Chapter 4

Toxoplasma gondii and Schizophrenia: A Relationship That Is Not Ruled Out

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Additional information is available at the end of the chapter

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Abstract

Over recent years, it has been proposed that some diseases of unknown origin, such as schizophrenia, may be caused by persistent chronic infections coupled with a genetic component and may be perpetuated by the immune system. This hypothesis is supported by epidemiological and biological evidence on the exposure of schizophrenics to infectious diseases during prenatal or postnatal periods, including *Toxoplasma gondii*, chlamydia, human herpes virus, human endogenous retroviruses, parvovirus B19, mumps, and flu viruses. This growing list of microbes will undoubtedly continue to increase in the future. Linking infection to schizophrenia is a complex challenge that requires further experimental and epidemiological research. *T. gondii* is the infectious agent that has most frequently been related to neuropsychiatric disorders, including schizophrenia, and it is considered to represent a highly useful model to analyze the influence of a microorganism on human behavior and the development of psychiatric disease. It may also help to detect patient subpopulations susceptible to treatment with specific antimicrobials by improving definition of the differential phenotype of the disease, and it offers the possibility of a preventive approach.

Keywords: schizophrenia, *Toxoplasma gondii*, antibodies, behavior, cytokine, neurotransmitter, gene-infection interaction

1. Introduction

Over the past few years, it has been proposed by some authors that schizophrenia may be caused by central nervous system (CNS) disorders during neurodevelopment (i.e., congenital) or during the postnatal period, at least in some patient subgroups [1]. These disorders may be related to environmental exposure to toxic products, radiation, stress, fetal hypoxia,

nutritional problems, infections (especially when chronic and persistent), and/or, according to more recent data, gut microbiota [2, 3]. Any of these exposures could possibly affect cognitive functions and behavior patterns with important neuropsychiatric consequences, including irreversible neurological lesions leading to neuronal dysfunction, behavior problems, mental retardation, learning difficulties, or mood disorders [4–9]. Participation by microbial agents in the development of schizophrenia is suggested by medical evidence, with prenatal or perinatal infection being the most frequent cause of severe congenital malformations and mental impairment [10]. Their involvement is also supported by epidemiological evidence on the exposure of schizophrenic patients to *T. gondii*, chlamydia, human herpes virus, human endogenous retroviruses, parvovirus B19, and rubella, mumps, or influenza viruses, among other microorganisms [11].

According to current pathogenic models, microorganisms may produce various inflammatory and/or immunological disorders in the infected brain, giving rise to neurotransmitter synthesis disorders with important clinical repercussions [7]. Schizophrenia has been related to the production of inflammatory cytokines that alter the synthesis of dopamine and other neurotransmitters [12] and to fetal neuronal tissue damage due to the transplacental transfer of maternal antibodies, which might underlie development of the disease decades later [13]. This association with inflammatory and immunologic disorders has been observed in studies of animal models and human cells. Thus, maternal infection of mice and rats during pregnancy was associated with behavioral disorders in the offspring that were very similar to those reported in schizophrenic patients. Various studies in murine models revealed an association between prenatal infection and marked deficits in sensory information processing, in the expression of certain neurotransmitters (e.g., dopamine) and of cytokines, and in the immune function, all of which emerged in the offspring. Their onset is at an age equivalent to human adolescence and is earlier, with more severe effects, in male *versus* female rats, and these alterations can be reverted by the administration of antipsychotic drugs. In short, the fetus can be damaged by numerous infectious agents, whether or not they are primarily neurotropic, which may favor in a direct or immune-mediated manner the development of neurological damage, disorders in neurotransmitter expression, and modifications in sensory information processing [14].

There is intense and increasing research interest in the relationship between schizophrenia and infectious agents. Irreversible mild or severe neurophysiologic alterations may result from fetal infection, maternal infection with secondary fetal involvement *via* inflammatory and/or immunological mechanisms, or postnatal infection and may lead to the emergence of schizophrenia over the years. The full elucidation of these associations may allow specific antimicrobial treatments to be added to current symptomatic (or antipsychotic) treatments for these patients [5], potentially offering a preventive and curative approach to the disease, given that they would act on known and treatable etiologic factors.

T. gondii is the infectious agent that has most frequently been related to neuropsychiatric disorders, including schizophrenia, and it is considered to represent a useful model to analyze the influence of a microorganism on human behavior and the development of psychiatric disease [15]. It is an obligate intracellular protozoa belonging to the *Coccidia* subclass of the phylum *Apicomplexa* and causes toxoplasmosis. Its definitive hosts are cats and other felines, which

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are the only animals in which the sexual stage of their life cycle takes place (in intestines), forming oocysts that are eliminated through the feces. Hot-blooded vertebrates such as birds and other mammals, including humans, are intermediate hosts. Humans can become infected by various pathways, such as: the intake of undercooked meat containing latent forms of the parasite (bradyzoites in tissue cysts), fresh food (e.g., fruit and vegetables), or water contaminated with oocysts from cat feces; blood transfusions; transplantation of solid organ or stem cells, or transplacental transmission. Upon reaching tissues, *T. gondii* rapidly replicates in the form of tachyzoites until tissue proliferation and expansion of the parasite are impeded by the immune response, after which its replication slows and it remains in tissue cysts in latent or bradyzoite form. Cysts are most frequently found in skeletal muscle, myocardium, CNS, and eyes and are responsible for persistent infection [16, 17].

