

***Toxoplasma*, testosterone, and behavior manipulation: the role of parasite strain, host variations, and intensity of infection**

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Abstract *Toxoplasma gondii* is an intracellular parasite involved in the etiology of various behavioral and hormonal alterations in humans and rodents. Various mechanisms, including induction changes of testosterone production, have been proposed in the etiology of behavioral alterations during *T. gondii* infection. However, controversy remains about the effects of *T. gondii* infection on testosterone production; in some studies, increased levels of testosterone were reported, whereas other studies reported decreased levels. This is a significant point, because testosterone has been shown to play important roles in various processes, from reproduction to fear and behavior. This contradiction seems to indicate that different factors—primarily parasite strains and host variations—have diverse effects on the intensity of *T. gondii* infection, which consequently has diverse effects on testosterone production and behavioral alterations. This paper reviews the role of parasite strains, host variations, and intensity of *T. gondii* infection on behavioral alterations and testosterone production, as well as the role of testosterone in the etiology of these alterations during toxoplasmosis.

Keywords *Toxoplasma gondii*, testosterone, behavior manipulation, parasite strain, host variations, intensity of infection, neurologic and psychiatric disorders

Introduction

Toxoplasmosis is one of the most common zoonotic diseases worldwide. It is estimated that up to a third of the world's human population is latently infected by *T. gondii*. Felines, including the domestic cat, are the only definitive host, and various warm-blooded animals and humans are intermediate hosts. Transmission of *T. gondii* occurs via the oral route and congenital transmission (Tenter et al., 2000; Montoya and Liesenfeld, 2004). Moreover, sexual transmission of *T. gondii* was observed in animal models of toxoplasmosis (Liu et al., 2006; Arantes et al., 2009; de Moraes et al., 2010; Dass et al., 2011; Lopes et al., 2013; Wanderley et al., 2013). Although, approximately 25% to 30% of the world's human population is infected by *T. gondii*, the most common form of infection is latent (asymptomatic) (reviewed by Robert-Gangneux and Dardé, 2012). However, latent toxoplasmosis can induce

various hormonal and behavioral alterations in humans and rodents and may be involved in the etiology of different neurologic and psychiatric disorders (Dalimi and Abdoli, 2012; Flegr, 2013a, 2013b; Webster et al., 2013; McConkey et al., 2013; Abdoli et al., 2014).

Various mechanisms have been proposed in the etiology of behavioral alterations and neuropsychiatric disorders during *T. gondii* infection, including hormonal manipulation (increased testosterone [Flegr et al., 2008a, 2008b, 2013a; Lim et al., 2013]), neurotransmitter alteration (particularly increased dopamine [Stibbs, 1985; Skallová et al., 2006; Gaskell et al., 2009; Prandovszky et al., 2011] and decreased serotonin [due to reduction of tryptophan] (Flegr, 2013b)), hippocampus and amygdala abnormalities [Vyas et al., 2007; Hermes et al., 2008; Mitra et al., 2013], decreased tryptophan, and increased kynurenic acid (Schwarcz and Hunter, 2007).

In the subject of *Toxoplasma* and testosterone, Lim et al. (2013) published a remarkable article showing the relationship of latent *T. gondii* infection, testosterone, and behavioral alterations in experimentally infected male rats. The results of this study showed that concentrations of testicular testosterone, mRNA expression of luteinizing hormone receptor

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(LHR), and steroidogenic enzymes (StAR, P450scc, 3 β -HSD, P450c17a, and 17 β -HSD) were significantly increased in the testicles of infected animals 6 and 8 weeks post-infection. Moreover, infection significantly attenuated the innate fear of the infected animals of a smell of bobcat urine but didn't affect this fear in castrated infected animals.

