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REVIEW

Influence of latent *Toxoplasma* infection on human personality, physiology and morphology: pros and cons of the *Toxoplasma*–human model in studying the manipulation hypothesis

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SUMMARY

The parasitic protozoan *Toxoplasma gondii* infects about one-third of the population of developed countries. The life-long presence of dormant stages of this parasite in the brain and muscular tissues of infected humans is usually considered asymptomatic from the clinical point of view. In the past 20 years, research performed mostly on military personnel, university students, pregnant women and blood donors has shown that this 'asymptomatic' disease has a large influence on various aspects of human life. *Toxoplasma*-infected subjects differ from uninfected controls in the personality profile estimated with two versions of Cattell's 16PF, Cloninger's TCI and Big Five questionnaires. Most of these differences increase with the length of time since the onset of infection, suggesting that *Toxoplasma* influences human personality rather than human personality influencing the probability of infection. Toxoplasmosis increases the reaction time of infected subjects, which can explain the increased probability of traffic accidents in infected subjects reported in three retrospective and one very large prospective case-control study. Latent toxoplasmosis is associated with immunosuppression, which might explain the increased probability of giving birth to a boy in *Toxoplasma*-infected women and also the extremely high prevalence of toxoplasmosis in mothers of children with Down syndrome. *Toxoplasma*-infected male students are about 3 cm taller than *Toxoplasma*-free subjects and their faces are rated by women as more masculine and dominant. These differences may be caused by an increased concentration of testosterone. *Toxoplasma* also appears to be involved in the initiation of more severe forms of schizophrenia. At least 40 studies confirmed an increased prevalence of toxoplasmosis among schizophrenic patients. *Toxoplasma*-infected schizophrenic patients differ from *Toxoplasma*-free schizophrenic patients by brain anatomy and by a higher intensity of the positive symptoms of the disease. Finally, five independent studies performed in blood donors, pregnant women and military personnel showed that RhD blood group positivity, especially in RhD heterozygotes, protects infected subjects against various effects of latent toxoplasmosis, such as the prolongation of reaction times, an increased risk of traffic accidents and excessive pregnancy weight gain. The modern human is not a natural host of *Toxoplasma*. Therefore, it can only be speculated which of the observed effects of latent toxoplasmosis are the result of the manipulation activity of the *Toxoplasma* aimed to increase the probability of its transmission from a natural intermediate to the definitive host by predation, and which are just side effects of chronic infection.

Key words: behaviour, parasite, polymorphism, Rhesus factor, personality questionnaire, toxoplasmosis.

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Toxoplasma as the model organism for studying the parasite manipulation hypothesis

Toxoplasma gondii is a parasitic protozoan whose effects on human behaviour, personality and other phenotypic traits have been studied most thoroughly, often in the context of the manipulation theory, the theory suggesting that many parasites change the phenotype of their host to increase their chances of transmission to a new host by, for example, predation. There are various reasons why this particular protozoon has become a favoured model for evolutionary parasitologists, biologists and also psychiatrists.

First of all, *Toxoplasma* is a very common parasite both in developed and developing countries, and some forms of diseases caused by *Toxoplasma* infection have very serious impacts on human health; taken together, all forms of toxoplasmosis are a serious socio-economic burdens throughout the world (Pappas et al., 2009; Torgerson and Macpherson, 2011). It is also important to note that the study of the influence of toxoplasmosis on the behaviour of laboratory animals has a very long tradition; this includes a series of about 20 studies that started in the laboratory of William M. Hudtchison in the early 1980s, followed by studies by Joanne P. Webster and Manuel Berdoy in the 1990s, which were succeeded by several other teams (for reviews, see Skallová et al., 2006; Webster, 2007; Webster and McConkey, 2010).

Toxoplasma is an excellent model for studying the manipulation hypothesis as it is trophically transmitted from an intermediate to a definitive host by predation. In contrast to behavioural patterns induced by directly or, more commonly, sexually transmitted parasites, the behavioural patterns induced by a trophically transmitted parasite are relatively easy to recognize (Parker et al., 2009). For example, in a sexually transmitted parasite, the parasite's and the host's genes have similar interests: they both 'try' to program the host to increase the probability of host reproduction. In contrast, the interests of the host and its trophically transmitted parasite radically differ. The intermediate host, e.g. the mouse, needs to survive (and reproduce) for as long as possible while the parasite, e.g. *Toxoplasma*, 'wants' the definitive host (here, a cat) to kill and

