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COMMENTARY

Parasite-altered feeding behavior in insects: integrating functional and mechanistic research frontiers

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ABSTRACT

Research on parasite-altered feeding behavior in insects is contributing to an emerging literature that considers possible adaptive consequences of altered feeding behavior for the host or the parasite. Several recent ecoimmunological studies show that insects can adaptively alter their foraging behavior in response to parasitism. Another body of recent work shows that infection by parasites can change the behavior of insect hosts to benefit the parasite; manipulations of host feeding behavior may be part of this phenomenon. Here, we address both the functional and the underlying physiological frontiers of parasite-altered feeding behavior in order to spur research that better integrates the two. Functional categories of parasite-altered behavior that are adaptive for the host include prophylaxis, therapy and compensation, while host manipulation is adaptive for the parasite. To better understand and distinguish prophylaxis, therapy and compensation, further study of physiological feedbacks affecting host sensory systems is especially needed. For host manipulation in particular, research on mechanisms by which parasites control host feedbacks will be important to integrate with functional approaches. We see this integration as critical to advancing the field of parasite-altered feeding behavior, which may be common in insects and consequential for human and environmental health.

KEY WORDS: Adaptive plasticity, Compensatory feeding, Ecoimmunology, Host manipulation, Host–parasite interactions, Self-medication

Introduction

Parasites live at the expense of their hosts, and at least 50% of species on Earth are parasites (see Glossary; Price, 1980; Windsor, 1988; Poulin and Morand, 2004). The ubiquity of parasites and the intimacy of their interactions with their hosts generate enormous biological impacts. For example, infectious viruses, bacteria and fungi are famous for their influence on the population dynamics of their hosts (Lefèvre et al., 2009b; Lafferty and Kuris, 2012), the evolution of host resistance (e.g. Ebert, 1994; Woolhouse et al., 2002) and even the evolution of sex (Morran et al., 2011). Until recently, however, few studies considered the possible proximate influence of parasitism by micro- or macroparasites on the feeding behavior of their hosts. This topic is now gaining some deserved attention with the rapid development of fields such as ecoimmunology (see Glossary; e.g. Rolff and Siva-Jothy, 2003; Schmid-Hempel, 2011), medication behavior (e.g. de Roode et al., 2013; Abbott, 2014) and parasite manipulation of hosts (e.g. Moore, 2002; Thomas et al., 2005; Libersat et al., 2009; Hughes et al.,

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2012). The host's feeding behavior is likely to be an important factor in host–parasite interactions because it has strong effects on the fitness of both hosts and parasites, with possible conflicts between an optimal host diet versus a diet optimal for parasitic survival (Maure et al., 2016). In theory, parasite-induced changes in the feeding behavior of their hosts could benefit the fitness of the host, parasite, both or neither (Poulin, 1995; Hurd, 2001; Moore, 2012).

Here we discuss changes in feeding behavior of insects induced by infections from their parasites (including microbial pathogens) that are adaptive for either host or parasite. Most studies that show a fitness benefit of altering host feeding behavior (either to the benefit of the host or parasite) lack a mechanistic understanding of the initiation of the behavior (Table 1). Conversely, many mechanistic studies do not address how parasite-altered feeding behavior might be adaptive for either party (Table 1). Therefore, our aim here is to integrate both functional and mechanistic frontiers in this field of research in hopes of guiding future research.

Parasite-altered feeding behavior of hosts: functional frontiers

We first use existing evolutionary theory as the basis for our functional perspective on parasite-altered feeding behavior, and we focus on insect hosts because of their suitability for experimental work in this field. Some earlier works (e.g. Poulin, 1995) focused on the question of whether these and other host behaviors are truly adaptations. Rather than revisiting this question, we move to more specific areas of evolutionary theory as guideposts for applying a functional approach, which tests fitness benefits of phenotypic traits. Coevolutionary theory (see Glossary) considers reciprocal adaptation between interacting species, and predicts the existence and potential escalation of adaptive antagonistic traits in hosts and their parasites (e.g. Kraaijeveld et al., 1998; Sasaki and Godfray, 1999). Even more pertinent to parasite-altered feeding behavior is an explicit consideration of adaptive plasticity theory (see Glossary), which predicts alternative adaptive phenotypic responses (e.g. feeding behavior and underlying physiology of the host) by a single genotype to different environmental conditions (e.g. imposed by parasites).

We identify four basic, functional types of parasite-altered feeding behavior of hosts (Fig. 1). Some of the existing terminology in the literature reflects the idiosyncrasies of particular sub-disciplines (e.g. anti-parasite medication behavior, de Roode et al., 2013; Abbott, 2014); thus, we advocate terms that can be applied more broadly: prophylaxis, therapy (see Glossary), compensation and manipulation. The first three are behavioral changes that are adaptive for the host. In this context, 'prophylaxis' refers to feeding changes prior to parasite infection, whereas 'therapy' refers to feeding responses after infection (de Roode et al., 2013). 'Compensation' refers to changes in feeding that redress physiological deficits imposed by either prophylaxis or therapy (or other physiological distress) (Singer et al., 2014). By contrast,

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Adaptive plasticity theory
Branch of evolutionary theory explaining and predicting how an environmentally induced change in behavior or phenotype during an individual's lifetime improves its prospects for survival and reproduction (adaptive plasticity). Adaptive plasticity is specifically expected when individuals can experience detectably different environments and there is a predictable trade-off in the adaptive value of alternative phenotypes among these environments.

Coevolutionary theory
Branch of evolutionary theory explaining and predicting reciprocal adaptive evolution among interacting species. When there is a highly specific host–parasite interaction from both parties' perspectives, coevolutionary theory predicts an arms race with escalation of both host defensive traits and parasite offensive (exploitation) traits. If there is asymmetry in specificity, then coevolutionary theory predicts an advantage to the more specific player (usually the parasite).

Density-dependent prophylaxis
A behavioral or phenotypic change that increases anti-parasite resistance in unparasitized hosts when they reach high population density. High host density is likely to be associated with an increased risk of parasitism.

Ecoimmunology
A new field integrating immunology with ecology and evolution. Here, we are particularly concerned with the effects of diet on animals' immunological responses to parasites and pathogens.

Medicinal therapy
Adaptive change in the intake of pharmacological substances by a host in response to infection by a parasite and resulting in anti-parasite resistance.

Neuropeptide
These peptides generally act as neuromodulators in the central and peripheral nervous system as well as regulatory hormones when released into the hemolymph. They act by binding to specific signal-transducing membrane receptors, inducing intracellular responses.

Nutritional therapy
Adaptive change in nutrient intake by a host in response to infection by a parasite and resulting in anti-parasite resistance.

Parasite
A micro- or macroorganism that lives in or on another organism and benefits by deriving nutrients at the host's expense. This definition includes pathogens as parasites.

Parasitoid
A parasite that develops within or on a single host, typically killing the host.

Therapy
Change in feeding behavior that: (1) increases the fitness of infected hosts, (2) decreases the fitness of uninfected hosts, (3) is detrimental to the parasite and (4) is preferentially enacted by the host in response to infection.

'manipulation' describes feeding changes in the host that are adaptive for the parasite (Moore, 2002; Thomas et al., 2005; Libersat et al., 2009; Hughes et al., 2012).

This language advantageously accommodates multiple functional mechanisms, such as alternative dietary mechanisms, e.g. medicinal versus nutritional therapy (see Glossary; Singer et al., 2014). Our suggested terminology also accommodates alternative life-history mechanisms of prophylaxis and therapy (as proposed by de Roode et al., 2013). For example, therapeutic changes in feeding behavior may have a social versus individual basis or may function via trans-generational versus cis-generational processes (Box 1). Because evidence for prophylaxis, therapy, compensation and manipulation as functional components of parasite-altered feeding behavior in insects is still somewhat new and patchy, we agree with Raubenheimer and Simpson (2009) that the time is right to adopt a

lexicon that reflects and does not limit conceptual developments in this field of study.

Prophylaxis and compensation

Adaptive plasticity theory predicts the existence of prophylactic foraging changes in response to cues that predict the risk of parasitism in insects, and several recent ecoimmunological studies support this prediction. For example, upon seeing parasitoid wasps (see Glossary), female *Drosophila melanogaster* flies switch their oviposition preference from low- to high-ethanol substrates (Kacsoh et al., 2013), a behavioral change that pre-emptively confers resistance to their larval offspring against some of their lethal parasitoids (Milan et al., 2012). This case study is significant because it proves the existence of trans-generational prophylaxis (de Roode et al., 2013), thus raising the question of how widespread it is. In holometabolous insects, trans-generational prophylaxis might be especially common, because ovipositing adults often have better opportunities to deploy pre-emptive defenses than do larvae. We further expect trans-generational prophylaxis to evolve in holometabolous insects in response to the risk of attack by parasites, such as insect parasitoids, that are not transmitted from mother to offspring. Vertically transmitted parasites, in contrast, are expected to induce trans-generational therapy (rather than prophylaxis) because offspring would respond directly to infections acquired from parents (de Roode et al., 2013).

