Curr Clin Micro Rpt (2015) 2:163–172
DOI 10.1007/s40588-015-0024-0

PARASITOLOGY (A VAIDYA, SECTION EDITOR)

Neurological and Neuropsychiatric Consequences of Chronic *Toxoplasma* Infection

Jaroslav Flegr[1]

Published online: 28 September 2015

Abstract The neurotropic pathogen *Toxoplasma gondii* infects about one third of human population. For a long time, it is well known that both acute and latent (life-long) forms of toxoplasmosis are associated with specific neurologic and neuropsychiatric symptoms. Here, the possible effects of latent toxoplasmosis on neurological and psychiatric disorders are surveyed and some general methodological problems of corresponding studies are discussed.

Keywords Toxoplasmosis · Cohort studies · Ecological studies · Neuropsychiatric diseases neurological disorders · Parasite infection

Introduction

Toxoplasma gondii is a protozoan parasite related to *Plasmodium*. Asexual reproduction of *Toxoplasma* can be accomplished in any warm-blooded animal, bird, or mammal, but sexual reproduction can occur only in its definitive host, i.e., any species of the feline family. The products of sexual reproduction, hundreds of millions highly resistant oocysts in feces of an infected cat, can survive in humid soil for more than a year. They can also accumulate in paratenic hosts, for example, in invertebrate animals filtrating sea water (oysters, etc.). The products of asexual reproduction in warm-blooded intermediate hosts are the rapidly dividing tachyzoites in the first stage of an infection and the slowly dividing bradyzoites contained in the so called "tissue cysts" in later stages of the infection. Tissue cysts wait in a parasitophorous vacuole of transformed cells within the intermediate host for a predator or an omnivore that eats up the intermediate host. Depending on the type of predator, either sexual (in a cat) or asexual (in other species) cycle of reproduction will start first in intestinal cells of the host and then in many other types of host cells. For the biology of *Toxoplasma*, see [1, 2].

Toxoplasma is a very successful parasite. For example, it infects probably one third of human population of both developing and developed countries. The prevalence of infection, toxoplasmosis, decreases in young age strata in North America and in many European countries. However, this decrease is probably more than compensated for by the increase of prevalence in China and other heavily populated Asian countries [3]. The most important routes of infection are contact with soil contaminated with oocytes, eating unwashed vegetables, or drinking contaminated water and eating raw or undercooked meat containing tissue cysts. Toxoplasmosis can additionally be transmitted with transplanted organs and probably also during unprotected sex of an infected man with a non-infected women [4].

Toxoplasma is an intracellular parasite which can actively enter any nucleated cell in the body. It disseminates through the host body with infected mobile cells, such as dendritic cells and monocytes. Using this Trojan horse strategy, it can even enter immunoprivileged organs, testes, the eyes, and especially the brain. Here, it infects many types of cells, including neurons, Purkinje cells, and microglial cells [2]. Bradyzoites slowly divide within cysts formed in the parasitophorous vacuole for the rest of the host's life and probably elicit no inflammatory response. Spontaneously or in response to various external stimuli, such as viral infections, some cysts can rupture. Some bradyzoites transform to

This article is part of the Topical Collection on *Parasitology*

✉ Jaroslav Flegr
Flegr@cesnet.cz

[1] Faculty of Science, Biology Section, Charles University in Prague, Viničná 7, Praha CZ-12844, Czech Republic

tachyzoites and infect new cells, and some others are ingested by mononuclear cells and induce an inflammatory response [5]. Many neurological symptoms of latent toxoplasmosis, such as headaches, are probably manifestations of inflammatory processes in the brain triggered by ruptures of *Toxoplasma* cysts [6].

Toxoplasmosis is kept in its latent stage by the host's immune system. In immunocompromised individuals, e.g., AIDS patients or patients after transplantation or under anticancer therapy, latent toxoplasmosis transforms into its active form. If untreated, the active form usually results in toxoplasmic encephalitis, which often lead to death of the host [7–9]. The combination of sulfadiazine and pyrimethamine supplemented with folinic acid (for protection against demyelinization) or clindamycin with pyrimethamine is used for effective treatment of acute toxoplasmosis or for its prevention in immunocompromised subjects [7]. However, no effective method of elimination of the parasites contained in tissue cysts and therefore final treatment of latent toxoplasmosis is presently available. There are some indications, however, that either certain antimalarials, such as atovaquone [10–12], or antipsychotics, reviewed in Table 5 of [6], can inhibit growth or even kill bradyzoites in tissue cysts.

In contrast to acute and congenital toxoplasmosis, latent toxoplasmosis was considered harmless or even asymptomatic for a very long time. It was supposed that unsterile immunity accompanying the latent infection represents a useful protection for women against infection in pregnancy and therefore against serious health consequences of congenital toxoplasmosis. New data, however, clearly show that latent toxoplasmosis is neither asymptomatic nor harmless. The earlier anecdotal observations of increased incidence of various disorders in subjects with latent toxoplasmosis have been confirmed by ecological as well as case-control studies performed in patients and recently also in a cohort of nonclinical subjects. Individuals with positive results of serological tests for latent toxoplasmosis, i.e., those with moderate levels of (high-affinity) IgG and low or undetectable concentrations of IgA and IgM anti-*Toxoplasma* antibodies, have been shown to express higher probability of suffering from gastrointestinal, endocrinological and metabolic (including diabetes), fertility, immunological, and especially neuropsychiatric disturbances; for a review, see [13••].

Association of Toxoplasmosis With Mental Health Disorders

Subjects with various neuropsychiatric disturbances, namely schizophrenia (SCH), bipolar disorder (BD), obsessive compulsive disorder (OCD), unipolar depression (UD), drug abuse disorder (DAD), suicides, homicides, generalized anxiety and panic disorders (AD), personality disorders (PD), and mood disturbances, have been reported to be more often infected with *Toxoplasma* than normal controls (Table 1).

Schizophrenia The association of toxoplasmosis with mental health disorders has been reported already in the middle of the past century [24]. It was observed that acute toxoplasmosis sometimes reminds mental disorders, being accompanied by positive psychiatric symptoms, like hallucinations and delusions. Based on this, serological surveys were performed in psychiatric hospitals showing that the prevalence of latent toxoplasmosis in patients, especially those with schizophrenia, was usually higher than the prevalence in normal population. It was often speculated that schizophrenia patients could have higher probability of *Toxoplasma* infection. However, the results of several prospective studies (surveyed in [15••]) as well as a discovery of enhanced synthesis of dopamine in the brains of infected hosts and other indirect indices suggested that toxoplasmosis could cause schizophrenia in predisposed subjects. This model is also supported by the fact that both schizophrenia and toxoplasmosis have one common risk factor, namely a contact with cats in childhood [25, 26]. Results of the first modern meta-analyses showed that being *Toxoplasma* seropositive increases the probability of schizophrenia about 2.7 times (odds ratio (OR) 2.73; CI_{95} 2.21–3.38) [14, 27]. However, the most recent prevalence studies often found decreased, rather than increased, prevalence of toxoplasmosis in schizophrenia patients [28, 29]. A new meta-analytic study based on 43 case-control studies showed overall OR to be just 1.81 (CI_{95}=1.51–2.16) and this OR even decreased to 1.43 (CI_{95}=1.21–1.70) when publication bias was properly controlled [15••]. It was suggested that increasing concerns regarding patients' rights could be responsible for such a decrease [30•]. Only the patients who voluntarily sign the informed consent, therefore, likely the patients with less serious forms of schizophrenia, can be included into any contemporary scientific study. Several studies showed that patients with latent toxoplasmosis express more serious positive symptoms of schizophrenia [31–34]. Changes in brain morphology—namely the decrease of gray matter density bilaterally located within the caudate, median cingulate, thalamus, and occipital cortex, and in the left cerebellar hemispheres—which are typical for schizophrenia, have been observed only in *Toxoplasma*-infected patients, not in *Toxoplasma*-free patients [28]. It was also observed that *Toxoplasma*-infected subjects had a 15× higher probability of having a continuous course of disease [35•] and a mortality rate five times higher [36] than *Toxoplasma*-free subjects. Indeed, it was confirmed that a highly increased prevalence of toxoplasmosis can be found in blood samples of male schizophrenia patients collected for various clinical purposes, not for scientific experiments [30•]. Also, the recent meta-analytic study showed that the highest OR were reported from studies performed in Africa (N=2, OR=3.74), then South America

