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Small cells with big implications: Microglia and sex differences in brain development, plasticity and behavioral health

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Abstract

Brain sex differences are programmed largely by sex hormone secretions and direct sex chromosome effects in early life, and are subsequently modulated by early life experiences. The brain's resident immune cells, called microglia, actively contribute to brain development. Recent research has shown that microglia are sexually dimorphic, especially during early life, and may participate in sex-specific organization of the brain and behavior. Likewise, sex differences in immune cells and their signaling in the adult brain have been found, although in most cases their function remains unclear. Additionally, immune cells and their signaling have been implicated in many disorders in which brain development or plasticity is altered, including autism, schizophrenia, pain disorders, major depression, and postpartum depression. This review summarizes what is currently known about sex differences in neuroimmune function in development and during other major phases of brain plasticity, as well as the current state of knowledge regarding sex-specific neuroimmune function in psychiatric disorders.

Introduction

How sex differences in the brain are established and maintained:

Gonadal hormones: Gonadal hormones, also called sex hormones, belong to the class of steroid hormones and include three major subclasses: androgens, estrogens, and progestins. Gonadal hormones are all synthesized from the common precursor, cholesterol, in several different endocrine tissues. These include the ovaries, which largely but not exclusively synthesize estrogens and progestins, the testes, which largely but not exclusively synthesize androgens, and the adrenal glands, which largely produce the closely-related stress and electrolyte regulating hormones, glucocorticoids and mineralocorticoids, but also produce

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sex hormones. These steroid hormones are hydrophobic, and when released into the bloodstream, they are carried by soluble steroid hormone binding globulins. Given their hydrophobic nature, steroid hormones readily cross the blood brain barrier and bind to their receptors to influence brain development and function (Stumpf & Sar, 1976). The brain, too, synthesizes steroid hormones, called 'neurosteroids'. The brain possesses all of the necessary enzymes to synthesize steroid hormones de novo from cholesterol (Kimoto et al., 2001; Hojo et al., 2004). Thus, gonadally-derived and locally-derived hormones can modulate brain function in concert or independently.

Steroid hormones largely exert their effects on target cells by crossing the plasma membranes of cells via diffusion and binding to intracellular receptors located largely in the nucleus. Classical steroid hormone receptors include the androgen receptor, estrogen receptor alpha, estrogen receptor beta, and the progesterone receptor. Upon hormone binding, these intracellular receptors dimerize and undergo a transformational change that allows the hormone-receptor dimer to bind to hormone response elements on the DNA to regulate gene transcription (King & Greene, 1984; O'Malley & Tsai, 1992). This mode of steroid hormone-receptor action is a relatively slow process since it depends upon gene transcription and translation of new proteins. Beyond their role as transcription factors, steroid hormone-receptor complexes can have more rapid, non-genomic effects, often via activation of second messenger cascades (reviewed in Woolley, 2007). Hormones also act on non-nuclear receptors that are membrane-bound, including the G-protein coupled estrogen receptor (e.g., GPR30), estrogen receptor X, membrane progestin receptors and possibly others (Toran-Allerand, 2004; Thomas Pang, 2012). Membrane-associated estrogen receptors and progestin receptors can influence neural physiology within seconds to minutes (e.g., Kelly & Levin, 2001; Mermelstein & Micevych, 2008). For the purposes of this review on sex differences in the neuroimmune system, it is important to note that both neurons as well as immunocompetent cells in the brain, including microglia and astrocytes, have been shown to express receptors for all three major classes of hormones (e.g., Brinton et al., 2008; Garcia-Ovejero et al., 2002; Sierra et al., 2008; Spense & Voskul, 2012; see Table 1).

The Organizational/Activational model of hormonally-regulated behavior: Sex-typical hormone exposure regulates the display of sex-typical physiological and behavioral outcomes throughout the lifespan, including during development and during the period in which the outcome is observed, usually in adulthood. This two-pronged role for steroid hormones was defined by Phoenix et al., (1959) in a series of experiments showing that both early life as well as adult hormones was crucial to the display of sexual behavior, which has since come to be known as the "Organizational/Activational" model of hormone action. During particular windows of development, dubbed 'critical' or 'sensitive' periods, hormone exposure leads to sex-typical "organization" of the brain, including the establishment of sexually-dimorphic gene expression, cell birth, death, migration, differentiation and circuit wiring and refinement. Critical or sensitive periods are so named because hormones cannot induce such organizational effects if the timing of exposure is outside of that period. There is now also evidence to suggest that puberty is a second "mini-organizational" period for completing and/or refining the sexual differentiation process (Sisk, 2017; Sisk & Zehr, 2005). In the case of both male- and female-typical behaviors, adult concentrations of

circulating hormones are the second necessary component for the full complement of sex-typical physiological or behavioral phenotypes to manifest. These “activational” hormones act on the sex-typical brain that resulted from the organizational effects established during ontogeny.

Sexual differentiation—Sexual differentiation is the name for the organizational process by which the brain develops sex-biased characteristics during a critical period of early life. Brain sexual differentiation is a largely permanent process: Sex differences in the size, shape, and function of the brain are established early in development and remain relatively stable throughout life. Sexual differentiation begins with sex determination, which depends first upon sex hormone complement— in mammals, either XX in genetic females or XY in genetic males. The gene *sex determining region of the Y chromosome* (*SRY*) initiates the sex determination process by coding for the protein testis determining factor (TDF). TDF is a secreted signal that programs the differentiation of the bipotential gonadal tissue into testes in males. In females, the lack of TDF allows differentiation of the bipotential gonad into ovaries along a default program in the absence of any intervening signals.

Male-typical sexual differentiation depends upon secretion of androgens during the perinatal window in males. The testes secrete androgens, which in turn act to differentiate the internal and external genitalia as well as the brain. In humans, male androgen levels are elevated in utero, and the process of brain sexual differentiation is largely complete by birth. In contrast, rodent sexual differentiation begins during the late prenatal period, around embryonic day (E) 18.5, and extends into the early postnatal period (Reviewed in McCarthy et al., 2008). Moreover, in rodents but not primates, the dominant effects of sexual differentiation are accomplished by the actions of the hormone estradiol (Bakker & Baum, 2008), which is locally metabolized in the brain from testosterone by the enzyme p450 aromatase (Naftolin et al., 1971; Roselli & Resko, 1993).

Early life androgen exposure promotes a process called masculinization, wherein a male typical phenotype is programmed. Behavioral outcomes of this masculinization process include a strong motivation to mount sexually receptive females, intromit, and ejaculate, and additionally to engage in male-male aggressive behaviors (Fig. 1; Reviewed in Yang & Shah, 2016; Hull & Dominguez, 2007). Genetic females (both humans and rodents) can be shunted toward a masculinized path of sexual differentiation by exogenous or atypical androgen exposure. In rodents, females can be masculinized by exogenous testosterone or estradiol administered during the prenatal period or first 10 postnatal days (McCarthy, 2008). In humans, this role for androgens in disrupting female-typical development is best evidenced by the condition congenital adrenal hyperplasia (CAH), in which an enzyme deficiency leads the adrenal glands to produce high levels of androgens. Girls and women with CAH show partial masculinization of the genitalia, as well as masculinized play behavior in childhood and masculinization of spatial reasoning (Berenbaum et al., 2012; Berenbaum and Hines, 1992; Pasterski et al., 2011).

Additionally, early life androgen exposure in males leads to a parallel, but mechanistically distinct process, called defeminization, whereby the male brain is rendered incapable of engaging in female-typical sexual behaviors. The process of defeminization has been shown

to be distinct from masculinization, because steroid hormones induce different downstream effectors to induce the two processes and can be dissociated by manipulating these effectors (Todd et al., 2005). In the absence of androgen exposure, the female brain undergoes feminization. In females, the ovaries are largely quiescent during the perinatal period, and thus feminization has been considered a default process (Jost et al., 1973). However, at least in mice, females lacking functional aromatase activity to synthesize estrogens do not show entirely wildtype female sexual behavior, and pre-pubertal estrogen exposure rescues sexual behavior deficits, indicating a possible role for estrogens in the feminization process (Bakker & Baum, 2008; Brock et al., 2011). The nature of this 'feminization' process by estrogens remains unelucidated. Outcomes in females that are programmed in the absence of androgen exposure include strong motivation to perform sexual solicitation and take the reflexive sexually receptive posture known as lordosis, as well as the motivation to engage in maternal behavior following pregnancy and parturition (Lonstein & De Vries, 2000; Beach et al., 1976; Zemlan & Adler, 1977).

Recent work from Nugent et al. (2015) suggests that, although the female differentiation process proceeds along a default program without the necessity of an active hormonal signal, the female brain is actively prevented from undergoing masculinization via epigenetic means. In the rat medial preoptic area, females have higher levels of DNA methylation than males, and this methylation acts to silence male-typical patterns of gene expression (Nugent et al., 2015). When methylation is inhibited in the female POA, masculinization of the nucleus and adult sexual behavior results. Additionally, methylation appears to be crucial to maintaining the organizational period for sex differences: Interfering with DNA methylation after the critical period for sexual differentiation has occurred can "reopen" the organizational capacity of steroid hormones on the brain (Nugent et al., 2015). There are other examples in which permanent sexual differentiation appears reversible via relatively limited genetic manipulations (e.g., Kimchi et al., 2007), thus there may be many active signals that repress a feminine phenotype and/or masculine phenotype outside the critical period for sexual differentiation.

