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# THE RELATIONSHIP OF TOXOPLASMA GONDII WITH NEUROCHEMISTRY IN PSYCHOPATHOLOGIES WITH EMPHASIS ON SCHIZOPHRENIA: BIBLIOGRAPHIC REVIEW

# A RELAÇÃO DE TOXOPLASMA GONDII COM A NEUROQUÍMICA EM PSICOPATOLOGIAS, COM ÊNFASE NA ESQUIZOFRENIA: REVISÃO BIBLIOGRÁFICA

# LA RELACIÓN DE TOXOPLASMA GONDII CON LA NEUROQUÍMICA EN PSICOPATOLOGÍAS, CON ÉNFASIS EN LA ESQUIZOFRENIA: REVISIÓN BIBLIOGRÁFICA

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## ABSTRACT

Toxoplasma gondii (T. gondii) is an obligate intracellular parasite. It is estimated that one-third of the world's population is affected, making it one of the most prevalent human parasites. Studies indicate a possible correlation between Toxoplasma gondii and psychopathologies such as schizophrenia, anxiety, depression and bipolar disorder, indicating dopaminergic and morphological alterations, thus causing changes in the behavior of those infected. This work aims to describe from a bibliographic review, the possible connection between Toxoplasma gondii with cases of psychopathologies. An integrative bibliographic search was carried out in the following databases: Pubmed, Lilacs, Scholar Google, Medline and Scielo. The articles went through an evaluation to be included or discarded; these were evaluated by inclusion and exclusion criteria. The requirement was to have been produced between 2010 and 2025 exclused studies published in the Portuguese language. A survey of clinical cases addressed

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in scientific papers was carried out seeking symptomatology, reasons that led to the possible correlation of toxoplasmosis and psychological disorders. According to the results obtained, it is noted that the multifactorial occasion of psychopathologies becomes inconclusive about the real correlation between Toxoplasma Gondii and psychopathologies, since there are no neurochemical methods and also variables such as socioeconomic, geographic, epidemiological, genetic factors, age, lifestyle and gender do not corroborate to attest this link, although there is evidence that makes this connection possible.

**Keywords:** Toxoplasma. Psychopathologies. Depression. Schizophrenia.

## RESUMO

Toxoplasma gondii (T. gondii) é um parasita intracelular obrigatório. Estima-se que um terço da população mundial seja afetada, tornando-o um dos parasitas humanos mais prevalentes. Estudos indicam uma possível correlação entre Toxoplasma gondii e psicopatologias como esquizofrenia, ansiedade, depressão e transtorno bipolar, apontando alterações dopaminérgicas e morfológicas, causando assim mudanças no comportamento dos infectados. Este trabalho tem como objetivo descrever, a partir de uma revisão bibliográfica, a possível conexão entre Toxoplasma gondii e casos de psicopatologias. Foi realizada uma busca bibliográfica integrativa nas seguintes bases de dados: PubMed, LILACS, Google Scholar, Medline e SciELO. Os artigos passaram por uma avaliação para serem incluídos ou descartados; estes foram analisados por critérios de inclusão e exclusão. O requisito foi que tivessem sido produzidos entre 2010 e 2025, excluindo estudos publicados no idioma português. Foi realizado um levantamento de casos clínicos abordados em artigos científicos, buscando a sintomatologia e os motivos que levaram à possível correlação entre toxoplasmose e transtornos psicológicos. De acordo com os resultados obtidos, observa-se que a origem multifatorial das psicopatologias torna inconclusiva a correlação real entre Toxoplasma gondii e essas condições, uma vez que não existem métodos neuroquímicos suficientes e também porque variáveis como fatores socioeconômicos, geográficos, epidemiológicos, genéticos, idade, estilo de vida e gênero não corroboram para atestar esse vínculo, embora existam evidências que tornam essa conexão possível.