Primary infection usually takes place during childhood, when only a small percentage of people show symptoms, which are mild and include general discomfort, lethargy, cervical lymphadenopathy, and/or eye disease, among others. Most parasitized individuals remain asymptomatic for a long time period, even throughout their life, and host the latent form of *T. gondii*. However, chronic infection can be reactivated in immunocompromised individuals (AIDS, transplanted, and oncology patients, etc.), giving rise to various symptoms and even, in death. This reactivation is often associated with nervous system symptoms, such as Guillain-Barré syndrome, diffuse encephalopathy, meningoencephalitis, or brain abscesses [17, 18]. Human parasitizations, although generally considered asymptomatic, may cause behavioral disorders and the development of a psychiatric disease such as schizophrenia due to damage resulting from the initial infection, from the host immune response to the parasite, or from the persistence of cysts in the CNS [19]. Accordingly, the concept of asymptomatic chronic parasitization is currently under debate [20].

T. gondii is a plausible candidate as an infectious origin of schizophrenia and has attracted considerable research attention for the following reasons: the possibility of its transplacental transmission; its marked neurotropism; its capacity for persistent infection, remaining in latent form but with the possibility of reactivation; its association with brain development disorders and anomalies; its relationship with behavior disorders in animal and human models; and *in vitro* evidence of the inhibition of its growth in cell culture by antipsychotic drugs.

2. Epidemiologic data on the association between toxoplasmosis and schizophrenia

One of the first approaches adopted to explore a possible relationship between *T. gondii* infection and schizophrenia was to analyze epidemiological data on the two diseases. Initial conclusions were as follows:

- Both have a familial incidence. This is explained in the case of schizophrenia by the possible participation of certain genes in its pathogeny [21], and in the case of toxoplasmosis by the possible common exposure of family members to the parasite, although a genetic influence has also been proposed [22].

- There is a relatively high frequency of stillborns among both schizophrenic [23] and parasitized [24] mothers.
- Both diseases typically show a decreased prevalence in geographic areas with small populations of felines [25, 26].
- Initial symptoms in both diseases commonly manifest between the second and third decade of life [27, 28].
- The prevalence of both diseases is higher among populations with lower socioeconomic level and living in overcrowded conditions [29, 30].

These and other published findings indicate that the two diseases have some similar features and may even be epidemiologically related. However, they are inadequate to establish etiological relationships, and a pathophysiological approach is required to explore causality.

3. Studies based on the detection of anti-*Toxoplasma gondii* antibodies

For more than six decades, the relationship between schizophrenia and toxoplasmosis has been explored by studying a specific immune response [31]. Various meta-analyses have demonstrated a significantly higher prevalence of anti-*T. gondii* antibodies in schizophrenic patients than in controls, with odds ratios ranging between 2.7 [11, 32–34] and 1.8 [35].

In the natural time course of toxoplasmosis, IgM antibodies against *T. gondii* are the first to be detected in serum, a few days after infection. These are usually negativized between weeks 4 and 12 but can remain detectable for months or even years in a large number of patients. IgG antibodies are detected at around 2 weeks later than IgM antibodies, reaching a maximum level in the 2nd to 3rd month and persisting throughout life in residual titers. The presence of IgM antibodies in the absence of IgG indicates recent infection, while the presence of IgG indicates chronic infection, especially in the absence of IgM. The reactivation of a persistent infection can be accompanied by increased IgG and/or IgM values, although these antibodies can be undetectable in immunocompromised patients [36].

Most studies have centered on the humoral immune response, comparing anti-*T. gondii* IgG and IgM antibodies between schizophrenic patients (in different clinical/therapeutic situations) and controls. This method is widely employed because of the ease with which samples (usually serum, occasionally cerebrospinal fluid) can be gathered and the high degree of reproducibility, specificity, and sensitivity obtained. Many of these studies reported higher levels of antibodies (IgG and, in some studies, IgM) against *T. gondii* in patients with schizophrenia than in other populations, including patients with a different psychiatric disorder [32, 37–51]. However, findings have been inconsistent [52, 53], and account should be taken of the publication bias against studies without significant results [11].

Clinical manifestations differ between seropositive and seronegative schizophrenic patients, with a predominance in the former of positive symptoms (delirium, hallucinations, disorganized thinking), cognitive disorders (abstract thinking difficulties, disorientation, attention

deficit), and agitation [50, 54]. Some researchers also observed that patients with schizophrenia and anti-*T. gondii* antibodies had a significantly higher risk of dying from natural causes [55] and were more likely to attempt suicide [56] in comparison with seronegative patients.

The above studies suggest a strong association between these diseases, with a significantly higher frequency of chronic parasitization in schizophrenic patients than in other population groups. However, if schizophrenia is a consequence of chronic CNS infection, which usually takes place at an early age, the question arises as to why it typically appears between the second and third decades of life. According to Yolken et al. [51], a significant increase in IgG titers observed in patients with a first schizophrenia episode may be compatible with a reactivation of the infection (previously in latent phase) that becomes clinically manifest in the onset of the disease *via* an immune-mediated mechanism. Some authors proposed that the immunoglobulins may cross the blood-brain barrier in this situation and react with brain tissue antigens due to their molecular mimicry with *T. gondii* antigens. This is similar to observations in such autoimmune diseases as systemic lupus erythematosus or in paraneoplastic syndromes [57]. Associations with the presence of anti-*Toxoplasma* IgM are less well documented [35], although Monroe et al. [58] reported in their meta-analysis a significant 1.7-fold greater likelihood of *T. gondii* IgM antibodies in patients with acute psychosis than in controls. It was concluded that *T. gondii* IgM antibodies may indicate either an acute/recent infection or a reinfection, possibly with a different genotype.

However, although a strong association has been described between schizophrenia and parasitization, these studies do not provide evidence to confirm the hypothesis on the infectious etiology of schizophrenia, and a causal relationship has not been demonstrated. Contact with *T. gondii* may be favored by the anomalous behavior, disorganized lifestyle, and/or weaker socioeconomic situation of schizophrenics, with infection being the consequence rather than the cause of their disease, which may explain the positive serological results [50].