Despite the dominance of the "organizational" hormonal theory of sexual differentiation, there is increasing evidence that some sex differences established during ontogeny are also programmed by other contributing factors, including sex chromosome effects and maternal-fetal interactions. For example, studies using the four core genotype mouse model, in which sex chromosome complement and gonadal hormone status are dissociated, certain sexually dimorphic phenotypes (e.g., pain sensitivity, alcohol consumption, metabolic status) appear to be more programmed by sex chromosome status than hormonal status (reviewed in Arnold, 2017). The placenta is another key contributor to sex differences in brain development, both at baseline and in response to stressors, and sex differences in placental function emerge prior to the onset of gonadal hormone secretion (Nugent and Bale, 2015). This review will not exhaustively describe these sex differences or the mechanisms downstream of hormones for establishing these sex differences, but we point interested readers to other excellent reviews on these topics (Arnold, 2017; McCarthy et al., 2017; Nugent and Bale, 2015). Herein, we will narrow in on sex differences in the neuroimmune system across the developmental, pubertal and adult windows. Recently emerging evidence suggests that there are significant sex differences in neuroimmune function that may mediate

the establishment and maintenance of sex differences in brain function and behavioral outcomes later in life. These sex differences may also confer sex-biased risk for brain-based disorders, particularly those related to mental health.

A primer on immune cells in the developing brain:

Before we explore what is known (and still unknown) about neuroimmune cells as both sexually differentiated and sexual differentiat*or*, we must briefly describe the origin and development of immunocompetent cells within the CNS. Immunocompetent cells within the brain include microglia, which are tissue resident macrophages of the CNS (Kettenmann et al., 2011); mast cells, which are also innate immune cells that, in the periphery, are associated with allergy, atopy, tissue edema, and itch (Silver & Curley, 2013); astrocytes, which are derived from neural stem cells, but are capable of inflammatory signaling, antigen presentation, and phagocytosis (Dong & Benveniste, 2001); perivascular macrophages, which have a similar developmental origin to microglia and communicate peripheral information to endothelial cells of the blood brain barrier (Faraco et al., 2017); and meningeal and choroid plexus immune cells, including monocytes, mast cells, neutrophils, dendritic cells, and T cells, and which can influence brain physiology and behavior across the blood brain barrier (Herz et al., 2017; Meeker et al., 2012). Each of these other cell types has been implicated in normal CNS function the response to injury, and the pathophysiology of autoimmune and neurodegenerative conditions, and in many cases gonadal hormones modulate their function in these contexts (Brinton et al., 2008; Garcia-Ovejero et al., 2002; Spense & Voskuhl, 2012; Wu et al., 2013) see table 1 for a summary). Because most work on central immune cells has focused on microglia, the bulk of this review will focus on microglia and known sex differences in their function.

Microglia are the most abundant innate immune cell of the brain, comprising approximately 8–12% of total brain cells (Kettenmann et al., 2011). Unlike other brain cells, however, microglia are not derived from the ectoderm. Instead, microglia progenitors are peripheral in origin and invade the brain early in ontogeny. These microglia become entrapped behind the developing blood brain barrier and constitute a locally sustaining and long-lived cell population within the brain (Ajami et al., 2007; Ginhoux et al., 2010). Starting at E8.5–9.5 in rodents, microglia progenitor cells derived from the yolk-sac begin to infiltrate the fetal neural tissue through the nascent vasculature (Ginhoux et al., 2010; Stremmel et al., 2018). Similarly to microglia in rodents, microglia in humans appear early in neural development, around 4.5 weeks of gestation (Verney et al., 2010). Microglia in the immature brain have recently been phenotyped in several studies and shown to have distinct gene expression signatures during ontogeny. Thus, microglia can be classified as belonging to one of several stages of development, including the progenitor phase (~E9.5-E14), embryonic phase (~E14-E18), the perinatal phase (~E18-Postnatal day (PN) 9), and the more mature phase that begins to appear at PN28 and endures to adulthood (Bennett et al., 2016; Matcovitch-Natan et al., 2016; Thion et al., 2017).

The pre-microglia progenitor is developmentally distinct from most other resident tissue macrophages in terms of gene expression (Bennett et al., 2018; Hoeffel et al., 2015; Sheng et al., 2015). Once microglia progenitors infiltrate the brain, they differentiate into early

microglia and colonize the entirety of the brain through migration and local proliferation (Bennett et al., 2016; Matcovitch-Natan et al., 2016). Colonizing microglia are typically amoeboid in shape, and over the course of the first weeks of postnatal life, microglia become fully ramified in shape. In rodents, this transition to a ramified morphology is complete around the end of the 2^{nd}-3^{rd} postnatal week, which is also accompanied by increased expression of Tmem119 (Bennett et al., 2016; Dalmau et al., 1998, 1997). Microglia density peaks approximately 3 weeks after birth; microglia number decreases to adult levels 4–5 weeks after birth (Kim et al., 2015; Nikodemova et al., 2015). Microglia appear to use local microenvironment signals to determine the density at which they seed the brain, as cultured microglia transplanted into a brain genetically depleted of microglia via cell survival factor (CSF) 1 receptor knockout rapidly assume a wild-type distribution of cells (Bennett et al., 2018). With the exception of the initial infiltration of the pre-microglia yolk-sac derived progenitors, the microglia population is largely sustained by proliferation throughout life, with little to no contribution of peripheral macrophages under basal conditions (Ajami et al., 2007). Across the remainder of the lifespan, microglia completely turn over approximately twice, with apoptotic cell death and new cell genesis occurring in a ‘coupled’ process (Askew et al., 2016).

Microglia function during development:

Microglia sample their local microenvironment by extending and retracting their many processes (Nimmerjahn, 2005). In doing so, microglia sense debris, dead or dying cells, and pathogens in the brain; engulf deleterious or foreign materials in phagosomes; and digest and eliminate this debris within phagolysosomes (reviewed in (Kettenmann et al., 2011). Within the context of brain injury or infection, microglia home to sites of inflammation and contribute to brain repair or host defense and recruit other immune cells to the site of active infection or degeneration (reviewed in Kettenmann et al., 2011). As such, microglia had long been dismissed as “garbage collectors” or defenders against rare viral or bacterial infections of the brain. And yet, a recent surge of evidence also suggests that microglia actively regulate brain development and physiology by a) sculpting the developing brain early in life and into adulthood, and b) regulating normal developmental processes in the brain by secretion of cytokines, chemokines, and other canonical immune molecules.

Microglia contribute to brain function as soon as they infiltrate the neural tissue, engulfing apoptotic cells as early as the second prenatal week (Kierdorf et al., 2013). During brain development, microglia also engulf and digest (phagocytose) cells and synapses, release diffusible molecules that stimulate synapse formation, cell genesis, and myelin production, and mediate neurite outgrowth (Cunningham et al., 2013; Hagemeyer et al., 2017; Miyamoto et al., 2016; Parkhurst et al., 2013; Pont-Lezica et al., 2014; Schafer et al., 2012; Ueno et al., 2013; Wakselman et al., 2008). Through activation of the complement cascade, microglia phagocytose presynaptic elements in the dorsolateral geniculate nucleus of thalamus in an activity-dependent manner (Schafer et al., 2012). Microglia also phagocytose postsynaptic elements in the developing brain, and recent work has identified astroglia-derived interleukin (IL) 33 as a factor that regulates microglial synaptic phagocytosis (Vainchtein et al., 2018). However, the strength of past studies that examined microglia synaptic engulfment has recently been questioned. During development, a recent study shows that microglia

phagocytized presynaptic, but not postsynaptic elements, largely by engaging in 'trogocytosis', or nibbling away small bits of presynaptic elements (Weinhard et al., 2018a). Weinhard et al. demonstrated that, while under light sheet microscopy, postsynaptic densities appeared to co-localize with microglia however, when examined using serial electron microscopy microglia were not engulfing the post-synaptic element. These data suggest that standard microscopy techniques may be inadequate to definitively determine whether microglia are pruning post-synaptic elements under homeostatic or diseased conditions.

Microglia also support developmental cell genesis. Microglia support neurogenesis and oligodendrogenesis by producing IL-1β, tumor necrosis factor alpha (TNFα), interferon gamma (IFNγ), IL-6 and insulin-like growth factor 1 (IGF1) (Hagemeyer et al., 2017; Shigemoto-Mogami et al., 2014). Recent research has found that a Cd11c+ population of microglia, previously thought to be dendritic cells, may be primarily responsible for supporting oligodendrogenesis (Hagemeyer et al., 2017; Wlodarczyk et al., 2017). Microglia also regulate neurogenesis by mediating progenitor pool size in the subventricular area: Microglia phagocytose healthy neural progenitor cells at the end of the period during which robust neurogenesis occurs, and depleting microglia during this window increases the size of the progenitor pool (Cunningham et al.,2013). In the case of the Cunningham et al. study, it would appear that microglia eliminate healthy living cells, because many engulfed cells do not express apoptotic markers (Cunningham et al., 2013). However, the mechanism or "tags" that regulate microglia phagocytosis of progenitor cells remains unknown.

In the young adult brain, microglia also clear apoptotic cells: 42% of these cells were PSA-NCAM+, a marker of neural progenitor cells, and 28% were POMC+, a marker of post-mitotic differentiating newborn neurons (Abiega et al., 2016; Sierra et al., 2010). Within the hippocampus, developmental cell death is at least partly mediated by microglia through Cd11b and DAP12 (Wakselman et al., 2008). Microglia also contribute actively to the cell death process by delivering free radicals to apoptosis-committed cells to complete the cell death process (Marin-Teva et al., 2004). Last, microglia support spinogenesis and synaptogenesis. Microglial physical contact with developing synapses, as well as microglial-derived prostaglandin E2 (PGE2), brain-derived neurotrophic factor (BDNF), IL-1β and IL-10 all regulate spinogenesis and synaptogenesis across several brain regions during development (Lenz et al., 2013; Lim et al., 2013; Miyamoto et al., 2016; Parkhurst et al., 2013).

