

Decrease of psychomotor performance in subjects with latent 'asymptomatic' toxoplasmosis

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SUMMARY

Toxoplasma gondii is known to induce specific behavioural changes in its intermediate hosts. This is usually considered to be an evolutionary adaptation aimed to increase the probability of transmission of the parasite into its definitive host, the cat, by predation. In rodents an increase of reaction time as well as many other specific behavioural patterns have been observed. Here we report the results of our double blind study showing the significantly longer reaction times of 60 subjects with latent toxoplasmosis in comparison with those of 56 controls. Moreover, the existence of a positive correlation between length of infection and mean reaction time suggested that slow and cumulative effects of latent toxoplasmosis rather than a one-step (and possibly transient) effect of acute toxoplasmosis disease are responsible for the decrease of psychomotor performance of infected subjects. To our knowledge, this is the first study confirming the existence of such parasite-induced changes in human behaviour that could be considered in evolutionary history of the human species as adaptive from the point of view of parasite transmission.

Key words: manipulation hypothesis, parasite, human, reaction times, *Toxoplasma gondii*, behaviour, evolution.

INTRODUCTION

Toxoplasma gondii is a heteroxenic coccidian parasite of felids with an unusually wide range of intermediate and paratenic hosts, including humans. After a short phase of acute toxoplasmosis the infection proceeds into its latent phase when cysts are formed and these survive for the rest of the host's life, mainly in neural and muscular tissues of infected subjects. In immunocompetent subjects the latent phase of infection is considered asymptomatic and harmless. The prevalence of latent toxoplasmosis is very high in most developed and developing countries in the world, usually ranging from 30 to 70% (Schassan & Kaskara, 1971; Perea & Borobio, 1974; Develoux *et al.*, 1988; Frenkel & Ruiz, 1980; Petithory *et al.*, 1996).

T. gondii is a classical model for the study of the manipulation hypothesis. Specific behavioural effects of latent toxoplasmosis which can be interpreted as special adaptation of the parasite to increase the probability of its transmission from intermediate to definitive host by carnivorousness have been demonstrated in numerous studies with laboratory mice and rats. Infected mice have impaired motor performance (Hutchison, Aitken & Wells, 1980*b*; Hay

et al. 1983*a*), deficit in learning capacity and memory (Witting, 1979), higher activity levels both in novel and familiar environments (Hutchison, Aitken & Wells, 1980*a*; Hay, Hutchison & Aitken, 1983*b*; Hay *et al.* 1984*b*; Hay, Aitken & Arnott, 1985), lower ability to discriminate between familiar and novel surroundings (Hutchison *et al.* 1980*a*; Hay, Aitken & Graham, 1984*a*), and longer reaction times (Hrdá *et al.* 2000). Infected rats have higher activity levels (Webster, 1994), lower neophobia (Webster, Brunton & Macdonald, 1994), reduced learning capacity (Witting, 1979) and lowered level of avoidance of a cat odour (Berdoy, Webster & Macdonald, 2000). In human hosts, only indirect evidence for the existence of behavioural changes, namely, the shifts in personality profiles in subjects with latent toxoplasmosis have been observed (Flegr *et al.* 1996; Flegr, Kodým & Tolarová, 2000).

A specific change that could be highly adaptive from the point of view of the life-cycle of *T. gondii* would be an increase in the reaction time of infected intermediate hosts. Under natural conditions such changes can increase the probability that an infected intermediate host would be captured and eaten by a cat. In a modern human such changes would be non-productive from the point of view of *T. gondii* transmission, however, they still could exist here. To search for this specific change in the behaviour of *Toxoplasma*-infected subjects we measured the psychomotor performance of men and women immuno-

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logically tested for latent toxoplasmosis. Here we report the results of a comparison of simple reaction times in a set of 116 subjects with and without latent toxoplasmosis.

MATERIALS AND METHODS

Subjects

The experimental set consisted of 69 men and 47 women, the donors of thrombocytes at the Institute of Haematology and Blood Transfusion, Prague. During the thrombocyte separation sessions the donors were asked to take part in a reaction time test. The tests were carried out in the morning (to avoid possible diurnal differences in performance), after the end of the thrombocyte separation session under standard laboratory conditions. The method of recruitment of subjects as well as the data handling was in accordance with all current rules in Czech legislation.

