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Decreased level of psychobiological factor novelty seeking and lower intelligence in men latently infected with the protozoan parasite *Toxoplasma gondii* Dopamine, a missing link between schizophrenia and toxoplasmosis?

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Abstract

Toxoplasma gondii, a parasitic protozoan, infects about 30–60% of people worldwide. The latent toxoplasmosis, i.e. life-long presence of cysts in the brain and muscular tissues, has no effect on human health. However, infected subjects score worse in psychomotor performance tests and have different personality profiles than *Toxoplasma*-negative subjects. The mechanism of this effect is unknown; however, it is supposed that presence of parasites' cysts in the brain induces an increase of the concentration of dopamine. Here we search for the existence of differences in personality profile between *Toxoplasma*-positive and *Toxoplasma*-negative subjects by testing 857 military conscripts using a modern psychobiological questionnaire, namely with Cloninger's Temperament and Character Inventory (TCI). ANCOVA showed that *Toxoplasma*-positive subjects had lower Novelty seeking (NS) scores

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($P = 0.035$) and lower scores for three of its four subscales, namely Impulsiveness ($P = 0.049$), Extravagance ($P = 0.056$) and Disorderliness ($P = 0.006$) than the *Toxoplasma*-negative subjects. Differences between *Toxoplasma*-negative and positive subjects in NS was inversely correlated with duration of toxoplasmosis estimated on the basis of concentration anti-*Toxoplasma* antibodies ($P = 0.031$). Unexpectedly, the infected subjects had also lower IQ ($P_2 = 0.003$) and lower probability of achieving a higher education ($P_2 < 0.0000$). Decrease of NS suggests that the increase of dopamine in brain of infected subjects can represent a missing link between toxoplasmosis and schizophrenia.

Keywords: Toxoplasmosis; Schizophrenia; Dopamine; Manipulation hypothesis; TCI; IQ; Parasite; Behavior

1. Introduction

About 30–60% of the population in both developed and developing countries is infected with the parasitic protozoon *Toxoplasma gondii*. Definitive hosts of *Toxoplasma* are various species of felids and the intermediate host can be virtually any mammal or bird species, including humans. The human hosts usually acquire infection by consumption of raw or undercooked meat containing tissue cysts of *Toxoplasma* or by ingestion of food contaminated by cat feces containing *Toxoplasma* oocysts. In an immunocompetent human the acquired toxoplasmosis, characterized by rapid reproduction of tachyzoites in cells of different tissues, is a relatively mild disease. Usually, it is unrecorded or is misdiagnosed as a common viral or bacterial disease. Within weeks or months the tachyzoits disappear and tissue cysts form in various tissues, mainly in the brain and muscles. The latent toxoplasmosis, i.e. life-long presence of these cysts and presence of anamnestic concentrations of anti-*Toxoplasma* antibodies in immunocompetent subjects, is considered asymptomatic and harmless (Remington and Krahenbuhl, 1982). However, a recent study on blood donors showed that subjects with latent toxoplasmosis have significantly impaired psychomotor performance (prolonged simple reaction times) in comparison with *Toxoplasma*-negative subjects (Havlíček et al., 2001). It is also known that subjects with latent toxoplasmosis express specific changes in some personality factors measured with 16PF questionnaire (Flegr and Hrdý, 1994; Flegr et al., 1996, 2000). The differences in psychomotor performance and personality factors increase with duration of infection (Havlíček et al., 2001; Flegr et al., 2000). Animal studies have shown specific behavioral changes in *Toxoplasma*-infected rodents. Infected mice have impaired motor performance (Hutchison et al., 1980b; Hay et al., 1983a), deficits in learning capacity and memory (Witting, 1979), higher activity levels both in novel and familiar environments (Hutchison et al., 1980a; Hay et al., 1983b, 1984b, 1985) lower ability of discrimination between familiar and novel surroundings (Hutchison et al., 1980a; Hay et al., 1984a), and longer reaction times (Hrdá et al., 2000). Infected rats have higher activity levels (Webster, 1994), lower neophobia (Webster et al., 1994), reduced learning capacity (Witting, 1979) and reduced specific predator avoidance

(Berdoy et al., 2000). The neurophysiological mechanism of these changes is unknown. However, it can be related to increased concentrations of dopamine observed in brain of chronically infected mice (Stibbs, 1985).