In addition, the growing evidence for density-dependent prophylaxis (see Glossary) as a physiological immunological defense against pathogens in insects (e.g. Reeson et al., 1998; Wilson et al., 2001; Triggs and Knell, 2012) raises the question of whether there might be associated prophylactic or compensatory feeding changes in these host species. The first case of density-dependent prophylaxis showed that *Spodoptera exempta* caterpillars reared at high densities were more resistant to nucleopolyhedravirus than those reared alone (Reeson et al., 1998). A recent study of nutritional immunology of *S. littoralis* caterpillars shows differences among the nutrient intake targets that optimally support alternative immune responses (e.g. phenoloxidase versus lysozyme activity), which were different from the optimal nutrient intake target for insect growth (Cotter et al., 2011). Although this study found no shifts in feeding behavior that directly support or compensate for the upregulation of the host's specific immunological defenses, this possibility needs further testing (Cotter et al., 2011). To our knowledge, density-dependent prophylactic feeding changes and associated compensatory feeding responses are strictly hypothetical at present.

Therapy and compensation

In contrast to the limited study of prophylactic changes in foraging behavior, therapeutic changes in foraging behavior in response to parasites have been investigated experimentally in several cases of medicinal and nutritional therapy (reviewed in de Roode et al., 2013; Abbott, 2014; see Box 1). Abbott (2014) has refined the set of criteria for defining therapeutic self-medication based on adaptive plasticity theory (*sensu* Singer et al., 2009), and here we extend them to other types of therapy. These criteria require demonstrating that the putatively therapeutic change in behavior: (1) increases the fitness of infected hosts, (2) decreases the fitness of uninfected hosts, (3) is detrimental to the parasite and (4) is preferentially enacted by the host in response to infection. A recent case study exemplifies this functional approach to medicinal therapy by showing explicit support for these criteria: wood ant workers (*Formica fusca*) infected with the fungus *Beauveria bassiana*

Table 1. Studies of parasite-altered foraging behavior in insects organized by functional categories

Functional category	Host species	Parasite species	Behavioral change	Physiological basis of behavioral change	Reference
Trans-generational medicinal prophylaxis	*Drosophila melanogaster*	*Leptopilina boulardi* *Leptopilina heterotoma*	Change in oviposition preference for high-alcohol food	Visual stimulus of parasitic wasps mediated by neuropeptide F and memory formation	Milan et al., 2012; Kacsoh et al., 2013
Medicinal therapy	*Grammia incorrupta*	*Exorista mella*	Increased consumption of pyrrolizidine alkaloids	Partially known: related to a change in gustatory responses in sick host	Bernays and Singer 2005; Singer et al., 2009
Medicinal therapy	*Formica fusca*	*Beauveria bassiana*	Selective consumption of reactive oxygen species	Unknown	Bos et al., 2015
Trans-generational medicinal therapy	*Danaus plexippus*	*Ophryocystis elektroscirrha*	Change in oviposition preference for high toxin plant	Unknown	Lefèvre et al., 2010
Nutritional therapy	*Spodoptera littoralis*	Nucleopolyhedrovirus (NPV)	Increased protein consumption	Unknown	Lee et al., 2006
Nutritional therapy	*Spodoptera exempta*	*Bacillus subtilis*	Increased protein consumption	Unknown	Povey et al., 2009
Nutritional therapy	*Spodoptera exempta*	Nucleopolyhedrovirus (NPV)	Increased protein: carbohydrate ratio by decreasing carbohydrate intake	Unknown	Povey et al., 2013
Illness-induced anorexia	*Gryllus texensis*	*Serratia marcenscens*	Overall reduced food intake to decrease lipid consumption	Partially known: related to trade-offs between digestion and immune function	Adamo et al., 2008, 2010
Social medicinal therapy	*Apis mellifera*	*Ascophaera apis*	Increased resin collection	Unknown	Simone-Finstrom and Spivak 2012
N/A	*Apis mellifera*	*Paenibacillus larvae*	N/A	N/A	Simone-Finstrom and Spivak, 2012
Nutritional compensation	*Tenebrio molitor*	*Hymenolepis diminuta*	Increased nutrient intake	Vitellogenesis in host fat body downregulated by parasite-produced molecule; in ovary, egg development disrupted by host-derived inhibitor of juvenile hormone (Hurd, 2001)	Ponton et al., 2011a
Therapy	*Cryptotermes secundus*	Undescribed mite	Increased feeding time	Unknown	Korb and Fuchs, 2006
Manipulation?	*Apis mellifera*	Deformed wing virus (DWV)	Increase in number of foragers and foraging behavior; behavioral changes were more pronounced in DWV hosts versus *N. ceranae* infected hosts	Unknown; linked to in the vitellogenin–juvenile hormone regulatory network; infected bees show upregulation of octopamine pathways (Mayack et al. 2015)	Natsopoulou et al., 2016
Manipulation?	*Apis mellifera*	*Nosema ceranae*			
Manipulation?	*Platyprepia virginalis*	*Thelaira americana*	Switch in food preference from lupine to poison hemlock	Unknown	Karban and English-Loeb, 1997
Manipulation?	*Manduca sexta*	*Cotesia congregeta*	Perturbation of nutrient regulation	Unknown	Thompson and Redak, 2005; Thompson et al., 2005
Mechanical manipulation	*Lutzomyia longipalpis*	*Leishmania mexicana*	Increased feeding time and rate	Mechanical blockage of anterior midgut with promastigote secretory gel (PSG)	Rogers and Bates, 2007
Genomic manipulation	*Lymantria dispar*	*Lymantria dispar* NPV	Maintenance of foraging cues	Host induced to secrete a virally encoded enzyme	O'Reilly et al., 1992
Chemical manipulation	*Anopheles gambiae*	*Plasmodium falciparum*	Increased biting duration and frequency	Parasite reduces apyrase activity	Koella and Packer, 1996; Koella et al., 1998
Mechanical manipulation	*Glossina* spp.	*Trypanosoma brucei brucei*	More frequent probing and more voracious feeding	Parasites collect around mechanoreceptors in the labrum	Jenni et al., 1980
Chemical/genomic manipulation	*Manduca sexta*	*Cotesia congregeta*	Decreased feeding	Rise in octopamine levels – mechanism underlying the surge in octopamine remains unknown; parasite-induced cytokine storm and changes in host immune response genes	Adamo, 1998, 2005; Adamo et al., 2016
Manipulation	*Frankliniella occidental*	Tomato spotted wilt virus	Increased feeding rate	Unknown	Stafford-Banks et al., 2014; Stafford et al., 2011

Adaptive plasticity in host feeding behavior:

Parasite

Prophylaxis/ compensation

Host Manipulation

Therapy compensation
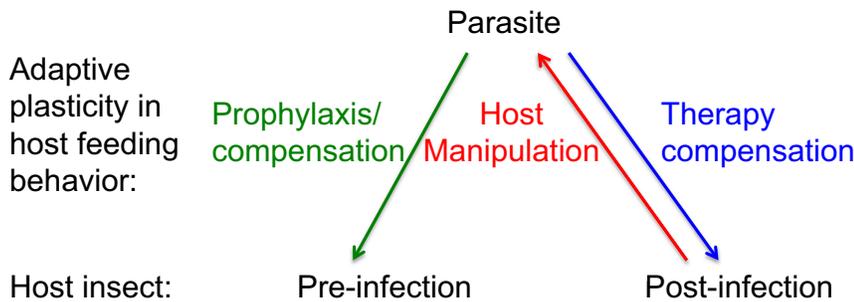
Host insect:

Pre-infection

Post-infection

Fig. 1. Alternative functional pathways of parasite-altered feeding behavior in insects. Arrows associated with prophylaxis (green), host manipulation (red) and therapy (blue) point to the beneficiary of fitness increases.

preferentially ingested liquid diets containing the putative medicinal substance, H_2O_2 (4), which increased the survival of infected workers (1) but decreased the survival of uninfected workers (2), and reduced the spore viability of the fungal pathogen (3) (Bos et al., 2015). Further testing of these criteria can identify additional cases of therapeutic feeding behavior as well as distinguish therapy from compensation, which does not necessarily confer fitness costs to uninfected hosts (2) (Abbott, 2014). Information on physiological mechanisms underlying feeding behavior (Box 2) is also critical for discerning therapy and compensation. In light of the growing evidence for therapeutic changes in foraging, we expect the existence of associated compensatory foraging in insects. However, research in this field has tended to emphasize medicinal or nutritional therapy over compensation (Singer et al., 2014; Shikano and Cory, 2016). It is possible, however, that some cases reported as 'macronutrient self-medication' (e.g. Povey et al., 2009, 2013) might more accurately represent cases of nutritional compensation (Shikano and Cory, 2016). In contrast to cases of medicinal and nutritional therapy (Box 1), there is also increasing support for illness-induced anorexia as a type of therapeutic change in infected insect hosts (Adamo, 2006; Adamo et al., 2010), but a definitive test using the criteria above has yet to be conducted.

