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We Could All Use Some Placebo

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Our brains are notoriously deceptive. We hit the snooze button because it feels right, though we know that it will probably not make a difference in our alertness. Magicians distract us for a split second and are able to move cards right under our noses without us noticing. Strokes in one side of our parietal cortex can preclude us from acknowledging anything in the world on the opposite side.[1] In these situations, and many others, we believe we are perceiving the world around us as it is, but we are often only perceiving our brain's interpretation thereof. Philosophers and scientists have been fascinated with this discrepancy – between the mind and the physical world – for millennia, perhaps most famously by René Descartes in the 17th century. In *Discourse on Method*,[2] Descartes thought that he could not be sure about anything he perceived, but he was forced to accept that, by denying everything, he was in fact thinking, concluding that "I think, therefore I am".

The discrepancy between the mind and the body continues to captivate us with such phenomena as the placebo effect: a physiological or psychological effect that results from a treatment – the placebo – that should be innocuous in the context it is used in. Indeed, investigating the mechanisms underlying the effects of expectations of treatments, or beliefs about improvement, on the body may shed light upon the nature of the mind itself. Hence, it serves to ask not only how the mind influences the brain, but also what it is about our mind-body interface that allows for the placebo effect. While advances in neurophysiology and psychology have begun to reveal the mechanisms underlying the placebo effect, many questions remain. Importantly, the answers to these questions may help us hone our minds and allow us to realize our full potentials.

But perhaps the first question we should ask is, if innocuous treatments are yielding effects, how do we know that they really are innocuous? Placebos are usually chosen and designed in reference to a test treatment. Depending on the situation, placebos can range from sugar pills in the place of pharmaceutical pills, to unplanned dialog instead of directed tutorials. For instance, a placebo surgery could involve anaesthetizing and opening the patient as usual, but without making any surgical intervention. Similarly, consuming inert sugar pills may distend the stomach minutely, but neither this nor the sugar is expected to have any effects on something like pain perception. In effect, placebos are a control condition, one which allows experimenters to differentiate the effects of undergoing the process of the treatment, from the treatment itself.

Control conditions are very important to establish the validity of a test, and placebos have been used in biomedical experimentation ever since it was found that people's health can change with their beliefs and expectations. True to its etymological roots from Latin, meaning "I will please", our understanding of the word is usually in the positive light.[3] As already mentioned, among the most common colloquial references includes unexpected improvements, such as pain-killing, that sugar pills can bring while under the impression that one is being treated. In an effort to maintain these etymological roots, most have called the mechanistically-distinct[4] negative effects of an inert treatment "nocebos", stemming from the Latin for "I will harm". However, as Stewart-Williams and Podd argued,[5] this only creates ambiguity and confusion, since the dichotomy of "placebo" versus "nocebo" would contrast to the word "treatment", which is used regardless of its positive or negative effects. To avoid this confusion, the word "placebo" will take on the more general definition in this essay.

The most straightforward but incomplete explanation of the placebo effect is that people can change their behaviours when undergoing a treatment. We have brains that are complex enough to understand that we are being treated, and we naturally have expectations and feelings about the treatment. Whether it is conscious or not, expectations and feelings could dispose us to change our behaviours and thereby change our health. For instance, our treatment could incite a new-found hope for longevity and as a consequence we begin to eat better and to exercise consistently. These are behaviours that may drastically improve our quality-of-life irrespective of the treatment. But this explanation cannot account for how expectations and feelings alone have also yielded notable changes in psychology and physiology.

Somewhat expectedly, placebo effects seem to be more prevalent with the treatment of medical conditions that are known to have a major psychological or neurological aspect. We generally presume that at least some aspect of our psychology is dependent on our disposition. After all, we have all experienced how, as a motivational card put it, "time flies by but moments last forever", particularly if that time is amusing and the moments are boring. Accordingly, the placebo effect is relatively prevalent in neurological and psychological conditions such as nausea, headaches, and Parkinson's disease.[6] In Parkinson's disease, deep-brain stimulation that is used to alleviate the symptoms surprisingly tends to work better when the patient is aware that they are receiving deep-brain stimulation.[7] In other words, the treatment does not work without the "placebo component"; the innocuous portion of the treatment – which includes being told one is being treated – is a

key determinant of the outcomes of the treatment. It is as if the patient's brain is sub-consciously cooperating with the deep-brain stimulation to control the condition.

