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Sex differences in the neuroimmune system

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While sex differences in the peripheral immune response have been studied extensively, sex differences in the *neuroimmune* response, including glial activation and associated cytokine production in the brain, is a recently emerging field. Advances in our understanding of sex differences in the neuroimmune response have important implications for understanding how neural circuits are shaped during early brain development, how activation of the immune system may impact cognitive function and behavior, and how inflammation may be associated with the risk of mental health disorders that have strong sex-biases. The goal of this mini review is to highlight recent work in the field of sex differences in neuroimmune function, with a particular focus on how microglia function is influenced by age and sex hormone exposure.

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Introduction

Sex is a biological variable that significantly affects all aspects of an organism, including the immune system. An individual's biological sex is determined as male or female by the differential presence of the sex chromosomes in each cell, the differentiation of the reproductive organs, and the subsequent production of sex-specific steroid hormones that organize the brain as male or female. Every cell has a sex; thus, biological sex differences can influence the *physiological* characteristics of the immune response that determine recognition, clearance, and transmission of pathogens, as well as the neuroimmune response to environmental insults. Gender, on the other hand, is an individual's identity as male or female with reference to social and cultural differences, rather than biological differences, *per se*. Gender differences can influence behaviors that impact the risk of exposure to pathogens, can restrict or promote access to healthcare, and can influence other behaviors that affect the course or duration of an infection in men and women. While both sex and gender have a critical role in determining the neuroimmune response in males and females, the focus of this review will be on biological sex differences in the neuroimmune response and their influence on the brain and behavior throughout the lifespan.

Sex differences in microglia number and function in the developing brain influence sex differences in neural circuit formation

A critical period is defined as a period of development wherein a system maintains a heightened sensitivity to particular stimuli in order to develop in a specific manner. Some of the most compelling evidence for critical periods comes from the early studies of sexual differentiation of the brain and behavior [1]. These studies elegantly demonstrate the powerful role of sex steroid hormones during perinatal development in organizing the brain and behavior as either male or female. These experiments also reveal that, as sex hormones increase during puberty, the sexually dimorphic neural circuits that were organized during the critical period of development are 'activated' inducing sex-specific behaviors. Since the time of this groundbreaking work, two lines of research have provided significant insight into the mechanisms responsible for sexual differentiation of neural circuits during the critical period of development. First, studies by Lenz and colleagues [[2,5,6]] demonstrated that the resident immune cells of the brain, microglia, are a fundamental mechanism for the development of sexually dimorphic neural circuits in the preoptic area (POA) that underlie *sex-specific behaviors*. Specifically, during the critical period of sexual differentiation, microglia within the POA release the immune signal, prostaglandin E_2 (PGE_2), which masculinizes neural circuits in the male POA and is necessary for the expression of male sex behavior later in life [[2,5,6]]. Furthermore, both estradiol and PGE_2 masculinize the number and morphology of microglia in the female brain, and inhibition of microglial function prevents adult male sex behavior later in life [[2,5,6]]. These findings were the first to directly link sex differences in microglia number and morphology with the development of the sexually dimorphic neural circuits that underlie sex-specific reproductive behaviors. The second line of research has investigated how sex differences in microglia number and morphology influence the development of neural circuits in regions that do not (yet) have a clear role in sexually dimorphic behaviors. For example, neonatal male rats have significantly more microglia than females in the parietal cortex, CA1, CA3, dentate gyrus (DG), and amygdala [3,4••]; and, compared to females, a larger

percentage of microglia in males have an amoeboid morphology, indicating a more immature 'phenotype' [3]. These sex differences in microglia number and morphology are evident on postnatal day 4 (P4) and are the result of increased testosterone-mediated cell proliferation in the male brain, and *not* the result of decreased cell survival in the female brain [4••]. In fact, neonatal female rats treated with estradiol have increased microglia cell proliferation, similar to that seen in males [4••], indicating that microglia can respond to sex steroid hormones to influence their number, and perhaps function, but it is not clear how this occurs. Several groups have shown that steroid hormone receptor expression is either extremely low or undetectable on microglia during early brain development [2,5,6], suggesting that cross-talk between microglia and other neural cells that express steroid hormone receptors may be necessary to produce sex differences in microglia number and phenotype in the developing brain. Similarly, exposure to Bisphenol A, a synthetic estrogen mimetic, from P6 to P12, increases the number of microglia in both male and female rat dentate gyrus and amygdala by P12 [7]. Thus, exposure to environmental factors that mimic sex steroid hormones, particularly testosterone (or estradiol), can also induce the process of brain masculinization by influencing the number of microglia in the developing brain (Figure 1).

