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Review article

Why are behavioral and immune traits linked?

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ABSTRACT

Through behavior, animals interact with a world where parasites abound. It is easy to understand how behavioral traits can thus have a differential effect on pathogen exposure. Harder to understand is why we observe behavioral traits to be linked to immune defense traits. Is variation in immune traits a consequence of behavior-induced variation in immunological experiences? Or is variation in behavioral traits a function of immune capabilities? Is our immune system a much bigger driver of personality than anticipated? In this review, I provide examples of how behavioral and immune traits co-vary. I then explore the different routes linking behavioral and immune traits, emphasizing on the physiological/hormonal mechanisms that could lead to immune control of behavior. Finally, I discuss why we should aim at understanding more about the mechanisms connecting these phenotypic traits.

Contents

1. Introduction

When trying to understand how the mechanisms regulating behavior have evolved, an important force to take into consideration is disease. Through behavior, animals interact with their abiotic (e.g. drinking) and biotic (e.g. fighting, mating) surroundings, where exposure to different forms and intensity of pathogens can occur. Individual differences in behavioral patterns will be associated with differences in the likelihood of encountering parasites (Lymbery, 2015). For instance, within an animal group, the more gregarious individuals have the

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highest risk of exposure to contact-transmitted pathogens due to increased social contacts. Thus, the cost to sociality imposed by disease risk should lead to selection of mechanisms that optimize the benefits obtained from engaging in social behaviors considering the animal's abilities to deal with disease burden. In this paper, I will provide examples of co-variation between immune and behavioral traits and explore different mechanisms that may underlie the relationship between these phenotypic traits. I will focus particularly on the importance of the immune system in bringing about variation in behavior. While more traditionally seen as a reactive system, switching from surveillance mode to being activated when necessary to respond to an invasion, immune molecules (e.g., cytokines) are also known to be essential for the development of the brain and for functions such as memory and learning (Bilbo and Schwarz, 2012). I argue here that some of the molecules involved in immune defense and communication are the same ones affecting behavior prior to an invasion. I discuss the possibility that these molecules may serve a broader function in shaping behavioral traits.

2. Behavioral traits co-vary with immune traits

Whether placed under the term personality, behavioral syndrome, coping style or temperament, we currently know that animals display individual differences in behavior that are consistent over time and across contexts (Réale et al., 2010). This type of behavioral variation should be associated with variation in pathogen and parasite exposure (Barber and Dingemanse, 2010). Indeed, traits such as exploratory behavior, risk-taking, boldness and extraversion have been linked to differences in susceptibility to infection. In pumpkinseed sunfish (*Lepomis gibbosus*), bolder animals had higher prevalence of trematodes than fish of the same species classified as shy (Wilson et al., 1993). The same relationship was found for bold feral cats (*Felis catus*) and immunodeficiency virus (Natoli et al., 2005) and bold deer mice (*Peromyscus maniculatus*) and Sin Nombre virus (Dizney and Dearing, 2013). Nightingales (*Luscinia megarhynchos*) displaying more risk-taking behaviors had more intense infections and were more likely to be infected by protozoan blood parasites than conspecifics displaying less risk-taking behaviors (Marinov et al., 2015). Recently, risk-taking personality in rock lizards (*Iberolacerta cyreni*) was found to covary with blood parasite infection intensity (Horváth et al., 2016). The relationship between the personality trait and parasite prevalence will depend on the host-parasite system and context being tested (Kortet et al., 2010). For example, while high exploratory behavior and activity in Siberian chipmunks (*Tamias sibiricus*) were associated with increased tick load (Boyer et al., 2010), wood frog (*Lithobates sylvaticus*) tadpoles showing high exploratory behavior and activity had lower trematode load (Koprivnikar et al., 2012). While in the chipmunks the behavior increased exposure, in the tadpoles the behavior allowed for parasite avoidance. These types of relationships also affect humans. Human subjects scoring high in extraversion and openness to experience had increased incidence of hospitalization due to illness or accident (Nettle, 2005). This relationship in humans led some researchers to suggest that in regions where disease prevalence has been historically high, selection of certain personality traits that are linked to lower levels of exposure may have occurred. In an analysis combining worldwide epidemiological data, with data on personality and sexual behaviors, Schaller and Murray (2008) found that increased disease prevalence was correlated with low scores on extraversion and on openness to experience. Thus, heterogeneity in behavior within and across populations and species seems, in many contexts, to be associated with heterogeneity in parasite burden (refer to Segerstrom, 2000, and Friedman, 2008, for more extensive reviews).

