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REVIEW ARTICLE

The known and missing links between *Toxoplasma gondii* and schizophrenia

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Abstract *Toxoplasma gondii*, an intracellular protozoan parasite, has a striking predilection for infecting the Central Nervous System and has been linked to an increased incidence of a number of psychiatric diseases. Several in vitro and in vivo studies have shown that *T. gondii* infection can affect the structure, bioenergetics and function of brain cells, and alters several host cell processes, including dopaminergic, tryptophan-kynurenine, GABAergic, AKT1, Jak/STAT, and vasopressinergic pathways. These mechanisms underlying the neuropathology of latent toxoplasmosis seem to operate also in schizophrenia, supporting the link between the two disorders. Better understanding of the intricate parasite-neuroglial communications holds the key to unlocking the mystery of *T. gondii*-mediated schizophrenia and offers substantial prospects for the development of disease-modifying therapies.

Keywords *Toxoplasma gondii* · Schizophrenia · Mental illness · Psychosis · Host-pathogen interaction

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Introduction

Schizophrenia and other psychiatric diseases are chronic mental disorders with a reaching impact on the human society. Worldwide, about 2 billion people suffer from brain related illnesses, such as dementia, Alzheimer's disease, depression, epilepsy, schizophrenia, stroke, or chronic pain. The overall cost of brain disorders in Europe has been estimated at €798 billion in 2010 (Gustavsson et al. 2011). Despite the far-reaching implications of mental diseases, their pathoetiological mechanisms remain incompletely understood due to the complexity of their pathogenesis. Indeed, genetic predisposition does not fully account for neuropsychiatric diseases; immunity, infection and other environmental factors, and socioeconomic status have also been implicated in the development of these diseases (Kendler and Diehl 1993; Lohmueller et al. 2003).

With the increasing dual burden of infectious and psychiatric diseases on human population the realization of the contribution of and interaction between these diseases and our understanding of them will form the basis for any future public health program. The effects of central nervous system (CNS) infections on the behavior of the infected individuals have been well documented. For example, borna virus has been associated with schizoaffective disorder and mania (Hans et al. 2004), HIV was linked to cognitive impairment and psychosis (Kalichman et al. 2000), rabies virus can cause hydrophobia (Bentivoglio et al. 2011). Also, *Brucella suis* can contribute to cognitive and emotional disturbances (Eren et al. 2006), *Leptospira* might trigger psychotic symptoms (Semiz et al. 2005), *Mycobacterium tuberculosis* can cause anxiety and depression (Vega et al. 2004), and streptococcal infections have been linked to obsessive-compulsive disorder and pediatric autoimmune psychoses (Swedo et al. 2004). Further, the neurotropic parasite *Toxoplasma gondii* (*T. gondii*) was linked

to behavioral changes in rodents, chimpanzee, and humans (Vyas et al. 2007; Flegr et al. 2011; Ingram et al. 2013; Poirotte et al. 2016). Elucidating the role of these microbial infections in neuropsychiatric diseases has been difficult to achieve probably due to the multifaceted nature of these diseases.

The past decade has marked exciting developments in understanding the important role specific pathogens can play in the development of these diseases (Jones-Brando 2003; Flegr 2007; Fekadu et al. 2010; Brooks et al. 2015). The aim of this review is to discuss the underlying pathophysiologic mechanisms by which *T. gondii* contributes to neuropsychiatric illness with an emphasis on processes or molecules that are known to alter brain function in schizophrenia, and hence are of interest for neuropsychiatric disease development. Although the exact molecular and cellular mechanisms underpinning the association between latent toxoplasmosis and schizophrenia remains poorly understood many neuropathologic commonalities between *T. gondii* infection and schizophrenia point out to a plausible relationship as explained in this review. Understanding the connection between *T. gondii* infection and psychiatric diseases will teach us a great deal about pathogenesis of these illnesses and may offer suggestions for improvement including testable hypothesis for future investigations and therapeutics' discovery.

