

A comprehensive assessment of toxoplasmosis and its dormant impact on psychotic disorders (Review)

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Abstract. Toxoplasmosis is a pathological condition induced by the parasite, *Toxoplasma gondii* (*T. gondii*), which has a notable affinity for the cellular components of the central nervous system. Over the decades, the relationship between toxoplasmosis and the development of psychiatric disorders has generated profound interest within the scientific community. Whether considering immunocompetent or immunocompromised patients, epidemiological studies suggest that exposure to *T. gondii* may be associated with a higher risk of certain psychiatric disorders. However, there are extensive debates regarding the exact nature of this association and how *T. gondii* is involved in the pathogenesis of these disorders. Toxoplasmosis has long been considered an asymptomatic infection among immunocompetent patients. However, there appears to be an association between chronic brain infection with *T. gondii* and alterations in patient neuronal architecture, neurochemistry and behavior. The present review aimed to compile statements and pathophysiological hypotheses regarding the potential association between toxoplasmosis and psychotic disorders. Further research is necessary for understanding the potential relationship of *T. gondii* infection and psychotic disorders.

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1. Introduction

Exploring the involvement of infectious agents in the emergence of psychotic disorders is vital for understanding the intricate origins of these conditions. Various viral infections, such as herpes simplex virus, Epstein-Barr virus, influenza virus, cytomegalovirus, retrovirus and coronavirus, have been linked to psychotic disorders (1). Additionally, infections caused by the *Toxoplasma gondii* (*T. gondii*) parasite have also been implicated in the development of these disorders (acute and chronic psychotic episodes) (2).

T. gondii is an intracellular protozoan parasite that has infected approximately a third of the global human population (3). *T. gondii* was first identified over 110 years ago in the tissues of a North African rodent, *Ctenodactylus gundi*, by Nicolle and Manceaux in 1908, and has a complex life cycle involving intermediate and definitive hosts. In intermediate secondary hosts, the parasite engages in asexual reproduction, with the rapid division of tachyzoites and the slower division of bradyzoites, followed by their encystment in tissues (3). Blood transfusions, eating undercooked or raw meat, consumption of tainted food or water, receiving an organ donation and vertical transmission from an acutely infected pregnant woman to the fetus are all possible routes of infection in humans.

The seroprevalence of *T. gondii* infection varies across countries and is associated with various sociodemographic and risk factors, including age, ethnicity, residential location, pet ownership, water supply and pregnancy status (2). A high prevalence of toxoplasmosis has been reported in Africa, Southeast Asia, the Middle East, Central/Eastern Europe and Latin America. The prevalence of *T. gondii* infection varies widely, with reported rates in Asia ranging 13.3-85.3%, in Europe 40.0-76.0%, in Africa 21.7-74.8% and in North America 7.3-26.5% (4).

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Seropositivity for *T. gondii* has been distinctly associated with an elevated risk of physical health conditions (ophthalmological complications such as chorioretinitis; pulmonary complications such as pneumonia; and neurological complications such as seizures) and is notably linked with a heightened risk of several mental health disorders, with schizophrenia being the most highly associated disorder (5,6). There is also a link between socioeconomic status and the risk of *T. gondii* infection. Generally, individuals with lower incomes or from marginalized communities are more likely to be exposed to risk factors associated with toxoplasmosis, such as limited access to medical care, poor nutrition and inadequate housing conditions. Individuals working in agriculture, hunting or in frequent contact with domestic or wild animals may be more exposed to *T. gondii* and may therefore have an increased risk of infection (7). In urban environments, the risk of infection may be associated with factors such as contact with stray cats and exposure to contaminated food, while in rural settings, interactions with farm animals and consumption of raw or undercooked meat can increase the risk of infection (8). A recent study supported the notion that farming activities (such as gardening and agriculture) are significant factors associated with the seroprevalence of *T. gondii*, adding valuable insights to the current understanding of infection (9). Additionally, poor hygiene and a lack of access to clean drinking water can contribute to the spread of infection (10,11). Although the general consensus is that there is no direct connection between age and *T. gondii* infection, in a study by Teimouri *et al* (9) it was demonstrated that age is a relevant risk factor for *T. gondii* infection. The study established a clear association between *T. gondii* infection and age in psychiatric patients, indicating a notable increase in infection in individuals >30 years old compared with those ≤30 years old.

