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Neuroinflammation and schizophrenia: The role of *Toxoplasma gondii* infection and astrocytic dysfunction

Abigail Everett, Hany M. Elsheikha *

Faculty of Medicine and Health Sciences, School of Veterinary Medicine and Science, University of Nottingham, Sutton Bonington Campus, Loughborough LE12 5RD, UK

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ABSTRACT

Obligate intracellular pathogens such as the protozoan *Toxoplasma gondii* exploit host cell mechanisms to facilitate their survival and replication. While *T. gondii* can infect any nucleated mammalian cell, it exhibits a particular affinity for central nervous system cells, including neurons, astrocytes, and microglia. Among these, astrocytes play a pivotal role in maintaining neuroimmune balance, and their infection by *T. gondii* induces structural and functional alterations. Emerging evidence suggests that these changes may contribute to the pathophysiology of schizophrenia (SCZ). Although a direct causal link between *T. gondii*-induced astrocytic dysfunction and SCZ remains unproven, infection has been associated with increased kynurenic acid production, elevated dopamine levels, and heightened inflammatory cytokines—all of which are implicated in SCZ pathology. Additionally, *T. gondii* infection disrupts crucial neurobiological processes, including *N*-methyl-D-aspartate receptor signaling, blood-brain barrier integrity, and gray matter volume, further aligning with SCZ-associated neuropathology. This review underscores the need for targeted research into *T. gondii*-mediated astrocytic dysfunction as a potential factor in SCZ development. Understanding the mechanistic links between *T. gondii* infection, astrocytic alterations, and psychiatric disorders may open new avenues for therapeutic interventions.

1. Introduction

Toxoplasma gondii is a heteroxenous protozoan responsible for toxoplasmosis, a widespread parasitic infection worldwide (Elsheikha et al., 2021). While felids are the definitive hosts for *T. gondii*, this zoonotic parasite can establish latent infections in various mammalian species. The rapidly replicating stage of the parasite, known as the tachyzoite, invades macrophages and dendritic cells, enabling its spread to various tissues, including immune-privileged sites such as the brain (Elsheikha et al., 2021; Gazzinelli et al., 1993). In immunocompetent individuals, the host immune response effectively controls the systemic infection (Weiss and Dubey, 2009). The parasite then transitions into a slow-replicating form called the bradyzoite, which persists in tissue cysts within the host's neural and muscle tissues (Elsheikha et al., 2021). In pregnant women, *T. gondii* infection can lead to congenital toxoplasmosis, leading to fetal disabilities, birth defects, or miscarriage (Elsheikha, 2008).

Although *T. gondii* has been linked to various neuropsychiatric disorders, including bipolar disorder, obsessive-compulsive disorder, aggressive behavior, Parkinson's disease, and Alzheimer's disease, its connection to schizophrenia (SCZ) remains one of the most extensively studied (Elsheikha et al., 2016; Elsheikha and Zhu, 2016; Kazemi Arababadi et al., 2024; Virus et al., 2021). Over the past three decades, SCZ research has explored multiple theories, including the dopamine hypothesis, disruptions in glutamine and tryptophan metabolism, genetic predisposition, prenatal infections, and inflammation (Elsheikha et al., 2016; Elsheikha and Zhu, 2016). Recent reviews have highlighted the role of astrocytes in central nervous system (CNS) health and disease (Endo et al., 2022; Gradisnik and Velnar, 2023; Lee et al., 2023), yet their involvement in SCZ pathology, particularly in the context of *T. gondii* infection, remains largely underexplored. As key regulators of neuroimmune signaling, neurotransmitter balance, and synaptic plasticity, astrocytes are significantly affected by *T. gondii* infection. Given the parasite's ability to alter brain function and behavior, as well as its influence on astrocytic function, *T. gondii* may contribute to SCZ development. The parasite disrupts glutamate homeostasis, promotes neuroinflammation, and alters synaptic pruning and metabolite levels—all features commonly associated with SCZ. Additionally, genetic susceptibility, such as Disrupted-in-Schizophrenia-1 (*DISC1*) mutations, may exacerbate the effects of *T. gondii*, further disrupting *N*-methyl-D-

* Corresponding author.
E-mail address: Hany.Elsheikha@nottingham.ac.uk (H.M. Elsheikha).

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aspartate receptor (NMDAR) signaling and neuronal connectivity.

This review explores the role of astrocytes in SCZ pathology, emphasizing how *T. gondii* manipulates these cells and how the resulting immune response contributes to both parasite propagation and SCZ development. We examine the role of astrocytes in CNS immune responses, including cytokine release, immune cell recruitment, and inflammation, which contribute to neuronal damage and synapse remodeling. Additionally, we discuss neurotoxic inflammation and how astrocytes attempt to counteract the proinflammatory response—an effect that paradoxically benefits *T. gondii*. A deeper understanding of astrocyte-mediated neuroinflammation may pave the way for new therapeutic approaches for SCZ.

