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Abstract: Toxoplasmosis is a highly spread and clinically heterogeneous disease, with a wide range of clinical manifestations ranging from a completely asymptomatic infection to multi-organ involvement, sometimes fatal, especially in non immunocompetent individuals. Once the parasite enters the body, after a brief period of circulation in the body fluids, it forms tissue cysts and establishes a chronic infection. Latent toxoplasmosis has always been considered subclinical or with non-specific symptoms, but in recent years, this belief has been questioned. In fact, it is possible to observe some personality and behavioral changes, Intellectual Quotient and psychomotor performance reduction as well as development of neuropsychiatric disorders (schizophrenia, schizophrenia spectrum disorders, and Parkinson's disease) in probably genetically predisposed individuals. The mechanisms by which Toxoplasma gondii leads to such changes are far from being elucidated. T. gondii has a strong tropism for the Central Nervous System with preferential localization in cerebral hemispheres, basal ganglia, cerebellum and brain stem. In particular, this parasite affects neurons and glial cells, both directly (see tissue cysts production and proteins homologous to the tyrosine hydroxylase and dopamine D2 receptor) and indirectly (see antibodies, cytokines-mediated effects). Over the years, a great number of serological, pharmacological, epidemiological and behavioral studies have been carried out, aimed at establishing an etiopathogenetic association between T. gondii infection and development of some behavioral changes and neuropsychiatric disorders. This paper reviews and highlights neurobiological, epidemiological and pharmacological data relating infection with T. gondii to neuropsychiatric diseases.

To: Professor A.H. Kaye

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23th March, 2012

Dear Editor,

We should greatly appreciate your kind consideration of the enclosed manuscript "**Toxoplasmosis and Neuropsychiatric Diseases: is there a clear relationship ?**", Authors: Silvia Fabiani, Barbara Pinto and Fabrizio Bruschi, for its publication as a Review in the Journal of Clinical Neuroscience.
The submitting authors warrant that the article is original, does not infringe upon any copyright or other proprietary right of any third party, and is not under consideration by another journal. All submitting authors have contributed to the work, seen and approved the submitted version.

Yours faithfully,

Prof. Fabrizio Bruschi

on behalf of the submitting authors

Toxoplasmosis and Neuropsychiatric Diseases: is there a clear relationship?

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Abstract

Toxoplasmosis is a highly spread and clinically heterogeneous disease, with a wide range of clinical manifestations ranging from a completely asymptomatic infection to multi-organ involvement, sometimes fatal, especially in non immunocompetent individuals. Once the parasite enters the body, after a brief period of circulation in the body fluids, it forms tissue cysts and establishes a chronic infection. Latent toxoplasmosis has always been considered subclinical or with non-specific symptoms, but in recent years, this belief has been questioned. In fact, it is possible to observe some personality and behavioral changes, Intellectual Quotient and psychomotor performance reduction as well as development of neuropsychiatric disorders (schizophrenia, schizophrenia spectrum disorders, and Parkinson's disease) in probably genetically predisposed individuals. The mechanisms by which *Toxoplasma gondii* leads to such changes are far from being elucidated. *T. gondii* has a strong tropism for the Central Nervous System with preferential localization in cerebral hemispheres, basal ganglia, cerebellum and brain stem. In particular, this parasite affects neurons and glial cells, both directly (see tissue cysts production and proteins homologous to the tyrosine hydroxylase and dopamine D_2 receptor) and indirectly (see antibodies, cytokines-mediated effects). Over the years, a great number of serological, pharmacological, epidemiological and behavioral studies have been carried out, aimed at establishing an etiopathogenetic association between *T. gondii* infection and development of some behavioral changes and neuropsychiatric disorders. This paper reviews and highlights neurobiological, epidemiological and pharmacological data relating infection with *T. gondii* to neuropsychiatric diseases.

Keywords: *T. gondii;* schizophrenia; schizophrenia spectrum disorders; Parkinson's disease.

Abbreviations: Abs, antibodies - **ACTH**, adrenocorticotropic hormone - **Ags**, antigens - **AIDS,** Acquired Immune Deficiency Syndrome - **α7nAch**, α7-nicotinic acid - **B-end**, Beta-endorphin - **CB1R**, type I cannabinoid receptor - **CMV**, *Cytomegalovirus* - **CNS**, Central Nervous System - **CRF**, corticotropin-releasing factor - **CT**, Congenital Toxoplasmosis - **DC**, Dendritic Cell - **DOPA**, dopamine - **D_2R**, DOPA receptor - **EIA**, Enzyme ImmunoAssay – **ELISA**, enzyme-linked immunosorbent assay - **GABA**, gamma-aminobutyric acid - **GM-CSF,** Granulocyte Macrophage Colony-Stimulating Factor – **HAART**, highly active anti-retroviral therapy - **5-HIAA**, 5-iydroxy-3-indole acetic acid - **HIV**, HumanImmunodeficiency Virus - **HLA,** Human Leukocyte Antigen - **HPA axis**, Hypothalamic-Pituitary-Adrenal axis - **HSV1, HSV2**, *Herpes virus* 1 and 2 - **5-HT**, 5-hydroxytryptamine - **ID/IDPs** ImmunoDeficit and ImmunoDeficient patients - **IDO**, indoleamine

2,3-dioxygenases - **IFN**, interferon - **Ig**, immunoglobulin - **IL**, interleukin - **IQ**, Intellectual Quotient - **IS**, Immune System - **KP**, kynurenine pathway - **KYNA**, kynureic acid - **L-KIN**, L-kynurenine - **Mø**, macrophage – **MRI**, magnetic resonance imaging - **NE**, norepinephrine - **NF-kB**, Nuclear Factor-KappaB - **NMDA**, N-methyl D-aspartate - **NK**, Natural Killer - **NO**, nitric oxide - **NS**, Novelty Seeking - **PD**, Parkinson's disease - **16-PF**, Cattell's 16-factor personality questionnaire – **PG**, prostaglandin - **PKU**, phenylketonuria - **QUIN**, quinolinic acid - **SFDT**, Sabin-Feldman dye test - **SLE**, Systemic Lupus Erythematosus - **TCI**, Character Inventory personality Test - **TDO**, thryptophan 2,3-dioxygenase - **TE**, *Toxoplasma* Encephalitis - **TGF**, Transforming growth factor – **TH**, tyrosine hydroxylase - **Th1**, **Th2**, T helper 1 and 2 - **TLR**, Toll-like receptor - **TNF,** tumor necrosis factor - **TRP,** tryptophan - **VBM**, voxel-based-morphometry

1. Introduction

Toxoplasmosis is a widespread parasitic disease, although differences between Countries exist partly due to different environmental, socio-economic and cultural habits. It is caused by *Toxoplasma gondii*, an obligate intracellular protozoan belonging to the phylum *Apicomplexa*. Within the species *T. gondii*, studies of gene sequencing have allowed the identification of different genotypes (the classical I, II, III, as well as recombinant and exotic genotypes) with different clinical implications. Re-infection with genotypes other than those involved in a primary infection is also possible (Boothroyd and Grigg 2002).[1] The life cycle of *T. gondii* has three infectious phases: sexual replication in felines (mainly the cats) which are the definitive hosts, exogenous (oocysts) and asexual replication in warm-blooded animals, including humans, that represent the intermediate host. Human beings can be infected by ingestion of cysts contained in tissues of infected animals after consumption of raw or undercooked meat, mainly sheep and goats (Latin-French model), or swine (Anglo-Saxon model), or by accidental ingestion of mature oocysts following contact with cats or cat litter boxes or, as in the tropical model, by consumption of water or fresh vegetables and fruit washed with contaminated water. Infection can also occur through maternal-fetal transmission which causes Congenital Toxoplasmosis (CT) or blood transfusions, solid organ or hematopoietic cell transplantation and laboratory accidents. Clinically, toxoplasmosis is usually responsible for both acute and chronic infection, as well as reactivation in non immunocompetent individuals. In the immunocompetent subjects, infection is asymptomatic in more than 80% of cases, although in a 10-20% of subjects negligible symptomatic forms can be observed. The situation is more severe in CT and in non immunocompetent patients who may undergo a neuropsychiatric involvement with numerous sequelae (disorientation, anxiety, depression and schizofrenic psychosis). Novel research is focusing on the possible link between exposure to *T. gondii* and development of neuropsychiatric disorders such as schizophrenia and Parkinson's disease (PD). If a firm association between *Toxoplasma* infection and neuropsychiatric disorders will be established, this would lead to novel methods for their prevention and treatment. This review will focus on neurobiological, epidemiological, and pharmacological data relating infection with *T. gondii* to neuropsychiatric diseases.

2. The origins of the infective theory on the etiology of neuropsychiatric disorders

The idea that psychotic disorders might be etiologically related to bacterial diseases dates from the late 19th century. Kraepelin first (Kraepelin 1919),[2] in 1896, postulated that toxins secreted by infectious agents may cause an organic brain pathology. Some years later Menninger (1994),[3] following the 1918-1919 influenza pandemic, theorized a viral etiology for encephalitis and schizophrenia and only later, attention shifted to parasites. Several infectious agents have been

involved to explain the etiology of psychiatric disorders. Although the cause of disorders has not been fully elucidated, the interaction between pathogens and host genes seems to play an important role. Genetic background does not completely explain the development of neuropsychiatric disorders and it is likely that, in past years, its role in the etiopathogenesis of the disease may have been overestimated (Torrey 1992).[4] Indeed, affected individuals show a higher rate of parasite infection with *Taenia solium*, *Giardia duodenalis*, *Ascaris spp*., *Trichinella spp.*, *Toxoplasma gondii*, and *Plasmodium malariae*, compared to general population. Other potentially involved infectious diseases are pneumonia, urinary tract infections, including pyelonephritis acquired during pregnancy, sepsis, legionellosis, syphilis, chlamydiosis, typhoid fever, diphtheria, retrovirus infections, as well as infection caused by microorganisms such as *Herpes virus* 1 and 2 (HSV1, HSV2), *Cytomegalovirus* (CMV), *Borna virus*, *Borrelia burgdorferi*, *Streptococcus spp*. (Strick 2004).[5] Among the infectious agents, *T. gondii* has received more attention for its localization in the Central Nervous System (CNS) during infection.

3. The role of *T.gondii* on etiopathogenesis of psychiatric disorders

3.1. Neurobiology studies

The mechanisms by which *T. gondii* could cause psychiatric symptoms are not fully known. As previously mentioned, both host and parasite factors should be taken into account (Table 1).

