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Host Manipulation by *Toxoplasma gondii*

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Abstract

Many parasites have evolved adaptive mechanisms for manipulation of host phenotypes, including behavior, to increase their chances of transmission from infected to noninfected hosts (Holmes and Bethel 1972). Very conspicuous behavioral changes are induced by parasites that are transmitted from intermediate to definitive host by predation because induced behavioral patterns increase biological fitness of the manipulating parasite but decrease fitness of the carrier – the infected animal. An already classical model for studying manipulative activity of parasites is the heteroxenous coccidian *Toxoplasma gondii,* whose life cycle includes transmission from intermediate host (any warm blooded animal) to definitive host (any feline species) by predation. *Toxoplasma* is known to modify not only the behavior of its intermediate animal hosts but also the behavior and personality of infected humans. The mechanisms most probably responsible for the observed behavioral changes are increase of dopamine, increase of testosterone in males and hypomethylation of certain regulatory elements of key genes in amygdala of infected hosts.

The first indices of manipulation activity of *Toxoplasma* appeared in 60-70s of the 20th century. Hutchison and his coworkers and successors published about 20 papers showing that congenital, acute and even chronic toxoplasmosis have specific impacts on the behavior of infected mice. The infection was associated with hyperactivity in an open field (Hay et al. 1984b; Hay et al. 1983), increased voluntary wheel running (Hay et al. 1985), decreased ability to discriminate between familiar and novel stimuli (Hay et al. 1984a), impairment of motor performance and coordination (Hutchison et al. 1980a), and impairment of memory resulting in learning deficits (Piekarski et al. 1978; Witting 1979), for review see (Hutchison et al. 1980b; Skallová et al. 2006). In nineties, the manipulation activity of *Toxoplasma* started to be systematically studied by Joanne Webster in Oxford on a more suitable animal model, the rat (*Rattus norvegicus*). In contrast to short-lived and toxoplasmosis sensitive mice, in this toxoplasmosis tolerant animal, acute toxoplasmosis quickly proceeds into its latent stage (as usually occurs in humans) in which all clinical symptoms of disease disappear but some specific behavioral symptoms of the parasite manipulation remain apparent for a long time. Infected rats express deficits in learning (Piekarski et al. 1978; Witting 1979), decreased neophobia and increased trappability (Webster et al. 1994), hyperactivity in a familiar environment (Webster 1994) and an increased exploration of a novel object (Berdoy et al. 1995). The most impressive product of manipulation activity described on this stage of research in rats, which was later confirmed also in mice and humans, is the so called Fatal attraction phenomenon, i.e. change their native, inborn fear of the odor of cats into an attraction to this odor (Berdoy et al. 2000). 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 (Vyas et al. 2007).

Some of the toxoplasmosis-associated behavioral changes weaken or even disappear with time from the infection and differ depending on strain of *Toxoplasma* and the species or strain of host. For example, the maximum reduction of mouse

activity and maximum impairment of reaction times of infected mice were observed at the peak of pathological symptoms and disappeared before 12 weeks post infection (Hrdá et al. 2000). The fatal attraction phenomenon that was observed in mice 2 months after infection with two Type II strains of *Toxoplasma* (Prugniaud and ME49) did not exist in ME49 after another 5 months; on the other hand, only this strain experienced impaired spatial working memory (Kannan et al. 2010). The *Toxoplasma* infection very often has different, frequently even contrasting, effect on behavior of males and females (Xiao et al. 2012). The Fatal attraction phenomenon was observed only in females of Balb/c mice while a decrease in preference for novel food was observed only in male mice. Infected female mice expressed higher activity in open field test while infected males lower activity. A gene expression study revealed that *Toxoplasma* infection altered the expression of genes involved in the development of the forebrain, neurogenesis, and sensory and motor coordination in females, while in male mice, infection led mainly to modulation of genes associated with olfactory function (Xiao et al. 2012). Large *Toxoplasma* strain specific differences were also observed in the concentration of various neurotransmitters in the brains of artificially infected animals, suggesting that Type I strains of *Toxoplasma* probably express the strongest manipulative activity (Abdoli 2013; Xiao et al. 2013). It is not clear yet, which of the *Toxoplasma*-associated behavioral changes are products of manipulative activity of the parasite aimed to increase the probability of the transmission in latent phase of infection, and which are the product of other manipulative activities of parasite, e.g. of the down-regulation of the host immune functions, and which are just transient side-effects of passed acute infection. The most convincing evidence for the manipulative nature of some of the observed toxoplasmosis-associated changes was obtained on other experimental model, namely on humans (Flegr 2013b).

