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## Chapter

# Neuroimmunopathology in Toxoplasmic Encephalitis

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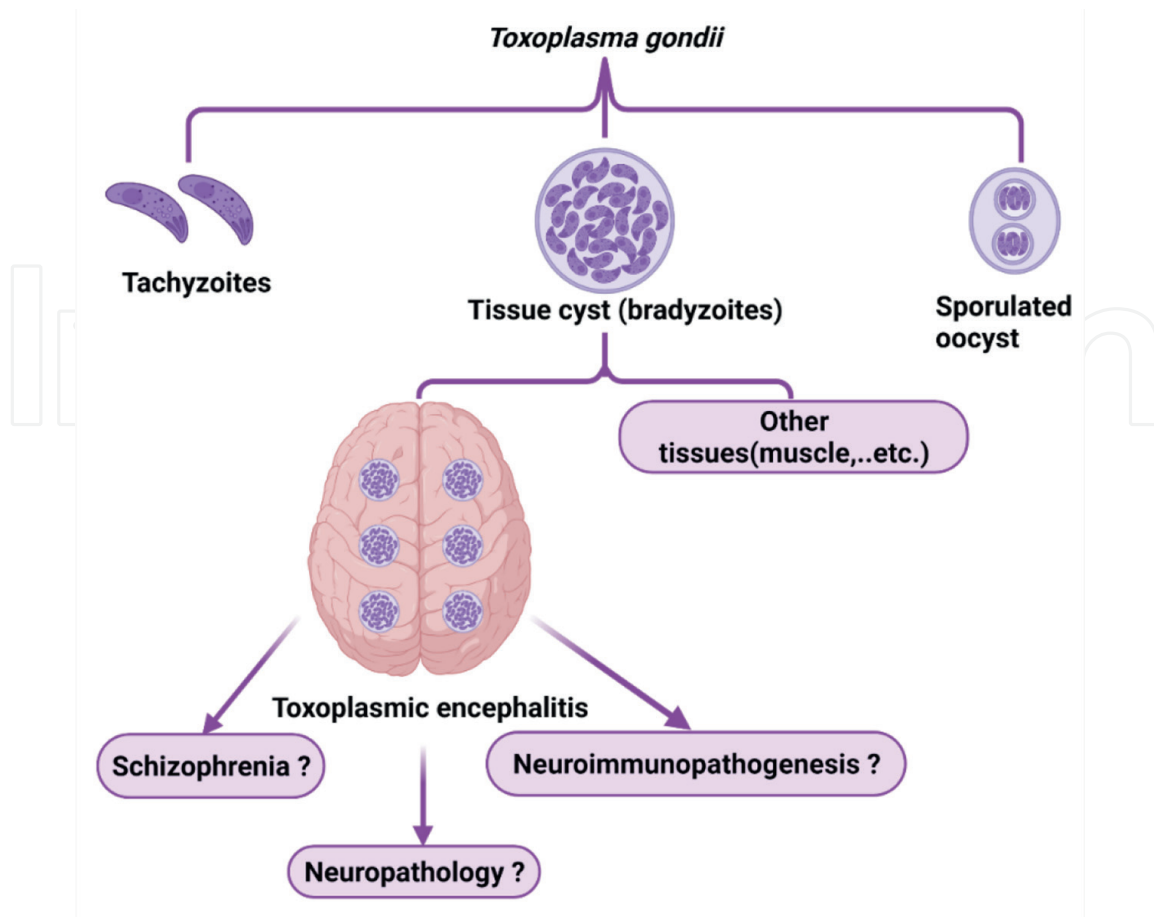
## Abstract

*Toxoplasma gondii* is a zoonotic protozoan parasite that causes mortality because of significant neuropathology. It is widespread in neonatal infections. Although the neuroimmunopathogenesis of toxoplasmic encephalitis (TE) has been studied for many years, it is still not completely understood, showing the disease's severity. The urge to write this chapter comes at this stage. The sections covered in this chapter show the pathogenesis that has been established and characterized so far. The involvement of astrocytes and microglia in the development of neuropathology, which begins with tachyzoites crossing the blood-brain barrier during acute infection, has been explored. The molecular mechanism between schizophrenia and TE has been thoroughly proven. Uncovering the molecular pathogenesis of TE is critical for both understanding neuropathology and elucidating the link between neuropsychiatric diseases. Each part covered here is expected to contribute to developing novel therapeutic agents for the treatment and maybe prevention of neuropathology. The pathogenesis of the steady progression of encephalitis has been meticulously revealed. Thus, this chapter will offer significant insight into developing novel treatments for all organisms suffering from this disease.

**Keywords:** *T. gondii*, immunopathogenesis, neuropathology, toxoplasmic encephalitis, cerebral toxoplasmosis

## 1. Introduction

*Toxoplasma gondii* (*T. gondii*), an obligate intracellular protozoan parasite, is closely related to public health because its zoonotic nature infects all warm-blooded animals [1, 2]. The severity of *T. gondii* infections is directly proportional to the infected host's immunity level. While the infection is subclinical in immunocompetent people, it causes lethal toxoplasmic encephalitis (TE) in immunocompromised people because of tissue cyst reactivation [3, 4]. *T. gondii*-related neuropathology is not only restricted to TE. *T. gondii* infections have been linked to neuropsychiatric and behavioral problems, including schizophrenia and bipolar disorders, as well as significant mental illnesses, including depression and obsessive-compulsive disorder [5–7]. Even though



**Figure 1.**  
The association between schizophrenia and schizophrenia mediated by *T. gondii*.

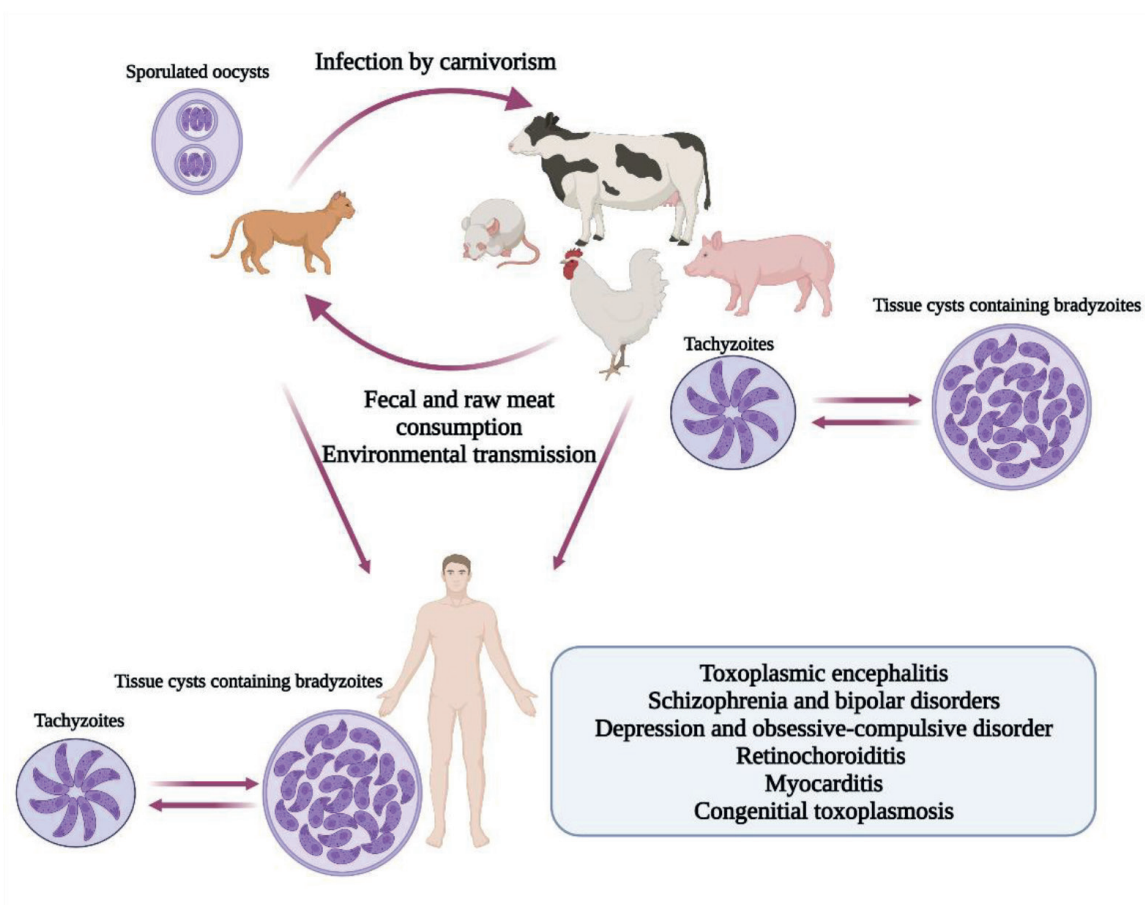
neuroimmunopathogenesis and neuropsychiatric disorders in TE and the pathogenesis of neuropsychiatric disorders have been studied for a long time, they are still among the issues that are still unclear and have many questions (**Figure 1**).

