Opinion

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Adaptive host manipulation by *Toxoplasma gondii*: fact or fiction?

Amanda R. Worth, Alan J. Lymbery, and R.C. Andrew Thompson

School of Veterinary and Biomedical Science, Murdoch University, South Street, Murdoch 6150, Australia

It is widely accepted that behavioural changes induced by *Toxoplasma gondii* are an adaptation of the parasite to enhance transmission to its cat definitive host. In our opinion, this explanation requires a rethink. We argue that the experimental evidence that observed behavioural changes will enhance transmission to cats is not convincing. We also argue that cats and sexual reproduction may not be essential for transmission and maintenance of this parasite. Thus, the selection pressure to infect a cat may not be sufficiently strong for the evolution of adaptive host manipulation to have occurred in order to enhance predation by cats.

Toxoplasma gondii and behaviour – why question the link?

Based partly on experimental studies in rodents, attention has recently turned to the potential causative association between *Toxoplasma gondii* and abnormal behaviour, personality changes, and mental disorders in humans [1]. It is widely accepted that *T. gondii*-induced behavioural changes in rodents are an example of adaptive manipulation to enhance transmission to cats (Box 1) (e.g., [2,3]). The story goes that if *T. gondii* finds itself in a rat, but wants to get into a cat, the parasite can manipulate the behaviour of the rat host in order to increase its chances of being caught and eaten by a cat. This appealing explanation is treated as entrenched dogma in this field and forms the foundation to guide future research. However, in our opinion this widely accepted view is not based on solid evidence, and requires reappraisal.

This article therefore aims to scrutinise the evidence from past studies and to question the assumptions underlying the idea that *Toxoplasma*-induced behavioural changes are an adaptation of the parasite. Firstly, we argue that due to inconsistencies in experimental design and conflicting results from past studies, there are no hard experimental data to support adaptive manipulation by *T. gondii*. Secondly, we question the underlying assumption that manipulation of rodent behaviour to enhance transmission to cats will be adaptive for the parasite. Specifically, we focus on whether cats and the sexual cycle of the parasite are essential, as presumed. We believe that questioning the accepted dogma will allow new perspectives to be considered – ultimately providing a sound foundation for future research.

Corresponding author: Worth, A.R. (A.Worth@murdoch.edu.au).
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There is no evidence that behavioural changes increase transmission to cats

Inconsistencies between past studies

Much support for adaptive manipulation by *T. gondii* is based on reports that only behaviours that could enhance transmission to the definitive host are altered (e.g., [4–6]). However, there are many conflicting results from past studies (Table 1), and it is impossible to draw sound conclusions based on what behaviours are or are not affected. A range of behavioural changes that may lead to enhanced predation by the definitive host have been reported in *T. gondii*-infected rodents, including increased activity level, decreased anxiety, impaired motor performance and reaction time, and inappropriate responses to cat odours. However, these findings are not consistent across all studies (see Table 1 for details). Behaviours that are not obviously related to enhanced predation are also affected (e.g., impaired learning and memory, and changes in dominance, social interaction and mate choice). The inconsistencies in experimental design between studies make it difficult to interpret the conflicting results, and it is premature to report that only behaviours related to enhanced predation by the definitive host are affected.

Could such appropriate behavioural changes be coincidental?

One reason the accepted explanation is so popular is that it tells an appealing story. If the parasite is currently in a rat, but needs to get into a cat, it makes sense for the parasite to manipulate the behaviour of its rat host to improve its chances of getting into a cat! Discovering that *T. gondii* makes rodents less afraid of cat odour [4,7] further embedded this idea. It could be argued that such a 'perfect' manipulation could not have come about without the necessary selective pressures, therefore providing support for the idea that *Toxoplasma* manipulates rodent behaviour to enhance predation by cats.

However, evidence from *Eimeria vermiformis*, a parasite that does not require predation to complete its life cycle, suggests otherwise. Mice infected with *E. vermiformis* show a similar decrease in avoidance of cat odour as *T. gondii*-infected rodents [8]. In the case of *E. vermiformis*, this cannot be argued to benefit the parasite – if the parasitised mouse is caught by a cat the parasite will die too. Instead, the decrease in cat-odour avoidance is interpreted as a coincidental side effect of a general reduction in anxiety and fearfulness [8]. If this behavioural change can be induced by *E. vermiformis* without being

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Box 1. What is adaptive manipulation?