Manipulation

Parasite manipulation of host feeding behavior has received very limited study in insects. Hence, our discussion of functional aspects of manipulation is mostly hypothetical. We expect selection to favor parasite manipulation of host feeding behavior when the host's normal diet creates a suboptimal environment for the parasite's

fitness. On the basis of coevolutionary theory (Hughes et al., 2012) and previous work (Adamo, 2002, 2013; Moore, 2002; Thomas et al., 2005; Escobedo et al., 2009; Helluy, 2013), we expect to see highly sophisticated manipulations of host feeding behavior by parasites with high host specificity. Host-specific parasitoid wasps, which infect a wide range of insects such as caterpillars, beetles, cockroaches and ants, are well known for manipulating the physiology of their insect hosts (Beckage and Gelman, 2004), and are likely candidates for subtle manipulations of host feeding behavior as well. To distinguish manipulation of host feeding behavior from mere disruption and dysfunction owing to parasitic infection, experiments will need to demonstrate that the parasite-altered behavior not only benefits the parasite, but also that the parasite-altered behavior is regulated or controlled physiologically by the parasite. For example, the wasp *Cotesia congregata* uses multiple mechanisms to suppress feeding by its caterpillar host, thus preventing the wasp larvae from being eaten by the host as they emerge and pupate on its integument (Adamo, 1997, 2005; Adamo

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Box 1. Life-history variation in therapeutic feeding responses to parasites

Adapting the scheme of de Roode et al. (2013) for animal medication behavior to our lexicon, the case of nutritional therapy by *Spodoptera littoralis* caterpillars exemplifies individual rather than social therapy. An individual *S. littoralis* caterpillar infected with a nucleopolyhedrovirus selects a protein-rich diet, which increases its probability of survival (Lee et al., 2006). By contrast, the case of medicinal therapy by *Apis mellifera* (honeybee) colonies represents social therapy. Honeybee colonies infected with the fungus *Ascophaera apis* increase the number of foragers collecting medicinal resin, resulting in a colony-wide decrease in infection intensity (Simone-Finstrom and Spivak, 2012). Compared with the cis-generational therapy in the previous examples, therapeutic behavior can also have trans-generational effects in which the behavioral change benefits the offspring. For example, trans-generational medicinal therapy has been discovered in the beloved monarch butterfly (*Danaus plexippus*). Monarch butterflies infected with the protist *Ophryocystis elektroscirrha* prefer to lay their eggs on plants containing high levels of toxins that reduce the parasite burden and virulence in offspring (Lefèvre et al., 2010).

Box 2. Regulation of insect feeding behavior in uninfected hosts

Insect chemoreception information is integrated in the central nervous system, and the balance between stimulatory and inhibitory signals arising from chemoreceptors determines whether a food is accepted or rejected (Simpson, 2013). Proximately, the change in chemoreceptor activity determines food intake choices. In uninfected hosts, chemoreceptor sensitivity changes as negative feedback accrues throughout a meal (Douglas and Simpson, 2013), and a major source of negative feedback is volumetric feedback provided by stretch receptors on the alimentary canal or body wall (Bernays and Chapman, 1973, Roessingh and Simpson, 1984).

Studies of physiological regulation of nutrient intake show that chemoreceptor sensitivity changes with the physiological state of the insect (Simpson et al., 1991; Zanotto et al., 1996). In unparasitized insects, changes in nutrient intake are attributed to blood-borne signals that feed back to modify the activity of excitatory and inhibitory chemoreceptors in the taste system (Chyb and Simpson, 1990; Chapman and de Boer, 1995; Lee et al., 2008; Simpson and Raubenheimer, 2012). Concentrations of dietary components in the hemolymph provide the basis for such signals (Simpson and Raubenheimer, 2012), and parasite-induced changes in host hemolymph metabolites have been observed in other systems (Thompson, 1986; Kearns et al., 1994; Senderskiy et al., 2014).

The physiological demands of parasite infection can generate resource competition between the parasite and host or among alternative physiological functions (e.g. immune response and reproduction) within the host (Smith and Holt, 1996; Moret and Schmid-Hempel, 2000; Cotter et al., 2011; Ponton et al., 2013). Nutritional therapy or compensation could enable a host to alleviate physiological resource limitation and increase host survival by aiding the immune response (Lee et al., 2006; Povey et al., 2009, 2013; Ponton et al., 2011b).

et al., 2016). It is possible that host-specific pathogens might manipulate host feeding behavior in such a way as to promote transmission to new hosts, as hypothesized for insect vectors of plant viruses for example (Blanc and Michalakis, 2016), and this deserves further investigation.

Parasite-altered feeding behavior of hosts: physiological frontiers

Experimental tests of evolutionary theory are crucial for resolving questions about the functional significance of parasite-altered host feeding behavior (i.e. whether the host or the parasite benefits from the change). However, understanding the physiological (including genomic and epigenetic) mechanisms underlying changes in feeding behavior is crucial for informing function, e.g. distinguishing therapy from compensation, as well as for identifying potential applications to issues such as public and environmental health. Currently, little is known about the physiological bases of prophylaxis, therapy, compensation and manipulation in cases of parasite-altered feeding behavior of insects (Table 1). Regardless of the functional outcome, parasite-altered feeding behavior must act proximately via the host's nervous system (Schmid-Hempel, 2011; Simpson, 2013), which entails modulation of chemoreception and feedbacks on other physiological processes of food rejection and intake. We therefore see the study of modulation of the host's chemoreception as a major research frontier for explaining how parasite-infected hosts can adaptively modify the quality or quantity of food intake. Parasite manipulation of host feeding behavior warrants further study along several physiological frontiers: direct and indirect manipulations of host resources, and biochemical, genomic and mechanical mechanisms.

Physiological mechanisms underlying prophylaxis, therapy and compensation

Parasite-altered feeding behavior can manifest as changes in food intake quality or quantity. Altered dietary choices based on food quality, which indicates the effects of food on the growth and development of the consumer, are based on physiological responses to a combination of several food components, such as macro- and micronutrients, toxins and non-digestible material (Simpson and Raubenheimer, 2012). It is important to note that a food's quality for a consumer is not absolutely determined by properties of the food; rather food quality is also a product of the consumer's physiological needs. In host–parasite interactions, the infection state of the host can determine the effect of any given food on the host's fitness (i.e. food quality). For example, infected hosts might experience increased fitness from consuming a higher ratio of protein to carbohydrate than the optimal ratio for uninfected hosts. Mechanisms responsible for the adaptive modification of the quality or quantity of food intake are therefore based on physiological feedbacks from post-ingestive processes to the host's sensory system (Simpson and Raubenheimer, 2012).

Uncovering the physiological feedbacks that change the chemosensory response in parasitized hosts is a research priority. Changes in gustatory response are likely to mediate feeding changes associated with functional mechanisms discussed above. The finding of parasite-induced changes in gustation in the woolly bear caterpillar, *Grammia incorrupta* (formerly *G. geneura*) (Bernays and Singer, 2005), as part of the physiological mechanism underlying medicinal therapy (Singer et al., 2009) opens the door for further study along these lines. Although there are other examples of parasitized insects changing their feeding choices with respect to nutrients and plant secondary metabolites, studies investigating

changes in gustation are limited. We therefore turn to the more extensive literature on physiological regulation of feeding in uninfected insects (Box 2). Based on the current understanding of feeding regulation in unparasitized insects (Behmer, 2009; Simpson and Raubenheimer, 2012), it would follow that shifting demands for nutrients and changes in blood metabolite levels could feed back on chemoreception as the basis for nutritional therapy and compensation in parasitized hosts.