**Palavras-chave:** Toxoplasma. Psicopatologias. Depressão. Esquizofren.

## RESUMEN

Toxoplasma gondii (T. gondii) es un parásito intracelular obligado. Se estima que un tercio de la población mundial esté afectada, lo que lo convierte en uno de los parásitos humanos más prevalentes. Los estudios indican una posible correlación entre Toxoplasma gondii y psicopatologías como esquizofrenia, ansiedad, depresión y trastorno bipolar, señalando alteraciones dopaminérgicas y morfológicas, lo que ocasiona cambios en el comportamiento de los infectados. Este trabajo tiene como objetivo describir, a partir de una revisión bibliográfica, la posible conexión entre Toxoplasma gondii y casos de psicopatologías. Se realizó una búsqueda bibliográfica integradora en las siguientes bases de datos: PubMed, LILACS, Google Scholar, Medline y SciELO. Los artículos fueron evaluados para ser incluidos o descartados; estos fueron analizados mediante criterios de inclusión y exclusión. El requisito fue haber sido publicados entre 2010 y 2025, excluyendo estudios escritos en idioma portugués. Se llevó a cabo un levantamiento de casos clínicos abordados en artículos científicos, buscando la sintomatología y los motivos que llevaron a la posible correlación entre toxoplasmosis y trastornos psicológicos. Según los resultados obtenidos, se observa que la naturaleza multifactorial de las psicopatologías vuelve inconclusa la correlación real entre Toxoplasma gondii y estas condiciones, ya que no existen métodos neuroquímicos suficientes y además variables como factores socioeconómicos, geográficos, epidemiológicos, genéticos, edad, estilo de vida y género no corroboran esta relación, aunque existen evidencias que la hacen posible.

**Palabras clave:** Toxoplasma. Psicopatologías. Depresión. Esquizofrenia.

## 1 INTRODUCTION

*Toxoplasma gondii (T. gondii)* is an obligate intracellular parasite that infects mammals and many other warm-blooded animals, including cats and other felines as definitive hosts for sexual reproduction, and it is the only mammals known to release oocysts in their feces (MILLER et al., 2009). It is estimated that one-third of the world's population is affected by this pathogen, making it one of the most common human parasites (HALONEN et al., 2013).

In the intermediate host, the parasite can lead to a lifelong latent infection in various tissues, including muscles, the eye, and the central nervous system, where persistent cysts form. According to Saadatina and Golkar (2012), humans become infected by ingesting cysts in tissues infected with *T. gondii* (undercooked infected meat) or oocysts in water, or through environmental exposure.

Although an acute infection is commonly asymptomatic or presents with nonspecific symptoms such as fatigue or lymphadenopathy, it can sometimes lead to toxoplasmic encephalitis. In the case of congenital toxoplasmosis, most lesions are seen in the eyes and brain (e.g., intracranial calcifications, hydrocephalus). The parasite is not eliminated, and after an acute symptomatic phase, the parasite will cause a latent infection that is commonly considered asymptomatic (SAADATINA and GOLKAR, 2012).

As described by Fuglewicz et al. (2017), there are indications of behavioral or psychological consequences. Evidence is also strong for an association between *T. gondii* infection and schizophrenia. Furthermore, increased immunity to *T. gondii* by interglobulin G (IgG), but not immunoglobulin M (IgM), was found among patients with schizophrenia. According to Kar and Misra (2004), interest in the possible link between T. gondii and depression was sparked by a case report describing a patient with depression who possibly remitted after antibiotic treatment aimed at combating T. gondii infection.

Subsequent studies have investigated the possible link between *T. gondii* infection and depression but have not yet provided a clear consensus on this association. Several studies have found positive associations between depressive symptoms and seropositivity (CARRUTHERS, SUZUKI, 2007). *Toxoplasma gondii* uses a complex mechanism to gain access to the brain. Once gained, it invades a variety of brain cells, including astrocytes and neurons, where it forms cysts (CARRUTHERS, SUZUKI, 2007). *Toxoplasma gondii* can then establish a continuous infection within the central nervous system (CNS), manipulate host behavior, and can cause neurological and psychiatric problems in some infected individuals (HALONEN, 2013).