This section will detail the immunopathogenesis of TE and examine potential mechanisms. Thus, it will shed light on the researchers' goals about what should be considered in the management of the TE process and what should be focused on in future studies. In addition, the intricate criteria needed for the differential diagnosis will be thoroughly covered. Therefore, considering the neuroimmunopathogenesis of the disease and the diagnosis concurrently will facilitate a better understanding of TE.

Tachyzoites, the active life form of *T. gondii*, cannot be entirely eliminated in the brain, unlike in other organs, despite activating a robust immune system upon reaching the brain. At this stage, they convert into a bradyzoite form inside a tissue cyst and continue to grow as a chronic infection, presenting no symptoms throughout the host's life [2, 8]. To reach the brain, this tissue cyst stage must first cross the blood-brain barrier (BBB). This point, the BBB's transitional phase, will be considered the first step (**Figure 2**).

## 2. Why is toxoplasmic encephalitis so important?

Toxoplasmosis is far more dangerous in immunocompromised people than in healthy people. Multiple organ involvement is possible in cases of acute toxoplasmosis

**Figure 2.**

The *T. gondii* life cycle. There are two phases in the life cycle: sexual in the definitive host and asexual in intermediate hosts. Unsporulated oocysts are shed in the cat's feces. Intermediate hosts get infected after eating contaminated food or drink. Oocysts evolve into tachyzoites in the small intestine after consumption. When the host's immune system is compromised, tachyzoites induce the acute stage of infection and develop into tissue cyst bradyzoites. Bradyzoites may either remain dormant for the host's life or convert to tachyzoites. Consuming undercooked meat with tissue cysts is one of the primary transmission routes in humans. Clinical signs of the disease include encephalitis, schizophrenia, bipolar disorders, depression, obsessive-compulsive disorders, retinochoroiditis, myocarditis, and fetal abnormalities following transplacental infection in immunocompromised people.

in immunocompromised people. Systemic diseases are often observed with severe pneumonia and retinochoroiditis, but encephalitis is the most common clinical finding [9]. The neuroimmunopathogenesis should be fully explained at this point. There is evidence that toxoplasmosis can be reactivated in people with certain cancer types, including lymphoma, leukemia, and myeloma [10–12]. Organ transplantation also poses a significant risk of toxoplasmosis, which can be fatal. For example, transplanting a *T. gondii*-infected organ to an immunocompromised patient may reactivate the organ's latent infection. Furthermore, reactivating latent *T. gondii* infection because of immunosuppressive treatment after organ transplantation can cause a fatal condition [13]. Importantly, deaths have been reported in Acquired Immune Deficiency Syndrome (AIDS) patients with CD4 T lymphocyte cell counts <200 cells/ $\mu$ L and severe immunosuppression, resulting in the formation of reactivation-related TE [14, 15]. It has been reported, for example, that TE develops in approximately 30–40% of immunocompromised *T. gondii* seropositive ADIS individuals [16]. It is clear that this rate is extremely high. Actually, TE is quite crucial for patients of all ages. To differentiate between patients, it is evident that immunocompromised individuals are at a higher risk. A thorough analysis of the disease's molecular pathogenesis is required at this point. Otherwise, deaths caused by TE make us to disregard the primary disease.

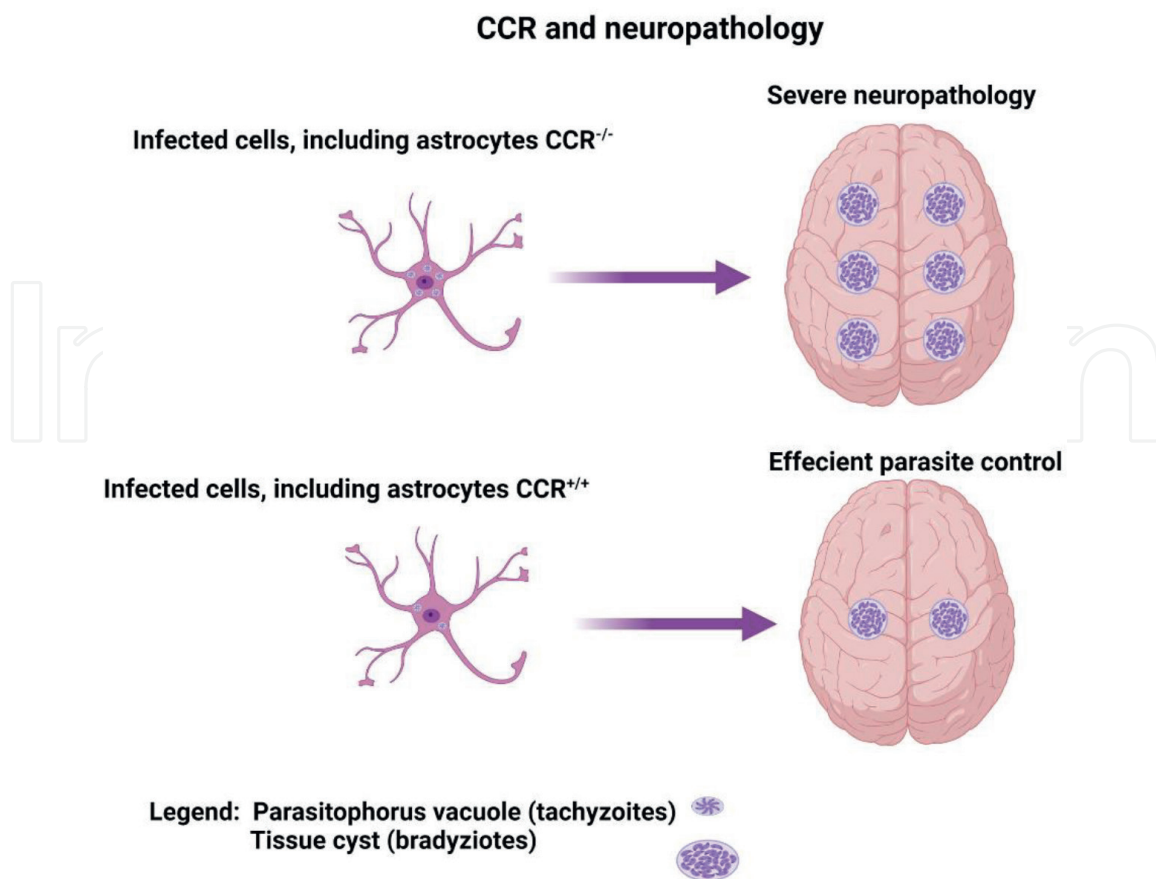
### 3. Crossing of the blood-brain barrier by *T. gondii* and molecular mechanism of damages