Perinatal sex differences in neuroimmune parameters:

Microglia: A growing body of research documents sex differences in microglia during development that are dynamic across the critical period for sexual differentiation. One of the first studies to compare male and female microglia found that females have more microglia in the hypothalamus, amygdala, and hippocampus shortly after the prenatal testosterone surge (Schwarz et al., 2012). However, in the early postnatal period, males have more microglia than females. Others have found that females have more microglia in the somatosensory area throughout perinatal development (Thion et al., 2017), though the function of this sex difference is unknown.

Males also have more microglia than females overall and more deramified, ameboid-shaped microglia in the developing preoptic area (POA). The POA is a brain a region that is crucial to the expression of male-typical sexual behavior in adulthood, as well as female-typical maternal behavior (reviewed in Lenz & McCarthy, 2010). Sex differences in POA microglia number and morphology are organized by exposure to estradiol, such that females treated neonatally with estradiol show rapid increases in the number of ameboid microglia in the POA (Lenz et al., 2013). This study is one of few cases in which the function of a sex difference in microglia has been determined. Male-typical synaptic patterning, namely an increase of dendritic spine synapses, depends on microglial release of the immune mediator PGE2 in the POA (Lenz et al., 2013). This synaptic patterning correlates strongly with masculine patterns of sexual motivation and sexual performance in adulthood (Amateau and McCarthy, 2004, 2002; Lenz et al., 2013; Wright and McCarthy, 2009).

We have also recently found that microglia phagocytose more cells in the neonatal female hippocampus than in the neonatal male hippocampus, but not before the prenatal testosterone surge (Nelson et al., 2017). This sex difference, too, is hormone-driven—estradiol treatment of females reduces phagocytic microglia to male-typical numbers (Nelson et al.,2017). Compared with males, females also show higher gene expression related to microglia phagocytosis, and the sex difference in microglia phagocytosis is directed at neural progenitor cells. Thus females could have lower levels of cell proliferation due to increased phagocytosis of progenitor cells. Others have found the rate of neurogenesis in the developing hippocampus is hormone-dependent and higher in males than it is in females (Bowers et al., 2010). However, it is unknown if there is a sex difference in the rest of the brain or later in development. Interestingly, although there was no difference in the number of phagocytic cups that contained pyknotic nuclei, there was a sex difference in the number of engulfed non-pyknotic nuclei (Nelson et al., 2017). However, we have not yet determined if the sex difference in phagocytosis of progenitor cells included apoptotic or healthy cells. Future studies are necessary to test for a mechanistic link between sex differences in microglia phagocytosis of progenitor cells and sex differences in neurogenesis. Additionally, how healthy cells are “tagged” for removal and if there are sex differences in such “tags” remains unknown.

In line with increased phagocytic capacity in females during development, another recent study has demonstrated that, in the neonatal hippocampus, female microglia express more CD68, a lysosomal marker used into indicate phagocytic capacity, in the second week postnatal that diminishes by puberty (Weinhard et al., 2018b). Moreover, this female-biased phagocytic capacity correlates with a transient sex difference in synapse number in the neonatal hippocampus, though the two phenomena have yet to be mechanistically linked (Weinhard et al., 2018b). Several labs have found that a) female microglia are more developmentally mature than male microglia across development and b) females have higher expression of inflammatory, phagocytic, and immune genes than males (Hanamsagar et al., 2017; Thion et al., 2017), though it is unknown whether this in maturity alters the rate of any normal developmental processes, such as cell genesis, death, synaptic patterning, etc., between the sexes.

Considering the differences between the main hormonal effector of sex differentiation of the brain between rodents and humans (i.e. estradiol vs testosterone), it is important to determine whether sex differences in human microglia development bear similarity to that seen in rodents. A landmark study of human microglial maturation found that while microglia gene expression was distinct across developmental stages, in the mid-gestation human brain, microglia gene expression did not differ by sex (Thion et al., 2017). However, another study, using a much larger cohort than Thion et al., 2017, found higher expression of microglia markers in males compared with females in whole brain tissue over development (Werling et al., 2016). Further research is needed to determine whether sex differences found in rodents map onto sex differences found in humans. Additionally, it remains unknown whether microglia are sexually differentiated throughout the brain or only in specific brain areas during development.

Lastly, it is important to determine how sex differences in microglia arise. Sex steroids could have direct or indirect effects on microglia depending on whether microglia themselves express sex steroid receptors (see Table 1). This may also be important for understanding differences in development sex differences of microglia in humans compared to rodents (i.e. testosterone vs estradiol driven). Some groups have found that microglia enriched from the whole brain express the gene for estrogen receptor alpha (ESR1) at low levels early in life and higher levels in adulthood (Crain et al., 2013). However, other groups found that neonatal microglia in the hippocampus do not express ESR1 or ESR2, the gene for estrogen receptor estrogen receptor beta, or androgen receptor; rather, other cells express sex steroid receptors (Turano et al., 2017). Similarly, estrogen receptor alpha staining was not seen in microglia in the neonatal POA, where strong sex differences in microglia properties have been demonstrated (Lenz et al., 2013). Others have found that microglia express several steroid hormone receptors in adulthood (Sierra et al., 2008). Thus, microglia likely express sex steroid receptors in a region-specific, time-dependent, and/or context dependent manner (such as after injury, stress, etc), and more work is needed to appreciate the subtleties of hormone sensitivity in microglia. Figure 2 summarizes what is currently known (or hypothesized) about sex differences in microglia during development.

Immune molecules: There are also sex differences in several immune molecules in the developing brain, and some of these sex differences have been shown to actively contribute to the sexual differentiation process. Above, we have discussed the case of PGE2 in the medial preoptic area, which is derived from microglia and also from neurons, and leads to male-typical dendritic spine patterning that underlies sexual behavior (Lenz et al., 2013). Another such example is a case in the developing anteroperiventricular nucleus of the preoptic area (AVPV), which is a sexually dimorphic nucleus that controls female hormonal cyclicity. During the perinatal period, increased cell death in the male AVPV leads to a smaller AVPV in males compared with females (Sumida et al., 1993). A study by Krishnan et al., (2009) demonstrated that an immune-related molecule, tumor necrosis factor (TNF) family member repressor protein (TRIP), is necessary for this developmental sex difference in cell death of GABAergic cells to occur. TRIP prevents the TNFα-activated cell survival cascade in males, leading to higher rates of cell death, whereas in females, TRIP is not

expressed and thus cell death is lower (Krishnan et al., 2009). It is unknown which cell type produces this signal, though microglia may be the most likely candidate.

Beyond these examples, there are several other studies that document sex differences in immune molecules, though the functional significance of these sex differences is still unknown. Within the hippocampus and cortex, female rats have higher concentrations of IL-1β and IL-1 receptor antagonist, and IL-1 receptor through life (Schwarz et al., 2012). On the other hand, male rats produce higher concentrations of CCL4 and CCL20 at PN0 than females, but not at other time points. Some chemokines and chemokine receptors, such as CCL22 and CCR4, are higher in females at P4, but higher in males at P60. Although these data were not collected from isolated microglia, several studies have found sex differences in immune gene expression in isolated microglia. Microglia-specific gene expression studies have found that whole brain microglia from females express more IL-1β, TNFα, IL-6, IL-10, P2X5, and P2Y4 at PN3, but not at later time-points (Crain et al., 2013, 2009). The consequences of these sex differences may be highly relevent for the physiological responses of microglia and their regulation of brain development or in response to early life perturbations, but have not been investigated to date.

Astrocytes: There are also sex differences in astrocyte number and morphology in the developing brain. In the rat POA, male astrocytes are more morphologically complex than female astrocytes; estradiol drives this effect (Amateau and McCarthy, 2002). In the nearby arcuate nucleus, a hypothalamic region that regulates pituitary function, male astrocytes are more stellate than female astrocytes (Mong and McCarthy, 2002). This sex difference is apparent at birth, remains so throughout life, and is also driven by organizational gonadal hormone effects (Mong and McCarthy, 2002). Extensive work by Garcia-Segura, Barreto, and colleagues has assessed sex differences in astrocytes and their inflammatory capacity throughout life, including in the context of healthy adulthood, injury, or animal models of neurodegenerative diseases (reviewed in Acaz-Fonseca et al., 2016). In the context of development, primary astrocytes derived from the neonatal cerebral cortex of males, females, or females treated with male-typical androgen exposure showed differential responses to immune challenge, with male and masculinized female astrocytes producing more inflammatory molecules, such as IL-6, TNFα, and IL-1β (Santos-Galindo et al., 2011). Such differences in the astroglial response to immune challenge may indicate that astrocytes participate in early life programming of the brain and behavior by stress, infection, or similar insults. A recent study has shown that astrocyte-derived IL-33 directs microglial synaptic pruning during development (Vainchtein et al., 2018), but it has not yet been determined whether there are sex differences in astroglial function in this context that could be relevant to sex-specific synaptic patterning. However, this study highlights the importance investigating crosstalk between different immunocompetent cell types in the developing brains of both sexes rather than studying one cell type in isolation.

Mast cells: Mast cells are peripherally-derived innate immune cells of hematopoetic origin that reside in various tissues, including the gut, skin, airway, and brain (reviewed in Silver Curley & Silver). They are best appreciated as contributors to type I hypersensitivity conditions, including food allergy, atopy, and asthma, as well as the response to parasitic

infections (Abraham and St John, 2010). Mast cells within the brain are most abundant during early life in both rodents and humans (Dropp, 1979; Khalil et al., 2007; Masliniska et al., 2001). Like microglia, mast cells rapidly respond to inflammatory stimuli by releasing cytokines, prostaglandins, and proteases (Silver and Curley, 2013), but mast cells also engage in bolus release of granules containing histamine and serotonin (Wernersson and Pejler, 2014). Mast cells are also known to regulate microglia function in response to inflammation. For example, mast cell degranulation, when triggered by immune challenge or a mast cell secretagogue, activates microglia release of pro-inflammatory cytokines, effects that can be blocked *in vitro* by co-administration of mast cell inhibitors (Dong et al., 2017; Zhang et al., 2016). Males express a mast cell specific gene, mast cell protease 2, in the developing POA, whereas females do not (Nugent et al., 2015), suggesting that sex differences in mast cells could contribute to sexual differentiation in this brain area. Additionally, mast cell numbers in the brain have been shown to increase during courting and reproduction in birds (Silverman et al., 2002) and to be a source of gonadotropin-releasing hormone (GnRH) (Khalil et al., 2003). Thus, mast cell dynamics may contribute to sex-specific brain function in ways that have not yet been reported.

