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Understanding the placebo effect from an evolutionary perspective

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ABSTRACT

A placebo is a treatment which is not effective through its direct action on the body, but works because of its effect on the patient's beliefs. From an evolutionary perspective, it is initially puzzling why, if people are capable of recovering, they need a placebo to do so. Based on an argument put forward by Humphrey [Great expectations: the evolutionary psychology of faith-healing and the placebo effect. In: Humphrey, N (2002). *The mind made flesh*. Oxford University Press, Oxford. 255–285], we present simple mathematical models of the placebo effect that involve a trade-off between the costs and benefits of allocating resources to a current problem. These models show why the effect occurs and how its magnitude and timing can depend on different factors. We identify a particular aspect of belief which may govern the effect and conclude that a deeper understanding of why the placebo effect exists may allow it to be invoked more easily in the future.

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Medicine is not only a science; it is also an art. It does not consist of compounding pills and plasters; it deals with the very processes of life, which must be understood before they may be guided.

Philipus A. Paracelsus

1. Introduction

Humphrey (2002, p. 256) defines a placebo as “a treatment which, while not being effective through its direct action on the body, works when and because:

- the patient is *aware* that the treatment is being given;
- the patient has a certain *belief* in the treatment, based, for example, on prior experience or on the treatment's reputation;
- the patient's belief leads her to *expect* that, following the treatment, she is likely to get better;
- the *expectation* influences her capacity for self-cure, so as to hasten the very result that she expects.”

The resulting improvement in the patient's health is known as the placebo effect, which is well established in medical circles for some conditions (Evans, 2003; Vallance, 2006), though the causes are poorly understood (Benedetti, Pollo, Lopiano, Lanotte, Vighetti, &

Rainero, 2003; Olshansky, 2007). Some (e.g., Hróbjartsson & Gøtzsche, 2004) argue that most findings are simply the result of reporting bias, whilst others assert that the effect has both a psychological and physiological basis (e.g., Wager et al., 2004). The magnitude of the effect can be modulated by many factors, such as the colour of pills and the size of doses; injections or surgery tend to produce a stronger effect than pills (Olshansky, 2007). The manner of the physician administering the treatment (e.g., reassuring or formal) can also affect outcomes (Di Blasi, Harkness, Ernst, Georgiou, & Kleijnen, 2001); Walach and Jonas (2004) list 18 ways to enhance healing responses based on the placebo effect.

If the placebo effect is ubiquitous in modern humans, it has presumably persisted for considerable evolutionary time. If individuals are capable of recovering without external aid, why do they rely on an external cue?

Bendesky and Sonabend (2005) argue that “at some point in the history of human evolution, brain development reached a certain level that allowed sick people to understand they could get ‘better’. [...] These individuals had probably less prolonged illnesses, [...] or else felt better, which would have a similar effect [to] ‘really’ being better.” This line of reasoning does not explain why the placebo effect exists. Just as animals do not need to understand that they must breathe in order to do so, it is not clear why individuals should require an understanding of their illness for their immune system to operate on it.

Many discussions and models of the placebo effect focus on the extent to which the effect occurs consciously (expectancy theory) or subconsciously (through conditioning and psychoimmunological

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effects). Much of this work has been neatly summarised by Stewart-Williams and Podd (2004), who conclude that these alternatives need not be mutually exclusive. We share this view and prefer to regard the effect in the holistic sense of an individual receiving an external cue, which may trigger a self-generated recovery (or, for that matter, a deterioration). Our aim at this stage is not to identify specific mechanisms in the brain by which the effect occurs, but to understand at a more fundamental level *why* the effect should have survived the seeming evolutionary pressure against it (i.e., why the effect exists at all) when one would expect that individuals who get better without the need for an external trigger would have a higher fitness.

Humphrey (2002) provides a verbal argument as to why the effect occurs, from the perspective of evolutionary biology. We summarise this argument in Section 2. In subsequent sections, we clarify Humphrey's suggestion using formal models and identify its strengths and weaknesses. This allows us to make predictions about when the effect (or the reverse effect) should occur by drawing out important distinctions about the type of belief that a patient has in a treatment.

2. Humphrey's concept

Natural selection will tend to favour organisms which are able to manage their resources effectively. As McNamara and Buchanan (2005) hypothesize, "the processes that allow redistribution of physiological resources should distribute resources optimally to maximise fitness." By drawing a parallel between the internal workings of an organism and the management of resources in a national health service, Humphrey (2002) points out that there are sometimes limitations on the use of resources due to budgets, triage systems, and so on. Just as a hospital administrator must manage resources based on risks of what might happen next, we can expect the immune system to take account of potential future infections when managing resources. Humphrey does not present a formal model but suggests that optimal trade-offs will predict how an organism should allocate resources to defence and repair. How much effort to put into current health and how the effort is traded off against other needs (including potential future requirements) are fundamental to this paper.

