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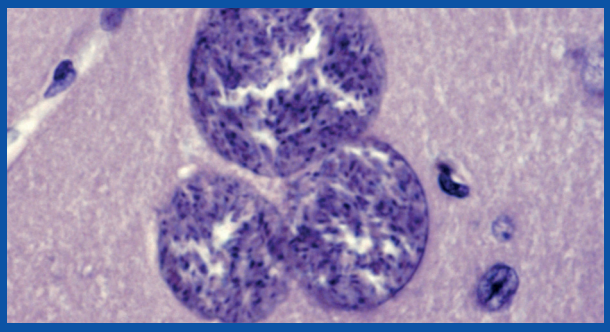


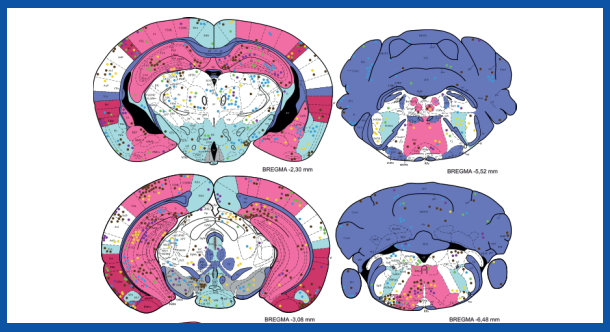

Special Issue

Effects of Latent Toxoplasmosis: Three Decades of Studies

Guest Editors:

Jaroslav Flegr
Faculty of Science, Charles University, Prague, Czech Republic

Ivan Fiala
Institute of Parasitology, Biology Centre of the Czech Academy of Sciences
České Budějovice, Czech Republic

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Special Issue on Toxoplasmosis
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Re-assessing host manipulation in *Toxoplasma*: the underexplored role of sexual transmission – evidence, mechanisms, implications

Ashkan Latifi, Jaroslav Flegr and Šárka Kaňková

Department of Philosophy and History of Sciences, Faculty of Science, Charles University; Viničná 7, 128 00, Prague, Czechia

Abstract: Latent infection with *Toxoplasma gondii* (Nicolle et Manceaux, 1908) has been repeatedly correlated with behavioural and physiological changes in both humans and animals. While classically regarded as a parasite transmitted via ingestion or vertical (transplacental) transmission, accumulating evidence suggests that sexual transmission may also contribute to its epidemiology. This review explores the hypothesis that some behavioural effects of toxoplasmosis – especially those related to attraction, sexual activity, and mate choice – may have evolved to facilitate sexual transmission of the parasite. We summarise findings from animal models and human studies that show modified sexual preferences, altered sexual activity, enhanced attractiveness in infected individuals, and elevated prevalence of *T. gondii* in groups exhibiting high sexual activity or non-traditional sexual behaviour patterns. Particular attention is given to the role of testosterone, which may mediate both behavioural changes and reproductive consequences, such as shifts in offspring sex ratios and fertility outcomes. Direct detection of the parasite in semen and evidence of transmission through insemination in non-human species further support the plausibility of this route. The observed behavioural effects may also intersect with mechanisms previously thought to enhance predation risk, such as altered fear responses to felid odours. Taken together, these findings point to the possibility that sexual transmission, while likely secondary in humans, may have played a more substantial role in the evolutionary history and current ecology of *T. gondii* than previously appreciated. This perspective also provides an alternative interpretative framework for understanding the broad spectrum of phenotypic changes associated with latent toxoplasmosis. Further interdisciplinary research is required to clarify the relative contribution of sexual transmission to the parasite's life cycle and to assess its implications for public health and theory of host-parasite coevolution.

Key words: review, toxoplasmosis, manipulation, sexual behaviour, testosterone, sexually transmitted diseases, parasite manipulation.

BACKGROUND

Toxoplasmosis, a disease caused by the protozoan parasite *Toxoplasma gondii* (Nicolle et Manceaux, 1908), has been extensively studied since its discovery. The sexual reproduction of this parasite occurs exclusively in the intestinal epithelium of felines, producing oocysts that are excreted in faeces. After excretion, oocysts require exposure to air and environmental conditions for sporulation, a process that usually takes 1 to 5 days, after which they become infectious to a broad range of warm-blooded hosts, including humans. Once ingested, sporozoites are released from oocysts in the intestine, where they invade host cells and differentiate into tachyzoites, initiating the acute phase of toxoplasmosis.

In immunocompetent individuals, postnatal infection typically triggers a strong immune response that halts the spread of tachyzoites and promotes the formation of tissue cysts containing slowly replicating bradyzoites. The encysted bradyzoite stage marks the beginning of the latent phase of infection, which can persist for life and is commonly referred to as latent toxoplasmosis. For more information see Dubey and Jones (2008), Bogitsh et al. (2005) and other articles in this issue.

Toxoplasma gondii (hereafter called *Toxoplasma*) is known for its ability to manipulate host behaviour in ways that enhance its own transmission. In rodents, its important natural intermediate hosts, infection leads to behavioural changes that increase the risk of predation by felids – the parasite's definitive hosts. These changes include the loss of innate fear and even a heightened attraction to cat odour, a phenomenon described as "fatal attraction" (Berdoy et al. 2000, Vyas et al. 2007a). By increasing the probability that infected rodents are eaten by cats, *Toxoplasma* enhances its chances of transmission through the predation route. Nevertheless, these manipulations are not limited to rodents; similar effects have been observed in other animals such as chimpanzees (Poirotte et al. 2016).

