Effect of *Toxoplasma gondii* upon neophobic behaviour in wild brown rats, *Rattus norvegicus*

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SUMMARY

The effect of *Toxoplasma gondii* on neophobic behaviour (the avoidance of novel stimuli) was assessed in four groups of wild rats with naturally occurring *Toxoplasma* infection. Two groups were placed in individual cages and tested in a series of experiments which examined the effect of *Toxoplasma* on the rat's reaction to 3 food-related novel stimuli (odour, food-container, food). A trappability study was performed on the other two groups to test whether *Toxoplasma* had an effect on probability of capture. The results show that low neophobia was significantly associated with positive *Toxoplasma* titres in 3 out of 4 groups. We suggest that differences between infected and uninfected wild rats arise from pathological changes caused by *Toxoplasma* cysts in the brains of infected rats. Such behavioural changes may be selectively advantageous for the parasite as they may render *Toxoplasma*-infected rats more susceptible to predation by domestic cats (the definitive host of *Toxoplasma*) and, as a side-effect, more susceptible to trapping and poisoning during pest control programmes.

Key words: host–parasite interactions, wild rats, *Toxoplasma gondii*, neophobic behaviour.

INTRODUCTION

Parasite-altered host behaviour has recently become the focus of particular attention, although there still remains a lack of studies on wild hosts. One parasite which has become of much interest in the laboratory is *Toxoplasma gondii*, the causal agent of toxoplamosis. *Toxoplasma* is an intracellular protozoan with world-wide distribution, of which the definitive host is the cat (Hutchinson *et al.* 1969). Chronic toxoplasmosis is characterized by the presence of resistant tissue cysts which can be found in virtually every organ, most commonly in the brain. Metabolic products from these cysts can cause inflammatory changes in the perivascular tissue of rodent brains and progressive deposition of necrotic material, which can lead ultimately to occlusion and subsequent sclerosis of cerebral blood vessels (e.g. Frenkel, 1972, 1974; Frenkel, Nelson & Arias-Stellas, 1975). Thus, despite the earlier consensus that *Toxoplasma* infection in rodents is asymptomatic (e.g. Beverley, 1976), more recent studies suggest that *Toxoplasma*-induced neural effects may interfere with normal CNS function and give rise to altered behaviour patterns (Werner, Masihi & Senk, 1981; Hay *et al.* 1983*a*). Laboratory studies have reported that *Toxoplasma*-infected laboratory mice are less responsive than uninfected controls to novel stimuli in a Y-maze or their home cage (Hutchison *et al.* 1980*a*, *b*, *c*; Hay *et al.* 1983*a*, *b*). These authors suggest that their results could reflect an impairment of recognition memory, that is, the ability to recognize, and thus discriminate between, novel stimuli and stimuli which have been encountered recently.

Wild rats (*Rattus norvegicus*, Berkenhout) are subject to intensive control and eradication regimes through poisoning and trapping (Barnett & Cowan, 1976; Berdoy & Smith, 1993) but are amongst the most neophobic mammals known (wild mice, in contrast, are neophilic; Meehan (1984)). This strong avoidance of novel stimuli is thought to be a significant impairment to the efficacy of eradication programmes (e.g. Barnett *et al.* 1975; Brunton, Macdonald & Buckle, 1993). The possible disruption of wild rats' discriminatory abilities by *Toxoplasma* infection could thus have profound consequences on their survival. However, although wild rats constitute a significant *Toxoplasma* reservoir for humans and domestic animals (Webster, 1994), the impact of *Toxoplasma* infection on their behaviour is unknown.

We tested the hypothesis that brown rats suffer from a diminished ability to discriminate novelty when infected with *Toxoplasma*. Our test of novelty detection was chosen for its naturalistic qualities, in contrast to the artificiality of laboratory experiments. In particular, we hypothesized that infection with *Toxoplasma* would affect (1) the rats' reactions to three food-related novel stimuli; odour, object and food, and (2) the propensity of rats to be captured in traps. Wild rather than laboratory rats were used because recent studies have revealed that laboratory rodent data, particularly neophobic behavioural data, cannot be generalized to that of wild rodents (rats:

Beck *et al.* 1988; Berdoy & Macdonald, 1991; mice: Gregory, Keymer & Clarke, 1990). Moreover, by using rats with naturally acquired *Toxoplasma* infection we avoided the possible artifacts arising from artificially induced inflammation and encephalitis caused by parasite inoculation (Hunter, Roberts & Alexander, 1992).