The study of *Toxoplasma* manipulation of human behavior started at early 90s of the past century. The first studies showed that personality profiles of subjects with latent toxoplasmosis (about one third of humans worldwide) specifically differ from personality profile of *Toxoplasma*-free subjects (Flegr and Hrdý 1994). The intensity of changes in some personality factors increases with time since the infection or

with decreases in anti-*Toxoplasma* antibodies. This suggests that these changes represent results of the cumulative effects of latent toxoplasmosis rather than transient after effects of passed acute infection. Some changes in personality are in the same direction in men and women, e.g., a decreased tendency for novelty seeking or decreased consciousness, while some are in the opposite direction in men and women, e.g., an increased Cattell's factor of pretension in men and decreased in women, increased Cattells' factor of superego strength in women and decreased in men (Flegr 2010). The changes in personality profile are associated with corresponding changes in infected subjects' behavior. For example, *Toxoplasma*-infected men scored lower in tidiness of their clothes than uninfected men, whereas infected women scored higher than uninfected women (Lindová et al. 2006). In experimental games (Dictator game and Ultimatum game) the infected male students expressed less altruism while infected women more than their non-infected pears (Lindová et al. 2010). Latent toxoplasmosis may even be responsible for differences in some cultural traits between countries. For example, the prevalence of toxoplasmosis explains a significant portion of the variance in aggregate neuroticism among populations, in the 'neurotic' cultural dimensions of sex roles and uncertainty avoidance (Lafferty 2006) as well as the variance in the incidence of suicides (Lester 2010).

An analogous version of the Fatal attraction phenomenon and the decreased psychomotor performance that were described originally in experimentally infected rodents were later observed in *Toxoplasma*-infected humans. In a double blind experiment, infected men rated the smell of highly diluted cat urine (but not urine of other four animals) as more pleasant and infected women as less pleasant than *Toxoplasma*-free subjects (Flegr et al. 2011). Both infected men and women have impaired reaction times (Havlíček et al. 2001) and express many specific defects in cognitive performance (Beste et al. 2014; Flegr et al. 2013; Pearce et al. 2012; Pearce et al. 2014; Priplatova et al. 2014; Stock et al. 2013), including in school achievements (Ferreira et al. 2013; Flegr et al. 2012b). Again, the impairment in reaction times increases with the time since infection when the age of subjects is statistically controlled. It is highly probable that observed changes in reaction times

(and also decreased capacity of long term concentration) are responsible for the observed about 2.6 times higher probability of traffic accidents and work place accidents observed in *Toxoplasma*-infected subjects in about 6 independent studies in past ten years (Flegr et al. 2002; Kocazeybek et al. 2009; Yereli et al. 2006). The subjects with Rh positive blood group are fully (heterozygotes) or at least partly (homozygotes) protected against deterioration of reaction times (Novotná et al. 2008), risk of traffic accidents (Flegr et al. 2009) and many other effects of latent toxoplasmosis as well as against other detrimental factors as smoking, aging and fatigue, as demonstrated in subsequent studies (Flegr et al. 2012a). This byproduct of *Toxoplasma* manipulation activity research not only solved an old enigma surrounding the existence of the Rh polymorphism, but could become important in many fields of human physiology and for clinical practices in the future.