Toxoplasmosis and psychosis

Toxoplasmosis is one of the most common zoonotic diseases that has infected about one-third of the world's human population (Montoya and Liesenfeld 2004). *T. gondii* is a predominantly intracellular pathogen with a strict neurotropism. Key to *T. gondii* neuropathogenesis is its ability to transmigrate across the blood–brain barrier and to colonize brain cells of infected hosts. During acute infection these events cause direct structural neurological damage due to invasion, growth and exit of the tachyzoite stage of the parasite (Fig. 1a) from the infected host cells, and by forming cyst during latent infection, in amygdala, olfactory bulb, cerebellum, and the cortical regions (Berenreiterová et al. 2011; Haroon et al. 2012; Evans et al. 2014), this parasite can elicit several hormonal and behavioral alterations in humans and rodents (Flegr 2013) (Fig. 1b). *T. gondii* uses several mechanisms to manipulate the host's phenotype and increase aggressiveness of the infected male hosts (Flegr et al. 2003). For example, the parasite enhances the levels of the neurotransmitter, dopamine (DA) in the brains of infected rodents, via its own tyrosine hydroxylase (Flegr et al. 2003; Gaskell et al. 2009; Parlog et al. 2015). Also, *T. gondii* enhances the plasma levels of the steroid hormone, testosterone, in infected male hosts via increasing the number of luteinizing hormone receptors, which regulate the synthesis of testosterone in testes on Leydig cells (Lim et al. 2013;

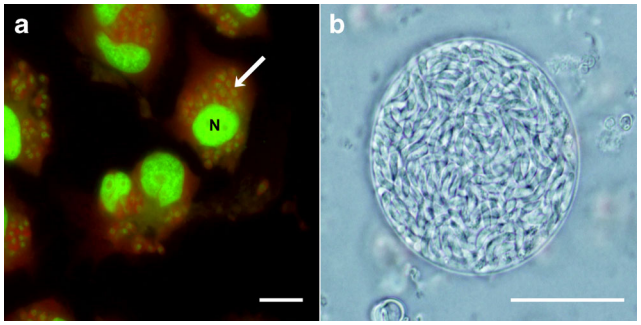

Fig. 1 Morphological appearance of the two life cycle forms of *Toxoplasma gondii*. **a** Acridine orange-stained human brain microvascular endothelial cells infected with *Toxoplasma gondii* RH strain. Note the presence of multiple tachyzoites (*green dots* indicated by the *arrow*), which are enclosed by a parasitophorous vacuole within host cell cytoplasm. N indicates host cell nucleus. Scale bar = 10 μm. **b** *Toxoplasma gondii* tissue cyst in the brain of infected mouse. Scale bar = 50 μm. This image was used with the kind permission of Dr. J.P. Dubey, Ph.D., USDA, Beltsville, MD, USA

Zghair et al. 2015). *T. gondii* hypomethylates the arginine vasopressin promoters in the medial amygdala of rats, leading to more activation of vasopressinergic neurons after exposure to cat odour, which leads to the reversion of fear into attraction, an evolutionary meachnaims meant to increase transmission of the parasite to its definitive felid hosts (Hari Dass and Vyas 2014). Further, latent infection with *T. gondii* was reported to cause dendritic retraction in the basolateral amygdala, possibly contributing to diminished fear and anxiety-like behavior in infected rodents (Mitra et al. 2013). Interestingly, time-dependent and gender-related differences have been detected in the levels of neurotransmitters. For example, DA release was found to be higher in acutely infected males, and a decrease in the noradrenergic system activity was found in females compared to slight increase in some brain areas of males. Also, acute invasion was associated with a rise in serotonin system activity, mostly in males (Flegr et al. 2008; Gatkowska et al. 2013).

Latent toxoplasmosis has been involved in psychiatric disorders, such as schizophrenia, autism, obsessive compulsive disorder (OCD), and bipolar disorder (Miman et al. 2010; Kusbeci et al. 2011; Taboas 2012; Sutterland et al. 2015). Schizophrenia in particular has received much attention and epidemiologic evidence supporting the link between latent toxoplasmosis and schizophrenia has been reported in many studies. *T. gondii* seropositive schizophrenic patients were found to experience poor course of schizophrenia and more severe positive psychopathology as indicated by the higher score on the Positive and Negative Symptom Scale (PANSS)-positive subscale (Holub et al. 2013). In young individuals, a link between infection with *T. gondii* and schizophrenia has been proposed based on the demonstration that *T. gondii* infection is associated with a high risk of developing schizophrenia, and children subjected to infection in utero are more likely to develop psychiatric disease than non-infected

children. *T. gondii* in utero infection affects fetal brain development and increases the vulnerability to develop 'true' schizophrenia later in life (Mortensen et al. 2007). The risk of developing schizophrenia or autism is not limited to prenatal exposure to *T. gondii*; congenital infection to other pathogens including influenza, rubella, measles, and cytomegalovirus has also been implicated in the etiology of this psychiatric disorder (Brown and Derkits 2010). *T. gondii* infection in the post-natal life could induce schizophrenia symptoms (i.e. not 'true' schizophrenia) by affecting brain function via, for example, altered dopamine transmission or causing neuro-inflammation. *T. gondii* infection can thus be a risk factor for schizophrenia in the young and the elderly. These epidemiological links are still debatable and better understanding of the neurophysiologic mechanisms underpinning these associations is needed if we are to develop better management of *T. gondii*-mediated psychiatric diseases.

