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CONCEPT

Mechanisms and Consequences of Infection-induced Phenotypes

# Inter-individual variation in parasite manipulation of host phenotype: A role for parasite microbiomes?

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## Abstract

1. Alterations in host phenotype induced by metazoan parasites are widespread in nature, yet the underlying mechanisms and the sources of intraspecific variation in the extent of those alterations remain poorly understood.
2. In light of the microbiome revolution sweeping through ecology and evolutionary biology, we hypothesise that the composition of symbiotic microbial communities living within individual parasites influences the nature and extent of their effect on host phenotype. The interests of both the parasite and its symbionts are aligned through the latter's vertical transmission, favouring joint contributions to the manipulation of host phenotype.
3. Our hypothesis can explain the variation in the extent to which parasites alter host phenotype, as microbiome composition varies among individual parasites. We propose two non-exclusive approaches to test the hypothesis, furthering the integration of microbiomes into studies of host–parasite interactions.

KEYWORDS
bacteria, behaviour, holobiont, host–parasite interactions, microbiome, symbionts, transmission, viruses

## 1 | INTRODUCTION

Parasite infection often induces changes in host morphology, physiology, performance or behaviour, making parasitism an important source of intraspecific variation in host phenotypic traits (McElroy & de Buron, 2014; Moore, 2002). In many cases, parasite-induced alterations in host phenotype are not merely pathological side effects, but are instead the product of natural selection (e.g., Lagrue et al., 2007; Moore, 1983; Yanoviak et al., 2008). Indeed, manipulation of host phenotype appears to be a widespread adaptive strategy that improves a parasite's chances of transmission and completing its life cycle (Hughes et al., 2012; Moore, 2002; Poulin, 2010). This strategy has had multiple independent evolutionary origins across a range of parasite taxa (Poulin, 2010). The underlying mechanisms remain unclear in most cases; the host's neural, endocrine and/or immunomodulatory systems may be targeted (Adamo, 2013; Herbison, 2017), while other parasites may directly alter the expression of host genes regulating particular behaviours (Grecias et al., 2020; Van Houte et al., 2013; Will et al., 2020).

Traditionally, the interaction between a manipulative parasite and its host has been viewed as a two-player game, with the parasite's genes having 'extended' phenotypic effects on host phenotype (Dawkins, 1982). However, hosts are frequently infected by two or more parasite species; depending on their respective transmission requirements, the interests of a manipulative parasite will either align or conflict with those of other parasites sharing its host (Cézilly et al., 2014). Synergistic or antagonistic effects among parasites can determine how strongly the manipulative influence of one parasite will be manifested as a modified host phenotype. Furthermore, it has been proposed that the host microbiome, that is, the community of symbiotic microbes harboured by an animal, might modulate the molecular crosstalk between a manipulative parasite and its host and influence the resulting alteration in host phenotype (Biron et al., 2015). For instance, certain microbes could counter attempts by parasites to manipulate host phenotype. Much evidence already exists that animal microbiomes affect their health, behaviour and general phenotype (Diaz Heijtz et al., 2011; Ezenwa et al., 2012; Feldhaar, 2011; Hooper et al., 2012), as well as affecting the host–parasite interaction more directly, by influencing the parasite's attraction to the host, infection success or virulence (Bernardo-Cravo et al., 2020; Cirimotich et al., 2011; Koch & Schmid-Hempel, 2012; Lutz et al., 2022; Oliver et al., 2005). It is plausible that host microbiomes also affect the outcome of host manipulation attempts by parasites. Therefore, the net impact of a manipulative parasite on the phenotype of its host is likely to vary depending on which other parasites infect the host and the composition of the host's microbiome.

Here, following from an earlier suggestion (Dheilly, Poulin, et al., 2015), we propose that the parasite's own microbiome, that is, the symbiotic microbial community living within a parasite and distinct from that living within host tissues, is also a key element in the manipulation of host phenotype by parasites. Our hypothesis is that, all else being equal, the presence or abundance of certain microbes within a manipulative parasite determines the magnitude of the changes induced in host phenotype. We begin by highlighting how the phenotypic changes induced by manipulative parasites show much intraspecific variation that remains mostly unexplained. We follow this with a brief overview of parasite microbiomes, which are distinct from host microbiomes but nevertheless not uniform across all conspecific parasite individuals. We then present our hypothesis that parasite microbiomes contribute to host manipulation and account for some of the variation in the extent of host phenotypic change, as well as its underlying assumptions and the existing evidence in support. Finally, we propose a framework for testing the hypothesis and discuss its wider implications.

