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Primer

Parasite manipulation of host behavior

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Some parasites have evolved the ability to precisely control the behavior of animals in ways that enhance the transmission of parasite genes into the next generation. This is the concept of the 'extended phenotype' first conceived by Richard Dawkins in 1982. It states that the behavior we observe in animals is due not only to the expression of their genes, but also to the genes of parasites infecting them. In such cases, the behavior is an extended phenotype of the parasite.

Examples of effective manipulation of animal behavior by parasites range from the zombie ant fungi (Figure 1), *Ophiocordyceps unilateralis*, which cause ants to bite leaves from where the fungal spores are released onto ant trails, to the apicomplexan, *Toxoplasma gondii*, which induces a strong and fatal attraction in mice to cats, which favors parasite transmission to its final host in these multi-host cycles. In these two examples, the manipulators (one a fungus, the other an apicomplexan) are both microbes. Manipulation of host behavior can be also induced by macro-parasites. For example, nematomorph worms induce crickets and other terrestrial insects to commit suicide in water to enable the exit of the parasite from its body into an aquatic environment. The worms can only complete their lifecycle and reproduce in water, which is why they induce such behavior. Such suicidal behavior in water has convergently evolved with mermithid nematodes, which also induce this behavior. Another notable group are baculoviruses that cause the induction of the 'summit disease' where infected caterpillars climb to the outer limbs of trees before being killed and liquefied to ensure virions are spread over the leaves that uninfected caterpillars will eventually eat. Other animals capable of manipulation are parasitic wasps that cause spiders to spin elaborate webs, while others elicit bodyguard behavior in the host for the protection of the wasp's cocoons.

These examples are just a small sample of the overall diversity of parasites known to manipulate host behavior in order to enhance their own transmission. In recent years, increased attention has been paid to parasite manipulation of host behavior, driven in part by exciting new examples and a better understanding of the critical role such manipulation plays in the life cycle of the parasite. Another reason for the increased focus is the realization that such parasites are essentially neuroengineers, capable of controlling the central nervous systems of the hosts they infect. As such, parasites that have evolved to control behavior represent independent experiments in evolution where genes in two organisms (host and parasite) both control the same brain.

Evolution of behavioral manipulation

Perhaps the most important question around parasites that control behavior is why such manipulation arose in the first instance. In the last 30 years, increased attention on the ecology and evolution of parasites in general has resulted in some very important insights that have caused a major rethink of their importance. We now know, for example, that parasitism is the most common life history trait to have evolved, having appeared during evolution more frequently than other modes of feeding, such as carnivory or herbivory. As many as half of all known species on Earth are parasitic. Ecological surveys, notably in estuaries, salt marshes and rainforests, are revealing the importance of parasites in food webs, energy flow and ecosystem functioning. Hence, parasitic taxa have arisen repeatedly to become hyperdiverse and are tightly enmeshed in food webs. The essential challenge for each of these many millions of species is achieving onward transmission from one host to another.

The vast majority of parasitic taxa are able to effectively transmit without evolving complex behavioral manipulation. In the normal course of animal behavior from resting to foraging to mating behaviors, parasites do manage to effectively transit from the current host to the next host without manipulating behavior. Where behaviors do change, it is often the

Figure 1. Zombie ant.
A dead *Camponotus atriceps* ant and the fungus *Ophiocordyceps unilateralis s.l.* growing from its head. The fungus has manipulated the ant to bite the leaf of a Brazilian rainforest plant before killing it's host in what is known as the zombie-ant manipulation (photo: David Hughes).