Prophylaxis and therapy

Hormones and neuropeptides (see Glossary) warrant attention as potential mediators of prophylactic or therapeutic changes in feeding by insects in response to parasites. Research on other aspects of parasite-altered behavior of insects has shown the important role of hormones and neuropeptides in escape (Lefèvre et al., 2009a), reproductive (Roy et al., 2006) and grooming behaviors (Libersat et al., 2009). The increased foraging behavior in bees infected with *Nosema ceranae* is linked to changes in the vitellogenin–juvenile hormone regulatory network, which affects the timing of a bee's switch from nursing to foraging activities (Nelson et al., 2007). Infection results in an accelerated shift from nursing to foraging behavior, and can benefit the colony because infected bees spend less time with the brood and young workers, and more time with foragers and older workers (Seeley, 1982). In addition, infected bees show upregulation of octopamine pathways, and this neurohormone is linked to changes in foraging behavior (Mayack et al., 2015). Although the adaptive significance of the behavioral change remains untested, the authors suggest that this may be a parasite-induced change in behavior that enables the parasite to obtain energy for reproduction.

Neuropeptides are important neuromodulators that can accumulate in parasitized insects (Zitnan et al., 1995) and influence feeding behavior in unparasitized insects (reviewed in Audsley and Weaver, 2009; Caers et al., 2012). Therefore, they are likely candidates for mediating parasite-induced changes in insect feeding behavior. Neuropeptides have been shown to regulate the quantity of ingested food (Wei et al., 2000; Maestro et al., 2001; Downer et al., 2007; Al-Anzi et al., 2010), exhibit myoactivity on the visceral muscles of the gut, and may act elsewhere, such as the central nervous system (CNS) or gut stretch receptors (Audsley and Weaver, 2009). Neuropeptides are involved in the case of trans-generational prophylaxis by *D. melanogaster* flies discussed above (Kacsoh et al., 2013). While a visual cue initiates the behavioral change in *D. melanogaster* oviposition, neuropeptide F mediates the lasting effects of the oviposition behavior for 4 days after parasitoid exposure (Kacsoh et al., 2013). However, examples of neuropeptides as mediators of prophylactic or therapeutic changes in feeding are lacking. This is likely to be a case in which absence of evidence is not evidence of absence, because the functions of neuropeptides are complex and their mechanisms of action, interactions with each other, and secretion are still poorly understood.

Therapeutic anorexia

Rather than increasing food intake, a host may adaptively decrease its intake of some or all food in response to parasitism. This anorexic response could be achieved through changes in blood nutrient composition (imposed by the parasite) to reduce the quantity of food intake by progressively reducing phagostimulatory input during a meal and desensitizing gustatory receptors (Simpson and Simpson, 1992). The mechanism by which food intake is reduced could also involve increased blood osmolality, prolonged intervals between feeding or decreased duration of feeding bouts (Simpson, 1995).

This anorexia could serve a therapeutic function by decreasing mobility and thus conserving host energy stores to be used by other host processes. Alternatively, reduced feeding during infection may be a means to ameliorate the trade-off in physiological allocation between immune function and other physiological processes (Smith and Holt, 1996), such as digestion (Adamo et al., 2008, 2010). Crickets (*Gryllus texensis*) experimentally infected with a bacterial pathogen (*Serratia marcescens*) reduce their food consumption, specifically their intake of a high-lipid food (Adamo et al., 2010). After consuming a diet high in lipid (34% fat), which increases the hemolymph lipid concentration in uninfected crickets, infected crickets show reduced resistance against the pathogen compared with their counterparts on the control diet (10% fat). This relationship is mediated by monomeric apolipophorin III, a lipid transport protein in the hemolymph that increases in concentration on a high-lipid diet (Adamo et al., 2010). Further mechanistic study of illness-induced anorexia in other systems is needed to determine whether it plays a general role in ameliorating trade-offs between digestion and immunological defense.

Compensation

Compensatory changes in feeding by infected hosts are especially likely to involve physiological mechanisms modifying the quantity of food intake. For example, increased food intake by infected hosts can compensate for extra energetic or nutrient costs imposed by the growing parasites (Ponton et al., 2011a,b). Although reduced fecundity often accompanies infection (Hurd, 1993, 2001), Ponton et al. (2011a) showed that the increase in nutrient intake in infected beetles was able to compensate for parasite-induced reduction in fecundity. In this case, the mechanism is currently unknown, but the authors hypothesize that the dual increase in protein and carbohydrate consumption results in part from blood-borne nutrient feedback. It is also unknown whether volumetric feedbacks are altered with infection in insects to benefit the host. Perhaps the threshold for stretch receptors in infected hosts could change to modify the volume of intake, possibly combating infection by alleviating trade-offs in resource allocation (Box 2). Hypothetically, parasite-induced alteration of stretch receptor sensitivity could thus prolong a meal to increase food intake in service of compensation or therapy.

Physiological mechanisms underlying manipulation
Resource manipulations

Parasites and insect hosts may compete for existing and ingested resources (Schaub, 1992; Adamo, 1997), which may facilitate changes in host feeding behavior. Hosts often respond to the physical presence of parasitic infection by economizing on their resources, e.g. reducing egg production or increasing foraging activity. Parasites could exploit this standard response and use it to gain increased transmission (e.g. increased foraging increases exposure to predation for hosts of parasites with complex life cycles involving multiple hosts) or to prolong survival (the host invests more into maintenance). Pre-existing compensatory mechanisms of hosts can therefore be readily hijacked by parasites.

The depletion of a host's internal resources by the parasite may lead to compensatory feeding, further increasing resources for the parasite (Raubenheimer and Simpson, 1993; Lefèvre et al., 2008a). Apparent manipulation of a host's quantity of food intake could be a byproduct of the parasite's ingestion of host resources, resulting in volumetric feedbacks and increased host feeding rate or duration. Alternatively, parasites could increase their hosts' feeding on a particular resource when the nutritional requirements of hosts and parasites differ. Parasite manipulation of resources (Polak, 1996; Ponton et al., 2011b) can change host hemolymph composition and alter chemoreception through blood-borne feedbacks. Thompson and colleagues (Thompson and Redak, 2005; Thompson et al., 2005) have demonstrated the effects of parasitism by *Cotesia congregata* wasps on blood metabolite levels of their *Manduca sexta* caterpillar hosts, concluding that the observed changes create an optimal environment for the parasite and cause physiological dysfunction of nutrient regulation for the host. This example raises the question of whether this type of breakdown in nutrient regulation in parasitized hosts may act in similar systems to curb host defenses, such as nutritional therapy or compensation, which could otherwise be deployed against the parasite.

Chemical and genomic manipulations

Parasites may adaptively manipulate the feeding behavior of the insect host by introducing molecules that directly alter host physiology (i.e. chemical manipulation; Moore, 2002; Thomas et al., 2005). Hymenopteran parasitoids inject their hosts with venom and hormones that act as neuromodulators (Beckage, 1997). These parasite-derived factors have the ability to alter host development (Jones et al., 1986; Dover et al., 1995; Steiner et al., 1999; Cole et al., 2002), induce immunosuppression (Beckage and Gelman, 2004) and drastically alter host behavior (Thomas et al., 2002, 2003; Libersat et al., 2009; Hughes et al., 2008; de Bekker et al., 2014; Takasuka et al., 2015). Although none has yet been identified, these same factors may play a role in altering host feeding behavior. Identifying parasite-derived factors that control host behavior via the CNS (neuropharmacological factors; Adamo, 2013) is key to elucidating the mechanisms involved in manipulation.

Alternatively, manipulation of host feeding behavior may result from parasites inducing the host to make factors that benefit the parasite (i.e. genomic manipulation). Such factors are known to influence other aspects of host behavior; for example, the baculovirus *Lymantria dispar* nucleopolyhedrovirus induces its caterpillar host to secrete a virally encoded enzyme into the hemolymph, causing the host to climb to an elevated position prior to death, which increases viral transmission once the host disintegrates or liquefies (O'Reilly et al., 1992). In this example, foraging behavior is indirectly targeted because the virally encoded enzyme inactivates one of the host's major hormones, 20-hydroxyecdysone, a hormone that is thought to induce many caterpillars to climb down from their foraging positions in the treetops to hide in bark or leaf litter (Hoover et al., 2011). However, to our knowledge, there are no known examples of such factors directly influencing feeding behavior by the host. Proteomics approaches to studying the genome-wide changes in protein expression of the insect host CNS caused by parasites (Biron et al., 2005, 2006; Ponton et al., 2006; Lefèvre et al., 2008b) provide a unique opportunity to explore host-derived factors responsible for host manipulation, and we expect this approach to increasingly yield insight into physiological mechanisms of host manipulation by parasites.

