Institute of Parasitology, Biology Centre CAS
Folia Parasitologica 2023, 70: 020
doi: 10.14411/fp.2023.020

Folia Parasitologica
http://folia.paru.cas.cz

Research Article OPEN ACCESS

Parasitic manipulation or side effects? The effects of past *Toxoplasma gondii* and *Borrelia* spp. infections on human personality and cognitive performance are not mediated by impaired health

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Abstract: Bacteria *Borrelia burgdorferi* s. l. and even more the protist *Toxoplasma gondii* Nicolle et Manceaux, 1908, are known to affect the behaviour and mental health of their animal and human hosts. Both pathogens infect a significant fraction of human population, both are neurotropic and survive in the host's body for a long time. While latent infections were thought to be clinically asymptomatic, recent studies suggest otherwise, revealing adverse effects on human health. It was hypothesised that the specific behavioural effects of these pathogens may be side effects of general health impairments in infected individuals. This hypothesis was tested using about one hour-long survey consisting of questionnaires and performance tests on a cohort of 7,762 members of the internet population. Results showed that individuals infected with *T. gondii* reported worse physical and mental health, and those infected with *Borrelia* spp. reported worse physical health than uninfected controls. Furthermore, infected and noninfected individuals differed in several personality traits, including conscientiousness, pathogen disgust, injury disgust, Machiavellianism, narcissism, tribalism, anti-authoritarianism, intelligence, reaction time, and precision. While the majority of behavioural effects associated with *Borrelia* infection were similar to those associated with *Toxoplasma* infection, some differences were observed, such as performance in the Stroop test. Path analyses and nonparametric partial Kendall correlation tests showed that these effects were not mediated by impaired health in infected individuals, contradicting the side effects hypothesis.

Keywords: toxoplasmosis, borreliosis, manipulation hypothesis, behaviour, personality, side effects hypothesis

This article contains supporting tables (Table S1) online at http://folia.paru.cas.cz/suppl/2023-70-020.pdf

Toxoplasma gondii Nicolle et Manceaux, 1908, and *Borrelia* spp. are neurotropic pathogens that are widely distributed among the human population. In the Czech Republic, both anti-*Toxoplasma* and anti-*Borrelia* IgG antibodies have a prevalence of approximately 15–35% in individuals' sera, with variations depending on age and sex ratio in specific population samples (Flegr and Horáček 2018). Histological data and knowledge regarding reactivation of toxoplasmosis in immunocompromised individuals, e.g., AIDS patients (Luft and Remington 1992), suggest that *Toxoplasma*-seropositive subjects carry dormant but viable parasites in tissue cysts in various organs throughout their lives. The presence of anti-*Toxoplasma* IgG antibodies in the serum is thus viewed as evidence of either latent asymptomatic or, much more rarely, chronic symptomatic toxoplasmosis (Robert-Gangneux and Darde 2012). The situation regarding *Borrelia* is less clear, but it is known that IgG seropositivity typically persists for about 10–20 years (Kalish et al. 2001). Moreover, viable *Borrelia* spirochetes have been shown to survive for decades in biofilms in human liver, heart, kidney, and brain, even after extensive antibiotic treatment (Sapi et al. 2019). This suggests that latent or chronic borreliosis might also persist for many years after the end of the acute active phase of infection.

It has long been known that *Toxoplasma*-seropositive individuals have a higher likelihood of developing psychiatric disorders, including schizophrenia (Torrey et al. 2012, Sutterland et al. 2015). Furthermore, these individuals show differences in personality traits (Flegr and Hrdý 1994, Flegr and Horáček 2018) and performance in cognitive tests (Havlíček et al. 2001) when compared to uninfected controls. Similar behavioural changes have been observed in laboratory animals infected with *Toxoplasma*, supporting the idea that the infection is the cause rather than the effect of these changes (Hodková et al. 2007a).

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Notably, in humans, the differences between infected and uninfected individuals tend to become more pronounced over time and are inversely correlated with the level of anti-*Toxoplasma* IgG antibodies (Flegr and Havlíček 1999). These findings suggest that the observed behavioural changes are the result of a gradual accumulation of effects that occur over years of latent infection, rather than a consequence of the (decreasing) impact of the brief period of acute infection.

The behavioural changes observed in *Toxoplasma*-infected animals and humans have been a subject of interest in many studies. Specifically, infected mice and rats have exhibited changes in innate fear of cat smell, with infected individuals displaying attraction to this smell (Berdoy et al. 1995, Vyas et al. 2007). Furthermore, infected rodents and primates (Poirotte et al. 2016), including humans (Flegr et al. 2011, 2018), have shown prolonged reaction times (Hrdá et al. 2000), possibly increasing the chance of transmitting the parasite to noninfected hosts, i.e. predators. While the adaptiveness of these changes in parasites with complex life cycles remains difficult to prove (Cezilly et al. 2010), it has been demonstrated in various cases, such as the well-known fish-manipulating trematode *Euhaplorchis californiensis* Martin, 1950 (Shaw et al. 2009) or the ant-manipulating trematode *Dicrocoelium dendriticum* (Rudolphi, 1819) (Carney 1969). Thus, the observed behavioural changes in *Toxoplasma*-seropositive individuals are commonly interpreted as the product of the parasite's adaptive manipulative activity (Moore 2002).

Much less is known about the behavioural effects of anti-*Borrelia* IgG seropositivity. Unlike *Toxoplasma*, *Borrelia* seropositivity does not seem to be strongly associated with psychiatric disorders (Grabe et al. 2008, Hernández-Ruiz et al. 2020, Tetens et al. 2021, but see Bransfield 2018a). While some transient behavioural changes have been observed in individuals with current or recent Lyme disease (Makara-Studzinska et al. 2017, Hündersen et al. 2021, Tetens et al. 2021), it is unclear whether these effects persist much longer after the resolution of infection.

From a clinical perspective, latent *Toxoplasma* infection or *Borrelia* IgG seropositivity are typically deemed asymptomatic and insignificant. However, recent studies have shown that seropositive individuals are generally in worse health and have a higher incidence of many diseases than their seronegative counterparts (Flegr et al. 2014, Flegr and Escudero 2016). The underlying cause of behavioural changes observed in those with latent infections is a subject of ongoing investigation, with the most widely suggested explanation being non-specific side effects of impaired health.

In this study, we capitalise on the fact that a substantial fraction of the Czech population has been screened for toxoplasmosis and Lyme disease in the past and have knowledge of their serological status. By gathering self-reported data and administering psychological questionnaires, we explore differences in cognitive performance and personality traits (Big Five personality traits, political beliefs, dark triad traits, and disgust, i.e., traits that have been found to correlate with latent toxoplasmosis infection or are suspected to do so) between individuals who are seropositive and seronegative for *Toxoplasma* and *Borrelia*.