Sometimes, the benefits of ignoring sickness or pain can outweigh the benefits of an immediate response. For example, an individual with a fever or a broken leg should still spend its resources on movement to safety when approached by a predator. Running an immune system can be costly in terms of energy (Owens & Wilson, 1999), and there is an increased risk of developing an autoimmune disease if an individual attempts to tackle an illness when he or she is already physically stressed (Råberg et al., 1998). These effects could reduce the optimal level of effort put into fighting an illness at a particular point in time. Houston, McNamara, Barta, and Klasing (2007) further identify that individuals should make a trade-off between investing energy in immune defence and storing it as reserves to prevent starvation. Similarly, trade-offs can be made in relation to the timing and allocation of resources to defence and repair (Shudo & Iwasa, 2001; Medley, 2002; McNamara & Buchanan, 2005). Thus, external cues should sometimes influence whether, when, and the extent to which an organism devotes resources to dealing with a problem (combating an illness or healing an injury), and so may also affect subjective measures (such as pain) which influence behaviour.

The common currency for making optimal trade-offs is the individual's expected number of offspring; in behavioural ecology, this is termed reproductive value (RV; see Fisher, 1958; McNamara & Houston, 1986). Humphrey argues that, rather than triggers having only a general effect, individuals will gain a greater benefit if they can act according to their personal situation. An individual's state (i.e., its

internal state and the external world) can affect RV (Houston & McNamara, 1999) and, with it, their optimal trade-offs and resulting behaviour, which includes the timing and magnitude of effort put into health. Immediate health can be traded off against many different factors, such as storing energy to reduce the risk of starvation or predation, reproductive effort, or holding back resources to deal with potential future ailments. By focusing on some of these trade-offs, we identify how perceived state should affect the operation of the immune system and thus how the placebo effect can be induced.

In summary, optimal behaviour is dependent on both the state of the animal (internal) and the state of its environment (external). Regarding physiology as a component of behaviour, it follows that the amount of effort put into health should be governed by the perceived state of the world and the perceived state of the focal individual. Any treatment which modifies either of these perceptions may therefore induce (or inhibit) the placebo effect.

The rest of this paper illustrates the above points by providing specific examples. In the next section, we use a formal framework to show that the state of the environment should influence when to get well, even if resources are sufficient to fight off an illness immediately.

3. The importance of environmental cues

In this section, we demonstrate that the operation of the immune system should depend on external cues; we do this by identifying how expectations and cues can mediate between long-term and short-term gains. Our analysis first considers a simple world with only two states and two available actions, before considering a more general situation.

3.1. Environment-dependent recovery

We assume that, at any given time, the individual knows which of two environmental states is being faced: the environment is either good (e.g., safe from predators) or bad (i.e., some kind of stressor is present, such as a predator or sexual competitor).

We assume a potentially chronic infection which is not life threatening, but which reduces an individual's reproductive success (i.e., expected number of offspring surviving to maturity) relative to that of a healthy individual whilst the infection is present. An infected individual could mount an intensive immune response which would overcome the illness, but would pay a significant short-term cost in order to do so.

We divide time into discrete units and assume a constant probability of survival per unit of time, assuming that infection does not affect survival. The reproductive success of an individual (per unit of time) depends on both its health and the external environment. For simplicity, we make the binary assumption that the focal individual is either infected or free from infection; if an individual is infected, a second infection will not develop. When infected, the individual can mount an immune response (to overcome the infection in the coming time step) or maintain a chronic level of infection.

The reproductive success per unit of time is contingent on both the individual's health and its environment, as shown in Table 1. Reproductive success (per unit of time) increases from left to right and from top to bottom in the table ($m_s < d_s < u_s$, $m_n < d_n < u_n$, $m_s < m_n$, $d_s < d_n$, $u_s < u_n$).

Table 1
Reproductive success per unit of time

	Mount response (infected)	No response (infected)	Uninfected
Stressor	m_s	d_s	u_s
No stressor	m_n	d_n	u_n

We denote the probability that a stressor is present per unit of time by p and the probability of escaping a new infection per unit of time, given the individual is uninfected, by q . We assume that p and q do not change over time and that there is a fixed probability of survival per unit of time.