The case of pain presents a more varied mind-body interaction in which not only awareness, but also distraction, expectation, and emotion can affect perception.[8,9] Some conditions involving pain, such as allodynia, the perception of pain through a normally non-painful stimulus, do not entail any known mechanical changes in the area of pain.[8,10] Instead, they are thought to stem from changes in both the way that nerves signal and the way those signals are processed.[10] Indeed, brain regions that contribute to the processing and perception of pain sensations are directly affected by emotions and feelings. A multitude of brain imaging studies point towards an array of interacting brain areas to yield these effects. Some of these areas are involved in higher-level cognition: areas of the prefrontal, insular, and anterior cingulate cortices are involved in contemplating, perceiving, planning, and expecting perceptions[6,11-13] and components of the limbic system such as the amygdala contribute towards perceiving pain and relating it to memories and conditioning.[14-16]

These and other areas responsible for higher-level cognition interact with one another and with more evolutionarily ancient areas of the brain to bring about psychological and physiological changes. In particular, the thalamus is involved in coordinating sensations, including pain, and can affect how those sensations are perceived.[11,12,17] This means that phenomena such as emotion could act on the thalamus to alter how pain perception occurs, for instance, by lowering the pain threshold. Alternatively, the thalamus and the higher-level cognitive areas can signal the hypothalamus, which is responsible for the hormonal and neural control of basic physiological parameters such as heart rate, hunger, and sexual impulse,[11,12] and the brainstem, which provides further neural control over basic physiological parameters.[6,12] Ultimately, signals from these areas project throughout the body and are capable of effecting physiological and psychological changes, through both hormones and nerves. Hence, the sensation of pain could hypothetically be modified by emotion at any one of these levels to dramatically impact its perception, and the explanations behind the effects of distraction and expectation are analogous.

While the mechanisms underlying the placebo effect are coherent in conditions with clear neurological etiologies, studying its appearance in other contexts has revealed the astonishing interconnectedness within our bodies. One such more puzzling context is the gastrointestinal system, where the placebo effect appears relatively commonly in conditions such as ulcerative colitis,[18] dyspepsia,[19] and reflux esophagitis.[20] In fact, the mind and the gut are connected quite strongly; just as in the case of pain perception, the gastrointestinal system is regulated by both neural and hormonal signals. Therefore, emotions could ostensibly impact the gastrointestinal system through the same general mechanisms as a more neurological phenomenon such as pain.[21] Let us take the example of dyspepsia, colloquially known as indigestion, which can occur as a result of both decreased gastrointestinal motility as well as enzyme function. Often, the cause of dyspepsia is unclear, but psychological factors, such as stress and anxiety, are believed to be contributors.[19] Stress and anxiety activate not only hormonal stress-signaling pathways, but also the sympathetic nervous system, which is responsible for a fight-or-flight response and opposes a rest-and-digest response. Together, these signals will depress gastrointestinal function not only by decreasing gastrointestinal muscle function but also by reducing the

production and release of enzymes and other secretions.[12,21] This means that a dyspeptic patient spending time in a physician's office expecting to improve could relieve the stress that may be partially responsible for the condition. Even if the feelings were not the sole cause of the illness, this could improve gastrointestinal function enough to no longer yield discomfort.

