Schizophrenia and *Toxoplasma gondii*: an undervalued association?

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The existence of an association between schizophrenia and an infection by the protozoan parasite *Toxoplasma gondii* has been suspected since the 1950s. Two significant phenomena first garnered the attention of the psychiatric community toward toxoplasmosis, the illness precipitated by an infection of the parasite. Transient symptoms of acute toxoplasmosis sometimes resemble the clinical picture of paranoid schizophrenia. Many studies have also found an increased seroprevalence of toxoplasmosis in clients of mental health institutions in comparison with members of control populations. We have had to wait until the first decade of our millennium for several independent research teams to make discoveries that would shed light on the possible mechanisms that link the *Toxoplasma* parasite to schizophrenia.

Infectology and psychiatry appear to be two unrelated branches of medicine that seem to have only a few topics in common. The main aim of the present article is to show that this understanding could change in the near future.

In the 1990s, Torrey and Yolken revived and promoted the infectious hypothesis of schizophrenia by pointing out the one risk factor that toxoplasmosis and schizophrenia have in common: contact with cats [1]. According to their two meta-analytic studies, the seroprevalence of toxoplasmosis in schizophrenia patients is significantly higher than in controls [2,3], while being *Toxoplasma* positive (to have anamnestic anti-*Toxoplasma* antibodies) increases by about 2.7-times (95% CI: 2.10–3.60) the chance that a subject will also be diagnosed with schizophrenia. Similar results (odds ratio [OR]: 2–4.4) have likewise been reported by four studies performed in China [4]. These ORs are most likely undersized due to a sampling bias accompanying all modern prevalence studies. The increased concern for patients' rights allows only subjects willing to voluntarily participate in a scientific study, that is, mostly the patients with less severe forms of schizophrenia, to be involved in surveys. The prevalence of toxoplasmosis in clinical serological samples of male patients is about two-times higher than in the general population [5]. There is only one prospective study published so far showing that the infection by *Toxoplasma* had preceded the onset of schizophrenia in the US military personnel by 6–36 months [6].

Distinct & more serious clinical picture of toxoplasmosis-associated schizophrenia

The clinical picture of schizophrenia in *Toxoplasma*-infected and *Toxoplasma*-free subjects differs in several respects. *Toxoplasma*-infected individuals score higher on the positive and negative syndrome scale. Specifically, they have more severe positive symptoms of schizophrenia as shown in three independent studies [7–9]. Another recent study revealed that *Toxoplasma*-infected patients have a 15-times higher probability of having a continuous course of disease than *Toxoplasma*-free patients [10]. Typical morphological changes described in the brain of schizophrenia patients, namely the decrease of grey matter density bilaterally located within the caudate, median cingulate, thalamus and occipital cortex and in the left cerebellar hemispheres,

EXPERT REVIEWS

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can be detected only in *Toxoplasma*-positive patients [11]. These patients also spend more time in hospitals during the occurrence of a schizophrenia episode [9]. Similarly, the difference in the mean age of schizophrenia onset between men (23.5 years in Czech Republic) and women (27 years) were observed only in *Toxoplasma*-infected subjects and not in the three-times as large population of *Toxoplasma*-free subjects (23 years for both men and women) [9]. This difference seems to be in agreement with the fact that Czech men usually acquire the *Toxoplasma* infection during their childhood, while Czech women undergo a second peak of incidence of infections at the age of 25–30. The second peak can be caused by transmission of *Toxoplasma* from infected men during non-protected sex [12], suggesting not only that toxoplasmosis, but also indirectly a certain form (the *Toxoplasma*-associated) of schizophrenia could be in fact a sexually transmitted disease. It is also possible that other changes observed in schizophrenia patients, for example, changes in a prepulse inhibition or in a sense of smell, are actually linked with (or even caused by) toxoplasmosis, rather than schizophrenia [13].

