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Biology

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Scientific article for use with Question 7.

Fearless Mice and Insect Zombies

Protozoa Could Be Controlling Your Brain

1. The ancient debate surrounding the existence of free will appears unresolvable, a metaphysical question that generates much heat yet little light. Common sense and volumes of psychological and neuroscientific research reveal, however, that we are less free than we think we are. Our genes, our upbringing and our environment influence our behaviors in ways that often escape conscious control. Understanding this influence, the advertisement industry spent approximately half a trillion dollars worldwide in 2010 to shape the buying decisions of consumers. And extreme dictatorships, such as that in North Korea, remain in power through the effective use of insidious and all-pervasive forms of propaganda. Yet nothing approaches the perfidy of the one-celled organism *Toxoplasma gondii*, one of the most widespread of all parasitic protozoa. It takes over the brain of its host and makes it do things, even actions that will cause it to die, in the service of this nasty hitchhiker. It sounds like a cheesy Hollywood horror flick, except that it is for real.

2. We know that illness in general can slow us down, incapacitate us and, in the worst case, kill us. Yet this organism is much more specific. Natural selection has given rise to pathogens that infiltrate the nervous system and change that system's wiring to achieve its ultimate purpose, replication—like a computer virus that reprograms an infected machine.

3. Such is the case with *T. gondii*. It sexually reproduces only in the intestines of cats yet can maintain itself indefinitely in any warm-blooded animal. Infected cats shed millions of their oocysts in their feces. Taken up by all kinds of animals, including dogs, rodents and humans, they infect muscle and the brain to escape attacks by the host's immune system. Hidden away, they remain dormant as cysts, surrounding themselves with a tough cell wall. Yet this quiet stage of infection, called toxoplasmosis, is deceptive. Violating all rules of good hospitality, these invaders make the host's brain do things counterproductive to its own survival.

4. Toxoplasmosis has been most thoroughly studied in rats and mice. Both species have a deep-seated, innate fear of cats for obvious reasons. Spray a bit of cat urine into a corner, and the rodent will avoid this location, well, like the plague. In contrast, an infected animal loses its innate fear of cats. By some measures, it even appears to be mildly attracted to the smell of felines. This is an unfortunate turn of events for the rodent, because it is now more likely to be successfully hunted by a cat. On the other hand, this is a great deal for *T. gondii*. When the cat devours the sick critter and its contaminated brain, *T. gondii* moves into its final host, where it reproduces, completing its life cycle. Not quite what the romantics have in mind when they write about "the circle of life"!

5. The behavioral manipulation induced by *T. gondii* is quite specific. The infected rodent doesn't look sick; its weight is normal; it moves about normally, possibly a bit more frantically than other mice; it grooms itself; and it interacts routinely with its conspecifics. Think how different this case is from what happens in rabies, another nasty infection. The animal loses its instinctual shyness, aggressively attacking others (the proverbial mad dog), thereby spreading the rabies virus through its bite. But because *T. gondii* can reproduce only in felines, it wants its host to be eaten by cats, not by just any carnivore. And because cats hunt live prey and do not eat carrion, *T. gondii* must not immediately kill its temporary host.

Rodents Aren't Superheroes

6. How does *T. gondii* effect its insidious changes in the host? Experiments by Joanne P. Webster of Imperial College London, Robert Sapolsky of Stanford University and others have shown that infected rats or mice do not turn into the murine equivalent of Siegfried, the hero of Wagner's Ring who knew no fear. No, they still avoid open spaces, remain nocturnal creatures, retain their aversion to the urine of other predators and learn to fear a tone associated with a foot shock. Might the protozoa have stunted their smell? After all, if they cannot smell anything anymore, they would not know how to avoid places smelling of cat urine. But infected mice still avoid food if it smells different—an aversion that arose partly because for centuries humans have been trying to control rodents by poison. The infected mice also respond appropriately to the smell of their littermates.

7. Clues about how the parasites affect the animal come from several observations. First, the density of cysts in the amygdala is almost double that in other brain structures involved in odor perception. Parts of the amygdala have been linked to anxiety and the sensation of fear. Second, the genome of *T. gondii* contains two genes related to mammalian genes involved in the regulation of dopamine, the molecule associated with reward and pleasure signals in the brain, including in ours. So perhaps the creepy protozoa makes suicidal activities, such as hanging around places frequented by cats, feel more pleasurable for the infected rodent?