Table 1 Association between latent toxoplasmosis and 11 neurological and neuropsychiatric disorders

	Case-control—patients	Ecological study	Cross sectional—general population[a]
Schizophrenia	More than 50 studies OR=2.73 (CI_{95}=2.21–3.38) [14]; now OR=1.81 (CI_{95}=1.51–2.16) [15••]	Europe: p=0.02 (posit. correlation) [13••], non-Europe: nesign. (negat. correlation) [13••]	All: OR=2.47, p=0.02, N=10/4 Women: OR=2.10, p=0.32, N=4/2 Men: OR=3.67, p=0.15, N=6/2
Bipolar disorder	11 studies, OR=1.52 [15••] (CI_{95}=1.06–2.19)	Europe: p=0.01 (posit. correlation) [13••], non-Europe: nesign. (posit. correlation) [13••]	All: OR=1.10, p=0.72, N=50/9 Women: OR=1.57, p=0.07, N=25/9 Men: OR=0.04, p=0.02, 25/0
Obsessive compulsive disorder	2 studies, OR=3.40 (CI_{95}=1.73–6.68) [15••]	Europe: p=0.02 (posit. correlation) [13••], non-Europe: p<0.001 (posit. correlation) [13••]	All: OR=1.49, p=0.04, N=62/15 Women: OR=1.63, p=0.05, N=24/9 Men: OR=1.73, p=0.09, N=38/6
Unipolar depression	9 studies, OR=1.21 (CI_{95}=0.86–1.7) [15••]	Europe: nesign. [13••], non-Europe: nesign. [13••]	All: OR=1.30, p=0.10, N=109/23 Women: OR=1.25, p=0.24, N=66/19 Men: OR=0.48, p=0.01 N=43/4
Drug abusing disorder	4 studies, OR=1.91 (CI_{95}=1.49–2.44) [15••]	Europe: p=0.07 (posit. correlation), non-Europe: p=0.1 (negative correlation)	All: OR=1.30, p=0.50, N=19/4 Women: OR=0.51, p=0.32, N=9/1 Men: OR=3.29, p=0.01, N=10/3
Anxiety disorder	1 study, OR=2.25 (CI_{95}=1.11–4.53) [16]	N.A.	All: OR=1.87, p<0.01, N=173/50 Women: OR=1.73, p=0.01, N=111/42 Men: OR=1.40, p=0.22, N=62/8
Panic disorder	N.A.	Europe: p=0.02 (posit.), non-Europe: p=0.1 (negative correlation) [13••]	All: OR=0.81, p=0.40, N=53/7 Women: OR=0.81, p=0.44, N=37/7 Men: OR=0.06, p=0.06, N=16/0
Self-directed violence	About 10 studies, mostly significant, no meta-analysis, OR about 2	Europe: 3 studies [13••, 17, 18]: signif. positive correlations, non-Europe: p=0.005, negat. correlation [13••]	Women: OR=1.53 (CI_{95}=1.27–1.85) [22]
Autism	1 study, OR=7.2 (CI_{95}=1.56–33.7) [23••]	N.A.	All: OR=5.12, p<0.01, N=6/5 Women: OR=4.28, p=0.10, N=1/1 Men: OR=8.78, p<0.01, N=5/4
Epilepsy	6 studies, OR=2.5 (CI_{95}=1.27–3.9) [19•]	World: p=0.001, posit. [20], Europe: p=0.03 [13••], posit., non-Europe: p=0.007, posit. [13••]	All: OR=1.17, p=0.82, N=6/2 Women: OR=0.18, p=0.99, N=3/0 Men: OR=1.93, p=0.27, N=3/2
Migraines	1 study, OR=2.11 (CI_{95}=1.16–3.84) [21]	N.A.	All: OR=1.27, p=0.02, N=181/34 Women: OR=1.71, p=0.05, N=32/9 Men: OR=1.07, p=0.51, N=149/55

N shows the number of *Toxoplasma*-free/number of *Toxoplasma*-infected subjects with particular disorder

[a] Except these for self-directed injury, all other results were obtained in two cross-sectional questionnaire studies performed on Czech nonclinical population. Study A—psychiatric disorders: 25,293 responders, 2619 provided information about their toxoplasmosis status (1117 *Toxoplasma*-free men and 106 infected men; 1131 *Toxoplasma*-free women and 265 infected women); study B—epilepsy and migraines: 4712 responders, 1046 provided information about their toxoplasmosis status (268 *Toxoplasma*-free men and 48 *Toxoplasma*-infected men; 540 *Toxoplasma*-free women and 190 *Toxoplasma*-infected women). Nonparametric partial Kendall correlation test with age as a confounding variable was used to compute significance when number of subjects reporting particular disorder was at least 8; otherwise, Fisher exact test was used

(N=4, OR=2.48), Asia (N=6, OR=2.06), the Middle East (N=11, OR=2.04), Europe (N=12, OR=1.53), and the USA (N=7, OR=1.25) [15••]. Various explanations for this order could be suggested. However, the probable existence of a gradient in patient right concerns seems to be a relatively parsimonious one.

All published case-control studies compared the prevalence of toxoplasmosis in schizophrenia patients and in healthy controls. It is possible that toxoplasmosis could trigger schizophrenia only in subjects with certain (possibly rare) predispositions and therefore usual case-control studies provide highly biased odds ratios for a general population. As far as I am aware, only one unpublished case-control study compared the prevalence of schizophrenia patients in a cohort of *Toxoplasma*-infected and *Toxoplasma*-free subjects in nonclinical population (the members of Facebook page "Guinea pigs" [37]). The reason for the lack of studies is that because of the incidence of schizophrenia is less than 1 %, a very large number of subjects must be involved in this type of observation studies. Among 2619 participants, only 6 women and 8 men reported to be diagnosed with schizophrenia. The OR was 2.47, p=0.02 (partial Kendall Tau, age controlled).