## 2 | VARIATION IN HOST PHENOTYPIC ALTERATIONS

Classical examples of host manipulation by parasites are often presented as though the outcome is fixed and inevitable: hairworm-infected crickets find water and jump into it (Thomas et al., 2002), and ants infected by *Ophiocordyceps* fungi climb up vegetation to die in an elevated location (Andersen et al., 2009). These examples suggest that manipulative parasites canalise the behaviour of their hosts towards a narrow range of outcomes, with limited variability. However, the reality is that for most phenotypic traits measured on a continuous scale, the extent to which a trait is altered by infection varies greatly, even among individual parasites from the same population.

We illustrate this using data from Nakagawa et al. (2015) compiled from 202 experimental studies on the effect of parasite infection on host behaviour, in which simple behaviours measured on a continuous scale (e.g. time spent moving, running speed, response to stimulus, microhabitat preferences) were quantified for both infected and control animals (Figure 1). The parasites in these studies were all helminths (platyhelminths, nematodes or acanthocephalans), whereas the hosts were mostly arthropods. The studies were split in two subsets, those in which behavioural changes induced by a parasite were believed a priori to influence its transmission success (i.e. the parasite must be transmitted by predation of its current host by a definitive host), and those in which behavioural changes induced by infection are unlikely to be adaptive for the parasite and may simply be the outcome of pathology. This categorisation was based on the known transmission mode of the parasite, and on information and predictions presented in the original studies. Although the mean value of behavioural traits was often altered by infection (see Nakagawa et al., 2015), the variation in trait expression

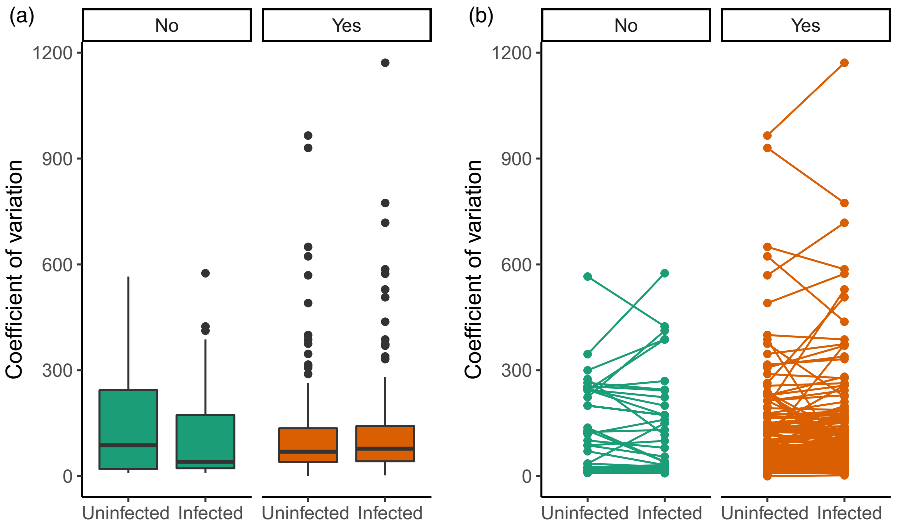

**FIGURE 1** Variability (coefficient of variation) in the phenotypic traits of animals, for both uninfected individuals and individuals infected by helminth parasites, presented both (a) pooled across studies (median and interquartile range) and (b) separately by study. Data shown separately for studies where behavioural changes induced by the parasite can influence its transmission success (yes, $N = 161$, orange), and those where behavioural changes induced by infection cannot benefit the parasite (no, $N = 41$, green). Data from Nakagawa et al. (2015) compiled from 202 experimental studies.

remained large, whether measured in hosts infected by manipulative parasites expected to benefit from alterations in the host or in hosts infected by other types of parasites (Figure 1). There is definitely no evidence that manipulation by parasites results in standard, repeatable changes in host phenotype.

This intraspecific variation in the extent of phenotypic changes induced by manipulative parasites has been attributed to the genetic and non-genetic (e.g. age or body condition) characteristics of both host and parasite, as well as environmental factors (Thomas et al., 2011). Yet, much of the variation remains unexplained. Here, we propose that in addition to the host microbiome (Biron et al., 2015), the parasite microbiome can also play a role in modulating the magnitude of phenotypic changes induced in the host.

