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Neuroendocrine-immune circuits, phenotypes, and interactions

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ABSTRACT

Multidirectional interactions among the immune, endocrine, and nervous systems have been demonstrated in humans and non-human animal models for many decades by the biomedical community, but ecological and evolutionary perspectives are lacking. Neuroendocrine-immune interactions can be conceptualized using a series of feedback loops, which culminate into distinct neuroendocrine-immune phenotypes. Behavior can exert profound influences on these phenotypes, which can in turn reciprocally modulate behavior. For example, the behavioral aspects of reproduction, including courtship, aggression, mate selection and parental behaviors can impinge upon neuroendocrine-immune interactions. One classic example is the immunocompetence handicap hypothesis (ICHH), which proposes that steroid hormones act as mediators of traits important for female choice while suppressing the immune system. Reciprocally, neuroendocrine-immune pathways can promote the development of altered behavioral states, such as sickness behavior. Understanding the energetic signals that mediate neuroendocrine-immune crosstalk is an active area of research. Although the field of psychoneuroimmunology (PNI) has begun to explore this crosstalk from a biomedical standpoint, the neuroendocrine-immune-behavior nexus has been relatively underappreciated in comparative species. The field of ecoimmunology, while traditionally emphasizing the study of non-model systems from an ecological evolutionary perspective, often under natural conditions, has focused less on the physiological mechanisms underlying behavioral responses. This review summarizes neuroendocrine-immune interactions using a comparative framework to understand the ecological and evolutionary forces that shape these complex physiological interactions.

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No longer are we confined to considering solely what happens in the brain following the injection of immune modulators, or what happens in the immune system after interfering with neurotransmitter or neuroendocrine systems. Instead, the questions of what evolutionary advantages or disadvantages a response confers to an organism have become important considerations.

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[–Michael Harbuz (1993). "Neuroendocrine-immune interactions" Trends in Endocrinology and Metabolism.]

1. Introduction

The quote above is significant because it emphasizes the foresight that the late Michael "Mick" Harbuz possessed as a young biomedical researcher while contributing to the nascent field of psychoneuroimmunology (PNI). He realized that evolutionary forces are important in shaping crosstalk between the brain and neuroendocrine system. As integrative and comparative physiologists, we often take for granted that organisms coordinate multiple physiological systems to meet the demands of everyday life, as well as adjust to unexpected environmental and social challenges. There is an implicit assumption that crosstalk between different physiological systems is the norm, rather than the exception. Several decades ago, this was not so. In fact, it was rare to consider integration of multiple physiological systems when investigating a core physiological problem. Many scientists were invested in their own "research silos", which prevented them from navigating outside their area(s) of expertise (and comfort level). Although barriers were continually being broken down by advances in some fields, such as PNI (also referred to as pyschoneuroendocrinology), many scientists were reluctant to "look outside the box" (Ader, 2000; Ader and Cohen, 1981). Several disciplines did not receive significant integration with each other until more recently. The modern integrative biologist, now more so than ever, is faced with the challenging task of understanding multiple physiological and genetic systems of organisms using such disciplines as endocrinology, neuroscience, animal behavior, immunology, biomechanics and bioengineering, genetics and genomics, and cell and molecular biology.

This synoptic approach is greatly amplified by studying organisms in their natural environment. Given that coordination between multiple physiological systems is complex to understand in a controlled laboratory setting, assessing the role of extrinsic and intrinsic factors in shaping these functional interactions adds an even greater challenge and layer of complexity. For example, environmental threats, such as predation and storms, can alter the circuitry of neuroendocrine-immune-behavior "supersystems" by activating the "fight-or-flight" response, which triggers the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system to release glucocorticoids and catecholamines from the adrenal glands, respectively, into the circulation. These hormones, in turn, regulate the immune system through suppression, enhancement, or re-distribution of immune cells throughout the body (Dhabhar, 2002; Dhabhar and McEwen, 1999; Martin, 2009). Assuming that these different responses by the immune system optimize survival, the mechanisms underlying the effect of glucocorticoids are certainly not uniform, and vary in relationship to the magnitude and duration of the stressor, as well as the life-history stage, early-life experiences, and behavior of the stressed animal.

2. Neuroendocrine-immune (NEI) interactions

It is becoming increasingly apparent that the endocrine system and its myriad connections with the nervous system are regulated by input from the immune system and vice versa (Fig. 1). Survival of an organism is predicated upon the ability of cells, tissues, and organs to communicate with each other to maintain homeostasis and to carry out important life-history functions, such as reproduction, growth, migration, and molt. A primary component of this web or nexus of interactions is mode of communication in the form of bioregulatory signals: neurotransmitters, classical blood-borne hormones, and cytokines/chemokines. The other necessary components are the receptors that bind to these chemical mediators at target cells, tissues, and organs. Importantly, the existence of this type of crosstalk is critically dependent upon this dynamic relationship. Crosstalk is effectively eliminated when either signal or receptor is absent. Modulation of the response can occur at the level of signal production or at the level of receptors. Moreover, these bioregulators and receptors are not tied to one physiological system. For example, immune cells are responsive to hormonal and neural stimulation, and have the capacity to produce endocrine secretions and neurotransmitters, while endocrine cells possess receptors for cytokines and neurotransmitters (Besedovsky and del Ray, 1996; Raison et al., 2002). Conversely, microglia from the CNS are well known to secrete cytokines that have widespread effects upon neuroinflammatory responses in the brain and behavior (Streit et al., 2004). Moreover, a variety of endocrine cells are responsive to soluble cytokines/chemokines, which allow for fine-tuning of other physiological processes during immune challenge (Blalock, 1994a; Petrovsky, 2001). Previous separation of these three distinct systems has largely been a semantic issue; now there is evidence of complete integration of NEI interactions in a variety of vertebrate and invertebrate taxa (Adamo, 2006; Ader and Cohen, 1981; Bilbo and Klein, 2012; Demas et al., 2010; Demas and Carlton, 2015; Engelsma et al., 2002; Kaiser et al., 2009; Ottaviani, 2011).

