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Abstract

The parasite *Toxoplasma gondii* is thought to be prevalent in humans, although the infection is typically latent. Cats are the definitive hosts of the parasite and it is believed the parasite is transmitted to humans through contact with cat feces. *T. gondii* is of particular interest to researchers because of its proposed effects on the central nervous system in humans. The parasite is able to enter the central nervous system and affect dopamine metabolism. Increased dopamine levels in infected cells primarily cause changes in the components of the limbic system. This has led to the proposed effects of increased impulsivity and aggression in people with active *T. gondii* infections. One of the most interesting effects of *T. gondii* in humans is its proposed contribution to schizophrenia. Schizophrenia alone is not well understood as to what causes the illness. There are studies that have hypothesized an increased level of *T. gondii* antibodies is correlated with increased risk for development of schizophrenia. This hypothesis is intriguing and requires further investigation.
Introduction

Toxoplasma gondii is a fairly common parasite in the United States, possibly infecting about forty million Americans, although most of the infections remain latent and never cause any problems (Centers for Disease Control and Prevention (CDC), 2018). However, an active T. gondii infection is dangerous especially for pregnant women and immunocompromised individuals because these populations are at risk for reactivation of the T. gondii infection and development of life-threatening toxoplasmic encephalitis (Carruthers and Suzuki, 2007). Many of the symptoms are typical flu-like symptoms such as fever and muscle aches and pains, but in more serious infections, T. gondii can infect neurons, and this could interfere with dopamine- and glutamate-mediated neurotransmission. The consequences of these changes in humans can be extreme. In congenital infections of T. gondii for example, the parasitic infection can cause severe neurological and ophthalmologic disease (Carruthers and Suzuki, 2007).

Physiological changes are only part of the danger of T. gondii infection. Perhaps the most intriguing aspect of T. gondii is its ability to alter behavior in rats and also in humans. It has been suggested that this protozoan parasite could be a contributing factor to altering human behaviors such as increasing aggressiveness and impulsivity. T. gondii may also have a role in depression, anxiety, and most interestingly schizophrenia. Since the 1950s, research on T. gondii infection as a contributing causal factor to schizophrenia has increased. Presented here are studies examining physiological and behavioral effects of T. gondii infection in rats and exploring if similar effects can be found in humans. Also presented here is an assessment of a possible cause and effect relationship between T. gondii and schizophrenia. In order to
understand this parasite and its effects, we will first present the basic biology of the *T. gondii* parasite, including its life cycle, hosts, reproduction, and mechanisms of infection.

**Life Cycle and Reproduction of Toxoplasma gondii**

**Hosts and Primary Forms**

Toxoplasmosis is an infection caused by a single-celled, intracellular protozoan parasite *Toxoplasma gondii*. The definitive hosts of the parasite are members of the family *Felidae* which consists of domestic cats and their relatives and these hosts can infect most warm-blooded species of animals. The primary forms of *T. gondii* are oocysts, tachyzoites, and bradyzoites. Oocysts are only produced in cats, which are the definitive hosts, and then passed in the feces and ingested by other animals to cause infection. The tachyzoites are the rapidly multiplying form of *T. gondii* which localize to muscle tissues and the central nervous system where they change into tissue cyst bradyzoites. The bradyzoites are the slowly multiplying, encysted form of the parasite and cause the host immune response to occur. The bradyzoites will transform back into tachyzoites when entering a new host (Nguyen, 2006). The tachyzoite is the life stage of the parasite which causes physiological and behavioral changes in the host during an active infection.

**Life Cycle and Reproduction**

The life cycle of *T. gondii* begins with unsporulated oocysts being shed in the feces from an infected cat. Intermediate hosts are then infected after ingestion of soil, water, or plant material contaminated with oocysts. The oocysts become tachyzoites shortly after ingestion by the intermediate hosts and localize in the neural and muscle tissues before developing into tissue cyst bradyzoites. More cats can become infected by consuming intermediate hosts, such
as birds, that have tissue cyst bradyzoites. Other animals for human consumption such as pigs, sheep, and certain birds can be infected with tissue cysts after ingestion of sporulated oocysts in the environment. This results in infection of the human after ingestion of contaminated meat. Once in the human, *T. gondii* forms tissue cysts which persist throughout the host’s lifetime (CDC, 2018). Reproduction of the parasite only occurs sexually in cats, while asexual reproduction occurs in intermediate hosts (Luna, 2016). Figure 1 is a depiction of the life cycle of *T. gondii* beginning with fecal oocysts from cats and ending in tissue cysts in humans.