MATERIALS AND METHODS

Reaction to food-related novelty

Experimental studies on the effect of novelty on feeding were performed on two groups of 30 rats (referred to as C1 and C2) placed within individual cages. C1 rats were trapped from an enclosure population (see below), and C2 rats were trapped from three UK farmstead populations (1 Shrewsbury; 2 Oxfordshire). Each cage measured $1 \times 0{\cdot}5 \times 0{\cdot}5$ m and contained a wooden nest-box, two metal feeding bowls, and water *ad libitum*. The bowls were placed on each side of a wooden tray under plastic covers to protect them from the rain. Surgical gloves were worn when handling anything in the cages in order to minimize the rats' contact with human odour. Cages were arranged with alternative rows of males and females and placed within an outdoor enclosure.

Neophobia levels in each rat were assessed in a series of three experiments which tested the respective contributions of a novel smell, a novel food-container and a novel food to the neophobic response of each rat and an overall 'Neophobia Index' score was then calculated. Three experiments were necessary to determine whether a neophobic response was general or specific, since neophobia may vary depending upon the type of stimulus (Meehan, 1984), and to determine whether a neophobic response was transient or consistent (Hay *et al.* 1984).

Fifty grams of whole-wheat were placed in two metal feed bowls (referred to as familiar bowls) within each cage and the quantity consumed per rat per night was calculated by weighing the uneaten residue each day. This provided data on each rat's mean grain consumption (hoarding was minimal). During control and experimental periods, the positions of the food bowls within each pair were alternated nightly to control for any position preference. One familiar bowl always contained unmanipulated whole-wheat to allow the rats a choice of food. All grain was weighed and replenished each day.

Experiment 1: novel smell. The protocol described for control days was continued for 15 days except for two days (6 and 12) on which one food bowl was handled without surgical gloves in order to present a novel odour.

Experiment 2: novel bowl. After 5 control days (identical bowls and food), one familiar bowl was exchanged for a novel white plastic bowl. Daily consumption from each bowl was measured until all rats ate from the novel bowl (26 days).

Experiment 3: novel food. After 5 control days (identical bowls and food), the grain in one familiar bowl was replaced with wheat mixed with oil and blue dye. This novel bait is the base-bait used for the poison calciferol (Sorex, Ltd). This protocol was continued for 18 days.

Rats were then ranked according to the number of nights until their consumption of novel food (or at the novel bowl) was similar (at 95% confidence) to that of control nights. These latencies to normal feeding were categorized as: 0 days, < 5 days or $\geqslant 5$ days and were allocated an ordinal score of 0, 1 and 2. The results for each individual rat for these three novelty conditions were assumed to give an overall Neophobia Index score ranging from 0 to 6. For example, a rat allocated a rank of 2 in each of the three experiments would have a score of 6.

Reaction to traps

To test whether *Toxoplasma* affected the trappability of rats, a field study was performed on two groups of rats (referred to as T1 and T2) which examined the relationship between *Toxoplasma* infection and order of capture. Forty 'Bledorberry' live-traps were placed at each site in areas likely to be used by rats. Each trap was pre-baited with whole-wheat for 7 nights prior to 20–24 trap-nights at each site.

T1 was a rat population maintained under naturalistic conditions within a large (266 m^2) outdoor enclosure. These rats were descended from 5 surviving rats trapped from a Hampshire farm after an eradication treatment had been completed. The enclosure 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 (Berdoy, 1994). T2 rats were trapped from 6 farmsteads around Oxfordshire. *Toxoplasma* infection had been previously detected in each population at prevalences similar to that found in other UK farmstead wild rat populations (35% mean; Fisher's exact test, $P = 0{\cdot}54$; Webster (1994)).

An estimation of minimum rat population density at each site was obtained by census-baiting. This involved the provision of whole-wheat each night and measurement of the amount taken. Twenty-two bait trays were placed at each site immediately before and after trapping sessions in areas likely to be encountered by rats (bait trays were removed during trapping-sessions in an attempt to minimize alternative food sources). All bait trays were covered to prevent access to non-target animals and to protect them from rain. Population size was determined by dividing the total nightly grain uptake from bait

trays by the mean daily intake of individual adult wild rats, which is 10% of body weight (i.e. 28 g: Meehan (1984)).