All previous human studies used Cattell's 16PF to estimate personality profiles of experiment subjects. Presently, however, several personality questionnaires are available which might be better suited for searching for biological agent-induced personality changes and for the neurological mechanism of the personality factor shift. For example, Cloninger's Temperament and Character Inventory (TCI) questionnaire (Cloninger et al., 1994) provides the personality factors that are supposed to be correlated with concentration of particular neurotransmitters in the brain tissue. Cloninger's psychobiological model (Cloninger et al., 1993) based on neuropharmacological studies in humans and animals recognizes four dimensions of temperament, namely Harm avoidance (HA), Novelty seeking (NS), Reward Dependence (RD) and Persistence (PE), and three dimensions of character, i.e. Self-directedness (SD), Cooperativeness (C) and Self-transcendence (ST). Dimensions of temperament, defined as individual differences in emotion-based habit patterns, are moderately heritable, stable from childhood through adulthood, and structurally consistent in different cultures and ethnic groups. In contrast, character is weakly heritable but moderately influenced by sociocultural learning. It develops in a stepwise manner from infancy through late adulthood, and the timing and rate of transition between levels of maturity depend on antecedent temperament configuration and sociocultural education (Svrakic et al., 1996). On the basis of neuropharmacological, neuroanatomic and biochemical data, each dimension of temperament has been related to specific central neurotransmitters: HA to GABA (γ-aminobutyric acid) and serotonin, NS to dopamine, RD to norepinephrine and PE to glutamate and serotonin (Cloninger et al., 1993). The dimension NS, which should negatively correlate with concentration of dopamine in the ventral midbrain, has four subscales: Exploration excitability (NS1), Impulsiveness (NS2), Extravagance (NS3) and Disorderliness (NS4). The level of the factor Novelty seeking was reported to be associated with certain alleles of dopamine transporter and receptors (Benjamin et al., 1996; Ebstein et al., 1996). These results, however, are still controversial (Paterson et al., 1999).

The aim of our study is to search for the existence of differences in personality profile between *Toxoplasma*-positive and *Toxoplasma*-negative subjects using a modern psychobiological questionnaire. For this purpose, a group of 857 military conscripts was serologically tested for latent toxoplasmosis and their personality profile was monitored with the TCI questionnaire.

2. Methods

2.1. Subjects

All personality testing was performed at the Central Military Hospital at Prague. Personality data were collected during regular psychological examinations of conscripts (men), aspirants to three military specializations, namely the military guards (guards), the military castle-guards (presidential guards) and the military drivers (drivers). All subjects were asked to voluntarily participate in the research project and to sign the informed consent form. Approximately 80% consented to the use of the results of their psychological and serological tests for the toxoplasmosis research and provided 5 ml of blood for serological examination. The recruitment of experimental subjects was performed during six drafts between January 2000 and July 2001. Only subjects aged 19–21 were included in the data set. By this, we not only obtained a more age-homogeneous experimental set of 857 men but also excluded an important category of potential outliers, i.e. the subjects who successfully avoided regular compulsory military service for more than 3 years, and also all subjects with higher (university) education. The number of subjects with higher education was low ($N = 7$) and their presence in the experimental set would have caused imbalance in the experimental design.

2.2. Personality tests

Personality testing was performed with a computerized form of the TCI (Cloninger et al., 1994) translated by Kožený and Tišanská (1998) with modification of two questions and with the Cloninger validization scale substituted with the Eysenck's Lie scale EPQ/R. The actual Czech version of the questionnaire is available at http://www.prfdec.natur.cuni.cz/flegr/cloninger/cloninger02. The final questionnaire (Preiss and Klose, 2001) contained all 226 items of TCI and 12 items of the Lie scale. The subjects received written instructions to press the Yes or No key for particular items, depending whether the sentence on computer screen characterized their usual and most probable behavior or feelings in described situations.

Testing of intelligence was performed with the Otis questionnaire (Otis, 1954) modified and translated by Vacíř (1973). The modified Otis test is a standard verbal intelligence test used by the Czech Army. It consists of 32 questions focused on an understanding of given relationships, linguistic sensitivity, and developed vocabulary. It requires definition of concepts as expressed by the closest descriptive characteristics, selection of concepts according to common characteristics of objects, choice of antitheses, rejection of disparate concepts and explanation of proverbs.

