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Review

Rats, cats, people and parasites: the impact of latent toxoplasmosis on behaviour

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ABSTRACT – The manipulation hypothesis states a parasite may alter host behaviour for its own benefit, often by enhancing its transmission rate through the food chain. This paper reviews studies on the potential impact of one parasite, *Toxoplasma gondii*, on host behaviour, both on rodents, where altered responses may be proposed to benefit the parasite, and humans, where altered responses may arise as a side-effect of infection with no current adaptive significance. © 2001 Éditions scientifiques et médicales Elsevier SAS

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1. Introduction

According to the manipulation hypothesis, a parasite may be able to alter the behaviour of a host for its own selective benefit, usually by enhancing its transmission rate. The hypothesis requires that such behavioural modification be a sophisticated product of parasite evolution aimed at host manipulation rather than an accidental by-product of other physiological activities of the parasite [1–3]. Classic examples concern transmission through the food chain, where a parasite is immature in the intermediate host, which must be eaten by a predatory definitive host before the parasite can reach maturity and complete its life cycle. The parasite thus manipulates the behaviour of its intermediate host so as to ensure its transmission to the correct definitive host. This review examines a series of studies on the potential impact of one parasite, *Toxoplasma gondii*, on host behaviour: both on intermediate hosts, where altered behavioural responses may be proposed to benefit the parasite, and on incidental hosts, where altered behavioural responses may arise as a side-effect of infection with no selective value.

T. gondii is an intracellular apicomplexan protozoan with worldwide distribution capable of infecting all endothermic vertebrates [4]. A consideration of its transmission route provides an indication of why it may be predicted to alter host behaviour. *T. gondii* has an indirect life cycle (*figure 1*), where members of the cat family (Felidae) are the only known definitive hosts able to shed oocysts with their faeces [5]. These oocysts contaminate the surrounding environment; a 20-g cat stool can contain between 2 and 20 million oocysts, and after faecal decomposition, the local soil contamination can be as high as 100 000 oocysts/g and remain infectious for more than 1 year [6]. If oocysts are ingested by another cat, viable organisms are released which invade intestinal epithelial cells, where they undergo both an asexual and sexual cycle. In contrast, if oocysts are ingested by a non-feline host, such as a wild rodent, bird, or human, an extra-intestinal cycle is observed, where asexual reproduction occurs and small thin-walled cysts form in all nucleated cells, particularly those of the brain. If a naive cat then consumes infected intermediate host prey, the *T. gondii* life cycle is completed.

Prevalence levels are frequently very high across species, reaching, for example, 45.6% in domestic and feral cats [6], 20–60% in wild rodents [7, 8], 13.4–66.7% in wild birds [6, 9] and 22–84% in humans [10]. Four distinct forms of its associate disease, toxoplasmosis, exist. The first, congenital toxoplasmosis, occurs via vertical transmission from infected mother to offspring. Serious foetal damage and malformation, including microcephaly, intracerebral calcification, and/or spontaneous abortion frequently result from congenital infection within humans and several other mammals [4, 11]. The second form is acute postnatally acquired toxoplasmosis, which is characterized by the occurrence of *T. gondii* tachyzoites in blood and other tissues. Whilst most symptoms of acute toxoplasmosis are relatively mild and harmless, and are often missed or misdiagnosed as minor viral infections, a broad spectrum of clinical symptoms from enlarged lymph nodes, fever, headache, to serious neurological complica