Mechanisms for Human Infection

*T. gondii* infects about forty million people in the United States, but very few people have symptoms because a healthy person’s immune system normally is able to prevent the parasite from becoming active and causing illness. Infection occurs in humans through eating undercooked, contaminated meat such as pork, lamb, or venison, not washing hands thoroughly after handling contaminated meat, using contaminated utensils to prepare other food, drinking contaminated water, swallowing the parasite through contact with cat feces containing *T. gondii* through cleaning a litterbox, touching or ingesting anything that has come into contact with cat feces, or ingesting contaminated soil. Vertical transmission occurs through congenital transmission from mother to child during pregnancy. Horizontal transmission occurs through infected organ transplants or blood transfusions. Cultural habits also play a role in infection because of the food choices made by some cultures to ingest animals that are more likely to be infected. There are also geographical areas where the environment is more likely to have contaminated material (CDC, 2018).

Symptoms and Treatment

There are three strains of *T. gondii*, type I being the most aggressively growing strain and types II and III the less aggressive, but still disease-causing strains (Carruthers and Suzuki, 2007). Although most infections are latent and have no symptoms, those infections that do produce symptoms result in flu-like symptoms with swollen lymph glands and muscle aches and pains that last for one month or more. Ocular symptoms include reduced or blurred vision, pain with bright light, redness of the eyes, and tearing (CDC, 2018). Other general symptoms of an infection can occur such as cervical lymphadenopathy, fever, malaise, night sweats, myalgia,
sore throat, and rash (Nguyen, 2006). The biggest danger is for pregnant women and immune compromised patients because their risk of infection and developing symptoms is greater due to decreased immunity. The part of the body that is most affected in humans is the brain (Mendez, 2017).

Treatment for those who are infected and showing symptoms is not necessary, but there are medications available for treatment such as sulphadiazine and pyrimethamine. Sulphadiazine and pyrimethamine are frequently used in combination for treatment of *T. gondii* infections because these drugs have synergistic activity against the replicating form of *T. gondii*, the tachyzoites. Sulphadiazine and pyrimethamine inhibit the parasite enzymes dihydropteroate synthase (DHPS) and dihydrofolate reductase (DHFR) (Bilgin et al., 2013). DHPS is an enzyme involved in the folate synthesis pathway which is essential for synthesizing amino acids required for function and growth of bacteria and parasites (Hall and Petek, 2012). DHFR is an enzyme involved in the reduction of dihydrofolate to tetrahydrofolate. Tetrahydrofolate is a precursor for purine synthesis, and purines are necessary in DNA synthesis and replication (Gagné, 2014). Inhibition of DHPS and DHFR by sulphadiazine and pyrimethamine therefore inhibits the growth and replication of the tachyzoite form of the *T. gondii* parasite.

**Effects of *T. gondii* on Rats**

The *T. gondii* parasite sparks interest among researchers because of its proposed unusual ability to alter not only the behavior of rats, but possibly that of humans as well. Rats are more ideal for use in studies on *T. gondii* instead of mice because *T. gondii* infection is very virulent in mice, whereas infection in rats in a more accurate representation of the clinical condition in humans (Bay-Richter et al., 2019). It has been proposed that rats infected with the
parasite lose fear of cats because they lose fear of the smell of cat urine, which normally serves as a danger signal for rats. Instead, the rats feel a sort of sexual attraction to the smell of the cat urine because *T. gondii* can cause changes in neural activity in certain areas of the brain which control fear (Bucklin, 2016). One study demonstrates that *T. gondii* infected rats display an attraction specifically for feline urine while maintaining their aversion to urine of other predators (Bay-Richter et al., 2019). Another study performed in 2000 by Berdoy et al. used test pens with four different scents in each corner, rat urine, water, rabbit urine, and cat urine, to test how *T. gondii* infection affected the amount of times the infected rats visited each of the four sites. As can be seen in Figure 2, infected rats visited the sites with water, rat urine, or rabbit urine about the same amount as the uninfected control rats. The figure also shows that infected rats visited the corner of the pen with cat urine significantly more than the uninfected rats, enforcing the hypothesis that *T. gondii* alters the behavioral response of rats to cat urine (Berdoy et al., 2000).