Two principally different physiological mechanisms responsible for the association between toxoplasmosis and schizophrenia have been suggested. Based on direct evidence in mice [38] and indirect evidence in humans, namely an

observed lower personality factor of novelty seeking [39, 40], it was suggested that increased concentration of dopamine is responsible for schizophrenia in predisposed subjects [39]. It was confirmed that the dopamine uptake inhibitor GBR 12909 interferes with specific behavioral effects of toxoplasmosis in infected mice [41]. An increased concentration of dopamine in the acute phase of infection was also observed in mice [42•]. Gaskell and Smith [43] have shown the genome of *Toxoplasma* contains two genes for tyrosine hydroxylase, the rate limiting enzyme of the dopamine synthesizing pathway. Indeed, an immunofluorescence study has demonstrated a high concentration of dopamine in *Toxoplasma* tissue cysts and their surroundings [44], but see also [45, 46]. It is well known that increased levels of dopamine in certain brain structures is responsible for typical positive symptoms of schizophrenia, namely for hallucination and delusions [47]. Also, nearly all antipsychotic drugs that are currently used for the treatment of schizophrenia are either dopamine antagonists or inhibitors of dopamine transport [48].

The second hypothesis suggests that an increased concentration of kynurenic acid is responsible for the onset of schizophrenia in *Toxoplasma*-infected subjects [49]. Increased levels of this product of degradation of tryptophan could be responsible for the inhibition of glutamine and nicotine neurotransmitter receptors, which is believed to play an important role in the cognitive impairment symptoms of schizophrenia (Schwarcz and Hunter [49]). While dopamine upregulation is mostly considered as a part of the manipulation activity of *Toxoplasma* [50], the tryptophan degradation is part of vertebrate host defense against various pathogens, including *Toxoplasma* [51].

Bipolar disorder A meta-analysis performed by Sutterland and Fond [15••] found 11 studies searching for an association between BD and showed that the overall OR was 1.52 (CI_{95}= 1.06–2.19). For example, a recent French study found 76.9 % of prevalence in 110 patients and 48.2 % prevalence in 106 controls, suggesting that infected subjects have about a 2× higher risk of bipolar disorder (OR=2.17, CI_{95}=1.09–4.36) than *Toxoplasma*-free subjects [52]. An ecological study showed an association between the prevalence of toxoplasmosis and the BD burden in 29 European countries and a similar trend for 59 non-European countries [13••]. Recent infection or reactivation of infection could play a role in BD, as the mania patients experienced increased levels of anti-*Toxoplasma* IgM antibodies but not IgG antibodies [53]. It was also observed that cognitive functions are correlated with the concentration of anti-*Toxoplasma* IgM antibodies in *Toxoplasma*-infected subjects with BD, but not in patients with SCH or in controls [54]. *Toxoplasma*-infected patients treated with antipsychotics with anti-*Toxoplasma* activity presented less lifetime depressive episodes than patients treated with other antipsychotics. Such a difference was not found in BD *Toxoplasma*-free patients and in SCH *Toxoplasma*-infected or SCH *Toxoplasma*-free patients [55]. In our cross-sectional study performed on nonclinical population of 2619 subjects, 59 individuals reported to be diagnosed with bipolar disorder. Total OR was 1.1, p=0.7. However, OR in women was 1.25 (p=0.07), while OR for men was 0.04 (p=0.02)—all 25 male BD patients were *Toxoplasma*-free.

Obsessive Compulsive Disorder An ecological study showed a very strong correlation between incidence of toxoplasmosis and the obsessive compulsive disorder-related burden in European (p=0.02) and especially in non-European countries (p<0.0001) [13••]. The prevalence of toxoplasmosis could explain 18 and 36 % of the between-country variability in OCD-related burden in Europe and outside Europe, respectively. The results of two case-control studies on the relation of OCD and toxoplasmosis have been published with overall OR of 3.40 (CI_{95}=1.73–6.68) [15••]. Our internet study performed on a nonclinical population found 77 subjects with OCD. The OR was 1.49, p=0.04. Another of our unpublished studies performed on a nonclinical population showed that infected men expressed a significantly higher OCD score measured with OCI-R [56] in comparison with non-infected men (Fig. 1).

Unipolar Depression Based on observed tryptophan depletion, which results in a decrease of serotonin level in *Toxoplasma*-infected subjects and increased rates of suicides and suicide attempts (see below), it was speculated that an association between toxoplasmosis and major depression could exist [57, 58]. However, a systematic review of modern literature found 10 studies searching for this association with an overall OR 1.21 (CI_{95}=0.86–1.7) [15••]. Only one technically problematic study found a positive result. When this study was omitted from the meta-analysis, the OR decreased to 1.01 (CI_{95}=0.80–1.28). Additionally, the ecological study found no association between toxoplasmosis and major depression [13••]. Our cross-sectional study performed on a nonclinical population found a nonsignificant association with toxoplasmosis, OR=1.30, p=0.10. Infected men even seem to be protected against unipolar depression—only 4 patients were found in *Toxoplasma*-infected subjects while 43 were found in *Toxoplasma*-free individuals (OR=0.48, p=0.01). This pattern indicates that toxoplasmosis has specific effects on mental functions, rather than a generally negative effect on mental health.

Drug Abuse Disorder A meta-analytic study [15••] found four studies reporting increased risk of drug abuse disorder in *Toxoplasma*-infected subjects with overall OR 1.91 (CI_{95}=1.49–2.44). An ecological study found a positive correlation of the prevalence of toxoplasmosis with alcohol use disorder-related burden explaining 13 % of the between-

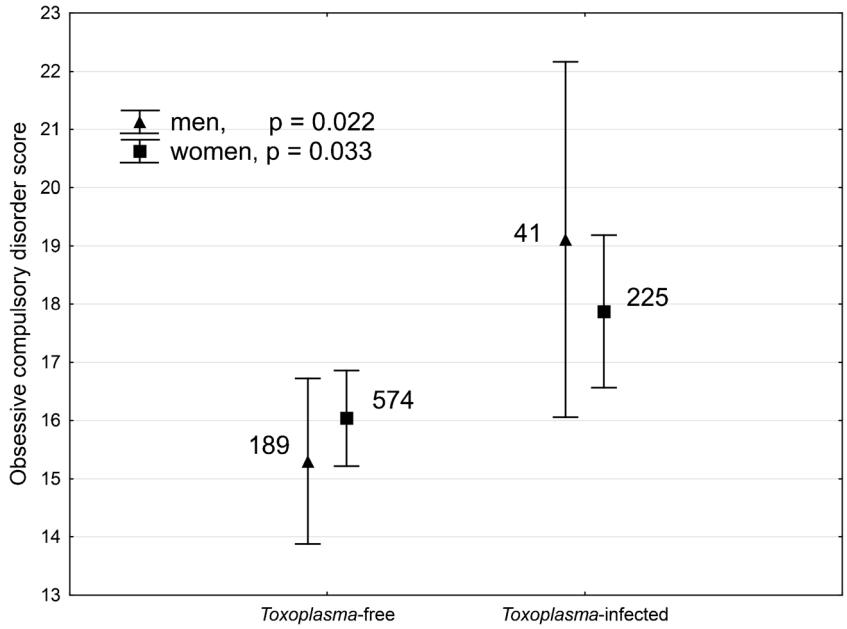

Fig. 1 Difference in intensity of obsessive compulsory disorders symptoms between *Toxoplasma*-infected and *Toxoplasma*-free nonclinical subjects

country variability (p=0.07) in European countries but a negative correlation explaining 5 % variability (p=0.1) in non-European countries. A cross-sectional study performed on a cohort of 1040 nonclinical subjects showed a nonsignificant trend for increased risk of DAD (OR=1.40, CI_{95}=0.38–5.62). However, the study also showed lower risk of alcohol use disorder in infected subjects, which was in agreement with the reported lower novelty seeking in *Toxoplasma*-infected subjects [39, 40].