Since the 1950s, it has been known that the prevalence of toxoplasmosis in schizophrenic patients is exceptionally high. It was later shown that toxoplasmosis increases

the concentration of dopamine in the brain of infected hosts, including humans, and its genome even contains unique genes for enzymes (tyrosine hydroxylases) that play an important role in dopamine synthesis (HESTER, et al., 2012; KAR, MISRA. 2004; NAK, et al., 2018).

Increased dopamine concentrations in certain brain regions play a fundamental role in the origin and progression of schizophrenia and in the inhibition of dopamine receptors, which underlie the function of all modern drugs used in the treatment of schizophrenia (HOLLIMAN, 1997).

According to Neves et al. (2011), the parasite presents multiple morphologies depending on its habitat or evolutionary stage. The infective forms that the parasite presents during its biological cycle are: tachyzoites, bradyzoites, and sporozoites. Tachyzoites are the form found in the acute form of the infection, presenting an arch-like shape. The bradyzoite form is found in various tissues such as the nervous, retinal, skeletal, and cardiac muscles. They are generally found in the chronic form of the infection. They are also called cystozoites. The sporozoite form is found inside oocysts, which are discarded in the feces of non-immune felines.

The life cycle of *T. gondii* has an asexual phase, which occurs in most animals, and a sexual phase, which occurs in felines. The asexual cycle occurs in numerous intermediate hosts and consists of two distinct life stages depending on the phase of infection: acute or chronic (FLEGR, et al., 2013).

After an unknown number of divisions and mechanisms that are still unclear, the *T. gondii* tachyzoites within the cells give rise to another evolutionary stage called bradyzoite. This infectious form has as its main biological characteristic the ability to reproduce slowly (bradi- = slow, in Greek) (De Souza, et al., 2006).

According to De Souza et al. (2006), the sexual phase occurs only in felines, with the domestic cat being the most important host, from an epidemiological point of view, for human toxoplasmosis. This cycle most often begins with the ingestion of tissue cysts through carnivory. After ingestion, several highly complex cycles occur until the generation of micro and macrogamonts, the fusion of which results in oocysts that are eliminated in the host's feces and disseminated in the environment, infecting mammals (including humans) and birds when ingested through water or food. These oocysts release sporozoites in the digestive tract, which then infect intestinal epithelial cells, giving rise to the tachyzoites of the acute phase of the infection.

According to De Souza et al. (2006), *T. gondii* is notable for its ability to invade a wide variety of host cells. Invasion is an active process that depends on the parasite's motility and

the sequential secretion of proteins from secretory organelles, micronemes, rhoptries, and dense granules. *T. gondii* can invade and multiply within any type of nucleated cell, including epithelial cells and blood leukocytes.

Schizophrenia (SZ) is one of the most challenging mental health problems in the world. Statistics released by international health organizations agree that its prevalence affects approximately 1% of the population, with a slight male preponderance. Over the past two decades, evidence has accumulated that this disorder arises from several brain developmental disorders involving genes and proteins that support the formation and function of large neural networks (TANDON et al., 2010).

The pathophysiological mechanisms involved are complex and unclear; it is believed to be the result of a combination of genetic and environmental factors (Javier et al., 1997). According to Javier et al. (1997), special attention has been paid to the role of dopamine (DA) in neurons of the brain's mesolimbic pathway. DA has been implicated in studies on neurotransmitters and their relationship with schizophrenia.

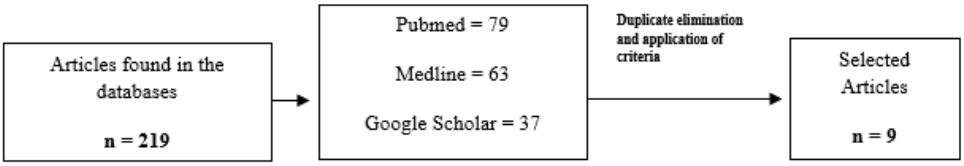
Furthermore, psychotropic drugs such as cocaine and amphetamines have been shown to cause DA release and often exacerbate the psychotic symptoms of the disease. The "dopaminergic schizophrenia" hypothesis proposes that overactivation of dopamine D2 receptors is the cause of schizophrenia symptoms. Here, we describe the possible relationship between Toxoplasma gondii and cases of psychopathology, especially the association between toxoplasmosis and schizophrenia.