However, there are controversial issues about the effect of *T. gondii* infection on testosterone production; in some studies, it increased (Hodková et al., 2007a; Kaňková et al., 2007a, 2007b; Flegr et al., 2005, 2008a, 2008b, 2013a; Shirbazou et al., 2011; Lim et al., 2013) and in other studies it decreased the level of testosterone (Oktenli et al., 2004; Kaňková et al., 2011; Khaki et al., 2011; Abdoli et al., 2012), and related hormones influencing testosterone production were reported (Stahl and Kaneda, 1998a; 1998b; Stahl et al., 1985, 1994, 1995; Oktenli et al., 2004). This is a significant point, because testosterone is one of the important sex hormones in men and rather small amount in women. Testosterone in men is mainly produced by the Leydig cells of the testes and, in women, is produced by the ovaries and placenta. Also, the adrenal cortex secretes this hormone in both sexes. Testosterone is involved in several physiologic processes, including: the development of secondary sexual trait and reproductive function in males, as well as behavioral and socio-emotional parameters etc in both sexes (Eisenegger et al., 2011). These opposing results (increased levels of testosterone in some studies and decreased levels in other reported) are most likely due to the different *T. gondii* strains, doses, and routes of parasite inocula, as well as variation in host susceptibility to infection, which would consequently affect the intensity of *T. gondii* infection and behavioral alterations (Innes, 1997; Montoya and Liesenfeld, 2004).

The aim of this paper is to explain the role of: i) parasite strains and host variations on the intensity of *T. gondii* infection and behavioral alterations, ii) the intensity of *T. gondii* infection on testosterone production, and iii) testosterone in the etiology of behavioral manipulation during *T. gondii* infection.

Factors influencing the intensity of *T. gondii* infection

Although *T. gondii* induces behavioral and hormonal alterations in humans and rodents, different influencing factors including virulence of the parasite strains, host variations in susceptibility to infection and intensity of the infection seem have varying effects on behavioral alterations during *T. gondii* infection. The use of different *T. gondii* strains, doses and hosts in experimental studies may directly affect the course of infection and consequently the behavioral parameters. In this regard, Dubey et al. (2012) examined the pathogenesis of toxoplasmosis in mice, using different strains (transgenic, out-bred, and in-bred), infected with different doses and strains of *T. gondii*. They showed that type II and

III *T. gondii* strains were less virulent than type I strains. Pathogenesis increased with increasing doses of the parasite. Moreover, infectivity and pathogenicity of toxoplasmosis in C57BL/6 mice was higher than the other strains (Swiss Webster, C57/black, and BALB/c).

Evidence that parasite strain influences outcome of *T. gondii* infection and behavior manipulation

T. gondii consists of three main genotypes, designated I, II and III, with some differences in virulence and epidemiological patterns. Type II strains are the most common in human and animal infections, while type III strains are most frequent in avian hosts. In general, as observed in experimental models, type I strains (such as RH and GT-1) are highly virulent, causing the death of mice in less than 10 days after inoculation of < 10 tachyzoites ($LD_{100} \approx 1$). In contrast, strains of type II (such as ME49 and PRU) and type III (such as VEG, NED, and CEP) have lower virulence than type I strains (mice infected with type II or III strains survive after inoculation of > 10^3 tachyzoites ($LD_{50} > 10^3$)) (Dardé, 2008).

In vitro and *in vivo* studies have shown that gene expression during infection with type I strains is higher than with types II and III (Xiao et al., 2011; Hill et al., 2012; Stutz et al., 2012; Xiao et al., 2013). Xiao et al. (2011) examined the transcriptional profile of human neuroepithelioma cells in response to three major strains of *T. gondii* using microarray analysis. They found, type I infection exhibited the highest level of differential gene expression and largely affects genes related to the central nervous system. Type II infection had a smaller number of gene expression and did not alter the expression of a clearly defined set of genes. Type III infection had intermediate effects on gene expression and largely altered those genes which affected nucleotide metabolism. Another study by Xiao et al. (2013) showed that human neuroepithelioma cells, infected with a type I strain, displayed abnormalities in two neuropeptides (PROK2 and TAC1) and three neurotransmitter systems (dopamine, glutamate and serotonin), while type III infection led to change in tryptophan 2,3-dioxygenase (TDO) in the kynurenine pathway. Nevertheless, the type II strain did not have a significant affect on infected cells relative to uninfected cells. Moreover, it has been recently hypothesized that infection with different strains of *T. gondii* may differently influence the etiology of neuropsychiatric disorders (Abdoli, 2013), as more involvement of type I strains in the course of such disorders was observed (Xiao et al., 2009; Groër et al., 2011). In this regard, Xiao et al. (2009) observed that the risk of developing adult schizophrenia and psychotic disorders in children of 219 pregnant women infected with type I strains of *T. gondii* was significantly higher than the 618 matched unaffected control mothers (OR = 1.94; CI 1.08–3.46; $p = 0.03$). The highest risk for

