discussion of what they call ‘learned placebo effects’, Schedlowski & Pacheco-López describe their understanding of how this response evolved:

“It can be hypothesized that this capacity was acquired during evolution as an adaptive strategy in order to protect the organism and prepare it for danger. For example, the exposure to a specific antigen and its categorization as an allergen might be centrally associated (i.e., a learning process) with a specific environment or food. An adaptive response is then elicited (i.e., a memory process), consisting first of behavioral modifications to avoid the place or food associated with the antigen. If avoidance is not possible, the organism will try to reduce the contact with the allergen, for instance by coughing or sneezing. At the same time, the immune system may prepare the body for interaction with the antigen, e.g. by mast cell degranulation or antibody production.” (15)

An example of this phenomenon in humans can be seen in an experiment that exposed asthmatic children to either a vanilla odor only, an inhaler only, or a vanilla odor paired with an inhaler twice a day for 15 days. Afterwards, the children who had been exposed to the paired odor and inhaler had increased pulmonary function after being exposed only to the vanilla odor, while children in the other conditions did not (16). Another experiment exposed subjects in the experimental condition to an immunosuppressive drug paired with a distinctively-flavoured drink (green-coloured strawberry milk plus 1 drop lavender oil) over four sessions. After acquisition, these subjects were given the same drink but paired with placebo pills instead of the immunosuppressive pills, and afterwards, several measures indicated a significant dip in their immune functions (17).

While some have argued that conditioned placebo responses are always mediated by expectations (18), evidence suggests that the conditioning process often occurs without, or despite, individual awareness. In one experiment, conditioned placebo responses were shown in subjects who had acquired an association between lemon lime Kool-Aid and a drug that reduced
their cortisol levels, even though poor guesses as to whether they were receiving the drug or placebo capsule on any given day suggests that participants were unaware of what condition they were in (19). Another experiment elicited conditioned placebo responses in participants through pairing an injection with a drug that increases growth hormones (participants in the control condition were injected with saline solution), and found that even when subjects were told to expect that they were being injected with a drug that decreases growth hormones, their levels showed an increase (20). This suggests that at least in terms of conditioned placebo responses related to endocrine functions, the effect can occur unconsciously.

2b. Cognitive Placebo Responses

Cognitive placebo responses are likely to have evolved much later than conditioned responses, as they are mediated by expectations and belief. Most research on cognitive placebo responses involves placebo analgesia (pain relief), since it is easy to control in an experimental paradigm and shows a strong placebo response. An important component of research into cognitive placebo analgesia responses is the hidden treatment paradigm, because administering treatment covertly (usually through an IV from an infusion machine in another room) eliminates individual expectations, providing a good model for representing the placebo effect. Results from research involving this paradigm suggest that the relief from painkillers and anti-anxiety drugs regularly involves a significant placebo component as well as the effect of the active ingredient (2, 21, 22). These experiments also demonstrate that cognitive placebo analgesic responses can be very powerful, indicating that “telling a patient that a painkiller is being injected (actually a saline solution) is as potent as 6–8 mg of morphine” (23). See Figure 1 (to the right) for a comparison of the effect of

Figure 1. from (2)
open and hidden injections and interruptions of morphine treatment on pain intensity.

Apart from many types of pain, cognitive placebo responses can also impact inflammation, asthmatic reactions, as well as tremors, rigidity, and bradykinesia (slowness of movements) in Parkinson’s patients (24-26). In a double-blind experiment that examined the effects of expectation on Parkinson’s patients implanted for deep brain stimulation, motor performance consistently declined when the stimulator was turned off, and continued to decline when the stimulator was left on but patients were told that it was being turned off. Additionally, when the patients were subsequently told to expect an improvement in their motor performance, the decline in performance was entirely reversed (20). In a demonstration of long term cognitive placebo responses, a large double-blind surgery trial investigating the effectiveness of transplanting human embryonic dopamine neurons in the brains of Parkinson’s patients assessed individual’s quality of life a year later. What predicted a significant improvement in quality of life was not the actual treatment group that individuals had been assigned to (real surgery or sham surgery), but the treatment group they believed they had been assigned to (27).

Neuroscientific evidence has shown that cognitive placebo analgesia responses often involve the release of endogenous opioids or the endocannabinoid system (28), while nocebo hyperalgesia responses (which lead to an increase in pain rather than pain relief) activate either CCK-ergic systems or pathway linked to anxiety in the brain (29, 30). Additional evidence for these pathways can be found in research demonstrating that placebo analgesic responses are blocked by the opioid antagonist naloxone or by the CB1 cannabinoid receptor antagonist rimonabant, while nocebo hyperalgesia can be blocked by either the CCK antagonist proglumide or the anti-anxiety drug diazepam (6, 30).