Some antipsychotic drugs, namely fluphenazine, haloperidol and mood stabilizer valproic acid [14,15] were found to be rather powerful and very specific inhibitors of *Toxoplasma* reproduction during *in vitro* cultivation. Goodwin *et al.* [16] reported inhibitory activity of fluphenazine, trifluoperazine and thioridazine but no activity of haloperidol or clozapine. It seems possible that some therapeutic activities of these antipsychotic drugs could be mediated by inhibition of mental disorder-associated infections. If so, the anti-microbial side effects of drugs should be taken into consideration in treatment of *Toxoplasma*-infected patients or in the process of searching for new antipsychotic and/or new antiparasitic drugs.

Differences in the prevalence of toxoplasmosis between countries explain a significant part of the variability between countries in the total disease burden within Europe when important confounding variables (income per capita, latitude, mean humidity) are controlled [17]. It must be reminded that an observed association of the prevalence of toxoplasmosis, with bipolar disorder and especially with obsessive-compulsive disorder was even stronger than that with schizophrenia.

Dopamine as the probable link between toxoplasmosis & schizophrenia

The neurotransmitter dopamine is known to play an important role in old as well as in some new theories of schizophrenia [18,19]. The increased concentration of dopamine in specific parts of the patients' brain is presumed to be responsible for the positive symptoms of this mental disorder, that is, hallucinations and delusions. Nearly all modern antipsychotics either decrease the dopamine concentration or downregulate the activity of its receptors on neural cells [20]. The key role of dopamine in the association between toxoplasmosis and schizophrenia was suggested in 2003 on the basis of decreased novelty seeking observed in infected people and as well as in laboratory mice later on [21,22]. This increased production of dopamine was originally considered to be a product of chronic brain tissue inflammation because similar behavioral symptoms were also observed in subjects infected with another neurotropic pathogen, human cytomegalovirus [23]. However, in 2009 Gaskell *et al.* identified two genes for rate-limiting enzymes of dopamine synthesis, tyrosine hydroxylases, in the genome of *Toxoplasma* [24] with a following study demonstrating that these genes are expressed in the brain tissue of an infected host as well as likely being responsible for the overproduction of dopamine in tissue cysts of *Toxoplasma* [25]. It is highly probable that the increased concentration of dopamine in the cysts and their surroundings is responsible for the positive symptoms of schizophrenia observed in some patients with acute schizophrenia, as well as for the observed association between latent (chronic) toxoplasmosis and schizophrenia. It is not clear whether the induction of the positive symptoms of schizophrenia is a part of the so-called 'manipulative activity' of *Toxoplasma* or just an effect of a chronic brain infection. In order to reproduce sexually, *Toxoplasma* needs to get from its intermediate host, for example, mouse or human, to its definitive host, which is a feline, by predation. Dopamine seems to interfere with processes of recognition of novelty, which results in a decrease of novelty seeking in neophilic species like mice and humans and in an increase of novelty seeking in neophobic animals like rats [26]. It is possible that these resulting behavioral changes could increase the probability of predation of mice or our human ancestors by felines. In *Toxoplasma*'s evolutionary past, dopamine was most likely produced only by activated immunocytes in locally damaged brain tissue in or near the sites of *Toxoplasma* infection. Only later did *Toxoplasma* improve its capacity to increase dopamine production by evolving or capturing through horizontal gene transfer its own tyrosine hydroxylases. If this is true, toxoplasmosis-associated schizophrenia is then just a side effect of the increased level of dopamine. The enhancement of the dopamine synthesis itself, however, could be a biological adaptation of *Toxoplasma* for manipulation within the intermediate host behavior, namely for increasing the probability of cat's predation of infected prey due to the deteriorated ability of infected hosts to recognize what is new in their environment.