The cross-talks between *T. gondii* and brain cells

Different psychopathologic mechanisms can substantiate the link between *T. gondii* infection and neuropsychiatric disorders. These include abnormal neurotransmitter metabolism (Stibbs 1985; Skallova et al. 2006; Gaskell et al. 2009; Prandovszky et al. 2011), dysregulated tryptophan metabolism (Schwarcz and Hunter 2007; Notarangelo et al. 2014), immunological changes (Prandota 2010), and hormonal (testosterone) alteration (Lim et al. 2013; Zghair et al. 2015). *T. gondii* infection also induces abnormalities in specific regions of the brain (e.g., hippocampus and amygdala) that are involved in the etiology of various neuropsychiatric disorders (Vyas et al. 2007; Mitra et al. 2013; Evans et al. 2014). Neuroinflammation and the imbalance between pro- and anti-inflammatory cytokines seem to be the main mechanisms that underpin the various pathways linking *T. gondii* and schizophrenia. Herein, we discuss how the activation of pro-inflammatory cytokines in response to *T. gondii* infection contributes to the pathogenesis of schizophrenia via its effects on various aspects of the brain function and structure (Fig. 2).

Alteration of neurotransmitter balance

Abnormality in the level of extracellular neurotransmitter concentrations has remained the core hypothesis supporting the link between latent toxoplasmosis and behavioral alterations. Dysregulation of the neurotransmitter DA has been implicated in psychiatric disorders, such as schizophrenia, bipolar disorder, OCD, and addiction in humans (Kim et al. 2003; Berk et al. 2007; Van Os and Kapur 2009; Ingram et al. 2013; Volkow et al. 2013; Brisch et al. 2014), and the ability of *T. gondii* to interrupt DA equilibrium has been documented in vivo and in vitro (Stibbs 1985; Skallova et al. 2006; Vyas et al. 2007; Prandovszky et al. 2011). Dopamine is produced by host neural cells, but the parasite is also able to augment dopaminergic function (Prandovszky et al. 2011). *T. gondii* can increase DA levels in rodents (Stibbs 1985) through the inflammatory release of DA by increasing cytotoxic nitric oxide (NO) and other inflammatory cytokines such as Interleukin-2 (IL-2) and IL-6, which are produced by activated leukocytes at sites of local inflammation in the infected brain (Miller et al. 2009). Also, increased DA release can occur via direct parasite's production. This proposition was supported by the discovery of two genes, *AAH1* and *AAH2*, in *T. gondii* genome encoding for two isoforms of aromatic amino acid hydroxylases AAH (tyrosine and phenylalanine hydroxylases), which catalyze phenylalanine (Phe) to Tyrosine (Tyr) and Tyr to 3,4 dihydroxyphenylalanine (L-Dopa) (the precursor to DA), which alters DA pathway and leads to alteration in the behaviour of *T. gondii*-infected host (Gaskell et al. 2009). Interestingly, the antipsychotic, dopamine-blocking agents, haloperidol and the mood stabilizer valproic acid were found to inhibit *T. gondii* growth in vitro (Jones-Brando et al. 2003; Goodwin et al. 2008, 2011), whereas DA stimulates tachyzoite propagation (Guo et al. 2010; Strobl et al. 2012). This has led to the assumption that the effects of drugs used in the treatment of schizophrenia and other psychoses may be potentiated through their toxic effect on the parasite in infected individuals (Webster et al. 2006; Strobl et al. 2012). However, this is only relevant for treating *T. gondii* and *T. gondii*-induced schizophrenia symptoms because most people with schizophrenia are not infected with *T. gondii*.

The induction of indoleamine 2,3-dioxygenase (IDO) enzyme by IFN-γ is another example of the modulation of host neurotransmission by *T. gondii*-associated immune activation. The cytokine-mediated expression of IDO of the tryptophan/kynurenine metabolism leads to the depletion of plasma tryptophan (Try), which may interfere with brain 5-HT(serotonin) synthesis, and increase production of anxiogenic and depressogenic Try catabolites (Schwarcz and Pellicciari 2002; Leonard and Maes 2012). A dramatically increased concentration of two neuroactive metabolites, quinolinic acid (QA) and kynurenic acid (KA), was observed in the brain of mice infected with a type II *T. gondii* strain (Notarangelo et al. 2014). In human patients, excessive QA and KA levels have been correlated with a number of neurodegenerative disorders, depression, schizophrenia, and non-fatal suicidal self-directed violence (Schwarcz et al. 2001; Schwarcz and Pellicciari 2002; Guidetti and Schwarcz 2003; Guilleminet al. 2006; Okusaga et al. 2016). Produced primarily by microglia, QA binds to glutamate N-methyl-D-aspartate receptors (NMDARs) inducing excitotoxicity and oxidative stress (OS) in the brain (Schwarcz and Pellicciari 2002; Guillemin et al. 2005). The KA, which is produced primarily in astrocytes, is a potent antagonist of NMDARs and attenuates glutamatergic neurotransmission at excitatory synapses, leading to alteration of the