The study aims to test the side effects hypothesis, i.e., the hypothesis that any differences in personality and cognitive performance between the two groups disappear when controlling for the effect of worse physical and psychological health in seropositive subjects. In the exploratory segment of our research, we sought to discern variations in behavioural traits by employing the Dark Triad Test (DTT) and the Three Domain Disgust Scale (TDDS). The Dark Triad in psychology encompasses three negative personality traits: Machiavellianism, characterised by manipulative behaviour; narcissism, marked by excessive self-love or self-centredness; and psychopathy, defined by a lack of empathy and remorse. We hypothesise that the DTT's evaluation of Machiavellianism, narcissism and psychopathy might be influenced by heightened levels of aggression, dominance and diminished superego strength, traits previously observed in individuals infected with *Toxoplasma* or *Borrelia* (Flegr et al. 1996, 2014, Hodková et al. 2007b, Bransfield 2018b, Coccaro et al. 2016).

To further explore whether personality differences might predispose individuals to infection rather than just being a result of it, we employed the Three Domain Disgust Scale (TDDS). The extended version of TDDS we used in our study also includes an "injury disgust" scale (related to disgust elicited by injuries). The TDDS gauges individual variations in disgust sensitivity across three core domains: pathogen (related to disease and contamination), sexual (linked to mating and sexual behaviours), and moral (associated with social and moral transgressions). Our focus was on determining if variations in the pathogen disgust scale could affect the susceptibility to *Toxoplasma* and *Borrelia* infections.

MATERIALS AND METHODS

Participants

We recruited participants for an electronic survey comprised of various questionnaires and performance tests, some of which were relevant to the present study, through Facebook and Twitter. The project was promoted as "studying interconnections between moral attitudes, cognitive performance, and various biological, psychological, and sociodemographic factors." Prior to beginning the first questionnaire, participants were explicitly informed that the study was anonymous, and they could withdraw at any time. They were also provided with the following information: "We will investigate which biological and psychological traits influence your performance test scores and moral attitudes. We will measure your memory, speed, ability to concentrate, and intelligence." Participants were required to confirm that they were over 15 years old and provide informed consent by clicking the corresponding button to participate in the study. From March to July 2022, 8,800 subjects participated in our study. A significant majority (95.5%) engaged in March, and all had responded by the end of July. Most took less than an hour to complete the survey, but many did not answer every question. The Institutional Review Board of the Faculty of Science, Charles University, approved the project and the process of obtaining informed consent (No. 2021/4).

Questionnaires and tests

We utilised a battery of psychometric tests to measure the cognitive performance of our study participants. The Cattell 16PF test (variant A, scale B) (Cattell and Mead 2008) was employed to assess their *intelligence*, while a modified Meili test (Meili 1961, Flegr et al. 2012a) was used to evaluate their *memory*. During the Meili test, participants were presented with a list of 12 words (knife, frog, pump, chain, tree, collar, ice, glasses, arrow, train, bars, rifle) for 24 seconds. In the middle of the survey approximately 20 minutes later, they were required to identify these words from a list of 24 words.

To assess psychomotor performance, we employed the Stroop test. The Stroop test is a cognitive assessment that measures selective attention, cognitive flexibility and processing speed by requiring individuals to inhibit an automatic response in favour of a more deliberate task. In our adaptation of the test, we aimed to assess two key parameters: the speed of information processing (*reaction time*) and the precision of this processing (*precision of reaction*). The test consisted of three parts, each separated by time needed to read new instructions and rest periods.

In part A, participants were required to select a specific word (e.g., "red") with their pointing device from a set of four words ("red," "green," "blue," "brown") displayed in the same order in the central part of the screen. The words were written in red, green, blue or brown font, and the meaning of the words did not match the font colour. The command specifying which word they were supposed to select was written in the upper part of the screen and participants were instructed to ignore the colour and focus only on the word. Part B was similar to part A, except participants were instructed to select a word based on its font colour, ignoring the word's meaning. Part C was similar to part A but with the added complexity that the command specifying which word the participant should select was always written in a different colour, which did not match the meaning of the word or the colour of the displayed stimuli.

At the beginning of each part, probands received instructions about the rules of the following subtest, informed about how many times the test would run (always five times), and were asked to react as quickly as possible. The probands could start each part of the Stroop test by pressing a "Start test" button. Additionally, a more straightforward variant of the reaction time test was conducted, in which the subjects were required to press a button that corresponds to a specific character (A, B, C or D) presented in the same order in black font. This test was administered eight times at the beginning of the experiment.

The present study utilised various measures to evaluate individual differences in personality traits. Specifically, the Ten Items Personality Inventory (Gosling et al. 2003) was employed to assess five personality traits, *extroversion*, *agreeableness*, *conscientiousness*, *emotional stability*, and *openness to new experiences*. In addition, the Czech version of the Three Domain Disgust Scale (TDDS) (Tybur 2009) was used to measure four facets of disgust, namely, *pathogen disgust*, *sexual disgust*, *moral disgust*, supplemented with the *injury disgust* scale (Kupfer and Le 2018).

Furthermore, the Czech version of the Short Dark Triad test (SD3) (Jones and Paulhus 2014, Mejzlíková et al. 2018) was used to assess three aspects of the dark triad, i.e., *Machiavellianism*, *narcissism*, and *psychopathy*. Lastly, the Political Beliefs and Values Inventory (PI34) (Kopecky et al. 2022) was administered to measure four aspects of political attitudes, specifically, *tribalism*, *economic egalitarianism*, *cultural liberalism*, and *anti-authoritarianism*.

In the anamnestic part of the questionnaire, participants responded to 11 questions concerning their physical health and four questions related to mental health. The questions covered a range of topics including the frequency of infectious diseases, headaches, physical pains, chronic or recurring physical problems, frequency of physician visits, frequency of feeling tired, neurological diseases, number of drugs prescribed by a physician (not for mental health), how many times they used antibiotics in the past year, how many times they spent more than a week in a hospital in the past five years, and how long they expected to live. Along similar lines, they were asked four questions concerning their mental health (frequency of suffering from depression, anxiety, other mental health problems, and how many kinds of drugs prescribed by a physician for mental health problems they were currently using). Participants responded using six-item Likert scales, with the exception of questions related to the number and kinds of medications being used (for details, see Flegr et al. 2021).

Physical and mental sickness indices were computed as the mean Z-score of the corresponding 11 or 4 questions, respectively. In this part of the survey, respondents were also asked about their age, sex ("you were born (officially) as"; males coded as 1, women coded as 0), education (ordinal scale 1–10: 1 – Basic education only, 2 – Basic education plus studying at secondary school, 3 – Secondary education including vocational training (without A-levels), 4 – Complete secondary education or higher vocational training (A-levels or diploma), 5 – Complete secondary education or higher vocational training, plus studying for a bachelor's degree, 6 – Bachelor's degree (BA, BSc), 7 – Studying for a master's degree, 8 – Master's degree (MA, MSc, MBA, MD, LL.M, MEng, etc.), 9 – Master's degree, plus studying for a doctoral degree, 10 – Doctoral degree (PhD, DPhil, EdD, etc.), and whether they were infected with *Toxoplasma* and/or *Borrelia*: "Are you infected with toxoplasma? (feline parasite especially dangerous for pregnant women", "Have you had borreliosis, Lyme disease? (tick-borne disease)" (1: "I do not know, I am not sure, I have not been tested," 2: "No, I was tested and the result was negative," 3: "Yes, I was tested and the result was positive"). For both toxoplasmosis and borreliosis, the questionnaire was preset to indicate as a default the first response ("I do not know, I am not sure, I have not been tested"). Infected individuals were coded 3, noninfected ones 2.