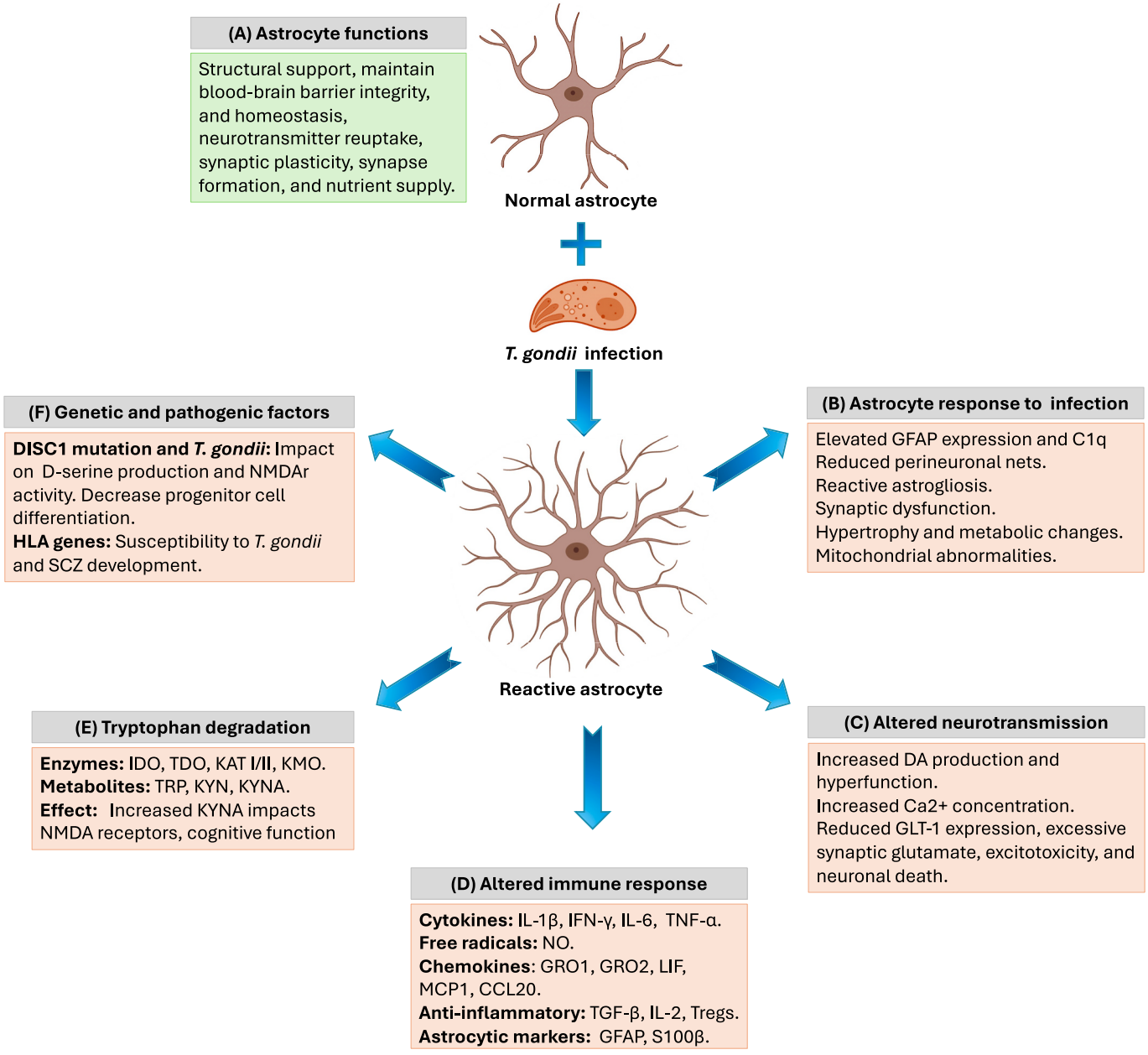

Fig. 1. Schematic representation of astrocyte-mediated mechanisms linking *T. gondii* infection to SCZ pathology. Astrocytes are essential for CNS homeostasis, and their dysfunction may contribute to neurodevelopmental disorders such as SCZ. (A) In a healthy state, astrocytes regulate synaptic activity, maintain ECM integrity, support brain development, and participate in synaptic pruning. (B) During *T. gondii* infection, astrocytes facilitate parasite replication and cyst rupture. GFAP forms a protective barrier, while C1q modulates immune responses that influence synapse density and cyst integrity. Infection triggers astrocytes to release proinflammatory cytokines, contributing to neuroinflammation, which may influence SCZ pathogenesis. (C) *T. gondii*-induced astrocytic dysfunction disrupts dopamine (DA) and glutamate regulation, both critical in SCZ. The parasite elevates proinflammatory cytokines and NO, leading to synaptic abnormalities. Additionally, DA metabolism in astrocytes activates *T. gondii* TgCDPK1, promoting parasite dissemination. (D) Prenatal *T. gondii* infection alters astrocyte function and structure, potentially increasing SCZ risk by disrupting synapse formation. Proinflammatory cytokines (IL-1β, TNF, IFN-γ) enhance immune responses but may also damage neurons and astrocytes. Conversely, anti-inflammatory mechanisms (e.g., TGF-β, Tregs) limit damage but promote *T. gondii* persistence. The parasite also activates IDO, increasing kynurenine production and Treg differentiation, fostering immune tolerance. (E) *T. gondii* manipulates the kynurenine pathway in astrocytes by degrading tryptophan and increasing KYNA production. Elevated KYNA interferes with synaptic signaling and neurotransmitter release, contributing to cognitive deficits and SCZ pathology. Cytokine-driven alterations in TRP metabolism further affect long-term CNS function. (F) Mutant *DISC1* gene predisposes individual to glutamatergic dysfunction and NMDAR hypofunction by reducing D-serine availability. Additionally, human leukocyte antigen (HLA) genes are risk factors for susceptibility to both *T. gondii* infection and SCZ. Credit: Astrocytes and *T. gondii* images used in the figure are sourced from BioRender.com.

2. Roles of astrocytes in CNS function, development, and SCZ

2.1. Astrocytes: beyond supportive functions

Astrocytes, once considered merely supportive to neurons, are now recognized for their diverse array of critical functions in the CNS. They are essential for many processes (Fig. 1A), including maintaining water and electrolyte balance, regulating neurotransmitter reuptake, modulating the CNS immune response, providing nutrients to neurons, and forming the blood-brain barrier (BBB) (Bernstein et al., 2015; Chang et al., 2021). Additionally, astrocytes connect to both pre- and post-synaptic compartments, forming a tripartite synapse that allows them to modulate synaptic activity (Casanova, 1991). Their end-feet also make contact with endothelial cells around CNS capillaries, influencing BBB permeability and the interaction between peripheral and CNS immune responses (Muller, 2019).

2.2. Dysregulation of astrocytic functions and altered synaptic connectivity in SCZ