Evidence also suggests that the prefrontal cortex plays an important role in cognitive placebo analgesic effects, as temporary or permanent inhibition to the area disrupts the response (31-33). In line with this, it has been shown that individuals who have prefrontal impairment due to Alzheimer’s disease require additional painkillers to feel pain relief since they no longer experience the cognitive placebo component of analgesia (34). In Parkinson’s disease, cognitive placebo responses appear to be mediated by the release of dopamine in the dorsal striatum (35),
although significant dopamine release only occurs if individuals believe there is a high likelihood (over 75% in one experiment) that they will be receiving an active intervention (36). This is consistent with data demonstrating that in general, placebo responses are greater in clinical trials where the likelihood of being in an active treatment group is higher, suggesting that the higher individual expectations are that they will be receiving an active treatment, the better their outcomes are (37).

Some research has indicated that the line between conditioned and cognitive placebo responses may not be so clear cut. There’s no doubt that conditioning procedures can impact the strength and duration of placebo analgesic responses (38), and can even determine whether the analgesic response is mediated by opioids or non-opioids (39). Additionally, similar brain areas appear to mediate conditioned and cognitive analgesic responses (33). However, this data is consistent with evidence that suggests that conditioned analgesic responses are mediated by expectations (40, 41). This hypothesis is corroborated by the fact that conditioned analgesic responses can be overridden by a suggestion of hyperanalgesia (20). Research that demonstrates an impact on pain by unconscious classical conditioning has been recently reported, however, suggesting that either unconscious cognitive mechanisms mediate this effect, or that cognition isn’t always involved in analgesic placebo responses (42).

2c. Network Placebo Responses

While the existence of conditioned and cognitive placebo responses is widely agreed upon, the third type of placebo response I describe here has received no mention in the placebo literature to date. While this third type of placebo response does not fall directly out of known causal placebo processes as the conditioned and cognitive placebo responses do, it involves unique features that cannot be explained by conditioned and cognitive placebo responses, and so is better off placed in a new category.

Before introducing the network placebo response, it is necessary to describe what a symptom network is and how it contrasts with an alternative picture of illness, the latent variable model. The work of a group of psychometricians from the University of Amsterdam led by Denny
Borsboom highlights the way in which the tools used to measure psychiatric phenomena rely implicitly on a model of psychiatric conditions as latent variables (43-45). A latent variable can be thought of as a single underlying cause that leads to the expression of many symptoms. In contrast, a symptom network lacks a single common cause, but involves an illness which is constituted by symptoms that causally influence each other within a network. An example can be seen in the interrelatedness of symptoms of Major Depressive Disorder (MDD), in which trouble sleeping leads to fatigue which leads to difficulties in concentration which leads to thoughts of inferiority and worry which leads back to trouble sleeping (46).

As psychometricians, Borsboom and colleagues are primarily concerned with how we might better measure the presence of mental disorders, but this model has interesting implications for intervention as well. While the latent variable model suggests that intervention should occur at the level of the common cause (e.g. antibiotics treating a bacterial infection), symptom network models suggest that intervention can occur at many sites within the network, since the symptoms are embedded in causal networks with each other. The widespread assumption that latent variables underlie mental disorders has contributed to many attempts to find a common pathway that explains efficacious treatment of MDD through both antidepressants and psychotherapy, which taken together have been largely unsuccessful (47-50). The symptom network model suggests that this search may be in vain, since there may be several distinct routes of intervention that can positively or negatively impact a disorder like MDD, which is in fact what the evidence shows (50). This suggests that, at least in terms of MDD, the symptom network model better explains the data than the latent variable model.

Returning to the placebo effect with this discussion of symptom networks in mind, there appears to be a handful of psychosomatic conditions that consistently show robust placebo responses, and that also share the feature with MDD of being responsive to various psychological and physical treatments (51-54). These conditions include irritable bowel syndrome, chronic fatigue syndrome, and panic disorder, among others (55-59). MDD has been found to be very responsive to placebo treatments as well (60). This indicates that these conditions might also be

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4 It should be noted that a recent meta-analysis suggests that placebo responses in chronic fatigue syndrome are not as big as once thought (59).
better thought of as symptom networks rather than as constituted by latent variables, since there appear to be multiple potential sites of intervention. Interestingly, each of these conditions has strong links to immune deficiencies, suggesting a relationship to conditioned placebo responses (61-67). Anxiety and mood disorders are also consistently implicated in these psychosomatic conditions, suggesting that cognitive placebo responses may play a role too (68-70). Placing this in a larger literature that has been describing the connections between the immune system and mood disorders for decades, it appears that disorders that occur at the margins of the mind and body may be important sites of interaction between conditioned and cognitive placebo responses (71, 72). Despite this link, network placebo responses can not simply be reduced to conditioned and cognitive placebo responses.