Data analyses

The effects of toxoplasmosis and borreliosis were tested with a nonparametric partial Kendall test controlled either for sex and age or for sex, age, physical health, and mental health using the program Explorer v. 1.0 (Flegr and Flegr 2021). The effect of multiple tests was controlled with the Benjamini-Hochberg procedure (FDR = 0.10). The results of the nonparametric analysis were confirmed with a parametric path analysis using Jamovi 2.2.5 (Jamovi 2021), PATHj module (Galuci 2021) and yEd Graph Editor (yWorks GmbH, https://www.yworks.com/products/yed, accessed 5. 11. 2022). The dataset is available at Figshare (Flegr 2022a).

Technical notes: Except for the Discussion section, we use "toxoplasmosis" ("borreliosis") or *Toxoplasma*- (*Borrelia*-) in-

Table 1. Differences in health and behavioural variables between female and male, *Toxoplasma* negative and positive, and *Borrelia* negative and positive participants. This table shows the arithmetic means and standard deviation (SD) of variables listed in the row headings for subpopulations specified in the column headings. The health indices and reaction times were computed as mean Z-scores (a higher score means worse health and longer, i.e., worse, reaction times); for other units, see Materials and Methods.

	Women		Men		*Toxoplasma*-		*Toxoplasma*+		*Borrelia*-		*Borrelia*+	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Physical sickness	0.04	0.54	-0.09	0.51	0.09	0.60	0.21	0.61	0.06	0.58	0.15	0.57
Mental sickness	0.05	0.80	-0.10	0.72	0.03	0.82	0.19	0.92	0.07	0.83	0.10	0.88
Education	6.08	2.22	5.92	2.31	6.27	2.31	6.24	2.13	5.94	2.30	6.26	2.27
Intelligence	9.00	1.93	9.49	1.86	8.98	1.99	9.16	1.95	8.94	1.96	9.30	1.87
Memory	7.61	2.26	7.20	2.52	7.71	2.19	7.51	2.33	7.60	2.25	7.54	2.34
Reaction time	0.01	0.48	0.00	0.48	-0.04	0.41	0.04	0.44	-0.02	0.44	0.06	0.47
Precision	13.15	2.66	13.31	2.68	13.45	2.30	13.15	2.61	13.34	2.30	13.45	2.25
Extroversion	4.35	1.62	3.97	1.56	4.39	1.59	4.37	1.69	4.32	1.60	4.30	1.53
Agreeableness	4.86	1.18	4.37	1.19	4.85	1.20	4.87	1.23	4.72	1.20	4.83	1.21
Conscientiousness	5.40	1.35	4.92	1.43	5.42	1.35	5.19	1.40	5.32	1.41	5.20	1.47
Emotional stability	4.12	1.49	4.48	1.45	4.16	1.49	4.15	1.47	4.22	1.46	4.21	1.55
Openness to new experiences	5.00	1.30	4.99	1.22	5.12	1.28	4.98	1.26	5.04	1.29	5.09	1.24
Pathogen disgust	3.77	1.10	3.47	1.09	3.76	1.13	3.62	1.14	3.67	1.15	3.54	1.08
Sexual disgust	3.55	1.21	2.31	0.98	3.29	1.29	3.36	1.30	3.19	1.33	3.26	1.35
Moral disgust	4.90	1.18	4.65	1.28	4.77	1.30	4.93	1.22	4.84	1.17	4.85	1.28
Injury disgust	4.12	1.51	3.89	1.51	4.02	1.55	3.74	1.62	3.90	1.52	3.90	1.49
Machiavellianism	2.83	0.63	3.10	0.64	2.97	0.65	2.79	0.62	2.98	0.67	2.87	0.63
Narcissism	2.46	0.69	2.59	0.67	2.58	0.68	2.47	0.69	2.59	0.68	2.51	0.66
Psychopathy	2.34	0.55	2.67	0.54	2.45	0.59	2.39	0.59	2.47	0.58	2.44	0.55
Tribalism	2.92	0.62	2.91	0.65	2.99	0.62	2.93	0.65	3.01	0.62	2.93	0.63
Economic egalitarianism	3.11	0.60	2.98	0.70	3.12	0.62	3.09	0.64	3.08	0.65	3.09	0.64
Cultural liberalism	4.07	0.64	4.11	0.67	4.06	0.68	4.03	0.67	4.04	0.69	4.04	0.66
Anti-authoritarianism	3.11	0.46	3.38	0.50	3.16	0.50	3.16	0.46	3.17	0.50	3.18	0.49

fection or seropositivity as an abbreviation for "reported past anti-*Toxoplasma* (*Borrelia*) seropositivity." Additionally, we use the term "effect" throughout the manuscript in the statistical sense, which refers to an observed association – the difference between the true population parameter and its null hypothesis value. We distinguish between cause and effect only in the Discussion section. In the result section, "$p << 0.001$" denotes $p < 0.000001$.

RESULTS

The raw dataset contained 4,942 women (mean age = 43.16, SD = 12.52) and 2,820 men (mean age = 39.80, SD = 12.42). Toxoplasmosis status (codes: negative = 2, positive = 3) was reported by 796 women (190, i.e., 24.0 % were positive) and 166 men (20, i.e., 12.0 % were positive). The effect of sex on *Toxoplasma* seropositivity was significant (OR = 0.437, $C.I._{95}$ = 0.252–0.724, $p < 0.001$). *Toxoplasma*-infected women were older (45.0, SD = 10.16) than *Toxoplasma*-free women (42.2, SD = 11.5), p = 0.001, Cohen d = 0.26. Likewise, *Toxoplasma*-infected men were older (42.7, SD = 12.5) than *Toxoplasma*-free men (39.5, SD = 10.3), p = 0.218, Cohen d = 0.26.

Borreliosis status (codes: negative = 2, positive = 3) was reported by 1,247 women (519, i.e., 41.6 % were positive) and 531 men (163, i.e., 30.7 % were positive). The effect of sex on *Borrelia* seropositivity was highly significant (OR = 0.621, $C.I._{95}$ = 0.497–0.775, $p << 0.001$). *Borrelia*-infected women were older (45.8, SD = 12.7) than *Borrelia*-free women (42.8, SD = 12.8), p = 0.001, Cohen d = 0.32. *Borrelia*-infected men were also older (44.4, SD = 12.8) than *Borrelia*-free men (37.9, SD = 12.8), $p<< 0.001$, Cohen d = 0.51.

We found a positive association between *Toxoplasma* and *Borrelia* positivity in 431 *Borrelia*-negative subjects, 59 (13.7 %) reported to be *Toxoplasma*-positive, while in 150 *Borrelia*-positive subjects, 52 (34.7 %) reported to be also *Toxoplasma*-positive (OR = 3.35, $C.I._{95}$ = 2.17–5.16, $p << 0.001$). The association was evident in both women (OR = 3.30, $C.I._{95}$ = 2.08–5.23, $p << 0.001$) and men (OR = 2.28, $C.I._{95}$ = 0.53–9.75, p = 0.488), however, it was significant only in women.