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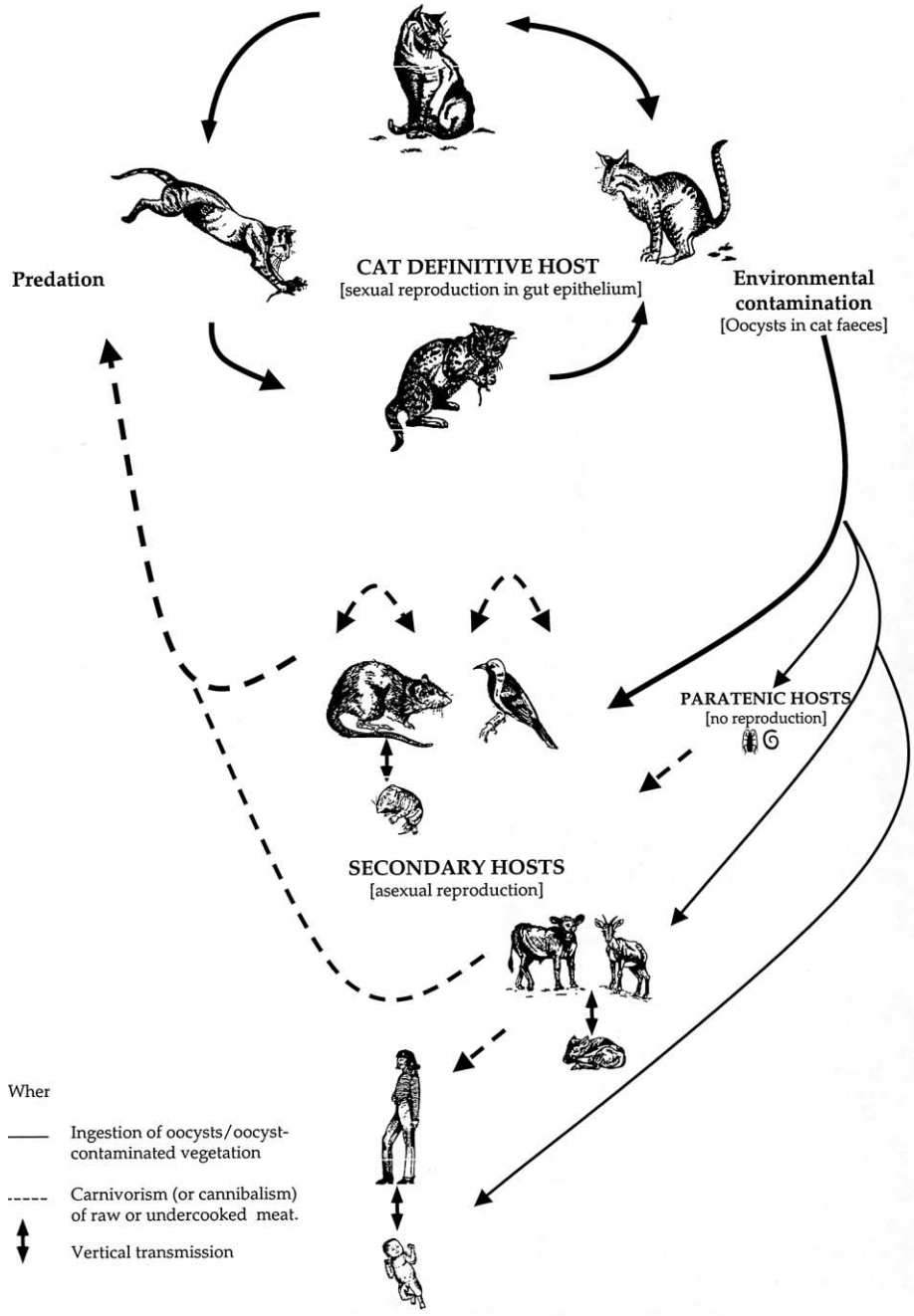

Figure 1. Schematic life cycle of *Toxoplasma gondii*. A consideration of the indirect life cycle of *T. gondii* provides an indication of why this parasite may be predicted to alter host behaviour. Members of the cat family are the definitive hosts, which shed oocysts with their faeces to contaminate the environment (and may also be transiently passed through invertebrate paratenic hosts). Unbroken arrows: if another cat ingests these oocysts, viable organisms are released which invade intestinal epithelial cells, where they undergo both an asexual and sexual cycle. In contrast, if oocysts are ingested by secondary hosts, such as wild rodents and birds (intermediate hosts) or humans and domestic livestock (accidental hosts), an extraintestinal cycle is observed where asexual reproduction occurs and small thin-walled cysts form in all nucleated cells, particularly those of the brain. Unbroken double arrows: in some species, vertical transmission also occurs, which in the case of rodents, can accentuate the intermediate host reservoir; broken double arrows: as can intra-specific transmission via cannibalism. Broken arrows: carnivores, including humans, are then infected through consumption of live prey or infected undercooked meat. If this carnivore is another cat, the *T. gondii* life cycle is completed. (Figure; J.P. Webster original).

