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ORIGINAL ARTICLE

Decreased level of novelty seeking in blood donors infected with Toxoplasma

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Abstract

OBJECTIVES: *Toxoplasma gondii*, a parasitic protozoan, infects about 30–60% of people worldwide. *Toxoplasma* is known to induce behavioral changes and an increase of dopamine in mice. The presence of anti-*Toxoplasma* antibodies (latent toxoplasmosis) is also a risk factor for schizophrenia. Latent toxoplasmosis in men (male soldiers) is associated with lower novelty seeking. As the novelty seeking is supposed to negatively correlate with level of dopamine, the observed effect was interpreted as indirect evidence of increased dopamine levels in subjects with toxoplasmosis. However, it is also possible that the observed effect was caused by association of both novelty seeking and *Toxoplasma* infection with a third factor, e.g. size of place of residence.

METHODS: Personality profile of 290 blood donors (205 men and 85 women) were measured by Cloninger's TCI (Temperament and Character Inventory) and their blood samples were assayed for the presence of anti-*Toxoplasma* antibodies. Difference between *Toxoplasma*-infected and *Toxoplasma*-free subjects was tested with ANCOVA method with gender, size of place of residence, and age as covariates.

RESULTS: The present analysis revealed that lower novelty seeking was associated with latent toxoplasmosis both in men and women. The effect of infection on novelty seeking remained significant even after adjustment for size of place of residence ($p<0.01$).

CONCLUSION: Decreased novelty seeking in *Toxoplasma*-infected subjects have been already confirmed in three independent populations (male soldiers and male and female blood donors). These findings suggest that the local inflammation-induced increase in dopamine in the brain of infected subjects can represent a missing link between toxoplasmosis and schizophrenia.

Abbreviations
TCI – temperament and character inventory
ELISA – enzyme linked immunosorbent assay
ANCOVA – analysis of covariance
NS – novelty seeking
CMV – Cytomegalovirus
IL-2 – interleukin 2
CSF – colony stimulating factor

Introduction

The protozoan parasite *Toxoplasma gondii* specifically influences the behavior of intermediate hosts. Infected mice have impaired motor performance, deficits in learning capacity and memory, higher activity levels both in novel and familiar environments, lower ability of discriminating between familiar and novel surroundings, and longer reaction times. Infected rats have higher activity levels, lower neophobia, reduced learning capacity and reduced specific predator avoidance. For review see [46]. Humans with latent toxoplasmosis have significantly deteriorated psychomotor performance (prolonged simple reaction times) in comparison with *Toxoplasma*-negative subjects [22] and are at higher risk of traffic accidents [15]. Subjects with latent toxoplasmosis are known to show specific changes in some personality factors as measured by the16PF questionnaire [16, 19, 17] and Cloninger's TCI (Temperament and Character Inventory) [18]. Recently, changes in the TCI factor novelty seeking were used for monitoring possible shifts in dopaminergic activity in the brain of infected men [18]. Increase in dopamine levels in infected subjects was expected based on direct measurement of neurotransmitter levels in animals [39] and the reported positive correlation between schizophrenia and toxoplasmosis [30, 36, 26, 27, 49, 44] or risk factors of *Toxoplasma* infection [42, 41, 43]. The background level of dopamine in the basal ganglia is expected to negatively correlate with the psychobiological factor novelty seeking as measured with Cloninger's TCI questionnaire [7, 48, 37, 20, 21]. Therefore, lower novelty seeking in the subset of *Toxoplasma*-infected subjects was interpreted as an indirect indicator of increased dopamine levels in brain tissue. An important caveat of the study was a failure to adjust for size of place of residence. The risk of *Toxoplasma* infection in the Czech Republic is known to correlate negatively with size of place of residence [24]. Since several psychobiological factors, including novelty seeking, also seem to correlate with this variable, it is difficult to tell to what extent the negative correlation between novelty seeking and latent toxoplasmosis can be biased by the correlation between novelty seeking and size of place of residence and between size of place of residence and the risk of *Toxoplasma* infection. The previous study was performed on military conscripts (men). There are no data concerning relationship between toxoplasmosis and novelty seeking in women.