Table 1 shows the mean scores for variables related to performance and personality for all subjects as well as separately for women, men, *Toxoplasma*-negative subjects, *Toxoplasma*-positive subjects, *Borrelia*-negative subjects, and *Borrelia*-positive subjects. Many behavioural variables had an irregular distribution. Therefore, we used nonparametric multivariate tests, namely partial Kendall correlation tests, to search for associations between *Toxoplasma* or *Borrelia* seropositivity and health, cognitive performance, and personality of the participants (Table 2, left part). The results showed that *Toxoplasma*-seropositive subjects reported to be in worse physical and mental health, and *Borrelia*-seropositive subjects to be in worse physical health than their corresponding controls.

The tests also revealed several significant associations between the infections and behavioural variables, with many of these associations remaining significant even after correction for multiple tests. The right part of Table 2 shows the results of analogical analyses performed with partial Kendall correlation tests controlled not only for sex and age but also for physical and mental health. A comparison of the left and right parts of the table shows only very small differences. This suggests that poor physical or

Table 2. Association of infections with physical and mental health and various behavioural traits. The first two columns of the table show the effects (partial Kendall τ) controlled only for sex and age, while columns 3 and 4 show the results controlled for sex, age, physical health, and mental health. (The effects of infections on mental health were controlled only for sex, age and physical health, and the effects of infections on physical health were controlled only for sex, age and mental health). Negative τ indicates a negative association with the infection, while positive τ indicated positive associations. Significant effects are printed in bold, and asterisks indicate the effects significant after the correction for multiple tests.

	Controlled for sex and age		Controlled for sex, age and health	
	Toxoplasmosis	Borreliosis	Toxoplasmosis	Borreliosis
Physical sickness	**0.058***	**0.049***	0.042	**0.052***
Mental sickness	**0.055***	0.000	0.038	-0.018
Education	-0.001	**0.049***	0.005	**0.052***
Intelligence	**0.066***	**0.111***	**0.071***	**0.113***
Memory	-0.011	0.015	-0.006	0.019
Reaction time	0.038	0.010	0.036	0.009
Precision	-0.024	**0.037***	-0.022	**0.036***
Extroversion	-0.016	-0.023	-0.010	-0.020
Agreeableness	-0.003	0.016	0.002	0.018
Conscientiousness	**-0.091***	**-0.066***	**-0.085***	**-0.065***
Emotional stability	-0.003	0.002	0.018	0.006
Openness to new experiences	**-0.047**	0.018	-0.044	0.020
Pathogen disgust	**-0.048**	**-0.049***	**-0.051**	**-0.052***
Sexual disgust	-0.024	-0.032	-0.024	-0.033
Moral disgust	0.009	-0.015	0.012	-0.015
Injury disgust	**-0.056***	0.002	**-0.056***	0.001
Machiavellianism	**-0.072***	-0.030	**-0.077***	-0.031
Narcissism	-0.044	**-0.039***	-0.043	**-0.037***
Psychopathy	-0.007	0.028	-0.014	0.027
Tribalism	**-0.047**	**-0.065***	**-0.049**	**-0.068***
Economic egalitarianism	-0.026	0.002	-0.033	0.000
Cultural liberalism	-0.006	0.024	-0.005	0.024
Anti-authoritarianism	0.017	**0.038***	0.019	**0.038***

mental health does not play a mediating role in the association between infections and behavioural variables. The same analyses were performed separately for women and men (Table 3).

We utilised a structural equation modelling approach to delve deeper into the relationship between infections, health and behavioural variables. By employing path analysis, we confirmed the results of the (nonparametric) partial Kendall correlation tests for all investigated behavioural variables, which were significantly associated with the infections in the partial Kendall tests. The direct effect of infections persisted as significant or the effects of impaired health and the infection on a behavioural trait were in opposite directions (Figs. 1, 2). The comparison of AIC values for the full models and models excluding the direct effect of infection, presented in Supplementary Table 1, demonstrated that the full models exhibited better fit to the data than the corresponding models without the direct effect of infections on personality and performance. Hence, both the more robust nonparametric and the more sensitive parametric methods do not support the existence of a mediating effect of impaired health.

One counterintuitive finding that has emerged from the current study and several previously published studies (Flegr and Havlíček 1999, Flegr et al. 2013) is the positive correlation between seropositivity and intelligence. In light of this, we hypothesised that this effect might be mediated by other variables, such as conscientiousness, which could be influenced not only by infection but also by factors such as age or health status. Path analyses were conducted to

Table 3. Association of infections with physical and mental health and various behavioural traits in women and men. This table shows partial Kendall τ controlled for age. A negative τ indicates a negative association with the infection, while a positive τ indicates a positive association. Significant effects are printed in bold. Asterisks indicate effects that remain significant after a correction for multiple tests.

	Women		Men	
	Toxoplasmosis	Borreliosis	Toxoplasmosis	Borreliosis
Physical sickness	**0.068***	**0.061***	-0.001	0.018
Mental sickness	**0.073***	0.025	-0.059	**-0.069**
Education	0.004	0.011	-0.025	**0.137***
Intelligence	**0.057***	**0.092***	**0.137***	**0.157***
Memory	-0.012	0.012	0.006	0.023
Reaction time	0.025	-0.011	**0.108**	0.055
Precision	-0.005	0.033	**-0.157***	0.041
Extroversion	-0.014	-0.021	-0.032	-0.026
Agreeableness	0.011	0.007	**-0.125**	0.045
Conscientiousness	**-0.094***	**-0.078***	-0.064	-0.023
Emotional stability	-0.019	-0.007	0.077	0.027
Openness to new experiences	**-0.056**	0.016	0.013	0.017
Pathogen disgust	-0.043	**-0.057***	-0.075	-0.030
Sexual disgust	-0.025	-0.030	-0.025	-0.028
Moral disgust	-0.007	-0.029	0.103	0.015
Injury disgust	-0.050	-0.011	-0.077	0.033
Machiavellianism	**-0.059***	-0.030	**-0.150***	-0.030
Narcissism	**-0.055**	**-0.047***	0.011	-0.017
Psychopathy	0.000	**0.042**	-0.037	-0.024
Tribalism	-0.031	**-0.071***	**-0.141***	-0.047
Economic egalitarianism	-0.026	-0.005	-0.029	0.019
Cultural liberalism	-0.019	-0.003	0.074	**0.085***
Anti-authoritarianism	0.019	0.038	0.006	0.034