Overall, these studies show that males generally appear to have higher basal microglia and neuroimmune tone in the developing brain, but in very few cases have these sex differences been linked to sex differences in brain development, physiology, or later life behavior. This is one area in which research on sex differences in neuroimmune function needs to expand and focus future inquiry. The following section focused on sex differences in neurodevelopmental disorders is arguably the best reason to focus on developmental sex differences in neuroimmune parameters, as they may give tremendous insight into the pathophysiology of these complex and often debilitating disorders.

Relevance to sex differences in developmental disorders:

Almost every mental health disorder has a neurodevelopmental component. Environmental factors such as prenatal stress, early life adversity, prenatal inflammation/immune activation, altered prenatal steroid environment, famine, and maternal obesity all increase the risk for developing a mental health disorder (Andersen, 2015; Baron-Cohen et al., 2015; Brown, 2011; Brown et al., 2014; Canetta et al., 2014; Godfrey et al., 2017; Kosidou et al., 2015; Zeanah et al., 2009). Furthermore, there are sex differences in many mental health disorders that have a neurodevelopmental origin. More males are diagnosed with Autism Spectrum Disorder (ASD) and Tourette Disorder than females, whereas more females than males are diagnosed with anxiety, mood disorders, and Rett Syndrome (Bandelow and Michaelis, 2015; Kessler et al., 2012; Kim et al., 2011; Robertson, 2008; Wingate et al., 2014). Additionally, it is more common for males to be diagnosed with schizophrenia (1.4:1) and males often have more severe negative symptoms (Abel et al., 2010). Interestingly, perturbations that increase the risk for these disorders also alter microglia function, which may mean that microglia mediate some of the effects of perinatal perturbations.

Neurodevelopmental disorders have a multifactorial origin that includes many contributors beyond the immune system or neuroimmune dysfunction, which are beyond the scope of this review. However, a large body of research has shown that there are significant alterations in

the microglia and immune system in many disorders with a neurodevelopmental origin. Some studies have found increased microglia number and/or density in post-mortem brain samples from patients with schizophrenia, autism, and Tourette disorder. In living human patients, PET scans using the ligand that binds translocator protein (TSPO) have been used to infer microglial (and astroglial) activation in various neuropathological conditions. TSPO is likely indicative of both increases in microglia proinflammatory tone as well as phagocytosis (Karlstetter et al., 2014). In several studies of people with neurodevelopmental disorders, TSPO binding is elevated relative to non-affected control participants (Bloomfield et al., 2016; Fillman et al., 2013; Laskaris et al., 2016; Lennington et al., 2016; Morgan et al., 2012, 2010; Suzuki et al., 2013). However, several studies have also found no change in TPSO binding or even decreased binding in schizophrenia (Collste et al., 2017; Coughlin et al., 2016; Hafizi et al., 2016). TPSO binding density must be interpreted cautiously because changes in binding are context-dependent, because other cell types express TPSO, and because there is high individual variability within healthy populations (see Notter et al., 2017) for an in-depth review). Transcriptomic analysis of brain tissue from people with ASD and Tourette Disorder shows a strong microglia and immune component in the altered transcriptome (Gandal et al., 2018; Lennington et al., 2016; Werling et al., 2016). Several mouse studies have shown some microglia involvement in Rett Syndrome, an X linked disorder with a similar phenotype to ASD, though the centrality of the microglia involvement in the disorder has not proved consistent across studies (Derecki et al., 2012; Maezawa and Jin, 2010; Schafer et al., 2016; Wang et al., 2015). Yet no studies to date have analyzed human tissue from Rett Syndrome patients. All these studies analyzed adults because many symptoms of these disorders are diagnosed later in life (with the exception of ASD and Tourette Disorder, which show symptoms early in life). Many mental health disorders with a developmental component are also associated with peripheral immune changes. These changes include altered immune responses and increased levels of circulating cytokines (Ashwood et al., 2011; Careaga et al., 2017; Goldsmith et al., 2016; Miller et al., 2011; Pramparo et al., 2015).

Perinatal immune activation—Several epidemiological studies noted that mothers that experienced infection during pregnancy had a higher risk of their offspring developing schizophrenia (Mednick et al., 1988). These findings gave rise to the maternal immune activation hypothesis of neurodevelopmental disorders. It has since become clear that maternal infection and general maternal immune activation/inflammation can increase risk of offspring developing schizophrenia as well as ASD (Brown, 2012; Brown et al., 2014). For example, maternal infection with influenza or Poly I:C immune challenge altered pre-pulse inhibition of the acoustic startle response in offspring (a behavior associated with schizophrenia) and decreased offspring exploratory behavior and social interaction (Shi et al., 2003). Many studies have replicated these findings in rodents using systemic poly I:C (a viral mimetic); lipopolysaccharide (LPS), a bacterial endotoxin; exogenous cytokines; live bacterial infection; intact viruses (Bilbo and Schwarz, 2012; Meyer, 2014); or intrauterine LPS (Makinson et al., 2017) as immune challenges. Many of these studies also found that both male and female offspring show behavioral changes following prenatal maternal immune challenge (Lin et al., 2012; Meyer et al., 2008; Smith et al., 2007; Van den Eynde et al., 2014). One study found that males only show decreased social play behavior following

prenatal immune challenge with LPS (Taylor et al., 2012). A recent prenatal poly I:C study has shown sex-specific effects on microglia development and function, as well as sex-specific behavioral impairments that bear relevance to schizophrenia and autism (Hui et al., 2018). Makinson et al. (2017) showed that intrauterine inflammation increased microglia numbers, TNFα expression, and induced anxiety-like behavior equally in male and female offspring, but led to greater secondary inflammatory response to adult immune challenge in males, suggesting that male microglia were more robustly "primed" by prenatal inflammation. Similarly, two studies in humans noted that high maternal inflammation during pregnancy (as measured by c-reactive protein levels) increased risk for ASD and schizophrenia, but the risk was increased in both males and females (Brown et al., 2014; Canetta et al., 2014). Several factors in rodents influence prenatal immune activation: for example, timing of challenge, presence of specific gut microbiota, and maternal production of IL-6 and IL-17 (Choi et al., 2016; Kim et al., 2017; Meyer, 2006, 2006; Smith et al., 2007). Due to the variability in challenges used, it is difficult to determine whether perinatal immune challenges have sex-specific effects.

How do microglia fit in to the picture of early life inflammation? Since microglia are the primary resident immune cell of the brain, it makes sense to hypothesize that microglia mediate maternal or neonatal immune activation effects on development. Recent research based on comprehensive transcriptome analysis has shown that maternal immune activation affects the maturation of microglia (Matcovitch-Natan et al., 2016). Furthermore, neonatal immune challenge alters maturation of microglia only in males, not in females (Hanamsagar et al., 2017). Hui et al. (2018) recently showed that adult male offspring of poly I:C challenged dams showed more deramified microglia compared to controls, increased physical interaction of microglia with synapses, increased cellular stress, and elevated inflammatory gene expression in the hippocampus, whereas females did not. In contrast, female microglia showed increased association with myelinated axons compared with male microglia following maternal immune challenge. In addition, while prenatally poly I:C-challenged males and females both showed decreased sociability in adulthood compared with control mice, only males showed increased anxiety and perturbations in pre-pulse inhibition of the acoustic startle response (Hui et al., 2018). Perinatal immune activation can also change microglial function by 'priming' microglia. When previous inflammation "primes" microglia, (Bilbo and Schwarz, 2012; Frick et al., 2013), a second hit of inflammation later in life can elicit exaggerated pro-inflammatory signaling that, amongst other effects, disrupts learning and memory and increases anxiety in adulthood (Niraula et al., 2017; Williamson et al., 2011; Wohleb et al., 2014). However, questions remain as to whether these changes in microglia alter behavior in a sex-specific manner and whether gene expression changes in microglia represent changes in microglia function. Figure 2 summarizes what is currently known (or hypothesized) about sex differences in microglia in response to early life perturbations.

Early life stress—In humans, prenatal stress increases the risk of the offspring developing a neurodevelopmental disorder such as schizophrenia, autism, and generalized externalizing symptoms (Bale et al., 2011). Male mice are particularly susceptible to the deleterious effects of early prenatal stress: They show altered emotionality, stress-induced corticosterone

release, and locomotor hyperactivity later in life (Bronson and Bale, 2014; Mueller and Bale, 2008). Little work has been done to identify *acute* effects of prenatal stress on microglia. Microglia isolated from prenatally stressed animals had higher expression of several "pro-inflammatory" cytokines than microglia isolated from control animals (Ślusarczyk et al., 2015). Prenatal stress potentially alters microglial colonization. Prenatal stress decreased the total number of microglia and amoeboid microglia most markedly in the corpus callosum (Gómez-González and Escobar, 2010) . In other areas, prenatal stress decreased amoeboid microglia and increased ramified microglia at PN1, but no changes in microglia were observed by PN10. Interestingly, these data suggest that microglia maturation is altered by prenatal stress, similarly to what is seen with maternal or postnatal immune challenge, in germ free mice, or following neonatal stress exposure (Delpech et al., 2016; Hanamsagar et al., 2017; Matcovitch-Natan et al., 2016; Thion et al., 2017). Further research is needed to determine whether microglia mediate the programming effects of maternal stress on behavior, or whether they simply react to an altered neural microenvironment. Several studies have analyzed the long-term effects of prenatal stress on microglia. Prenatal stress alters microglia morphology and increases the inflammatory response to LPS in adult males and females, suggesting that prenatal stress might "prime" microglia (Diz-Chaves et al., 2013, 2012). Another group found that, following maternal treatment with dexamethasone, a synthetic glucocorticoid, during pregnancy, microglia ramification in the medial prefrontal cortex was increased in males but decreased in females (Caetano et al., 2016). Thus, stress may impact microglia through mediating effects on the stress system and release of stress hormones, such as glucocorticoids.