8. What elevates this vignette about evolution and life in the wild to epic proportions for humanity is that about a tenth of the U.S. population is infected by *T. gondii* (in some countries, such as France, the infection rate is seven to eight times higher, possibly because of the widespread consumption of uncooked and undercooked meat). Human toxoplasmosis is usually considered to be symptom-free (what doctors refer to as asymptomatic). Exceptions are patients with a weakened immune system and the unborn (hence the need for pregnant women to avoid cleaning cat-litter boxes).

Parasite makes mice lose fear of cats permanently

9. People with schizophrenia are more likely than the general population to have been infected with *Toxoplasma*, and medications used to treat schizophrenia may work in part by inhibiting the pathogen's replication.

10. Schizophrenia is thought to involve excess activity of the neurotransmitter dopamine in the brain. This has bolstered one possible explanation for *Toxoplasma's* behavioural effect: the parasite establishes persistent infections by means of microscopic cysts that grow slowly in brain cells. It can increase those cells' production of dopamine, which could significantly alter their function. Most other suggested mechanisms also rely on the presence of cysts.

Persistent trait

11. Research on *Toxoplasma* has mainly used the North American Type II strain. Wendy Ingram, a molecular cell biologist at the University of California, Berkeley, and her colleagues investigated the effects of two other major strains, Type I and Type III, on mouse behaviour. They found that within three weeks of infection with either strain, mice lost all fear of cat odour —showing that the behavioural shift is a general trait of *Toxoplasma*.

Mice infected with toxoplasmosis lose their instinctive fear for the smell of cats—and the parasite's effects may be permanent.
Wendy Ingram/Adrienne Greene

12. More surprising was the situation four months after infection. The Type I pathogen that the researchers used had been genetically modified to provoke an effective immune response, allowing the mice to overcome the infection. After four months, it was undetectable in the mouse brain, indicating that no more than 200 parasite cells remained. "We actually expected that Type I wouldn't be able to form cysts, and therefore wouldn't be able to cause the behaviour change," explains Ingram.

13. But that was not the case: the mice remained as unperturbed by cat odour as they had been at three weeks. "Long after we lose the ability to see it in the brain, we still see its behavioural effect," says geneticist Michael Eisen, also at Berkeley.

14. This suggests that the behavioural change could be due to a specific, hard-wired alteration in brain structure, which is generated before cysts form and cannot be reversed. The finding casts doubt on theories that cysts or dopamine cause the behavioural changes of *Toxoplasma* infections.

Mind and matter

15. Joanne Webster highlights the worrying implication that if the behavioural changes of *Toxoplasma*-caused schizophrenia are fixed, treatments that are intended to target cysts might have no effect. However, she notes that mice are not the best model for *Toxoplasma* infection in humans, because they experience more severe symptoms and complications. Webster uses rats in her research.

16. Ingram says that her group is using mice because of the better genetic tools available to help to uncover the mechanism behind behavioural changes. However, she is not yet convinced of the link between *Toxoplasma* infections and schizophrenia. Her findings may actually weaken that link, because they seem to provide evidence against the dopamine hypothesis.

17. She notes that *Toxoplasma* infections are common around the world, but their prevalence varies by region, whereas schizophrenia rates are consistent at around 1% globally. Furthermore, it is possible that the increased rate of *Toxoplasma* infections among people with schizophrenia is caused by them being more likely to pick up the parasite, rather than by the parasite causing schizophrenia.

How To Make A Zombie Cockroach

18. Researchers have worked out the neurological trick used by a species of wasp to turn cockroaches into 'zombie slaves'. The discovery explains why, once stung, cockroaches can be led by a much smaller master towards certain death. Researchers have proven their theory by replicating the effect, and by using an antidote injection to release the cockroaches from their zombie state.

19. Zombie insects might sound like the B-movie plot device from heaven (or hell, depending on your cinematic preferences). But to the emerald cockroach wasp (*Ampulex compressa*), they're a tried and tested way to provide food for their hungry larvae.

