REVIEW ARTICLE

Manipulation of host behaviour by *Toxoplasma gondii*: what is the minimum a proposed proximate mechanism should explain?

Ajai Vyas¹ and Robert Sapolsky²

¹ School of Biological Sciences, Nanyang Technological University, 60 Nanyang Drive, 637551 Singapore;

² Department of Biological Sciences and Departments of Neurology and Neurological Sciences and of Neurosurgery, Stanford University, Stanford, California 94305, USA

Abstract: The behavioural manipulation hypothesis posits that parasites can change the behaviour of hosts to increase the reproductive fitness of the parasite. The protozoan parasite *Toxoplasma gondii* fits this description well. Sexual reproduction occurs in the cat intestine, from which highly stable oocysts are excreted in faeces. Grazing animals, including rodents, can then ingest these oocysts. The parasite has evolved the capacity to abolish the innate fear that rodents have of the odours of cats, and to convert that fear into an attraction. This presumably increases the likelihood of the rodent being predated, thereby completing the parasite's life cycle. The behavioural syndrome produced by *T. gondii* does not have any precedent in neuroscience research. This is not a case where the normal functioning of fear system have been altered. This is not even the case of the altering of fear towards predator odours, while leaving other kinds of fear intact. This is an unprecedented example of one component of the fear being eliminated (and replaced by a novel attraction), while appearing to leave other domains unchanged. An understanding of the neurobiological effects of *T. gondii* is beginning to emerge. One possibility is *T. gondii*'s preferential localisation to, and effects within the amygdala; this is particularly intriguing, given the role of this brain structure in the normal fear response. Obviously, far more must be understood, and the unique behavioural effects of *T. gondii* put very demanding constraints on any hypothesis we formulate to explain proximate neurobiological mechanisms.

Keywords: *Toxoplasma*, rat, innate fear, behavioural manipulation, amygdala, dopamine

The protozoan parasite *Toxoplasma gondii* can invade the rat brain and remove deep-seated fears from a rat's psyche (Berdoy et al. 2000, Sapolsky 2003). Why? So that the parasite can hitch-hike a ride to cat intestines (when fearless rat is eaten by the cat) and reproduce there. In order to appreciate these effects, one must begin by considering the nature of parasitism. The core of parasitism is the ability of an organism to exploit its host, in order to obtain the benefit of shelter, transportation, food, or the facilitation of reproduction. According to the manipulation hypothesis, a parasite can alter the behaviour of a host for its own selective benefit, usually by enhancing its transmission rate (Thomas et al. 2005). The hypothesis requires that such behavioural modification has emerged as a result of a high degree of selection for the host manipulation rather than an accidental by-product of other physiological activities of the parasite.

Classic examples of specific manipulation of host behaviour concern transmission through the food chain. Many parasites show sequential parasitism, moving from an intermediate host(s) to a definitive one, in which they

reproduce. Often, the benefit derived from the intermediate host is that it facilitates access to the definitive one. The parasite thus manipulates the physiology of the intermediate host so as to ensure its transmission to the correct definitive host. For example, *Plasmodium* infection of humans make infected individuals more attractive to mosquitoes (Koella 2005, Lacroix et al. 2005), the definitive host for the parasite. As a flip side, *Plasmodium* alters stretch receptors in a mosquito's abdominal wall, compromising sensation of a full stomach and hence increasing biting and probability of transmission. Other examples involve increasing the likelihood of the intermediate host being predated by the definitive one. For example, the parasitic worm *Echinorhynchus truttae*, after infecting fish, increases their respiratory rate (MacNeil et al. 2003). This forces the fish towards the more heavily oxygenated water at the surface, increasing the likelihood of it being predated by a raptor, the definitive host.

All of these are cases in which behaviour is altered through parasitic actions outside the central nervous system. While few in number, there are fascinating examples

where a parasite manipulates host behaviour by acting upon the central nervous system. The best known is the effects of rabies infections in mammals (Sapolsky 2003). Through mechanisms that have been studied with remarkable infrequency, the rabies virus is able to alter the function of pathways related to aggression. The consequence, of course, is aggressiveness, where the increased likelihood of the infected animal biting another facilitates the transfer of virion shed in the saliva.