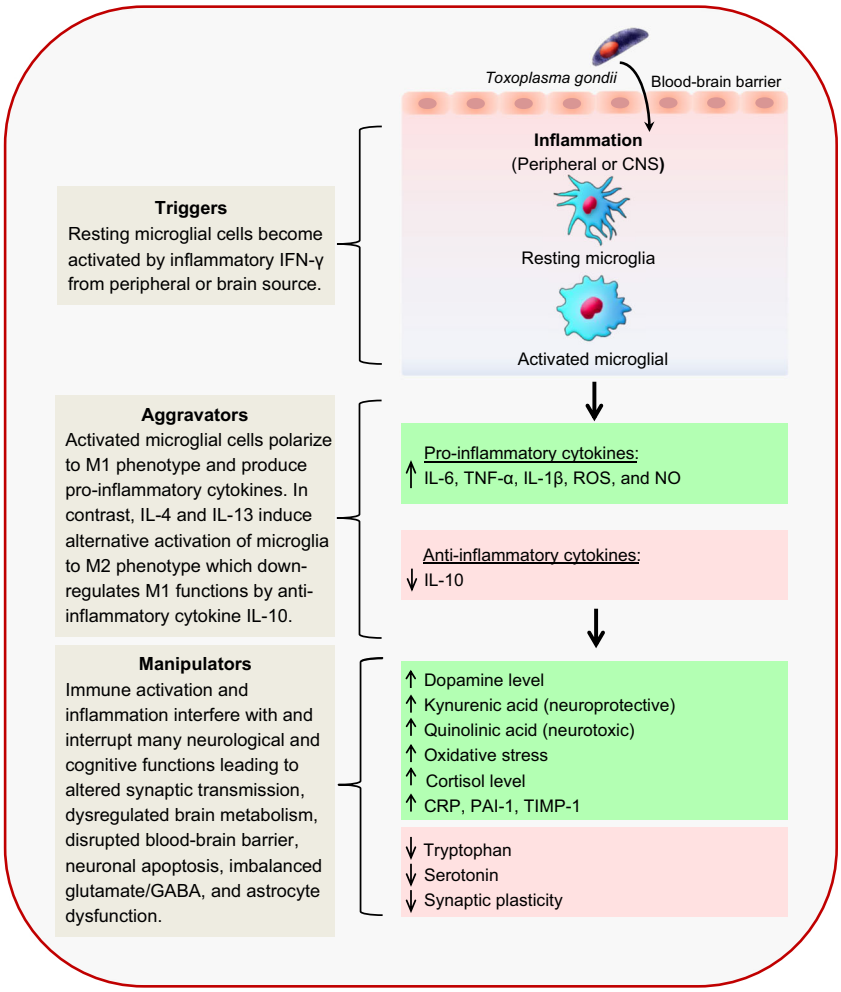

Fig. 2 Summary of the alterations associated with brain infection with the protozoan *Toxoplasma gondii*. Besides the direct physical damage associated with *T. gondii* infection on brain cells, the parasite disrupts a number of neurochemical processes and these are summarized here. Inflammatory and immune responses seem to be the main drivers for all cascade of events starting from activation of resting microglial cells, polarizing their immuno-regulatory functions, which cause many neurochemical changes, similar to those occurring in schizophrenia, leading to irregularities in mood, cognition and behaviour observed in some infected individuals. *Abbreviations: GABA* gamma-aminobutyric acid, *CRP* C-reactive protein, *PAI-1* plasminogen activator inhibitor 1, *TIMP-1* tissue inhibitor of metalloproteinases 1, *VCAM-1* vascular cell adhesion molecule 1, *TNF-α* tumour necrosis factor alpha, *ROS* reactive oxygen species, *NO* nitric oxide

