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Toxoplasmosis: Recent Advances in Understanding the Link Between Infection and Host Behavior

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Abstract

Humans, wildlife, and domestic animals are intimately linked through shared infections. Many parasites and pathogens use multiple host species, either opportunistically or sequentially, such that managing disease risk frequently requires a broader understanding of the ecological community. The coccidian protozoan *Toxoplasma gondii* infects more than one hundred species of vertebrates, ranging from bats to beluga whales. In humans, acute toxoplasmosis can have serious health consequences for immunocompromised individuals. Even amongst asymptomatic patients, however, toxoplasmosis has been linked to a range of behavioral alterations and conditions, such as changes in risk tolerance, neuroticism, mental illness, suicide, and accident proneness. Whether such links are causal or simply correlational has been the subject of intense study and debate; from an evolutionary standpoint, selection may favor parasite-induced alterations in host behavior that increase the likelihood a host is consumed by the definitive host—in this case a domestic or wild felid. Here, we examine current evidence for parasite-induced manipulations of host behavior, in both humans and other animals. We critically evaluate proposed mechanisms through which infection might influence host behavior, which range from inflammation in the brain to changes in hormones or neurotransmitters. Considering estimates that *T. gondii* may infect up to one-third of the global human population, we conclude by examining the implications of these changes for human behavior, individual fitness, and emergent cultural properties.

INTRODUCTION

Humans, wildlife, and domestic animals are often intimately linked through shared infection by parasites and pathogens. Nearly 70% of emerging human infections involve nonhuman hosts or vectors (1, 2), and growing evidence indicates that human infections are increasingly spilling into wildlife populations (e.g., measles in gorillas and tuberculosis in African elephants) (3, 4). These observations underscore the importance of transdisciplinary research to systematically tackle the pathways of transmission for multi-host pathogens and identify their consequences for public health and wildlife conservation (5). A prime example involves the coccidian protozoan *Toxoplasma gondii*, for which cats (both domestic and wild) function as the only known definitive hosts. According to the Centers for Disease Control, more than 40 million people in the United States carry *T. gondii*, although most individuals are relatively asymptomatic. Acute toxoplasmosis can be fatal for immunocompromised patients and lead to birth defects when acquired by pregnant women (6, 7). However, this parasite can also infect hundreds of species of endothermic vertebrates, ranging from bats to beluga whales (8, 9). Indeed, in a recent review of the literature, Lindsay & Dubey (10) document infection in canids, bears, raccoons, squirrels, rabbits and hares, skunks and fishers, beavers, woodchucks, moles, bats, deer, elk, sea otters, whales, dolphins, monkeys, wombats, koalas, bandicoots, elephants, hippopotamuses, raptors, owls, pigs, cattle, chickens, buffalos, and others.

In addition to its widespread geographic prevalence and broad host-species use, *T. gondii* has received increased attention because of its potential to influence the behavior of its vertebrate hosts (11). Often of interest is whether such induced behavioral alterations are evolutionarily adaptive for the parasite, that is to say, whether they enhance the likelihood that *T. gondii* is subsequently transmitted to a suitable felid host, which occurs through predation. In rats, for instance, infection can increase an individual's attraction to the smell of cat urine, with presumably adverse effects on long-term survival probability (12). But even for hosts that are (usually) less likely to be eaten by a cat, such as humans, the notion that a cryptic but widespread parasite might alter patterns of risk tolerance, neuroticism, mental illness, suicide, or accident proneness has elicited tremendous research interest and intrigue (13). Concurrently, links between infection and traffic collisions in threatened Australian marsupials and increased risk of shark attacks in sea otters highlight the relevance of *T. gondii* for wildlife conservation (14, 15).

In this article, we briefly review the life cycle and biology of *T. gondii* and its use of multiple transmission mechanisms to spread and reproduce. We then examine current evidence for parasite-induced manipulations of host behavior, in both humans and other animals, and evaluate alternative proposed mechanisms for how *T. gondii* is believed to influence host behavior, which range from inflammation in the brain to changes in hormones or neurotransmitters. We also examine the implications of these changes for human behavior, individual fitness, and emergent cultural properties. Finally, we conclude by highlighting outstanding issues and unanswered questions surrounding *T. gondii* and its link to host behavior. For more in-depth reviews on the biology, history, and epidemiology of *T. gondii*, we refer readers to work by Dubey (16), as these topics are beyond the scope of this review.

BIOLOGY AND TRANSMISSION OF *TOXOPLASMA GONDII*

Toxoplasma gondii has a multistage life cycle that involves sexual reproduction in felids, its primary host (**Figure 1**). It is transmitted to secondary hosts, primarily other vertebrate mammals, through oocysts found in cat feces. Secondary hosts may consume the oocysts directly (with feces) or through contaminated water or soil. After consuming oocysts, animals may experience an acute infection. In humans, this might present like a mild to moderate flu.