## 3 | PARASITE MICROBIOMES

Whether or not they are capable of host manipulation, parasites harbour their own microbiomes; these include microbial taxa acquired horizontally from the host or external environment, but also microbes distinct from those of the host or the environment (Dheilly et al., 2019; Jorge et al., 2020; Jorge, Dheilly, et al., 2022; Sinnathamby et al., 2018). Even parasitic worms with complex life cycles possess a core microbiota that persists across life stages and generations (Jorge et al., 2020; Jorge, Dheilly, et al., 2022). This implies that some microbes are vertically transmitted, something that has been demonstrated for particular microbial taxa, such as the bacteria *Neorickettsia* (Vaughan et al., 2012). Vertical transmission aligns the interests of the microbes with those of the parasite harbouring them. If the parasite survives and continues its life cycle, so do its symbiotic microbes; the vertically transmitted taxa among the latter would therefore benefit from the same alterations in host phenotype that improve parasite transmission. From this perspective, parasites and their symbiotic microbes can be thought of as holobionts, that is, integrated entities functioning as true evolutionary units (Bordenstein & Theis, 2015).

There is mounting evidence that the performance of a parasite in its interaction with the host is influenced by the microbes it harbours (Dheilly et al., 2019; Dheilly, Poulin, et al., 2015). For example, Martinson et al. (2020) have demonstrated that an intracellular bacterial symbiont improves the infectivity of a parasitic nematode towards its fly host; without this symbiont, the nematode shows greatly reduced infection success. It seems plausible that other phenotypic traits of parasites are similarly influenced by their microbiomes.

Importantly, the composition of parasite microbiomes varies among conspecific parasites from the same population. For example, in two species of parasitic trematode, different microbial taxa that form their core microbiome have different prevalence, that is, they are absent from some individual parasites. Thus, different subsets of the total pool of symbiotic microbes occur in different individuals (Jorge et al., 2020; Jorge, Dheilly, et al., 2022). Imperfect vertical transmission, microbial competition and some degree of horizontal transmission can generate these inter-individual differences. For instance, during the asexual proliferation of trematodes in their snail intermediate host, only a variable proportion of the resulting clonal infective stages leaving the snail have acquired *Neorickettsia* bacteria from the parent generation (Greiman et al., 2013). Variation in microbiome composition could therefore explain some of the variation in both the parasite's own phenotype and in its interaction with the host.

## 4 | PARASITE MICROBIOMES AND HOST MANIPULATION

Our hypothesis is that the presence of certain microbial taxa, or their (relative or absolute) abundance in an individual parasite, influences the nature and extent of its effect on host phenotype. From a holobiont perspective, the parasite and its microbes (at least the vertically transmitted ones) are in a partnership to alter host phenotype in ways that benefit them both. All key assumptions underpinning this hypothesis are met: parasites harbour distinct microbiomes whose exact composition varies among individuals; symbiotic microbes of parasites are known to affect their interaction with the host; and the host phenotypic changes induced by manipulative parasites display substantial and mostly unexplained variation.

Our hypothesis' main prediction is that parasites harbouring similar microbial communities induce similar phenotypic changes in their host (Figure 2). A parasite can harness an extra set of functional genes from its symbiotic microbes to achieve host manipulation (see Dheilly, Poulin, et al., 2015), however which genes are available depends on which microbes are present. Assuming no other sources of variation among host phenotypes (i.e. genetics, environmental factors), similar microbial communities should produce similar spectra of signalling and effector molecules, thereby triggering similar downstream phenotypic modifications.

There already exist evidence in support of our hypothesis indicating that specific microbes play key functions in initiating phenotypic changes in the hosts in ways that benefit the parasite in which they live. Herbivorous insects often rely on symbiotic microbes to modify the physiology of their host plant and facilitate their food intake (Frago et al., 2012; Kaiser et al., 2010). Entomopathogenic nematodes rely on symbiotic bacteria of the genera *Xenorhabdus* and *Photorhabdus* to kill their insect host and convert their cadaver into suitable food for nematode growth (Goodrich-Blair & Clarke, 2007). Even more remarkable, an RNA virus carried by the parasitoid wasp *Dinocampus coccinellae* and released into the beetle host invades the beetle's nervous tissue and is responsible for the behavioural manipulation that results in the beetle protecting the parasitoid's pupa after it emerges from the host (Dheilly, Maure, et al., 2015). Our hypothesis goes one step further by proposing that manipulation of the host can be enhanced not just by one, but by multiple symbiotic microbes harboured by the parasite. Some well-studied manipulative parasites, such as the cestode *Schistocephalus solidus*, harbour rich microbial communities (Hahn et al., 2020, 2022). We argue that the

