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Thirty years of studying latent toxoplasmosis: behavioural, physiological, and health insights

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Abstract: In this article, I recount the journey of discovering the effects of latent toxoplasmosis on human psychology, behaviour, morphology, and health as I observed it from the closest perspective over the past 30+ years, during which our laboratory has been intensely focused on this research. I trace how we moved from the initial observations of differences between infected and uninfected individuals in certain personality traits to the systematic study of similar differences in behaviour, both in the laboratory and in everyday life, as well as in physiological and even morphological traits. This eventually led us to investigate the causal relationships behind these observed associations and their molecular basis. I describe some of the unexpected discoveries our research revealed – whether it was the impact of toxoplasmosis on the human sexual index, the prenatal and postnatal development, the sexual preferences and behaviour, the modulatory effect of blood Rh factor on toxoplasmosis, or the discovery of sexual transmission of toxoplasmosis. In exploring whether the toxoplasmosis-associated effects were merely side effects of an ongoing latent infection, we gradually uncovered that seemingly asymptomatic toxoplasmosis has profound (and certainly not positive) effects on the mental and physical health of infected individuals. The article also includes three separate boxes that discuss some key methodological challenges we encountered along the way, such as how to distinguish the effect of infection from mere statistical association, or how to differentiate parasitic manipulation from a simple side effect.

Keywords: *Toxoplasma*, personality, behaviour, mental health, morbidity, schizophrenia, physical health, chronic toxoplasmosis, sex ratio, Rh factor, dopamine, testosterone, manipulation, parasite.

How it all started

In the beginning was the Word. This time it was three words *The Selfish Gene*. When I arrived at the Faculty of Science in Prague in 1991 after a year's internship at the University of Tokyo, and quickly anchored myself in the Department of Parasitology, I was just reading (for the fifth time, I guess) this most famous work by Richard Dawkins. Having focused on parasites for my master's and doctoral theses, I was naturally drawn to the sections about parasites that manipulate host behaviour to enhance their transmission to other, uninfected hosts within their life cycle.

Originally, I assumed that at my new-old workplace I would focus mainly on molecular phylogenetics. But then chance intervened and directed perhaps the most important branch of my professional career in a completely different direction. The department had been conducting research on toxoplasmosis for many years, including testing a newly prepared antigen for diagnostic kits. Every time a new batch of antigen arrived, it was customary to test it first on the department staff. And so, soon after joining the department, I learned that I belong to that third of humanity that is a lifelong host to the parasite *Toxoplasma gondii* (Nicolle et Manceaux, 1908).

Toxoplasmosis changes the human mind

Toxoplasma gondii is a protozoan parasite that infects roughly one-third of the human population (Tenter et al. 2000, Pappas et al. 2009). Its definitive hosts, where it can reproduce sexually, are felines, while its intermediate hosts, where it reproduces only asexually, include any warm-blooded animal. Toxoplasmosis, the disease caused by infection with *Toxoplasma*, has four basic forms. Immediately after infection, a person develops acute toxoplasmosis, which is usually accompanied by swollen lymph nodes in the neck and a range of more or less severe symptoms resembling those of tonsillitis. In most immunocompetent individuals, acute toxoplasmosis spontaneously transitions to latent toxoplasmosis, during which clinical symptoms disappear, but the parasite persists in tissue cysts in various organs of the intermediate host, likely for the host's entire life. As a result, the vast majority of infected individuals never find out they have had toxoplasmosis. In a small number of individuals with immune disorders or other predispositions, toxoplasmosis can progress to a chronic form, characterised by some clinical symptoms of acute toxoplasmosis that persist for a long time or recur repeatedly. The most severe form of toxoplasmosis is congenital

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toxoplasmosis, which occurs when a woman becomes infected just before or during pregnancy, and the infection is transmitted to the developing fetus. Depending on the stage of pregnancy at which the infection occurs and the timeliness of treatment, the outcome may be a miscarriage, or the birth of a severely affected child. If infection occurs during the third trimester, symptoms in the child are usually milder and typically involve sensory organ disorders, especially those affecting the retina.

BOX 1: What is latent toxoplasmosis

In this text, the term latent toxoplasmosis refers to the presence of anti-*Toxoplasma* IgG antibodies at concentrations exceeding the threshold used in diagnostic tests, while anti-*Toxoplasma* IgM antibodies are absent or present at concentrations below the diagnostic threshold. Generally, latent toxoplasmosis is considered a form of toxoplasmosis in which *Toxoplasma* persists long-term, possibly for life, in the infected organism in the form of tissue cysts. These cysts remain dormant, awaiting the host's predation by a definitive host (a cat) or a paratenic host (any carnivorous or omnivorous animal). Within these cysts, a specialised form of *Toxoplasma* – bradyzoites – divides slowly, without directly causing the typical symptoms of a clinically significant illness. However, individuals with latent toxoplasmosis may exhibit various nonspecific health-related symptoms, such as elevated levels of pro-inflammatory cytokines and psychological signs of chronic stress. *Toxoplasma*-seropositive individuals also display a significantly higher incidence of various diseases (Flegr et al. 2014a, Flegr and Escudero 2016) and often experience more severe disease progression than *Toxoplasma*-seronegative individuals (Flegr 2021).

It remains uncertain whether some individuals can fully eliminate the infection from their bodies. Over time, antibody levels typically decline, and in many individuals, they eventually fall below the critical threshold for a positive diagnostic test. This seroconversion from positive to negative is not uncommon in our repeatedly tested cohorts of experimental subjects. Furthermore, serological surveys show that the seroprevalence of toxoplasmosis increases with age in younger populations, plateaus in middle-aged groups, and then declines in those over 50 (Flegr 2017). This indicates that the true prevalence of latent toxoplasmosis may substantially surpass its measured seroprevalence and could be significantly higher than the often-cited global and local estimates.

Toxoplasma is an interesting protozoan in every way. What interested me most about it, however, was that in its life cycle, it has to get from its intermediate host, any warm-blooded animal, into the stomach and then the intestines of the final host, a feline. It is therefore a suitable model organism for studying parasitic manipulation. Since humans are among its intermediate hosts, discovering its manipulative activity would be much more interesting than if the target of parasitic manipulation were an ant or an amber snail. And most importantly, studying the manipulation hypothesis on the *Toxoplasma*-human model was very simple, cheap, and fun. All that was needed was to search my memory and identify elements of behaviour that seemed strange to me and that could increase the risk of a natural host becoming prey to a feline. Then, it was simply a matter of preparing a set of relevant questions, administering them to a few hundred students and colleagues, testing for latent toxoplasmosis, and statistically evaluating the significance of the differences in responses between infected and uninfected individuals. At that time, the proportion of infected people among students was about 24 %, so there were enough infected people among them. Currently, only about 10% of students are infected, so similar studies are much more difficult to conduct and must include significantly more people.

To prevent the students from figuring out the purpose of our strange set of questions, we decided to mix them in with about 180 questions from the standard Cattell 16PF personality questionnaire. And that was another great piece of luck. The answers of the infected and uninfected participants to the ten originally selected questions did not differ much, but there were differences in the psychological factors measured by the standard questionnaire (Flegr and Hrdý 1994). It could have been a coincidence – perhaps an artifact of multiple tests. But as subsequent studies on other groups over the years confirmed, it was anything but a coincidence. We subsequently demonstrated similarly altered psychological profiles in groups of conscripts, pregnant women, blood donors, and applicants for service in the professional army.

Of course, we considered the possibility that the differences in psychological profiles between infected and uninfected individuals might not be caused by the infection itself, but rather that individuals with certain personality traits may be more susceptible to infection (Flegr et al. 1998). Since conducting a randomised experiment in humans – where we would recruit a hundred uninfected people into a double-blinded experiment, expose half to *Toxoplasma*, and give the other half a placebo – might run into a few... issues with the ethics review board, we had to find another way to determine the causal direction of the observed differences. In collaboration with clinical laboratory staff, we sent our personality questionnaire to former patients for whom data on the timing of acute toxoplasmosis were available, and then measured whether the observed differences increased, disappeared, or remained the same over time since infection.