Recognition of NEI interactions began with biomedical research that occurred in the early twentieth century, starting with basic neuroendocrine interactions. Four decades of neuroimmunological research by Hugo Besodovsky and colleagues provided firm support of cross-talk between neuroendocrine and immune systems (Besedovsky and del Ray, 1996). In 1975, Robert Ader and Nicholas Cohen demonstrated behavioral conditioning of the immune system in rats (Ader and Cohen, 1975), which provided strong evidence that the nervous system can directly affect immune functioning. Edwin Blalock further proposed an immunoregulatory role for the brain and a sensory function (coined "the sixth sense") for the immune system (Blalock, 1994b). Taken together, a solid body of research has categorized NEI interactions, but has yet to gain traction by comparative and integrative physiologists.

NEI crosstalk in vertebrate and invertebrates animals is a recent area of investigation that has started to garner attention from a comparative perspective (Demas et al., 2010; Demas and Carlton, 2015). Although this comparative approach has largely focused upon vertebrates, recent research on invertebrates in this field has exploded. Some of the important insights that have been highlighted in previous reviews are that vertebrates and invertebrates share analogous mechanisms for coordinating NEI interactions and homeostasis (Adamo, 2006, 2008; Demas et al., 2010), and the seemingly disparate fields of PNI and ecoimmunology can benefit from each other (Demas and Carlton, 2015). Specifically, ecoimmunology is an integrative field that involves understanding the proximate and ultimate factors that regulate variation of immunity within ecological and comparative contexts (sensu Demas and Nelson, 2012). In contrast, PNI is the study of interactions between physiological processes and the nervous system and immune systems, with particular emphasis upon human health and disease (Ader, 2000). Importantly, PNI can inform ecoimmunologists about the mechanistic underpinnings of the brain and immune system, whereas ecoimmunology can provide insight to PNI by examining NEI interactions in free-living organisms, illuminating life-history and energetic tradeoffs, and exploring integration with disease ecology and epidemiology (Demas and Carlton, 2015).

The purpose of this review is to emphasize NEI relationships from ecological and evolutionary perspectives, and to assess the effect of behavior in interacting with NEI circuits. First, we introduce terminology that will assist us in understanding the complexity of these interactions. NEI feedback loops are key regulators of homeostasis. Collectively, the actions of NEI circuitry upon organismal physiology, morphology, and behavior produce a collective *NEI phenotype*. Second, we evaluate the importance of behavior in shaping NEI interactions in wild populations. The role of behavior in mediating NEI interactions is rooted in the fields of psychoneuroimmunology/psychoneuroendocrinology (Dantzer and Kelley, 2007; Demas and Carlton, 2015). Lastly we focus on three areas of research that have attracted significant interest in the fields of

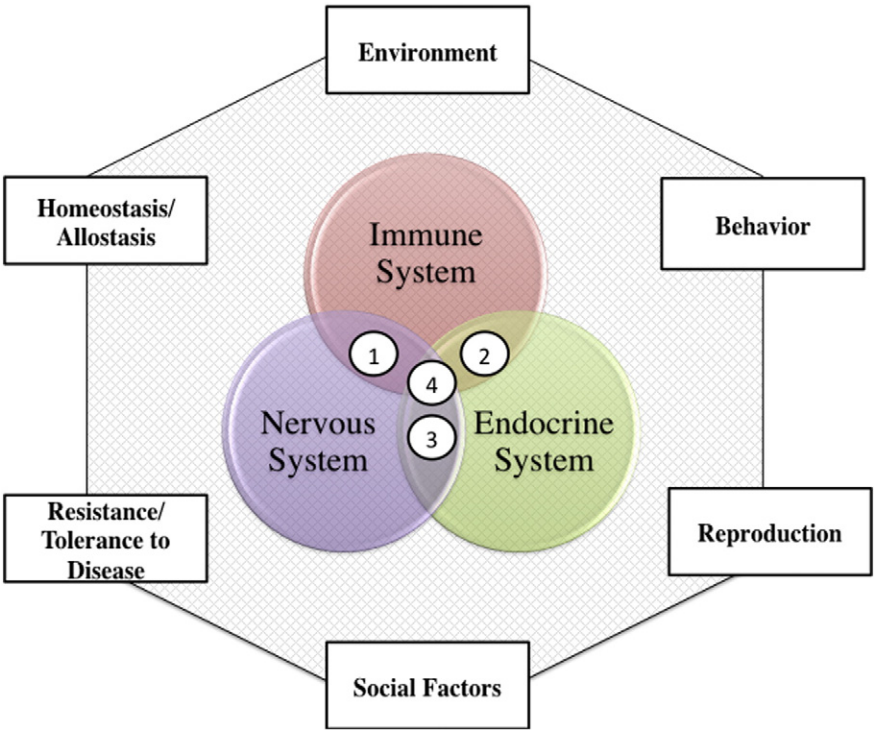

Fig. 1. Neuroendocrine-immune interactions involve multi-directional crosstalk that is mediated by extrinsic (environmental, social factors) and intrinsic (resistance/tolerance to disease, homeostasis and allostatic load, reproductive status, behavior) factors. First-order interactions involve 1.) direct interactions between the nervous and immune systems (e.g., sympathetic innervation of immune tissue, activation of microglia or specific nuclei in brain from cytokines), 2.) endocrine-immune interactions (e.g., hormonal regulation of immunity, cytokine/chemokine activation of endocrine cells), and 3.) classic interactions between the nervous and endocrine systems (e.g., activation and modulation of hypothalamic-pituitary units, neuromodulation by hormones). 4.) Second-order interactions involve all three systems interacting to produce a physiological effect(s). These sustained interactions involve a high degree of coordination to generate complex neuroendocrine-immune phenotypes.

ecoimmunology and PNI: (1) HPG axis and immunity, (2) modulation of sickness behavior, and (3) metabolic signals and immunity. Of course, there are many other interesting aspects of NEI dynamics that we will not have the opportunity to review (e.g. gut-microbe interactions and maternal effects). The upcoming special edition "Neuroendocrine-Immune Interactions: Implications for Integrative and Comparative Physiologists" in *Hormones & Behavior* will showcase these topics from experts in the field.