We are interested in the optimal operation of the immune system once an infection is acquired and a stressor is present, i.e., how to maximise lifetime reproductive success. If an acute immune response is mounted, we can calculate the change in expected lifetime RV (relative to not responding) based on the change in per-episode reproductive success for each episode that the individual remains alive. This can be done for different strategies, specifically, immediate responses to infection and delaying response until no stressor is present.

In Appendix A (available on the journal's website at www.ehbonline.org), we show that for a high probability of surviving longer than the stressor is present, it is better to have a delayed response (i.e., wait until no stressor is present) than have no response at all if:

$$d_n - m_n < \frac{q(p(u_s - d_s) + (1-p)(u_n - d_n))}{1-q},$$

and it is better to delay responding (than have an immediate response in the presence of a stressor) if:

$$d_s - m_s > d_n - m_n. \quad (1)$$

Assuming that it is better to make a response at some point (so the former condition is satisfied), condition (1) will be satisfied if an immune response is highly detrimental to short-term reproductive success in a bad environment (i.e., with a stressor present). Because it can be best to delay response when a stressor is present, we see that from the perspective of optimal behaviour, *activation of the immune system should be influenced by external cues*. When viewed from this perspective, the immune system's tendency to work less well under conditions of stress may be considered a design feature rather than a defect, as the more general adaptation is that of the immune system calibrating the intensity of its activity to current circumstances.

3.2. Medication

We have identified that with high survival rates, it can be best to delay the immune response when conditions are stressful. In this subsection, we assume that this condition (inequality 1) holds and consider an individual that is infected when a stressor is present (so that rather than recovering immediately, the response is delayed until the stressor is no longer present).

We further suppose that an individual receives a cue (such as a pill or some other form of 'medication') which, it believes, means that it is less costly to mount an immune response. Because a stressor is present, this means that the perceived value of response under stress, m_s , is increased and it may no longer be best to delay the immune response. Under such circumstances, the immune system should be triggered into action immediately (despite the stressor still being present). If the cue only alters the expectations of the individual (without affecting the actual payoffs), then under such circumstances, *the placebo effect will be triggered*. This is because decisions are based on expected, rather than actual, payoffs.

An individual's belief in a placebo could be a conditioned belief, from the expectation of health following previous treatments (especially if there has been an active component in previous treatments), or a conscious change in perceptions, for instance, from having been told that a consequence of the treatment is that it will be able to recover more easily. Many papers assume one of these or compare the two (e.g. [Montgomery & Kirsch, 1997](#); [Voudouris, Peck, &](#)

[Coleman, 1989](#)) but do not identify why the effect exists. Here, we can see why the effect exists: the payoff matrix drives outcomes, which means that beliefs tend to be self-fulfilling (i.e., if an individual believes that it should combat an illness, then, because it acts on that belief, it tends to get better).

The effort level of each individual should be optimised to correspond to its perceived overall state (both internal and external). This perception can depend on many possible types of cue. Unlike the environmental cue, the supply of medication can often be readily controlled by the focal individual. Consequently, a self-reinforcing effect can occur in which the individual chooses to take the medicine in order to help get well and waits until the medicine is taken before fully activating its immune system, thus reinforcing the effect of the medicine (and the belief in it for future occasions) even if it is a placebo.

In this light, a parallel might be drawn between the use of witch doctors and the use of medicines, with the effect of the latter potentially being increased (in a placebo-like manner) by knowledge that the medicine will do some good through active (i.e., 'real') components (see [Humphrey & Skoyles, 2012](#); [Kaptchuk, 2011](#)). Thus, medicines which do have some direct action on the body may also be enhanced by placebo-related effects (a possible downside to the use of medicines is also discussed in Section 5).

3.3. The general effect of perceptions

The state of the world includes external factors, such as temperature or food supplies, and internal factors, such as energy reserves or nutrients. Decisions (in the most abstract sense, so including the action of the immune system) should depend on the expected value of each possible action, which in turn depends on the perceived state of the world. Consequently, an altered perception of any of those factors (internal, external, or expected future rewards) can, in theory, affect the optimal response of the immune system.

In Appendix B (available on the journal's website at www.ehbonline.org), we assume that an individual has a disease which is potentially life threatening and that the effort put into recovery can be chosen from a continuous scale. By assuming two possible sources of mortality, the disease and other sources, we show that recovery effort level will often positively correlate with how good the individual perceives the world to be (e.g., probability of food supplies). In other words, if an individual believes (falsely or not) that its situation has improved, it can be expected to put more resources into fighting the disease; i.e., the placebo effect should be induced. Although this is expected to improve health with respect to the disease, the behaviour is suboptimal with respect to total mortality if the situation has not really improved. [Fig. 1](#) illustrates how the level of effort put into health can affect total mortality rate in different environments and thus how the effort put into health should change according to the perceived environmental conditions. In this case, the effort put into health should increase by more than 80%; it is easy to identify situations where the effect should be even larger.