In the cerebellum, Perez-Pouchoulen *et al.* [8] showed that males have more microglia with very thin, long processes than females in the granule layer, even up until P17; however, there was no sex difference in the number of microglial phagocytic cups. Similarly, in the ventrolateral periaqueductal grey (vLPAG), Doyle *et al.* [9] found that females had a greater number of microglia with thicker and more branches, but there was no sex difference in the *total* number of microglia. Thus, there are clear sex differences in microglia morphology in the cerebellum and vLPAG, but, unlike in the preoptic area, it is not clear yet how these sex differences in morphology translate to sex differences in the function of these cells, how they influence surrounding neural cells, or how they impact sex differences in behavior later in life. Conversely, in the neonatal hippocampus, Nelson and colleagues [4••] found that female microglia phagocytose neural progenitor cells at higher rates than male microglia. Female microglia also had higher expression of genes related to phagocytic pathways compared to males; however, there were no sex differences in microglia morphology, indicating a clear sex difference in microglia function, without a discernable sex difference in cell morphology. These data highlight the enormous amount of heterogeneity in sex differences of microglial cells that is dependent upon the microenvironment of the brain region examined.

Collectively, these data suggest that there can be fundamental differences in the function of microglia between males and females, which can alter the way in which they interact with developing neural circuits in their unique microenvironments, but are independent (to some degree) from their function as traditional 'immune cells'. While there is much that remains to be discovered, so far we know that microglia have an essential role in modulating sex differences in the development of neural circuits, including those underlying sex-specific behaviors and those that do not. Microglia are influenced by the differential hormonal milieu of the developing brain, impacting how they carry out these important developmental processes during the critical period of sexual differentiation of the brain and beyond [2,10]. Thus, drugs that deplete microglia or block microglial function during early brain development can have permanent sex-dependent effects on later-life sexual and social behaviors [2,11,12].

Sex differences in microglia: how is risk conferred following early-life immune activation?

During the early neonatal period (P4), males have more microglia with an amoeboid morphology than females in a number of brain regions important for cognition, memory, and emotion processing [3]. But, compared to males, female microglia show significant increases in the expression of a number of cytokines and chemokines including IL-10, IL-1f5, CCL22, CCR4, CXCL9, and IL-1β protein in many of these same regions at this same age [3]. These findings suggest that males and females have fundamental differences in microglia number and phenotype during early neonatal development, thus microglial activation could underlie sex differences in the vulnerability caused by early-life immune activation. Indeed, Bolton and colleagues [13] found that *in utero* exposure to air pollution delays the maturation of microglia resulting in an exaggerated response to subsequent lipopolysaccharide (LPS) treatment (i.e. increased number of microglia with thick, long processes) in juvenile males, but not females. These male mice also had decreased cortical volumes in the parietal cortex, which the authors suggest is the result of increased microglia-neuronal interactions in this region [13]. Furthermore, when *in utero* exposure to air pollution was paired with maternal stress, male offspring exhibit impaired hippocampal-dependent learning, increased expression of the pro-inflammatory cytokine interleukin (IL)-1β, and decreased expression of the anti-inflammatory cytokine IL-10 as adults [14] — effects that are not seen in females. These data support previous findings that increased IL-1β expression in the brain results in hippocampal-dependent learning deficits, specifically in adult males (reviewed in [15]). Stress-induced activation of inflammatory molecules within the placenta also occurs in a sex-dependent manner [16]. Following chronic maternal stress, pro-inflammatory cytokine expression is significantly increased in male, but not female fetuses.