The causal relationship between toxoplasmosis and schizophrenia is not simple. Schizophrenia is not caused by only one main, environmental or genetic, etiological factor, rather it is a typical disorder caused (or rather co-caused) by many environmental and genetic factors, which are both additive and interchangeable in their effects. In such multifactorial disorders, the question of whether a particular factor, for example, toxoplasmosis, just modifies the course of schizophrenia, or whether it causes certain forms of schizophrenia, does not make much sense. The best that could be said is that the observed strength of association between these two 'unrelated' disorders suggests that *Toxoplasma* infection is probably a relatively important cause of severe forms of schizophrenia in subjects with other environmental and genetic predispositions.

Expert opinion

The prevalence of toxoplasmosis in younger subjects has decreased from about 20 – 25% to about 10% in the USA and many European countries during the past 15 years. Throughout the same time, the prevalence increased from about 5% to >10% in some large Asian countries, like China. On the whole, the public health impact of toxoplasmosis, including its psychiatric sequels, is most likely increasing in the modern world [17]. No method of treatment for latent toxoplasmosis is currently available. In light of present discoveries, intensive searching for new antiparasitic drugs able to kill dormant stages of the *Toxoplasma* in bodies of people with latent toxoplasmosis is therefore critically needed. Phylogenetic affinity of *Toxoplasma* and the results of *in vitro* studies suggest that antimalarials and certain categories of antipsychotics might be the drugs of the first choice.

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References

Papers of special note have been highlighted as:
• of interest
•• of considerable interest

1. Torrey EF, Yolken RH. Could schizophrenia be a viral zoonosis transmitted from house cats. Schizophr Bull 1995;21(2):167-71

• **This is the first study suggesting that schizophrenia could be caused by a pathogen transmitted by cats.**

2. Torrey EF, Bartko JJ, Lun ZR, Yolken RH. Antibodies to *Toxoplasma gondii* in patients with schizophrenia: A meta-analysis. Schizophr Bull 2007;33:729-36

•• **The first meta-analytic study showing that toxoplasmosis increases risk of schizophrenia.**

3. Torrey EF, Bartko JJ, Yolken RH. *Toxoplasma gondii* and other risk factors for schizophrenia: An update. Schizophr Bull 2012;38(3):642-7

• **The second meta-analytic study confirming that toxoplasmosis increases risk of schizophrenia.**

4. Zhou P, Chen ZG, Li HL, et al. *Toxoplasma gondii* infection in humans in China. Parasite Vector 2011;4:165

5. Flegr J, Priplatova L, Hampl R, et al. Difference of neuro- and immunomodulatory steroids and selected hormone and lipid concentrations between *Toxoplasma*-free and *Toxoplasma*-infected but not CMV-free and CMV-infected schizophrenia patients. Neuroendocrinol Lett 2014;35(1):20-7

6. Niebuhr DW, Cowan DN, Millikan AM, et al. Risk of schizophrenia and antibodies to Toxoplasma gondii among U.S. military personnel. Schizophr Bull 2007;33:243-4

• **A prospective case–control study showing that *Toxoplasma gondii* infection preceds an onset of schizophrenia.**

7. Wang HL, Wang GH, Li QY, et al. Prevalence of Toxoplasma infection in first-episode schizophrenia and comparison between Toxoplasma-seropositive and Toxoplasma-seronegative schizophrenia. Acta Psychiatr Scand 2006;114:40-8

• **A study showing more severe clinical picture of *Toxoplasma*-infected schizophrenia patients.**

8. Yolken RH, Dickerson FB, Torrey EF. Toxoplasma and schizophrenia. Parasite Immunol 2009;31:706-15

9. Holub D, Flegr J, Dragomirecka E, et al. Differences in onset of disease and severity of psychopathology between toxoplasmosis-related and toxoplasmosis-unrelated schizophrenia. Acta Psychiatr Scand 2013;127:227-38

• **A study showing more severe clinical picture of *Toxoplasma*-infected schizophrenia patients.**

10. Celik T, Kartalci S, Atas O, et al. Association between latent toxoplasmosis and clinical course of schizophrenia - continuous course of the disease is characteristic for *Toxoplasma gondii*-infected patients. Folia Parasitol (Praha) 2015;62