BOX 2: Association *vs.* causality in the case of toxoplasmosis

In the case of zoonoses, determining whether an infection is the cause of a specific phenotypic trait, such as certain behaviours, can be achieved through randomised experiments. If the trait develops exclusively or preferentially in individuals we have experimentally infected with a particular parasite and not, or to a significantly lesser extent, in the control group that received a placebo, we can conclude that the infection is the cause of the trait. However, conducting such experiments on humans is often ethically unfeasible. Therefore, our judgments regarding the direction of causality – whether the observed association between infection and, for example, behavioural changes – is due to the infection causing the behavioural change or whether certain behaviours increase the risk of acquiring toxoplasmosis must be based on observational studies using Bradford Hill's nine criteria for causality (Hill 1965).

In the case of the association between toxoplasmosis and behavioural traits, the results of all studies conducted to date suggest that the infection is the cause of the observed changes, rather than the behavioural traits being the cause of the infection. This conclusion is strongly supported by experimental studies on laboratory animals, which show that infection induces the same or very similar behavioural changes as those observed in humans (*criteria of experiment* and *consistency*).

Among the observational studies in humans, longitudinal studies are particularly valuable as they allow us to apply the *temporality criterion*. These studies have demonstrated that infection precedes behavioural changes, such as the onset of schizophrenia in soldiers (Niebuhr et al. 2008) or involvement in traffic accidents (Flegr et al. 2009). Another important *criterion is the biological gradient* (also known as the *criterion of dose-response* or *accompanying variance*). If the infection is the cause of the changes, the intensity of the infection (or the severity and duration of the illness) should positively correlate with the degree of expression of the trait. Several studies on human volunteers have confirmed that this criterion is met in the case of toxoplasmosis. For example, the intensity of the observed behavioural changes correlates with the time elapsed since the infection (i.e., the duration of exposure to latent toxoplasmosis) or with the concentration of antibodies against *Toxoplasma*. Furthermore, other criteria – *strength of association, consistency, plausibility, coherence,* and *analogy* – also support the conclusion that the infection is indeed the cause of the behavioural changes.

It turned out that the first option was true – the difference increased over time since infection (Flegr et al. 1996, 2000). This supports the hypothesis that the observed differences arise as a result of the cumulative effect of latent toxoplasmosis, not the fading effect of acute toxoplasmosis (which would gradually disappear), nor are they pre-existing psychological predispositions to infection (in which case the differences would remain the same after filtering out the effect of age).

However, later studies showed that some observed differences in the personality, such as changes in novelty seeking and intelligence, decrease with time since infection and are therefore perhaps a transient consequence of the acute phase of the disease (Flegr et al. 2003). However, this is not certain – in these latter studies, we no longer had data on when the participants were infected so we could only roughly estimate this from the levels of anti-*Toxoplasma* IgG antibodies. This is a very inaccurate method, as antibody levels decrease at different rates in different people, or in some cases, do not decrease at all. Moreover, antibody concentration is not only affected by time since infection, but probably also by the intensity of the infection – for example, the number of *Toxoplasma* cysts that have formed in the host's tissues. A positive correlation between antibody levels and the intensity of personality changes may not be due to the gradual disappearance of these changes over time since infection. Instead, it might reflect that individuals exposed to repeated infections, reactivation of the infection, or simply a stronger initial infection – resulting in higher antibody levels – exhibit more pronounced personality changes than those who experienced a single, less severe infection.

One of the questionnaires we used to study the differences in the psyche of infected and uninfected individuals was Cloninger's Temperament and Character Inventory (TCI). We hypothesised that infected individuals would have lower values of the personality traits "harm avoidance" and possibly "persistence". However, it turned out that the main differences were in the personality trait "novelty seeking", in which infected individuals repeatedly had lower values than uninfected individuals (Flegr et al. 2003, Skallová et al. 2005). This unexpectedly linked our research to studies on the connections between *Toxoplasma* and certain psychiatric disorders, particularly schizophrenia, initiated and led by Fuller E. Torrey – see his article in the Special Issue on Toxoplasmosis of Folia Parasitologica (Torrey 2024). His team showed in numerous studies that the prevalence of toxoplasmosis is significantly higher among patients with schizophrenia than in the general population (Torrey and Yolken 2003, 2005, Torrey et al. 2007). Other studies have indicated that individuals who had contact with cats in childhood are at increased risk of schizophrenia (Torrey 2005, Torrey et al. 2015) and that many antipsychotic drugs used to treat schizophrenia inhibit the reproduction of *Toxoplasma gondii* (Jones-Brando et al. 2003).

Our results regarding reduced novelty seeking supported the hypothesis of a causal relationship between toxoplasmosis and schizophrenia. Research indicates that **low novelty seeking correlates with high basal inter-signal dopaminergic tone**, meaning elevated background concentrations of dopamine. This increased baseline dopamine

can lead to **compensatory postsynaptic dopamine receptor hyposensitivity** – a decrease in the sensitivity or number of dopamine receptors on the postsynaptic neurons. As a result, when dopamine release is stimulated, there is **lower reactive dopaminergic activity** due to the reduced receptor responsiveness (Cloninger et al. 1993, Ruegg et al. 1997, Costa et al. 2014). It is also known that high dopamine levels in certain areas of the brain are found in patients with schizophrenia (Derincon and Bonilla 1983, Schulz et al. 2022). In 2003, based on our results regarding the decrease in novelty seeking in infected individuals, we published the hypothesis that the reason for the higher risk of schizophrenia in individuals with latent toxoplasmosis is the increased concentration of dopamine in their brain tissue (Flegr et al. 2003).

Originally, we assumed that dopamine is secreted by leukocytes in local inflammatory foci resulting from brain infection, and we subsequently supported this hypothesis with several studies in mice (Skallová et al. 2006, Hodková et al. 2007a). However, in 2009, our British colleagues showed that the whole phenomenon is much more interesting. They demonstrated that *Toxoplasma* carries genes for the key enzyme of dopamine synthesis, tyrosine hydroxylase, in its genome (Gaskell et al. 2009), and that high concentrations of dopamine are found in *Toxoplasma* cysts in brain tissue and in their vicinity (Prandovszky et al. 2011). It is therefore possible that dopamine is the main tool by which *Toxoplasma* affects the behaviour of its host, see also article by Postolache et al. (2025) and others in this Special Issue on Toxoplasmosis.

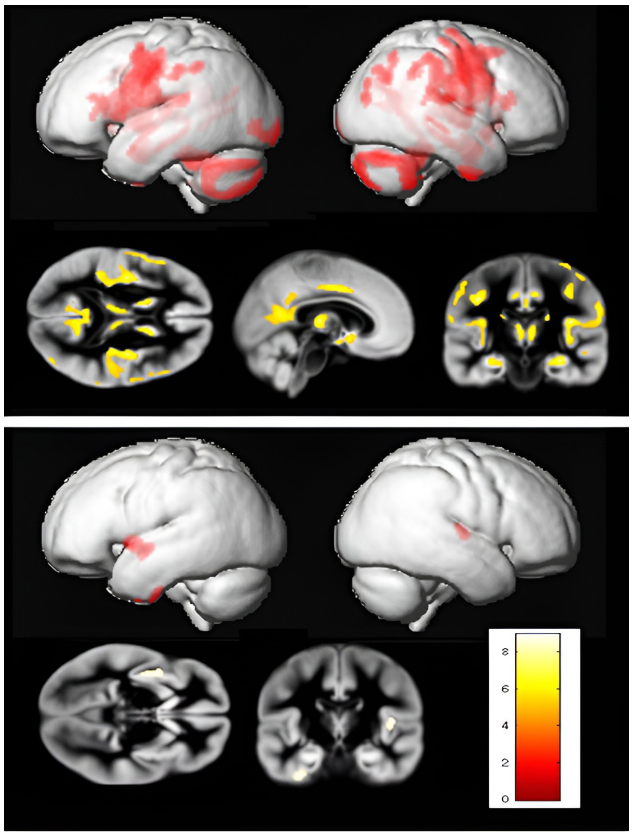

Fig. 1. Differences in grey matter density between *Toxoplasma*-infected and uninfected individuals with schizophrenia (top half) and without schizophrenia (bottom half). Coloured regions indicate areas where grey matter density is significantly lower in infected individuals compared to uninfected ones. Data were obtained using magnetic resonance imaging. The results show that *Toxoplasma*-positive individuals without schizophrenia exhibit practically no reduction in grey matter density – something we, the *Toxoplasma*-positive controls, were quite pleased about!