A good example of why reduction doesn’t work can be seen in an experiment led by Ted Kaptchuk involving a group of individuals suffering from irritable bowel syndrome (IBS). Participants were enrolled in a clinical trial and randomized to either the control condition (no treatment) or the open-label placebo treatment condition, where participants knowingly took two “placebo pills” (the bottle was marked with these words) twice a day while thinking about how powerful the placebo effect can be. At the end of three weeks, the open-label placebo group had significant improvements compared to the control group on both measures of symptom reduction and quality of life (73). While conditioned and cognitive placebo responses both appear to be related to the placebo phenomena that occurred in this experiment, it is also clear that neither response adequately explains this data. Conditioned placebo responses are unable to account for the outcomes since there is no unconditioned stimulus in the experiment that reliably produces a response and underlies the acquisition phase (e.g. Pavlov’s dog food that the bell is paired with). Similarly, the expectations and beliefs that typically underlie cognitive placebo responses are inconsistent with the participants’ knowledge that they are taking sugar pills, and so cognitive placebo responses cannot explain the outcomes either.

Conceiving of this as a network placebo response, however, better explains why such a robust placebo response might occur in response to an open label placebo treatment. If IBS consists a network of interactive symptoms, both psychological and somatic, then the condition involves multiple sites of intervention that can be impacted through both psychological and physical
treatments. In this experiment, several minor effects on symptoms, induced by the repeated act of focusing on the efficacy of the placebo pills, the ritual of taking them twice a day, and knowledge that one has the support of the clinical team, might lead to significant relief overall through the interaction of different symptom effects, each of which are initiated by a combination of conditioning or expectations. This explanation is consistent with another placebo experiment involving patients with IBS that demonstrated that the more ritual, sympathy, and support built in to the patient-healer interaction, the better the clinical outcomes were. In the most intensive condition, which also included treatment with fake acupuncture, the effect was better than any pharmaceutical ever tested for IBS (74).

While much is still unknown about network placebo responses, the evidence suggests that a new category is warranted. Placebo effects in these conditions appear to be important sites of overlap and perhaps interaction between conditioned and cognitive placebo responses, but are not adequately explained by them. Thinking of these conditions as symptom networks and conceiving of the placebo responses they involve as network placebo responses better explains why these conditions are so sensitive to placebo treatments. If a condition is constituted by causal relationships between symptoms, as opposed to a single common cause, we would expect to see larger placebo responses, since there are multiple avenues of intervention that might provide relief, and this is precisely what we do see.

Section 3.
Returning to the Three Goals

3a. Demarcation

The account of the placebo effect laid out in the previous section has little trouble demarcating the placebo effect from other types of effects, at least in theory. Any clinical outcome that can be attributed to either classical conditioning or expectancies counts as a placebo response on this account. If the response only involves classical conditioning, then it is a conditioned placebo response, while if it only involves expectancies or beliefs, it is a cognitive placebo response. If it
involves both, it may be either an additive effect of both conditioned and cognitive responses (in pain relief, for example) or if it occurs within a complex network of symptoms, it is a network placebo response.

Within practice, there is likely to be many occasions in which it is unclear what the causal processes that led to a placebo response are. This is often the case in clinical trials, when the placebo group shows a significant improvement, but there are many factors, related to conditioning, expectations, or other factors (e.g. regression to the mean, patient bias, etc), that could be responsible. There is also a limited amount of research related to the causal mechanisms that contribute to network placebo responses, and since both conditioned and cognitive responses are likely to be involved, the causal processes that underlie these responses will often be underdetermined.

It is possible, and perhaps likely, that with time and additional research, the boundaries around these three types of responses will shift. It may turn out that network placebo responses can be explained by reference to conditioned and cognitive placebo responses, or that all three responses can be collapsed into a single mechanism\(^5\). Such changes should be welcomed, as it is often the case that once we have more information about the explanatory relevant features of a phenomenon, we start to redraw the boundaries, a process that William Bechtel has deemed ‘reconstituting the phenomenon’ (75). While this account may be less stable than one which relies on the form or effect of a placebo treatment, it is certainly worth sacrificing for the degree of explanatory relevance gained.

**3b. Explanation**

Since the importance of developing an account based on causal processes was already discussed in detail at the start of this paper, I will provide minimal justification here for how this account

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\(^5\) Some have suggested that conditioned and cognitive placebo responses may operate through the same immune pathways (5) or that they make up the unconscious and conscious components of one placebo response (74), but there is currently insufficient evidence to support either position.
contributes to the goal of explanation. In comparison to previous accounts, the account of the placebo effect as constituted by conditioned, cognitive, and network placebo responses relies explicitly on the causal processes that underlie placebo effects to give it shape, except in the case of network placebo responses where the mechanisms are still unknown. This leads to an account that is able to explain several important features of the phenomenon.