In Appendix B (available on the journal's website at www.ehbonline.org), we also provide a formal model showing that it should also be possible to induce the placebo effect by modifying perceived payoffs (i.e., the value of being well or remaining unhealthy). In Appendix C (available on the journal's website at www.ehbonline.org) we show that the perception of the current situation (compared to how things are likely to be in the future) can also affect the optimal amount of effort put into health.

By considering the risk of starvation (as well as disease), [Houston et al. \(2007\)](#) analyse the effect of energy reserves and food availability on immune defence. By identifying the behaviour which maximises RV, they show that the optimal allocation of energy to immune defence increases with energy reserves. Consequently, if an animal

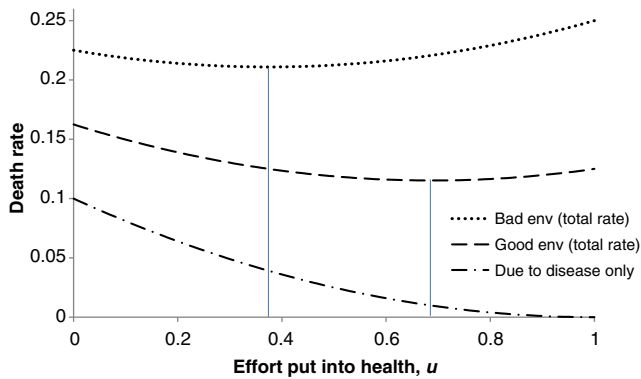


Fig. 1. Effort put into health should alter with environmental conditions. The death rate due to disease, D , decreases with effort put into health, u . The death rate from other sources (such as starvation or predation), M , decreases with the quality of the environment, a , and increases with u . In a bad environment, the optimal value of u is low (indicated by the vertical bar on the left) because there is a high rate of mortality from other sources, so it is best not to increase that rate still further by putting much effort into health (indicated by the right vertical bar). $D(u) = (1-u)^2/10$. $M(a, u) = \frac{1+u}{20a}$. Bad environment: $a=0.4$, $u^*=0.375$. Good environment: $a=0.8$, $u^*=0.6875$.

were to believe that its resources were higher than they really were, it would (suboptimally) put more effort into immune defence.

4. Cues which promise no health benefit

The complexity of the world means that the prioritisation of tasks may not always be perfect. In this section, we identify how prioritisation processes, in conjunction with mental limitations, could result in a placebo effect.

We assume that there is a link between mental priorities and physical behaviours—specifically the action of the immune system. We have limited mental resources, so it is not surprising that tasks will occasionally be overlooked or incorrectly prioritised. Any prompt which causes an individual to reevaluate its priorities may therefore induce the placebo effect. A regular prompt (such as a daily pill) may have more effect over time than a single prompt, as might a stronger provocation to reevaluate priorities (such as big, bright red pills or an operation; these might also serve to increase the perceived priority of the health issues).

If it takes time or effort to check priorities, then too many reevaluations (reprioritisations) would reduce the overall fitness of the individual. However, if illnesses tend to get worse with time, a slightly higher than optimal rate of reprioritisation could result in the health of an individual being increased. Thus, if we regard a placebo as a trigger to reevaluate priorities, then too many placebos may have a positive effect on health but (counterintuitively) at the expense of RV, just as people who devote much of their lives to eating healthily and training at a gym may not achieve as much as others, despite living for longer.

A placebo in this case amounts to a change in expectation not directly related to the illness (or treatment) but to whether it is worth reprioritising tasks. One realistic cue for reprioritisation of tasks is a perceived change in the environment. Returning to the stressor model of Section 3.1, we note that for high survival rates and little chance of reinfection, a perceived deterioration in the environment (expecting stressors to become more likely) can trigger the body to fight an illness (see end of Appendix A, available on the journal's website at www.ehbonline.org), effectively caused by priorities having changed. Thus, *cues which promise no health benefit can result in an improvement in health*; relating the cue to the effect, it is natural to term this the placebo effect.

The mindset of this section accords with Humphrey's concept of managing resources in a health service, though it has somewhat side-stepped his definition of expectations, instead focusing on the limitations of the health service administrator (to use Humphrey's analogy). The act of prayer or meditation may have similar consequences in terms of recognising priorities and acting accordingly; for a discussion of prayer in relation to the placebo effect, see Jantos and Kiat (2007) and Kohls, Sauer, Offenbacher, and Giordano (2011).