Analogous behavioural changes have also been documented in humans. These include alterations in personality traits (Flegr and Hrdý 1994, Kopecký et al.

Address for correspondence: Šárka Kaňková, Faculty of Science, Charles University, Viničná 1594/7, 128 00 Prague. E-mail: sarka.kankova@natur.cuni.cz. ORCID ID: 0000-0002-3087-7538.

2022), increased risk-taking behaviour (Johnson and Johnson 2021), and shifts in sexual attraction patterns (Borráz-León et al. 2022). Although these changes may be maladaptive in modern contexts, in ancestral environments they could have increased exposure to predators and thereby facilitated transmission, much like in rodents.

In addition to their established role in increasing predation risk, certain *Toxoplasma*-induced behavioural changes may also serve a different purpose – enhancing the parasite's potential for sexual transmission. *Toxoplasma* can be transmitted via semen or mating in several animal species, including rodents, goats, sheep, rabbits and dogs (Liu et al. 2006, Arantes et al. 2009, Lopes et al. 2013, Santana et al. 2013, Consalter et al. 2017). In these hosts, viable parasites have been identified in semen and infection has occurred after natural or artificial insemination. This raises the possibility that some parasite-induced behavioural changes – particularly those involving sexual activity or attractiveness – may have evolved to facilitate sexual transmission of the parasite.

Sexual transmission could theoretically also occur in humans. Several lines of evidence support this hypothesis. *Toxoplasma* cysts have been detected in the semen of infected men, providing direct biological evidence of the parasite's potential to be transmitted during sexual activity (Tong et al. 2023). In addition, latent toxoplasmosis in a sexual partner has also been identified as a risk factor for infection in women attending assisted reproduction centres (Hlaváčová et al. 2021a). Furthermore, men infected with *Toxoplasma* tend to exhibit elevated testosterone levels, which are likely responsible for their heightened attractiveness to women, particularly in terms of perceived dominance and masculinity (Flegr et al. 2005, 2008b, Borráz-León et al. 2022). These traits may significantly contribute to the likelihood of sexual transmission of *Toxoplasma*.

This review explores the emerging hypothesis that *Toxoplasma* may be sexually transmitted in humans and that some of the phenotypic, and specifically behavioural, changes observed in infected individuals may serve to enhance this transmission route. Specifically, we aim to:

1. Summarise evidence for sexual transmission in both animals and humans.
2. Review data suggesting that *Toxoplasma* manipulates host behaviour to facilitate sexual transmission.
3. Examine candidate physiological mechanisms – especially the role of testosterone – that might underlie these behavioural effects.

Together, these lines of inquiry may help clarify the potential significance of sexual transmission in the life cycle of *Toxoplasma* and provide an alternative interpretative framework for understanding the phenotypic, particularly behavioural, alterations observed in infected hosts.

SEXUAL TRANSMISSION OF TOXOPLASMOSIS

Toxoplasma can be transmitted through multiple routes. Although the most common routes of *Toxoplasma* transmission include contact with cat faeces (containing oocysts) or consumption of undercooked meat (containing tissue cysts), increasing evidence suggests that *Toxoplasma* can also be transmitted sexually.

Animal studies indicate that *Toxoplasma* can penetrate the blood-testis barrier, a capability also observed in some other pathogens but not commonly associated with protozoan parasites. The presence of parasite DNA in semen has been demonstrated in dogs, rabbits, rams, goats and deer (Liu et al. 2006, Santana et al. 2013, Bezerra et al. 2014, Koch et al. 2016, Rouatbi et al. 2019, Mazzoni Baldini et al. 2022). In rats, *Toxoplasma* disrupts the blood-testis barrier and forms cysts in the epididymis during latent infection (Dass et al. 2011). Similarly, cysts have been detected in mouse testes (Tyebji et al. 2020).

In addition to rodents, viable parasites have also been isolated from the semen of dogs (Arantes et al. 2009) and goats (Wanderley et al. 2015), and *Toxoplasma* transmission occurred after insemination of their females with sperm containing tachyzoites. Artificial insemination with tachyzoite-containing sperm has resulted in infection in rabbits (Liu et al. 2006) and sheep (De Moraes et al. 2010, Consalter et al. 2017).

Sexual transmission has also been studied in animals under natural conditions. Males were allowed to mate with female sheep and goats (Lopes et al. 2013, Santana et al. 2013). In both cases, the parasite was transmitted. After natural mating with males with latent toxoplasmosis, female rats also became infected and transplacental transmission occurred to their offspring (Dass et al. 2011, Abdulai-Saiku et al. 2017). While many animal studies have been conducted examining *Toxoplasma* in relation to possible sexual transmission, research directly addressing this route in humans remains limited.