neuronal oscillations, cognitive defects and schizophrenia-like symptoms (Schwarcz and Pellicciari 2002; Guillemin et al. 2005; Kegel et al. 2014; Goff 2015; Howes et al. 2015). However, a recent study revealed that kynurenine pathway alteration in acutely *T. gondii*-infected mice might not fully reflect changes observed in the brain of schizophrenia patients (Notarangelo et al. 2014), suggesting that other mechanisms might contribute to schizophrenia pathogenesis in individuals infected with *T. gondii*. Indeed, recent evidence showed that Type II ME49 *T. gondii* directly interferes with GABA signalling in the brain by inducing global changes in the distribution of glutamic acid decarboxylase 67 (GAD67), a key enzyme that catalyzes the neuronal biosynthesis of gamma-aminobutyric acid (GABA) in the brain (Brooks et al. 2015). GABA is the major inhibitory neurotransmitter in the brain and can be secreted from *T. gondii*-infected dendritic cells (DCs), which promotes parasite dissemination by stimulating motility of infected DCs through GABAergic signalling pathways (Fuks et al. 2012).

The effects of infection with representative strains of *T. gondii* on the expression of genes coding for neurotransmitter and neuropeptide systems (NNS) in human neuroepithelioma cells was studied using microarray (Xiao et al. 2013). Compared to controls, cells infected with type I strain showed alterations in the gene transcription and protein levels of three neurotransmitter systems (dopamine, glutamate and serotonin) and two neuropeptides (PROK2 and TAC1). Infection with type III changed the critical enzyme, TDO2, in the kynurenine pathway, whereas type II caused no significant abnormalities in the NNS. Interestingly, levels of mRNA encoding for TDO2 are elevated in the brain of individuals with schizophrenia (Miller et al. 2004).

Metabolic alterations

IFNγ, produced by T cells, natural killer cells infiltrating the brain, and by resident microglia (Suzuki et al. 2005), is the main component of the anti-*T. gondii* immune response (Hunter and Sibley 2012). It primes phagocytes to produce toxic intermediates that suppress the growth of the parasite, but also increases the activity of IDO. Interestingly, this enzyme depletes Try, which is necessary to limit the replication of *T. gondii* tachyzoites, but on the other hand it interferes with brain 5-HT synthesis and causes alteration in the kynurenine

pathway of Try metabolism, which has been linked to schizophrenia as stated above. Of note, patients suffering from immune activation and inflammation, critical factors in the pathogenesis of toxoplasmosis, were found to have elevated serum levels of Phe together with an elevated Phe to tyrosine ratio (Phe/Tyr), which was associated with neuropsychiatric symptoms, such as depression and mood changes (Neurauter et al. 2008). The associations between immune and inflammatory activation and the disturbed Phe metabolism is most likely a consequence of a reduced conversion of Phe to Tyr by the aromatic amino acid phenylalanine 4-hydroxylase (PAH). Given the oxidative stress associated with both *T. gondii* infection and neuropsychiatric disorders it is reasonable to expect that metabolites, such as 5,6,7,8-tetrahydrobiopterin (BH4), which acts as an antioxidant as well as a cofactor for PAH in mammals are rapidly destroyed (Widner et al. 2001). As a consequence, the BH4-dependent enzyme PAH loses its activity, leading to increased concentration of Phe and Phe/Tyr ratio, characteristics of neuropsychiatric disorders.

A recent untargeted LC-MS-based metabolomic's study identified 19 metabolites that are differentially regulated in the serum of *T. gondii*-infected mice compared to controls. Among these compounds, 5 were detected in the ESI+mode. These include kynurenine, serotonin, glycerophosphocholine, choline, and N-Acetyl-DL-tryptophan, which play key roles in mediating host-pathogen interaction as described above (Zhou et al. 2016). A similar metabolomics approach in BALB/c mice during infection with *T. gondii* Pru strain revealed alteration in the metabolism of amino acids, organic acids, carbohydrates, fatty acids, and vitamins in the brain of infected mice (Zhou et al. 2015).

Inflammatory markers

Elevated levels of pro-inflammatory cytokines, e.g. IL-1, IL-6 and tumour necrosis factor alpha (TNF-α), and Th-1-derived cytokines, such as IL-2 and interferon gamma (IFN-γ) have been reported in the cerebral spinal fluid (CSF) and serum of individuals with schizophrenia. Recent evidence suggests that levels of C-reactive protein (CRP) are increased in the brain of schizophrenia patients adds to the evidence of activated immune response in schizophrenia. CRP is a protein involved in acute phase response and is considered a generic marker of inflammation. Increased levels of peripheral CRP in schizophrenia was found to be independent of confounding factors, such as smoking or body mass index (Dickerson et al. 2013). Also, a positive association exists between serotiters to *T. gondii* infection and circulating CRP levels in schizophrenia (Hinze-Selch et al. 2007). Levels of CRP remain elevated regardless of treatment with antipsychotic medications (Suvisaari et al. 2011) and were associated with the severity of cognitive impairment (Dickerson et al. 2007), suggesting that interventions that are able to lower CRP levels could benefit schizophrenia patients.