The studies published mainly at the beginning of 21st century shed some light on the physiological mechanisms of *Toxoplasma* manipulation. *T. gondii* possesses two unique genes for key enzymes that catalyze the synthesis of the important neurotransmitter dopamine (Gaskell et al. 2009). These genes are expressed in *Toxoplasma* bradyzoites in tissue cysts in the brains of infected animals; a large amount of dopamine is produced there and is exported to the surrounding neural tissue (Prandovszky et al. 2011). The level of dopamine in the brain is known to negatively correlate with the personality trait of novelty seeking, one the traits that is significantly lower in *Toxoplasma*-infected subjects. The increased level of dopamine, or rather resulting imbalance in concentration of dopamine between different parts of brain could also explain the tight connection between schizophrenia and toxoplasmosis, a phenomenon studied for more than 50 years (Willner 1997). It is known that the imbalance in dopamine concentration plays a key proximal role in schizophrenia. Nearly all modern antipsychotic drugs either decrease the level of dopamine in brain of schizophrenic patients or inhibit binding of this neurotransmitter to its receptors (Nikam and Awasthi 2008). Results of recent studies suggest that toxoplasmosis plays an important role in the onset of schizophrenia in a significant portion of genetically predisposed patients. Moreover, the clinical picture of schizophrenia in *Toxoplasma*-infected patients differs from that

of *Toxoplasma*-free patients. For example, the decrease in gray matter density in the brain occurs only in *Toxoplasma*-infected patients (Horacek et al. 2012a), Fig. 1 and the same is true for gender differences in the onset of schizophrenia – on average, a 3-year delay of the onset of the disease exists only in *Toxoplasma*-infected subjects (Holub et al. 2013). *Toxoplasma*-infected schizophrenia patients express more severe positive symptoms of the psychiatric disease (more frequent or intense hallucinations, delusions) than *Toxoplasma*-free subjects (Holub et al. 2013; Wang et al. 2006).

