Opinion

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How and why *Toxoplasma* makes us crazy

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For a long time, a latent toxoplasmosis, the lifelong presence of dormant stages of *Toxoplasma* in various tissues, including the brain, was considered harmless for immunocompetent persons. Within the past 10 years, however, many independent studies have shown that this parasitic disease, with a worldwide prevalence of about 30%, could be indirectly responsible for hundreds of thousands of deaths due to its effects on the rate of traffic and workplace accidents, and also suicides. Moreover, latent toxoplasmosis is probably one of the most important risk factors for schizophrenia. At least some of these effects, possibly mediated by increased dopamine and decreased tryptophan, are products of manipulation activity by *Toxoplasma* aiming to increase the probability of transmission from intermediate to definitive host through predation.

On teaching an old disease new tricks

No-one was probably concerned with the parasitic protozoon *Toxoplasma gondii* during the first 20 years after its discovery in 1908 in the rodent *Ctenodactylus gundi* [1]. However, when its detrimental effects on the retina were discovered, toxoplasmosis (Box 1) became a disease of interest for ophthalmologists. Following the discovery of congenital toxoplasmosis in 1939, concern spread among obstetricians and then to a plethora of specialists with the rise of transplantation medicine, oncology, and the AIDS epidemic, when encephalitis began killing immunosuppressed patients. In the past 20 years an association between latent toxoplasmosis and serious psychiatric and neurological diseases [2–10] has been discovered, forcing psychiatrists and neurologists to open parasitological textbooks more and more often. And, most probably, this is not the end of the story. But let us start from the beginning.

The first indices of the role of toxoplasmosis in psychiatric diseases were found in the early 1950s (reviewed in [2]). Studies performed in various countries showed increased seroprevalence of toxoplasmosis in psychiatric patients. It was speculated as to whether toxoplasmosis causes psychiatric disease or whether the psychiatric disease or hospitalization in a mental facility increases the probability of *Toxoplasma* infection. A study performed on US soldiers found that the first occurrence of anti-*Toxoplasma* antibodies was detected in frozen blood samples collected from subjects that were later demilitarized because of their psychiatric disease 6 months and often even 2–3 years before the onset of the schizophrenia [11]. This suggests that toxoplasmosis may cause schizophrenia in subjects with genetic and non-genetic predispositions rather than the alternative hypothesis that schizophrenia increases the probability of *Toxoplasma* infection. The same conclusions can be deduced from the fact that, in *Toxoplasma*-free schizophrenics, the onset of disease is the same for female and male patients (at 23 years), whereas in *Toxoplasma*-infected schizophrenics the disease starts about 3 years later in females (at 27 years) than in males (at 23.5 years) [12]. In the Czech population, males and females are usually infected before the age of

Glossary

Bradyzoites: slowly dividing and sessile form of the parasite contained in tissue cysts during the latent phase of toxoplasmosis.
Correlation study: a study aiming to reveal a statistical association between two factors (e.g., toxoplasmosis and suicides) by comparison of their occurrence in various populations (e.g., various countries).
Definitive host: the host species in which sexual reproduction of the parasite takes place.
Dopamine: a monoamine neurotransmitter and member of the catecholamine family that plays a fundamental role in many neurologic processes including reward-driven learning. Abnormal levels of dopamine are characteristic for many neurological and psychiatric diseases, such as Parkinson disease and schizophrenia.
Incidence of parasitosis: the number of new infections during a fixed period (e.g., 1 year) in a particular population.
Intermediate host: the host species in which only asexual reproduction of the parasite takes place.
Manipulation hypothesis: the hypothesis claiming that many species of parasites evolved an ability to increase the probability of transmission from their intermediate to definitive hosts by modifying the phenotype, typically the behavior, of the infected host.
Oocysts: the dormant form of the parasite, the product of its sexual reproduction in intestinal cells of infected cats. Thick-walled oocysts can survive in dropping-contaminated soil for years.
Prevalence of a parasite: the percentage of infected hosts in a particular population. It is dependent on the incidence and duration of the infection.
Tachyzoites: the rapidly dividing and motile form of the parasite contained in various host cells, including macrophages, during the acute phase of toxoplasmosis.
Tissue cysts: transformed host cells containing a parasitophorous vacuole with a population of slowly dividing bradyzoites. Raw or undercooked meat with tissue cysts is an important source of infection for definitive and intermediate hosts.
Schizophrenia: a common (prevalence 0.5–1%) and serious psychiatric disease characterized by a complex of positive (hallucinations, delusions), negative (e.g., social withdrawal), and general symptoms (cognitive deficits). In most cases, modern antipsychotic drugs successfully cure the positive symptoms of schizophrenia which are caused mainly by an increased concentration of dopamine [25].