2.3. Immunological tests for toxoplasmosis

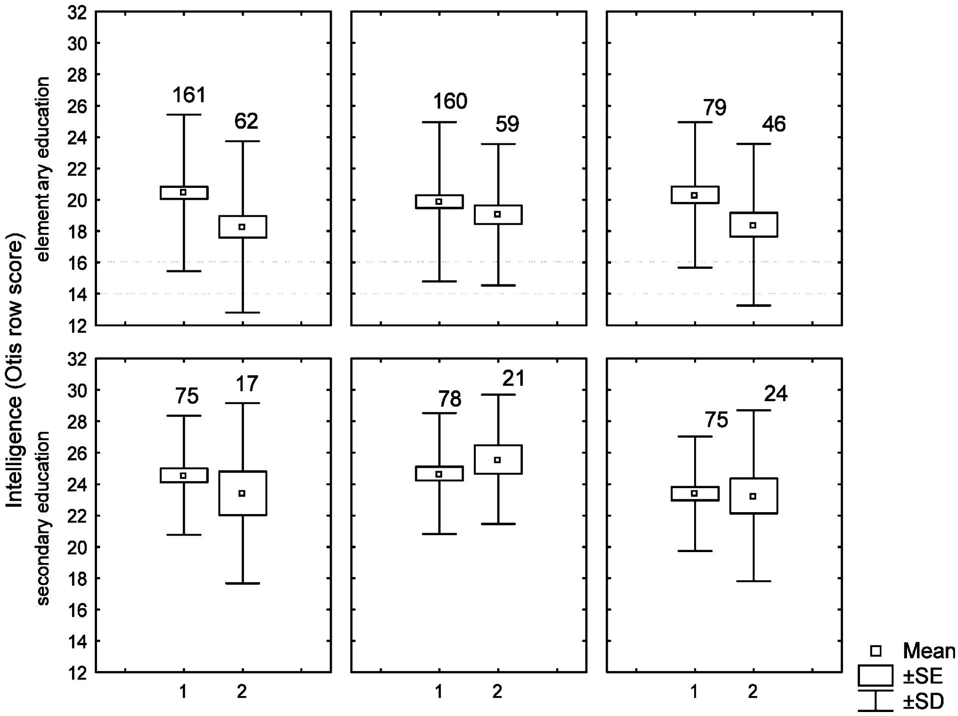
All serological tests were carried out in the National Reference Laboratory for Toxoplasmosis, the National Institute of Public Health, Prague. Specific IgG and IgM antibody titres for toxoplasmosis were determined by ELISA (IgG: SEVAC, Prague, IgM: TestLine, Brno), optimized for early detection of acute toxoplasmosis (Pokorný et al., 1989) and with complement fixation test (CFT) (SEVAC, Prague) which is more sensitive and, therefore, more suitable for the detection of old *T. gondii* infections (Warren and Sabin, 1942). The titre of anti-*Toxoplasma* antibodies in sera was measured in dilutions between 1:8 and 1:1024. The subjects with negative results of IgM ELISA (positivity index < 0.9) and either CFT titres equal or higher than 1:8 or absorbance in IgG ELISA >0.250, i.e. approximately 10 IU/ml were considered latent-toxoplasmosis positive.

2.4. Statistics

Software package R v. 1.4.0 was used for comparison of alternative ANOVA models and for evaluation of statistical test assumptions. Statistica® v.6.0 was used for all other statistical testing, i.e. for Log-linear analyses, ANCOVA, linear regression, and nonparametric 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. Prior to nonparametric regression, the personality factors were standardized with respect to variables of profession, draft term, education and intelligence by computing standardized residuals using an ANCOVA test. The same approach was also used for standardization of the intelligence in respect to the variables profession, draft term and education. The residuals were used also in descriptive statistics (Figs. 2 and 3). We used nonparametric Kendall tests for testing correlations between anti-*Toxoplasma* antibodies titres (five-points ordinal scale 1, 2, 3, 4, 5 for titres 1:8, 1:16, 1:32, 1:64, and 1:128, respectively) and the standardized residuals of personality factors.

3. Results

The experimental sample consisted of 857 men, aspirants to three different military professions, namely 315 guards, 318 presidential guards and 224 drivers. 567 (66.2%) subjects achieved elementary education and 290 (33.8%) secondary education. The sample comprised 628 (73.3%) *Toxoplasma*-negative subjects and 229 (26.7%) subjects with latent toxoplasmosis. Fig. 1 shows the prevalence of toxoplasmosis in aspirants to different military professions. The results of log-linear analysis with factors defined as military profession (1), draft term (2), education (3) and toxoplasmosis (4) indicated the existence of three statistically significant interactions, namely education–toxoplasmosis, military profession–draft term, and education–draft term interactions. The model that included also the toxoplasmosis–education interaction (21 43 32) explained the existing variability far better than the model without the interaction (21 32), ($\chi^2 = 191.35$, 2 d.f., $P < 0.0000$). The reasons for existence of military profession–draft term and education–draft term interaction were obvious, being caused by seasonal differences in army needs of particular military professions and by difference in draft term of subjects with elementary and secondary education. On the other hand, no similar explanation exists for the highly significant interaction between toxoplasmosis and education, i.e. for pronounced underrepresentation of subjects with secondary education among *Toxoplasma*-positive conscripts. Among 626 *Toxoplasma*-negative conscripts 36.3% subjects had finished secondary education while among 229 *Toxoplasma*-positive conscripts the frequency of subjects with secondary education was only 27.1%.