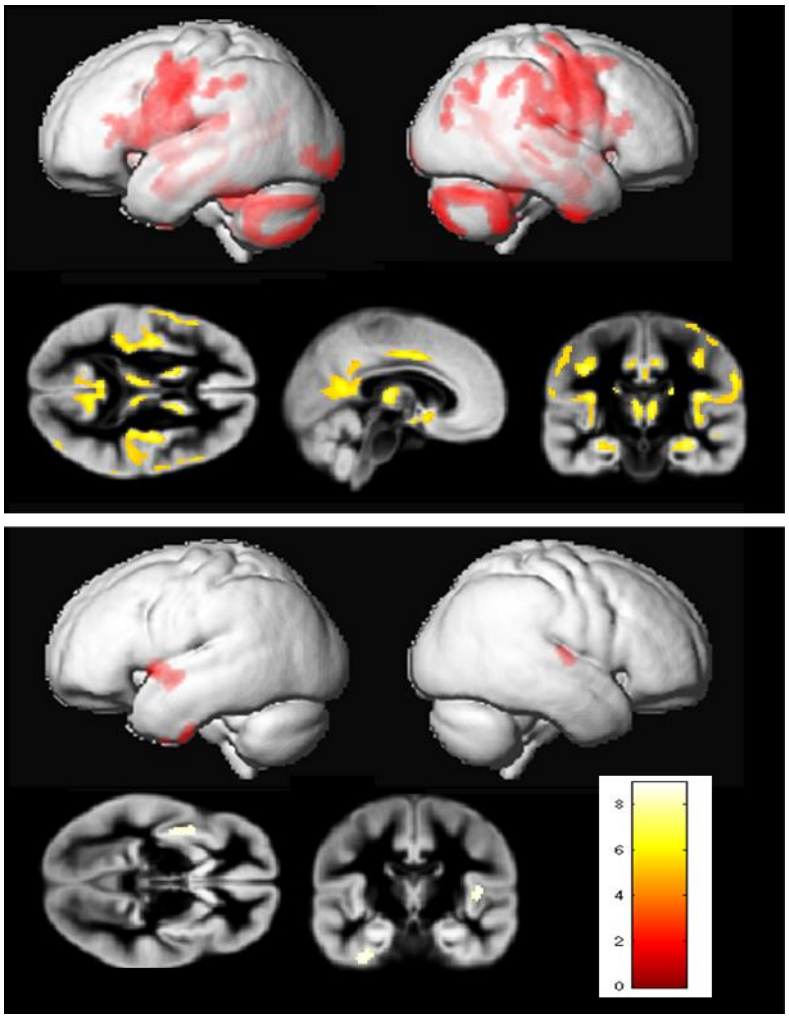

Fig. 1 The regional gray matter volume reduction in schizophrenia for *Toxoplasma*-infected subjects (upper image), and *Toxoplasma*-free (lower image) subjects. Significant results ($P < 0.05$, FWE, cluster

50 voxels) are displayed on study specific 3D template and mean image slices. L or R, left or right hemisphere; the intensity of color reflects difference in gray matter density between schizophrenia and control subjects, the bar in the lower left corner represents T value for slices. *Toxoplasma*-infected patients but not *Toxoplasma*-free patients had reduced grey matter density in specific regions of a brain in comparison with corresponding controls (Horacek et al. 2012b).

Men with latent toxoplasmosis have increased levels of free testosterone while women have decreased levels (Flegr et al. 2008). It has been observed in a rodent model that *Toxoplasma* induces synthesis of this steroid hormones in the testes of infected males (Lim et al. 2013). Increased levels of testosterone could explain why *Toxoplasma* infected men are in average 3 cm taller than their *Toxoplasma*-free peers and their photos are also rated as more masculine and dominant by female raters (Flegr et al. 2005). It is possible that the increased level of testosterone results in higher competiveness, which may also at least partly explain the higher risk of traffic accidents (however, this was observed also in female drivers) or the increased probability of birthing sons in women and in mice females with relatively recent *Toxoplasma* infection (Kaňková et al. 2007a; Kaňková et al. 2007b). It is also not clear whether increased levels of testosterone are a symptom of manipulation activity by *Toxoplasma* aimed to increase its chance for successful transmission, or a part of its struggle with the host immune system (testosterone is known to have a potent immunosuppressive activity), or whether it is just some nonadaptive side effect of the parasitic infection. In *Toxoplasma*-infected rats, however, the Fatal attraction phenomenon (loss of the fear response to cat odor and its change into an attraction) can be observed only in intact, not castrated males (Lim et al. 2013). It can be also speculated that increased levels of testosterone in males, resulting in increased sexual activity, could result in increased efficiency of sexual transmission of *Toxoplasma*. Viable parasites were frequently observed in seminal fluid of infected males and sexual transmission of toxoplasmosis from infected male to female during sexual intercourse was observed in many animal species. In humans, only indirect evidence for sexual transmission

of toxoplasmosis exists (Flegr 2013a; Flegr et al. 2014a). It can probably occur only in acute or post-acute phase of the infection and therefore the unprotected sex is probably only a marginal risk factor of toxoplasmosis. However, it can play an extremely important role in acquiring the most devastating form of toxoplasmosis, congenital toxoplasmosis, i.e., in transmission of the parasite from mother in acute phase of the infection to a developing embryo. It is indicative that about two thirds of *Toxoplasma* infections in pregnant women cannot be explained by the known risk factors.

