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► **To cite this version:**

Janice Moore, Shelley S. Adamo, Frédéric Thomas. Manipulation: expansion of the paradigm. *Behavioural Processes*, 2005, 68 (3), pp.283-287. 10.1016/j.beproc.2004.10.005 . hal-02521317

HAL Id: hal-02521317

<https://hal.science/hal-02521317>

Submitted on 5 Apr 2024

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Manipulation: expansion of the paradigm

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The comments in this journal range from the scholarly and thoughtful to the daring and imaginative. Some have been enticingly brief – one begs for more – and some have contained errors. They comprise over 70 pages of typescript (not including references), with topics ranging from proteomics to culture, castration to predation.

This far-flung exuberance of commentary, along with our initial manuscript, is unfettered by peer review. In this volume, then, we see scientific thinking in progress, all sparkling creativity visible, all warts exposed. It is a sight to behold, and well worth the price of admission. For detail and verification, however, we urge the reader to seek out the primary – and in some cases, “historic” (by scientific timelines) – literature. There is no substitute. Combes (2001) and Moore (2002) have produced thorough reviews of this literature, with comprehensive bibliographies; search engines can address the interim.

Given this breadth of commentary, a detailed response is impossible. We would therefore like to return to some concepts that we hope to emphasize. Perhaps the most important is this: As we gaze towards the fu-

ture, armed with new tools and hoping to tease out ever more complex nuances, older and perhaps more fundamental challenges remain unanswered. Which hosts are important in natural life cycles? Parasites may survive in many species of hosts, but they often thrive to varying extents. Do we know that the host–parasite associations we study are those that are most influential, evolutionarily and ecologically speaking, in the natural world? For that matter, what about the propensity of many parasites (and hosts) to form genetic isolates or strains? Do we understand geographic variation in the ways that parasites alter hosts and in the hosts’ responses (see also Wellnitz)? What is the role of physiological (and ultimately, phylogenetic) constraint in how much alteration occurs? What are the roles of parasite intensity, host age, host sex? How are hosts exposed to the parasite? The manner of infection itself can have profound influences on parasite establishment and effects on hosts. Several authors cite the importance of ecological context in the study of altered behaviors (e.g. Biron et al., Combes, de Jong–Brink and Koene, Helluy and Holmes, Klein, Rigaud, and Webster).

Two acanthocephalan examples, both examined in detail, can illuminate the difficulties that attend this area of research, and the fact that even “simple” questions may have complex answers. The *Moniliformis moniliformis*-rodent association is one of a handful of

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intensively investigated helminth systems, because of its tractability in the laboratory, *M. moniliformis* is the best-known acanthocephalan. We know from laboratory studies that it can infect many (but not all) cockroach species with varying degrees of success, that it can alter several behaviors in most of them (including the escape response), that it can behaviorally castrate male cockroaches, eliminating their response to female pheromone, and that cockroaches may take defensive action in the form of altered thermal preference. We have tested for the effects of cockroach phylogeny on these alterations, and found no evidence for such effects (Moore 2002 and references therein, Guinnee and Moore, 2004). In short, we know quite a bit, but we do not know which of these species is/are important in this life cycle in nature, and if that importance varies geographically. We perhaps are more confident with the acanthocephalan *Plagiorhynchus cylindraceus*, which infects terrestrial isopods. In this case, we know that the acanthocephalan induces behavioral alterations, we know that in the laboratory, birds eat more infected than uninfected isopods, we know that nestlings in the field are infected at levels that can best be explained by preferential predation on infected isopods (Moore, 1983), but as Nickol points out in this volume, if infection covaries with other traits that make intermediate hosts desirable prey, manipulation may not be the sole explanation for enhanced predation on those hosts.

Indeed, covariation of altered traits themselves may thwart Cézilly and Perrot-Minnot's intriguing suggestion that we examine such traits separately. That said, it is difficult not to smile just imagining the elegance and creativity of the experiments – most of them not yet designed – that will succeed in overcoming that obstacle. As many contributors agree, there is a high likelihood that many parasite–host associations exhibit several affected traits (e.g. Cézilly and Perrot-Minnot, Dunn, Helluy and Holmes, Klein).