![Figure 2](image.png)

*Figure 2. Mean numbers of visits to the four scented areas in the outdoor pens over one night.*

It has been speculated that the ability of *T. gondii* to modify the behavior of its intermediate host has evolved because this increases its chances of entering a cat, the definitive host (Yong, 2008). This is known by some as the manipulation hypothesis where a parasite manipulates the behavior of its intermediate host to enhance its transmission into the definitive host (Webster, 2007). Sexual reproduction of *T. gondii* can only occur in feline hosts, so there are strong selective pressures on the parasite to evolve mechanisms to enhance its transmission into the definitive feline hosts from the intermediate hosts to complete its life cycle (Webster, 2007). In a study by Bay-Richter et al. (2019), *T. gondii* infected rats displayed increased levels of the cytokines IL-4, IL-6, IL12-p70, GLP-1, IL-1α, and CM-CSF, cytokines known to be associated with anxiety-like behaviors, which the researchers suggest is one of the probable causes of alteration of rat behavior.

The results of the study by Bay-Richter et al. (2019) show that elevation of the mentioned cytokines may be directly related to anxiety-like behavior through the use of various behavioral tests such as the light-dark box test. In this test, the rat is placed in a box where one half of the box is dark and has a lid while the other half is white, open, and brightly illuminated. The rat is able to move freely between the compartments because of the presence of an open door. As Figure 3 shows, both the healthy control rats (FRL) and genetically vulnerable rats (FSL) spent less time in the white compartment of the box if they were infected with *T. gondii*. The Flinders sensitive line (FSL) rats are rats which have been shown to display symptoms of depression and anxiety due to a genetic predisposition (Bay-Richter et al., 2019). *T. gondii* causes anxiety-like behaviors to increase, and in this test, an anxious rat prefers to be in the safety of the dark, enclosed half of the box. This may seem contradictory to the effect of *T.*
*gondii* increasing rat preference for cat urine, but it is likely that these are two different, unrelated effects. The increased preference for cat urine is an evolutionary advantage for the parasite, but the increased anxiety in *T. gondii* infected rats could be a side effect caused by the host responding to the parasite. This increased anxiety was also associated with increased levels of cytokines known to be involved in anxiety-like behaviors.


Webster (2007) presented additional plausible hypotheses for the alterations in the behavior of rats infected with *T. gondii*, such as histopathological, immunological, and neuromodulatory changes. In infected rats, multi-focal lesions and histopathological changes in the cyst-containing regions of the brain have been observed. Some of these histopathological changes include inflammatory granulomatous changes of perivascular areas of the brain,
progressive deposition of necrotic material, and vesicular occlusion and sclerosis (Webster, 2007). Supplementing the hypothesis of increased levels of cytokines in infected rats causing behavioral changes, Webster (2007) proposed that latent toxoplasmosis can cause permanently increased levels of mRNA of the cytokines TNFα and IL-10. It is probable that the local immune response in the brain required to keep T. gondii dormant, may alter the levels of these cytokines and those listed by Bay-Richter et al. (2019) resulting in changes in neuromodulator levels (Webster, 2007). In turn, neuromodulation could be the main mechanism of changing the expression of host behavior. Blocking the N-methyl-D-aspartic acid receptors in the amygdala, which are normally anxiogenic, and use of serotonin antagonists causes rats to become fearless to cat urine, in a similar manner to T. gondii infected rats (Webster, 2007). Some of the main neurotransmitters proposed by Webster (2007) to cause these types of behavioral changes in infected rats are homovanillic acid, norepinephrine, and dopamine. These hypotheses of how T. gondii modifies behavior in rats has led researchers to study the effects of T. gondii on human behavior with these hypotheses as starting points.