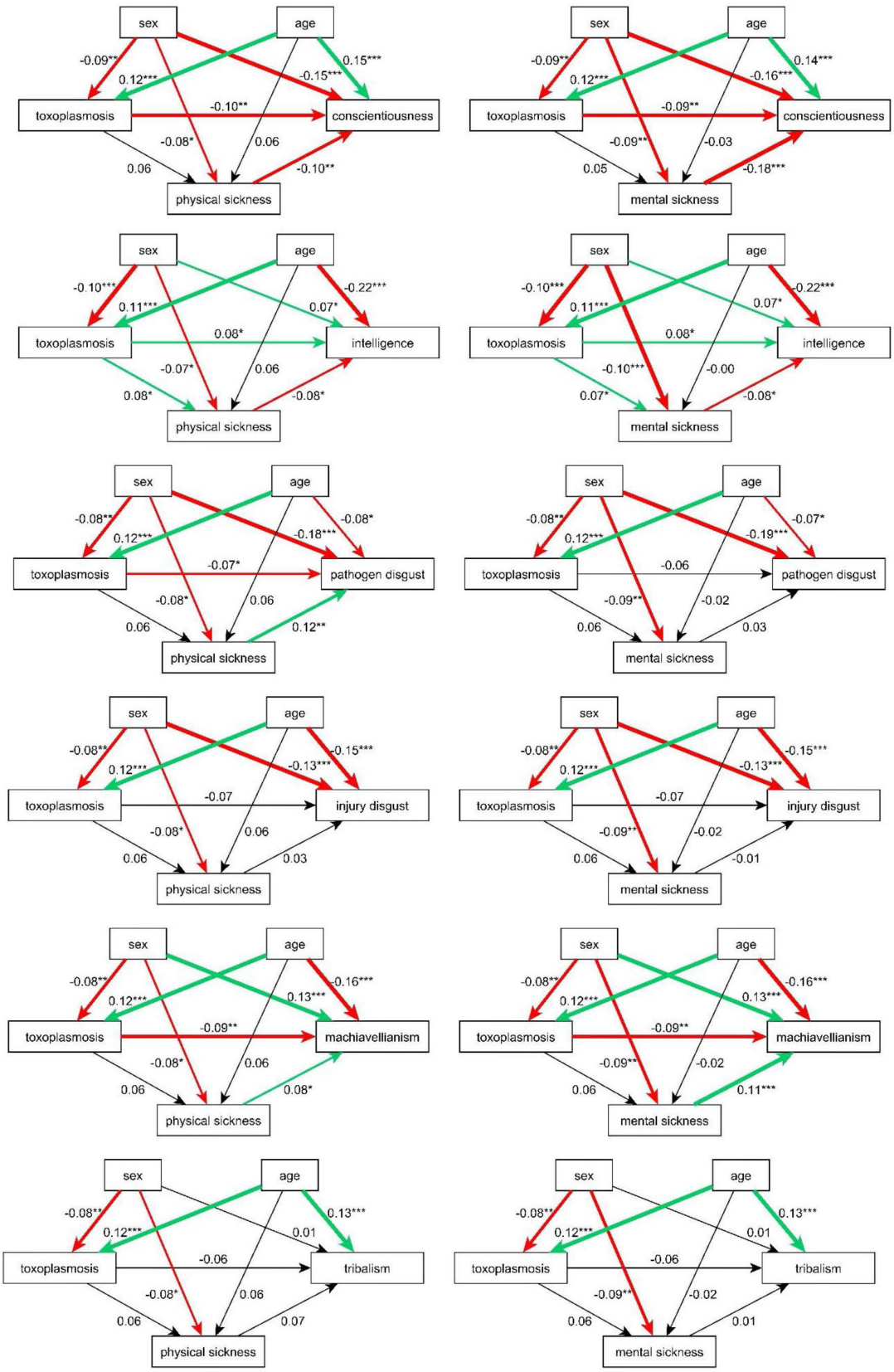

Fig. 1. The results of path analyses for toxoplasmosis: investigation of possible mediating effects of physical or mental health. Green arrows show positive, red arrows negative, and black arrows nonsignificant correlations. The numbers (standardised path coefficients) and arrow widths indicate the strength of correlations. The number of asterisks (one, two or three) indicates their significance (0.05, 0.01 and 0.001, respectively). Men are coded with 1, women with 0; therefore, a negative path coefficient indicates that, for example, men scored lower on conscientiousness than women did.

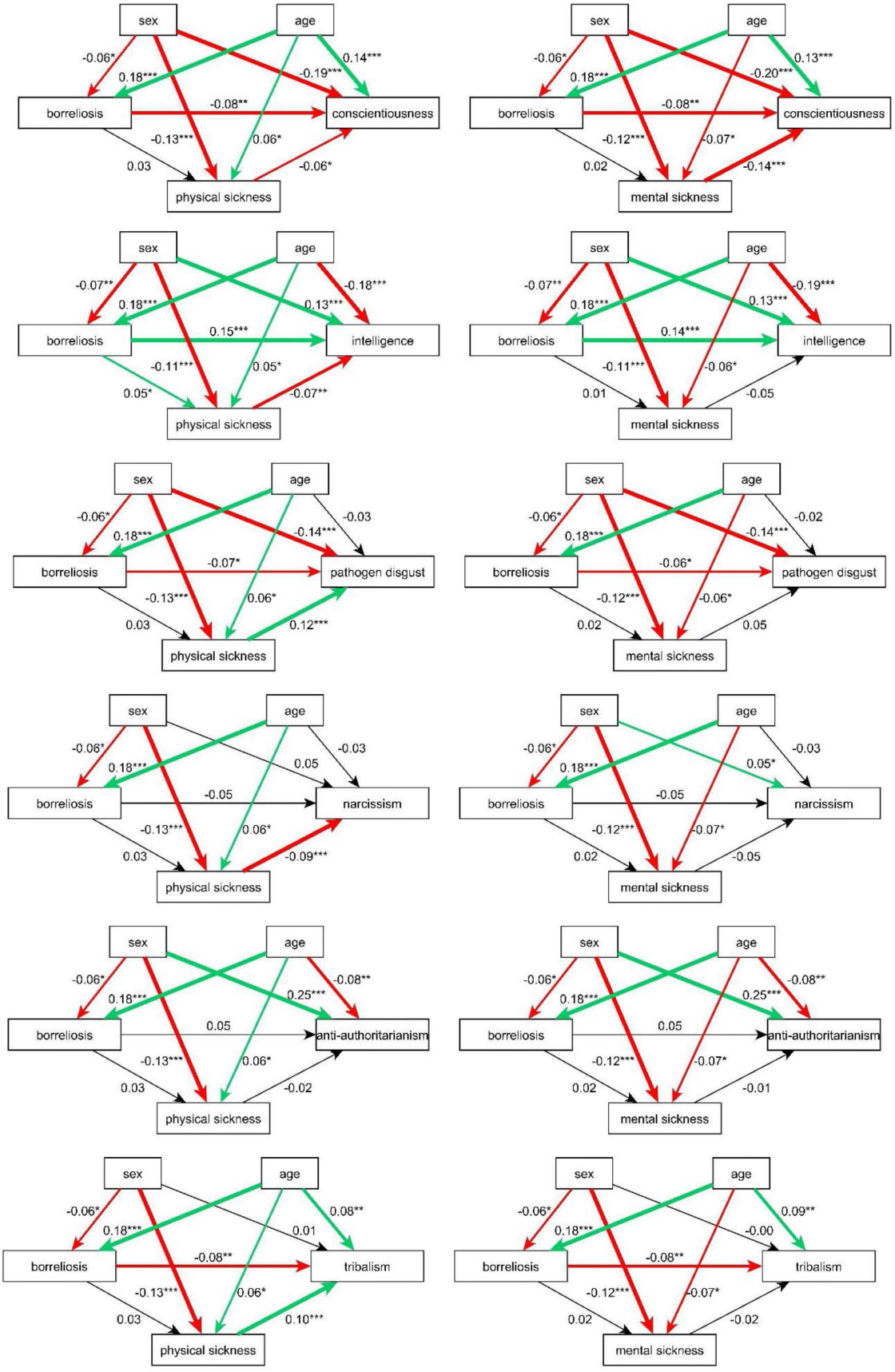

Fig. 2. The results of path analyses for borreliosis: investigation of possible mediating effects of physical or mental health. For legend, see Fig. 1.