11. Horacek J, Flegr J, Tintera J, et al. Latent toxoplasmosis reduces gray matter density in schizophrenia but not in controls: Voxel-based-morphometry (VBM) study. World J Biol Psychiatry 2012;13:501-9

• **A study showing more severe clinical picture of *Toxoplasma*-infected schizophrenia patients.**

12. Flegr J, Klapilová K, Kaňková Š. Toxoplasmosis can be a sexually transmitted infection with serious clinical consequences. Not all routes of infection are created equal. Med Hypotheses 2014;83:286-9

13. Priplatova L, Sebankova B, Flegr J. Contrasting effect of prepulse signals on performance of Toxoplasma-infected and Toxoplasma-free subjects in an acoustic reaction times test. PLoS One 2014;9(11): e112771

14. Jones-Brando L, Torrey EF, Yolken R. Drugs used in the treatment of schizophrenia and bipolar disorder inhibit the replication of *Toxoplasma gondii*. Schizophr Res 2003;62:237-44

•• **The first study showing that some antipsychotic drugs inhibits growth of *Toxoplasma*.**

15. Fond G, Macgregor A, Tamouza R, et al. Comparative analysis of anti-toxoplasmic activity of antipsychotic drugs and valproate. Eur Arch Psychiatry Clin Neurosci 2014; 264(2):179-83

• **Another study showing that some antipsychotic drugs inhibits growth of *Toxoplasma*.**

16. Goodwin DG, Strobl JS, Lindsay DS. Evaluation of five antischizophrenic agents against *Toxoplasma gondii* in human cell cultures. J Parasitol 2011;97:147-51

17. Flegr J, Prandota J, Sovickova M, Israili ZH. Toxoplasmosis - A global threat. Correlation of latent toxoplasmosis with specific disease burden in a set of 88 countries. PLoS One 2014;9(3):e90203

•• **A study indicating that prevalence of toxoplasmosis positively corelates with incidence and morbidity of many diseases, including cardiovascular diseases and some forms of cancer.**

18. Willner P. The dopamine hypothesis of schizophrenia: current status, future prospects. Int Clin Psychopharmacol 1997; 12(6):297-308

19. Fallon JH, Opole IO, Potkin SG. The neuroanatomy of schizophrenia: circuitry and neurotransmitter systems. Clin Neurosci Res 2003;3(1-2):77-107

20. Nikam SS, Awasthi AK. Evolution of schizophrenia drugs: A focus on dopaminergic systems. Curr Opin Invest Drugs 2008;9:37-46

21. Flegr J, Preiss M, Klose J, et al. Decreased level of psychobiological factor novelty seeking and lower intelligence in men latently infected with the protozoan parasite Toxoplasma gondii. Dopamine, a missing link between schizophrenia and toxoplasmosis? Biol Psychol 2003;63:253-68

•• **The first study suggesting that increased level of dopamine could be associated with latent toxoplasma infection.**

22. Skallová A, Kodym P, Frynta D, Flegr J. The role of dopamine in Toxoplasma-induced behavioural alterations in mice: an ethological and ethopharmacological study. Parasitology 2006;133:525-35

23. Novotná M, Hanušová J, Klose J, et al. Probable neuroimmunological link between Toxoplasma and cytomegalovirus infections and personality changes in the human host. BMC Infect Dis 2005;5:54

24. Gaskell EA, Smith JE, Pinney JW, et al. A unique dual activity amino acid hydroxylase in Toxoplasma gondii. PLoS One 2009;4:e4801

•• **The study showing that *Toxoplasma* contains genes for dopamine synthetizing enzymes.**

25. Prandovszky E, Gaskell E, Martin H, et al. The neurotropic parasite Toxoplasma gondii increases dopamine metabolism. PLoS One 2011;6(9):e23866

26. Hodková H, Kodym P, Flegr J. Poorer results of mice with latent toxoplasmosis in learning tests: impaired learning processes or the novelty discrimination mechanism? Parasitology 2007;134:1329-37