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Facultative virulence: A strategy to manipulate host behaviour?

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Abstract

Examples of behavioural manipulation by parasites are numerous, but the processes underlying these changes are not well characterized. From an evolutionary point of view, behavioural changes in infected hosts have often been interpreted as illustrations of the extended phenotype concept, in which genes in one organism (the parasite) have phenotypic effects on another organism (the host). Here, we approach the problem differently, suggesting that hosts, by cooperating with manipulative parasites rather than resisting them, might mitigate fitness costs associated with manipulation. By imposing extra fitness costs on their hosts in the absence of compliance, parasites theoretically have the potential to select for cooperative behaviour by their hosts. Although this 'mafia-like' strategy remains poorly documented, we believe that it has substantial potential to resolve issues specific to the evolution of behavioural alterations induced by parasites.

Keywords: Extended phenotype; Mafia-like strategy; Manipulation; Parasite; Virulence

Why do certain bird species accept cuckoo eggs and nestlings in their nest despite the dramatic cost such a behaviour has to their own fitness? From the relationship between the great spotted cuckoo (*Clamator glandarius*) and its magpie host (*Pica pica*), Soler et al. (1995) suggested a fascinating explanation: cuckoos force the bird host to tolerate non-self eggs by making the consequences of rejection more damaging than acceptance (Fig. 1, see also Zahavi, 1979). In this host–parasite system, the host can raise at least some of its own young along with those of the cuckoo. Soler et al. (1995) showed that ejector magpies suffered from considerably higher levels of nest predation by cuckoos than acceptors, i.e. the cuckoo retaliates, 'punishing' ejector hosts. As a result, the frequency of 'acceptor genes' is more likely to increase in the host population than 'rejector genes' are. Although conceptually appealing, there is currently no example other than cuckoo–magpie interactions to support such a mafia strategy among host–parasite systems. Thus, the relevance of this scenario among typical parasites invites exploration.

Parasite-induced alterations of host behavioural phenotypes have been reported in a wide range of protozoan and metazoan parasites (Combes, 1991; Poulin, 1998; Poulin and Thomas, 1999; Moore, 2002). Because these changes frequently increase the probability of infective stages encountering their next host, they are often thought to be the sophisticated products of parasite evolution aimed at host manipulation rather than accidental side effects (Barnard, 1990; Lafferty, 1999; Berdoy et al., 2000; Poulin, 1995). Despite the increasing evidence of such parasitic adaptations, underlying reasons as to why infected hosts capitulate and act in ways that benefit the parasite remain enigmatic in most cases. Although there is some evidence for parasite interference with host neuroendocrine signaling systems (Helluy and Holmes, 1990; De Jong-Brink, 1995; Adamo and Shoemaker, 2000; Overli et al., 2001; Helluy and Thomas, 2003), in the majority of cases, the mechanisms of behavioural change are unknown. The 'manipulation hypothesis' *sensu stricto* stipulates that host behaviour is simply 'under parasitic control', with no reference to mechanism.

In contrast, parasitized hosts are also known to engage in behavioural defenses. Self-medication, kin-selected suicide and changes in thermal preferences are only a few of many behavioural strategies that can benefit the parasitized host at the