Insert Table 1

In general, both direct and indirect effects of *T. gondii* infection on the CNS must be considered. The former are due to parasite cysts in neurons, microglia and astrocytes, the latter are essentially due to three factors: (1) production of proteins homologous to aromatic aminoacid hydroxylase and D2R, with increase of DOPA synthesis and TRP degradation and decrease of serotonin synthesis (Henriquez et a. 2009);[9] (2) induction of endocannabinoids through the CB1R activity on basal ganglia, substantia nigra, globus pallidus, caudate nucleus, putamen (Melamede 2009);[10] (3) immune response. Over all, *T. gondii* is a strong stimulator of the immunity. After proliferation of tachyzoites during the acute stage, the parasite gives rise to tissue cysts and establishes a chronic infection. The delicate balance between host immunity and the parasite's evasion mechanisms of the immune response is the basis of the sub-clinical infection (Carruthers and Suzuki 2007).[6] Only when parasite and host factors are in balance, an asymptomatic chronic infection results. A key role in maintaining the latency of chronic infection is carried out mainly by interferon-gamma (IFN-γ), interleukin 12 (IL-12), and tumor necrosis factor-alpha (TNF-α) produced by macrophages (Møs),

dendritic cells (DCs), and natural killer cells (NK cells), activated by *T. gondii* itself. They have a key role in controlling the parasite growth, induction of T helper 1 (Th1) cell expansion and development of cytotoxic CD8+ T cells which have an essential role in the development of tissue cysts. On the contrary, Th2 cytokines have been related to a down-regulation in Mø activation and, consequently, to a decreased ability of these cells in controlling the parasite growth. Type-2 cytokines such as IL-4, IL-10 and IL-13, are thought to have a role also in the control of the inflammatory response and in preventing a further progression of toxoplasmosis. All these mediators could be also induced by *T. gondii* directly in the brain. Thus, IFN-γ, IL-12, TNF-α, IL-4 and IL-10, together with IL-1 and IL-1ß, IL-2, IL-6, GM-CSF (Granulocyte Macrophage Colony-Stimulating Factor) and IL-17 and IL-23, are variably expressed by microglia cells, astrocytes, infiltrating CD4+ and CD8+ T cells (Henriquez et al. 2009).[9] Since these cytokines may influence mood and behaviour through their ability to modulate neurotransmission, the idea that latent infection is clinically asymptomatic should be reconsidered. As tachyzoites induce more intense inflammatory cytokine responses in host cells than do bradyzoites, proliferation of tachyzoites in the brain following cysts rupture could be related to the onset of schizophrenia (Carruthers and Suzuki 2007) [6] and other mental diseases. Indeed, a high total immunoglobulin (Ig) G level together with the absence or a low level of IgM, which is a key indicator of acute acquired infection, was clearly demonstrated in serological studies (Wang et al. 2006).[11] The above situation is found in the sera of patients with first-onset schizophrenia, who are not in the acute stage of infection. The main characteristics of patients with first-onset schizophrenia are: increased concentrations of anti-*T. gondii* IgG, increased levels of IL-6 and IL-1ß, lack of anti-*T. gondii* IgM. It is important to underline the role of IL-1ß and IFN-γ in the astrocytes activation that, as microglia cells activation, inhibits tachyzoite replication through production of high levels of nitric oxide (NO) (Peterson et al. 1993).[12]

Many neurobiological mechanisms are involved in the etiopathogenic link between *T. gondii* and schizophrenia: histopathological abnormalities (cysts, granulomatous reactions of perivascular areas, progressive deposition of necrotic material); involvement of the immune response with increased expression of cytokines that stimulate (TNF-α, IL-1) or inhibit (IL-10 and Transforming Growth Factor β, TGF-β) the inflammatory response and interfere with neuromodulatory processes, as well as development of a humoral and cell-mediated immune response that keeps infection with *T. gondii* in a state of latency; neuromodulatory changes involving alterations in the N-methyl D-aspartate (NMDA) receptor and in the concentration of molecules such as serotonin and dopamine (DOPA) that alter the locomotor activity, behavior, memory, learning and brain flood flow.

In general, neurological and psychic involvement is easily explained by the neurotrophic behavior of *T. gondii* (Zhu et al. 2007; Zhu 2009)[13,14] that acts on both neurons and glial cells, mainly at the

level of the astrocytes (Halonen et al. 1996; Cotter et al. 2001; Doyle and Deakin 2002).[15,16,17] In cerebral toxoplasmosis, especially in non immunocompetent patients, the neuropathological involvement is serious, sometimes showing acute necrotizing encephalitis and formation of glial nodules. Unfortunately, in most studies it was not possible to identify the protozoan in the brain (Conejero-Goldberg et al. 2003).[18] A recent study using a voxel-based-morphometry (VBM) of magnetic resonance imaging (MRI) shows that latent toxoplasmosis reduces grey matter volume in schizophrenic subjects, but not in the controls, bilaterally in the caudate, median cingulate, thalamus and occipital cortex and in the left cerebellar hemisphere, by both direct and indirect effects (Horacek et al. 2011).[19] In addition to a direct action on the brain tissue, antibodies (Abs) directed against self-antigens (self-Ags) or cytokine-mediated effects also seem to be implied. Specific receptors for cytokines are present in many brain areas. The presence of these receptors seems to confirm the hypothesis that cytokines have a direct influence on neuronal function. The most likely mechanism of action thought to be involved in schizophrenia is affecting neurotransmission in specific brain areas such as the limbic-thalamic-cortical circuit of DOPA, 5-hydroxytryptamine (5-HT), gamma-aminobutyric acid (GABA) and glutamate. Schizophrenic patients show abnormal levels of neurotransmitters, especially glutamate, GABA, and DOPA (Yolken et al. 2009).[20] Drugs that increase DOPA release such as amphetamines, may also induce psychotic symptoms in patients with psychiatric illness or trigger psychotic episodes in healthy subjects.

Imaging studies show an increased DOPA release in the limbic system, whereas anti-psychotic drugs seems to improve the positive symptoms of schizophrenia and schizophrenia spectrum disorders by blocking the D_2 subtype of the DOPA receptor (D_2R). Similarly, drugs such as ketamine and phenylciclidine which work as glutamate antagonistat the NMDA receptor, reproduce the positive as well as the negative and cognitive symptoms associated with schizophrenia. In addition, a growing number of studies have shown that infection with *T. gondii* involves the synthesis of DOPA and other neurotransmitters. Indeed, this parasite possesses genes encoding proteins homologous to the tyrosine-hydroxylase (TH) and to the D_2R (Henriquez et al. 2009; Zhu 2009).[9,14]

3.2. The role of dopamine (DOPA)

DOPA is one of the most important biological molecules produced by the body. The enzyme TH which catalyzes the formation of L-tyrosine to L-dihydroxyphenylalaline (L-DOPA), is the rate limiting factor in the synthesis of DOPA within the brain. It is induced during the production of the bradyzoites (Gaskell et al. 2009).[21] L-DOPA is then converted to DOPA by the enzyme DOPA decarboxylase. Studies on animal models suggest that *T. gondii*, like other infectious agents, may

interfere with the synthetic pathways of DOPA in specific areas of the host CNS. In particular, Stibbs (1985) first suggested the hypothesis of a link between *T. gondii* and this molecule.[22]

In a study on mice infected with the C56 strain of *T. gondii*, mice brains were analyzed by neurochemical analyses and compared to control mice. No changes in serotonin or 5-hydroxy-3-indole acetic acid (5-HIAA) level were found in infected animals. Norepinephrine (NE) level were found a 28% lower in mice with acute infections compared to control, but remained unchanged in chronic infections, whereas homovanilic acid, the main metabolite of DOPA, showed a 40% increase in acute but not in chronic infection. DOPA levels were not altered in acute infections, but were higher in mice with chronic infection than controls (Stibbs 1985).[22]

At present, it is not clear whether these alterations are directly induced by the parasite on the brain or they are the result of unknown complex neuro-immuno-endocrine interactions. In any case, *Toxoplasma* appears to cause abnormalities in catecholamine metabolism. These abnormalities could be a factor contributing to psychological, behavioral and motor changes found in experimentally infected rodents. Similar studies were carried out by Webster (Webster 2001, 2007; Webster et al. 2006).[23,24,25]

Huber *et al*. (2007)[26] suggested that parasitic infection might contribute to the increase of the DOPA level in mice brain. Flegr (Flegr et al. 1996; Flegr 2007) [27,28] and, more recently, Zhu (2009)[14] hypothesized that DOPA is the missing link between schizophrenia and toxoplasmosis. The first explained the psycho-behavioral patterns found in animals and humans infected with *T. gondii* as due to alterations in the levels of cytokines (mainly IL-2) and DOPA (particularly in mesocortical area). Zhu (2009)[14] focused his attention on the release of DOPA in the *nucleus accumbens* of individuals with latent toxoplasmosis. Indeed, this DOPA release in this brain area could damage the brain region of the fornix because of the activation of retro-hyppocampal region. As consequence, the development of psychosis could occur.

3.3. The role of tryptophan (TRP) and the kynurenine pathway (KP) in psychiatric syndroms

Many studies have evaluated the TRP involvement in the onset of psychotic syndroms. TRP is an essential amino acid necessary not only as a component of proteins, but also as a precursor of neurochemical mediators such as serotonin and melatonin. In particular, Hinze-Selch *et al*. (2007) [29] observed an interaction of *T. gondii* with effectors of the immune system (IS), including IFN-γ and indoleamine 2,3-dioxygenase (IDO), possibly involved in the T-cell/IFN-γ-dependent degradation of TRP that is needed for the parasite replication. The IS seems to have elaborated a mechanism to degrade TRP to N-formylkynurenine in order to interfere with the growth and survival of the parasite (Fig. 1).

Insert Fig. 1

The Hinze-Selch study (2007) [29] showed that administration of L-kynurenine (L-KIN) induces a depressive-like behavior in mice. Kynurenic acid (KYNA) is a L-TRP catabolite likely involved in the development of schizophrenia, which has received attention during years (Schwarcz and Hunter 2007; Dion 2009).[30,31] The synthesis of KYNA begins with the opening of the ring of TRP by the enzyme IDO and/or tryptophan 2,3-dioxygenase (TDO). The reaction product of these two enzymes, L-KYN, is converted irreversibly into KYNA. In the brain, this process takes place almost exclusively in astrocytes, which then rapidly release newly produced KYNA into the extracellular environment, where this metabolite can influence surrounding neurons (Schwarcz and Hunter 2007).[30] It is note-worthy, that the mRNA for TDO is elevated in the brain of individuals with schizophrenia and a concomitant increased density of TDO positive astroglial cells in the patient's white matter has been observed (Miller et al. 2004).[32] Since the TDO is an enzyme responsible for the biosynthesis of KYNA, this could lead to an increased level of KYNA in the brain of patients with psychiatric disorders.