Clinical relevance

Research of manipulation activity by *Toxoplasma* started as typical basic research in the field of evolutionary parasitology. Results obtained during past 20 years, however, showed that this activity of the parasite could have an important effect on human wellbeing and that latent toxoplasmosis could have an even larger public health and economic impact than other forms of toxoplasmosis put together. For example, just the increased risk of traffic and work place accidents could be together responsible for a similar number of deaths as malaria. Schizophrenia, which affects about 1% humans, represents huge economic burden. The prevalence of toxoplasmosis also explains large part of between-countries differences in the incidence of other serious psychiatric and nonpsychiatric diseases, including obsessive–compulsive disorder, epilepsy, suicides, and cardiovascular diseases (Flegr et al. 2014b), see Fig. 2. At least some of the observed associations between these diseases and toxoplasmosis can be caused by manipulation activity of the parasite. Presently, no effective method of treatment of, or vaccination against, toxoplasmosis exists. However, the results of manipulation activity studies suggest that more effort should be focused not only on prevention and treatment of *Toxoplasma* infection, but also to prevention of manipulative activity of this common parasite in future.

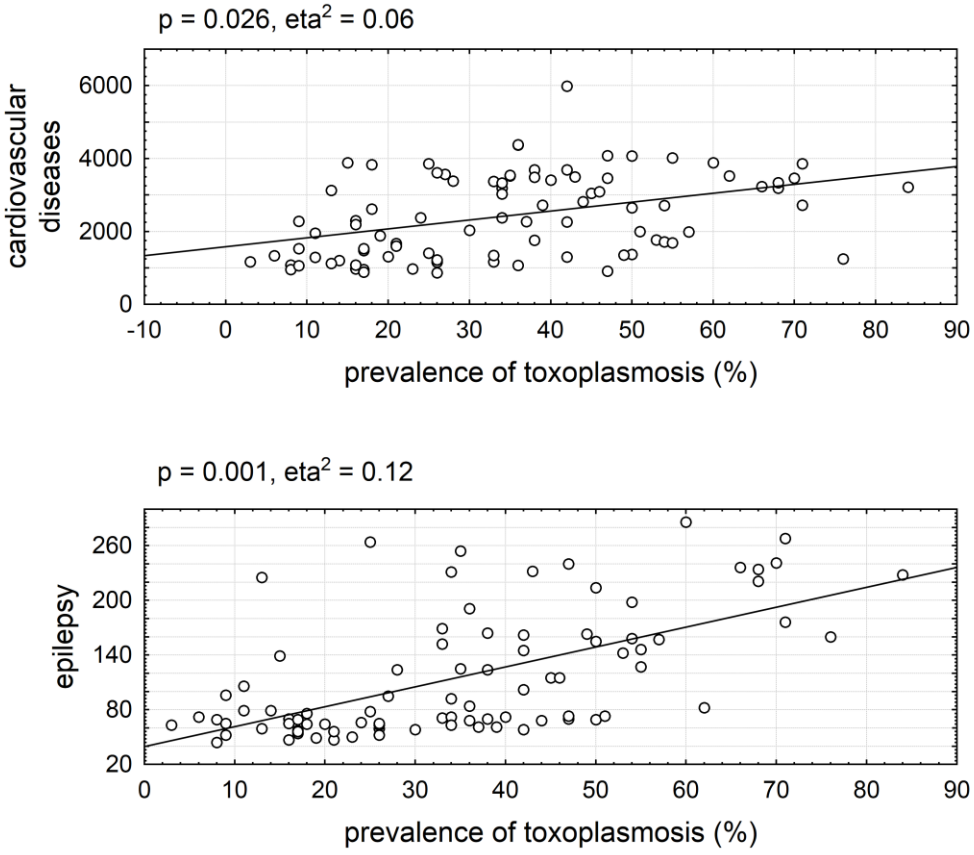

Fig. 2 Correlation of prevalence of toxoplasmosis with and cardiovascular diseases and epilepsy-attributed morbidity for 88 WHO-member countries. The axes show prevalence of toxoplasmosis (%) in women of childbearing age and y-axes the number years of 'healthy' life lost by virtue of being in a state of poor health or disability due to particular disease per 100,000 inhabitants in 2004 (Flegr et al. 2014b).

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