subsequent psychoses was observed for the samples with affective psychoses that were exposed to type I *T. gondii* (OR = 5.24; CI 1.69–16.49; $p = 0.005$). Interestingly, there was no significant association between other genotypes of *T. gondii* and risk of psychoses in adult offspring. Groër et al. (2011) also found that the risk of anxiety, depression and schizophrenia spectrum disorders was increased in mothers with higher titers of *T. gondii* IgG antibody during 16-25 weeks pregnancy. Interestingly, the depression and anxiety scores were highest in the women with serotype I *T. gondii*, but it was not statistically significant.

Kannan et al. (2010) studied the effects of two type II strains of *T. gondii* (ME49 and PRU) on mouse behavior. The results showed that mice infected with either strain were significantly more attracted to cat odor than non-infected animals at two months post-infection. Moreover, only PRU-infected mice exhibited hyperactivity; in contrast, ME49-infected mice showed impaired spatial working memory.

Evidence that host variations influence outcome of *T. gondii* infection and behavior manipulation

Various warm-blooded animals and humans can become infected with *T. gondii*. Rodents, especially rats and mice, are the species most routinely used as experimental models in toxoplasmosis research. Other species, such as New and Old World monkeys, are very sensitive to toxoplasmosis; sheep are intermediately sensitive, while cattle, horses, deer, pigs, and goats are resistant to the infection (Innes, 1997). These species, however, are less commonly used as experimental models in toxoplasmosis research. Except in immunosuppressed status, the most common forms of toxoplasmosis in both humans and rats are latent (asymptomatic) (Sulliran and Jeffers, 2012); therefore, rats provide the most appropriate model for human toxoplasmosis investigation. Indeed, infection in mice is more acute than rats, because while infection with the RH strain (belonging to type I strains) is always fatal in mice, rats develop latent infection without any therapy (Innes, 1997; Dubey and Frenkel, 1998).

Several studies have been carried out on *Toxoplasma* and behavior (for review, see Worth et al., 2013), but some contradictory results have been reported. For example, in some studies, hypoactivity of *T. gondii*-infected mice was found (Hutchison et al., 1980; Skallová et al., 2006), while in others, hyperactivity was reported (Hay et al., 1983, 1984). A comparison of the learning capacity of *T. gondii*-infected rats and mice showed that although infected rats and mice had lower learning capacity than non-infected animals, mice were more affected than rats (Witting, 1979). Recent studies also reveal that the aversion of *T. gondii*-infected rats to cat odor decreased in comparison with non-infected animals (Berday et al., 2000; Vyas et al., 2007; Lamberton et al., 2008). Moreover, infected male rats were more attractive in terms of

mate choice to females than non infected animals (Dass et al., 2011). In contrast, infection of male mice with *T. gondii* does not increase attractiveness to females (Soh et al., 2013). Opposite results in behavioral alterations in rat and mice may be due to the intensity of *T. gondii* infection, which depends on the parasite strains and host variations.

It is also evidenced that host genotype variations affect the outcome of *T. gondii* infection. For example, human leukocyte antigen (HLA)-DQ3 gene is a genetic marker of susceptibility to development of toxoplasmic encephalitis, but HLA-DQ1 is a resistance marker (Suzuki et al., 1996; Mack et al., 1999). Recent studies, in the subjects of latent toxoplasmosis, have shown that physiologic and behavioral alterations that occurs during latent toxoplasmosis depend on Rh blood group of the infected subjects, while, RhD-positivity protects against several physiologic and behavioral alterations during the latent toxoplasmosis (Novotná et al., 2008; Flegr et al., 2008; Kaňková et al., 2010). In this regard, Kaňková et al. (2010) observed that RhD-negative mothers (at pregnancy week 16) with latent toxoplasmosis have significantly more weight than RhD-negative infected mothers, or *Toxoplasma*-free RhD-positive or RhD-negative mothers (Kaňková et al., 2010). Moreover, it is observed that the RhD molecule has protective role against toxoplasmosis-induced behavioral alterations in men and women (Flegr et al., 2008; Novotná et al., 2008).