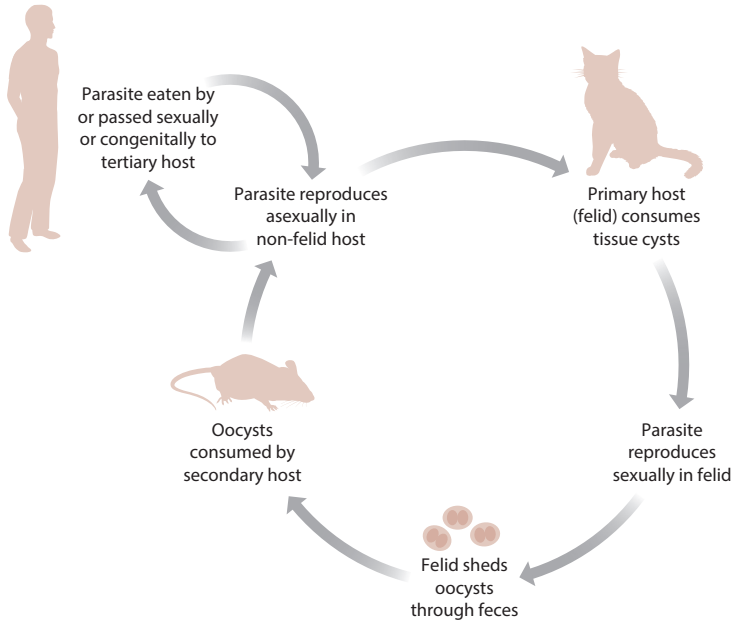

Figure 1

Parasite life cycle. The primary host of *Toxoplasma gondii* is a felid, in which the parasite can sexually reproduce. The felid sheds the parasite in the form of oocysts through feces, which can be consumed by a secondary host, such as a rodent. The parasite can also take an alternative turn in its life cycle if the secondary host is consumed by a tertiary host, who also contracts the parasite. The secondary and tertiary host can also pass the parasite to others congenitally or sexually.

Fecal–Oral Transmission

Fecal–oral transmission is the most common pathway through which *T. gondii* is spread from the primary host to secondary hosts. Only felids can actually transmit oocysts (although oocysts can also be produced in the lab) (17). As an oocyst enters a cell, it becomes a tachyzoite and reproduces quickly using endodyogeny, a process by which a single parasite produces two daughter cells that eventually consume the initial parasite. Tissue cysts form and the tachyzoite becomes a bradyzoite, which reproduces slowly using endodyogeny within the tissue cyst. Tissue cysts can form anywhere in the host body, including muscles, organs, and the brain, and all stages of the parasite can form tissue cysts.

Cats are most likely to be infected by consuming tissue cysts filled with bradyzoites, which can occur when they prey upon infected secondary hosts. Consuming just a single bradyzoite can effectively infect a cat, but fewer than 30% of cats shed oocysts after ingesting tachyzoites and sporozoites (18, 19). Once a cat becomes infected, *T. gondii* can reproduce sexually within the new felid, and its life cycle is complete. Tissue cysts can remain viable within a secondary host for months (20), which helps to enhance the likelihood of consumption by a felid primary host.

Alternative Pathways

Alternatively, *T. gondii* can take an indirect pathway to reach another felid through a tertiary host. There is evidence of at least three alternate routes. First, an animal can become infected by eating

another animal infected with *T. gondii*. Specifically, the consumption of tissue cysts in an infected animal (whether they are filled with tachyzoites or bradyzoites) can cause infection in the tertiary host. However, the parasite is not as effective at infecting tertiary hosts through the consumption of meat as it is at infecting cats (the primary or definitive host).

Although eating one bradyzoite can infect a cat, eating 100 bradyzoites may not be enough to infect a mouse. Dubey (21) showed that mice could be infected through the consumption of tachyzoites, but again, it required high doses of the parasite and differed by strain of *T. gondii*. Instead, it seems the infection can be mitigated or eliminated through the digestion process. In contrast, consumption of a single oocyst is sufficient to infect a mouse. Mice do not become immune to *T. gondii*, and new tissue cysts continue to be formed among chronically infected mice (22, 23). For humans, the likelihood of infection by consuming tissue cysts is further reduced via thorough cooking, which can kill the parasite. Humans can contract *T. gondii* from consuming undercooked meat such as cows, pigs, and deer (9).

The other two ways that *T. gondii* can spread are through semen, if the secondary host is male, and through congenital transmission, if the secondary host is a pregnant female (**Figure 1**). Of course, these two routes can also be connected. There is evidence that *T. gondii* can act as a sexually transmitted infection in rats (24), dogs (25), sheep (26), and even humans (27). Interestingly, researchers found that uninfected female mice were more attracted to infected male mice than to uninfected male mice, which is counter to most evidence that disease reduces mate preference (24). Finally, the secondary host (if female) could pass the parasite on to its unborn offspring. In humans, congenital *T. gondii* is associated with miscarriage and severe birth defects. There are also high levels of mortality among congenitally infected mice; infection can be passed on to at least 10 generations of mice (28).