Although the blood-brain barrier (BBB) is a solid barrier between blood and brain tissue, *T. gondii*'s superior tactics for crossing this barrier and reaching the brain have yet to be completely disclosed. However, it is still unclear whether neuroinvasion occurs via hiding within or as a direct tachyzoite outside the cell. The actual huge issue begins right here. Because TE, one of the most severe forms of the disease that may lead to death, develops when tachyzoites cross through the properly functioning BBB during acute infection [14]. The BBB is lined by microvascular endothelial cells, which are highly specialized. The key characteristics of this barrier are low pinocytic activity, restricted fenestration, and high trans-endothelial resistance. Thus, it functions as a structural and functional barrier with minimal permeability. Additionally, pericytes, microglia, and astrocytes are closely associated with BBB endothelial cells and substantially contribute to sustaining BBB activity [17–20]. It has been proven conclusively that the first transmission of *T. gondii* to the central nervous system (CNS) occurs primarily through the cortical capillaries [21]. It is crucial at this point to explore how this dissemination occurred. There is evidence that *T. gondii* manipulates gene expression in brain endothelial cells to cross the BBB via a “Trojan horse” strategy. *T. gondii* in cells expressing CD11b may play a significant role in the intracellular trafficking of the BBB [22]. In the same research, the percentage of CD45+/CD11bc+ cells infected with *T. gondii* tachyzoites was 13 times greater at the beginning of infection when compared with the population percentages. In this work, CD45+/CD11bc+ cells, both infected and uninfected, show the ability to breach the BBB in an in vitro culture model. Uninfected cells respond identically to infected cells, which is a surprise topic of debate at this level. Similar increases in the expression of intercellular adhesion molecule 1 and monocyte chemoattractant protein-1 were reported after infection of brain endothelial cells with *T. gondii* tachyzoites within 2 and 12 hours, respectively [22]. CD11c- CD11b+ monocytes and CD11c+ CD11b+/- dendritic cells are the progenitor cells that facilitate the switch to the “Trojan horse” approach [23]. Although extracellular free-moving tachyzoites can cross the BBB without an intermediate, they can also do so *via* a variety of other mechanisms. Infection of the microvascular endothelium of the brain by tachyzoites, and their subsequent reproduction in the CNS is one potential approach [24]. Toxophyllin and protease expressions have been observed to assist the passage of *T. gondii* through the BBB. It has been shown that this transition is accomplished by destroying BBB cells [23, 25]. Because of this destruction, the BBB's permeability and integrity have been disrupted. Importantly, BBB disruption induces irreversible neurodegeneration and neuropathology in TE. In TE, *T. gondii* directly damages the blood-brain barrier (BBB) by inducing apoptosis in endothelial cells [26], while *T. gondii*-mediated oxidative stress (OS) [27] and nitrosative stress (NS) [28] also induce the same damage. Therefore, it is crucial to uncover the intricate processes involved in the pathophysiology of BBB degradation. It has been shown that von Willebrand Factor, closely related to a disintegrin and metalloprotease with thrombospondin 1 repeats family 13 (ADAMTS-13), plays an essential role in BBB permeability [29]. In addition, it has been underlined that ADAMTS-13 has neuroprotective roles by disclosing and decreasing BBB damage in the brains of small ruminants attacked with border disease virus [30] and listeric encephalitis [31]. Similarly, the expression of ADAMTS-13 has strongly shown BBB destruction in TE, and its neuroprotective activities have been described [26]. These results show that ADAMTS-13 has essential functions in the

BBB and neuronal parenchyma in disclosing the degree of BBB damage and reducing neuropathology. This essential initial step must be fully disclosed. Because a thorough understanding of the processes by which tachyzoites cross the BBB will aid in developing more focused therapies for preventing fatal brain injury. The primary aim should be to maintain the integrity of the BBB and prevent tachyzoites from entering the brain parenchyma during the acute infection phase. Thus, chronic TE may be avoided even before it begins.

#### 4. Molecular mechanism of neuropathology caused by *T. gondii*

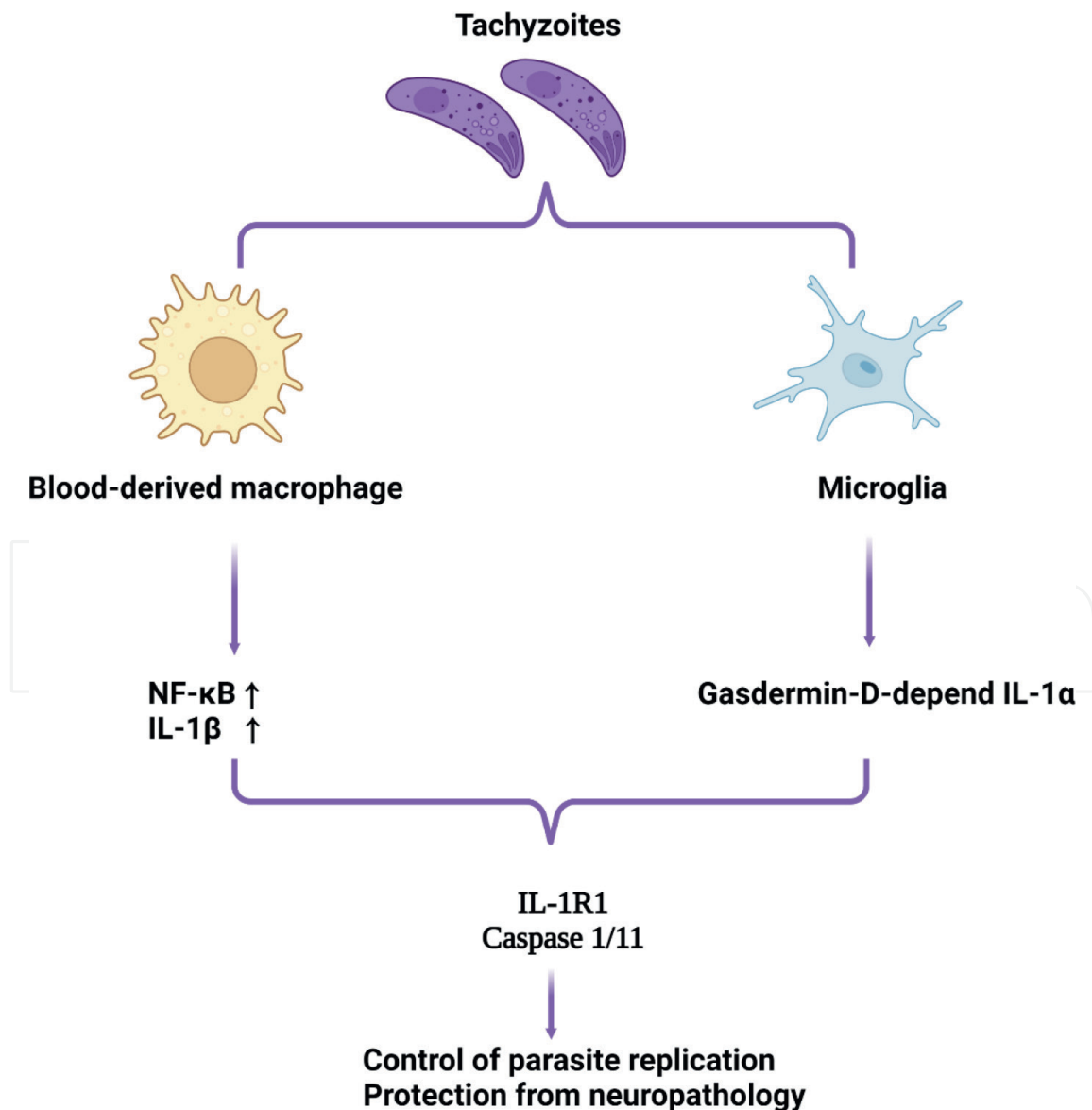
Tachyzoites that reach the brain parenchyma after improved strategies have crossed the BBB may induce severe neuropathology and host mortality. Although the molecular pathways of neuropathology are continuously investigated, there are still several unanswered questions. Chemokine (C–C motif) receptor 2 (CCR2), a crucial chemokine receptor with a microbicidal function, has a tight relationship with the parasite burden in the brain. In mice whose CCR2 receptor was experimentally blocked, the immune system cells in the brain were markedly inactive, resulting in a considerable increase in the parasite load in the brain [32]. In conclusion, the CCR2 receptor is necessary to regulate parasite replication in peripheral organs and the CNS in particular (**Figure 3**). Although the deadly TE produced by the reactivation of latent tissue cysts in the brain has been investigated for many years, the molecular mechanism of reactivation is still unknown.



**Figure 3.**  
The role of CCR2 in TE.

The significance of nitric oxide (NO) generation in chronic TE is remarkable since it must be in a delicate balance. This section focuses on two distinct topics. The first is NO's neuroprotective impact, while the second is its neurotoxic and neuropathological consequences, which may be severe. During *T. gondii* infection, nuclear factor kappa B and inflammatory cytokines are overexpressed in blood-derived macrophages. IL-1 $\alpha$  was overexpressed in microglia and IL-1 $\beta$  in macrophages during infection compared with control groups. In TE, IL-1R1, gasdermin-D-dependent IL-1 $\alpha$ , and caspase-1/11 have been demonstrated to control parasite multiplication, limit neuroinflammation, and regulate immune cell multiplication infiltration [33]. This research shows that alarmin IL-1 $\alpha$ , produced by microglia, works hard to reduce the neuropathology found in TE (**Figure 4**).