3. NEI circuits

Homeostasis is the ability of organisms to maintain internal stability even in the face of environment change. NEI feedback loops act to maintain homeostasis through negative feedback—effector molecules produced from NEI cascades feedback to inhibit their own production. In contrast, positive feedback involves an unstable process where the product stimulates the NEI cascade to generate more product, leading to runaway amplification. In some cases, to halt the amplified cycle, the feedback loop is broken by induction of a change in state that diverges from homeostasis. Understanding these two types of feedback are critical for understanding most physiological feedback loops, including NEI interactions.

At a basic level, a simple circuit is a closed path through which signals flow. A basic electrical circuit includes (1) a voltage source (battery), (2) the load (the work done by the circuit; e.g., turning on a light bulb), and (3) a conductive path (route through which electrons move). Importantly, a closed circuit forms a loop (e.g., from negative side to positive side of the voltage source). Do NEI circuits behave in a similar fashion to electrical circuits? On the one hand, the major components observed in an electrical circuit are also seen in NEI circuits. For example, endocrine, immune, and/or neural cells that produce various bioregulatory signals (hormones, cytokines, neurotransmitters) act as the voltage source. Similarly, the cumulative physiological effect resulting from receptors binding to these chemical signals (release of another bioregulator, signal transduction, and/or physiological effect; e.g., muscle contraction) would represent the load. The conductive path would either be local (autocrine, paracrine) or blood-borne (endocrine) whereby chemical signals traverse to reach target cells/tissue. On the other hand, modeling feedback loops using electrical circuits is quite complicated (but certainly achievable) and involves the use of additional components of a circuit (transistors, resistors, and capacitors). Modeling of NEI feedback loops using advanced electrical engineering concepts could increase our understanding of biological feedback systems, but is certainly beyond the scope of this review.

For the sake of simplicity, we distill NEI interactions into two broad types of circuits: (1) long loop interactions, and (2) local interactions (Besedovsky and del Ray, 1996). Long loop interactions entail processes that involve signaling across multiple organ systems. For example, an immunogen that stimulates the immune system leads to production of pro-inflammatory cytokines from various immune cells (e.g., macrophages), that in turn affect *distant* neuroendocrine structures. In contrast, local interactions involve NEI dynamics that occur within the same tissue or organ (e.g., brain, immune organ). A salient comparison involves the effect of peripheral versus local glucocorticoids upon immune function. In developing zebra finch (*Taeniopygia guttata*), corticosterone is the major circulating glucocorticoid. However, in thymic tissue, cortisol is the predominant glucocorticoid (Schmidt et al., 2009, 2010; Schmidt and Soma, 2008; Taves et al., 2016a), which suggests that local steroids may produce different effects from those of systemic steroids. In neonatal and postnatal mice, local concentrations of corticosterone are elevated in thymus, liver, spleen, and/or brain relative to circulating levels (Taves et al., 2015). Lymphoid-derived corticosterone is not produced de novo from cholesterol, but regenerated from adrenal metabolites (Taves et al., 2016b), which does not alter circulating levels since inactive metabolites (11-deoxycorticosterone) with little glucocorticoid activity are used. Conversely, this regeneration mechanism

permits higher glucocorticoid concentrations to accrue locally that would otherwise passively track circulating levels. Local elevation of glucocorticoids regulates selection of immunocompetent T-cells, while systemic levels are low to presumably minimize the detrimental effects of chronic glucocorticoid exposure during development (Taves et al., 2015). Taken together, the relationship between glucocorticoids and immune function is altered depending upon which NEI circuit is employed (long-loop (peripheral) versus local circuit).

Understanding the dynamics of NEI circuits can provide key insights upon whole organismal processes. Importantly, long loop and local interactions work together to regulate homeostasis. Major inputs into the overall circuit include environmental factors, social interactions, as well as pathogens, whereas primary outputs include immunological responses and hormonal and behavioral changes (Fig. 2). Local NEI interactions occur within brain as well as autocrine/paracrine interactions within various immune tissues. Dysregulation in any of these circuits can lead to pathology and increased susceptibility to disease (Bilbo and Klein, 2012; Jara et al., 2006; Masek et al., 2003; Petrovsky, 2001). Alternatively, we argue that some alterations in NEI circuits are not necessarily detrimental, but can derive potential fitness benefits in certain environmental and social contexts (see below).