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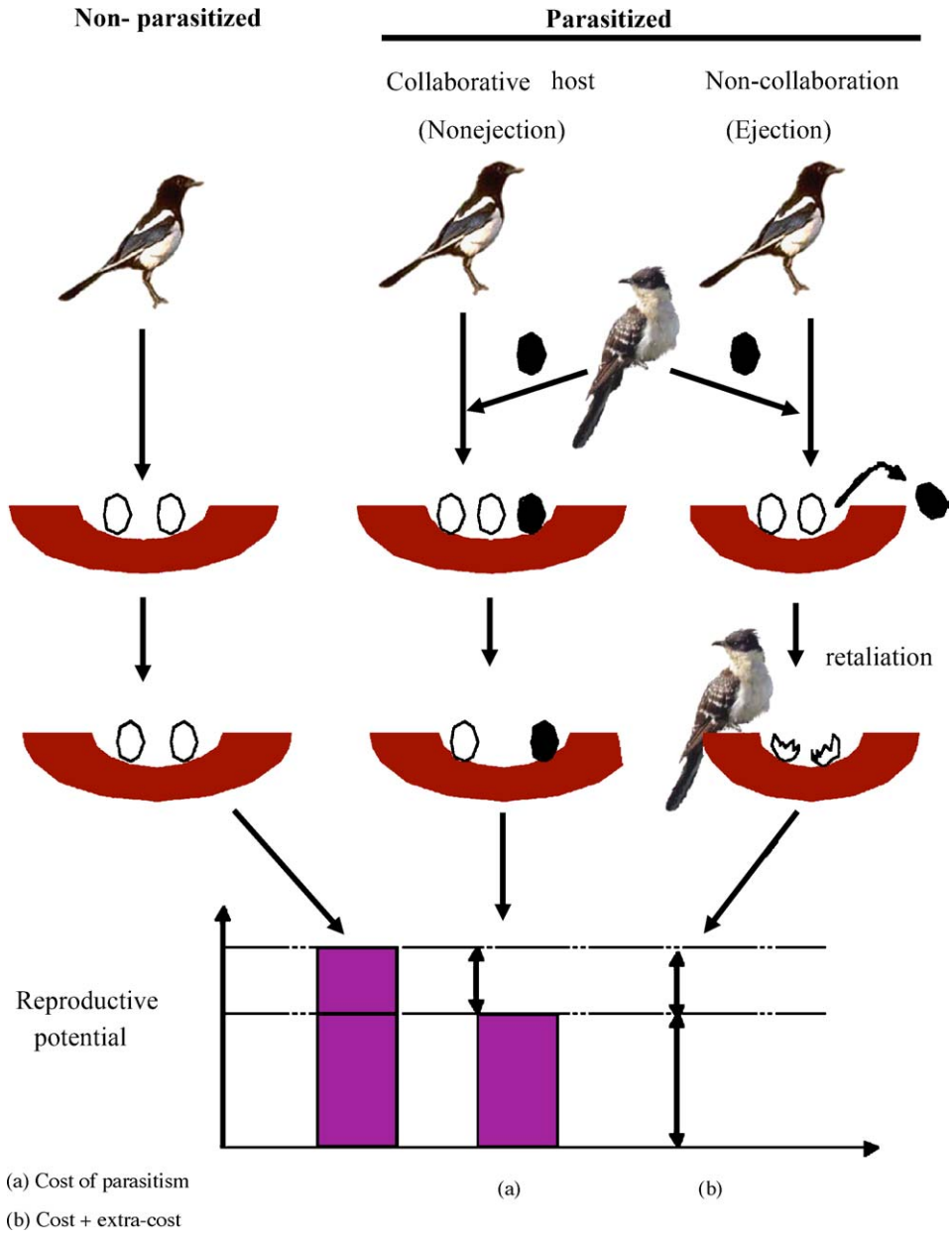

Fig. 1. Mafia behaviour in the cuckoo *Clamator glandarius* parasitizing the magpie host *Pica pica* (inspired from Soler et al., 1995).

expense of the parasite (Moore, 2002). Lost in this dichotomy of parasite manipulation and host defense is a third, seldom-explored, possibility: that hosts, by cooperating with manipulative parasites rather than resisting them, might mitigate fitness costs associated with that manipulation. In this scenario, the parasite might adjust its strategy of host exploitation (i.e. facultative virulence, with virulence referring here to the trade-off between host exploitation and successful parasite transmission) to the degree of compliance displayed by the host.

Why would the host be a compliant hostage? With few exceptions, parasitic manipulation dramatically reduces host fitness. However, if the host opposes manipulation and does not behave as 'expected' from the point of view of the parasite, parasites could phenotypically increase their virulence even more, thus making any non-cooperative behaviour even less profitable for the host. Thus, a 'mafia-like strategy' could in theory force the host to accede to manipulation in a large range of systems (Thomas et al., 2005; Wellnitz, 2005).

1. Host–parasite interactions and state-dependent models

For a mafia-type manipulation mechanism to evolve, both the host and the parasite must be able to adjust their life history decisions (considered here *sensu lato*) in a state-dependent manner. There is abundant evidence that free-living organisms are able to recognize fitness-related environmental cues, including parasitic infection, and to adjust their strategic decisions accordingly. For instance, once infected by a harmful parasite (i.e. killer or castrator), several host species have been shown to

change their physiology or their behaviour in a way that maximizes immediate reproductive effort (Minchella and Loverde, 1981; Polak and Starmer, 1998; Adamo, 1999; Agnew et al., 1999). Behavioural fevers or chills, certain cases of anorexia, grooming, self-medication, the use of natural disinfectants and repellents, and, in extreme case, adaptive 'suicide' in order to reduce risk of parasitic infection for kin (see Moore, 2002, for a synthesis) illustrate the large diversity of host responses that have evolved because they reduce the detrimental fitness consequences of infection. If hosts can recognize that they are parasitized and then change their behaviours in order to accommodate their own defensive actions, they should also be able to recognize that they are parasitized and behave in a cooperative fashion when warranted.