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Keywords: *Toxoplasma*; toxoplasmosis; schizophrenia; mental illness; manipulation hypothesis; behavior.

1471-4922/$ – see front matter
 http://dx.doi.org/10.1016/j.pt.2013.01.007

Box 1. Four distinct forms of toxoplasmosis

Toxoplasmosis has several forms that differ from a clinical point of view. Acute toxoplasmosis, which is characterized by the rapid reproduction of tachyzoites in cells of different tissues of the host body, is usually a self-limited disease. Malaise, fever, fatigue, headache, and cervical lymphadenopathy are typical symptoms of this form of disease. In sensitive individuals it can be accompanied also by transient psychiatric symptoms [79], and in immunocompromised subjects it can even have a fatal outcome. In a small fraction of individuals, acute toxoplasmosis can take a chronic course – the symptoms of acute toxoplasmosis persist or periodically return for many years. In most cases the activated immune system causes transition of acute toxoplasmosis into latent toxoplasmosis. In this stage of disease, tissue cysts with slowly reproducing bradyzoites are formed and survive in various tissues of the body, including the brain, for many years or until the end of the life of the host. The presence of these cysts induces local inflammation in the infected tissues, and the bradyzoites release various antigens and other molecules, for example, dopamine, into surrounding tissues. The presence of living parasites protects the host against new infection; however, after natural or artificial immunosuppression (AIDS; immunosuppression in oncological or transplantation patients), the latent toxoplasmosis quickly transits into a new, severe acute phase, and without radical and rapid treatment the patient usually dies of encephalitis. In the case of infection of a woman immediately before pregnancy or in the first trimester of pregnancy, the infection is transmitted from mother to fetus in about 10% of cases, resulting in either abortion or serious malformations of the fetus, including hydrocephalus and microcephalus. If the infection of the mother occurs in the third trimester, the probability of infection of the fetus is much higher, ~50–60%. However, the resulting symptoms of congenital toxoplasmosis are usually much milder, sometimes only causing various ophthalmologic defects such as chorioretinitis or intracranial calcifications.

Humans can acquire *Toxoplasma* infection by eating tissue cysts in undercooked or raw meat from an infected intermediate host, or by ingestion of oocytes with, for example, unwashed vegetables or drinking water contaminated with the feces of an infected cat. Acute toxoplasmosis resulting from the infection by oocytes usually has a worse course than acute toxoplasmosis acquired from tissue cysts [80]. During the past 20 years, the prevalence of toxoplasmosis in young people (monitored usually in pregnant women) has decreased by about 1% per year in many developed countries [81]. This decrease is probably due to the consumption of cooled and frozen meat, a procedure that kills bradyzoites in tissue cysts. In some countries the prevalence of toxoplasmosis is rising. It can be speculated that this increase can be attributed to either an increase in the number of households owning cats (China) or by current trends to consume organic food (Western Australia).

nine. However, a second peak of incidence of infection occurs around the ages of 25 to 30 in women [13]. This second peak (Box 2) could explain the later onset for toxoplasmosis-associated schizophrenia in females.

The strongest evidence for the causal role of *Toxoplasma* in triggering schizophrenia comes from a recent magnetic resonance imaging (MRI) study showing that differences in brain morphology, originally thought to be characteristic of schizophrenia patients – namely the decreased density of gray matter in particular parts of the brain – are actually present only in the subpopulation of *Toxoplasma*-infected patients [14]. In *Toxoplasma*-free schizophrenics no such changes were observed. It seems far more probable that toxoplasmosis induces changes in the brain gray-matter density than that the decrease of gray-matter density influences the risk of *Toxoplasma* infection, especially when no differences in gray matter were observed between *Toxoplasma*-infected and *Toxoplasma*-free healthy controls (Box 3). The absence of these differences in normal subjects also suggests that toxoplasmosis can trigger schizophrenia only in individuals with particular predispositions; the same is also suggested by the simple fact that 30% of people are infected with *Toxoplasma* whereas only 0.5–1% of people develop schizophrenia during their lifetime [15]. Nevertheless, toxoplasmosis increases the risk of schizophrenia roughly 2.7 times (OR, 2.73; CI_{95} 2.21–3.38), which is more than any 'gene for schizophrenia' that has been described so far (OR, 1.09–1.24) [16].