We now turn to an example central to this review, namely the manipulation of host behaviour by *Toxoplasma gondii*. This protozoan is an intracellular pathogen of mammals and birds. It is probably the most successful endoparasite in the mammalian world (Webster 2001) (depending on the country, 15–90% of humans contain this parasite). The sexual phase of its life cycle is restricted to the intestine of cats (Felidae), while the asexual phase can be maintained in virtually any endothermic vertebrate (Dubey 1998). The asexual phase involves rapid proliferation of tachyzoites (tachy = rapid) inside virtually all enucleated cells. Soon, the immune system is activated, and this triggers tachyzoites to differentiate into slow-dividing bradyzoites (brady = slow), preferentially in the brain (Dubey 1998, Webster 2001). This preferential localisation is probably the key to the behavioural manipulation. Tissue cysts containing bradyzoites are resistant to gastric juices and can initiate a next round of infection when eaten in raw meat. When a warm-blooded animal is eaten by cats, bradyzoites differentiate into sexually active gametes, zygotes and finally to oocysts in intestinal epithelium. These oocysts are shed with faeces, initiating a fresh round of infection (Dubey 1998).

Once bradyzoites are formed, infection is usually viewed as being clinically asymptomatic. Yet, a small but highly provocative literature suggests that *T. gondii* blocks the instinctual fear of cats in infected rodents (Berdoy et al. 2000, Vyas et al. 2007a, Webster 2007). Rodents have a fearful aversion to cat pheromones; this is seen even among laboratory bred rodents with no prior exposure to cats, demonstrating this to be a hard-wired behaviour. However, *T. gondii*-infected rats lose their aversion to cat pheromones and, in fact, show an attraction to the odour. One would presume that this behavioural alteration, when occurring in a naturalistic setting, would greatly increase the likelihood of rodents being predated by cats, thereby introducing *T. gondii* into its definitive host. Related to this, *T. gondii* infection in rodents causes them to become less neophobic and more willing to approach a novel object or odour (Webster 1994).

How specific are these effects?

The answer to this question is important for several reasons. Firstly, specificity can put important constraints on possible neurobiological mechanisms. Separate, but

closely related, neural systems mediate aspects of olfaction, emotions and escape behaviour. Thus, specificity of effects of *T. gondii*, or the lack of it, can implicate different brain systems. In its most pure definition, a behavioural manipulation is a change induced by the parasite for increasing its own reproductive fitness (Thomas et al. 2005). In practical situations though, behavioural manipulation is very difficult to differentiate from an accidental physiological changes, a “by-product” that happened to be ‘co-incidentally beneficial’ for the parasite (Poulin 1995). It is plausible that these physiological by-products of parasitism were recruited and refined by parasites to result in selective behavioural manipulation. In this evolutionary perspective, a very specific behavioural change means that it has emerged as a result of a high degree of selection for the host manipulation rather than accidental by-product of other physiological activities of the parasite. For example, if *T. gondii* induces a non-specific drive in rodents towards investigating odours of all sorts, the attraction towards cat odours would be considerably less interesting.

All this raises the issue of specificity, which can take a number of forms. The parasite can cause a general sickness behaviour in rodents; or it can cause a general decline in the ability to detect odours; or parasite can cause a specific change in emotional valence of the cat odour.

Are the behavioural effects of *Toxoplasma gondii* mere sickness behaviour?

The most parsimonious explanation will be that *T. gondii* makes its rodent host sick, thus reducing the rodent’s physiological ability to mount an effective defence response. In rodents, sickness behaviour manifests itself as reduced weight (because of high calorie consumption on top of usually high basal metabolism) and ruffled unkempt appearance of coat (reduced self-grooming). It is also likely that non-aversive memory tasks will be compromised if sickness is causing a general compromise in adaptive behaviours. Moreover, behaviours that are energetically expensive are likely to be compromised in a sick rodent. This includes maintaining social status and the ability to compete for mates. Both of these require appropriate function of the limbic system and also high energy expenditure that a sick animal is unlikely to spare.

