Infection, Genetics and Evolution xxx (2011) xxx–xxx

Contents lists available at ScienceDirect

Infection, Genetics and Evolution

journal homepage: www.elsevier.com/locate/meegid

Review

Intraspecific variability in host manipulation by parasites

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ARTICLE INFO

Article history:
Received 21 December 2010
Accepted 23 December 2010
Available online xxx

Keywords:
Coevolution
Genetic effect
Environmental effect
Local adaptation
Phenotypic plasticity
Acanthocephalans
Cestodes
Trematodes

ABSTRACT

Manipulative parasites have the capacity to alter a broad range of phenotypic traits in their hosts, extending from colour, morphology and behaviour. While significant attention has been devoted to describing the diversity of host manipulation among parasite clades, and testing the adaptive value of phenotypic traits that can be manipulated, there is increasing evidence that variation exists in the frequency and intensity of the changes displayed by parasitized individuals within single host-manipulative parasite systems. Such variability occurs within individuals, between individuals of a same population, and across populations. Here we review the non-genetic (i.e. environmental) and genetic causes of variability in host behaviour manipulation, discuss its evolutionary significance, and propose directions for further researches.

Contents

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doi:10.1016/j.meegid.2010.12.013

1. Introduction

Many parasitic organisms (e.g. virus, fungi, bacteria, protozoans, nematodes, nematomorphs, trematodes, cestodes, acanthocephalans and insect parasitoids) have developed the ability to manipulate the phenotype of their hosts to increase their own probability of transmission (Moore, 2002; Thomas et al., 2005; Lefèvre et al., 2009), or their own probability of survival within a given host (Brodeur and McNeil, 1992; Harvey et al., 2008). Phenotypic alterations displayed by parasitized hosts are extremely diversified, ranging from small changes in the frequency or duration of a given activity to the display of novel, and sometimes spectacular behaviours, physiologies and/or morphologies. Manipulative parasites are usually categorized by the type of phenotypic alterations displayed by the host. For example, a given trophically transmitted parasite species renders its intermediate host more vulnerable to predatory definitive hosts (e.g. crickets parasitized by hairworms jump into water). It is now increasingly recognized that within each host–parasite association, substantial variation exists in the frequency and intensity of the changes displayed by parasitized individuals, even within a single population (Bauer et al., 2000; Cézilly et al., 2000; Thomas et al., 2005; Poulin, 2010). Despite the increasing effort being invested in the study of host manipulation by parasites, few studies have explored the causes and outcomes of this intraspecific variability.

Classically, three main categories of factors (parasite-, host- and environmental factors) could *a priori* generate intraspecific variability in the traits associated with host manipulation by parasites (Fig. 1).

Distinction between genetic and non-genetic components of variation is important in host–parasite relationships. Individual parasites belonging to different populations are expected to differ in the way they exploit their hosts, because of local adaptation phenomena (reviewed in Lambrechts et al., 2006). Parasites are better adapted to the host with which they have coevolved (local host) than with hosts from foreign populations. The outcome of who is locally adapted to whom is influenced by several factors, one of the most important being the relative migration rate of hosts and parasites between populations (Gandon et al., 1996). This co-evolutionary scenario is based on genetic variation of traits under selection, for both hosts and parasites, which has been extensively studied for infectivity and virulence (Greischar and Koskella, 2007). However, an increasing number of studies reveal that variation due to environmental conditions could be more important than genetic variation (Wolinska and King, 2009), thereby hiding the co-evolving process, or at least creating geographic mosaics of local adaptations. Finally, a potentially significant part of intraspecific variation in host manipulation may also result from both the host and the parasite being able to maximise their lifetime reproductive success through adaptive state-dependent responses (i.e. strategic plasticity). Surprisingly, these aspects of host–parasite coevolution have received little attention for parasite-induced manipulation.