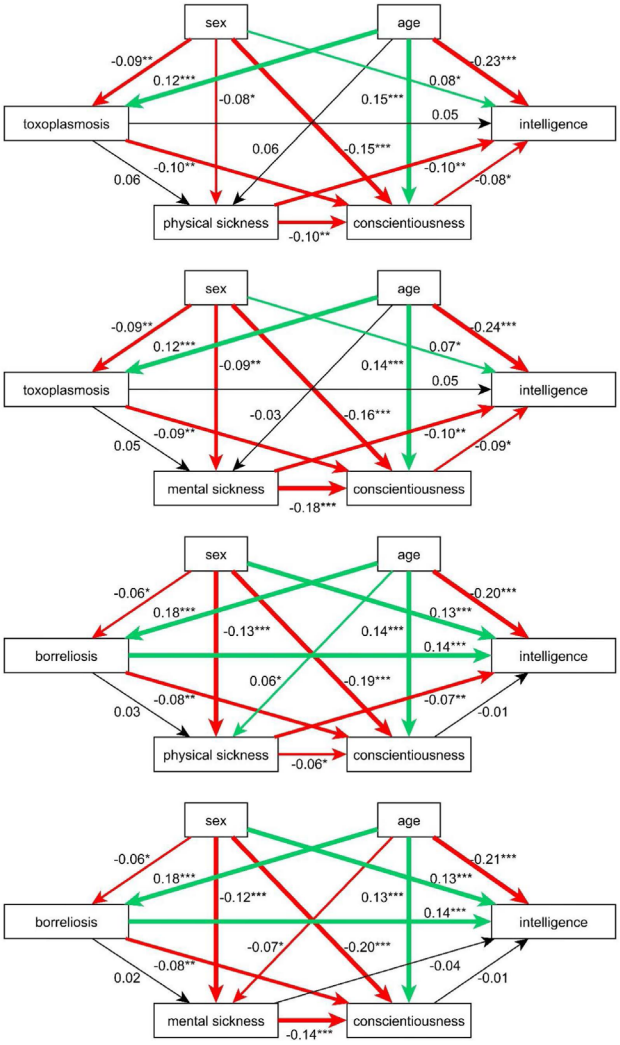

Fig. 3. Path analysis: search for a mediating effect of conscientiousness on intelligence. For legend, see Fig. 1.

investigate this hypothesis, and the results are presented in Fig. 3. The models included six variables: age, sex, infection status, physical and mental health, conscientiousness, and intelligence. The findings were different for borreliosis and toxoplasmosis.

Regarding toxoplasmosis, the findings partially support a conscientiousness-mediated model. Specifically, when both conscientiousness and physical or mental illness were included in the analysis, the direct effect (i.e., the path coefficient) decreased from 0.08 to 0.05, rendering it statistically non-significant. Therefore, the results suggest that toxoplasmosis negatively affects conscientiousness and conscientiousness negatively affects intelligence test results, and these two negative relations could result in a positive relationship between toxoplasmosis and intelligence. However, it is likely that the indirect effect is weaker than the direct effect of toxoplasmosis on intelligence. Additionally, toxoplasmosis was found to increase mental illness, which, in turn, was linked to decreased conscientiousness. Nevertheless, this conscientiousness-mediated positive effect of mental sickness on intelligence was outweighed by a much stronger direct negative effect of mental sickness on intelligence (Fig. 3).

For borreliosis, the path analysis did not provide evidence for a conscientiousness-mediated model. Specifically, when conscientiousness and physical or mental health were included in the analysis, the direct positive effect of the infection on intelligence remained unchanged (Fig. 3, lower portion).

We conducted a comparable analysis to explore whether education might mediate the association between infections and intelligence. This analysis revealed a strong positive correlation between education and intelligence, with a path coefficient greater than 0.4 (results not shown). Nevertheless, we observed no link between *Toxoplasma* or *Borrelia* seropositivity and education. As such, education is unlikely to account for the positive relationship between infections and intelligence.

DISCUSSION

In the confirmatory phase of this study, we tested the hypothesis that the differences in cognitive performance and personality traits between individuals who tested positive or negative for anti-*Toxoplasma* or anti-*Borrelia* IgG antibodies were merely the side effects of the impaired physical or mental health of the infected subjects. Our findings indicate that seropositive subjects had poorer overall health; however, the results from our multivariate nonparametric tests and path analyses provide evidence against the side effects hypothesis. Specifically, our relatively large dataset demonstrated that the strength of all associations between seropositivity and behavioural traits remained relatively constant regardless of whether physical and mental health were controlled for or not. Additionally, for several outcome variables, the effects of seropositivity and impaired health on behavioural variables exhibited opposite directions.

In the exploratory part of our study, we confirmed the existence of some previously described effects, found novel effects, and assessed discrepancies between our findings and previously published data. With regards to toxoplasmosis, we replicated previous findings indicating that infected individuals reported poorer physical and mental health compared to corresponding controls. This finding is consistent with the results of similar questionnaire-based studies and other empirical studies, such as cross-sectional studies conducted on serologically tested volunteers (Flegr and Escudero 2016) and ecological (correlative) studies performed in 88 countries worldwide or in 29 European countries (Flegr et al. 2014).

We have also confirmed a lower level of conscientiousness but not higher extroversion among seropositive individuals. In a previous study conducted by Lindová et al. (2012), the Big Five personality traits were evaluated using a different personality questionnaire (NEO-PI-R) in a considerably younger population of university students whose *Toxoplasma* status was serologically tested immediately prior to the study. These differences in the experimental design may partially account for the divergent results obtained in the two studies, particularly the lack of an associ-

ation between toxoplasmosis and extroversion in our current investigation. We replicated the previously reported effect of *Toxoplasma*-seropositivity on psychomotor performance. The effects were nonsignificant in women but significant and relatively strong in men, showing longer reaction times and lower precision (higher number of errors) compared to *Toxoplasma*-seronegative men. Our findings are consistent with those of other studies, such as Flegr et al. (2012b) and Gale et al. (2020). Additionally, both *Toxoplasma*-positive men and women scored higher on intelligence tests than their *Toxoplasma*-negative counterparts.

