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## Zombie Ants and Fearless Mice: Parasites and the Brain

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*A truly successful parasite is commensal, living in amity with its host, or even giving it positive advantages... A parasite that regularly and inevitably kills its hosts cannot survive long, in the evolutionary sense, unless it multiplies with tremendous rapidity ... It is not pro-survival.*

Mr Spock, Star Trek 2 (cited in Moore 2002)

*I cannot persuade myself that a beneficent & omnipotent God would have designedly created the *Ichneumonidae* [parasitic wasps] with the express intention of their [larvae] feeding within the living bodies of caterpillars, or that a cat should play with mice.*  
Charles Darwin, in a letter to Professor Asa Gray, 22 May 1860.

### Introduction

We have long been morbidly fascinated by the thought that parasites could take over our bodies and, even worse, our minds. A parasite growing inside us is a common plot of science fiction including, of course, the horror film *Alien*. However, scientists are revealing that the imagination of science fiction writers is surpassed by the reality of the bizarre ways that parasites can exquisitely manipulate the behaviour of their hosts, in species as varied as ants, crickets, snails, fish, mice, and perhaps even humans (Hughes *et al.* 2012; Hughes & Libersat 2019; Moore 2002). As many as half the known species on earth are parasitic. The parasitic way of life has arisen repeatedly.

The essential challenge for each of these millions of parasite species is getting from one host to the next in their lifecycle (Hughes & Libersat 2019). One of the pioneers in the subject, Janice Moore, has noted that until the 1980s scientists tended not to study the evolutionary biology of parasites and their hosts, and in particular the ways that parasites might influence the behaviour of their hosts (Moore in Hughes *et al.* 2012). Part of the problem historically is that parasitology, the science of parasites, had been dominated by a focus on disease, not wider evolutionary issues. Many animal behaviourists also seemed to be deterred by the scary nature of complex parasite lifecycles, through multiple hosts, with a multitude of life stages each with a long name impossible to remember. Today parasite manipulation is one of the hottest topics in biology.

### Parasite takeover

I will start by introducing some of the many examples of host manipulation by parasites of a wide range of host animal species. Parasites are effectively neuroengineers, capable of controlling the central nervous system of their host, changing its behaviour (Hughes & Libersat 2019). The stories are extraordinary but *how* the parasite changes the behaviour of the host is usually a mystery. In some, however, we are discovering in detail how parasites manipulate their host's hormones, immune systems and nerves to take control (Adamo 2013). Later in the talk I will return to some of these intensively studied parasite-host systems to explore the ways parasites rule their hosts. One of the most intriguing aspects of behavioural manipulation is that parasites that live in the gut or body cavity of the host can still have an impact on behaviour. One mechanism may be by influencing the immune system, releasing molecules that are able to get through the blood-brain-barrier and thus impact behaviour.



Mice and rats infected by the brain parasite, *Toxoplasma gondii*, a protozoan, lose their healthy fear of cats and become easy prey (see later). This kind of manipulation is common for parasites that have complicated life-cycles with different hosts that require the parasitized host to be eaten by the next animal host in the cycle. It is in these parasite-host interactions that we are most likely to see behavioural manipulation of the host.

## **Tempting wriggling morsels**

A pulsating stripy maggot on a leaf caught the attention of a German naturalist in the 1830s. It turned out to be the tentacle of a snail. It pulsates at about 70 strokes a minute. But it was not what it seemed: the ‘maggot’ was the sporocyst stage of a parasite worm *Leucochloridium paradoxum* which migrates inside the snail it is infecting to fill the snail’s tentacle. In the tentacle it dances, attracting the attention of a bird to eat it; the bird is the next host that the worm needs to reach to complete its lifecycle. *Leucochloridium* has become a textbook example of parasite behavioural manipulation as the worm was said to cause the normally shade-seeking snail to climb high up a plant, on to a sunlit leaf, conspicuous to any bird looking for food. However, it was only in 2015 that two Polish scientists demonstrated that the worm sporocyst really does influence the snail’s behaviour in this way (Wesołowska & Wesołowski 2014). The pulsating visual show should attract birds but that step has not been critically tested.

## **Fake red ‘berries’**

In the rainforest canopy of Central and South America, a parasitic nematode worm which infects turtle ants needs to be eaten by its next host, a fruit-eating bird (Hughes *et al.* 2008). Living inside the turtle ant, the nematode turns the ant’s normally matt-black abdomen into a bright red swollen ‘berry’. The red ‘berry’ is full of nematode eggs. The nematode also changes the behaviour of the ants so that they continually wave their ‘berry’ abdomen in the air as they walk in the high canopy, increasing the chance that they will be spotted easily by a bird looking for fruit. The nematode also weakens the link of the ‘berry’ to the rest of the ant, making it an easy morsel to eat without danger from the strong defensive spines of the ant’s front half. After being eaten by the bird, the nematode eggs will be deposited in the bird’s faeces near another ant nest, ready to be carried into the nest by workers and infect ant larvae. The changes to the ant’s appearance and behaviour could be said to be the result of the nematode’s genes acting on the ant, an extended phenotype beyond the animal’s own phenotype as proposed by Richard Dawkins in his book *Extended Phenotype* (Dawkins 1982). Parasites provide compelling examples of extended phenotypes, with the parasites’ genes affecting their host’s behaviour in both dramatic and subtle ways.

