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1 **Studying placebo effects in model organisms will help us understand them in**

2 **humans**

3

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5

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10 **Abstract**

11 The placebo effect is widely recognized, but important questions remain, for  
12 example whether the capacity to respond to a placebo is an evolved, and potentially  
13 ubiquitous trait, or an unpredictable side-effect of another evolved process.

14 Understanding this will determine the degree to which the physiology underlying  
15 placebo effects might be manipulated or harnessed to optimize medical treatments.

16 We argue that placebo effects are cases of phenotypic plasticity where once  
17 predictable cues are now unpredictable. Importantly, this explains why placebo-like  
18 effects are observed in less complex organisms such as worms and flies. Further, this  
19 indicates that such species present significant opportunities to test hypotheses that  
20 would be ethically or pragmatically impossible in humans. This paradigm also  
21 suggests that data informative of human placebo effects pre-exists in studies of  
22 model organisms.

23

24 **Keywords:** *Caenorhabditis*; *Drosophila*; nocebo effect; phenotypic plasticity, placebo  
25 effect.

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

38

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

49

50 Placebo effects, real responses to false cues, potentially stand at odds with the view  
51 that, for adaptive reasons, organisms respond only to true environmental cues. In  
52 placebo effects, phenotypic responses are seen in the absence of a biologically active  
53 agent. Most frequently associated with placebo control conditions in clinical trials of  
54 drugs, placebo effects actually represent a broader class of responses. Hence,  
55 ‘placebo’, ‘placebo control’ and ‘placebo effect’ refer respectively to sham/dummy  
56 treatments, a control process for a set of experimental artifacts, and legitimate  
57 neurophysiological events. Here we argue that what we currently recognize as the  
58 placebo effect is the result of humans as a species changing our environment such  
59 that cues that once accurately predicted the future environment no longer do so, *i.e.*  
60 we have made the environment lie. Placebo effects are not therefore artifacts or  
61 anomalies, but rather are examples of phenotypic plasticity that evolved to respond  
62 to what were once predictable cues in our environment.

63

64 Placebo effects result from a broad range of environmental stimuli that goes beyond  
65 traditional ideas of sham tablets only. In fact, the range of information that can  
66 influence the response to a sham treatment is broad and includes many  
67 environmental and psychosocial variables, such as verbally communicated  
68 expectations of an effect, previous experience of an effect (learning), manipulated  
69 learning (conditioning), context such as the ‘white coat effect’, and emotional  
70 responses such as hope and anxiety. All are manifest in responses via a number of  
71 discrete biological processes, including dopamine (2), opioid (3), and cannabinoid (4)  
72 pathways, with similar pathways often observed for both placebo effects and the  
73 drug they are mimicking (2, 5). This has collectively been described as “the new

74 physiology of the doctor-patient relationship” (6). This emergent viewpoint is  
75 shifting thinking around the placebo effect away from vague self-reported and  
76 subjective responses towards robust and directly measured biological events.  
77  
78 Arguably, if the placebo effect is *biologically real* in humans, it evolved for a purpose.  
79 An evolutionary case can be made for a response that can reduce the severity of  
80 subjective symptoms, thereby allowing the organism to better cope with survival-  
81 relevant situations. For example, if pain is tolerated for longer it might allow an  
82 individual to produce greater muscle force and therefore running speed and/or  
83 physical strength to capture prey or avoid predation, both potentially life-critical  
84 contexts.  
85  
86 However, whilst anecdote abounds, it is rare that placebo effects are reliably  
87 observed in any contemporary life-critical context in humans (although the ethical  
88 constraints of administering experimental placebo treatments in such contexts must  
89 be acknowledged). This appears slightly at odds with the idea that traits closely  
90 linked to fitness are likely to be the most responsive to environmental variation. This  
91 presents a paradox; if placebo effects occurred only in relation to subjective  
92 symptoms, no matter how unpleasant to the individual (e.g. pain, fatigue and  
93 depression), it is doubtful they would have been sufficiently responsive to natural  
94 selection for the placebo effect to earn its place in contemporary human biology.  
95  
96 There are exceptions. For example, Benedetti and co-workers (7) reported the  
97 effects of sham oxygen on pain, fatigue and performance among subjects

98 experiencing chronic exposure to severe hypoxia at 3,500m of altitude. Whilst the  
99 main outcome variable of the study was hypoxia induced pain, the ability of subjects  
100 to produce physical work at reduced perception of fatigue suggests that even life-  
101 critical functions such as oxygen supply are placebo responsive.

102

103 Another interesting exception is Parkinson's disease (PD), which although not life  
104 critical *per se*, reduces lifespan in the majority of patients. In fact, examining the  
105 table of contents of books on placebo effects, PD stands out from the list of  
106 otherwise ostensibly subjective conditions like the proverbial sore thumb.

107

108 The role of dopamine in PD has long been recognized. Increasingly the role of the  
109 same neurotransmitter is recognized in placebo responses in many scenarios.

110 Benedetti and co-workers analysed the effects of a placebo in PD patients,  
111 specifically the effects on dopamine release in the striatum and the modification of  
112 neuronal activity in both the thalamus and subthalamic nuclei. In naïve patients, a  
113 first placebo administration resulted in no change in neural or clinical measures.