A number of findings argue that *T. gondii* effects are not mere reflections of generic sickness. Rats infected with *T. gondii* do not lose weight, demonstrating comparable growth rates between control and infected animals (Vyas et al. 2007a). Moreover, none of the publications on this subject, including from our own group, indicates a disruption of self-grooming or appearance of unkempt coat (Berdoy et al. 1995, 2000, Webster et al. 2006, Vyas et al. 2007 a, b, Webster 2007). Additionally, we find that non-aversive learning, dependent on the hippocam-

pus and presumably important for survival, is not compromised (Vyas et al. 2007a). This is indicated by intact spatial learning of infected rats in a Morris water maze. It has been reported that infected mice take longer time to discern previously visited and unvisited arms in a radial arms maze (Hodková et al. 2007). This could suggest a deficit in spatial memory. An equally plausible explanation could be that infected mice have reduced awareness of the novelty in the environment. Finally, previous studies elegantly show that neither social status nor the ability to compete for mates is altered in infected rats (Berdoy et al. 1995), both behaviours that are typically impaired as a component of generic sickness behaviour.

Do the behavioural effects reflect a generalized compromise in olfaction?

A direct experimental observation of reduced fear of cats would require a comparison of predation rates between control and infected animals. Since this experiment would be ethically tenuous, behavioural tasks have mainly relied on cat odours as a source of aversive stimuli (Berdoy et al. 2000, Webster et al. 2006, Vyas et al. 2007 a, b). Then, it becomes imperative to ask if the effects of *T. gondii* on aversion to cat odour is merely an olfactory effect. In this version of non-specificity, infected rats do not fear cat odours because they cannot smell them. From the perspective of fitness, it will be sufficient for the parasite to block the perception of all odours, so that infected rats cannot smell an approaching cat. Yet, such an approach will have significant evolutionary cost for the parasite. It is possible that many of the infected rats would be predated by predator species in which *T. gondii* cannot reproduce. Predation of infected animals by non-host predators thus represents a probabilistic cost for the parasite (Poulin et al. 2005).

Several experiments suggest that effects of *T. gondii* on aversion to cat odour is not merely an olfactory effect. A) Infected mice retain an aversion to food with a novel odour and are capable of learning from olfactory cues provided by their social group (Vyas et al. 2007a). B) Loss of fear in infected animals is restricted to odours of the definitive host, the cat. Infected rats retain the aversion to odours of predators that do not serve as definitive host of *T. gondii*, like mink (Lamberton et al. 2008). C) The response of infected rats to cat odour is linked to the dose of cat odour in a subtle and non-monotonic way (Vyas et al. 2007b). Infected animals do not differ from control animals when cat odour is presented in very high or very low ranges of concentration; instead, the behavioural manipulation is restricted to middle ranges of cat odour strength. D) Lastly, and perhaps most importantly, *T. gondii* does not merely cause the selective destruction of a behaviour (i.e., the loss of aversion) but, instead, creates a new behaviour (i.e., the gain of what was termed a “fatal attrac-

tion” to the pheromones; Berdoy et al. 2000). These observations collectively suggest that the effects of *T. gondii* infection are not due to mere impairment of olfaction. Instead, the effects of infection rather reflect a specific change in defensive and mnemonic behaviours.

Do the behavioural effects then reflect a generalized disruption of defensive behaviours?

Can the behavioural effects of *T. gondii* then be explained by a generic disruption of defensive behaviours? Looking from a neurobiological perspective, there are substantial reasons to predict that this is the case. Several investigators have done brilliant work in deciphering the neural circuits of innate fear to cat odours (Canteras et al. 1997, Dielenberg et al. 2001, Dielenberg and McGregor 2001, Adamec et al. 2005, Blanchard et al. 2005, Staples et al. 2008). The circuitry detailed by these extensive experiments consists of two forebrain pathways impinging on the medial hypothalamic zone. Many stations of this circuit either overlap or run parallel to brain regions important for other aspects of defensive behaviours such as anxiety or learned fear. Since neural architecture seems to be shared between these different aspects of defensive behaviours, it is logical to assume that any manipulation of innate fear to cat odour will also affect anxiety and learned fear. Interestingly, the effects of *T. gondii* run counter to this simple neurobiological assumption. Infected rats retain the ability to form learned association between a foot-shock and sound tone (Vyas et al. 2007a). This demonstrates that they retain the ability to learn and express novel fears. Similarly, infected and control rats exhibit a comparable tendency to avoid venturing out in open lighted spaces, traditionally thought to be anxiogenic (i.e. producing anxiety) (Vyas et al. 2007a). Thus, infection does not alter anxiety. Infected mice retain the ability to learn aversion to unfamiliar food (Vyas et al. 2007a). And very importantly, as described earlier, infected animals even retain the aversion to odours from predators that eat rats but do not serve as the definitive host of the parasite (Lamberton et al. 2008).