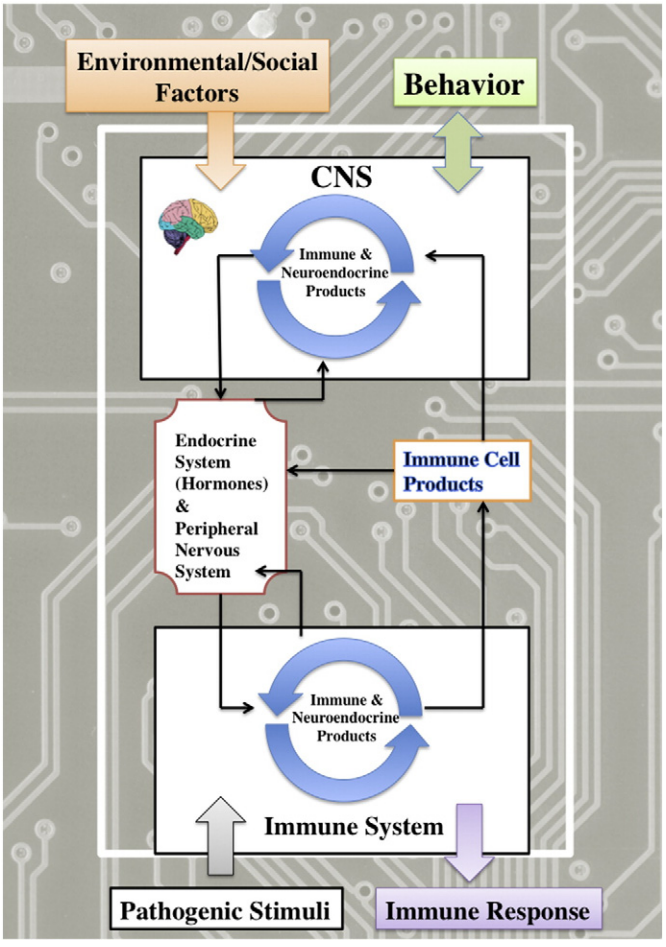

Fig. 2. Prototype of a neuroendocrine-immune (NEI) circuit. The circuit represents a flow of signals and is defined by local (blue arrows) and long-loop (black arrows; multi-system) interactions that are altered according to extrinsic inputs (environment, social factors, pathogens). Primary outputs include immune responses, hormone secretions, activation of the peripheral nervous system, and behavioral alterations. Importantly, behavior can act as an input or output in the circuit. The white box encloses systems involved specifically with NEI interactions from the rest of the body. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
Adapted from Besedovsky and del Ray (1996).

A theoretical framework for examining NEI interactions is bow tie architecture (Ottaviani, 2011; Ottaviani et al., 2008). This involves conceptually modeling a wide variety of stimuli that are converted into fine-tuned responses by passing through or "fanning into" a core integrating center, termed the "knot". Although limited by evolutionarily conserved elements that are mostly immutable, the knot is able to integrate a wide range of stimuli (e.g., immune, social, physical, and hormonal) and convert them into fine-tuned biological responses that "fan out" from the knot and feedback to various physiological parameters. The advantage of this approach is the identification of core elements that are highly conserved, and thus less likely to change within and between individuals, populations, and species. It should be noted that the bowtie method is purely conceptual and does not necessarily identify precise circuitry and pathways that are necessary to understand specific NEI interactions. Nonetheless, comparing multiple methods of conceptualization using a combination of NEI circuits and bow tie modeling will undoubtedly enhance our understanding of the evolution of complex NEI interactions.

4. NEI phenotypes

We can define the *NEI phenotype* as the collective actions of NEI feedback loops in regulating the physiology, morphology, and behavior of an organism. The concept of distinct and predictable NEI interactions towards pathogenic challenge or environmental/social factors has led to the hypothesis that multiple NEI phenotypes occur within populations (Nazar et al., 2015). The classic example of NEI phenotypes involves Lewis and Fischer (F344) rats. These two inbred strains exhibit opposing susceptibility to autoimmune disease and tumors, which have been linked to altered HPA axis function (Sternberg et al., 1989; Stohr et al., 2000). Specifically, Lewis rats display heightened Th1-pro-inflammatory responses, are more vulnerable to inflammatory and autoimmune dysfunction, and exhibit lower baseline glucocorticoid levels than Fisher rats (Sternberg et al., 1989; Stohr et al., 2000). Female Sprague-Dawley rats apparently differ in their immune and endocrine responses to inflammatory challenge depending upon which vendor they originate from (Bodnar et al., 2015). Similar dichotomies in NEI phenotypes have been reported in captive birds (Japanese Quail, *Coturnix coturnix*). Quail with the lowest corticosterone profiles exhibited heightened inflammatory responses, reminiscent of Lewis rats whereas "Fischer-like" quail displayed the opposite response (Nazar et al., 2015). In a healthy population of humans, baseline epinephrine output (but not cortisol or sex hormone concentration) correlated inversely with pro-inflammatory cytokine production, and two phenotypes of low vs. high-responders could be identified (Elenkov et al., 2008).

The lingering questions that remain for integrative and comparative physiologists involve NEI phenotypes in wild populations. Does selection favor certain NEI phenotypes over others in different environmental or social settings? How flexible are NEI interactions in general? Do NEI phenotypes in some cases constrain the evolution of behavior/personality? And how best do we characterize and measure NEI phenotypes? How are NEI phenotypes related to individual variation in disease susceptibility and exposure rates? For example, do superspreaders (individuals that disproportionately spread disease through increased transmission/infectiousness) have altered NEI phenotypes compared with other members of the population? Do NEI phenotypes within individuals change according to season, sex, or lifespan? Tackling these types of questions is important for understanding NEI interactions from ecological and evolutionary perspectives.

If we focus on single physiological systems for a moment, then there is ample evidence of plasticity *within* endocrine, immune, and neural systems. For example, among wild populations, there is clearly variation in HPA axis responsiveness within species (Romero, 2002; Wingfield et al., 1997; Wingfield and Romero, 2001; Wingfield et al., 1992), as well are their being immunological differences across populations (Adelman et al., 2010, 2013; Ardia, 2007; Matson, 2006; Møller et al.,

2006; Owen-Ashley et al., 2008). However, evidence for life-history variation in NEI interactions (in this case, between glucocorticoids and immunity) is scant. In house sparrows (*Passer domesticus*), glucocorticoid treatment suppresses cell-mediated immunity in birds inhabiting temperate, but not tropical, regions (Martin et al., 2005). In a reciprocal NEI interaction, plasma glucocorticoid level following bacterial lipopolysaccharide challenge is higher in Siberian hamsters (*Phodopus sungorus*) adapted to short day lengths (winter-like conditions) versus long day lengths, suggesting a photoperiodic effect (Carlton and Demas, 2015). In tree lizards, corticosterone suppresses wound healing only during periods of energy limitation, implying a reorganization of the NEI circuit when resources are abundant (French et al., 2007). Among wild male Norway rats (*Rattus norvegicus*), there is variability in circulating testosterone and corticosterone levels depending upon whether an animal is wounded and/or infected with Seoul virus (Easterbrook et al., 2007). This pathogen increases aggression in male hosts, which leads to increased salivary transmission through wounding during male-to-male combat. These studies suggest that NEI interactions are not static and exhibit plasticity to accommodate changes in the environment.

