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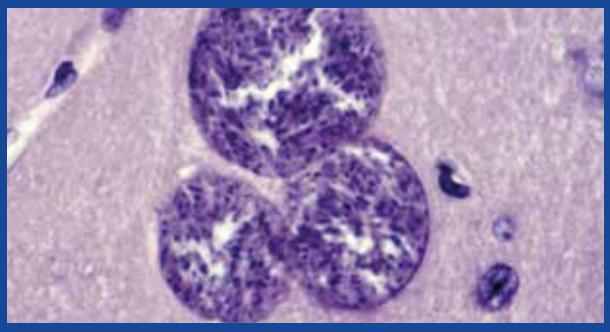


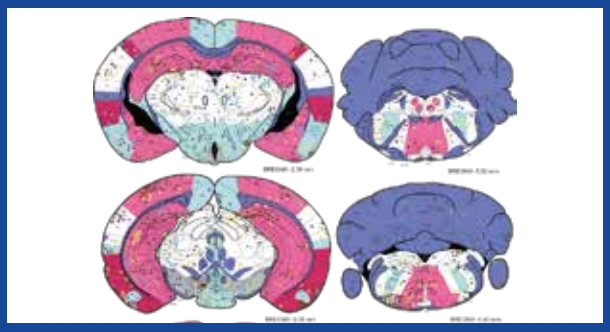

Special Issue

Effects of Latent Toxoplasmosis: Three Decades of Studies

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Special Issue on Toxoplasmosis

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Who makes the decisions? Uncovering the evolutionary implications and clinical applications of *Toxoplasma gondii's* Fatal Feline Attraction

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Abstract: Here I recount my research journey on the coccidian protist *Toxoplasma gondii* (Nicolle et Manceaux, 1908), a ubiquitous parasite capable of infecting all warm-blooded animals as intermediate or secondary host, but with only members of the Felidae as its definitive host. I describe my initial studies into its epidemiology and persistence within the UK, and how this led on to a series of biologically and ethically appropriate studies into *T. gondii*'s apparent specific manipulation of its rat intermediate host to facilitate transmission to its feline definitive host. I then describe how this prompted searches into the potential mechanisms of action behind such manipulation and what this raises in terms of behavioural changes, from the subtle to severe, across other secondary hosts including humans.

Keywords: Toxoplasmosis, manipulation, rats, behaviour, intermediate host, definitive host

On commencing my doctoral research at Oxford University, my original plans were to elucidate the transmission dynamics and zoonotic impact of leptospirosis in the UK. This spirochaete, primarily that of *Leptospira icterohaemorraghia*, evoked fear in many of my fellow Oxford students and staff – namely amongst the various rowing teams and individual enthusiasts, due to its infamous reputation across both scientific literature and the media as reputedly prolifically circulating amongst wild rat, *Rattus norvegicus* (Berkenhout), populations and thereby contaminating the local waterways.

After designing a complex set of studies, multiple field surveys and endless hours spent over a wide range of different diagnostic tests, it soon became apparent that this infectious agent, whilst undoubtedly still of profound zoonotic health implications across much of the world, was really rather rare amongst the wild rats of Oxfordshire and the surrounding regions (Webster et al. 1995). However, these same rats, frequently gleaming with apparent health overtly, were found to be hosts to almost every other infectious agent imaginable, from helminths to Hanta viruses (Webster and Macdonald 1995).

Indeed, one of the most consistently prevalent parasites was that of the protozoan *Toxoplasma gondii* (Nicolle et Manceaux, 1908), with around 35% of rats seropositive across all sites examined (Webster 1994a). Furthermore, one of the benefits of working within Oxford was that we had space, including a working farm adjacent to Wytham woods, which enabled us to perform unique sets of naturalistic studies. One immediate opportunity was the existence of very large (266 m^2) naturalistic outdoor enclosures (Fig. 1A–C). Within one of these was a breeding population of rats, originally seeded by six locally-wild-caught *R. norvegicus* (of unknown infection status) for previous food-selection behavioural studies by my colleagues.