While infected rats show a deficit in conditioned fear when foot shock is used an unconditioned stimulus, *T. gondii* affects learned fear expressed after conditioning to the cat odour (Vyas et al. 2007b). In uninfected rodents, exposure to cat odour causes acquired changes in the behaviour related to learning. For example, when rats are exposed to a worn cat collar in a test situation, they subsequently show avoidance in the same situation when presented with an unworn cat collar that is free of cat odour. This shows that rats have been conditioned to the test situation; in other words, animals demonstrate learned fear to a stimulus merely because of its historical association with cat odour and not because of actual odour present. *T. gondii* infection not only reduces aver-

sion to cat odours, but also blunts learning driven by the cat odour. Since effects on learning are not dependent on the physical presence of odour during the testing, it can be argued that the effects of *T. gondii* are not merely dependent on sensory perception of the odour or arising out of generic malaise.

Despite these examples of anxiety and conditioned fear being maintained in *T. gondii*-infected rats, the parasite does have some effects in this area. Indeed, a report indicates that *T. gondii* reduces anxiety in rats when tested with an exploration-based anxiety test, but not when a social interaction-based anxiety test is used (Gonzalez et al. 2007); this distinction is certainly consonant with *T. gondii*'s effects on the response to cat odours, in that increased exploration on the part of an infected rat would increase the likelihood of *T. gondii* completing its life cycle, whereas increased amounts of social interactions with other rats would not. Similarly, absence of effects in one learned fear task does not necessarily indicate that infection effects will not be discerned in other tests or if a different training sequence is used. Given the endless permutation and combinations in design of experiments, it is very difficult to provide an evidence of absence.

These observations collectively suggest that the behavioural effects of *T. gondii* infection are very specific. It is likely that mechanisms of behavioural change have been shaped by intense selection pressure on the parasite, and are likely to be equally specific. The specificity is likely to put important constraint on possible neurobiological mechanisms.

What are the proximate mechanisms?

There are practical incentives for us to understand them. Several animal models of psychiatric condition use innate fear to cat odours as a paradigm (Dielenberg and McGregor 2001, Woodson et al. 2003, Adamec et al. 2005, 2009, Mitra et al. 2009). The promise of these animal models is based on the fact that innate fear provides a hard-wired, instinctual, and ethologically relevant paradigm to dissect fear pathways of the brain. This points to an evolutionarily ancient realm of emotions, etched into the brain because of intense selection pressure. These characteristics have resulted in some excellent investigations into neural and hormonal underpinnings of the innate fear, including pathways of the brain, sub-types of neurotransmitter and hormone receptors, interaction between hormones and neurons and so on. Yet, metaphorically speaking, *T. gondii* has 'known' all along what specific neurons in which specific brain regions to target for a selective knock-out of one particular innate fear. Important to study of fear as these animal models are, selective perturbation by *T. gondii* provides an unmatched opportunity to understand mechanisms involved (Sapolsky 2003). It raises the possibility that, at some level of analysis, neural substrates of innate aversion to felines can be completely

dissociated from substrates of other aspects of fear and defensive reactions. In other words, it points to a set of neural mechanisms or substrates that is dedicated only to the processing of cat odours.

The majority of brain cells are comprised of either neurons or glia. Traditionally, glial cells are thought to play a supporting and nourishing role for electrically active neurons. *In vitro* and *in vivo* studies show that *T. gondii* invades glial cells with greater frequency than neurons (Peterson et al. 1993, Halonen et al. 1996, Gonzalez et al. 2007). Cysts containing *T. gondii* are distributed in a wide variety of brain regions, including areas important for olfaction, emotions, learning and hormone secretion (Gonzalez et al. 2007, Vyas et al. 2007a). Hence a very selective tropism on the part of the parasite is not indicated. However, the cysts are observed to occur more frequently in limbic structures like the amygdala and nucleus accumbens (Gonzalez et al. 2007, Vyas et al. 2007a), structures that play pivotal roles in modulating emotional processes. The role of the amygdala in mediating defensive behaviours has been very intensely studied. The amygdala plays a crucial part in imparting emotional valence to environmental stimulus in a species-typical manner. For example, upon removal of the amygdala, monkeys lose their instinctual fear of snakes and indiscriminately "pick up a comb, a live snake or a piece of banana" (Kluver and Bucy 1938). For humans, the amygdala becomes active during processing of facial expressions (Adolphs 2008). Indeed, a recent study reports that development of learned fear in rat pups to an odour depends on an intact amygdala (Moriceau et al. 2006). Moreover, the presence of the mother during conditioning diminishes the amygdala activation, resulting in development of a net attraction rather than aversion to the odour (Moriceau et al. 2006). Given the importance of the amygdala in emotional processing, the presence or subtle tropism of parasites to the amygdala is exciting.