Sting in the brain: a toxic injection renders cockroaches submissive.
Libersat

20. The wasp, which lives in tropical regions of Africa, India and the Pacific Islands, relies on cockroaches for its grisly life cycle. But unlike many venomous predators, which paralyse their victims before eating them or dragging them back to their lair, the wasp's sting leaves the cockroach able to walk, but unable to initiate its own movement.

21. The wasp then grabs the cockroach's antenna and leads it back to the nest. The cockroach walks "like a dog on a leash", says Frederic Libersat of Ben-Gurion University of the Negev in Israel, who led the research and has previously described the wasps' behaviour in detail. Once home, the merciless wasp lays an egg on the docile cockroach's belly, and the larva, once hatched, devours the hapless insect.

Toxic cocktail

22. But although the zombie cockroach phenomenon has been well documented, Libersat and his colleagues still didn't know how exactly the wasps pull off the trick. "We know the wasp injects a rich cocktail of toxins," Libersat says. But it was unclear how the venom could alter the victims' behaviour so subtly.

23. The researchers knew that the wasps tend to sting the cockroaches once to subdue them, then adminster another, more precise sting right into their victim's brain. So they suspected that the venom might work by blocking a key chemical messenger.

24. The results of their latest experiment, published in the *Journal of Experimental Biology*, support that theory. The researchers report that the venom works to block a neurotransmitter called octopamine, which is involved in preparations to execute complex behaviours such as walking.

25. Libersat and his team found that they could restore spontaneous walking behaviour in stung cockroaches by giving them a compound that reactivates octopamine receptors in the insects' central nervous system. This, they conclude, means that the wasp venom probably blocks these receptors.

26. What's more, the researchers discovered that injecting unstung cockroaches with a compound that blocks these receptors produced a similar effect to that of the venom.

Undead-End: Fungus That Controls Zombie-Ants Has Own Fungal Stalker

27. An unsuspecting worker ant in Brazil's rainforest leaves its nest one morning. But instead of following the well-worn treetop paths of its nest mates, this ant stumbles along clumsily, walking in aimless circles, convulsing from time to time.

28. At high noon, as if programmed, the ant plunges its mandibles into the juicy main vein of a leaf and soon dies. Within days the stem of a fungus sprouts from the dead ant's head. After growing a stalk, the fungus casts spores to the ground below, where they can be picked up by other passing ants.

29. This strange cycle of undead life and death has been well documented and has earned the culprit the moniker: "zombie-ant" fungus—even in the scientific literature. But scientists are just learning the intricacies of this interplay between the *Ophiocordyceps* parasitic fungus and the Camponotini carpenter ants that it infects. Fossil evidence implies that this zombifying infection might have been happening for at least 48 million years. Recent research also suggests that different species of the fungus might specialize to infect different groups of ants across the globe. And close examination of the infected ant corpses has revealed an even newer level of spooky savagery—other fungi often parasitize the zombie-ant fungus parasite itself.

ZOMBIE-ANT FUNGUS FEAST: New research is uncovering how zombie-ant fungus might control its hosts. But this parasite also has its own fungal threats.
Image: Wikimedia Commons/David Hughes/ Maj-Britt Pontoppidan/PLoS ONE

30. "We have advanced a great deal in understanding how the fungus controls ant behavior," David Hughes, an assistant professor of entomology and biology at The Pennsylvania State University, says. Every few months scientists are discovering yet another peculiar trait that, added together, make this parasite one of the most insidious infections—or perhaps that honor goes to the parasite that ultimately kills the killer parasite.

Deadly infection

31. This clever *Ophiocordyceps* fungus depends on ants to reproduce and spread, but it has found an abundant host animal. As Hughes notes, ants have been incredibly successful, currently comprising an estimated half of all insect biomass worldwide.

32. One of the first clues that a tropical carpenter ant has become infected with *Ophiocordyceps* is that it will leave the dry tree canopy and descend to the humid forest floor, staggering over debris and plants. "Infected ants behave as zombies," Hughes and his colleagues wrote in a 2011 *BMC Ecology* paper describing some of the latest findings. The ant will walk randomly, displaying "convulsions that make them fall down and thus preclude them from returning to the canopy," they noted, comparing the stumbling gait with a "drunkard's walk."