However, it is observed that *T. gondii* infection has differing effect on gene expression (Xiao et al., 2012), neurotransmitter levels (Gatkowska et al., 2013), testosterone production and behavior parameters in males and females (Flegr et al., 2008a, 2008b, 2013a).

Evidence for decreased testosterone during *T. gondii* infection

There is a great deal of direct and indirect evidence that testosterone levels decrease in humans and rodents during acute toxoplasmosis (Stahl et al., 1985, 1994, 1995; Stahl and Kaneda, 1998a; 1998b; Oktenli et al., 2004; Kaňková et al., 2011; Khaki et al., 2011; Abdoli et al., 2012; Dalimi and Abdoli, 2013). For example, reduced concentration of serum testosterone was reported in *T. gondii*-infected male and female mice (Kaňková et al., 2011). Similarly, impaired reproductive functions, along with transient reduction of serum and testicular testosterone, were reported in male rats infected with high doses of the RH strain of *T. gondii* (Khaki et al., 2011; Abdoli et al., 2012). Oktenli et al. (2004) demonstrated that total and free testosterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) levels decreased in male patients during acute toxoplasmosis.

In addition to decreasing testosterone, the impairment of thyrotropin-releasing hormone (TRH) and thyroid-stimulating hormone (TSH), as well as decreased serum thyroxine (T4), were reported in *T. gondii*-infected mice (Stahl and

Kaneda, 1998a, 1998b). Thyroid hormone levels play an important role in testicular development and function, and the alteration of these hormones (particularly hypothyroidism) negatively affects gonadotropin secretion, thus adversely affecting reproductive function quality (Choksi et al., 2003; Wagner et al., 2008). Moreover, hypothalamic–pituitary axis dysfunction, along with hypogonadotropic hypogonadism, was reported in *T. gondii*-infected female mice (Stahl et al., 1985; Stahl et al., 1994; Stahl et al., 1995). At the same time, however, dysfunction of the hypothalamic–pituitary axis negatively affects thyroid and sex steroid hormone levels (Achermann and Jameson, 1999; Choksi et al., 2003).

Evidence for increased testosterone during *T. gondii* infection

Unlike the findings for acute toxoplasmosis, there are some direct and indirect evidence for increased testosterone in human and animal models with latent toxoplasmosis (Hodková et al., 2007a; Kaňková et al., 2007a, 2007b; Shirbazou et al., 2011; Flegr et al., 2005, 2008a, 2008b, 2013a; Lim et al., 2013). In this regard, Lim et al. (2013) reported that production of testicular testosterone increased significantly in rats with latent *T. gondii* infection. In human subjects, a study consisting 91 male and 174 female university students showed that the concentration of salivary testosterone increased in *T. gondii*-infected men and decreased in infected women when compared to *Toxoplasma*-negative controls (Flegr et al., 2008a). These results were confirmed in another study by the same group of the researchers (Flegr et al., 2008b). Zghair et al. (2013) examined the seroprevalence of toxoplasmosis and the levels of sex hormones (total testosterone, free testosterone and follicle stimulating hormone (FSH)) in 400 healthy men in Baghdad. They showed, seropositive men had significantly higher levels of total and free testosterone ($p < 0.05$), but, the level of FSH was not significantly changed. Also, an increased concentration of testosterone was reported in *Toxoplasma*-infected men and women in Iran (Shirbazou et al., 2011). Increased concentration of testosterone in men with latent toxoplasmosis (Flegr et al., 2008a, 2008b, 2013a; Shirbazou et al., 2011; Zghair et al., 2013), along with the remarkable observation of an increased synthesis of testicular testosterone in latent *T. gondii*-infected male rats (Lim et al., 2013), suggests that latent toxoplasmosis stimulates Leydig cells to increase the production of testosterone.