In addition, the timing and duration of NEI interactions are important caveats to consider. Again, we use the well-studied example of glucocorticoids and immunity to illustrate this point. Stress-induced elevation in glucocorticoids can significantly alter virtually every component of immune function—cellular proliferation, cytokine production, antibody production, and innate immune defenses, but timing is critical (Dhabhar, 2002; Martin, 2009). Acute exposure to a stressor has been shown to actually enhance some aspects of immunity. Mice exhibit enhanced delayed type-hypersensitivity when subjected to 2 h of stress compared with unstressed controls (Dhabhar and McEwen, 1999). This effect is attributed to glucocorticoids because adrenalectomy abolishes the immunoenhancing effect, and replacement with glucocorticoids reinstates it (Dhabhar, 2002; Dhabhar and McEwen, 1999). Therefore, caution is warranted when evaluating NEI interactions at different temporal scales.

5. NEI circuits and behavior

If NEI circuits involve precise regulation from multiple physiological systems, then one can make the prediction that NEI phenotypes will tend to coincide with specific behaviors. It is also well known that behavior can influence transmission of disease, as well as susceptibility to infection by altering host physiology (Hawley et al., 2011). Importantly, these two effects can exhibit covariation since many aspects of reproductive and social behavior of hosts are regulated by endocrine mediators, such as androgens and glucocorticoids, that can, in turn, regulate interactions between behavior and physiology (Hawley et al., 2011). Behavioral changes, such as flight-or-fight responses or social defeat, result in immune modulation and simultaneous changes in endocrine profiles (Bailey et al., 2007; Dhabhar, 2002). However, linkages of these physiological responses to corresponding alterations in contact rates and disease resistance is often lacking. Conversely, stimulation of the NEI circuit by infection or immunogens can produce stereotypical and adaptive changes in behavior that are collectively termed *sickness behavior* (discussed below). In addition, maternal immune challenge can also affect personality of offspring and predisposition to disease (Butler et al., 2012; Grindstaff, 2016; Khan et al., 2014). Thus, behavior affects NEI interactions and vice versa (Fig. 2.). These relationships have been clearly delineated by PNI since its inception in the early 1980s (Ader and Cohen, 1981), but a comparative perspective has been noticeably lacking.

Laboratory mice (*Mus musculus*) are social animals and have been used as a model to demonstrate behavioral effects upon NEI interactions. Males that are aggressive towards conspecifics exhibit higher serum levels of corticosterone, a slower rate of parasite clearance, and develop peak parasitemia earlier compared with less-aggressive males (Barnard et al., 1993), indicating that a high social status may carry costs in terms of increased susceptibility to disease. Alternatively, mice that are subjected to repeated social defeat exhibit increased anxiety behavior, enhanced cytokine secretion, and enhanced detection and clearance of pathogens (Bailey et al., 2007; Kinsey et al., 2007; Powell et al., 2009).

Using a comparative genomics approach, house mice (*Mus musculus*), stickleback fish (*Gasterosteus aculeatus*), and honey bees (*Apis mellifera*) exposed to a territorial intrusion exhibit a similar upregulation in NF-kappa-β, a transcription factor responsible for initiating a pro-inflammatory response (Rittschof et al., 2014) as well as altered neuroendocrine signaling of Egr1, a transcription factor sensitive to gonadotropin secretion in the brain (Yang et al., 2007). These findings suggest that in species where social behavior has independently evolved, the effect of social stimuli upon genetic factors that mediate immune and neuroendocrine responses is highly conserved.

It should also be noted that immune-behavior interactions can occur in the absence of infection. Although pro-inflammatory cytokines, such as IL-1 and TNF, are typically associated with development of an inflammatory response (Ashley et al., 2012; Medzhitov, 2008), there is increasing evidence that these cytokines play a role in mediating physiological and behavioral processes in healthy animals. For example, cytokine secretion is tied to biological rhythms and the sleep/wake cycle (Opp, 2005), and experimental sleep loss leads to the induction of a pro-inflammatory response in brain and peripheral tissues (Ashley et al., 2016; Dumaine and Ashley, 2015; Faraut et al., 2012). Whether such an inflammatory response is adaptive (at the least in the short term) remains to be seen. A modest increase in IL-1 protein levels is associated with learning in rats, but excessive levels can inhibit learning and memory (Williamson et al., 2011). On a chronic level, pro-inflammatory cytokines lead to the development of a variety of mood disorders in humans, including depression (Dantzer, 2009). The role of cytokines in mediating "normal" behaviors is poorly understood, and virtually unexplored in free-living animals.

6. HPG axis and immunity

Sex differences in immunity abound in the medical literature and have long been recognized as important contributions to variation within and among species (Klein, 2000a, 2000b; Klein et al., 2015). One of the more controversial hypotheses debated among behavioral ecologists and evolutionary biologists is the immunocompetence handicap hypothesis (ICHH), which was formulated by Folstad and Karter (1992). This hypothesis employs NEI interactions to explain how some sexually-selected traits in male vertebrates are honestly enforced. These interactions involve pleiotropic effects of the steroid hormone testosterone upon physiology and morphology. On the one hand, testosterone putatively suppresses the immune system in an obligate fashion (the cost or handicap). On the other hand, testosterone acts to enhance the quality of some sexually-selected traits important for female choice (the benefit). High-quality males can "afford" to endure the *obligate* costs of immunosuppression because they possess genes with high resistance (or tolerance) to infection. In contrast, low-quality males lacking these genes are thus unable to withstand testosterone-induced immunosuppression, which enforces honesty. This "double-edged sword" highlights the bidirectional effects of testosterone upon male physiology, morphology, and behavior. This relationship can be visualized using an NEI circuit (Fig. 3A).