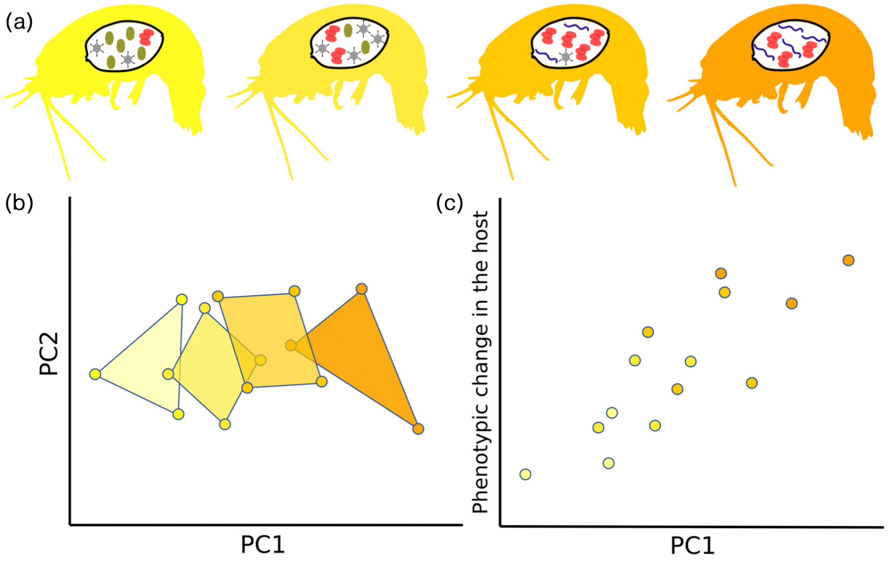

FIGURE 2 Hypothetical effect of parasite microbiomes on host phenotypic manipulation, illustrated for an amphipod infected by a juvenile acanthocephalan parasite which must reach its definitive host via predation to develop into an adult worm. Other factors (host and parasite genetics, host microbiome, etc.) that may also influence the magnitude of host phenotype manipulation are excluded from this example. (a) The presence and/or abundance of particular symbiotic microbes (different symbols) within the parasite affects the extent of host phenotypic change, with progressively darker shades of yellow representing hosts displaying more pronounced phenotypic alteration. (b) In a principal coordinates analysis of parasite microbial community composition, parasites inducing similar phenotypic changes in their hosts (delimited by hulls with the same yellow shading) harbour similar microbial communities. (c) The principal coordinate, PC1, capturing the greatest amount of variation in the composition of microbial communities within parasites correlates positively with the extent of phenotypic change induced in the host.

net influence of parasite infection on host phenotype results from the combined effects of multiple microbial symbionts whose interests align with those of the parasite.

## 5 | LOOKING AHEAD

We propose two non-exclusive approaches to test our hypothesis that parasite microbiomes contribute to host manipulation. First, one could characterise the microbiomes of both host and parasite at different stages of the manipulative process (before, during and after the onset of phenotypic changes in the host). Simultaneously, complementary -omics approaches (transcriptomics, metabolomics, proteomics) can be deployed to identify candidate effector molecules, determine which of the participating genomes they originate from, and ascertain what role they play (if any) in host manipulation through gene silencing using RNAi or CRISPR/Cas9 (see Biron et al. (2015) for a similar suggestion to characterise the host microbiome).

Second, direct manipulation of parasite and/or host microbiomes is also a powerful route to demonstrate the causal effect of microbes on host manipulation. Antibiotic exposure can be used to disrupt the microbiota of parasitic worms (e.g. Jorge, Froissard, et al., 2022; Martinson et al., 2020). Changes in the ability of a parasite to manipulate host phenotype following the experimental deletion of certain microbes from its microbiome would provide strong evidence that symbiotic microbes within parasites contribute to modification of the host phenotype.

If symbiotic microbes living within a parasite can influence parasite phenotype (e.g. Dheilly, Poulin, et al., 2015: Martinson et al., 2020), why not also host phenotype? Instead of just an extended phenotype (genes of one organism having phenotypic effects on another organism), we may have a hyper-extended phenotype with the nested arrangement of parasite microbes within a parasite, itself within a host. Microbial genes may have phenotypic effects on the parasite, which indirectly lead to phenotypic changes in the host, as well as having direct phenotypic effects on the host. This view firmly places host manipulation by parasites into the complex multi-level eco-evolutionary framework (e.g. McFall-Ngai et al., 2013; Miller et al., 2018) resulting from the recent recognition of the role of microbiomes in the study of species interactions.

### AUTHORS' CONTRIBUTIONS

All authors contributed to the development of the ideas. R.P. led the writing of the manuscript, with critical input from F.J. and P.M.S.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## DATA AVAILABILITY STATEMENT

No original data were used in this manuscript. Data used in Figure 1 were published by Nakagawa et al. (2015).

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