Investigating the effects of latent toxoplasmosis on mental health

We subsequently spent many years researching the relationship between toxoplasmosis and psychiatric disorders in collaboration with psychiatrists, primarily Jiří Horáček and David Holub. We showed that schizophrenia in infected and uninfected individuals may represent two quite different diseases. First of all, the so-called positive symptoms of the disease, delusions and hallucinations, are more frequent and severe in infected individuals than in uninfected individuals, and the hospitalisation of schizophrenic patients with toxoplasmosis is also significantly longer on average (53 days vs. 39 days in men and 80 days vs. 47 days in women). While schizophrenia starts about 2 years later in infected women than in infected men, in *Toxoplasma*-uninfected individuals, it starts at about the same age in both men and women, i.e., just before the age of 24 (Holub et al. 2013).

The most interesting difference, however, is that changes in the internal structure of the brain characteristic of patients with schizophrenia (Glahn et al. 2008, Fornito et al. 2009), namely reduced grey matter density in certain areas of the brain, occur only in patients infected with *Toxoplasma*, not in uninfected patients, Fig. 1 (Horáček et al. 2012). It is important to note that, in controls – individuals without schizophrenia – there were no apparent differences in brain microanatomy between infected and uninfected individuals.

In the following years, we investigated which other psychiatric disorders have a different course or occurrence in infected and uninfected individuals. We showed that these differences extend to conditions such as obsessive-compulsive disorder, with symptoms related to this disorder being more pronounced in *Toxoplasma*-infected individuals, even within the non-psychiatric population (Flegr and Horáček 2017). Important results were also provided by our internet study conducted on more than 3,600 individuals who had been tested for toxoplasmosis in the past. The study showed that in the Czech population, toxoplasmosis-associated disorders included autism (OR = 4.78), schizophrenia (OR = 1.86), antisocial personality disorder (OR = 1.63), learning disabilities (OR = 1.59), and anxiety disorder (OR = 1.48) (Flegr and Horáček 2020).

Our research in the field of psychiatry received unexpected international recognition in 2014 when our team was awarded the Ig Nobel Prize for "investigating whether it is mentally hazardous to own a cat." The immediate impetus for this award, "for research that makes you laugh and then makes you think," was a publication by American authors who showed that the strongest predictor of major depression is being bitten by a cat (Hanauer et al. 2013). In their

study, they suggested that toxoplasmosis might be the cause and cited our results. By the time I set off to Harvard University to receive a diploma and the well-deserved award of 10 trillion Zimbabwean dollars, I already knew from my own results that the award might not have been entirely deserved. The correlation between depression and cat injury did exist, but it was not about being bitten by a cat; it was about being scratched by a cat, which often accompanies a bite, and the cause was not toxoplasmosis, but cat scratch disease (Flegr and Hodný 2016, Flegr et al. 2018b). This disease is caused by bacteria of the genus *Bartonella* that get into scratches from the feces of cat fleas.

Latent toxoplasmosis has a number of negative impacts on mental health, including the level of depressiveness. It significantly increases, among other things, the risk of avoidant personality disorder, but does not significantly increase the risk of major depression (Flegr and Horáček 2020) and in some cases even reduces it (Flegr 2015), see also the articles in Special Issue on Toxoplasmosis of Folia Parasitologica. The question of the influence of pet ownership and injuries caused by these animals on mental and physical health has interested us for a long time. It turns out that owning a cat, and even more so sustaining injuries caused by a cat (and to a lesser extent by a dog), has a notably strong negative influence on human health. The observed effects are different from the effects associated with toxoplasmosis (Flegr and Vedralova 2017, Flegr and Preiss 2019). In my next life, I plan to explore this issue thoroughly – unless, of course, I fall in love with cats again and end up putting this project on hold, just like I did in this life.

Investigating the effects of latent toxoplasmosis on reaction times and cognitive performance

In parallel with studying the associations between toxoplasmosis and the personality traits of infected individuals, we also examined its associations with psychomotor performance, specifically reaction times. It is clear that a slowed-down mouse would find its way into a cat's stomach much more easily than a normally agile mouse. It is therefore not surprising that one of the manifestations of toxoplasmosis in infected rodents is prolonged reaction times (Hrda et al. 2000). We tested the slowing down of infected individuals in two ways – by reaction time tests performed on computers in the laboratory, and by analogy of predation experiments.

In the simplest computer tests, we sat the subjects (students, blood donors, soldiers) in front of a computer screen on which we projected visual stimuli at irregular intervals, to which these people were to react as quickly as possible by pressing a button. In other studies, people were to respond similarly to acoustic stimuli. Some tests were much more complex, and people had to first evaluate, based on the type of stimulus, whether or not to press the button. For example, in the Stroop test, they had to press the button with the word "green" written on it as quickly as possible. The remaining three buttons were labeled with the words "red," "blue," and "brown," and the words were written in colours that did not match the meaning of the words. The general conclusion from many such studies was simple – infected individuals performed worse than uninfected individuals (Havlíček et al. 2001, Příplatová et al. 2014, Flegr et al. 2024a). Our conclusion was later confirmed by a number of other studies, and finally by a meta-analytical study that combined the results of previously published articles (de Haan et al. 2021).

However, the most interesting result of these studies was the discovery of the associations between the Rh factor and performance in reaction time tests among *Toxoplasma*-positive and *Toxoplasma*-negative individuals. Most of the studies were conducted by then Ph.D. students Jan Havlíček and Martina Novotná on blood donors. For blood donors, data on Rh phenotype and genotype were available, so we could also test the effect of Rh on reaction times using their data. The same thing has probably been tested by many researchers before us, and like us, they probably didn't find any interesting effect of the Rh phenotype. This effect only became apparent when we analysed infected and uninfected individuals separately (Flegr et al. 2008a, Novotná et al. 2008).

It turned out that uninfected Rh-negative individuals (i.e., Rh-negative homozygotes) have excellent, extremely short reaction times (about 265 ms). In contrast, infected Rh-negative individuals have very poor reaction times (about 300 ms). In Rh-positive individuals, the effect of toxoplasmosis depends on whether they are heterozygous or homozygous. Uninfected Rh-positive homozygotes have much worse reaction times than uninfected Rh-negative homozygotes (about 280 ms), but infected Rh-positive homozygotes have about the same poor reaction times as Rh-negative, *Toxoplasma*-infected individuals (about 293 ms) (Novotná et al. 2008).

However, the most interesting group is the Rh-positive heterozygotes, who inherited the allele for Rh negativity from one parent and the allele for Rh positivity from the other. Uninfected Rh-positive heterozygotes have about the same reaction times as uninfected Rh-positive homozygotes (about 280 ms). However, infected Rh-positive heterozygotes have nearly as good reaction times as uninfected Rh-negative individuals (about 270 ms) (Novotná et al. 2008).

This effect, or any other biological effect of the Rh phenotype, apart from the well-known immunisation of Rh-negative mothers by the blood of Rh-positive newborns, had not been previously described. However, we later demonstrated it in approximately 20 studies, whether focusing on reaction times, intelligence, or health status.