The main aim of the present study was to establish whether the psychological effect of latent toxoplasmosis was evident after adjustment for an important confounder, i.e. size of place of residence and can be detected both in men and women. For these purposes, 290 blood donors were tested for latent toxoplasmosis and examined with Cloninger's TCI questionnaire.

Materials and methods

Subjects

During the thrombocyte separation sessions, about eight hundred donors of thrombocytes at the transfusion units of Institute of Haematology and Blood Transfusion, Prague and Zbraslav hospital, Prague were asked to voluntarily participate in the research project and to sign the informed consent form. Five hundred thirty one (about 70%) consented to provide their psychological data and provided 5 ml of blood for serological examination. They were given Cloninger TCI questionnaire and stamped envelope with address of department of parasitology at the Faculty of Science, Charles University. Two hundred ninety questionnaires (54.7%) were filled and returned to our address.

Reliable information on the size of place of residence was available for 270 subjects, divided into three categories: those living in villages and small cities (<10 thousand population), those living in larger cities (10–50 thousand population), those living in large cities (50–100 thousand population) and those living in the Czech capital, Prague (1.2 million population). The results of all analyses were virtually the same if the study subjects were divided into three categories (<10 thousand, 10–100 thousand, >100 thousand). For purpose of Log-linear analysis we divided the subjects to two categories <50 thousand and >50 thousand. The recruitment of subjects and the data handling was in accordance with current rules in Czech legislation.

Personality tests

Personality testing was performed with TCI (Temperament and Character Inventory) [8] as translated by [25], with translation of two questions being modified and Cloninger's validation scale being substituted with Eysenck's Lie scale EP/R. The final questionnaire [35] contained all 238 TCI items and 12 Lie scale items. The subjects received written instructions to answer the YES or NO for particular items, depending on whether the sentence in the questionnaire characterized or did not characterize their usual and most probable behavior or feelings in the given situations.

Immunological tests for toxoplasmosis

All serological tests were carried out in the National Reference Laboratory for toxoplasmosis of the National Institute of Public Health, Prague. Specific anti*Toxoplasma* IgG and IgM antibody concentrations were determined by ELISA (IgG: SEVAC, Prague, IgM: TestLine, Brno), optimized for early detection of acute toxoplasmosis [34], and complement fixation test (CFT) (SEVAC, Prague) which is more sensitive and therefore more suitable for the detection of old *T. gondii* infections [45]. Titres of antibodies to *Toxoplasma* in sera were measured at dilutions between 1:8 and 1:1024. The subjects with negative results of IgM

ELISA (positivity index<0.9) and CFT titres higher than 1 : 8 were considered latent-toxoplasmosis positive.

Statistical analysis

The Statistica® v.6.0 general linear models module was used for all statistical testing, i.e., for Log-linear analyses, ANCOVA and linear regression. The results of testing of ANCOVA assumptions, namely of the testing of normality of data distribution, normality of residuals and homogeneity of variances, were nonsignificant for all studied models.

Results

Two hundred ninety blood donors (205 men and 85 women) were tested for specific immunity against *Toxoplasma*. The prevalence rates of *Toxoplasma* infections in men and women were 34.1% and 27.1%, respectively. Log-linear analysis of the categorical factors *Toxoplasma* infection, gender, and size of place of residence revealed only one significant interaction, namely decreased prevalence of toxoplasmosis in inhabitants of large cities (Chi2=4.71, df=1, p=0.030). Results of ANCOVA showed that *Toxoplasma* infection was associated with lower novelty seeking scores, *Fig.1* (F1,254=6.922, p=0.009, factors: gender, size of place of residence, age). *Toxoplasma* infection was also associated with lower self-transcendence scores (12.8 vs. 14.5, F1,254=5.18, p=0.024, nonsignificant after Bonferroni correction for multiple statistical tests). The results also showed significant interaction between gender and *Toxoplasma* infections with respect to reward dependence (F1,254=4.07, p=0.045, nonsignificant after Bonferroni correction for multiple statistical tests), *Fig.2*. For the particular subfacets responsible for the effects see the *Table 1*. The effects of toxoplasmosis on personality traits were stronger in women then in men

Table 1. Difference between *Toxoplasma*-negative and *Toxoplasma*-positive subjects in TCI factors. Last two columns show the results of ANCOVA with size of living place, gender, and age and *Toxoplasma* infection as the independent factors.