There are recent suggestions that parasites are also able to perceive a large set of environmental variables and to respond in a state-dependent manner thereby maximizing their lifetime reproductive success (Lewis et al., 2002; Davies et al., 2002; Pfenning, 2001). For instance, parasites are expected to recognize many physiological and biochemical conditions of their internal host environments that are of selective importance (e.g. age and sex of the host and presence or absence of other parasites). There are also good reasons to believe that parasites are able to perceive numerous cues about the external environment of their hosts (e.g. host population density and the presence of predators) by detecting changes that occur inside their hosts upon meeting conspecifics (sexual partners or competitors) or predators (Thomas et al., 2002). Poulin (2003) recently provided empirical evidence that the environmental perception of parasites can be much more sophisticated than traditionally thought: the trematode *Coitocaecum parvum* from New Zealand is able to accelerate its development and rapidly reach precocious maturity in its crustacean intermediate host in the absence of chemical cues emanating from its fish definitive host. Juvenile trematodes can also mature precociously when the mortality rate of their intermediate hosts is increased (Poulin, 2003). These results show that growth decisions and developmental strategies in this parasite are plastic, and conditional upon the opportunities for transmission evaluated by the parasite itself. More generally, these results suggest that parasites can exploit several sources of information in their immediate and external environment. In this manner, they may also be able to evaluate some of the behavioural phenotypes displayed by the host they are infecting (e.g. photophilia and hyperactivity), and they may be able to assess the extent to which the host is cooperative.

2. Mafia strategy

Hosts infected with debilitating parasites are under pressure to evolve not only ways of eliminating the parasites (host immunity in the broadest sense), but also ways of compensating for parasite effects when elimination is impossible. For instance, it has been theoretically (Hochberg et al., 1992) and empirically (Minchella and Loverde, 1981; Polak and Starmer, 1998; Adamo, 1999; Agnew et al., 1999) demonstrated that hosts unable to resist infection by other means (immunological resistance and/or inducible defences) are favoured by selection if they partly compensate for the parasite-induced losses by adjusting their life history traits (e.g. precocious reproduction). In the present context, we suggest that such hosts should also be favoured by selection if, by adopting particular phenotypes (e.g. altered behaviours), they can reduce the virulence of their parasite. Although these particular phenotype(s) may also considerably reduce the survival of the infected host (e.g. behavioural alterations induced by trophically transmitted parasites), they do not necessarily reduce host fitness in an equivalent fashion: a reduction in survival is not synonymous with a reduction in fitness. From an evolutionary point of view, the key parameter to consider is net fitness and not survival. In this way, a host that cooperates with the parasite, even to the point of displaying suicidal (manipulated) behaviour, could be favoured if it only had reduced fecundity compared to complete castration faced by an uncooperative host.

By imposing extra fitness costs in the absence of compliance, parasites have (in theory) the potential to select for cooperative behaviour in their hosts. Of course, such cooperative behaviours do not necessarily result from conscious choices or appreciation of the computational structure underlying the problem to be solved. Over time, selection is expected to produce population-specific phenotypic plasticity and to act on patterns of condition-dependent expression of behaviour, causing individuals to behave differently when infected. Moreover, in relatively long-lived hosts with sophisticated nervous systems (e.g. vertebrates), the infected host might learn how to behave in ways that limit extra-parasitic costs.

There are undoubtedly many host–parasite systems in which there is little opportunity for evolution of a mafia-type strategy of manipulation. For instance, numerous parasites induce behavioural changes in their hosts by impairing the functioning of particular organs, i.e. making the host 'handicapped'. Because in these cases, the link between parasite action (i.e. physical damages) and host behavioural change most likely is causal, there is a priori no need to invoke facultative virulence to understand why host behaviour was altered. Numerous parasites traditionally considered as manipulators probably fall within this category (e.g. parasites increasing host vulnerability to predators by encysting in eyes or in locomotor organs) (Combes, 1991, 1998; Moore, 2002). In the mafia-type strategy, the link between parasite presence and altered host behaviour is, by definition, indirect. The resultant virulence is expressed on a continuum ranging from minor to severe effects on the host, including castration, offspring destruction and/or reduction of its sexual attractiveness.