Oxidative stress and stress-activated signalling pathways

The innate immune system generates reactive oxygen species (ROS) and reactive nitrogen species (RNS) to aid in the destruction of foreign pathogens. On the other hand, most of the inflammatory mediators are potentially toxic for neurons (Zindler et al. 2010). For instance, scientific evidence points to ROS-mediated oxidative damage as a key pathogenic pathway involved in infection-mediated neuropathy (Gao et al. 2014). Pro-inflammatory cytokines associated with *T. gondii* infection induce the activation of apoptosis through microglial activation and subsequent production of ROS and increased RNS. *T. gondii* also activates immune cells (Jones et al. 2006) and a host of inflammatory actions through Jak/STAT pathway, and induces neuronal expression and activation of NADPH oxidase (NOX2) enzyme. NOX2, in turn, can produce large amounts of ROS (Sun et al. 2007), primarily superoxide known to be connected to seizures, stroke and neurodegenerative diseases (Vasconcelos et al. 2014). Also, a number of schizophrenia susceptibility genes are involved in the life cycle of *T. gondii* (Carter et al. 2009), whereby these genes have a role in immunity, but also regulate binding to the integrin system, which could influence AKT1 signaling, preventing host cell death, but also modulating dopamine-dependent behavior (Tan et al. 2008).

The activation of NMDA receptor has also been known to trigger oxidative stress in schizophrenia through glutamate, which is actively taken up into astrocytes and is converted into glutamine. Alterations in glutamine increase calcium influx into neurons, which may contribute to excitotoxicity, NMDA antagonism in schizophrenia and altered neurotransmission. The imbalance in the glutamatergic neurotransmission leads to further production of ROS and RNS, which subsequently leads to nitrosative damage to DNA, proteins and lipids. These finding indicate that a high degree of degenerated neurons and cognitive impairment are expected to be associated with the presence of *T. gondii* in the brain.

Neuronal damage and apoptosis

Intracerebral *T. gondii* infection was found to activate neurotoxic microglia CCR9+Irg1+ in C57BL/6 J mice and increased TNF-α mRNA expression that promoted neuronal apoptosis and thus facilitates neurodegeneration (Li et al. 2006). Considering the neuroinflammation hypothesis, the possible relevance of activated microglia in the pathophysiology of schizophrenia is increasingly recognized (Van Berckel et al. 2008; Gao et al. 2014). Microglias play a role in controlling *T. gondii* infection in the brain (Blanchard et al. 2015), possibly through the kynurenine pathway (Notarangelo et al.

2014), whereby differences of the microglial immune response to different strains of *T. gondii* have been found (Glaser et al. 2011). Alternatively, IL-6 production of macrophages reverts the inhibition of *T. gondii* replication caused by astrocytes and microglial cells and may be involved in the mechanism of reactivation of latent infection in patients with AIDS (da Silva and Langoni 2009). IL-6 has been found to be increased in schizophrenia patients (Miller et al. 2011). Another hypothesis links CD8 T-cell downregulation with the mental effects of toxoplasmosis (Bhadra et al. 2013), which can be caused by the kynurenine pathway.

IFNγ is known to induce expression of VCAM-1 in endothelial cells to allow recruitment of cytotoxic T cells to the site of *T. gondii* infection (Wang et al. 2007). This is associated with the formation of collagen-like structures, which guides lymphocyte migration (Wilson et al. 2009). Also excessive cytokine responses to *T. gondii* infection may cause neuronal apoptosis and glial damage, decreasing the neurotrophic support and inducing structural changes (Fabiani et al. 2015). This is in line with recent findings that showed signs of CNS tissue damage, demyelination and increased apoptosis in experimentally infected mice (Tomasik et al. 2015), indicating that infection may be associated with exacerbated brain pathology. These findings are relevant to the previously reported decrease in the density of grey matter (the regions containing neuronal cell bodies and almost all synaptic connections) of *Toxoplasma* seropositive schizophrenic patients compared with seronegative schizophrenic patients (Horacek et al. 2012; Tomasik et al. 2015). Also, alterations in synaptic, dendritic and axonal organization have been linked to macroscopic features observed in the brain of schizophrenic patients, such as decreased cortical volume (Harrison 1999). Further, myelin abnormalities have been described in schizophrenia and linked to abnormal neural connectivity and functional impairment (Flynn et al. 2003).