tions can occasionally occur in humans and may even result in death within several small mammalian species [12, 13]. In some human cases the third form, chronic toxoplasmosis, may develop, where the symptoms of acute toxoplasmosis described above persist for many years. However, in the vast majority of cases all symptoms spon

taneously disappear within weeks or months and develop instead into the fourth form, latent toxoplasmosis, where *T. gondii* survives as dormant but viable bradyzoites within tissue cysts which remain for the host's lifetime [14]. These can recrudesce to cause severe neurological disease if the host becomes severely immunosuppressed due to, for example, AIDS or chemotherapy in humans [15]. However, within immunocompetent human and animal hosts, latent toxoplasmosis is generally believed to be asymptomatic and of no clinical or epidemiological interest [16, 17]. Indeed, latent toxoplasmosis has even been considered beneficial for humans, as it protects pregnant women from acute toxoplasmosis and hence their children from congenital toxoplasmosis. Yet, in contrast to the extensive research performed on the clinical sequelae of acute and congenitally acquired *T. gondii* infection, minimal research to date has focused on latent toxoplasmosis and/or the cyst form of the parasite, despite the vast number of humans and animals infected [18]. Moreover, there are a number of reasons why one may expect to observe behavioural alterations in individuals with latent toxoplasmosis, as the parasite would benefit from enhancing transmission rates from intermediate to definitive host, and having a predilection for host brain tissue, is situated in an ideal position in which to achieve such manipulation.

2. 'Parasite manipulation': evidence from rodent models

Recent studies have demonstrated that wild rodents can represent not only a highly prevalent, but also a persistent intermediate host reservoir for *T. gondii* [7, 8]. For example, a breeding rat population derived from wild caught individuals, maintained in an enclosure which prevented any contact with cats and hence direct oocyst contamination, was found to maintain a *T. gondii* infection prevalence similar (at a mean of 35%) to that of wild populations [8]. This suggested that the infection reservoir could persist through, in part, vertical transmission (supplemented through cannibalism and insect paratenic host horizontal transmission). Vertical transmission is also believed to predominate in wild mice and bank-vole populations [7]. As such a prevalent and persistent intermediate host reservoir exists, it may therefore be expected to benefit *T. gondii* if it could enhance its subsequent transmission rate from this to the cat definitive host. Moreover, as sexual reproduction can be accomplished only in the definitive host, there might be strong selective pressure to evolve such a mechanism. There is now a convincing body of evidence to suggest that *T. gondii* may achieve such manipulation.

In some initial studies, Piekarski [19] and Witting [20] found that laboratory mice inoculated with *T. gondii* showed significantly diminished learning capacity and memory in double-training maze experiments than did their uninfected counterparts. Whilst any disruption to normal behaviour in such prey species may be predicted to influence predation rate, a more specific method for *T. gondii* could be to alter intermediate host activity and exploratory levels, since cats are immediately attracted to moving and exposed objects and show little interest, or cannot see, stationary or hidden ones [21]. A series of studies by Hay, Hutchinson and colleagues thus investigated the potential effect of postnatal and congenital toxoplasmosis (from both acutely and chronically infected dams) on laboratory mouse activity and exploratory behaviour via recording each individual's entry into marked squares on a cage floor, Y-shaped maze and/or on running wheels [22–26]. Infected mice were found to be more active than their uninfected counterparts [24, 26]. Likewise, infected mice showed a smaller but consistent relative preference for more exposed or novels areas of apparatus [23, 24, 26], and spent significantly less time grooming, a typical 'displacement activity', before investigating such novel areas than did their uninfected counterparts [24]. Such selective effects appear to exclude explanations of behavioural abnormalities in terms of lowered motivation or general debility, since these could not be expected to produce consistently increased levels of one behavioural category consistent with decreases in other categories. A more likely explanation may be that *T. gondii*-infected mice interact with their environment and novel stimulation arising from it in a different way from uninfected mice.