Adaptive manipulation refers to parasite-induced changes in host behaviour that benefit the parasite, often through enhanced transmission to the next host in the life cycle of the parasite [3]. It is important to acknowledge that the literature concerning adaptive manipulation is not without its controversies and disagreements over what constitutes true adaptive manipulation (see [24] for more information). In general, it is considered that behavioural changes observed in parasite-infected hosts could be explained by one of three phenomena:

1. The parasite itself does something specific and direct to the host, in order to alter behaviour to its own benefit.
2. The host changes its own behaviour in order to eliminate or minimise the effect of infection.
3. The change in host behaviour is the coincidental result of pathology or immune response.

The latter two phenomena may coincidentally benefit the parasite; for example, increased energy requirements whilst fighting an infection may cause the host to forage more, increasing the risk of predation, and thus increasing the chance of the parasite spreading to a new host. However, behavioural changes that are host-mediated (e.g., caused by an immune response or an increased energy requirement) are likely to be nonspecific and occur in response to a range of pathogens. Therefore, we do not think it makes sense to consider these changes to be adaptive manipulation, even if they do have coincidental benefits for the parasite. Nonetheless, as mentioned previously, there is some contention about what should be considered 'adaptive manipulation', and all we can do is clearly define what we mean by this term.

The first explanation in the above list is the classical interpretation [3] and this is what we mean in this article when we refer to 'adaptive manipulation'. This definition implies both of the following:

- that behavioural changes benefit the parasite (adaptive),
- that behavioural changes are caused by a direct and specific action of the parasite on the host (manipulative).

of benefit to the parasite, the same may be true for *T. gondii* – the decreased fear of cat odour may be co-incidental, rather than an adaptation to enhance transmission to cats.

Do observed behavioural changes actually translate into an increased predation rate?

Many researchers have suggested that the observed behavioural changes will increase the likelihood of the affected host being caught by a cat, benefitting the parasite by enabling it to complete its sexual cycle. However, it is notoriously easy to interpret behavioural changes to fit your expectations, so any inference based on behavioural changes should be treated with caution. There is no direct evidence (either from predation studies or observed mortality in the wild) that rodents infected with *T. gondii* actually do get caught by cats more often, although it could be argued that the finding that infected rodents are less afraid of cat odour (specifically urine) [4,7], provides strong indirect evidence. However, we do not agree with this, as a decreased fear of cat urine does not necessarily guarantee enhanced predation by cats. In nature, an infected rat that is not averse to the scent of cat urine may spend more time in places where a cat has been, but not necessarily more time near an actual cat, which will smell of 'cat fur', and not urine. 'Cat fur' odour elicits a much stronger aversion in normal rats [9], and this aversion may be unaffected by *T. gondii* [4]. Furthermore, stimuli such as the sound and movement of a cat may be important additional cues that rodents use to avoid predation.

The importance of establishing that behavioural changes in the host do actually lead to an increase in predation rate was demonstrated by Webster *et al.* [10] in a study of behavioural changes in tenebrionid beetles infected with the rat tapeworm *Hymenolepis diminuta*. Infected beetles were more likely to be exposed, rather than hidden under a box, and this was assumed to increase the likelihood that infected beetles would be eaten by the definitive host of the parasite – the rat. Nevertheless, a subsequent predation experiment demonstrated that there was no difference in predation rate of infected versus uninfected beetles. Their results 'emphasise the need for caution before active parasite manipulation is inferred from behavioural changes without direct demonstration of enhanced transmission' [10].

If behavioural changes induced by *T. gondii* do not actually lead to an increase in predation rate, there is no reason to think this is adaptive manipulation. In the case of *T. gondii* infected rodents, a rigorous predation experiment would not be possible due to ethical issues. However, this does not change the fact that inferring enhanced transmission based only on behavioural changes is dangerous, and any conclusions drawn in such a way are limited.

Increased transmission to cats may not increase parasite fitness

The accepted explanation that *T. gondii* manipulates host behaviour to enhance transmission to cats is based on the assumption that completion of the sexual cycle in the cat definitive host is essential for the parasite, or increases the fitness of the parasite. This increase in fitness may be in the form of short-term benefits (by increasing transmission to new hosts) and/or long-term benefits of sexual reproduction (which could be difficult to define, see [11,12] for discussions). However, there is a growing belief (e.g., [13,14]) that cats and sexual reproduction are not essential for the survival, transmission, and maintenance of *T. gondii* in a population, bringing into question the importance of the sexual cycle.

