

## Effects of *Toxoplasma* on Human Behavior

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**Although latent infection with *Toxoplasma gondii* is among the most prevalent of human infections, it has been generally assumed that, except for congenital transmission, it is asymptomatic. The demonstration that latent *Toxoplasma* infections can alter behavior in rodents has led to a reconsideration of this assumption. When infected human adults were compared with uninfected adults on personality questionnaires or on a panel of behavioral tests, several differences were found. Other studies have demonstrated reduced psychomotor performance in affected individuals. Possible mechanisms by which *T. gondii* may affect human behavior include its effect on dopamine and on testosterone.**

*Key words:* personality test/reaction time/dopamine/testosterone

### Introduction

*Toxoplasma gondii* is the most common protozoan parasite in developed nations. Following the initial acute phase of infection, the parasite assumes a latent form. Up to 80% of the population may be infected, depending on eating habits and exposure to cats.<sup>1</sup> The dormant form of *T. gondii* is found predominantly in nervous and muscle tissues in infected hosts. Until recently, latent infections in humans were assumed to be asymptomatic. Results of animal studies and recent studies of personality profiles, behavior, and psychomotor performance, however, have led to a reconsideration of this assumption.

### Personality Profile and Behavior

Since 1992, a series of studies have been carried out in the Czech Republic comparing the personality characteristics of individuals who have anamnestic antibodies to

*T. gondii*, and are thus assumed to have a latent infection, and those without such antibodies. The personality questionnaires used in these studies have been Cattell's 16-personality factor (16PF) questionnaire<sup>2–6</sup> and Cloninger's Temperament and Character Inventory (TCI) personality test.<sup>7,8</sup>

The subjects tested with Cattell's 16PF have included students and faculty in the Department of Biology at Charles University ( $n = 243, 200, 107,$  and  $255$  in various studies), military conscripts ( $n = 475$ ), blood donors ( $n = 55, 268, 190$ ), individuals known to have had symptomatic toxoplasmosis in the past ( $n = 190$  and  $230$ ), and women tested for toxoplasmosis during pregnancy ( $n = 191$ ).

Consistent and significant differences in Cattell's personality factors were found between *Toxoplasma*-infected and -uninfected subjects in 9 of 11 studies, and these differences were not the same for men and women. After using the Bonferroni correction for multiple tests, the personality of infected men showed lower superego strength (rule consciousness) and higher vigilance (factors G and L on Cattell's 16PF). Thus, the men were more likely to disregard rules and were more expedient, suspicious, jealous, and dogmatic. The personality of infected women, by contrast, showed higher warmth and higher superego strength (factors A and G on Cattell's 16PF), suggesting that they were more warm hearted, outgoing, conscientious, persistent, and moralistic. Both men and women had significantly higher apprehension (factor O) compared with the uninfected controls.

The subjects tested with Cloninger TCI (5 studies) have included military conscripts ( $n = 857$ ), blood donors ( $n = 205$  and  $85$ ), and university students ( $n = 163$  and  $87$ ). In 3 of these 5 studies, both men and women showed a decrease in the novelty-seeking factor on the Cloninger TCI.<sup>7,8</sup>

In general, differences in personality factors were greater in subjects in older age groups. In order to ascertain whether there was any correlation between personality change and duration of infection, personality test (16PF) data were available on 190 men and 230 women in whom acute toxoplasmosis had been diagnosed in the previous 14 years. After the age of subjects was controlled for, superego strength (factor G) was found to significantly decrease in men ( $P = 0.017$ ,  $t$ -test, 1 tailed)<sup>5</sup> and increase in women ( $P = 0.010$ ,  $t$ -test, 1 tailed)<sup>6</sup> in relation to the duration of infection.

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Differences in behavior between infected and uninfected subjects were also examined using a panel of simple behavioral tests. For example, experiments designed to measure suspiciousness rated the person's willingness to taste a strange liquid, to let one's wallet be controlled by the experimenter, and to put one's signature on an empty sheet of paper. Similarly, experiments designed to measure self-control rated whether the person came early or late for the testing, how accurate the person's guess was as to the contents of his or her own wallet, the time used to answer the computerized questionnaire, and the person's knowledge of social etiquette. The composite behavioral factors Self-Control and Clothes Tidiness, analogous to Cattell factors Q3 (perfectionism) and G (superego strength), showed a significant effect of the toxoplasmosis–gender interaction, with infected men scoring significantly lower than uninfected men and a trend in the opposite direction for women. The effect of the toxoplasmosis–gender interaction on the composite behavioral variable “Relationships” (analogous to factor A, warmth) approached significance; infected men scored significantly lower than uninfected men, whereas there was no difference among women.<sup>9</sup> All ratings were done by raters blind to the person's *T. gondii* infection status.

### Psychomotor Performance

Because animal studies have demonstrated that mice infected with *T. gondii* have impaired motor performance,<sup>10,11</sup> human studies were carried out on volunteer blood donors. A computerized simple reaction time test (reaction to the appearance of a white square) was given to 60 adults positive for antibodies to *T. gondii* and 59 adults negative for such antibodies. Those with latent infection performed significantly more poorly (analysis of covariance,  $P = 0.011$ ) and appeared to lose their concentration more quickly, although the effect of the infection was modest and explained less than 10% of the variability in performance.<sup>12</sup> Similar results were recently obtained in 2 (unpublished) studies performed on 439 blood donors and 623 military servicemen.