33. The clumsiness cannot, however, be blamed on the ant. "While the manipulated individual may look like an ant, it represents a fungal genome expressing fungal behavior through the body of an ant," the researchers noted in the paper. Hence the zombie designation.

34. Evans suggests that a nerve toxin spurred on by the fungus is at least partly to blame, "judging from the uncoordinated movements and hyperactivity of the ants infected," he says. Ants that have been dissected at this stage of infection reveal heads already full of fungal cells.

35. Eventually, an affected ant will stop on the underside of one leaf, roughly 25 centimeters from the forest floor, and clamp down on the leaf's main vein. (This position appears to be optimal for the fungus's later stage in which it ejects spores onto the soil directly below.) Biting leaves is not normal ant behavior. The zombies' bites are synchronized near noon (possibly cued by clock genes in the fungus) and usually occur in a north-northwestern orientation.

36. Scientists have found that the fungus also triggers atrophy in its victim's muscles—specifically those around its mandibles. This atrophy is prompted by metabolites that purge the muscle cells of mitochondria and sarcoplasmic reticulum (which provide energy and signals), according to the *BMC Ecology* research. Perhaps counterintuitively, when the infected ant bites onto the leaf vein in its so-called "death grip" this atrophy causes it to have lockjaw, leaving it there to die. This seemingly small detail is crucial to the fungus's success. "Without the death grip," Hughes explains, "the ant would fall to the ground," destroying the launching point for the fungus's spores.

37. By that stage, cells from the fungus have grown even more numerous in the ant's body. They have proliferated around the ant's brain and between surrounding muscle fibers but have not entered the brain, glands or muscles, making the manipulation all the more amazing.

38. Ants appear to die within six hours after their final bite. About two to three days later a fungal stalk will start to emerge from the back of the ant's head. After maturing over the course of weeks the stalk's head will shoot spores onto the soil below. Researchers have also discovered that this relatively slow-growing fungus can have its main stem broken off and regrow it later. Foraging worker ants can unwittingly pick up spores as they pass by.

39. The death of an ant outside of its colony and subsequent growth of the fungal stalk might be key adaptations of the fungus, researchers have hazarded. "Ants quickly remove dead nest mates so that dying in the nest would not allow sufficient time for stalk development and spore release" before the dead host ant was ejected, Hughes and his colleagues noted in their *BMC Ecology* paper.

40. The doomed ants do not wander too far afield, often ending up within meters of their familiar territory. And large groups of dead ants are commonly found near colonies. These graveyards can contain anywhere from 50 to hundreds of corpses, says Sandra Andersen, currently of the University of Oxford's Department of Zoology, who has studied many of these sites. If a nearby colony is new, there is not likely to be as large a graveyard—yet.

41. Ants' complex and large social groups are thought to be one of the keys to their global abundance. The fungus has capitalized on ants' social behavior. "Sociality can be thought of as evolution's winning lottery ticket," Hughes says. But "this zombie fungus is natural selection's tax man."

42. The zombie fungus, however, cannot live without the winning ants' continued success. It appears to be an obligate parasite, requiring a specific, local species of ant for it to inhabit, grow and propagate its spores.

A specialized but global threat

43. The ants best known for getting zombified by the *Ophiocordyceps* fungus are tree-dwelling carpenter ants found in Brazil and Thailand, but the fungus is thought to be broadly distributed in tropical areas around the globe. In fact, the full range of strange behavior—observed in Sulawesi, Indonesia—was first described in the scientific literature by Alfred Russell Wallace in the 19th century.

44. Although many ants in different areas are similarly infected and dispatched in this strange way, the species of fungus infecting them is not at all the same. "Instead of one variable species, there may be tens or even hundreds," says Harry Evans, a principal scientific officer at the Center for Agricultural Bioscience International. In a 2011 paper published in *PLoS ONE*, Evans, Hughes and Simon Elliot (of the Department of Animal Biology at the Federal University of Vicosa in Brazil) described four new species of the *Ophiocordyceps* fungus that were found in just a small section of rainforest in Brazil's southeastern state of Minas Gerais. Each of these species was associated with a different *Camponotus* ant species, denoting a high degree of specialization.