The sexual cycle is not essential for transmission or maintenance of T. gondii

Despite the existence of a sexual phase in the life cycle, the genetic structure of *T. gondii* is essentially clonal, with three main lineages predominating, at least throughout North America and Europe [13,15]. *T. gondii* is unique in that it has a very wide host range and can be transmitted directly between intermediate hosts, completely bypassing the definitive host (Figure 1) [13]. Theoretically, *T. gondii* could be maintained in a population, in the absence of cats, via repeated vertical transmission [16] and/or repeated carnivory [14], resulting in clonal reproduction of the parasite. The clonal population genetic structure suggests that these 'non-cat' routes of transmission happen often (Box 2), and that sexual reproduction occurs only rarely.

Previously, it has been argued that the lack of *T. gondii* in cat-free island populations [17] is good evidence that cats are an essential part of the life cycle of the parasite.

Table 1. Summary of behavioural changes in rodents infected with *T. gondii*

Behaviour	Reported results[a]	Host/s[b]	Possible reasons for inconsistencies[c]	Rat Refs	Mouse Refs
Activity level	Increased		Dose/strain of parasite? Type of behaviour test? Time post-infection?	[25]	[26–30]
	Decreased			[31]	[23,31–33]
	Not affected			[4,34]	[23,29]
Learning	Impaired		Host species? Type of behaviour test?	[31]	[31]
	Not affected			[4]	
Memory	Impaired		Host species? Type of behaviour test?		[29,31]
	Not affected			[4,31]	[35]
Social interactions	Increased		Time post-infection? Type of behaviour test?	[34]	[36]
	Not affected			[5,34]	[35]
Preference for novelty	Decreased		Host species? Type of behaviour test?		[26,32]
	Increased			[5,37]	[33]
	Not affected				[35]
Time spent near cat urine	Increased		Time post-infection?	[4,7,38]	[4,29]
	Not affected				[29]
Time spent near cat fur	Increased		Host species? Type of behaviour test?	[4,7]	
	Not affected			[4]	
Anxiety	Decreased		Host species?	[34]	[30]
	Not affected			[4]	[35]
Motor coordination	Impaired		n/a		[35,39]

Past studies have investigated various behaviours and have reported contrasting results. Studies have used different experimental designs, for example, different combinations of the following: host species, *T. gondii* strain, type of behaviour test, time post-infection, dose and stage of parasites, and route of infection, making it difficult to interpret the collective results.

[a]Results as reported by the authors of the study.

[b]The host(s) in which the reported behavioural change has been found.

[c]Our interpretation of which experimental factors may help explain the contrasting results, based on details of each study in the behaviour category.

Theoretically, however, *T. gondii* could become established in a new population in the absence of cats, if it was transferred there within an intermediate host. Evidence to support this idea has been found in the cat-free Svalbard Islands, Norway, where the parasite has been detected in the arctic fox [18]. It is thought that *T. gondii* might have been introduced to these islands by migratory geese that became infected elsewhere and were eaten by arctic foxes when they returned to Svalbard. Once introduced, *T. gondii* infection could be maintained on these islands by vertical transmission and carnivory [18].