The increased prevalence of toxoplasmosis in schizophrenics was demonstrated by at least 50 studies (for reviews and a meta-analytic study see [2,16,17]). However, some studies completed recently in developed countries did not find such an increase [14,18]. It can be speculated that this negative result could be due to an increased concern about the rights of patients. In the past, all patients of a particular hospital were automatically included in the study. Currently, only the patients who are able and willing to sign the informed consent document participate in studies. Data suggest that *Toxoplasma*-infected men are more suspecting, and that *Toxoplasma*-infected men and women are less cooperative and conscientious than their *Toxoplasma*-free peers [19,20]. Moreover, *Toxoplasma*-infected schizophrenia patients express more severe symptoms of psychosis than *Toxoplasma*-free patients [12,21–23]. Higher suspiciousness and lower cooperativeness and conscientiousness of infected subjects, as well as more severe clinical symptoms in *Toxoplasma*-infected schizophrenia patients, decrease the probability of including *Toxoplasma*-infected schizophrenics in the study.

How toxoplasmosis increases the risk of schizophrenia

The physiological mechanism behind the association between toxoplasmosis and schizophrenia is unknown. It is, however, probable that increased concentration of the neurotransmitter dopamine in specific parts of the brain plays a central role. The fundamental role of increased concentration of dopamine in schizophrenia is rarely doubted [24]. Nearly all modern antipsychotic drugs either inhibit dopamine receptors or decrease the level of dopamine in the brain [25]. The increased level of dopamine in the brains of mice infected with *Toxoplasma* was described in 1985 [26]. Indirect evidence of increased levels of dopamine in humans with toxoplasmosis, namely their lower scores for Clonger's personality factor of novelty-seeking, were later observed in soldiers and in blood donors [27,28]. The most parsimonious explanation of increased levels of dopamine in the brains of *Toxoplasma*-infected hosts is the production of this neurotransmitter by particular subpopulations of brain cells responding to interleukin-2 produced by activated leukocytes at sites of local inflammation in the infected brains [29,30]. This hypothesis was supported by the results of a study showing decreased level of novelty-seeking in subjects infected with cytomegalovirus, a herpetic virus that also causes inflammation foci [30]. However, in 2009 Gaskell *et al*. showed that the genome

Box 2. Is toxoplasmosis a sexually transmitted disease?

Parasitologists often suppose that young women, more often than young men, acquire the infection by manipulation of raw meat when they start cooking after marriage. This conjecture is supported by extremely high prevalence of toxoplasmosis observed many times in workers in slaughterhouses and sometimes in cooks; however, it has never been rigorously tested. Current results show that *Toxoplasma* is easily transmitted from males to females by an ejaculate in many animal species [82]. This suggests that a second possible source of infection in women (but probably not men) could be unprotected sex between partners. This alternative route of infection can be extremely serious because unprotected sex may lead not only to infection but also to pregnancy, and may therefore result in congenital toxoplasmosis. The existence of this route might explain the low effectiveness of educational campaigns aiming to lower the risk of congenital toxoplasmosis [83] and also the fact that up to two-thirds of infections could not be explained by known risk factors [84].

of *Toxoplasma* contains two genes for the enzyme tyrosine hydroxylase, the key enzyme for synthesis of dopamine [31]. Another study showed that the bradyzoites in tissue cysts express these enzymes and release dopamine into surrounding tissue [32]. Distribution of cysts (Figure 1) within brains is relatively random, possibly reflecting the site of entrance of activated dendritic cells containing parasites [33] into the brain ([34], reviewed in [35]) The difference between individuals in the localization of cysts could be one of the reasons why schizophrenia develops in less than 3% of *Toxoplasma*-infected subjects.