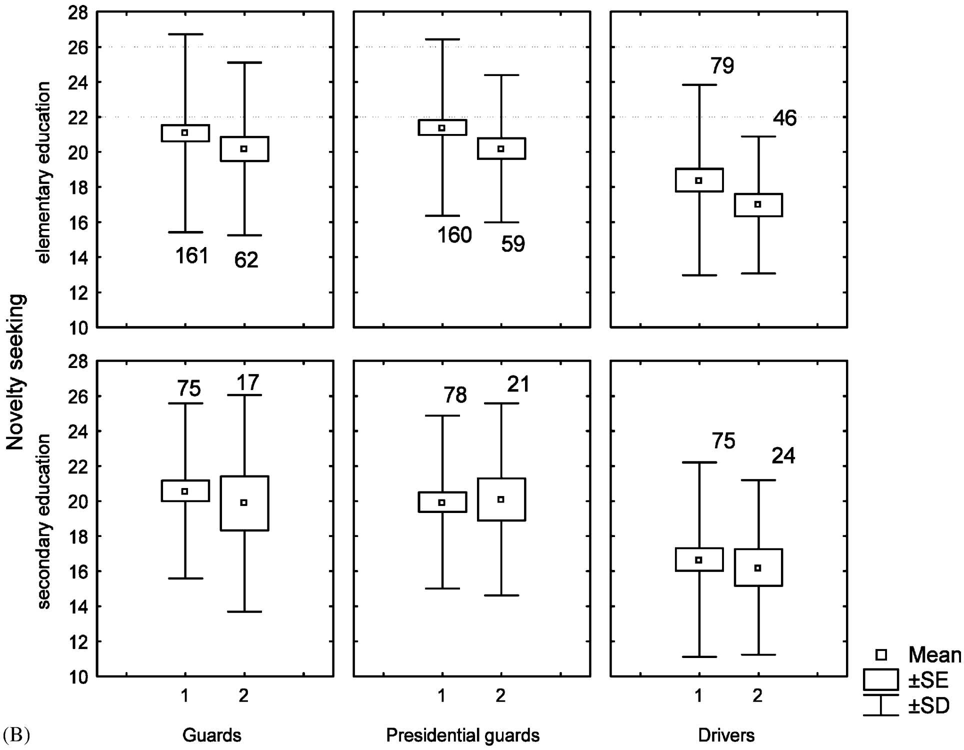


(A)

Fig. 1. Differences between *Toxoplasma*-negative (1) and *Toxoplasma*-positive (2) subjects in the factors verbal intelligence (A) and Novelty seeking (B).

Toxoplasma-positive subjects scored significantly lower in the test of verbal intelligence than the *Toxoplasma*-negative subjects, Fig. 1A. The statistical effect of toxoplasmosis on intelligence was highly significant even after the effects of military profession, education and draft term were controlled (ANOVA, $F_{1,810} = 8.73$, $P = 0.003$). As some of the personality factors (Lie score, HA, RD, C, ST) were correlated with factor intelligence, we included intelligence measured with the Otis test among confounding factors in further analyses.

The result of ANCOVA tests for all seven personality factors, i.e. four factors of human temperament (HA, NS, RD, PE) and three factors of human character (SD, C, ST), showed that after elimination of effects of military profession, draft term, education, and intelligence only the factor Novelty seeking (NS), was lower in *Toxoplasma*-positive subjects ($F_{1,809} = 3.78$, $P = 0.052$), Fig. 1B. The decrease of Novelty seeking was apparent in three of four of Novelty seeking subscales (NS2-Impulsiveness: $F_{1,809} = 3.719$, $P = 0.054$, NS3-Extravagance: $F_{1,809} = 3.254$, $P = 0.072$, NS4-Disorderliness: $F_{1,809} = 7.163$, $P = 0.008$). In contrast, the *Toxoplasma*-positive subjects scored slightly higher in the subscale NS1-Exploration excitability (NS1: $F_{1,809} = 2.318$, $P = 0.128$). *Toxoplasma*-positive subjects had also a slightly



(B)

Fig. 1 (*Continued*)