TCI facets and subfacets	Toxo negative		Toxo positive			
	M	SD	M	SD	F1,254	P
Novelty seeking (NS)	19.82	6.11	17.53	5.92	6.92	0.009
Harm Avoidance (HA)	14.69	6.47	15.22	5.92	0.06	0.812
Reward Dependence (RD)	14.95	3.56	14.97	3.66	0.05	0.821
Persistence (PE)	4.52	2.03	4.39	1.97	0.11	0.739
Self-directedness (SD)	26.66	6.97	28.38	7.20	3.66	0.057
Cooperativeness (CO)	29.10	6.03	28.97	5.40	0.03	0.857
Self-transcendence (ST)	14.43	6.03	12.77	5.53	5.18	0,024
Lie score	3.98	2.06	4.32	1.94	1.59	0.209
Exploration Excitability NS1)	5.60	2.42	5.01	2.31	2.38	0.124
Impulsiveness (NS2)	4.52	1.88	4,01	1.82	2.73	0.100
Extravagance (NS3)	5.22	2.39	4.52	2.44	3.78	0.053
Disorderliness (NS4)	4.48	2.11	3.91	2.18	3.73	0.055
Worry/pessimism (HA1)	4.45	2.32	5.03	2.12	3.04	0.083
Fear of Uncertainty (HA2)	3.57	1.87	3.51	1.77	0.30	0.587
Shyness (HA3)	4.00	2.36	3.94	2.20	0.20	0.657
Fatigability (HA4)	2.68	2.10	2.73	1.94	0.04	0.848
Sentimentality (RD1)	6.35	1.97	6.43	2.20	0.01	0.905
Attachment (RD3)	4.97	1,85	4.77	2.09	0.41	0.521
Dependence (RD4)	3.63	1.31	3.76	1.30	0.33	0.569
Responsibility (SD1)	5.24	1.82	5.74	1.47	5.40	0.021
Purposefulness (SD2)	4.75	1.83	4.97	1.97	0.84	0.360
Resourcefulness (SD3)	3.60	1.41	3.50	1.36	0.38	0.536
Self-Acceptance (SD4)	5.79	2.62	6.05	2.85	0.65	0.419
Enlightened 2nd Nature (SD5)	7.30	2.52	8.13	2.50	6.77	0.010
Acceptance (CO1)	6.41	1.57	6.44	1.55	0.03	0.860
Empathy (CO2)	4.39	1.60	4.08	1.32	1.93	0.166
Helpfulness (CO3)	6.30	1.27	6.39	1.22	0.80	0.372
Compassion vs Revenge (CO4)	6.46	2.66	6.39	2.84	0.17	0.678
Integrated Conscience (CO5)	5.55	1.43	5.67	1.38	0.26	0.613
Self-Forgetfulness (ST1)	6.09	2.38	5.47	2.41	4.64	0.032
Transpersonal Identification (ST2)	2.99	1.90	2.70	1.81	1.89	0.170
Spiritual Acceptance (ST3)	5.35	3.26	4.60	2.93	3.36	0.068