As indicated above, parasites are also known to be concentrated in the nucleus accumbens (Gonzalez et al. 2007). This brain structure is involved in processing of reward and pleasure (Carlezon and Thomas 2009). Natural rewards, like sex and food, enhance the concentration of the neurotransmitter dopamine in the nucleus accumbens (Pfaus 1999, Kelley 2004), and such increase plays a crucial role in mediating reward. In fact, a rat can be easily induced to self-administer drugs that increase dopamine in the nucleus accumbens (Hoebel et al. 1983, Carlezon et al. 1995), indicating that such dopamine provides for permissive valence of rewards. Given the role of the nucleus accumbens in processing of positive and permissive aspects of reward, the presence or subtle tropism of parasites to this structure is important.

On the other hand, a more parsimonious explanation will need to explain why other behaviours that depend on the amygdala and nucleus accumbens remain intact in

infected animals (Berdoy et al. 1995, Vyas et al. 2007a). Moreover, *T. gondii* is by no means absent from other brain regions, including those that are not involved in defensive behaviours or reward (Gonzalez et al. 2007, Vyas et al. 2007a).

Regardless of subtle tropism or not, it is unlikely that direct damage of the brain structures is involved in the behavioural change. Although encephalopathy and gross lesions have been observed in brains of immune-compromised hosts (Gagne 2001), these outcomes are rare in immune-competent animals. The possibility of direct physical damage is also mitigated by the fact that the cyst burden in infected rat brains is usually of only a modest degree (Freyre et al. 2003, Vyas et al. 2007a). The number of parasites in the brain is grossly outnumbered by the number of brain cells. It appears more plausible that as-yet-unknown neuroactive substances are secreted either from *T. gondii*-containing cysts or from infected host cells. Because of the smaller number of parasites compared to brain cells, the latter possibility seems more likely, thereby inducing the host to provide for the bulk of metabolic cost (Poulin et al. 2005, Thomas et al. 2005).

According to a recent report, *T. gondii* contains two genes that are homologues of important mammalian enzymes (Gaskell et al. 2009). Both of these genes can function as the mammalian enzyme tyrosine hydroxylase. Tyrosine hydroxylase is the rate-limiting enzyme in the synthesis of neurotransmitter dopamine. As we discussed in an earlier paragraph, dopamine plays a crucial role in mediating positive valence of rewarding environmental stimuli (Hoebel et al. 1983, Carlezon et al. 1995, Carlezon and Thomas 2009). Because *T. gondii* can potentially supply a rate-limiting enzyme in dopamine synthesis, it is possible that infected cells synthesize greater amounts of this key neurotransmitter. It is tempting to hypothesize that greater dopamine secretion by infected cells provide for a hyper-rewarding state in the brain and blunts the negative valence associated with cat odour. Indeed, an earlier report indicates greater availability of dopamine in infected mouse brains (Stibbs 1985). Work with human volunteers suggests that *T. gondii* infection affects personality traits known to be associated with dopamine (Flegr et al. 2003, Skallová et al. 2005). These reports provide an indirect evidence for role of dopamine in behavioural change after *T. gondii* infection. Moreover, treating infected rats with dopamine antagonist, haloperidol, diminishes behavioural effects of infection, suggesting a role of dopamine transmission in *T. gondii* effects (Webster et al. 2006). An alternative explanation has also been discussed regarding effects of dopamine antagonists. Haloperidol also inhibits the replication of *T. gondii* (Jones-Brando et al. 2003). It is thus plausible that effects of haloperidol are caused by both dopamine antagonism and inhibition of *T. gondii* replication.

Do we know sufficient about proximate mechanisms?