**Proposed Effects of T. gondii in Humans**

**Potential Link to Schizophrenia**

Schizophrenia is a complicated disease for which the cause is not specifically known. Schizophrenia is not caused by just one main, environmental, or genetic factor, but it is a disease caused by multiple factors which are additive in their effects. Since the 1950s, it has been proposed that toxoplasmosis, the disease manifestation of T. gondii infection, may be a contributing cause of schizophrenia because sometimes the transient symptoms of toxoplasmosis resemble the clinical signs of paranoid schizophrenia. (Flegr, 2015). As previously
stated, cats are the definitive hosts of the *T. gondii* parasite, and a study by Torrey and Yolken (1995) pointed out that the risk factor common to both schizophrenia and toxoplasmosis is contact with cats. The questions being addressed in human studies are, once infected with *T. gondii*, which parts of the human body are most affected, and what changes does the parasite cause that can lead to schizophrenia?

**Entering and Infecting the Central Nervous System**

Some of the main influences of *T. gondii* on human behavior include pseudo-kinase proteins involved in the virulence of the parasite, changes in dopamine metabolism, changes in trait aggression and impulsivity, and the possible contribution to schizophrenia and other mental disorders (Cook et al., 2015). *T. gondii*, like other brain invading parasites, must cross the blood brain barrier to be able to affect cells within brain tissues. *T. gondii* has three methods for crossing the blood brain barrier: paracellular crossing, transcellular crossing, and by an infected immune cell crossing the blood brain barrier and bringing the parasite with it.

Paracellular entry occurs when *T. gondii* crosses through the tight junctions of endothelial cells (Mendez, 2017). The parasite traverses the intestinal or placental epithelium as a free parasite by paracellular migration and enters circulating cells such as macrophages or dendritic cells (Carruthers and Suzuki, 2007). Transcellular migration occurs when a cell becomes infected, replicates, and lyses or egresses from the basolateral side. Tachyzoites are the form of the parasite which cross the blood brain barrier (Mendez, 2017). Once *T. gondii* tachyzoites have crossed the blood brain barrier and entered the central nervous system, the parasite persists as cysts mostly in neurons and astrocytes. The major difference between infection of these two cell types is that astrocytes are typically able to clear infections caused by intracellular parasites.
such as *T. gondii*, but neurons are unable to clear *T. gondii* infections on their own. Therefore, *T. gondii* infection may initially be present in astrocytes and neurons, but persistent infection occurs in neurons where the majority of cysts are (Mendez, 2017).

**Contribution of Pseudo-Kinases to Virulence**

One of the characteristics of *T. gondii* that is perhaps the most striking is its ability to infect almost any type of warm-blooded animal. Reese et al. (2011) raised the question of how *T. gondii* is able to infect various types of cells in a host of warm-blooded animals. *Toxoplasma gondii* secretes many different proteins into host cells from organelles the parasite has called rhoptries and dense organelles. One of these proteins is ROP18 which is a catalytically active kinase that phosphorylates and inactivates host GTPases involved in the immune system. ROP16 is another protein which is a tyrosine kinase that phosphorylates the STAT proteins in the host (Reese et al., 2011). STAT proteins are intracellular transcription factors which are involved in cell immunity, proliferation, apoptosis, and differentiation. ROP5 is another protein which acts as a catalytically inactive pseudo-kinase and was found to act independently of ROP16 and ROP18. Although all three proteins are involved in the virulence of the *T. gondii* parasite, ROP5 appears to play a larger role than ROP 18 in *in vivo* infection. It is proposed that ROP5, as a catalytically inactive pseudo-kinase, may function in a similar manner to other known pseudo-kinases as a molecular scaffold which can coordinate signal transduction. Reese et al. (2011) suggested that differences in the virulence of different strains of *T. gondii* are caused by how ROP5 interacts inside the host cells, and how it can interact with other parasite proteins to affect host signaling. There are different copy numbers and different alleles of the ROP5 protein in the different strains of the *T. gondii* parasite, and this diversity of ROP5 as well
as other parasitic proteins is what allows *T. gondii* to infect a multitude of warm-blooded animals (Reese et al., 2011).