Infection with *T. gondii* in the CNS is accompanied, in direct response to the parasite or, more likely, in response to an inflammatory reaction, to a strong activation of glial cells, particularly astrocytes, resulting in a high synthesis of KYNA. Even a moderate induction of the concentrations of endogenous KYNA in the brain is able to inhibit the NMDA receptors for glutamate and the α7-nicotinic acid (α7nAch) receptors for acetylcholine. This effect is increased in people with high activity of the enzyme TDO in the brain, i.e. in individuals with genetic predisposition to the development of schizophrenia. In schizophrenic patients, in fact, the level of KYNA is significantly higher than in controls. As a result of the inhibitory activity exerted by KYNA on NMDA or α7nAch receptors, a reduction in glutamatergic and nicotinergic neurotransmission can be observed, which is believed to play an important role in the cognitive and sensory impairments observed in schizophrenia.

The increase of KYNA levels probably involves also the IS. It is interesting to note that in schizophrenic patients transcripts of TDO are higher as a result of the Th2 response, which is abnormally activated in these subjects. In turn, infection with *T. gondii* is predominantly associated during the acute phase to a Th1 response and to a low Th2 response in the chronic phase. Therefore, an increase in Th1-type cytokines in patients with psychiatric symptoms may also be induced by the pro-inflammatory response during infection with *Toxoplasma*. It is thus possible that an altered balance between Th1 and Th2 in both directions, may contribute to the production of KYNA and to the development of schizophrenia (Schwarcz et al. 2001).[33]

The early sensitization of the IS, after exposure to infectious agents, may contribute to the risk of developing schizophrenia. This would generate the imbalance of the immune response found in these patients. The IS involvement could lead to the accumulation of KYNA in the CNS, thus inducing cognitive dysfunction and psychotic symptoms due to its antagonistic action against the NMDA receptor (Schwarcz et al. 2001). [33] The intense pro-inflammatory immune response induced by *Toxoplasma* could be self-defeating, since the overproduced cytokines decrease the neurotrophic support by inducing neuronal apoptosis and glial damage (Hinze-Selch et al. 2007).[29]

On this basis, the elucidation of the interaction between the IS and the TRP metabolism in the onset of schizophrenia following *T. gondii* exposure is an important goal, as well as the role of the hypotalamic-pituitary-adrenal (HPA) axis. Many cytokines, including IL-1β, IL-6 and TNF-α, produced during infection with *T. gondii* act on the HPA axis. As a consequence, the infection in peripheral tissues may contribute to immune-mediated events in the brain. However, since this parasite is present in the brain, it might also directly induce the production of immunological mediators.

Several studies have shown that in the brain of infected mice several transcripts of cytokines are induced, including IL-1β, IL-6 and TNF-α, that stimulate prostaglandin (PG) E_2or directly act on the hypothalamus. Although stimulation of the HPA axis has been linked to behavioral changes, no mechanism has yet been found. It is possible that the activation of the HPA axis may be indicative of an immunological activity affecting the brain without directly causing behavioral changes. The final products of the HPA axis are glucocorticoids, which act on the HPA axis with a feed-back mechanism by interfering with many other systems, i.e. by reducing the neuroplasticity and cellular resistance. This action may lead to an imbalance between glucocorticoids and mineralocorticoids and their high-density receptors as well to neuronal injury. In addition, the higher activity of HPA axis induces the involvement of the IS with activation of Møs, DCs and T cells and production of pro-inflammatory cytokines. In some cases, antagonists of glucocorticoids, such as RU486 and ketoconazole, have been shown to function as antidepressants. Moreover, glucocorticoids affect the TRP metabolism by increasing the levels of TDO in the liver, and the level of IDO in immune cells. Therefore, alteration of TRP metabolism, neuroendocrine deregulation through the HPA axis, and interference with the IS, appear closely related (Henriquez et al. 2009) (Fig. 2).[9]

Insert Fig. 2

3.4. Serological studies

According to the infectious theory of psychiatric disorder pathogenesis, it should be relevant to demonstrate an increased rate of anti-*T. gondii* Abs in patients with neuropsychiatric disorders

compared to healthy individuals. Interestingly, most of the serological studies have been conducted in China where, until recently, the keeping of cats as pets has been uncommon and where the prevalence of *T. gondii* Abs in the general population is still quite low (Remington et al. 2001).[34] In such a situation, the higher prevalence of seropositivity in patients with schizophrenia may be more highlighted. By contrast, in a EU countries like Ireland, where cats are ubiquitous and where the prevalence of *T. gondii* antibodies in the general population is known to be high (Stanford et al. 1990),[35] a modest increase in the seroprevalence among patients with schizophrenia may be less apparent (Zhu et al. 2003, 2007; Torrey et al. 2007; Yolken et al. 2009; Zhu 2009).[36,13,37,20,14]

After the first "serological study" performed by Kozar (1953) in Poland,[38] several other studies have followed. In particular, a meta-analysis by Torrey (Torrey et al. 2007) [37] on data from more than twenty-three studies performed over the period 1953-2005 in seventeen different Countries from Asia, Europe, North and South America, included 3,873 patients with schizophrenia and 7,046 controls. This study evaluated the prevalence of Abs to *T. gondii* detected by serological analysis of sera samples using different diagnostic tests, in individuals with schizophrenia. An OR of 2.73 (95% CI 2.10 to 3.6, Chi-square = 263, df = 1, $p < 0.000001$) was found, indicating a moderate association between infection with *T. gondii* and schizophrenia, substantially higher than the OR found in most meta-analyses on specific genes or environmental factors (i.e. obstetric complications, OR ≈ 2) associated with risk of schizophrenia. Since 2005, many other studies provided evidence consistent with an association between the prevalence of Abs to *T. gondii* and schizophrenia, as well as other psychiatric disorders (Fig. 3).

Insert Fig. 3

Recently, there has been an increasing interest on the comparison of *T. gondii* seropositivity between patients with chronic and acute schizophrenia. Whether *T. gondii* infection is specifically relatable to first-onset schizophrenia (Yolken et al. 2001; Wang et al. 2006; Hinze-Selch et al. 2007) [48,11,29] or rather to chronic schizophrenia has not yet been clarified (Delgado 1979; Delgado and Garcia 1979; Alvarado-Esquivel et al. 2006).[49,50,40] Most studies oriented towards the first hypothesis. Hinze-Selch (2007)[29] postulated that the lower prevalence of IgG Abs detected in patients with chronic schizophrenia may be due to treatment of these patients with immunomodulating antipsychotic drugs (see later). However, since high rates of Abs can be observed both in first-onset patients and patients with chronic disease, it is also possible that the persistence of high Ab titers may favor the chronic evolution of the illness.

Wang (Wang et al. 2006, 2008),[11,51] analyzing the serological status of schizophrenic patients, found clinical differences between individuals with *T. gondii* infection and *Toxoplasma*-free

individuals. These differences could be explained by considering the different clinical patterns of psychiatric disorder during latent infection in asymptomatic subjects. It should be noted, however, that the disease itself could facilitate the exposure to the parasite. Patients with schizophrenia showing "positive symptoms" or agitation are exposed, to a greater extent, to various infectious agents, including *T. gondii*. On the other hand, patients with "negative symptoms", being inactive and less interested in the personal care are at risk of infection, mainly by ingestion of infected food. For this reason, both *Toxoplasma*- seronegative and -seropositive schizophrenic patients show an increased risk of being infected because of their abnormal behavior (Table 2).

Insert Table 2

"Positive symptoms" (also known as "psychotic symptoms") and agitation reflect an excess or distortion of normal functions and are mainly present during the acute stage of schizophrenia. These symptoms can be pharmacologically treated with anti-psychotic drugs and mood stabilizers (haloperidol, risperidone, fluphenazine and valproic acid) which also act against *T. gondii* infection, *in vitro*. "Negative symptoms" refer to a diminishment or absence of characteristics of normal function. They may appear months or years before "positive symptoms".

On the whole, these studies linked infection with *T. gondii* in adults to schizophrenia. Nonetheless, a number of unanswered questions still remain on serological evidence of *Toxoplasma* infection, as well as in the interpretations of results: a) lack of standardization of methods, in particular the individuation of cut-off values; b) bias in selection of individuals enrolled in the study, small sample sizes; c) assessment of the antibody pattern, with no direct isolation of the infective agents or their DNA in body fluids of infected individuals; d) lack of anti-*Toxoplasma* Abs in many patients with schizophrenia, which could indicate a lack of association between *T. gondii* infection and schizophrenic disease; e) poor predictive value of seropositivity to *Toxoplasma* against schizophrenia; most seropositive individuals do not show schizophrenia, whereas only some individuals after exposure to the infective agent develop the disease. Other factors, including host genetic susceptibility, different *T. gondii* genotypes, different ways of infection, the stage of infection may alter the outcome of infection (Henriquez et al. 2009);[9] f) difficulty in dating the infection.

The assessment of the timing of infection is very important to understand whether *T. gondii* Abs are present before the onset of psychiatric illness. This would clarify whether the infection by this parasite in schizophrenic patients is the cause of the disorder or rather is the result of a "at risk" behavior in psychiatric patients. This hypothesis has been advanced by several authors (Zhu et al. 2003; Alvarado-Esquivel et al. 2006, Wang et al. 2006, 2008; Zhu et al. 2007; Zhu

2009).[36,40,11,51,13,14] A Spanish study (Garrido and Redondo 1968)[52] showed that the higher rate of Ab positivity to *T. gondii* found in inpatients with schizophrenia is not dependent on psychiatric disorders but on their exposure to the parasite while working in the hospital gardens contaminated with feces of infected cats. In addition, a further risk of exposure in institutionalized psychiatric inpatients was through contaminated food at hospital cafeteria. These considerations, however, cannot explain the cases of first-episode schizophrenia. In addition, the possibility that the infection occurs as a result of behavioral changes is not consistent with studies showing an increased risk of schizophrenia in the offspring of mothers infected during pregnancy (Brown et al. 2005; Brown 2006, 2008, 2009; Mortensen et al. 2007a; Mortensen et al. 2007b; Brown and Derkits 2010; Brown and Patterson 2011).[53,54,55,56,57,58,59,60] Some studies have partially avoided problems due to timing of infection by taking into account serological samples prior to onset of psychiatric symptoms.

In a study by Niebuhr *et al*. (2008),[61] a cohort of U.S. military personnel was considered. For these subjects, serum samples were obtained at military accession and every two years. A clinical evaluation of personnel excluding psychiatric disease was available. In this study, the time range from serum sample collection to the date of diagnosis varied from 11 years before to 1 year after diagnosis. Healthy subjects were matched in a 3:1 ratio with patients (N=180 individuals) with a diagnosis of schizophrenia and analyzed by evaluating the rate of IgG Abs against *T. gondii* and other infectious agents. Psychiatric patients had a higher seropositivity for *T. gondii* (hazard ratio = 1.24, p = 0.01) compared to controls. However, a further analysis showed slightly increased rates of anti-*Toxoplasma* IgG Abs two or three years before the diagnosis of schizofrenia Concentrations significantly increased 6 months preceding the onset of the diseases and remained high even after the diagnosis. The question of whether changes in lifestyle consequent to schizophrenia may or may not have contributed to the exposure to the parasite still remains unresolved. Moreover, no increased risk of schizophrenia was observed at other time intervals before diagnosis.

