
Received: 20 September 2017
Accepted: 1 November 2017

Subject Areas:
developmental biology, evolution, health and disease and epidemiology

Keywords:
Caenorhabditis, Drosophila, nocebo effect, phenotypic plasticity, placebo effect

Author for correspondence:
Simon C. Harvey
e-mail: simon.harvey@canterbury.ac.uk

Evolutionary biology

Studying placebo effects in model organisms will help us understand them in humans

Simon C. Harvey and Chris J. Beedie
School of Human and Life Sciences, Canterbury Christ Church University, Canterbury CT1 1QU, UK

The placebo effect is widely recognized but important questions remain, for example whether the capacity to respond to a placebo is an evolved, and potentially ubiquitous trait, or an unpredictable side effect of another evolved process. Understanding this will determine the degree to which the physiology underlying placebo effects might be manipulated or harnessed to optimize medical treatments. We argue that placebo effects are cases of phenotypic plasticity where once predictable cues are now unpredictable. Importantly, this explains why placebo-like effects are observed in less complex organisms such as worms and flies. Further, this indicates that such species present significant opportunities to test hypotheses that would be ethically or pragmatically impossible in humans. This paradigm also suggests that data informative of human placebo effects pre-exist in studies of model organisms.

The non-living environment does not lie. What you see, feel or smell is what you get. It therefore pays to behave, develop and respond appropriately. If it is raining then use an umbrella, and if you know what the future has in store—perhaps because you can see nothing but black clouds—then you should prepare accordingly and take your umbrella. The key is the predictability; if a cue can be used to accurately assess what the future holds then responding appropriately is the best strategy. Predictable cues make it possible for organisms to evolve ways to modify their biology to maximize fitness. We see this in various types of phenotypic plasticity where single genotypes produce, via changes in development or physiology, different phenotypes in response to the environment [1]. Such responses range from short-term modifications of physiology to trans-generational effects that persist for many generations.

The key difference between a direct response to the environment and phenotypic plasticity is that the latter relies on the detection of a cue. Hence, an organism’s response to food might be a direct response to glucose in the bloodstream or an indirect, and phenotypically plastic, response arising from the smell of food. Phenotypic plasticity is ubiquitous. Organisms that are not responsive to environmental conditions were long ago out-competed by mutants that can accurately tailor their biology to the conditions they will experience. This ubiquity also suggests that phenotypic plasticity is evolutionarily ancient, and hence for metazoans will be grounded in the basics of the nervous and endocrine systems that control and regulate life.

Placebo effects, real responses to false cues, potentially stand at odds with the view that, for adaptive reasons, organisms respond only to true environmental cues. In placebo effects, phenotypic responses are seen in the absence of a biologically active agent. Most frequently associated with placebo control conditions in clinical trials of drugs, placebo effects actually represent a broader class of responses. Hence, ‘placebo’, ‘placebo control’ and ‘placebo effect’ refer respectively to sham/dummy treatments, a control process for a set of experimental
The role of dopamine in PD has long been recognized. Increasingly, the role of the same neurotransmitter is recognized in placebo responses in many scenarios. Benedetti and co-workers analysed the effects of a placebo in PD patients, specifically the effects on dopamine release in the striatum and the modification of neuronal activity in both the thalamus and subthalamic nuclei. In naive patients, a first placebo administration resulted in no change in neural or clinical measures. However, in patients previously administered the anti-Parkinson’s drug apomorphine, the number of repeated exposures to apomorphine predicted both the neural and clinical responses of patients to placebos. Critically, these effects were of the same magnitude as those elicited by the drug itself, suggesting a significant role for learning in the placebo response observed [2].

Placebo responses have also been observed in response to nutritional treatments that were presented, but not actually ingested [8]. For example, athletes who were not glucose deficient show performance increases when glucose is introduced to the mouth and then withdrawn without being ingested, this ‘glucose rinsing’ also resulting in clear neurophysiological responses. An analogous effect has been observed with caffeine rinsing [9]. These placebo effects can be understood in terms of the body responding to a predictable cue—detecting glucose or caffeine in the mouth normally indicates that it will soon be available in the intestine—by altering resource allocation.

If placebo responses seen in humans are the result of phenotypic plasticity, then placebo-like effects should be observable in other species—particularly in cases where the environment has been altered to disrupt its reliability. This is the case, and placebo-like effects are seen in a variety of model systems. Importantly, these examples are directly linked to fitness and rely on widely conserved signalling pathways.

Although not addressing placebo effects per se, Ader & Cohen [10] reported the conditioned immunosuppression of rats, whilst Sokolowsa et al. [11] demonstrated how a ‘probe dose’ of 10% of the normal dose of morphine triggered morphine-like effects, again in rates. However, placebo effects have to date been largely studied in humans, and when not in humans, in vertebrates. Little or no work to date has examined the possibility of placebo effects in simple invertebrate model organisms. However, it is plausible that such species experience similar responses.