Childhood adversities are estimated to cause ~40% of all childhood onset mental health disorders and ~25% of adult onset disorders (Green et al., 2010). There have been several reviews outlining how early life adversity "programs" behavior (see Andersen, 2015; Chen and Baram, 2016). Here, we will focus on how the immune system may moderate the early life programming effects of exposure to adverse experiences and whether there are sex specific interactions of early life adversity and the neuroimmune system.

Adversity during infancy and childhood has a long-term impact on internalizing and externalizing behaviors, as well as other cognitive behaviors in both rodents and humans (Andersen, 2015; Chen and Baram, 2016; Teicher and Samson, 2016). Early postnatal stress in rodents increases microglia density in the hippocampus (Delpech et al., 2016; Roque et al., 2015). Like other challenges that alter immune function, postnatal stress alters microglia development and function (Delpech et al., 2016). Such stress exposure can also increase the number of circulating peripheral monocytes; however, these monocytes do not appear to infiltrate the brain (Delpech et al., 2016). In addition to the acute developmental effects of early postnatal adversity, there are long-term effects on the immune system. Maternal separation stress in newborn rats increases the concentration of circulating IL-1β and IL-6 and decreases the number of parvalbumin interneurons in adolescent rats, as discussed further below (Brenhouse and Andersen, 2011; Wieck et al., 2013). Interestingly, maternal separation seems to disrupt social behavior and decrease parvalbumin expression earlier in females than it does in males (Holland et al., 2014), which may stem from the aforementioned basal sex differences in microglia maturation in the brain (Hanamsagar et al., 2017). However, little work has been done to assess sex differences in how early life

stress programs the immune system. The sensitive period of sex-specific programming in the brain overlaps with the period of early life adversity, however, suggesting effects of early life stress may be sexually dimorphic.

Maternal diet—Because 36% of adults in the US are obese and many more are overweight, interest in how maternal obesity affects neurodevelopment is growing. Obesity increases adverse outcomes of pregnancy such as maternal infection, preterm birth, inflammation, and gestational diabetes (Marchi et al., 2015; Norman and Reynolds, 2011). Adverse effects related to obesity during pregnancy are also known risk factors for neurodevelopmental disorders (see Perinatal Immune Activation). However, how obesity affects fetal neurodevelopment and later-life neurological function in humans is still unclear. Godfrey et al. (2018) conclude that, at this stage, the evidence is mixed: Some studies find that obesity increases the risk of the offspring developing ADHD, ASD, and cerebral palsy, whereas others find no correlations. Many confounding factors need to be assessed to determine the true effect of obesity on offspring, such as presence or absence of comorbid conditions, such as diabetes, high blood pressure, preeclampsia, or autoimmune disorders.

Many studies in rodents have shown that maternal weight gain induced by a high-fat diet altered neurodevelopment and behavior in offspring. High-fat diets have been found to increase circulating and hippocampal IL-1β neonatally, concomitant with an increase in microglia density as well as decreased spatial memory performance and increased anxiety (Bilbo and Tsang, 2010). Similarly, data in non-human primates showed that high-fat diet early in pregnancy increased anxiety responses in females (Sullivan et al., 2010). In rodents, dietary intervention during lactation is capable of preventing brain inflammation and social behavior deficits and anxiety following gestational high fat diet (Kang et al., 2014). Some of fetal and sex effects of high-fat diet may be mediated by exposure to maternal glucocorticoids: Male fetuses of rodent dams on a high-fat diet had higher levels of corticosterone and females had lower levels compared with respective controls (Chin et al., 2017). Maternal high-fat diet has also been shown to alter spine density, dendritic remodeling, and myelination in offspring (Graf et al., 2016; Janthakhin et al., 2017; Rincel et al., 2018), but future work is needed to mechanistically link microglia to high-fat diet-induced neurodevelopmental and behavioral outcomes.

Juvenile and adolescent sex differences in neuroimmune parameters:

Markedly less experimental attention has been directed at microglia function and sex differences in microglia during the peripubertal and adolescent period, yet this topic is likely an important one to investigate. The adolescent period is gaining increasing attention as an overlooked mini critical period during which sex-specific organization of the CNS and resulting behavior is refined (reviewed in (Lenroot and Giedd, 2010; Sisk, 2017; Walker et al., 2017)). Additionally, many neuropsychiatric disorders typically manifest during puberty (for example, schizophrenia, depression, eating disorders, substance abuse, and migraine). Thus, adolescents and young adults may be especially vulnerable to exogenous perturbations that are associated with risk for neuropsychiatric or neurological disorders (Lenroot and Giedd, 2010; Walker et al., 2017).

What little work has been devoted to microglia during this period suggests that sex differences are apparent. In the aforementioned article by Schwarz et al (2012), male and female microglia were compared in the early pubertal period (PN30). Schwarz et al. found that females had a greater number of microglia with thick branches (which indicate a "reactive" phenotype) in several brain regions, including the parietal cortex, amygdala, and CA3 region of the hippocampus. Also, in the AVPV nucleus, a robustly sexually differentiated brain region (discussed above in "**Perinatal sex differences in neuroimmune parameters")**, more new cells are born in females than in males during the peripubertal period, when this region becomes functional and responsible for controlling pulsatile hormone release in females (Ahmed et al., 2008). Interestingly, of the new cells added to the AVPV during adolescence, almost half are either astrocytes or microglia (Mohr et al., 2016). Together, these two studies suggest that there are sex differences in adolescent immunocompetent cells that could contribute to sex-specific brain function later in life.

Several recent studies have shown adolescent sex differences in the neuroimmune response to previous early life perturbations. One such perturbation is a two-hit model of inflammation: neonatal E. coli infection and juvenile endotoxin challenge. Using this protocol, Osborne et al. (2017) found that elevated concentrations of IL-1β persist in the hippocampus and prefrontal cortex of juveniles at PN24. In response to a second hit of inflammation with LPS, both males and females show an exaggerated IL-1β response in the hippocampus if previously infected with E. coli, whereas only females show increases in the prefrontal cortex (Osborne et al., 2017). However, this exaggerated inflammatory response was unaccompanied by deficits in hippocampal-dependent learning during the juvenile period, Thus, the behavioral consequences of this persistent and sex-specific inflammation remain unknown.

Maternal separation stress has also been used to assess sex-specific immune function (as mentioned above). Following 3 weeks of daily maternal separation stress in rats, Grassi-Oliveria et al. (2016) found evidence of persistent peripheral inflammation, with males but not females showing decreases in anti-inflammatory IL-10 concentrations in the early juvenile period (PN25) (Grassi-Oliveira et al., 2016). Moreover, the authors found significant correlations between behavioral performance on a win-shift cognitive task assessed in adulthood and juvenile peripheral cytokine levels in females but not males. These data suggest that sex-specific responses to systemic inflammation during the juvenile period may predict adolescent behavioral outcomes. However, it should be noted that central levels of cytokines or microglia function were not reported in this study, thus future research is needed to address whether early life stress impacts the neuroimmune systems of males and females differentially.

Though much less researched, there is also evidence that males and females show differential neuroinflammatory priming effects in response to juvenile stress (Pyter et al., 2013). Following adolescent stress coupled with adult immune challenge with LPS, males and females show elevated proinflammatory gene expression in the hippocampus following LPS. Yet only males showed evidence of stress-induced priming of the neuroinflammatory response, with greater TNFα, IL-1β, iNOS, and NFkB elevations to LPS following previous adolescent stress exposure (Pyter et al., 2013). Interestingly, estradiol concentrations in

females were correlated with gene expression for the microglia marker Cd11b. Estradiol and Cd11b expression were not correlated in stress-exposed animals, however, implying dysregulation in the relationship between female-typical hormones and microglia in response to stress.

We have recently found that adolescent rats show behavioral changes as a result of early life microglia loss. Specifically, we depleted microglia from the brains of male and female rats during the early postnatal period (PN1–10), and subsequently allowed microglia to repopulate the brain. When assessed between PN28–29, we found that both males and females that experienced early life microglial loss showed changes in social play behaviors, with microglia-depleted males and females displaying reduced social chasing compared with vehicle rats, and depletion female rats showing increased social exploration (Nelson and Lenz, 2016). In the open field test on PN30–32, microglia-depleted males and females both showed evidence of locomotor hyperactivity, and only females showed increases in center entries, indicating a reduced anxiety-like response (Nelson and Lenz, 2016). A similar study by Van Ryzin et al. (2016) also found anti-anxiety and hyperactive phenotypes in juvenile males and females that experienced early life microglia depletion (Van Ryzin et al., 2016). This study also showed that microglia-depleted males and females exhibit impaired performance on a T-maze alternation task as well as decreased fear behavior and increased risk-assessing behaviors in a predator odor exposure during the juvenile period (Van Ryzin et al., 2016). These data indicate that juvenile behaviors are sensitive to the effects of microglia programming in the developing brain, and that some but not all behavioral outcomes show sex-specific effects. Future work is necessary to determine which aspects of juvenile brain function are altered in microglia-depleted animals. Nevertheless, it is clear that microglia contribute to sex-specific programming of behavior observed in proximal developmental periods, such as puberty, and thus future studies focused on microglia and development should strive to connect neuroanatomical effects of microglia to behavioral outcomes throughout the lifespan.