The anti-parasitic action of NO is diminished in C57BL/6 mice vulnerable to chronically infected *T. gondii*, and TE, which leads to mortality, occurs because of the reactivation of tissue cysts [34–38]. NO plays a significant role in the shift from acute to chronic infection. There have been investigations into the critical functions of NO in the shift from acute to chronic infection. In a nutshell, NO causes the conversion



**Figure 4.**  
*IL-1R1 and Caspase 1/11-mediated pathway for TE attenuation.*

of tachyzoite to bradyzoite forms and attempts to regulate the course of the illness [34–36, 38–43]. It has been shown that a reduction in inducible nitric oxide synthase (iNOS) expression is linked to tissue cyst reactivation [34, 37, 38]. However, the focus of this section will be on the occurrence of neuropathology induced by NO generated over physiological limitations, because it has been proven that NO causes significant neuropathology rather than having neuroprotective characteristics. Despite the emphasis on the consequences of iNOS-derived NO generation in TE, it was shown that NO was not only iNOS-derived. Endothelial nitric oxide synthase (eNOS)-derived NO produced from endothelial cells infected with tachyzoites, and neuronal nitric oxide synthase (nNOS)-derived NO expressed by neurons also induces neuropathology at an unavoidable level [28]. It has been shown that all NO sources play a part in disease pathogenesis, explaining why the NS has progressed to such a severe level (Figure 5).

Apoptosis causes neuropathology found in TE, as shown by high caspase 3 expression and suppression of B-cell lymphoma-extra-large (Bcl-xL) expression, which has anti-apoptotic characteristics. The observed apoptosis is driven both extrinsically by the expression of Tumor necrosis factor receptor 1 and caspase 8 and internally by the production of caspase 9, which is a component of the apoptosome complex. *T. gondii* inhibiting Bcl-xL is exceptionally notable. The most surprising discovery in this research is that Purkinje cells were susceptible to intrinsically caused apoptosis. Thus, intrinsically caused apoptosis has been identified as one reason for Purkinje cell death in TE patients [26]. Pathological neurofilament (NF) accumulation in neurodegenerative cerebral diseases, particularly in injured neurons, is the most fundamental sign of acute neuroparenchymal destruction [44–46]. The critical element to understand in this section is that NF accumulates to pathological levels during the acute stage. TE had a large amount of

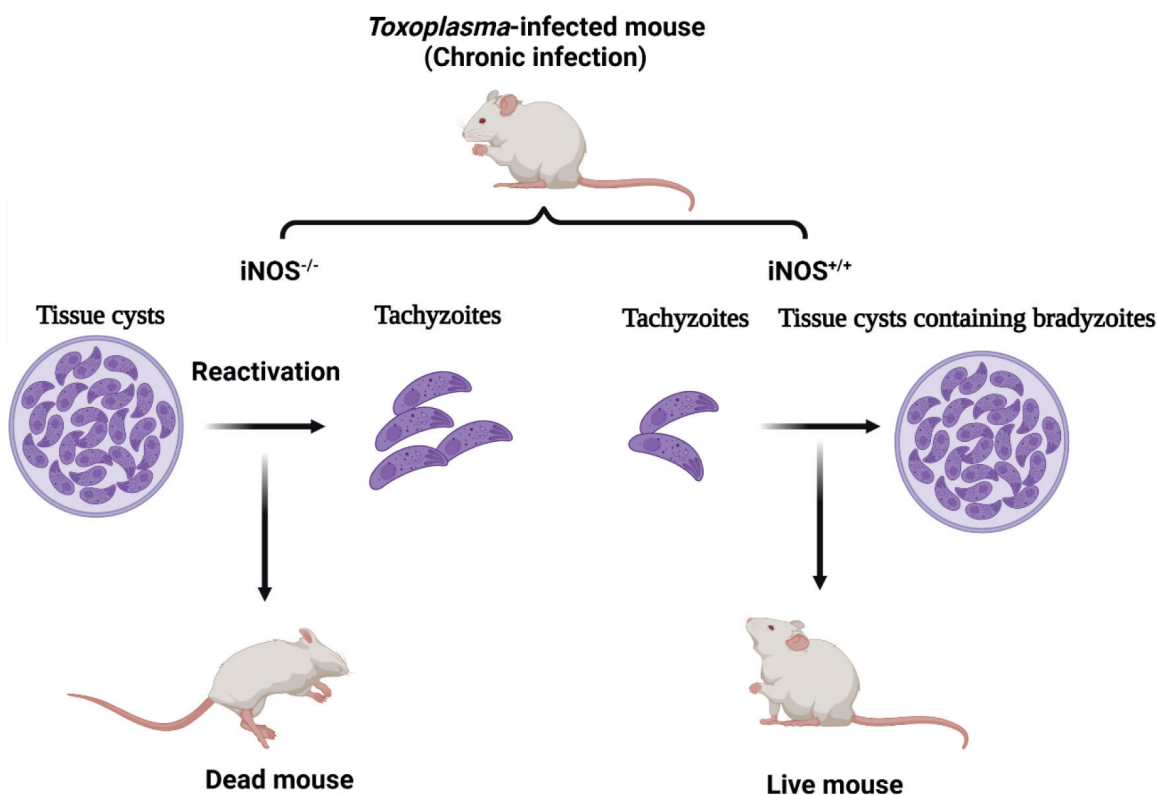


Figure 5.  
The role of iNOS in TE survival.