The two recognized forms of toxoplasmosis in humans include postnatal acquired toxoplasmosis, which occurs after birth, and congenital toxoplasmosis, which results from prenatal infection when a pregnant mother contracts the disease. There are also two types of postnatal acquired toxoplasmosis: Lifelong latent toxoplasmosis, which has historically been assumed to be clinically asymptomatic in immunocompetent individuals, and transient acute toxoplasmosis, which is characterized by a variety of specific and non-specific symptoms (lymphadenopathy, and flu-like symptoms including fever, headache and muscle pain (12,13). According to McLeod *et al* (14), *T. gondii* can harm patients receiving chemotherapy, organ transplant recipients and individuals with immunological deficiencies such as HIV/AIDS. However, in healthy individuals, the initial infection only causes moderate symptoms such as fever, enlarged lymph nodes or weakness in the muscles (15). In patients with total immunity, acute infections are typically cured on their own, but tachyzoites frequently become bradyzoites and remain latent within tissue cysts. *T. gondii* can undergo a transformation into intracellular cysts, residing in organs such as the liver, muscles and neuronal cells, persisting throughout the lifetime of the host. It has also been suggested that a correlation exists between chronic brain infection with *T. gondii* and alterations in patient neuronal architecture, neurochemistry and behavior (16,17).

While observational and epidemiological studies (2,14,18,19) have suggested a potential association between toxoplasmosis and psychosis, the intricate interplay of multiple factors contributing to this relationship remains unclear. Current research indicates that individuals with toxoplasmosis may have a higher risk of developing psychotic symptoms, possibly due to the ability of the parasite to affect neurotransmitter function and neural pathways in the brain (2). However, establishing a definitive causal relationship between toxoplasmosis and psychosis requires further investigation, particularly through longitudinal studies that can track individuals over time, to provide more robust evidence.

Acute toxoplasmosis can manifest symptoms resembling psychotic disorders, particularly when accompanied by positive psychiatric symptoms such as hallucinations and delusions (5). Previously, the latent form of *T. gondii* infection was considered to be devoid of significant sequelae, with only reactivation of the infection posing a real threat (20). However, an increasing body of evidence suggests that persistent and latent infection may contribute to various neurological and psychiatric disorder symptoms. For instance, individuals with latent toxoplasmosis exhibit specific alterations in psychomotor performance, characterized by decreased learning and memory capacity and significantly prolonged reaction times, and demonstrating lower IQ levels and a reduced probability of attaining higher education (21).

Given the profound influence of *T. gondii* on human health, numerous investigations have explored its lifecycle, immunology and pathogenesis. However, the present review specifically aimed to examine the role of *T. gondii* in the development of psychosis, as suggested by Zhu in 2009 (21), focusing on its pathophysiological mechanisms in psychiatry, its gene-environment interactions and current treatment modalities.

Psychotic disorders involve a lot of work regarding psychiatric evaluation, but often the main cause of the affliction can be overlooked; therefore, a deeper understanding of potential co-existing factors, such as infectious diseases (including toxoplasmosis), with such clinical manifestations is necessary.

2. Literature search methods

A literature review was performed using the PubMed (<https://pubmed.ncbi.nlm.nih.gov/>), Google Scholar (<https://scholar.google.com/>), Science Direct (<https://www.sciencedirect.com/>), Elsevier (<https://www.elsevier.com/>), Springer Link (<https://link.springer.com/>) and Medscape (<https://www.medscape.com/>) databases, searching for studies regarding toxoplasmosis and psychiatric disorders. The search words included '*toxoplasma*', 'risk factors', 'mental health', 'gene-environment interactions', 'pathophysiology', 'psychosis' and 'schizophrenia'. The included studies were published in the last five decades, published in English, conducted on humans and animal subjects, conducted on subjects ≥18 years old (for the human studies) and contained data about instances of toxoplasmosis that can present a similar symptomatology to psychotic disorders.

3. Pathophysiology of *T. gondii* in psychiatry

For over a century, various genetic theories have been presented to explain the causes of schizophrenia. It is well-known that the interaction between the genetic composition of an individual and the environment has a significant role in the development of schizophrenia. Based on the family clustering of cases, Emil Kraepelin proposed in 1919 that a 'hereditary predisposition' should be considered, stating 'I know a very great number of cases in which several brothers and sisters were attacked with dementia praecox'. Moreover, Kraepelin proposed additional hypotheses, such as 'infections in the years of development' (22).