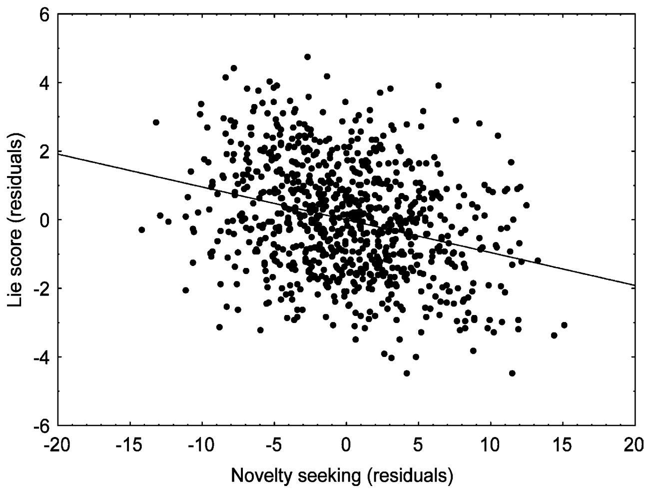


Fig. 2. Negative correlation between factors Novelty seeking and Lie score. The effects of confoundings military profession, draft term, education and intelligence were controlled independently for both factors.

higher Lie-score (L) ($F_{1,809} = 4.121$, $P = 0.09$). However, the lie score was negatively correlated with the factor Novelty seeking Fig. 2, ($\beta = -0.29$, $F_{1,855} = 80.86$, $P <$ 0.000). After the elimination of the effects of Novelty seeking, intelligence, military profession, draft term and education, the difference in Lie score between *Toxoplasma*-positive and *Toxoplasma*-negative subjects disappeared ($F_{1,808} = 1.49$, $P = 0.223$).

To obtain a more precise estimation of the effects of latent toxoplasmosis it is necessary to eliminate possible effects of both confounding factors and also their interactions. Therefore, we compared sums of squared residuals of models that included the factors military profession, draft term, education and binary interactions of these confoundings, and either included or not the effect of toxoplasmosis. Again, the model that included also the effect of toxoplasmosis was significantly better (i.e. explained a significantly greater part of total variability) only for the factor Novelty seeking and three of its subscales (NS: $F_{1,836} = 4.46$, $P = 0.035$, NS1: $F_{1,836} = 1.80$, $P = 0.180$, NS2: $F_{1,836} = 3.89$, $P = 0.049$, NS3: $F_{1,836} = 3.66$, $P = 0.056$, NS4: $F_{1,836} = 7.59$, $P = 0.006$). Similar results were obtained when the models also included the effects of intelligence and interactions between intelligence and other confounding factors (results not shown).

In our experience, some of the questions of the TCI questionnaire are relatively difficult for subjects with lower intelligence to understand. Therefore, we performed all analyses including only 789 subjects who achieved Otis raw score of 14 and higher. The raw score 14 corresponds to the IQ 70 for subjects with elementary education. In this subset the effects of latent toxoplasmosis on Cloninger personality factors were stronger, although qualitatively the results were approximately the same as for the total data. Statistical significance of ANOVA tests of difference of sum of squared residuals was 0.031, 0.753, 0.045, 0.071, 0.011 for factors NS, NS1, NS2, NS3, and NS4, respectively.

The association between personality factors and toxoplasmosis could be caused either by induction of a personality factor shift by toxoplasmosis or by increased probability of *Toxoplasma* infection in subjects with a particular combination of personality factors. Only in the former case is the correlation between personality factor and duration and intensity of *T. gondii* infection expected to exist. The duration and intensity of *Toxoplasma* infection can be roughly estimated on the basis of concentration of anti-*Toxoplasma* antibodies. Therefore, we tested the correlation between levels of antibodies and either Novelty seeking or intelligence in the subset of *Toxoplasma*-positive subjects. We computed the modified Novelty seeking factor (NS^M) for all subjects by subtracting the NS1 subscale from NS, i.e. by removing the effect of only the NS subscale in which *Toxoplasma*-positive subjects scored (nonsignificantly) higher than *Toxoplasma*-negative subjects (see Section 4). The Kendal test showed no correlation between CFT titres and NS^M or intelligence adjusted with respect of the factors military profession, draft term and education (Fig. 3). On the other hand, a linear regression test for *Toxoplasma*-positive subjects suggested a negative correlation between NS^M and concentration of anti-*Toxoplasma* antibodies measured with IgG ELISA ($\beta = -0.13$, $F_{1,223} = 3.83$, $P = 0.052$) (Fig. 4). After removing subjects with rather recent or intensive