A recent meta-analytic study (de Haan et al. 2021) reported a mild impairment of cognitive functions in *Toxoplasma*-positive subjects but, for some unknown reason, this study excluded all studies that used IQ questionnaires. When the intelligence of 191 women tested for toxoplasmosis during pregnancy was essayed with the Cattel 16PF test, those who were *Toxoplasma*-positive scored higher than those who were *Toxoplasma*-negative (Flegr and Havlíček 1999). In a study of 857 military conscripts (men), *Toxoplasma*-positive subjects scored significantly worse on the OTIS intelligence test (Otis 1954). However, this effect was likely a transient effect of recent acute toxoplasmosis rather than a cumulative effect of latent toxoplasmosis, as intelligence negatively correlated with anti-*Toxoplasma* antibody titre (and therefore positively with the duration of infection). In another study of 502 male soldiers tested with two IQ tests (Wiener Matrizen-Test, i.e., nonverbal general intelligence test, and OTIS verbal intelligence test), RhD-positive *Toxoplasma*-infected subjects scored lower, while RhD-negative *Toxoplasma*-infected subjects scored higher on intelligence than their *Toxoplasma*-free peers (Flegr et al. 2013). To summarise, *Toxoplasma*-positive and *Toxoplasma*-negative subjects usually differ in their performance in intelligence tests, but the direction of the effect varies between studies and may be a side effect of other effects of the infection or possibly due to an unknown variable independently influencing both intelligence and the probability of being seropositive.

We observed no significant effect of *Toxoplasma* positivity on memory, as assessed by a modified Meili test. This finding contrasts with several recent studies that have reported impairments in certain memory functions in *Toxoplasma*-positive individuals (Mendy et al. 2015a, b, Wyman et al. 2017, Gale et al. 2020, Wiener et al. 2020). In terms of political attitudes, our results sharply contrast with those of a recent study by Kopecky et al. (2022). Specifically, we found a negative association between *Toxoplasma* positivity and tribalism (i.e., tribal conscientiousness and loyalty, exaltation of one's own tribe or nation over other groups), which was not significant in path analysis.

In contrast, a study using the same method and conducted earlier (2016–2018) found a positive association between *Toxoplasma* positivity and tribalism. We can only speculate as to the reasons for this change. For instance, it is possible that a significant shift in political attitudes occurred in the Czech population following the onset of the Russian invasion of Ukraine. Path analysis revealed that both *Toxoplasma* seropositivity and tribalism were positively associated with age. However, the effect of age alone does not explain the marked differences between the current and previous studies.

To our knowledge, no prior studies have investigated the relationship between toxoplasmosis and the dark triad traits or disgust. We discovered that *Toxoplasma*-positive individuals, particularly men, demonstrated lower scores on Machiavellianism, and *Toxoplasma*-positive women scored lower on narcissism. We incorporated the dark triad test into our survey since we speculated that impaired health could influence an individual's life strategy, leading to a shift from a slower to a faster life strategy (Sýkorová and Flegr 2021), which, in turn, could affect some of these traits. However, our findings demonstrated that the impacts of toxoplasmosis and impaired health on these traits were in opposition to one another.

We discovered a robust negative correlation between *Toxoplasma* positivity and pathogen disgust and injury disgust (the latter being non-significant in path analysis). It is plausible that higher levels of pathogen and injury disgust may protect individuals against *Toxoplasma* infection. It is noteworthy that pathogen disgust displayed a negative correlation with both *Toxoplasma* and *Borrelia* positivity, whereas injury disgust was only correlated with *Toxoplasma* positivity. One can mitigate the risk of *Toxoplasma* infection by avoiding the consumption of raw meat and by maintaining better hygiene standards. Nevertheless, it is not clear how heightened pathogen disgust could reduce the risk of *Borrelia* infection (i.e., tick bites).

A possible explanation is that pathogen disgust correlates with disgust towards ectoparasites, a hypothesis which finds support for instance in Lorenz et al. (2014). It is challenging to explain how injury disgust could decrease the risk of *Toxoplasma* infection. *Toxoplasma* can be transmitted through blood, but in modern times, this transmission route is relatively infrequent. One hypothesis is that a greater propensity to consume raw meat is linked with decreased disgust in general (including injury disgust), as raw meat digestion can trigger disgust (Angyal 1941). An alternate explanation is provided by the results of the path analysis, which demonstrated that injury disgust exhibited correlations with age and sex that could potentially influence both the probability of becoming *Toxoplasma* seropositive and the differences in injury disgust.

In the present study, we confirmed that *Borrelia*-positive individuals reported to be in worse physical but not mental health than the corresponding controls (see also Flegr and Horáček 2018). In contrast to toxoplasmosis, behavioural effects of borreliosis (i.e., Lyme disease) have received less attention, possibly due to the focus on clinically important symptomatic neuroborreliosis or post-treatment neuropsychiatric syndrome that is affecting about 10–20 % of antibiotically treated patients (McAuliffe et al. 2008, Hündersen et al. 2021, Marvel et al. 2022, but see Halperin 2014). These conditions can lead to various negative outcomes, including attention and memory impairments, executive function deficits, and lower perceived quality of life (McAuliffe et al. 2008, Hündersen et al. 2021), which are often associated with psychiatric conditions such as de-

pression, panic attacks, psychotic states, bipolar disorder, and dementia (Fallon et al.1992, Scotti and Weber 1995).

Furthermore, changes in brain structure and function have also been reported in such cases (Oksi et al. 1996, Marvel et al. 2022). It is plausible that such changes may persist even long after infection, particularly in untreated patients or those who did not receive post-treatment clinical intervention. It should be noted, though, that, leaving out individual case studies, changes in personality, including those related to dark triad, disgust or political beliefs have not been previously studied in relation to borreliosis (see Flegr and Horáček 2018 for some negative findings). Therefore, the part of our study concerning the behavioural effects of *Borrelia* seropositivity had an explorative character and the observed associations cannot be compared with previously published data. If nothing else, it should be noted that the positive association of intelligence with *Borrelia* positivity was nearly two times stronger than the equivalent association with *Toxoplasma* positivity (τ 0.111 vs. 0.066).

In contrast to the findings with *Toxoplasma*, *Borrelia*-positive male subjects showed higher scores in achieved education (only men) and precision, as demonstrated by their ability to select a greater number of targets correctly in the Stroop test. This might seem surprising concerning the negative effect of neuroborreliosis on memory. However, these results are consistent with earlier studies revealing unaffected working memory task accuracy in patients with post-treatment borreliosis syndrome (Marvel et al. 2022). Similar to the situation with *Toxoplasma*, we found no effect of *Borrelia* positivity on memory. Moreover, *Borrelia*-positive individuals, both men and women, scored lower in conscientiousness, pathogen disgust and tribalism compared to their *Borrelia*-negative counterparts. These negative associations were also detected in *Toxoplasma* positivity.

In contrast to *Toxoplasma*, we found no significant association between Machiavellianism and *Borrelia* positivity in either test, while the association between narcissism and *Borrelia* was only significant in the Kendall correlation test. We also discovered a positive association between *Borrelia* (but not *Toxoplasma*) positivity and anti-authoritarianism, which may be moderated by age and sex. Overall, the majority of behavioural effects associated with *Borrelia* seropositivity resembled those of *Toxoplasma* seropositivity. Nonetheless, there were several differences, some of which were marked, notably the performance in the Stroop test.