Since 1950, there has been a proposed link between schizophrenia and *T. gondii* infection (23,24). Furthermore, numerous studies have substantiated the association between *T. gondii* infection and various mental health disorders, including schizophrenia, bipolar disorder, suicide attempts, personality disorders and instances of self-directed violence (14,20-22,25,26). The pathophysiology behind the influence of *T. gondii* on psychiatric conditions is multifaceted. It has been suggested that the parasite may induce an immune response or directly affect neurotransmitters such as dopamine, contributing to symptoms observed in schizophrenia and other disorders (27,28). One of the compelling hypotheses regarding the neuromodulatory effects of *T. gondii* infection revolves around the ability of the parasite cysts to disrupt dopamine metabolism (27). The detection of significant dopamine levels within *T. gondii* tissue cysts, coupled with an increased dopamine release from infected dopaminergic cells, underscores the potential influence of this parasite on neural cell function. The observation of *T. gondii* cysts in brain regions rich in dopamine, such as the amygdala and nucleus accumbens, raises concerns regarding the potential disruption of essential brain functions. Altered dopamine levels induced by the parasite in these critical regions may lead to a spectrum of behavioral changes and neurological dysfunctions, affecting processes related to movement control, reward, pleasure, motivation, cognition and the fear response (27).

Gaskell *et al* (29) identified two genes in the *T. gondii* genome responsible for encoding tyrosine hydroxylase, a key molecule involved in dopamine synthesis. Notably, Prandovszky *et al* (27) reported in 2011, utilizing both *in vitro* and *in vivo* methods, that *T. gondii* cysts enclosed within neurons not only expressed tyrosine hydroxylase but also produced dopamine. Additionally, after being stimulated by the immunological response, the infected cells exhibited a 3-fold increase in dopamine release compared with uninfected cells. In 2000, Berdoy *et al* (30) demonstrated that a mouse model infected with *T. gondii* displayed altered behavior, leading to a fatal attraction to feline predators. These findings propose that an overabundance of dopamine generated by the parasite might disrupt vital brain function, thereby directly influencing the behavior of the host organism.

Flegr (5) mentioned the potential influence of *T. gondii* on psychomotor performance. The study findings revealed that individuals with latent infection exhibited slower reaction times, scored lower on standardized computerized tests and appeared to experience faster declines in concentration.

In 2015, Celik *et al* (31) conducted a study that included 94 patients with schizophrenia, which revealed a notable seropositivity rate of 46% for anti-*T. gondii* IgG antibodies, with no significant sex-based differences. A further analysis based on illness status demonstrated a markedly higher seropositivity rate of 72% among 'chronic' patients, compared with 22% in the 'partial remission' group, while no positive cases were observed in the 'remission to a great extent' group. The prevalence of toxoplasmosis was significantly higher in patients with chronic illness compared with those in the partial remission and remission to a great extent groups. Additionally, the presence of latent toxoplasmosis was significantly higher in patients lacking awareness of their schizophrenia compared with those who were aware of their illness. These findings underscore a potential negative association between toxoplasmosis seroprevalence (including latent toxoplasmosis) and the clinical course of schizophrenia, emphasizing the need for further research to elucidate the intricate relationship between *T. gondii* infection and the manifestation of symptoms in patients with schizophrenia.

A study has investigated the impact of *T. gondii* tissue cysts on neuronal morphology and central nervous system pathology, which revealed significant alterations (31). In examining the impact of *Toxoplasma*-induced lesions, Parlog *et al* (32,33) uncovered compromised local connectivity, as indicated by changes in fiber density, disruptions in fiber continuity and decreased levels of the synaptic proteins, postsynaptic density protein 95 and synaptophysin. In a study exploring the effect of chronic infection on central nervous system pathology, David *et al* (34) documented alterations in neuronal morphology, specifically a decrease in dendritic spines, alongside changes in network activity. When investigating latent *Toxoplasma* infection in the context of schizophrenia, Horacek *et al* (6) employed whole-brain voxel-based morphometry of gray and white matter, and revealed a notable reduction in gray matter volume among *Toxoplasma*-positive individuals compared with *Toxoplasma*-negative individuals. These findings highlight the intricate influence of *Toxoplasma* infection on neuronal structure and overall brain morphology, particularly in chronic infection, and its association with schizophrenia.

Parlog *et al* (33) also elucidated the profound impact of chronic *T. gondii* infection-induced neuroinflammation on the synaptic physiology and morphology of non-infected neurons. This study was the first to demonstrate that chronic infection instigates alterations in protein expression within both presynaptic and postsynaptic compartments of mature synapses. In addition, their analysis further revealed that chronic *T. gondii* infection detrimentally affects neuronal structure by diminishing dendritic complexity and inducing modifications in dendritic spine number, distribution and morphology. Similar outcomes have been observed in various brain structures and components of the enteric nervous system (32,33,35). Additionally, using a rat model, Mitra *et al* (36) demonstrated that *T. gondii* induces dendritic arborization retraction in basolateral amygdala neurons to manipulate the fear response of the host.