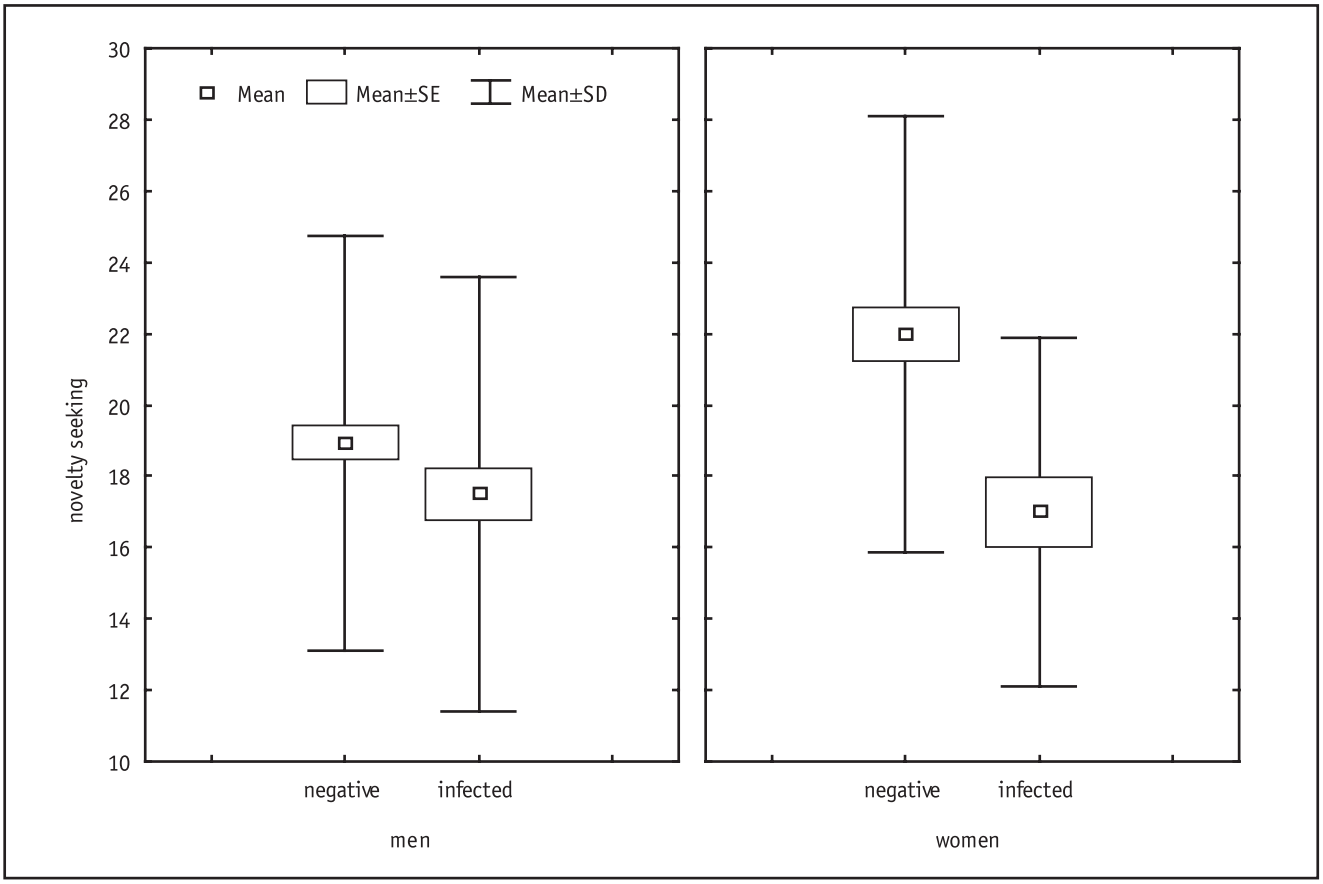

Figure 1. Novelty seeking in blood donors infected with *Toxoplasma gondii*.

