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REVIEW

Parasite-induced alterations of sensorimotor pathways in gammarids: collateral damage of neuroinflammation?

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Summary

Some larval helminths alter the behavior of their intermediate hosts in ways that favor the predation of infected hosts, thus enhancing trophic transmission. Gammarids (Crustacea: Amphipoda) offer unique advantages for the study of the proximate factors mediating parasite-induced behavioral changes. Indeed, amphipods infected by distantly related worms (acanthocephalans, cestodes and trematodes) encysted in different microhabitats within their hosts (hemocoel, brain) present comparable, chronic, behavioral pathologies. In order to evaluate the potential connection between behavioral disturbances and immune responses in parasitized gammarids, this Review surveys the literature bearing on sensorimotor pathway dysfunctions in infected hosts, on the involvement of the neuromodulator serotonin in altered responses to environmental stimuli, and on systemic and neural innate immunity in arthropods. Hemocyte concentration and phenoloxidase activity associated with melanotic encapsulation are depressed in acanthocephalan-manipulated gammarids. However, other components of the arsenal deployed by crustaceans against pathogens have not yet been investigated in helminth-infected gammarids. Members of the Toll family of receptors, cytokines such as tumor necrosis factors (TNFs), and the free radical nitric oxide are all implicated in neuroimmune responses in crustaceans. Across animal phyla, these molecules and their neuroinflammatory signaling pathways are touted for their dual beneficial and deleterious properties. Thus, it is argued that neuroinflammation might mediate the biochemical events upstream of the serotonergic dysfunction observed in manipulated gammarids – a parsimonious hypothesis that could explain the common behavioral pathology induced by distantly related parasites, both hemocoelian and cerebral.

Key words: host behavioral manipulation, helminth, cerebral parasite, serotonin, neurodegeneration.

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Introduction

Reflecting on the intricate relationship between immune and neural systems, Adamo proposed that the behavioral changes induced by some parasites in their hosts to facilitate transmission could stem from adaptations aimed at defeating host defense mechanisms (Adamo, 2002). This is known as the 'neuroimmune hypothesis' of parasitic manipulation. Following infection, the central nervous system (CNS) relies on glial cells – the resident immune cells – to express cytokines and other mediators in the course of neuroinflammation – a process which appears to have both beneficial and deleterious effects on host tissues (Bentivoglio et al., 2011; O'Callaghan et al., 2008). Indeed, chronic neuroinflammation has been associated with neural dysfunction and specific behavioral disturbances in vertebrate hosts infected by various cerebral parasites (Bentivoglio and Kristensson, 2007; Hemachudha et al., 2002; Henriquez et al., 2009; Hamilton et al., 2008; Klein, 2003; Rozenfeld et al., 2003; Sciutto et al., 2007). The possible relationship between immune function and parasite-mediated behavioral changes has also been explored in invertebrates, including in helminth-infected gammarids (Adamo, 2002; Adamo, 2012; Adamo, 2013; Lefèvre et al., 2009; Thomas et al., 2005). In an effort to shed additional light on the connection between parasite-induced altered behavior and CNS neuroinflammatory processes, the present paper surveys extensively the behavioral, neural and immune aspects of the association between gammarids (Crustacea, Amphipoda) and their manipulative helminths.

Specifically, this article reviews evidence showing that, (a) manipulative hemocoelian helminths (acanthocephalans and cestodes) and cerebral trematodes induce alterations of sensorimotor pathways in their gammarid hosts, (b) the biogenic amine serotonin (5-hydroxytryptamine, 5-HT) mimics aspects of the altered behavior induced by parasites, and (c) serotonergic disruption in the gammarid brain mediates some cases of altered behavior in infected gammarids. In subsequent sections, the potential mode of action of serotonin is debated. It is argued that altered cue-oriented behavior in infected individuals could result from erroneous sensory information followed by correct central integration and motor response. The biochemical events upstream of the serotonergic dysfunction are considered in the light of the neuroimmune hypothesis, and the following questions are addressed. What information is available about the immune response to manipulative helminths in gammarids? More generally, what do we know about defenses deployed against pathogens in arthropods? Could Toll receptor signaling and cytokine cascades be implicated in the aminergic dysfunction? Are systemic immune challenges such as those presented by hemocelian acanthocephalans potentially triggering CNS neuroinflammation? Some cerebral parasites, in particular *Toxoplasma gondii*, also alter responses to environmental stimuli in their vertebrate hosts. What insights can we gain from these host–parasite associations? Evidence from these various fields converge to support the neuroimmune hypothesis and to suggest possible avenues of research.

Characterization of altered sensorimotor pathways induced by helminths in gammarids

Acanthocephalans (spiny-headed worms) require two hosts to complete their life cycle: an arthropod intermediate host and a vertebrate definitive host. In the species mentioned below, the gammarid becomes infected when it ingests acanthocephalan eggs released with the feces of the final host. The larva passes through the intestinal wall of the gammarid to encyst in the hemocoel (the body cavity), where it grows into a stage (cystacanth) infective to the definitive host. The worm becomes adult and reproduces in the intestine of vertebrates that prey upon infected gammarids.

In North America, the larval acanthocephalan *Polymorphus paradoxus*, which develops in the hemocoel of the freshwater *Gammarus lacustris* (Fig. 1A), alters the escape behavior of infected gammarids (Table 1). When mechanically disturbed, an uninfected individual is negatively phototactic and dives towards the bottom of the lake to hide in the mud (Bethel and Holmes, 1973; Holmes and Bethel, 1972). In contrast, upon disturbance, an infected gammarid is positively phototactic, and thus swims towards the surface, skims the water and then clings with the claws of its gnathopods (first thoracic appendages) to floating material, remaining motionless in a flexed posture (Fig. 1A). In addition, infected gammarids are more photophilic than uninfected ones. Therefore, two aspects of the photic behavior are manipulated in infected individuals: a chronic component, the photophilic behavior, and a phasic component, the positive phototactism as a response to mechanical disturbance. Habitat shift toward zones of higher illumination and aberrant escape behavior make *P. paradoxus*-infected gammarids more susceptible to predation by mallard ducks, muskrats and beavers, definitive hosts of the acanthocephalan (Bethel and Holmes, 1977). *Polymorphus marilis*, a parasite of diving ducks, also induces behavioral alterations in infected *G. lacustris* but does not affect the escape behavior. Gammarids harboring *P. marilis* are photophilic but negatively phototactic when disturbed. Moreover, they do not exhibit the clinging behavior induced by *P. paradoxus* at the end of an escape sequence (Bethel and Holmes, 1973).