LINKING *TOXOPLASMA GONDII* AND HOST BEHAVIORAL CHANGES IN RODENTS

Many parasites can induce physiological or behavioral changes within infected hosts. In some cases, such changes are the by-product of infection, such as reductions in energetic reserves, fatigue, or changes in body condition (i.e., morbidity). In other cases, however, induced changes are hypothesized to also play a role in promoting pathogen transmission (29, 30). In infection by the rabies virus, for example, shifts in the behavior and biting frequency of infected hosts increase the chances of viral spread (i.e., through broken skin and entry into the bloodstream of another host). Similarly, horsehair worms (nematomorphs) can cause their cricket hosts to seek out aquatic environments wherein the worm can reproduce, often leading to the unfortunate drowning of the terrestrial cricket. Among multi-host parasites that depend on predation as a mechanism to move from one host to another (i.e., trophic transmission), parasite-induced manipulations of host behavior, physiology, and appearance have been widely studied. Alterations in host behavior or appearance that increase the likelihood of a host being consumed by an appropriate downstream host can offer a selective advantage for transmission. For instance, trematode worms that infect the brains of estuarine fish have been linked to erratic swimming behavior and conspicuous movements, which increase the chance infected fishes are consumed by water birds—the parasite's definitive host in which sexual reproduction occurs (31).

For *T. gondii*, the definitive hosts are cats, both domestic and wild. If infection can induce behavioral alterations that increase the likelihood an infected host is ultimately eaten by a felid, then such induced changes may be selectively advantageous. A core challenge, however, is determining the degree to which infection induces such changes or is simply correlated with them. In the

absence of experimental research or longitudinal surveys of hosts both before and after infection, it is entirely plausible that certain behaviors enhance the likelihood of parasite exposure in the first place, rather than emerging as a consequence of infection. This emphasizes the importance of using a wide range of research approaches and examining the link between infection and behavior across a range of host taxa, including those for which experimental infections can be conducted. In the section below, we first explore evidence for parasite-induced behavioral manipulations in the behavior of rodents before extending this line of inquiry to humans.

Behavioral Changes in Rodents

The interest in behavioral changes among hosts carrying *T. gondii* has often focused on rodents, the ideal cat prey. In the case of *T. gondii*, there is evidence of behavioral changes among rodents that increase their likelihood of consumption by a cat. For example, Gatkowska et al. (32) found that infected rodents are more likely to spend time in open, exposed areas, which could increase consumption by cats (or any other predator). After experimentally infecting the rodents, the authors examined the behavior of exposed and unexposed animals in an arena designed for the experiment. Specifically, infected male C57BL/6 (H-2b) inbred mice that were 10–12 weeks old were infected with the ME49 strain of *T. gondii*. Infected and noninfected mice were placed in an arena where researchers observed their behavior. The open-field test was used to examine whether infected mice would spend more time in an exposed area of the enclosure, which could increase their predation risk. Infected mice preferred the more exposed, central part of the arena compared with noninfected mice. Infected mice also engaged in fewer grooming behaviors and displayed reduced exploratory activity. Using light microscopy, the authors also counted cysts in duplicate samples three weeks and six weeks post-infection, finding parasite cysts in both the hippocampus and amygdala of infected mice.

Fatal feline attraction. In addition to spending more time in open spaces, rodents also show an increased attraction to the smell of cats—a phenomenon referred to as fatal feline attraction. In one study, Berdoy et al. (33) compared infected and noninfected rats' fear of cat urine, rat urine, no urine, and rabbit urine. The researchers divided 2 × 2-m outdoor pens into 16 individual cells. The corners of each cell contained one of four scents: used straw bedding containing the rat's own urine, fresh straw bedding with water for a neutral smell, fresh bedding treated with undiluted cat urine, and fresh bedding treated with undiluted rabbit urine (to represent a nonpredatory mammal). Smell location was counterbalanced across cells. The researchers infected rats with a low-virulence RRA Beverley strain of *T. gondii*. Infected rats then underwent *T. gondii* IgG antibody tests. Rats that were dosed but failed to test positive for *T. gondii* were excluded from the study, leaving 23 infected and 32 uninfected rats. Rats' nocturnal behavior was monitored for 670 h. Uninfected rats displayed aversion to areas with cat urine, whereas infected rats showed less aversion and no avoidance of areas with cat urine. They visited the cat odor significantly more than the control group and more than they visited the rabbit and neutral odors. The infected and uninfected rats spent similar time in the rabbit-, neutral-, or rat-scented locations.

Vyas et al. (34) provided some of the most compelling evidence for fatal feline attraction, finding that mice and rats showed an increased attraction toward cat urine and smell (on a cat collar), although they did not show other forms of cognitive impairment. In one study, the researchers compared rodent attraction to bobcat urine versus rabbit urine. In another trial, they compared rodent attraction to a cat collar that had been worn by a cat versus a cat collar that had not. The researchers infected 8-week-old male Long-Evans rats and 7-week-old female BALB/c mice with

a Prugniaud strain of *T. gondii*. They used a circular (rather than square) arena and found that infected mice and rats spent more time than uninfected rodents in the cat quadrants. They found no differences between the infected and uninfected rodents on learned fear, anxiety, olfaction, or non-aversive learning, leading them to suggest that fatal feline attraction is supported over alternative explanations, such as general reductions in fear or cognitive impairment.