Exploratory analyses of our data revealed a pronounced positive correlation between *Toxoplasma* and *Borrelia* seropositivities (OR = 3.35). This association was not significant among the smaller male subset, where toxoplasmosis prevalence was notably lower than in women. Specifically, only seven out of 92 *Borrelia*-free men and three out of 19 *Borrelia*-infected men were infected with *Toxoplasma* in our sizable sample. This observation aligns with a previous study that reported a similar association (OR = 3.10) in a large population sample (Flegr and Horáček 2018). Historically, two primary explanations for this association have been suggested (Flegr and Horáček 2017). Firstly, latent toxoplasmosis is known to exert specific immunomodulatory effects on both humans and mice (Kaňková et al. 2010, Flegr and Stříž 2011), potentially heightening vulnerability to other infections, including borreliosis. Secondly, a shared vector for both pathogens might exist. While ticks are not conventionally linked to human *Toxoplasma* infections, *Toxoplasma* DNA has been identified in *Ixodes ricinus* Linnaeus, the predominant European tick, at a rate almost identical to *Borrelia* (12.6% versus 12.7%) (Sroka et al. 2009). Moreover, both pathogens were detected in 2.3% of all ticks and 3.8% of adult female ticks. Prior research has also confirmed the transmission of *Toxoplasma* by three tick species: *Dermacentor variabilis* (Say), *D. andersoni* Stiles, and *Amblyomma americanum* (Linnaeus) (Woke et al. 1953).

The main limitation of the present study is that the participants self-reported their serostatus. Although we instructed them to rely solely on laboratory test results, this method is still prone to errors. Nevertheless, it is a reasonable and cost-effective way to collect data from a large number of participants, which is necessary for certain types of analyses. This method is also more reliable for detecting old *Toxoplasma* and *Borrelia* infections than laboratory tests, as the level of anamnestic IgG antibodies decreases below the detection threshold of standard serological tests in a large fraction of subjects who were infected more than 10 years ago (Kodym et al. 2007). However, some participants may have confused the pathogens, misinterpreted the test results, or confused IgG and IgM seronegativity. Additionally, some individuals may have acquired the infection after having previously tested negative. It is important to note, though, that such stochastic noise disproportionately more often result in the Type II error – the failure to detect an existing effect than in the Type I error – detecting a non-existent effect (Flegr and Horáček 2017).

Another limitation of our study is the overrepresentation of women in our sample. This may be due to self-selection, as those who were more altruistic and curious may have been more likely to participate voluntarily. Additionally, studies have shown that *Toxoplasma*-infected women tend to be more altruistic than their uninfected peers, while *Toxoplasma*-infected men tend to be less altruistic (Lindová et al. 2010), explaining also why the seroprevalence of toxoplasmosis in our sample was much higher in women than in men. As a result, caution should be taken when generalising our findings to the wider Czech population. However, it should be noted that this is a common issue in studies that rely on voluntary participation, and it was demonstrated that offering payment for participation increase selection bias even more significantly (Aruguete et al. 2019).

An additional challenge in our study was that the bulk of the data was gathered in March 2022, during which the Czech Republic faced a pronounced COVID-19 wave. Concurrently, the well-being of many was impacted by the unfolding events in Ukraine. It is plausible that responses related to physical health might have been influenced by recent experiences with COVID-19, while mental health responses (anxiety and depression) could have been affected by the current epidemiological situation and the war in

Ukraine. This raises the question of how generalisable the findings are to a more typical situation. However, only future studies can address this question.

In previous studies, we demonstrated an association between having had COVID-19 and toxoplasmosis (Flegr 2021), and between having had COVID-19 and borreliosis (Flegr et al. 2022). However, we also showed that individual variants of SARS-CoV-2 likely differ in this regard. In the current study, we asked participants if they had contracted COVID-19. By spring 2022, many individuals who had contracted COVID-19 did not have laboratory confirmation, some had mild cases post-vaccination, and others had been infected multiple times. Moreover, it became evident that merely having COVID-19 had a relatively minor effect on an individual's physical and mental condition; the actual course of the disease and the time since infection were more crucial (Flegr and Latifi 2023, Latifi and Flegr 2023).

Preliminary analysis from the current study did not show any significant association between COVID-19 and either *Toxoplasma* or *Borrelia*. We opted not to include the relevant COVID-19-related variables in our models. Incorporating them would have required further subgroup divisions, especially among those with *Toxoplasma* and *Borrelia* infections based on their COVID-19 history. This would not only lead to smaller sample sizes in each category but also introduce the risk of overparametrisation, necessitating a substantially larger overall sample for robust analysis. We acknowledge that uncontrolled variables might have increased the overall variability in our target variables, thereby increasing the risk of false-negative results in some tests.

In conclusion, our results suggest that the behavioural effects of latent toxoplasmosis and borreliosis are direct effects of the infections rather than side effects of impaired health of the infected subjects. However, it should be emphasised that neither path analysis nor any other statistical method can conclusively confirm the validity of a model. For instance, such techniques cannot rule out the involvement of unknown factors that are not accounted for in the models. Furthermore, statistical analyses of observational data cannot establish causality in particular associations, meaning that they cannot determine the direction of arrows connecting pairs of variables in the model. For example, no statistical method can determine whether the positive association between intelligence and *Toxoplasma* or *Borrelia* seropositivity is the result of a positive (direct or indirect) effect of higher intelligence on the risk of infection or vice versa. Only an experimental study, which is not feasible for ethical reasons, could distinguish between these two fundamentally different models.

Moreover, neither observation nor experiment can decide whether a particular behavioural change is a side effect of some process associated with the infection or the product of the parasite's manipulation activity. It is common for researchers to consider a behavioural change that positively affects the biological fitness of the parasite as evidence that the parasite is manipulating its host. Nevertheless, it should be acknowledged that nonspecific side effects may also increase the biological fitness of a parasite (Flegr 2022b). In contrast, statistical analyses of data obtained from observational and experimental studies can disprove or fundamentally question the validity of certain models, as demonstrated in our analysis. Our more robust nonparametric and more sensitive parametric methods both failed to support the existence of a mediating effect of impaired health. Neither method yielded any evidence of such an effect, implying that impaired health is unlikely to act as a mediator in this context.

Acknowledgments. We would like to thank Anna Pilátová for the final revisions of our text. This research was supported by the Czech Science Foundation, grant number 22-20785S. Our sponsor had no involvement in the study design, the collection, analysis and interpretation of data, the writing of the report, or in the decision to submit the article for publication.

Author Contributions statement. Designed research (JF, JT), performed research (JF, JH, JT), contributed new reagents or analytical tools (JF), analysed data (JF, JH), wrote the paper (JF, JH, JT).

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Received 13 June 2023 Accepted 31 October 2023 Published online 28 November 2023

Cite this article as: Flegr J., Ullmann J., Toman J. 2023: Parasitic manipulation or side effects? The effects of past *Toxoplasma gondii* and *Borrelia* spp. infections on human personality and cognitive performance are not mediated by impaired health. Folia Parasitol. 70: 020.