In Europe, two species of amphipods, *Gammarus pulex* and *Gammarus roeseli*, have been thoroughly studied as hosts of three manipulative acanthocephalans: *Pomphorhynchus laevis* and *Pomphorhynchus tereticollis*, which are both fish parasites, and *Polymorphus minutus*, which is carried by birds (Table 1). The acanthocephalans affect various sensory pathways in their hosts: mechanical, photic, geotactic and olfactory, in different combinations (Table 1). Particularly intriguing is the differential effect of *P. laevis* on the behavior of *G. pulex*, a native species, and *G. roeseli*, an invasive species in central France (Bauer et al., 2005; Tain et al., 2007). Whereas *P. laevis* induces a strong photophilic behavior in *G. pulex*, it does not affect the photic behavior of *G. roeseli* (Table 1). Tain and colleagues suggest that local strains of *P. laevis* may have co-evolved with the dominant intermediate host *G. pulex*, allowing the behavioral manipulation to become established (Tain et al., 2007). Interestingly, *P. minutus* seems to have similar behavioral effects on *G. pulex* and *G. roeseli*, hinting that the great dispersal range of birds, definitive hosts of *P. minutus*, may result in less specificity in the relationship between *P. minutus* and its gammarid hosts (Bauer et al., 2005). A cestode, *Cyathocephalus truncatus*, with a life cycle similar to that of acanthocephalans, also affects the photic behavior of *G. pulex* (Franceschi et al., 2007).

The life cycle of *Microphallus papillorobustus* (Trematoda) requires three hosts for its completion. A first intermediate host, a mollusk in which asexual reproduction occurs, is intercalated between the final hosts, aquatic birds, and the second intermediate hosts, gammarids. In the brackish waters of southern France, the relationship between *M. papillorobustus* and its two sympatric hosts, *Gammarus aequicauda* and *Gammarus insensibilis*, is exquisitely complex (Helluy, 1983a). *Microphallus papillorobustus* larvae are present within the brain of gammarids (Fig. 1B–E) or attached to nerves in the thorax and abdomen (Helluy, 1982). In *G. aequicauda*, *M. papillorobustus* encysts mostly in the thorax and abdomen, while in *G. insensibilis*, *M. papillorobustus* encysts mostly in the brain (Helluy, 1983b). Field data and experimental infections show that *M. papillorobustus*

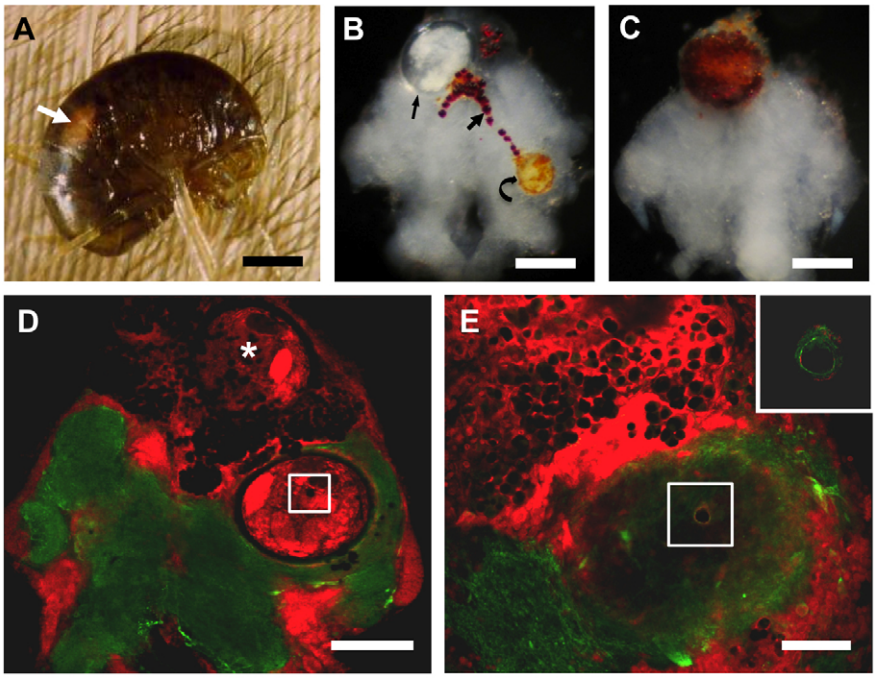

Fig. 1. Helminths and gammarids. (A) *Gammarus lacustris* infected by the hemocelian larval acanthocephalan (cystacanth) of *Polymorphus paradoxus* (arrow) (modified from Helluy, 1988). (B–E) Brains of *Gammarus insensibilis* parasitized by the cerebral larva (metacercaria) of *Microphallus papillorobustus* (modified from Helluy and Thomas, 2010). The thin arrow in B indicates a mature metacercaria in the protocerebrum, while the curved arrow points to a young larva partially melanized in a gammarid with altered behavior; carotenoid-rich lipid droplets are present at the surface of the brain (thick arrow). In C, a dead metacercaria is encapsulated and melanized in the protocerebrum of a normal gammarid; lipid droplets dot the surface of the encapsulated larva. Brains in B and C are whole mounts viewed with a stereomicroscope. In D, two metacercariae, one melanized and dead (asterisk), the other under attack, are encysted in the brain of a gammarid with altered behavior; a glutamine synthetase antibody (green) labels glial cell bodies and processes, while cell nuclei are stained with propidium iodide (red) in this confocal microscope optical section. E is a magnified view of the posterior metacercaria seen in D; a perforation through the cyst wall (boxed) appears lined with glial processes. Anterior is up. Scale bars: A, 2 mm; B–D, 200 μm; E, 80 μm.

Table 1. Helminth-induced behavioral, neural and immunological alterations in gammarids

Gammarus species	Helminth parasite	Altered behavior			Clinging	Altered 5-HT levels	Hemocyte no. and PO activity
		Photic	Geotactic	Olfactory			
G. lacustris	*Polymorphus paradoxus* (A)	Yes[1,9,11,12]			Yes[1,9,11,12]	Yes[15]	
G. lacustris	*Polymorphus marilis* (A)	Yes[1,9]			No[1,9]	No[15]	
G. pulex	*Pomphorhynchus laevis* (A)	Yes[2,3,6,7,18,19]	No[6,18]	Yes[5]		Yes[18,19]	Depressed[7,17]
G. pulex	*Pomphorhynchus tereticollis* (A)	Yes[18,19]	No[18]	Yes[16]		Yes[18]	Depressed[7]
G. pulex	*Polymorphus minutus* (A)	No[6,18]	Yes[4,6,7,18]		Yes[4]	No[18]	Depressed[7,17]
G. roeseli	*Pomphorhynchus laevis* (A)	No[3,19]				No[19]	Enhanced[17]
G. roeseli	*Polymorphus minutus* (A)		Yes[4,14]		Yes[4]		
G. pulex	*Cyathocephalus truncatus* (C)	Yes[8]	No[8]				No change[8]
G. insensibilis	*Microphallus papillorobustus* (T)	Yes[10]	Yes[10]		No[10]	Yes[13]	

Both chronic changes in response to light (shift in light preferendum toward zones of higher illumination, i.e. photophilia) and acute changes (reversed phototactism from negative to positive upon disturbance) are regrouped under the heading 'Altered photic behavior'.

Parasites: A, acanthocephalan; C, cestode; T, trematode.

5-HT, 5-hydroxytryptamine (serotonin); PO, phenoloxidase.