When these had finished, I had the opportunity to examine the seroprevalence of *T. gondii* in this unique population, which had been isolated from any direct exposure to cats, and hence direct oocyst contamination, for around three years. To my surprise I found a similar seroprevalence levels of 35%, matched to their free-ranging fully wild counterparts (Webster 1994a). This indicated that *T. gondii* could persist in wild rat populations without continued contact with their feline definitive hosts.

Whilst the potential role of oocyst contamination from insect paratenic hosts, and also bradyzoite transmission through the occasional cannibalism amongst the rat colony members, could not be wholly excluded here, it appeared that congenital transmission was likely to be the predominant route for transmission here (Webster 1994a). Such findings helped to explain the consistency and persistence of a large wild rat intermediate host reservoir for *T. gondii*.

Whilst the epidemiology of infection persistence was of keen interest, an enduring research passion for me, and very much the focus on my undergraduate training and research specialities, were the behavioural and neurosciences – and

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Fig. 1. Taking the laboratory to the field – large (266 m^2) naturalistic enclosures with wild *Rattus norvegicus* (Berkenhout). **A** – the breeding colony of *R. norvegicus*, originally seeded from six wild caught rats with naturally-acquired infections, were free to display natural behavioural traits, activities and develop social hierarchies comparable to that of free-ranging wild rats; **B** – rats had both nest boxes provided and were free to dig their own burrows; **C** – the rats were completely separated from external contacts or contamination, though here both a passing farm cat and enclosure rat are showing great interest in each other through the narrow fencing (photos M. Berdoy).

the existence of such consistently high levels of *T. gondii* in these rodent reservoirs thereby sparked a new line of enquiry for me. As stated in the "manipulation hypothesis," certain parasites can manipulate the behaviour of their hosts to increase the transmission rate to the subsequent hosts (Holmes and Bethel 1972, Poulin 1994). Whilst numerous fascinating cases of parasite manipulation in insect hosts were already known (Holmes and Bethel 1972, Moore et al. 2005, Adamo and Webster 2013), there were very few documented cases of such manipulation (as distinct from simple parasite-induced pathology/'disease') in mammalian hosts – with rabies being the notable exception.

I suspected *T. gondii*, being indirectly-transmitted, would be an ideal parasite to display such manipulation: since sexual reproduction of *T. gondii* occurs only within the feline definitive host, there should be strong selection pressure for this parasite to enhance transmission from the large reservoirs of rodent intermediate hosts to cats, via enhanced predation, and thereby complete its life cycle. Furthermore, as *T. gondii* has a tropism for the intermediate host's brain, where bradyzoites may persist potentially for the host's lifetime, this places *T. gondii* in an ideal location to achieve such manipulation.

To begin to test the hypothesis that *T. gondii* can specifically manipulate the behaviour of its rat intermediate host to facilitate transmission to the feline definitive hosts, we undertook a series of non-invasive behavioural assays. Indeed, wild rats represented an ideal model host to study this as, contrary to mice for instance, immunocompetent *T. gondii*-infected rats do not suffer overt morbidity nor mortality (Kaushik et al. 2012, Webster et al. 2013).

To start, we again took 'the laboratory to the field', by using very large individual outdoor pens with video cameras and infra-red lights above, and filmed the rat's behavioural patterns over each 12-hour night. *Toxoplasma gondii*-infected rats were significantly more active than their uninfected counterparts. This was true irrespective of whether these were wild rats with naturally occurring parasite loads, or experimental rats, for which parasitic histories were tightly controlled (Webster 1994b).

Increased activity/movement amongst infected rats, relative to their uninfected matched counterparts, is consistent with the manipulation hypothesis since cats, as the predatory definitive hosts, show little interest in (and potentially cannot detect) stationary objects but are immediate attracted by moving ones (Hubel and Wiesel 1962). A parasitised rat experiencing general malaise, on the other hand, may be expected to reduce its activity and perhaps remain in a burrow beyond the reach of predators.