**Dopamine Metabolism**

Parasite proteins such as the ROP proteins can affect signaling in the host cells. One important signaling molecule affected by the *T. gondii* parasite is the neurotransmitter dopamine. The amygdala and hippocampal areas of the brain are part of the limbic system and dopaminergic neurons in other portions of the brain receive information from these areas (Haber and Fudge, 1997). These other portions of the brain with dopaminergic neurons are the nucleus accumbens and ventral tegmental area (Haber and Fudge, 1997). In a study by Prandovsky et al., it was found that the levels of dopamine in the brains of mice chronically infected with *T. gondii* were elevated by fourteen percent, while the levels of other neurotransmitters remained the same (2011). Dopamine staining revealed that the neurotransmitter localized primarily in the *T. gondii* tissue cysts. To exclude the possibility that a neurotransmitter other than dopamine was causing these results, exogenous serotonin was added, and this did not affect the dopamine staining, confirming dopamine, or possibly the precursor to dopamine, L-DOPA, was causing the staining. Not only were dopamine levels increased in infected cells, but dopamine release levels were also elevated in infected cells. Tyrosine hydroxylase, the rate-limiting enzyme in dopamine synthesis, was found to be localized in the tissue cysts of the brains of mice chronically infected with *T. gondii* (Prandovsky et al., 2011).

Gaskell et al. (2009) identified two genes for tyrosine hydroxylases in the genome of *T. gondii*. These genes are likely responsible for the increased production of dopamine in *T. gondii*
tissue cysts (Flegr, 2015). The increased dopamine synthesis could be a biological adaptation of
*T. gondii* to manipulate the behavior of intermediate hosts to enhance transmission. Dopamine
has been known to play a role in schizophrenia. The increased levels of dopamine caused by *T.
gondii* infection in specific areas of the brain may be responsible for some of the positive
symptoms of schizophrenia such as delusions and hallucinations (Flegr, 2015).

Why is alteration of dopamine metabolism an important feature of the *T. gondii*
parasite? Dopamine metabolism mediates host behavior based on levels of dopamine and its
release. Increases in dopamine synthesis may also be a contributing factor to schizophrenia.
Areas of the brain that are particularly susceptible to changes in dopamine levels are the
nucleus accumbens and ventral tegmental area which receive information from parts of the
limbic system (Haber and Fudge, 1997). These areas play roles in movement in the basal
ganglia, reward to stimuli, pleasure, and dependency in the nucleus accumbens and
hippocampus, motivation and cognition, and species and stimuli specific fears in the amygdala.
Therefore, changes in dopamine metabolism in the amygdala help to explain how *T. gondii*,
through altering dopamine levels and release, can cause rats to lose their fear of cat urine.

**Trait Aggression and Impulsivity**

In addition to its effects on rats, dopamine changes caused by *T. gondii* may be
responsible for aggression and impulsivity changes in normally healthy adult humans. Cook et
al. studied how *T. gondii* infection may cause or worsen trait aggression or impulsivity directly,
or through host immune activation (2015). In rats, elevated dopamine release in the nucleus
accumbens was correlated with increased firing of ventral tegmental neurons, and this was
observed during aggressive encounters. Blocking the dopamine receptors of rats in these brain
areas caused anti-aggressive effects. This conclusion reached by others contradicts the results from Cook’s study. Cook suggests lower dopamine production and storage capacity may be associated with increased aggression (Cook et al, 2015). Another explanation is that pro-inflammatory cytokines and anti-inflammatory signals may both be responsible for these behavioral effects. Pro-inflammatory cytokines induce increased breakdown of tryptophan. Tryptophan is necessary for *T. gondii* replication, and pro-inflammatory cytokines serve as a major line of defense against the *T. gondii* parasite because they break down tryptophan. A consequence of breaking down tryptophan is decreased serotonin synthesis because serotonin is synthesized from tryptophan. Cook hypothesizes that this immune reaction to *T. gondii* infection, breakdown of tryptophan, leads to impulsivity and aggression via decreased serotonin synthesis (2015). Anti-inflammatory signals are released from the parasite to decrease the host immune response, resulting in a temporary reactivation of the *T. gondii* infection because tryptophan levels would increase, allowing the parasite to replicate again. It is therefore not the parasite directly causing increased aggression and impulsivity, but rather the host’s immune response to the parasite.