In order to determine whether such behavioural alterations were consistent across rodent species, Piekarski , Witting, and colleagues [19, 20] repeated their experiments upon laboratory rats, and found that whilst learning capacity was also reduced in some individuals, this was much milder and rarer than observed for laboratory mice. Potential explanations for these differences may be the higher infection rate of *T. gondii* in the brains of mice than rats during latent toxoplasmosis, as well as the formers' increased potential for severe morbidity during the acute phase of infection. Indeed, in both these studies, whilst the general health and behaviour of laboratory rats was unaffected by infection, laboratory mice often showed signs of acute infection, and were observed to run in circles with their heads bent to one side when moving and sitting [19, 20]. Similar clinical symptoms of acute, as distinct from latent, toxoplasmosis amongst laboratory mice have also recently been identified by Hrda and colleagues [27]. These authors concluded that experiments with more resistant animals, such as rats, provide a better model in which to study the potential manipulatory activity of *T. gondii*.

Webster, Berdoy and colleagues have performed a series of studies on the potential impact of *T. gondii* on rat behaviour [28–32]. Such studies had an advantage in that, in contrast to the artificiality of most laboratory-based experiments, particular attention was paid to testing each hypothesis using wild or wild hybrid rats maintained under naturalist habitats and/or social conditions.

In an initial study, the activity levels of both wild-trapped rats with naturally occurring parasite loads, and purpose-bred wild/laboratory hybrid rats with experimentally induced parasite loads were investigated [28]. Replication using each of these combinations ensured elimination of a number of potential biases such as, for example, generalised encephalitis due to artificial parasite inoculation, differences in past parasitic histories, and/or inherent behavioural differences between laboratory and wild rats

[32, 33]. Since rats are nocturnal, the activity of each individual, maintained within large (1 × 1 m) outdoor cages containing nest boxes, food and water supplies, were video-taped for 10 h each night. *T. gondii*-infected rats were found to be significantly more active than their uninfected counterparts. In contrast, the activity levels of wild and hybrid rats either naturally or artificially infected with a variety of direct life cycle parasites (*Leptospira* spp., *Cryptosporidium parvum*, *Coxiella burnetti*, *Hymenolepis nana*, *Syphacia muris*) were not altered. This is consistent with the manipulation hypothesis, because directly transmitted parasites do not require a definitive host in order to complete their life cycle, and thus would not be expected to alter host activity levels as any increase in predation rate would result in death of both host and parasite [2, 28].

The effect of *T. gondii* on the neophobic (fear of novelty) response in rats was also examined [29, 31]. This thus differed from the laboratory mouse studies [23, 24, 26], since whilst mice are neophilic species, wild rats, in contrast, are amongst the most innately neophobic mammals known and react to novel stimuli with extreme caution and often total avoidance [33]. It is this neophobia that makes wild rats so notoriously difficult to control through human predation regimes such as trapping and poisoning [32, 33]. The experimental design was again chosen for its naturalistic qualities. Firstly, wild rat reactions to three food-related novel stimuli were recorded, as measured by the length of time taken until consumption of food associated with an unfamiliar smell, constituents or container, and compared with individual baseline data. *T. gondii*-infected rats were found to be significantly less neophobic towards each of the novel stimuli. In contrast, there were no differences in neophobic behaviour between rats infected or not with any direct life-cycle parasite investigated, as for the activity study [28] described above. The propensity of wild rats to be captured in live traps was then investigated. Whilst results were inconclusive from farmyard populations, rat populations maintained within captive environments where all individuals could eventually be caught showed a clear relationship between trappability and *T. gondii* status, with infected rats significantly more likely to be trapped first [29]. Finally, the propensity of rats to approach a mildly fearful object within such a captive environment was recorded by direct observation, and again *T. gondii*-infected rats were significantly more likely to approach the object than their uninfected counterparts [31].