Psychomotor test

Psychomotor performance was investigated by a computer version of a simple reaction time test. This test is widely used in studies of behavioural effect of viral infections (Smith *et al.* 1989; Hall & Smith, 1996). A white square (1 × 1 cm) appeared in the centre of the black computer display at irregular intervals ranging from 1 to 8 sec. The subject had to respond to the square immediately after it appeared on the display by pressing a key on a special keyboard. A 1-min training exercise was followed by a 3-min test. The computer measured and recorded reaction times of each trial. After the experiment a mean reaction time for each minute of the test and total mean reaction time for the whole 3 min of the test were computed omitting all outliers i.e. values more than 2.5 s.d. away from the raw mean reaction time for the particular subject. At the time of reaction time testing neither the subjects nor the researcher were aware of the results of the immunological assessment of toxoplasmosis.

Immunological tests for toxoplasmosis

All serological tests were carried out in the National Reference Diagnostic Laboratory for Toxoplasmosis, the National Institute of Public Health, Prague. Specific IgG and IgM antibody titres for toxoplasmosis were determined by ELISA, optimized for early detection of acute toxoplasmosis (Pokorný *et al.* 1989) and with complement fixation tests (CFT) which are more sensitive and therefore more suitable for the detection of old *T. gondii* infections (Warren & Sabin, 1942). The titre of anti-*Toxoplasma* antibodies in sera was measured in dilutions between 1:8 and 1:1024. The subjects with CFT titres between 1:8 and 1:128 were considered latent-toxoplasmosis positive. No subjects with titres equal

or higher than 1:256 or with other indications of recent acute toxoplasmosis (e.g. high titres in IgG and IgM ELISA) were involved in the study.

Statistics

The Statistica® v. 5.0 program was used for all statistical testing including evaluating statistical test assumptions, namely the normality of data distribution, homogeneity of variances, and interaction by covariates (parallelism). The women had slightly longer reaction times than men in the 3rd min of the test (ANCOVA, $F_{1,111}$, $P = 0.038$). However, after the Bonferroni correction for multiple tests no statistically significant differences between men and women were observed either in reaction time, or in the prevalence of latent toxoplasmosis, and therefore both sexes were analysed together. Without a logarithmic transformation, the distributions of reaction times were slightly asymmetrical and also the distribution of residuals of ANOVA tests were significantly skewed (independent variables TOXO and SEX, Shapiro-Wilk normality test, $W = 0.9691$, $P = 0.009$). However, the results of all tests performed on transformed and non-transformed data were similar and therefore only the results for the non-transformed data are reported in the present study.

An analysis of covariance (ANCOVA) was used to study the effects of toxoplasmosis (independent variable TOXO), and age of subject (confounding variable AGE), on reaction time in the 1st, 2nd and 3rd min of the test (dependent variables). ANCOVA with repeated measures (reaction times in the 1st, 2nd and 3rd min of the test) was used for estimation of the effect of toxoplasmosis in the whole 3 min test and both ANCOVA and ANOVA with repeated measures for the study of the possible interaction between toxoplasmosis and duration of test (by *post hoc* tests). Scheffé tests were used for the *post hoc* comparison of differences in reaction times in the 1st, 2nd and 3rd min for *Toxoplasma*-negative and positive subjects. The effect of the elimination of the effect of age was negligible in *post hoc* tests i.e. the results of these tests were identical for ANCOVA and ANOVA. For testing of correlation between the 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 reaction time we used nonparametric Kendall tests. The effect of age was controlled by using residuals of regression between age (independent variable) and reaction time (dependent variable) instead of raw reaction times in our Kendall test.

RESULTS

The results of the simple reaction time test for 56 *Toxoplasma*-negative and 60 *Toxoplasma*-positive subjects are shown in the Fig. 1. The results of one-

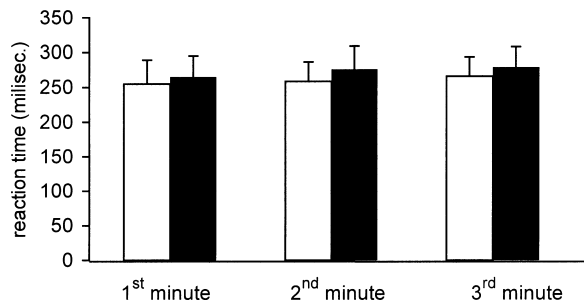


Fig. 1. Mean reaction time (in msec) in 1st, 2nd and 3rd min of the test. Error bars show standard deviation. Light columns, non-infected; dark columns, infected subjects.