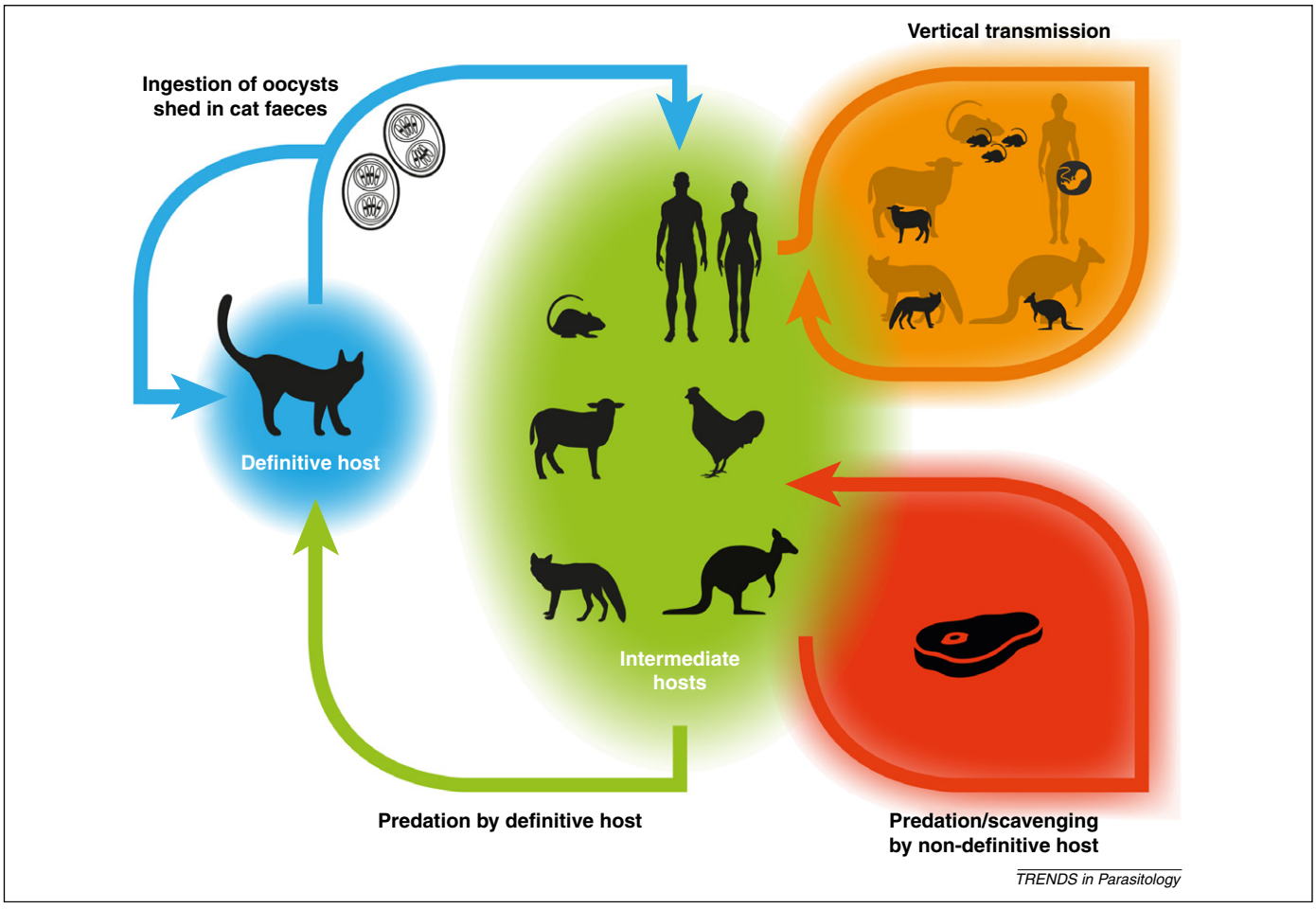

Figure 1. The life cycle of *Toxoplasma gondii*. The flow chart shows a variety of intermediate hosts and three routes of transmission to intermediate hosts: ingestion of oocysts from cat faeces, ingestion of tissue cysts via predation/scavenging, and vertical transmission from mother to offspring.

Is the sexual cycle important enough for the evolution of adaptive manipulation?

Although the sexual cycle of the parasite is not essential for maintaining *T. gondii* in the population, it may still exert sufficient selective pressure for the evolution of adaptive manipulation if it contributes disproportionately to parasite fitness in the short term (by enhancing successful transmission to new hosts) or in the long term (by introducing genetic variation). In the short term, it has been suggested that cats are pivotal to the transmission of *T. gondii* as they shed millions of oocysts into the environment, providing a large, persistent reservoir of infection for intermediate hosts [19]. However, there are other opportunities for transmission to intermediate hosts, and production of oocysts in a cat may not necessarily result in the greatest dissemination of the parasite.

For example, we now know that vertical transmission occurs in many species (Box 2). In mice, *T. gondii* can be transmitted vertically even during chronic maternal infection, and probably occurs for the life of the breeding female [20]. One female mouse, if she survives long enough, has the potential to pass the parasite to many of her offspring, in multiple litters.

