Association Between Latent Toxoplasmosis and Schizophrenia

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Abstract
Toxoplasma gondii, a protozoan parasite, is known to establish a lifelong latent infection in humans. This infection, termed latent toxoplasmosis, has been implicated in various neurological and psychiatric disorders, including schizophrenia. Schizophrenia is a complex psychiatric disorder characterized by disruptions in thought processes, perceptions, and social behavior. While its exact etiology remains elusive, studies have increasingly explored the potential role of infectious agents in its development and progression. Epidemiological studies have shown an association between toxoplasma infection and an increased risk of schizophrenia development. Moreover, several plausible pathways have been proposed through which Toxoplasmosis may exert its influence on the central nervous system, including alterations in neurotransmitter levels, immune response dysregulation, and neuroinflammation. Understanding the intricate relationship between latent toxoplasmosis and schizophrenia could pave the way for novel therapeutic interventions and preventive strategies for individuals at risk.

This review aims to consolidate current knowledge regarding the relationship between latent toxoplasmosis and schizophrenia. It synthesizes findings from epidemiological studies, clinical observations, and experimental research investigating the prevalence of toxoplasmosis in individuals with schizophrenia compared to the general population. Additionally, it examines the potential mechanisms through which T. gondii infection might contribute to the pathogenesis of schizophrenia, including neuroimmune responses, neurotransmitter alterations, and neurodevelopmental effects.

Introduction
Toxoplasma gondii (T. gondii) is an obligatory intracellular parasite that infects warm-blooded animals, including humans [1]. It causes toxoplasmosis in intermediate hosts (humans and other Mammals) [2]. It commonly resides in cats and their feces, and it can be transmitted to humans through ingestion of sporulated oocysts, contact with contaminated soil with sporulated oocysts, water, or undercooked meat containing the parasite’s cysts [1,3]. There has been some scientific interest in exploring the potential link between T. gondii infection and schizophrenia (SCZ) [4,5], a chronic mental disorder characterized by a range of symptoms including hallucinations, delusions, disorganized thinking, and cognitive impairment [6]. However, the exact relationship between T. gondii infection and schizophrenia remains a topic of debate and ongoing research.

Several studies have suggested a potential association between T. gondii infection and an increased risk of developing schizophrenia or experiencing more severe symptoms in individuals who already have the condition [7]. However, it’s essential to note that while
these studies show correlations, they do not necessarily establish a direct cause-and-effect relationship.

The mechanisms underlying how *T. gondii* might influence the development or progression of schizophrenia are not yet fully understood [8]. Some researchers propose that the parasite may impact the brain and behavior by altering neurotransmitter levels or affecting the immune system, potentially contributing to the onset or exacerbation of schizophrenia symptoms in susceptible individuals [9]. It’s crucial to approach this topic with caution, as the relationship between *T. gondii* infection and schizophrenia is complex and multifaceted. More research is needed to determine the exact nature of this relationship, including whether the parasite plays a causal role in the development of schizophrenia or if other factors contribute to this association. It’s unclear if Toxoplasmosis has the biggest correlation with schizophrenia or if research on the disease is just more prevalent. To investigate this, we conducted a review search to look for any connections between toxoplasmosis and schizophrenia.

**Toxoplasmosis**

The parasite *Toxoplasma gondii* is an obligatory intracellular coccidian parasite that causes toxoplasmosis. Even though the disease affects a large number of people globally, most human infections are asymptomatic. Still, it is a frequent opportunistic infection in immunocompromized individuals, individuals with human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), and those who have received organ transplants [2,10].

**Classification of Toxoplasma gondii**

Toxoplasmosis is an intracellular obligatory protozoal infection that is caused by the protozoan parasite *T. gondii*. *T. gondii* is under the kingdom: Protista, phylum: sporozoa (Apicomplexa), class: Coccidia, order: eucoccidiorida, and family: Sarcocystidae [11,12].