Several years later, it was realized that the obligate nature of immunosuppression by testosterone could be evaded if a mutant evolved resistance to testosterone-induced suppression of immunity. In response, the original hypothesis was revised to posit that immunosuppression by testosterone is an adaptive response to permit reallocation of resources from immunity to development and maintenance of costly sexual ornaments (Wedekind and Folstad, 1994). Despite this revision, a number of shortcomings in ICHH have been identified. First, many sexually-selected traits in males are not dependent upon androgens (Owens and Short,

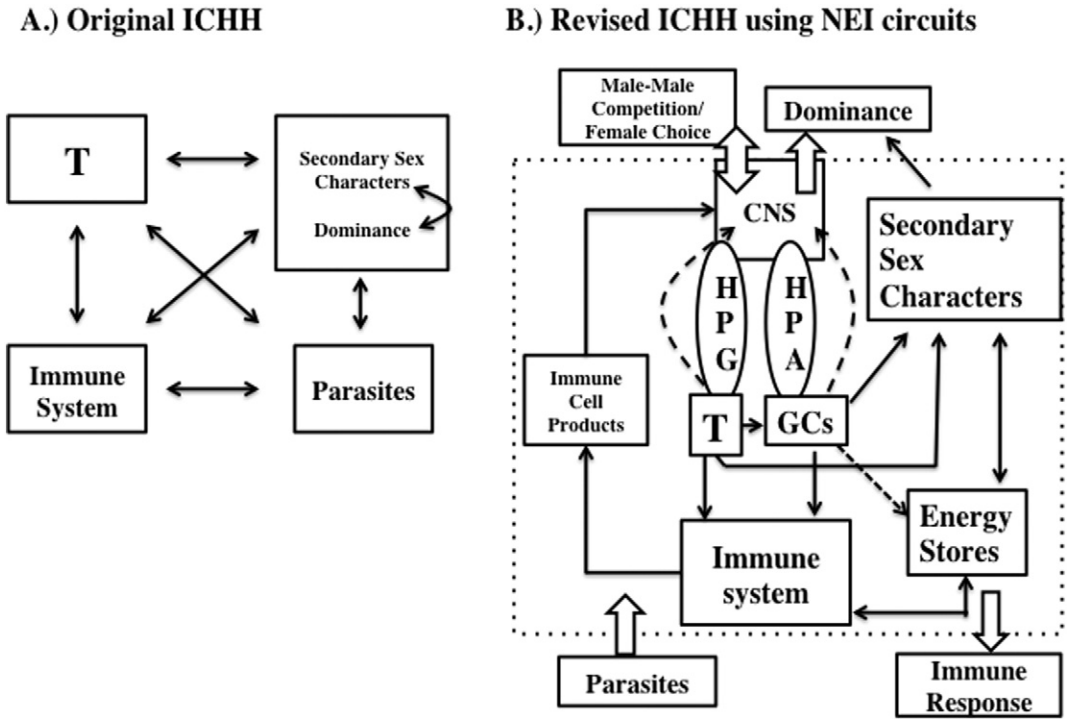

Fig. 3. Conceptual model of (A) original ICHH hypothesis from Folstad and Karter (1992) and reconfigured as a (B) NEI circuit, which takes into account the organization and interconnections that occur among neural, endocrine, and immune systems. These interactions promote the regulation of the production of sexually-selected traits at the expense of suppressed immune function through direct (T) and indirect (glucocorticoids, energy availability). Dotted lines represent negative feedback effects.

1995). Second, immunosuppression occurs in some species, but not others, so the immunosuppressive effect is quite variable (Hasselquist et al., 1999; Roberts et al., 2004, 2007). Third, in studies that employ the use of Silastic implants to chronically elevate circulating levels of testosterone, baseline glucocorticoids are also increased, suggesting a potential indirect effect of immunosuppression by stress hormones (Casto et al., 2001; Evans et al., 2000; Owen-Ashley et al., 2004). In addition, the effect of testosterone upon the immune system may be indirectly mediated by energetic state (Alonso-Alvarez et al., 2007; Demas, 2004; Ruiz et al., 2010). The original ICHH circuit can be modified to accommodate connections between the HPG and HPA axis, as well as a role for energy availability in mediating tradeoffs between immunity and sexual signaling (Fig. 3B).

Another common criticism of the ICHH is that it only applies to vertebrates, since invertebrates lack the ability to produce testosterone. However, trade-offs between invertebrate immunity and sexual signaling are similar to those seen in vertebrates. Thus, other hormones produced by invertebrates could perform the same function as testosterone by reducing immunity while enhancing sexual signaling, and a number of studies have had mixed success in discovering such an analogous hormone. For example, juvenile hormone can promote traits important for dominance and sexual signaling while decreasing immunocompetence, and ultimately survival (Contreras-Garduño et al., 2009; Gonzalez-Tokman et al., 2012; Rantala et al., 2003). Although seemingly acting like testosterone, juvenile hormone is produced by both sexes whereas testosterone is the major sex hormone of male, but not female, vertebrates. Thus, this difference raises the question whether sexual signaling and immunity of females are affected in the same way as males by juvenile hormone secretion. Other studies have proposed that melanin, a pigment, is a potential candidate to mediate the tradeoff between immunity and sexual signaling. In damselflies (*Calopteryx splendens*), melanin is used for sexual signaling but also regulates immunity (Cotter et al., 2008; Siva-Jothy, 2000). Lastly, it has been proposed that reliability of some exaggerated traits is regulated by sensitivity to insulin/IGF signaling pathways during growth, such that honest signaling is a byproduct of the growth mechanism, as shown in male rhinoceros beetles, *Trypoxylus dichotomus* (Emlen et al., 2012; Warren et al., 2013). Taken together, these studies demonstrate the importance of NEI interactions in shaping the evolution of secondary sex characteristics in invertebrates and vertebrates to permit the assessment of the reliability of a potential partner's health and genetic resistance to parasites.