## 2 METHODS

This is a narrative literature review. A search was conducted in the PubMed, Lilacs, Medline, Scholar Google, and Scielo databases. This study included clinical case articles and case-control studies written in English between 2010 and 2025, reporting patient symptoms and the reasons for the possible correlation between toxoplasmosis and schizophrenia and other psychological illnesses and disorders. Articles not in English, systematic reviews and meta-analyses, and articles published outside the timeframe were excluded. The search was conducted using the keywords: toxoplasmosis, psychopathology, neurochemistry, depression, and schizophrenia. First, articles were selected based on their title, year, and abstract. Afterward, duplicates were removed, and articles were selected based on the following parameters: title; author; year; results; and discussion. The methodology workflow is illustrated in Figure 1:

**Figure 1**

*Workflow of the article search and selection methodology*




## 3 RESULTS AND DISCUSSION

A total of 219 articles were found in the databases related to the delimited approach, which were recorded in quantitative correspondence after delimitation of the inclusion criteria, configured according to the variables described, with: Pubmed (79), Medline (63), Google Scholar (37), Lilacs (23), Scielo (17). After screening the records obtained by searching the databases, 9 studies met the proposal of the current study, described in Table 1.

**Table 1**

*Articles selected after filtering*

| **Study Title** | **Author** | **Year of Publication** | **Main Results** |
|---|---|---|---|
| Toxoplasmosis as a cause for behaviour disorders – overview of evidence and mechanisms | FEKADU, et al. | 2010 | The proposition that in some cases, *T. gondii* infection can cause mental and behavioral disorders seems plausible. *T. gondii* infection is associated with various mental and behavioral disorders, ranging from personality changes to severe disorders such as schizophrenia. These findings are also supported by plausible mechanisms that may lead to these mental and behavioral changes. |
| Toxoplasma gondii antibody titers and history of suicide attempts in patients with schizophrenia. | OKUSAGA, et al. | 2011 | Serology for *T. gondii* may become, with interaction with vulnerability genes, a candidate biomarker for a subgroup of schizophrenic patients with a tendency to attempt suicide. |
| Toxoplasma gondii Infection and Self- directed Violence in Mothers | PEDERSEN, et al. | 2012 | The study results are consistent with the hypothesized association between *T. gondii* infection and self-directed violence and, together with other converging evidence and better |

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| | | | understanding of the underlying mechanisms, if confirmed in future studies. |
| Influence of latent Toxoplasma infection on human personality, physiology and morphology: pros and cons of the Toxoplasma–human model in studying the manipulation hypothesis | FLEGR, et al. | 2013 | There are several objective reasons why *Toxoplasma gondii* is now used as the most important model for studying manipulative activity in humans. However, the most important are the subjective reasons. This organism, however, still requires research teams to engage in a systematic study of its influence on the human host. |
| Latent toxoplasmosis is associated with neurocognitive impairment in young adults with and without chronic HIV infection | Ene, et al | 2016 | Worse cognitive performance was observed in young patients with latent toxoplasmosis, both with and without chronic HIV infection. It is suggested that latent toxoplasmosis may be a potential confounding factor in attributing the cause of cognitive impairment to HIV. |
| Association of Toxoplasma gondi infection with schizophrenia and its relationship with suicide attempts in these patients | ANSARI-LARI, et al. | 2017 | A positive relationship between *T. gondii* infection and schizophrenia was observed in the present study. Furthermore, we observed a significantly lower rate of suicide attempts in male patients infected with T. gondii than in uninfected men. The evidence is mixed, and further studies, particularly prospective ones, are clearly needed. |
| Immunoglobulinsub- class distribution inbipolar disorder and schizophrenia:potential relationship with latent Toxoplasma Gondii infection. | HADAMI, et al. | 2018 | A limitation of our study is that we did not perform simultaneous sequential immunology monitoring during the stable and active phases of the disease in the same patients with bipolar disorder and schizophrenia. Furthermore, patients and controls were not matched for age and sex, which may influence the data. |
| Randomized controlled trial of adjunctive Valproate for | IBRAHIM, et al | 2019 | There were no statistically significant differences between the valproate and placebo groups regarding changes in |