In further support of fatal feline attraction, Kaushik and colleagues (35) tested whether attraction of *T. gondii*–infected rats to feline odor differed between domestic (*Felis silvestris catus*) and wild cats, such as cheetahs (*Acinonyx jubatus*) or pumas (*Felis concolor*). To do this, the authors conducted trials in which infected and uninfected rats were allowed 5 min to enter and explore arenas with designated feline odor zones and neutral zones. Both male ($n = 15$) and female ($n = 15$) Lister hooded rats were infected with two wild-type Pru (type II) strains of *T. gondii*. They used a two-choice paradigm involving an apparatus with two arms containing different types of cat urine. One arm always contained domestic cat urine, and the other contained urine from one of the two wild cats. Rats started the trial in the apparatus' neutral zone, which faced away from the arms containing cat urine, and were given 5 min in the apparatus. The location of odors within the two arms was randomized to avoid positional bias, and all apparatuses were wiped down to remove odors before and after each test. Automated tracking was used to track rats' movement, and activity was measured as the number of entrances into and the time spent in zones with the different feline odors. The authors found that among rats that entered a feline zone at least once, the infected rats spent more time in the wild cat zone than in the domestic cat zone, but their preference for puma or cheetah did not differ. Both infected and uninfected rats avoided felid odor, but uninfected rats did so to a greater degree.

The case against felid specificity. Although this parasite clearly has behavioral effects that may or may not be adaptive for its life cycle, other studies suggest that the change in fear response to cat urine is a more general phenomenon related to a reduced fear of all predators (36). Boillat et al. (36) suggested that *T. gondii* reduces predator aversion without selectivity toward cats. Their study also suggested that infection lowers anxiety and increases explorative behaviors, which can further increase predation risk (we discuss these alternative mechanisms in the next section). They reported a positive correlation between the severity of the behavioral alterations and cyst load, which indirectly reflects the level of inflammation during brain colonization.

Strain differences. One important issue with the potential to influence the consistency of observed experimental results involves the specific strain of *T. gondii* used in different studies. For example, the VEG (type III) strain of *T. gondii* results in higher IgG levels of antitoxoplasma than the ME-49 (type II) strain (37). The VEG strain also has a greater impact on tissue cyst burden in the central nervous system, reduction in long-term memory, mobility, and greater aversion to cat odor than the ME-49 strain (37). To test whether the genotype of *T. gondii* strains influences behavior change in rodents, Bezerra et al. (37) assessed the effect of chronic infection by developing ME-49 and VEG strains in BALB/c mice. An ELISA (enzyme-linked immunosorbent assay) test was used to assess humoral immune responses, and real-time polymerase chain reaction was used to quantify parasite loads in the central nervous system. Based on behavioral tests (passive avoidance, open-field, Y-maze) that assessed learning and memory, locomotor activity, and aversion to feline odor, the researchers found that, compared with mice infected with the ME-49 strain, mice infected with the VEG strain had a higher IgG level of antitoxoplasma and higher tissue burden of *T. gondii* in the central nervous system, as well as reduced long-term memory, lower mobility, and lower aversion to feline odor.

LINKING *TOXOPLASMA GONDII* AND HOST BEHAVIORAL CHANGES IN HUMANS

Just as *T. gondii* has been linked to changes in rodent behavior, significant behavioral changes have also been associated with the parasite in humans. Of course, one primary difference between studies in humans versus those in rodents is that research typically must use correlational or case-control designs, which limits the ability to determine whether the parasite is causing behavioral changes. Yet *T. gondii* is associated with a suite of behavioral changes in humans. These changes could be considered an accidental by-product of the parasite's evolutionary adaptation within vertebrates frequently consumed by cats (such as rodents), but such manipulations could also increase the likelihood of a primate being consumed by a wild felid.

Indeed, a recent study demonstrated that chimpanzees showed a decreased aversion toward leopard urine when infected with *T. gondii* (38). Interestingly, the chimpanzees showed no such decrease in their aversion to the urine of tigers and lions, which are not natural predators. Poirotte et al. (38) examined the origin of *T. gondii*–induced changes in humans by performing olfactory tests on chimpanzees, as these primates are regularly preyed upon by wild felids. The authors presented one type of urine at a time (human, leopard, tiger, and lion) to 33 male and female chimpanzees (9 *T. gondii* infected and 24 uninfected) living in Gabon. The authors found no difference between infected and uninfected chimpanzees in response to urine from feline hosts that chimpanzees do not encounter in nature, such as tigers and lions. However, infected chimpanzees did display a loss of aversion to the urine of leopards, which are a natural predator.