Anxiety Disorder One case-control study [16] revealed increased incidence of anxiety disorder (OR=2.25, CI_{95}=1.11–4.53) and a nonsignificant increase of posttraumatic stress disorder (OR=1.68, CI_{95}=0.88–3.21) in *Toxoplasma*-infected subjects. This association was stronger for infected subjects with higher concentrations of anti-*Toxoplasma* antibodies (OR=1.68, CI_{95}=0.88–3.21), suggesting that increased anxiety can be understood as an aftereffect of acute toxoplasmosis, rather than the effect of latent toxoplasmosis [59]. A higher anxiety score was also reported in *Toxoplasma*-infected pregnant women enrolled in a study of postpartum thyroiditis [60]. A trend suggesting a positive association between toxoplasmosis and panic disorder was observed in an ecological study performed on the set of 29 European countries (p=0.02, 10 % of explained between-country variability) [13••]. On the other hand, no association between toxoplasmosis and generalized anxiety disorder or panic disorder in cross-sectional study performed on 1846 nonclinical subjects [61]. Studies on the interaction between anxiety and toxoplasmosis should take into consideration that *Toxoplasma* could have an opposite effect on men and women. It was observed among laboratory-infected mice that infected males expressed less while infected female mice more anxiety in open field test than controls [41]. *Toxoplasma*-gender interaction was also observed when personality and fear were studied in human models [59, 62]. Our cross-sectional study performed on a nonclinical population, however, showed a positive association between latent toxoplasmosis and anxiety disorder both in women (OR=1.73, p=0.01) and in men (OR=1,40, p=0.22). Only a nonsignificant positive association between toxoplasmosis and posttraumatic stress disorder was observed in our study (OR=1.36, p=0.15, 59 *Toxoplasma*-free and 13 *Toxoplasma*-infected patients).

Violence and Self-Directed Violence One study showed the association between toxoplasmosis and homicides [63] and more than 10 studies showed the association between toxoplasmosis and suicides or suicide attempts. Some case-control studies were performed on subjects with mental health problems [64, 65] and some on nonclinical populations [66, 67]. A large prospective cohort study performed on 45,788 Danish women that were pregnant between the years 1992 and 1995, and who were observed until the year 2006, showed that an infected woman had about a 1.53-fold increased probability of self-directed violence and a 2.05-fold higher probability of suicide than a *Toxoplasma*-free woman. Two correlation studies showed that the incidence of suicides in Europe correlated with the prevalence of toxoplasmosis in any particular country [17, 68]. A larger ecological study performed in 29 European countries confirmed this trend, and at the same time, it showed a negative association between the incidence of suicides and the prevalence of toxoplasmosis in 59 non-European countries (p=0.005, 14 % explained between-country variability) [13••].

Autism A possible association between toxoplasmosis and autism spectrum disorders was suggested [23••, 69–71]. Patients with autism have persistent neuroinflammation,

hypercytokinemia, and specific gastrointestinal abnormalities [72–74]. A similar spectrum of symptoms also occurs in mice with chronic toxoplasmosis and further in *Toxoplasma*-infected subjects. It was also suggested that an increased prenatal level of testosterone could be associated with both toxoplasmosis and autism [75]. Only one case-control study has been published so far. Prandota et al. [23••] found 23.9 % prevalence in 46 children with autism spectrum disorder and 4 % prevalence in 50 controls. They also found markedly increased levels of interferon γ and NO in *Toxoplasma*-infected participants. In our internet-based study, we found only 6 *Toxoplasma*-free and 5 *Toxoplasma*-infected individuals with autism (OR=5.12, $p<0.01$); however, 21 *Toxoplasma*-free and 8 *Toxoplasma*-infected subjects also reported Asperger's syndrome (OR=2.36, $p<0.01$). These two associations were much stronger for men than for women (see Table 1).

Personality Disorder An association between toxoplasmosis and personality disorder was observed in 896 patients with schizophrenia, major depression, schizoaffective disorder, or bipolar disorder (OR=1.90, CI_{95}=1.19–3.03) [76]. Our cross-sectional study performed on a nonclinical population of 2619 subjects found a significant association between toxoplasmosis and antisocial personality disorder (OR=2.76, CI_{95}=1.11–6.68) and borderline personality disorder (OR=4.12, CI_{95}=1.09–15.48) only in men.

Neurological Diseases

For historical reasons, the associations of latent toxoplasmosis with various mental health disorders are being studied more often than with other disorders and diseases. It is, however, very probable that the association with certain neurological disorders are even stronger than with mental health disorders. Most often, the associations of toxoplasmosis with epilepsy, headaches, and migraines are reported.

Epilepsy Toxoplasmosis has been reported to be associated with cryptogenic epilepsy, i.e., the epilepsy without any known cause. A meta-analytic study published in 2015 found six case-control studies comparing the prevalence of toxoplasmosis in patients with cryptogenic epilepsy and in controls [19•]. Overall OR was 2.25 (CI_{95}=1.27–3.9). The existence of an association between toxoplasmosis and epilepsy was also supported by the results of two ecological studies. The first one showed a correlation between the prevalence of latent toxoplasmosis and the incidence of cryptogenic epilepsy on a set of 16 European and non-European countries (r=0.98, p=0.001) [20], while the second showed a correlation between the prevalence of latent toxoplasmosis and cryptogenic epilepsy disease burden on the set of 29 European countries (r=0.82, p=0.025) and the set of 59 non-European countries (r=0.97, p=0.007) [13••]. *Toxoplasma* cysts containing slowly dividing bradyzoites persist and grow in the brain of an infected host. They eventually rupture, releasing many bradyzoites that infect surrounding cells. Bradyzoites and components of killed cells induce local inflammation, the process that could produce microglial scars (glial nodules). It is widely believed that these scars are the main cause of cryptogenic epilepsy in *Toxoplasma*-infected subjects [19•, 77]. Only six *Toxoplasma*-free and two *Toxoplasma*-infected subjects in 1046 participants of a smaller study reported to suffer epilepsy; therefore, the observed positive associations were not significant (see Table 1).

Recurrent Headaches and Migraines Acute toxoplasmosis is frequently accompanied with many neurological signs, which nearly always include headache [7, 78]. In immunocompetent subjects with acquired toxoplasmosis, the most frequent symptoms of the disease are lymphadenopathy and headache [21, 79]. Latent toxoplasmosis, the seemingly asymptomatic form of the disease, is probably accompanied by chronical local inflammation in foci that are usually localized in different places than the tissue cysts of the parasite [5, 80] and with an activation of immune system both inside and outside an infected brain [2, 81]. An increased concentration of certain immunomodulators and immunoeffectors, like interferon γ, tumor necrosis factor, and nitric oxide, are very often associated with various forms of headaches, including migraine; for a review, see [21, 82]. At present, migraine is usually considered to be a neurogenic inflammation disorder [83].