2. Evidence for genetically based variation in phenotypic alterations

2.1. The parasite point of view

The case of the New-Zealand trematode *Curtuteria australis* is among the best documented examples of genetically based variation in behavioural manipulation. Metacercariae of this parasite accumulate in the foot of the cockle *Austrovenus stutchburyi* (intermediate host) and heavily parasitized hosts lose their ability to burrow into the mud. This behavioural manipulation favours parasite transmission since manipulated cockles are on average 5–7 times more likely to be captured by oystercatchers (definitive host) than unparasitized buried cockles (Thomas and Poulin, 1998). Leung et al. (2010) found that some genotypes of *C. australis* have the tendency to encyst in the distal section of the cockle's foot, where their impairing effect on the host burrowing behaviour is the highest. Conversely, other genotypes encyst in the proximal section of the foot and have less, or no, impact on cockle burrowing activity. The presence of more or less manipulative genotypes may reflect different transmission strategies. Encysting at the top of the foot is efficient for host manipulation but also risky because those metacercariae are more likely to be eaten by foot-cropping benthic fishes, which are not suitable definitive hosts (Mouritsen and Poulin, 2003). Genotypes that encyst in other sections of cockle foot can be considered as hitchhikers since they benefit from the manipulation of others without paying the costs of the manipulation (Poulin, 2010). Thus, when one strategy is only advantageous in the presence of individuals using an alternate strategy, trade-offs among different parasite strategies can lead to the selection of multiple genotypes with different strategies.

Using experimental infections of *Gammarus pulex* by the acanthocephalan *Pomphorynchus laevis*, Franceschi et al. (2010a) have recently compared levels of behavioural alteration induced by different parasite families (sibships). In this system, parasitized gammarids typically become photophilic, are more attracted by predator odours and are more often found in the river current than uninfected individuals. These alterations favour parasitic transmission to fish predators, the definitive hosts (Lagrue et al., 2007). Interestingly, important within-population variation in behavioural manipulation occurs in this system, with some infected gammarids showing, for example, a complete phototaxis reversal whereas others behave like unparasitized individuals (Tain et al., 2007). Such within-population variation might be at least partially under genetic control given that Franceschi et al. (2010a) found significant among-families differences in the intensity of early behavioural manipulation.

In parasite species with distinct sexes, the intensity of host phenotypic alterations can be influenced by the parasite gender. An example is the association between the acanthocephalan *Acanthocephalus lucii* and its intermediate host, the isopod *Asellus aquaticus*. As the parasite becomes infective to the definitive host (e.g. the fish *Perca fluviatilis*), the respiratory operculae of isopods become darkly pigmented (Benesh et al., 2008b), with small isopods infected by a male parasite having darker abdominal pigmentation than those infected by a female (Benesh et al., 2009). Many acanthocephalan species are sexually dimorphic in size even during their larval stages, and it is assumed that the benefits of being large are higher for females than males (Benesh and Valtonen, 2007). This sexual dimorphism might lead to divergent manipulative strategies. For instance, because male parasites invest less in growth than females, they may have more resources available to allocate toward modifying host pigmentation, and/or may have less to gain than females by remaining in and growing mutually with the host (Benesh et al., 2009).

2.2. The host point of view

With few exceptions, phenotypic manipulation dramatically reduces host fitness (Moore, 2002). Therefore natural selection should favour host individuals to resist infection by manipulative parasites, and/or to tolerate manipulative effects. Heterogeneity in the capacity to oppose manipulation could result from hosts having within or between populations different means to defend themselves against manipulative parasites. While some hosts could be resistant to parasitism, others could be resistant to

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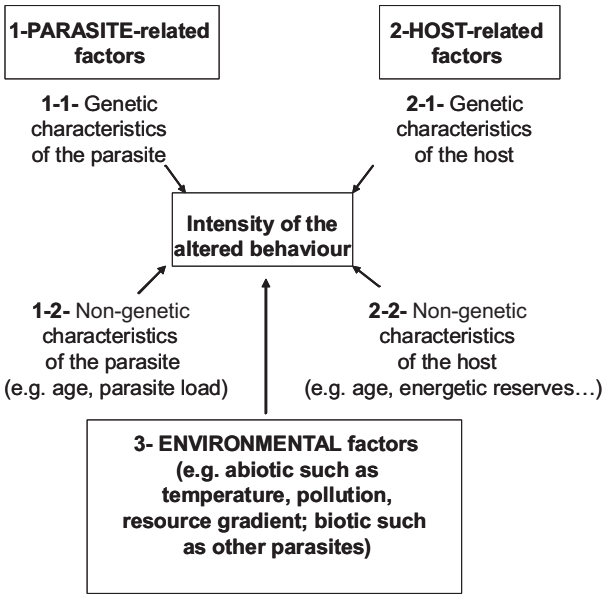