eat the infected intermediate host. Some toxoplasmosis-associated behavioural changes, e.g. the prolongation of reaction times in the infected hosts (Hrdá et al., 2000), are rather simple and therefore difficult to recognize from the side effects of the parasitic disease. Other changes, however, are relatively complex and specific, e.g. the fatal attraction phenomenon, i.e. the loss of the fear response to cat odour (and not, for example, to dog odour) in infected rodents (Berdoy et al., 2000). The existence of such complex behavioural patterns suggests that the observed toxoplasmosis-associated changes are the products of the parasite's manipulative activity rather than side effects of the acute toxoplasmosis (Poulin, 1995). This is further supported by the fact that the intensity of some of the observed behavioural changes increases with the length of time since the onset of infection (Flegr et al., 1996; Havlíček et al., 2001). If the observed behavioural patterns were merely the side effects of the acute form of infection, their intensity would decrease over time from the moment of the infection.

The probable role of *Toxoplasma gondii* in the origin and progress of some important psychiatric diseases, including schizophrenia, is another reason why this protozoan has become the most important model for studying the influence of a parasite on human behaviour. Schizophrenia afflicts about 0.5–1% of the population in all countries worldwide and its health and socioeconomic impacts are extraordinary (Saha et al., 2005). Since the 1950s it has been known that the prevalence of toxoplasmosis in schizophrenic patients is unusually high (Torrey et al., 2007). This systematic research was initiated and developed by Edwin F. Torrey from the Stanley Research Institute and Robert H. Yolken from the Johns Hopkins University, who showed that the connection between schizophrenia and toxoplasmosis is very strong and that the *Toxoplasma* infection is most probably a very significant (but not exclusive) cause of schizophrenia (Torrey and Yolken, 1995; Torrey and Yolken, 2005). The effect of latent toxoplasmosis on the risk of schizophrenia is stronger than that of any schizophrenia-associated gene variant identified in genome-wide analyses (The International Schizophrenia Consortium, 2009). A prospective study performed on personnel of the American Army revealed that specific anti-*Toxoplasma* antibodies show up in the serum of subjects before they contract schizophrenia (Niebuhr et al., 2007). It was shown later that toxoplasmosis increases the concentration of dopamine in the brain of infected hosts, including humans (Flegr et al., 2003), and its genome even contains unique genes for enzymes (tyrosine hydroxylases) that play an important role in the synthesis of dopamine (Gaskell et al., 2009). The increased concentration of dopamine in certain regions of the brain is believed to play a key role in the origin and progress of schizophrenia and the inhibition of dopamine receptors is the basis of the function of all modern drugs used in the treatment of schizophrenia (Tandon et al., 2010). Other studies have shown that the symptom profiles of *Toxoplasma*-infected and *Toxoplasma*-free schizophrenia patients differ and the positive symptoms of the disease (hallucinations, delusions) are more severe in *Toxoplasma*-infected patients (Wang et al., 2006). Modern imaging techniques revealed that the morphology of the brain of schizophrenics differs from that of controls by having a lower density of grey matter (GM) in certain parts of the brain (Shenton et al., 2001). A magnetic resonance imaging (MRI) study published in 2011 showed that these differences (reduction of GM volume bilaterally in the caudate, median cingulate, thalamus and occipital cortex, and in the left cerebellar hemisphere) are observed only in *Toxoplasma*-infected patients while *Toxoplasma*-free patients (as well as *Toxoplasma*-infected controls) have the same brain morphology as *Toxoplasma*-free controls (Horacek et al., 2012). This observation suggests that toxoplasmosis can induce morphological changes in the brain of genetically predisposed subjects, which, possibly together with a toxoplasmosis-associated imbalance in the levels of dopamine and other neurotransmitters, e.g. serotonin (Henriquez et al., 2009) or nitric oxide (NO) (Kaňková et al., 2010a), can result in schizophrenia.