## **Suicidal crickets**

When the parasite’s first host lives on land and the next host in the cycle lives in water, the parasite has a problem. Parasitic hairworms in crickets cause their hosts to make suicidal jumps into water, releasing the hairworms to find a partner. It has been suggested that the mechanism may be indirect, by the parasite causing the crickets to be more attracted to light and thus more likely to end up jumping into water. A nematode infesting ants similarly causes them to jump into water, where the nematode needs to be for the next stage of its lifecycle. The cricket and ant, infested by very different parasites, both of which cause their hosts to end up in water, are illustrations of the common pattern of convergence in parasite-host manipulations in different hosts and parasite combinations.

## **Zombie Ants**

Some parasites do not need a different host but still need to spread their infective stage far and wide to infect the next cohort of hosts. This is the case for a range of extraordinary fungi that attack insects. In the tropical rainforest in Thailand, as mid-day approaches, some carpenter ants leave their tasks high in the canopy, start to turn into zombies, staggering like horror film ‘mummies’, and walk down to the forest floor. These are ants infected with the fungus *Ophiocordyceps unilateralis* (Hughes *et al.* 2011). The ants climb onto the underside of a leaf about 25 cm above an ant trail. At noon the fungus causes the ant to grasp the mid-rib of the leaf with their mandibles in a ‘death grip’ before being killed by the fungal parasite. The fungus rapidly grows a mushroom from the dead ant’s head. The mushroom then releases a ‘snow’ of fungal spores onto the trail being walked on by other ants of this species of carpenter ant, infecting them. The fungal parasitism has been going a long time:



in fossils in Germany, rocks laid down in tropical times 48 million years ago contain fossil leaves with the characteristic leaf-rib scars left by ‘death-gripping’ ants. The fungus fills the body of the ant, growing deep into the muscles. The precise nature of how the fungus causes the behavioural changes in the ant is being investigated by Hughes and other scientists (Fredericksen *et al.* 2017).

## **Zombie Cockroaches: the wasp stings twice**

A very different kind of zombie results from a deadly ballet between a female parasitic jewel wasp *Ampulex compressa* and a large cockroach *Periplaneta americana* (Libersat & Gal 2014). If you have ever tried to catch a cockroach alive, you will be impressed. The wasp delivers precision doses of neurotoxins as it stings the head of the cockroach. The wasp’s larvae will feed on the living but immobilized host.

How does the wasp vanquish the cockroach? The wasp stings twice. The wasp’s first sting to the cockroach’s body (thorax) immobilizes it. The first sting temporarily knocks-out central motor circuits, blocking motor output to the cockroach’s forelegs for 1-2 minutes so it does not run away. This gives time for the wasp to make a second, longer sting into the cockroach’s head. The wasp uses sensors on its stinger to locate a particular part of the cockroach brain, the command centre responsible for initiating walking. The wasp precisely injects a cocktail of neurotoxins directly into it. After the second sting, the cockroach shows a peculiar behavioural change: instead of escaping, it spends 30 minutes grooming excessively, most likely because of an insect neurotransmitter (dopamine) in the venom. While the cockroach grooms, the wasp goes off to dig her burrow. A long-lasting effect of the head-sting is a lethargic state called hypokinesia which, while it does not paralyze the cockroach, prevents it from self-initiating walking.

The head-sting venoms contain opioid drugs which target neurons in the command centre specifically responsible for initiating and maintaining walking, without affecting the function of the central pattern generator motor centres. The wasp exploits the separation of central nervous systems into command centres and central pattern generation circuits so she can ‘walk’ the cockroach, too big for her to move by brute force, to her burrow. This is especially interesting for animal behaviour researchers because in most systems it is hard to ‘dissect’ behaviours in this way. The wasp venoms reveal the hidden neural circuits. The stepping circuit is a ‘central pattern generator’, a phenomenon first investigated by the German neuroethologist Erich von Holst. Central pattern generators have been found in animals of all kinds (Katz 2016). They produce rhythmic motor patterns such as walking in cockroaches, feeding in lobsters, courtship song in fruit flies, swimming in sea slugs, fish and tadpoles, and walking and breathing in mammals, including us. It means that we don’t have to consciously think about each step or each breath, they happen ‘automatically’.

The jewel wasp’s venoms have attracted interest from pharmacologists. The hypokinesia immobilization is temporary (if the cockroach was not being eaten alive by the wasp larva, it could walk away when the venom drug wears off). A newly found class of venom peptides, ampulexins (Moore *et al.* 2018), which target the cockroach’s dopamine circuits might one day provide leads for drugs that might be used to treat the dopamine-deficiency in Parkinson’s disease in humans. The jewel-wasp venom, like those of other parasitic wasps, contains an astonishing array of some 250 molecules, including ampulexins and precursors which are only activated once injected, hijacking control of the host’s brain by introducing a ‘storm’ of the host’s own neurochemicals (Arvidson *et al.* 2019).