4. Seroprevalence studies in mothers and newborns

The possible transplacental transmission of *T. gondii* has attracted considerable attention in seroprevalence studies. Maternal infection during the first or second trimester of pregnancy can lead to severe problems in the offspring, including intracranial calcifications, chorioretinitis, blindness, deafness, hydrocephaly, microcephaly, mental retardation, psychomotor retardation, pancytopenia, or epilepsy. The timing of the transmission is an influential factor: early maternal infection less frequently affects the fetus but is associated with a more severe congenital toxoplasmosis that may result in intrauterine death and miscarriages, while later maternal infection (third trimester) increases the risk of affecting the fetus but is associated with offspring who are asymptomatic [17]. Complications, possibly including schizophrenia, can appear decades later in patients with initially undetected infection due to its reactivation [59].

This type of study can be classified into two groups: those on the presence of antibodies in pregnant women and the development of schizophrenia in their offspring; those on the pres-

ence of antibodies in newborns and their later development of schizophrenia. Among the former, Brown et al. [60] and Blomström et al. [61] demonstrated associations between increased anti-*Toxoplasma* IgG levels in pregnant mothers and risk of schizophrenia in their offspring, although other researchers published discrepant results [62]. Xiao et al. [63] observed a significant association between the presence of maternal antibodies against type I *T. gondii* (but not against types II or III) and the onset of psychotic disorders in the offspring. Among the latter group of studies, Mortensen et al. [59] demonstrated that newborn levels of anti-*T. gondii* IgG levels (from the mother) were significantly higher in individuals who developed schizophrenia in adulthood.

Published data suggest that schizophrenia risk in offspring is associated with persistent maternal infection by *T. gondii* but is not directly related to acute maternal infection [64]. If this were the case, a significant association could be expected between the presence of IgM in the serum of mothers and/or newborns and the presence of the disease, which has not been demonstrated [60]. However, this relationship may be masked by the low frequency of anti-*Toxoplasma* IgM detection in pregnant women [24, 65].

As noted above, increased maternal IgG levels can cross the placenta (unlike IgM antibodies) and may damage fetal brain development by molecular mimicry [60, 64]. However, the presence of maternal IgG may indicate a reactivation of latent infection due to the impact of immune system disorders on protozoan replication control during pregnancy [66]; hence, brain development could also be impaired by transplacental transmission and/or the passage of inflammatory cytokines to the fetus [67, 68].

The majority of schizophrenic patients do not have anti-*Toxoplasma* antibodies, and the majority of seropositive patients are not schizophrenic. Therefore, *T. gondii* would only explain a minority of cases. Other factors under investigation that may explain why only some parasitized individuals develop schizophrenia include genetic susceptibility, the infective genotype of the parasite, the existence of different infection pathways, and the timing of toxoplasmosis onset [20, 33, 63].

5. Studies based on *Toxoplasma gondii* nucleic acid detection

Studies of animal brain biopsies have shown *T. gondii* to have high neurotropism, with the capacity to infect glial cells (especially microglia and astrocytes) and neurons, forming persistent cysts in brain tissue [69]. Although no tropism for specific brain regions has been observed, with cysts being detected in many areas, the most frequently parasitized regions are the hippocampus, thalamus, cerebral cortex, cerebellum, olfactory bulb, and, especially, the amygdala [70–73].

However, the presence of brain cysts can only be detected in *postmortem* biopsies, explaining the few studies of this type and the predominance of serological techniques for the detection of chronic infection by *T. gondii* in humans. The presence of glial anomalies, including a reduced amount of astrocytes, has been reported in the brains of schizophrenic patients [74], and it has been speculated that these may possibly result from infection by *T. gondii* [31].

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Imaging techniques have revealed a lower density of gray matter in certain brain regions of schizophrenic patients [75], which may be directly related to the infection, given that non-parasitized schizophrenic patients were found to have the same brain morphology as healthy controls [76].

One of the few studies of *postmortem* brain biopsies found no parasite DNA in any subject (14 schizophrenic patients and 26 healthy controls) [77]. There appear to be three possible explanations: first, there was truly no association with the infection; second, the biopsies missed infected brain areas; and finally, the sensitivity of the nucleic acid detection technique might be inadequate. In addition, the detection of parasite DNA only demonstrates the presence of the parasite not its possible effect on the parasitized individual and would not establish an etiological relationship with schizophrenia. Thus, the detection of parasite DNA in brain tissues does not distinguish between asymptomatic patients with latent parasitization and those with encephalitis [17].

A study of blood samples detected parasite DNA in 33 out of 101 samples from schizophrenic patients *versus* 2 out of 55 samples from controls, a significant difference [46]. In contrast, Gutiérrez-Fernández et al. [32] detected parasite DNA in only 1 out of 128 blood samples from schizophrenic patients and in none of 143 samples from controls (nonsignificant difference). However, although the presence of parasite DNA in blood indicates acute infection [17], it does not necessarily signify infection of the brain, and no relationship was found between anti-*Toxoplasma* IgM and schizophrenia in the aforementioned study [46].

6. Studies on behavioral disorders in animals and humans

Research on this issue has included experimental animal studies, mainly in rats and mice. Parasitized animals have shown various behavioral changes, becoming more active, expressing less fear when examining new stimuli, reducing their natural aversion to cat odor or even becoming attracted to it, and demonstrating reduced learning ability and attention or memory deficits [78–83]. According to the "behavioral manipulation hypothesis," these disorders in their intermediate hosts (rodents) represent an evolutionary adaptation of the parasite, facilitating their capture by their definitive host (felines) and completing their life cycle [84, 85]. Although the mechanism by which *T. gondii* induces these behavioral changes is poorly understood, various possibilities have been proposed. It may be due to a direct effect on tissue cysts in specific brain areas such as the amygdala or hippocampus, given that the host response to predator odors was changed by the parasite in male rats infected with *T. gondii* by inducing hypomethylation of the neuropeptide arginine vasopressin in the posterodorsal part of the medial amygdala, an important node of the extrahypothalamic vasopressin system that contains a large number of arginine vasopressin neurons. This epigenetic manipulation produced a greater activation of vasopressinergic neurons after exposure to cat odor, leading to the reversion of fear into attraction [86]. It may also result from the effect of a more diffuse and wider involvement of brain tissues, with no apparent changes, that nevertheless give rise to a series of neurophysiological disorders. Changes may also result from inflammation (encephalitis) caused by the immune activation induced by parasitization, which would increase