Fig. 1. Factors influencing the intensity of the manipulation in hosts parasitized by manipulative parasites.

manipulation. The latter would be a tolerance mechanism (see Råberg et al., 2009), since it reduces the effects of parasitism rather than the parasite burden of the host. Several recent studies demonstrated that animals show genetic variation not only for resistance to parasites and pathogens but also tolerance (Ayres and Schneider, 2008; Blanchet et al., 2010), and this could be important in natural populations (Svensson and Raberg, 2010). There is, at the moment, little empirical or experimental evidence for this hypothesis in parasite manipulation. Hamilton et al. (2006) showed, with respect to a non-natural case of host behaviour manipulation (the dog roundworm, *Toxocara canis* in lab mice), that the host genotype indeed matters: two laboratory inbred strains of mice were not equally sensitive to behavioural changes induced by the roundworm.

Franceschi et al. (2010b) found that *G. pulex* hosts from four naturally parasitized populations were equally sensitive to parasite-induced behavioural changes, following experimental infection by *P. laevis* from six different geographic origins. However, hosts from an additional population where the parasite does not naturally occur (i.e. a naive population where hosts and parasites did not co-evolved) were highly sensitive to parasite-induced behavioural changes. The difference in manipulation intensity between the naive hosts and those with co-evolving parasites suggests that resistance to manipulation can evolve. But the absence of variation between co-evolved host populations suggests that this resistance cannot overcome a threshold, which could limit a red-queen or arms race process. Alternatively, there might be variation in the parasite's ability to manipulate the host that parallels variation in host resistance to manipulation, leading to equivalent levels of manipulation.

When parasitic transmission relies on a sex specific characteristic of the host, manipulative strategies are often influenced accordingly. For example, certain mermithid nematodes infecting mayflies depend on the female specific behaviour for their transmission, since parasite eggs are laid only when the host visits an aquatic environment for oviposition. Remarkably, when the parasite infects a male host, it feminizes it both at the morphological and the behavioural levels (Vance, 1996). Turning males into functioning females also occurs in arthropods infected by *Wolbachia* bacteria (Engelstädter and Hurst, 2009).

2.3. Are there local adaptations in manipulative parasites?

To our knowledge, only one study has investigated local adaptation of manipulative parasites to their host. Using a full reciprocal design of infection under controlled conditions, Franceschi et al. (2010b) found strong variation in the intensity of manipulation between six host (*G. pulex*) and parasite (*P. laevis*) populations. Some parasite populations induced a strong manipulation whereas others failed to do so. As described above, host populations were similar in their sensitivity to manipulation. Despite such a geographic variation, no comprehensive pattern of local adaptation was identified for behavioural manipulation, while a mosaic of parasite local adaptations was found for their capacity of infecting hosts. This suggests that the two traits are not evolving in parallel. Infectivity, i.e. the combination between the parasite ability to infect hosts and the host ability to resist parasites, is known to have strong genetic bases in many host–parasite systems (reviewed in Greischar and Koskella, 2007; Schulte et al., 2010). The absence of local adaptation for behavioural manipulations suggests that a genetic basis similar to the "matching alleles" or "gene for gene" interactions generally invoked to account for variation in infectivity is unlikely to explain variability in manipulation intensity in the *G. pulex–P. laevis* system.

3. Numerous non-genetic variations in phenotypic alterations

3.1. The environmental context and state-dependent responses

Host–parasite coevolution occurs in a heterogeneous environment. Therefore, on a large geographical scale, populations of a parasite species infecting different host populations experience distinct selective forces because of variable external conditions, following the general principles of the geographic mosaic concept of coevolution (Thompson, 2005). Thomas et al. (2010) argued that this phenomenon could favour the evolution of multidimensional manipulations. Intensity of host manipulation is also likely to have evolved, and be maintained, in response to spatially heterogeneous factors affecting the probability of transmission. For instance, manipulation intensity should be sensitive to the fact that in some areas, suitable definitive hosts correspond to species with different foraging strategies, and/or can be outnumbered by non-host predators. Similarly, because differences in microhabitats available for manipulation of intermediate hosts, a given manipulation intensity may perform differently among sites. Alternatively, theory predicts that in heterogeneous environments, local populations might be permanently maladapted because of migration from other habitats with contrasting selection pressures (e.g. sink populations). In host–parasite associations, the causes of the environment heterogeneity could result from both abiotic and biotic factors, but most of the time it arises from variations in the conditions or traits of hosts and parasites themselves. For example, as pointed out by Poulin (2010), the expression of host manipulation cannot be considered independent of the initial phenotypic characteristics of the host, since it is measured as a change in those initial characteristics.