Could subtle alterations in psychomotor performance have any effects on human behavior? To test this, sera were collected in a Prague hospital from 146 individuals deemed to have been responsible for causing, either as a driver or as a pedestrian, a motor vehicle accident. These sera were compared with 446 control sera collected by random sampling in Prague. The difference in seroprevalence of toxoplasmosis in these 2 samples suggests that *Toxoplasma*-infected subjects have a 2.65 times higher risk of traffic accidents than *Toxoplasma*-free subjects (Mantel–Haenszel test for age-stratified data, chi-square = 21.45,  $P < 0.0001$ ).<sup>13</sup> Confounding factors could not be ruled out that might lead to both exposure to *T. gondii* and vehicle accidents.

A higher incidence of *T. gondii* antibodies among drivers involved in traffic accidents was also found in a recent study in Turkey. Among 185 such drivers, the rate of *T. gondii* IgG antibodies was 24.3% and IgM antibodies, 3.2%; among 185 age-matched controls, the rate of IgG antibodies was 6.5% and IgM antibodies, 0.5% (chi-square,  $P < 0.05$ ).<sup>14</sup>

Studies have also examined possible relationships between *T. gondii* infections and intelligence, education, and memory. Initial reports of associations with intelligence and education<sup>3,7</sup> were found to be spurious when all confounding factors were taken into account.<sup>8</sup> Two unpublished studies found no association between infection and short-term memory.

### Discussion

Is it reasonable to expect that latent infection with *T. gondii* could have an effect on human behavior and possibly even transcultural differences<sup>15</sup>? The studies reviewed suggest that *T. gondii* may have subtle effects on personality and psychomotor performance. If so, this would be consistent with the effects of *T. gondii* on rodent behavior, as described in the accompanying article by Webster.

In the rodent model, the effects of *T. gondii* are best explained in evolutionary terms by the manipulation hypothesis, ie, the parasite changes the behavior of the rodent in such a way as to increase the chances of the parasite's getting into a feline and completing its life cycle. Humans are dead-end hosts for *T. gondii*, because the chances that a human being will be eaten by a feline are infinitesimally small. Among our primate ancestors, however, this was not always the case,<sup>16</sup> as suggested also by contemporary studies of the frequency with which monkeys and apes are eaten by large felines in Africa. For example, a study performed in the Ivory Coast confirmed that primates account for a large proportion of leopards' diet and revealed the predation pressure exerted by large felines on 8 different monkey and 1 chimpanzee species.<sup>17</sup> In addition, parasites are not aware that they have entered dead-end hosts, so they are likely to exert whatever effects they do in any host. In this regard, it is interesting to consider the increase in traffic victims among *T. gondii*-infected humans as a contemporary example of manipulation activity of a parasite. It is also possible that the effects of the parasite are not due to the manipulation in an evolutionary sense but merely due to neuropathological or neuroimmunological effects of the parasite's presence.

Alternate explanations for the effects of *T. gondii* on humans cannot be ruled out. It is possible, eg, that individuals with certain personality characteristics behave in a manner that makes it more likely that they will become infected. For example, it was found that specific risk factors for *Toxoplasma* infection, such as contact with cats and the eating of raw or undercooked meat, were also related to some of Cattell's personality factors. However,

these personality factors were different from those related to *Toxoplasma* infection.<sup>4</sup> Confounding factors must also be considered as possible explanations. For example, in some countries, infection with *T. gondii* occurs more commonly in rural areas that is also where individuals are likely to have less education and consequently score lower on tests of verbal intelligence.<sup>18</sup> This can produce a spurious association between *T. gondii* infection and intelligence.

If latent *T. gondii* infections are exerting effects on human personality characteristics and behavior, what is the possible mechanism? It is known that *T. gondii* increases dopamine in rodents<sup>19</sup> and also that treating the rodents with a selective dopamine uptake inhibitor differentially alters the behavior of the infected and uninfected rodents.<sup>20</sup> Also the observed low level of novelty seeking in humans infected with *Toxoplasma* or cytomegalovirus is supposedly associated with high dopamine levels in the ventral midbrain.<sup>7,8</sup> The mechanism of the dopamine increase by *T. gondii* is not known but may involve the inflammatory release of dopamine by increasing cytokines such as interleukin-2.<sup>21,22</sup> The dopamine imbalance between the mesolimbic and mesocortical regions in the brain is suspected to play a role in the development of schizophrenia,<sup>23,24</sup> which could explain the observed association between schizophrenia and toxoplasmosis (see related articles in this issue of *Schizophrenia Bulletin*).

It is also possible that differences in the level of testosterone may be responsible for the observed behavioral differences between *Toxoplasma*-infected and *Toxoplasma*-free subjects. A lower second- to fourth-digit length ratio,<sup>25</sup> greater body height in men,<sup>25</sup> longer duration of pregnancy,<sup>26</sup> and higher sex ratio (ie, more male births)<sup>27</sup> suggest that *Toxoplasma*-infected subjects have a higher level of testosterone. High levels of steroid hormones have been associated with lower cellular immunity.<sup>28,29</sup> Thus, the most parsimonious explanation of the observed high testosterone–toxoplasmosis association is a higher risk of *Toxoplasma* infection in subjects with higher levels of testosterone and therefore a weaker immunity. Alternatively, in an evolutionary sense, the behavioral changes induced by *T. gondii* could be side effects of the organism's increase in testosterone in order to impair the cellular immunity of the host and thus increase the chances of surviving in the host organism.

The results obtained during the past 15 years strongly suggest that latent toxoplasmosis influences the behavior not only of rodent hosts but also of humans. The neurophysiological mechanisms and practical effects of these behavioral changes, however, are still to be elucidated.

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