[1]Bethel and Holmes, 1973; [2]Bakker et al., 1997; [3]Bauer et al., 2000; [4]Bauer et al., 2005; [5]Baldauf et al., 2007; [6]Cezilly et al., 2000; [7]Cornet et al., 2009; [8]Franceschi et al., 2007; [9]Holmes and Bethel, 1972; [10]Helluy, 1984; [11]Helluy, 1988; [12]Helluy and Holmes, 1990; [13]Helluy and Thomas, 2003; [14]Haine et al., 2005; [15]Maynard et al., 1996; [16]Perrot-Minnot et al., 2007; [17]Rigaud and Moret, 2003; [18]Tain et al., 2006; [19]Tain et al., 2007.

larvae migrate to the brain in both juvenile and adult stages of *G. insensibilis*, but only in juvenile stages of *G. aequicauda*, hinting at the retention of juvenile characteristics (pedogenesis) in adult *G. insensibilis* (Helluy, 1983b). Moreover, only cerebral metacercariae manipulate gammarid behavior and modify the responses of the host to various environmental stimuli (Helluy, 1984). One metacercaria is sufficient to elicit changes in behavior but up to a dozen cysts are found within the brain protruding in the head cavity. Brain-infected gammarids are photophilic and negatively geotactic, as well as positively phototactic when disturbed (Helluy, 1984). Live mature larvae (Fig. 1B) but not dead, melanized ones (Fig. 1C) induce the altered behavior (Helluy, 1982; Kostadinova and Mavrodieva, 2005; Thomas et al., 2000), demonstrating that it is not the mechanical pressure of the cyst on cerebral tissue that affects responses to sensory stimuli in gammarids.

Parasites do not induce sluggishness or a general pathological state in gammarid hosts. Only specific behaviors are modified. For example, gammarids harboring manipulative helminths continue to engage in behaviors requiring highly sophisticated sensorimotor integration such as eating, molting and forming precopula (Bollache et al., 2001; Thomas et al., 1996). In addition, the larvae do not induce behavioral alterations from the start of the infection. It is only after a few weeks, when the cysts are mature and infective to the definitive hosts, that the behavioral responses are changed [acanthocephalans (see Bethel and Holmes, 1974); cestodes (Franceschi et al., 2008); trematodes (Helluy, 1982)]. Therefore, the parasites are modulating host behavior with precise timing and in very subtle ways (Helluy and Holmes, 2005). Gammarids infected by manipulative helminths are preyed upon significantly more than uninfected individuals by potential definitive hosts of the parasites such as birds for *P. paradoxus*-infected gammarids (Bethel and Holmes, 1977) and *M. papillorobustus*-infected gammarids (Helluy, 1984) and fish for *P. tereticollis*-infected gammarids (Perrot-Minnot et al., 2007) and *C. truncatus*-infected gammarids (Knudsen et al., 2001).

The survey above shows that infection by distantly related parasites (acanthocephalans, cestodes, trematodes) living in different microhabitats within the gammarids (brain and hemocoel) induces similar behavioral pathologies characterized by the alteration of sensorimotor pathways (Table 1). Parasite-induced changes in responses to environmental stimuli (photic, geotactic, olfactory and mechanical) imply that modulation of afferent signals is taking place, whereas altered motor responses are illustrated by flexed posture and clinging behavior in the *P. paradoxus*–*G. lacustris* system.

Serotonin reproduces aspects of the altered behavior induced by helminths in gammarids

The similarity between the flexed posture induced by *P. paradoxus* in *G. lacustris* (Fig. 1A) and the flexed abdominal posture induced by serotonin in lobsters (Livingstone et al., 1980) prompted a study in which serotonin was administered to uninfected *G. lacustris* to assess the effects of the monoamine in gammarids (Helluy and Holmes, 1990). Serotonin injected into the hemocoel of uninfected *G. lacustris* elicited the photopositive, clinging and skimming responses to disturbance characteristic of *P. paradoxus*-infected individuals (Helluy, 1988; Helluy and Holmes, 1990). The behavioral effects induced by the most effective hemolymph concentration (10 µg per individual weighing about 100 mg) culminated about 1 h after injection. Other neurotransmitters were tested in an attempt to reproduce the clinging behavior in uninfected gammarids but only serotonin had an effect; GABA, noradrenaline, dopamine and octopamine, at similar concentrations, failed to induce the clinging behavior in uninfected gammarids (Helluy and Holmes, 1990). In lobsters, the biogenic amine octopamine produces an extended posture (Livingstone et al., 1980). Not surprisingly, octopamine suppressed the clinging behavior in *P. paradoxus*-infected *G. lacustris*. However, octopamine had no effect on the photic behavior of infected individuals (Helluy, 1988; Helluy and Holmes, 1990).

Similar results were obtained in another *Gammarus* species, *G. pulex*. Hemocoel injection of octopamine had no effect on the photic behavior of *G. pulex* (Tain et al., 2006). Only injections of 5-HT (5 µg per individual) produced a significant change in photic behavior in the gammarids, inducing a pronounced shift from photophobic to photophilic behavior that mimicked the behavior of *G. pulex* parasitized by *P. tereticollis* or *P. laevis*. In contrast, the geotactic behavior of *G. pulex* was not affected by 5-HT (Tain et al., 2006). In yet another amphipod, *Echinogammarus marinus*, phototaxis and geotaxis increased significantly in a dose-dependent manner with exposure to serotonin (Guler and Ford, 2010). In this study, the biogenic amine was delivered not by a one-time injection into the hemocoel but by dilution in the seawater medium (10 ng l^{-1}

to 10 μg l^{-1}) over a period of weeks. Moreover, exposure to fluoxetine, but not to the anticonvulsant carbamazepine or the analgesic diclofenac, also significantly altered phototaxis and geotaxis activity in gammarids. Fluoxetine, better known as Prozac and Sarafem, is a selective serotonin reuptake inhibitor (SSRI) and a widely prescribed anti-depressant that prolongs the effects of serotonin in the synaptic cleft (Guler and Ford, 2010). Injection of serotonin also modifies the behavior of decapod crustaceans. Serotonin, but not dopamine or octopamine, changes locomotor and phototaxic behavior in the crab *Carcinus maenas* (McPhee and Wilkens, 1989).

Collectively, the evidence to date demonstrates that serotonin modulates sensorimotor pathways in crustaceans. Remarkably, in all experiments performed, exposure to serotonin reversed the photic behavior from negative to positive.

Serotonin levels are altered in the CNS of gammarids infected by manipulative helminths

The data presented so far indicate that serotonin modulates crustacean behavior but not that serotonin actually mediates parasite-induced manipulation of host behavior. The biogenic amine could be mimicking some other substance actually underlying the behavioral manipulation. However, evidence obtained through immunocytochemistry and proteomics tends to implicate serotonin as a mediator of the altered behavior induced by manipulative helminths.