Currently, the biological role of the RhD molecule (part of the transmembrane ion pump) is not known, nor is it clear how polymorphism in the corresponding RHD gene can be maintained in populations over the long term. Our results do not answer the first of these questions, but they do answer the second. Polymorphism was maintained in human populations, in which almost everyone was infected with toxoplasmosis in the recent past, by selection in favor of heterozygotes (Flegr et al. 2020, 2021). In my next-but-one life, I will probably give up on toxoplasmosis research and devote myself fully to studying the function of the Rh molecule and Rh polymorphism.

The effect of latent toxoplasmosis on the risk of traffic accidents

Predation studies compare the occurrence of a parasite in prey captured by a predator with its occurrence in individuals of the same species in the same location that were not captured. It is clear that humans are not very often preyed upon by felines these days. However, they are quite often involved in traffic accidents, and it can be assumed that the probability of a traffic accident and a "predation accident" are influenced by similar characteristics of the victim. To find out whether people infected with *Toxoplasma* have a higher risk of traffic accidents than uninfected people, Jan Havlíček spent several years visiting the emergency departments of Prague hospitals and recruiting participants for our study among the victims of traffic accidents (Flegr et al. 2002).

After evaluating the data, we found that the prevalence of toxoplasmosis in this sample was significantly higher than in a sample of Praguers of the same age, indicating approximately a 2.7 times higher probability of an accident in infected individuals compared to uninfected individuals. The increased probability of a traffic accident applied to both infected drivers and infected pedestrians who were hit by a car. Among infected individuals, the lowest risk of traffic accidents was found in those with the lowest antibody titers – likely indicating a long-ago infection (OR = 1.86, 95% CI = 1.14–3.03). The risk was higher in those with medium titers (OR = 4.78, 95% CI = 2.39–9.59), and highest in those with the highest titers, suggesting a more recent infection (OR = 16.03, 95% CI = 1.89–135.66).

Since the correlation is the opposite for reaction times, with reaction times gradually worsening with time since infection, it is likely that infected individuals gradually adjust their driving style to compensate for their impaired reaction times due to toxoplasmosis.

In the case of the correlation between toxoplasmosis and traffic accidents, the probability that a traffic accident would cause infection is very small. However, it is not zero, as it cannot be ruled out that antibodies or even *Toxoplasma* itself could be transmitted to an injured driver through blood transfusions. Moreover, it cannot be ruled out that some third factor, such as a higher tendency to take risks or lower tolerance for delayed gratification, could simultaneously increase the likelihood of a car accident and a *Toxoplasma* infection.

Therefore, in cooperation with psychologists from the Central Military Hospital, we conducted a prospective study to rule out this possibility. Upon entering compulsory military service, 3890 future military vehicle drivers were tested for toxoplasmosis. After a year and a half, when they were leaving for civilian life, we checked the military police records to see if the originally infected drivers had more traffic accidents than the originally uninfected drivers (Flegr et al. 2009). They did, but it turned out that this only applied to drivers with Rh-negative blood type and again mainly to those who had high antibody levels at the start, so they were probably infected not long before starting military service (or had a very severe infection). For these individuals, the probability of a traffic accident was 16.7%, about six times higher than for Rh-positive, *Toxoplasma*-uninfected individuals.

Two meta-analytical studies published in 2018 and 2019 on data from 9 (Gohardehi et al. 2018) and 11 (Sutterland et al. 2019) studies on association between toxoplasmosis and traffic accidents confirmed our results. Additionally, it has been shown over time that toxoplasmosis probably also increases the risk of workplace accidents (Alvarado-Esquivel et al. 2012). *Plasmodium* Marchiafava et Celli, 1885 is considered to be the parasitic protozoan that currently causes the most deaths. In 2020, 619,000 people died from malaria (and this number is decreasing quite rapidly from year to year). In contrast, 1,350,000 people die each year in traffic accidents, and another 20–50 million suffer non-fatal injuries. From this data, it can be estimated that if toxoplasmosis were eradicated, the number of traffic fatalities might be reduced by 450,000. Since toxoplasmosis not only increases the risk of traffic accidents but also a wide range of prevalent and often fatal diseases, such as cerebrovascular disease and ischemic heart disease (see below), *Toxoplasma* is almost certainly a bigger killer than all species of *Plasmodium* combined.

Latent toxoplasmosis changes the behaviour of infected individuals

Our favorite experimental material has always been students at the Faculty of Science. They were willing to come to our laboratory repeatedly, where they not only filled out questionnaires and took performance tests, but also participated in various ethological experiments. And most of the time, they were even so kind as to tolerate (albeit probably with some teeth-gnashing) the fact that we often didn't tell them for several years whether or not they were infected. They understood that for the results of our experiments to be credible, they had to be double-blinded; neither the experimenter nor the subjects could know who was infected and who was not during the course of the experiments.

We started with ethological experiments mainly to find out whether *Toxoplasma* affects the actual behaviour of an infected person, or just what they write about their behaviour in questionnaires. From the questionnaires, we found that infected men are more suspicious and messier than uninfected men, while infected women are more trusting and tidier than uninfected women. To find out if this is also the case in real life, we prepared a panel of tests that measured these two personality traits (Lindová et al. 2006).

In the case of suspiciousness, for example, we asked students to taste an unknown liquid from a laboratory beaker (it was water, but the students couldn't know that) and to sign a blank piece of paper (we shredded the paper in front of them immediately after the experiment). The highlight was an experiment in which we weighed them, asked them to put away all metal objects, and hold one "electrode" in each hand, seemingly connected to a dusty device with a dial set to 3000 volts, and asked them to press the button on one of the electrodes "when they were ready", Fig. 2.

The experiments showed basically the same differences in psychological traits as the personality questionnaires had previously shown: infected men were more suspicious,

Fig. 2. In this "resistance experiment", we measured how long it would take for students to gather the courage to press the button. The display on the device showed a value of 3000 volts, but in reality, the electrodes were not connected to the machine.

and infected women were less suspicious than uninfected individuals of the corresponding sex.

Perhaps the most popular part of the testing among the students was the experimental games (Lindová et al. 2010). At that time, this method was mainly used by experimental economists, while psychologists used them much less often. In these games, the experimental subjects play among themselves for real money, and the strategy they choose in the game can reveal a lot about their personality traits. Successful players could take home up to a few hundred crowns from the testing, while unsuccessful players sometimes received only a consolation prize of 20 crowns (about one US dollar at the exchange rate at that time). When paying out the reward at the end of the testing morning, we offered them the option to bet their total winnings on one of the colours in roulette. If red came up, their winnings would double, while if black came up, they would lose everything and only get the consolation prize of 20 crowns.

During our experiments, the students played, for example, the Dictator game. In this game, 12 people sat in isolated cubicles at computers, and the control computer divided them into pairs, with one of the pair being the dictator and the other the subordinate. The dictator was given 10 crowns and could send any part of this amount (including 0 crowns) to the subordinate. The students played the game repeatedly, but each time with a different anonymous opponent. The results showed that infected individuals were less generous in the role of dictator than uninfected individuals.

More interesting results were obtained in the Trust game. In this game, the investor received 10 crowns and could send any part of this amount to the entrepreneur. On the way to the entrepreneur, the computer tripled the amount. The entrepreneur could send any part of the received amount (including 0 crowns) back to the investor. It turned out that in this game, infected men are less generous and infected women are more generous in the role of entrepreneurs than uninfected individuals of the corresponding sex. For women, the effect was not significant, but the *Toxoplasma*-sex interaction was significant (Lindová et al. 2010).

The effect of latent toxoplasmosis on physical resilience and endurance

In addition to the effect of latent toxoplasmosis on mental characteristics, we also monitored its effect on physical characteristics in students. First and foremost, we were interested in how infected individuals would fare in physical endurance tests. Our questionnaire studies indicated that infected individuals tend to give up prematurely. Again, this could be a trait that helps an infected mouse end up in a cat's stomach. In three independent studies, male *Toxoplasma*-infected students and faculty reported that when they are physically attacked and start to defend themselves, at a certain point, they experience a sudden impulse to stop defending themselves, as if their subconscious mind urges them to surrender. Uninfected male, but not female, students reported this experience significantly less often (Flegr 2010).