**Proposed Link to Schizophrenia**

**Overview of schizophrenia.** Perhaps one of the most debatable and controversial effects of *T. gondii* infection in humans is the possible link between *T. gondii* and increased risk of schizophrenia. Schizophrenia is a mental disorder in which the person interprets reality abnormally and it may result in hallucinations, disordered thinking, delusions, and behavior that impairs their ability to function from day to day (Mayo Clinic, 2018). Although there is not a definite cause of schizophrenia, issues with normal brain neurotransmitters such as dopamine
and glutamate may contribute to the disorder. The Mayo Clinic lists increased immune system activation from inflammation or autoimmune diseases, and pregnancy complications such as exposure to toxins or viruses that can affect brain development of the fetus as other potential risk factors for schizophrenia. There are increasing studies producing results which indicate \textit{T. gondii} plays a role in schizophrenia along with other environmental and genetic factors.

\textbf{Prevalence of schizophrenia and \textit{T. gondii}.} Schizophrenia affects about one percent of the population of the United States, while \textit{T. gondii}, normally in a latent form, affects about eight percent of the population, although the numbers of those infected with latent \textit{T. gondii} vary because of lack of testing for the parasite for normally healthy adults. The prevalence of \textit{T. gondii} varies between countries with some studies stating it is 10 to 30\% in North America, Southeast Asia, and Northern Europe, 30 to 50\% in Central and Southern Europe and Northern Africa, and the highest prevalence of the parasite is found in areas where the climate is more tropical including South America and tropical African countries (Esshili et al, 2016). One could argue that it is mere coincidence that there is an association between \textit{T. gondii} and schizophrenia because of the prevalence percentage of the parasite, but there are multiple studies that support an association between schizophrenia and \textit{T. gondii} as a sort of cause and effect relationship. Some hypotheses for how \textit{T. gondii} contributes to schizophrenia include increased dopamine synthesis and changes in tryptophan synthesis.

\textbf{Tryptophan changes in \textit{T. gondii} infection.} It has already been stated that \textit{T. gondii} requires tryptophan in order to replicate. What is so significant about tryptophan that the parasite cannot replicate without it? The immunological reaction to \textit{T. gondii} may disrupt tryptophan metabolism by the infected cells secreting large amounts of kynurenic acid (KYNA)
through the indoleamine-2,3-dioxygenase (IDO)-mediated tryptophan degradation pathway (Burgdorf et al., 2019). Latent *T. gondii* causes production of the enzyme IDO and another enzyme, tryptophan dioxygenase (TDO), in astrocytes. These enzymes are responsible for breaking down tryptophan which prevents the parasite from replicating and keeps it in the latent form. Degradation of tryptophan by IDO produces kynurenine. Kynurenine is either metabolized to KYNA which is an antagonist of the glutamate N-methyl-D-aspartate (NMDA) receptor and nicotinic receptors or hydroxylated to quinolinate which is a potent NMDA neurotoxic agent (Burgdorf et al., 2019). The NMDA receptors are glutamatergic receptors, which are excitatory, so antagonizing or inhibiting the NMDA receptors results in decreased excitability meaning the *T. gondii* infection will remain latent. High levels of KYNA have been found in the cerebrospinal fluid of schizophrenic individuals, indicating these same individuals may have a latent *T. gondii* infection. This study by Burgdorf et al. (2019) thus shows that in addition to dopaminergic neurotransmission, glutamatergic neurotransmission is also affected by *T. gondii*.