Likewise, Flegr et al. (39) showed that men infected with *T. gondii* rated the smell of cat urine as more pleasant than did uninfected men, although they did not report differences in the pleasantness of hyena, horse, or tiger urine. Infected women showed the opposite pattern of results, rating the cat urine smell as less pleasant than uninfected women did. These findings contrast with other studies showing stronger effects for wild compared with domestic cats.

The majority of behavioral changes in humans also suggest decreases in cognitive functioning (40, 41). Using a double-blind study, Gajewski and colleagues (40) examined cognitive impairment in infected but asymptomatic older adults. The study included healthy participants aged 65 years and older who tested positive (IgG $>$ 50 IU/ml) or negative (IgG $=$ 0 IU/ml) for *T. gondii*. Participants were given a computer-based working-memory test along with standardized memory and executive cognitive function psychometric tests. Infected adults displayed lower performance in working and verbal memory (regarding immediate recall, delayed recognition, and recall from long-term memory as assessed by a word fluency test) but not executive cognitive function. Those who were *T. gondii* positive also reported lower quality of life.

Flegr et al. (42) further reported that latent toxoplasmosis was associated with prolonged reaction times in infected subjects; evidence of this association can be observed outside the laboratory, including the likelihood of a person getting into a car accident. The authors compared the seroprevalence of latent toxoplasmosis in subjects involved in traffic accidents to that of the general population. Results showed a significantly higher seroprevalence among individuals in the traffic accident group. Indeed, an increase in traffic accidents is one of the more consistent associations related to *T. gondii* infection in humans (42–44), although it is yet unclear whether this increase stems from slower reaction times or increased risk-taking behavior (45). Using autopsy data, Samojłowicz et al. (45) demonstrated that *T. gondii*–infected individuals were more likely to die from risky behaviors (such as riding a motorcycle without a helmet) than those who were not infected.

The main concern with human models is determining why complex behaviors occur. In the case of traffic accidents, the association with *T. gondii* could result from slower reaction times,

decreased fear of taking risks (similar to rodents' choice to remain in open areas), or different reward structures. For example, Stock et al. (41) found humans with latent toxoplasmosis had a greatly reduced response to monetary rewards compared with adults without latent toxoplasmosis. So, infection could also be altering the risk-versus-reward payoff of engaging in certain behaviors.

T. gondii is associated with a higher frequency of suicide attempts in humans (46), another complex behavior. Ling et al. (46) used secondary country-level seropositivity data available from women and suicide rate data from 20 European countries based on the European Mortality Database. When stratified for age, seroprevalence was significantly positively correlated with suicide rates for women aged 60 and older. After adjusting for GDP, seroprevalence was also significantly and positively correlated with suicide rates for women aged 45–59 years old. Hungary and France, which had the first- and third-highest seropositivity rankings, also had the first- and fourth-highest suicide rankings, respectively. In contrast, the United Kingdom showed the lowest seroprevalence ranking (twentieth) and ranked sixteenth in suicide rates.

Likewise, Yagmur et al. (43) used ELISA to measure the seropositivity level for anti-*Toxoplasma* IgG and IgM antibodies in 200 people who had attempted suicide and compared them to 200 healthy volunteers. Results showed that the seropositivity level for anti-*Toxoplasma* IgG antibodies among participants with suicide attempts (41%) was significantly higher than in the control group (28%). The authors concluded that toxoplasmosis is a potential contributing factor in suicide attempts in humans. Finally, meta-analytic evidence of the relationship between *T. gondii* and suicide showed that the odds of suicide in people with *T. gondii* were 43% higher than in noninfected individuals (47).

In notable contrast, a birth-cohort study examining the relationship between *T. gondii* and human behavior change showed no difference in schizophrenia or major depression, personality, or reduced cognitive performance, although there was some evidence of increases in suicide attempts (48). The results are quite compelling but do raise the question of why *T. gondii*–positive individuals would attempt suicide more despite displaying no change in personality, cognitive function, or mental illness.

Mental Illness

Another potential mechanism for the increase in risky behavior or accidents could be the association between *T. gondii* and mental illness in humans, including schizophrenia (49, 50), depression (51, 52), bipolar disorder (53), and obsessive-compulsive disorder (OCD) (54). Arias et al.'s (50) meta-analysis also showed a significant association between schizophrenia and *T. gondii*, such that schizophrenia was 2.7 times more frequent in people with *T. gondii* markers such as IgG antibodies or messenger RNA. In another meta-analysis of case-control studies, Sutterland and colleagues (49) detected significant relationships between *T. gondii* and schizophrenia, bipolar disorder, OCD, and addiction but not major depression. Of all of the relationships, *T. gondii* was most strongly related to schizophrenia.

In contrast to the Sutterland study (49), other research has provided support for the link between *T. gondii* and depression. Alvarado-Esquivel and colleagues (51) used a case-control study on individuals who had attended a psychiatric hospital in Durango City, Mexico, for depression. Using ELISA, the authors analyzed sera for anti-*Toxoplasma* IgG and IgM antibodies of patients suffering from mixed anxiety and depressive disorder (cases) and healthy controls in the general public. The prevalence of anti-*Toxoplasma* IgG antibodies was significantly higher among cases compared with controls, and seroprevalence was significantly higher in female cases compared with female controls.