Changes in the personality profile of humans with latent toxoplasmosis

The personality profile of *Toxoplasma*-infected subjects was studied using three standard psychological questionnaires, i.e. Cattell's 16PF, Cloninger's TCI, NEO-PI-R (Big Five), and one special psychological questionnaire, Toxo94, that searched for specific changes expected to occur in subjects infected by the parasite transmitted from prey to predator (Flegr, 2007). Several studies have shown that infected men exhibited lower scores on Cattell's factor G – superego strength (they have tendency to disregard rules) and higher scores on Cattell's factor L – protension (they are more suspicious and jealous). In women, the shift in these two factors is opposite to that of men; they mainly show a positive shift in Cattell's factor A – affectothymia (they are more warm-hearted, outgoing and easy-going than the more reserved, detached and critical *Toxoplasma*-free women). With a new version of Cattell's questionnaire (v. 5), the infected men showed increased, rather than decreased, scores on superego strength [(Flegr, 2010b) for an explanation of discordant results between studies, see chapter 4]. Cloninger's TCI showed that infected subjects, both men and women, have decreased scores on factor NS – novelty seeking, i.e. a lower tendency to search for new stimuli (Flegr et al., 2003; Skallová et al., 2005). Ethopharmacological studies have shown that lower novelty seeking scores are characteristic for individuals with an increased concentration of dopamine in the brain tissue, which is in an agreement with the increased synthesis of dopamine in tissue cysts of *Toxoplasma* found in the brain of infected hosts and with results of ethopharmacological studies performed with *Toxoplasma*-infected mice (Hodková et al., 2007; Skallová et al., 2005). Some studies also suggest that infected subjects have higher scores on Cloninger's ST – self-transcendence (Novotná et al., 2005; Skallová et al., 2005). The NEO-PI-R questionnaire showed more extraversion in infected subjects, both men and women, and less conscientiousness in comparison with *Toxoplasma*-free subjects (Lindová et al., 2012).

On the basis of predictions of the manipulation theory and introspection of the *Toxoplasma*-infected author, a special questionnaire called Toxo94 was constructed (Flegr, 2010b). This questionnaire consisting of only 10 questions was distributed to several groups of subjects tested for toxoplasmosis, such as two large groups of university students and a group of women screened for toxoplasmosis during pregnancy (Flegr, 2010b). The results showed that infected men more often reported that diplomacy is not their strong point, that their instinctive (reflex) behaviour under imminent danger is rather slow and passive, that they believe that some people have the power to impose their will on others with hypnosis or through other means and that when they are attacked, physically or otherwise, or when they should fight for something important, they stop fighting at a certain moment because their own subconsciousness betrays them and they loss the will to fight back. The infected women more often report that diplomacy is not their strong point, that their instinctive (reflex) behaviour under imminent danger is rather slow and passive, that they believe that some people have the power to impose their will on others with hypnosis or otherwise and that they have a weak instinct for self-

preservation: in situations where somebody else might be afraid, for example being alone in a forest at night or in an empty house, they remain calm.

Influence of latent toxoplasmosis on human behaviour

Toxoplasma-infected subjects have prolonged reaction times, as measured by a test of simple reaction times (Havlíček et al., 2001). The psychomotor performance gets worse with the level of development of the infection (estimated on the basis of a decrease in the concentration of specific anti-*Toxoplasma* antibodies). The performance of the subjects in the 3 min simple reaction time test suggests that toxoplasmosis impairs long-term concentration ability rather than maximum performance. The largest performance decrease in the test occurred in RhD negative subjects while the performance of RhD-positive heterozygotes was not influenced by the infection (Flegr et al., 2010; Novotná et al., 2008). The impaired psychomotor performance of infected subjects can explain the higher risk of traffic accidents and work accidents observed in four retrospective studies (Alvarado-Esquivel et al., 2012; Flegr et al., 2002; Kocazeybek et al., 2009; Yereli et al., 2006) and one prospective study (Flegr et al., 2009). The risk of traffic accident is again increased in RhD-negative drivers (Flegr et al., 2009). A double-blind observational study showed that *Toxoplasma*-infected men scored lower in clothes tidiness than uninfected men, whereas infected women scored higher (but not significantly so) than uninfected women (Lindová et al., 2006). Similarly, infected men scored lower and infected women scored higher in sociability. These outcomes match the results of the personality questionnaires. The infected rural male students scored higher in suspiciousness while infected rural female students scored lower in suspiciousness than their non-infected peers (Lindová et al., 2006), which again agrees with the results obtained with Cattell's 16PF questionnaire. However, the very opposite was true for students of urban origin – infected male students showed lower and infected female students higher suspiciousness than their *Toxoplasma*-free peers. Using the method of experimental games, it was shown that both infected men and infected women were less altruistic than *Toxoplasma*-free subjects in the Dictator game while in the Trust game, the infected men were less altruistic and infected women were more altruistic than *Toxoplasma*-free men or women (Lindová et al., 2010).