As is amply clear from the previous discussion, we do not yet know the precise mechanisms of behavioural change. What we have is an inventory of potential mechanisms. A few members of that inventory are, as discussed in previous paragraphs, subtle tropism and regulation of dopamine synthesis.

It can also be hypothesized that *T. gondii* can inactivate olfactory receptors important for cat odour detection. There is a multitude of olfactory neurons expressing specific receptors that innervates nasal epithelium in mammals (Touhara and Vosshall 2009). Each of the neurons expresses only one receptor, and respond to one specific ligand in the olfactory environment. Biologically relevant odours are believed to activate several such olfactory neurons, and activation of a combination of them gives rise to perception of an odour. It is possible that *T. gondii* can alter the function of olfactory neurons expressing specific receptors for the cat odour. However, we do not know which molecules in cat odour act as ligand for these receptors, nor whether there are even olfactory receptors that specialize in detection of cat odour (Dielenberg and McGregor 2001).

Another possibility could be that *T. gondii* causes changes in levels of circulating testosterone. A recent study reports that infected human males have greater concentration of testosterone than control volunteers (Flegr et al. 2008). It can be envisaged that higher concentration of testosterone causes animals to tone down defensive responses. This, again, is an untested possibility. Moreover, not all defensive behaviours are compromised by the *T. gondii* infection, and *T. gondii*'s behavioural effects are not restricted to males. Several other possibilities can be included in this inventory of potential mechanisms. These include alteration in emotional valence of cat odour, brain re-wiring and reduction of stress hormone secretion. These possibilities will need to be systematically tested in future studies

None of these possibilities completely explains the specificity of *T. gondii* effects. The remarkable specificity presents a great challenge when trying to map out proximate mechanisms. It raises the possibility that, at some level of analysis, neural substrates of aversion to cat odours can be completely dissociated from substrates of other defensive behaviours. In other words, it points to a neurobiological system that is dedicated only to processing of the cat odours, and that *T. gondii* influences such a hypothetical system. Moreover, it suggests that such influences represent a subtle, dose-dependent conversion of that innate fear to attraction, rather than a blunt ablation of fear. These requirements put very demanding constraints on any hypothesis we formulate to explain proximate mechanisms and will shape future work on this subject.