In addition to the direct effects of *Toxoplasma* on testosterone, there are also some phenotypic traits that may be influenced by latent toxoplasmosis due to the production of testosterone in infected individuals (Flegr, 2010, 2013a). For example, the faces of infected men in photographs are rated by women raters as more masculine and dominant (Hodková et al., 2007a). *Toxoplasma*-infected men are taller in stature than non-infected men, and both men and women who are

infected have a lower second-to-fourth digit length ratio (2D:4D ratio) (Flegr et al., 2005). This ratio is negatively correlated with prenatal testosterone, which means that, individuals with lower 2D:4D ratios were exposed to higher levels of prenatal testosterone (Lutchmaya et al., 2004; Hönekopp et al., 2007). On the other hand, individuals with high levels of pre-birth testosterone may be more susceptible to post-birth *Toxoplasma* infection due to the immunosuppressive effects of testosterone.

Human sex ratio at birth (the ratio of boy to girl at birth) is around 0.51 in most populations. This ratio is believed to be influenced by several factors, such as stress, immunosuppression, and maternal endocrine disruption (James, 2008, 2010). It has been observed that the probability of giving birth to a boy increases in pregnant women with high levels of anti-*Toxoplasma* IgG antibodies (250 boys per 100 girls); in contrast, women with low levels of anti-*Toxoplasma* IgG antibodies gave birth to more girls than boys (Kaňková et al., 2007a). These observations have been confirmed in mouse models of toxoplasmosis, in which the elevated sex ratio occurred at the early phases of infection, but then decreased in later phases (Kaňková et al., 2007b). The effects of latent toxoplasmosis on the increased sex ratio of recently infected females, and decreased sex ratio of females infected for a long time, can be explained by the endocrine hypothesis. In this hypothesis, increased levels of estrogen and testosterone are present in recently infected females, and decreased levels of these hormones are found in long-term infection (James, 2008, 2010).

The role of testosterone in the etiology of behavioral alterations during latent toxoplasmosis

An increased concentration of testosterone during latent toxoplasmosis can result in different consequences, including the induction of behavioral alterations. Testosterone plays different roles in behavioral parameters (Eisenegger et al., 2011; Montoya et al., 2012); the administration of exogenous testosterone can reduce fear in both humans and rodents (Aikey et al., 2002; van Honk et al., 2005; Hermans et al., 2006). Meanwhile, a decreased level of testosterone can have the opposite effect; for example, reduced testosterone due to castration has been shown to significantly increase innate fear of predator odor in male rats (King et al., 2005). Moreover, elevation of testosterone increased transmission potential and intensity of different parasites (Hughes and Randolph, 2001; Mougeot et al., 2006; Cox and John-Alder, 2007; Grear et al., 2009). Interestingly, some similar effects were observed in *T. gondii*-infected rodents. For example, higher activity and less neophobic fear were observed in *T. gondii*-infected rats (Webster, 1994; Berdoy et al., 1995). The aversion of *T. gondii*-infected rats to cat odor decreased in comparison with non-infected animals (Berdoy et al., 2000; Vyas et al., 2007;

Lamberton et al., 2008). Increased spontaneous activities in the wheel running test and worse scores in the learning tests were observed in mice with latent *T. gondii* infection (Hodková et al., 2007b).

These indications, along with evidence of increased testosterone during latent toxoplasmosis raise an important question: Does testosterone play a role in the etiology of behavioral alterations during latent toxoplasmosis? The answer to this question was directly demonstrated in the study of Lim et al. (2013), where infection with *T. gondii* increased testosterone levels in male rats and attenuated innate fear of infected animals to cat urine, but didn't affect loss of fear in castrated animals. These results confirm the involvement of testosterone in the etiology of behavioral alterations during latent toxoplasmosis.