45. This hint at such vast diversity and specialization also contains broader implications for assumptions about fungus numbers in general. "We may need to increase fungal diversity estimates by these sorts of factors," Evans notes.

Ancient scourge

46. The zombifying fungus's vast geographic distribution also hints at the possibility that it has been possessing ants at least since before many of the continents split apart. But these delicate organisms have not been discovered in fossils. Other examples of parasitism have been found preserved in amber dating back 150 million years, and they reveal the parasite and host as a common arrangement—but not any evidence of actual behavior manipulation.

47. Research published in *Biology Letters* in 2010 describes a 48-million-year-old fossilized leaf from Germany that bears the distinctive scars of a bite from an ant's mandible on its main vein. The researchers, led by Hughes, describe the find as perhaps "the first example of behavioral manipulation in the fossil record." During that time period the region of Germany would have been similar in climate to the areas of Thailand where contemporary zombie-ant fungus has been documented.

A parasite's parasite

48. The zombie-ant fungus is not the end of the parasitizing line, however—it meets its own death at the work of yet another parasite.

49. Andersen and her colleagues have found that a different breed of fungi grow over the ant corpse *and* the emerging fungus stalk. By covering the original fungus and its stalk, this secondary fungus—or hyperparasite—effectively prevents the zombie-ant fungus from ejecting its spores. "It looks like they completely sterilize it," Andersen says of the second-level parasite.

50. Even these hyperparasites seem to be specialized for growing on specific parasitizing fungi. "They're not really growing on anything else" in the area, Andersen says. This makes the hyperparasite another obligate parasite, which depends on the zombie-ant fungus, which depends, in turn, on the carpenter ant colony. "Once you're very successful, something else will take advantage of it," she notes. "It's really a little ecosystem in its own [right]."

51. The zombie-ant fungus's doom, of course, is little consolation for the infected ant. But the castration of the ant-killing fungus means that it will not go on to turn other local ants into zombies. This hobble might, in fact, be one of the reasons the zombie-ant fungus has been so successful over the long term. As a deadly infection, it could severely damage an ant colony. But, if another parasite renders more than half of its mature spores infertile (and more still failing to reproduce due to other interferences), that creates a sort of equilibrium with a colony. According to the research by Andersen and her colleagues (published in May 2012 in *PLoS ONE*), the actual reproduction rate for each mature zombie-ant fungus organism is a little more than one new mature organism, thus allowing the species and local population to sustain itself as long as there are ants nearby to infect.

52. In addition to the fungicidal fungi, scientists have also seen small bugs laying their eggs in the infected ant corpse, where their larvae can then eat the growing fungus. These bugs include specialized gall midges (in the Cecidomyiidae family) and a species that appears to be new to science, Hughes says. "It seems their entire nutrition comes from eating the fungus that manipulates ant behavior."

53. Are such hyper-specialized hyperparasites a freak occurrence? Apparently not: "We have found it all over the world, and most [ant] cadavers have hyperparasites exploiting the zombie-ant fungus at some stage," Hughes notes. And Anderson suspects "the more people study parasites, the more examples we'll find." Even if they are hiding in darker corners.

54. Indeed, Evans, Hughes and others continue to hunt for more bizarre, opportunistic organisms. Evans is collecting more zombie ants in Brazil, as part of what he and Hughes have unofficially dubbed the "World Ant Tour." The hunt may be a race against time, however. When Evans returned to a field site in Ghana where he had found different genera of possessed ants in the 1970s, "we could not find any of the forest sites," he says. They were "all cleared, gone and largely invaded by exotic weeds. In fact, the same thing occurs every time I revisit the places that I have worked over the past 40-plus years," he notes.

55. Learning about zombie-ant funguses is not simply an exercise in outré science. As Hughes notes, discovering more about both the fungus and the ant behavior and signaling dynamics could add to research about pest control for agriculture. "Lots of the pure discoveries we make have great import for food security and the challenges farmers in tropical countries face from insects and fungi that infect their crops," he notes. But garnering such knowledge will require more zombie corpses to collect and study.

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