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Sex Differences in the Neuroimmune System

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Abstract

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.

Keywords

sex differences; microglia; cytokines; mental health; neurodevelopment; hormones

1. 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

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Conflict of Interest

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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.

2. 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] 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 E₂ (PGE₂), which masculinizes neural circuits in the male POA and is necessary for the expression of male sex behavior later in life [2]. Furthermore, both estradiol and PGE₂ 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]. 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.

In the cerebellum, Perez-Pouchoulen, VanRyzin, and McCarthy [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, Eidson, Sinkiewicz, and Murphy [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].

3. 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-1 β 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)-1 β , 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-1 β 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. These male mice have altered dopamine receptor expression in the prefrontal cortex and nucleus accumbens, and as a result, exhibit hyperactivity – a behavioral effect that is ameliorated by maternal anti-inflammatory treatment [16]. Using a model of intrauterine inflammation, Makinson and colleagues [17] found that neonatal males exhibit increased expression of IL-1 β , TNF- α , C1q, C3, and TGF- β , and have an exaggerated cytokine response to an immune challenge in adulthood – effects which are not seen in females. Collectively, these data indicate that males may be more vulnerable to early-life immune activation than females, possibly via sex differences in the function of microglia and their expression of pro-inflammatory molecules (e.g. males show exaggerated levels) during early brain development, leading to cognitive and behavioral deficits.

Stress induces pro-inflammatory cytokine expression in the brain by increasing microglial activation [18,19] and alters a number of biological processes involved in the neuroimmune response in a sex-dependent manner, including cell-to-cell communication [20], epigenetic regulation of gene expression [21], and the inflammatory response in the male and female hippocampus [22,23]. For example, following chronic prenatal stress, male mice show increased basal levels of the pro-inflammatory cytokine TNF- α in the hippocampus as adults, an effect that is not seen in females [22,23]. Males exposed to prenatal stress also show increases in the number of microglia with an activated morphology (i.e. more and thicker branches) in the dentate gyrus in response to LPS as adults, whereas prenatal stress in females causes an increase in the basal levels of activated microglia, which is unaffected by treatment with LPS in adulthood [22,23]. However, after exposure to prenatal stress, both males and females show increased basal levels of IL-1 β expression in the hippocampus as adults suggesting that at least some consequences of prenatal stress can be similar between males and females [22,23]. In a different model of early-life stress, following maternal separation (MS), male rats showed significant decreases in the number of parvalbumin-containing interneurons in the prefrontal cortex and increases in circulating levels of TNF α as adolescents – effects that were not seen in females [24]; however, both males and females

had similar learning deficits on a cognitive task [24]. Similarly, prenatal alcohol exposure produces exaggerated expression of IL-1 β and IL-6 in the hippocampus in response to an LPS immune challenge in adulthood, but to a significantly greater extent in males than females. But, both males and females show deficits in recognition memory as adults [25]. These data demonstrate that sex differences in the neuroimmune response can differ depending on the type of immune challenge and, while there can be sex differences in the neuroimmune response in the brain and periphery, this does not always reflect a sex difference in behavior. Therefore, some sex differences in the neuroimmune response may result in similar outcomes in males and females.

Still, there are many cases in which sex differences in the neuroimmune system *do* lead to different outcomes in males and females. Morphine, for example, is more effective at decreasing pain sensitivity in males compared to females. Doyle et al. [9] proposed that this sex difference in morphine effectiveness is driven by sex differences in microglia activity. As mentioned above, females have more microglia with an activated phenotype in the vIPAG compared to males, which may account for the attenuated response to morphine in females. Furthermore, *blocking* TLR4 receptor activation decreases the development of morphine tolerance in males, but not females. Sorge and colleagues [26] proposed that microglia might not even be required for pain processing in female mice at all. Instead, female mice may preferentially initiate changes in adaptive peripheral immune cells, as opposed to microglia, resulting in increased pain sensitivity following injury. Interestingly, however, in the absence of adaptive immune cells, females engage microglial pathways typically used by males to process pain sensitivity following injury [26].

These studies highlight that early-life exposure to a wide range of immune challenges, including early-life inflammation, stress, or drugs of abuse can have negative consequences for brain development and behavior that are likely driven by sex differences in microglia. The data so far indicate that, under certain circumstances, males may be uniquely vulnerable to the negative effects of early-life immune activation. However, in some cases, females are also vulnerable. Indeed, sex differences in the neuroimmune response have been shown to have an important role in the risk of stress- and anxiety-related mood disorders that are more common in women than in men [18]. In fact, ovarian hormones have been shown to alter expression of IL-1 [27] and, following early-life stress, cognitive impairments in adolescents can be predicted by sex and cytokines [28]. Thus, dysregulation of glial function caused by early-life immune activation, stress, or trauma may result in cognitive dysfunction in a sex-dependent manner, resulting in the sex-specific emergence of many disorders, including schizophrenia, Alzheimer's Disease, or other types of dementia later in life [29]. The jury is still out on exactly *how* sex differences in the neuroimmune system confer sex differences in vulnerability to the negative consequences of early-life immune activation. Future research aimed at elucidating the role of microglia-neuronal communication in brain regions important for cognition, memory, and emotion processing in males and females are likely to provide significant advancements in our understanding of the relationship between sex differences in the neuroimmune response and the risk for mental health disorders.