We then tested whether *T. gondii* could override strongly innate traits. Neophobia – the ability to detect/fear of novelty, where rodents are the most neophobic mammals known, was again the focus of many of my fellow researchers at Oxford, who were examining the behavioural resistance of rodents towards pesticides. As responsiveness to novelty is likely to be important to wild rats in terms of survival against predation as well as poisoning, we decided to combine our non-invasive behavioural research. Wild rats infected with *T. gondii* (again alone among the plethora of parasites naturally infecting these wild rats) were found to have significantly reduced reactivity to each of three food-related novel stimuli (odour, food-container, food) (Webster et al. 1994), or to a mildly-fearful novel object in their environment (Berdoy et al. 1995), relative to their *T. gondii*-negative counterparts.

As it became clear that this parasite could even alter innate behaviour in their intermediate hosts, we then decided to examine the potential ultimate obstacle militating again successful transmission to the feline definitive host – the fear of felines itself. Whilst direct predation studies would obviously be unethical, we sought a biologically meaningful proxy for feline risk. Laboratory rats with no exposure to cats for hundreds of generations still show significant behavioural and physiological aversion to the odour of cats' urine (Zangrossi and File 1992, File et al. 1993, Hogg and File 1994).

Returning to the large outdoor enclosure, my colleague Manual Berdoy and I set up individual (2 m × 2 m) open-topped pens, within which each corner contained 15 drops of one of four distinct odours deposited within nest boxes: the rat's own smell (own urine-soiled woodchip bedding), neutral smell (fresh woodchips treated with water), cat odour (fresh woodchips treated with undiluted cat urine) and rabbit odour (fresh woodchips treated with undiluted rabbit urine). Rabbit odour was used as a control for a mammalian non-predator. The position of the four smells

Fig. 2. Cordelia – a much loved pet.

was changed between each test to avoid positional biases, and the rats were then videotaped from above going about their normal activities and explorations over each 10-hour night (a mere 670 hours of subsequent viewing for blinded data scoring!).

As predicted, uninfected rats showed a strong aversion to the cat-treated areas. In contrast, *T. gondii*-infected rats showed no such aversion, and to our surprise, an actual significant attraction to the cat-treated areas (Berdoy et al. 2000). Such findings suggested that *T. gondii* appears to subtly alter the rats' cognitive perception of predation risk, turning their powerful behavioural and physiological innate aversion to predator odour into a definitive, host-specific 'suicidal attraction'. Here we formulated the 'Fatal Feline Attraction' hypothesis (http://www.independent.co.uk/news/science/professor-joanne-webster-the-scientist-who-uncovered-fatal-feline-attraction-8102715.html). This highly replicated 'Fatal Feline Attraction' model has become a canonical example of mammalian host manipulation, taught across schools and universities worldwide. Indeed, Jaroslav Flegr even observed an equivalent feline odour attraction amongst in his male *T. gondii*-infected human subjects (Flegr et al. 2011, Flegr 2025).

Taking this further, we then tested whether the 'Fatal Feline Attraction' of *T. gondii*-infected rats differed according to the type of feline odour used, specifically whether it came from domestic cats (*Felis catus* Linnaeus) or wild cats – cheetahs (*Acinonyx jubatus* [Schreber]) or pumas (*Felis concolor* [Linnaeus]) (both of which were kept [as pets] by an individual living in rural Hertfordshire who kindly allowed us to collect their urine!). Here we moved from direct observation to that of the relative ease of automated video tracking tools. We also used laboratory rats, and specifically that of the Lister-hooded rats who were not only easier to track by the automated cameras, given their unique markings, but had been shown to behaviourally most similar to wild rats (Webster et al. 2013).

Our findings demonstrated that all cat odours are not equal: infected rats had a stronger preference for wild cat odour over that of domestic cats, an effect that did not differ significantly according to the type of wild cat odour used (Kaushik et al. 2014). These results may imply, for instance, that wild cats have greater capacity to be definitive hosts for *T. gondii* relative to domestic cats, consistent with the known persistent oocyst-shedding of many wild cat species in contrast to domestic cats (Dubey 1995), and/or that the former have longer/stronger co-evolution histories with the parasite.