| | | | |
|---|---|---|---|
| cognitive remediation in early course schizophrenia | | | cognitive function in patients with early-onset schizophrenia, positive or negative symptom scores, or daily functioning scores at baseline or end of the study. No significant differences were observed between valproate and placebo in toxoplasmosis serological status or toxoplasmosis-related cognitive dysfunction. |
| *Toxoplasma gondii* Seropositivity in patients with depressive and anxiety disorders | NIENKE, et al. | 2021 | The present study does not support the hypothesis that *T. gondii* seropositivity is associated with depressive or anxiety disorders, or with aggressive and suicidal thoughts. Considering previous studies and new findings, it seems unlikely that T. gondii seropositivity plays a significant role in the risk of affective disorders, suicidal thoughts, and aggressive thoughts. |

Ibrahim et al. (2019) conducted a randomized, double-blind, placebo-controlled study to compare the effects of valproate or placebo as adjuncts to risperidone treatment in patients with early-onset schizophrenia. Cognitive variables, clinical characteristics, and general function, as well as indicators of toxoplasmosis infection, were also assessed. Although valproate was tolerated by the participants, no significant differences were detected between the groups regarding cognitive function, psychopathology, or quality of life scores. Furthermore, no differential effects of valproate were found among toxoplasmosis-seropositive patients, which contradicts previous studies indicating that the infection is associated with impaired motor performance, deficits in learning and memory, reduced ability to discriminate between familiar and novel environments, and longer reaction times.

Nienke et al. (2021) failed to observe a significant association between *Toxoplasma gondii* and psychological disorders. The authors extended their findings, showing no association with either self-reported depressive symptoms or observer-assessed depression diagnoses using standardized psychiatric interview diagnoses. Although significant associations between seroprevalence and depressive symptoms were found in some studies, according to Nienke et al. (2021) and most of the articles used for their scientific basis, they found no association between toxoplasmosis and depression (De BIES et al., 2021).

Previous inconsistencies could not explain the differences in age distribution since older individuals are more virulent, nor could the hypothesis that states that T. gondii strains differ in virulence and in the ability to influence human behavior (NIENKE et al., 2021; De BIES, et al., 2021).

> In line with our findings on depressive state, we found no associations between T. gondii seropositivity and anxiety disorders. This was consistent with population-based studies of 1,846 and 7,712 participants, respectively, which found no association between T. gondii and generalized anxiety (De BIES, et al., 2021).

According to Nienke et al. (2021), the fact that seroprevalence varies greatly due to various factors such as age and even region currently makes it impossible to relate T. gondii to neurochemical changes in patients, thus preventing correlations with anxiety, increased aggression, depression, and schizophrenia from being established.

According to Flegr et al. (2013), the study of Toxoplasma gondii correlations has several impediments, since it is impossible to study the morphology of brains affected by Toxoplasma gondii without altering the patients' lifestyles. In his studies, he proposed several ways in which T. gondii altered both the behavior and phenotype of patients. *Toxoplasma gondii* could interact with dopamine production in the brain, altering aspects of patients' ego. Most physiological processes are regulated at multiple levels, from the molecular to the psychological. If, for example, *Toxoplasma gondii* causes an increase in dopamine concentration in certain brain regions, dopamine-synthesizing cells in other areas of the brain may degenerate. Therefore, at a certain stage of infection, we may paradoxically detect a decreased, rather than an increased, level of dopamine in the brains of infected individuals. If toxoplasmosis induces a decrease in superego strength, it could increase the tendency of certain individuals to lie when completing a questionnaire, and thus, we may detect an apparent increase, rather than a decrease, in superego strength in these subjects in study questionnaires (FLEGR, et al., 2013).