Even if the host has some fitness compensations when collaborating, conflicts might exist between host and parasite concerning the level of host compliance that is optimal for both partners. A priori, the more the host complies, the more parasite fitness is maximized. However, excessive levels of compliance are likely to be counter-selected in the host population. Imagine, for instance, a trophically transmitted parasite constraining (e.g. through facultative castration) its host to behave in a way that increases its risk of predation by definitive hosts. Hosts displaying very high levels of compliance (e.g. always behaving aberrantly) also experience a high risk of being eaten

before reproducing. Extreme cooperative behaviours are thus unlikely to be favoured by selection because individuals with such extreme responses are less likely to transmit their genes compared to individuals displaying intermediate levels of compliance. Even within intermediate ranges of compliance, conflict between the host and the parasite is likely to persist. From the host perspective, the optimal compliance level should be the lowest possible (i.e. the minimum required to avoid extra-parasitic costs), while from the parasite perspective, the optimal host compliance level is expected to be higher, until the point at which the benefits of complying become so small that compliance behaviours are not favoured by selection. Whether extra-parasitic costs are proportional to the host compliance level or respond to threshold values is a key parameter to understanding the evolutionary compromise involved in adjusting the behaviour of a host once it is infected. Further theoretical and empirical studies are needed to understand the nature of this compromise and which partner is primarily responsible for the level of compliance in such interactions.

3. Future directions

Few scientists have investigated host–parasite interactions for mafia-like manipulation (Soler et al., 1998). This paper explored an extension of the mafia hypothesis from brood parasites to parasites that manipulate their hosts. Several things are necessary for this to work. First, the behavioural change of the host must be plastic or under host control. Second, the level of virulence must be facultative for the parasite. Third, the level of behavioural change of the host must be detectable by the parasite. Fourth, compliance must have a net benefit for the host. Fifth, there must be an axis of virulence unrelated to transmission (e.g. castration) that the parasite uses as 'punishment' for non-compliance. At least all these conditions are needed for the hypothesis to evolve in a system.

One method of investigation would be to place infected hosts in situations of forced non-compliance, and to compare the fitness of these non-compliant hosts to that of hosts that are allowed to express parasite-induced behaviour. Knowing that manipulative costs, if they exist, should in theory be lower for parasites in cooperative hosts, we might even expect the transition from pure manipulation to mafia strategies of manipulation to be favoured by selection. We have here considered an up-regulation of virulence as a mean of invoking a mafia strategy. Conceivably, parasites could also retaliate via the release of toxins and/or by products as opposed to just host 'exploitation'. Similarly, we address mafia strategy from the parasite point of view. However, in certain situations, such as when the death of the host also results in (reproductive) death of the parasite, it may be the host that is imposing the mafia strategy on the parasite. Finally, we suggest that investigators begin to examine the fitness of compliant (and forcibly non-compliant) hosts when possible in order to distinguish between a cooperative host and a truly manipulated one.

Unfortunately, very few studies have investigated the fitness of manipulated hosts in natural conditions; indeed, very few studies have demonstrated enhanced transmission as a result of parasite-induced behavioural alterations. Moreover, although a theoretical consideration encourages one to contemplate the costs associated with manipulation, to date, such costs have rarely been measured. From an evolutionary point of view these considerations are relevant as they suggest that behavioural changes in infected hosts, even when they result in clear fitness benefit for the parasite, are not necessarily an illustration of the extended phenotype of the parasite alone (sensu Dawkins, 1982, i.e. parasite genes expressed in host phenotypes). They can be the direct product of natural selection acting on the host genome as well. Until recently, the ability of parasites to assess and respond to external stimuli has been greatly underestimated. The recognition of such ability opens the door to an increasingly sophisticated approach to the behavioural interactions of hosts and parasites. Research on the mafia strategy of manipulation has significant potential to resolve issues specific to the evolution of behavioural alterations induced by parasites, and the dynamic interaction of both parasites and hosts in the expression of such behaviour.

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References

Adamo, S.A., 1999. Evidence for adaptive changes in egg-laying in crickets exposed to bacteria and parasites. Anim. Behav. 57, 117–124.

Adamo, S.A., Shoemaker, K.L., 2000. Effects of parasitism on the octopamine content of the central nervous system of *Manduca sexta*: a possible mechanism underlying host behavioural change. Can. J. Zool. 78, 1580–1587.

Agnew, P., Bedhomme, S., Haussy, C., Michalakis, Y., 1999. Age and size at maturity of the mosquito *Culex pipiens* infected by the microsporidian parasite *Vavraia culicis*. Proc. R. Soc. Lond. B 266, 947–952.

Barnard, C.J., 1990. In: Barnard, C.J., Behnke, J.M. (Eds.), Parasitism and Host Behaviour. Taylor and Francis, London, UK, pp. 1–33.