In another study, (Amminger et al. 2007)[62] the presence of anti-*T. gondii* Abs was evaluated in 105 young individuals at risk for developing schizophrenia because of the presence of behavioral changes at an early age. Eighteen of these patients were positive to anti-*Toxoplasma* Abs. Seropositivity correlated with the presence of positive psychotic symptoms and, in general, with more severe psychiatric disorders. In this context, a special approach to substantiate a link between *T. gondii* infection and mental diseases are studies of prenatal exposure to *T. gondii* and its effects on neurological development.

3.5. Studies on prenatal exposure to *T. gondii* as risk factor for the onset of psychiatric disorders and schizophrenia in adult individuals: the neurodevelopmental theory

Prenatal exposure to *T. gondii* is a risk factor for schizophrenia or schizophrenia-related diseases (Brown et al. 2005; Brown 2006, 2008, 2009; Mortensen et al. 2007a; Mortensen et al. 2007b; Brown and Derkits 2010; Brown and Patterson 2011).[53,54,55,56,57,58,59,60] According to the neurodevelopmental theory, the stage of highest risk for exposure to infection seems to be the late first or early second trimester (Fatemi SH 2005),[63] when the mesolimbic system, the thalamus and the entorhinal cortex are rapidly growing and nearly all the neurons of the cerebral cortex, have been generated but have not yet migrated to the target structures nor arranged and connected to form synapses. Alterations at this stage of active development can lead to an inappropriate and incomplete migration, an altered position, a reduction or a change in the connections, with consequent neurodevelopmental impairment. In addition to the production and migration from the depths to the surface of neurons, occurring in prenatal period, the differentiation and maturation of glial progenitors continue for an extended period after birth, throughout childhood (Stiles and Jernigan 2010).[64] Gray matter tissue, which consists of all the neurons and other supporting cell-types, first increases in volume in childhood and after peaking around puberty, starts to decrease (Paus 2005).[65] Indeed, adolescent period represents another critical step because of the possibility of an excessive elimination of synapses and loss of plasticity. This erroneous development during 2 critical time points (early brain development and adolescence) has been well explained by the ‘‘2-hit’’ model proposed by Keshavan (Keshavan 1999; Keshavan and Hogarty, 1999).[66,67] Anomalies during these stages would not immediately cause symptoms of the disease, becoming apparent after a latency ranging from one to three decades. Neurodevelopment of the hippocampus area, prefrontal cortex, and of dopaminergic neurons of the segmental ventral midbrain plays a key role in physiological and pathological interactions, since genetic and/or epigenetic early lesions of the hippocampus, interacting with the neurodevelopment of the dorsolateral prefrontal cortex, may lead to the alteration of several neurobiological phenomena, including DOPA dysregulation and impaired working memory. Rodent models have confirmed these considerations (Lipska and Weinberger 2000; Lipska et al 2002).[68,69] Several authors have dealt with research on the neurodevelopmental theory. A special contribution was provided by Brown who has recently reviewed this topic (Brown and Derkits 2010).[59]

In 2005, Brown (Brown et al. 2005)[53] reported data of a study aimed at assessing the relationship between maternal *Toxoplasma* Abs and risk of schizophrenia in a large birth cohort born between 1959 and 1967 in California. Maternal serum specimens from pregnancies giving rise to 63 cases of schizophrenia and other schizophrenia spectrum disorders and 123 matched (2:1) comparison subjects were taken. Results showed a higher seropositivity for *Toxoplasma* in offspring in cases compared to controls ($p = 0.051$; OR = 2.61, range 1.00 to 6.82). The same cohort was the subject of a long-term follow-up to further assess the neuropsychological and executive function.

Individuals exposed to *in utero* infection exhibited a lower performance in all tests showing particularly executive dysfunction, impaired reasoning, impaired problem-solving and an inability to use appropriate contextual information to formulate and implement adaptive behaviors. All of these changes, would result from structural and functional alterations in the prefrontal cortex, which occurred in pre-natal period (Brown 2009).[56]

Mortensen (Mortensen et al. 2007b)[58] was very interested in determining the effects of prenatal exposure to *Toxoplasma* on children neurodevelopment. This Author evaluated a cohort of children born in Denmark since 1981 and analyzed blood samples collected during the first days of life for the presence of anti-*Toxoplasma* IgM and IgG, as part of a screening program to detect phenylketonuria (PKU). In this study, the serological samples of 71 subjects who developed early-onset schizophrenia (onset before 18 years), 342 individuals with schizophrenia spectrum or mood disorders and 684 controls were examined. No significant association with schizophrenia spectrum or mood disorders was found in control subjects, whereas among patients with schizophrenia, there were increased levels of anti-*T. gondii* IgG ($p = 0.045$, OR = 1.79, range 1.01 to 3.15) compared to controls. It is note-worthy that in these studies no increase in IgM Ab rate was detected, thus suggesting that either in mothers or in children there was no acute infection. Several Authors (Mortensen et al. 2007a, 2007b; Clarke et al. 2009; Brown and Derkits 2010; Brown and Patterson 2011),[57,58,70,59,60] have sought possible explanations for the association between pre-natal infection with *T. gondii* and development of schizophrenia by focusing on both the direct effect of infection on the fetus and the effect mediated by cytokines and Abs produced by mothers after infection. These nonspecific reactions, immediately activated after infection, would both be involved in fetal and placental damage by acting against the fetal-placental unit and resulting in impaired fetal development of the brain that represents a potential risk factor for the onset of schizophrenia in adulthood.

An important role seems to be played by maternal IgG induced by *T. gondii* during a latent infection, which would have a direct effect on the fetus, similarly to what occurs on the CNS in paraneoplastic manifestations, in which the symptoms, including psychiatric manifestations, would be related to the levels of circulating tumor-specific Abs. It has been shown that Abs *versus* self-ags can interact with cognitive and behavioral manifestations, being essential in the pathogenesis of the alterations of the CNS found in diseases such as Systemic Lupus Erythematosus (SLE), partly due to the binding of Abs with the NMDA receptor. These observations could, by analogy, suggest a possible mechanism by which anti-*Toxoplasma* IgG interact in the brain in the development of schizophrenia. In particular, since the parasitic infection contracted *in utero* leads to a decreased expression of NMDA receptors, which are essential factors for normal brain development, and to increased levels of DOPA and homovanillic acid, it could be argued that neurotransmitter

mechanisms may act through the reactivation of maternal infection. It is also possible that the presence of maternal Abs against *T. gondii* indicate an increased sensitivity to infection by other infectious agents which could interact with this protozoa in determining brain alterations. The presence of anti-*Toxoplasma* IgG in mothers might therefore reflects a "at risk" lifestyle that could increase the risk of exposure of children after birth. It is likely that women with anti-*Toxoplasma* Abs have cats or use to eat undercooked meat.

In any case, maternal infection during the gestational period increases the risk of psychiatric disorders. Therefore, it should be prevented to effectively avoid induction of neurobehavioral disorders and psychiatric illnesses.

The neurodevelopmental theory does not take into account only infections occurring in prenatal period, but also involves interfering factors during childhood. Generally, the infection contracted in childhood is not well documented and rarely a follow-up of children at risk for schizophrenia is made. Some researchers tried to overcome these limitations. In particular, Dalman *et al*. (2008)[71] examined a cohort of 1.2 million children born between the early 70s and mid 80s in Sweden. In his study, Dalman consulted national registries on Hospital admissions for CNS infections of children aged 0-12 years and registries relating to psychiatric hospitalization up to 2002 of the same individuals during adulthood. It is likely that many cases of mild meningitis/encephalitis underwent improper diagnosis. Since this study describes the risk associated with register-based CNS infections requiring hospital treatment, mild cases may also go unnoticed. The study also shows that viral, bacterial or parasitic CNS infections during childhood could be associated with development of schizophrenia and nonaffective psychosis in later life.

Both prenatal and perinatal exposure to *Toxoplasma* or exposure during childhood, play an important role in the development of behavioral and neuropsychiatric disorders, probably due to the interaction of the pathogen in a particularly vulnerable period of neurobiological development. Some Authors investigated for a possible link between *T. gondii* genotypes and risk of psychosis, showing a greater influence of the type I genotype in increasing the risk of this disease. Xiao *et al*. (2009)[8] developed an enzyme immunoassay (EIA) using polymorphic polypeptides specific for the three genotypes of the parasite and derived from dense granules (GRA5, GRA6 and GRA7) to determine whether the parasite genotype is a risk factor for disease. Type-specific Abs in the serum of 219 pregnant women whose children later developed schizophrenia and affective disorders in adult life were detected. Results were compared to data obtained by 618 control mothers. The offspring of mothers with a serological pattern consistent with type I *Toxoplasma* infection was found to have a significantly increased risk for developing psychosis in comparison with control mothers (OR = 1.94, with 95% CI 1 0.08 to 3.46, p = 0.03). The risk is particularly high for

"affective" psychosis (OR = 5.24, with 95% CI 1.67 to 16.5, p = 0.005). In contrast, no association was found between maternal Abs against different genotypes and risk of psychosis in the offspring.

3.6. Pharmacological studies

Based on neurobiological and serological evidence of a possible link between *T. gondii* and neuropsychiatric disorders, many pharmacological studies were carried out aimed at showing that treatment with anti-*Toxoplasma* drugs may lead to an improvement of neuropsychiatric symptoms (Webster et al. 2006; D'Angelo et al. 2009)[25,72] and that some antipsychotic drugs and mood-stabilizing agents can inhibit the replication of tachyzoites (Pezzella et al. 1997; Jones-Brando et al. 2003; Skallovà et al. 2006; Webster et al. 2006; Torrey and Yolken 2007; Treuer et al. 2007; Goodwin et al. 2008, 2011; Zhu 2009) (Table 3).[73,74,75,25,76,77,78,79,14]

Insert Table 3

There are also some negative findings, especially about anti-*Toxoplasma* drugs and their potential positive effects on schizophrenia symptoms (Dickerson et al. 2009; Shibre et al. 2010).[80,81] The interpretation of data from these studies is not always easy. First of all, these studies are not able to detect any effect of intervention; in addition, severe conditions of patients affected by chronic disorders hamper the possibility to detect any additional modest pharmacological effect; finally, the effect of *T. gondii* is likely to be irreversible (Fekadu et al. 2010).[82]

Nevertheless, behavior changes related to an increased DOPA level are observed following infection with *T. gondii.* These alterations are also induced by several drugs administered to seronegative mice. The mechanism of action appears to be related to alterations of the neurotransmitter pathways. Many drugs inhibit *Toxoplasma* replication and host brain cells invasion. Anti-*Toxoplasma* properties can be correlated with the inhibitory effect on ion calcium making tachyzoites able to invade cells. Tachyzoite diffusion is inhibited by agents that block calcium channels and by calmodulin antagonists (Pezzella et al. 1997; Pezzella-D'Alessandro et al. 2001).[73,83]

In patients with acute schizophrenia, higher levels of Th1-type cytokines are also observed. Cytokines level go back normal values after administration of antipsychotic drugs. Based on these observations, the anti-*Toxoplasma* effect of anti-psychiatric drugs should be taken into account, as well as anti-psychotic potential effects of anti-infective drugs in order to achieve better therapeutic applications in the treatment of psychiatric diseases

3.7. Epidemiological studies

Nonspecific pathogenic aspects should be considered in epidemiologic studies linking schizophrenia to *Toxoplasma* disease (Torrey and Yolken 2007; Yolken et al. 2009).[76,20] There are several areas of similarity between toxoplasmosis and schizophrenia as well as areas in which epidemiological aspects are dissimilar (Table 4).