> *When a subject recognizes some personality change that he or she does not like, for example a toxoplasmosis-associated increase in extroversion, he or she may try, consciously or unconsciously, to mask this change when filling out the questionnaire and he or she may even compensate for the real personality change by switching from extroversion to introversion (FLEGR, et al., 2013).*

Toxoplasmosis frequently influences personality factors in different populations (rural and urban populations). However, the direction of a factor's effect can vary between populations (FLEGR et al., 2013). Analysis of the effect of a factor in heterogeneous

populations finds a significant increase in variance in certain dependent variables, rather than a significant difference between the population means of a particular variable. Thus, Flegr et al. (2013) concludes that many variables are related to this correlation, such as sex, age, area of residence, and even the large genotypic variability of populations.

According to Fekadu et al. (2010), based on existing evidence, studies indicate that *T. gondii* infection may be the cause of various mental and behavioral disorders. The suggested involvement of *T. gondii* ranges from subtle neurobehavioral impairments to severe manifestations of schizophrenia requiring inpatient care.

> The risk of schizophrenia is elevated among those exposed to infection during the postnatal period. The likelihood of T. gondii involvement is also demonstrated by the higher seroprevalence of T. gondii antibodies among those with schizophrenia compared with controls. 19 Pedersen, et al., (2012).

Despite this, there are several problems with their hypotheses, such as epidemiological inconsistencies. *Toxoplasma gondii* is a ubiquitous parasite, affecting nearly a third of the world's population, with marked geographic variation. However, psychiatric disorders currently attributable to or associated with *T. gondii* are not as prevalent in areas of high seroprevalence and do not exhibit such marked geographic variation in the preceding period (PEDERSEN et al., 2012).

According to Fekadu et al. (2010), if *T. gondii* causes psychiatric disorders as proposed, it can only cause such disorders in a fraction of the individuals it infects. Furthermore, psychiatric disorders are complex conditions resulting from multiple interacting risk factors, one of which may be *T. gondii* infection. It has also not been possible to demonstrate a link between *T. gondii* infection and the timing of onset of these psychiatric conditions.

This profile has only been demonstrated in severely immunodeficient individuals, where reactivation of the infection resulted in toxoplasma encephalitis (TLE), which can be identified in the brain (PEDERSEN et al., 2012). According to Pedersen et al. (2012), this link is also quite difficult due to differences in socioeconomic status and health coverage, thus precluding a global study of cases that fit this correlation.

A study by Ene et al. (2016) found worse performance in the domains of verbal fluency, learning and memory, and information processing speed in elderly individuals who tested positive for anti-Toxoplasma IgG antibodies and were HIV-negative. Furthermore, the authors found a higher relationship between impairment among HIV-negative and Toxoplasma-positive young adults compared to HIV-negative and Toxoplasma-negative adults, as well as

a main effect for Toxoplasma in the entire sample, demonstrating that the pathogen may be a potential confounder in attributing the cause of neurocognitive impairment to HIV.

Finally, Ansari-lati et al. (2017) studied articles with patients who received treatment for schizophrenia, bipolar disorder, or depression. The authors reported particularly strong odds of a history of suicide attempts in individuals who had elevated levels of IgM, but not IgG, antibodies to *T. gondii.*

## 4 CONCLUSION

Psychopathologies present a multifactorial spectrum of occurrence, which makes the true correlation between *Toxoplasma gondii* and psychopathologies inconclusive. Although important clinical/laboratory diagnostic methods exist for detecting the pathogen, specific neurochemical and genetic methods are needed to correlate psychopathologies, as well as correlate the diagnosis with patients' socioeconomic, geographic, epidemiological, and demographic variables. Therefore, experimental studies with larger cohorts and robust statistical tests should be conducted to better understand the relationship between *Toxoplasma gondii* and psychopathologies.

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