Parasite load and body condition

Rats were either (a) killed with CO_2 and bled by cardiac puncture, or (b) anaesthetized with Metofane (C-Vet Ltd, Bury St Edmunds), weighed, sexed, individually marked (by ear punch), and (< 0·5 ml) blood was taken from the tail prior to release at point of capture (the second 30 T1 rats trapped were released, but recaptured rats were not included in data analysis). *Toxoplasma* antibodies (IgG) were determined by the indirect latex agglutination test (Toxoreagent, Eiken; Tsubota *et al.* (1977)) and confirmed by enzyme-linked immunosorbent assay (Voller, Bidwell & Bartlett, 1976). Titres of $\geqslant 1:16$ and $\geqslant 1:10$ respectively were considered positive (Jackson, Hutchison & Siim, 1986; Webster, 1994).

The body condition of rats was assessed to test whether behavioural differences between the infected and uninfected rats were dependent on general health. Rat weights, to the nearest gram, and head–body lengths, to the nearest 0·5 cm, were used to calculate a condition index based on the allometric relationship between body weight (W, g) and length (L, cm), i.e.

$$W = aL^n.$$

All data were used for linear regression of log W and log L to calculate mean values for a and n, which can then be used to predict expected W from L (Le Cren, 1951). Data from males and females were pooled as there was no significant sex difference in the estimation of W from L (males: $\log W = 2{\cdot}44 \log L - 0{\cdot}8$: $r^2 = 0{\cdot}87$; females: $\log W = 2{\cdot}45 \log L - 0{\cdot}8$ $r^2 = 0{\cdot}81$: $Z = 0{\cdot}16$, $P < 0{\cdot}05$). Body condition scores were calculated as the ratio of observed weight:expected weight, thus condition scores have a mean of 1.

SAS proc. GLM (SAS Inst. 1988) were used to test for interaction effects between rat groups, novelty experiments, neophobia indices, and parasite loads. Residual plots were inspected to check that deviations from normal errors were not extreme. For models involving binomial responses, logistic regression was applied using SAS proc. CATMOD.

Rat numbers used in the analysis of C1 and C2 populations were both less than 30 because insufficient blood for serological analysis was obtained from 8 (C1) and 5 (C2) individuals.

RESULTS

Reaction to food-related novelty

The sex ratio and weight distribution were matched between groups C1 and C2 (sex: $\chi^2 = 3{\cdot}3$, D.F. = 2, $P = 0{\cdot}19$; weight, mean (S.E.): C1 = 284·8 (6·5); C2 = 263 (18·6); Kruskal–Wallis: H = 2·03, D.F. = 2, $P = 0{\cdot}36$). The relationship between Neophobia Index and *Toxoplasma* infection was also matched between rat groups: there was no significant interaction term in a regression of proportion of *Toxoplasma* positives versus Neophobia Index and rat group (SAS proc. GLM, $F_{1,8} = 0{\cdot}07$, $P = 0{\cdot}80$). Data from the two groups could thus be pooled and the regression repeated (omitting the group interaction term).

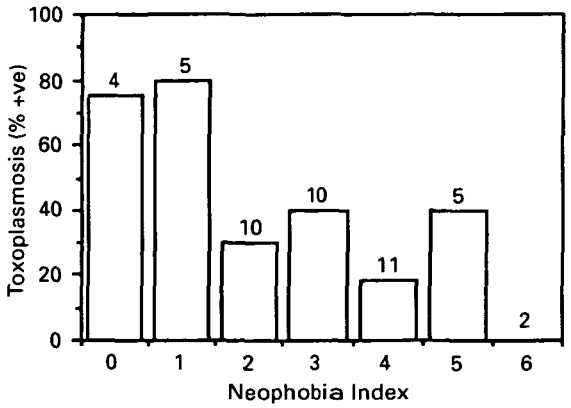

Fig. 1. Prevalence (%) of *Toxoplasma*-positive rats within each Neophobia Index category. The numbers above the columns represent the number of rats sampled within each Neophobia Index category. The proportion of *Toxoplasma*-positive titres declined significantly with the neophobia index score (SAS proc. GLM, $F_{1,46} = 5{\cdot}46$, $P = 0{\cdot}04$). □, % + ve toxoplasmosis (groups C1 and C2).