Using immunocytochemical methods, Maynard and colleagues studied the nerve cord of *G. lacustris* and found that the number of serotonergic varicosities is augmented significantly in individuals infected by *P. paradoxus* but not in individuals infected by *P. marilis* when compared with uninfected individuals (Maynard et al., 1996). The level of 5-HT immunoreactivity is also increased significantly in the brain of *G. pulex* infected by *P. laevis* and by *P. tereticollis* but not in the brain of *G. pulex* infected by *P. minutus* (Tain et al., 2006; Tain et al., 2007) (Table 1). Finally, *P. laevis* infection has no effect on 5-HT immunoreactivity in the brain of *G. roeseli* (Tain et al., 2007). As mentioned above, *P. laevis* inverses the photic behavior in the local species *G. pulex*, but not in the invasive species *G. roeseli*, whereas the geotactic behavior but not the photic behavior is altered in *P. minutus*-infected *G. pulex* (Table 1). When evaluated together with the behavioral data, the results suggest that higher serotonin levels in the gammarid CNS correlate with strong photopositive behaviors as induced by *P. paradoxus* in *G. lacustris*, and by *P. laevis* and *P. tereticollis* in *G. pulex* (Lefèvre et al., 2009). Altered serotonin levels are not observed in systems with weaker or no effects of the parasite on the photic behavior of its gammarid host, such as *P. marilis* in *G. lacustris*, *P. minutus* in *G. pulex*, or *P. laevis* in *G. roeseli* (Table 1).

Patterns of serotonergic immunocytochemical labels were compared in the brain of uninfected *G. insensibilis* and *G. insensibilis* infected by the cerebral trematode *M. papillorobustus* (Helluy and Thomas, 2003). The intensity of the serotonergic signal was significantly decreased in the optic neuropils (Fig. 2), but increased in the olfactory lobes (Fig. 2) and the deutocerebrum in brain-infected individuals. In addition, the paired serotonergic tritocerebral giant neurons (TGNs; Fig. 2A) showed pronounced (Fig. 2B–E) signs of degeneration in the presence of the parasite (Helluy and Thomas, 2003). The paired TGNs are the two largest cells of ~40 serotonergic neurons; with their projections to all brain regions and to the nerve cord, these giant neurons invite comparisons with the mammalian serotonergic raphe nuclei. The axon length (2-D projection) of the TGNs from cell body to lateral projections was significantly shorter in the brain of *M. papillorobustus*-infected *G. insensibilis* than in the brain of uninfected individuals (S.H., unpublished data). In some extreme cases of degeneration, axon and projections were too deformed to be traced and measured (Fig. 2D,E). Interestingly, degeneration of the TGNs was not observed in the brain of *G. pulex* harboring the acanthocephalan *P. laevis* and TGN axon length was not modified in that host–parasite association (Tain et al., 2006). Proteomics tools also point to the involvement of serotonin in the trematode–gammarid system: the enzyme aromatic-L-amino acid decarboxylase, part of the synthetic pathway of serotonin (and dopamine), is expressed at higher levels in the brain of *G. insensibilis* infected by *M. papillorobustus* than in uninfected brains (Ponton et al., 2006).

In brief, serotonin exposure mimics aspects of the behavior induced by parasites. Moreover, disruption of the serotonergic

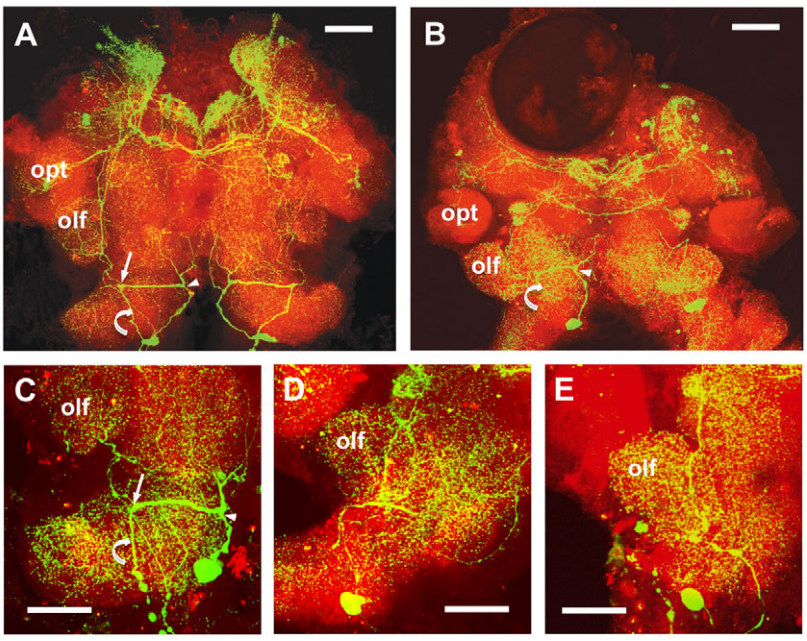

Fig. 2. Distribution of serotonin in brains of *Gammarus insensibilis*. (A) Brain of a normal uninfected gammarid. (B–E) Brains of *Microphallus papillorobustus*-infected gammarids with altered behavior. Serotonergic tritocerebral giant neurons (TGNs) are enlarged in C–E. The arrowheads point to projections of the TGNs to medial brain areas. The straight arrows indicate the branching of the lateral projections of the TGNs to olfactory (olf) and optic (opt) areas, while the curved arrows show the posterior trajectory of the axons to the nerve cord. Whereas the cell body of TGNs is clear in all pictures, B–E present different degrees of degeneration of the TGN neurites in infected individuals. Brains were subjected to immunocytochemical treatment for serotonin (green); neuropile tangles are labeled with a synapsin antibody (red). Lateral is left and anterior is up. Stacks of confocal optical sections through whole brains are presented in all images [A and B (modified from Helluy and Thomas, 2003)]. Scale bars: 100 μm.

system has been documented in helminth/gammarid systems involving hemocoelian acanthocephalans and a cerebral trematode. Thus, it is likely that 5-HT is actually involved in sensorimotor alterations induced by manipulative parasites in gammarids. However, additional evidence should be sought from experiments attempting to 'cure' the altered behavior in infected individuals with serotonin blockers such as methysergide (see Aréchiga et al., 1990).

Speculation on the mode of action of serotonin

In infected gammarids, clinging consists of the sustained flexion of the claw of the gnathopods onto any material, accompanied by extreme flexion of abdominal segments (Fig. 1A). It is reasonable to assume that the mechanism underlying flexion, a basic posture, is similar among crustaceans. Livingstone and colleagues found that serotonin increases the firing rate of the tonic flexor motoneurons and depresses the activity to the extensor muscles in the abdomen of lobsters, possibly through the modulation of driver or command neurons in the nerve cord (Livingstone et al., 1980). Acting at presynaptic sites, serotonin also facilitates transmitter release at the neuromuscular junction. Interestingly, in the same sensorimotor circuit, Strawn and colleagues demonstrated that the firing pattern in the sensory neurons is also strongly enhanced in the presence of serotonin upon stimulation of the cuticle (Strawn et al., 2000). Thus, in decapod crustaceans 5-HT modulates posture at the sensory, central and motor levels of the pathway.