Flegr et al. (2014a) proposed the hypothesis that *Toxoplasma* can be sexually transmitted in humans, citing multiple indirect lines of evidence. Since then, additional findings – mainly from the past decade – have provided further support for this possibility. The key arguments are summarised below:

1. *Toxoplasma* has been detected in semen and testicular tissue of various animal species, including humans (Moura et al. 2007, Tong et al. 2023). Additionally, *Toxoplasma* DNA has been identified in vaginal swabs from women, further supporting the potential for sexual transmission (Faroughi and Amini 2021). Tachyzoites and cysts have been identified in the testes of men, often those who are HIV-positive (Nistal et al. 1986, Haskell et al. 1989).
2. A significant proportion – up to two-thirds – of *Toxoplasma* infections observed in pregnant women cannot be accounted for by established risk factors associated with toxoplasmosis (Boyer et al. 2005, Petersen et al. 2010). Furthermore, serological testing of fathers of children with congenital toxoplasmosis revealed a high prevalence of toxoplasmosis (36%) compared to an average seropositivity rate of 9.8% in boys and men aged 12–49 years (Contopoulos-Ioannidis et al. 2015). In addition,

testing fathers of children under one year of age revealed a high prevalence of recent infection (13%). These findings raise the possibility of additional, possibly sexual, transmission routes. Consistent with this possibility, latent toxoplasmosis in a sexual partner has been identified as a risk factor for infection in women visiting assisted reproduction centres (Hlaváčová et al. 2021a).

3. Several risk factors have been identified that correlate with a higher prevalence of toxoplasmosis. These include a higher frequency of unprotected sexual intercourse among women prior to pregnancy (Flegr et al. 2014a). In women, certain factors – such as engagement in sex work and a history of genital injuries – have been associated with an increased risk of *Toxoplasma* infection (Alvarado-Esquivel et al. 2015). For men, sexual promiscuity has been noted as a significant factor (Alvarado-Esquivel et al. 2021), along with the practice of anal sex without condom use among men who have sex with men (Prasetyo et al. 2014).
4. Epidemiological data indicate a positive correlation between the prevalence of sexually transmitted diseases (STDs) and the prevalence of latent toxoplasmosis across countries (Flegr et al. 2014b). Furthermore, being HIV positive has been linked to an increased likelihood of contracting toxoplasmosis (Meisheri et al. 1997). This association may imply that similar transmission dynamics could exist for both types of infections.
5. Over the past three decades, the incidence of toxoplasmosis has declined in developed countries. This trend may be partly attributable to behavioural changes following the AIDS pandemic, including the adoption of safer sex practices, which could have reduced the frequency of transmission through potential sexual routes (Flegr et al. 2014a).
6. An unusual secondary peak in *Toxoplasma* incidence has been reported among women aged 25 to 35 years, whereas no such peak is observed in men of the same age group (Kodym et al. 2001). This sex-specific divergence suggests the existence of a female-specific risk factor – likely sexual transmission of the parasite from infected male partners in the context of stable relationships. Supporting this hypothesis, the onset of schizophrenia – a condition statistically associated with *Toxoplasma* infection (Torrey et al. 2007) – occurs 2 to 3 years later in infected women compared to uninfected women and both infected and uninfected men. This delay is consistent with a higher incidence of *Toxoplasma* infection in women after age 25, coinciding with increased rates of unprotected sexual intercourse after marriage or long-term partnership formation (Holub et al. 2013).

In the context of sexual transmission, a recent hypothesis also proposes that oral sex may represent a route of transmission for toxoplasmosis (Kaňková et al. 2020). The authors suggested that swallowing ejaculate containing *Toxoplasma* tissue cysts during oral sex could, at least hypothetically, result in infection via a mechanism similar to that of ingesting undercooked meat. Bradyzoites, which are the form of the parasite found in tissue cysts, are known to be better adapted to oral transmission and are significantly more resistant to degradation by proteolytic enzymes than tachyzoites (Jacobs et al. 1960). Kaňková et al. (2020) also speculate that the parasite may not necessarily need to pass through the stomach and intestines; instead, local lesions in the oral epithelium could serve as potential entry points into the bloodstream. Their article also presents empirical data showing that men and women engaging in oral sex (fellatio) with male partners exhibit increased rates of toxoplasmosis compared to control groups.

Additional indirect findings lend further plausibility to this potential transmission route. For instance, in adolescents aged 10 to 14 years – an age group where oral sexual activity may precede penetrative intercourse – the prevalence of toxoplasmosis is significantly higher in females than in males (Kodym et al. 2001). Moreover, a recent study reported the presence of *Toxoplasma* cysts in a substantial proportion of male ejaculate samples (Tong et al. 2023). However, one experimental study administering ejaculate from *Toxoplasma*-infected human males to mice via the oral route found no evidence of transmission, suggesting species-specific barriers or limited efficiency of this route (Ullmann et al. 2024). These findings suggest that while *Toxoplasma* may be present in human semen, its potential for transmission via this medium remains in need of further research. Nonetheless, given that various forms of oral sex are reported in a number of species, e.g., chimpanzees, macaques, goats, sheep, brown bears and fruit bats (Tan et al. 2009, Sergiel et al. 2014, Sugita 2016, Brooker et al. 2020, Prokop et al. 2024), the presence of a pathogen in ejaculate could represent an evolutionary adaptation for the horizontal spread of infectious diseases (not just toxoplasmosis) within host populations.

THE SEXUAL BEHAVIOUR OF UNINFECTED INDIVIDUALS TOWARDS *TOXOPLASMA*-INFECTED INDIVIDUALS

In numerous species, female mate choice is characterised by discriminating behaviour that reflects a preference for males exhibiting specific traits. This selectivity often leads to avoidance of potential mates showing signs of infection. Such behaviours appear to have evolved as adaptive mechanisms aimed at ensuring that females mate with males possessing genetic traits that confer resistance to parasitic infections. Additionally, such behaviours may reduce the risk of infection for the females themselves. For instance, females may exhibit reluctance to copulate with or approach males showing signs of infection.