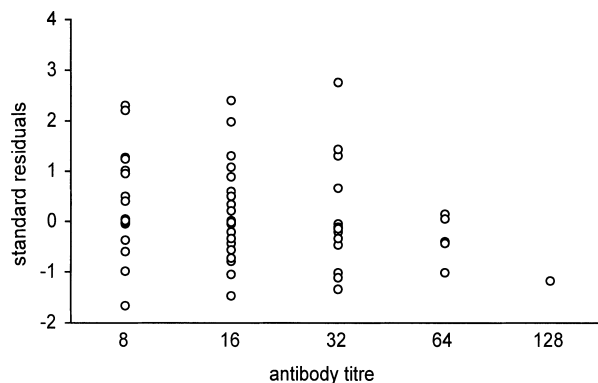


Fig. 2. Correlation between antibody titre and mean reaction time in the whole 3-min interval of the test. The abscissa shows standard residuals of simple linear regression between the age and total mean reaction time, the ordinate shows the antibody titre measured with CFT.

sided ANCOVA tests (with elimination of a possible effect of age) showed that *Toxoplasma*-positive subjects had significantly longer reaction times in the second ($F_{1,113} = 7.6$, $P = 0.0034$, $R^2 = 0.084$) and third ($F_{1,113} = 4.8$, $P = 0.015$, $R^2 = 0.076$) min as well as in the whole 3 min interval of the test (ANCOVA with repeated measures, $F_{1,113} = 5.41$, $P = 0.011$). In the 1st min of the test the difference between *Toxoplasma*-positive and *Toxoplasma*-negative subjects was not significant ($F_{1,113} = 2.0$, $P = 0.079$, $R^2 = 0.037$). *Post hoc* comparison (with two-tailed Scheffé test) showed that a significant reduction of psychomotor performance occurred between the 1st and 3rd min ($P = 0.030$) but not between the 1st and 2nd min ($P = 0.91$) in the *Toxoplasma*-negative and between the 1st and 2nd min ($P = 0.015$) but not between the 2nd and 3rd min ($P = 0.95$) in the *Toxoplasma*-positive subjects.

To reveal whether the difference in reaction times between *Toxoplasma*-negative and *Toxoplasma*-positive subjects increases or decreases with duration of the *T. gondii* infection, we measured the correlation between reaction times and the anti-*Toxoplasma* IgG antibodies titres. The moment of *T. gondii* infection

is usually not known for most subjects with latent toxoplasmosis. Statistically, however, it can be indirectly estimated based on the level of IgG antibodies, which is usually very high during acute toxoplasmosis but which decreases within months or several years after the infection (Konishi, 1989). After removing the effect of age, a one-sided nonparametric correlation analysis of data from 60 *Toxoplasma*-positive subjects revealed the existence of a negative association between the level of anti-*Toxoplasma* antibodies and the mean reaction time in the 1st (Kendall tau = -0.175 , $P = 0.019$), 2nd (Kendall tau = -0.078 , $P = 0.024$) and 3rd (Kendall tau = -0.193 , $P = 0.038$) min as well as in the whole 3 min interval (Kendall tau = -0.183 , $P = 0.014$) of the test (Fig. 2).

DISCUSSION

In a double blind study we demonstrated the deterioration of psychomotor performance (increase of reaction times) of subjects with latent toxoplasmosis. The differences between *Toxoplasma*-positive subjects and *Toxoplasma*-negative controls were rather low in the subjects with high level of anti-*Toxoplasma* antibodies and increased with decrease of the antibody level (i.e. with duration of *T. gondii* infection).

In the 1st min of the test there is no significant difference in psychomotor performance between *Toxoplasma*-negative and *Toxoplasma*-positive subjects. The prominent reduction in psychomotor performance occurred between the 1st and 3rd min of the test but not between the 1st and 2nd min in the *Toxoplasma*-negative subjects and between the 1st and 2nd min but not between the 2nd and 3rd min of the test in the *Toxoplasma*-positive subjects. This suggests that the *Toxoplasma*-positive subjects probably get tired more quickly than *Toxoplasma*-negative controls. It indicates that *Toxoplasma*-positive subjects have a deteriorated ability of long-term concentration rather than prolonged simple reaction time under the optimal conditions of maximum concentration of the 1st min of the test.