Proteomic signature of brain tissues

Data generated from high-throughput proteomic techniques have furthered our understanding of the *T. gondii*-schizophrenia interface. Tomasik et al. (2015) revealed increases in the levels of CRP, IL-1β, IFNγ, plasminogen activator inhibitor 1 (PAI-1), tissue inhibitor of metalloproteinases 1 (TIMP-1), and vascular cell adhesion molecule 1 (VCAM-1). These features overlapped between mice chronically infected with *T. gondii* and "postmortem" brain samples of schizophrenic patients. This signature of immune activation (indicative of neural damage) and tissue repair molecules are implicated in several mechanisms in the pathogenesis of schizophrenia and toxoplasmosis. Immune activation-induced damage and tissue remodeling processes during *T. gondii* brain infection are controlled by matrix metalloproteinases, enzymes that degrade extracellular matrix proteins, and their inhibitor TIMP-1 produced by astrocytes and microglia (Clark et al. 2011). Increased TIMP-1 level was shown in both animal models and schizophrenic patients and overexpression of TIMP-1 can impair long-term potentiation (LTP) in the prefrontal cortex (Okulski et al. 2007). Extracellular matrix abnormalities and resulting LTP-like plasticity deficits are likely to contribute to the pathophysiology of schizophrenia and result in impaired information processing in patients (Berretta 2012). The exact role of PAI-1 in *T. gondii* infection and schizophrenia-related mechanisms is unknown. But, similar to TIMP-1, PAI-1 can control the matrix metalloproteinase activity and degradation of extracellular matrix proteins. However, excessive PAI-1 may lead to accumulation of collagen and scar formation (Ghosh and Vaughan 2012). Increased levels of PAI-1 may also be linked to reduced neurotrophic support in the brain of schizophrenic patients, because PAI-1 is involved in brain-derived neurotrophic factor maturation in the hippocampus (Mou et al. 2009). Further studies are required to investigate the exact impact of elevated PAI-1 on brain function.

Epigenetic modification

Promoter hypomethylation of the neuropeptide arginine vasopressin (AVP) gene in the medial amygdala was observed in male rats infected with *T. gondii*. This epigenetic manipulation induced more activation of vasopressinergic neurons after exposure to cat odour and, thus, initiates the reversion of fear into attraction (Hari Dass and Vyas 2014). Loss of fear in the infected animals can be rescued by systemic hypermethylation (i.e., administration of L-methionine). More interestingly, this 'fatal attraction phenomenon' can be recapitulated by inducing hypomethylation via directed intracerebral delivery of methylation inhibitor into the medial amygdala in noninfected rats (Hari Dass and Vyas 2014).

Gaps in knowledge and future priorities

Even though several evidence suggest that *T. gondii* infection contributes to psychiatric diseases in humans and influence the behaviour of humans and animals many questions remain to be addressed.

Abnormal transmitter release

Therapeutic drugs for the treatment of psychiatric disorders have been developed and categorized largely on the basis of their effects on neurotransmitter release and resulting receptor stimulation. Interestingly some of these drugs are also effective in treating *T. gondii* infection. This stresses the implications of the hypotheses that address the dynamic nature of neurotransmitter dysregulation during *T. gondii* infection. *T. gondii* interacts with host cells and activates sets of infection-

specific and host-specific genes and proteins. Some of these proteins are secreted into extracellular fluids as neurotransmitters (e.g. dopamine) to modify and modulate signals between neurons and other brain cells. Whether this reflects an adaptive advantage to the host or enhances the fitness of the parasite is not clear. Better understanding require tools that are able to assess neurotransmitter release at high spatial and temporal resolution, which will then enable the elucidation of the role of infection related-neurotransmitter dysfunction in the development of symptoms of neuropsychiatric disorders, and also may refine neuro-pharmacological mechanisms to serve as targets for new treatment approaches. Irregularities of other neurotransmitters, including serotonin, glutamate, and GABA have also been implicated in schizophrenia. Hence, it is important to investigate preferential tropism of the parasite for specific neuronal populations and subpopulations (i.e. GABAergic or dopaminergic).