Furthermore, the fine detail facilitated by automated tracking revealed that, whilst infected rats spent relatively more of their time in wild cat zones compared to domestic cat zones, they actually moved more slowly when within the wild cat zone (Kaushik et al. 2014). Thus, rather than 'freezing' in a fear response, infected rats appeared to maximise their time exploring the wild cat zones, a behaviour that under natural conditions would likely increase their risk of predation. These results raised further questions about the mechanism of action and mode of discrimination in 'Fatal Feline Attraction' as well as about the role of wild cats in the transmission of *T. gondii* both today and in our evolutionary past.

A little aside, and the beauty of using the rat model for *T. gondii* study since, unlike mice, no overt morbidity is induced, it was written into our licencing that these rats, at least the uninfected ones, could be released as pets following a veterinary check at the end of each study, and thus, as well as myself, so many of my friends and colleagues were the proud owners of these delightful creatures (Fig. 2).

Alternative explanations – parasite pathology *versus* manipulation

As with any apparent parasite manipulation of host behaviour, it is essential to consider alternative potential explanations for the behavioural changes observed. Indication in support of the specificity of *T. gondii* behavioural changes in the rats studied above was that there were no such behavioural changes observed in association with a broad range of directly-transmitted parasites, where death of host by predation would also result in death of parasite, with which the wild rats were naturally infected/co-infected, nor laboratory rats experimentally infected (Webster 1994b, Webster et al. 1994). Likewise there were no differences in food-intake, and hence apparent hunger which may have explained any enhanced risk-taking exploratory behaviours between infected and uninfected rats (Webster et al. 1994).

Furthermore, the 'Fatal Feline Attraction' toward the smell of urine was specific to that of the Felidae only, with no attraction/difference between infected and uninfected rat's responses to rabbit (non-predatory mammal) (Berdoy et al. 2000), nor dog (Kannan et al. 2010), mink (Lamberton et al. 2008), or fox (McGregor et al. 2002) (all predatory mammal) odours. This subtle ability to distinguish between the odours of a definitive and a non-definitive host of *T. gondii* indicates that this is a specific alteration in the cognitive perception of the predation risk by the rat, rather than a more general destruction of a behavioural trait or of olfaction.

Moreover, the behavioural changes observed amongst *T. gondii*-infected rats appeared to be specific towards only those behavioural traits likely to enhance transmission

Fig. 3. Fatal feline attraction assay within the laboratory using automated tracking of Lister-hooded *Rattus norvegicus* (Berkenhout) (photo M. Kaushik).

to cats via predation. For instance, we also examined the social behaviour and dominance hierarchies of the rats in the original 266 m^2 outdoor breeding colonies, since social 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. Here we had to go back to observing the individual-identifiable rat social interactions within their stable free-ranging colonies from an external vantage point to the side of the 100 m^2 outdoor enclosure by binoculars over multiple 10-hour nights.

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) were found between infected and uninfected rats (Berdoy et al. 1995). 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 from rodent to feline, rather than simply causing a generalised illness and/or global change in host behaviour.

Beyond rodents – parasite constraint versus manipulation

Toxoplasma gondii is a ubiquitous parasite capable of infecting all warm-blooded animals, and despite the apparent specificity of the behavioural changes documented in rodents, it is implausible that such behavioural changes would only be displayed in potential intermediate host species such as rodents (or birds), but instead be apparent in a broad range of infected mammalian secondary host species. Such changes may be termed as parasite 'constraint' rather than manipulation, as they arise as side-effect of prior selection in intermediate hosts (although such constraints may remain, for some host-parasite systems, adaptive) (Moore and Gotelli 1990).