The ability to recognize fitness-related environmental cues to adjust strategic decisions is of great adaptive value in animals including parasites (e.g. Thomas et al., 2002a). Hosts of different ages might plastically 'decide' to resist manipulation to greater or lesser degrees (Poulin, 2010). Because such a decision is influenced by reproductive expectancy, which is not entirely determined by age, other variables could intervene in a state-dependent response. Host longevity following infections can also strongly influence the success of a fixed manipulative strategy (e.g. Poulin, 1994), and this should exert selective pressure on parasites to adapt their

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manipulative decisions to the age of their hosts. It is predicted that parasites should secure transmission by enhancing their manipulative effort when the life expectancy of their host decreases (Thomas et al., 2002a). The finding of Poulin (1993) that the intensity of manipulation in fish parasitized by trematodes is greater when the intermediate hosts become older could be explained by state-dependent decisions.

An abundant literature reveals the density-dependent nature of parasites responding to intraspecific competition. Among manipulative parasites, individuals of the trematode *C. australis* adjust their strategy in a state-dependent manner, according to the number of manipulative metacercariae already involved in the manipulation (Leung et al., 2010). New infective larvae are more likely to contribute to manipulation by migrating toward the distal part of the cockle foot when a threshold number of encysted parasites has been achieved.

Similarly, manipulative parasites could respond through adaptive phenotypic plasticity to external variables. For parasites, a potentially large number of direct and indirect cues may provide accurate information about the host external environment (see Thomas et al., 2002a). Parasites can for instance have a reliable indicator of the population density of their host by detecting physiological changes that occur inside their hosts when interacting with conspecifics. Manipulative parasites that rely on predation for their transmission could benefit from perceiving these cues when their optimal manipulative effort is theoretically influenced by the density of manipulated hosts (Poulin, 1994; Thomas et al., 2002a). Several studies (e.g. Poulin, 2003; Lagrue and Poulin, 2007; Loot et al., 2008) suggest that trophically transmitted parasites, when inside intermediate hosts, can perceive cues emanating from the definitive host, and adjust accordingly their life history decisions. Manipulation intensity could therefore be plastic, and conditional upon the opportunities for transmission evaluated by the parasite itself. Exploring the potential for strategic plasticity in parasites and identifying the mechanisms used to gain information from their external environment would be a promising approach to understand variation in manipulation intensity.

3.2. Potential (but understudied) sources of variation

3.2.1. The parasitic load

Parasitic load is likely to influence the intensity of host manipulation, especially when behavioural alterations come from parasites impairing the function of a specific host organ. For example, with the trematode *C. australis* which encysts in the foot of cockles (see above), the more metacercariae there are encysted in the tip of the foot, the more the foot's function is handicapped (Thomas and Poulin, 1998). However, manipulation intensity and the probability of capture by the final host are not always positively correlated with parasite load, as evidenced in *Diplostomum spathaceum* (Trematoda), an eye fluke of fish (Seppälä et al., 2005). Finally, it is predicted that conflict between conspecific parasites could occur inside the host because not all of them are mature/transmissible at the same time. In such a case, immature/non transmissible stages are expected to decrease the intensity of the manipulation induced by mature/transmissible individuals (see Sparkes et al., 2004). This prediction has received recent experimental support in the acanthocephalan *P. laevis* of different ages co-infecting *G. pulex* (Dianne et al., 2010).