We also attempted to explore this phenomenon experimentally. In the study, we used a Hand grip test and a Weight-holding test. In the first test, the subjects tried to repeatedly squeeze a metal ergometer. Performance in this test depends on both hand strength and resistance to the pain caused by the strong grip of the ergometer. In the second test, we measured the length of time the subjects were able to hold a 5 kg weight in their outstretched arms. Our results only partially confirmed our hypothesis – infected individuals, both men and women, did perform worse than uninfected individuals, but the effect was significant only in men and, as usual, only in Rh-negative individuals.

However, a surprise of this study was that Rh-positive infected individuals performed better than uninfected individuals in both tests. In the hand grip test, this improvement in performance was very significant. Unfortunately, we did not have genetic data available in this study to determine whether this improvement in performance in infected individuals, as in the case of reaction times, applies only to Rh-positive heterozygotes or also to Rh-positive homozygotes.

The effect of latent toxoplasmosis on morphological traits: is testosterone behind it all?

Infected and uninfected male students also differed in morphological traits. First, it was shown that infected male students were on average 3 cm taller than uninfected students and had a lower 2D:4D index, meaning they had a relatively shorter 2nd finger compared to the 4th finger (Flegr et al. 2005). When women were asked to rate the masculinity and dominance of men in photographs, infected students scored higher in these traits (Hodková et al. 2007b). It is known that traits such as increased perceived masculinity and dominance, a lower 2D:4D ratio, and, depending on timing, even greater height in young men are associated with elevated testosterone levels. This led us to

hypothesise that *Toxoplasma* infection might increase the levels of this sex hormone (Hodková et al. 2007b).

Subsequent analysis of saliva samples supported this hypothesis, showing that infected men have higher testosterone levels on average than uninfected men (Flegr et al. 2008b,c). An interesting finding was that in infected women, testosterone levels were conversely lower than in uninfected women, and in mice, testosterone levels were lower in both infected females and infected males (Kaňková et al. 2011). The results in mice, therefore, contrast with those in rats (Lim et al. 2013). As discussed in the article by A. Vyas in this issue (Vyas 2024), infected male rats have higher testosterone levels than uninfected males.

The likely explanation for lower testosterone levels in infected women and both male and female mice is the deteriorating health status of infected individuals over time. To verify this hypothesis, it will be important to determine whether male mice exhibit elevated testosterone levels shortly after infection and whether infected men show reduced testosterone levels a significant time after the infection.

One intriguing phenomenon related to the modulation of testosterone levels was discovered by Šárka Kaňková while analysing questionnaire data from gynecological clinics. She found that women shortly after infection give birth to significantly more sons, whereas women long after infection give birth to significantly more daughters (Kaňková et al. 2007a). This effect is quite strong. Women with high titers of anti-*Toxoplasma* IgG antibodies give birth to 260 sons for every 100 daughters. In another study, it was found that the prevalence of toxoplasmosis is the third most strongly correlating factor with the sex ratio at birth out of 15 tested factors, following son preference and fertility and preceding maternal age, polygyny intensity, wealth, latitude, humidity, sanitation rate, parasite stress, nutritional stress, contraceptive use, health status, cat ownership, and meat consumption (Dama et al. 2016).

The study of the impact of toxoplasmosis on the sex ratio later led Šárka Kaňková and her team to a series of other discoveries. For example, she found that women with toxoplasmosis have greater difficulty conceiving (Kaňková et al. 2015), toxoplasmosis significantly affects the course of pregnancy (Kaňková and Flegr 2007), with Rh positivity again protecting against some of these effects (Kaňková et al. 2010). Children born to mothers with toxoplasmosis exhibit slower motor development in the first 18 months after birth (Kaňková et al. 2012). Infected men more frequently face fertility issues, likely due to a reduced sperm count in their ejaculate (Hlaváčová et al. 2021a).

As is often the case, the most epidemiologically significant discovery was a side outcome of our research on the effects of toxoplasmosis on human reproduction. We found that toxoplasmosis almost certainly transmits sexually from an infected man to a woman. It became evident that toxoplasmosis in men significantly increases the likelihood that their female partners will also be infected (Hlaváčová et al. 2021b). Our study suggests that this may not be reciprocal – toxoplasmosis in women did not affect the likelihood of their male partners becoming infected. This finding undermines the possibility that the correlation arises from a common source of infection. The prevalence of toxoplasmosis in various countries correlates with the incidence of sexually transmitted diseases in those countries (Flegr et al. 2014a), and the likelihood that a pregnant woman will be infected positively correlates with the amount of unprotected sex she had with her partner before conception (Flegr et al. 2014b).

Perhaps the strongest evidence for the existence of sexual transmission of toxoplasmosis in humans is the discovery that the ejaculate of infected men contains a large number of *Toxoplasma* tissue cysts, detectable immunohistochemically and with modern molecular biological techniques (Tong et al. 2023). Given these findings, as well as results of many animal studies, it may be appropriate to consider toxoplasmosis as a sexually transmitted disease (STD) (Flegr et al. 2014b). Why might the sexual transmission route be clinically significant? Primarily because during unprotected sex, both the transmission of the infection and conception can occur simultaneously. If the mother becomes infected around the time of conception or during the first trimester, and acute toxoplasmosis develops, the parasite may be transmitted to the fetus, potentially leading to congenital toxoplasmosis – the most severe form of the disease. In more than half of congenital toxoplasmosis cases, the source of infection cannot be identified, hinting at the possibility of an alternative transmission pathway, potentially involving sexual transmission. Our results further suggest that toxoplasmosis could be transmitted from man to woman not only via penilo-vaginal intercourse but also through oral sex (Kaňková et al. 2020). While conception is not a risk in this case, some couples switch to this form of sex during pregnancy, which could still increase the risk of congenital toxoplasmosis.

The influence of latent toxoplasmosis on sexual behaviour

Our long-term research has focused on human sexual behaviour, not only in relation to the sexual transmission of toxoplasmosis but also its transmission through predation. Joanne P. Webster from Oxford University, who started studying the manipulative activity of *Toxoplasma* around the same time as we did (Webster 1994, Webster et al. 1994), described the so-called fatal attraction phenomenon in 2000 (Berdoy et al. 2000). She demonstrated that while uninfected rats avoid areas with the smell of cat urine, infected rats are drawn to such areas. The same phenomenon was later confirmed in infected chimpanzees (Poirotte et al. 2016), who were attracted to the scent of large feline predators' (leopard) urine and related phenomen was recently described in hyenas (Gering et al. 2021). Results of this study showed that *Toxoplasma*-infected hyena cubs approach lions more closely than uninfected cubs and have higher rates of lion mortality.

We did not have the resources needed to study the fatal attraction phenomenon in chimpanzees (and, to say the truth, not even in rats), so we had to make do with our students. We asked them to rate the pleasantness and intensity of a range of unknown scent samples, including diluted urine samples from six mammal species. Two independent

studies showed that individuals infected with *Toxoplasma* rated the scent of diluted cat urine as more pleasant than uninfected individuals did (Flegr et al. 2011, 2018a). However, it must be admitted that in the first study, we found increased attractiveness of cat odor in infected men and decreased attractiveness in infected women, whereas in the second study, which used higher urine concentrations, the opposite was true.

We believe this might be due to the fact that the dependence of cat urine scent attractiveness on its intensity follows an inverted U-shaped curve, with attractiveness being high at medium intensity and low at both low and high concentrations (Vyas et al. 2007). Additionally, since women generally have a more sensitive sense of smell, the U-shaped curves for men and women may be shifted relative to each other, with women reaching peak attractiveness at a lower concentration than men.