Astrocytes play a crucial role in brain development and synaptic plasticity by regulating the extracellular matrix (ECM) through the secretion of various molecules, such as chondroitin sulfate proteoglycans (CSPGs) (Wiese et al., 2012). The ECM serves as a scaffolding that supports synapse formation, maturation, and plasticity. In individuals with SCZ, alterations in astrocyte function, particularly in the formation and remodeling of the ECM, are thought to contribute to synaptic dysconnectivity, a hallmark of the disorder (Pantazopoulos et al., 2015). One key aspect of astrocytic dysfunction in SCZ is the reduced secretion of CSPGs into the ECM. These molecules are essential for the formation of perineuronal nets (PNNs), which envelop certain synapses and provide structural support, regulating synaptic plasticity, and influencing the survival and development of neurons and neuronal circuit (Chelini et al., 2018). In SCZ patients, the decreased secretion of CSPGs by astrocytes leads to a reduction in the density and integrity of PNNs, disrupting the scaffolding required for efficient synaptic transmission. This structural alteration is thought to underlie the synaptic dysfunction observed in SCZ, including decreased dendritic spine density, hypomyelination, and reduced gray matter volume—prominent features in post-mortem studies (Leza et al., 2015; Pantazopoulos et al., 2010). These changes in synaptic structure and function are considered to contribute to the cognitive and emotional disturbances commonly seen in SCZ patients, such as impaired memory, attention, and emotional regulation.

2.3. Role of T. gondii in altering astrocytic functions and synaptic connectivity

Infection by *T. gondii* can impact the immune system, neuronal signaling, and synaptic plasticity, all of which may contribute to the pathophysiology of SCZ. *T. gondii* primarily infects astrocytes in the brain, and this infection can lead to significant alterations in astrocytic function. One key mechanism through which *T. gondii* might influence synaptic connectivity is by modulating the immune response. The infection activates the host's immune system, triggering the release of pro-inflammatory cytokines and other immune mediators. Chronic inflammation resulting from *T. gondii* infection can exacerbate astrocytic dysfunction, impairing their ability to maintain the ECM and regulate synaptic plasticity. Elevated levels of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), disrupt the secretion of CSPGs and reduce the formation of PNNs, which in turn impair synaptic connectivity and contributes to cognitive dysfunction in SCZ (Mallya and Deutch, 2018). Furthermore, *T. gondii* infection can directly interfere with neuronal signaling and synaptic plasticity by altering astrocytic communication with neurons. Astrocytes release gliotransmitters, such as glutamate and ATP, which modulate synaptic activity and plasticity. By affecting the release of these gliotransmitters, *T. gondii* may induce an imbalance in excitatory and inhibitory neurotransmission, exacerbating the synaptic dysfunction observed in SCZ. This disruption of synaptic signaling may contribute to the cognitive and behavioral symptoms commonly seen in the disorder (Feinberg, 1982).