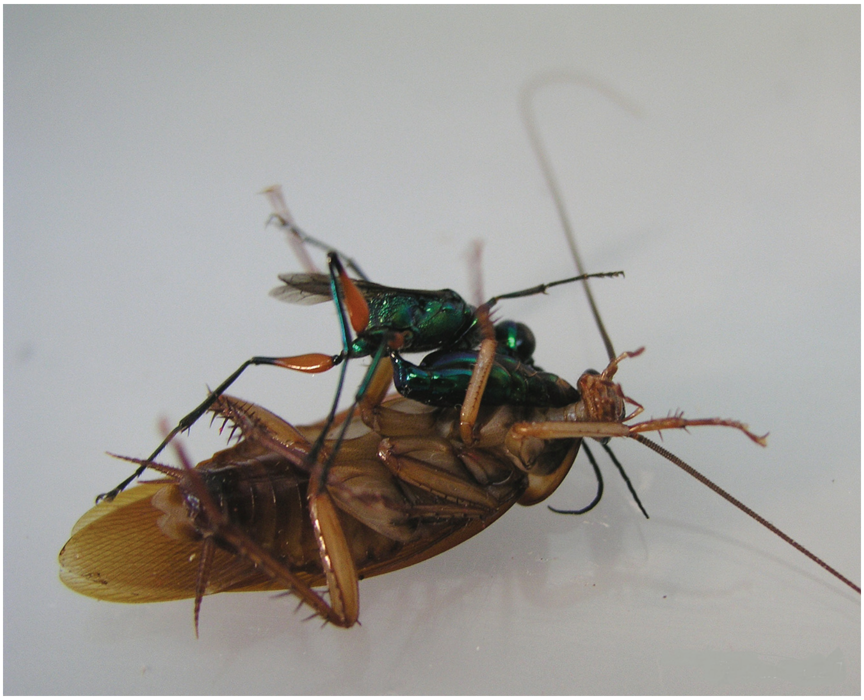

Figure 2. Direct brain injection.
The wasp *Ampulex compressa* stings the cockroach *Periplaneta americana* in the head and injects venom into the brain (photo: Frederic Libersat).

result of generalized sickness and not considered to be an adaptive change in host behavior driven by the parasite genes. So, what are the conditions that explain the evolution of the types of complex behavioral manipulation mentioned above? One important driver is the life history of the parasite. For example, the worms (nematodes and hairworms) that induce terrestrial crickets and ants to jump into water require aquatic larval insects (e.g. mosquito larvae) as a next host so parasite mating and egg laying occurs in water. These infected larval insects mature into adults that leave the water and die in the woods to be eaten by crickets or ants. This presents the parasite with a challenge to get back into the water. This challenge is solved by evolving the ability to coerce your terrestrial host to commit suicide in water. A similar argument has been made for parasites that transmit via predation. The parasite was likely only infecting the prey animal but then transitioned to a multi-host cycle as they began to infect the predators that continuously consume prey. With this scenario in mind, it was likely that parasites of prey animals that evolved to also exploit the predators that ate that prey did better than those who solely infected prey and had their lifecycle cut short by predators. Once predators became part of the lifecycle, any parasites that could reduce the natural tendency of prey to flee predators would have a higher fitness. Over time, behavioral manipulation became part of the lifecycle leading to the impressive phenomenon where male rodents infected with *Toxoplasma gondii* are sexually attracted to cats, approaching them, only to be eaten.

Another illustrative case study are the zombie ant fungi (Figure 1). These are microbial fungal parasites in the genus *Ophiocordyceps.* One species complex, *Ophiocordyceps unilateralis s.l.*, contains hundreds of species that infect carpenter and spiny ants (genera *Camponotus* and *Polyrhachis*, respectively). In what is one of the most complex examples of behavioral manipulation, ants infected by the fungus leave their colonies and bite into vegetation (leaves and twigs) that are above the trails of the colony. The adaptive significance is that fungi infecting insects require the host to be dead before the fungus grows out from the body to produce spores and achieve onward transmission. However, ants and other social insects have a suite of hygienic behaviors to reduce transmission inside the nest. Once a nestmate dies, other ants rapidly break up and remove the cadaver from the nest. To circumvent this problem, the fungi manipulate ants to leave the nest before death and die above the foraging trails that the colony must use each day to secure resources. The parasite has evolved behavioral manipulation to exploit a weak spot in the colony ensuring its transmission.

The ability to control a worker ant to leave its colony requires overcoming the strong ties the individual has to its siblings in the larger group because of kin selection and collective behavior. It is impressive enough that this has arisen once, but in fact colony desertion and subsequent elevation have arisen four times independently — twice among the fungi (*Pandora* and *Ophiocordyceps*), once in trematodes and once in an insect parasite of ants (Strepsipterans). The first three examples all cause the ants to bite the vegetation and the last just controls the ant to hold on to the vegetation. These examples demonstrate the importance of parasite life history. In both fungal genera, transmission is not possible inside the nest because these fungi only grow from cadavers a day or two after death. Because dead ants are quickly removed and disposed of, transmission would not occur. Thus, to transmit, the fungi control ants to bite vegetation over trails near the colony before killing the ant to produce spores from the cadaver. The trematodes infecting ants also induce this biting behavior but do not kill the ant. In this example the parasite has three hosts: snail, ant and cow. The infection passes on from snail to ant as the latter consume the slime balls of snails. The challenge to go from ant to cow is hard, as cows are vegetarian. The parasite thus controls its ant host to attach to grass. It doesn't kill the ant though, allowing it to repeatedly return to the nest to avoid high temperatures that would harm the parasite, returning to the grass blade in cooler temperatures. The final example, the strepsipteran, is a small male insect (the females infect crickets) that must emerge from the ant to fly, for its short five-hour life as an adult, to find a female who remains inside its cricket host. There, the male mates with the female through her head. The reason for causing the ant to leave the nest and ascend vegetation is to provide the fragile small male strepsipteran an unencumbered launch pad from which to begin its maiden (and terminal) flight. These examples again highlight the importance of life history when considering the parasites that control animal behavior.