Despite the existence of many case reports and the obvious relation between toxoplasmosis, encephalitis, and headache, only one case-control study on the relation between headache or migraine and latent toxoplasmosis could be found in PubMed and Web of Science. Koseoglu and Yazar [21] showed that prevalence of toxoplasmosis in 104 patients with migraine was 44.2 % while in 50 healthy controls, or in 50 patients with headache due to rhinosinusitis, the prevalence was 26.0 and 24 %, respectively. This corresponds to OR=2.1, CI_{95}=1.16–3.84. In our internet-based study performed on 1046 internet users, 181 *Toxoplasma*-free and 64 *Toxoplasma*-infected subjects reported migraine (OR=1.27, p=0.02).

Other Neurological Disorders The relation between latent toxoplasmosis and Alzheimer's disease, Parkinson's disease, brain tumors, attention concentration deficit, hyperactivity, anorexia, Down syndrome, idiopathic intracranial hypertension, pseudotumor cerebri, aseptic meningitis, facial nerve palsy (Bell's palsy), hearing loss, and anosmia was also reported to exist—for a review, see [13••, 84]. Results of our cross-sectional study performed on 2619 nonclinical subjects suggest that the potential associations of latent toxoplasmosis

with multiple sclerosis, sense of motion problems, tics, fasciculation, posttraumatic stress disorder, primary insomnia, and learning disabilities deserve more attention in the future.

Methodological Issues Relating to the Study of Toxoplasmosis Disorders Associations

Acute toxoplasmosis spontaneously proceeds to the latent phase in nearly all infected subjects in Europe and North America. However, in subjects with impaired immunity or infected with a highly virulent strain of *Toxoplasma*, toxoplasmosis never turns latent and retains a chronical course with persisting or aperiodically returning symptoms of acute toxoplasmosis instead. Virulent strains of *Toxoplasma* are common in South America, where the highest diversity of *Toxoplasma* strains and also an extremely high prevalence of toxoplasmosis exists [85–87]. Due to the selection for the highest virulence within individual hosts superinfected with several genetically distinct strains of the parasite [88], the mean parasite virulence increases in centers of higher biodiversity and abundance of parasitic fauna. Therefore, one must be very careful with generalizations of results reported in individual case studies as well as results of case-control studies performed in South America. These studies might concern chronical, rather than latent, toxoplasmosis.

Another serious complication of the study of toxoplasmosis disorder associations concerns a sieve effect that could strongly influence the results of case-control studies. This effect can cause both false-negative and false-positive results. The course of toxoplasmosis is different in a subpopulation of subjects with certain, possibly rare predispositions. A case for this is the subjects with a certain genotype or subjects infected with a certain pathogen, e.g., cytomegalovirus [89]. Therefore, toxoplasmosis could trigger a particular disorder only in this small subpopulation, not in the general population which we are usually interested in. However, when we run a case-control study by comparing the frequency of toxoplasmosis in patients with a particular disease and in healthy controls, the obtained positive results are related to the subpopulation with the predisposition, not the general population. False-negative results could be obtained in some cases, such as when the course of the studied disorder is more serious in *Toxoplasma*-infected than in *Toxoplasma*-free subjects. It is possible that subjects with a more severe form of a disease cannot enter or refuse to enter the study. This can be the case of schizophrenia, see above, and possibly also some neurodegenerative disorders [90]. It is also possible that a more severe toxoplasmosis-associated form of a disorder, e.g., of borderline disorder, is more often classified as another disease, e.g., schizophrenia, and therefore, *Toxoplasma*-infected patients are not enrolled in studies of personality disorders.

The sieve effect can be avoided by using an alternative design, i.e., the cohort study, in which incidence of a particular disorder is compared between populations of *Toxoplasma*-infected subjects and *Toxoplasma*-free controls. Such studies are much more difficult to perform, and especially for rare disorders, they require extremely a large number of participants. Therefore, they are much rarer than studies that use a case-control design. Some problems occur even in these studies. Modern diagnostic methods for toxoplasmosis, which are based on the presence of anti-*Toxoplasma* antibodies, have very good specificity and a relatively good sensitivity. However, the level of anamnestic antibodies irregularly decreases as time passes from the moment of infection [91]. On the basis of the results of randomization tests, it was estimated that about 5–10 % of false-negative subjects occur in populations of birth-giving age women that had been diagnosed by two independent serological methods (IgG ELISA and complement fixation reaction) in the National Reference Laboratory [92]. In higher age strata, the number of seemingly *Toxoplasma*-free but actually *Toxoplasma*-infected subjects is probably higher. If the studied disorder needs a long time to fully develop, then false-negative subjects could have the highest incidence of the disorder and the case-control study could wrongly provide a false-negative instead of a positive association between toxoplasmosis and the disorder. This paradoxical effect of toxoplasmosis was already shown to exist [92] and could possibly explain an observed negative association between toxoplasmosis and multiple sclerosis [93].

Another highly undervalued problem of the toxoplasmosis research is the difference between men and women, both in the physiological and behavioral effects of toxoplasmosis and in the prevalence of toxoplasmosis [59]. When toxoplasmosis has opposite effects on men and women, the association could not be detected if the mixed sample of men and women is studied and sex is not included into the statistical model. Because a typical clinical picture of certain disorders differs, the men and women with the same disorder could be often diagnosed differently. Such clinical praxis could result in a seemingly opposite effect of toxoplasmosis (or any other epidemiological factor) on men and women. This can be the case, for example, of pairs of disorders such as tics-muscle fasciculation and possibly also schizophrenia-bipolar disorder. When the prevalence of toxoplasmosis and incidence of a particular disorder differ between men and women, then the analysis of a mixed sample could provide a false-positive result. Last but not least, behavioral response of men and women on chronical stress is the opposite. In contrast to men, who seem to use more individualistic and antisocial (e.g., aggressive, hostile) forms of coping with stress, women are more likely to seek and provide social support joined with others and verbalize toward others or toward one's self [94]. A recent biological (evolutionary) theory similarly distinguishes between the male "fight-or-flight" response and the female "tend-and-befriend" reaction to stress [95]. Opposite behavioral reactions to toxoplasmosis-

associated mild but continuous stress could result in different psychiatric diagnoses for men and women with the same disorder and the dissimulation (product tendency not to verbalize own problems) could result, for example, in a seemingly lower incidence of unipolar disorder in *Toxoplasma*-infected men.

Conclusions

A large part of the information concerning the associations between latent toxoplasmosis and neurological disorders was obtained in case studies or case-control studies of not fully satisfactory design, and therefore, it could be relevant only to a subpopulation of atypical subjects. In spite of this, some associations definitely exist even in the general population. The causal relation between *Toxoplasma* infection and the disorder has been analyzed by prospective studies only for schizophrenia. These studies have confirmed that the infection is the cause of the disorder. It is highly desirable to study the relation between toxoplasmosis and (not only) neurological disorders with prospective cohort studies performed on non-clinical population. It is even more desirable to search for a method of treatment of latent toxoplasmosis by destroying tissue cysts of the parasite and to decrease frequencies of infections by performing suitable epidemiological precautions.