Adult sex differences in neuroimmune parameters:

Few studies, either in the healthy brain or following perturbations, have assessed microglia and neuroimmune signaling in both males and females and compared the sexes. Yet some studies that compare males and females show notable adult sex differences in microglia or neuroimmune function. In general, the data suggest that microglia within the adult brain have a more activated or basally primed phenotype in *females*. The hallmark sex differences survey experiment by Schwarz et al. (2011) found that adult females showed evidence of more primed microglia than males in the hippocampus, parietal cortex, and amygdala. Additionally, females have increased cortical/hippocampal levels of IL-10, the IL-10 receptor antagonist, IL-16, IL-1α, CD11b, and TOLLIP genes and IL-1β protein in adulthood, whereas males have higher expression of the genes for IL-18, chemokine receptor CCR4, and the chemokine CCL22 in adulthood (Schwarz et al., 2012). Two studies by Bollinger et al. investigated sex differences on the effects of acute versus chronic stress on microglia in limbic areas of the rat brain, as will be discussed below (Bollinger et al., 2017, 2016).,These studies also documented several notable baseline sex differences in microglia. In the medial prefrontal cortex, Bollinger et al. (2016) showed females have a

higher baseline ratio of primed to ramified microglia as well as higher baseline levels of fractalkine (CX3CL1), which is a microglia regulator released by neurons, compared with males. In a follow-up study, Bollinger et al., (2017) investigated additional brain regions, including the amygdala, orbitofrontal cortex, and hippocampus, and found evidence of mild basal sex differences in neuroimmune parameters, including higher baseline expression of CD40, CD200, and arginine genes in the amygdala in females than in males. Correlation matrices of gene expression and microglia morphology suggested that microglial activation is more correlated across corticolimbic brain regions in males under basal conditions than in females (Bollinger et al., 2017). Another recent transcriptomic study compared male and female mouse hippocampus at 3 (young adult), 12 ('middle age') and 24 months of age (old) and found that sex differences were detectable at each age examined (Mangold et al., 2017). Interestingly, the particular inflammatory genes that showed sex differences in expression were age specific, and that male and female gene expression become increasingly divergent as mice age (Mangold et al., 2017). The functional significance of these basal sex differences remains uninterrogated, but such studies are certainly warranted given sex differences in stress-related psychiatric disorders (and likely underway).

Relevance to sex differences in brain-based disorders with adolescent or adult onset:

Pain—Sex differences in neuroimmune parameters in the adult CNS may be relevant for pain-related disorders. In the periaqueductal gray of the rat, females have a more reactive microglia morphology than males at baseline (Doyle et al., 2017). In response to LPS, female microglia show an exaggerated activation response relative to males as well as a greater elevation in IL-1β concentration (Doyle et al., 2017). Moreover, this sex difference in microglia predicted a reduced female response to morphine via the toll-like receptor 4, which may have implications for sex difference in pain perception, pain treatment, or susceptibility to opioid abuse. Not only do sex differences in microglia correlate with pain-related neurobiology, but a recent study has implicated differing immune cell types in the spinal cord on the induction of pain hypersensitivity following nerve injury in male and female mice. Sorge et al (2015) found that nerve injury was associated with microglial activation in both males and females, but that microglia-inhibiting interventions prevented only the induction of allodynia in males and had no effect on females (Sorge et al., 2015). Rather, in females, T cells of the adaptive immune system appeared to drive the development of pain hypersensitivity. These data illustrate why it is important to study both males and females, even when their end phenotypes (e.g., mechanical pain sensitivity) are the same. Different biological mechanisms may drive a similar behavioral or functional outcome, which would mean that different intervention or treatment strategies may be necessary for males and females in a variety of brain-based disorders.

Microglia in the developing brain are also implicated in sex-specific behavioral outcomes in adult rodents. Following transient early postnatal microglia depletion, both male and female rats showed hyperactivity and evidence of decreased anxiety-like behavior (Nelson and Lenz, 2016; VanRyzin et al., 2016) and decreased behavioral despair (Nelson and Lenz, 2016). In contrast, only microglial-depletion females showed a blunting of the acute stress response in adulthood (Nelson and Lenz, 2016), whereas only males showed evidence of impaired sexual behavior (VanRyzin et al., 2016), similar to inhibiting microglia with

minocycline during the early neonatal period (Lenz et al., 2013). Together, these data show that sex differences in how microglia shape brain development and long-term function may have previously unappreciated implications for sex differences in behavior throughout life.

Anixety and mood disorders: Anxiety and mood disorders are more common in females than in males, and inflammatory processes have been linked to mood dysregulation and anxiety and depression. This section will summarize what is known about the mechanisms underlying sex differences in anxiety and depression with a focus on potential crosstalk between biological sex and inflammation as contributing factors.

Major depressive disorder (MDD) has been associated with high concentrations of peripheral cytokines in humans (e.g., morning IL-6) (Alesci et al., 2005) and diminished natural killer activity relative to those observed in healthy controls (reviewed in Irwin and Miller, 2007; Réus et al., 2015)). People who are diagnosed with immune disorders (such as allergy, asthma, and multiple sclerosis) are also diagnosed with depression at higher rates than control populations (Himmerich et al., 2008; Ortega et al., 2004; Siegert, 2005). MDD also appears to worsen the course of non-psychiatric diseases such as HIV (reviewed in Arseniou et al., 2014; Irwin and Miller, 2007). Allergic rhinitis, too, may confer vulnerability to MDD (Chen et al., 2013).

MDD is hypothesized to have a large immune and/or microglia component to the disorder, and these neuroimmune parameters may be sex-specific. Studies have found increased TSPO binding in the patients with depression as well as increased microglial density and increased peripheral macrophage infiltration in depressed suicides (Holmes et al., 2018; Setiawan et al., 2015; Torres-Platas et al., 2014). Depression severity correlated positively with TSPO density in the anterior cingulate cortex, a crucial mood- and emotion-regulating brain region (Setiawan et al., 2015). Surprisingly, serum inflammatory markers did *not* correlate with TSPO density in the brain; these data suggest that peripheral and central immune activation are somewhat independent (citation here? Or is citation in previous sentence sufficient?). In humans, IL-6 concentrations are elevated in patients with MDD relative to controls, and in individuals with “treatment-resistant” MDD , pharmacological antidepressants do not effectively reduce IL-6 levels (Hodes et al., 2014).

Women are more susceptible than men to developing depressed mood following immune activation (Moieni et al., 2015). Recent studies of brain tissue from people with MDD showed that males and females have dramatically different transcriptomic signatures associated with the disorder (Labonté et al., 2017; Seney et al., 2018). Interestingly, both men and women with depression showed dramatic shifts in gene sets associated with microglia within the brain, but in opposite directions: Men with MDD show increases and women with MDD show decreases in microglia-related gene expression (Seney et al., 2018). Further, similar transcriptional changes are seen in a rodent model of depression induced by chronic variable stress (Labonté et al., 2017).

In animal studies, chronic stress paradigms have been used to investigate environmentally-driven onset of mood dysregulation. Most studies of microglial involvement in mood-related behavior have used only males, yet the female bias in depressive disorder prevalence

warrants the addition of female animals to psychoneuroimmunological research. A series of studies by Bollinger et al. (2016; 2017) compared the microglial response to acute and chronic restraint stress in males and females. Results showed complex region- and sex-dependent relationships between stress and microglia/neuroimmune function. Highlights of Bollinger et al.'s findings include that chronic stress had opposite effects on cross-correlations between measures of microglia morphological changes in corticolimbic regions, including the amygdala, hippocampus, and orbitofrontal cortex. Stress decreased correlations in males and increased them in females (Bollinger et al., 2017). In the medial prefrontal cortex, female microglia (both microglia-related gene expression and morphology) were impacted by chronic stress, whereas male microglia were not affected (Bollinger et al., 2016). In a different study with a similar foundational question, chronic variable stress elicited sex specific effects on microglia function, such that stress in males more dramatically altered microglia morphology, increased microglia expression of the CSF receptor, *Csf1r,* and the fracktalkine receptor (*Cx3cr1)*, and more putative phagocytosis of dendritic inclusions compared to microglia in females (Wohleb et al, 2017). These studies underscore how complicated studies of sex by environment interactions become, especially once multiple brain regions are considered. We have only just begun to appreciate the complex dynamics underlying stress-induced dysfunction of the neuroimmune system across sexes, but the question is of clear importance given the prominent sex differences in depression incidence, symptomology, and severity.

Repeated social defeat stress (RSDS) is another rodent model of environmentally-induced anxiety and depression. RSDS has been carried out mostly in male mice to date, because the model relies upon the sexually dimorphic display of intra-male aggression which females do not endogenously display. Despite the downside of not being able to easily utilize the model in females, RSDS has given fantastic insight into the neuroimmune contributions to mood dysregulation. Experimenters place a male C57BL/6J mouse in an enclosure with a larger, aggressive male CD-1 mouse who attacks the first mouse; this encounter is repeated daily for 7–10 days (Golden et al., 2011). RSDS resembles the psychosocial stress of repeated bullying and abuse, which are associated with the development of depression and anxiety in humans (Brunstein Klomek et al., 2007; Campbell, 2002; Huhman, 2006). Although RSDS elicits depressive-like and anxiety-like behavior from most mice, a substantial minority of mice are resilient to social defeat stress (Golden et al., 2011), making RSDS an excellent model to study the mechanisms of stress susceptibility and resilience.