Importantly, the account is able to explain why placebo responses can happen as a result of either unconscious or conscious triggers, and how those triggers can range from Kool-Aid to fake acupuncture to open label sugar pills. Similarly, the account explains how measures as diverse as pain, white blood cell count, and fatigue can all be impacted by placebo treatments. The account also explains nocebo effects as well as it does placebo effects, since conditioning can lead to either positive or negative clinical outcomes, and expectations can be led in both directions as well. Additionally, the account is able to explain why it is that we see such large placebo effects in conditions that involve both psychological and somatic symptoms, especially when those symptoms are linked to both immune and anxiety pathways. In the next section (not included within this writing sample), I will say more about how the account is able to explain related placebo phenomena such as clinician empathy, placebo by proxy, alternative medicine, and positive psychology.

3c. Direction

Perhaps the most important goal that the account is able to contribute to is that of pointing towards future directions for research. It’s clear that both conditioned and cognitive placebo responses require a lot more investigation with regards to the details of the causal mechanisms underlying them, as well as in terms of how they might be harnessed to produce the most beneficial effects. The promise of harnessing conditioning placebo responses so that pharmacological doses can be lowered and harmful side effects can be avoided has already been noted (1, 76) and additional explorations of the impact of prescribing open label placebo pills are being explored (73, 77). Quite a bit of excitement has also been generated over the possibility of conditioned placebo responses occurring while individuals are receiving chemotherapy, especially since conditioned stimuli related to the chemotherapy context often trigger
symptomatic responses such as nausea long after treatment, but it is too early to say if conditioned placebo responses induced during chemotherapy can impact cancer progression (78-81). These and other possibilities for harnessing the placebo effect to benefit individuals will be discussed in more detail in chapter five.

In terms of placebo research, however, is likely that the most untapped potential lies within network placebo responses. The analysis of this third type of response given in the previous section suggests that placebo researchers ought to spend more time exploring conditions that arise at the boundaries of the psychological and the somatic, since we can anticipate increased placebo responsiveness there. Some conditions that have not been investigated, but according to this account can be expected to be sensitive to placebo treatments, are those that are often grouped under functional somatic syndromes or bodily distress syndromes, including multiple chemical sensitivity, the sick building syndrome, repetition stress injury, the Gulf War syndrome, and chronic whiplash (82, 83). Other psychological disorders related to anxiety should also be explored in terms of their relations to placebo responses, including obsessive compulsive disorder, post-traumatic stress disorder, social anxiety, trichotillomania, and sexual dysfunction.

In addition, network placebo responses carry implications for what kinds of treatments should be given priority when conditions are made up of psychosomatic symptom networks. While both psychological and pharmacological treatments are available for psychosomatic conditions that fall under the domain of the DSM, like depression and panic disorder, those that are primarily thought of as medical conditions are primarily treated by pharmacological means. Perhaps for this reason, individuals suffering from conditions like irritable bowel syndrome, chronic fatigue syndrome, and other functional somatic syndromes, who rarely respond well to treatment, are often met with disdain by health care professionals who see their suffering as ‘all in their heads’. One clinician complains that “the suffering of these patients is exacerbated by a self-perpetuating, self-validating cycle in which common, endemic, somatic symptoms are incorrectly attributed to serious abnormality, reinforcing the patient’s belief that he or she has a serious disease” (83).
If psychosomatic conditions do not fit within a latent variable model where one treatment would be expected to fix the problem, then it should come as no surprise that the pharmacological one-size-fits-all treatments available to individuals with these conditions are minimally effective. This (and the nocebo-minefield attitude expressed above) might help explain why individuals suffering from psychosomatic ailments are very likely to seek alternative forms of treatment outside the medical model (84). If, on the other hand, these psychosomatic conditions are better thought of as complex symptom networks, then we would expect to see limited positive results from a single treatment, and better results when multiple treatments are used in conjunction. This aligns with evidence that both psychological and pharmacological treatment of depression consistently leads to greater improvements than treatment with one or the other alone (50). This suggests that psychosomatic conditions might require both psychological and somatic treatments to ensure the best clinical outcomes. As two placebo researchers recently observed, “the bias against merely symptomatic treatments has contributed to neglect of the contextual variables that can powerfully affect the outcomes of such treatments” (85).

**Conclusion.**

In this chapter, I have presented an account of the placebo effect that describes the phenomenon as made up of three types of responses: conditioned placebo responses, cognitive placebo responses, and network placebo responses. Conditioned placebo responses are mediated by classical conditioning, cognitive placebo responses are mediated by expectations and beliefs, while network placebo responses occur in conditions that are constituted by complex symptom networks, and involve the interplay of both conditioned and cognitive placebo responses. I argue that this account is better able to meet the goals of demarcation, explanation, and direction than other available accounts of the placebo effect.
References.

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