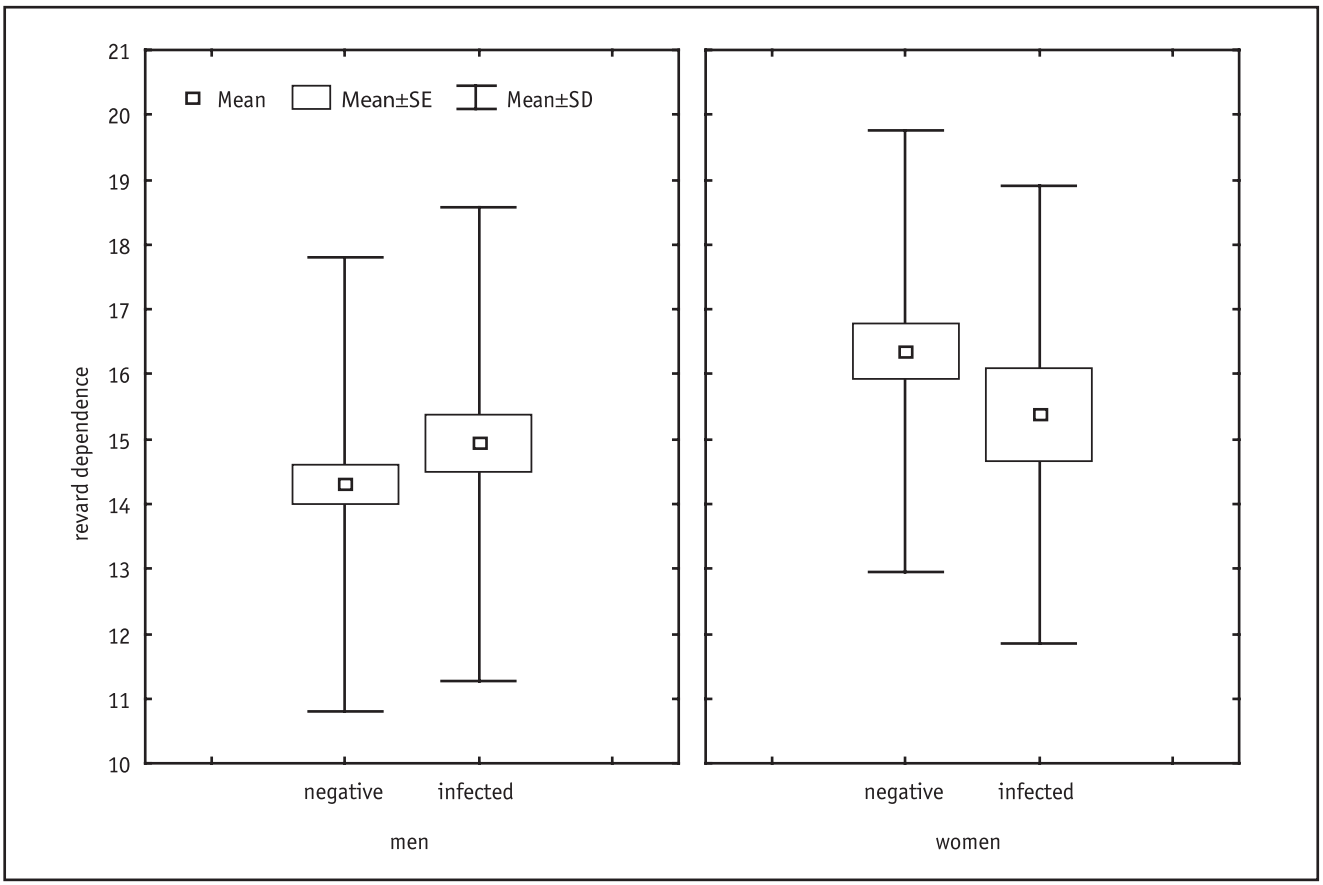

Figure 2. Reward dependence in blood donors infected with *Toxoplasma gondii*.

(novelty seeking: men p=0.099, women p=0.021, self transcendence: men p=0.14, women p=0.038).

Previous studies showed that novelty seeking scores negatively correlated with concentration of specific anti-*Toxoplasma* antibodies in *Toxoplasma*-infected subjects. Here, we find no correlation between personality factors and concentration of anti-*Toxoplasma* antibodies.

Discussion

Our results confirmed that *Toxoplasma*-infected subjects, both men and women, had lower scores in the psychobiological factor novelty seeking than the *Toxoplasma*-free subjects. The lower values of all four NS subscales (NS1-NS4) suggest that the *Toxoplasma*-infected subjects have on average little or no need for novel stimulation, prefer familiar places, people, and situations, are more reflective, tend to require more detailed information when making an opinion and are not easily distracted. *Toxoplasma*-infected subjects are also more reserved, slow, controlled; they do not waste their energy and feelings. They tend to be organized, methodical, and prefer activities with strict rules and regulations.

In the contrast to previous study that showed slightly increased level of self-transcendency we found here lowered level of this factor in the infected subjects. Subjects with low level of self-transcendency are more rational and materialistic, have lower spirituality, self-identification with nature or cosmos. The opposite influence of toxoplasmosis on the same personality factors in different experimental sets (men vs. women, students vs. military conscripts) was already reported in previous studies. We suppose that the overcompensation of toxoplasmosis induced-change as part of ego-defense mechanism can cause that some people (for example women, residents of small cities) behave in the opposite way to their natural drive commands. Differences in five other TCI personality factors and in Eysenck Lie score were not significant after the effects of confounding variables were controlled. Lower number of subjects in the present experimental set, 290 men and women vs. 857 men in previous study, was probably responsible for failure to find any correlation between novelty seeking and concentration (titre) of anti-*Toxoplasma* antibodies in the infected subject.