Insert Table 4

3.8. Behavioral studies

Research on behavioral and cognitive changes induced by *Toxoplasma* were derived from *in vivo* studies on animals. The first observations showing a worsening of learning capacity and memory of *Toxoplasma*-infected laboratory rodents go back to the '70s (Witting 1979; Piekarski 1981).[86,87] Later, different studies (Webster 2001, 2007; Webster et al. 2006)[23,24,25] have underlined that mice infected with *T. gondii* were more active than controls, especially with regard to the exploration of new environments, and less phobic against cat urine than controls while the response to urine of animals other than predators, such as rabbits, is not altered by infection with *Toxoplasma*. This attitude increased the risk of predation by cats which, however, are not attracted by mice with reduced activity. Several investigators studied the ability of the parasite in manipulating host behavior to facilitate the completion of its life cycle and propagation. Vyas *et al*. (Vyas et al. 2007; Vyas and Sapolsky 2010),[88,89] in their studies, showed that infection with *T. gondii* not only blocks the innate aversion of rats and mice for cat urine, but even converted the aversion to feline odors into attraction to the pheromones. Flegr, in his first works conducted on animal models, showed that infection with *T. gondii* is likely to induce behavioral changes by acting on the dopaminergic system. These alterations are supposed to occur also in humans (Table 5).

Insert Table 5

Flegr was one of the Authors who most dealt with the effects of infection by *T. gondii* on human personality and behavior. Using personality tests and questionnaires of evaluation, such as the Cattell's 16-factor personality questionnaire (16PF) and the Cloninger's Temperament and Character Inventory personality test (TCI), he studied differences in personality factors in *Toxoplasma*-positive and *Toxoplasma*-negative subjects. Infected individuals showed changes in personality profile, in particular in one dimension of temperament, namely, Novelty Seeking (NS). NS has been suggested to be related to dopaminergic activity and it consists of the following four subscales: Exploratory excitability (NS1), Impulsiveness (NS2), Extravagance (NS3), Disorderliness (NS4). As a consequence, NS is strongly related to risk behavior, such as drug addiction, extravagance,

impulsiveness, and lack of control. From these studies, gender differences have emerged. Infected men appeared more likely to disregard rules and were more expedient, suspicious, jealous, and dogmatic, compared to uninfected men. On the contrary, women were more warm hearted, outgoing, conscientious, persistent, and moralistic and with higher warmth and higher superego strength. Males and females showed also differences in self-control tests and suspiciousness. In addition, both men and women had significantly higher apprehension, compared with the uninfected controls.

These results look more a curiosity than a matter of scientific and medical importance and should be replicated in other populations as well as evaluated by other methods. Many authors also wonder whether the latent infection with *Toxoplasma* may affect cross-cultural differences. An important point to be considered, however, is the difficulty in determining whether the observed correlations are due to infection with the protozoan or whether certain personality characteristics are more susceptible to exposure to *T. gondii*. Flegr hypothesized that at the basis of these psycho-behavioral aspects there were mechanisms involving the DOPA pathway as well as mechanisms involving steroid hormones that are increased in individuals infected with *Toxoplasma*. This could lead a reduction in host cellular immunity resulting in an increased risk of infection and/or increase the chances of survival of the parasite in the body.

By using psychobiological questionnaires, Flegr found longer reaction time, increased exposure to risk factors, and increased hazard of traffic accidents in individuals infected with *T. gondii*. In particular, serum samples from 146 individuals involved in motor vehicle accidents as drivers or as pedestrians were analyzed and compared with 446 control sera randomly collected in the city of Prague. The difference in *Toxoplasma* seroprevalence in these two groups suggested a 2.65 times higher risk of being involved in road accidents in subjects infected with the parasite compared to uninfected controls ($\chi 2 = 21.45$, $p < 0.0001$) (Flegr et al. 2002).[97]

Yereli (Yereli et al. 2006),[98] in Turkey, replicated Flegr's results by measuring the titer of IgG and IgM Abs in 185 car drivers involved in traffic accidents and in 185 controls. The results showed a 24.3% positivity for IgG and a 3.2% positivity for IgM in the first group compared to a 6.5% of positivity for IgG and a 0.5% IgM positive in the control group ($p<0.05$). Again, it should be defined whether the infection with *T. gondii* is responsible for the observed behavioral changes or, rather, are the psychological and behavioral abnormalities to determine a higher risk of both exposure to traffic accidents and to infection.

In order to evaluate if exposure to *T. gondii* could be associated with predisposition to risk behavior and to major mortality rate, Dickerson (Dickerson et al. 2007)[99] studied a group of 358 (16.2%) schizophrenic patients with positivity for anti-*Toxoplasma* Abs, higher in females than in males (21.9% and 12.7%, respectively; $p<0.03$). These subjects were followed-up for a 5-years

period (from 1999 up to2004). It is estimated that individuals with schizophrenia have a 20% reduction in life expectancy compared to general population. However, the reason for untimely death are not known, even though some predisposing factors have been hypothesized, including cigarette smoking, obesity, hypertension, diabetes, drug and alcohol addiction. In general, these aptitudinal characteristics are commonly found in schizophrenic subjects, and although in recent years there has been a greater control of these risk factors, mortality among these patients is still increased. So far, there is no data related to a possible association between infection by specific infectious agents and risk of premature death in the patients with schizophrenia.

Dickerson's study focuses on this aspect, trying to understand whether there is an association between *Toxoplasma* infection and increasing mortality. Among schizophrenic subjects seropositive for *T. gondii*, a mortality rate of 8.6% was found, while mortality among subjects without serological evidence of infection was 1.7% ($\chi 2 = 8.6$, $p < 0.003$). Overall, the mortality rate was almost 5-fold in schizophrenic patients with seropositivity for *T. gondii* than in seronegative subjects. Dickerson examined the independent contribution given by seropositivity for *Toxoplasma* to mortality by analyzing demographic parameters such as age, race, sex, and clinical trials that may contribute to mortality in this selected population. For this study, Cox proportional hazard analysis was used. A positive association between seropositivity to *Toxoplasma* and death from natural causes (hazard ratio = 4.70; 95% CI 1.27 to 17.31, p = 0.020) was found, regardless of socio-demographic factors such as race, sex, education level, age at study entry, lenght of the disease, cigarette smoking, diabetes diagnosis at the time of initial assessment. In the Cox regression model, the level of education was considered a predictor of mortality: individuals with higher levels of education were, in fact, less likely to die of natural causes during the follow-up (hazard ratio = 0.57, 95% CI 0.60 to 0.99, *p* = 0.041). The reasons for this increase in mortality observed in individuals infected with *T. gondii* are not completely known. Studies on larger populations would also be important to determine the association between the *Toxoplasma* infection and other risk factors. Finally, there is a clear need to extend the research to other populations, in order to further define the relationship between infection and increased mortality.

Arling and Yolken (Arling et al. 2009)[100] investigated for a possible link between seropositivity for *T. gondii* and the suicide attempt, which certainly correlates with psycho-behavioral disorders. In particular, they compared three different groups (Group I: 99 patients with recurrent mood disorders with a history of attempted suicide, Group II: 119 patients with mood disorders without a history of attempted suicide, Group III: 39 healthy controls). The Ab rates were highest among psychiatric patients with a history of attempted suicide (p = 0.004) and a predictive association between seropositivity for *Toxoplasma* and history of attempted suicide was found (OR = 1.55; 95% CI 1.14 to 2.12, p = 0.006). Three other studies followed these considerations and linked the history of

suicide attempts with *T. gondii* seropositivity (Lester 2010; Yagmur et al. 2010).[101,102] The study led by Ling and colleagues (Ling et al. 2011) [103] is the most recent. The Authors suggest that a positive relationship between rates of infection with *T. gondii* and suicide is apparent in women of postmenopausal age ($p = 0.007$). Obviously, further investigations are needed.

The above studies show that several psychological and behavioral effects caused by *T. gondii* occur also in humans. It is conceivable that future research confirms in humans the "behavioral manipulation" hypothesis already demonstrated in animal models. Studies on primates living in Ivory Coast (Africa), where primates account for a large proportion of leopard's diet, seem to confirm this theory. These studies, that recorded the frequency with which monkeys and apes are eaten by large felines in Africa, revealed the predation pressure exerted by large felines on 8 different monkey and 1 chimpanzee species (Flegr 2007).[28] Sea Otters of California, following infection with *T. gondii* developed behavioral changes that make them easier prey for sharks that, like humans, are intermediate hosts of the parasite (Miller et al. 2002; Kreuder et al. 2003).[104,105] In favor of the behavioral theory (i.e. a change in behavior induced by *Toxoplasma*) in humans and animals there is also a recent study published by Da Silva and Langoni (2009).[106] It is possible that the observed behavioural changes are a consequence of the neuro-pathological or neuro-immunology effects induced by the presence of the parasite in the brain. The distributions of *T. gondii* cysts and histopathological lesions in the brains may explain numerous behavioral abnormalities observed in the chronically infected rodents (Berenreiterova´ et al. 2011).[107]

On the whole, behavioral studies seem to support the hypothesis of a link between infection with *T. gondii* and the onset of neuropsychiatric disorders. However, a number of questions remain unanswered, concerning the reason why many individuals with serological evidence of infection with *T. gondii* are asymptomatic, whereas only a small number of individuals manifest psychiatric disorders with behavioral changes. Possible factors involved are the genotype of the host, the virulence of the infecting agent, the timing of infection, the way of infection. It is also possible that *T. gondii* is one of the factors affecting brain development *in utero* or during childhood, thus inducing genetically susceptible individuals to develop psychosis. The clarification of these points would lead to the understanding of the role of *T. gondii* in human neuropsychiatric diseases as well as a key step for their prevention and for therapeutic treatment.

4. The role of *T.gondii* in the etiopathogenesis of Parkinson's disease

A distinction should be made based on the type of patients: Parkinson's disease (PD) patients with Acquired Immune Deficiency Syndrome (AIDS) seropositive for *T. gondii*, and immunocompetent PD patients seropositive for *T. gondii*.