Altogether, a vast bed of studies hint at the mechanisms underlying the influence of psychology on either neurological or gastrointestinal conditions. Though the findings are still vague and jumbled, we have made progress away from supernatural or metaphysical explanations. Furthermore, the same sorts of studies have elucidated the relationship between the mind and other major systems,[22] such as the cardiorespiratory[12] or immune systems.[23] Understanding the strength of the mind's grip on the body is thus increasingly within reach. It serves to recall times when one has been frightened and one's heart begins to race, or when one is confronted with a sad situation and one's breathing becomes heavier. These situations are obvious examples of when pieces of information, such as a loud sound or a morsel of bad news, can have almost instantaneous effects on our bodily functions. Similarly, the placebo effect is not a mystical phenomenon, but simply one that is more complex.

Despite the advances in our understanding of the mind's connection to the body, we are left with the question of what it is about us humans that allows the placebo effect to manifest itself so strongly. Relative to their size, humans have among the largest brains, and areas of the brain that are responsible for goal-setting and data interpretation are especially large.[24,25] These functions being so highly-developed means that we humans also have among the greatest of self-reflective abilities. With respect to the placebo effect, our brains allow us to understand that we have a condition that is potentially treatable, how we should be feeling with this condition, that we have health professionals caring for us, and that we are being treated to alleviate our condition. Hypothetically, all of this humanly understanding could affect areas of our brains that control our feelings and our expectations, and thereby influence areas that control our bodily functions.

But to believe that we owe our profound self-reflection and consciousness for being the sole "victims" of the placebo effect would be misguided. The placebo effect is fundamentally the result of applying an inert substance – a negative control treatment. Yet, negative controls are used not only in clinical trials that include humans, but in every experiment in which they are possible or ethical to use. It becomes difficult to tease apart the differences between a negative control treatment and a placebo treatment when it comes to studies that use animals with higher cognitive abilities, such as mammals. After all, though non-human mammals may have more primitive brains than us in some ways, many of the same communication pathways between the information-processing, emotion, and the physiological regulatory systems remain in place. For instance, handling mice frequently can be distressing for the mice, and it is entirely conceivable that they would be affected in many of the same ways that we discussed. Of course, they are unlikely to anticipate what their treatment might affect, whereas we do. Therefore, our higher cognitive abilities, while not being obligatory for the placebo effect, may certainly deepen it.

What seems to distinguish the placebo effect from the effects of a negative control then is the existence of the mind itself. When a phenomenon identifiable as the mind exists, we call

it “the placebo effect”: an unexpected effect of an innocuous treatment due to the expectations, beliefs, and feelings of a being. The use of the term “placebo effect” becomes a bit of a stretch when considering molecular or cellular experiments, wherein treatments no longer include any recognizable form of mind. In these cases, the results of a negative control simply are accounted for as peculiar intractable biochemical phenomena. Hence, the placebo effect cannot be defined as we initially did; it is not only the effect resulting from an innocuous treatment but particularly it is the effect resulting from an innocuous treatment occurring through changes in beliefs, expectations, or emotions, and thereby potentially physiology, in a manner which either unexpected or otherwise indirect. By definition then, the placebo effect can only exist in situations where any sort of mind can be defined, one with cognitive phenomena such as beliefs, expectations, or emotions.

This is where further studying the placebo effect can provide some traction to the mind-body problem. In one iteration, the problem is to determine how a network of neurons, switches, or whatever else, acquires a mind. If we are able to explain the differences between a negative control and a placebo, we should be able to explain the difference between an unconscious system and a conscious one. We might begin with an organism that is widely accepted to possess consciousness, such as mice. As we discussed, mice can be stressed by being handled and this can have physiological consequences.[26] But we also mentioned that the mice are unlikely to anticipate the results of an innocuous treatment and thus any effects will not be able to be as profound as humans’ effects are able to be.