Acknowledgments I would like to thank to J. Prandota, A. Vyas, E.F. Torrey, and Ch. Lotterman for their help with preparing the manuscript.

Compliance with Ethics Guidelines

Conflict of Interest The author declares that the work was supported by project UNCE 204004 (Charles University in Prague) and the Czech Science Foundation (Grant No. P303/11/1398).

Human and Animal Rights and Informed Consent This article contains no studies with human or animal subjects performed by the author.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Tenter AM, Heckeroth AR, Weiss LM. *Toxoplasma gondii*: from animals to humans. Int J Parasitol. 2000;30(12-13):1217–58.
2. Costa da Silva R, Langoni H. *Toxoplasma gondii*: host-parasite interaction and behavior manipulation. Parasitol Res. 2009;105: 893–8.
3. Pappas G, Roussos N, Falagas ME. Toxoplasmosis snapshots: global status of *Toxoplasma gondii* seroprevalence and implications for pregnancy and congenital toxoplasmosis. Int J Parasitol. 2009;39:1385–94.
4. 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.
5. Hermes G, Ajioka JW, Kelly KA, Mui E, Roberts F, Kasza K, et al. Neurological and behavioral abnormalities, ventricular dilatation, altered cellular functions, inflammation, and neuronal injury in brains of mice due to common, persistent, parasitic infection. J Neuroinflammation. 2008;5:48.:48.
6. Prandota J. The importance of *Toxoplasma gondii* infection in diseases presenting with headaches. Headaches and aseptic meningitis may be manifestations of the Jarisch-Herxheimer reaction. Int J Neurosci. 2009;119(12):2144–82.
7. Mamidi A, DeSimone JA, Pomerantz RJ. Central nervous system infections in individuals with HIV-1 infection. J Neurovirol. 2002;8(3):158–67.
8. Matinella A, Lanzafame M, Bonometti MA, Gajofatto A, Concia E, Vento S, et al. Neurological complications of HIV infection in pre-HAART and HAART era: a retrospective study. J Neurol. 2015;262(5):1317–27.
9. Mwanza JC, Nyamabo LK, Tylleskar T, Plant GT. Neuro-ophthalmological disorders in HIV infected subjects with neurological manifestations. Br J Ophthalmol. 2004;88(11):1455–9.
10. Ferguson DJ, Huskinson-Mark J, Araujo FG, Remington JS. An ultrastructural study of the effect of treatment with atovaquone in brains of mice chronically infected with the ME49 strain of *Toxoplasma gondii*. Int J Exp Pathol. 1994;75(2):111–6.
11. Araujo FG, Huskinson-Mark J, Gutteridge WE, Remington JS. In vitro and in vivo activities of the hydroxynaphthoquinone 566C80 against the cyst form of *Toxoplasma gondii*. Antimicrob Agents Chemother. 1992;36(2):326–30.
12. Shubar HM, Lachenmaier S, Heimesaat MM, Lohman U, Mauludin R, Mueller RH, et al. SDS-coated atovaquone nanosuspensions show improved therapeutic efficacy against experimental acquired and reactivated toxoplasmosis by improving passage of gastrointestinal and blood-brain barriers. J Drug Target. 2011;19(2):114–24.
13.•• 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). **This publication shows that prevalence of toxoplasmosis in general population correlates with the incidence and morbidity of many disorders, including the neurological disorders.**
14. 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.
15.•• Sutterland AL, Fond G, Kuin A, Koeter MW, Lutter R, van Gool T, et al. Beyond the association. *Toxoplasma gondii* in schizophrenia, bipolar disorder, and addiction: systematic review and meta-analysis. Acta Psychiatr Scand. 2015;132(3):161–79. **This is an excellent systematic review and meta-analytic study concerning a subset of neuropsychiatric disorders.**
16. Markovitz AA, Simanek AM, Yolken RH, Galea S, Koenen KC, Chen S, et al. *Toxoplasma gondii* and anxiety disorders in a community-based sample. Brain Behav Immun. 2015;43:192–7.
17. Lester D. Predicting European suicide rates with physiological indices. Psychol Rep. 2010;107:713–4.
18. Ling VJ, Lester D, Mortensen PB, Postolache TT. *Toxoplasma gondii* seropositivity and completed suicide in 20 European countries. Biol Psychiatry. 2011;69:500.
19.• Ngoungou EB, Bhalla D, Nzoghe A, Darde M-L, Preux P-M. Toxoplasmosis and epilepsy—systematic review and meta analysis. PLoS Neglect Trop D. 2015;9(2). **Excellent meta-analytic study showing association between toxoplasmosis and epilepsy.**
20. Palmer BS. Meta-analysis of three case controlled studies and an ecological study into the link between cryptogenic epilepsy and chronic toxoplasmosis infection. Seizure. 2007;16(8):657–63.