Influence of *Toxoplasma* on the human phenotype

In addition to its influence on personality profile and behaviour, *Toxoplasma* is known to affect other phenotypic traits in humans. For example, infected male university students (age 19–22 years) have increased concentrations of testosterone (Flegr et al., 2008a; Flegr et al., 2008b) and, from photographs, their faces are rated as more masculine and dominant by females (Hodková et al., 2007). In contrast, infected female students have decreased levels of testosterone – which corresponds to decreased levels of testosterone in infected male and female mice (Kaňková et al., 2011). Infected male students are 3 cm taller than non-infected male students and both male and female students have a lower index finger to ring finger ratio (Flegr et al., 2005b), which is considered as an indication of being exposed to higher concentrations of testosterone during pregnancy (Manning, 2002). The increased concentration of testosterone was also recently reported in *Toxoplasma*-infected men, women (Shirbazou et al., 2011) and rats (Vyas, 2013). It should be noted, however, that recent studies performed on two independent populations did not find increased levels of testosterone in infected male soldiers and immunology clinic patients (see Table 1). An alternative explanation for the observed increase in the level of testosterone in males (and expected increase in the level of oestrogen) was suggested by James (James, 2010). He proposed that high testosterone and high oestrogen individuals are more susceptible to any infection, including the *Toxoplasma* infection. This model can explain the increased concentration of testosterone in men; however, it cannot explain the increased concentration of testosterone in laboratory-infected rodents.

The infected students differ from non-infected students in various morphological traits; however, at least some of the observed differences could be caused by differences between the populations of students coming from towns and from villages (where the prevalence of latent toxoplasmosis is much higher than

Table 1. Concentration of steroid hormones in *Toxoplasma*-infected and *Toxoplasma*-free subjects

	Men								Women							
	Toxoplasma free			*Toxoplasma* infected					*Toxoplasma* free			*Toxoplasma* infected				
	N	Mean	s.d.	*N*	Mean	s.d.	τ	*P*	*N*	Mean	S.D.	*N*	Mean	s.d.	τ	*P*
Immunology clinic patients																
Testosterone	26	15.16	5.99	12	14.40	4.11	–0.029	0.796	128	1.21	0.61	65	1.37	0.79	0.064	0.186
Cortisol	26	200.90	82.60	13	204.90	74.15	0.040	0.717	129	226.10	125.40	65	226.80	125.40	–0.021	0.661
Estradiol	26	0.0986	0.0417	13	0.1013	0.0309	0.066	0.556	129	0.2049	0.2537	65	0.2985	0.3811	0.066	0.169
Military personel																
Testosterone	50	15.87	4.55	50	15.19	3.04	–0.032	0.526	46	1.49	0.53	47	1.52	657.40	–0.029	0.682
Cortisol	50	542.50	122.30	50	466.90	108.30	–0.269	**0.000**	46	712.80	365.80	47	741.90	342.70	0.039	0.578
Estradiol	50	0.1146	0.0271	50	0.1123	30.70	–0.091	0.178	46	0.2883	0.3457	47	0.3009	0.3416	0.028	0.687
Students 2003–2006																
Testosterone 1	68	0.393	0.234	22	0.496	0.251	0.161	**0.026**	143	0.272	0.274	29	0.252	0.400	–0.282	**0.007**
Testosterone 2	68	0.349	0.242	21	0.428	0.219	0.152	**0.035**	133	0.272	0.248	28	0.230	0.379	–0.142	**0.003**
Students 2007–2010																
Testosterone 1	64	0.776	0.845	9	0.840	0.707	0.116	0.148	148	0.361	0.505	22	0.738	1.165	–0.186	**0.000**
Testosterone 2	63	0.561	0.645	8	0.489	0.222	0.060	0.461	155	0.186	0.136	24	0.176	0.115	–0.241	**0.000**
Cortisol 1	67	4.820	3.538	9	5.003	4.306	0.013	0.868	148	5.456	3.322	25	4.177	3.983	–0.137	**0.007**
Cortisol 2	67	3.049	1.630	9	2.040	1.236	–0.197	**0.013**	149	2.929	1.586	24	3.118	2.434	0.030	0.559

The concentration (nmol l^{-1}) of total hormones was determined in serum of immunology patients and military personal, and that of free hormones was determined in saliva of university students. Two samples were collected, the first at 09:00 h (before ethological and psychological testing of students) and the second at 11:30 h. Statistical significance of the effect of toxoplasmosis on hormone concentration was estimated with a partial Kendall test, with age of subjects as covariate. Significant results are shown in bold. (J.F., Š. Kaňková, M. Bičíková and J. Klose, unpublished.)