Similarly, Wadhawan et al. (52) investigated the association between *T. gondii* IgG serointensity and dysphoria/hopelessness in a nonclinical population. The study used a large sample of Old Order Amish individuals ($n = 777$) with a mean age of 42.4 and made up of 61.4% female and 38.6% male participants. The authors used a depression screening questionnaire and ELISA testing to measure *T. gondii* IgG serointensity. Results showed a significant association between serointensity and dysphoria/hopelessness.

Hamdani et al. (53) explored the relationship between past exposure to *T. gondii* and bipolar disorders in a French case-control study by comparing the prevalence of IgG and IgM antibodies in 106 healthy participants and 110 participants with bipolar disorders. Individuals who were seropositive for IgG antibodies to *T. gondii* also had higher odds of having bipolar disorder.

Finally, Miman et al. (54) used a case-control study to examine the association between *T. gondii* and OCD. They found that 20 of the 42 OCD patients studied tested positive for IgG antibodies (48%), whereas only 19 of the 100 individuals in the control group had the antibodies. Clearly, there is a strong association between *T. gondii* infection and mental health outcomes. It is difficult to disentangle the array of mental health conditions associated with *T. gondii* because many have strong comorbidity with one another.

From Individuals to Societies: Culture-Level Effects

Insofar as *T. gondii* infection might influence individual behavior, it could also have interesting effects at a societal level, considering that some nations and regions have higher prevalence of the parasite in humans than others. Lafferty (55) explored the association between culture and latent *T. gondii* infection by investigating whether the parasite's subtle effect on individual personality alters aggregate personality at the population level. To test this, the author used preexisting country-level *T. gondii* prevalence data, published country-level data on cultural dimensions and aggregate personality, and data from an independent assessment of aggregate neuroticism. Lafferty found that aggregate neuroticism (measure for individual personality) increased significantly with *T. gondii* prevalence. The author concluded that *T. gondii* could be one of many factors that influence human culture.

Maseland (56) tested whether cultural attitudes affect institutions and economic performance. The author used *T. gondii* prevalence rates as an instrument for cultural variation owing to its ability to affect individual attitudes and societal values. They found that higher prevalence of *T. gondii* was related to (*a*) lower institutional quality and (*b*) lower economic performance at the cultural level. The author used country-level *Toxoplasma* seroprevalence data from pregnant women collected in previously published studies, along with World Values Survey data for culture measures.

The parasite has also been associated with an increase in entrepreneurship at the societal level (57, 58). Johnson et al. (57) collected primary survey data and saliva from college students and professionals at entrepreneurship events and secondary country-level *T. gondii* data and data from the Global Entrepreneurship Monitor. Results from a saliva-based assay found that students who tested IgG positive for *T. gondii* were more likely to major in business and more likely to have an emphasis in management and entrepreneurship. Among professionals at entrepreneurship events, those who had started their own business were more likely to be *T. gondii* positive. Lastly, they found that *T. gondii* infection prevalence was a consistent, positive predictor of entrepreneurial activity and intentions on a global scale. The authors concluded that there is a link between *T. gondii* infection and complex human behaviors, including those related to business and entrepreneurship.

More recently, Lerner et al. (58) examined the relationship between *T. gondii* and entrepreneurship by using longitudinal data covering Denmark's female population. Their results showed that *T. gondii* infection is associated with the likelihood of becoming an entrepreneur and is linked to

other outcomes, such as venture performance. Overall, the data covered 11,433 economic ventures founded by 16,068 women, 1,831 of whom were *T. gondii* positive. *T. gondii*–positive women were 29.2% more likely to subsequently enter into entrepreneurship than *T. gondii*–negative women. *T. gondii*–positive women were also 26.6% more likely to pursue multiple ventures in comparison to the negative group. *T. gondii*–positive women were also 134% more likely to start a venture by themselves, as opposed to including other people. *T. gondii* also had a significant and negative relationship with an entrepreneur staying with her venture. This, on average, corresponds to a shortening of an entrepreneur's persistence by approximately 1.1 years for *T. gondii*–positive individuals. The mean venture persistence across all observations is 4.09 years. Thus, infection appears to reduce persistence with a venture by approximately 25% from the mean value.

MECHANISMS FOR MANIPULATION: HIJACKING THE BRAIN?

Although there is little consensus on the specific changes in inflammation, hormones, or neurotransmitters (59), the reality is that there need not be any specific change to increase the likelihood of transmission. If entering the brain sometimes but not always causes changes in behavior that favor transmission, the likelihood of *T. gondii* infecting the brain could be selected for even if some of the changes do not favor or disfavor transmission. Such changes in the brain (especially those inferred from rodent models) could also explain the increase in mental illness in humans with toxoplasmosis.