No one system is going to give us all the answers, and even if it does, there is no guarantee that those answers are generally applicable to the larger universe of parasites and hosts. Moreover, embedded in this swath of fundamental questions, and almost impossible to overcome, is the problem of observer bias. Most behavioral alterations that have been reported are those that are most readily noticed by visual observers (i.e., humans). However, a large proportion of animals rely primarily on non-visual information about other organ-

isms. What are we missing? (It is notable that one of the most outstanding exceptions to this visual bias, the odor alterations of red grouse infected with *Trichostrongylus tenuis*, was first “reported” by hunting dogs (Hudson et al., 1992).) In addition to agreement about ecological topics, we find much agreement among our colleagues about the importance of the study of proximate mechanisms in parasitic manipulation (e.g. Biron et al., Cézilly et al., Hurd, De Jong-Brink and Koene, Helluy and Holmes, Klein, Nichol, and Webster). If we know the physiological mechanisms that mediate changes in host behaviour, for instance, we may be able to determine whether a host response plays a role (e.g. Klein). In these cases, changes in host behaviour may also be a compromise between host and parasite (e.g. Hurd), with some benefit for the host. Unfortunately, as Hurd points out, in many cases we do not understand the mechanisms that underlie normal behaviour, much less how those mechanisms are subverted by parasites or in response to them. Therefore, examining how parasites alter host behaviour will sometimes require the discovery of previously unknown phenomena in uninfected animals, such as novel connections between immune, endocrine and nervous systems.

To help organize information about proximate mechanisms, we suggested dividing them into direct and indirect effects, a scheme seconded by others (e.g. Biron et al., De Jong-Brink and Koene, Klein). We used this division because parasites can influence host behaviour only if they are able to alter the functioning of the nervous system (including sensory structures) or the musculoskeletal system. Parasites can have direct effects on host behavior by invading and destroying neurons and muscles and/or by the production of molecules capable of interacting with receptors on neurons and muscle cells. The effects of activating these receptors may be immediate (e.g. change in cell membrane potential) and/or delayed (e.g. change in gene transcription). Both immediate and delayed effects can produce changes in host behavior (Carew, 2000). Parasites can have indirect effects by inducing other host systems, such as the immune and endocrine systems, to secrete neuroactive compounds. Parasites can also have indirect effects by altering the functioning of host metabolism (e.g. altering the amount and quality of nutrients reaching the host's nervous system). The division of parasitic effects into direct and indirect mechanisms helps us make sense of the bewildering array

of connections between host and parasite, not all of which are related to changes in host behavior (e.g. see Beckage, 1993; Adamo et al., 1997).

Sometimes it can be difficult to assess whether physiological changes in the host will result in changes in behavior. For example, parasites often affect host gene regulation, as Combes points out. Unfortunately, whether these changes influence host behavior is often unclear, especially when the products of the genes in question are unknown or poorly understood. This difficulty reflects the gap in our understanding of how genes and behavior interact, a gap that may be narrowed by new technical advances, such as proteomics (Biron et al.).

Some indirect mechanisms may be used by parasites more often than others. We suggested that immune-neural connections may be especially vulnerable to parasitic manipulation, a suggestion also made by Klein and Helluy and Holmes. Neuroimmunological mechanisms should be considered as possible mediators of behavioral change in any host/parasite system. The contribution of endocrine changes should not be overlooked either (Helluy and Holmes). Hormones have connections to both the immune and nervous systems (Sapolsky, 1992).

Commentators (e.g. de Jong-Brink et al., 1999) recognized that discovering how parasites alter host behavior is difficult. For example the interpretation of physiological studies is not always straightforward. There can be problems in interpreting parasite-induced changes in immunohistochemical staining (Adamo, 2002, de Jong-Brink et al., 1999). Determining whether a parasite or host is secreting a specific compound is challenging, usually requiring advanced biochemical techniques and in vitro culture (e.g. see Adamo, in press). Complicating the issue is the demonstration by de Jong-Brink et al. (2001) that parasites can use more than one physiological mechanism to alter a single host behavior (see also Helluy and Holmes).

Diverse selective regimes may nonetheless result in convergent manipulation mechanisms. Although different types of parasites (e.g. parasitoids and trophically transmitted parasites (TPP)) may be under different kinds of selection pressures (see Kuris), they may still use similar mechanisms for the manipulation of host behavior. For example, rabies (a pathogen, Hemachudha et al., 2002), the trematode *Trichobilharzia ocellata* (a TPP, de Jong-Brink et al., 2001)

and *Cotesia congregata* (a parasitoid; Adamo, in press) all appear to manipulate host behavior, in part, by manipulating immune-neural connections in the host. Conversely, similar transmission pathways and similar behavioral changes may result from a variety of mechanisms (Moore, 1993). Pathogen or parasite type appears to be a poor predictor of the proximate mechanisms mediating parasite control.