In situations analogous to those seen in human experiments above, the perception of food matters in model organisms. A widespread means of extending lifespan is to reduce the overall calorific intake while preserving vitamin/mineral needs and avoiding starvation [12]. This lifespan-extending response to calorific or dietary restriction (DR) is seen widely in eukaryotes, and represents potentially the most viable non-pharmacological means of extending human life and health-span [13]. In the nematode worm Caenorhabditis elegans and the fruit fly Drosophila melanogaster, DR via a range of methods extends lifespan, with lifespan extensions of up to 50% observed in C. elegans. The regulation of the DR response is complex, but work in many systems demonstrates the involvement of insulin-like signalling and the highly-conserved mTOR (mechanistic target of rapamycin) pathway [14]. The life-extending effects of DR can however be blocked in both worms and flies by the smell of food alone [15,16]. Hence in situations where there is a mismatch between perception and reality, the standard DR response is not seen. In these cases,
the smell of food is therefore acting as a placebo, or more correctly what is termed a ‘necob’, a negative placebo response resulting in no lifespan extension.

Likewise, work on C. elegans shows that the neuronal perception of cold, rather than the system-wide effects of temperature on cellular function per se, is critical for cold stress survival. Low temperatures damage C. elegans and can kill them, with adult worms dying if they are exposed to temperatures lower than 5°C for prolonged periods [17,18]. This mortality can be greatly reduced, or even blocked, by habituation—worms exposed to low, but non-stressful temperatures are then highly resistant to subsequent acute cold stress [17,18]. Critically, this habituation is a result of the worms’ perception of temperature as opposed to the environmental reality, as disruption of specific neurons can replicate the habituation response in the absence of any temperature change [18,19]. The response, in this case the survival or not of a subsequent stress, is therefore based not on the temperature itself, but on the perception of temperature. This perception of temperature then feeds into the insulin-like signalling pathway [18,20], one of the core highly-conserved pathways that regulate nutrient allocation and lifespan in eukaryotes.

Hence, in both worms and flies we can observe placebo effects; there is an expectation of something and a subsequent set of changes that (should) optimize fitness under the expected condition. Critically though, the trigger is neuronal and hence can be separated from the actual environment that is being perceived or expected. The reality of environmental temperature is less positive than the signal, and it is the signal to which the organism responds; temperature sensation in a light- and pheromone-sensing neuron produces a robust effect on insulin signalling that controls experience-dependent temperature habituation. Likewise, the reality of reduced caloric intake is less critical to survival than the perception, suggesting a calorie-independent mechanism for lifespan extension by caloric restriction.

It is increasingly clear that the biology underpinning the placebo effect in humans could have significant clinical and societal impacts. One reason that we know so much about the neurophysiological response to placebo treatments among PD patients is that we are able to conduct research on real-time neuronal activity by using the electrodes implanted for the treatment of the disease itself via deep brain stimulation. PD might not be, as is suggested above, an exception, it might simply be the medical condition in humans in which it has been easiest to secure relevant data. In PD therefore, the response to placebos is less a problem for clinical trials and/or a unique opportunity for placebo effect researchers, but a potential clue to future treatments. Far from controlling for the placebo effect in clinical trials, scientists should in fact be seeking to understand and harness the biological processes that in many cases constitute to a substantial percentage of the overall effectiveness of the drug when compared to no-treatment. In short, this field of study could become important and impactful.

However, the study of placebo responding in humans is plagued by ethical, logistical and cost issues. Scenarios such as PD in which conventional medical treatment facilitates easy and reliable access to brain activity are rare. There are many questions that might be asked in humans with relative ease, for example we should be able to answer the question of whether all individuals respond similarly to non-ingested glucose mouthwash, arguably a direct neuronal prediction. But these are not the critical questions; placebo responses that require a cognitive prediction are more problematic to study. For example, those effects that result from anticipation or expectation of an effect, which might be moderated by a number of affective and cognitive factors such as environmental cues, emotion, memory, sensation and perception.

That placebo responses might be open to study and to systematic manipulation in simple model organisms could significantly enhance our understanding of the response in humans. We therefore propose five hypotheses that could be tested in animal models. (i) Placebo-like effects are ubiquitous responses to a set of standardized environmental cues across organisms (i.e. we would expect to see placebo effects to a similar type of cue across numerous organisms). (ii) Placebo-like responses will be limited to certain types of species-relevant environmental information such as temperature and energy availability (i.e. we would expect to see evolved responses in life-critical contexts). (iii) The capacity to respond to a novel placebo-like cue can be acquired through evolution within a species and/or learning within an organism. (iv) A threshold magnitude of information (e.g. temperature, energy availability) is required to elicit a placebo-like effect (this threshold is likely related to the significance of the information in critical survival terms). (v) The threshold magnitude for a placebo-like cue can be experimentally modified to enhance the dose–response relationship. Several of the above questions might be addressed by experimental evolution in model systems that should be able to test the levels of predictability required to maintain and modify responses. Critically, this paradigm also suggests that a wealth of data informative of human placebo effects already exists in studies of model organisms, and several of the hypotheses might be amenable to secondary analysis.

Data accessibility. This article has no additional data.

Author contributions. S.C.H. and C.J.B. drafted the manuscript and gave final approval for publication.

Competing interests. We have no competing interests.

Funding. S.C.H. is supported by the Leverhulme Trust (RPG-2016-040).

References


