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# How and why *Toxoplasma* makes us crazy

**Jaroslav Flegr**

Faculty of Science, Charles University in Prague, Prague 128 44, Czech Republic

**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

*Corresponding author:* Flegr, J. (flegr@cesnet.cz).

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### 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].

**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