inflammatory cytokines in the rodent brain, such as tumor necrosis factor alpha (TNF-α), interleukin-1β (IL-1β), IL-10, interferon gamma (IFNγ), C-reactive protein, tissue inhibitor of metalloproteinases 1 (TIMP-1), or vascular cell adhesion molecule 1 (VCAM-1), similar to observations in *postmortem* biopsies of schizophrenic patients. Finally, the behavioral changes have also been related to neurochemical mechanisms, with an increase in dopamine and homovanillic acid and a decrease in norepinephrine levels [73, 84, 85, 87–90].

Any of the above mechanisms in rodents could also produce behavioral changes in the brains of other intermediate hosts, including humans. Thus, research in humans also suggests that toxoplasmosis may alter behavior, psychomotor abilities, or personality, with the corresponding clinical consequences [84]. These disorders would be more related to latent rather than acute toxoplasmosis, given that its emergence, frequently several years after primary infection and not during the acute phase, would indicate that it results from slow and possibly accumulative changes induced by parasite activity [91–93]. The study by Horacek et al. [76] demonstrates that, in seropositive schizophrenic patients, latent parasitization is associated with a significant reduction in gray matter volume in specific brain areas (cortical regions, hippocampus, and caudate nucleus), which is not observed in seronegative patients.

Reinforcing the relationship between the parasite and the psychiatric disease, it has been demonstrated that haloperidol, an antipsychotic drug that blocks D2 dopaminergic receptors in the mesolimbic system and often used in the symptomatic treatment of schizophrenia, inhibits the replication of tachyzoites in cell cultures *in vitro*. This effect may at least partly be due to the capacity of this drug to inhibit calcium transport, blocking cell ion channels [94]. The interaction between tachyzoites and host cells is calcium-dependent; hence, cell invasion capacity can be inhibited by the presence of drugs that block calcium channels, such as haloperidol [95]. Experimental studies with rodents have also demonstrated that some behavioral changes caused by the infection are reverted by using the antipsychotic, and that there are fewer parasitized neurons and glial cells after the treatment; this is observed using immunohistochemical techniques [96]. It is therefore possible that its therapeutic effect can be explained in patients with schizophrenia by various mechanisms, given that on the one hand, it blocks dopamine, whose levels are often elevated in schizophrenia patients parasitized with *T. gondii* [89, 97], and on the other hand, it can inhibit parasite replication in brain cells [96]. Other antipsychotic drugs such as fluphenazine, thioridazine, trifluoperazine, or zuclopenthixol, and mood stabilizers, e.g., valproic acid, were also found to inhibit *T. gondii* proliferation in cell cultures [94, 98, 99].

Antipsychotics are especially indicated in patients with a predominance of positive symptoms and agitation (as in the acute phase of schizophrenia), which are significantly more frequent in those parasitized with *T. gondii*, as noted above. The greater effectiveness of these drugs in these situations may be due not only to their dopamine blocking effect but also to their anti-*Toxoplasma* activity. Thus, these treatments were found to reduce anti-*Toxoplasma* antibody levels in seropositive schizophrenic patients, indicating their antiparasitic effect [44]. These findings suggest that these drugs may possibly have a beneficial effect on schizophrenic patients parasitized with *T. gondii*.

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Studies to date on the possible effect in these patients of drugs with anti-*Toxoplasma* activity (e.g., pyrimethamine, sulfadiazine, azithromycin, or trimethoprim-sulfamethoxazole) have not demonstrated significant improvements in psychotic symptoms [100, 101]. In fact, drugs used to treat toxoplasmosis are largely active during the tachyzoite replication phase, and their effectiveness against bradyzoites in tissue cysts is drastically reduced once chronic infection by *T. gondii* is established [102].

The etiological relationship between parasitization and schizophrenia has not yet been established, despite the above data on behavioral changes in animals or humans and on the effects of antipsychotic drugs on symptoms. In addition, differences in behavioral disorders between humans and rodents may mean that results in animal models cannot be extrapolated to humans. It should also be borne in mind that the mild behavioral modifications associated with the infection cannot necessarily be considered symptoms of a psychotic disease.

7. The role of proinflammatory cytokines

The host response to the parasitization of glial cells and neurons involves the activation of immune system cells, including T lymphocytes (CD4+ and CD8+), B lymphocytes, NK cells, macrophages, and dendritic and glial cells. These produce a wide variety of inflammatory cytokines such as IFNγ, interleukins (IL-1, IL-1β, IL-2, IL-4, IL-6, IL-10, IL-12, IL-15, IL-17, IL-18, IL-23), granulocyte macrophage colony-stimulating factor (GM-CSF), and/or TNFα [69, 103]. These cytokines halt protozoan proliferation and limit their replication, playing a key role in regulating the infection of host cells, thereby favoring the formation of tissue cysts and the development of the chronic latent form [20]. These and other inflammatory responses have also been reported in schizophrenia [104] and are therefore involved in brain disorders both in this disease and in *T. gondii* infection [105].