Dopamine is the major suspect responsible for the association between toxoplasmosis and schizophrenia; however, it is not the only suspect. For example, infected male students also express an increased concentration of testosterone in saliva [36,37]. It was originally speculated that subjects with higher concentrations of testosterone would have a higher probability of *Toxoplasma* infection due to the immunosuppressive effects of steroid hormones. This immunosuppression hypothesis of testosterone–toxoplasmosis association was later indirectly supported by the fact that a higher concentration of testosterone was not observed in two independent studies performed on different populations [28]. Moreover, both artificially infected male and female mice expressed significantly lower concentrations of testosterone [38]. However, recently published results of experiments performed on male laboratory rats (the representatives of species that respond to toxoplasmosis the most similarly to humans) showed that testosterone increases in males after infection [39]. This study showed that the mechanism of upregulation of testosterone involves the increase of luteinization hormone receptors on Leydig cells, in other words the receptors that regulate the synthesis of testosterone in testes. Therefore, *Toxoplasma* can increase the concentration of testosterone in males but not in females, which agrees with the observed lower level of testosterone in *Toxoplasma*-infected female students [36]. The opposite shift of testosterone concentration in *Toxoplasma*-infected men and women could explain why many personality factors are also shifted in opposite directions in men and women following *Toxoplasma* infection [19,40].

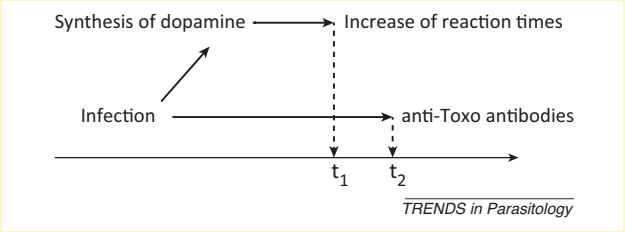
Tryptophan, or rather kynurenic acid, as well as other biologically active products of the metabolism of tryptophan, may be responsible for behavioral effects of toxoplasmosis. Tryptophan is an essential amino acid for many parasites, including *Toxoplasma*. One of the protective roles of interferon γ is the induction of the synthesis of indoleamine 2,3-dioxygenase, the enzyme that metabolizes tryptophan into *N*-formylkynurenine [41]. The decrease in the availability of tryptophan could result not only in the starvation of parasites [42], and inhibition of their growth, but also in the decrease of the concentration of the neurotransmitter serotonin, which is synthesized from tryptophan. The decrease in tryptophan also results in an increase of kynurenic acid [43], an antagonist of the glutamatergic NMDA (*N*-methyl-D-aspartate) receptor, which plays an important role in schizophrenia. Kynurenic acid may be responsible for, or contribute to, memory defects and other cognitive symptoms characteristic of schizophrenia patients, including the increase of dopaminergic tension [44,45]. At the same time, the decrease in the concentration of serotonin could be responsible for depression and irritability observed in patients [46]. Depression, possibly caused by inhibition of parasite growth by tryptophan starvation, can be responsible for the increased risk of suicides observed in psychiatric patients with high concentrations of anti-*Toxoplasma* antibodies [47,48]. Increased prevalence of toxoplasmosis (41% vs 28%) was also observed in subjects hospitalized after suicide attempt [49]. A correlation study showed that the incidence of suicides in Europe correlates with prevalence of toxoplasmosis in any particular country [50,51]. The most convincing evidence for the relationship between toxoplasmosis and risk of suicide so far was provided by a prospective study performed on 45 788 Danish women that were pregnant between the years 1992 and 1995, and who were observed until the year 2006 [52]. The infected woman had about a 2-fold higher probability of suicide and 1.5-fold increased probability of suicide attempt than the *Toxoplasma*-free women. Although many symptoms of toxoplasmosis, including change in personality factors [53] and prolongation of reaction times [54], increase with decreasing concentrations of anti-*Toxoplasma* antibodies, and therefore increase with probable length of time since the onset of infection, the risk of suicide decreases with decreasing concentration of anti-*Toxoplasma* antibodies. This indicates that the observed behavioral changes and reaction times changes are most probably the cumulative effects of latent toxoplasmosis, whereas the increased risk of suicide could represent more probably the transient effect or after-effect of acute *Toxoplasma* infection.