2.4. Alterations in synaptic pruning and the potential role of T. gondii

Synaptic pruning is a crucial process during brain development that involves the elimination of excess synapses to refine neural circuits. Astrocytes play a central role in this process, mediating synapse elimination through phagocytosis of synaptic components or by releasing of factors such as transforming growth factor-beta (TGF-β), which trigger astrocytic remodeling. In SCZ, abnormal synaptic pruning during adolescence is thought to contribute to the onset of the disease. Insufficient or excessive pruning can lead to altered synaptic connectivity and cognitive deficits (Takahashi and Sakurai, 2013).

T. gondii infection may influence synaptic pruning in several ways. The parasite alters immune responses, including the activation of microglia and astrocytes, which can impair their role in synaptic pruning. For example, increased activation of TGF-β by *T. gondii* could lead to excessive or misdirected pruning of synapses, disrupting the normal fine-tuning of neural circuits. This disruption may result in the over-elimination or improper maintenance of synaptic connections, potentially contributing to the cognitive and functional impairments observed in SCZ. Furthermore, *T. gondii*-induced changes in astrocytic metabolism and gliotransmitter release could alter the signals that regulate pruning, further exacerbating synaptic abnormalities (Feinberg, 1982; Takahashi and Sakurai, 2013).

3. Astrocytic responses to *T. gondii* infection

Astrocytes provide an ideal environment for *T. gondii* replication, particularly in fetal brain tissue (Halonen et al., 1996). During *T. gondii* infection, the glial fibrillary acidic protein (GFAP) forms a physical barrier around the parasite (Fig. 1B), a process initiated by TGF-β (Cekanaviciute et al., 2014). The complement protein C1q, which is recognized by astrocytes as a marker for infection and synapse remodeling, accumulates around cysts with compromised walls, potentially triggering an immune response. This increased presence of C1q (Fig. 1B) may contribute to the pruning of adjacent synapses and a reduction in dendritic spine density, although the mechanisms behind cyst degeneration and parasite reactivation are not fully understood (Xiao et al., 2016).

Astrocytes play a crucial role in coordinating the immune response within the CNS during *T. gondii* infection. Upon encountering tachyzoites, astrocytes release proinflammatory cytokines such as TNF-α, IL-6, IL-1α, IL-1β, and interferon-gamma (IFN-γ), and granulocyte/macrophage colony-stimulating factor (GM-CSF) (Cekanaviciute et al., 2014; Fischer et al., 1997). The potential implications of these cytokines on the pathogenesis of SCZ and *T. gondii* infection are discussed in the subsequent sections.

4. Mechanisms of *T. gondii*-induced astrocytic alterations in SCZ development

4.1. The dopamine hypothesis

The dopamine hypothesis of SCZ originated from the discovery of elevated dopamine levels in SCZ patients (Fond et al., 2013; Seeman and Kapur, 2000). Astrocytes play a key role in regulating dopaminergic transmission in the brain by degrading extracellular dopamine and influencing NMDAR activity (Fig. 1C). Initially, the cause of dopaminergic hyperfunction was unclear, but subsequent research revealed that *T. gondii* upregulates dopamine production in astrocytes. This process occurs through the activation of two genes, *AAH1* and *AAH2*, which

encode tyrosine hydroxylase enzymes. These enzymes convert tyrosine or phenylalanine into L-dopa, ultimately increasing dopamine levels (Elsheikha and Zhu, 2016; Gaskell et al., 2009).

During *T. gondii* infection, activated leukocytes produce nitric oxide (NO) and proinflammatory cytokines, which further elevating dopamine levels (Elsheikha and Zhu, 2016). Supporting evidence shows that mice with chronic *T. gondii* infection exhibit higher dopamine levels (Fond et al., 2013) and increased densities of *T. gondii* tissue cysts in brain regions with elevated dopamine (Strobl et al., 2012).

Calcium (Ca2+) plays a crucial role in intracellular signaling within astrocytes, where Ca2+ waves generated in the endoplasmic reticulum (ER) modulate neuronal activity and homeostasis (Miterauer and Baer, 2020). Dopamine stimulates the egression of *T. gondii* from the parasitophorous vacuole by activating Ca2+ signaling. Specifically, dopamine or IFN-γ induces the ER fusion with the vacuole, triggering a significant influx of Ca2+ and facilitating parasite release (Melzer et al., 2008). This increase in Ca2+ concentration also activates *T. gondii* calcium-dependent protein kinase 1 (TgCDPK1), which promotes the secretion of micronemes, enhancing the parasite's mobility, egress, dissemination, and host-cell invasion (Fig. 1C) (Lourido et al., 2010).