Over time, it became evident that this attraction arises because *Toxoplasma* reprograms the host's brain so that stimuli that would normally induce fear in infected individuals also elicit sexual arousal (Dass and Vyas 2014), as described in A. Vyas's article in this issue (Vyas 2024). It occurred to us that a similar connection between fear and sexuality might also be present in masochism, where sexual arousal is associated with one's own fear, helplessness, humiliation, and pain, as well as in sadism, where sexual arousal is associated with others' fear, helplessness, humiliation, and pain. We therefore began testing the hypothesis that *Toxoplasma*-infected individuals would be more frequently or intensely aroused by these stimuli than uninfected individuals.

For anyone who imagines that we set up a torture chamber in the basement of the Faculty of Science and observed how much *Toxoplasma*-infected and uninfected individuals enjoyed being tortured, I am sorry to disappoint you. We initially chose the prosaic method of an online questionnaire. Although it wasn't entirely prosaic – the questionnaire included about a thousand questions covering all possible aspects of sexual life and several standard psychological questionnaires. Completing the questionnaire took respondents over an hour and a half, and some slower respondents spent several hours on it. It seems, however, that they didn't consider it too much of a hardship (we asked them this at the end of the questionnaire). We collected responses from more than 60,000 respondents, which is about half a percent of the entire population of the Czech Republic. I "modestly" note that the most famous dataset on sexual issues, Kinsey's Reports, included in its broader form 18,000 respondents, and its number of questions was much smaller than ours.

The analysis of the collected data confirmed our hypothesis – infected men (but not women) were significantly more aroused by masochistic sex than uninfected men (Flegr and Kuba 2016). A more detailed analysis showed that arousal by violence correlated positively with toxoplasmosis in women ($p = 0.014$), and factors arousal by submission and masochism ($p = 0.004$), arousal by raping ($p = 0.001$), and arousal by sexual bondage ($p < 0.0005$) correlated positively with toxoplasmosis in men. Generally, infected subjects expressed relatively high attraction to non-conventional sexual practices, especially certain SM-related practices. However, they also reported engaging in such activities less frequently than *Toxoplasma*-free subjects (Flegr 2017), which we attributed to their poorer health status preventing them from fully realising their preferences, as discussed below.

The influence of latent toxoplasmosis on animal behaviour – our animal studies

Studying the manipulative activity of toxoplasmosis in infected people had many advantages, but it also had certain drawbacks. If the research did not involve internet-based studies, data collection usually required several years. This was quite problematic, as the projects were typically conducted by undergraduate and postgraduate students for their theses. As a result, data collection was often carried out by a different cohort of students than those who eventually included it in their theses. Moreover, methodologically, these projects were rather monotonous – apart from statistical techniques, the students and subsequent doctoral candidates did not learn many modern methods. This was why we frequently conducted parallel studies on the manipulative activities of toxoplasmosis in rodents, both those captured in the wild and laboratory mice that we infected in the lab.

The advantage of these laboratory experiments was that we could control the infection of the rodents, ensuring that the observed behavioural changes were due to the infection and not some unknown factor that correlated with both the studied behavioural variable, such as motor activity or novelty-seeking tendency, and the risk of toxoplasmosis infection. However, a significant drawback was that these experiments were much more expensive than human studies and were subject to increasingly stringent regulations each year. In contrast, our experimental subjects (humans) did not need to be purchased – they mostly participated in our studies without demanding a reward. When we did compensate them for some of the more time-consuming experiments, the amount was much lower than the cost of one inbred mouse from a controlled breeding facility. Another advantage of human study participants was that they housed and fed themselves, while feeding and housing mice in certified breeding facilities cost a significant amount per day.

Despite these challenges, some results from animal studies were quite fundamental and would have been difficult to obtain from human volunteers. For example, detailed maps of *Toxoplasma* tissue cyst locations in various brain structures created by PhD student Mirka Pečálková (Fig. 3), or data on the effects of dopamine agonists and antagonists on the behavioural effects of toxoplasmosis studied by students Anna Skallová and Hana Hodková (Hodková et al. 2007a, Skallová et al. 2006). I must also mention the findings on the impact of infection on the primary sex ratio conducted by Šárka Kaňková, which confirmed that shortly after infection, females mice give birth to an excess of sons, while later after infection, they give birth to an excess of daughters (Kaňková et al. 2007b). This confirmed her earlier discovery regarding infected women, as mentioned above.

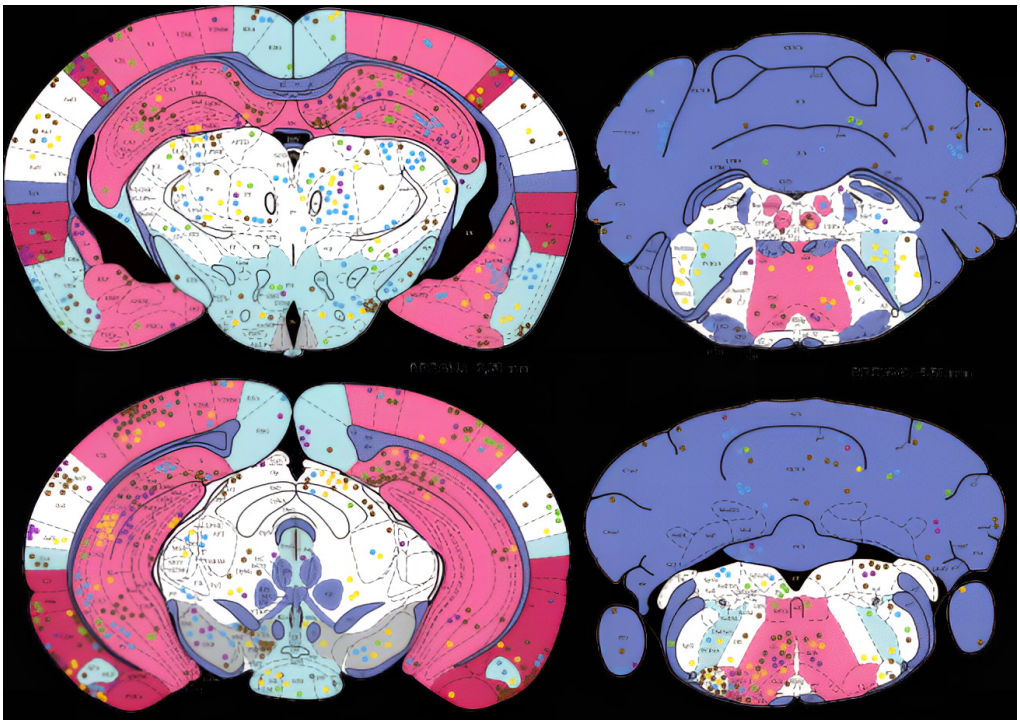

Fig. 3. This diagram shows the locations of tissue cysts in the forebrain of five infected CD1 mice. Each coloured circle represents a single cyst, with different colours indicating cysts from different mice. Cyst density is classified into five levels: very high (red), high (pink), medium (white), low (blue) and very low (dark blue). For the record, our PhD student Mirka Pečálková-Berenreiterová examined 1,600 slices from each brain under 200 × magnification. I solemnly swear that this Herculean task was her own idea and she even cunningly pretended to enjoy it the entire time!

Everything is different? Behavioural effects of toxoplasmosis as side effects of impaired health in infected individuals?

Our research on the impact of latent toxoplasmosis on human behaviour began 30 years ago as a study of the manipulation hypothesis on the somewhat atypical *Toxoplasma*-human model. Over time, we and other researchers in this field have found considerable evidence that *Toxoplasma* manipulates the behaviour of various animal species, including humans. However, as more and more results accumulated on our computer hard drives, it became clear that much of what we thought we knew might be different.

BOX 3: Manipulation or side effects?