Results of many studies suggest that latent toxoplasmosis could play an important role in a much broader spectrum of psychiatric and neurological disorders, such as bipolar disorder [3], personality disorder [4], Parkinson disease [5], Alzheimer disease [6], obsessive–compulsive disorder [7], cryptic epilepsy [8], recurrent migraines [9], autism [10], and even brain tumors [55,56]. The prevalence of toxoplasmosis in a particular country correlates with incidence of homicides, suggesting that the toxoplasmosis could be also responsible for the most serious defects in social behavior [57].

Box 3. How does one distinguish between cause and effect in epidemiology?

Based on the existence of a statistical association between two phenomena, we cannot determine which of the phenomena is the cause and which the effect – in other words, whether event *A* causes event *B*, or whether event *B* causes event *A*. Not only are we unable to determine whether event *A* causes *B*, or vice versa, there often is an (unknown) event *C* that causes both *A* and *B*. To determine causation we usually rely on additional information. Sometimes common sense is enough. For example, if statistical testing shows us that the reaction time of a person is related to his/her age, we do not assume that a slower reaction time causes an older age. Nevertheless, even in this case we cannot forget the distinct possibility that there may exist another phenomenon, *C*, which is related to both age and the tested reaction time. For example, younger people generally are better trained in rapid reactions (and especially in quickly reacting to stimuli on a screen and pressing buttons) from playing video games and texting. Sometimes it helps to use the criterion of temporality. If phenomenon *A* always precedes phenomenon *B*, then it is not very likely that *B* could be the cause of *A*. But even the criterion of temporality is not completely infallible (Figure I). Usually, we observe neither *A* nor *B* directly, but determine them based on other phenomena *A*′ and *B*′. For example, we do not observe *Toxoplasma* infection directly (the presence of the parasite in the human), but instead determine infection status based on the presence of specific antibodies that the immune system creates to fight the parasite. However, it takes some time for the body to create antibody levels that are sufficiently high for us to detect them; it might happen that we observe a worsened reaction time in a person before we determine *Toxoplasma* infection, and, based on the criterion of temporality, we might (erroneously) conclude that worsened reaction time increases the risk of infection. Even the gold standard, the result of experimental infection with *Toxoplasma*, is not infallible – infection inocula can be contaminated with an unknown virus responsible for the observed behavioral effects. In fact, some data suggest that contact with a cat, rather than toxoplasmosis, is the risk factor for schizophrenia in some populations [85].

In general, we have to comply with a rule explicitly described only in the first half of the 20th century by Sir Karl Raimund Popper: in science (and in epidemiology too), hypotheses cannot be proven – only refuted. We only consider a hypothesis to be (conditionally) true when it has survived a sufficiently long onslaught of intensive attempts to refute it.



Figu1re I. An example of the failure of the temporality criterion. In a test, we may find that some people have longer reaction times before we detect (using the antibody test) that they have toxoplasmosis, even if/though the prolongation of reaction times is due to toxoplasmosis (Toxo). This is a hypothetical and perhaps unlikely example. It is more likely, but not certain, that specific antibodies appear before the infected person attains a longer reaction time.

Why *Toxoplasma* changes human behavior and personality

Behavioral effects of toxoplasmosis began to be studied because *Toxoplasma* represents a classical model for studying the so-called manipulation hypothesis [58]. In its life cycle, this parasite needs to be transmitted from an intermediate host, any warm-blooded animal, to the definitive host, the feline predator. Similarly to many other parasites that are also transmitted by predation, *Toxoplasma* is known to manipulate the behavior of their hosts to increase the probability that the host is captured by a predator. It has been found that *Toxoplasma* can prolong the reaction times of infected rodents, and change their spontaneous activity, vigilance, and ability to recognize novel stimuli [59,60]. All these changes can increase the risk that the infected rodent will be captured and eaten by a predator, including a definitive host of *Toxoplasma*, the cat. However, *Toxoplasma* seems to be able to induce such changes that specifically increase the probability that the host will be captured by feline predator. Since the year 2000 [61], approximately ten studies have been published showing that *Toxoplasma* infection of rodents is able to change their native, inborn fear of the odor of cats into an attraction to this odor. The infected mice and rats visit more often and stay longer in places containing the odor of cat urine. Conversely, they are not attracted by the odor of urine of other species [62].