4.2. The glutamate hypothesis

MK-801, also known as dizocilpine, is a non-competitive NMDAR antagonist. Blocking the NMDARs on astrocytes induces both positive and negative SCZ symptoms (Chang et al., 2021; Martins-de-Souza et al., 2011), suggesting that NMDAR hypofunction plays a role in the disorder. The glutamate hypothesis of SCZ posits that NMDAR hypofunction leads to an accumulation of glutamate in the synaptic cleft, although the precise mechanism remains unclear (Mei et al., 2018). Under normal conditions, astrocytes regulate glutamate levels in the synaptic cleft by using the GLT-1 transporter protein to remove excess glutamate. However, during *T. gondii* infection, the expression of GLT-1 is downregulated (David et al., 2016), leading to an accumulation of glutamate in the synapse (Fig. 1C). This glutamate buildup creates a neurotoxic environment, which can result in excitotoxicity and neuronal death (Wohlfert et al., 2017). Elevated glutamate levels also trigger the release of intracellular Ca2+ from the ER, promoting cyst rupture and benefiting the parasite (Fritschi et al., 2021).

5. Peripheral vs. CNS immune responses to *T. gondii* infection

The intricate interplay between *T. gondii* infection, astrocytic dysfunction, and SCZ pathophysiology highlights the need for a nuanced understanding of immune responses across both peripheral and central compartments. Immune activation following *T. gondii* infection differs significantly between the systemic circulation (serum) and the CNS, including cerebrospinal fluid (CSF) and brain tissue. While *T. gondii*-induced neuroinflammation has been implicated in SCZ, most studies have focused on systemic cytokines, chemokines, and other inflammatory mediators in serum (Dupont et al., 2012; Elsheikha et al., 2021; Leza et al., 2015; Liu et al., 2006), with limited exploration of direct immune alterations within the CNS. However, systemic inflammation does not necessarily mirror CNS-specific immune activity, as the BBB restricts the passage of many immune mediators.

Given *T. gondii*'s ability to establish persistent infections in the brain, dissecting compartment-specific immune responses is critical for understanding its role in neuroinflammation and neuropsychiatric disorders such as SCZ. Future research should prioritize the analysis of CSF and post-mortem brain tissue in *T. gondii* infection models. Longitudinal tracking of immune markers in both serum and CSF may help clarify the dynamic interplay between peripheral and central immune responses, shedding light on the contribution of neuroinflammation to SCZ and guiding the development of targeted therapeutic interventions for CNS-specific immune dysregulation.

6. Balancing act: the dual role of inflammatory and anti-inflammatory responses in *T. gondii* infection and SCZ pathogenesis

The proinflammatory response to *T. gondii* infection involves significant immune activation and inflammation. Tachyzoites elicit a robust systemic immune response, leading to the upregulation of genes encoding proinflammatory cytokines such as IL-1β and IL-6, along with chemokines such as GRO1, GRO2, LIF, and MCP1, which that recruit immune cells to the infection site (Fig. 1D) (Carruthers and Suzuki, 2007). Interestingly, elevated levels of these cytokines, together with TGF-β, are also observed during SCZ exacerbation, suggesting that *T. gondii*-induced inflammation may contribute to the onset and severity of SCZ symptoms (Leza et al., 2015).

A central cytokine in *T. gondii* infection is IFN-γ, which disrupts the parasitophorous vacuole containing tachyzoites. By interacting with the interferon-inducible GTP-binding protein IGTP, IFN-γ promotes early egression of tachyzoites, limiting their ability to infect host cells (Melzer et al., 2008). Additionally, IFN-γ and IL-1β, stimulate NO production, which inhibits tachyzoite replication (Carruthers and Suzuki, 2007). However, this prolonged inflammation can be detrimental, leading to neuronal and astrocytic damage.

Dysfunction of the BBB is a hallmark of chronic SCZ, with elevated ICAM-1 and albumin levels in CSF indicating increased permeability (Chang et al., 2021; Muller, 2019). Moreover, astrocytes, critical components of the BBB, undergo morphological changes such as deformation and swelling of their end-feet, which may further compromise BBB integrity and contribute to SCZ pathogenesis (Uranova et al., 2010).

The CNS is highly sensitive to inflammation, and excessive immune responses can lead to neuronal damage. While clearing *T. gondii* from the CNS is critical, maintaining brain integrity requires tight regulation of inflammation. Astrocytes, essential for CNS homeostasis, play a key role in this balance by initiating anti-inflammatory responses to mitigate damage while supporting parasite clearance (Fig. 1D). IFN-γ activates GP130, a receptor for IL-6 family cytokines, which restricts *T. gondii* growth in astrocytes and reduces brain damage. Without GP130, astrocytes become more susceptible to apoptosis in response to proinflammatory cytokines such as TNF-α (Drogemuller et al., 2008).