Parasitic manipulation falls under the category of xenoadaptations. Unlike adaptations, xenoadaptations do not increase the biological fitness of the carriers of the traits themselves but rather benefit the carriers of the associated genes, which can be members of the same or a different biological species. The genes responsible for parasitic manipulation are the product of the parasite's evolution and are physically present in its genome. However, the phenotypic expression of these genes is part of the host's phenotype. Parasitic manipulation can manifest as changes in the host's morphology, such as the formation of galls that provide shelter for the parasite's larvae, or as behavioural changes that increase the likelihood of transmission of the parasite from the infected host to an uninfected one within its lifecycle.

In the case of toxoplasmosis, behavioural changes in the infected host often increase the likelihood of being preyed upon by a predator. For *Toxoplasma*, the ideal predator is a feline species, which serves as the definitive host where *Toxoplasma* can undergo sexual reproduction. However, any warm-blooded predator or omnivore can function as a paratenic host, accumulating different genetically distinct strains of *Toxoplasma*. This process facilitates the eventual transmission of multiple *Toxoplasma* strains to a definitive host, often a top predator like a large cat species, where these genetically diverse strains can recombine through sexual reproduction.

A fundamental question in the study of parasitic manipulation is whether the observed changes in the host are the result of manipulation by the parasite or merely side effects of the parasitic infection. This question becomes particularly urgent and challenging in parasites that are transmitted through predation. Almost any pathological process triggered by a parasite can alter the host's behaviour, reducing its viability and increasing its risk of predation. Researchers often rely on "predation experiments" to distinguish between manipulation and side effects. These experiments observe whether infected individuals are more frequently preyed upon than uninfected individuals. In the case of toxoplasmosis, such experiments conducted on semi-wild rats suggest that manipulation might be at play. However, as previously mentioned, a positive result in a predation ex-

periment does not rule out the possibility that the increased susceptibility to predation is merely a side effect of the host's deteriorating health. Similarly, a negative result in a predation experiment does not rule out the possibility of manipulation. Behaviour that might have been advantageous for the parasite in the past may now be neutral or even disadvantageous, particularly if the host's environment has changed significantly, such as through the disappearance of certain paratenic hosts. In human parasites, predation experiments are not feasible, as human environments and lifestyles have dramatically changed in recent evolutionary history, effectively eliminating most natural predators.

One potential way to determine whether a certain trait in parasitised individuals is the result of manipulation or merely a side effect of the infection is to study the impact of superinfection frequency (infection of an already infected host) on the expression of that trait. In cases of high superinfection frequency, the average virulence of the parasites tends to increase, as natural selection favors strains that do not spare their hosts, given that competing strains may cause the host's death. Consequently, the expression of traits that are merely side effects of the pathological processes in the infected organism also increases. However, if a trait is the result of parasitic manipulation, the frequency of superinfections should have the opposite effect on the virulence of the parasites and thus on the expression of the trait (Flegr 2013). In such cases, parasites would benefit more from investing resources in reproduction rather than manipulation, effectively shifting the costs of manipulation to competitors sharing the same host. To my knowledge, no such study has yet been conducted on *Toxoplasma* or any other parasite.

The first indications actually appeared in the 1990s during our research on the effects of toxoplasmosis on personality profiles. Strikingly often, we found that toxoplasmosis would influence a particular personality trait in one direction for men and in the exact opposite direction for women. Initially, we speculated that men (or conversely, women) might be unwilling to acknowledge the personality changes that began to manifest after infection. They might subconsciously resist admitting these changes and, as a result, respond untruthfully in the questionnaires by answering relevant questions in the opposite manner. To test this hypothesis, we attempted to replace personality questionnaires with ethological experiments (Lindová et al. 2006, 2010). However, over time, these experiments showed that our working hypothesis was likely incorrect. The opposite shifts in the respective personality traits were evident not only in the questionnaire responses but also in the actual behaviour of infected men and women.

A new hypothesis that could explain the opposite effects of toxoplasmosis on men and women was proposed about 10 years later by my then-PhD student Jitka Lindová. At that time, she was also studying psychology and noticed that the traits oppositely influenced by toxoplasmosis in men and women were similar to those oppositely affected by chronic stress. Based on this, she proposed her stress-coping hypothesis (Lindová et al. 2006, 2010). According to this hypothesis, *Toxoplasma* induces mild but long-term stress in infected individuals. It is known that men and women cope with chronic stress in opposite ways. Stressed women seek help from others and are willing to provide help to others. In contrast, men under chronic stress tend to withdraw, neither seeking help nor providing it (Matud 2004, Kelly et al. 2008). The hypothesis presumes that latent toxoplasmosis, which doctors believe does not harm infected individuals, actually does harm them, causing long-term chronic stress.

The basic premise of the stress-coping hypothesis is that latent toxoplasmosis negatively affects the health of infected individuals. We began systematically studying this premise about 10 years ago. It soon became apparent that it was likely true. Once again, we turned to our favored questionnaire studies. At that time, as part of our citizen science project, we already had access to a community of thousands of our "Labbunnies," i.e., people willing not only to fill out our online questionnaires but also to help spread them via social media. It was therefore not difficult for us to obtain samples of, say, 15,000 respondents, a significant percentage of whom had been tested for toxoplasmosis in the past for various reasons.

The first study conducted on 1,153 toxoplasmosis-free and 333 toxoplasmosis-infected individuals showed that infected individuals scored significantly worse on 28 of 29 health-related variables than uninfected individuals (Flegr and Escudero 2016). Toxoplasmosis was associated most strongly with musculoskeletal ($\tau = 0.107$, $P < 0.0005$), followed by neurological ($\tau = 0.088$, $P < 0.0005$), immune ($\tau = 0.085$, $P < 0.0005$), metabolic ($\tau = 0.079$, $P < 0.0005$), respiratory ($\tau = 0.068$, $P = 0.0001$), allergic ($\tau = 0.053$, $P = 0.004$), digestive system ($\tau = 0.052$, $P = 0.004$), and mental health disorders ($\tau = 0.050$, $P = 0.008$).

Respondents also checked which specific diseases had been diagnosed in them in the past. It turned out that 76 of a list of 134 disorders reported by at least 10 participants of the study occurred significantly more often in infected individuals than in uninfected individuals, and only one occurred significantly more often in uninfected individuals. Disorders that occurred more frequently in infected individuals included bronchitis, acquired immunodeficiencies except AIDS, both diarrhea and constipation, mononucleosis, allergies, amoebiasis, celiac disease, weight loss, recurrent abortion, hypothyroidism, leukemia, cervical uterine cancer, tics, fasciculation, learning disabilities, depression (in men), autism, osteoporosis, scoliosis, and asthma.

The second study was based on data published annually by the WHO on their website. The WHO continuously monitors the incidence of various diseases and their impact on public health (mortality and morbidity measured as Disability Adjusted Life Years, DALYs) in individual member countries. Using this data and the known prevalence of latent toxoplasmosis in 88 countries, we conducted a correlation study (Flegr et al. 2014a). This study showed that out of the 128 diseases monitored by the WHO, the disease