In the past 20 years nearly all changes observed earlier in infected rodents were found also in infected humans. Recently, even the analogy of the fatal attraction phenomenon, in other words the increase of relative attraction to the odor of cat urine, was observed in humans [63]. Infected male students rated the odor of diluted cat urine as more pleasant than did non-infected students. No significant difference in rated pleasantness between *Toxoplasma*-infected and non-infected students was observed for the odor of four other animal species.

Toxoplasmosis-associated behavioral changes cannot influence the risk of predation by cats on modern humans. Some such changes – for example, the prolongation of reaction times in men and women and decrease of willingness to follow social rules in infected men – could, however, be responsible for the observed increase of the probability of traffic or work accidents observed in five independent studies [64–68]. The situation may have been very different in our ancestors, because primates, including apes, constitute an important part of the prey of large cats. Currently, the most important definitive host of *Toxoplasma* is the domestic cat, and the most important intermediate hosts are small rodents. However, the existence of about 600–1000 million domestic cats is a recent outcome of their modern domestication [23]. It is highly probable that another feline species was the major definitive host of *Toxoplasma* several hundred years ago [69]. It is possible that *Toxoplasma* is better adapted for the manipulation of behavior in primates than in rodents. Moreover, *Toxoplasma* cannot recognize the brain of humans as opposed to that of a rat, and cannot determine if its manipulation activity will be unproductive.

It is highly probable that only a part of the observed behavioral effects of toxoplasmosis are a product of the manipulation activity of the parasite. Some of the effects are the result of pathological changes accompanying the reproduction of parasites inside the host cell, and some are the effects of altered levels of lymphokines that the

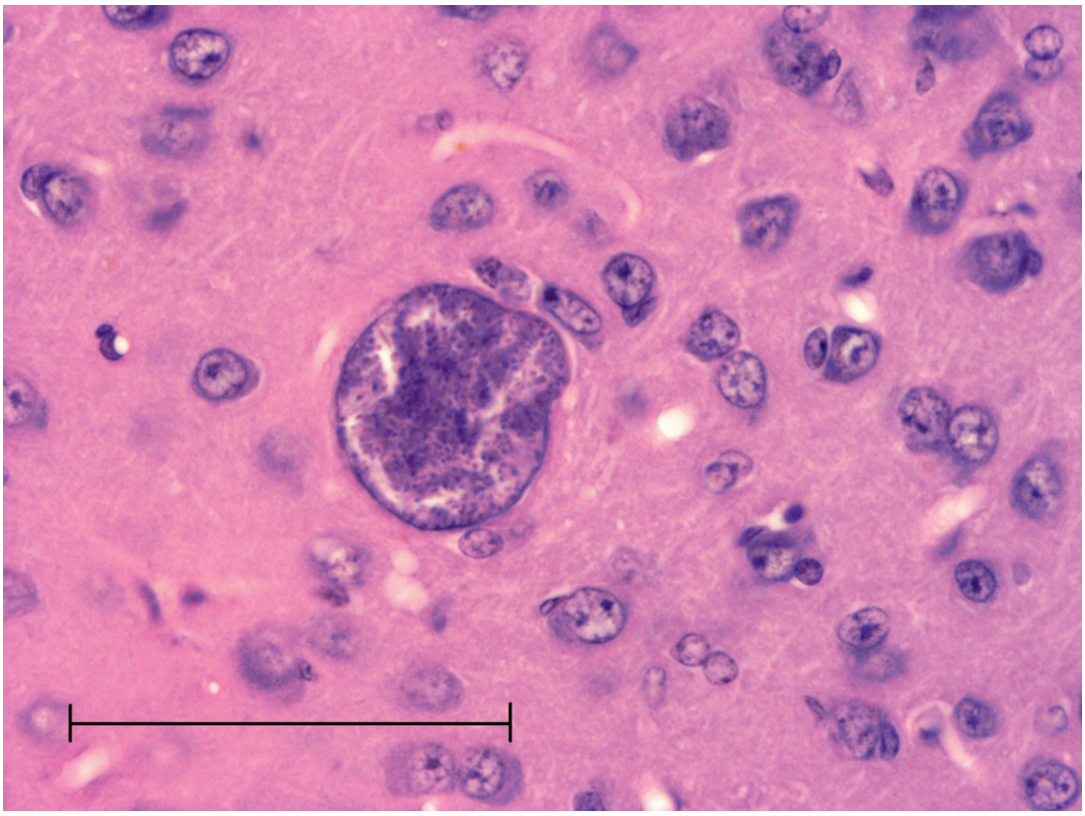


Figure 1. *Toxoplasma gondii* tissue cyst in the brain of chronically infected CD1 mice. Scale bar, 100 μm.