in Prague) (Kodym et al., 2000). Infected pregnant women have an increased probability of giving birth to a boy; the shift in the sex ratio is especially high in women with relatively recent latent infection. The women with high levels of anti-*Toxoplasma* IgG antibodies (but with low levels of IgM antibodies) gave birth to 250 boys per 100 girls while the women with low levels of anti-*Toxoplasma* IgG antibodies gave birth to more girls than boys (Kaňková et al., 2007b). The same effects have been confirmed in mice infected with *Toxoplasma* in the laboratory (Kaňková et al., 2007a). Pregnant women with toxoplasmosis have increased weight gain: in the subpopulation of RhD-negative *Toxoplasma*-infected women, the weight gain was nearly twice as high in the 16th week of pregnancy as in other pregnant women (Kaňková et al., 2010b). The rate of early fetal development is lower and the length of pregnancy is about 1.5 days longer in *Toxoplasma*-infected than in non-infected mothers (Flegr et al., 2005a; Kaňková et al., 2010b). The children of *Toxoplasma*-infected mothers have lower rates of motor development in the first 18 months of life (Kaňková et al., 2012). Most differences in the reproduction-associated traits between infected and non-infected women can be explained as being a result of immunosuppression and the resulting (expected) decrease in the stringency of embryo quality control (Neuhäuser and Krackow, 2007), which has been observed in both humans (Flegr and Stříž, 2011) and mice (Kaňková et al., 2010a) with latent toxoplasmosis. A large proportion of embryos with various developmental defects, as well as a large percentage of more immunogenic male embryos, are aborted in the early weeks of pregnancy. In immunosuppressed *Toxoplasma*-infected women, a fraction of such embryos are saved. This phenomenon can explain not only the decreased rates of prenatal and postnatal development of children of infected mothers but also the increased sex ratio in their offspring. The lower stringency of embryo quality control can also explain the observation published in the early 1960s of a dramatically higher prevalence of toxoplasmosis in mothers of children with Down syndrome, 84% *versus* 32% in controls (Hostomská et al., 1957).

An endocrine hypothesis for the increased sex ratio of recently infected women and decreased sex ratio of women infected for a long time – namely, originally (before the infection) higher oestrogen and testosterone levels in *Toxoplasma* infection-sensitive subjects and a reduced concentration of these hormones as consequence of long-term infection – has also been suggested (James, 2008; James, 2010). The increased sex ratio of recently infected women can also be explained by Catalano's stress hypothesis, i.e. selective abortion of male embryos of chronically stressed women (Catalano et al., 2012). It should be noted that the immunological and the endocrine or stress hypotheses are compatible as the increased level of steroids is known to impair the function of the immune system.

An analogous effect to the fatal attraction phenomenon (Berdoy et al., 2000; Kannan et al., 2010; Webster and McConkey, 2010) was observed in *Toxoplasma*-infected humans. Infected men rated the smell of cat urine as relatively more pleasant while infected women rated it as relatively less pleasant compared with non-infected controls (Flegr et al., 2011). Using urine from four other animal species (tiger, dog, horse, brown hyena), a similar but weaker effect was observed for hyena urine. Like the cat, the hyena is a member of the Feliformia suborder; however, it is not known whether any representatives of this superfamily other than cats (family Felinidae) can be definitive hosts of *Toxoplasma*. The fatal attraction phenomenon was not observed with tiger urine. This is rather surprising because large cats are definitive hosts of *Toxoplasma*, and monkeys and apes are a regular component of their prey. It may be that the difference in the effects of the smell of cat and tiger urine on human behaviour is due to the fact that the important pheromone felinine is present in the urine of small cats (Felinae subfamily) but absent in the urine of large cats (Pantherinae subfamily) (Hendriks et al., 1995). It is, however, possible that chance strongly influences which of the urine samples is active in the fatal attraction test. In our study (Flegr et al., 2011), samples of five individuals of each species were used in smell-rating experiments. However, the relative attractiveness of particular samples can still depend on the sample concentration and the time elapsed from sample collection. It has been observed that the effect of toxoplasmosis on olfactory preference follows an inverted-U function – the effect on mice is not observed when using either a high or a very low amount of cat urine (Vyas et al., 2007). Therefore, the results of odour studies partly depend on the dilution of the samples tested. In this context, interesting side results were obtained in one of our evolutionary psychology studies run in parallel with the fatal attraction study. We found that the smell of urine of men and of women in the fertile phase of the menstrual cycle was relatively more pleasant for *Toxoplasma*-infected male raters (Fig. 1). No significant effect of toxoplasmosis was observed with urine of women in infertile phases of the menstrual cycle. It is possible that the smell of strange male urine might signal a potential danger, which is not avoided to the same extent by infected men – as has been suggested in a similar context by the stress-coping hypothesis (Lindová et al., 2010).