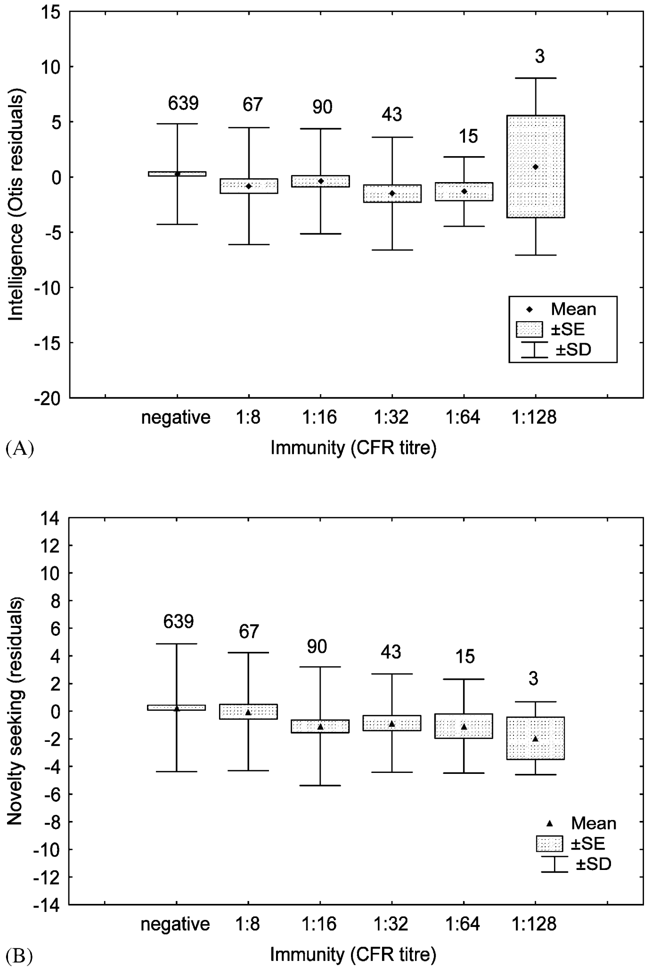


Fig. 3. Correlation between anti-*Toxoplasma* immunity measured with CFT and (A) intelligence and (B) Novelty seeking. The y-axis shows standard residuals of intelligence or Novelty seeking obtained by ANCOVA for military profession, draft term, education and for the factor Novelty seeking as well as intelligence as independent variables. The "negative" group consists of *Toxoplasma*-negative subjects. The group with lowest antibody titres (1:8) consists of subjects with the longest duration of *Toxoplasma* infection.

toxoplasmosis (IgG ELISA >1.8) the negative correlation was even stronger ($\beta=-0.16$, $F_{1,177}=4.71$, $P=0.031$). Although the correlation between antibody concentration and intelligence was not significant, Fig. 3A suggests that the influence of toxoplasmosis on human personality is stronger in subjects with a higher concentration of antibodies.