These studies thereby suggest that *T. gondii* can alter a strongly innate behaviour, such as neophobia, amongst infected intermediate hosts. A subsequent study took this idea further by examining whether *T. gondii* affect the rats' perception of cat predation risk [30]. The response to cat odour was chosen as a measure because this is known to elicit a strong innate aversive reaction even amongst laboratory rodents that have never been in contact with a predator. Individual wild/laboratory hybrid rat behaviour was again video-recorded throughout each 10-h night within purpose-built outdoor (2 × 2 m) pens. Wooden nest boxes were positioned in each corner of the pen, and each contained either: (1) the rat's own bedding; (2) fresh neutral bedding treated only with a few drops of plain water; (3) bedding treated with a few drops of cat urine; or (4) bedding treated with drops of rabbit urine. Rabbit urine was used as a control, as it represents a mammalian smell, but is that of a herbivore rather than a predator, thus controlling for reaction to smells in general. The results showed that uninfected rats showed a strong aversion to the cat-treated areas. In contrast, infected rats showed, not simply a reduction in their cat-aversion, but actually a preference for cat-treated areas. This preference continued throughout the night, and was most apparent amongst the most active rats. These results suggest that there is also a significant divergence in the perceived response to cat predation between infected and uninfected rats. Uninfected individuals show a significant and innate avoidance of cat-scented areas, whilst infected rats show a significant (presumably suicidal) preference for cat-treated areas [30].

Finally, these authors looked to see whether the effect of *T. gondii* was general or specific, i.e. does the parasite simply alter all types of behaviour or, as in accordance with the manipulation hypothesis, only those aimed at increasing its transmission through cat predation? [31]. Social behaviour was examined because status and mating success are the result of hard competition in this species, and therefore any disruption of them would be a good indicator of generalised illness, whilst at the same time there is no obvious benefit to the parasite's transmission rate through altering this behaviour. Breeding colonies were maintained within large (266 m^2) outdoor enclosures which provided the rats with features that they would normally encounter in the wild, such as sufficient space, a diverse social environment and a dispersed food supply, whilst facilitating the collection of detailed data upon known individuals. Rats were observed by binoculars from the vantage points of raised huts positioned outside the perimeter fence of each enclosure. No difference in either the social status (as indicated by their position within a dominance hierarchy), nor mating success (as indicated by the number of mating chases, copulatory events, and ejaculations) was found between infected and uninfected rats. Thus, in accordance with the manipulation hypothesis, the effect of *T. gondii* does appear to be specific to those behavioural categories that may increase its transmission, rather than simply causing a generalised illness and/or global change in host behaviour.

In summary, these studies, carried out under different experimental conditions suggest that infected rodents do behave differently for a suite of behaviour that may make them more likely to by predated on by cats, the parasite's definitive host, and such behavioural manipulation does appear to be specific rather than generalised.

3. 'Parasite constraint': evidence from human models

Humans obviously do not represent intermediate hosts for *T. gondii*, as they are rarely preyed upon by cats. Instead humans may become infected with the parasite accidentally, and any behavioural alterations induced may be termed as parasitic 'constraint' [2], as they arise as a

side-effect of prior selection in intermediate hosts (although such constraint may remain, for some host–parasite systems, adaptive). One may still expect to observe behavioural alterations in latently infected humans, as it is unlikely that any parasite would have the recognition and modulatory mechanisms able to restrict expression to within only those hosts likely to be predated. As latent toxoplasmosis is highly prevalent within human populations [10], any impact upon human host behaviour could have significant clinical and economic implications. Clear differences between rodents and humans as models can also be exploited to help elucidate the precise mechanisms of this parasite. For example, while the average life span of a rodent is a similar length to that of acute acquired toxoplasmosis (in rodents and humans), any behavioural alterations observed in human subjects several years after infection could be indicative of slow cumulative changes induced by the activity of the parasite.

