Did parasite manipulation influence human neurological evolution?

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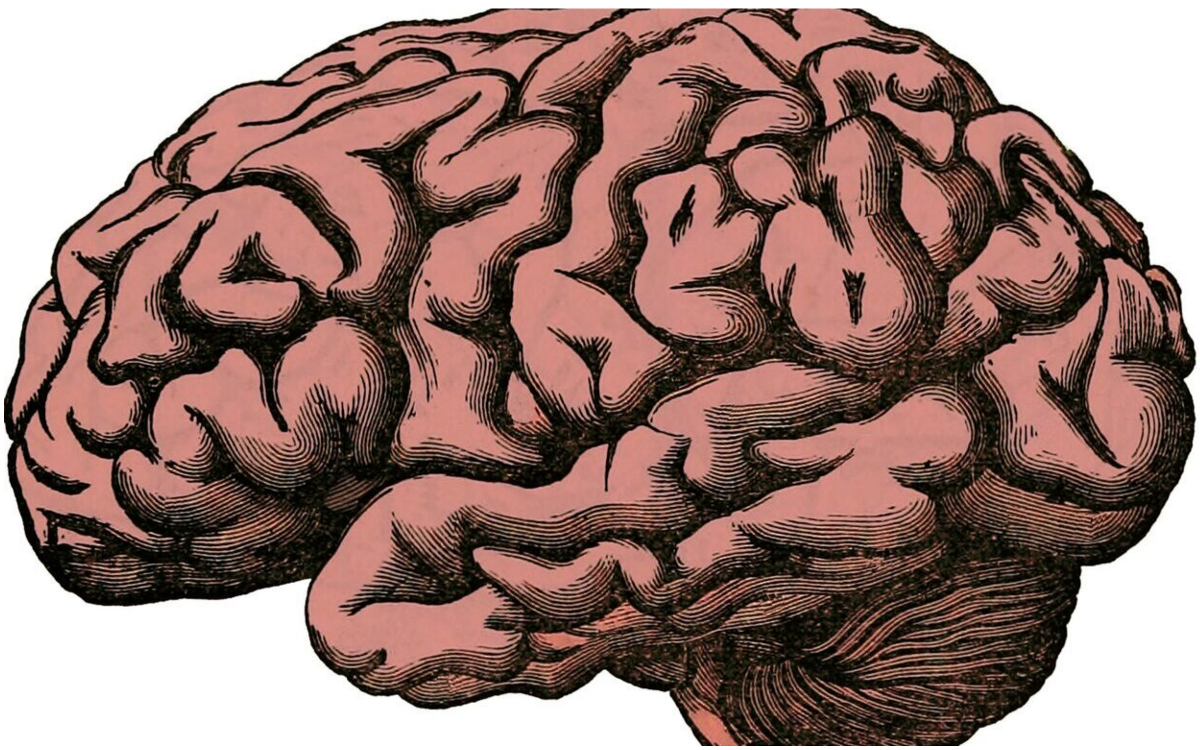

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It seems so obvious that someone should have thought of it decades ago: Since parasites have plagued eukaryotic life for millions of years, their prevalence likely affected evolution. Psychologist Marco Del Giudice of the University of New Mexico is not the first researcher to suggest that the evolution of the human brain could have been influenced by parasites that manipulate host behavior. But tired of waiting for neurologists to pick up the ball and run with it, he has published a paper in the *Quarterly Review of Biology* that suggests four categories of adaptive host countermeasures against brain-manipulating parasites and the likely evolutionary responses of the parasites themselves. The idea has implications across a host of fields, and may explain human psychology, functional brain network structure, and the frustratingly variable effects of psychopharmaceuticals.

Detailed and gruesomely readable, the paper is a work of theory intended to provide a roadmap for deeper study that is likely to be agonizingly complex, and which will eventually require the involvement of neurologists, evolutionary biologists, psychologists, parasitologists and many others.

Manipulating host behavior

Many parasites manipulate host behavior in order to increase reproductive success and to spread across wider areas. Dr. Del Giudice cites such examples as Toxoplasma gondii, which hitches a ride in a rat and induces epigenetic changes in the rodent's amygdala. These changes diminish its predator aversion around cats, the protozoan's intended destination, and the only animal in which it can reproduce. (As a side effect, it can infect humans—people are a reproductive dead end for T. gondii, but it is also believed to alter human behavior.)

Del Giudice also cites rabies, which increases production of infectious saliva and induces the host's aversion to water, which further concentrates the saliva, and then engenders violent aggression to increase the likelihood of biting, a transmission route. And many sexually transmitted pathogens are known to manipulate host sexual behavior.

The point is that parasites are really bad for hosts, and it therefore stands to reason that the evolution of modern humans includes protective countermeasures that were selected for success and likely shaped the stupefyingly complex central nervous system.

The paper is organized by four countermeasures hosts have evolved against manipulative parasites: restricting access to the brain; increasing the costs of manipulation; increasing the complexity of signaling; and increasing robustness. Within each category, Del Giudice suggests evolutionary responses by parasites to these countermeasures.