immune system of the host uses in its response to parasites. It is also possible that some of the observed effects represent side effects of manipulation activity of *Toxoplasma* that aims to influence not the behavior but some other property of the host. Infected women and mice have more male than female offspring [70,71]. Infected women also have a higher probability to deliver children with a developmental defect, for example Down syndrome [72]. It was also observed that *Toxoplasma*-free children of infected mothers have slower prenatal and postnatal development [73,74]. A possible explanation for all of these phenomena is that *Toxoplasma* lowers the stringency of embryo quality control [75], probably through immunosuppression [76,77], and in this way increases the probability that more immunogenic male embryos and embryos with various developmental defects are not aborted, and instead survive until delivery. In some species, *Toxoplasma* is often transmitted from mother to offspring, therefore this manipulation activity could be primarily aimed at increasing the number of males, which migrate more often, and also longer distances, than do females in the great majority of mammal species [78], and are therefore better vectors for spreading *Toxoplasma*. Similarly, the offspring with developmental defects can infect cats with a similar, if not higher, likelihood than normal offspring. Because of the tight interconnection between the immune, hormonal, and nervous systems, any manipulation of the immune or endocrine systems of a host can easily result in changes in its behavior. Outstanding questions for further research in the field are presented in Box 4.

Box 4. Outstanding questions

- Does prognosis of *Toxoplasma*-infected and *Toxoplasma*-free schizophrenia patients and the optimal method of treatment of their mental disease differ?
- Is the anti-*Toxoplasma* activity of several antipsychotic drugs observed in *in vitro* tests (co)responsible for treatment of positive symptoms of schizophrenia?
- Can some antipsychotics or antimalarial drugs be used for treatment of latent toxoplasmosis?
- Is there a causal relation between a decrease of prevalence of toxoplasmosis and decrease of incidence of schizophrenia observed in some countries?
- Is there a causal relation between the incidence of epilepsy, heart diseases, cancer of mouth and esophagus, or violence, and the prevalence of toxoplasmosis in particular countries?
- Does Rhesus factor positivity (partly) protect patients against some symptoms of schizophrenia?
- Does sexual transfer of toxoplasmosis from man to woman play an important role in human infection?
- Shall we intensively search for a human or cat vaccine against *Toxoplasma*?
- Shall we intensively search for a method of treatment of latent toxoplasmosis?