Neurotransmitters

A wide variety of changes in the brain have been associated with *T. gondii.* For example, one study showed changes in dopamine, homovanillic acid, norepinephrine, serotonin, and 5-hydroxyindoleacetic acid among infected mice. Among these, dopamine has received the most attention (60, 61), possibly because schizophrenia is linked to unbalanced dopamine (62), and there is a consistent link between schizophrenia and *T. gondii* (63). In an excellent review on the topic, Webster & McConkey (64) focus on how altered dopamine levels have been reported for both *T. gondii* infection and schizophrenia, mentioning that several medications used to treat schizophrenia demonstrate anti–*T. gondii* properties.

Stibbs (59) measured levels of dopamine, homovanillic acid, norepinephrine, serotonin, and 5-hydroxyindoleacetic acid in mice with acute and chronic toxoplasmosis and in healthy controls. Mice with acute toxoplasmosis had increased levels of homovanillic acid and lower levels of norepinephrine, and mice with chronic infection had higher dopamine levels.

Prandovszky et al. (60) examined the relationship between *T. gondii* and dopamine metabolism in infected mice. Immunostaining of brain sections of *T. gondii*–infected mice with dopamine antibody showed intense staining of encysted parasites. These results showed that *T. gondii* significantly increases dopamine metabolism in neural cells of infected mice. The authors concluded that the parasite's effects on dopamine metabolism could explain the behavior changes in infected mice, and that these results could also be relevant in interpreting reports of psycho-behavioral changes in toxoplasmosis-infected humans.

Gaskell et al. (61) explored two genes contained in *T. gondii* that encode tyrosine hydroxylase, which produces L-DOPA. One of the genes is expressed, whereas the other is induced during bradyzoite formation at the cyst stage of the life cycle. Aligning rat and human enzymes revealed clear similarities between some factors related to rat tyrosine hydroxylase and to the *T. gondii* sequences. The authors concluded that *T. gondii* tyrosine hydroxylase has several possible biological roles; for example, the enzyme could be required for supply of tyrosine for protein synthesis, and synthesized tyrosine will be converted to L-DOPA.

Energy Consumption and Metabolites

Others argue that energy consumption and metabolites have the greatest effect on the behavioral manipulation of *T. gondii* (34). *T. gondii* has been associated with changes in at least nine metabolites: galactosylsphingosine, arachidonic acid, Lyso SM (d18:1), L-palmitoylcarnitine, calcitetrol, 27-deoxy-5b-cyprinol, L-homophenylalanine, oleic acid, and ceramide (d18:1/16:0) (65). *T. gondii* has also been linked to altered quinolinic acid (66) and kynurenine (67).

Okusaga et al. (67) examined whether *T. gondii* seropositivity and history of nonfatal suicidal self-directed violence would be stronger in schizophrenia patients with high plasma kynurenine levels. The authors measured anti–*T. gondii* IgG antibodies and plasma kynurenine in patients with schizophrenia and evaluated the relationship between nonfatal suicidal self-directed violence and kynurenine in patients who were either seropositive or seronegative for *T. gondii*. They showed that kynurenine was positively related to nonfatal suicidal self-directed violence in seropositive but not seronegative patients.

Ma et al. (65) investigated the molecular factors that contribute to the neurobehavioral changes in the cerebral cortex and other brain regions in *T. gondii*–infected animals and humans. The authors used mass spectrometry–based metabolomics to examine metabolomic signatures that discriminate between the cerebral cortexes of *T. gondii*–infected and uninfected mice. Results indicated that *T. gondii* induced the biosynthesis of unsaturated fatty acids to promote its own growth and survival, as demonstrated by upregulation of metabolites in the unsaturated fatty acid biosynthesis pathway as the infection progressed.

Notarangelo et al. (66) examined the role of endogenous compounds (stimulation of tryptophan degradation along the kynurenine pathway containing several neuroactive metabolites, including 3-hydroxykynurenine, quinolinic acid, and kynurenic acid) in the connection between toxoplasmosis and schizophrenia. They measured kynurenine pathway metabolites in both the brain and periphery of *T. gondii*–infected mice. Infected mice showed early decreases in tryptophan levels in the brain and serum, and these reductions were associated with elevated levels of kynurenine, 3-hydroxykynurenine, and quinolinic acid. Treatment with antiparasitic drugs (pyrimethamine and sulfadiazine) significantly reduced levels of hydroxykynurenine and kynurenic acid. The authors concluded that *T. gondii* infection enhances the production of kynurenine pathway metabolites in the brain.

Hormones

Changes to the endocrine system represent another pathway of changing behavior. *T. gondii* is also associated with higher levels of testosterone in men and women (68), although significant sex differences have also been reported (69). In support of the testosterone hypothesis, castrated male rats do not suffer from fatal feline attraction (70).