Extending this to a more primitive organism, the sea slug *Aplysia californica*, with its roughly twenty thousand neurons, is able to sense its environment and be conditioned to act differently.[27] For instance, certain innocuous treatments will decrease its gill-withdrawal reflex which is normally in place to prevent damage to the sensitive yet crucial gill.[27] This conditioning confers a sort of expectation: for the slug, withdrawing the gill becomes less important. Conversely to the higher-level cognitive processes invoked in humans and mice, here innocuous treatments are changing physiology through a relatively simple biochemical mechanism, by strengthening or weakening nerve-to-nerve signal transmission. The mechanism still involves interacting cells, though in a manner that is much more immediate and reflexive than processing the innocuous treatments and adjusting their effects within the neurological context of beliefs, expectations, and emotions. As a result, it seems less fitting to call innocuous treatments placebos in a case like this.

Nevertheless, the biochemical mechanism seems to encode some form of expectation through a feed-forward adjustment of nerve signaling. The slug senses no imminent danger with the innocuous treatment, and is able to adjust accordingly. This is ultimately analogous to expectation in more advanced nervous systems such as ours, but it merely happens to be simpler and more completely understood. In other words, the sea slug still senses the environment and adjusts to it as we do, but in a way that is much more direct and tractable. All we can conclusively state is that our nervous system is more complex and less understood. The slug is able to expect albeit in a way that is much less profound than our capabilities for expectation. We therefore do not have grounds for entirely dismissing the existence of a mind or of claiming that they cannot experience the placebo effect.

However, we can conclude that the sea slug’s mind is much less profound, and perhaps infinitesimally so. It exhibits features between that of an unconscious system and that of a

stupendously complex interacting network such as our brains. It is this complexity that makes using the words “mind” and “placebo” more fitting in humans. Human brains are cumulatively more complex than all other known brains. Our sensory modalities are more developed than sea slugs’. In our case, the sensations are largely processed through the thalamus and then throughout our entire cortex, which is extremely well-developed. The signals in our cortex arising from these sensations are then further processed through phenomena in our brain relating to our beliefs, expectations, and emotions. In humans, all these parts of our brains will be interacting much more intricately and complexly than in other nervous systems, giving rise to a more profound mind and thus, potentially more profound placebo effects.

Since humans are able to come deeply under the effect of placebos, scholars and physicians have suggested that using placebos can be viable for treatment. In fact, as was recently reviewed,[28] many scholars argue that the vast majority of benefits from pre-scientific medicine have hinged on the placebo effect. But now, as science trudges on and as our paradigms of healthcare have shifted from paternalistic to patient-centered,[29] several problems emerge from the suggestion to use placebos in treatments.

First, the unreliability of the placebo effect and our lack of understanding of its precise causes decreases the value of placebos as treatments. Placebos can have significant effects on health and feelings, but they are notoriously stochastic. Even in certain types of conditions, such as neurological ones, in which we know that the placebo effect tends to manifest more frequently, the effect is incompletely penetrant. As we have already seen, health can be affected by the patient’s expectations, their knowledge, their environment, or even how healthcare professionals approach them. Unfortunately, we do not currently have reliable ways of determining what patients will be affected in what way. Concomitant with a lack of knowledge about the precise neurophysiological mechanisms underlying the placebo effect, physicians are reluctant to prescribe the placebo effect.

However, these shortcomings do not generally stop physicians from using other forms of treatment. Stochasticity and a lack of understanding do not preclude treatment acceptance, as long as treatments both yield sufficient responses to pass appropriate statistical tests and avoid unjustified negative effects. Indeed, a former senior vice president of genetics research at GlaxoSmithKline has conjectured that 90% of drugs work in less than half of the people that use them.[30] Though it is important to note that treatment regulatory agencies such as the United States of America Food and Drug Administration often require substantiated and reliable hypotheses of a treatment mechanism to even begin human trials. This means that while the placebo effect may rival many drugs in terms of reliability, the mechanism remains too obscure for even the more liberal regulatory agencies.