REFERENCES

- ADAMEC R., FOUGERE D., RISBROUGH V. 2009: CRF receptor blockade prevents initiation and consolidation of stress effects on affect in the predator stress model of PTSD. *Int. J. Neuropsychopharmacol.* (online ahead of print).
- ADAMEC R.E., BLUNDELL J., BURTON P. 2005: Neural circuit changes mediating lasting brain and behavioral response to predator stress. *Neurosci. Biobehav. Rev.* 29: 1225–1241.
- ADOLPHS R. 2008: Fear, faces, and the human amygdala. *Curr. Opin. Neurobiol.* 18: 166–172.
- BERDOY M., WEBSTER J.P., MACDONALD D.W. 1995: Parasite-altered behaviour: is the effect of *Toxoplasma gondii* on *Rattus norvegicus* specific? *Parasitology* 111: 403–409.
- BERDOY M., WEBSTER J.P., MACDONALD D.W. 2000: Fatal attraction in rats infected with *Toxoplasma gondii*. *Proc. R. Soc. Lond., Ser. B. Biol. Sci.*, 267: 1591–1594.
- BLANCHARD D.C., CANTERAS N.S., MARKHAM C.M., PENTKOWSKI N.S., BLANCHARD R.J. 2005: Lesions of structures showing FOS expression to cat presentation: effects on responsivity to a cat, cat odor, and nonpredator threat. *Neurosci. Biobehav. Rev.* 29: 1243–1253.
- CANTERAS N.S., CHIAVEGATTO S., VALLE L.E., SWANSON L.W. 1997: Severe reduction of rat defensive behavior to a predator by discrete hypothalamic chemical lesions. *Brain Res. Bull.* 44: 297–305.
- CARLEZON W.A., Jr., DEVINE D.P., WISE R.A. 1995: Habit-forming actions of nomifensine in nucleus accumbens. *Psychopharmacol.* 122: 194–197.
- CARLEZON W.A., Jr., THOMAS M.J. 2009: Biological substrates of reward and aversion: a nucleus accumbens activity hypothesis. *Neuropharmacology* 56 (Suppl. 1): 122–132.
- DIELENBERG R.A., HUNT G.E., MCGREGOR I.S. 2001: “When a rat smells a cat”: the distribution of Fos immunoreactivity in rat brain following exposure to a predatory odor. *Neuroscience* 104: 1085–1097.
- DIELENBERG R.A., MCGREGOR I.S. 2001: Defensive behavior in rats towards predatory odors: a review. *Neurosci. Biobehav. Rev.* 25: 597–609.
- DUBEY J.P. 1998: Advances in the life cycle of *Toxoplasma gondii*. *Int. J. Parasitol.* 28: 1019–1024.
- FLEGR J., LINDOVÁ J., KODYM P. 2008: Sex-dependent toxoplasmosis-associated differences in testosterone concentration in humans. *Parasitology* 135: 427–431.
- FLEGR J., PREISS M., KLOSE J., HAVLÍČEK J., VITÁKOVÁ M., KODYM P. 2003: Decreased level of psychobiological factor novelty seeking and lower intelligence in men latently infected with the protozoan parasite *Toxoplasma gondii*. Dopamine, a missing link between schizophrenia and toxoplasmosis? *Biol. Psychol.* 63: 253–268.
- FREYRE A., FALCON J., CORREA O., MENDEZ J., GONZALEZ M., VENZAL J.M., MORGANES D. 2003: Cyst burden in the brains of Wistar rats fed *Toxoplasma* oocysts. *Parasitol. Res.* 89: 342–344.
- GAGNE S.S. 2001: Toxoplasmosis. *Prim. Care Update OB/GYNS* 8: 122–126.
- GASKELL E.A., SMITH J.E., PINNEY J.W., WESTHEAD D.R., MCCONKEY G.A. 2009: A unique dual activity amino acid hydroxylase in *Toxoplasma gondii*. *PLoS ONE* 4: e4801.
- GONZALEZ L.E., ROJNIK B., URREA F., URDANETA H., PETROSINO P., COLASANTE C., PINO S., HERNANDEZ L. 2007: *Toxoplasma gondii* infection lower anxiety as measured in the plus-maze and social interaction tests in rats. A behavioral analysis. *Behav. Brain Res.* 177: 70–79.
- HALONEN S.K., LYMAN W.D., CHIU F.C. 1996: Growth and development of *Toxoplasma gondii* in human neurons and astrocytes. *J. Neuropathol. Exp. Neurol.* 55: 1150–1156.
- HODKOVÁ H., KODYM P., FLEGR J. 2007: Poorer results of mice with latent toxoplasmosis in learning tests: impaired learning processes or the novelty discrimination mechanism? *Parasitology* 134: 1329–1337.
- HOEBEL B.G., MONACO A.P., HERNANDEZ L., AULISI E.F., STANLEY B.G., LENARD L. 1983: Self-injection of amphetamine directly into the brain. *Psychopharmacology* 81: 158–163.
- JONES-BRANDO L., TORREY E.F., YOLKEN R. 2003: Drugs used in the treatment of schizophrenia and bipolar disorder inhibit the replication of *Toxoplasma gondii*. *Schizophr. Res.* 62: 237–244.
- KELLEY A.E. 2004: Ventral striatal control of appetitive motivation: role in ingestive behavior and reward-related learning. *Neurosci. Biobehav. Rev.* 27: 765–776.
- KLUVER H., BUCY P.C. 1938: An analysis of some effects of bilateral temporal lobectomy in the rhesus monkey with special reference to “psychic blindness”. *J. Psychol.* 5: 33–54.
- KOELLA J.C. 2005: Malaria as a manipulator. *Behav. Process.* 68: 271–273.
- LACROIX R., MUKABANA W.R., GOUAGNA L.C., KOELLA J.C. 2005: Malaria infection increases attractiveness of humans to mosquitoes. *PLoS Biol* 3: e298.
- LAMBERTON P.H.K., DONNELLY C.A., WEBSTER J.P. 2008: Specificity of the *Toxoplasma gondii*-altered behaviour to definitive versus non-definitive host predation risk. *Parasitology* 135: 1143–1150.
- MACNEIL C., FIELDING N.J., HUME K.D., DICK J.T., ELWOOD R.W., HATCHER M.J., DUNN A.M. 2003: Parasite altered micro-distribution of *Gammarus pulex* (Crustacea: Amphipoda). *Int. J. Parasitol.* 33: 57–64.
- MITRA R., ADAMEC R., SAPOLSKY R. 2009: Resilience against predator stress and dendritic morphology of amygdala neurons. *Behav. Brain Res.* 205: 535–543.
- MORICEAU S., WILSON D.A., LEVINE S., SULLIVAN R.M. 2006: Dual circuitry for odor-shock conditioning during infancy: corticosterone switches between fear and attraction via amygdala. *J. Neurosci.* 26: 6737–6748.
- PETERSON P.K., GEKKER G., HU S., CHAO C.C. 1993: Intracellular survival and multiplication of *Toxoplasma gondii* in astrocytes. *J. Infect. Dis.* 168: 1472–1478.
- PFAUS J.G. 1999: Neurobiology of sexual behavior. *Curr. Opin. Neurobiol.* 9: 751–758.
- POULIN R. 1995: “Adaptive” changes in the behaviour of parasitized animals: a critical review. *Int. J. Parasitol.* 25: 1371–1383.
- POULIN R., FREDENSBORG B.L., HANSEN E., LEUNG T.L. 2005: The true cost of host manipulation by parasites. *Behav. Process.* 68: 241–244.
- SAPOLSKY R. 2003: Bugs in the brain. *Sci. Am.* 288: 94–97.
- SKALLOVÁ A., NOVOTNÁ M., KOLBEKOVÁ P., GAŠOVÁ Z., VESELÝ V., SECHOVSKÁ M., FLEGR J. 2005: Decreased level of novelty seeking in blood donors infected with *Toxoplasma*. *Neuroendocrinol. Lett.* 26: 480–486.
- STAPLES L.G., MCGREGOR I.S., APFELBACH R., HUNT G.E. 2008: Cat odor, but not trimethylthiazoline (fox odor), activates accessory olfactory and defense-related brain regions in rats. *Neuroscience* 151: 937–947.
- STIBBS H.H. 1985: Changes in brain concentrations of catecholamines and indoleamines in *Toxoplasma gondii* infected mice. *Ann. Trop. Med. Parasitol.* 79: 153–157.