Thus, infection of brain tissue by *T. gondii* produces activation of the Jak/STAT pathway, which is recognized as an important regulatory mechanism in CNS development, function, and disease progression [106, 107]. This pathway comprises three elements: a ligand receptor, the majority are receptors of cytokines such as IFNγ; Janus kinase (Jak) proteins associated with the receptor within the cell, which possess tyrosine-kinase activity; and signal transducer and activator of transcription (STAT) proteins, which act as transcription factors that move toward the cell nucleus after their phosphorylation, where they bind with regulatory sequences of genes designated gamma interferon activation sites (GAS) [108]. In mammals, the Jak/STAT pathway induces the transcription of genes that participate in multiple processes, including antimicrobial activity and the production of proinflammatory cytokines [109]. Among other effects, an increase is produced in the expression of NADPH oxidase enzyme (NOX2) and inducible nitric oxide synthase (iNOS). These enzymes are responsible for the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), which assist the destruction of foreign pathogens [110, 111] but have been linked to seizures, stroke, neurodegenerative diseases, and schizophrenia [111, 112] as a consequence of their toxic effect on neurons [113]. Scientific evidence points to ROS-mediated oxidative damage as a key pathogenic pathway involved in infection-mediated neuropathy. According to these findings, it can be

expected that a high degree of degenerated neuron degeneration and cognitive impairment is associated with the presence of *T. gondii* in the brain [111].

8. The importance of dopamine and other neurotransmitters

As already noted, some experimental animal and human studies concluded that behavioral changes may be explained by increased dopamine levels in the parasitized brain, and that these disorders could largely be resolved by administration of a dopaminergic receptor antagonist (e.g., haloperidol) or dopamine reuptake inhibitor (e.g., GBR-12909) [96, 114, 115]. It is therefore possible that dopamine represents the link between toxoplasmosis and schizophrenia [97]. This neurotransmitter is synthesized in the cytosol of neurons from L-tyrosine amino acid by the action of the tyrosine hydroxylase enzyme, which converts it to L-3,4-dihydroxyphenylalanine (L-DOPA). L-DOPA is in turn converted by the action of DOPA-decarboxylase (DDC) to dopamine, a precursor of norepinephrine (noradrenalin) and epinephrine (adrenalin) in the synthesis pathway of these catecholamines. It is subsequently packaged in vesicles and transported through the axon to the synapse, where it is released by exocytosis in response to an electrical stimulus. Dopamine is one of the main neurotransmitters in the prefrontal cortex and the mesolimbic system (mainly formed by the nucleus accumbens, amygdala, and hippocampus), where the presence of *T. gondii* tissue cysts is especially frequent [73].

The definitive mechanism by which *T. gondii* induces changes in the dopaminergic pathway has not been fully elucidated. However, an increase in dopamine with no modification of cellular tyrosine hydroxylase was demonstrated *in vitro* after parasitization of a rat pheochromocytoma cell line (PC12) and *in vivo* after the parasitization of mouse brains. This dopamine synthesis is attributable to the additional activity of the aromatic amino acid hydroxylase, which is encoded by two *T. gondii* genes [116] and has homologous activities to those of mammalian tyrosine hydroxylase, associated with the entry of cellular DDC enzymes into parasitophorous vacuoles (compartments formed by the parasite to invade the cell) and into tissue cysts (the protozoan encodes no enzyme with DDC activity) [114, 117]. Experiments in cell cultures have demonstrated that dopamine increases the replication of *T. gondii* tachyzoites [118]. This biochemical mechanism may play a role in the behavioral changes observed, which would result from the involvement of catecholaminergic neurons and consequent dopaminergic hyperactivity [19].

Parasitization in the fetal period may also impair the development of mesolimbic dopaminergic or prefrontal cortex neurons (inappropriate migration, altered position, reduced synapses, etc.) leading to neurodevelopmental disorders. Disease symptoms would not be induced immediately by these early anomalies but would rather manifest after a latency period of one to three decades. This is because the proliferation, migration, differentiation, and maturation of glial progenitor cells continue throughout childhood [119] and the volume of gray matter increases to a peak in puberty before beginning to diminish [120].

However, the hypothesis that increased dopamine levels or dopaminergic hyperactivity is the underlying cause of schizophrenia does not account for the negative symptoms in these

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patients, which are more likely to result from dopaminergic hypoactivity. Therefore, neurotransmitters other than dopamine may play an important role in the development of this disease. Thus, it has been proposed that deficits in glutamatergic brain systems also participate in the physiopathology of schizophrenia based on findings of higher kynurenic acid levels in patients with psychotic symptoms than in healthy controls [121]. Kynurenic acid is a metabolite of tryptophan with important biological effects on the nervous system, related to its antagonism for the glutamate receptor in the human brain (it is a glutamatergic NMDA receptor antagonist). Increased kynurenic acid levels due to blockade of NMDA receptors in glutamatergic neurons have been related to changes in dopamine level in different brain areas. These modifications include cortical dopaminergic hypoactivity and mesolimbic dopaminergic hyperactivity, which would explain the negative and positive symptoms in patients. This relationship between glutamate pathway disorders and dopamine level changes may explain the presence of different symptoms in the psychosis [122].

Indoleamine-2,3-dioxygenase and therefore the metabolism of tryptophan, a precursor metabolite in serotonin (and melatonin) synthesis, are induced by the proinflammatory cytokines released in response to *T. gondii* infection, especially IFNγ [123]. Tryptophan is an essential amino acid for the parasite, and decreased levels inhibit its growth and replication capacity [124]. However, induction of this metabolite in turn increases kynurenic acid levels and therefore alters dopamine levels through the glutamatergic receptor antagonist effect of this acid [114]. Tryptophan degradation also reduces serotonin levels, which has been related to a higher incidence of depression and suicide [125, 126], as also observed in patients with high anti-*T. gondii* antibody levels [56].

Patients with schizophrenia also show anomalous levels of gamma-aminobutyric acid (GABA), another important neurotransmitter [20], which is synthesized from glutamate by the action of glutamic acid decarboxylase (GAD) [127]. GABA activates $GABA_A$ receptors, which are ion channels, and $GABA_B$ receptors, which are G-protein-coupled receptors [128]. It is the main neurotransmitter with inhibiting effect in the CNS, regulating dopaminergic activity and playing a key role in the reduction of neuronal excitability throughout the nervous system. Dopaminergic neurons in basal ganglia would be directly inhibited by GABAergic neurons, so that any GABAergic hypofunction would be accompanied by an increase in subcortical dopaminergic activity, as observed in schizophrenia.