114 However, in patients previously administered the anti-Parkinson's drug  
115 apomorphine, the number of repeated exposures to apomorphine predicted both  
116 the neural and clinical responses of patients to placebos. Critically, these effects  
117 were of the same magnitude as those elicited by the drug itself, suggesting a  
118 significant role for learning in the placebo response observed (2).

119

120 Placebo responses have also been observed in response to nutritional treatment  
121 that were presented, but not actually ingested (8). For example, athletes who were

122 not glucose deficient show performance increases when glucose is introduced to the  
123 mouth and then withdrawn without being ingested, this 'glucose rinsing' also  
124 resulting in clear neurophysiological responses. An analogous effect has been  
125 observed with caffeine rinsing (9) These placebo effects can be understood in terms  
126 of the body responding to a predictable cue – detecting glucose or caffeine in the  
127 mouth normally indicates that it will soon be available in the intestine – by altering  
128 resource allocation.

129

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

136

137 Although addressing placebo effects *per se*, Ader & Cohen (10) reported the  
138 conditioned immunosuppression of rats, a study that whilst Sokolowska et al (11)  
139 demonstrated how a 'probe dose' of 10% of the normal dose of morphine triggered  
140 morphine like effects, again in rates. However, placebo effects have to date been  
141 largely studies in humans, and when not in humans, in vertebrates. Little or no work  
142 to date has examined the possibility of placebo effects in simple invertebrate model  
143 organisms. However, it is plausible that such species experience similar responses.

144



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

161

162 Likewise, work on *C. elegans* shows that the neuronal perception of cold, rather than  
163 the system-wide effects of temperature on cellular function *per se*, are critical for  
164 cold stress survival. Low temperatures damage *C. elegans* and can kill them, with  
165 adult worms dying if they are exposed to temperatures lower than 5°C for prolonged  
166 periods (17, 18). This mortality can be greatly reduced, or even blocked, by  
167 habituation – worms exposed to low, but non-stressful, temperatures are then  
168 highly resistant to subsequent acute cold stress (17, 18). Critically, this habituation is

169 a result of worm's perception of temperature as opposed to the environmental  
170 reality, as disruption of specific neurons can replicate the habituation response in  
171 the absence of any temperature change (18, 19). The response, in this case the  
172 survival or not of a subsequent stress, is therefore based not on the temperature  
173 itself, but on the *perception of temperature*. This perception of temperature then  
174 feeds into the insulin-like signaling pathway (18, 20), one of the core highly-  
175 conserved pathways that regulates nutrient allocation and lifespan in eukaryotes.

176

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

187

188 It is increasingly clear that the biology underpinning the placebo effect in humans  
189 could have significant clinical and societal impacts. One reason that we know so  
190 much about the neurophysiological response to placebo treatments among PD  
191 patients is that we are able to conduct research on real-time neuronal activity by  
192 using the electrodes implanted for the treatment of the disease itself, deep brain

193 stimulation. PD might not be, as is suggested above, an exception, it might simply be  
194 the medical condition in humans in which it has been easiest to secure relevant data.  
195 In PD therefore, the response to placebos is less a problem for clinical trials and/or a  
196 unique opportunity for placebo effect researchers, but a potential clue to future  
197 treatments. Far from controlling for the placebo effect in clinical trials, scientists  
198 should in fact be seeking to understand and harness the biological processes that in  
199 many cases constitute to a substantial percentage of the overall effectiveness of the  
200 drug when compared to no-treatment. In short, this field of study could become  
201 important and impactful.

202

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

214

215 That placebo responses might be open to study and to systematic manipulation in  
216 simple model organisms could significantly enhance our understanding of the

217 response in humans. We therefore propose five hypotheses that could be tested in  
218 animal models: 1) Placebo-like effects are ubiquitous responses to a set of  
219 standardized environmental cues across organisms (*i.e.*, we would expect to see  
220 placebo effects to a similar type of cue across numerous organisms); 2) Placebo-like  
221 responses will be limited to certain types of species-relevant environmental  
222 information such as temperature and energy availability (*i.e.*, we would expect to  
223 see evolved responses in life-critical contexts); 3) The capacity to respond to a novel  
224 placebo-like cue can be acquired through evolution within a species and/or learning  
225 within an organism; 4) A threshold magnitude of information (*e.g.*, temperature,  
226 energy availability) is required to elicit a placebo-like effect (this threshold likely  
227 related to the significance of the information in critical survival terms); and 5) The  
228 threshold magnitude for a placebo-like cue can be experimentally modified to  
229 enhance the dose-response relationship. Several of the above questions might be  
230 addressed by experimental evolution in model systems which should be able to test  
231 the levels of predictability required to maintain and modify responses. Critically, this  
232 paradigm also suggests that a wealth of data informative of human placebo effects  
233 already exists in studies of model organisms, and several of the hypotheses might be  
234 amenable to secondary analysis.

235

#### 236 **Competing interests**

237 We have no competing interests.

238

#### 239 **Authors' contributions**

240 SH and CB drafted the manuscript and gave final approval for publication.

241

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244

245 **Data, code and materials**

246 No primary data are reported here.

247

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249

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