The host's immune response is another prime target for manipulation by parasites because host immune responses can influence neural function and reliably change the physiology and behavior of the host (i.e. psychoneuroimmunological mechanisms *sensu* Adamo, 2012, 2013). The link between the immune and nervous systems could be a major axis relating resource manipulation, chemical manipulation and genomic manipulation (Adamo, 2002, 2013; Schmid-Hempel, 2011; Adamo et al., 2016). For example, the parasitoid *C. congregata* suppresses host feeding

by inducing a currently unidentified host-derived molecule to manipulate immune–neural connections of its caterpillar host, *M. sexta* (Adamo, 2005). Wasp larvae inhibit the breakdown of octopamine (released during immune and stress responses in other insects; Adamo, 2010), which decreases the host caterpillar's feeding (Adamo, 1998, 2005) by disrupting the neural output of the frontal ganglion, which in turn disrupts host swallowing (Miles and Booker, 2000). However, while increased octopamine levels are necessary to arrest host feeding, they are not sufficient. Most recently, Adamo et al. (2016) found that a surge of insect cytokines (which is potentially induced by the parasitoid) as well as changes in the expression of host immune genes [i.e. *plasmatocyte spreading peptide* (PSP) and *spätzle*] play an important role in suppressing feeding behavior of the host after parasitoid larvae emerge and pupate on the host's body. This body of work demonstrates the redundancy and multi-functionality of physiological mechanisms responsible for parasite manipulation of host feeding behavior (Adamo et al., 2016).

Mechanical manipulations

Finally, we note the possibility that parasite manipulation of host feeding behavior may occur through mechanical or physical means (Molyneux and Jefferies, 1986; Hurd, 2003). Such manipulations include obscuring host phagoreceptors, blocking the host foregut and damaging host tissue. The protist parasite *Leishmania* impairs the sandfly vector's ability to fully engorge during a blood meal and therefore induces the vector to increase feeding time and frequency, increasing parasite fitness by enhancing transmission efficiency (Rogers and Bates, 2007; Jenni et al., 1980). The parasite causes a mechanical blockage of the host's anterior midgut with promastigote secretory gel. In another example, increased transmission of the malaria parasite is partially due to mechanical damage of mosquito salivary glands by parasite sporozoites. Mosquitoes with damaged salivary glands have reduced apyrase activity, which increases mosquito feeding attempts and transmission of the malaria parasite (Ribeiro et al., 1984, 1985; Koella and Packer, 1996; Koella et al., 1998). Therefore, where the parasite resides in the host and the tissue with which it interacts inform the mechanism of manipulation.

Conclusions

The field of parasite-altered feeding behavior in insects is burgeoning with new studies. We have argued that therapy, compensation, prophylaxis and manipulation are adaptive types of parasite-altered feeding behavior that will be most profitably studied by integrating functional and mechanistic approaches. To better understand and distinguish prophylaxis, therapy and compensation, further study of physiological feedbacks affecting host sensory systems is especially needed. For host manipulation in particular, research on mechanisms by which parasites control host feedbacks will be important to integrate with functional approaches. Although few empirical examples exist, parasite manipulation of host feeding behavior may be subtle and thus more common than indicated in the literature.

To expand the study of this field, we propose some new research questions that stem from the above discussion. The functional genomics revolution offers great promise for identifying proteomic pathways underlying changes in foraging by infected hosts. How do these pathways compare among cases of prophylaxis, therapy, compensation and manipulation? Are some physiological feedbacks more commonly modified as anti-parasite defenses or easier to manipulate than others? To what extent might they be predicted by the phylogenetic relationships of parasites and hosts? How can

informatics and other advanced approaches shed new light on the critical issue of modulation of neural pathways underlying changes in host foraging? Lastly, given recent findings of the surprisingly potent role of the host microbiome in modifying host physiology and behavior, including anti-parasite defenses in insects (Oliver et al., 2014), it will be of interest to investigate how microbial mutualists might mediate parasite-altered feeding behavior in insects (Ponton et al., 2013).

We close by discussing the potential relevance of parasite-altered feeding in insects to human and environmental health. Several observations of dietary effects on insect host or parasite fitness are quite suggestive (Moore, 2002; McArt et al., 2014). In a recent example, Hien et al. (2016) showed that variation in the plant source of nectar meals consumed by malaria-carrying *Anopheles coluzzi* mosquitoes modified the infection prevalence and intensity as well as fitness components of the mosquito host and *Plasmodium* parasite. This observation raises the question of whether parasite-altered nectar feeding behavior occurs in this system, which would putatively link variation in ecological communities to variation in public health. Turning to the critical ecosystem service of pollination, recent evidence shows medicinal effects of floral nectar chemistry on bumblebees infected with an intestinal parasite (*Crithidia bombi*) (Richardson et al., 2015), as well as changes in bumblebee pollination behavior in response to floral nectar chemistry (Richardson et al., 2016). To the extent that bumblebees engage in medicinal therapy (Barrachi et al., 2015), parasite-altered foraging behavior may play a role in the dynamics of plant pollination in both agricultural and non-agricultural ecosystems. In summary, parasite-altered feeding behavior in insects is a topic of both basic and applied interest, offering great opportunities for experimental research in comparative physiology to inform ecology, evolution, and human and environmental health.

References

Abbott, J. (2014). Self-medication in insects: current evidence and future perspectives. *Ecol. Entomol.* **39**, 273-280.

Adamo, S. (1997). How parasites alter the behaviour of their insect host. In *Parasites and Pathogens: Effects on Host Hormones and Behaviour* (ed. N.E. Beckage), pp. 231-245. New York: Chapman & Hall.

Adamo, S. A. (1998). Feeding suppression in the tobacco hornworm, *Manduca sexta*: costs and benefits to the parasitic wasp *Cotesia congregata*. *Can. J. Zool.* **76**, 1634-1640.

Adamo, S. A. (2002). Modulating the modulators: parasites, neuromodulators and host behavioral change. *Brain Behav. Evol.* **60**, 370-377.

Adamo, S. A. (2005). Parasitic suppression of feeding in the tobacco hornworm, *Manduca sexta*: parallels with feeding depression after an immune challenge. *Arch. Insect Biochem. Physiol.* **60**, 185-197.

Adamo, S. A. (2006). Comparative psychoneuroimmunology: evidence from the insects. *Behav. Cog. Neurosci. Rev.* **5**, 128-140.

Adamo, S. A. (2010). Why should an immune response activate the stress response? Insights from the insects (the cricket *Gryllus texensis*). *Brain Behav. Immun.* **24**, 194-200.

Adamo, S. (2012). The strings of the puppet master: how parasites change host behavior. In *Host Manipulation by Parasites* (ed. D. Hughes, J. Brodeur and F. Thomas), pp. 36-51. Oxford, UK: Oxford University Press.

Adamo, S. A. (2013). Parasites: evolution's neurobiologists. *J. Exp. Biol.* **216**, 3-10.

Adamo, S. A., Roberts, J. L., Easy, R. H. and Ross, N. W. (2008). Competition between immune function and lipid transport for the protein apolipophorin III leads to stress-induced immunosuppression in crickets. *J. Exp. Biol.* **211**, 531-538.

Adamo, S. A., Bartlett, A., Le, J., Spencer, N. and Sullivan, K. (2010). Illness-induced anorexia may reduce trade-offs between digestion and immune function. *Anim. Behav.* **79**, 3-10.

Adamo, S. A., Kovalko, I., Turnbull, K. F., Easy, R. H. and Miles, C. I. (2016). The parasitic wasp *Cotesia congregata* uses multiple mechanisms to control host (*Manduca sexta*) behaviour. *J. Exp. Biol.* **219**, 3750-3758.

Al-Anzi, B., Armand, E., Nagamei, P., Olszewski, M., Sapin, V., Waters, C., Zinn, K., Wyman, R. J. and Benzer, S. (2010). The leucokinin pathway and its neurons regulate meal size in *Drosophila*. *Curr. Biol.* **20**, 969-978.

Audsley, N. and Weaver, R. J. (2009). Neuropeptides associated with the regulation of feeding in insects. *Gen. Comp. Endocrin.* **162**, 93-104.