RSDS has dramatic effects upon both the peripheral and central immune system. Adoptive transfer of the immune system from mice exposed to RSDS to naïve controls induces a depressive and anxiety-like phenotype in the naïve animals (Hodes et al., 2014). Both central and peripheral immune function appear to contribute to the onset and maintenance of mood dysregulation following RSDS. Peripheral monocytes respond to RSDS by proliferating, adopting a more pro-inflammatory (and glucocorticoid-resistant) phenotype, and traveling to the brain (McKim et al., 2017, 2016; Wohleb et al., 2013, 2011). There, peripheral monocytes engage with blood-brain barrier endothelial cells, promote microglial morphological and inflammatory gene expression changes, and induce anxiety behavior by releasing IL1β that acts on endothelial cells (McKim et al., 2017; Sawicki et al., 2015; Wohleb et al., 2013; 2014). Communication between the central and peripheral branches of

the immune system may contribute to stress-related psychological disorders, such as depression and anxiety (Weber et al., 2017; Yirmiya et al., 2015). The cytokine IL-6 participates in this crosstalk and acts on various CNS cells, including microglia (Hodes et al., 2014; Menard et al., 2017). The intensity of the leukocyte IL-6 response to the initial bout of RSDS predicts later stress susceptibility or resilience: Stress-susceptible mice tend to secrete more IL-6 following social stress than stress resilient mice (Menard et al., 2017). Depleting leukocyte-derived IL-6 or sequestering IL-6 from entering the brain similarly promotes resilience to RSDS, implicating peripheral to central signaling by this cytokine in depression susceptibility. Stress-induced catecholamine activity at the β-adrenoceptor also (at least partly) mediates microglial proinflammatory changes and adoption of an anxiety-like phenotype following RSDS (Wohleb et al., 2011).

A downside of the RSDS model is that it does not allow for studies of biological sex, as adult male mice typically cannot be induced to attack females, and females do not show intra-sex aggression. But several modifications of the RSDS have recently been validated to adapt the task for use in female mice (Harris et al., 2017; Takahashi et al., 2017). Chemogenetic manipulations using designer receptors exclusively activated by designer drugs (DREADDs) enable researchers to induce male mice to attack adult female conspecifics by activating the ventrolateral portion of the ventromedial hypothalamus, a pro-aggression node in the brain (Lee et al., 2014; Lin et al., 2011; Takahashi et al., 2017). Another recently identified approach to elicit female-directed aggression from male mice is the application of male odorants to female mice (Harris et al., 2017). These adaptations of RSDS might allow neuroscientists to determine the neurological bases of sex differences in mood and anxiety disorder course and prevalence. Additionally, adaption of RSDS to female mice will allow researchers to determine similarities and differences between RSDS induced- and chronic variable stress induced-depression and anxiety.

Although these RSDS models have not been implemented in any yet-published mechanistic studies in females, a recent study in mice using RSDS in males alongside chronic variable stress manipulations in females has shown that resilience to chronic stress in males is linked to estrogen receptor alpha-associated gene networks in the nucleus accumbens (Lorsch et al., 2018). This study showed that chronic stress alters estrogen receptor alpha in the nucleus accumbens, that overexpression of estrogen receptor alpha promotes resilience to chronic stress, and that males and females show differential transcriptional networks related to estrogen receptor alpha following chronic stress. Interestingly, in addition to estrogen receptor genes, several immune genes were uncovered as differentially expressed in resilient versus susceptible mice following stress (Lorsch et al., 2018). Additionally, gene ontology analyses showed that overexpression of estrogen receptor alpha in both males and females led primarily to decreases in expression of genes associated with the immune response and inflammation in the brain, but that increases in gene expression were different in males and females (Lorsch et al., 2018). This study shows that sex-specific hormone receptor interactions can both promote resilience to mood-related dysfunction as well as contribute to stress-induced mood dysregulation.

Neuroimmune parameters in the maternal brain:

Pregnancy and the postpartum period are associated with dramatic sex-specific plasticity in the brain, yet this association is often overlooked. During pregnancy and immediately following parturition, maternal hormones induce plasticity in the brain to promote the onset of maternal behavior (Bridges, 2015; Dulac et al., 2014; Numan, 2007). Many of these same hormones, including estrogens, progesterone, oxytocin, and glucocorticoids are known to exert effects on microglia and inflammatory signaling in other contexts (Garcia-Ovejero et al., 2005; Lenz & McCarthy, 2015). We recently profiled microglia number and morphology over the course of normal, healthy pregnancy in rats and found significant shifts in microglia properties in limbic regions of the brain (Haim et al., 2017). In late pregnancy and extending into the early postpartum period, we found significant decreases in the overall number of microglia in the prefrontal cortex, hippocampus, nucleus accumbens, and amygdala (Haim et al., 2017). This decrease in microglia number was driven by a reduction in microglia proliferation but no change in microglia death. Interestingly, these effects on microglia were not observed in the motor cortex, suggesting regional specificity, potentially as a result of differential sensitivity of limbic and non-limbic brain regions to hormones. Finally, we observed elevations in IL-6 and IL-10 concentrations in the postpartum hippocampus. Another research group has documented similar pregnancy-related changes in neuroimmune parameters, including increases in expression of the CD11b, IL-4, BDNF, and IL-6 in the postpartum prefrontal cortex and decreased microglia staining in the hippocampus (Sherer et al., 2017). This same group has shown that the inflammatory gene expression in the brain in response to immune challenge with LPS during pregnancy is also blunted, suggesting central immunosuppression (Sherer et al., 2017).

Relevance to postpartum depression: As discussed above in the section on major depression, there are clear links between stress, depression and anxiety and neuroimmune dysregulation. As with major depression, stress during pregnancy is a major risk factor for postpartum depression (PPD) (Beck, 2001). In women with postpartum depression, peripheral immune changes have been documented, including mild changes in serum IL-6 and IL-10 (Simpson et al., 2016), which are cytokines we observed to be altered in the rodent brain over the course of healthy pregnancy (Haim et al., 2017). Another study found a host of inflammatory mediators to be suppressed during late pregnancy in women who went on to develop postpartum depression (Bränn et al., 2017). Peripheral immune cells have different gene expression signatures in women with postpartum depression and those without (Segman et al., 2010). Yet other studies have found little relationship between immune mediators in women and postpartum depression (Blackmore et al., 2014, 2011). Thus, at this stage, studies have been somewhat contradictory and hard to compare due to the trimester in which women were studied, the demographics of the sample population, and level of stress exposure in women (see review by (Osborne and Monk, 2013)). An additional caveat is that imaging of possible microglia “activation” as measured by TSPO binding in the context of major depression has showed little correlation between peripheral inflammatory markers and central markers of inflammation (Setiawan et al., 2015), therefore peripheral immune changes may not be a good marker for neuroimmune changes occurring in the peripartum brain. Future studies in which TSPO imaging of brain inflammatory

changes in new mothers with PPD or measuring CSF cytokine levels in samples obtained from mothers undergoing epidural anesthesia may be more informative.

Hormonal imbalances following childbirth, including rapid declinations in estrogen and progesterone levels, blunted oxytocin levels, and elevated corticotropin releasing factor levels have also been associated with risk for postpartum depressive symptoms (reviewed in (Schiller et al., 2015)). Microglia are known to be responsive to estrogens in the context of development (Lenz et al., 2013; Nelson et al., 2017)) and in adulthood (Loram et al., 2012). Further, as discussed above, resilience to stress-induced mood dysregulation is conferred by higher levels of estrogen receptor tone in the brain, and increased estrogen receptor function downregulates immune-related gene expression in females (Lorsch et al., 2018). Together, these data suggest that crosstalk between hormones of pregnancy and neuroimmune parameters may contribute to the onset of postpartum depression and/or resilience to the disorder, and they warrant future inquiry in both animal models and human patient populations.

Conclusions:

where do we go from here?

To date, most rodent studies that investigate neuroimmune contributions to brain development and plasticity have only focused on males. The small subset of studies that has compared the sexes is clear proof that such studies are warranted, because in many cases, sex differences in behavioral outcomes or underlying biochemical processes are found. Microglia have been shown to be hormone sensitive during brain development and throughout life, and clearly show phenotypic differences both at baseline and in response to perturbations. Sometimes these sex differences in neuroimmune function are complicated and not easy to interpret, but this complexity does not mean they should be ignored or dismissed. The data published to date on sex differences in microglia and neuroimmune signaling suggest that microglia could be actively playing a role in setting up sex-specific neural circuitry and resulting brain physiology. In doing so, microglia may contribute to sex differences in psychiatric disorder risk or symptomology. It is time to include males and females in all studies as a matter of course, and report findings so that consistencies and converging evidence can accrue and show that sex-specific mechanisms are at play during brain development, plasticity, and in brain-based disease states.

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Highlights

- Sex differences in the brain are programmed by early life exposure to hormones and sex chromosome genes, and sex differences in brain and behavior are also modulated by hormones in the pubertal and adult period.
- There are normal sex differences in immunocompetent cells in the brain, such as microglia, astrocytes, and others, that contribute to normal, sex specific brain function and sex differences in the brain's response to perturbations.
- Neuroimmune cells and their activity are implicated in many psychiatric and neurological disorders with sex biases in prevalence, and sex differences in these neuroimmune cells may underlie these sex biases in disorder risk or resilience.