Serotonin also modulates photoreceptor activity in crustaceans (Aréchiga et al., 1990; Rodríguez-Sosa et al., 2006). For example, the firing frequency of action potentials is increased in the caudal photoreceptors in crayfish upon exposure to serotonin (Rodríguez-Sosa et al., 2006). It is tempting to speculate that serotonergic modulation of visual pathways changes the nature of incoming information to optic areas of the CNS. The altered firing pattern in visual neurons would provide erroneous information on the intensity of the photic stimulus to the gammarid CNS. The CNS would respond correctly to the modified sensory signal and direct infected hosts towards what appears to be a dark and safe environment. The same principle could apply to olfactory stimuli. Indeed, serotonin is known to modulate olfactory pathways in both insects (Dacks et al., 2008) and vertebrates (Liu et al., 2012). Predator odor would be encoded in chemosensory neurons in a way that signals another scent, making water permeated by fish odorous molecules attractive to *P. laevis*-infected gammarids (see references in Table 1).

Immune response in gammarids and other arthropods

Invertebrates lack the adaptive arm of the immune system and do not possess immunoglobulins. However, they have developed a variety of modalities to respond to pathogen infection (Hoffmann and Reichhart, 2002; Iwanaga and Lee, 2005; Nappi and Christensen, 2005; Ottaviani et al., 2007). Depending on the invader, an arthropod may deploy the following components of the innate immune system: phagocytosis, encapsulation by hemocytes, phenoloxidase (PO) activity leading to melanin synthesis, lectins or agglutinins, Toll signaling cascades, nitric oxide (NO), reactive intermediates of oxygen (ROI) and nitrogen (RNI), pro-inflammatory cytokines, as well as antimicrobial and antifungal peptides. In addition, it is suggested that carotenoids (Fig. 1B,C) may play a role in scavenging free radicals and cytotoxic molecules in crustaceans (Cornet et al., 2007; Gaillard et al., 2004; Perrot-Minnot et al., 2011).

Phenoloxydase enzymatic pathway and hemocyte concentration

One of the main components of the arthropod innate immune system is the prophenoloxidase (proPO) cascade that leads to the synthesis of melanin (Cerenius and Söderhäll, 2004; Jiravanichpaisal et al., 2010; Nappi and Christensen, 2005). This pathway provides a general defense mechanism against a large range of pathogens including macroparasites. Upon infection, proPO undergoes a limited proteolysis by a serine protease to yield the active form of the enzyme, PO. While the resulting melanin physically isolates the parasites, its synthesis generates highly reactive and toxic quinone intermediates as well as superoxide and hydroxyl radicals (Nappi and Christensen, 2005). These molecules have enzymatic and DNA-damaging properties and contribute to the destruction of parasites. Melanization occurs in both insects and mammals along some common metabolic pathways but is used for immune defense only in arthropods. Semi-granular and granular hemocytes synthetize proPO in crustaceans (Cerenius and Söderhäll, 2004). Both cell types were identified in the amphipod *Echinogammarus stammeri* (Dezfuli et al., 2008).

Aspects of the immune response have been thoroughly studied in two gammarid species (*G. roeseli* and *G. pulex*) harboring three acanthocephalan species and a cestode (Table 1). Manipulative acanthocephalans strongly depress hemocyte count and PO activity in their hosts (Cornet et al., 2009; Rigaud and Moret, 2003), while the cestode appears to evade host immune response possibly through molecular mimicry (Franceschi et al., 2007). It is interesting to consider the whole gamut of permutations documented for helminth species, gammarid host species, host behavior and host phenoloxydase activity (Table 1). In brief, *P. laevis*, *P. tereticollis* and *P. minutus* alter the behavior of *G. pulex* (Bakker et al., 1997; Cezilly et al., 2000) and depress its PO activity (Cornet et al., 2009; Rigaud and Moret, 2003), thus avoiding melanization and death. Only 0.17% of *P. laevis* larvae recovered from the hemocoel of *E. stammeri* (N=18,710) were partially or totally melanized (Dezfuli et al., 2008). The cestode *C. truncatus* also alters the behavior of *G. pulex*, but with no apparent effect on PO activity (Franceschi et al., 2007). In another host, *G. roeseli*, the acanthocephalan *P. laevis* does not induce alterations of behavior (Bauer et al., 2000), but actually increases the PO activity of the host (Rigaud and Moret, 2003).

When studies on brain serotonin immunocytochemistry are also taken into consideration, it appears that behavioral manipulation, in particular altered photic behavior, is accompanied by changes in serotonin levels in the CNS, decreased hemocyte concentrations and depressed PO activity (e.g. *P. laevis* in *G. pulex*). When acanthocephalans fail to induce behavioral changes (e.g. *P. laevis* in *G. roeseli*), serotonin levels are not altered, but hemocyte concentrations are increased and PO activity is enhanced (Lefèvre et al., 2009) (Table 1). Taken together, the evidence presented above seems to indicate that manipulative acanthocephalans may raise serotonin levels in the CNS, but depress aspects of the host defense responses. Let us turn to other components of the immune system that are phylogenetically conserved in arthropods but have not yet been investigated in gammarids.

NO and other free radicals

The synthesis of the gaseous molecule NO from L-argininine is catalyzed by the enzyme nitric oxide synthase (NOS). A ubiquitous member of the immune and nervous systems, NO is a potent molecule with deleterious properties towards pathogens ranging from viruses to metazoans (Rivero, 2006). In *Drosophila*, NO may be implicated in the destruction of parasites through various

pathways (Carton et al., 2009). As an essential signaling molecule, it may be involved in mediating *Drosophila* spp. innate immune signaling pathways producing cytotoxic molecules (Nappi and Vass, 2001). However, NO can also interact with certain melanin precursors including tyrosine and dopamine and with reactive intermediates of oxygen such as superoxide anion (O_2^-) and hydrogen peroxide (H_2O_2) to generate toxic compounds (Carton et al., 2009).

It is revealing to examine the interplay between the different components of the innate immune response, in particular the connection between NO levels and PO/melanogenic activity. For instance, NO production is augmented in the presence of hemocyte-mediated melanotic encapsulation of a parasitoid wasp in *Drosophila melanogaster* (Nappi et al., 2000) but it is also increased in the absence of melanotic encapsulation in *Drosophila paramelanica* (Carton et al., 2009). In both cases the host mounts an effective defense against the macroparasite, suggesting some involvement of NO in the host immune response (Carton et al., 2009). In another insect, *Galleria mellonella*, stimulation of NO production is also independent of PO activity (Krishnan et al., 2006). As emphasized by Adamo and shown by the examples cited above, various components of the innate immune response are deployed independently by infected hosts (Adamo, 2004). Therefore, it is plausible that a long co-evolutionary history has led to the attenuation of biochemical cascades leading directly to parasitic death through melanotic encapsulation, and to the enhancement of other pathways of the innate immune system (e.g. reactive oxygen and nitrogen species and cytokine production), eliciting secondary pathologies favorable to invaders.