**Relationship between IgG antibodies against *T. gondii* and schizophrenia.** One study used neonatal blood samples that had been stored on filter papers and compared them to current blood samples from the same subjects if they were still living (Mortensen et al., 2007). The researchers compared levels of IgG antibodies for *T. gondii* in the samples from the adult subjects from whom the neonatal samples were taken at an earlier time and compared them to the levels of IgG antibodies for *T. gondii* in control subjects without the parasite. It was found that subjects who later developed schizophrenia had significantly elevated levels of IgG antibodies against *T. gondii* compared to the control subjects, suggesting there is an association
between the parasite and the disorder. This finding was also apparent in a similar study by Esshili et al. where IgG antibody to *T. gondii* was 74.8% in schizophrenic patients compared to 53.8% in the control subjects (Esshili et al., 2016). Subjects who later developed bipolar affective disorder or other affective disorders did not have elevated IgG antibodies against *T. gondii*. The main conclusion reached from Mortensen’s study is that there is a significant correlation between elevated levels of IgG antibodies against *T. gondii* and the diagnosis of schizophrenia in the same subjects before the age of eighteen (2007).

**Interpretation of Mortensen et al. (2007) and Esshili et al. (2016) study results.**

Perinatal infection by other viruses or parasites such as rubella or cytomegalovirus were ruled out as the cause of increased antibody levels in these two studies because the levels of IgM antibodies, which are the first antibodies to respond to a new infection, were low in those subjects later diagnosed with schizophrenia. This is not to say that perinatal *T. gondii* infection causes schizophrenia to develop later, but rather that the conclusions of the study are one way to interpret the results. There are many possibilities for elevated antibodies at this stage and the cause of schizophrenia is not known. Instead, the elevated levels of IgG antibodies against the parasite are likely to indicate cat ownership since cats are the only definitive hosts of *T. gondii*. A further interpretation given by Mortensen (2007) is that exposure to a cat during early childhood is associated with increased risk of schizophrenia developing later in the child’s life. Although these are interpretations of the results, *T. gondii* is a plausible parasite to cause persistent neuropsychiatric diseases such as schizophrenia because of its known ability to alter key neurotransmitter levels such as dopamine and glutamate, as well as its ability to affect neurons and cognitive function. *T. gondii* in culture has also been shown to be inhibited by
some antipsychotics and mood stabilizers frequently used as treatments for mental disorders such as schizophrenia (Mortensen et al., 2007).

A second study already mentioned that more recently explored the relationship between *T. gondii* and schizophrenia was performed in Tunisia, a country located in northern Africa between the Sahara Desert and the Mediterranean Sea. This study was performed similar to Mortensen’s study by observing the IgG antibody levels against the parasite in both schizophrenic subjects and control subjects. Eshilli found the rate of infection by *T. gondii* in schizophrenic patients was statistically higher than in control patients, also claiming that the parasitic infection increased the risk for schizophrenia by about 2.5 times (2016). This is not to say *T. gondii* is a direct cause or indicator for development of schizophrenia, but it may be involved as a cofactor along with other factors such as genetics and environment. *T. gondii* does have a direct impact on the brain and immune system mechanisms and affects neurotransmission, as previously discussed. *T. gondii* will typically infect both neurons and astrocytes within the brain, and these infected astrocytes and other microglia will produce pro-inflammatory cytokines. The pro-inflammatory cytokines can then alter the glutamatergic neurotransmission which is a change observed in schizophrenic patients. The important part of the parasite’s life cycle here is the bradyzoite which, during the development, could directly alter dopamine biosynthesis which is observed in persons with psychotic disorders (Eshili et al., 2016).

**Treatments and What They Target**

In the study by Eshili et al. (2016), schizophrenic patients were treated with either a typical antipsychotic such as Haloperidol, Fluphenazine, or Chlorpromazine, with an atypical
antipsychotic such as Risperidone, Olanzapine, or Amisulpride, or with both typical and atypical antipsychotic medications. Over half of the patients were also taking anticholinergic medications (Esshili et al., 2016). There are several anti-psychotic drugs and mood stabilizers which have anti-\textit{T. gondii} effects, although the medications were not originally prescribed to target the parasite. Haloperidol functions by inhibiting the effects of dopamine though competitively blocking post-synaptic dopamine receptors in the brain. This prevents neurotransmission through dopamine and can relieve delusions or hallucinations (DrugBank, 2019d). Haloperidol is used primarily to treat schizophrenia and other forms of psychosis.