Burkinshaw [34] performed one of the earliest investigations into the potential effect of *T. gondii* on human cognitive performance. Skin and serological tests were performed on a population of certified 'mental defectives' from a single institution, and 55 infected individuals from 698 tested were detected, with the incidence of positive reactions rising with increased patient age. As this infection prevalence distribution was similar to that found within the 'normal' population, and in no cases could the authors find that the mental defect could be definitely attributed to toxoplasmosis, they concluded that toxoplasmosis is not a common cause of mental defect. However, whilst such early studies were of value in that they did highlight a potential link between cognitive performance and parasitism, their experimental design may be too crude to allow any valid conclusions to be drawn. Firstly, these studies did not control for type of *T. gondii* infection; congenital, acute, chronic or latent. Indeed there is no doubt that congenital toxoplasmosis alone can reduce intellectual function, where, in some regions up to 9% of cases of mental retardation are associated with congenital *T. gondii* infection [35]. Secondly, whereas the effects of latent toxoplasmosis may be expected to be subtle (as for the rodent studies described above), these authors only investigated effects in terms of gross mental retardation so as to warrant patients to be institutionalised as 'mental defects'. Moreover, within this categorisation, the individual levels of disability ranged widely from 'a vegetative idiot with as estimated social quotient of 2 up to a neurotic girl with an intelligence quotient of 104 (whilst) overweighted with high-grade imbeciles for administrative reasons'. Finally, the aetiology of many of the patients mental retardation was already known, and due to factors quite distinct from *T. gondii* infection, such as several cases of known brain injury, phenylketonuria, Down's syndrome, cerebral palsy, familial mental defect related to incest, tubercular meningitis etc.

Unfortunately, many of these same criticisms can also be directed at some of the subsequent human studies aimed to associate cognitive performance with *T. gondii* infection. For example, Paul [36] reported a change of personality in several children associated with *T. gondii* infection, and Elias and Porsche [37] found that the prevalence of *T. gondii* infection amongst patients of another institution for severe mental disorder was 30% higher than that of the general population. However, in neither study was any distinction made between congenital or postnatally acquired infection. Likewise, whilst Langset [38] observed a very high incidence of infection (71.5%) in a group of children that had been assessed to be slow learners, any habits of the children that may potentially influence risk of infection, such as social status and environmental conditions, were not accommodated for.

Nevertheless, a few studies have attempted to control for factors such as social status, onset and type of infection, etc., and suggest that behavioural alterations may indeed be displayed in humans with latent toxoplasmosis.

The first systematic investigation on small children with latent toxoplasmosis regarding their cognition compared the social background, physical behaviour and intelligence quotients of infected children with those of uninfected (seronegative) children [39]. Whilst there were no social differences between groups, the infected children had on average a lower IQ (93) than the controls (110).

More recently, Flegr and colleagues investigated potential differences in personality profiles between humans with latent toxoplasmosis and uninfected controls [40–42]. Based on questionnaires measuring personality factors, differences between infected and uninfected groups were detected. For example, infected men had lower 'superego' and higher 'protension' scores, which the authors concluded implied that they had a higher tendency to disregard rules of their society and were more suspecting, jealous and dogmatic. With some tests (though not all) infected men also had lower intelligence scores than uninfected men. Infected women, on the other hand, were found to have higher 'affectothymia' and 'superego strength' scores, which were suggested to imply they were more warm-hearted, out- and easy-going, but also more conscientious, persistent, moralistic and staid. Both infected men and women had higher guilt proneness than their uninfected counterparts.

Whilst such effects may be indicative of subtle differences in personality profile between infected and uninfected humans, such studies alone do not distinguish cause from effect, since human studies obviously preclude the experimental manipulation open to laboratory rodent studies. However, the authors proposed that if *T. gondii* induces behavioural alterations, then the intensity of change should increase with the duration of infection. If such behavioural characteristics were present before infection, no such correlation should exist. They tested this again with questionnaire profiles and related the results to either clinical records on date of acute phase of infection (two experimental sets) or antibody levels present (one experimental set), where low levels of antibody titres were assumed here to indicate older infections. 'Superego' strength scores were lowest amongst men, and highest amongst women, with low antibodies and/or an increased duration since acute infection, consistent with that found in their previous studies. The authors thus concluded that the observed changes in personality profile of infected humans were induced by the parasite, rather than that any

shift in personality factor influenced the probability of being infected with *T. gondii* [40–42].

The potential impact of *T. gondii* on human psychomotor performance has also been investigated using a simple computerised 3-minute reaction test [43]. Whilst there were no significant differences in psychomotor performance between individuals with latent toxoplasmosis and uninfected controls throughout the first minute of testing, infected individuals showed a decrease in performance earlier, in the second minute of the test, than did their uninfected counterparts. The intensity of this decrease was again correlated with decreased antibody levels. The authors thus concluded that *T. gondii* also affects the ability for long-term concentration [43].