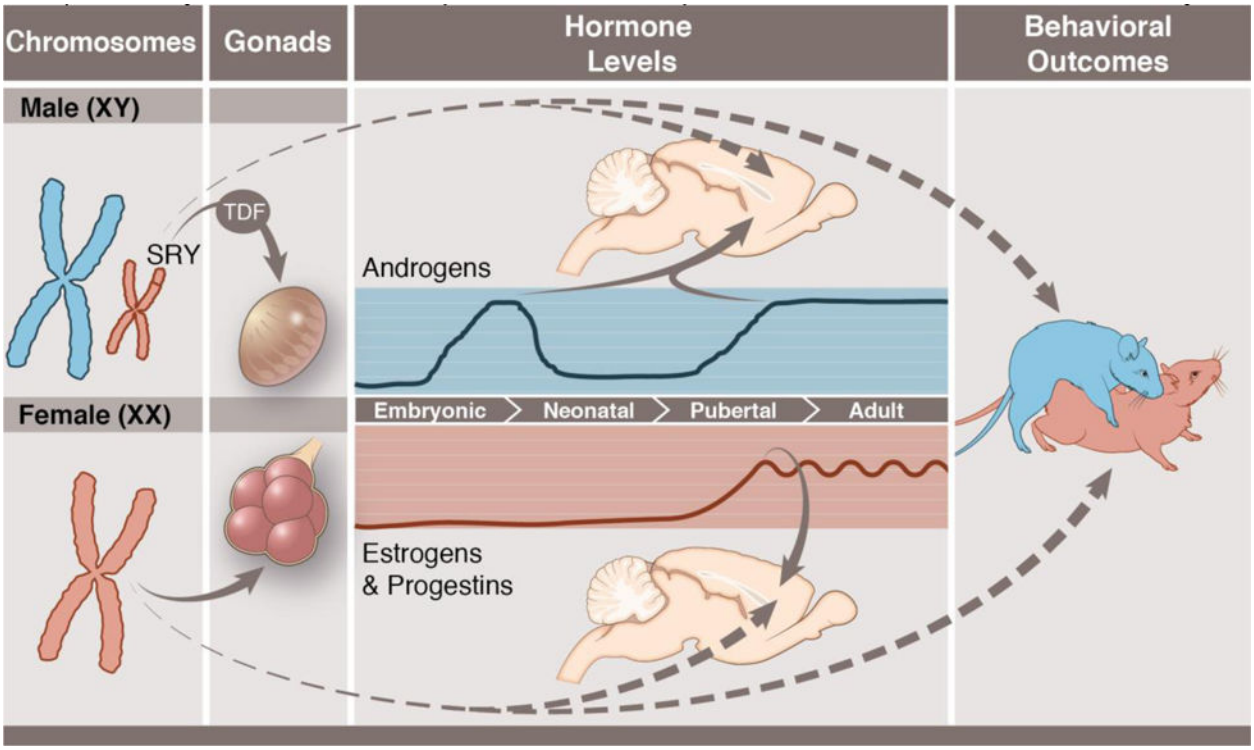

Figure 1: Sexual differentiation of the brain and behavior.

Male typical (top; blue) and female typical (bottom; pink) sexual differentiation. Sex chromosome complement (XX in females; XY in males) leads to sex determination. The Y-chromosome gene, SRY, codes for the protein testicular determining factor (TDF), which programs the bi-potential gonads to differentiate into testes (left). In rodents, the testes begin secreting androgens during the late embryonic period, and these androgens lead to sexual differentiation of the brain and other tissues (middle). In the rodent brain, androgens are converted into estrogens, and estrogens masculinize the brain. In genetic females, the gonads differentiate into ovaries, and the ovaries are largely quiescent in the perinatal period (middle), thus brain feminization occurs largely in the absence of active hormonal signals. At puberty, both male and female gonads produce sex-typical hormone secretions, namely high androgen levels and high but pulsatile estrogen and progestin levels in females. Both early life (organizational) and post-pubertal (activational) hormones contribute to sex differences in behavior, most notably male mounting behavior (blue rat) and female lordosis behavior (pink rat) (right). Sex chromosomes can also have independent effects on brain organization as well as adult sex differences in behaviors (dashed lines). Anthony S. Baker, CMI, Reproduced with the permission of The Ohio State University.

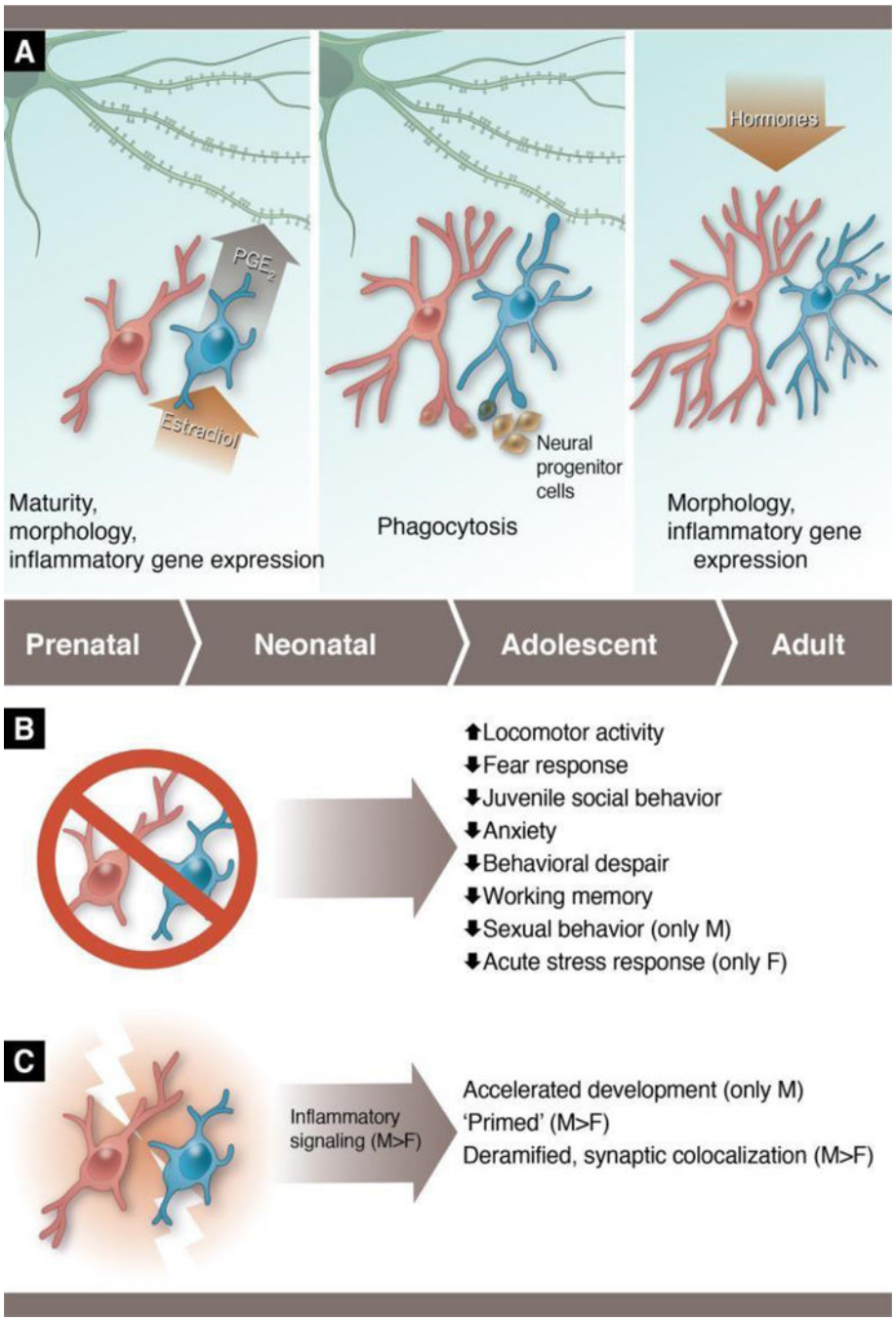

Figure 2: Sex differences in microglia across different developmental windows and conditions.

(A) During the perinatal period (left panel), males have more microglia than females, and the microglia are in a more activated and immature form. Microglia in the male preoptic area respond to the masculinizing hormone, estradiol, by releasing the inflammatory lipid, prostaglandin E2 (PGE2), and PGE2 is responsible for programming male-typical dendritic spine genesis/maintenance that is necessary to display adult copulatory behavior. During the perinatal-juvenile period (middle panel), female microglia appear to show a higher level of phagocytic activity in the hippocampus than male microglia. Female microglia target neural

progenitor cells at a higher rate than males, and higher phagocytosis in females is also correlated with reduced dendritic spines in the hippocampus at this time, though they have not been causally linked to date. In adulthood (right), female microglia are hormone responsive and show hyper-ramification relative to males. (B) Studies in which microglia have been depleted early in life demonstrate lifelong behavioral changes in both males and females, with sex-specific effects being seen in some outcomes. (C) Studies in which microglia are stimulated early in life show that male microglia are more responsive than female microglia. Male microglia depicted in blue and female microglia in pink throughout. Figure based on data from Bollinger et al., 2016; 2017; Hanamsagar et al., 2017; Hui et al., 2018; Lenz et al., 2013; Makinson et al., 2017; Nelson & Lenz, 2016; Nelson et al., 2017; Schwarz et al., 2011; Van Ryzin et al., 2016, Weinhard et al., 2018b). Anthony S. Baker, CMI, Reproduced with the permission of The Ohio State University.

Table 1:

Immunocompetent cell types in the brain: Location, function, sex differences and hormonal responsiveness.

Cell type	Location in CNS	Neuroimmune function in CNS	Known sex differences	Hormone receptor expression
Microglia	Parenchyma	Secretion of cytokines, chemokines, growth factors; phagocytosis; antigen presentation; injury response; autoimmune/degenerative conditions	Yes: number, signaling and phenotype across life	ERα,β; AR; PR
Astrocytes	Parenchyma	Secretion of cytokines, chemokines, growth factors; phagocytosis; antigen presentation	Yes: morphology and inflammatory signaling across life	ERα; AR; PR
Perivascular macrophages	Parenchyma	BBB function; humoral communication across BBB; injury response; autoimmune/degenerative conditions	Unknown	Unknown, but hormones influence their function
Mast cells	Parenchyma; meninges; choroid plexus	Immune surveillance, host defense; Behavioral effects; contribute to injury response; autoimmune/degenerative conditions	Yes: mast cell protease 2	ERα
T & B cells, granulocytes; monocytes; dendritic cells	Meninges; choroid plexus; parenchyma?	Immune surveillance, antigen presentation; host defense; Behavioral effects; contribute to injury response; autoimmune/degenerative conditions	Unknown	ERα (T & B cells); ERβ (dendritic cells)