The proportion of rats with positive *Toxoplasma* titres declined significantly with the Neophobia Index score (GLM, $F_{1,46} = 5{\cdot}46$, $P = 0{\cdot}04$). Thus low neophobia scores were associated with positive *Toxoplasma* infection (Fig. 1). There were no significant differences in antibody titres between neophobia indices (Kruskal–Wallis: H = 8·62, D.F. = 6, $P = 0{\cdot}19$).

The relationship between *Toxoplasma* and neophobia did not differ significantly between each of the three novelty experiments performed (GLM, $F_{1,3} = 0{\cdot}32$, $P = 0{\cdot}74$). The overall proportion of *Toxoplasma*-positive rats declined significantly with the latency to normal feeding (GLM, $F_{1,7} = 10{\cdot}6$, $P = 0{\cdot}01$). Thus minimal or no neophobia toward food-related novelty was associated with positive *Toxoplasma* titres in all three tests.

Mean grain consumption per rat per night (calculated using values from unmanipulated individual feeding rates) did not differ between groups (Mann–Whitney U: $Z = -0{\cdot}86$, $P = 0{\cdot}38$), or between *Toxoplasma*-infected and uninfected individuals (Mann–Whitney U: $Z = -1{\cdot}52$, $P = 0{\cdot}12$). Similarly, there was no correlation between the mean quantity of grain eaten (either during experimental or control periods) and neophobia indices (Spearman's rho = −0·22, $n = 47$, $P = 0{\cdot}10$).

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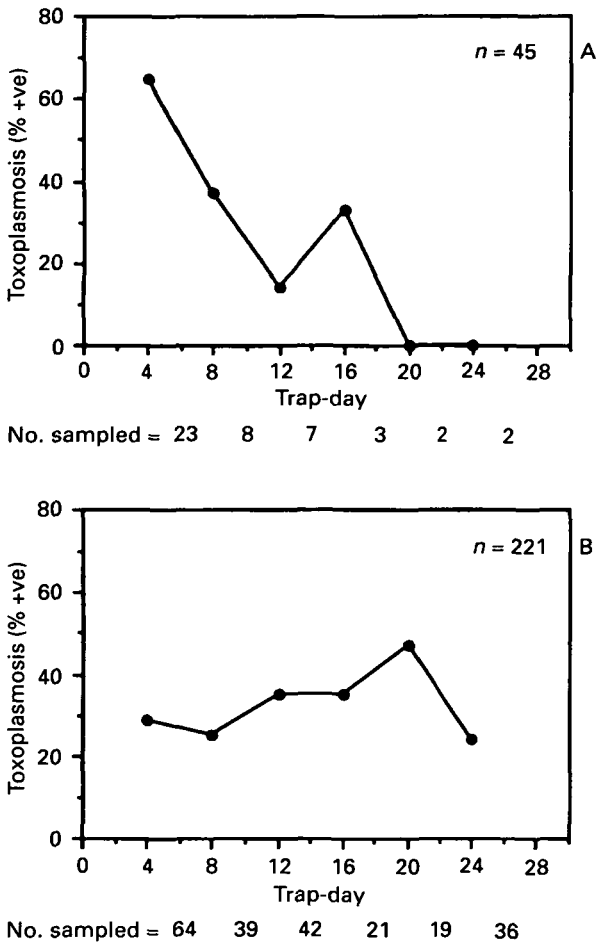

Fig. 2. Relationship between toxoplasmosis and trap-night within (A) T1 (enclosure) and (B) T2 (farmstead) wild rats.

Reaction to traps

T1 (enclosure rats) showed a clear relationship between trappability and *Toxoplasma* status, with infected rats being significantly trapped first (Fig. 2A). Census-bait data prior to trapping indicated that there were approximately 50 rats present within the T1 enclosure population. Approximately half of the population ($n = 23$ rats) were trapped within the first 4 days, whilst the remaining half ($n = 22$ rats) took up to 21 days to trap, with the few most neophobic rats being unable to be trapped at all. Fifteen of these first 23 rats trapped were infected (65% infected; trap-night average = 7·5), whereas only 5 of the 22 trapped over the subsequent 21 days were infected (22% infected; trap-night average = 1·4: $\chi^2 = 8{\cdot}22$, D.F. = 1, $P = 0{\cdot}004$).