If instead, this one female mouse is caught by a cat, the opportunity for her offspring to become infected is gone. If the cat in question had not been previously exposed to *T. gondii*, the parasite will be able to produce oocysts, and has the opportunity to spread to new hosts, although these oocysts must survive in the environment until they are ingested by an appropriate host species. Conversely, if the cat had been infected previously, and is thus immune to reinfection [21], the parasite will not be transmitted further. It could be argued that transmission of *T. gondii* from mother to offspring may be more beneficial (at least in the short term) than the parasite taking its chances in a cat, where it may or may not have the opportunity to spread to new hosts. Clearly, relying on logic and reasoning to infer which route of transmission is the most important is not enough, as arguments can be made for either case. A well-parameterised model could help us better understand the importance of each transmission route to the short-term spread of *Toxoplasma*. However, without such supporting evidence, we feel it is important to at least question the entrenched belief that transmission via cats is 'pivotal'.

In the long term, sexual reproduction may be essential for the persistence of *T. gondii*, by maintaining the genetic variation required to allow adaptation to changing environments. However, it appears that sexual reproduction only occurs rarely, and rare occurrences of sexual reproduction may be enough to provide long-term benefits. If this is the case, we need to consider whether the selective

Box 2. The importance of vertical transmission

Vertical transmission has been demonstrated in many mammalian hosts, including humans, dogs [40], rodents [20], sheep [41], and marsupials [42] and is likely to be a common route of transmission in nature [41]. The idea that vertical transmission may be important in the life cycle of *T. gondii* is not new. In 1997, Johnson [16] suggested that repeated vertical transmission may be a natural life cycle for some strains of *T. gondii*, as has been found in the closely related parasite *Neospora caninum*. Theoretically, repeated vertical transmission (from mother to daughter, to daughter's daughter, etc.) could maintain the parasite in a population [16], and the resultant asexual reproduction would agree with the observed 'clonal' population genetic structure [41].

There is also empirical evidence to support the idea that vertical transmission is an important route of transmission. In a survey of UK farmsteads, Webster [43] found that the prevalence of *T. gondii* in wild rats was high (25–60%) regardless of whether cats were present or absent at the site, indicating that continual contamination of the site with oocysts was not a prerequisite for high levels of infection.

Furthermore, the prevalence of *T. gondii* in a captive rat population that was known to be cat-free for 2.5 years prior to sampling was 44%, and there was no association between *T. gondii* infection and either age or sex of the rats. Environmental transmission (via ingestion of oocysts, carnivory, scavenging, and/or ingestion of paratenic hosts) is predicted to result in a defined pattern of prevalence in wild rats, where prevalence is higher in males than females (due to differences in space use) and higher in older animals than in young animals (as older animals have had more exposure to the environment) [43]. As no such pattern was found by Webster [43], it was concluded that vertical transmission, rather than environmental transmission, accounted for the high prevalence of *T. gondii*.

These findings support the idea that vertical transmission is common enough to maintain the parasite at high levels in a population, and therefore that cats are not essential for the transmission and maintenance of *T. gondii*.

pressure to increase sexual reproduction by increasing transmission to cats is sufficiently strong to have led to adaptive host manipulation of rodent behaviour.

Concluding remarks

In our opinion, the accepted dogma that *T. gondii* manipulates host behaviour to increase transmission to cats, tells an appealing story but does not stand up to scrutiny. The behavioural changes reported vary between studies, and it is difficult to interpret past results due to inconsistencies in experimental design between studies. There is also no direct evidence that *T. gondii*-infected rodents actually get caught by cats more often. Furthermore, cats are not essential to the life cycle of *T. gondii*, and we see no compelling reason to expect this parasite to have adapted to enhance its transmission to cats. Having multiple routes of transmission and such a wide host range make *T. gondii* unique and successful [14,22], perhaps eliminating the need for this parasite to enhance transmission by adaptive manipulation.

In light of the questionable assumptions and the inconsistent evidence that underlie the accepted dogma, we believe the effect of *T. gondii* on rodent behaviour is not yet well understood, and this field is in need of reappraisal. Given that research into human behaviour is based at least partly on findings in rodents, it is vital that we have a good understanding of how rodent behaviour is affected by *T. gondii*, before we extrapolate to other species. Therefore, future research should focus on filling the gaps in our fundamental understanding of this phenomenon in rodents. It has been suggested that observed behavioural changes may be nonspecific byproducts of the response to infection by the host [23], rather than the result of direct action by the parasite. Such hypotheses deserve more attention. We hope that this article will encourage readers to question the accepted dogma; we believe this will allow new perspectives to be considered and will bring us closer to the ultimate goal of elucidating the mechanism(s) by which *T. gondii* induces behavioural changes.

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