Parasite molecules that interact with host cells

Molecules, such as DA are known to mediate the interaction between *T. gondii* and brain cells and contribute to the behavioural changes in mice or psychiatric symptoms in infected humans (Stibbs 1985; Prandovszky et al. 2011). During its life cycle, *T. gondii* injects certain secreted proteins into the host cell whose properties may be relevant to the above perspective. For instance, toxolysin is a metalloprotease with homology to insulysin (Hajagos et al. 2012), which degrades certain growth factors (Guo et al. 2010), while certain rhoptry proteins (e.g. ROP16 and ROP18) possess kinase activity, which may influence key functions within the signalling networks (Saeij et al. 2006). On the other hand, less is known concerning the effects of *T. gondii* on key processes in schizophrenia, including neuregulin signaling that affects demyelination (Brinkmann et al. 2008; Buonanno et al. 2008) or glutamate N-methyl-D-aspartate (NMDA) receptor function, which is involved in the synaptic changes implicated in schizophrenia (Carter 2006, 2007; Ogden and Traynelis 2011). Also, calcium channels play a key role in this scenario, whereas *DISC1*, a key schizophrenia gene resides at the centre of a hub controlling many of these processes (Bradshaw and Porteous 2012). Further, the degree to which *T. gondii*-derived molecules alter host's signalling pathways or modulate neural circuitry still needs further investigation.

T. gondii and brain function: mixed messages

Giving the complex nature of host-parasite interaction within the brain it is reasonable to expect many pathological mechanisms through which *T. gondii* infection contributes to the development of psychiatric diseases. But what was not expected is the potential beneficial role of the parasite on the cognition and memory of affected host. Let us elaborate, even though *T. gondii* has not yet been detected in the brain of schizophrenic patients the parasite cysts have been detected in the memory processing areas, such as hippocampus and amygdala of infected mice (Haroon et al. 2012). This explains why anti-*T. gondii* IgG positive individuals exhibited impaired memory performance and infected mice exhibited memory impairment in the passive avoidance task, and lost their anxiety-like behaviour towards cat's urine (Ingram et al. 2013). In striking contrast, the same pathogen can have a neuroprotective effect. Interferon gamma (IFN-γ)-activated microglial cells play a pivotal role in neuronal protection by stimulating the production of transforming growth factor beta-1, which inhibits inducible nitric oxide synthase (Rozenfeld et al. 2005). Interestingly, immune-inhibition associated with latent *T. gondii* infection was found to ameliorate learning and memory deficits in Tg2576 transgenic mouse model of Alzheimer's disease and protected against neuronal degeneration, as evidenced by a reduction in cerebral β-amyloid deposition and increased anti-inflammatory cytokines (Jung et al. 2012).

Towards stratified psychiatry

Psychiatric diseases are polygenic in nature and are derived from interactions between environmental factors, individual's immune response, mutational events in several genes, and epigenetic modifications (Sullivan et al. 2003). It is important to recognize the complexity associated with the understanding of these multifactorial diseases, which requires integration of interdisciplinary methodologies. High-dimensional data is needed to identify new biomarkers to stratify disease risk in psychiatric patients via the analysis of the interactions that occur at different levels of the biological system, from genetic variations to metabolic pathways, and their relationship to distinct phenotypes of psychiatric disease or an infection status. Identification of genetic variants linked to disrupted biological functions caused by a psychiatric disease state and/or due to exposure to *T. gondii* can provide direct evidence that these genes and the connecting pathways are related to disease susceptibility. In the emerging era of 'personalized medicine' stratification of patients based on disease-specific genetic signatures that accurately identify at risk individuals will become an important tool of disease susceptibility testing and may enable clinicians to accurately predict the course of the illness (i.e. prognosis) or response to therapy. Clinical psychiatrists are encouraged to keep abreast of developments in this increasingly important area.

Conclusions and perspectives

Great strides have been made in deciphering the molecular mechanisms involved in toxoplasmosis and schizophrenia,

although these areas remain incompletely defined and sometimes controversial. However, knowledge generated in recent years starts to offer fresh perspectives and opens a new avenue for examining the links between the pathogenesis of schizophrenia and latent toxoplasmosis. Herein, we have evaluated available data from in vitro and in vivo (animals and humans) studies to summarize the commonalities between schizophrenia and latent toxoplasmosis. Both entities manifest enhanced neuroinflammation, which underpins disrupted neurotransmission, increased production of *L*-kynurenine (and its neuroactive metabolites), hormonal imbalance, tissue remodeling processes, the ability of *T. gondii* to alter rodent neural connectivity and fear behavior, and impairs human cognition, and the high PANSS score and reduced grey matter density, of seropositive schizophrenic patients. These links support the latent toxoplasmosis-schizophrenia connection theory, but some of these and other, yet unknown, hypotheses remain to be validated. These hypotheses are only a starting point for exploring potential mechanisms, with the aim of uncovering cellular pathways affecting parasite replication that also can be targeted for the development of schizophrenia-modifying therapies. Finally, we speculate that stratification of schizophrenic patients into phenotypic subgroups that share a distinct set of pathophysiologic mechanisms and treatment responses, and that correlate with a specific state of infection will enhance the management of these disorders. Parasitologists will increasingly need to collaborate with psychiatrists to realize the full potential of these data.

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