Accordingly, an increasing body of work has been observing such apparent changes, indeed more as a 'by-product' of which may have no adaptive value to the parasite. For example, California sea otters, *Enhydra lutris nereis* Meriam, with moderate to severe toxoplasmic encephalitis, have been observed to be 3.7 times more likely to be attacked by sharks than their *T. gondii*-uninfected counterparts (Miller et al. 2004).

Our own research examined Dopey Fox Syndrome, a recently characterised presentation of clinical neurological signs in red foxes (*Vulpes vulpes* Linnaeus), for which a causative agent had not yet been identified. Such wild foxes have been reported to exhibit abnormal behavioural traits, ranging from the relatively subtle, including apparent lack of fear, increased affection and potentially increased interaction with and injuries from domestic cats, to the more pathological including constant pacing, facial muscle twitching and ocular abnormalities or blindness.

Given the *T. gondii* is prevalent amongst wild fox populations and given their long lifespans (relative to rodents), they acquire 'trickle' infections which may be more akin to human *T. gondii* exposure, we felt that *V. vulpes* may provide a key opportunity to further understand the impact of *T. gondii* (and co-infecting neurotropic pathogens) on behaviour beyond intermediate host species. In partnership with local fox rescue centres, a modified, epidemiological and ethically appropriate form of the Fatal Feline Attraction behavioural assay was performed within large outdoor enclosures, where infected foxes were indeed found to show a near-significant trend towards time spent within areas with cat (but not dog) urine (Milne et al. 2020a).

Furthermore, we also observed a significantly higher prevalence of both *T. gondii* (in combination with a recently identified Circovirus) amongst those foxes with the most severe behavioural abnormalities, requiring them to be maintained within the sanctuary environments, relative to those free-ranging foxes without apparent behavioural pathologies (Milne et al. 2020a).

Given the encouraging results from our 'Dopey Fox' study, we then tried to expand further and test the potential evidence of a Fatal Feline Attraction association amongst *T. gondii*-infected large herbivores and big cats across the plains of Botswana. Encouragingly, working with colleagues at my new research home of the Royal Veterinary College, we did find a very high proportion of wildlife to be seropositive – across the potential intermediate hosts of zebras, wildebeest, tsessebes, to the scavengers of the spotted hyenas, and most excitingly of all, a near 100% seroprevalence across the lion and cheetah big cats definitive hosts (J.P. Webster and A. Wilson, unpublished data).

Our aim was thus to examine behavioural changes in these infected large herbivore intermediate hosts that may make them more susceptible to big cat predation, such as increased activity or risk-taking behaviours aways from their herds. Alas, the importance of the herd effect dampening out the individual, combined with limited and misbehaving radio tracking collars, put paid to these plans, at least for now.

Of course, humans are animals too, and *T. gondii* is also highly prevalent amongst human populations, and as discussed in detail in this volume (Torrey 2024, Flegr 2025), we may predict and do indeed observe similar behavioural changes from subtle to severe amongst *T. gondii*-infected humans relative to their uninfected counterparts.

Toxoplasma gondii in rodents as a model for human schizophrenia

With increasing pressure to understand transmissible agents, renewed recognition of infectious causation of both acute and chronic diseases is occurring, and the 21st century has seen a proliferation of studies and meta-analyses examining the potential associations between *T. gondii* infection and a wide variety of cognitive and neuropsychiatric disorders in humans. These include, for example, Alzheimer's disease, bipolar disorder, epilepsy and obsessive-compulsive disorder (Torrey 2024). However, whilst the strength of evidence for some of these disorders is variable and/or questionable (Milne et al. 2020b), such studies and meta-analyses have repeatedly demonstrated consistent and continued support for a link between *T. gondii* and schizophrenia (see also Torrey 2024, Flegr 2025) this issue).