Barrachi, D., Brown, M. J. F. and Chittka, L. (2015). Weak and contradictory effects of self-medication with nectar nicotine by parasitized bumblebees. *F1000Research* **4**, 73.

Beckage, N. E. (1997). New insights: How parasites and pathogens alter the endocrine physiology and development of insect hosts. In *Parasites and Pathogens: Effects on Host Hormones and Behavior* (ed. N. E. Beckage), pp. 3-36. Boston, MA: Springer US.

Beckage, N. E. and Gelman, D. B. (2004). Wasp parasitoid disruption of host development: implications for new biologically based strategies for insect control. *Annu. Rev. Entomol.* **49**, 299-330.

Behmer, S. T. (2009). Insect herbivore nutrient regulation. *Annu. Rev. Entomol.* **54**, 165-187.

Bernays, E. A. and Chapman, R. F. (1973). Regulation of feeding in *Locusta migratoria*: internal inhibitory mechanisms. *Ent. Exp. Appl.* **16**, 329-342.

Bernays, E. A. and Singer, M. S. (2005). Insect defences: taste alteration and endoparasites. *Nature* **436**, 476.

Biron, D. G., Marché, L., Ponton, F., Loxdale, H., Galéotti, N., Renault, L., Joly, C. and Thomas, F. (2005). Behavioural manipulation in a grasshopper harbouring hairworm: a proteomics approach. *Proc. R. Soc. Lond. B.* **272**, 2117-2126.

Biron, D. G., Ponton, F., Marché, L., Galeotti, N., Renault, L., Demey-Thomas, E., Poncet, J., Brown, S. P., Jouin, P. and Thomas, F. (2006). Differential expression of the proteomes of a host and its manipulative parasite at different stages of their biochemical interaction. *Insect. Mol. Biol.* **15**, 731-742.

Blanc, S. and Michalakis, Y. (2016). Manipulation of hosts and vectors by plant viruses and impact of the environment. *Curr. Opin. Insect. Sci.* **16**, 36-43.

Bos, N., Sundström, L., Fuchs, S. and Freitak, D. (2015). Ants medicate to fight disease. *Evolution* **69**, 2979-2984.

Caers, J., Verlinden, H., Zels, S., Vandersmissen, H. P., Vuerinckx, K. and Schoofs, L. (2012). More than two decades of research on insect neuropeptide GPCRs: an overview. *Front. Endocrinol.* **3**, 151.

Chapman, R. F. and de Boer, G. (1995). *Regulatory Mechanisms in Insect Feeding*. New York: Springer.

Chyb, S. and Simpson, S. J. (1990). Dietary selection in adult *Locusta migratoria*. *Ent. Exp. Appl.* **56**, 47-60.

Cole, T. J., Beckage, N. E., Tan, F. F., Srinivasan, A. and Ramaswamy, S. B. (2002). Parasitoid-host endocrine relations: self-reliance or co-optation? *Insect Biochem. Mol. Biol.* **32**, 1673-1679.

Cotter, S. C., Simpson, S. J., Raubenheimer, D. and Wilson, K. (2011). Macronutrient balance mediates trade-offs between immune function and life history traits. *Func. Ecol.* **25**, 186-198.

de Bekker, C., Merrow, M. and Hughes, D. P. (2014). From behavior to mechanisms: An integrative approach to the manipulation by a Parasitic Fungus (*Ophiocordyceps unilateralis* s.l.) of its host ants (*Camponotus* spp.). *Integr. Comp. Biol.* **54**, 166-176.

de Roode, J. C., Lefèvre, T. and Hunter, M. D. (2013). Self-medication in animals. *Science* **340**, 150-151.

Douglas, A. E. and Simpson, S. J. (2013). Nutrition. In *The Insects: Structure and Function* (ed. R.F. Chapman S.J. Simpson and A.E. Douglas), pp. 81-106. Cambridge, UK: Cambridge University Press.

Dover, B. A., Menon, A., Brown, R. C. and Strand, M. R. (1995). Suppression of juvenile hormone esterase in *Heliothis virescens* by *Microplitis demolitor* calyx fluid. *J. Insect Physiol.* **41**, 809-817.

Downer, K. E., Haselton, A. T., Nachman, R. J. and Stoffolano, J. G. Jr (2007). Insect satiety: sulfakinin localization and the effect of drosulfakinin on protein and carbohydrate ingestion in the blow fly, *Phormia regina* (Diptera: Calliphoridae). *J. Insect Physiol.* **53**, 106-112.

Ebert, D. (1994). Virulence and local adaptation of a horizontally transmitted parasite. *Science* **265**, 1084-1086.

Escobedo, G., Lopez-Griego, L. and Morales-Montor, J. (2009). Neuroimmunoendocrine modulation in the host by helminth parasites: a novel form of host-parasite coevolution? *Neuroimmunomodulation* **16**, 78-87.

Helluy, S. (2013). Parasite-induced alterations of sensorimotor pathways in gammarids: collateral damage of neuroinflammation? *J. Exp. Biol.* **216**, 67-77.

Hien, D. F. d. S., Dabiré, K. R., Roche, B., Diabaté, A., Yerbanga, R. S., Cohuet, A., Yameogo, B. K., Gouagna, L.-C., Hopkins, R. J., Ouedraogo, G. A. et al. (2016). Plant-mediated effects on mosquito capacity to transmit human malaria. *PLoS Pathog.* **12**, e1005773.

Hoover, K., Grove, M., Gardner, M., Hughes, D. P., McNeil, J. Slavicek, J. (2011). A gene for an extended phenotype. *Science* **333**, 1401-1401.

Hughes, D. P., Kronauer, D. J. C. and Boomsma, J. J. (2008). Extended phenotype: nematodes turn ants into bird-dispersed fruits. *Curr. Biol.* **18**, R294-R295.

Hughes, D. P., Brodeur, J. and Thomas, F. (2012). *Host Manipulation by Parasites*. Oxford, UK: Oxford University Press.

Hurd, H. (1993). Reproductive disturbances induced by parasites and pathogens of insects. In *Parasites and Pathogens of Insects* (ed. B. Thompson and B. Federic), pp. 87-105. San Diego, CA: Academic Press.

Hurd, H. (2001). Host fecundity reduction: a strategy for damage limitation? *Trends Parasitol.* **17**, 363-368.

Hurd, H. (2003). Manipulation of medically important insect vectors by their parasites *Annu. Rev. Entomol.* **48**, 141-161.

Jenni, L., Molyneux, D. H., Livesey, J. L. and Galun, R. (1980). Feeding behaviour of tsetse flies infected with salivarian trypanosomes. *Nature* **283**, 383-385.

Jones, D., Jones, G., Rudnicka, M., Click, A., Reckmalleczewen, V. and Iwaya, M. (1986). Pseudoparasitism of host *Trichoplusia ni* by *Chelonus* spp. as a new model system for parasite regulation of host physiology. *J. Insect Physiol.* **32**, 315-328.

Kacsoh, B. Z., Lynch, Z. R., Mortimer, N. T. and Schlenke, T. A. (2013). Fruit flies medicate offspring after seeing parasites. *Science* **339**, 947-950.

Karban, R. and English-Loeb, G. (1997). Tachinid parasitoids affect host plant choice by caterpillars to increase caterpillar survival. *Ecology* **78**, 603-611.

Kearns, J. Y., Hurd, H. and Pullin, A. S. (1994). Effect of metacestodes of *Hymenolepis diminuta* on storage and circulating carbohydrates in the intermediate host, *Tenebrio molitor*. *Parasitology* **108**, 473-478.

Koella, J. C. and Packer, M. J. (1996). Malaria parasites enhance blood-feeding of their naturally infected vector *Anopheles punctulatus*. *Parasitology* **113**, 105-109.

Koella, J. C., Sorensen, F. L. and Anderson, R. A. (1998). The malaria parasite, *Plasmodium falciparum*, increases the frequency of multiple feeding of its mosquito vector, *Anopheles gambiae*. *Proc. R. Soc. Lond. B.* **265**, 763-768.

Korb, J. and Fuchs, A. (2006). Termites and mites – adaptive behavioural responses to infestation? *Behaviour* **143**, 891-907.

Kraaijeveld, A. R., van Alphen, J. J. M. and Godfray, H. C. J. (1998). The coevolution of host resistance and parasitoid virulence. *Parasitology* **116**, S29-S45.

Lafferty, K. D. and Kuris, A. M. (2012). Ecological consequences of manipulative parasites. In *Host Manipulation by Parasites* (ed. D. Hughes, J. Brodeur and F. Thomas), pp. 158-171. Oxford, UK: Oxford University Press.