**Toxoplasmosis Life Cycle and Route of Transmission**

Toxoplasmosis has a complex life cycle in which a cat is considered the final host and humans and other mammals as intermediate hosts [13]. Toxoplasmosis is commonly acquired through the ingestion of contaminated food or the drinking of contaminated water, with an infective stage of *T. gondii* (sporulated oocysts), and humans can also be infected with the infection through eating undercooked meat or undercooked milk that contains tissue cysts (bradyzoite) as mentioned in Figure 1. *T. gondii* has three morphological stages, including tachyzoites, bradyzoites, and oocysts. Some parasites transform into tissue (bradyzoite) in response to host immune system attacks, which initiate the latent or chronic phase of the disease [14]. There are additional reports of congenital transmission of toxoplasmosis, which takes place when toxoplasmosis is still in its acute phase. A tachyzoite stage from the mother infects the fetus by crossing the placenta [15] and may cause hematological anomalies, hepatosplenomegaly, convulsions, mental and psychomotor impairment, vision and hearing loss, or even death [16]. The life cycle of toxoplasmosis includes an asexual reproduction cycle (which occurs in intermediate hosts) and a sexual reproduction cycle (which occurs in the final host) [17].

**Figure 1: Life Cycle of Toxoplasmosis** [18]
Toxoplasmosis is typically asymptomatic or symptomatic, primarily seen in immune-competent people, with severe variants that manifest as encephalitis or multiple organ involvement; immunocompromised hosts are more likely to experience these manifestations [3,19]. T. gondii parasites produce tissue cysts in various vital organs, mainly the brain and muscles. Therefore, almost all available medications cannot cure the tissue cysts [20,21]. Over one-third of people globally are thought to be infected with chronic toxoplasmosis [22]. At this point, the emergence of several mental illnesses has been linked to the ability of neurotropic pathogens, such as protozoal (T. gondii), bacterial (Chlamydia), or viruses (Bornavirus, and Herpesviridae), to establish chronic infections within brain tissue [23,24]. So, T. gondii is regarded as a neurotropic pathogen that causes persistent brain infections and is linked to mental diseases [25].

Schizophrenia
Schizophrenia is a chronic neuropsychiatric disease with an unknown cause [6]. Family members of affected individuals are more likely to experience schizophrenia, which implies that genetic factors may contribute to the disease’s etiology [26]. Infected people exhibited psychotic signs such as decreased motivation and expressiveness as well as cognitive deficiencies like memory loss and slowed cognitive processing speed, as well as hallucinations, delusions, and disordered speech [27,28]. Chronic toxoplasmosis has been proposed as a possible important etiological factor in certain instances of schizophrenia in studies on infectious agents [29,30].

Relation between Toxoplasmosis and Schizophrenia
Several studies in the literature suggest a link between toxoplasmosis and schizophrenia. Studies have not yet dismissed this association [31]. So this study studied the possibility that latent toxoplasmosis contributes to schizophrenia. According to many researchers, they approved this. T. gondii has a strong affinity for the neurological system (particularly astrocytes and glia cells), as well as its known link to inherited brain disorders. For an extended period, scientists focused their attention on possible connections between parasite exposure and the development of serious mental illnesses [29,32]. Although there has been discussion about a connection between toxoplasmosis and schizophrenia since 1950, further research into this and other links has just lately been conducted [29].

Toxoplasm gondii may have a role in the genesis of schizophrenia. There are four important things to think about in this regard: first off, it has been established that genes influence mice’s susceptibility [29]. T. gondii can transmit genetic patterns transplacentally [33]. Second, neurotransmitter abnormalities may be brought on by schizophrenia. For instance, research on animals has demonstrated how T. gondii affects neurotransmitter disorders depending on dopamine and serotonin levels [34]. Third, a neurodevelopmental condition linked to T. gondii is schizophrenia. Prenatal infections may be the source of this, and it may take an extended period for it to become active again before reactivating [25]. Fourth, behavioral abnormalities in infected animals with toxoplasmosis are consistently suggested by the connection between toxoplasmosis and schizophrenia in animal models [35]. According to a review done by Fabiani et al. [36], the primary neurobiological alterations brought on by latent toxoplasmosis in humans are congruent with the pathophysiology of neuropsychiatric disorders like mood disorders and schizophrenia. Moreover, another study done by Prandovszky et al. [37] on toxoplasmosis in mammalian dopaminergic cells has been demonstrated to consistently increase dopamine-dependent K+ secretion. Cysteine-containing areas of the diseased rats’ brains were strongly stained in the same study when dopamine-specific antibodies were used to stain them. The limiting enzyme in the synthesis of dopamine, tyrosine hydroxylase, was also discovered inside intracellular cysts. The study’s overall conclusion was that toxoplasmosis is crucial for raising dopamine metabolism in neurons.