Estato et al. (71) examined the effect of cysts resulting from chronic acquired toxoplasmosis on neuroinflammation. The authors infected albino mice with the ME-49 strain of *T. gondii* and measured their cerebral blood flow 10, 40, and 180 days after infection. Infected mice had decreased cerebral blood flow at 10 and 40 days postinfection, but those differences were eliminated by 180 days postinfection. They also found that *T. gondii*–infected mice had significant capillary rarefaction and neuroinflammation. The authors concluded that some *T. gondii*–induced behavior change may be the result of neuroinflammation and microcirculatory dysfunction.

Flegr et al. (69) looked for evidence of latent toxoplasmosis-associated differences in testosterone concentration among *Toxoplasma*-infected patients and uninfected controls. Compared with controls, *Toxoplasma*-infected men had a higher concentration of testosterone, and *Toxoplasma*-infected women had a lower concentration of testosterone. The authors concluded

that the testosterone shift in men compared with in women may explain the observed gender specificity of behavioral shifts in infected human subjects.

Zouei et al. (68) explored the association between latent toxoplasmosis and testosterone concentration in *Toxoplasma*-infected humans and controls. They collected blood samples and analyzed sera for presence of anti-*Toxoplasma* IgG antibodies. Testosterone concentration was significantly higher in infected subjects compared with in controls. The authors concluded that *Toxoplasma* can affect the mean concentration of serum testosterone in humans.

Lim et al. (70) examined whether testosterone is responsible for *T. gondii*–associated behavior change, specifically, whether it enhances sexual attractiveness and reduces innate fear of cat odor in infected male rats. Results showed that *T. gondii* infection enhanced expression of genes involved in facilitating testosterone synthesis, which resulted in greater testicular testosterone production in male rats. The authors concluded that augmentation of testosterone synthesis by *T. gondii* may manipulate rats' behavior.

Immune Response

T. gondii–induced behavioral effects could also be the result of a local immune response in the brain to keep *T. gondii* dormant, resulting in changes in cytokines and neuromodulators (64, 72). *T. gondii*–infected rats have increased levels of certain cytokines that are associated with anxiety-like behaviors (73). Bay-Richter et al. (73) infected Flinders resistant line and Flinders sensitive line rats with *T. gondii* ME49 and examined neurological changes by using light microscopy post-mortem. They found that infection altered the expression of cytokines and IL-1α and that the change was greater for genetically vulnerable animals.

SUMMARY AND OUTLOOK

Over the past 30 years, extensive research has examined the potential link between *T. gondii* infection and behavioral alteration in different species. Disentangling causation from correlation represents a long-standing challenge in this line of inquiry, alongside potential issues surrounding reporting bias in favor of more sensational results, whether by scientists or the media. Experimental exposure studies, particularly using laboratory model species such as rats and mice, have provided some of the most compelling evidence for parasite-induced behavioral alteration. In general, these studies have found broadly that infecting rodents with *T. gondii* causes general behavioral changes and reduced avoidance of cat odor. Nonetheless, whether infection actually enhances transmission (i.e., via increased predation of infected hosts) under natural conditions remains undemonstrated, limiting conclusions about whether infection-induced changes are adaptive for the parasite. Despite the large range of vertebrate secondary hosts for *T. gondii* in nature, most experimental infection studies have focused on laboratory breeds of mice and rats, with comparatively little work performed on other host taxa.

Studies on the link between human behavior and infection have also expanded dramatically in scope and number in recent years, with suggested correlations between *T. gondii* and mental illness, car accidents, risky behavior, and entrepreneurship. Although typically correlational, these findings broadly parallel those from experimental animal model systems. The most consistently reported linkages are between infection and car accidents, suicide, and mental illness. Of particular importance have been longitudinal cohort studies able to track individuals through time, both before and following exposure to *T. gondii*. However, birth cohort studies raise the need for additional research using randomly selected, longitudinally studied human populations in an effort to examine within-person changes in personality, mental illness, and behavior resulting from *T. gondii* infection (48).

Research into the potential mechanisms linking *T. gondii* infection and behavior has typically focused on one of three domains: generalized inflammation, alteration in endocrine signaling, and changes in neurotransmitter pathways. Dopamine and testosterone changes stand out as having the most compelling evidence, although there is no clear consensus as to whether one is dominant. This could instead suggest that the behavioral effects of *T. gondii* have multiple mechanisms, which remains an underexplored possibility. Additional topics that warrant additional investigation include the relative importance of the genetic strain or lineage of *T. gondii*, as well as the role of exposure pathways in affecting observed effects. Recent studies have shown or suggested, for instance, that *T. gondii* genotype can affect infection and behavior changes (21, 37), although the potential for the exposure pathway (e.g., oocysts from soil or water versus from contaminated meat) to influence subsequent effects in hosts remains relatively unknown.

There is little doubt that *T. gondii* causes behavioral changes in rodents with the potential to promote transmission. The neurological or hormonal changes that facilitate those changes (as well as the specificity of the changes) are still up for debate. The effects of the parasite on humans are less certain, but it is clear from the extant data that *T. gondii* poses a risk to humans beyond those who are pregnant or immunocompromised. Future research should continue to explore the risk factors resulting from *T. gondii* infection.

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Errata

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