21. Koseoglu E, Yazar S, Koc I. Is *Toxoplasma gondii* a causal agent in migraine? Am J Med Sci. 2009;338:120–2.
22. Pedersen MG, Mortensen PB, Norgaard-Pedersen B, Postolache TT. *Toxoplasma gondii* infection and self-directed violence in mothers. Arch Gen Psychiatry. 2012;69(11):1123–30.
23.•• Prandota J, Elleboudy NAF, Ismail KA, Zaki OK, Shehata HH. Increased seroprevalence of chronic toxoplasmosis in autistic children: special reference to the pathophysiology of IFN-gama and NO overproduction. Int J Neurol Res. 2015;1(3):102–22. **The first case-control study showing significant association between toxoplasmosis and autism.**
24. Minto A, Roberts FJ. The psychiatric complications of toxoplasmosis. Lancet. 1959;1180–2.
25. Fuller TE, Rawlings R, Yolken RH. The antecedents of psychoses: a case-control study of selected risk factors. Schizophr Res. 2000;46:17–23.
26. Torrey EF, Simmons W, Yolken RH. Is childhood cat ownership a risk factor for schizophrenia later in life? Schizophr Res. 2015;165(1):1–2.
27. Torrey EF, Bartko JJ, Yolken RH. *Toxoplasma gondii* and other risk factors for schizophrenia: an update. Schizophr Bull. 2012;38(3): 642–7.
28. Horacek J, Flegr J, Tintera J, Verebova K, Spaniel F, Novak T, 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.
29. Hinze-Selch D, Daubener W, Eggert L, Erdag S, Stoltenberg R, Wilms S. A controlled prospective study of *Toxoplasma gondii* infection in individuals with schizophrenia: beyond seroprevalence. Schizophr Bull. 2007;33:782–8.
30.• Flegr J, Priplatova L, Hampl R, Bicikovia M, Ripova D, Mohr P. 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. **This study shows that prevalence of toxoplasmosis in male schizophrenia patients is very high even today, if clinical samples routinely collected for various clinical purposes are examined.**
31. Wang HL, Wang GH, Li QY, Shu C, Jiang MS, Guo Y. Prevalence of *Toxoplasma* infection in first-episode schizophrenia and comparison between *Toxoplasma*-seropositive and *Toxoplasma*-seronegative schizophrenia. Acta Psychiatr Scand. 2006;114:40–8.
32. Amminger GP, McGorry PD, Berger GE, Wade D, Yung AR, Phillips LJ, et al. Antibodies to infectious agents in individuals at ultra-high risk for psychosis. Biol Psychiatry. 2007;61:1215–7.
33. Yolken RH, Dickerson FB, Torrey EF. *Toxoplasma* and schizophrenia. Parasite Immunol. 2009;31:706–15.
34. Holub D, Flegr J, Dragomirecka E, Rodriguez M, Preiss M, Novak T, 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.
35.• Celik T, Kartalci S, Atas O, Akarsu GA, Unal S. Association between latent toxoplasmosis and clinical course of schizophrenia—continuous course of the disease is characteristic for *Toxoplasma gondii*-infected patients. Folia Parasitol. 2015;62. **This study shows that *Toxoplasma*-infected schizophrenia patients have 15× higher probability of having continuous course of disease than *Toxoplasma*-free patients.**
36. Dickerson F, Boronow J, Stallings C, Origoni A, Yolken R. *Toxoplasma gondii* in individuals with schizophrenia: association with clinical and demographic factors and with mortality. Schizophr Bull. 2007;33:737–40.
37. Kankova S, Flegr J, Calda P. The influence of latent toxoplasmosis on women's reproductive function: four cross-sectional studies. Folia Parasitol. 2015;62.
38. Stibbs HH. Changes in brain concentrations of catecholamines and indoleamines in *Toxoplasma gondii* infected mice. Ann Trop Med Parasitol. 1985;79:153–7.
39. Flegr J, Preiss M, Klose J, Havlíček J, Vitáková M, Kodym P. 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.
40. Skallová A, Novotná M, Kolbeková P, Gašová Z, Veselý V, Flegr J. Decreased level of novelty seeking in blood donors infected with *Toxoplasma*. Neuroendocrinol Lett. 2005;26(5):480–6.
41. 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.
42.• Gatkowska J, Wieczorek M, Dziadek B, Dzitko K, Dlugonska H. Sex-dependent neurotransmitter level changes in brains of *Toxoplasma gondii* infected mice. Exp Parasitol. 2013;133(1):1–7. **Excellent study showing influence of latent and acute toxoplasmosis on concentration of various neurotransmitters including dopamine in mice.**
43. Gaskell EA, Smith JE, Pinney JW, Westhead DR, McConkey GA. A unique dual activity amino acid hydroxylase in *Toxoplasma gondii*. PLoS ONE. 2009;4:e4801.
44. Prandovszky E, Gaskell E, Martin H, Dubey JP, Webster JP, McConkey GA. The neurotropic parasite *Toxoplasma gondii* increases dopamine metabolism. PLoS ONE. 2011;6(9):e23866.
45. Wang ZT, Harmon S, O'Malley KL, Sibley LD. Reassessment of the role of aromatic amino acid hydroxylases and the effect of infection by *Toxoplasma gondii* on host dopamine. Infect Immun. 2015;83(3):1039–47.
46. Tan D, Soh LJT, Lim LW, Daniel TCW, Zhang XD, Vyas A. Infection of male rats with *Toxoplasma gondii* results in enhanced delay aversion and neural changes in the nucleus accumbens core. Proc R Soc Biol Sci Ser B. 2015;282(1808).
47. Willner P. The dopamine hypothesis of schizophrenia: current status, future prospects. Int Clin Psychopharmacol. 1997;12(6):297–308.
48. Nikam SS, Awasthi AK. Evolution of schizophrenia drugs: a focus on dopaminergic systems. Curr Opin Investig Drugs. 2008;9:37–46.
49. Schwarcz R, Hunter CA. *Toxoplasma gondii* and schizophrenia: linkage through astrocyte-derived kynurenic acid? Schizophr Bull. 2007;33:652–3.
50. Barnard CJ, Behnke JM. Parasitism and host behaviour. New York: Taylor and Francis; 1990.
51. MacKenzie CR, Heseler K, Muller A, Daubener W. Role of indoleamine 2,3-dioxygenase in antimicrobial defence and immuno-regulation: tryptophan depletion versus production of toxic kynurenines. Curr Drug Metab. 2007;8(3):237–44.
52. Hamdani N, Daban-Huard C, Lajnef M, Richard JR, Delavest M, Godin O, et al. Relationship between *Toxoplasma gondii* infection and bipolar disorder in a French sample. J Affect Disord. 2013;148(2-3):444–8.
53. Dickerson F, Stallings C, Origoni A, Vaughan C, Katsafanas E, Khushalani S, et al. Antibodies to *Toxoplasma gondii* in individuals with mania. Bipolar Disord. 2014;16(2):129–36.
54. Dickerson F, Stallings C, Origoni A, Katsafanas E, Schweinfurth L, Savage C, et al. Antibodies to *Toxoplasma gondii* and cognitive functioning in schizophrenia, bipolar disorder, and nonpsychiatric controls. J Nerv Ment Dis. 2014;202(8):589–93.
55. Fond G, Boyer L, Gaman A, Laouamri H, Attiba D, Richard JR, et al. Treatment with anti-toxoplasmic activity (TATA) for *Toxoplasma* positive patients with bipolar disorders or schizophrenia: a cross-sectional study. J Psychiatr Res. 2015;63:58–64.
56. Foa EB, Huppert JD, Leiberg S, Langner R, Kichic R, Hajcak G, et al. The obsessive-compulsive inventory: development and validation of a short version. Psychol Assess. 2002;14(4):485–96.