Behavioral alterations in *T. gondii* infected rodents may facilitate parasite transmission from the infected intermediate rodents to the feline definitive host, as proposed in the 'manipulation hypothesis' (Webster, 2007; Webster et al., 2013). Recently, Dass et al. (2011) reported that infection with *T. gondii* affects the mating behavior of brown rats by enhancing the sexual attractiveness of infected males to uninfected females. Moreover, the parasite was observed in the epididymis and semen of infected males and the vaginal lavage of females after mating with infected males, resulting in active infection in female rats. These results confirm that sexual transmission of *T. gondii* in rats can occur via a mechanism consistent with the manipulation hypothesis, i.e. that the parasite alters host behavior for its own benefit, usually by enhancing its transmission rate. Rodents are a natural persistent intermediate host reservoir for *T. gondii* (Dubey and Frenkel, 1998); hence manipulation of rodents' behavior may cause an increased risk of predation and therefore increased transmission of the parasite to the final host.

At the same time, testosterone plays a pivotal role in male fertility and sexual attractiveness (Achermann and Jameson, 1999; Vyas, 2013). It also has immunosuppressive effects, which consequently increase susceptibility to microbial and parasitic infection (Klein, 2000; Roberts et al., 2001; Muehlenbein and Bribiescas, 2005; Nava-Castro et al., 2012). Therefore, increased testosterone levels during latent toxoplasmosis may indirectly help the transmission of the organism by enhancing mating opportunities between infected males and uninfected females, and also via manipulation of rodents' behavior as described above.

In addition to studies on the influence of *T. gondii* on rodents' behavior, different studies have been conducted on the influence of latent toxoplasmosis on human behavior. Interestingly, these parameters were often reported to be opposite in infected men and women (Lindová et al., 2006; Flegr, 2007; Lindová et al., 2010). For example, the scores of infected men were lower, and infected women were higher in sociability factors (Lindová et al., 2006). When *T. gondii*-

infected and -uninfected individuals were tested with Cattell's personality factors, infected women showed higher warmth and higher superego strength; in contrast, infected men showed lower superego strength and higher vigilance (Flegr, 2007). Flegr (2007) also suggested that the personality profiles of infected men and women are different and concluded that infected women are warm-hearted, conscientious, outgoing, persistent, and moralistic and infected men are more likely to disregard rules and were more expedient, suspicious, jealous, and dogmatic. Gender difference in behavior and personality parameters of *T. gondii*-infected men and women may be partially related to the difference in testosterone concentrations as it was found that infected men have a higher and infected women have a lower level of salivary testosterone than *T. gondii* negative controls (Flegr et al., 2008a, 2008b, 2013a).

Testosterone is an important influencing factor in behavior and personality, in both sexes. As observed in the majorities of studies, increased testosterone was associated with antisocial, aggression, and dominance behaviors (for reviews see, Booth et al., 2006; Eisenegger et al., 2011; Montoya et al., 2012).

The other mechanisms of gender difference in behavioral alterations during toxoplasmosis can be related to difference in gene expression and neurotransmitter levels (Xiao et al., 2012; Gatkowska et al., 2013). As observed in male mice, *T. gondii* infection altered those genes associated with olfactory function. In contrast, infection in females led to modulation of those genes associated with the development of the forebrain, sensory and motor coordination neurogenesis (Xiao et al., 2012). Gatkowska et al. (2013) have found several changes in neurotransmitter levels of *T. gondii* infected male and female mice. For example, infection in males mainly led to increased dopaminergic and serotonergic activity, while infection in females led to decreased noradrenergic system activity.