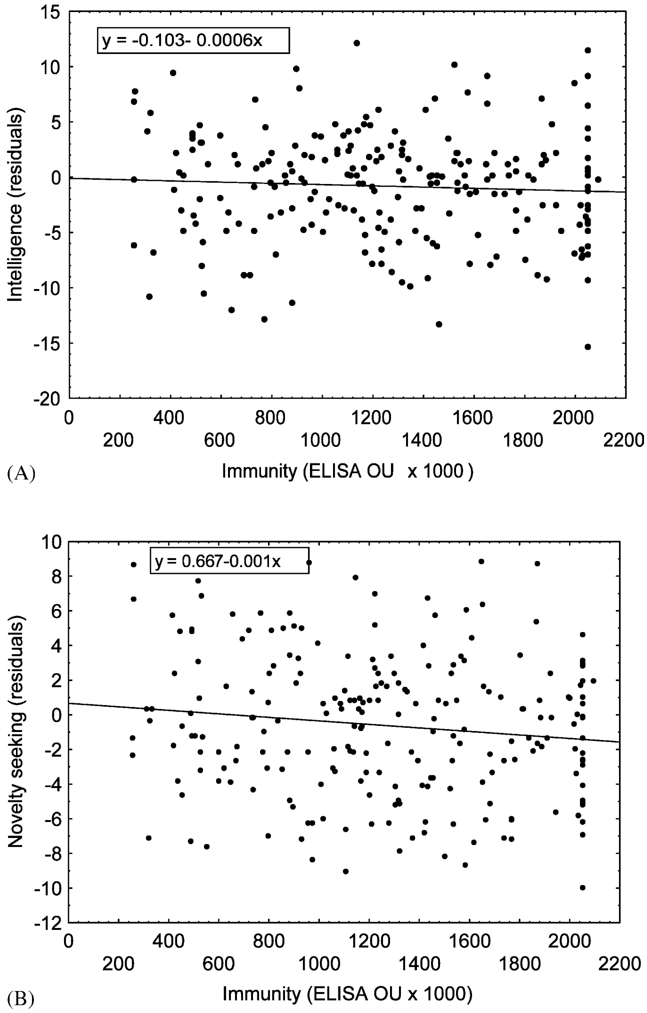


Fig. 4. Correlation between concentrations of anti-*Toxoplasma* antibodies measured with ELISA and (A) intelligence and (B) Novelty seeking. The y-axis shows standard residuals of intelligence or Novelty seeking obtained by ANCOVA for military profession, draft term, and education and for the factor Novelty seeking also intelligence as independent variables.

4. Discussion

Analysis of a sample of 857 conscripts showed that *Toxoplasma*-positive subjects were significantly overrepresented among people with only elementary education, had significantly lower verbal intelligence and significantly lower factor of Novelty seeking. The lower values of three of four NS subscales (NS2-NS4) suggest that the *Toxoplasma*-positive subjects are on average more reflective, tend to require more detailed information when making an opinion and are not easily distracted.

Toxoplasma-positive 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. Differences in six other TCI personality factors and in Eysenck Lie score were not significant after the effects of confounding variables were controlled. Difference in Novelty seeking between *Toxoplasma*-positive and *Toxoplasma*-negative subjects decreased with the anti-*Toxoplasma* antibodies level, the indirect indication of duration and intensity of *Toxoplasma* infection.

The NS1 (Exploratory excitability) was slightly higher in *Toxoplasma*-positive subjects. It has already been demonstrated by others that NS1 has only a low correlation with other NS subscales (Hansenne et al., 2001). The results of factor analysis have shown that the NS1 subscale loads on the factor HA rather than Novelty seeking (Hansenne et al., 2001). After removing the subscale NS1 from the NS scale, the statistical significance of difference in the modified factor of Novelty seeking increased to $P = 0.004$.

The unexpected result of our study was observed underrepresentation of *Toxoplasma*-positive subjects among conscripts with higher than elementary education, and significantly lower verbal intelligence of *Toxoplasma*-positive subjects. The results of the Otis intelligence test were lower for *Toxoplasma*-positives even in the subset of aspirant drivers. In the Czech Army, the profession of military drivers is highly valued by conscripts and, therefore, they are highly motivated to achieve good results in the tests. Therefore, the difference in intelligence rather than lower motivation and lower effort by tested subjects seems to be a more probable explanation for lower scores of *Toxoplasma*-infected subjects in the intelligence test. The lower intelligence of *Toxoplasma*-positive men (Flegr et al., 1996) and higher intelligence in *Toxoplasma*-positive women (Flegr and Havlíček, 1999) was observed in our previous studies. These differences were measured with Cattell's B factor computed on the basis of 13 items, i.e. with a relatively rough test, and the differences were not significant after Bonferroni correction for multiple statistical tests. A lower IQ of *Toxoplasma*-positive subjects was also observed in children with subclinical congenital toxoplasmosis in the early seventies (Saxon et al., 1973; Alford et al., 1974). The incidence of congenital toxoplasmosis in European countries is relatively low. A recent study performed in the Czech Republic showed an incidence about 5 per 100 000 birth per year (Kodym et al., 2001). Therefore, small and moderate decrease of mean intelligence of many subjects with latent (acquired) toxoplasmosis rather than pronounced decrease of intelligence of rare subjects with subclinical congenital toxoplasmosis possibly present in our experimental set is the more probable explanation of lower IQ observed in the *Toxoplasma*-positive conscripts.