In light of this, it might be expected that uninfected females would avoid mating with *Toxoplasma*-infected males as a protective behaviour. However, some studies suggest that rather than being avoided, *Toxoplasma*-infected males may be preferred by females, possibly due to parasite-induced changes that enhance their attractiveness, and, in turn, facilitate transmission.

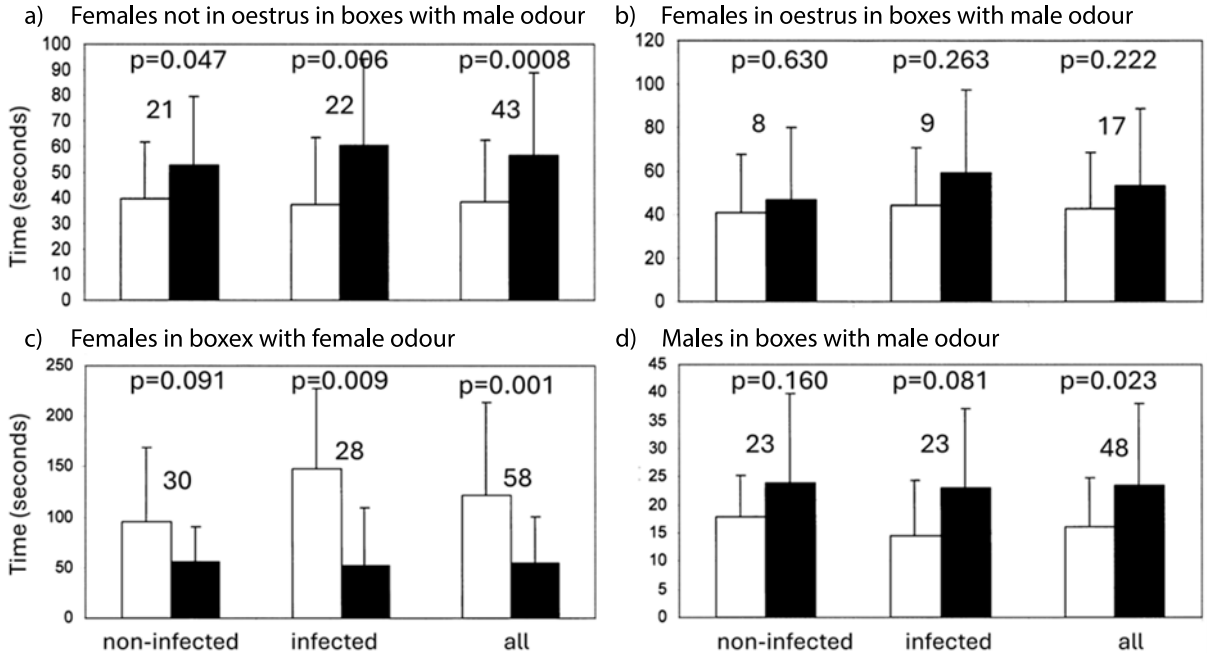

Fig. 1. Odour preference test. Infected and uninfected mice were placed in test aquaria with fresh bedding (sawdust) and two enclosed boxes (8 × 8 cm) with circular openings 3 cm in diameter. One box contained bedding from aquaria housing infected males or females, and the other from uninfected animals of the same sex. During a 10-minute test, the time (in seconds) that each mouse spent inside either of the boxes was recorded. The graphs show the mean time spent in seconds and the corresponding standard deviation. White bars indicate the time spent in boxes with bedding from uninfected animals, and black bars indicate the time spent in boxes with bedding from infected animals. The numbers above the bars indicate the two-tailed *t*-test p-values and the number of animals in each group (Hodková 2006).

Animal Model Studies

Female rats exhibit avoidance behaviours towards male rats infected with parasites, particularly when detecting infection-related chemosensory cues. Typically, parasite load is negatively associated with chemosensory signals, male secondary sexual characteristics and mate preference (Sarabian et al. 2018, Lopes et al. 2022). Males with higher parasite loads tend to display reduced secondary sexual traits and are generally perceived as less attractive to females (Penn and Potts 1998, Møller et al. 1999). The primary neural structures involved in detecting these cues and mediating avoidance responses include the vomeronasal organ, olfactory bulb, hypothalamic nuclei and medial amygdala. It is likely that specific proteins present in the urine of infected male rats serve as key informational cues for this sensory system, as suggested by Baum and Kelliher (2009).

However, *Toxoplasma* infection appears to alter this typical avoidance response. Female rats possess sensorial and neural mechanisms that enable them to detect odours emitted by infected male rats (Kavaliers et al. 2005). Vyas (2013) argued that rather than triggering avoidance, these odours can induce attraction behaviours in female rats. Given the ongoing evolutionary arm race between host and pathogen, it is plausible that *Toxoplasma* may manipulate host behaviour by enhancing the attractiveness of infected males, potentially overriding natural avoidance responses. Such manipulations may facilitate both sexual and vertical transmission (i.e., transmission from mother to offspring), thereby increasing the likelihood of parasite persistence in host populations.