Some problems do remain with the current human studies. For example, the use of declining antibody titres as indicative of duration of infection [40–43] cannot accommodate for groups with repeated exposure to *T. gondii*. Likewise, zero titres could be taken as either unexposed individuals or, in contrast, individuals with the longest duration of infection and hence those predicted to show the greatest effect; indeed viable tissue cysts are known to remain even when antibody responses have disappeared [44]. Similarly, it may be a little optimistic to conclude that *T. gondii* affects the ability for long-term concentration from only two minutes of testing [43]. Nevertheless, the studies do suggest that the behaviour of humans with latent toxoplasmosis is different from that of their uninfected counterparts, and that any alterations could have important clinical and/or educational repercussions.

4. Functional explanations and mechanisms

The studies reviewed here suggest that *T. gondii* can alter host behaviour. Such modulation appears restricted and specific to only those behavioural categories likely to influence predation rate of intermediate hosts, whilst simultaneously being displayed in other paratenic or accidental hosts. These results obviously raise questions as to the evolution, epidemiology and potential mechanisms of *T. gondii*'s actions.

As with all examinations of traits that appear to support the manipulation hypothesis, alternative explanations must be considered [2, 32]. Firstly, one may propose that the observed effects simply represent the consequences of a generalised response to parasitism. However, this appears unlikely, at least in the context of the rat studies reviewed here, both due to the specificity of the response [31] and the fact that no behavioural differences were observed between individuals infected with any of the direct life-cycle parasites examined, where enhanced predation would result in death of both host and parasite [28, 29]. Likewise, it is unlikely that the observed behavioural alterations were simply a side-effect of cyst-induced encephalitis, since two of the direct life-cycle parasites (*C. burnettii* and *Leptospira icterohaemorrgiae*) have been reported to result in encephalitis and toxic confusional states, but left the behaviours reviewed here intact [28, 32].

Secondly, one could propose that the observed behavioural alterations in parasitised hosts may not be the result of natural selection favouring transmission efficacy, even if the consequences are the same, but may be due instead to other aspects of the host–parasite association. For example, parasitised animals may have special requirements as a result of being parasitised, such as increased hunger, and in meeting these requirements, behave differently from uninfected conspecifics, which may entail risk including increased exposure to predators. This too is unlikely to apply to *T. gondii*, since no differences in food intake (and hence hunger or energy requirements), condition indices, other parasite loads, or growth rates between infected and uninfected individuals were reported in any of the reviewed studies. Another alternative may be that the observed changes are of benefit to the host rather than the parasite. For instance, it has been suggested that where prevention of infection is impossible, suicidal responses on the part of infected hosts may be adaptive if they protect the host's close kin from infection. However this too is unlikely in the *T. gondii* system, as such suicidal behaviour tends to be restricted in response to parasites where kin–kin direct horizontal transmission risk is high (see references cited in [1]). Nevertheless, as it is at least theoretically possible that predation by cats could prevent kin–kin transmission via cannibalism amongst infected rats, any realistic evaluation requires a more detailed understanding than is currently available of the fitness consequences for manipulation and any potential suicide alleles in this system.

Thirdly, it is feasible that alterations may have arisen during the evolution of host and parasite taxa and therefore may reflect the history of the lineage rather than particular adaptations for the transmission of a parasite in a particular host. *T. gondii*-induced behavioural changes may have been adaptive in the ancestral association in which they arose, in presumably earlier murids and avians, but regardless of their origin, now characterise descendants of the association in which they appear to have both beneficial and non-beneficial consequences. A clear illustration of this may be the reduced psychomotor performance reported amongst latently infected humans [44], which will not influence parasite transmission and hence can have no adaptive significance to the parasite. In contrast, any equivalent increase in reaction times in a small rodent or bird intermediate host could have a significant impact upon their likelihood of predation by the feline definitive host, and hence would be subject to strong selective pressure under the original natural conditions. Likewise, even within potential intermediate hosts such as rodents, an example of a disadvantageous side-effect of parasite-altered behaviour is that, although parasitised rodents may be more susceptible to predation, the predator may not be a suitable definitive host for the parasite. This has been suggested to be an unavoidable cost of altered behaviour [1]. Such an effect may be illustrated here by the study on the effect of *T. gondii* on neophobia levels in wild rats [29]. Reduced neophobia may make the infected rat more prone to cat predation, but it also seems sure to make the infected rat more prone to vermin-control regimes by humans. Such consequences

cannot fit the manipulation hypothesis since, even if poisoned rats were more easily caught by cats, the parasite would be disadvantaged if the cats then succumbed to secondary poisoning.