Differences between *Toxoplasma*-negative and positive subjects in Novelty seeking decreased with a decline of concentration of anti-*Toxoplasma* antibodies. Generally, the concentration of specific antibodies decreases with the duration of *Toxoplasma* infection. Therefore, the differences in Novelty seeking between *Toxoplasma*-negative and positive subjects probably decreased with duration of infection. This result contrasted with previous results obtained by the 16PF personality questionnaire. The differences in 16PF personality factors between *Toxoplasma*-negative and positive subjects significantly increased both with duration of infection (for subjects diagnosed with acute toxoplasmosis 24–300 months before the study (Flegr et al., 1996, 2000)) and with a decrease of anti-*Toxoplasma* immunity (Flegr et al., 2000). Also, the differences in psychomotor performance between *Toxoplasma*-negative and positive subjects significantly increased with decline of anti-*Toxoplasma* immunity (Havlíček et al., 2001). Such a difference in trends can be explained by difference in nature of personality factors measured by Cloninger TCI test and Cattel 16PF test. Personality factors monitored with 16PF are derived by factorial analyses of personality descriptors (Nezami and Butcher, 2000). It is highly probable that such complex factors develop only slowly in human ontogeny and also respond only slowly to external factors, including the *Toxoplasma* infection. Therefore, the intensity of changes of these factors can correlate with the duration of toxoplasmosis. On the other hand, TCI factors, namely four temperament factors including Novelty seeking, are derived on the basis of biological data and at least some of them are tightly connected with concentrations of a particular neurotransmitter in the brain tissue (Cloninger et al., 1993). Therefore, they can quickly respond to changes in concentrations of neurotransmitters. Changes in TCI factors induced by *Toxoplasma* infection can in fact be instant. The observed positive correlation between intensity of personality factor changes and the concentration of anti-*Toxoplasma* antibodies may reflect the positive correlation between intensity of personality factor changes and intensity of *Toxoplasma* infection (or individual innate resistance to infection) rather than a negative correlation between intensity of personality factor changes and duration of infection. It is also possible that infected people have the capacity to develop compensation for changes in neurotransmitter levels in the course of the infection. Such compensation can be relatively difficult for changes in rather complex 16PF factors and practically impossible for psychomotor performance parameters.

Because of ethical reasons, it is not possible to perform infection experiments with human subjects. Without such experiments, however, it is not possible to decide whether a causal relation exists between *Toxoplasma* infection and personality factor changes. Theoretically, *Toxoplasma* can induce the personality changes, personality factors can influence the probability of *Toxoplasma* infection or an unknown third factor, such as the socioeconomic status of the subject, can influence both personality factors and probability of *Toxoplasma* infection. In our view, however, the most parsimonious explanation of our results is that the parasite infection, namely the presence of bradyzoites in tissue cysts in brains of infected subjects, induces changes in neurotransmitter level, which results in changes in TCI personality factors. This conclusion is based on five lines of indirect evidence:

1) The level of Novelty seeking appears to return to population norms with decrease of anti-*Toxoplasma* immunity. Such a correlation between the intensity of personality change and anti-*Toxoplasma* immunity can hardly be found if the level of Novelty seeking influences the probability of infection or if an unknown

factor independently influences both Novelty seeking and the probability of *Toxoplasma* infection.

2) The decrease of novelty seeking has been observed in *Toxoplasma*-infected rodents experimentally infected with *Toxoplasma* (Hutchison et al., 1980a; Hay et al., 1984a).
3) The consumption of raw or undercooked meet is the major source of *Toxoplasma* infection in Czech Republic (Flegr et al., 1998). The consumption of raw or undercooked meat is not a standard habit in Czech cuisine. Therefore, high Novelty seeking (or low HA) rather than low Novelty seeking would be more tightly associated with a higher probability of contracting *Toxoplasma* infection.
4) Novelty seeking is expected to be correlated with low basal dopaminergic activity (low basal firing rates of dopaminergic neurons being associated with postsynaptic supersensitivity and higher novelty seeking score, and inversely higher dopaminergic baseline activity being associated with relative postsynaptic downregulation and lower novelty seeking score) (Cloninger et al., 1993; Wiesbeck et al., 1995; Ruegg et al., 1997; Gerra et al., 2000; Suhara et al., 2001; Hansene et al., 2002). The increased level of dopamine has already been observed in mice experimentally infected with *Toxoplasma* (Stibbs, 1985).
5) Increased levels of dopamine in certain areas of the brain can play an important role in patients with certain forms of schizophrenia (Creese et al., 1976; Carlsson, 1988; Sawa and Snyde, 2002). In many countries, one of two major risk factors for acquired toxoplasmosis is breeding of pet cats in the home (Frenkel et al., 1995; Flegr et al., 1998; Fan et al., 2001). It has recently been shown that contact with cats is also an important risk factor in schizophrenia (Torrey and Yolken 1995; Torrey et al., 2000; Torrey and Yolken, 2002). Many studies have also directly demonstrated frequent association between acute toxoplasmosis and schizophrenia or higher prevalence of latent toxoplasmosis in patients with schizophrenia than in the normal population (Minto and Roberts, 1959; Robertson, 1965; Kramer, 1966; Ladee et al., 1966; Yolken et al., 2001). These results, as well as our indirect indices for increased level of dopamine in the brain of infected subjects, suggest that *T. gondii* can be an etiological agent in at least some forms of schizophrenia.

The results of animals' studies and the nature of the personality changes associated with toxoplasmosis in men suggest that a possible relation between latent toxoplasmosis and an increase of dopamine level in the brain of infected subjects deserves future study.

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