Indeed, rather than diminishing attractiveness, *Toxoplasma* infection appears to enhance certain traits, which might potentially increase mating success. For example, research by Dass et al. (2011) demonstrated that uninfected female rats preferentially selected *Toxoplasma*-infected males over their uninfected counterparts. Furthermore, infected males experienced greater mating opportunities despite exhibiting similar reproductive parameters. Similar results were also observed in female and male mice, which spent more time near closed boxes filled with bedding from nests of infected male mice (Hodková 2006), see Fig. 1.

Human studies

Toxoplasma has been shown to influence various aspects of sexual attraction and behaviour in infected individuals. A study conducted by Flegr et al. (2005) revealed that men infected with *Toxoplasma* were, on average, taller than their uninfected counterparts. Given that body height is a well-documented factor in female mate preferences – with women generally favoring taller men (Stulp et al. 2013) – the observation that *Toxoplasma*-infected men are taller may reflect parasite-driven changes in traits linked to male attractiveness.

In addition to height, research has explored the relationship between *Toxoplasma* infection and perceived masculinity and dominance in men. Research by Hodková et al. (2007) demonstrated that infected male university students

were rated by female students as significantly more dominant and masculine compared to their uninfected peers. Another key finding is that infected men exhibit lower 2D : 4D ratios (Flegr et al. 2005), a marker linked to early developmental influences of testosterone, the dominant androgen that governs the prenatal and pubertal development of masculine physical and behavioural characteristics (Šebánková and Flegr 2024). While 2D : 4D ratios have been associated with various biological and behavioural traits, their role in attractiveness and dominance remains multifaceted.

Some studies have found that individuals with lower 2D : 4D ratios tend to be perceived as more dominant, though not necessarily more attractive. For instance, research by Schaefer et al. (2024) found that these early developmental influences shaping facial structure contribute to perceptions of masculinity but do not necessarily enhance attractiveness. Similarly, Neave et al. (2003) reported that while certain facial features affected by these early developmental influences may signal dominance, attractiveness does not always correlate with these traits. In another study, Flegr et al. (2019) showed that although women report finding dominance in men attractive, they actually rated male faces with dominant features as unattractive – especially when evaluating them as potential long-term partners.

These findings suggest that the relationships among dominance, masculinity and attractiveness in humans are more complex than initially suggested. Moreover, it should be noted that in non-human mammals, the natural hosts of *Toxoplasma*, the relationship between dominance and attractiveness may be much more straightforward and strongly positive.

These findings collectively indicate that *Toxoplasma* infection may shape traits associated with male masculinity and dominance. Yet, the extent to which such traits contribute to male attractiveness or affect female mate choice likely varies across species and contexts.

THE SEXUAL BEHAVIOUR OF *TOXOPLASMA*-INFECTED INDIVIDUALS

Toxoplasma infection has been associated with altered sexual behaviours in infected individuals, potentially leading to differences in sexual behaviour and interactions compared to uninfected counterparts. A growing body of research suggests that these behavioural changes may result from a combination of hormonal, neurobiological and evolutionary mechanisms that may facilitate the parasite's transmission.

Studies by Flegr and Kuba (2016) and Flegr (2017) have shown that latent toxoplasmosis significantly influences sexual preferences and behaviours. Infected individuals, particularly men, report stronger tendencies toward masochism, rape fantasies, bondage, same-sex experiences, and anal sex. Women with latent toxoplasmosis also report higher attraction to violent sexual practices and same-sex experiences. However, despite their heightened inclinations, infected individuals tend to engage in these behaviours less frequently than uninfected individuals. This discrepancy suggests that while *Toxoplasma* may increase sexual arousal and fantasies, the physical and psychological effects of chronic infection may inhibit actual participation (Flegr et al. 2014b, Escudero et al. 2021).

Toxoplasma infection has also been associated with increased sexual promiscuity in men, as observed in a study by Alvarado-Esquivel et al. (2021). The study found that men with latent toxoplasmosis reported a higher number of sexual partners, suggesting a link between infection and riskier sexual behaviours. Notably, this association was not observed in women. Two potential mechanisms have been proposed: first, a testosterone-driven increase in sexual desire, and second, a possible adaptive response to declining health, where individuals adopt a fast life history strategy to maximise reproductive opportunities before their condition worsens (Sýkorová and Flegr 2021).

Toxoplasma may also promote its sexual transmission indirectly by reducing male fertility, which can lead to repeated mating attempts by infected males. Research by Hlaváčová et al. (2021b) suggests that infected men experience higher rates of fertility problems, including reduced sperm concentration and motility. While these fertility impairments may result from direct parasitic effects on reproductive organs, they may also stem from behavioural adaptations triggered by infection. Paradoxically, men with reduced reproductive capability may increase their sexual activity as a compensatory response, inadvertently promoting the parasite's sexual transmission. However, the negative physical and psychological effects of chronic infection may constrain their ability to act on these impulses (Mcinnes 2003, Flegr 2017).

One possible explanation for these behavioural shifts, as well as for the phenotypic changes discussed in the previous chapter, is the influence of *Toxoplasma* on testosterone levels. Research indicates that infected men often have elevated testosterone concentration, which could drive increased libido (Flegr et al. 2008a, Borráz-León et al. 2021). This mechanism will be addressed in greater detail in a dedicated chapter later in the present review article.