Advantages and disadvantages of the *Toxoplasma*–human model for studying the manipulation hypothesis

The greatest advantage of the *Toxoplasma*-human model for studying the manipulation hypothesis is the convenience of obtaining empirical data. Practically any clinical, ethological, anthropological or psychological study could be supplemented with testing the experimental subject for the presence of anamnestic anti-*Toxoplasma* antibodies and with the comparison of the data from *Toxoplasma*-infected and *Toxoplasma*-free subjects. Moreover, all pregnant women are being screened for toxoplasmosis in some countries. Here, we could just ask the women tested to provide informed consent for the use of their clinical data or to complete a special, e.g. psychological, questionnaire.

The human is a long-living animal, especially in contrast with laboratory rodents. This is another very important advantage in manipulation hypothesis studies (but see Webster et al., 2013). Acute toxoplasmosis is usually only a mild disease in humans, a short event in a long human life. The life-long latent toxoplasmosis is mostly considered asymptomatic from the clinical point of view. Therefore, there is little risk of mistaking manifestations of *Toxoplasma*'s manipulative activity for side effects of the parasitic disease suffered. The possible side effects of acute infection can be identified by searching for a positive or negative correlation between the time elapsed from the infection (which can be derived from the patient medical records or estimated from the concentration of anamnestic antibodies) and the intensity of the observed *Toxoplasma*-associated phenotypic changes. Of course, the existence of such a positive correlation cannot distinguish whether the observed changes are manifestations of the manipulative activity or only symptoms of the chronic disease. In the case of human parasites, we cannot run a predation study, i.e. we cannot tell whether the manipulation activity objectively increases the efficiency of parasite transmission from intermediate to definitive host by comparing the prevalence of the parasite in intermediate hosts captured and eaten by the definitive host with that in a population of the intermediate host living in the

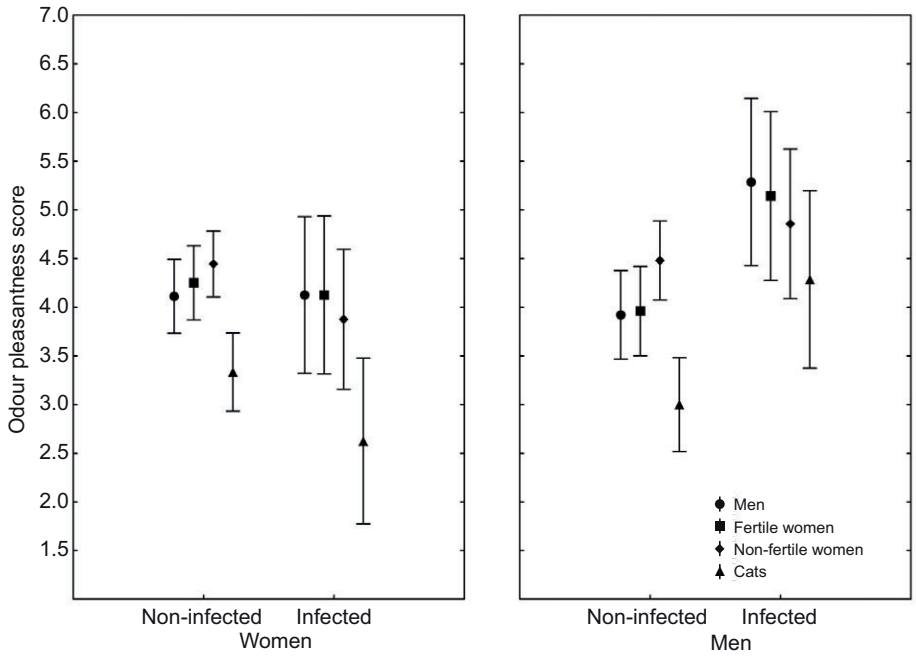

Fig. 1. Differences between *Toxoplasma*-infected and *Toxoplasma*-free men and women in the odour pleasantness scores attributed to urine samples of men, fertile and non-fertile women, and cats. The signs denote the mean raw scores attributed by a particular population to the samples tested (at least five samples from different individuals of the same species were used); the vertical bars denote 0.95 confidence intervals. Higher scores were attributed to urine samples with a more pleasant smell (in comparison with other urine samples). The statistical significance of the toxoplasmosis–sex interaction for men, women in the fertile phase of the menstrual cycle, women in the non-fertile phase of the menstrual cycle and cats was 0.021, 0.021, 0.067 and 0.006, respectively. The urine odour was rated by 36 *Toxoplasma*-free women, 9 *Toxoplasma*-infected women, 26 *Toxoplasma*-free men and 7 *Toxoplasma*-infected men on a 7-point scale. (J.F., P. Lenochová, Z. Hodný and M. Vondrová, unpublished.)