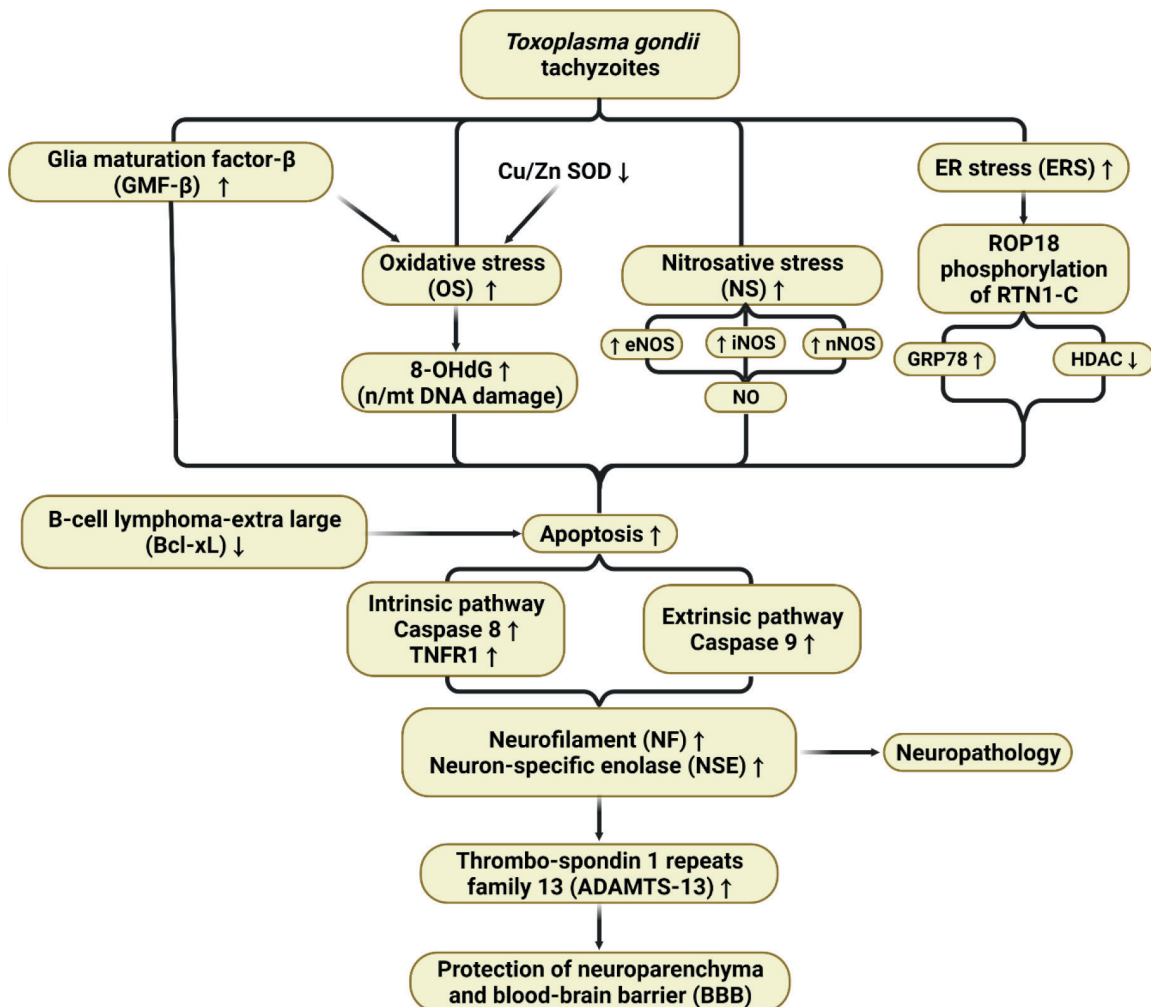


NF buildup in the chronic TE stage. The occurrence of degeneration and necrosis in acute neuroparenchymal structures owing to tissue cyst reactivation was the cause. As a result, it has been shown that monitoring NF accumulations may evaluate and track neuropathology in acute TE. Consequently, it has been demonstrated that the degree of neuropathology in acute TE may be identified and tracked by monitoring NF accumulations [28]. In experimental models of ischemia in rats, neuron-specific enolase (NSE) may be employed as a quantifiable marker to determine the degree of neuronal injury [47]. NSE is a good-quality marker for assessing TE-related neuropathology's severity and disease follow-up. NSE strongly showed the severity of *T. gondii*-mediated neurodegenerations in neuroparenchymal structures [27]. This is a significant result because, given the absence of a successful therapy for TE that has yet to be addressed entirely, it will play an essential role in assessing neuroprotective drugs.

It is widely established that oxidative stress (OS) plays a significant part in the molecular process of neurodegeneration/neuropathology in TE. Glutathione reductase and 8-hydroxy-2'-deoxyguanosine have been expressed at pathological levels in TE, and the expression of Cu/Zn superoxide dismutase (SOD), a critical endogenous enzymatic antioxidant that protects cells against OS-related apoptosis, is similarly hindered. Therefore, OS and n/mt DNA damage produced by OS shows severe neuropathology mediated by *T. gondii*, because a reduction in antioxidant enzyme activity provides crucial insight into the neuropathogenesis of TE [27]. Glia maturation factor (GMF)-mediated proinflammatory responses have been found to play a crucial role in the neuropathogenesis of neurodegenerative and demyelinating diseases and produce severe neuropathology [48–51]. In addition, it has been shown that elevated GMF expressions play a crucial role in the neuropathogenesis of Alzheimer's disease, a severe neurodegenerative disorder [48, 52]. Dincel's 2017 research found abnormal levels of GMF-b expression, a severe proinflammatory cytokine, in reactive glial cells and specifically in gliosis foci in the brain tissues of animals. This research showed a relationship between GMF overexpression in glial cells in TE and neuronal damage. It has been explained that the subsequent neurotoxicity is GMF-mediated neuropathology that has not been documented in TE before [53]. Uncovering a novel GMF-mediated proinflammatory mechanism is a significant step forward to our knowledge of neuropathogenesis.

The pathogenesis of TE has been linked to an enhanced unfolded protein response and extended ER stress. In the model created with *T. gondii*, type I strains showed that Roptry protein 18 (ROP18) is associated with the N-terminal portion of endoplasmic reticulum (ER)-associated protein called reticulon 1-C (RTN1-C), an ER protein expressed in the CNS [54]. As a result of ROP18 phosphorylation of RTN1-C, it has been explained that it triggers ER-stress-mediated apoptosis in neuronal cells. In addition to these findings, it has been demonstrated that ROP18 phosphorylation of RTN1-C increases glucose-regulated protein 78 acetylation by decreasing the activity of histone deacetylase. These results have been associated with neuronal apoptosis [54]. These findings clearly show that ER stress and ROP18 expression play critical roles in the pathogenesis of TE, and treatment modalities should focus on this target (**Figure 6**).

The neuropathology found in TE is critical. Although the neuropathology associated with chronic toxoplasmosis is thought to be resolved, we should not ignore their neuropsychiatric consequences. Any reactivation of tissue cysts intimately linked to the immune system might end in mortality. Although the aim here is to reduce neuropathology and avoid permanent damage, we should not ignore that the goal is



**Figure 6.**  
 Mechanism underlying the significant apoptosis seen in TE.

to eliminate tissue cysts. Because as long as the existence of tissue cysts in the brain persists, patients cannot avoid the risk of death.

## 5. Critical roles of astrocytes in toxoplasmic encephalitis

Astrocytes exert considerable effort to maintain control over *T. gondii*. Although the expression of gamma interferon (IFN-γ) has been proven to significantly regulate *T. gondii* in the brain, the molecular mechanism behind these protective actions is not well known. A comprehensive analysis revealed that IFN-gamma-induced GTPase (IGTP) suppressed the replication of *T. gondii* tachyzoites in astrocytes. Therefore, IGTP protects TE *via* astrocyte-mediated mechanisms [55]. However, it has been established that the signal transducer and activator of transcription 1 are required for IFN-gamma to suppress parasite multiplication in astrocytes (STAT1). Experimentally, it has been shown that in animals devoid of STAT1 expression, astrocytes cannot suppress *T. gondii* replication and, thus, cannot prevent neuropathology [56]. It has been shown that the orphan nuclear receptor regulates STAT1 signaling and host defense in astrocytes. In TE, astrocytes play a crucial role in developing a robust resistance to the parasite and complicated molecular pathogenesis [57]. It has been discovered that astrocytes' glycoprotein 130 (gp130) expression plays a crucial

role in mice with the experimental TE model. An experiment with animals lacking gp130 showed that apoptosis in astrocytes increased, and inflammatory lesions could not be avoided. However, it has been shown that gp130 expression by astrocytes is not required for *T. gondii* regulation in these cells. In summary, it has been shown that astrocyte-expressed gp130 alleviates neuropathology but does not prevent parasite replication [58].

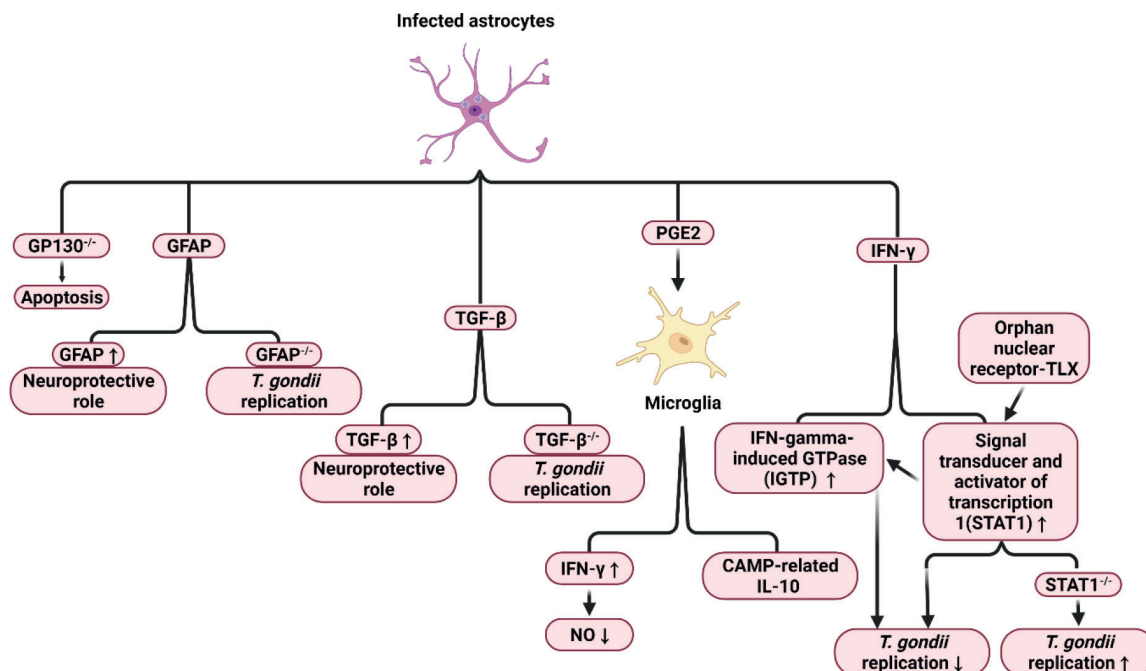
The importance of astrocytes in the immunopathogenesis of TE cannot be overstated. Astrocytes are among the cells infected by tachyzoites in both *in vivo* and *in vitro* experiments. *In vivo* investigations have shown that tachyzoites target and infect astrocytes after invading the brain. Activated astrocytes have been demonstrated to decrease parasite multiplication in TE and, as a result, help alleviate severe neuropathology such as necrosis [59–63]. Mice have been demonstrated to have little chance of surviving in TE, which was established in mice whose glial fibrillary acidic protein (GFAP) expressions were suppressed, and astrocyte numbers were lowered in an experiment [58]. This condition may be described as follows: in mice without a protective astrocyte population, the efficiency of GFAP, an essential immunoregulatory, would be reduced. As a result, parasite replication rises, and because of this replication, more widespread and severe inflammatory lesions develop, resulting in increased neuropathology severity [58, 64]. Severe GFAP expressions from astrocytes were identified in a potential tissue cyst reactivation. This robust expression shows that astrocytes exert effort to prevent neuropathology in the neuroparenchyma. Therefore, it has been shown that astrocytes function as immunomodulatory and immune effector cells in TE [28].