Lee, K. P., Cory, J. S., Wilson, K., Raubenheimer, D. and Simpson, S. J. (2006). Flexible diet choice offsets protein costs of pathogen resistance in a caterpillar. *Proc. R. Soc. Lond. B* **273**, 823-829.

Lee, K. P., Simpson, S. J. and Wilson, K. (2008). Dietary protein-quality influences melanization and immune function in an insect. *Func. Ecol.* **22**, 1052-1061.

Lefèvre, T., Roche, B., Poulin, R., Hurd, H., Renaud, F. and Thomas, F. (2008a). Exploiting host compensatory responses: the 'must' of manipulation? *Trends Parasitol.* **24**, 435-439.

Lefèvre, T., Thomas, F., Schwartz, A., Levashina, E., Blandin, S., Brizard, J. P., Le Bourligu, L., Demettre, E., Renaud, F. and Biron, D. G. (2008b). Malaria *Plasmodium* agent induces alteration in the head proteome of their Anopheles mosquito host. *Infect. Genet. Evol.* **8**, S12-S13.

Lefèvre, T., Adamo, S. A., Biron, D. G., Missé, D., Hughes, D. and Thomas, F. (2009a). Invasion of the body snatchers: The diversity and evolution of manipulative strategies in host-parasite interactions. *Adv. Parasitol.* **68**, 45-83.

Lefèvre, T., Lebarbenchon, C., Gauthier-Clerc, M., Missé, D., Poulin, R. and Thomas, F. (2009b). The ecological significance of manipulative parasites. *Trends Ecol. Evol.* **24**, 41-48.

Lefèvre, T., Oliver, L., Hunter, M. D. and de Roode, J. C. (2010). Evidence for trans-generational medication in nature. *Ecol. Lett.* **13**, 1485-1493.

Libersat, F., Delago, A. and Gal, R. (2009). Manipulation of host behavior by parasitic insects and insect parasites. *Annu. Rev. Entomol.* **54**, 189-207.

Maestro, J. L., Aguilar, R., Pascual, N., Valero, M.-L., Piulachs, M.-D., Andreu, D., Navarro, I. and Bellés, X. (2001). Screening of antifeedant activity in brain extracts led to the identification of sulfakinin as a satiety promoter in the German cockroach. Are arthropod sulfakinins homologous to vertebrate gastrins-cholecystokinins? *Eur. J. Biochem.* **268**, 5824-5830.

Maure, R., Thomas, F., Doyon, J. and Brodeur, J. (2016). Host nutritional status mediates degree of parasitoid virulence. *Oikos* **125**, 1314-1323.

Mayack, C., Natsopoulou, M. E. and McMahon, D. P. (2015). *Nosema ceranae* alters a highly conserved hormonal stress pathway in honeybees. *Insect Mol. Biol.* **24**, 662-670.

McArt, S. H., Koch, H., Irwin, R. E. and Adler, L. S. (2014). Arranging the bouquet of disease: floral traits and the transmission of plant and animal pathogens. *Ecol. Lett.* **17**, 624-636.

Milan, N. F., Kacsoh, B. Z. and Schlenke, T. A. (2012). Alcohol consumption as self-medication against blood-borne parasites in the fruit fly. *Curr. Biol.* **22**, 488-493.

Miles, C. I. and Booker, R. (2000). Octopamine mimics the effects of parasitism on the foregut of the tobacco hornworm *Manduca sexta*. *J. Exp. Biol.* **203**, 1689-1700.

Molyneux, D. H. and Jefferies, D. (1986). Feeding behavior of pathogen-infected vectors. *Parasitology* **92**, 721-736.

Moore, J. (2002). *Parasites and the Behavior of Animals*. Oxford, UK: Oxford University Press.

Moore, J. (2012). A history of parasites and host, science and fashion. In *Host Manipulation by Parasites* (ed. D. Hughes J. Brodeur and F. Thomas), pp. 1-9. Oxford, UK: Oxford University Press.

Moret, Y. and Schmid-Hempel, P. (2000). Survival for immunity: the price of immune system activation for bumblebee workers. *Science* **290**, 1166-1168.

Morran, L. T., Schmidt, O. G., Gelarden, I. A., Parrish, R. C., II and Lively, C. M. (2011). Running with the Red Queen: host-parasite coevolution selects for biparental sex. *Science* **333**, 216-218.

Natsopoulou, M. E., McMahon, D. P. and Paxton, R. J. (2016). Parasites modulate within-colony activity and accelerate the temporal polyethism schedule of a social insect, the honey bee. *Behav. Ecol. Sociobiol.* **70**, 1019-1031.

Nelson, C. M., Ihle, K. E., Fondrk, M. K., Page, R. E. and Amdam, G. V. (2007). The gene vitellogenin has multiple coordinating effects on social organization. *PLoS Biol.* **5**, 673-677.

Oliver, K. M., Smith, A. H. and Russell, J. A. (2014). Defensive symbiosis in the real world – advancing ecological studies of heritable, protective bacteria in aphids and beyond. *Func. Ecol.* **28**, 341-355.

O'Reilly, D. R., Brown, M. R. and Miller, L. K. (1992). Alteration of ecdysteroid metabolism due to baculovirus infection of the fall armyworm *Spodoptera frugiperda*: host ecdysteroids are conjugated with galactose. *Insect Biochem. Mol. Biol.* **22**, 313-320.

Polak, M. (1996). Ectoparasitic effects on host survival and reproduction: the *Drosophila-Macrocheles* association. *Ecology* **77**, 1379-1389.

Ponton, F., Lefèvre, T., Lebarbenchon, C., Thomas, F., Loxdale, H. D., Marché, L., Renault, L., Perrot-Minnot, M. J. and Biron, D. G. (2006). Do distantly related parasites rely on the same proximate factors to alter the behaviour of their hosts? *Proc. R. Soc. Lond. B* **273**, 2869-2877.

Ponton, F., Lalubin, F., Fromont, C., Wilson, K., Behm, C. and Simpson, S. J. (2011a). Hosts use altered macronutrient intake to circumvent parasite-induced reduction in fecundity. *Int. J. Parasit.* **41**, 43-50.

Ponton, F., Wilson, K., Cotter, S. C., Raubenheimer, D. and Simpson, S. J. (2011b). Nutritional immunology: a multi-dimensional approach. *PLoS Pathog.* **7**, e1002223.

Ponton, F., Wilson, K., Holmes, A. J., Cotter, S. C., Raubenheimer, D. and Simpson, S. J. (2013). Integrating nutrition and immunology: a new frontier. *J. Insect Physiol.* **59**, 130-137.

Poulin, R. (1995). "Adaptive" changes in the behaviour of parasitized animals: a critical review. *Int. J. Parasitol.* **25**, 1371-1383.

Poulin, R. and Morand, S. (2004). *Parasite Biodiversity*. Washington, DC: Smithsonian Institution Press.

Povey, S., Cotter, S. C., Simpson, S. J., Lee, K. P. and Wilson, K. (2009). Can the protein costs of bacterial resistance be offset by altered feeding behaviour? *J. Anim. Ecol.* **78**, 437-446.

Povey, S., Cotter, S. C., Simpson, S. J. and Wilson, K. (2013). Dynamics of macronutrient self-medication and illness-induced anorexia in virally infected insects. *J. Anim. Ecol.* **83**, 245-255.

Price, P. W. (1980). *Evolutionary Biology of Parasites*. Princeton, NJ: Princeton University Press.

Raubenheimer, D. and Simpson, S. J. (1993). The geometry of compensatory feeding in the locust. *Anim. Behav.* **45**, 953-964.

Raubenheimer, D. and Simpson, S. J. (2009). Nutritional PharmEcology: doses, nutrients, toxins, and medicines. *Integr. Comp. Biol.* **49**, 329-337.

Reeson, A. F., Wilson, K., Gunn, A., Hails, R. S. and Goulson, D. (1998). Baculovirus resistance in the noctuid *Spodoptera exempta* is phenotypically plastic and responds to population density. *Proc. R. Soc. Lond. B* **265**, 1787-1791.

Ribeiro, J. M. C., Rossignol, P. A. and Spielman, A. (1984). Role of mosquito saliva in blood vessel location. *J. Exp. Biol.* **108**, 1-7.

Ribeiro, J. M. C., Rossignol, P. A. and Spielman, A. (1985). Salivary gland apyrase determines probing time in anopheline mosquitoes. *J. Insect Physiol.* **31**, 689-692.