Simultaneously, the anti-inflammatory cytokine TGF-β is upregulated during infection (Fig. 1D), directing immune cells to infected sites while preventing unnecessary neuronal damage (Cekanaviciute et al., 2014). TGF-β also enhances T regulatory cell (Treg) production, suppressing excessive inflammation by inhibiting naive T cell activation and limiting proinflammatory cytokines such as IL-2, TNF-α, and IFN-γ. Interestingly, elevated TGF-β levels are also observed in individuals with SCZ (Corsi-Zuelli and Deakin, 2021). Astrocytes regulate Treg-mediated immune suppression via IL-2 signaling, and disruptions in this pathway can result in Treg dysfunction and excessive phagocytosis (Corsi-Zuelli and Deakin, 2021; Xiao et al., 2016).

Despite its protective function, this anti-inflammatory response may also facilitate *T. gondii* persistence. IL-1β-activated astrocytes can downregulate CCL20, a chemokine that recruits Tregs, inadvertently creating a more permissive environment for the parasite (Akkouh et al., 2020). Moreover, *T. gondii* manipulates anti-inflammatory pathways to sustain its presence, enhancing the production of indoleamine 2,3-dioxygenase (IDO). IDO degrades tryptophan into kynurenine, promoting the differentiation of FoxP3(+) Tregs over T helper cells (Fig. 1D), fostering immune tolerance toward the parasite (Mezrich et al., 2010).

7. Markers of astrocytic inflammation/activation in SCZ: the roles of GFAP and S100β

GFAP is a key marker of astrocytic activation and inflammation in the CNS (Fig. 1D) (Kubesova et al., 2015). Produced by astrocytes in response to cell damage, GFAP contributes to the proinflammatory process by increasing NO production (Esshili et al., 2020). During

T. gondii infection, GFAP plays a protective role by forming a physical barrier, mediated by TGF-β, to limit neuroinflammation (Cekanaviciute et al., 2014). While GFAP+ astrocytes are essential in CNS infections, data on soluble GFAP levels in CSF during acute *T. gondii* infection remain scarce. Future research is needed to clarify how GFAP levels correlate with infection stage and neuroinflammatory responses.

Interestingly, elevated GFAP concentrations have been detected in the prefrontal cortex of SCZ patients, often correlating with symptom severity (Kim et al., 2018; Ranganathan et al., 2022). However, variability in GFAP measurements among SCZ patients may stem from genetic differences and regional brain variations (Kim et al., 2018). Given the shared neuroinflammatory mechanisms in *T. gondii* infection and SCZ, GFAP could serve as a relevant biomarker, but its precise role, particularly in CSF, warrants further investigation.

Another key astrocytic marker, S100β, has dual roles in neuroinflammation and neuroprotection (Fig. 1D). It interacts with the receptor for advanced glycation end products (RAGE), triggering free radical, NO, and glutamate production—factors that can contribute to neuronal damage (Langeh and Singh, 2021). Despite these inflammatory effects, S100β also exerts neuroprotective functions by reducing microgliosis and suppressing TNF-α (Langeh and Singh, 2021). Increased S100β concentrations in SCZ patients' CSF are linked to BBB hyperpermeability (Chang et al., 2021) and poorer responses to therapeutic treatments (Rothermundt et al., 2009).

8. *T. gondii* and the kynurenine pathway: disruption in tryptophan metabolism and KYNA overproduction in SCZ

The parasite manipulates the kynurenine pathway in astrocytes to degrade tryptophan, leading to increased kynurenic acid (KYNA) production (Fig. 1E). Initially, tryptophan is converted to kynurenine (KYN) by enzymes such as IDO and tryptophan 2,3-dioxygenase (TDO) (Schwarcz et al., 2012). Astrocytes then metabolize KYN to KYNA via kynurenine aminotransferases (KAT I and KAT II) (Miuller and Schwarz, 2007). The parasite's dependence on tryptophan for survival drives this metabolic shift, disrupting host neurochemical balance (Xiao et al., 2018).

The accumulation of KYNA, released by astrocytes, antagonizes NMDA and α7nACh receptors, significantly impairing synaptic signaling. By inhibiting glutamate release, KYNA disrupts excitatory-inhibitory neurotransmission (Beggiato et al., 2014; Wu et al., 2010). Additionally, KYNA suppresses dopamine release (Miuller and Schwarz, 2007), a key mechanism underlying cognitive impairments in SCZ. Elevated KYNA levels in the CSF and post-mortem brains of SCZ patients suggest that dysregulation of this pathway contributes to the disorder's cognitive deficits (Kubesova et al., 2015; Linderholm et al., 2012; Miuller and Schwarz, 2007; Sathyasaikumar et al., 2011).