4. Gene-environment interactions in schizophrenia

This section introduces the intricate relationship between *T. gondii* infection and the etiology of schizophrenia, underscoring the ‘parasite x genotype x stress’ interaction model. This model is a subset of the broader gene-environment interaction framework in schizophrenia and is instrumental in elucidating how genetic susceptibility, environmental factors and infectious agents interlace to influence the onset and progression of this complex psychiatric condition (37). The hypothesis that toxoplasmosis may contribute to schizophrenia is challenged by the fact that only a minority of those with *T. gondii* infection develop the disease. However, this discrepancy can be explained by individual differences in the response to *T. gondii*, notably that only infections resulting in cyst formation in the brain lead to behavioral alterations linked to the parasite. Furthermore, it has been demonstrated that not all *T. gondii*-exposed rats develop brain cysts and subsequent behavioral changes, suggesting a similar pattern may exist in humans where only a subset of those seropositive for *T. gondii* progress to the active form of infection that causes cyst formation (30,33-35).

Abdoli highlights the relevance of parasite strains in contributing to the severity of *T. gondii*-induced alterations, particularly in the context of neuropsychiatric disorders, mentioning the existence of three strains with different levels of virulence and epidemiological behaviour. Strain I is mainly associated with psychotic disorders such as schizophrenia and is more virulent than strains II and III. Furthermore, pregnant women infected with strain I had a significantly higher risk of their offspring developing schizophrenia and other psychotic disorders compared with unaffected mothers (38).

Genetic predispositions are critical in determining susceptibility to *T. gondii*, with genes such as disrupted-in-schizophrenia 1 (DISC1) playing a role in the host immune response against *T. gondii* and influencing the dopaminergic system. It was revealed that individuals homozygous for the DISC1 Phe607 variant had higher levels of serum anti-*T. gondii* IgG, thus linking genetic predisposition to the immune response (39). Studies on DISC1 animal models indicated that stress, particularly psychosocial isolation, is a prerequisite for the manifestation of behavioral abnormalities, even when *T. gondii* infection is not factored in, resonating with human studies that have identified stress as a trigger for psychosis (39-41).

5. Treatment

Treatment with antipsychotic medications in patients with schizophrenia has been linked to both the inhibition of *T. gondii* tachyzoite replication and increased levels of anti-*T. gondii* IgG antibodies (42,43). The parasite x genotype x stress model suggests a paradigm shift in schizophrenia treatment towards addressing underlying microbial infections and therefore tailoring psychiatric diagnoses to specific pathogens, potentially utilizing specific blood tests for more precise diagnoses. However, future research is needed to explore the variance in schizophrenia symptoms in relation to specific microbial infections and the timing of these infections (37).

In 2011, Goodwin *et al* (42) investigated the efficacy of antipsychotic medications against *T. gondii*, suggesting the therapeutic potential of fluphenazine and thioridazine and highlighting the complex nature of pharmacological interventions. Other commonly used antipsychotics, chlorpromazine and clozapine, are able to inhibit the replication of *T. gondii* (44). However, clinical trials on individuals with schizophrenia treated with anti-*T. gondii* agents such as trimethoprim (45) or azithromycin (46), showed limited improvement in the disease. By contrast, a study involving animals indicated that haloperidol or pyrimethamine plus dapsone were effective in mitigating behavioral changes due to *T. gondii* infection (44).

6. Conclusions

In the examination of behavioral changes related to *T. gondii* infection, research has revealed notable changes during the acute stage, suggesting a temporary, non-specific inflammatory response which appears in both the acute and chronic stages of infection, suggesting a multi-faceted interaction between *T. gondii* and neuronal dysfunction. Despite the extensive use of experimental mouse models, the exact mechanisms underlying this condition remain incompletely understood and require further clarification. The complex nature of the effects of *T. gondii* on cerebral functions suggests that a single mechanism cannot solely explain the behavioral and neuropsychological disorders associated with this infection. An increasing amount of evidence suggests that chronic *T. gondii* infection can impact both the structure and function of neuronal structures and can have a powerful impact on the behavior of the host. Several *in vitro* and *in vivo* techniques have been used to investigate the notable neuronal changes induced by the persistent presence of the parasite.

The potential association between certain microorganisms and the incidence of schizophrenia offers a promising direction for the improvement of preventive and therapeutic strategies. This relationship highlights the complex interaction between parasite growth, tissue lesions, inflammatory responses and host and parasite genotype influences, collectively influencing the severity of associated diseases.

In conclusion, the complexity of the effects that *T. gondii* exerts on behavioral and neuropsychiatric disorders highlights the importance of further investigations into its mechanisms. Understanding this intricate relationship may enable the development of enhanced strategies targeting both the prevention and management of associated disorders.

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Competing interests

The authors declare that they have no competing interests.

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