The wasp does not always have its way. High-speed film of stinging attempts shows that the cockroach is able to kick back and escape about half the attacks, to live another day (Catania 2018).

## **Fearless mice**

Darwin mentioned cats and mice in his doubts about a beneficent God but it was worse than he thought: he didn’t know about the protozoan parasite *Toxoplasma gondii* which manipulates mice and rats to lose their fear of cats, the host in which the parasite can reproduce sexually (Adamo 2012; Vyas 2015). Early observations from the 1990s demonstrated that rodents infected with *Toxoplasma* showed behaviours likely to increase the chance of being eaten by a cat. These behaviours include greater activity, exploration of novel areas, but also a dramatic change in response to cat odour, including the odour of urine. Instead of being fearful, the male rodents may even be sexually attracted to approach their predator. The response was quite specific as the odours of non-feline predators still produced appropriate fear responses in the rodents. Most other behaviours such as feeding



and sexual behaviour were otherwise normal in infected rodents. The parasite forms cysts in the rodent's brain, in both glia and neurons. The research on toxoplasma's effects on its hosts is fascinating but not all scientists are convinced (Worth *et al.* 2013).

Humans can also be infected by toxoplasma, by picking up parasite eggs from cat faeces for example. About 15-85% of the adult human population is chronically infected. As in rodents, toxoplasma forms cysts in the human brain (but humans are a dead-end host as the parasite cannot sexually reproduce in us). A wide variety of effects of this infestation have been claimed, including greater aggressiveness and impulsivity (leading, in one study to an apparent increase in the likelihood of being knocked over by traffic). However, most studies are small and we should be cautious in the conclusions drawn (Martinez *et al.* 2018).

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## General reading

### Popular science books

- Simon, M (2018) *Plight of the Living Dead: What real-life zombies reveal about our world--and ourselves*. Penguin.  
Wyatt, TD (2017) *Animal behaviour: A very short introduction*. OUP  
Zimmer, C (2003) *Parasite Rex: Inside the bizarre world of nature's most dangerous creatures*. Arrow.  
Zuk, M (2008) *Riddled with Life: Friendly worms, ladybug sex, and the parasites that make us who we are*. Houghton

### Books and special collections of papers

- Special issue of *Integrative and Comparative Biology*, Vol 54, Issue 2. Parasitic manipulation of host phenotype, or how to make a zombie. Free, available at [www.academic.oup.com/icb/issue/54/2](http://www.academic.oup.com/icb/issue/54/2)  
Dawkins, R (1982) *The extended phenotype*. San Francisco, CA: WH Freeman.  
Hughes, DP, Brodeur, J & Thomas, F (eds.) (2012) *Host manipulation by parasites*. Oxford: Oxford University Press.  
Moore, J (2002) *Parasites and the behavior of animals*. New York: Oxford University Press.

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Adamo, SA (2013) Parasites: evolution's neurobiologists. *The Journal of Experimental Biology* 216: 3-10.  
Arvidson, R, et al (2019) Parasitoid jewel wasp mounts multipronged neurochemical attack to hijack a host brain. *Molecular & Cellular Proteomics* 18: 99.  
Catania, KC (2018) How not to be turned into a zombie. *Brain Behavior and Evolution* 92: 32-46.  
Fredericksen, MA, et al (2017) Three-dimensional visualization and a deep-learning model reveal complex fungal parasite networks in behaviorally manipulated ants. *Proceedings of the National Academy of Sciences of the United States of America* 114: 12590-12595.  
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Katz, PS (2016) Evolution of central pattern generators and rhythmic behaviours. *Phil Trans R Soc B Biol Sci* 371.  
Libersat, F & Gal, R (2014) Wasp voodoo rituals, venom-cocktails, and the zombification of cockroach hosts. *Integrative and Comparative Biology* 54: 129-142.  
Martinez, VO, de Mendonça Lima, FW, de Carvalho, CF & Menezes-Filho, JA (2018) *Toxoplasma gondii* infection and behavioral outcomes in humans: a systematic review. *Parasitology Research*: 1-7.  
Moore, E, Arvidson, R, Banks, C, Urenda, J, Duong, E, Mohammad, H & Adams, ME (2018) Ampulexins: A New Family of Peptides in Venom of the Emerald Jewel Wasp, *Ampulex compressa*. *Biochemistry*.  
Vyas, A (2015) Mechanisms of host behavioral change in *Toxoplasma gondii* rodent association. *PLoS Pathog* 11: e1004935.  
Wesołowska, W & Wesołowski, T (2014) Do *Leucochloridium* sporocysts manipulate the behaviour of their snail hosts? *Journal of Zoology* 292: 151-155.  
Worth, AR, Lymbery, AJ & Thompson, RCA (2013) Adaptive host manipulation by *Toxoplasma gondii*: fact or fiction? *Trends in Parasitology* 29: 150-155.