It should be emphasized that the clinical evaluation of patients with AIDS is more complex, since it is necessary to discriminate between Human Immunodeficiency Virus (HIV)-related neuropsychiatric manifestations and manifestations associated with toxoplasmosis. In particular, as previously mentioned, it is known that extra-pyramidal disorders related to Parkinson's syndrome can be caused directly by the HIV. Nonetheless, it is well known that infection with *Toxoplasma* in HIV-positive patients can induce a marked brain involvement. A number of studies on HIV-positive patients have suggested a relationship between toxoplasmosis and PD, while only a study assessed a link between toxoplasmosis and PD in immunocompetent patients (Miman et al. 2010).[108]

In general, patients with HIV infection may present almost all types of movement disorders. Berger, in 1984, firstly reported involuntary movements in patients with AIDS (Berger et al. 1984).[109] Two years later, studies by Navia on 27 AIDS-patients with cerebral toxoplasmosis have followed (Navia et al. 1986).[110] To explain the PD symptoms in these patients several mechanisms have been hypothesized including the inhibition of the nigrostriatal dopaminergic pathways which cross the internal capsule, mechanical compression or destruction of the striatum or the *substantia nigra*, destruction of postsynaptic striatal neurons and cardiovascular transient diseases in the anterior choroidal artery.

MRI of the patients showed a lesion with ring enhancement in the right lenticular nucleus, which could account for the parkinsonian symptoms in the left side of the nucleus. In these patients, the anti-*Toxoplasma* therapy has been successful on parkinsonian symptoms, showing reduction and later disappearance of MRI lesions. Nath *et al*. (1987),[111] Noël *et al*. (1992),[112] Mirsattari *et al*. (1997)[113] and Hirose (2000),[114] also, studied HIV-positive patients with opportunistic infections by *T. gondii* with cerebral involvement. Recent studies were carried out by Maggi (2000) [115] and Murakami (Murakami et al. 2000) [116] on patients with AIDS and *Toxoplasma* infection who developed extrapyramidal disorder, choreoathetosis, dystonia, emiballismo, parkinsonism after formation of brain granulomatous lesions. In these subjects, PD develops only when the lesions involve the basal ganglia bilaterally.

The specific location of opportunistic lesions in direct and indirect striatal-pallid pathways, likely associated with HIV-related neurotoxicity, might contribute to clinical manifestations. A major study by Mattos (Mattos et al. 2002),[117] performed on 2,460 HIV-positive patients followed-up for a period of 14 years (1986-1999), related to the development of neurological disorders in 42.8% of patients and of the onset of involuntary movements in 2.7% of subjects. Motor disorders include parkinsonism (50%), hemichorea-hemiballism (21.4%), myoclonus (14.2%), painless legs moving toes (PMLT) (7.2%), hemidystonia (3.6%) and Holmes' tremor (3.6 %).

Probably, brain toxoplasmosis may be considered a potentially treatable complication of AIDS. Therefore, early diagnosis and treatment are important determinants (factors) in preventing

mortality and morbidity. In patients with AIDS, particularly in Countries with high prevalence of toxoplasmosis, the appearance of movement disorders may be the first event leading to the diagnosis of cerebral toxoplasmosis. Currently, cerebral toxoplasmosis should be considered in the differential diagnosis of symptomatic PD, especially when unusual features, such as the one-sidedness of the symptoms are present. In recent years, there has been a decrease in the cases of PD and other involuntary movements in patients HIV positive. This phenomenon may be related to the introduction of highly active anti-retroviral therapy (HAART) which resulted in a drop in the mortality rate for AIDS and the incidence of various opportunistic infections, including CMV disease, atypical mycobacterial infection, and toxoplasmosis. Taken together, these factors will result in a reduction of neurological complications of AIDS. In any case, the situation of patients with AIDS is extremely complex and it is difficult to determine the true etiology of any damage to the CNS. Damage can be, indeed, induced by opportunistic infections (toxoplasmosis, cryptococcosis, CMV infection, tuberculosis, progressive multifocal leukoencephalopathy), drugs, neoplastic lesions with mass effect, direct or indirect effect of HIV.

A different situation is present in patients without AIDS, in which *T. gondii* has been until now considered responsible for acute and latent infections, in most cases completely asymptomatic. Over the years, the dogma of the latent infection with *T. gondii* has been overcome. In particular, many of the above studies have assessed the prevalence of *Toxoplasma* infection in patients with schizophrenia and other serious psychiatric disorders. More recently, analyzing the pathophysiological basis of PD and alterations in neurotransmission pathways due to its involvement mainly at the level of the dopaminergic neurons, a likely interaction between *Toxoplasma* and PD has been suggested. To date, only two serologic studies supporting this hypothesis have been published (Celik et al. 2010; Miman et al. 2010).[118,108]

Miman's study considered 52 patients with PD and 40 healthy subjects. All of the patients underwent MRI before the study and their results were normal. Clinical course of PD group was as expected by the natural course of disease and none of the patients showed lymphoadenopathy. Clinical evaluation focused on the analysis of personal and family history and neurological and physical conditions of the participants. Patients with a history of neurological diseases, Parkinson-plus syndrome, head injury, substance abuse, schizophrenia, depression, epilepsy, migraine, brain surgery, previous encephalitis or meningitis, clinical evidence of immunodeficiency or other immunological alterations (diabetes mellitus, leukaemia, lymphoma or other malignancies), as well as a history of alcoholism were excluded from the study. Anti-*T. gondii* IgG and IgM Abs were measured by the micro-enzyme-linked immunosorbent assay (ELISA) technique. A significant difference in IgG positivity rate of the two groups (42.3% among patients and 22.5% among healthy controls, $p = 0.006$) was found.

In the Celik's study (Celik et al. 2010),[118] serum samples from 50 patients with PD and 50 controls were analyzed for the presence of anti-*Toxoplasma* IgG by Sabin-Feldman dye test (SFDT). The results of this study revealed *Toxoplasma* seropositivity rates of 50% in PD patients and of 40% in controls. No statistically significant difference was then detected supporting a link between PD and toxoplasmosis.

However, further studies involving greater number of patients are needed. It is likely that the degeneration of dopamine-producing neurons, together with the production of this neurotransmitter by *T. gondii* and tissue inflammation, can cause PD. Other studies are needed which investigate the action of drugs used in *Toxoplasma* infection therapy on the outcome of PD. A confirmation of the link between toxoplasmosis and PD would open new therapeutic perspectives for the cure of this widespread neurodegenerative disease.

5. Discussion

The interest in studying the role of *T. gondii* and other infectious agents in the etiology of some neuropsychiatric diseases has so far been limited for several reasons:

1) Lack of knowledge of the molecular biology of *T. gondii* and of the pathophysiological mechanisms of the parasitic disease; the protozoan genome sequencing has recently allowed a better knowledge of infection biology; the development of assays for Abs against specific proteins of the parasite have shown the existence of different strains with different pathogenicity. Numerous markers of pathogenicity have been studied, including the protein kinases specific for *T. gondii*;

2) Lack of knowledge on "evolutionary terms". Recently, infectious agents have been recognized to alter host behavior to increase its own survival and reproduction. *T. gondii* is an example of evolutionary adaptation. Several behavioral studies on animal models have been carried out;

3) Lack of knowledge of the neurobiology mechanisms by which *T. gondii* causes psychotic symptoms;

4) Further studies are needed on the microbial and human genomes for a better knowledge of neuropsychiatric disorders resulting from multiple genome interactions.

Despite these limitations, research on this topic has become prominent in the last decades. As stated by Yolken and Torrey[7] the idea that *T. gondii* may cause some neuropsychiatric disorders is still actual for a variety of reasons:

a) many studies have reported a higher prevalence of Abs to *T. gondii* in individuals with schizophrenia

b) psychotic symptoms are frequently observed in individuals with adult toxoplasmosis

c) epidemiological studies show many similarities between cerebral toxoplasmosis and schizophrenia

d) antipsychotic drugs known to be effective in schizophrenia also inhibit the parasite replication

e) infection with *T. gondii* has been shown to induce high levels of dopamine in experimentally infected animals; schizophrenia also induces an increase in the DOPA levels

f) a number of studies have shown that individuals with schizophrenia had higher frequency of cat contact during childhood, compared to controls.

Strain's parasite, timing and source of infection and genetic host factors represent potential links between infection with *T. gondii* and neuropsychiatric diseases. *T. gondii* has a strong tropism for the NCS, in which it is widely distributed, although with a preference for certain regions represented primarily by the cerebral hemispheres, followed by the basal ganglia, the cerebellum and the brainstem. In addition, this parasite affects both neurons and glial cells, due to both direct and mediated effects by Abs, cytokines and proteins encoded by genes of the parasite with homology to the tyrosine hydroxylase and to D_2R. In this way, the parasite may interfere with the synthesis and function of DOPA and DOPA-related neuronal signaling pathways. The particular way by which *T. gondii* interacts with CNS cells and dopaminergic and non-dopaminergic (i.e. serotoninergic) neurotransmission pathways, may in part explain the wide range of clinical manifestations in cerebral toxoplasmosis. In particular, the aspects mentioned above are also involved in schizophrenia and schizophrenia-spectrum disorders as well as in PD. In fact, schizophrenia involves both neurons and glia, affecting many areas of the brain. It is also a disease characterized by relevant neurotransmitter changes, particularly involving DOPA, glutamate and GABA. PD also causes several injuries of the CNS, most importantly a microscopic depigmentation in the *pars compacta* of the *locus niger*, which contains the cell bodies of dopaminergic neurons whose projections are directed to the *striatum*. Thus, the neuronal loss is a major point in evolution of PD, with important consequences on neurotransmitter pathways.

Recently some authors suggest a new hypothesis in the neurological field: "Could *Toxoplasma gondii* have any role in Alzheimer disease?" In a study, led on 34 patients with Alzheimer disease and 37 healthy individuals, a significant difference between the serum anti-*T. gondii* IgG levels was found (44.1% and 24.3%, respectively) (Kusbeci et al. 2011).[119] Neuroinflammatory mechanisms might contribute to the cascade of events leading to neuronal degeneration. If confirmed, a positive correlation between toxoplasmosis and Alzheimer disease may lead to new approaches for management.

As a consequence of the great number of works based on this matter, the hypothesis based on pathophysiological relationships between *T. gondii* infection and development of psychiatric disturbances, such as schizophrenia, and neurological disorders, such as PD or even Alzheimer's disease, are in progress and become always more strong.