Berdoy, M., Webster, J.P., Macdonald, D.W., 2000. Fatal attraction in rats infected with *Toxoplasma gondii*. Proc. R. Soc. Lond. B 267, 1591–1594.

Combes, C., 1991. Ethological aspect of parasite transmission. Am. Nat. 138, 866–880.

Combes, C., 1998. Parasitism, The Ecology and Evolution of Intimate Interactions. The University of Chicago Press, London.

Davies, C.M., Fairbrother, E., Webster, J.P., 2002. Mixed strain shistosome infections of snails and the evolution of parasite virulence. Parasitology 124, 31–38.

Dawkins, R., 1982. The Extended Phenotype. Oxford University Press, Oxford.

De Jong-Brink, M., 1995. How schistosomes profit from the stress responses they elicit in their hosts. Adv. Parasitol. 35, 177–256.

Helluy, S., Holmes, J.C., 1990. Serotonin, octopamine and the clinging behaviour induced by the parasite *Polymorphus paradoxus* (Acanthocephala) in *Gammarus lacustris* (Crustacea). Can. J. Zool. 68, 1214–1220.

Helluy, S., Thomas, F., 2003. Effects of *Microphallus papillorobustus* (Platyhelminthes: Trematoda) on serotonergic immunoreactivity and neuronal architecture in the brain of *Gammarus insensibilis* (Crustacea: Amphipoda). Proc. R. Soc. Lond. B 270, 563–568.

Hochberg, M.E., Michalakis, Y., de Meeüs, T., 1992. Parasitism as a constraint on the rate of life-history evolution. J. Evol. Biol. 5, 491–504.

Lewis, E.E., Campbell, J.F., Sukhdeo, M.V.K., 2002. Parasite behavioural ecology in a field of diverse perspectives. In: Lewis, E.E., Campbell, J.F., Sukhdeo, M.V.K. (Eds.), The Behavioural Ecology of Parasites. CAB International, New York, USA.

Lafferty, K.D., 1999. The evolution of trophic transmission. Parasitol. Today 15, 111–115.

Minchella, D.J., Loverde, P.T., 1981. A cost of increased early reproductive effort in the snail *Biomphalaria glabrata*. Am. Nat. 118, 876–881.

Moore, J., 2002. Parasites and the Behavior of Animals. Oxford University Press, New York, USA.

Overli, O., Pall, M., Borg, B., Jobling, M., Winberg, S., 2001. Effects of *Schistocephalus solidus* infection on brain monoaminergic activity in female three-spined sticklebacks *Gasterosteus aculeatus*. Proc. R. Soc. Lond. B 268, 1411–1415.

Pfenning, K.S., 2001. Evolution of pathogen virulence: the role of variation in host phenotype. Proc. R. Soc. London B 268, 755–760.

Polak, M., Starmer, W.T., 1998. Parasite-induced risk of mortality elevates reproductive effort in male *Drosophila*. Proc. R. Soc. Lond. B 265, 2197–2201.

Poulin, R., 1995. 'Adaptive' changes in the behaviour of parasitized animals: a critical review. Int. J. Parasitol. 25, 1371–1383.

Poulin, R., 1998. Evolutionary Ecology of Parasites: From Individuals to Communities. Chapman & Hall, London.

Poulin, R., 2003. Information about transmission opportunities triggers a life history switch in a parasite. Evolution 57, 2899–2903.

Poulin, R., Thomas, F., 1999. Phenotypic variability induced by parasites: extent and evolutionary implications. Parasitol. Today 15, 28–32.

Soler, M., Soler, J.J., Martinez, J.G., Møller, A.P., 1995. Magpie host manipulation by great spotted cuckoos: evidence for an avian mafia? Evolution 49, 770–775.

Soler, J.J., Møller, A.P., Soler, M., 1998. Mafia behaviour and the evolution of facultative virulence. J. Theor. Biol. 191, 267–277.

Thomas, F., Brown, S.P., Sukhdeo, M., Renaud, F., 2002. Understanding parasite strategies: a state-dependent approach? Trends Parasitol. 18, 387–390.

Thomas, F., Adamo, S., Moore, J., 2005. Parasitic manipulation: where are we and where should we go? Behav. Process 68, 185–199.

Wellnitz, T., 2005. Parasite-host conflicts: winners and losers or negotiated settlements? Behav. Process 68, 245–246.

Zahavi, A., 1979. Parasitism and nest predation in parasitic cuckoos. Am. Nat. 113, 157–159.