In summary, if individuals sometimes need to reprioritise tasks (including dealing with health issues) and mental wiring has evolved to respond to ancestral cues for when it is best to reprioritise (e.g., following a change of environment), then a 'placebo' (such as a change of scenery) may trigger an individual into reevaluating its priorities. Such a trigger might have positive, negative, or neutral effects on health (so would be called a placebo in hindsight only if it happened to have a positive effect). However, if illnesses tend to get worse until they're dealt with, they will tend to move up the list during reprioritisation, so cues which lead to reprioritisation will tend to produce placebo effects.

When faced with a problem, the question is whether it is worth trying to find a solution. This applies to both internal problems (relating to health and the placebo effect) and external problems. For instance, faced with the 'problem' of understanding why the placebo effect occurs, even if none of the models in this paper were valid, *this paper* could effectively act as a cue which helps to sort out the problem by focusing attention on finding an explanation for the effect, which may in turn cause someone reading this to solve the problem. However, there is also a downside; if people believed the problem to be solved, they would put *less* effort into solving the problem, not more. In this way, the effect of a supposed aid (Humphrey's effect) could be reversed.

5. The reverse of Humphrey's effect

So far, we have considered how placebos can trigger the immune system into action by increasing the expected worth of getting better (be it through paying a lesser cost for fighting the ailment or altering priorities). Without any belief in the cue (i.e., the placebo), such effects would not exist. However, let us now assume that the patients have great confidence that the placebo will cure them.

Rather than increasing the placebo effect, too much belief in the power of a placebo could reverse its effect. This is because, if the individual believes that the (placebo) treatment will cure it, there is no need for its immune system to also exert effort on recovering from the ailment. In such a situation, because the placebo will have no effect on the body directly (and the immune system will do less), the health of the patient may decline, rather than improve, due to the use of the placebo.

As a possible example, the situation is summarised on a personal level in a book by Gavin (1989) who, having previously fought off many bouts of malaria in the jungle and a prisoner-of-war camp, recalled his thoughts on reaching a Westernised hospital with only a mild touch of malaria: "The job of getting me better was in their hands and I was certainly not going to be robbed of the pleasure of doing nothing about it myself." Days later, hardly able to think but vaguely aware of comments that he was almost dead, "the doctors had failed me, they couldn't look after me, the long promised treat of letting myself go was no treat at all. I was going to be stuck even now with the job of pulling myself round." Which, it would seem, is what then happened.

Thus, the *type* of belief in a placebo may considerably alter its effect. In situations where the immune system must be (further) activated, belief that a particular treatment or medication will fix the problem (on its own) may do more harm than good, whereas belief that the medication may only assist the immune system to fight the illness may help to activate the healing systems (as discussed in

Section 3.2). However, in situations where the individual is suffering from stress or its immune system is overactive, complete belief in a treatment may have beneficial effects. It is worth noting that rather than having direct access to information encoded in mental states (i.e., the particular content of a belief), the immune system may respond merely to one or a few physiological correlates of such states (i.e., the level of stress hormones). If so, different types of beliefs may be relevant only insofar as they are perceived to be more or less stressful. The risk of a treatment having deleterious consequences on a patient's health, depending on the patient's expectations, is related to another effect: that of the nocebo.

6. The nocebo effect

A nocebo (Latin for “I shall harm”) is a substance which is pharmacologically (medicinally) inactive but which a patient experiences as harmful due to negative expectations (reviewed by Hahn, 1997). Note that some people use the term to mean “all distressing symptoms that accompany placebo administration” (e.g., Barsky, Saintfort, Rogers, & Borus, 2002), whilst others define it in the latter manner but then refer to the placebo (nocebo) effects as occurring through positive (negative) expectations (e.g., Liccardi et al., 2004). As we have already alluded to possible negative outcomes of placebos in the previous section, we use the term nocebo here to relate to the harmful consequences of negative expectations, as summarised in Table 2.

Like placebo effects, there is evidence for the existence of nocebo effects, which are also poorly understood (Olshansky, 2007). Just like placebo effects, nocebo effects may be induced through conscious expectations or unconscious conditioning (Benedetti et al., 2003).