6. Conclusions

Over the years, research has identified *T. gondii* as a potential factor involved in the interaction among psychiatric vulnerability, genetic background, immunomodulation and neurotransmission systems. However, the etiopathogenetic association between this parasitic infection and development of some psychiatric illnesses and behavioral disorders such as schizophrenia, or neurological disorders such as PD, is still much debated. In any case, further studies in larger cohorts of patients with more rigorous method, the improvement of statistical method, and the ability to replicate results in distinct populations are required. Of course, we are just at a full speculative level. However, if future research will confirm the potential association between *T. gondii* infection and schizophrenia and Parkinson's disease development, new perspectives in preventive and therapeutic strategies for these two highly common neuropsychiatric disorders would open up. It is therefore important that studies in this area go forward because, as Bill Hutchinson used to say: "*Any organism that shares our brain with us is worthy of study*" (Ferguson 2009).[120]

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Figure Legends

Fig. 1. Tryptophan (TRP) metabolic ways, increased TRP degradation and consequent tachyzoites replication inhibition. Different responses such as astrocytes, immune system (IS) and Hypothalamic-Pituitary-Adrenal (HPA) axis activation, induced in the host by *T. gondii* infection, determinate an enzymatic regulation of indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO) levels, which are key elements in TRP degradation. In particular, production of IDO is induced, in the immune cells, through interferon-gamma (IFN- γ) dependent mechanisms, while TDO is mostly produced in the liver by glucocorticoids, following HPA axis stimulation. Glucocorticoids seem to increase the induction of IDO in astrocytes following exposure to IFN-γ. As a consequence, the immune activity induced by IFN-γ and by HPA axis, may reduce the concentration of TRP. Degradation products of TRP accumulated through the kynurenine pathways (KP) may result in an incresed dopaminergic tone. Host defense system may induce a lack of serotonin and an increase of the dopaminergic activity. This action could be at the basis of depressive and psychotic syndromes. In addition, the lack of enzyme induces catabolites production such as 3-hydrossikynurenine, urenine and antranilic, kynurenic, xanthurenic and quinolinic acids (QUIN). Some catabolites have been shown to alter neurons and neuron activity. The QA is an antagonist of the N-methyl-D-aspartate (NMDA) receptor. Like 3-hydrossikynurenin, it may cause neuronal death by involving O_2 reactive species, as well as epilepsy, convulsions and muscle cramps.

Fig. 2. Interaction between endocrine system, immune system (IS), neurotransmitters and neuromodulating pathways in the Central Nervous System (CNS). HPA axis, Hypothalamic-Pituitary-Adrenal axis; CRF, corticotropin-releasing factor; ACTH, adrenocorticotropic hormone; B-end, β-endorphin.

Fig. 3. IgG seropositivity against *T. gondii* among schizophrenic patients and control subjects

Figure

Fig. 1.

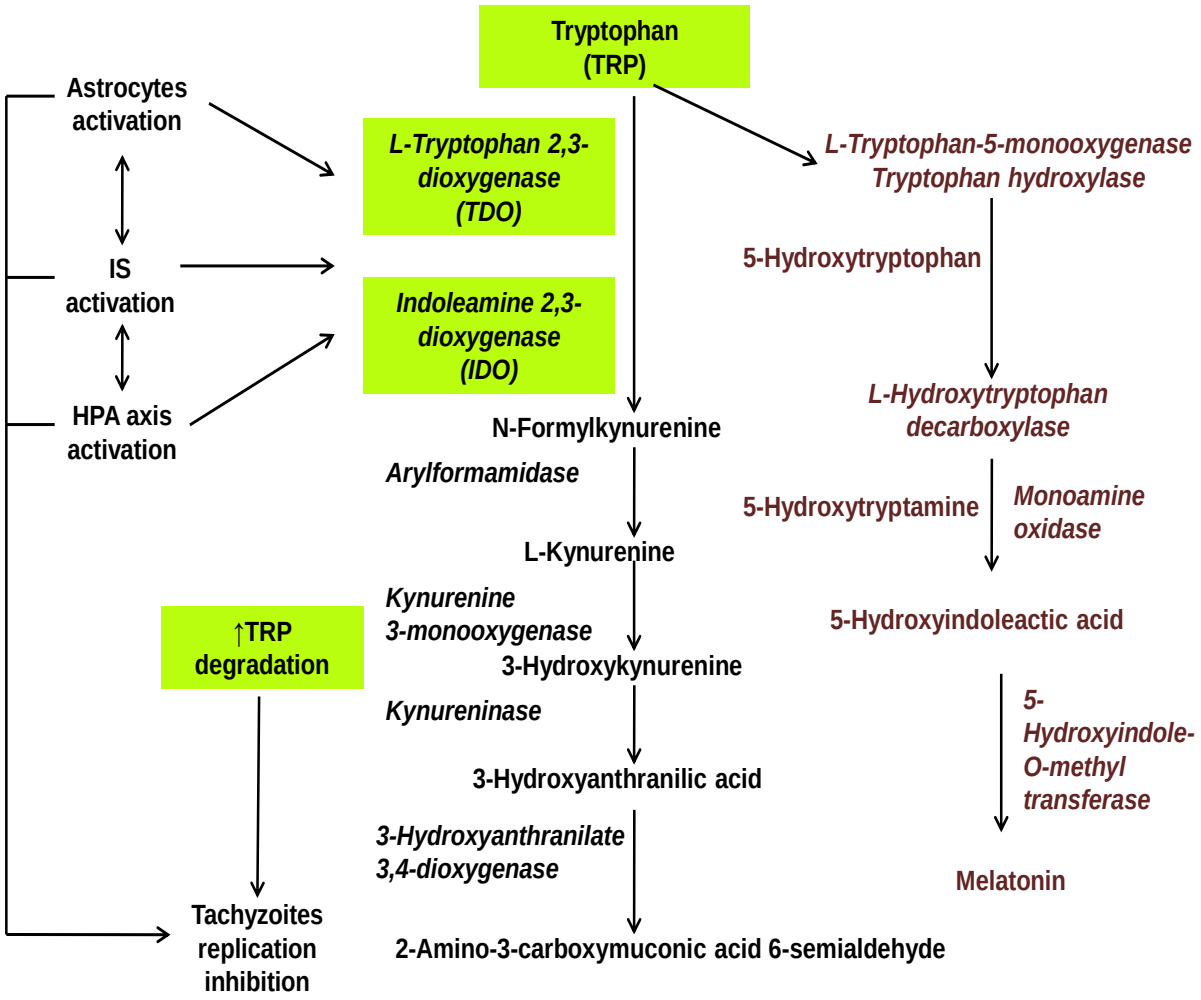
Tryptophan
(TRP)
Astrocytes activation
IS activation
HPA axis activation
L-Tryptophan 2,3-dioxygenase (TDO)
Indoleamine 2,3-dioxygenase (IDO)
L-Tryptophan-5-monooxygenase
Tryptophan hydroxylase
5-Hydroxytryptophan
L-Hydroxytryptophan decarboxylase
5-Hydroxytryptamine
Monoamine oxidase
5-Hydroxyindoleactic acid
5-Hydroxyindole-O-methyl transferase
Melatonin
N-Formylkynurenine
Arylformamidase
L-Kynurenine
Kynurenine 3-monooxygenase
3-Hydroxykynurenine
Kynureninase
3-Hydroxyanthranilic acid
3-Hydroxyanthranilate 3,4-dioxygenase
2-Amino-3-carboxymuconic acid 6-semialdehyde
↑TRP degradation
Tachyzoites replication inhibition

Fig. 2.

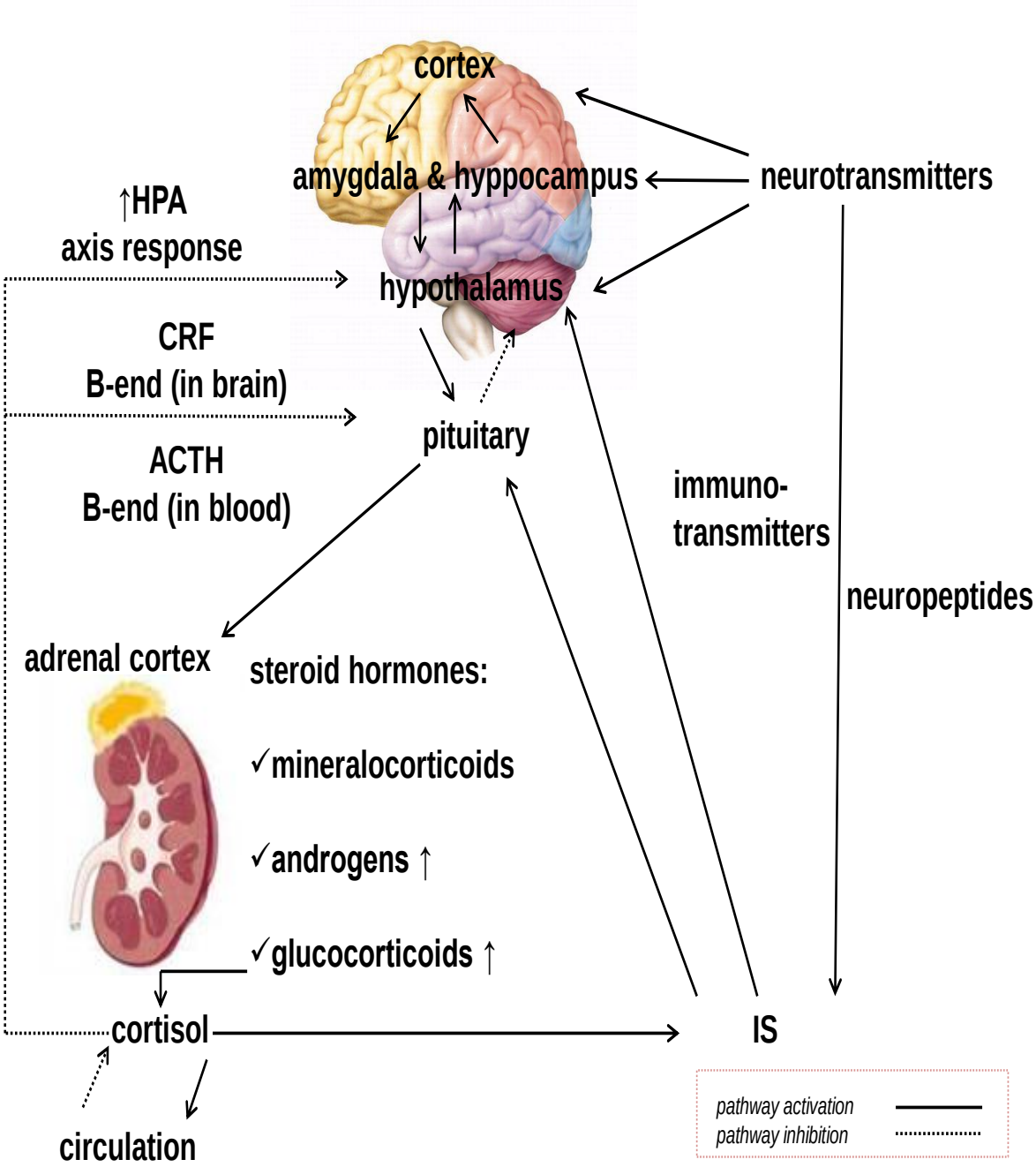
cortex
amygdala & hyppocampus
neurotransmitters
↑HPA
axis response
hypothalamus
CRF
B-end (in brain)
pituitary
ACTH
B-end (in blood)
immuno-
transmitters
neuropeptides
adrenal cortex
steroid hormones:
✓mineralocorticoids
✓androgens ↑
✓glucocorticoids ↑
cortisol
IS
circulation
pathway activation
pathway inhibition

Fig. 3.