More direct evidence of the involvement of this neurotransmitter in the etiology of schizophrenia derives from data on the reduction in neurons in the GABAergic system or in brain regions such as the hippocampus, temporal lobe, and prefrontal cortex of schizophrenic patients [129–131]. *Postmortem* molecular studies have demonstrated: a reduction in messenger RNA (mRNA) levels of isoform 67 of glutamic acid decarboxylase (GAD67) and of type 1 GABA transporter (GAT-1) in the prefrontal cortex of schizophrenics [132, 133]; an increase in subunit α2 of the $GABA_A$ receptor in the initial segment of the axon of pyramidal neurons [134]; and a reduced expression of the receptor $GABA_{B,}$ which regulates GABA release as a possible compensatory mechanism for GABAergic dysfunction [135]. As noted above, these findings may be the consequence of alterations during neurodevelopment in the differentiation and migration of these neurons toward their definitive localizations in the brain. This

would give rise to structural alterations and neurochemical dysregulation that would have a global effect on all of these neurotransmitters (dopamine, glutamate, serotonin, GABA) and would become manifest from adolescence onward, inducing the appearance of the disease. Once more, infection by *T. gondii* may play an important role in this process.

Outside the nervous system, GABAergic mechanisms have been observed in different tissues and peripheral organs, and GABA has also been found to exert a major role in the immune system, with important inter-regulatory functions between this and the CNS [136]. It has been reported that *T. gondii* infection is followed by an increase in the motility and migratory capacity of infected dendritic cells, permitting propagation of the parasite to different tissues, including the brain [128]. Although dendritic cells are considered guardians of the immune system, they can also, paradoxically, mediate in the spread of the parasite. This mechanism is produced by the induction in these cells of the GAD enzyme and therefore of GABA production and secretion, which in turn activate GABA receptors expressed by these same cells, stimulating their motility [137]. In experimental mouse models, inhibition of the GABAergic pathway by blockade of GABAA receptors or inhibition of the GAD enzyme markedly reduced the hypermotility and spread of *T. gondii*-infected dendritic cells and therefore of the parasite itself [137, 138]. Finally, it has also been reported that brain infection by *T. gondii* can interfere with the GABAergic system by inducing changes in the distribution of the GAD67 enzyme, although this event has been related more to possible neurological complications of toxoplasmic encephalitis, such as seizures [139], than to possible complications of latent toxoplasmosis, such as schizophrenia.

Accordingly, the inflammatory response of the host to parasitization, which aims to control parasite replication and alterations in differentiation and migration processes, can change levels of dopamine, tryptophan, kynurenic acid, serotonin, and GABA, leading to behavioral changes and giving rise to different psychotic symptoms.

In order to establish dopamine and other related neurotransmitters as a causal link between toxoplasmosis and schizophrenia development, it is necessary to confirm that this neurotransmitter is also involved in the disease genesis when there is infection by other pathogens [140], and this mechanism should also explain the possible contribution of *T. gondii* parasitization in other dopaminergic pathway diseases, e.g., Parkinson's disease [114].

9. The *N*-methyl-D-aspartate receptor hypofunction theory: anti-NMDAr antibodies

Encephalitis due to antibodies against the glutamatergic NMDA receptor (anti-NMDAr antibodies) is an autoimmune disease caused when antibodies produced by the host immune system identify NMDA receptors as foreign antigens. This receptor forms a heterotetramer between two GluN1 and two GluN2 subunits and participates in essential functions for reality perception, memory, and the control of unconscious activities. The disease is characterized by the hypofunction of NMDA receptors, which would account for the psychotic symptoms, personality changes, memory impairment, and psychomotor agitation

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[141, 142]. It usually arises during the course of a paraneoplastic process and is frequently associated with the development of ovarian teratomas, explaining its higher incidence among females [143, 144]. Likewise, 14–75% of patients with systemic erythematous lupus, another autoimmune disease, have been reported to manifest psychiatric symptoms related to the presence of the same antibodies [145, 146]. This involvement of anti-NMDAr antibodies (and other neurotransmission receptors) indicates an important link between immune abnormalities and altered neurotransmission in schizophrenia, major depression, or bipolar disorder [147, 148].

The presence of anti-NMDAr antibodies has been documented in schizophrenic patients in the absence of seizures, movement disorders, or other neurological signs or symptoms [149–151], although other researchers were unable to replicate these findings [152, 153]. For various reasons, the production of anti-NMDAr antibodies is a plausible mechanism to explain at least a percentage of schizophrenic cases [149]: several studies reported that 5–10% of cases are associated with the presence of these antibodies in serum and cerebrospinal fluid [150, 151, 154]; kynurenic acid is an antagonist of glutamate *via* blockade of NMDA receptors, as commented in the previous section, suggesting that it contributes to the pathogenesis of schizophrenia [122]; persistent blockade of NMDA receptors in experimental animals recreates clinical characteristics of schizophrenia [155]; selective elimination of subunit GluN1 of the NMDA receptor in neurons of the cortex and hippocampus in early postnatal development contributes to the pathophysiology of schizophrenia-related disorders in mice [156]; some of the genes associated with schizophrenia are related to the NMDA receptor [157]; NMDA receptors are reduced in medication-free schizophrenic patients [158]; blockade of the receptor with ketamine or phencyclidine produces psychotic symptoms [159, 160]; and *de novo* mutations (large chromosomal copy number changes) affect genes that encode one or more nucleotides among the glutamatergic postsynaptic proteins that form part of the receptor, providing insight into possible etiological mechanisms underlying schizophrenia [161].