3.2.2. Age and size of parasites

In many systems, the developmental stage of the manipulative parasites influences the intensity of behavioural changes displayed by the host. This phenomenon in itself can account for an important part of the natural variation in host manipulation because field samples often consist of a mixture of parasitized hosts containing differently aged parasites. For associations involving trophically transmitted parasites, behaviours increasing host vulnerability to definitive hosts usually occur only when the parasite larvae become infective for the definitive host (e.g. Helluy, 1984; Sparkes et al., 2006; Franceschi et al., 2008; Benesh et al., 2008a). Parasites can also induce behavioural alterations that conversely reduce predation risk on the host to avoid premature transfer. For example, copepods parasitized by the cestode *Schistocephalus solidus* have a reduced activity until infectivity for stickleback is attained, and then the opposite pattern is observed (Hammerschmidt et al., 2009). Taxa other than trophically transmitted parasites also demonstrate stage-dependent manipulations. In crickets parasitized by hairworms, Sanchez et al. (2008) found that sub-adult and adult worms do not induce the same behavioural alterations in parasitized crickets: the former induces an erratic behaviour which could serve to increase the probability of encountering a water body suitable for worm emergence. Then, fully mature worms induce the water-seeking behaviour which enables the parasite to physically enter water (Sanchez et al., 2008). Koella et al. (2002) showed that different stages of the malaria parasite *Plasmodium gallinaceum* differentially influence the host-seeking behaviour of its mosquito vector *Aedes aegypti*. Vectors parasitized with oocysts (which cannot be transmitted to the mammal host) pierce the skin less, whereas the reverse pattern is found with individuals infected with sporozoites (transmissible stage).

Although less documented, age-dependent manipulation can persist once infectivity is reached and such a phenomenon could be adaptive for the parasite. As larvae become older and usually larger, the relative benefits of remaining in the intermediate host decrease while the potential costs increase (Benesh et al., 2008a). For instance, the growing potential of cestode larvae in intermediate host copepods decreases with time because of resource depletion and within host space constraints (Benesh et al., 2008a; Shostak et al., 2008). In addition, the probability of natural host mortality presumably increases with time. Theoretical investigations suggest that the optimal time for switching manipulation results from a trade-off between increasing establishment probability in the next host and reducing mortality in the present host (Parker et al., 2008). Franceschi et al. (2008) demonstrated from the association between *G. pulex* and two populations of the acanthocephalan *P. laevis* that ageing affects the intensity of manipulation even among infective (i.e. cystacanth stage) parasites. In this case, older cystacanths induce a higher and less variable degree of manipulation compared with young ones. A similar phenomenon has been reported by Benesh et al. (2009) in isopods parasitized by the acanthocephalan *A. lucii*: alteration of isopod colouration only occurs after parasites become cystacanths, but maximum host alteration is not achieved immediately after attaining the cystacanth stage. Finally, at least two studies involving manipulative cestodes also support these ideas. Brown et al. (2003) found that large *Ligula intestinalis* plerocercoids alter more drastically the habitat selection of their fish hosts than small parasites, and Ness and Foster (1999) found that large *Schistocephalus solidus* also demelanized more sticklebacks than small ones. Since in these two parasites size is correlated with age, we can reasonably infer that older parasites induce stronger phenotypic alterations than young ones.

The possibility that senescence effects (i.e. reduced manipulation when parasites are too old) explains part of the variation in the intensity of manipulation has received very little attention. Theory predicts that for parasites, there should be a trade-off between manipulative and reproductive efforts (Poulin, 1994). Because parasites require transmission for reproduction, they should maintain manipulation of the host at a high level even if this

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leads to a reduction in fecundity, rather than decreasing the manipulative effort to keep a potential fecundity that would be useless in the absence of transmission. Accordingly, senescence effects would be rare. Sanchez et al. (2008) indeed found that when crickets harbouring a mature hairworm were experimentally prevented from reaching an aquatic area (where the adult parasites reproduce), the fecundity of the worm decreases through time but the manipulative effort exerted by the parasite is maintained. It is also possible that senescence effects are not common in natural conditions because host manipulation (timing, intensity, etc.) has evolved to ensure an efficient transmission prior to senescence. However, there are undoubtedly many instances in which not all manipulative parasites achieve successful transmission (e.g. not all intermediate hosts manipulated by trophically transmitted parasites are captured by predators) and senescence effects deserve to be explored.