Indeed, the first studies describing potential associations between latent *T. gondii* infection and human neuropsychiatric disorders, specifically that of schizophrenia, were published in the 1950s, even before the parasite life cycle was completely understood. Two beautiful publications that particularly sparked our interest here in terms of our own research avenues were: firstly the observation that *T. gondii* antibodies of schizophrenia patients treated with antipsychotic drugs were intermediate between those of patients never treated and those of control groups, with a significant further reduction in those patients undergoing current drug treatment, suggesting that antipsychotic treatment may affect *T. gondii* levels (Leweke et al. 2004); and secondly, that this theory was supported by the observation that many antipsychotic drugs commonly used in the treatment of schizophrenia were demonstrated to inhibit the replication of *T. gondii* tachyzoites in cell culture (Jones-Brando et al. 2003). One could therefore suspect that the antipsychotic and mood stabilising activity of some medications may be achieved, or at least augmented, through their inhibition of *T. gondii* replication and invasion in infected individuals.

Accordingly, this hypothesis was tested *in vivo* (Webster et al. 2006). In particular we predicted, again using our epidemiologically and clinically applicable 'Fatal Feline Attraction' protocol, that haloperidol, an antipsychotic used in the treatment of mental illnesses including schizophrenia and/or valproic acid, a mood stabiliser used in the treatment of mental illnesses including schizophrenia, both of which showed the strongest *in vitro* anti-tachyzoite properties (Jones-Brando et al. 2003), would be, at least, as effective in preventing the development of *T. gondii*-associated behavioural and cognitive alterations as the standard anti-*T. gondii* chemotherapeutics pyrimethamine with dapsone.

To again keep our studies as minimally stressful to our rats as possible, all drugs or placebo controls were given contained within fruit-flavoured jelly cubes (our rats liked blackcurrant flavour best of all), to which the rats had been previously habituated to eat daily. Accordingly we observed that, whilst *T. gondii* again appeared to alter the rats' perception of predation risk turning their innate aversion into a 'suicidal' feline attraction, the anti-psychotic drugs indeed proved at least as efficient, actually more so, than anti-*T. gondii* drugs in preventing such behavioural alterations (Webster et al. 2006).

Clues as to mechanisms of action

Such findings led us directly to ask how? What are the mechanism of action behind how this unicellular parasite can alter, indeed specifically and selectively manipulate host behaviour? (Webster and McConkey 2010, Webster et al. 2013). It was plausible that each of the drug treatments may function by directly minimising *T. gondii* replication and invasion of host brain cells, consistent with the tachyzoite inhibition demonstrated *in vitro* (Jones-Brando et al. 2003). Indeed both the number of *T. gondii* cysts, and more importantly the location of these cysts – with areas such as the amygdala and accumbens being feasibly proposed as ideal areas for which this parasite achieves such manipulation, given in their key roles in behaviour, reward and motivation – have been repeatedly proposed, albeit with inconsistent findings between studies (McConkey et al. 2013).

Another, not mutually exclusive, explanation for the effects of *T. gondii* and drug treatment on feline avoidance behaviour relates to their potentially neuromodulatory impact, either directly or indirectly (Kaushik et al. 2012). Indeed, the drug which had the greatest impact in preventing the development of these behavioural alterations in the rats was haloperidol, a drug whose mode of action is believed to involve acting as a dopamine D2 antagonist. Dopamine has repeatedly been proposed as one of the 'missing links' in elucidation of the potential association between schizophrenia and toxoplasmosis (Flegr et al. 2003), particularly since both disorders are characterised by raised levels of this neurotransmitter (Stibbs 1985, Torrey et al. 2000, Torrey and Yolken 2003, Torrey 2024, Flegr 2025 – this issue). Stibbs (1985) first reported that dopamine levels were elevated by 14% in mice chronically infected with *T. gondii* (Stibbs 1985), which has been subsequently documented in more recent studies (Mirzaeipour et al. 2021, Omidianet al. 2022).