Beyond hormonal changes, neurobiological mechanisms may also contribute to altered sexual behaviour. Studies have shown that *Toxoplasma* infection can lead to the demethylation of arginine vasopressin promoters within the amygdala, a process that may influence behaviour (Dass and Vyas 2014). Additionally, increased dopamine levels (Flegr et al. 2003, Prandovszky et al. 2011) have been linked to heightened sexual motivation (Hull et al. 2004), while reduced serotonin levels may contribute to decreased sexual satisfaction and engagement (Henriquez et al. 2009). These neurochemical shifts, combined with the broader health deterioration commonly observed in infected individuals (Flegr et al. 2024), could in part explain both an increased inclination toward certain sexual behaviours and a concurrent reduction in their actual execution.

It is also essential to consider that the relationship between *Toxoplasma* infection and sexual behaviours may function in both directions. While infection may influence sexual behaviours, certain sexual practices could also in-

crease the risk of acquiring the parasite. Behaviours such as promiscuity, oral sex and zoophilia may expose individuals to bodily fluids containing *T. gondii*, thereby elevating transmission risk. This reciprocal relationship emphasises the complex interplay between host behaviour and parasite transmission dynamics.

In summary, the effects of *Toxoplasma* infection on human sexual behaviour likely involve hormonal and neurobiological mechanisms. While elevated testosterone levels, neurochemical changes and health deterioration may contribute to shifts in sexual attraction and engagement, the exact nature and purpose of these changes remain subjects of ongoing investigation. Regardless of whether these behavioural alterations serve as an adaptive strategy for the parasite's transmission or arise as incidental byproducts of infection, they clearly illustrate the profound ways in which pathogens can shape host biology and behaviour.

HIJACKING SEXUAL PATHWAYS TO ALTER PREDATOR AVOIDANCE

Rodents

Rodents exhibit a natural aversion to the odour of cats, an adaptive response to predation risk. This aversion manifests as reduced locomotor activity and heightened avoidance responses, such as seeking refuge in hide boxes when exposed to cat odour. For example, research conducted by McGregor et al. (2002) demonstrated that the scent of cats triggers distinct defensive reactions in rats, whereas fox odour produces effects that resemble those of non-specific unpleasant odour.

Toxoplasma infection significantly alters the behaviour of infected rats, particularly their response to cat odour. Instead of maintaining their natural aversion, *Toxoplasma*-infected rats display an unexpected attraction to the scent of cats, a phenomenon referred to as "fatal attraction." Berdoy et al. (2000) were the first to describe this behavioural effect of *Toxoplasma* and proposed that the parasite modifies host behaviour to facilitate its transmission through predation by felines. Despite their attraction to cat odour, *Toxoplasma*-infected rodents continue to exhibit defensive responses to non-feline predators, which do not contribute to the parasite's transmission cycle. Vyas et al. (2007a) provide evidence that while aversion to feline scents is selectively diminished, the overall survival strategies against other threats remain intact.

In this respect, another study conducted by House et al. (2011) demonstrated that *Toxoplasma* disrupts neural pathways associated with defensive behaviour in rats. This research indicates that *Toxoplasma* alters the ventromedial and dorsomedial hypothalamus, critical components of the brain's defensive circuitry. When infected rats are exposed to cat urine – a potent stimulus that typically elicits avoidance behaviour – their neural activity is redirected towards the reproductive pathway. This pathway is primarily associated with sexual arousal and attraction, particularly involving the posterodorsal medial amygdala, which is anatomically adjacent to the defensive pathway.

These findings suggest a significant alteration in how infected rats perceive threats. Instead of exhibiting typical defensive behaviours like avoidance, these rats display altered responses, perceiving cat urine as a sexually arousing stimulus. This shift in perception highlights a remarkable manipulation of host behaviour by *Toxoplasma*, potentially enhancing its transmission through predation by cats, which are necessary for its life cycle. For further insights into this phenomenon, see Ajai Vyas's article (Vyas 2024) in this Special Issue on Toxoplasmosis.

Primates

Further investigations into the "fatal attraction" phenomenon have been conducted with primates, reinforcing the idea that *Toxoplasma* infection can influence olfactory preferences and behaviours across species. In particular, a study showed that the infected chimpanzees were attracted to the odour of their natural predator, the leopard, while the uninfected chimpanzees exhibited their typical avoidance behaviour (Poirotte et al. 2016).

Further studies extended this line of research to humans. In a study involving both *Toxoplasma*-infected and uninfected participants, Flegr et al. (2011) examined the perceived intensity and pleasantness of urine odours from various animals, including domestic cats, horses, tigers, brown hyenas and dogs. The results revealed a significant and robust effect of latent toxoplasmosis on how participants rated the odour of cat urine. This effect was sex-dependent: infected women rated the odour of cat urine as less pleasant compared to uninfected women, whereas infected men rated it as more pleasant than uninfected men.

Notably, this effect was specifically pronounced for cat urine odour, which is particularly relevant given the association between *Toxoplasma* and felids, the definitive hosts of this parasite. While the pronounced effect was not observed for odours from other animal species, a marginal trend emerged in responses to brown hyena odour. Brown hyenas, members of the suborder Feliformia, share a closer evolutionary relationship with felids, hinting at a possible underlying mechanism linked to their shared lineage.