Second, there is an ethical issue surrounding the misinformation that prescribing a placebo seems to entail. Today we recognize the patient as an autonomous person that has their own beliefs, expectation, and goals.[29] If physicians provide patients with less knowledge than they can have, or than they want to have, patients are being deprived of a basic human right: autonomy. Moreover, the patient-physician relationship fundamentally depends on honesty and trust in order to be effective. Patients divulge what they may view as their darkest secrets only because they instill trust in the physician, trust that was enkindled by adequate information, sound advice, and a verbal contract of confidentiality. If the patient

were to find out that they were being lied to – being informed that they were being treated while they were actually given a placebo – it would be a blow to the patient-physician relationship. Within our current system, so catastrophic would such a breach of trust be that it is seldom considered an option by physicians. But this may not have to stop physicians either. A number of studies have now used placebo treatments while overtly informing patients that they were taking a placebo.[31,32] And the placebo effect still occurred!

The perseverance of the placebo effect even when patients were aware of an absence of active treatment brings about two potential alternative ways to implement the placebo effect for its beneficence. On one hand, one may perhaps give a combination treatment of a placebo and an active treatment, while informing patients either that they will be receiving an additional treatment, or by outright telling them that they are also receiving a placebo. Either way, this should at least partly by-pass the ethical issues in withholding a standard evidence-based treatment. On the other hand, one may want to consider an inverse placebo trial, wherein the patient is told that they are receiving a placebo, but they are instead actually receiving the active treatment. Though this option does not avoid the problem of misinformation, it does avoid the problem of treatment. If knowingly taking a placebo can improve health, perhaps doing so in tandem with actual treatment will have additive benefits.

Even with these alternative experiments in mind, it is clear we have many questions to ask yet about how human nature makes us so susceptible to the placebo effect. But perhaps we can take away one more important lesson from the perplexity of the placebo effect: our perceptions are often amiss and, regardless of their accuracy, often have a strong influence on our physiology. Luckily, the deception of an optical illusion can sometimes be unseen once we are informed. Similarly, we saw that our pain threshold can change with our disposition. In the same way, we may want to un-see other illusions and sway our disposition in the preferable direction. This idea, of forcing behaviours to change our characters, has been entertained for millennia, such as by Aristotle:[33]

> *It is well said, then, that it is by doing just acts that the just man is produced, and by doing temperate acts the temperate man; without doing these no one would have even a prospect of becoming good. But most people do not do these, but take refuge in theory and think they are being philosophers and will become good in this way, behaving somewhat like patients who listen attentively to their doctors, but do none of the things they are ordered to do.*

Towards this same point, a number of studies have shown that forcing a smile by holding a pencil with one's teeth can make our dispositions more positive and can even make cartoons seem funnier.[34] On a more physical level, seemingly innocuous treatments have led to noteworthy improvements in physical exercise.[22] For one, verbal encouragement has been shown to increase peak muscle force production by 5%[35] and a multitude of studies have shown even greater gains for placebo treatments.[22] Moreover, verbal encouragement in exercise has also produced significant improvements in exercise endurance in certain cases.[36,37]

These results show that we often hold ourselves back on a physical level. Perhaps we are preventing ourselves from enjoying life and living life to the fullest. And this is not only due

to considerations for our responsibilities, but also due to logical reasoning, social norms, and mysterious subconscious feelings, which often turn out to be unnecessary or erroneous. Thoughts such as “I should be tired by now, so I will rest” or “normally this is not possible, so I will not try” are among those responsible for our inhibitions. Perhaps Diane van Deren can be our greatest exemplar for shedding this unnecessary inhibition.[38] Diane van Deren is an elite ultramarathon runner who is thought to be able to perform at such high levels in part because she has short-term memory loss. Instead of dwelling on how much distance she has left, or how much she has already run and how tired she must feel, she simply runs. She does not have the psychologically-decided or societally-accepted limits of human performance bearing down on her. So, if we cannot release our minds to be like Diane van Deren’s, perhaps we can at least hold a figurative pencil between our teeth, there is no way to know what benefits we will unleash. In the spirit of having argued against multiple words for the placebo effect, I facetiously suggest calling this the “temptado” effect, after the Latin for “I will try”.

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