57. Hsu PC, Groer M, Beckie T. New findings: depression, suicide, and *Toxoplasma gondii* infection. J Am Assoc Nurse Pract. 2014;26(11):629–37.
58. Flegr J. How and why *Toxoplasma* makes us crazy. Trends Parasitol. 2013;29(4):156–63.
59. Flegr J. Influence of latent *Toxoplasma* infection on human personality, physiology and morphology: pros and cons of the *Toxoplasma*-human model in studying the manipulation hypothesis. J Exp Biol. 2013;216(1):127–33.
60. Groer MW, Yolken RH, Xiao JC, Beckstead JW, Fuchs D, Mohapatra SS, et al. Prenatal depression and anxiety in *Toxoplasma gondii*-positive women. Am J Obstet Gynecol. 2011;204(5).
61. Gale SD, Brown BL, Berrett A, Erickson LD, Hedges DW. Association between latent toxoplasmosis and major depression, generalised anxiety disorder and panic disorder in human adults. Folia Parasitol. 2014;61(4):285–92.
62. Flegr J, Lenochová P, Hodný Z, Vondrová M. Fatal attraction phenomenon in humans: cat odour attractiveness increased for *Toxoplasma*-infected men while decreased for infected women. PLoS Negl Trop Dis. 2011;5(11):e1389.
63. Lester D. *Toxoplasma gondii* and homicide. Psychol Rep. 2012;111:196–7.
64. Arling TA, Yolken RH, Lapidus M, Langenberg P, Dickerson FB, Zimmerman SA, et al. *Toxoplasma gondii* antibody titers and history of suicide attempts in patients with recurrent mood disorders. J Nerv Ment Dis. 2009;197:905–8.
65. Okusaga O, Langenberg P, Sleemi A, Vaswani D, Giegling I, Hartmann AM, et al. *Toxoplasma gondii* antibody titers and history of suicide attempts in patients with schizophrenia. Schizophr Res. 2011;133(1-3):150–5.
66. Yagmur F, Yazar S, Temel HO, Cavusoglu M. May *Toxoplasma gondii* increase suicide attempt—preliminary results in Turkish subjects? Forensic Sci Int. 2010;199:15–7.
67. Zhang Y, Traskman-Bendz L, Janelidze S, Langenberg P, Saleh A, Constantine N, et al. *Toxoplasma gondii* immunoglobulin G antibodies and nonfatal suicidal self-directed violence. J Clin Psychiatry. 2012;73(8):1069–76.
68. Ling VJ, Lester D, Mortensen PB, Langenberg PW, Postolache TT. *Toxoplasma gondii* seropositivity and suicide rates in women. J Nerv Ment Dis. 2011;199:440–4.
69. Prandota J. Neuropathological changes and clinical features of autism spectrum disorder participants are similar to that reported in congenital and chronic cerebral toxoplasmosis in humans and mice. Res Autism Spectr Disord. 2010;4:103–18.
70. Prandota J. Autism spectrum disorders may be due to cerebral toxoplasmosis associated with chronic neuroinflammation causing persistent hypercytokinemia that resulted in an increased lipid peroxidation, oxidative stress, and depressed metabolism of endogenous and exogenous substances. Res Autism Spectr Disord. 2010;4:119–55.
71. Brown AS. Epidemiologic studies of exposure to prenatal infection and risk of schizophrenia and autism. Dev Neurobiol. 2012;72(10): 1272–6.
72. Prandota J. Gastrointestinal tract abnormalities in autism, inflammatory bowel disease and many other clinical entities may be due to *T. gondii* infection. Open Acc Sci Rep. 2012;1:256.
73. Prandota J. Idiopathic intracranial hypertension may be caused by reactivation of latent cerebral toxoplasmosis probably because of disturbances in the host and/or *Toxoplasma gondii* immune defense mechanisms. Effect of various medications and biologic agents. In: Gemma C, editor. Neuroinflammation pathogenesis, mechanisms, and management. New York: Nova; 2012. p. 274–336.
74. Prandota J. Idiopathic intracranial hypertension may be caused by reactivation of latent cerebral toxoplasmosis. Effect of various diseases and clinical states. In: Gemma C, editor. Neuroinflammation pathogenesis, mechanisms and management. New York: Nova; 2012. p. 337–43.
75. Abdoli A, Dalimi A. Are there any relationships between latent *Toxoplasma gondii* infection, testosterone elevation, and risk of autism spectrum disorder? Front Behav Neurosci. 2014;8.
76. Hinze-Selch D, Daubener W, Erdag S, Wilms S. The diagnosis of a personality disorder increases the likelihood for seropositivity to *Toxoplasma gondii* in psychiatric patients. Folia Parasitol. 2010;57:129–35.
77. Stommel EW, Seguin R, Thadani VM, Schwartzman JD, Gilbert K, Ryan KA, et al. Cryptogenic epilepsy: an infectious etiology? Epilepsia. 2001;42(3):436–8.
78. Wong WK, Upton A, Thomas MG. Neuropsychiatric symptoms are common in immunocompetent adult patients with *Toxoplasma gondii* acute lymphadenitis. Scand J Infect Dis. 2013;45(5):357–61.
79. Anand R, Jones CW, Ricks JH, Sofarelli TA, Hale DC. Acute primary toxoplasmosis in travelers returning from endemic countries. J Travel Med. 2012;19(1):57–60.
80. Berenreiterova M, Flegr J, Kubena AA, Nemec P. The distribution of *Toxoplasma gondii* cysts in the brain of a mouse with latent toxoplasmosis: implications for the behavioral manipulation hypothesis. PLoS ONE. 2011;6(12):e28925.
81. Flegr J, Stříž I. Potential immunomodulatory effects of latent toxoplasmosis in humans. BMC Infect Dis. 2011;11:274.
82. Prandota J, Gryglas A, Fuglewicz A, Zeslawska-Falenczyk A, Ujma-Czapska B, Szenborn L, et al. Recurrent headaches may be caused by cerebral toxoplasmosis. World J Clin Pediatr. 2014;3(3):59–68.
83. Waeber C, Moskowitz MA. Migraine as an inflammatory disorder. Neurology. 2005;64(10):S9–S15.
84. Prandota J. *T. gondii* infection acquired during pregnancy and/or after birth may be responsible for development of both type 1 and 2 diabetes mellitus. J Diabetes Metab. 2013;4(2):55.
85. Ajzenberg D. Type I, strains in human toxoplasmosis: myth or reality? Future Microbiol. 2010;5:841–3.
86. Wendte JM, Gibson AK, Grigg ME. Population genetics of *Toxoplasma gondii*: new perspectives from parasite genotypes in wildlife. Vet Parasitol. 2011;182(1):96–111.
87. Minot S, Melo MB, Li F, Lu D, Niedelman W, Levine SS, et al. Admixture and recombination among *Toxoplasma gondii* lineages explain global genome diversity. Proc Natl Acad Sci U S A. 2012;109(33):13458–63.
88. Hamilton WD. Altruism and related phenomena, mainly in social insects. Annu Rev Ecol Syst. 1972;3:193–232.
89. Novotná M, Hanušová J, Klose J, Preiss M, Havlíček J, Roubalová K, et al. Probable neuroimmunological link between *Toxoplasma* and cytomegalovirus infections and personality changes in the human host. BMC Infect Dis. 2005;5:54.
90. Celik T, Kamisli O, Babur C, Cevik MO, Oztuna D, Altinayar S. Is there a relationship between *Toxoplasma gondii* infection and idiopathic Parkinson's disease? Scand J Infect Dis. 2010;42(8):604–8.
91. Kodym P, Machala L, Roháčová H, Širocká B, Malý M. Evaluation of a commercial IgE ELISA in comparison with IgA and IgM ELISAs, IgG avidity assay and complement fixation for the diagnosis of acute toxoplasmosis. Clin Microbiol Infect. 2007;13:40–7.
92. Flegr J, Hrdá Š, Kodym P. Influence of latent 'asymptomatic' toxoplasmosis on body weight of pregnant women. Folia Parasitol. 2005;52:199–204.
93. Stascheit F, Paul F, Harms L, Rosche B. *Toxoplasma gondii* seropositivity is negatively associated with multiple sclerosis. J Neuroimmunol. 2015;285:119–24.
94. Lindová J, Kuběna AA, Šturcová A, Křivohlavá R, Novotná M, Rubešová A, et al. Pattern of money allocation in experimental games supports the stress hypothesis of gender differences in *Toxoplasma gondii*-induced behavioural changes. Folia Parasitol. 2010;57:136–42.
95. Taylor SE, Klein LC, Lewis BP, Gruenewald TL, Gurung RAR, Updegraff JA. Biobehavioral responses to stress in females: tend-and-befriend, not fight-or-flight. Psychol Rev. 2000;107(3):411–29.