Beyond responses to non-human animal odours, alterations in olfactory perception among infected individuals have also been observed in relation to human-derived scents. In this respect, Flegr (2013) reported that infected women – but not men – exhibited a pattern reminiscent of the fatal attraction phenomenon, showing a heightened perception of attractiveness in the scent of diluted human urine samples, particularly those from men. This finding suggests that *Toxoplasma* infection may influence olfactory-driven preferences even outside the context of felid predators – potentially linking attractiveness with subtle cues of danger in broader social environments. Alternatively, the enhanced response might reflect an increased sensitivity to sexually relevant chemosignals associated with male scent.

Another investigation into the role of toxoplasmosis in olfactory functions, involving 61 infected subjects and 62 uninfected controls, revealed that infected men performed better than their uninfected counterparts in standardised odour-identification tests (Flegr et al. 2018). Also, individuals infected with *Toxoplasma* exhibited a significantly

altered sensitivity to odours compared to their uninfected counterparts. Specifically, the infected male participants rated the intensity of various smells as lower than those who were not infected. Conversely, the female participants who were infected rated the intensity of these same smells as higher than their uninfected peers, indicating a divergent effect of the infection on odour perception between sexes. Furthermore, when assessing the pleasantness associated with specific odours, particularly that of cat urine, the results were notably different for men and women. Infected men reported a lower level of pleasantness for cat urine compared to uninfected men, reflecting a diminished positive response to this odour. In contrast, infected women rated the pleasantness of cat urine higher than uninfected women, suggesting that the infection may enhance the appeal or positive association with this particular smell among women (i.e., Flegr et al. 2018).

In the previous study (Flegr et al. 2011), the direction of the sex-specific effects of toxoplasmosis was reversed compared to the findings of the study discussed above (i.e., Flegr et al. 2018). The authors attributed this discrepancy between the two studies to the use of significantly lower urine concentrations in the earlier one. Vyas et al. (2007b) demonstrated that the relationship between the attractiveness of cat urine odour for *Toxoplasma*-infected rodents follows an inverted U-shaped curve based on the strength of the stimulus (Vyas et al. 2007b) and is likely influenced by additional factors (Abdulai-Saiku et al. 2018). Given the differences in olfactory sensitivity between men and women – and more generally, between males and females – it is possible that study outcomes will vary depending on the exact experimental setup, particularly the concentration of the urine.

Of course, one could also speculate that *Toxoplasma* manipulates the behaviour of infected hosts in a sex-specific manner – making males more susceptible to predation, while making females, who in some mammalian species can transmit the infection to developing embryos, less susceptible. However, this evolutionary explanation seems highly unlikely given the contrasting results of two studies (Flegr et al. 2011, 2018). The hypothesis may account for the findings of the initial study, which indicated that men exhibited a preference for cat odour, but not the opposite results of the second study which revealed that women but not men expressed a preference for cat odour.

These findings underscore the sex-specific effects of *Toxoplasma* on olfactory perception and raise questions about the underlying mechanisms driving these differences. For example, future research should encompass an exploration of how the parasite may influence olfactory receptors or neural pathways involved in the processing of smell. It is crucial to determine whether these alterations arise from direct effects on the olfactory system or through indirect influences on hormonal or neurotransmitter levels, or potentially both. Future studies should also examine whether different immune responses between infected males and females are responsible for observed differences in behavioural responses of men and women to toxoplasmosis.

Another potentially important but understudied aspect of *Toxoplasma*'s behavioural manipulation concerns its interaction with the host's sexual behaviour in the context of psychological stress. As noted above, *Toxoplasma* is capable of targeting specific brain structures such as the amygdala (Vyas et al. 2007a), resulting in a rewiring of neural circuits that normally mediate fear into those associated with sexual arousal. Latent toxoplasmosis has also been linked to elevated levels of chronic stress and anxiety in infected individuals (Flegr et al. 2024), and fear responses are known to be enhanced under stress (Nijholt et al. 2004, Li et al. 2015).

It is therefore plausible that the overlapping neural pathways for fear and sexual arousal may become increasingly conflated in infected individuals under conditions of chronic stress. This may lead to an enhanced coupling of fear and sexual excitation, which may be further amplified in individuals with comorbid anxiety or phobic disorders. If supported by future research, this would suggest that chronic stress partly acts as a modulator of *Toxoplasma*-induced sexual behavioural changes. Such findings could have implications not only for our understanding of the mechanisms underlying parasite-induced behavioural alterations, but also for the psychological processes shaping human sexual behaviour in the context of toxoplasmosis and chronic stress, such as anxiety disorders.

TESTOSTERONE AS A MEDIATOR OF EFFECTS OF LATENT TOXOPLASMOSIS ON SEX AND REPRODUCTION?

Toxoplasma infection and testosterone alterations

As mentioned in the previous text, changes in testosterone levels may represent the physiological mechanism underlying some of the observed associations in the domain of sexual behaviour and reproduction. However, the effects of *Toxoplasma* infection on testosterone levels in animals and humans are inconsistent, with some studies reporting increases and others decreases. This variability likely stems from differences in parasite strain, host genetics, infection intensity and species-specific responses (Abdoli 2014).