Based on a case-control study, it is not possible to tell whether there is a causal relation between two statistically associated factors (e.g. infection and lower novelty seeking scores) or to determine the direction of such a relation. Theoretically, the infection could induce personality changes, personality factors may have influenced the risk of infection and possibly a third factor, such as the socioeconomic status, may have played a role in both personality factors and the risk of infection. In our view, however, the most parsimonious explanation is that the infection, more precisely the presence of pathogens in the brain of infected subjects, induces changes in neurotransmitter levels, causing in turn changes in TCI personality factors. This hypothesis is based on several lines of indirect evidence:

a) Two different neurotropic pathogens, protozoon *Toxoplasma gondii* and Human Cytomegalovirus (CMV), with quite different life cycles and transmission routes are associated with the same psychobiological effect, namely with decrease of novelty seeking [31]. This makes the existence of a third factor responsible for both lower novelty seeking scores and higher risk of infection rather unlikely. Moreover, the existence of such a factor would cause a statistical association between *Toxoplasma* and CMV infections. However, CMV infection was detected with equal frequency among *Toxoplasma*-free and *Toxoplasma*-infected subjects [31].

b) The existence of correlation between novelty seeking scores and levels of specific anti-*Toxoplasma* antibodies was observed on previous studies [18, 31]. Such a correlation between the intensity of personality change and specific immunity could hardly be found if novelty seeking would influence the risk of infection or if an unknown factor would independently influence both novelty seeking and the risk of infection.

c) A decrease in neophilia, probably caused by lower ability of discriminating between familiar and novel surroundings, was also observed in mice experimentally infected with *Toxoplasma*. Therefore, the direction of the causal relation between novelty seeking-related behavioral changes and *Toxoplasma* infections has already been experimentally established in rodents.

d) Lower novelty seeking scores are expected to correlate with the background level of dopamine in the basal ganglia [7, 48, 37, 20, 21]. The increased level of dopamine was indeed observed in mice experimentally infected both with *Toxoplasma* [40] and CMV [32].

The specific neurological mechanism underlying the association between the infections and novelty seeking was not the subject of the present study. The available results of neuroimmunological studies, however, suggest that several cytokines engaged in inflammation processes, like interleukins 1, 2 and 6, directly influence the level and turnover of many neuromodulators, including dopamine [13, 23, 3, 51]. An extremely low concentration of interleukin 2 (IL-2) is able to potentiate dopamine release evoked by number of different stimuli, including K+ depolarization in mesencephalic cell cultures [2] and striatal slices [33]. Injections of IL-2 into the rat striatum have been shown to induce turning behaviors in rats that are typical of perturbation of the dopaminergic system [10] and subcutaneously administered IL-2 significantly increases locomotor activity of mice in the elevated plus-maze test [33]. Serious neuropsychiatric side effects demanding acute intervention regularly occur in oncological patients treated with IL-2 and lymphokine-activated killer cells [11, 47, 33]. Dormant forms of *Toxoplasma* and CMV persist in the brain of infected individuals for many years. The activation of acute disease in immunocompromised patients and immunohistochemical data obtained on mice [9] suggest that under normal conditions both diseases are kept in latent form by the host

immune system. Local immune processes in the brain of subjects with latent infections are probably accompanied by local disturbances in particular cytokine levels [4, 38, 12, 5, 14]. This can influence the background level of neuromodulators and secondarily some of the psychobiological factors.

It has been reported repeatedly that both toxoplasmosis and contact with cat, the definitive host of *Toxoplasma gondii*, are associated with higher risk of schizophrenia [30, 36, 26, 27, 49, 44, 42, 41, 43]. The background level of dopamine is supposed to play an important role in etiology of schizophrenia [50, 6, 38] and autoimmune-like effects on the dopamine system have been proposed as a possible mechanism involved in the pathogenesis of schizophrenia and Parkinson's disease [1]. Clinical investigations have detected increased levels of IL-2 in the CSF of schizophrenic patients manifesting symptoms of psychosis [28, 29]. It can be speculated that the local inflammation-induced increase in dopamine in the brain of infected subjects can be in fact the missing link between schizophrenia and *Toxoplasma* infection.

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