4. Age as a determinant of sex differences in the neuroimmune response: What do we know about the role of microglia?

Age, much like sex, is a critical determinant for *how* immune activation influences sex differences in the immune response. As previously mentioned, Bilbo and colleagues found that neonatally-infected male rats showed cognitive deficits in *adulthood* following an immune challenge that occurred around the time of learning, an effect that is not seen in females [15]. Using this same model, Osborne and colleagues [30] determined that *juvenile* males and females do not yet show these cognitive deficits, which suggests that there may be something unique about the brain at this younger age that protects cognitive function from the detrimental effects of early-life immune activation in males. Moreover, these findings could inform our understanding of the mechanisms responsible for why females continue to be “protected” even in adulthood. Indeed, age is an important factor that influences sex differences in the neuroimmune response (for a recent review see [31]). Following peripheral immune activation, adult male mice have a greater febrile response than females, an effect that is caused by a sex difference in cytokine expression in the brain at this age [32,33] - higher levels of IL-1 receptor *antagonist* (IL-1ra), an endogenous anti-inflammatory cytokine that attenuates the production of pro-inflammatory cytokines, including IL-1 β , in the hypothalamus, attenuates the febrile response in adult female rats [32]. Adult male mice also display greater and more prolonged hypothermic responses, greater fluctuations in body temperature, and more pronounced sickness behavior following peripheral LPS administration compared to female mice, a sex difference that only becomes apparent *after* puberty [34]. Similarly, de Souza and colleagues [35] found that following maternal immune activation, the astroglial marker S100B was increased in the prefrontal cortex of adolescent *male* rats; but in adulthood, S100B was increased in males *and* females, suggesting that circulating steroid hormones activated in puberty can regulate the neuroimmune response in females to alter the activity of neuroimmune cells. Indeed, following a foot shock stressor, Arakawa and colleagues [27] found that regularly cycling females showed stress-induced increases in IL-1 expression in the paraventricular nucleus (PVN) of the hypothalamus during the diestrous, proestrous, and estrous phases. No change in IL-1 expression was seen in the metestrous phase, however, estrogen receptor (ER)- β expression did increase [27]. Treatment with progesterone increased ER- β expression in ovariectomized females leading the authors to posit that high levels of progesterone during the metestrous phase sensitizes ER- β receptors, causing the observed attenuation of stress-induced increases IL-1 expression in the PVN [27].

Thus, every immune cell in the brain has the potential to respond differently to the same immunogenic challenge depending on the age of that cell and the associated hormonal milieu. Critical periods remain fundamental to our understanding of brain development and later-life behavior; however, recognizing that age is an important biological factor that influences sex differences in the neuroimmune response *throughout* the lifespan is necessary for elucidating how sex differences in neuroimmune function confer sex-specific vulnerability to early-life immune challenges.

6. Conclusions

The recent data summarized here only begin to elucidate the diverse mechanisms by which sex differences in microglia number and function may influence the establishment and maintenance of sex differences in the brain. What has been discovered to-date has been enormously instrumental in our understanding of how sex differences in the neuroimmune system can affect sexual differentiation of the brain and behavior and the vulnerability to early-life immune challenges, which increases the risk for mental health disorders. Future research must focus on understanding how early-life immune challenges may impact vulnerability to mental health disorders in a sex-dependent manner. Specifically, we still need to understand how sex influences microglia-neuronal interactions for the establishment and maintenance of healthy neural circuits and how these interactions may be perturbed following early-life immune challenge at various ages. This research will be crucial for advancing our understanding of how sex differences in the neuroimmune response may affect the brain and behavior across the lifespan.

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Highlights

- Sex differences in microglia number and function are evident early in the neonatal brain
- Microglia have an important role in establishing sex-specific behaviors later in life.
- Vulnerability to perinatal immune activation is dependent on sex difference in microglia
- Age significantly influences sex differences in the expression of the neuroimmune response

Figure 1. Microglia can be influenced by endogenous and exogenous factors in a sex dependent manner

Microglia initially colonize the brain early in development (embryonic day (E) 9-10 in rodents). During this time and into the postnatal weeks, microglia have an important role in forming neural circuits by initiating synapse formation, pruning aberrant synapses, and phagocytosing naturally dying cells. Around birth, testosterone production in males can influence the number and function of microglia in the developing brain, thus influencing many of these important neurodevelopmental processes. There are also many perinatal events that can program the function of microglia and later-life behavior in a sex-dependent manner. In general, males are more vulnerable to early-life insults including immune activation or stress. Later in life, microglia continue to have an important role in monitoring synapse function and formation, and thereby influencing cognitive function and behavior. During this time, microglia can be influenced by circulating sex steroid hormones, either testosterone in males, or estradiol and progesterone in females. Acute stress can also induce the activation of microglia in the brain via glucocorticoid secretion (CORT), and this can occur in a sex-dependent manner.