It has been revealed that astrocytic transforming growth factor-beta (TGF- $\beta$ ) signaling is crucial for suppressing the neuroinflammatory response in TE. It has been shown that inhibiting astrocytic TGF- $\beta$  signaling increases immune cell infiltration into the brain, resulting in severe neuronal damage. Inhibiting astrocytic TGF- $\beta$  signaling has no effect on CNS parasite burden in acute or chronic phases, suggesting a separate molecular mechanism in astrocytic TGF- $\beta$ -mediated neuroinflammation. Astrocytic TGF- $\beta$  signaling has a role in avoiding neuronal tissue damage in TE *via* astrocytic TGF- $\beta$  signaling [65].

*T. gondii*-infected astrocytes have been shown to express prostaglandin E2 (PGE2). PGE2 production by infected astrocytes has also been linked to microglia IL-10 expression reliant on cyclic adenosine monophosphate (cAMP). Finally, *T. gondii*-infected astrocytes suppress NO generation by IFN-gamma-activated microglia, and cAMP-dependent IL-10 expression by microglia contributes to neuropathology reduction (**Figure 7**) [66].

## 6. *T. gondii* and schizophrenia: Pathogenesis relationship

The relationship between *T. gondii* and schizophrenia has been investigated for decades. However, despite such studies and extensive meta-analyses, the relationship between the two diseases remains obscure. Because it is a current topic, this is regarded as a significant point. Kynurenic acid (KYNA), a metabolite of the kynurenine pathway derived from the breakdown of tryptophan, is synthesized by astrocytes [67–69]. In the pathogenesis of schizophrenia, impaired metabolism of the brain kynurenine pathway (KP) and consequently elevated kynurenate levels have been conclusively demonstrated [70]. In response to intense glial activation during TE, KYNA formation increases substantially. To summarize,

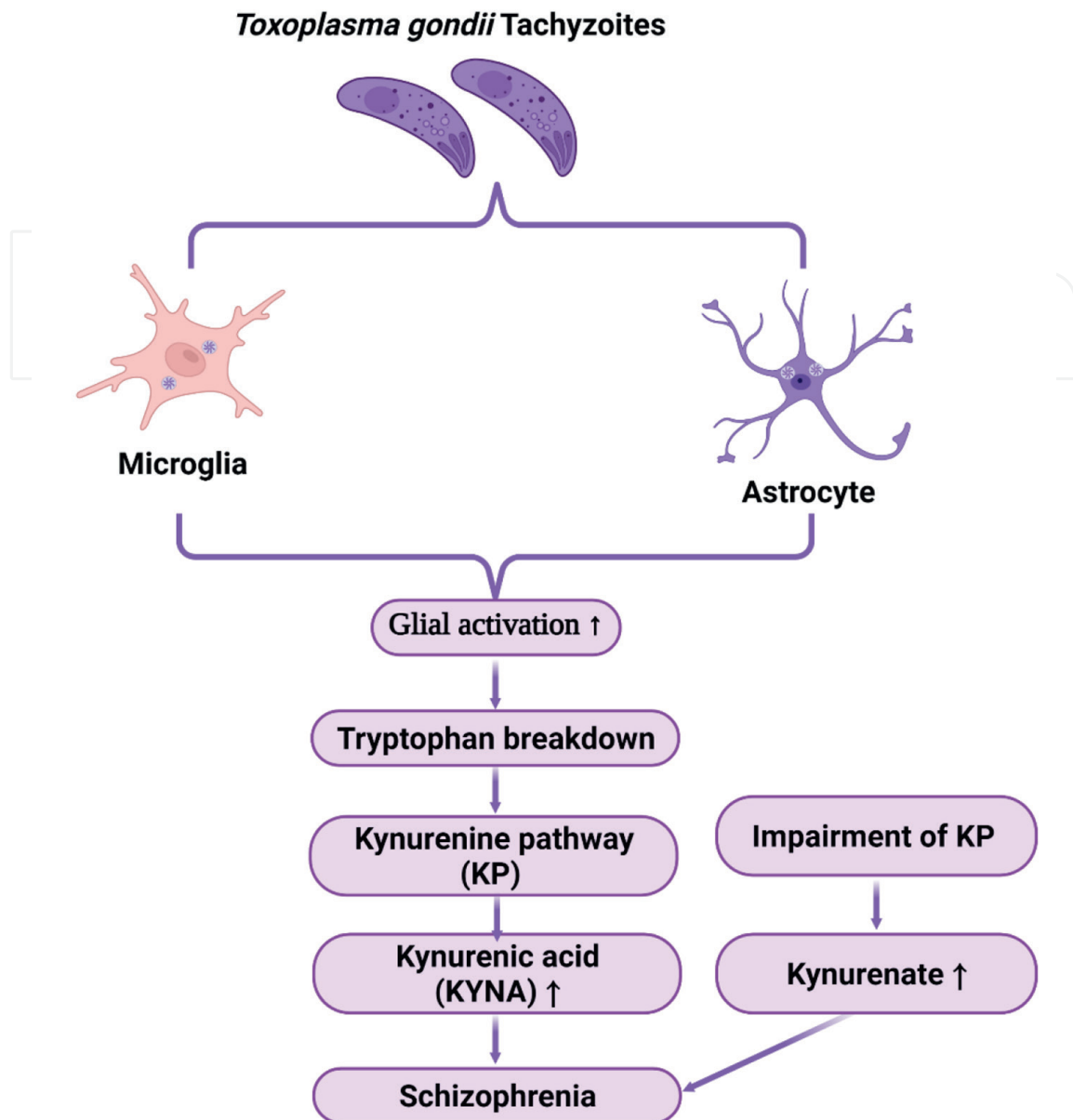


**Figure 7.**  
 TE severity and the roles of infected astrocytes.

KP metabolites play an essential role in the pathogenesis of *T. gondii*-mediated schizophrenia (Figure 8) [71].

The Matrix Metalloproteinase-9 (MMP-9) gene has been extensively studied in schizophrenia, and it has been demonstrated that the MMP-9 gene polymorphism may play a role in the pathogenesis of schizophrenia [72–74]. In TE, tachyzoite-infected astroglial cells increase the expression of Matrix Metalloproteinase-2 and -9 (MMP-2 and MMP-9). It has even been reported that the inflammatory development of encephalitis can be controlled by inhibiting MMP-2 and MMP-9 expression [75], because MMP-2 and MMP-9 expressed by astroglial cells have been shown to contribute to extracellular matrix degradation in brain tissue [76]. These findings show that MMP expression is essential in the pathogenesis of *T. gondii*-mediated schizophrenia (Figure 9).

The similarities between the pathogenesis of schizophrenia and TE are quite striking. There is an increase in NO production in schizophrenia [77] and neuropathology associated with OS [78, 79]. However, it has been demonstrated that the antioxidant enzyme SOD in the brain is significantly decreased in schizophrenia [80]. A considerable drop in the expression of the anti-apoptotic protein Bcl-2 has been discovered in the pathogenesis of schizophrenia [81], and apoptosis has been proven to play a crucial part in the process [82–84]. Similarly, cytokine-mediated neuronal damage has been documented in schizophrenia, and declines in the number and density of neurons have been reported [85]. When examining the pathogenesis of TE considering these data, it has been discovered that there are remarkable similarities, and their link is highlighted. Pathological levels of eNOS, iNOS, and nNOS-derived NO production have been observed in TE [28]. Moreover, it was shown that OS increased while SOD activity reduced considerably [27]. In addition, severe inhibition of the expression of Bcl-xL, an antiapoptotic protein, and triggering of apoptosis have been clearly demonstrated in TE models [26]. In TE, elevated GMF expressions, which induce proinflammatory responses in glial cells, revealed cytokine-mediated neuropathology [53] (Figure 10).