same area. Theoretically, it would be possible to compare the intensity of behavioural manifestations of toxoplasmosis in high-prevalence areas (with high rates of superinfections, i.e. new infections in hosts previously infected with *Toxoplasma*) with the intensity in low-prevalence areas (where the rates of superinfections are low). The virulence of non-manipulative parasites increases in the high-prevalence areas because in the competition between different genetic lines of the parasite in the body of a superinfected host, the winners are the lines with the highest rates of reproduction and therefore usually those with the highest virulence (Ewald, 1994). In contrast, the virulence of manipulative parasites decreases in the high-prevalence areas, because in the competition within the body of an infected host, the winners are the lines of non-manipulators that, instead of wasting resources in the manipulation activity, invest the maximum resources in reproduction (and leave the manipulation to their competitors). Such studies, however, should be performed in a long-term stable area and it is clear that the human is not a suitable model. Even studies conducted in some suitable model animal in a stable environment would not differentiate between the direct and indirect manipulation activity. It is highly probable that some of the observed effects, for example the shift of the sex ratio in infected humans and mice (Kaňková et al., 2007a; Kaňková et al., 2007b), are only side effects of the manipulative activity of *Toxoplasma*, primarily aimed at suppressing the activity of the immune system of the infected host and therefore increasing the survival of the parasite in the host organism.

For obvious reasons, a laboratory infection experiment using a *Toxoplasma*–human model to study the manipulation hypothesis is not feasible. This is an important obstacle to the study of the causal relationship between *Toxoplasma* infection and various toxoplasmosis-associated traits. For example, the lower NEO PI-R conscientiousness in infected subjects (Lindová et al., 2012) could be an effect of the infection or it may be that there is a higher probability of infection in persons with lower conscientiousness who may have a lower tendency to adhere to hygienic standards. In some cases, the causality direction is quite obvious. It is more probable that toxoplasmosis causes impairment of reaction times than the persons with longer reaction times having a higher probability of infection. Sometimes, a longitudinal study can help; however, a large number of subjects, preferably several thousand, would be needed for such a study when the incidence of the parasitosis is relatively low. Before the presence of genes for dopamine-synthesizing enzymes in the genome of *Toxoplasma* was revealed (Gaskell et al., 2009) and before an increased dopamine synthesis rate was found in *Toxoplasma* tissue cysts (Prandovszky et al., 2011), it was not possible to decide whether the positive association between toxoplasmosis and schizophrenia was more probably caused by the effect of *Toxoplasma* on the brain of predisposed individuals or by a higher risk of *Toxoplasma* infection in schizophrenics. The results of a prospective longitudinal study performed on US army personnel, however, showed that *Toxoplasma* infection often precedes the first episode of schizophrenia (Niebuhr et al., 2008).

An important hint concerning the causality can be provided by measurement of the correlation between the duration of *Toxoplasma* infection and the amount of observed phenotypic change. The existence of a positive correlation suggests that the difference observed between the infected and non-infected subjects is probably the effect of latent infection. A negative correlation suggests that the difference is a fading-out effect of past acute infection and the absence of any correlation is likely to indicate that subjects with a particular phenotype have an increased risk of infection. The published results of similar studies suggest that many statistical associations between latent toxoplasmosis and phenotypic traits are caused by the effect of toxoplasmosis on the host phenotype; however, some associations are probably caused by the effect of a particular trait on the risk of infection and certain associations by parallel effects of some third, known or unknown, factor on the host phenotype and on the risk of *Toxoplasma* infection.