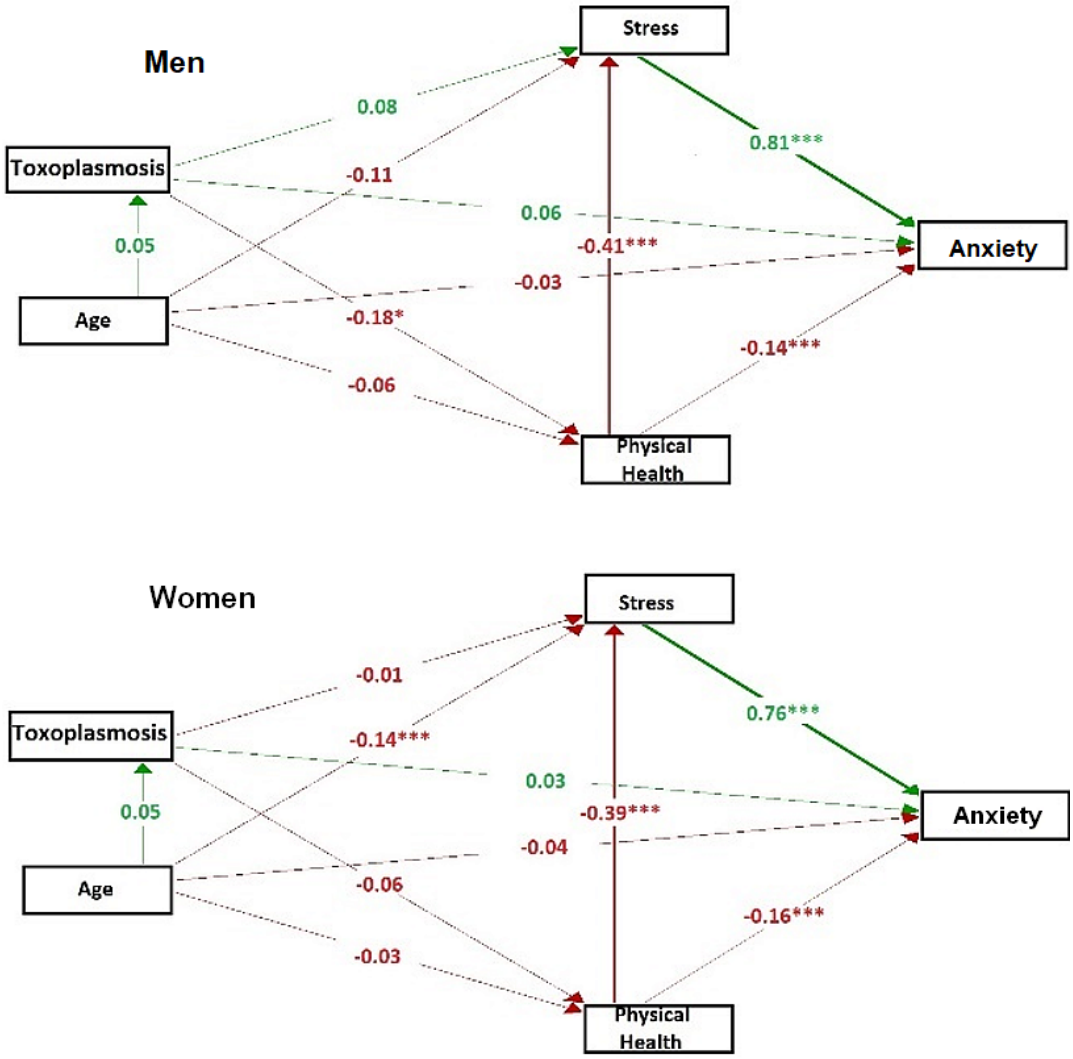

Fig. 4. The diagram shows the results of the path analysis. The path coefficients clearly indicate that toxoplasmosis primarily affects physical health, which in turn influences stress, and only then does stress impact anxiety.

burden of 23 correlated with the prevalence of toxoplasmosis in a given country (18 positively and 5 negatively). These often included very widespread and serious diseases such as prostate cancer, cerebrovascular disease, ischemic heart disease, inflammatory heart disease, epilepsy, and endocrine diseases. The effects were very strong. For example, in 29 European countries, differences in the prevalence of toxoplasmosis explained 23% of the differences in overall morbidity and mortality between these countries.

As a *Toxoplasma*-positive individual, these results naturally did not please me. Similar to accidents and mental illnesses, it turned out that the indirect consequences of toxoplasmosis could be extremely serious and that toxoplasmosis might not only be indirectly responsible for "just" hundreds of thousands of unnecessary deaths due to traffic and workplace accidents but also likely for millions of unnecessary deaths from many widespread diseases.

Our results regarding the indirect impact of latent toxoplasmosis on public health might be significant from both medical and economical perspectives. However, our primary aim was to verify the stress-coping hypothesis and to determine whether the observed toxoplasmosis-associated changes in behaviour and psyche of infected individuals are merely side effects of the stress caused by deteriorating health. We have tested this question in two studies, each providing somewhat different answers to a similar, though not identical, question.

In the first study, we focused on differences in psychological traits, including only a minimal number of tests studying the cognitive performance of respondents. The study confirmed that infected individuals are indeed less healthy than uninfected ones, while also showing that the observed differences in psychological traits remain unchanged even when statistically controlling for the effects of deteriorating health (Flegr et al. 2023). The results of this first study support the manipulation hypothesis, suggesting that the changes in the personality of infected individuals might not merely be byproducts of the disease but could be the result of specific manipulative activity by the parasite. Unfortunately, this study did not include the time-consuming Cattell questionnaire, which monitors the very factors that showed opposite shifts in infected men and women.

The second study (Flegr et al. 2024b) was more complex, as respondents filled out a detailed health questionnaire along with a stress assessment questionnaire and one tracking the main symptom of stress – anxiety. In this case, we primarily investigated the impact of latent toxoplasmosis on cognitive performance in a sample of 698 individuals previously tested for toxoplasmosis. The participants, 552 uninfected and 146 infected, underwent a broad panel of performance tests. We analysed the results using path analysis, a technique that allows for the identification of direct and indirect effects of the studied factors (Fig. 4).

This time, the study showed that *Toxoplasma* affects performance in cognitive tests only indirectly. It primarily affects the physical health of infected individuals; deteriorated health increases the intensity of stress, and stress directly or indirectly (via increased anxiety) impacts cognitive test performance. Lyme disease was used as a negative control in the study. Although there were significantly more individuals tested for Lyme disease than for toxoplasmosis (specifically 1057 uninfected and 527 infected), the impact of Lyme infection on physical health, stress, or anxiety could not be demonstrated. This study clearly showed that many behavioural manifestations of toxoplasmosis are merely side effects of chronic stress caused by the negative impact of toxoplasmosis on physical health.

An additional finding of the study was that some symptoms commonly associated with physical aging might also be influenced by the increasing likelihood of toxoplasmosis infection, rather than being solely a direct consequence of increasing age. This insight suggests that toxoplasmosis could play a contributing role in certain aspects of what is often attributed to natural aging processes.

What I learned along the way

When we began studying the influence of latent toxoplasmosis on human behaviour in the early 1990s, we had no idea where this line of research would ultimately lead us. I assumed it would be a short-term substitute scientific activity, allowing me to take a break from the molecular biology techniques I was intensely involved in at the time. The study of the manipulation hypothesis seemed like a purely academic project that might interest the public or a narrow circle of experts in evolutionary parasitology, but it would have no practical significance. In fact, several colleagues tried to selflessly convince me of this.

Today, it seems that these colleagues and I were profoundly mistaken in this regard. Even the discovery of the impact of Rh genotype on human health and cognitive performance could significantly contribute to understanding the function of the relevant membrane molecule and the role of Rh polymorphism in the future. Most importantly, we were gradually led to recognise that latent toxoplasmosis, generally considered harmless to individuals with an intact immune system, profoundly negatively affects both the mental and physical health of infected individuals. The main outcome of our three-decade-long effort is the realisation that seemingly harmless latent toxoplasmosis, affecting about 30% of the population in both developing and developed countries, is perhaps the most significant parasitic disease currently confronting humanity from the perspectives of both individual and public health. Notably, toxoplasmosis could potentially be significantly curtailed through the immunisation of domestic and feral cats, preferably with an oral vaccine.

If I were to distill the most important lesson from more than thirty years of experience, it would be this: ‘‘There are no unimportant scientific projects – only inattentive researchers.’’

Acknowledgment. I would like to express my deepest gratitude to the late Jaroslav Kulda, my former teacher and tolerant department head, who not only brought me to the Department of Parasitology but also provided a supportive and inspiring environment in which I could thrive. I am also deeply grateful to the dozens of fantastic colleagues, students and tens of thousands of volunteers who have contributed to our research on latent toxoplasmosis over the past 30 years. Their dedication, time and effort have been invaluable, and this acknowledgment serves as a token of my immense appreciation for their collective contributions.

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