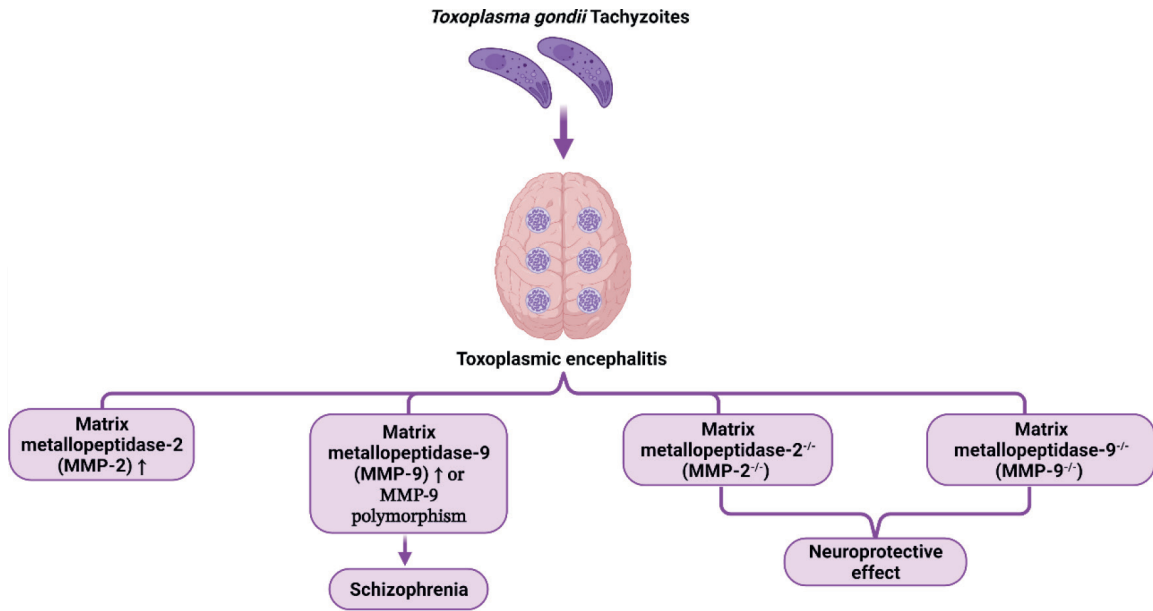


**Figure 8.**  
*T. gondii*-mediated KYNA elevation and its association with schizophrenia.

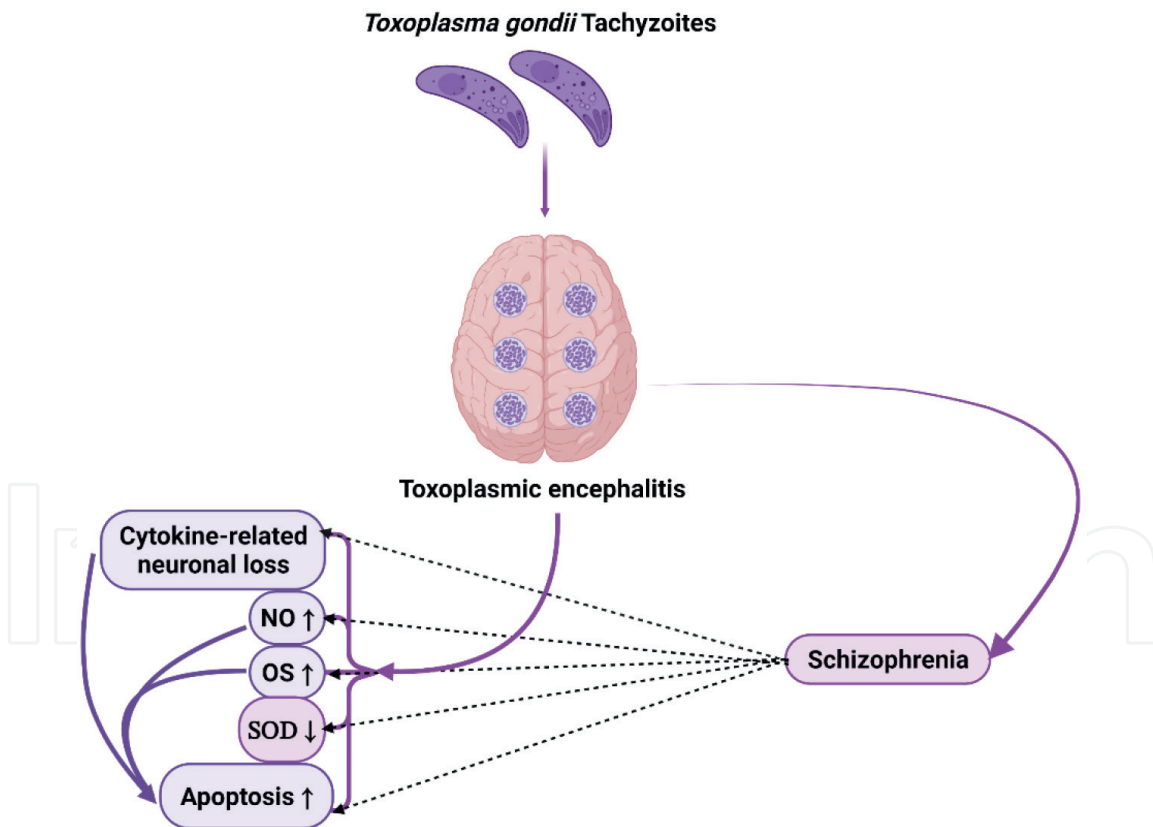
In a broad sense, the parallels between the pathogenesis of these diseases are highly remarkable. It also shows their close relationship. These investigations show the molecular mechanism behind the pathogenesis of schizophrenia mediated by *T. gondii*.

## 7. Neurohistopathological findings of toxoplasmic encephalitis

Nonsuppurative and/or necrotizing meningoencephalitis are among the fundamental histological findings in TE. The existence of tissue cysts is a crucial observation. It has been shown that tissue cysts may be found throughout the brain, with the increased density in the cerebral cortex, hippocampus, thalamus, and amygdala regions being a noteworthy histopathological finding. The histological findings are neuronal degeneration and necrosis, localized gliosis foci, hyperemia,



**Figure 9.**  
 Roles of MMP-2 and MMP-9 in TE neuropathology and schizophrenia.



**Figure 10.**  
 The reason why TE continues to be a major health issue.

perivascular mononuclear cell infiltration, and capillary endothelial hypertrophy. As shown earlier, Purkinje cells are very susceptible to *T. gondii* tachyzoites. Histopathologically, these cells are also shrunken, with eosinophilic cytoplasm and necrotic [26–28, 86–88].

## **8. Diagnosis of toxoplasmic encephalitis**

Multifocal necrotizing encephalitis is the main neuropathological sign of TE in people living with AIDS [89, 90]. However, from the start of the epidemic until more recent years, a number of publications have used the term “toxoplasma abscess” [91]. Human Immunodeficiency Virus (HIV)-related TE does not exhibit pus, contrary to the traditional definition of a brain abscess, which requires for an intraparenchymal pus accumulation. The four histological phases of the development of a brain abscess are early cerebritis, late cerebritis, early capsule formation, and late capsule formation. Pus may be seen in the latter three stages [92]. Additionally, an immunocompromised host may have a considerable delay in the progression of the phases of a brain abscess [93]. Thus, early cerebritis that more closely resembles necrotizing encephalitis is often seen in toxoplasmosis patients [92]. Although these lesions are considered abscesses in some studies, we think it is more appropriate to define “toxoplasmic encephalitis” as researchers who have worked with TE for many years.

### **8.1 Diagnostic categories**

There are important diagnostic criteria for TE. A differential diagnosis with diseases such as tuberculous meningitis or progressive multifocal leukoencephalopathy is required at this stage. In fact, the important points at this stage are early diagnosis and direct intervention, because it should never be forgotten that the time lost in neuropathology comes back with irreparable results [94].