The difference between *Toxoplasma*-positive subjects and *Toxoplasma*-negative controls was only 10, 17 and 13 msec on the 1st, 2nd and 3rd min of the test, respectively. In fact, even in the second min of the test the coefficient of determination R^2 was 0.084, and therefore the effects of latent toxoplasmosis explained only about 8.4% of total variability of reaction times in our experimental set. However, it must be stressed that our experimental set of *Toxoplasma*-positive subjects contained many subjects with relatively recent infections (i.e. the subjects whose psychomotor performance was changed only slightly in comparison with uninfected controls). It is also highly probable that the subset of *Toxoplasma*-

negative subjects was in fact contaminated with false negatives i.e. with subjects with very long infection (and very low level of anti-toxoplasma antibodies) (Flegr & Havlíček, 1999). Moreover, the length of infection is always positively correlated with the age of infected subjects. No statistical method exists that can eliminate the effect of age without at least partly removing also the effect of length of infection on the reaction times of experimental subjects. Therefore, our statistical tests probably downgraded the effects of latent toxoplasmosis on the psychomotor performance.

The increase of the differences between *Toxoplasma*-infected subjects and controls with the decrease of specific antibody levels (and therefore with the duration of infection) suggests that slow and cumulative effects of latent toxoplasmosis rather than a one-step and possibly transient effect of acute toxoplasmosis disease is responsible for the decrease of psychomotor performance of infected subjects. The physiological mechanism of the effect is not known. It is currently supposed that probably all infected people bear dormant stages of *T. gondii* i.e. bradyzoites in zoitocysts located mainly in the neural and muscular tissue, for the rest of their life (Remington & Krahenbuhl, 1982). The parasite can resume its pathogenic activity and even kill its host only after severe deterioration of the immune system, for example in AIDS patients (Grant *et al.* 1990; Ortona *et al.* 1991; Zufferey *et al.* 1993; Halonen, Lyman & Chiu, 1996; Arendt *et al.* 1999) or immunosuppressed transplantation patients (Figueiredo *et al.* 1983; Derouin *et al.* 1986; Gallino *et al.* 1996). Under normal conditions, latent toxoplasmosis is considered asymptomatic in human and even immunoprotecting pregnant women from acute toxoplasmosis (and their children from the danger of congenital toxoplasmosis). In mice, however, histopathological changes in cyst-containing regions of brain, including inflammatory granulomatous changes of perivascular areas, progressive deposition of necrotic material resulting finally in an occlusion and subsequent sclerosis of vessels, was observed (Werner, Masihi & Senk, 1981). Even in relatively resistant strains of mice the latent toxoplasmosis was accompanied by permanently increased levels of mRNA of the cytokines TNF-alpha and IL-10 (Arsenijevic *et al.* 1997).

AIDS patients with neurotoxoplasmosis usually express multifocal lesions mostly in basal ganglia and thalami (Sparacia *et al.* 1998). Histopathological data for immunocompetent subjects are not available. However, indirect observations suggesting a possible influence of 'asymptomatic' latent toxoplasmosis on human health are available in the literature from the late seventies. It was shown that latent *Toxoplasma* infection can diminish learning capacity of children (Hengst, 1979). The studies performed on 5 independent large experimental sets

showed that subjects with latent toxoplasmosis significantly differed in several personality factors from uninfected controls (Flegr & Hrdý, 1994; Flegr *et al.* 1996; Flegr & Havlíček, 1999). The personality changes increased with length of latent toxoplasmosis estimated on the basis of either antibody level (one experimental set) or date of acute phase of infections (two experimental sets) (Flegr *et al.* 1996, 2000), suggesting that the cumulative changes in personality profiles of infected subjects are induced by the parasite, rather than that a certain combination of personality factors influences an acquisition rate of *T. gondii* infection.

The behavioural changes associated with latent or chronic toxoplasmosis in humans and animals are usually studied and interpreted in the context of the manipulation hypothesis. Increase of reaction times and other changes observed in rodents can theoretically increase the chance of transmission of *T. gondii* into a definitive host, a cat. In modern human (but possibly not in his ancestors), this manipulation activity is unproductive for the parasite. However, the decrease of psychomotor performance or ability of long-term concentration of infected subjects can play an important role in many situations even in our modern world. Because of its extremely high prevalence (30–70% in most countries), latent toxoplasmosis, the mildest form of *T. gondii* infection, might in fact represent a very serious and highly underestimated public health problem.

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