Fluphenazine is also used in managing schizophrenia and functions through blocking post-synaptic mesolimbic dopamine receptors in the brain (DrugBank, 2019c). Chlorpromazine functions similarly to Haloperidol and Fluphenazine, and is used to treat schizophrenia, although unlike the other two drugs, Chlorpromazine has many other targets such as relieving restlessness before surgery and tetanus (DrugBank, 2019b). Risperidone and Olanzapine function similarly to the other drugs already described for schizophrenia. Amisulpride is slightly different from the other drugs in that at low doses it binds to and blocks pre-synaptic dopamine receptors which enhances dopaminergic transmission, while at higher doses it blocks post-synaptic dopamine receptors to prevent hyperactivity (DrugBank, 2019a).

Fluphenazine, Haloperidol, and the mood stabilizer valproic acid have been found to be powerful and specific inhibitors of \textit{T. gondii} reproduction during \textit{in vitro} cultivation (Flegr, 2015). Nearly all modern antipsychotics either decrease the dopamine concentration or downregulate the activity of its receptors on neural cells (Flegr, 2015). There may be causes other than \textit{T. gondii} infection for the increased dopamine levels seen in schizophrenic patients.
However, the drugs which decrease dopamine and have been found to inhibit replication of *T. gondii* provide evidence that *T. gondii* may likely be a contributing factor to schizophrenia.

**Conclusion**

*Toxoplasma gondii* is a parasite known to be transmitted from cats to humans most commonly through contact with cat feces. It is suggested this parasite infects almost forty million Americans, although most infections in humans are latent and never cause any problems because a healthy person’s immune system can normally fight off the infection. Pregnant women and immune compromised individuals are at much greater risk for reactivation of the *T. gondii* infection. Some of the most common ways humans are infected is through contact with contaminated cat feces, vertical transmission from mother to child, horizontal transmission through infected transplant organs, and through ingesting infected animals due to cultural beliefs or habits. *Toxoplasma gondii* has been of interest to researchers since the 1950s because of the effect it has on rats. Some studies have shown that rats infected with *T. gondii* lose their instinctual fear of cat urine, making them more likely to become prey. Furthering research on *T. gondii* has shifted to a focus on the proposed effects of the parasite in humans, and the possible link to schizophrenia.

The parasite can infect almost any warm-blooded species and can enter the central nervous system using pseudo-kinase proteins which inactivate host GTPases involved in the host’s immune system. Once in the central nervous system, the parasite is proposed to exert an effect on the dopaminergic neurons to increase dopamine neurotransmission. Areas of the human brain that are particularly susceptible to changes in dopamine levels are the amygdala, nucleus accumbens, and other limbic regions of the brain. Alterations of dopamine metabolism
may be linked to the increased aggressivity and impulsiveness associated with *T. gondii* infection. There have also been studies on the possibility of *T. gondii* having a role in schizophrenia. Schizophrenia as a disease is not well understood as to what its exact cause is, but it is well known that increased dopamine levels play a significant role.

Other proposed theories suggest that infected astrocytes and microglia in the brain release pro-inflammatory cytokines which alter the glutamatergic or dopaminergic neurotransmission, changes in which are associated with schizophrenia. There are anti-psychotic and mood stabilizer drugs such as Haloperidol which inhibit dopamine transmission. Haloperidol and other anti-psychotics used in the treatment of schizophrenia not only decrease dopamine but have also been shown to inhibit replication of *T. gondii*. *T. gondii* has been associated with increased levels of dopamine in both rats and humans, so it is likely that drugs such as Haloperidol decrease dopamine because they inhibit *T. gondii*. The studies presented here are only a few of many that provide increasing evidence for an association between *T. gondii* and schizophrenia. Further research is necessary to increase support of these findings and to enhance the understanding of schizophrenia as a disease itself.
References


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