#### *8.1.1 Histopathology-confirmed toxoplasmic encephalitis*

To establish the diagnosis clearly and definitively by histopathological examination, it is necessary to demonstrate the presence of *T. gondii* in brain biopsy or postmortem examination. Among the most commonly used methods, the priority is stereotactic computed tomography (CT)-guided needle biopsy. *T. gondii* tachyzoites or bradyzoites from tissue cysts can be seen at the margins of lesions by hematoxylin and eosin staining methods. However, the sensitivity can be significantly increased with immunohisto/cytochemical staining. Considering these histopathological methods, a definitive diagnosis can be made easily. However, the complications of brain biopsy should not be forgotten, and it should be done if necessary to make a definitive diagnosis. It should be recommended if there is no improvement in clinical findings after antitoxoplasma treatment and no progress is detected in imaging methods [94].

#### *8.1.2 Laboratory-confirmed toxoplasmic encephalitis*

For laboratory-confirmed TE, *T. gondii* DNA from cerebrospinal fluid (CSF) or brain biopsy material must be proven by nucleic acid amplification tests. The presence of serum *T. gondii* immunoglobulin G (IgG) antibodies also contributes significantly to diagnosing TE. Therefore, these two findings should be evaluated as a whole [94].

## 8.2 Important criteria for detecting suspected TE cases in immunocompromised patients

It has been extensively discussed above that immunocompromised patients are highly susceptible to TE, and serious pathology occurs in such cases. Here, we will focus on the steps to reveal a TE in these patients.

1. It should be considered when patients have clinical manifestations of massive brain lesions lasting up to 4 weeks, such as altered mental state, headache, or focal motor impairment [95].
2. Detection of the most common and diagnostic nodular lesions with perilesional edema and eccentric target sign in brain computed tomography (CT) scans is important. If any contradiction or negative result is seen at this stage, the patient should be referred to magnetic resonance imaging (MRI) without wasting time [96].
3. The clinical findings of patients receiving antitoxoplasma treatment with the suspicion of TE are followed closely, and a positive improvement is observed, and the improvement in neuropathology with imaging methods is an important advance for a definitive diagnosis.
4. The absence of *T. gondii* IgG antibodies and/or negative polymerase chain reaction (PCR) in blood samples/CSF taken from the patient does not completely exclude the possibility of TE. Instead, it requires redirection to other validation methods [97, 98].

Finally, it is worth mentioning that CNSToxoIndex evaluates the local synthesis of anti-toxoplasmic IgG in the CNS and their diffusion from blood as a consequence of blood-brain barrier disruption, and it is also a potent approach of TE diagnostics in HIV-positive individuals [99].

If a definitive diagnosis is desired, an important step in immunocompromised patients, lesions revealed by imaging methods should also be confirmed by histopathological and molecular methods.

## 9. Imaging features of toxoplasmic encephalitis

Imaging systems are of great importance in revealing the pathology caused by the diseases, both in the follow-up and diagnosis.

Since hematogenous distribution has a very important place in *T. gondii* infections, most of the lesions are seen in the basal ganglia, corticomedullary junction, white matter, and periventricular area [100]. The most accurate modality to diagnose TE is *via* magnetic resonance imaging (MR), which may also show the full scope of the illness. Infection of the brain produces lesions with poor attenuation on CT, low or high signal on T1WI (suggesting hemorrhagic components), and high signal on T2WI with surrounding edema. Currently, several important lesions in the imaging features of TE are very helpful in the diagnosis. Foremost among these, uniform nodular or



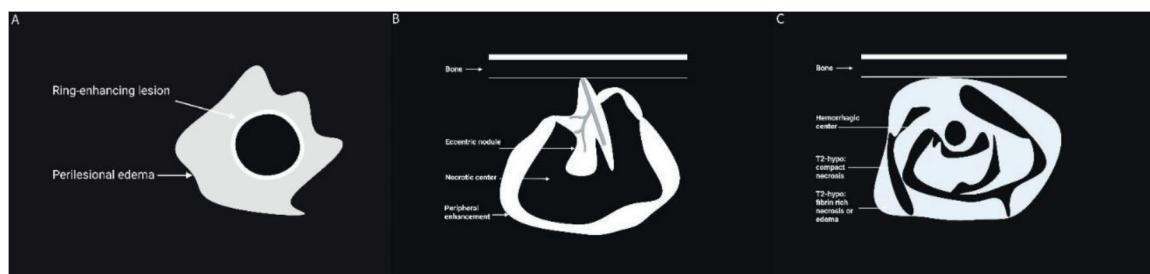
multifocal ring-enhancing lesions are seen, particularly in the cortex and periventricular white matter [100, 101]. Lesions from toxoplasmosis exhibit uniform nodular or ring enhancement [100, 101]. If there is poor enhancement, it may be modest or nonexistent in immunocompromised individuals depending on their cellular immune response. The “concentric target sign” in T2-weighted imaging and the “eccentric target sign” in postcontrast T1-weighted sequences are significant MRI findings reported in TE [100, 102–105]. In particular, this finding is considered pathognomonic.

Multiple lesions were seen in the bilateral basal ganglia, frontal, temporal, parietal, occipital, and cerebellar lobes, as well as ring enhancement on postcontrast sequence near edema and the development of “eccentric target sign” on an MRI of the brain with contrast. These lesions featured intra-lesional hemorrhagic foci and alternating hyper and hypointense zones on T2-weighted sequence, along with perilesional edema that was clearly visible and corresponded to the “concentric target sign” [105].

Susceptibility-weighted imaging (SWI) of hemorrhagic lesions commonly seen in TE was superior and more sensitive than GRE T2\*WI. It is emphasized that diffuse hemorrhage foci seen in TE and frequently detected in recent studies may also be because of the superior sensitivity of SWI in detecting hemorrhage [106].

The eccentric target sign linked histologically to a sizable necrotizing abscess. The enhancing rim histologically corresponded to a thick ring of histiocytic response with inflamed and proliferating vessels demarcated by immunostaining to Factor VIII related antigen of vascular endothelium, while the surrounding zone of necrosis caused the intermediate zone of hypointensity. On T2W images, the perilesional white matter edema with demyelination appeared as strong hyperintensities [107]. The ring-enhancing lesion’s periphery occasionally contained tissue cysts containing *T. gondii* bradyzoite, while the necrotic zone’s inflamed vascular zone contained diffusely dispersed tachyzoite forms that could be seen by immunohistochemistry using antibodies to tachyzoite-specific antigen (p30). Eccentric target sign, a characteristic of imaging, is thought to be strongly predictive of toxoplasmosis. Less than 30% of cases have this sign, which may be seen on postcontrast CT scans (asymmetric target sign) or T1W MRI scans [108]. There are three alternating zones in this: a centrally eccentric innermost enhancing core, a middle hypointense zone, and an outermost hyperintense enhancing rim. A leash of inflamed, leaking arteries that enter the lesion *via* a sulcus create the eccentric core [107].

Diffusion- and perfusion-weighted imaging (DWI and PWI) and spectroscopy may help distinguish toxoplasmosis from other disorders that mirror it, such as brain lymphoma and infections, especially in immunocompromised individuals. Toxoplasmosis may exhibit peripheral limited diffusion, but pyogenic abscesses often exhibit central restricted diffusion. PWI in toxoplasmosis is minimal, but high in



**Figure 11.** Ring-enhancing lesions surrounding hyperintensity, consistent with vasogenic edema, eccentric target sign, and concentric target sign.

lymphoma and other neoplasms. Toxoplasma and pyogenic abscesses both had an increased lipid-lactate peak in spectroscopy [109, 110]. PET-CT and thallium single-photon emission computed tomography often reveal increased uptake in lymphoma and decreased uptake in toxoplasmosis (**Figure 11**) [109, 111].

## 10. Conclusion

The mechanisms of neuroimmunopathogenesis, the most significant and complicated aspect of TE, were covered in this chapter, which was the product of much study and effort. Each part has been thoroughly evaluated and clarified. Therefore, the most fundamental aspect of avoiding neuropathology induced by TE, which may lead to mortality, is the investigation and complete disclosure of these processes. This book chapter, which discusses this extensive neuroimmunopathogenesis and will play an essential role in developing novel therapeutic medications, will make a significant addition to the body of literature. Furthermore, diagnostic methods that are critical are emphasized. The tricks of imaging methods are summarized, and key points are highlighted. It is hoped that considering all aspects of TE, which has a complex pathological mechanism, will make a significant contribution to the literature.

## Conflict of interest

The authors declare that there is no conflict of interests regarding the publication of this chapter.

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