Richardson, L. L., Adler, L. S., Leonard, A. S., Andicoechea, J., Regan, K. H., Anthony, W. E., Manson, J. S. and Irwin, R. E. (2015). Secondary metabolites in floral nectar reduce parasite infections in bumblebees. *Proc. R. Soc. Lond. B* **282**, 20142471.

Richardson, L. L., Bowers, M. D. and Irwin, R. E. (2016). Nectar chemistry mediates the behavior of parasitized bees: consequences for plant fitness. *Ecology* **97**, 325-337.

Roessingh, P. and Simpson, S. J. (1984). Volumetric feedback and the control of meal size in *Schistocerca gregaria*. *Ent. Exp. Appl.* **36**, 279-286.

Rogers, M. E. and Bates, P. A. (2007). Leishmania manipulation of sand fly feeding behavior results in enhanced transmission. *PLoS Pathog.* **3**, 818-825.

Rolff, J. and Siva-Jothy, M. T. (2003). Invertebrate ecological immunology. *Science* **301**, 472-475.

Roy, H. E., Steinkraus, D. C., Eilenberg, J., Hajek, A. E. and Pell, J. K. (2006). Bizarre interactions and endgames: Entomopathogenic fungi and their arthropod hosts. *Annu. Rev. Entomol.* **51**, 331-357.

Sasaki, A. and Godfray, H. C. J. (1999). A model for the coevolution of resistance and virulence in coupled host-parasitoid interactions. *Proc. R. Soc. Lond. B* **266**, 455-463.

Schaub, G. A. (1992). The effects of trypanosomatids on insects. *Adv. Parasitol.* **31**, 255-319.

Schmid-Hempel, P. (2011). *Evolutionary Parasitology: The Integrated Study of Infections, Immunology, Ecology, and Genetics*. New York: Oxford University Press.

Seeley, T. D. (1982). Adaptive significance of the age polyethism schedule in honeybee colonies. *Behav. Ecol. Sociobiol.* **11**, 287-293.

Senderskiy, I. V., Timofeev, S. A., Seliverstova, E. V., Pavlova, O. A. and Dolgikh, V. V. (2014). Secretion of *Antonospora* (*Paranosema*) *locustae* proteins into infected cells suggests an active role of microsporidia in the control of host programs and metabolic processes. *PLoS ONE* **9**, e93585.

Shikano, I. and Cory, J. S. (2016). Altered nutrient intake by baculovirus-challenged insects: self-medication or compensatory feeding? *J. Invert. Path.* **139**, 25-33.

Simone-Finstrom, M. D. and Spivak, M. (2012). Increased resin collection after parasite challenge: a case of self-medication in honey bees? *PLoS ONE* **7**, e34601.

Simpson, S. J. (1995). Regulation of a meal: chewing insects. In *Regulatory Mechanisms in Insect Feeding* (ed. R.F. Chapman and G. de Boer), pp. 137-156. Boston: Springer US.

Simpson, S. J. (2013). Mouthparts and feeding. In *The Insects: Structure and Function* (ed. R.F. Chapman, S.J. Simpson and A.E. Douglas), pp. 46-79. Cambridge, UK: Cambridge University Press.

Simpson, S. J. and Raubenheimer, D. (2012). *The Nature of Nutrition: A Unifying Framework from Animal Adaptation to Human Obesity*. Princeton, NJ: Princeton University Press.

Simpson, S. J. and Simpson, C. L. (1992). Mechanisms controlling modulation by hemolymph amino acids of gustatory responsiveness in the locust. *J. Exp. Biol.* **168**, 269-287.

Simpson, S. J., James, S., Simmonds, M. S. J. and Blaney, W. M. (1991). Variation in chemosensitivity and the control of dietary selection behaviour in the locust. *Appetite* **17**, 141-154.

Singer, M. S., Mace, K. C. and Bernays, E. A. (2009). Self-medication as adaptive plasticity: increased ingestion of plant toxins by parasitized caterpillars. *PLoS ONE* **4**, e4796.

Singer, M. S., Mason, P. A. and Smilanich, A. M. (2014). Ecological immunology mediated by diet in herbivorous insects. *Integr. Comp. Biol.* **54**, 913-921.

Smith, V. H. and Holt, R. D. (1996). Resource competition and within-host disease dynamics. *Trends Ecol. Evol.* **11**, 386-389.

Stafford, C. A., Walker, G. P. and Ullman, D. E. (2011). Infection with a plant virus modifies vector feeding behavior. *Proc. Natl. Acad. Sci.* **108**, 9350-9355.

Stafford-Banks, C. A., Yang, L. H., McMunn, M. S. and Ullman, D. E. (2014). Virus infection alters the predatory behavior of an omnivorous vector. *Oikos* **123**, 1384-1390.

Steiner, B., Pfister-Wilhelm, R., Grossniklaus-Burgin, C., Rembold, H., Treiblmayr, K. and Lanzrein, B. (1999). Titres of juvenile hormone I, II and III in *Spodoptera littoralis* (Noctuidae) from the egg to the pupal moult and their modification by the egg-larval parasitoid *Chelonus inanitus* (Braconidae). *J. Insect Physiol.* **45**, 401-413.

Takasuka, K., Yasui, T., Ishigami, T., Nakata, K., Matsumoto, R., Ikeda, K. and Maeto, K. (2015). Host manipulation by an ichneumonid spider ectoparasitoid that takes advantage of preprogrammed web-building behaviour for its cocoon protection. *J. Exp. Biol.* **218**, 2326-2332.

Thomas, F., Schmidt-Rhaesa, A., Martin, G., Manu, C., Durand, P. and Renaud, F. (2002). Do hairworms (Nematomorpha) manipulate the water seeking behaviour of their terrestrial hosts? *J. Evol. Biol.* **15**, 356-361.

Thomas, F., Ulitsky, P., Augier, R., Dusticier, N., Samuel, D., Strambi, C., Biron, D. G. and Cayre, M. (2003). Biochemical and histological changes in the brain of the cricket *Nemobius sylvestris* infected by the manipulative parasite *Paragordius tricuspidatus* (Nematomorpha). *Inter. J. Parasit.* **33**, 435-443.

Thomas, F., Adamo, S. and Moore, J. (2005). Parasitic manipulation: where are we and where should we go? *Behav. Proc.* **68**, 185-199.

Thompson, S. N. (1986). Effects of dietary carbohydrate on the nutritional physiology and blood sugar level of *Trichoplusia ni* parasitized by the insect parasite, *Hyposoter exiguae*. *Parasitology* **92**, 25-30.

Thompson, S. N. and Redak, R. A. (2005). Feeding behaviour and nutrient selection in an insect *Manduca sexta* L. and alterations induced by parasitism. *J. Comp. Physiol. A* **191**, 909-923.

Thompson, S. N., Redak, R. A. and Wang, L. W. (2005). Host nutrition determines blood nutrient composition and mediates parasite developmental success: *Manduca sexta* L. parasitized by *Cotesia congregata* (Say). *J. Exp. Biol.* **208**, 625-635.

Triggs, A. and Knell, R. J. (2012). Interactions between environmental variables determine immunity in the Indian meal moth *Plodia interpunctella*. *J. Anim. Ecol.* **81**, 386-394.

Wei, Z., Baggerman, G., Nachman, R. J., Goldsworthy, G., Verhaert, P., de Loof, A. and Schoofs, L. (2000). Sulfakinins reduce food intake in the desert locust, *Schistocerca gregaria*. *J. Insect Physiol.* **46**, 1259-1265.

Wilson, K., Cotter, S. C., Reeson, A. F. and Pell, J. K. (2001). Melanism and disease resistance in insects. *Ecol. Lett.* **4**, 637-649.

Windsor, D. A. (1988). Most of the species on earth are parasites. *Int. J. Parasitol.* **28**, 1939-1941.

Woolhouse, M. E. J., Webster, J. P., Domingo, E., Charlesworth, B. and Levin, B. R. (2002). Biological and biomedical implications of the co-evolution of pathogens and their hosts. *Nat. Genet.* **32**, 569-577.

Zanotto, F. P., Raubenheimer, D. and Simpson, S. J. (1996). Haemolymph amino acid and sugar levels in locusts fed nutritionally unbalanced diets. *J. Comp. Physiol. B* **166**, 223-229.

Zitnan, D., Kingan, T., Kramer, S. J. and Beckage, N. E. (1995). Accumulation of neuropeptides in the cerebral neurosecretory system of *Manduca sexta* larvae parasitized by the braconid wasp *Cotesia congregata*. *J. Comp. Neurol.* **356**, 83-100.