It is easy to imagine that nocebos operate in exactly the opposite way to placebos. Flaten, Simonsen, and Olsen (1999), for instance, state that “nocebo responses may be regarded as negative placebo responses.” This makes sense for a continuously measurable focal problem, such as the measurement of pain. The view is strengthened by the results of some studies which indicate that nocebos may have the opposite effect of placebos through their mediation of opioids (e.g., Benedetti, Amanzio, Vighetti, & Asteggiano, 2006). However, it is not clear that such an effect is always caused by the same mechanisms as the placebo effect. With the placebo effect, the focal individual will have a specific pain or ailment and may or may not be more able to recover after taking a placebo. Thus, the placebo effect can be said to act on a particular (focal) ailment. Nocebos, on the other hand, are said to be capable of producing deleterious effects in otherwise healthy individuals (Blackman, 2009).

From an evolutionary standpoint, we are able to see why an increased expectation of something bad, such as pain, may tend to result in that very outcome. From a mechanistic perspective, Benedetti, Lanotte, Lopiano, and Colloca (2007) write:

“Recent experimental evidence indicates that negative verbal suggestions induce anticipatory anxiety about the impending pain increase, and this verbally-induced anxiety triggers the activation of cholecystokinin (CCK) which, in turn, facilitates pain transmission.”

Table 2
Assigned reasons for outcomes based on the subject's expectations

		Subject's expectation	
		Good	Bad
Actual outcome	Good (improve)	Placebo	Call-to-arms (sometimes called placebo)
	Bad (deteriorate)	Anti-Humphrey (sometimes called nocebo)	Nocebo

Pain is not always a bad thing; it serves to warn and protect from further harm (Humphrey, 2002). Therefore, if an individual is entering a situation in which it may be hurt, it can be logical to sharpen the senses relating to such danger. In its simplest form, this can be regarded as a signal detection problem (Green & Swets, 1966). There are two possible errors: believing the situation to be safe when it is not and vice-versa. If expectations about the situation are modified, the optimal threshold for responding in a particular way will also be modified. Consequently, more false alarms (e.g., of seeming pain, which might otherwise have been put down to ‘pins-and-needles’) may be experienced.

As discussed in Section 4, drawing attention to a particular issue may result in more effort being applied to it. In situations where further attention is deleterious (such as suffering from stress), it is easy to see how feedback loops of self-reporting and action can result in the nocebo effect after a problem is reported to the focal individual. For instance, if a doctor tells a patient that he or she may have a heart attack due to stress, the patient may become more stressed. In its most extreme form (‘the fear of fear itself’), such feedback loops may cause panic attacks (Chambless, Caputo, Bright, & Gallagher, 1984).

Evans (2003) suggests that, rather than operating through the activation of an immune system, both placebo and nocebo effects may be due to the suppression of a particular type of immune response, as we now discuss.

7. Evans' suggestion

Jawed vertebrates such as mammals have two types of immune system: innate and acquired. For a summary of these systems and an evolutionary perspective on the mechanisms involved, see Beck and Habicht (1996) and Litman (1996).

The innate (or natural) immune system produces what is known as the acute response. This is a general, fast-acting response because the phagocytic white blood cells (macrophages) of the system are already active in the body prior to infection. The innate system is phylogenetically ancient, predating vertebrates to primitive multicellular organisms (Janeway, Travers, Walport, & Shlomchik, 2001; Litman, Cannon, & Dishaw, 2005). Immune cells are recruited to fight infection, and the process of inflammation can establish a physical barrier against further infection. The innate system also activates the acquired immune system in a process known as antigen presentation.

The acquired (or adaptive) immune system is a target-specific system which takes a number of days to mobilise when dealing with an antigen (antibody generator) which has not been encountered before (Beck & Habicht, 1996). The acquired system has an immunologic memory, resulting in subsequent encounters with a given antigen being dealt with more quickly. The acquired nature of the system means that, although it is slower, it can be more precise than the innate immune system and is therefore more able to deal with some types of ailment (particularly viruses and bacterial infections).

Inspired by Humphrey's concept of placebos working through modification of expectations, Evans (2003, 2005) makes a case that only conditions affected by the acute response are sensitive to placebos and that the placebo effect occurs through the suppression of the acute system. Evans' reasoning comes from a combination of empirical evidence and a hypothesis about how the placebo effect may operate through beliefs.

Evans argues that numerous conditions which have been shown to be responsive to placebos (such as pain, stomach ulcers, and swelling) are related to the acute response of the innate system, whereas bacterial and viral infections (which are dealt with by the acquired system) do not respond to placebos.