Whilst the manner in which *T. gondii* exerts its behavioural alterations is unknown, one could postulate that the same causal mechanisms are involved across all secondary hosts. Histopathological, immunological and/or neuromodulatory changes are all potential candidates. For example, whilst gross pathology alone is unlikely to account for the observed changes, as other behavioural characteristics are left intact, multifocular lesions and/or histopathological changes in the cyst-containing regions of the brain have been observed. These include inflammatory granulomatous changes of perivascular areas, progressive deposition of necrotic material and subsequent vesicular occlusion and sclerosis [45]. There is even correlational evidence that *T. gondii* cysts in brain tissue can trigger tumorigenic processes, as an increased frequency of latent *T. gondii* infection has been found in humans with some forms of meningioma brain tumour [46]. Indication of potential immunological involvement has also been suggested since, even in relatively resistant strains of mice, latent toxoplasmosis can be accompanied by permanently increased levels of mRNA of the cytokines' tumour necrosis factor-alpha and interleukin-10 [47]. Finally, neuromodulatory modulation may represent an ideal system whereby *T. gondii* could influence the expression of host behaviour. Changes in brain concentrations of catecholamines and indoleamines have been found in *T. gondii*-infected laboratory mice. Significant differences between infected and uninfected mice were found in homaovanillic acid, dopamine, and norepipephirine levels, all substances which mediate, amongst others, locomotor activity, mood, learning, memory and cerebral blood flow [48]. Moreover, these same neurotransmitters have been implicated in the pathogenesis of schizophrenia in humans [48], and indeed a recent study has reported significantly higher levels of *T. gondii* antibodies amongst first-incidence schizophrenic patients than occurs in the general public [49]. Furthermore, studies investigating the neurological basis of anxiety, which often use reaction by potential prey to cat stimuli as a model, have found that blocking the normally anxiogenic NMDA receptors in the amygdala, and/or provision of serotonin (5-HT) antagonists, causes rats to approach cats or cat odours 'fearlessly' [50, 51], in much the same way as *T. gondii*-infected rats were demonstrated to approach areas treated with cat urine [30]. One could thus speculate an anxiolytic (anxiety relieving) action of *T. gondii*. Such a mechanism would account for the altered general exploratory and activity behaviour reported here for infected rodents, and even perhaps the types of personality shifts reported for humans (reduced concern over implications of actions etc.), although not perhaps for the types of pathology characteristic of schizophrenic patients. Nevertheless, interpretations over potential mechanisms to explain some of the observed behavioural effects, such as sex-related effect, remain complex. For example, Flegr reported human personality factor shifts to be in opposite directions in men and women [40–42]. Such may reflect simply gender-based bias in questionnaire-based studies and design, rather than a real parasite-induced effect. However, whilst no such *T. gondii*-related sex effects were observed in the rodent studies as regards the standard behavioural measures, Hay [26] did study defecation as a stress measure index in his laboratory mice and also found a significant sex difference.

5. Conclusions and recommendations

In conclusion, latent toxoplasmosis, although frequently dismissed as asymptomatic and clinically unimportant in both humans and animals, does alter host behaviour, even if it is just as a side-effect from a previously selected response. Clearly, much research remains to be performed. For instance, actual predation rates by the feline definitive host are the real yardstick to measure any proposed behavioural manipulation amongst intermediate hosts. Suitable criteria must also be developed for estimating and acknowledging the potentially harmful effects of parasitic disease on human behaviour and cognition. However, what may be the most pressing need is an accurate elucidation of the mechanisms by which *T. gondii* may achieve such effects. A parasite such as this, highly prevalent within both the human and animal populations, with such a predilection for the central nervous system, should not be ignored.

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