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Bugs in the Brain

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LIKE MOST SCIENTISTS, I attend professional meetings every now and then, one of them being the annual meeting of the Society for Neuroscience, an organization of most of the earth's brain researchers. This is one of the more intellectually assaulting experiences you can imagine. About 28,000 of us science nerds jam into a single convention center. After a while, this togetherness can make you feel pretty nutty: For an entire week, go into any restaurant, elevator, or bathroom, and the folks standing next to you will be having some animated discussion about squid axons. The process of finding out about the science itself is no easier. The meeting has 14,000 lectures and posters, a completely overwhelming amount of information. Of the subset of those posters that are essential for you to check, a bunch remain inaccessible because of the enthusiastic crowds in front of them, one turns out to be in a language you don't even recognize, and another inevitably reports every experiment you planned to do for the next five years. Amid it all lurks the shared realization that despite zillions of us slaving away at the subject, we still know squat about how the brain works.

My own low point at the conference came one afternoon as I sat on the steps of the convention center, bludgeoned by information and a general sense of ignorance. My eyes focused on a stagnant, murky puddle of water by the curb, and I realized that some microscopic bug festering in there probably knew more about the brain than all of us neuroscientists combined.

My demoralized insight stemmed from a recent extraordinary paper about how certain parasites control the brain of their host.

Most of us know that bacteria, protozoa, and viruses have astonishingly sophisticated ways of using animal bodies for their own purposes. They hijack our cells, our energy, and our lifestyles so they can thrive. But in many ways, the most dazzling and fiendish thing that such parasites have evolved — and the subject that occupied my musings that day — is their ability to change a host's behavior for their own ends. Some textbook examples involve ectoparasites, organisms that colonize the surface of the body. For instance, certain mites of the genus *Antennophorus* ride on the backs of ants and, by stroking an ant's mouthparts, can trigger a reflex that culminates in the ant's disgorging food for the mite to feed on. A species of pinworm of the genus *Syphacia* lays eggs on a rodent's skin, the eggs secrete a substance that causes itchiness, the rodent grooms the itchy spot with its teeth, the eggs get ingested in the process, and once inside the rodent they happily hatch.

These behavioral changes are essentially brought about by annoying a host into acting in a way beneficial to the interlopers. But some parasites actually alter the function of the nervous system itself. Sometimes they achieve this change indirectly, by manipulating hormones that affect the nervous system. There are barnacles (*Saccalina granifera*), a form of crustacean, found in Australia that attach to male sand crabs and secrete a feminizing hormone that induces maternal behavior. The zombified crabs then migrate out to sea with brooding females and make depressions in the sand ideal for dispersing larvae. The males, naturally, won't be releasing any. But the barnacles will. And if a barnacle infects a female crab, it induces the same behavior — after atrophying the female's ovaries, a practice called parasitic castration.

Bizarre as these cases are, at least the organisms stay outside the brain. Yet a few do manage to get inside. These are microscopic ones, mostly viruses rather than relatively gargantuan creatures like mites, pinworms, and barnacles. Once one of these tiny parasites is inside the brain, it remains fairly sheltered from immune attack, and it can go to work diverting neural machinery to its own advantage.

The rabies virus is one such parasite. Although the actions of this virus have been recognized for centuries, no one I know of has framed them in the neurobiological manner I'm about to. There are lots of ways rabies could have evolved to move between hosts.

The virus didn't have to go anywhere near the brain. It could have devised a trick similar to the one employed by the agents that cause nose colds — namely, to irritate nasal-passage nerve endings, causing the host to sneeze and spritz viral replicates all over, say, the person sitting in front of him or her at the movies. Or the virus could have induced an insatiable desire to lick someone or some animal, thereby passing on virus shed into the saliva. Instead, as we all know, rabies can cause its host to become aggressive so the virus can jump into another host via saliva that gets into the wounds.

Just think about this. Scads of neurobiologists study the neural basis of aggression: the pathways of the brain that are involved, the relevant neurotransmitters, the interactions between genes and environment, modulation by hormones, and so on. Aggression has spawned conferences, doctoral theses, petty academic squabbles, nasty tenure disputes, the works. Yet all along, the rabies virus has "known" just which neurons to infect to make a victim rabid. And as far as I am aware, no neuroscientist has studied rabies specifically to understand the neurobiology of aggression.