Cytokines

Cytokines are signaling molecules of the immune system that play a central role in CNS inflammatory responses as well as in neurotransmitter modulation. Released by various cells including glia, these proteins bind with high affinity cell surface receptors and regulate the transcription of cellular genes. The pro-inflammatory cytokines IL-1α, IL-1β, IL-6 and TNF-α have been successfully labeled by immunocytochemistry in invertebrate brains (Sonetti and Peruzzi, 2004). However, few full-title invertebrate cytokines have been characterized so far (Malagoli, 2010). Ottaviani and colleagues argue that it is the structure of the cytokine helical proteins that is conserved across animal phyla rather than the sequence of nucleotides or amino acids (Ottaviani et al., 2007). Of great relevance for host–parasite systems is a member of the tumor necrosis factor (TNF) family, Eiger, identified in insects (Igaki et al., 2002). It is expressed in the fat body and implicated in melanization (Mabery and Schneider, 2010). Moreover, there is evidence for glial-derived prodegenerative TNF-α signaling in *Drosophila* (Keller et al., 2011). In crustaceans, the TNF superfamily gene, the TNF receptor superfamily gene, and the lipopolysaccharide (LPS)-induced TNF-α factor have been characterized in the shrimp *Liptopenaeus vannamei* (Wang et al., 2012). TNF is also present in the shrimp *Marsupenaeus japonicus* (Mekata et al., 2010) where it is constitutively expressed in the muscle, stomach, brain and gill. The expression of *MjTNF* is augmented in lymphoid organ cells following exposure to various immune stimulations including peptidoglycan, polycytidylic acid and LPS, suggesting a role for MjTNF in the innate immune defense in crustaceans (Mekata et al., 2010). Indeed, Vidal suggested that TNF might represent an ancient and central signaling molecule that acts as a key pro-inflammatory cytokine in the innate immune system of invertebrates and vertebrates (Vidal, 2010).

Immune response in the CNS

In invertebrates, as in vertebrates, the CNS lacks the adaptive arm of the immune system and relies on innate mechanisms based on the activation of resident glial cells (Streit et al., 2004; Bentivoglio et al., 2011). In vertebrates, glial cells respond to tissue injury and infectious agents with a complex panoply of molecules such as NO and inflammatory cytokines. Similar immune cascades are observed in invertebrates (Cooper, 2003; Peruzzi et al., 2004; Salzet, 2000). Microglia, present in the brain of mollusks (Peruzzi et al., 2004) and vertebrates, have not been described in arthropods (Freeman and Doherty, 2006). Doherty and colleagues define three types of glial cells in the brain of *Drosophila*: ensheathing glia, cortex glia and astrocytes (Doherty et al., 2009). Both ensheathing glia and astrocytes were clearly revealed by a glutamine synthetase antibody in the brain of *G. insensibilis* (Helluy and Thomas, 2010).

Cerebral metacercariae of *M. papillorobustus* elicit a robust immune response in the brain of infected gammarids (Thomas et al., 2000). Indeed, signs of melanization (Fig. 1) were observed in 13% of the brains (N=115) in *M. papillorobustus*-infected *G. insensibilis* (Helluy and Thomas, 2010). Astrocytes and their processes were abundant at the surface of the parasites while levels of NO synthase were elevated at the host–parasite interface in the brain of gammarids harboring mature cerebral larvae and demonstrating altered behavior (Helluy and Thomas, 2010). Schmid-Hempel coined the term ‘momentous molecular war’ in the context of parasite immune evasion (Schmid-Hempel, 2008). Momentous molecular war also seems particularly apt for describing host–parasite interactions in the brain of *M. papillorobustus*-infected *G. insensibilis* (Fig. 1D,E). We proposed that an ‘arm-wrestling’ contest is taking place in infected gammarid brains (Helluy and Thomas, 2010). The metacercaria would elicit a persistent attack from the host brain with deployment of cytokines, NO and other toxic molecules that interact with the parasite but also with the host serotonergic neurons, resulting in the behavioral pathology exhibited by parasitized gammarids. Well-protected within a thick cyst wall, most mature metacercariae would avoid encapsulation but some would succumb to the host defense mechanisms. When the protracted war is won by the host, perforations are poked in the wall of the cerebral cysts and melanin granules accumulate around the parasite (Fig. 1C–E).

Helminth immune recognition

The internal host environment is monitored by pattern recognition receptors (PRRs). These molecules detect pathogen-associated molecular patterns (PAMPs), and transmit the information to signaling receptors. These receptors in turn activate the synthesis of attack molecules. Helminths appear to interact with host signaling pathways through PRR lectins and through receptors belonging to the Toll family (Friberg et al., 2010; Mishra et al., 2009; Perrigoue et al., 2008). First discovered in *Drosophila*, this group of transmembrane proteins plays an important role in the innate immune system of both vertebrates and invertebrates. The Toll pathway is activated when excretory/secretory products released by helminths stimulate Toll receptors, ultimately leading to various defense responses such as production of antimicrobial peptides and melanization through the PO cascade (McTaggart et al., 2009). Seven Toll receptor genes have been identified in the crustacean *Daphnia pulex* by McTaggart and colleagues, who found that the Toll pathway was fairly well conserved between insects and *Daphnia* (McTaggart et al., 2009). A Toll receptor is expressed in various tissues in the shrimp *Litopenaeus vannamei* including hemocytes and the brain (Yang et al., 2007). Toll-like

receptors are found in neurons and glia in the vertebrate brain and induce the production of cytokines, enzymes and other inflammatory mediators (Hanke and Kielian, 2011; Lehnardt, 2010). Other pattern-recognition proteins have been characterized in crustaceans, namely β-1,3-glucan-binding protein, LPS- and β-1,3-glucan-binding protein (LGBP), and the masquerade-like protein (Cerenius and Söderhäll, 2004).

Insights from vertebrate systems

'In view of the data available to date, we are progressing towards a unifying concept of an immune response that is common to all metazoans' (Hoffmann and Reichhart, 2002). Thus, it is reasonable to survey vertebrates and their cerebral diseases in search of information and hypotheses regarding the role played by neuroimmune responses in helminth-induced sensorimotor alterations in gammarids.

Cerebral parasites

Toxoplasma gondii is an intracellular parasite that affects both neurons and glia (Gulinello et al., 2010; Henriquez et al., 2009). The host–parasite association involving the protozoan *T. gondii* in its rodent intermediate host offers striking similarities with the manipulative helminth–gammarid associations. In both systems, parasites are trophically transmitted and interfere with anti-predator strategies of the intermediate hosts. Transmission to the definitive hosts, cats for *T. gondii*, is presumably enhanced. Moreover, the stage responsible for the behavioral alterations of the intermediate host is not the initial developing/replicating parasitic stage but the mature parasite infective to the definitive host. It is a chronic, latent stage – namely, cystacanths (acanthocephalans) and metacercariae (trematodes) in gammarids, and bradyzoite cysts (*T. gondii*) in rats – that persists during the lifespan of the intermediate host. Bradyzoite cysts are formed once the acute infection accompanied by tachyzoite replication has been resolved (Gulinello et al., 2010).