Given the increased risk of particular behavioral phenotypes in acquiring parasites, studies have more recently focused on understanding whether certain behavioral traits may also be linked to differences in immune investment or responsiveness. Several cases of this association have been found in birds. For instance, when wild greenfinches (*Carduelis chloris*) were captured and brought into captivity, the 'calm' individuals were also the ones mounting the stronger immune responses (stronger antibody response to a novel antigen and stronger oxidative burst; Sild et al., 2011). House finches (*Haemorhous mexicanus*) that displayed social avoidance of conspecifics exhibiting disease symptoms also showed a reduced investment in immunity (Zylberberg et al., 2013). A different study on house finches found immune function to be reduced as novelty avoidance or surveying behaviors increased (Zylberberg et al., 2014), leading authors to conclude that house finches with increased risk-taking behaviors have higher investment in immunity. In zebra finches (*Taeniopygia guttata*), the portion of time birds spent resting was positively correlated with immune responsiveness (Lopes et al., 2014). A similar relationship was recently found in firebugs (*Pyrrhocoris apterus*), whereby the less active animals had higher immune responses (Gyuris et al., 2016). In adult male rhesus macaques (*Macaca mulatta*), high sociability (tendency to engage in affiliative social interactions) seemed to be associated with a more favorable progression of simian immunodeficiency virus disease (Capitanio et al., 1999).

Links between behavioral traits and immunity have also been found in humans. Using a functional genomics approach, Cole et al. (2007) found a relationship between loneliness and overexpression of pro-inflammatory genes. More recently, using a similar approach, Vedhara et al. (2015) collected peripheral blood samples from healthy volunteers and asked them to complete a personality test. The individuals were also asked to provide information on health behaviors (such as exercising, drinking and smoking) and current medication use, so that these could be controlled for. Based on the personality test, individuals were classified into five personality dimensions: Extraversion, Neuroticism, Openness, Agreeableness and Conscientiousness. When leukocyte gene expression was compared to these personality dimensions, the researchers found Extraversion to be associated with up-regulation of pro-inflammatory gene expression and Conscientiousness with down-regulation. Individuals suffering from depression show consistent behavioral changes, many of these having striking similarities with behavior symptoms of illness (Dantzer et al., 2008). Moreover, a meta-analysis found that the intensity of depressive symptoms varied linearly with markers of cellular immunity (Herbert and Cohen, 1993). Because of this overlap, ongoing research is studying possible links between inflammation and depressive behaviors (Dantzer et al., 2008; Wohleb et al., 2016). The findings point to an effect of pro-inflammatory cytokines on behavior. I will extend on this point in section *Immune traits affect behavior*.

The central question that arises from these studies is: what underlies these relationships? While the main view has been that personality somehow (potentially through biased pathogen exposure) drives the changes in immunity, other scenarios are possible.

3. How are behavioral and immune traits linked?

The simplest explanation for findings of co-variation between behavioral and immune traits is that these observations have been found by chance and do not reflect any physiological link. While this is possible given the correlative nature of many of these studies, the neural, endocrine and immune systems have been shown to be so intrinsically intertwined that it is hard to imagine that at least part of this co-variation would not be explained by some aspect of the underlying physiology. Assuming a causal relationship, possible mechanistic routes that explain co-variation between behavioral and immune traits are the following (Fig. 1):

1) Behavioral traits affect immune traits
2) Immune traits affect behavioral traits
3) A third factor simultaneously impacts behavioral and immune traits.

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