The release of particular chemical messengers, such as endorphins, in the brain can result in the reduction of pain and inflammation. Therefore, if the brain can be triggered (by a placebo) into releasing more of these chemicals, the apparent symptoms of an ailment will be

relieved to some degree. If this occurs earlier than is appropriate, deleterious consequences may result. However, aside from the possibility that placebos act only to reduce symptoms, Evans has three arguments for helping to suppress the innate immune response (after some time). Firstly, he argues that some disorders (such as arthritis) are caused by a failure to stop the acute response; in such conditions, a placebo effect would be genuinely beneficial. Secondly, although the acute response is useful in slowing the spread of pathogens whilst the acquired system gets fired up, the nitric oxide produced by the innate system (which reduces the rate at which bacteria divide) also tends to inhibit the lymphocytes of the acquired system when they arrive (Evans, p. 62). Finally, Evans argues that the speed and effectiveness of the acquired immune system will depend on the available resources (such as energy). Therefore, an organism which could mediate the acute response through knowledge of the available resources would have an evolutionary advantage. If the perception of available resources were modified artificially, we may expect to witness the placebo effect.

Whereas Humphrey talks generally in terms of the activation of the immune system, Evans regards the placebo effect as occurring through the suppression of the innate part of the immune system. It is not easy to ascertain whether the effect exists only for conditions affected by the acute response, principally because:

1. The body is very complex. For instance, it is difficult to know the extent to which depression relates to the acute response—as Evans (2003, p. 53) suggests.
2. The results of clinical studies can be far from easy to interpret, especially at the meta level.

The view that nitric oxide can play an important role in the placebo effect is reinforced by the review of Walach and Jonas (2004). If Evans' argument is correct, then the potential magnitude of placebo effects may have increased in recent history due to improved availability of resources. If a reliable supply of resources results in our acquired immune systems being more capable, then the 'parameters' of the innate system would be incorrectly tuned, tending to take too much action (and for too long). Thus, we again see that optimal defence involves a trade-off between priorities, with the allocation of resources being mediated by expectations.

8. Discussion and summary

We have shown that, rather than fight diseases unconditionally, it can be adaptive to wait for (what is perceived to be) a better opportunity. Placebos may act as cues that a better opportunity now exists. The placebo effect may therefore reduce to expectations about when it is worth trying to take action.

We have identified that the placebo effect could be induced in several ways, through modifying perceptions of (a) the external environment, (b) the cost of getting well, or (c) the value of being well (which accords with Nesse, 2005). In each case, the effect of a placebo is modulated by expectations; this accords with functional magnetic resonance imaging studies which show correlations between the placebo effect and regions of the brain (specifically the orbitofrontal cortex and dorsolateral prefrontal cortex) associated with expectation (Petrovic, Dietrich, Fransson, Andersson, Carlsson, & Ingvar, 2005; Wager et al., 2004).

Typically, the action of natural selection should tend to maximise the RV of individuals. Disease and damage can severely reduce RV, so the immediate relief of pain (or recovery from illness) is often a good proxy for fitness. However, relieving hunger and avoiding predation are also good proxies for fitness; the currency of RV takes all such factors into account. Because each factor must sometimes be traded off against others (if RV is to be maximised), we find that individuals should not always recover as quickly as possible; to do so would maximise the wrong currency.

There are two forms of explanation for the placebo effect:

1. Optimal behaviour (in terms of responsiveness to cues), caused by a trade-off between different aspects of fitness.
2. Suboptimal behaviour, caused by genetic deficiencies or recent circumstantial changes.

We have focused primarily on the first of these and have shown that it can be optimal not to take action at the point of affliction but act later, when triggered by a cue. However, while a delay of action may often be optimal, this does not imply that waiting for a useless pill before taking action is an optimal behaviour. What is adaptive is the general responsiveness to cues, not the responsiveness to useless pills.

In humans, conscious information about whether drugs have good or bad consequences can affect the rate of absorption of a drug, as shown by Flaten et al. (1999). Ader and Cohen (1975) have shown that the immune system of rats can be modified by Pavlovian conditioning, resulting in a placebo effect, and Evans (2003, p. 99) summarizes that, "many mammals seem to be subject to *something like* the placebo effect. To be specific, rats, mice, guinea pigs and dogs have been shown to be susceptible to a phenomenon known as *immune conditioning*." Stewart-Williams and Podd (2004) review the literature in terms of how learning and conditioning can shape and mediate the placebo effect. They conclude that conscious expectations (e.g., from verbal information) can sometimes mediate the effect but that conditioning can also shape the placebo effect in ways which are not conscious.