- THOMAS F., ADAMO S., MOORE J. 2005: Parasitic manipulation: where are we and where should we go? *Behav. Process.* 68: 185–199.
- TOUHARA K., VOSSHALL L.B. 2009: Sensing odorants and pheromones with chemosensory receptors. *Annu. Rev. Physiol.* 71: 307–332.
- VYAS A., KIM S.K., GIACOMINI N., BOOTHROYD J.C., SAPOLSKY R.M. 2007a: Behavioral changes induced by *Toxoplasma* infection of rodents are highly specific to aversion of cat odors. *Proc. Natl. Acad. Sci. U. S. A.* 104: 6442–6447.
- VYAS A., KIM S.K., SAPOLSKY R.M. 2007b: The effects of toxoplasma infection on rodent behavior are dependent on dose of the stimulus. *Neuroscience* 148: 342–348.
- WEBSTER J.P. 1994: The effect of *Toxoplasma gondii* and other parasites on activity levels in wild and hybrid *Rattus norvegicus*. *Parasitology* 109: 583–589.
- WEBSTER J.P. 2001: Rats, cats, people and parasites: the impact of latent toxoplasmosis on behaviour. *Microbes Infect.* 3: 1037–1045.
- WEBSTER J.P. 2007: The effect of *Toxoplasma gondii* on animal behavior: playing cat and mouse. *Schizophr. Bull.* 33: 752–756.
- WEBSTER J.P., LAMBERTON P.H., DONNELLY C.A., TORREY E.F. 2006: Parasites as causative agents of human affective disorders? The impact of anti-psychotic, mood-stabilizer and anti-parasite medication on *Toxoplasma gondii*'s ability to alter host behaviour. *Proc. R. Soc. Lond., Ser. B*, 273: 1023–1030.
- WOODSON J.C., MACINTOSH D., FLESHNER M., DIAMOND D.M. 2003: Emotion-induced amnesia in rats: working memory-specific impairment, corticosterone-memory correlation, and fear versus arousal effects on memory. *Learn. Mem.* 10: 326–336.

Received 2 January 2010

Accepted 19 March 2010