3.2.3. Age of the host

It is well established that the age of the host can be a crucial parameter in determining the expression of the manipulation. For instance, when the cercariae of the trematode *Microphallus papillorobustus* infect *Gammarus insensibilis*, they always migrate toward the brain, the condition for inducing behavioural changes (positive phototaxis, negative geotaxis and aberrant escape behaviour). Similar changes are observed with *Gammarus aequicauda* but only when gammarids are infected when young. In older gammarids, cercariae are unable to migrate toward the brain and thus remain in the abdomen where they have no effect on the host behaviour (Helluy, 1983). This is apparently the result of a physiological constraint (Helluy, 1983), but age-dependent manipulation may also result from adaptive decisions from the host that more or less oppose manipulation. In this respect, Poulin (1994, 2010) predicted that if the expected reproductive success of the host declines following the onset of maturity, intermediate hosts of long-lived parasites could benefit by opposing manipulation early in their adult life. Late in their reproductive life, the benefits of opposing manipulation by parasites would be much reduced. In accordance with this prediction, manipulative changes in certain freshwater fishes parasitized by manipulative trematodes are more intense in old host than in young hosts (Poulin, 1993).

3.2.4. Multiple infections

Hosts in natural conditions are often parasitized by a community of phylogenetically distinct parasites. These parasites may have shared or opposing interests for their transmission (Brown, 1999; Lafferty et al., 2000). Where there are conflicts of interest, certain parasites are able to sabotage the manipulation initiated by other parasites, effectively reducing the intensity of the manipulation induced by competitors (Cézilly et al., 2000; Thomas et al., 2002b; Haine et al., 2005).

3.2.5. Seasonality

For host-manipulative parasites that are active for long periods of time in ecosystems, seasonal variation in the manipulation intensity may exist. A compelling example comes from a parasitoid manipulating aphids in order to meet its different seasonal requirements. Brodeur and McNeil (1989) found that the behaviour of parasitized aphids varies as a function of the physiological state of the parasitoid. At the end of the season, potato aphids containing *Aphidius nigripes* larvae destined to enter diapause (dormancy) leave the host plant and mummify in concealed microhabitats. In contrast, during the rest of the growing season, the parasitoid induced the host to leave the aphid colony and mummify in the apical stratum of the plant canopy. In both situations, induced host behaviour would result in parasitized hosts mummifying in sheltered microhabitats, thereby reducing the negative effects of adverse climatic conditions and the actions of natural enemies (Brodeur and McNeil, 1992).

3.3. Potential (uninvestigated) sources of variation

3.3.1. Pollution

Pollution by toxic chemicals is now ubiquitous in the environment, especially in freshwater ecosystems (Gauthier-Clerc and Thomas, 2010). This phenomenon could influence the intensity of host manipulation in various ways. An immediate challenge would be to gather systematic information on how pollutants influence the host capacity to oppose manipulation as well as the manipulative capacities of parasites. Anthropogenic pollution also influences the infective stages of parasites outside their host (Poulin, 1992) and this has obvious evolutionary impacts (Lebarbenchon et al., 2008). For instance, pollutants reduce the lifespan of the free-living infective stages of many pathogens (Pietrock and Marcogliese, 2003) and we know that survival of infective stages in the external environment is a key driver of the evolution of parasite strategies (Walther and Ewald, 2004). Therefore, adverse conditions for infective stages resulting from pollution affect transmission success, and may be selecting for pathogen strains with different levels of virulence.

3.3.2. Energetic reserves of the host

Although never considered, displaying an aberrant behaviour is likely to be energetically expensive for the host. For example, crustaceans (*Gammarus* and *Artemia*) parasitized by bird helminths (trematodes, acanthocephalans and cestodes) are manipulated to move toward the air/water interface, notably when there is a mechanical disturbance in the water (like a foraging bird walking or swimming). Because this behaviour comes with energetic costs for the hosts, we can predict that hosts in poor condition will be less subject to intensive manipulation, even if they are genetically sensitive to manipulation and infected with a parasite having strong manipulative abilities. Interestingly, although trematodes, cestodes and acanthocephalans are phylogenetically distant, they all increase the level of energetic reserves of their hosts (especially lipids), suggesting that they physiologically manipulate their hosts in a way that allow them to afford for energetic dispenses associated to manipulated behaviours (Amat et al., 1991; Plaistow et al., 2001; Ponton et al., 2005). The hypothesis that heterogeneity in host energetic reserves induces variation in the host resistance in host manipulation deserves attention.