Maternal infection during brain development or infection during childhood may produce anti-NMDAr antibodies, while other environmental or genetic factors may influence the age of disease onset [149]. Certain pathogens have been associated with elevated anti-NMDAr antibodies [162, 163]. Thus, a *T. gondii*-infected mouse model showed a significantly higher increase in serum GluN2A autoantibodies among juvenile- *versus* adult-infected mice. Adolescence is a critical window in neurodevelopment, and the authors hypothesized that early infection would have greater effects on behavior and the brain in comparison with adult infection. It is possible that chronic infection with *T. gondii* affects pre- or postnatal brain development by altering synaptic maturation. An increase in NMDAr autoantibodies due to *T. gondii* exposure might underlie behavioral alterations in symptomatic individuals [164].

10. Studies on gene-infection interaction

Various studies have demonstrated the participation of numerous genes in schizophrenia, providing firm evidence on the involvement of genetics in the etiology of the disease

[165]. Some authors have described inheritability in >80% of cases, and schizophrenia has been associated with polymorphic variability in certain genes [21, 166–168]. However, the genetic hypothesis alone cannot explain the familial association of schizophrenia with other diseases, the seasonal peaks of schizophrenia births, the different prevalences among residents of urban and rural areas, discordant results between monozygotic and dizygotic twins or between dizygotic twins and full siblings, or correlations in adopted children, which are, however, consistent with an infectious etiology [1]. Schizophrenia is likely a genetically complex disease that does not follow a Mendelian transmission pattern but rather involves multiple genes, each with a small effect, which act in combination with epigenetic and environmental factors [169]. Accordingly, epidemiological findings suggest that a combination of intrinsic (genetic) and extrinsic or environmental factors, including infections, may participate in the origin of this disease, operating during the development of the individual at some time between conception and adolescence [7]. Tomonaga [170] proposed that persistent chronic infections or the expression of microbial proteins may directly and/or indirectly affect CNS functions in infected individuals, changing the expressions of genes related to schizophrenia and increasing the risk of suffering this disease or at least some of its varied clinical phenotypes.

Genes whose variants or polymorphisms have been associated with the risk of schizophrenia include some that encode proteins with important functions in neurodevelopment or neurodegeneration and in neuronal neurotransmission circuits. This is the case of the gene that encodes neuregulin 1 (NRG1), a key molecule in maintaining brain synaptic plasticity in adults, which has been related to schizophrenia etiology [171, 172], and the genes that encode catechol-O-methyltransferase (COMT) [173], proline dehydrogenase (PRODH) [174], dysbindin protein (DTNBP1) [175], a regulator of G4 protein (RGS4) [176], a regulator of potassium calcium channels (KCNN3) [177], and D-amino-oxidase complex (G72, DAAO) [178], among others [179]. The genes that encode these proteins are located in chromosomal regions that have been described as relevant for the study of schizophrenia, and many of these proteins participate in glutamatergic, dopaminergic, or serotonergic neurotransmission circuits.

Genetic polymorphisms that increase susceptibility to schizophrenia, including some of the above, have also been related to resistance or susceptibility to certain infections through their important role in the life cycle of some pathogens, including *T. gondii* [169, 179, 180]. Schizophrenia may possibly correspond to a model in which various genes may interact with microbial agents in a process that is probably mediated by the inflammatory and immune response of the individual, increasing the risk of developing psychiatric disease [169, 179–182]. It appears reasonable to assume that infections may interact, thereby changing the expressions of schizophrenia-related genes and increasing the risk of suffering this condition.

Various rodent [79, 183, 184] and human [185, 186] studies have supported the existence of genetic susceptibility to *T. gondii* parasitization, suggesting that if the parasite were one of the possible causes underlying schizophrenia development, this genetic susceptibility might also explain familial cases of schizophrenia [1]. As commented above, some *T. gondii* genes encode proteins with a similar activity to that of enzymes (e.g., tyrosine hydroxylase) in the cells of their intermediate hosts. Therefore, this parasite has genes that allow it to "manipulate" the

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behavior of the host and facilitate its capture by the cat, its definitive host, thereby favoring parasite survival. The presence of these genes is consequently an evolutionary advantage of *T. gondii* [19].

Genetic studies (in animals and humans) currently center on the possible presence of genes or specific allelic variants that interact with the genes of microorganisms that can infect the patient (gene-infection interaction hypothesis), increasing the risk of schizophrenia [187–189]. Thus, it has been demonstrated that a critical role in human congenital *T. gondii* infection is played by the *ALOX12* gene, which encodes arachidonate 5-lipoxygenase enzyme, which is involved in fatty acid metabolism and has been related to schizophrenia, at least in a Korean population [190, 191]. HLA-related genes such as *SGK1* on chromosome 6, which plays a role in regulating different brain functions [192] and mediates the effects of cortisol on hippocampal neurogenesis [193], have a modulating effect on some infectious agents, including *T. gondii*, consistent with the proposition that parasitization may modify the risk of schizophrenia [187]. In a study of mice parasitized with *T. gondii*, heterozygous deletion of the *Nurr1* gene (Nurr1 ± genotype), an orphan nuclear receptor essential for the development of mesencephalic dopamine neurons [194], predisposed the animals to behavioral disorders that involve dopamine neurotransmission associated with schizophrenia symptoms [195].

A further example in support of this hypothesis is the Akt cell signaling system. The *Akt* gene encodes a serine-threonine kinase with three isoforms (Akt1, 2, and 3), whose activation mediates cell survival processes and whose inhibition favors apoptosis. As commented above, the innate immune system induces a range of processes after infection of brain cells by *T. gondii*, including antimicrobial activity and the generation of ROS to assist in the destruction of foreign pathogens. However, increases in ROS concentrations activate the Akt system, which guarantees cell survival and allows the pathogen to persist and replicate within the infected cell. Akt is above all activated in pathophysiological situations in which ROS increase as the result of ischemia-reperfusion, playing an important role in the protection of the different cells and tissues involved, including nerve tissue [196]. On the other hand, Akt is known to affect dopaminergic signaling, and polymorphisms of the *Akt1* gene have been found to increase the risk of developing schizophrenia through its relationship with dopaminergic pathways of the prefrontal cortex [197].