It has been shown that the dopaminergic system contributes significantly to the development of schizophrenia and mood disorders. According to the dopamine hypothesis in bipolar disorder, the depressed phase is characterized by lower amounts of this neurotransmitter than the mania/hypomania phases [38,39]. Several epidemiological studies indicate that people with a variety of psychiatric and behavioral illnesses, such as schizophrenia, have a greater prevalence of toxoplasmosis [40]. In 2003, it was suggested that dopamine plays a crucial role in the correlation between toxoplasmosis and schizophrenia, based on the observation of reduced novelty seeking in both sick individuals and laboratory mice [41]. Initially, it was thought that the elevated dopamine production resulted from persistent inflammation of the brain tissue, as the same behavioral signs were also noted in subjects infected with another neurotropic disease [42]. However, a study discovered two genes for tyrosine hydroxylases, the rate-limiting enzymes of dopamine synthesis, in the genome of Toxoplasma [43]. A subsequent study showed that these genes are expressed in the brain tissue of an infected host and are probably also in charge of the excessive production of dopamine in Toxoplasma tissue cysts [37]. The symptoms of acute schizophrenia observed in some patients and the
correlation between latent toxoplasmosis and schizophrenia are most likely caused by an elevated level of dopamine in the cysts and their surroundings. It is unclear if Toxoplasma's alleged "manipulative activity" contributes to the production of symptoms of schizophrenia or if it is only a side effect of a persistent brain infection [44]. If this is accurate, elevated dopamine levels could be the cause of schizophrenia linked to toxoplasmosis. However, the increase in dopamine synthesis itself may be a biological adaptation of Toxoplasma for controlling the behavior of the intermediate host, specifically to raise the likelihood of cats preying on infected prey because infected hosts' capacity to detect changes in their surroundings is compromised.

Recently, Flegr & Horáček [45] found the biggest correlation between toxoplasmosis and schizophrenia is with autism, and it may have a significant impact on the etiopathogenesis of mental health issues. According to a study done by Liu et al. [46] in China, there was a greater seroprevalence of T. gondii infection among patients with mental illnesses. Mania, schizophrenia, depression, recurrent depressive disorder, and bipolar disorder have all been linked to T. gondii infection. Also, another study done in 2023, a meta-analysis has provided compelling evidence linking toxoplasmosis to some psychiatric conditions, including suicidal thoughts and behaviors, bipolar disorder, and schizophrenia. Here, we calculate the number of instances based on the portion of these illnesses that may be attributed to toxoplasmosis [47]. Numerous observational studies found a moderate to strong correlation between SC2 and toxoplasmosis. Even though significant mistakes in the methodology were found, more association studies are not warranted and are unlikely to alter this association.

**Conclusion**

In conclusion, there is no obvious link between toxoplasmosis and schizophrenia. Mainly caused by a single primary environmental or genetic etiological factor, schizophrenia is a typical condition that is co-caused by numerous additive and replaceable environmental and genetic components. The question of whether a specific component, such as toxoplasmosis, causes a particular kind of schizophrenia or only alters its course is not relevant in such complex illnesses. The most that can be concluded is that, in patients with additional environmental and genetic predispositions, Toxoplasmosis is likely a relatively substantial cause of severe forms of schizophrenia, based on the reported strength of the correlation between these two "unrelated" disorders.

**Future Directions**

Future research directions should focus on expanding our understanding of the mechanisms linking latent toxoplasmosis and schizophrenia, identifying potential therapeutic targets, and developing preventive strategies to mitigate the impact of *Toxoplasma gondii* on the onset and progression of schizophrenia. Collaborative, interdisciplinary research efforts are essential for advancing our knowledge in this field and potentially improving clinical outcomes for affected individuals.

**Conflict of Interest**

The authors declare that there is no conflict of interest regarding the research data and tools used in this study.

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**Author contributions**

All authors conceived this work and drafted and finalized this review article.

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