In both systems, responses to specific sensory stimuli are reversed in infected hosts. Depending on the host–parasite system, gammarids infected with manipulative helminths escape toward the source of light rather than away from it, and toward the odor of the predator definitive host rather than away from it (Table 1). *Toxoplasma gondii*-infected rodents exhibit a variety of sensorimotor deficits (Gulinello et al., 2010). In particular, infected rats are specifically attracted rather than repulsed by the odor of cat urine (Berdoy et al., 2000; House et al., 2011; Vyas and Sapolsky, 2010; Vyas et al., 2007). Remarkably, cat odor activates sexual arousal pathways (House et al., 2011) in *T. gondii*-infected rats. Thus, the olfactory behavior of parasitized rodents might be altered based on erroneous sensory information (odor of cat urine coded as sexual scent), as speculated earlier for helminth-infected gammarids. In humans, individuals with latent toxoplasmosis have impaired reaction times and reduced psychomotor performance (Flegr, 2007; Flegr, 2013). There is evidence of neurotransmitter dysfunction in both host–parasite associations. Dopamine levels are modified in mammals infected with *T. gondii* (McConkey et al., 2013; Prandovszky et al., 2011; Webster et al., 2013; Yolken et al., 2009) whereas serotonin has been incriminated in gammarids infected by manipulative helminths (see Table 1).

Toxoplasma gondii infection is accompanied by a continuous immune response involving the secretion of cytokines such as gamma interferon (IFN-γ) and TNF-α, proinflammatory mediators with potential neurotoxic activity (Henriquez et al., 2009). In addition, microglia activation leads to NO release, which, among other deleterious effects, can dramatically affect neurite outgrowth (Rozenfeld et al., 2003).

Trypanosomes are extracellular single cell organisms responsible for human African trypanosomiasis or sleeping sickness. These parasites are of interest in the context of helminth–gammarid systems in connection with reports of altered tryptophan, serotonin and melatonin metabolism (Vincendeau et al., 1999). In trypanosome-infected mice, correlative evidence suggests that astrocytic activation is responsible for the production of cytokines. Inflammatory cytokines such as IFN-γ, TNF-α and IL-1β, and anti-inflammatory cytokines such as IL-10 have been demonstrated both peripherally and centrally in trypanosome-infected mammals (Bentivoglio and Kristensson, 2007; Bentivoglio et al., 2011; Kristensson et al., 2010). Trypanosomes interfere with sleep–wake patterns at the level of the suprachiasmatic nucleus (SCN), a region of the hypothalamus that regulates circadian rhythms and is entrained by the light–dark cycle through retinal input. Moreover, glutamate receptor subunits that gate retinal afferents to the SCN show reduced expression in trypanosome-infected mice (Kristensson et al., 2010). Thus, trypanosomes could be said to interfere with photic input in the brain of their mammalian hosts.

The CNS of mammals harbors not only protozoans but also helminths such as the larval nematode *Toxocara canis* and the larval cestode *Taenia solium*. Cerebral toxocariasis increases the expression of inducible iNOS and of pro- and anti-inflammatory cytokines in the brain of mice (Hamilton et al., 2008; Holland and Hamilton, 2013). The larval stage of the flatworm *T. solium* causes neurocysticercosis (NC) when it encysts in the human brain, inducing what may be seen as a two-edged defense mechanism. The physiological processes that damage the parasites may also injure brain tissues through inflammation, necrosis and fibrosis, with significant clinical consequences (Sciutto et al., 2007). Much of the pathology of NC (epilepsy, chronic headaches) is believed to be associated with the host immune response to the cerebral larva (Alvarez et al., 2002). Astrocytic gliosis is notable around granulomas (Alvarez et al., 2002) and pro-inflammatory IL-1β and TNF-α cytokines have been detected in cerebrospinal fluid of NC cases (Sciutto et al., 2007). Moreover, upregulation of all Toll-like receptors occurs in NC-infected mice (Mishra et al., 2009).

Neuroinflammation and dysfunction of monoaminergic neuronal populations

Neuroinflammation, 'the activation of microglia and astroglia with attendant expression of proinflammatory cytokines and chemokines' (O'Callaghan et al., 2008), has been correlated with CNS pathology, although the cause and effect relationship between neurotoxicity and pro-inflammatory signals has been hotly debated in recent years (see O'Callaghan et al., 2008; Streit, 2010). However, an abundant literature sheds light on cytokine–neuromodulator interactions that could potentially affect behavior. Cytokines may increase or decrease the release of neurotransmitters, stimulate their uptake or affect neuronal development. For example, IL-1β augments the release of noradrenaline, dopamine and serotonin in the rat hypothalamus (Shintani et al., 1993), while TNF-α stimulates serotonin uptake by activating serotonin transporters (Mössner et al., 1998; Zhu et al., 2006). Interleukins and TNF-α can affect developing monoamine neurons at physiologically relevant concentrations (Jarskog et al., 1997). And cytokines are strongly implicated in the neuroinflammation hypothesis of depression through the enzyme that metabolizes tryptophan, the precursor of serotonin (Dantzer et

al., 2011; Catena-Dell'Osso et al., 2011; Myint and Kim, 2003). Pelletier and Siegel have surveyed the links existing between serotonin and TNF signalling (Pelletier and Siegel, 2009).

Is it reasonable to propose that a hemocoelian acanthocephalan representing a systemic challenge could induce neuroinflammation and CNS aminergic dysfunction? The answer is clearly yes. Indeed, there is evidence that peripheral inflammatory responses can result in chronic neuroinflammation and neurotoxicity (Qian et al., 2010; McCusker, 2013). Peripheral injection of the bacterial wall LPS causes long-term chronic neuronal degeneration. In fact, a single systemic administration of LPS results in severe loss of dopaminergic neurons over a period of months in mice (Qin et al., 2007). The large LPS molecules cannot readily reach the brain. However, the cytokine TNF-α produced at the periphery is transported through the blood–brain barrier and underlies the mechanism of LPS-induced toxicity to dopaminergic neurons in the substantia nigra (Qin et al., 2007). Intraperitoneal administration of LPS also increases extracellular 5-HT levels in specific brain parts (Mössner and Lesch, 1998). Moreover, the photic response of the SCN is affected by chronic systemic inflammation (Palomba and Bentivoglio, 2008).

Clearly, systemic immune stimulation can induce neuroinflammation, neurodegeneration and functional disturbances in the brain.

Conclusions

The literature surveyed indicates that specific sensorimotor processes are altered in helminth-infected gammarids, and that serotonin is likely to underpin some of these changes. As argued by Thomas and colleagues (Thomas et al., 2005) and Adamo (Adamo, 2012) it is doubtful that the amine is released directly by the parasites in surrounding host tissues, given the high concentrations required to induce behavioral effects experimentally. Albeit only correlative in nature, convergent evidence suggests the involvement of host defense responses upstream of the serotonin-mediated sensorimotor changes exhibited by infected amphipods.