Moreover, *T. gondii* infection alters the expression of enzymes involved in tryptophan degradation. Pro-inflammatory cytokines such as IL-6 and prostaglandin E2 enhance IDO activity, accelerating tryptophan breakdown and KYNA production (Kubesova et al., 2015). This creates a feedback loop in which increased KYNA levels exacerbate synaptic dysfunction, potentially worsening SCZ symptoms. Notably, prenatal *T. gondii* infection primes the CNS immune response, and when the parasite reactivates, it triggers heightened inflammation, disrupting synaptic maturation and pruning in the developing brain (Iaccarino et al., 2013).

Taken together, *T. gondii* infection and the resulting kynurenine pathway dysregulation significantly impact synaptic plasticity, contributing to SCZ pathophysiology (Fig. 1E). Whether through an active inflammatory response (type 1) or immune modulation (type 2), the resulting imbalance in kynurenine metabolites plays a critical role in the cognitive and behavioral abnormalities associated with SCZ. This pathway may serve as a mechanistic link between *T. gondii* infection and SCZ progression, highlighting potential therapeutic targets for future research.

9. Prenatal and early-life *T. gondii* infection: mechanisms, astrocytic dysfunction, and long-term implications for SCZ development

Prenatal and early-life *T. gondii* infection poses significant risks to maternal and fetal health, with growing evidence linking it to an increased likelihood of SCZ later in life. *T. gondii* tachyzoites can cross the placenta and infect the developing fetus, elevating SCZ risk (Miuller and Schwarz, 2007). However, given that SCZ is a chronic disorder that unfolds over decades, understanding how *T. gondii* infection and astrocyte-mediated immune responses contribute to its progression is crucial. This section examines how early-life infection affects neurodevelopment, synaptic function, and chronic neuroinflammation, predisposing individuals to SCZ.

9.1. Immune activation, chronic neuroinflammation, and temporal effects

Maternal *T. gondii* infection triggers the release of proinflammatory cytokines such as IL-1β, IFN-γ, and IL-6, which cross the placenta and disrupt fetal neurodevelopment (Leza et al., 2015). These cytokines activate microglia and astrocytes, leading to excessive reactive oxygen species and NO production, impairing synaptic maturation and neuronal survival. While acute infection has immediate neurodevelopmental consequences, the chronic neuroinflammation induced by *T. gondii* persists long after the initial infection. Sustained neuroinflammation during prenatal development primes the fetal immune system for long-term dysregulation, increasing vulnerability to psychiatric disorders later in life (Takahashi and Sakurai, 2013). Additionally, astrocyte-driven immune responses maintain a prolonged neuroinflammatory state, progressively impairing synaptic plasticity and neuronal function. This gradual neurodevelopmental disruption may contribute to the late-onset emergence of SCZ symptoms, particularly during adolescence, a critical period for synaptic remodeling.

9.2. Astrocytic dysfunction in the context of other glial cells

Astrocytes play a key role in maintaining extracellular homeostasis, modulating synapse formation, and regulating glutamate signaling. However, their role in cytokine production must be considered within the broader context of neuroimmune signaling. While astrocytes amplify inflammatory signals and influence neuronal health, microglia act as the brain's primary immune responders, initiating cytokine release. Astrocytes, in turn, sustain neuroinflammatory states by responding to microglial cytokines with increased production of inflammatory mediators, reinforcing a proinflammatory feedback loop. Beyond immune signaling, astrocytes are involved in glutamate excitotoxicity, synaptic pruning, and BBB integrity, making their dysfunction a critical component of SCZ pathology (Esshili et al., 2020). The interplay between astrocytes and microglia in *T. gondii*-induced neuroinflammation suggests that astrocyte dysfunction is not an isolated event but part of a larger dysregulation affecting glial communication and synaptic maintenance (Prieto-Villalobos et al., 2021).

9.3. Synaptic dysfunction, perineuronal nets, and progressive neural damage

T. gondii infection contributes to long-term synaptic dysfunction through astrocyte-mediated disruptions in PNN formation and glutamate signaling. PNNs, secreted by astrocytes, provide structural support for dendritic spine stabilization and synaptic maintenance. Early-life astrocyte damage reduces PNN volume in the ECM, impairing synaptic organization and plasticity. Importantly, SCZ patients exhibit reduced PNN density, correlating with decreased dendritic spine density and gray matter volume (Horacek et al., 2012; Leza et al., 2015).

Additionally, astrocytes regulate hemichannel and pannexon activity, essential for cellular signaling and extracellular ion balance.

Dysfunctional astrocytic hemichannels lead to excessive ATP and glutamate release, creating a hyperexcitable neuronal environment that increases susceptibility to neurodevelopmental disorders (Prieto-Villalobos et al., 2021). This mechanism may explain how prenatal and early-life *T. gondii* infection disrupts synaptic organization, particularly in SCZ-associated brain regions, such as the prefrontal cortex and hippocampus.