The story became even more interesting when it was discovered that *T. gondii* may even be able to produce its own dopamine to achieve such manipulation, rather than relying only on changes to host-produced dopamine. Dopamine is synthesised in two steps from its precursor amino acid tyrosine: tyrosine hydroxylase metabolism to produce L-DOPA and decarboxylation of L-DOPA by aromatic L-amino acid decarboxylase to dopamine. In some cells, dopamine is further metabolised to norepinephrine by dopamine beta-hydroxylase. Colleagues at Leeds University found that *T. gondii* encodes a protein with high

homology and showing similar catalytic properties to the tyrosine hydroxylases found in mammals – *TgTH* encoded by *TgAaaH1* and *TgAaaH2* (*T. gondii* aromatic amino acid hydroxylase), and that this *T. gondii* ortholog synthesises L-DOPA, the precursor to dopamine, as well as tyrosine (Gaskell et al. 2009).

Accordingly, working together we subsequently found that high concentrations of both *TgTH* and dopamine were detected in *T. gondii* cysts in the brain, and that infected dopaminergic cells released 350% more dopamine than uninfected cells (Prandovszky et al. 2011). However, the role of *T. gondii*-produced *TgTH* in the dopamine-dependent pathway remains controversial. Subsequent gene deletion and overexpression experiments in laboratory mice by another group indicated that the expression level of *TgAaaH2* did not affect the brain dopamine contents in *T. gondii*-infected mice, nor did the dopamine contents released by cultured dopaminergic cells (PC12) differ depending on infection with wildtype, *TgAaaH2*-knockout or *TgAaaH2*-overexpressing strains *in vitro* (Wang et al. 2015). Similarly, other laboratory mouse studies suggested that *TgAaaH2* may not be required to induce dopamine-dependent behavioural changes (Afonso et al. 2017, McFarland et al. 2018). Nevertheless, our own (currently unpublished) *TgTH* gene-overexpressing experiments in the more biologically and clinically-appropriate rat model (Hrdá et al. 2000, Webster et al. 2013, 2015), and using our more subtle and specific behavioural assays of the Fatal Feline Attraction, even when taken into the laboratory to enable automated behavioural tracking overhead equipment (Fig. 3) (Kaushik et al. 2012, Webster et al. 2013), research suggests it is perhaps too early to disregard the role of parasite-produced dopamine in such behavioural changes.

Furthermore, our examinations and meta-analyses of across the published literature, as well as our own behavioural study's findings, suggest that it is likely that a number of mechanistic pathways, including endocrine and neurotransmitter dysregulation (see also Vyas 2024) and the pro-inflammatory immune response to infection, including interactions between pathways as well as potentially trans-generational epigenetic changes, that are actually likely to act in parallel to explain the range of behavioural changes associated with *T. gondii* infection (Kaushik et al. 2012, Webster et al. 2013, Milne et al. 2020b).

Next steps

The last twenty years of my career has very much been dominated by disease control and research activities of another major parasite of humans and animals, that of the *Schistosoma* spp., but my fascination of *T. gondii* and its impact upon host behaviour very much remains. One reason of course is that it touches on core philosophical issues such as the existence of free will – how much of the behaviour displayed, be that of the rat or human host, is under control of that organism and how much instead by this amazing parasite within its both immunologically and mechanistically privileged site of the host brain.

Whilst the current work of my research group and I have tended to veer away from rodent behavioural studies, one area we are looking into relates to the potential implications and applications of reported temporal decreases in *T. gondii* seroprevalence across human populations (see also Flegr 2025), and how this may impact congenital toxoplasmosis and the range of overt or covert morbidities associated with this (Milne et al. 2023).

We have also long been intrigued by why some individuals, be it human or animal, appear to develop more severe behavioural morbidities whilst others remain minimal, and how this could be related to either differential strains of *T. gondii* circulating, or indeed the consequences of differential routes of infection (Webster et al. 2017) – warranting the need for improved and discriminatory diagnostic tools (Milne et al. 2020c).

I have no doubt that further research will reveal that the occult effects of latent *T. gondii* infection likely outweigh the recognised overt morbidity caused by toxoplasmosis, substantially raising the public and one health importance of this parasite – and if we are very fortunate, in the not-too-distant future we may even further understand its undeniably sophisticated mode or modes of action. Only when we have the awareness, the tools and a fuller appreciation of this major parasite will we ever hope to develop better preventative or potentially curative treatments against it.

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