Other researchers reported similar associations between schizophrenia risk and other human pathogens, supporting the gene-infection interaction hypothesis [198–201]. This research line on the effects of interaction between genes or genetic variants on the risk of schizophrenia related to *T. gondii* parasitization is highly likely to establish the true causes of the disease, at least in some types of patient.

11. Is there an etiological association between *Toxoplasma gondii* infection and schizophrenia development?

Numerous studies have contributed evidence on the involvement of toxoplasmosis in the pathogenesis of numerous CNS diseases, including bipolar disorder, depression, Alzheimer's disease, Parkinson's disease, and epilepsy [49, 202–204]. However, the main advances over

the past few years have been achieved by research on deciphering the molecular mechanisms underlying the physiopathology of schizophrenia.

This chapter analyzes data from *in vitro* and animal and human *in vivo* studies in order elucidate points of connection between *T. gondii* and schizophrenia. It can be concluded that infection by *T. gondii* is highly likely to be a cause of the disease for the following reasons: it is a neurotropic microorganism that persistently invades glial cells and neurons; it generates brain development anomalies; it reduces brain gray matter density; it elicits an inflammatory and immune response that alters neurotransmission systems; it affects cognitive function and behavior; and its replication is inhibited by some antipsychotics. All disorders reported for the parasite are associated with the development of psychotic symptoms. Furthermore, specific genetic polymorphisms linked to an increased risk of schizophrenia have also been associated with a higher likelihood of infection by this parasite. Nevertheless, despite all of the above evidence on this possible pathogenic association, one important

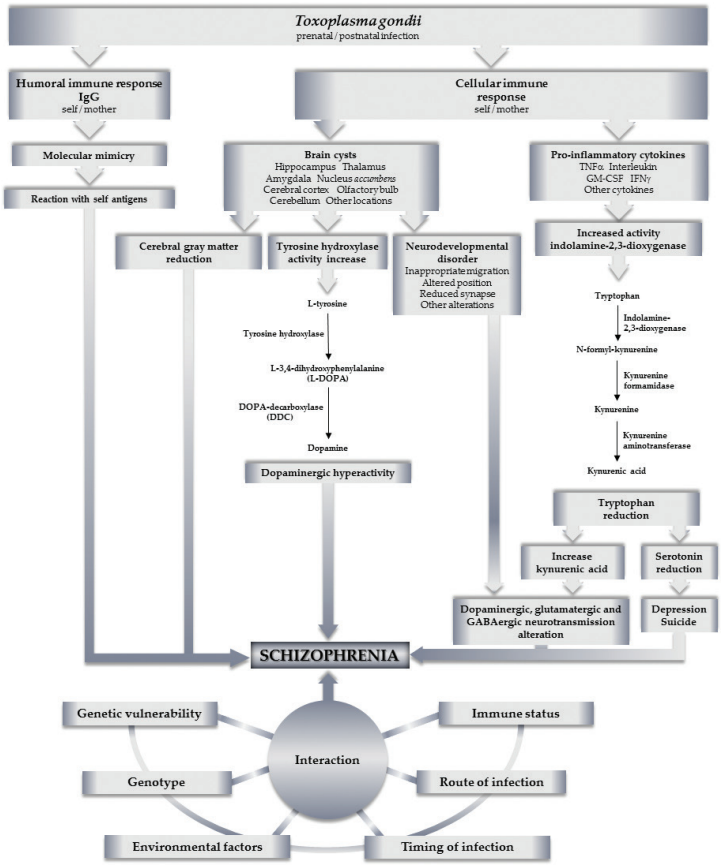

Figure 1. Likely involvement of infection by *Toxoplasma gondii* in the development of schizophrenia.

question remains to be resolved, which is why most individuals with signs of infection by *T. gondii* are asymptomatic and only a few develop psychiatric disorders.

Schizophrenia is a complex disease with innumerable symptoms, and its presentation and severity vary among patients. According to the infectious hypothesis of this disease (**Figure 1**), differences among patients would be influenced by their genetic predisposition or vulnerability, their immune status, the timing of parasitization (congenital, neonatal, or adult), the time interval since their first contact, and/or the particular brain area(s) affected. Characteristics of the infection also play a role, including its source (oocysts or tissue cysts), possible interactions with other infectious agents, and the genotype; thus, genotypes II and III more frequently establish chronic infections and show a greater expression of tyrosine hydroxylase genes in comparison with genotype I, and they may be more strongly related to behavioral changes [205].

Finally, the biology of schizophrenia must be fully elucidated to support the appropriate design of disease-modifying therapies or novel antipsychotic drugs. There appears to be sufficient evidence to suggest that schizophrenic patients with *T. gondii* infection could clinically benefit from a combined therapeutic approach based on the prescription of current or future antipsychotic drugs with antitoxoplasmic activity. However, published results have not been conclusive [206], and randomized controlled prospective trials are required in wider samples, stratifying schizophrenic patients into subgroups (e.g., by clinical phenotype, pathophysiological mechanism, or response to treatment) and in relation to specific types of *T. gondii* parasitization. Translational research must play a key role, with the involvement of psychiatric, neurologic, immunologic, biochemical, genetic, pharmacological, and microbiological investigators, among others, offering the possibility of using new and more effective methodologies. It appears highly likely that different causal agents are responsible for schizophrenia and that the pathogenic action of a particular microorganism such as *T. gondii* would only be relevant in certain patient subgroups, endorsing the need for personalized medicine.

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