3.3.3. Parasite trade-offs

Phenotypic traits are usually selected to optimize life history traits in response not only to the environmental variation discussed above, but also in response to internal trade-offs. In manipulative parasites, this has been shown in the acanthocephalan *P. laevis*, where parasites cannot optimize both their growth rate and their manipulative intensity: parasites that rapidly reach the infective stage do not induce behavioural changes at that stage, while parasites growing more slowly manipulate their host as soon as they reach the infective stage (Franceschi et al., 2010a). These types of trade-offs are common in parasites, especially for those with complex life-cycles because they have to cope with multiple hosts. In that case, optimization of life-history traits could be different according to the host, or conversely could be synergetic, as is the case in parasite adaptation to immune response (Hammerschmidt and Kurtz, 2005). This field of research is largely overlooked for behavioural manipulation. If this trait is costly (Poulin, 1994), potential trade-offs could exist between this trait and several others. In addition to growth rate in the intermediate

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host, other traits such as the ability to establish in the final host, the growth rate in the final host or fecundity could be constrained by the intensity of behavioural manipulation.

4. Concluding remarks and future directions

4.1. Technical avenue

As exemplified here, non-genetic and genetic sources influencing the intensity of manipulation are numerous but poorly studied. Specific studies should be undertaken to decipher the respective roles of these sources in various host–parasite associations. In the field, such studies require appropriate sampling schemes coupled with adequate statistics. Sampling should account for all possible sources of variation and should therefore be hierarchically structured, with several individuals being sampled in several habitats, themselves sampled in several populations (or localities). Such comparative and hierarchical sampling design can also be performed temporally to investigate the timing and progression of manipulation. By using appropriate statistics such as multilevel models (either Bayesian or frequentist methods, McMahon and Diez, 2007; Basañez et al., 2004; Byers et al., 2008) one can deconstruct variance in manipulation intensity among the main biological levels involved (individuals, habitats, populations, time), and one can also relate factors associated to each level to the observed variability (Byers et al., 2008; Diez and Pulliam, 2008). Obviously, the impressive numbers of variables that can potentially influence the intensity of manipulation in natural conditions are likely to interact, with potential additive, synergistic or antagonistic effects on the host manipulation intensity. Again a close hierarchical deconstruction of this variability using variance partitioning tools (Chevan and Sutherland, 1991; Heikkinen et al., 2005) could prove powerful in elucidatating the relative role of independent *vs*. joint effects of these various sources of variation.

In the laboratory, more specific tools could be used to dissociate the role of genetic factors on patterns of variability observed in the field. Notably, parasitologists now need to better embrace the field of quantitative genetics (Falconer, 1981) that allows inferring important parameters for assessing the evolutionary potential of quantitative traits. For instance, an often neglected source of variation among populations is genetic drift. Indeed, genetic drift by itself can generate patterns of phenotypic variance that can be mistakenly attributed to the effect of selection (Merilä and Crnokrak, 2001; Whitlock, 2008). In such a context, one can use appropriate breeding designs in the lab (i.e. common garden experiments) to measure and compare the genetic differentiation at neutral loci (i.e. "Fst", measured using microsatellites for instance) *vs.* the genetic differentiation at quantitative traits (i.e. "Qst", measured as the intensity of manipulation for instance), and to infer the role of natural selection *vs.* genetic drift (i.e. Qst/Fst comparison, Whitlock, 2008) on the differentiation in manipulation intensity among populations (Whitlock, 2008; Leinonen et al., 2008). Indeed, when the genetic differentiation among populations measured at quantitative traits is significantly greater than the genetic differentiation measured at neutral loci, we can generally assume that natural selection play a greater role than genetic drift in shaping observed patterns (but see Whitlock, 2008; Leinonen et al., 2008 for details). Surprisingly, no Qst/Fst comparisons have been performed on host–parasite interactions although these are rather straightforward experiments to perform. In addition, breeding design such as full-sib/half-design should now be performed and coupled with animal models (Kruuk and Hadfield, 2007; Wilson et al., 2009) to assess essential parameters such as heritability values of important traits (virulence, resistance, tolerance) and genetic correlation between traits ($r_{\text{virulence–resistance}}$, $r_{\text{virulence–tolerance}}$ and $r_{\text{resistance–tolerance}}$).