In addition to the direct effects of testosterone on behavioral parameters, testosterone is also linked to dopamine (Hull et al., 1997). Both testosterone and dopamine are increased during latent toxoplasmosis (Stibbs, 1985; Flegr et al., 2005, 2008a, 2008b, 2013a; Skallová et al., 2006; Hodková et al., 2007a; Kaňková et al., 2007a, 2007b; Gaskell et al., 2009; Shirbazou et al., 2011; Prandovszky et al., 2011; Lim et al., 2013), and both are important for male sexual behavior. Dopamine facilitates sexual activities of rodents such as sexual motivation, genital reflexes and copulation. The connection between dopamine and testosterone was observed in several researches (for review see, Hull et al., 1997; Hull et al., 2004). For example, it was observed that dopamine increased in gonadally intact male rats during exposure to estrous females, but no dopamine release occurred in castrated male rats in response to the female (Hull et al., 1995). It is also suggested that the connection between testosterone and dopamine is mediated by nitric oxide (NO); in other words, testosterone enhances production

of NO by upregulation of nitric oxide synthase in the medial preoptic area of the brain (MPOA); subsequently, NO promotes dopamine release in the MPOA and facilitates male sexual behavior (for reviews see Hull et al., 1997; Hull et al., 2004).

Complexity of the researches on *Toxoplasma* and behavior

Although the influencing of *T. gondii* infection on testosterone production and behavior manipulation has been demonstrated in different studies, but still there are many complexity and complication in this area. For example, different direct and indirect evidences show that infected men have higher and infected women lower testosterone levels than uninfected individuals (Flegr et al., 2008a, 2008b, 2013a; Zghair et al., 2013). On the other hand, testosterone has immunosuppressive effects (Roberts et al., 2001; Muehlenbein and Bribiescas, 2005). This evidence raises important questions: are humans (or indeed other animals) with naturally high levels of testosterone perhaps more susceptible to *Toxoplasma* infection due to the immunosuppressive effects of testosterone? Could testosterone level before infection play a role in predisposing humans to becoming infected? Moreover, behavioral traits associated with high testosterone may prompt these individuals to acquire the infection.

Gender difference in behavior alteration induced by *T. gondii* reveal the parasite uses diverse mechanisms for behavior alteration in males and females. So differences in testosterone, gene expression and neurotransmitter levels in *T. gondii* infected males and females arbitrate that the parasite has differing effects on males and females (Flegr et al., 2008a, 2008b, 2013a; Xiao et al., 2012; Gatkowska et al., 2013).

In human subjects, only two studies were evaluated for the types of *T. gondii* strains that reported infection with type I *T. gondii* strains that were more involved in the course of psychotic disorders (Xiao et al., 2009; Groër et al., 2011), while in other studies the types of *T. gondii* strains were not known.

Different mechanisms such as neurotransmitters and hormonal alterations, hippocampus and amygdala abnormalities and imbalance of the immune responses have been proposed in the etiology of behavioral alterations during *T. gondii* infection (for reviews, see Flegr, 2013b; Fabiani et al., 2013; McConkey et al., 2013; Webster et al., 2013). However, it seems that all of these mechanisms play a mixed role in the etiology of these alterations, for example, increased testosterone enhances dopamine levels (via nitric oxide), and both influence behavioral parameters (Hull et al., 1997; Dominguez and Hull, 2005). On the other hand, nitric oxide and other inflammatory effectors such as Interleukin-2 (IL-2) and IL-6 are innate defenses against *T. gondii* infection (reviewed by Miller et al., 2009). NO, IL-2 and IL-6 also elevate dopamine release (Alonso et al., 1993; Zalcman et al., 1994;

Petitto et al., 1997; Prast and Philippu, 2001; West et al., 2002).

Conclusion

In conclusion, among different mechanisms of *T. gondii* uses for behavioral alterations, increased testosterone level seems to play an important role. Several influencing factors including parasite strain, doses, and routes of parasite inocula, as well as host variations in susceptibility to infection may directly affect the course of infection and consequently affect testosterone production and behavioral alterations. Acute toxoplasmosis led to decreased testosterone and latent toxoplasmosis led to increased testosterone. Acute toxoplasmosis in rodents is often fatal, but latent toxoplasmosis can persist for long time. In humans, it is estimated that up to a third of the world's populations are latently infected with *T. gondii*. Therefore, alterations of testosterone during latent toxoplasmosis can affect several behavioral, physiologic and immunological parameters for a long time. These alterations in rodents can lead to increased transmission of the parasite, so the life cycle of the parasite is maintained in a natural condition.

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Compliance with ethics guidelines

Amir Abdoli declares that he has no conflict of interest.

This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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