Many of the empirical investigations of the placebo effect report subjective measures, such as pain. In this paper, rather than subjective outcomes, we have focused on the optimal functioning of the immune system and how effort put into health should be traded off against other behaviours. Subjective experiences such as pain are relevant to the functioning of an organism because they can mediate changes of behaviour; i.e., we see pain as one mediator of behaviour, affected by external cues because it then also affects the choice of appropriate behaviour. Although it would be preferable for empirical studies of the placebo effect to use less subjective and more objective measures, it may often be easier to identify the immediate effect of a placebo on a subjective measure, like pain, than on longer-term objective measures of health (which are subject to many more variables due to the longer time scale).

It is well known that the immune system operates less effectively under conditions of stress (Khansari, Murgo, & Faith, 1990), and it would be natural to assume that this is due to physiological limitations. Our models indicate that rather than being suboptimal, the reduced effectiveness of the immune system under conditions of stress may be adaptive.

Our models imply that alterations in expected reward (or punishment) can trigger the placebo effect. Expected reward can, to an extent, be measured by studying the levels of dopamine in an individual (Dayan & Abbott, 2001; Doya & Kimura, 2009). By applying this knowledge to the study of placebos, de la Fuente-Fernandez and Stoessl (2002) concluded that "the placebo effect in Parkinson's disease was triggered by the expectation of reward (i.e., the expectation of clinical benefit)."

We have identified how Humphrey's (2002) definition of a placebo can be expanded in terms of expectations: individuals need not have a belief in the treatment (which leads to an expectation of health) for an improvement in health to be promoted. For instance, the expectation can relate to what will be gained if health is achieved (Appendix B, available on the journal's website at www.ehbonline.org) or mental limitations (Section 4). More importantly, we have identified that rather than the placebo effect following simply from having positive expectations of health following a treatment, the particular type of belief in the treatment can, in theory, lead to positive or negative effects. For conditions where an increased

Table 3
Summary of how patient expectations should affect treatment outcomes

		Expected outcome of treatment	
		Good	Bad
Type of belief in how the treatment works	Works alone	Deteriorate (Anti-Humphrey effect)	Improve (call-to-arms)
	Affects immune system capability	Improve (placebo effect)	Deteriorate (nocebo effect)

immune response will promote health, a belief that the treatment should enable their immune system to fight more effectively should have positive effects; we have termed this the ‘Humphrey effect.’ In contrast, a belief that the treatment will cure them, without any need for the immune system to do anything, could have deleterious effect on the patient’s health: the ‘reverse Humphrey effect.’ The effects are summarised in Table 3. For conditions caused by an overactive immune system, the above outcomes are switched relative to the type of belief. Consequently, we suggest that future empirical work focusing on this factor may lead to a better understanding of how to invoke and control the placebo effect.

Whereas Humphrey’s suggestion is highly general, pitched in terms of expectations and the allocation of resources, Evans’ (2003) hypothesis—that the placebo effect occurs due to the inhibition of the innate immune system—may be closer to the biological truth. Whether Evans usurps Humphrey is largely an empirical matter, but, from a theoretical perspective, we have shown that there is good reason for the placebo effect to occur not only through the inhibition of the innate immune system but by the activation (or strengthening) of responses, depending on strategic information. Empirical data also appear to undermine Evans’ (2003, p. 134) suggestion that both placebo and nocebo effects are due to the suppression of the acute response. If positive expectations lead to the suppression of the acute response and negative expectations also lead to the suppression of the acute response, then patients could not be conditioned to respond in a positive (placebo) or negative (nocebo) manner with the same kind of stimulus. However, precisely this effect has been shown by pairing a stimulus with increased or decreased pain (Lorenz et al., 2005; Voudouris et al., 1989). Thus, there are both theoretical and empirical reasons to be dubious about Evans’ hypothesis.

From a theoretical perspective, we find a plethora of possible mechanisms and pressures for and against responses to placebos. This fits well with the conclusion of Benedetti, Carlino, and Pollo (2011) (from reviewing how placebos affect patients’ brains) that “there exists not a single, but many placebo effects, with different mechanisms” and that mechanisms of expectation, anxiety, and reward are all involved. As the workings of the brain and links with the healing systems of the body become better understood, many of the relevant mechanisms may be identified and perhaps then better controlled to our benefit (Walach & Jonas, 2004).

Clearly, much work remains to be done if the placebo effect is to be fully understood and utilized to work towards, as Jonas (2011) puts it, an optimal healing environment. We conclude by concurring with the words of Maier and Watkins (1998, p. 94) who state, in relation to the link between brain pathways and immune responses, “the function or adaptiveness of a set of mechanisms is often best appreciated in the context of the evolution of the mechanisms in question.”

Supplementary materials

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.evolhumbehav.2012.07.004>.

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