In acanthocephalan–gammarid associations, the altered photic behavior appears to be accompanied by changes in serotonin levels and by a decrease in PO activity and hemocyte concentration (Table 1). However, immune resources may be allocated independently (Adamo, 2004), and manipulative parasites are likely to elicit additional defense responses in infected amphipods, such as the activation of Toll signaling pathways and the production of cytokines – phenomena that have not yet been investigated in helminth-infected gammarids.

Looking ahead, the most promising research avenues may be those inspired by the common properties of the neuroimmune systems of vertebrates and invertebrates, and by the similarities presented by host behavioral manipulation in phyla as distantly related as crustaceans and mammals. Parasite-induced alterations of specific sensorimotor pathways are now well documented in both gammarids and rodents. Moreover, molecules that may underlie the pathogenesis of cerebral infectious diseases in vertebrates have been identified in crustaceans, many of them recently. Members of the Toll receptor family – incriminated in neurotoxic processes in mammals (Hanke and Kielian, 2011; Lehnardt, 2010) – have been found on hemocytes and in the brain of shrimps (Yang et al., 2007). NO, a potent molecule touted for its Janus-faced cytotoxic and cytoprotective properties (Calabrese et al., 2007), is prevalent across animal phyla. And cytokines, at the core of neuroinflammatory processes in mammals, are expressed in crustaceans; in particular, Eiger, a member of the TNF family (Mekata et al., 2010), is implicated in arthropod immune functions (Vidal, 2010).

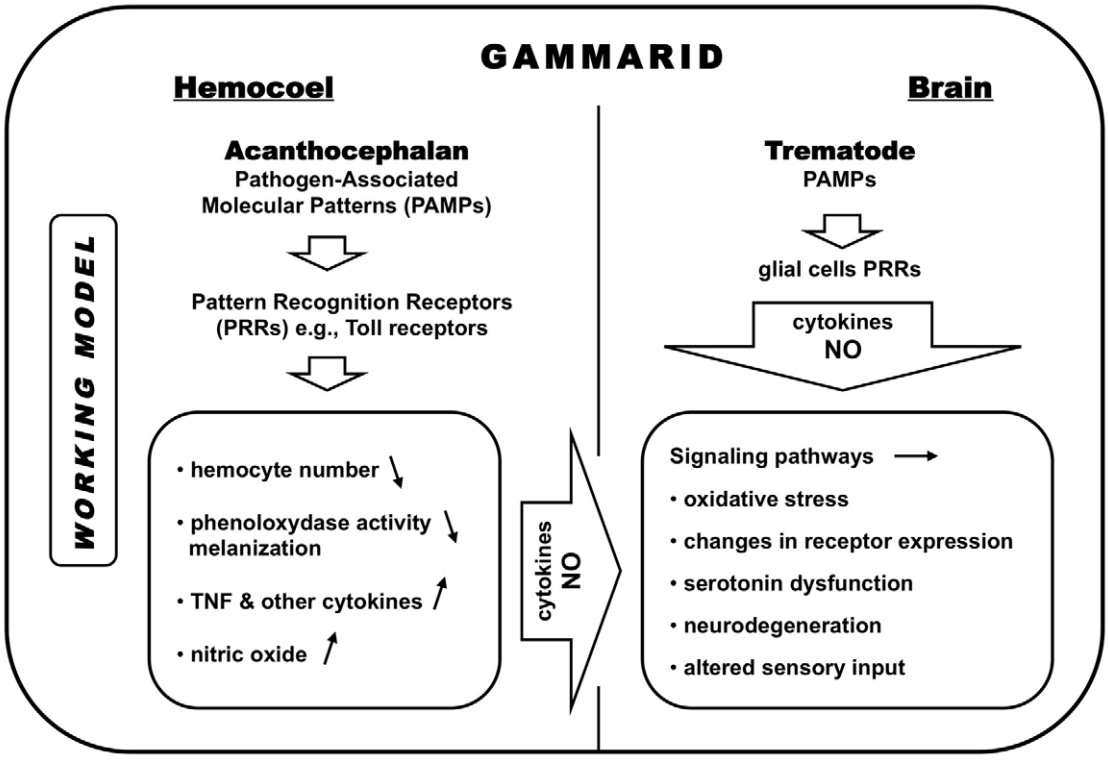

Fig. 3. Hypothetical mechanisms of action underlying altered sensorimotor processes in gammarids infected by manipulative helminths. NO, nitric oxide; TNF, tumor necrosis factor.

It is also clear that peripheral immune stimulation can cause neuroinflammation in the vertebrate CNS (Dantzer et al., 2011). Indeed, TNF-α elicited by a peripheral immune challenge can cross the blood–brain barrier and cause the degeneration of specific aminergic neuronal populations in mice (Qin et al., 2007), providing a potential mechanism for the neural effects of hemocelian helminths. Finally, evidence is accumulating that 'non-cell-autonomous events' are involved in diseases of the nervous system (Bentivoglio et al., 2011). In other words, non-neuronal cells, in particular astrocytes and microglia, are main players in the pathogenesis of chronic neurodegenerative diseases as well as in neuroinflammatory signaling in vertebrate brain infections. So, is there a link between serotonin dysfunction and neuroinflammation in helminth-infected gammarids? Solid proof is lacking as yet, but circumstantial evidence converges from diverse fields inviting further investigation of neuroimmune processes in manipulated gammarids (Fig. 3).

Even though so far the pathology caused by parasites in the brain appears widely disseminated (see Adamo, 2012; Adamo, 2013; Gulinello et al., 2010; Lefèvre et al., 2009; Vyas and Sapolsky, 2010), the reversed responses to stimuli induced by helminths in arthropods and by *T. gondii* in mammals imply that firing patterns are disrupted in specific sensorimotor circuits (House et al., 2011). Thus, it is essential to continue exploring the altered behavior of hosts with methods providing information on the localization of parasites' neuronal and immune effects in the CNS of manipulated hosts. Immunohistochemistry for the protein c-Fos revealed that neural activity is altered in limbic brain areas of *T. gondii*-infected rodents in response to cat odor (House et al., 2011). The same method could shed light on the sensorimotor pathways rerouted in the brain of manipulated gammarids. To initiate a search for cytokines, *in situ* hybridization with an Eiger RNA probe (see Igaki et al., 2002) could be applied to the CNS of trematode- and acanthocephalan-infected amphipods. These visualization techniques are particularly promising as the small size of the crustacean brain allows a comprehensive view of the entire structure. Gammarids are also amenable to ethopharmacological studies. Additional tests of the neuroimmune hypothesis would involve administration of anti-inflammatory drugs in an effort to 'cure' the altered behavior of infected hosts. Ultimately, helminth-induced behavioral manipulation in gammarids might provide a versatile invertebrate model of chronic infectious diseases with neuropathological and behavioral correlates.

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