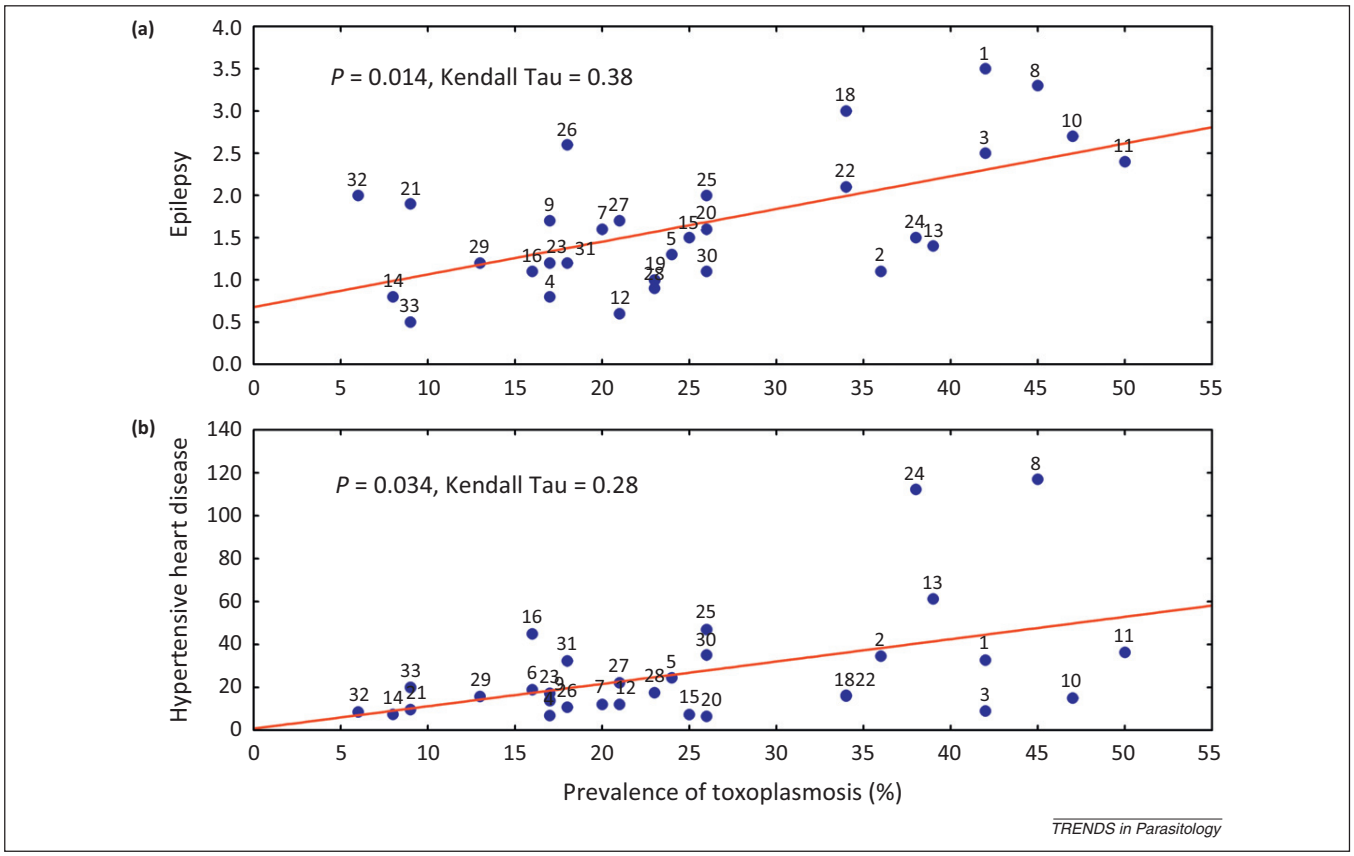


Figure 2. Correlation between prevalence of latent toxoplasmosis in pregnant women and the number of deaths due to epilepsy **(a)** or hypertensive heart disease **(b)** per 100 000 inhabitants of the listed European countries and Canada and USA. *P* values were calculated by partial Kendall regression with *per capita* gross domestic product (GDP) as a covariate without any correction for multiple tests. Countries: Albania 1, Austria 2, Belgium 3, Canada 4, Croatia 5, Czech Republic 6, Denmark 7, Estonia 8, Finland 9, France 10, Germany 11, Greece 12, Hungary 13, Iceland 14, Ireland 15, Italy 16, Lithuania 18, Montenegro 19, Netherlands 20, Norway 21, Poland 22, Portugal 23, Romania 24, Serbia 25, Slovakia 26, Slovenia 27, Spain 28, Sweden 29, Switzerland 30, Macedonia 31, UK 32, USA 33. Death rates are World Health Organization estimates for the year 2008; toxoplasmosis prevalence data are published estimates for the years 1999–2010 corrected for mean age of pregnant women in each country.

Concluding remarks

Currently, a study of the manipulation hypothesis remains at the periphery of the interests of parasitologists and absolutely out of the scope of interest of physicians. However, our experience from the study of behavioral effects of toxoplasmosis suggests that many effects of the manipulation activity of parasites could have a serious impact upon the mortality and morbidity of common parasitic diseases. Until now, only the behavioral effects of toxoplasmosis have been systematically studied. It is highly probable that similar or even more important impacts of other parasitic diseases will be discovered in the future. Malaria is considered to be the most important protozoan killer of man. However, when we take into account the hundreds of thousands of deaths that occur due to the increased probability of traffic accidents, working accidents, suicides, and possibly also other side effects of the infection (Figure 2), we are forced to admit that 'asymptomatic' latent toxoplasmosis could easily take malaria down from its throne. It is highly probable that a study of latent toxoplasmosis, a disease affecting about one third of the world population, still has its best years ahead.

Acknowledgments

The study was supported by projects of Grant Agency of the Czech Republic (Grant No. P303/11/1398 204004) and Charles University of Prague (UNCE 204004).

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