Despite how impressive these viral effects are, there is still room for improvement. That is because of the parasite's nonspecificity. If you are a rabid animal, you might bite one of the few creatures that rabies does not replicate well in, such as a rabbit. So although the behavioral effects of infecting the brain are quite dazzling, if the parasite's impact is too broad, it can wind up in a dead-end host.

Which brings us to a beautifully specific case of brain control and the paper I mentioned earlier, by Manuel Berdoy and his colleagues at the University of Oxford. Berdoy and his associates study a parasite called *Toxoplasma gondii*. In a toxoplasmic utopia, life consists of a two-host sequence involving rodents and cats. The protozoan gets ingested by a rodent, in which it forms cysts throughout the body, particularly in the brain. The rodent gets eaten by a cat, in which the toxoplasma organism reproduces. The cat sheds the parasite in its feces, which, in one of those circles of life, is nibbled by rodents. The whole scenario hinges on specificity: Cats are the only species in which toxoplasma can sexually reproduce and be shed. Thus, toxoplasma wouldn't want its carrier rodent to get picked off by a hawk or its cat feces ingested by a dung beetle. Mind you, the parasite can infect all sorts of other species; it simply has to wind up in a cat if it wants to spread to a new host.

This potential to infect other species is the reason all those "what to do during pregnancy" books recommend banning the cat and its litter box from the house and warn pregnant women against gardening if there are cats wandering about. If toxoplasma from cat feces gets into a pregnant woman, it can get into the fetus, potentially causing neurological damage. Well-informed pregnant women get skittish around cats. Toxoplasma-infected rodents, however, have the opposite reaction. The parasite's extraordinary trick has been to make rodents lose their skittishness.

All good rodents avoid cats — a behavior ethologists call a fixed-action pattern, in that the rodent doesn't develop the aversion because of trial and error (since there aren't likely to be many opportunities to learn from one's errors around cats). Instead feline phobia is hard-wired. And it is accomplished through olfaction in the form of pheromones, the chemical odorant signals that animals release. Rodents instinctually shy away from the smell of a cat — even rodents that have never seen a cat in their lives, rodents that are the descendants of hundreds of generations of lab animals. Except for those infected with toxoplasma. As Berdoy and his group have shown, those rodents selectively lose their aversion to, and fear of, cat pheromones.

Now, this is not some generic case of a parasite messing with the head of the intermediate host and making it scatterbrained and vulnerable. Everything else seems pretty intact in the rodents. The social status of the animal doesn't change in its dominance hierarchy. It is still interested in mating and thus, de facto, in the pheromones of the opposite sex. The infected rodents can still distinguish other odors. They simply don't recoil from cat pheromones. This is flabbergasting. This is akin to someone getting infected with a brain parasite that has no effect whatsoever on the person's thoughts, emotions, SAT scores, or television preferences but, to complete its life cycle, generates an irresistible urge to go to the zoo, scale a fence, and try to French-kiss the pissiest-looking polar bear. A parasite-induced fatal attraction, as Berdoy's team noted in the title of its paper.

Obviously, more research is needed. I say this not only because it is obligatory at this point in any article about science, but because this finding is just so intrinsically cool that someone has to figure out how it works. And because — permit me a Stephen Jay Gould

moment — it provides ever more evidence that evolution is amazing. Amazing in ways that are counterintuitive. Many of us hold the deeply entrenched idea that evolution is directional and progressive: Invertebrates are more primitive than vertebrates, mammals are the most evolved of vertebrates, primates are the genetically fanciest mammals, and so forth. Some of my best students consistently fall for that one, no matter how much I drone on in lectures. If you buy into that idea big-time, you're not just wrong, you're not all that many steps away from a philosophy that has humans directionally evolved as well, with the most evolved being northern Europeans with a taste for schnitzel and goose-stepping.

So remember, creatures are out there that can control brains. Microscopic and even larger organisms that have more power than Big Brother and, yes, even neuroscientists. My reflection on a curbside puddle brought me to the opposite conclusion that Narcissus reached in his watery reflection. We need phylogenetic humility. We are certainly not the most evolved species around, nor the least vulnerable. Nor the cleverest.