7. Acute phase response and sickness behavior

Host response to a pathogenic threat involves not only an assortment of cellular and humoral responses that include proliferation of lymphocytes, heightened monocyte trafficking, and increased cytokine and antibody production, but also a highly coordinated suite of physiological and behavioral alterations that allow hosts to cope with and eventually overcome infection (Adelman and Martin, 2009; Ashley and Wingfield, 2012; Dantzer and Kelley, 2007; Hart, 1988, 1990). Physiological changes include activation of the HPA axis, suppression of the HPG axis, reduced intestinal motility, fever, and acute phase protein release from the liver (Ashley and Wingfield, 2012; Dantzer, 2001; Dunn and Swiergiel, 1998; Hart, 1988; Kent et al., 1992; Maier and Watkins, 1998). Together, this altered physiological state is often termed the acute phase response (APR) to infection. In addition, the APR is accompanied by nonspecific behavioral symptoms that were historically considered maladaptive byproducts of infection: anorexia (reduction in food intake), adipsia (reduced thirst), reduced activity and soporific behavior, increased slow-wave sleep, anhedonia (inability to experience pleasure), hyperalgesia (decreased threshold to perceiving pain), general withdrawal from social activities and exploratory behavior, decreased libido, depression, and a disinterest in grooming behavior (for reviews, see Adelman and Martin, 2009; Ashley and Wingfield, 2012; Kent et al., 1992). In rodents, the APR decreases food intake, but not food hoarding behavior (Aubert et al., 1997; Durazzo et al., 2008), which suggests that immediate energy needs are decoupled from perceived future demands during an infection.

The idea that sickness behavior represents an actual host defense rather than a weakened host state was first eloquently demonstrated

by Matt Kluger and colleagues in the 1970s (Kluger, 1979; Kluger et al., 1975). When infected with bacteria, ectothermic animals raise body temperature by seeking out warmer microclimates. Kluger et al. discovered that desert iguanas (*Dipsosaurus dorsalis*) treated with bacteria had higher survival rates in warm than cool environments, suggesting that behavioral thermoregulation of fever has adaptive value (Kluger et al., 1975). In 1988, Benjamin Hart provided strong evidence that sickness behavior is an adaptive host behavioral strategy that redirects energy to fever and immune defenses at the expense of other behaviors, such as reproductive, social, and foraging behaviors (Hart, 1988).

This type of NEI circuit involves a series of local and long-loop interactions that begin with detection of an antigen by the immune system (Fig. 4). Recognition occurs when Toll-like receptors on macrophages and dendritic cells bind to pathogen-associated molecular patterns (PAMPs), which are conserved moieties on the surface of microbes. Activated immune cells release pro-inflammatory cytokines, most notably IL-1β, IL-6, and TNF-α. These cytokines promote recruitment of immune cells locally, but also signal the brain and liver that infection (or injury) is occurring through neural and endocrine pathways. In response, the brain induces metabolic, hormonal, and behavior changes, such as fever, sickness behavior, activation of the HPA axis, and suppression of the HPG axis. Glucocorticoids released from the adrenals act as a brake on immune system activation to prevent the APR from causing excessive damage to the body (Besedovsky and del Ray, 1996; Munck et al., 1984). In addition, glucocorticoids increase gluconeogenesis and lipolysis, which mobilizes energy that can be diverted to the immune system for fighting infection. The status of energy stores becomes more important as immune activation progresses and is conveyed through metabolic hormones, such as leptin and ghrelin (Carlton et al., 2012). Lower energy stores can lead to the termination of sickness behavior; otherwise, survival is drastically reduced once body mass (and energy stores) decreases below a minimum threshold (Ashley and Wingfield, 2012; Carlton and Demas, 2015).

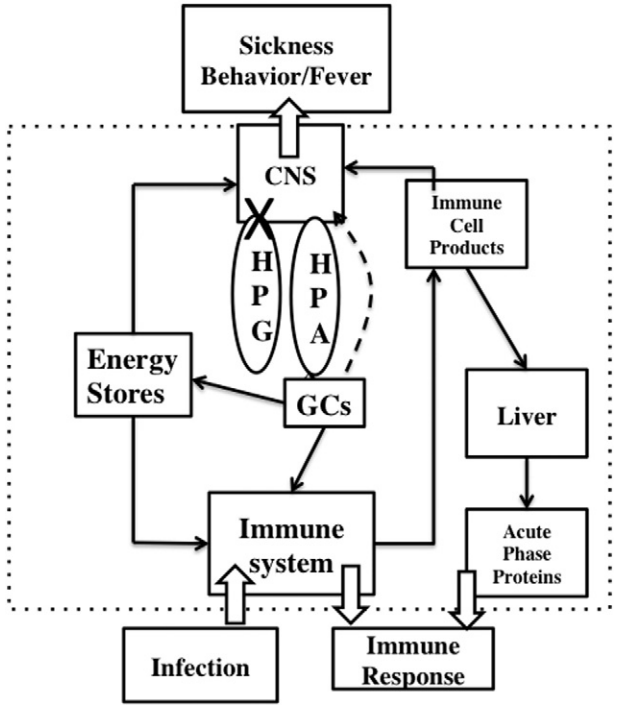

Fig. 4. NEI circuit depicting the acute phase response (APR) to infectious challenge. During an APR, the HPG axis is typically suppressed, whereas the HPA axis is activated. Glucocorticoids produced from the adrenals regulate energy stores as well as the immune system. The behavioral output of the APR circuit is expression of sickness behavior.