4.2. Evolution of manipulation

Unless more common-garden experiments are performed, it is clearly premature to conclude about the strength of genetic components underlying host manipulation. From our current knowledge it appears that variability of host manipulation arises from complex interactions between genomes, environment and the age of hosts and parasites. Evolution of host manipulation should then be considered within the framework of phenotypic plasticity rather than in a purely genetic framework. This is not surprising *per se* since many ecological interactions are mediated through phenotypic plasticity (see Fordyce, 2006 for review).

Advantages of being plastic should be particularly critical in manipulative parasite species exploiting habitats that are fragmented and heterogeneous in space and/or time. A potentially large number of manipulative parasite species experience such ecological conditions. Host manipulation usually occurs with intermediate hosts that often disperse less than definitive host species (and hence manipulative parasites). In addition, numerous manipulative parasites are not specific, either on their intermediate or final hosts. A high level of plasticity in host manipulative parasite systems is expected to reduce the likelihood of strict trait-for-trait pairwise coevolution between the host and the parasite, then leading to a diffuse coevolution between the two protagonists (Wolinska and King, 2009). Depending on the population considered, the relative contribution of genetic variation to phenotypic variation may however vary, and ultimately the strength and direction of selection. The coevolution could then be more or less diffuse depending on the populations and/or time considered.

Providing a 'moving target' for natural selection should not only slow down the adaptive response of the interacting protagonist, it is also expected to create a variable biotic environment that might favour the evolution of plasticity in the other members (i.e. reciprocal plasticity) (Fordyce, 2006). This could potentially explain the high number of conditional responses from both manipulative parasites and their hosts in determining the intensity of manipulation. The time/space scales over which plastic phenotypes in one member (the host or the parasite) are expressed can influence the evolutionary response of the interacting population. In the short term (i.e. within a generation), plasticity in one member may favour reciprocal plasticity, but on the long term, it might lead to shifting selective pressures across generations. Such temporal and spatial variations in the strength and direction of selection might be important for maintaining genetic variation in the populations of the mosaic.

Manipulating the host behaviour is a fluid interaction rather than a fixed trait in manipulative parasites. More findings either on local adaptation patterns or genetic and plastic variations on parasite ability to manipulate host behaviour (or host ability to resist manipulation) would provide helpful information on how this strategy of exploiting a host evolves. This information should be analyzed taking into consideration the theoretical prediction of a trade-off between manipulative effort and other functions, because maintenance of a variation on manipulation, due to phenotypic plasticity, could prevent the predicted "optimal manipulation effort" being reached in field populations.

4.3. Implications for predicting parasite dynamics

Determining factors that control the temporal and spatial dynamics of manipulative parasites is important for biodiversity conservation, human and animal health and economy, especially in a rapidly changing world. Predictive models require a precise understanding of the biological mechanisms underlying the dynamic of parasite populations (Wimberly et al., 2008). Among them, both host manipulation and parasite fecundity are of great

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importance as they maximise parasite opportunities for transmission. As mentioned above, theory predicts that these two variables are not independent since the energy invested by parasites into host manipulation is not available for other functions, especially fecundity (Poulin, 1994). Exploring the causes and the life history consequences of intensity variation in host manipulation may therefore help to directly or indirectly understand the spatial and the temporal dynamic of manipulative parasites.

We believe that understanding and predicting intraspecific variation in host manipulation is one of the most exciting research directions on manipulative parasites for the near future. At the moment, this promising area of research is clearly in its infancy. As for the study of multidimensional host manipulations (see Thomas et al., 2010), answers to many current and future questions about intraspecific variation in host manipulation might come as a result of convergence between scientific disciplines (e.g. evolutionary ecologists, parasitologists, physiologists and epidemiologists).

Ethical statement

No ethical problem.

Acknowledgements

We thank David Hughes for having corrected the English. F. Thomas and T. Rigaud received support from the French Agence Nationale de la Recherche (Project PARADIV and BODYGUARD). N. Franceschi was funded by a doctoral grant from the MENESR. S. Blanchet received financial supports from the CNRS (Centre National de la Recherche Scientifique) through a Projets Exploratoires/Premier Soutien.

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