T2 (farm rats) showed no relationship between trap night and *Toxoplasma* status (Fig. 2B). There was no evidence that either sex, weight, or age category influenced the relationship between proportion of *Toxoplasma*-positive rats and trap-day (ANCOVA on proportion of trapped rats versus trap-day, weighted by the number of rats trapped on each day: sex: $F_{1,27} = 1{\cdot}81$, $P = 0{\cdot}19$; weight: $F_{2,37} = 0{\cdot}02$, $P = 0{\cdot}97$; age category: $F_{2,35} = 0{\cdot}80$, $P = 0{\cdot}45$). However, there was a significant difference in the relationships between *Toxoplasma*-positive rats and trap-day between the six farm sites used to compose group T2 (ANCOVA, $F_{5,27} = 4{\cdot}11$, $P = 0{\cdot}006$), because one site showed a significant decline of *Toxoplasma*-positive rats over time (Spearman's rho = $-0{\cdot}52$, $n = 26$, $P < 0{\cdot}05$) similar to that found in the T1 enclosure population.

Census-bait daily grain consumption within the (T1) enclosure was significantly lower after trapping than before (Mann–Whitney U: $Z = -3$, $P = 0{\cdot}002$) but not significantly lower after trapping within (all but one of) the T2 farmsteads (Overall: Mann–Whitney U: $Z = -0{\cdot}21$, $P = 0{\cdot}88$, Table 1). This suggested that the majority of rats within the (T1) enclosure were trapped whereas only a small proportion of rats within (all but one of) the (T2) farmsteads were trapped. The one site within T2 that did show a significantly lowered census-bait mean after trapping (Mann–Whitney U: $Z = -3{\cdot}13$, $P = 0{\cdot}002$) was the same site that showed a similar distribution of infection pattern with trap night to that found in T1.

Body condition

There were no significant differences in body condition indices between groups C1 and C2 (Kruskal–Wallis: $H = 2{\cdot}67$, D.F. = 2, $P = 0{\cdot}26$), or between *Toxoplasma*-infected and uninfected individuals within groups C1 and C2 (Mann–Whitney U: $Z = -0{\cdot}94$, $P = 0{\cdot}35$). Similarly, there were no significant differences in rat condition indices between neophobia indices (Kruskal–Wallis: $H = 10{\cdot}01$, D.F. = 6, $P = 0{\cdot}12$).

DISCUSSION

Overall, wild brown rats with *Toxoplasma* infections were significantly less neophobic than uninfected rats. These findings are consistent with the laboratory mice studies (Hutchison *et al.* 1980*a*, *b*, *c*; Hay *et al.* 1983*a*, *b*), despite the contrasting feeding behaviour of the two species (rats are neophobic and mice neophilic).

Neophobia in food-related tests was affected by *Toxoplasma* in both populations (C1 and C2). However, trappability was correlated with positive *Toxoplasma* titres only in the small population of rats within the enclosure (T1). In this sense the aggregated results of the food-related trials appear to be a more sensitive measure of neophobia in wild rats. The absence of an effect of *Toxoplasma* on trappability of T2 (farmstead) rats may be due to differences in the sampling data between T1 and T2. As census-baiting indicated that the majority of rats within the T1 (enclosure) population were trapped, due to the lack of alternative food sources, the data provided an almost complete description of *Toxo-*

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Table 1. Mean nightly grain consumption (g) from census-bait boxes and estimated minimum population densities at each site before and after trapping

(Before and After refers to census-bait period relative to trapping session at each site. Values in parentheses are estimates of minimum rat population density at each site as derived from mean quantity of grain removed from bait boxes per night ($n = 7$ nights) divided by 28 g/rat (Meehan, 1984): see text for further details. *P* value refers to Mann–Whitney U test of difference between census-bait uptakes before and after trapping at each site, * represent a significant difference. F4 was the farmstead site within T2 which showed a similar relationship between *Toxoplasma*-positives and trappability to T1.)