Restricting access to the brain

For aspiring higher organisms, keeping parasites out of the central nervous system is like Immunology 101; as Del Giudice points out, the adaptive benefits of restricting access to the brain also apply to non-parasitic pathogens. So the blood-brain barrier comprises the first line of defense as a layer of physical and chemical security.

Parasites have evolved other options to manipulate behavior from outside of the brain: Some produce behavior-altering substances like dopamine and release them into the blood; some manipulate the secretion of hormones; others activate specific immune responses in order to manipulate the host. Del Giudice also cites a number of parasites that evolved methods of passing through the blood-brain barrier in order to reach the brain physically.

Increasing the costs of manipulation

Some parasites release certain neurochemicals to alter host behavior. As a countermeasure, hosts could adapt by increasing the amount of particular neurochemicals required to induce such responses, greatly increasing the metabolic cost to the parasites. Since hosts are generally much larger, this increased cost could be completely negligible to the host while overwhelming the parasite's ability to produce enough of the neuroactive substance.

Del Giudice adds, "Since present-day instances of manipulation are mostly of the indirect kind, selection to increase the costs of signaling would have peaked a long time ago, possibly in the early stages of brain evolution… Paradoxically, if those countermeasures were so effective that they forced most parasites to adopt indirect strategies, they would have rendered themselves obsolete, eventually becoming a net cost without any prevailing benefits. If so, they may have been selected out owing to the relentless pressure for efficiency."

Increasing the complexity of signals

The central nervous system uses neuroactive substances as internal signals between neurons, brain networks and between the brain and other organs. Parasites can hijack these pathways to alter behavior by producing overriding signals or, as Del Giudice points out, corrupting existing ones. This entails breaking the host's internal signaling code.

Thus, a more complex signaling code is more difficult for a parasite to break. Instances of such a complexity increase include the requirement of joint action of different neurochemicals, or releasing neuroactive substances in specifically timed pulses. Expanding the set of transmission molecules and their binding receptors also increases complexity. More elaborate internal signals increase the time required to break. From an adaptive standpoint, this can close off the parasite's options, forcing it to develop other means of manipulation.

However, rising complexity raises the metabolic costs for the hosts, though these costs are disproportionately more expensive for parasites. And Del Giudice points out that increasing the complexity of a system "tends to create new points of fragility," which may be exploited by adapting parasites.

Increasing robustness

Increasing the robustness of a system basically amounts to damage control. Higher organisms tend to evolve in such a way that they can maintain normal behavior functionality, even during attack by a parasite. Del Giudice discusses a number of passive, reactive and proactive robustness host strategies, including redundancy and modularity of systems; so-called bow-tie network architectures; feedback-regulated systems that detect perturbations of the system and make corrective adjustments; and the monitoring of nonspecific cues such as immune system activities that indicate the presence of a parasitic pathogen.

Largely, robustness adaptations are likely to exclude fixed physiological adjustments, and instead favor the development of "plastic responses triggered by cues of infection." The reason is that if brain physiology and behavior are adapted to function best in the presence of a pathogen, then its absence would lead to non-optimal behaviors and reduced survival.

Del Giudice includes in the paper a discussion of the constraints on the evolution of countermeasures by hosts. These include metabolic and computational constraints such as energy availability and small body size—animals with larger brains can more easily evolve higher levels of protective complexity. This is one reason that behavior-altering parasites are more commonly observed in insects, which have provided fundamental examples of parasite strategies and host countermeasures.

Psychopharmacology

Finally, the author includes a fascinating discussion of the implications of such adaptations for psychopharmacology. "Using psychoactive drugs to treat psychiatric symptoms is an attempt to alter behavior by pharmacological means. This is also what manipulative parasites do—even though, in the case of psychiatric treatment, the goal is to benefit the patient," Del Giudice writes.

Thus, adaptive responses to attacks by parasites could explain why antidepressants tend to induce tolerance in some patients—like parasites, the drugs seek to alter the organism's behavior, with the possibility that robust neural systems rebalance behavior pathways that have been altered by the drug. "It is worth considering the possibility that at least some of these reactive mechanisms may be specifically designed to detect and respond to parasite intrusions," Del Giudice writes. "If so, standard pharmacological treatments may unwittingly mimic a parasite attack and trigger specialized defensive responses." He adds that certain undesirable side effects of drugs could be metabolically expensive but useful adaptive features during a parasite infection, but detrimental to psychiatric treatment.

The paper is a theoretical exploration of the ideas surrounding parasitism as an evolutionary pressure, and as such, usefully illuminates how complex and difficult the question will be for researchers tackling the already challenging fields of neurophysiology and brain networks.

More information: Marco Del Giudice. Invisible Designers: Brain Evolution Through the Lens of Parasite Manipulation, *The Quarterly Review of Biology* (2019). DOI: 10.1086/705038

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