9.4. Long-term consequences and future directions

Prenatal and early-life *T. gondii* infection initiates a cascade of immune, astrocytic, and synaptic disruptions that increase susceptibility to SCZ. The interplay between maternal immune activation, chronic neuroinflammation, and astrocytic dysfunction creates an environment conducive to impaired synaptic development and long-term neuropsychiatric consequences. Importantly, *T. gondii*-induced inflammation suggests that SCZ does not arise from a single acute infection but rather from a sustained neuroinflammatory state that progressively alters neuronal and glial function over time. Future research should focus on identifying specific molecular targets within astrocytes, their interactions with microglia, and their influence on synaptic networks. Understanding these mechanisms could guide the development of targeted therapeutic interventions aimed at mitigating the neurodevelopmental impact of congenital and early-life *T. gondii* infection.

10. Genetic and pathogenic synergy in SCZ

This section explores how genetic and pathogenic factors interact in the development of SCZ (Fig. 1F). Extensive research has identified various genetic markers that predispose individuals to SCZ, with one significant gene being *DISC1*. The normal *DISC1* protein stabilizes the enzyme serine racemase (SR), which is essential for producing D-serine, a co-agonist at the NMDAR (Ma et al., 2013). However, a mutation in the *DISC1* gene, characterized by a premature C-terminal truncation, disrupts this binding, leading to reduced D-serine production (Wu and Barger, 2016). This mutation results in decreased D-serine levels, which are crucial for NMDAR activation alongside glutamate. Reduced D-serine levels and abnormal SR forms have been observed in SCZ patients (Hussaini and Jang, 2018).

The *DISC1*-mediated reduction in D-serine predisposes individuals to NMDAR hypofunction, a condition that can be further exacerbated by *T. gondii* infection. The parasite dysregulates glutamate control in astrocytes (David et al., 2016) and reduces D-serine levels (Acquarone et al., 2021). As described earlier, *T. gondii* infection increases tryptophan degradation, depleting resources required for parasite growth. While this inhibits *T. gondii* replication, it also leads to excessive KYNA production, which disrupts neuronal transmission. The combination of reduced NMDAR agonists (glutamate and D-serine) and increased NMDAR antagonist (KYNA from tryptophan breakdown) can lead to pronounced NMDAR hypofunction.

In mice with the mutant *DISC1* gene, researchers observed impaired progenitor cell differentiation (Terrillion et al., 2017), shorter dendritic branches (Wu and Barger, 2016), and deficits in memory, learning, social interaction, and elevated anxiety (Terrillion et al., 2017). Individuals carrying the mutant *DISC1* gene are predisposed to reduced NMDAR activity, which can be further aggravated by *T. gondii* infection, resulting in dysfunctional signaling networks that manifest as SCZ symptoms.

Epigenetic modifications also play a crucial role in SCZ pathology (Chen et al., 2015). *T. gondii* employs epigenetic modifications to block the transcription factor STAT1, which is responsible for recognizing IFN-γ and initiating immune responses through histone modifications (Nast et al., 2020). A genetic marker associated with susceptibility to *T. gondii* is the *HLA-DQ3* gene (Carruthers and Suzuki, 2007). HLA genes, part of the major histocompatibility complex (MHC), mediate immune responses. Interestingly, the HLA region on chromosome 6 is linked to SCZ susceptibility (Miuller and Schwarz, 2007), suggesting a potential connection between MHC-based genetic susceptibility to *T. gondii* and the development of SCZ.

11. Conclusions

The growing body of evidence suggests a link between *T. gondii* infection and SCZ, with astrocytes playing a pivotal role in this connection. *T. gondii* primarily infects astrocytes, altering their immune functions, promoting neuroinflammation, and disrupting essential processes such as glutamate homeostasis and synaptic remodeling—mechanisms also implicated in SCZ pathogenesis. Understanding the distinction between peripheral and central immune responses is crucial, as CNS-specific inflammation, blood-brain barrier dysfunction, and microglial activation may directly contribute to SCZ-related neuropathology. However, the precise causal mechanisms remain unclear. Future studies should focus on examining the direct effects of *T. gondii* on astrocytic proliferation, calcium signaling, and metabolic pathways. Longitudinal research, including CSF analysis, post-mortem brain tissue studies, and in vivo infection models, will be crucial in determining whether *T. gondii*-induced astrocytic dysfunction plays a role in SCZ onset or exacerbation. A better understanding of *T. gondii*-driven neuroinflammation could clarify the role of infection in SCZ and potentially lead to targeted therapeutic interventions aimed at mitigating inflammation-driven neuropathology. By bridging infectious disease and psychiatric research, this review highlights the importance of an integrated approach to studying neuroimmune interactions in psychiatric disorders.

CRediT authorship contribution statement

Abigail Everett: Writing – original draft, Formal analysis, Data curation. **Hany M. Elsheikha:** Writing – review & editing, Visualization, Supervision, Resources, Project administration, Conceptualization.

Declaration of competing interest

None.

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Data availability

No data was used for the research described in the article.

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