We emphasized the potential costs of proximate mechanisms in our review because these are rarely considered and never measured. However, other types of costs should be considered too (Poulin et al.). Nonetheless, Poulin et al. illustrate why we need to know physiological mechanisms to fully assess the costs of parasitic manipulation. They discuss a system in which an amphipod is infested with a trematode (*Microphallus papillorobustus*). They argue that parasitic manipulation is costly in this system because more trematodes are destroyed by the immune system when they infest the brain than when they infest the abdomen (Thomas et al., 2000). However, trematodes in the abdomen are exposed to the entire array of the host's immune system and may need to make an energetic investment in immunosuppression (e.g. secretion of immunosuppressive substances—see Beckage, 1998 for some examples of immune evasion by parasitoids). Trematodes in the brain may not need to make any investment in immunosuppression if amphipods have a blood–brain barrier (see Bundgaard and Abbott, 1992 for a brief review of invertebrate blood–brain barriers). Some of the trematodes in the brain may be encapsulated by the microglia that afford some protection to the central nervous system (Sonetti et al., 1994), but by investing nothing (or very little) in immune evasion they may have more energy for growth and subsequent reproduction than do the trematodes in the abdomen. Without knowing the mechanisms by which trematodes in the brain and abdomen evade host immunity, it is premature to conclude who is paying the greater ‘cost’ by residing in different areas of the host. Although cost/benefit analysis has provided a productive viewpoint in evolutionary ecology, in many associations we need to know far more than we do about actual costs and benefits (see Rigby et al., 2002).

Unfortunately, determining the costs of parasitic manipulation is not a trivial problem, as Poulin et al. and others discuss. For example, parasitic effects may have multiple functions. A secreted compound may

both suppress immunity and alter host behavior (e.g. see [Kavaliers et al., 1999](#)). It may not be possible to measure the costs of manipulating behavior as separate from the cost of surviving in the host. Hurd argued that parasitic manipulation should be studied from the perspective of the host's entire physiology, and not just its behavior.

Lafferty and Webster proposed that human behavior may be influenced by common pathogens such as *Toxoplasma gondii*. However, the relationship between *T. gondii* and human behavior needs to be interpreted cautiously ([Webster, 2001](#)). These studies rest on the assumption that exposure to *T. gondii* results in latent disease that lasts a life-time, and that antibody titre is an accurate measure of this exposure (e.g. [Havlíček et al., 2001](#)). However, the evidence that people with measurable antibody titre have a latent infection is not definitive. For example, the duration of chronic infection is unknown, although in some people it can be decades ([Remington and Cavanaugh, 1965](#); [Remington and Krahenbuhl, 1982](#)). In AIDS patients and other immunocompromised individuals (e.g. bone marrow transplant patients) some individuals with antibodies to *T. gondii* redevelop the acute form of the disease due to a loss of immune surveillance ([Ambroise-Thomas and Pelloux, 1993](#)). However, more than 50% of similarly immunocompromised individuals may not show signs of parasite reactivation ([Cohen, 1999](#); [Janitschke et al., 2003](#)). Seropositive individuals who do not show signs of *T. gondii* reactivation when immunocompromised may have cleared themselves of the parasite, or there may be other reasons for the lack of reactivation. Hopefully new techniques for detecting *T. gondii* parasites will resolve this problem. Until then, studies on the effects of latent *T. gondii* on human behavior should be evaluated cautiously. Despite these admonitory remarks about the effects of *T. gondii* on human behavior, the effect of infectious disease on human behavior (e.g. [Ledgerwood et al., 2003](#)) deserves to be further explored. Meanwhile, we concur with Helluy and Holmes and Hughes that invertebrates hold distinct advantages for researchers interested in studying how parasites manipulate host behavior.

In some host/parasite systems, all members of a parasitic species produce the same behavioral change in all hosts. For example, all *Manduca sexta* parasitized by the wasp *C. congregata* do not feed during parasitoid emergence ([Adamo et al., 1997](#)). However, in many

host/parasite systems, the effect of the parasite on the host is variable (Webster). This range in parasitic effect could be caused by a number of factors, ranging from differences in the manipulative abilities of the individual parasites to differences in the host–parasite interaction. For example, in rabies, the ability of the same viral strain to induce neuroimmunological changes varies depending on the individual ([Hemachudha et al., 2002](#)). Webster rightly points out that this variability is usually ignored, but may hold important clues about how parasites manipulate their hosts.

In the face of such diversity and subtlety, it is no wonder that scientists who study this phenomenon, when faced with the question, “Where do we go from here?” behave like mice dumped out of a burlap bag in the middle of a parking lot, scurrying in every direction. We suggest that the truth of that image, however inelegant, is the strength of our emerging field of study. This is no weakening paradigm (see also Cézilly and Perrot-Minnot, Webster, Helluy and Holmes, Hughes). Most of us also agree that a multidisciplinary approach is beneficial, if not essential, and that the “by-product” explanation does not inevitably have the stature of null hypothesis. In their comments, many of our colleagues enlarge the concept of manipulation to include such disparate systems and topics as social insects (Hughes), malaria (Koella), cleaning symbionts (Morand), host transfer (Helluy and Holmes), and mate choice (de Jong-Brink). From niche construction (Brown, Combes) to human and clinical considerations (Webster, Lafferty), to the world of mathematical models (Gandon). The idea that parasites influence host behavior not only thrives, but generates novel ways of viewing the natural world.

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