The last but yet very serious disadvantage of the human model is connected with extreme genetic polymorphism in the human population as well as with extreme heterogeneity of the environmental factors that affect individuals in the study population. Such genetic and non-genetic heterogeneity has a strong negative influence on the observed effect size of any factor studied, including latent toxoplasmosis. In statistics, the effect size is often estimated as the proportion of the total variability of a dependent variable (e.g.

of a personality factor) that can be explained by the independent variable studied (e.g. toxoplasmosis). While in studies performed on inbred laboratory animals or on F1 hybrids we can often see factors explaining a high percentage of the total variability of a particular behavioural variable, in ecological and evolutionary studies performed on outbreeding organisms, we mostly see factors explaining 2–7% of variability (Moller and Jennions, 2002); therefore, to find significant effects, we may need to use an order of magnitude larger samples than in inbred animal studies.

A large within-sample and between-samples variability of human populations is also the cause of the fact that various studies performed on different populations often provide different, even opposite, results. In laboratory experiments on inbred animals, we study genetically identical animals that have been exposed to very similar environmental factors during their lives. Therefore, they will probably react identically to the same factor, for example to *Toxoplasma* infection. In humans, the situation is very different for various reasons. For example, toxoplasmosis influences the human body and mind through several independent pathways. Infected men have a higher concentration of testosterone (Flegr et al., 2008a) and, therefore, are likely to be more competitive, but at the same time they have impaired reaction times (Havlíček et al., 2001). Therefore, if in one study a self-administered simple reaction time test is distributed to groups of 20 draftees during regular military testing while in another study the same test is individually administered by an attractive female PhD student to male university students, it can be expected that in the first study, the negative influence of toxoplasmosis on reaction times will prevail while in the second, the higher competitiveness of the infected students will prevail in the final effect (Flegr et al., 2008c). In both studies, we would find a significant effect of toxoplasmosis on performance in the test; however, in the first study the effect would be negative but in the second it would be positive.

Most physiological processes are regulated on various levels, from the molecular to the psychological. If, for example, *Toxoplasma* causes an increase in the dopamine concentration in certain regions of the brain, the dopamine-synthesizing cells in other areas of the brain may degenerate. Therefore, at a certain stage of infection, we can detect, paradoxically, a decreased, rather than an increased, level of dopamine in the brain of infected individuals. If toxoplasmosis induces a decrease in superego strength, it could increase the tendency of certain individuals to lie while filling out a questionnaire and therefore we could detect seemingly increased rather than decreased superego strength in these subjects in questionnaire studies. When a subject recognizes some personality change that he/she does not like, for example a toxoplasmosis-associated increase of extraversion, he/she may try, consciously or unconsciously, to mask this change while completing the questionnaire and he/she can even overcompensate for the real personality change by moving from extraversion to introversion.

Some biological theories suggest that a large part of the genetic polymorphism is sustained in a natural outbreeding population as a result of epistatic interactions and frequency-dependent selection (Flegr, 2010a; Mayr, 1963; Templeton, 2008). The particular alleles cannot be fixed or eliminated from the population because they increase a trait positively in the context of one genotype and negatively in the context of another, or because they are advantageous when rare and disadvantageous when common. The population cannot get rid of various mutations by selection and remains polymorphic, and its members react to the same stimuli in different, often even opposite, ways. This affects the results of our ethological and psychological studies. Toxoplasmosis quite often influences the same personality factor in different populations (men and women, rural and urban populations, or RhD-positive and RhD-negative subjects); however, the direction of the effect of a factor may vary between populations. When we study the effect of a factor on a heterogeneous population, we often find a significant increase of variance in certain dependent variables, rather than a significant difference between the population means of particular variables (see Poulin, 2013). For example, comparison of Cattell's 16PF personality profiles of young women screened for toxoplasmosis during pregnancy showed that infected females scored higher in intelligence and lower in guilt proneness than *Toxoplasma*-free females. At the same time, they differed in the variance of four other personality factors, namely surgency, protension, shrewdness and self-sentiment integration (Flegr and Havlíček, 1999). In technical articles, tests for equality of variance are commonly used only to check preconditions of the statistical tests. Our experience with real data and the present knowledge of the genetic architecture of phenotypic characters, however, suggest that many genetic and environmental factors influence the variance rather than the mean values of particular characters in polymorphic populations. Therefore, the results of the tests for equality of variance should be published as full-bodied results of such studies.

There are several objective reasons why *Toxoplasma gondii* is now used as the most important model for studying manipulative activity in humans, which are summarized in the first paragraphs of the present article. However, the most important are subjective reasons and also chance. A large number of parasitic organisms probably exist in helminths, protozoa, fungi, bacteria, archea and viruses that may influence the phenotype of their human host even more than the *Toxoplasma*. These organisms are, however, still waiting for research teams to engage in a systematic study of their influence on the human host.

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