Site	No. of rats trapped (*n*)	Quantity of grain consumed/night (g)		
		Before	After	*P*
T1 (enclosure)	45	1425 (51)	728 (26)	0·002*
T2 (farmsteads)				
Overall	221	999 (36)	860 (30)	0·886
F1	47	30 (1)	27 (1)	0·653
F2	5	506 (18)	544 (19)	0·055
F3	14	692 (25)	618 (22)	0·063
F4	38	894 (32)	396 (14)	0·002*
F5	34	1740 (62)	1454 (52)	0·177
F6	83	2132 (76)	2067 (74)	0·169

plasma-status and trap-night. In contrast, census-baiting indicated that trapping accounted for only a limited proportion of the rat populations within T2 (farmsteads). Indeed, the one site within T2 which did show a similar distribution pattern to T1 was the only one with minimal alternative food (and substantial reduction in bait census) and hence may also have provided a reasonably complete description of *Toxoplasma*-status and trap-night. Diminished trapping success is a well-known consequence of abundant alternative food on farms (e.g. Meehan, 1984).

The hypothesis that differences in neophobia between infected and uninfected wild rats are due primarily to pathological changes caused by the *Toxoplasma* parasite, is further supported by the exclusion of several alternatives. Our results showed, as did those of Hay *et al.* (1983*a*, *b*), that there was no relationship between the neophobic response, or *Toxoplasma* status, and the sex, weight, age, hunger (mean nightly grain consumption), or general body condition of individuals (see also Webster, 1994). Differences in neophobia between rats are also unlikely to be attributable to differences in time or state of *Toxoplasma* infection, or to prior behavioural differences which may have affected their susceptibility to infection, because rats in all populations presumably had either congenitally acquired infection (Webster, 1994) or endured endemic infection over several generations. All experimental rats were maintained within oocyst-free captive environments which would prevent any recent adult-acquired infections (Webster, 1994). Moreover, there were no significant differences in *Toxoplasma*-positive titres between neophobia indices, or across T1 and T2 populations.

Responsiveness, in particular to novelty, is obviously important in the avoidance of two major sources of mortality for farm rats, namely predation and poisoning. Diminished fear of scent, sound or sight of cats, for example, could impair the rat's survival and enhance the likelihood of the parasite reaching its feline definitive host. Thus, the behavioural traits which led the first 23 rats to be trapped before their companions from T1 could also have made them more likely victims of cats. Enhanced transmission to definitive host predation is a frequently cited selective consequence of parasite-induced host behaviour (see Moore & Gotelli, 1990), and indeed rats, like mice, constitute a significant part of the diet of cats (e.g. Fitzgerald & Karl, 1979). The diminished food-related neophobia amongst rats infected with *Toxoplasma*, however, also seems certain to make them more prone to poisoning. Standard poisoning procedures involve the addition of poison to a familiar bait (Meehan, 1984), and neophobia is invoked as a major impediment to successful rat control in some populations (e.g. Brunton *et al.* 1993). Any selective advantage to the parasite that might arise from increasing the rat's susceptibility to cat predation would not apply to the increased susceptibility to poison because even if narcotized rats were easily caught by cats, the parasite would be disadvantaged if the cats then succumbed to secondary poisoning. Although some species appear to have evolved 'host

suicide' in response to parasites which may be adaptive for host kin and increase their inclusive fitness (see Moore & Gotelli, 1990), it seems unlikely that this could explain our results because poisoning is a relatively recent addition to a rat's environment (Meehan, 1984). Thus we propose that diminished neophobia to novel food may be a side-effect of the parasite, the relevance of which to rat host survival will have only recently become important as comprehensive vermin control programmes have developed.

Our results also offer a testable explanation for the puzzling observation that prevalence of *Toxoplasma* in wild farm rats in the UK seldom rises above 35%, irrespective of rat population density, habitat-type, and exposure to cats (Webster, 1994). All the farms on which *Toxoplasma* prevalence has been measured were subject to regular rat control four times annually. We suggest that rat control generally kills a disproportionate number of individuals infected with *Toxoplasma*, and we thus predict a relationship between *Toxoplasma* prevalence and time elapsed since control. Our results indicate that *Toxoplasma* is yet one more of the suite of factors that might affect the 'behavioural resistance' of some farm rats to poisoning, and contribute to the individual differences in neophobia which characterize wild rats (Brunton *et al.* 1993).

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