A growing number of studies have demonstrated that animals modulate the expression of sickness behavior according to different life-history and environmental contexts that include season, latitude, sex, age, and parental demands (for review see Ashley and Wingfield, 2012). For example, there is seasonal modulation of the sickness response after bacterial lipopolysaccharide (LPS) challenge in birds and mammals (Bilbo et al., 2002; Owen-Ashley et al., 2006, 2008; Owen-Ashley and Wingfield, 2006), although there are exceptions to this rule (for e.g., Hegemann et al., 2012). This variation seems to be influenced by a combination of proximate factors that include testosterone (in males; Ashley et al., 2009), melatonin (Bilbo and Nelson, 2002), glucocorticoids (Goujon et al., 1995a, 1995b), insulin (Carlton and Demas, In press) and body condition (Carlton and Demas, 2015; Owen-Ashley et al., 2006, 2008; Owen-Ashley and Wingfield, 2006), which is partially mediated by leptin (Carlton and Demas, 2014)—a satiety hormone produced from adipose cells. From an ultimate perspective, sickness behavior represents an "opportunity cost" and thus conflicts with the expression of other activities important for reproductive and growth functions (sexual and social behavior, territorial defense, parental care, etc.; Ashley and Wingfield 2012; Owen-Ashley and Wingfield 2007). This creates an intriguing tradeoff between host responses to infection and future reproductive prospects that can favor modulation of the sickness response.

Social interactions can also influence the sickness response to LPS. If the benefit of "hiding" a sickness response from a potential mate outweighs the costs of losing the opportunity to mate, then one would predict social modulation of sickness behavior (Avistur and Yirmiya, 1999; Lopes, 2014). Indeed, male zebra finch (*Taeniopygia guttata*) injected with LPS and exposed to a novel female mask sickness behavior; they exhibit courting behaviors and activation of the HPG axis similar to control-injected males (Lopes et al., 2013). In rats, IL-1 injection suppresses mating behavior in female but not males rats, even though both sexes display a decrease in activity (Yirmiya et al., 1995). On balance, exposure to a receptive female in male mice exacerbates sickness behavior (Weil et al., 2006). Clearly, more research is needed to fully understand how social interactions affect modulation of NEI circuits.

8. Energetic signals and immunity

The immune system is tightly interwoven into the neuroendocrine system, sharing a common set of biosignaling molecules and genes. A fundamental tenet of ecoimmunology is that immune responses invoke energetic costs that potentially trade-off with other physiological processes, such as reproduction, development, growth, and sexual signaling (Demas and Nelson, 2012; Norris and Evans, 2000; Sheldon and Verhulst, 1996). It is generally accepted that a steady supply of energy is required to maintain necessary biological functions, and that energy is a limited resource (at least, in wild populations). Thus, energy available to organisms must be strategically allocated to competing physiological systems as well as future life-history demands (stored for later use). For example, a number of studies have demonstrated that immunological challenge can increase metabolic rate and/or lead to a decrease in reproduction and/or growth in a variety of vertebrate and invertebrate taxa (see Table 8.1; Demas et al., 2012). Mechanisms that underlie this strategic allocation of resources are poorly understood, but certainly are mediated by NEI crosstalk (Demas et al., 2010).

Leptin plays an important link in mediating energy homeostasis, and represents a key hormone that provides a signal that coordinates immune, neuroendocrine, and metabolic processes by conveying current energy availability (Carlton et al., 2012; Demas, 2004). Encoded by the *ob* gene, leptin is a peptide hormone produced by adipocytes that has anorexigenic effects upon appetite (Myers et al., 2008). In addition, leptin has well-described effects upon immune function (reviewed by Carlton et al., 2012), reproduction (Caprio et al., 2001; Tena-Sempere, 2007), and development (Briffa et al., 2015; Crespi and Unkefer, 2014). In mammals, experimental reductions in white adipose tissue via surgical removal (i.e., lipectomy) of specific white adipose tissue

depots impairs antibody production; immune function is restored following compensatory regrowth of the remaining fat pads (Demas et al., 2003). Interestingly, whereas lipectomy decreases circulating leptin by removing the source of the hormone, restoring the leptin signal via treatment with exogenous leptin restores lipectomy-induced immune suppression, even in the absence of increases in body fat (Demas and Sakaria, 2005). Collectively, these *signals* of energetic state, and not total energy per se, regulate investment in immune responses in a dynamic fashion. More research is needed to understand exactly how energy status is transduced into these energetic signals that regulate NEI interactions.

9. Conclusions & future directions

The study of NEI interactions has great potential to increase our understanding of how three major systems of the body coordinate activities to regulate homeostasis in the face of environmental and social changes. Probably the most obvious example of this integration is the stress response, which plays a critical role in mediating behavior, immunity, and physiology. The HPA and SNS axes are closely tied to the immune system, but our understanding of the constraints and advantages created by these tripartite interactions is still in its infancy.

One of the more pressing needs of this integrative field is interpreting the role that NEI interactions and cumulative output (referred to as NEI phenotypes) play in mediating susceptibility, resistance, and tolerance to disease. Do NEI phenotypes contribute to disease dynamics? Does one NEI phenotype reinforce or alter behavior (e.g., dominance) that increases the exposure rate to various pathogens as opposed to others? Do NEI phenotypes change over time, such as across life-history stages, and in response to disease? Is recovery from an infection contingent upon NEI phenotype? Understanding and managing the complexity of the interactions among neural, endocrine, and immune interactions will provide a significant challenge to predicting disease dynamics at an individual and population level. If the plasticity of these interactions is measured and understood, then our ability to predict disease outbreaks and identify management options could be enhanced. Finally, on a theoretical level, it would be useful to explore from an evolutionary standpoint how tightly-regulated physiological feedback loops are subject to selective pressures, such as global environmental change and emerging infectious diseases.

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