The mechanisms of control

Although the why-question is important, perhaps most biologists are keen to understand how parasites manipulate behavior. How does one organism so precisely control the nervous system and behavior of another, only distantly related animal? The examples mentioned above are complex, stereotypical and often highly synchronized on a daily or seasonal level. In the case of parasite microbes, it is a remarkable feat of evolution by natural selection that the organism without the brain controls the one with the brain. How?

Only recently have concerted efforts focused on discovering how parasites control animal behavior. Given the broad taxonomic diversity of manipulators from virus through fungi, apicomplexans, worms and parasitic insects, it is to be expected that the mechanisms of manipulation are diverse. What is emerging from the multiple examples is that the neuro-ethological manipulation can occur with the parasite outside of the host body, inside the body cavity and inside the host brain. For example, the hairworms that induce cricket suicide change the brain's neurochemistry despite being in the abdomen of the host. By contrast, other parasites, such as the trematodes that induce ants to bite grass to be eaten by cows, enter the brain to encyst in specific regions, for instance the olfactory lobe. It is noteworthy that the same type of manipulation — inducing ants to bite leaves — is induced by the zombie ant fungi without the fungus entering the brain. Some parasitic wasps, such as *Ampulex compressa*, injects its manipulative venom directly into the brain of the host to induce a compliant and obeying zombie for the wasp offspring (Figure 2).

In some examples, the genetic basis of behavioral manipulation is being investigated. A very clear example comes from the virus that manipulates caterpillars to remain exposed on leaf surfaces where the virus will kill them before liquefying their body to spread virions across the leaf. Rather neatly, it was discovered that a single gene encoding an enzyme known as ecdysosteroid UDP-glycosyl-transferase (EGT) is responsible. The function of the enzyme is to inactivate insect host ecdysosteroid hormones preventing insect moulting on the tree trunk. Furthermore, it keeps the insect feeding out on the leaves where it will die. Where parasites have bigger and more complex genomes, identifying which genes are critical to manipulation is more difficult, requiring multiple independent lines of evidence.

Transcriptomics, metabolomics, proteomics and histological studies are all useful approaches to complement genomic studies into the mechanisms of behavioral manipulation. Currently though, we only have a scattershot view with insights obtained from different systems. For example, we know from proteomic studies that WNT proteins are upregulated in the head of infected crickets at the time of behavioral manipulation when they jump into water. Multiple studies using metabolomics and biogenic amine profiling have shown that in diverse hosts infected by diverse taxa of parasites, changes in brain chemistry are evident. In one striking study, where caterpillars control ant behavior inducing them to be protective bodyguards, the changes in biogenic amines (notably dopamine) occurred simply by the parasite feeding its secretions to the attendant ants, reducing levels of dopamine in the ant brains. An exciting development is micron level histology to examine the interface between parasite and host. In the zombie ant fungi, for example, this has revealed that the microbes arrange themselves in a 3D network surrounding the muscle of the host which they both control and consume as they manipulate the ant's behavior.

Zombification by the wasp *Ampulex* involves a venom comprising different proteins, many of which could affect synaptic efficacy. The wasp might exert control over cockroach behavior through molecular cross-talk between venom components and molecular targets in the host brain, leading to broad-based alteration of synaptic efficacy and behavioral changes that promote successful development of the wasp progeny.

Conclusion

We are really just at the beginning of our exploration into parasites that have evolved adaptive manipulation of host behavior as a mechanism to move around the environment. There is something both unnerving and entrancing in the spectacle of an animal moving against its instinct to the drumbeat of a parasite inside its body. For biologists, the fact that such machinations have evolved repeatedly in the natural world offers us great opportunities to understand the why and how of manipulation and include such impressive adaptations into our framework for understanding evolution by natural selection. It is fair to say that evolutionary biologists have not considered parasite extended phenotypes as much as they could have. This is despite some noble beginnings as Alfred Russel Wallace, the co-discoverer of natural selection, was the first scientist to collect zombie ants in 1859. Now, with the exciting new tools that can be deployed for non-model organisms we are poised to fully understand just how parasite manipulation of host behavior occurs.

FURTHER READING

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