A recent meta-analysis of six animal studies found mixed results (Abdoli et al. 2024). Three studies in male animals (rats, mice and spotted hyenas) and two in female animals (mice and spotted hyenas) reported decreased testosterone levels, while two studies in male rats found increased levels. One study in female rats showed no significant change. Species differences may contribute to these inconsistencies, as rats are relatively resistant to toxoplasmosis, whereas mice are highly susceptible.

In humans, a systematic review and meta-analysis of 18 studies similarly found varying effects (Abdoli et al. 2024). Among 19 studies on males, 13 reported increased testosterone levels following latent toxoplasmosis, three found decreases and two showed no significant change. This meta-analysis indicated that infected males exhibited, on average, a 0.73-unit increase in testosterone, while infected females had a 0.55-unit increase compared to uninfected individuals. These findings suggest sex-specific effects,

although some studies report no significant differences in hormone levels between infected and uninfected women (Borráz-León et al. 2021).

Testosterone is known to have immunosuppressive properties, which may be exploited by pathogens to enhance their chances of survival within the host (Braude et al. 1999, Roberts et al. 2004, Foo et al. 2017, Roved et al. 2017). A decrease of testosterone levels in infected hosts may therefore represent a compensatory response to immune alterations caused by *Toxoplasma*. During acute infection, lower testosterone levels could enhance immune function, increasing host survival. Conversely, elevated testosterone in infected men may enhance visual and olfactory attractiveness (Flegr et al. 2008a,b), raising the possibility of parasite-driven manipulation to facilitate transmission from infected men to their uninfected sexual partners. If *Toxoplasma* does influence testosterone levels, the underlying purpose remains uncertain – whether to promote sexual transmission or suppress host immunity for its persistence (Roved et al. 2017).

Toxoplasma infection, testosterone, and sex ratios

The temporal dynamics of testosterone levels in infected hosts remain unclear, though indirect evidence suggests a systematic change over time – potentially involving an initial increase followed by an irreversible decline. High testosterone in females is often associated with an increased secondary sex ratio (proportion of male offspring) (James 2010). Studies in both humans and mice indicate a higher secondary sex ratio shortly after infection, with some human cases reaching a 2.6 : 1 ratio (260 sons per 100 daughters) (Kaňková et al. 2007a,b). However, over time, infected females tend to have more daughters (Kaňková et al. 2007a,b). An ecological study identified *Toxoplasma* prevalence as one of the stronger predictors of low secondary sex ratios – ranking third among 16 examined factors, after son preference and fertility rates (Dama et al. 2016).

A decline in testosterone levels over time may be explained by the deteriorating health status associated with chronic infection (Flegr et al. 2014b, Flegr and Escudero 2016), as poor health typically reduces testosterone production. Alternatively, host compensatory mechanisms may act later in infection to lower testosterone levels and counteract its immunosuppressive effects.

Despite clear associations between *Toxoplasma* infection and changes in testosterone levels, fundamental questions remain. Does *Toxoplasma* actively manipulate host hormone levels, or are these changes incidental effects of infection? If manipulation occurs, is the goal to enhance transmission – either alimentary or sexual – or to suppress the host's immune response for prolonged persistence? Alternatively, could individuals with naturally high testosterone and weaker immunity simply be more susceptible to infection? Given testosterone's immunosuppressive properties (Roberts et al. 2004, Foo et al. 2017), increased sexual transmission may be a secondary consequence rather than a primary adaptive strategy of the parasite.

Further research is needed to clarify the complex interplay between *Toxoplasma*, testosterone, immunity and host behaviour, shedding light on whether observed hormonal changes serve a functional role in parasite transmission or are merely byproducts of infection.

CONCLUSION

The findings reviewed in this article suggest that *Toxoplasma gondii* may exert a broader influence on host sexual behaviour and physiology than previously assumed. While its best-known behavioural effects have traditionally been interpreted in the context of predation facilitation, growing evidence indicates that some of these changes – particularly those related to sexual attraction, behaviour, and reproductive physiology – may also serve to enhance the parasite's sexual transmission.

Although alimentary and vertical transmission remain the primary pathways in humans, the detection of viable parasites in semen, behavioural alterations that may alter sexual activity or enhance certain physical traits related to sexuality and attractiveness (such as height and dominance), and epidemiological associations with certain sexual practices support the hypothesis that sexual transmission could represent an additional, evolutionarily significant route.

In humans – but not necessarily in other species – sexual transmission likely accounts for only a minority of cases. Nevertheless, it may have disproportionate clinical consequences. If infection occurs during unprotected sexual intercourse at the moment of conception, the parasite may bypass maternal immunity and directly infect the embryo, increasing the risk of congenital toxoplasmosis – the most serious and life-threatening form of the disease. In this context, even rare instances of sexual transmission may justify increased scientific and clinical attention.

The possibility of sexual transmission also offers a novel framework for understanding several phenotypic changes observed in infected individuals. It challenges the assumption that all behavioural modifications serve a single ecological purpose and instead highlights the likelihood of multiple, overlapping transmission strategies shaped by inclusive fitness and host-parasite coevolution.

To evaluate the epidemiological, evolutionary and clinical importance of this potential transmission route, further interdisciplinary research is needed. Integrating insights from behavioural ecology, parasitology, immunology and reproductive medicine will be essential to determine whether sexual transmission represents an overlooked but meaningful component of the parasite's life cycle – and how it may affect both public health and our broader understanding of host manipulation by *Toxoplasma*.

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