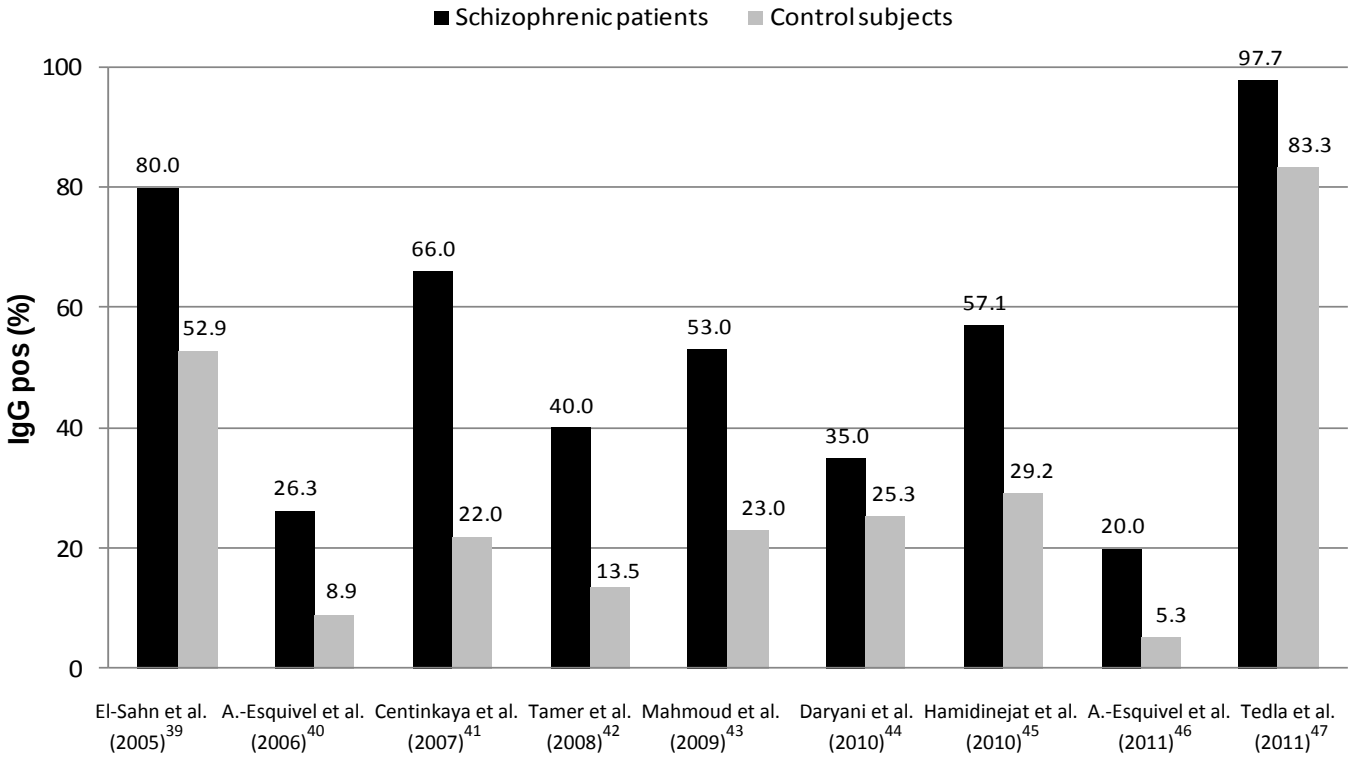
Schizophrenic patients
Control subjects
IgG pos (%)
100
80
60
40
20
0
80.0
52.9
26.3
8.9
66.0
22.0
40.0
13.5
53.0
23.0
35.0
25.3
57.1
29.2
20.0
5.3
97.7
83.3
El-Sahn et al. (2005)[39]
A.-Esquivel et al. (2006)[40]
Centinkaya et al. (2007)[41]
Tamer et al. (2008)[42]
Mahmoud et al. (2009)[43]
Daryani et al. (2010)[44]
Hamidinejat et al. (2010)[45]
A.-Esquivel et al. (2011)[46]
Tedla et al. (2011)[47]

Table 1. Host and parasite factors which could determine neuropsychiatric disorders development

Host factors	Parasite factors
• individual genetic susceptibility HLADQ3 locus is a marker of susceptibility to AIDS-related TE or post-congenital infection cerebral involvement; HLADQ1 locus is a marker of resistance;[6] regulatory genes of macrophage function, expression of T-cell determinants and transcription of cytokines are NF-kB, lymphotoxin, chemokine receptors and TLR[7] • host immune system • timing and duration of infection • area of infected brain	• way of infection • parasitic stage (tachyzoite, cysts, oocysts) • parasitic burden • single or multiple exposure • co-infection with other neurotrophic agents • strain virulence: - type I: involved in acute infections and ocular manifestations; it seems also involved in the development of schizophrenia[8] - type II: induces TE in IDPs and, CT with neuropsychiatric manifestations - type III: involved in animal infections - recombinant and exotic strains

AIDS, Acquired Immune Deficiency Syndrome - HLA, Human Leukocyte Antigen - NF-kB, Nuclear Factor-KappaB - TE, Toxoplasma Encephalitis - TLR, Toll-like receptor, IDPs, ImmunoDeficient patients

Table 2. Clinical symptoms of schizophrenia in *Toxoplasma*-seropositive and *Toxoplasma*-free individuals [11]

Toxoplasma-seropositive schizophrenia	*Toxoplasma*-seronegative schizophrenia
Prevalence of "positive symptoms":	*Prevalence of "negative symptoms":*
mania, disorganized behavior, hallucinations, ostentation, suspiciousness, persecution mania, mannerism, tic, exhibitionism, racing thoughts, poverty of judgment and awareness, difficulty in abstract thoughts, conventional/stereotyped thoughts, confusion, poor concentration, agitation, hostility, lack of cooperation, impulsivity	affective disorders, asociality, social withdrawal, loss of motivation, passivity, lack of spontaneity, difficulty moving, alteration or lack in motivation, lost of interest in everyday activities, poor determination/resolution, reduced ability to plan or carry out activities, worries, apathy, lack of emotion, poor or non-existant social functioning

Table 3. Anti-psychotic drugs, mood-stabilizing agents, and anti-*T. gondii* drugs in schizophrenia

Anti-psychotic and mood-stabilizing drugs that inhibit *T. gondii* replication[14,25,76,77,78,79] and reduce *T. gondii* Ab rates[29]		Anti-*Toxoplasma* drugs with positive effects on early-onset schizophrenia symptoms[25,72]
aripiprazole carbamazapine chlorpromazine clozapine fluphenazine haloperidol	quetiapine risperidone thioridazine trifluoperazine valproic acid ziprasidone	artemisinin compounds azithromycin ponazuril pyrimethamine-clindamycin pyrimethamine-sulfadiazine trimethoprim-sulfamethoxazole

Table 4. Epidemiologic similarities and differences linking *T. gondii* infection and schizophrenia

Factors	Toxoplasmosis	Schizophrenia
Genetic	Increased risk of infection in members of the same family, probably due to interaction between genetic (susceptibility genes) and environmental factors (exposure to contaminated food or infected cats); a transplacental transmission of the parasite up to 5 generations was showed in mice, according to a pseudogenetic pattern	Higher risk in first-degree relatives affected, even if any single gene involved has been definitely identified
Peak age of onset	20-30 years old, with early onset among males	
Stagionality	Patients born in winter or spring show a higher probability of contracting infectious diseases, including toxoplasmosis	
Stillbirth	Increased	
Socio-economic	Lower	
Residence rural, urban	Conflicting data	An association exists with being born or living in an urban area and the onset of schizophrenia
Geographical correlation	Geographical areas with a low prevalence of anti *T. gondii* Abs generally show a low prevalence of schizophrenia. The best example is provided by subjects from Papua, New Guinea where domestic and wild cats are still rare, prevalence rates for toxoplasmosis are low (2% or lower) and schizophrenia is poorly disseminated. A geographical association, however, is not found in countries such as France, Ethiopia and Brazil, where prevalence rates of toxoplasmosis are high and prevalence of schizophrenia is similar to the general population. This fact may be in relation to the timing of exposure to *T. gondii*, the route of infection, the parasite genotype more frequently found in the studied population, and the absence of cofactors required for the infection	
Contacts with cats	The seropositivity to *T. gondii* has increased together with the habit of keeping domestic cats; although cat keeping was documented in ancient Egypt, this practice became popular in the mid eighteenth century and since then it has increased. In	A positive correlation between schizophrenia and cat contact, especially during childhood is likely: • schizophrenic patients showed a higher frequency of exposure to cats from the age of six to ten (43%) years compared to control subjects (34%)[84] • in families whose members developed

	particular, it is important the possession of a kitten under the age of one year	schizophrenia or bipolar disorder, many individuals reported a past contact with or keeping cats. The number was especially higher (52% of subjects) during the period from birth up to 13 years old compared to controls (42%)[85] • Fifty-nine percent of the schizophrenic patients *versus* 20% of controls had cats during their childhood[43]

Table 5. Effects of *T. gondii* infection on mental capacity and animals and humans behavior

Animals	Humans
• Mice display impaired learning and memory[86,87] • Rats lose their innate aversion to cat odor and develop an effective feline attraction; moreover they are more active and less neophobic[23,24,25,88,89] • The administration of a DOPA re-uptake inhibitor will alter the behavior of the mice. Therefore, it is likely that infection with *T. gondii* causes behavioral changes by adjusting the dopaminergic system[27]	• Lower IQ scores; Anomalies in intelligence, education and memory [90] • Different personality profiles [27,28,90,91,92,93] • Differences between genders[95,95,96] • Implications on CNS[90] • Alterations in psychomotor performance, slower reaction times, higher exposure to risk, mainly involvement in road accident[97,98] • CT associated with mental retardation • Brain development alteration related to schizophrenia • Reports of psychiatric symptoms during acute infection • Psychiatric symptoms upon reactivation of latent infection in AIDS patients

AIDS, Acquired Immune Deficiency Syndrome - CT, Congenital Toxoplasmosis - DOPA, dopamine - IQ, Intellectual Quotient - NS, Novelty Seeking