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*Review*

# (Putative) Sex Differences in Neuroimmune Modulation of Memory


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The neuroimmune system is significantly sexually dimorphic, with sex differences evident in the number and activation states of microglia, in the activation of astrocytes, and in cytokine release and function. Neuroimmune cells and signaling are now recognized as critical for many neural functions throughout the life span, including synaptic plasticity and memory function. Here we address the question of how cytokines, astrocytes, and microglia contribute to memory, and specifically how neuroimmune modulation of memory differentially affects males and females. Understanding sex differences in both normal memory processes and dysregulation of memory in psychiatric and neurological disorders is critical for developing treatment and preventive strategies for memory disorders that are effective for both men and women. 

**Key words:** learning and memory; cytokines; females; microglial activation; neurogenesis; astrocytes; synaptic plasticity

Memory of places, events, and relationships between cues is critical for adapting to a rapidly changing world. The ability to vary memory strength as a function of importance—memories of dangerous or beneficial events should be strengthened—is a critical feature of memory encoding. Modulation of memory by co-occurring emotion, stress, or immune state can thereby increase or decrease memory strength as appropriate for current circumstances (Liang et al., 1986; Roozendaal et al., 2002). Given the fundamental nature of memory, it is somewhat surprising that memory function differs between males and females. Nevertheless, sex differences have been observed across a broad range of memory tasks including verbal memory (Kramer et al., 1988), context fear conditioning (Maren et al., 1994; Keiser et al., 2016), extinction of fear conditioning (Lebron-Milad et al., 2012), reward-related learning (Quinn et al., 2007), and spatial memory (Voyer et al., 2016), among others (see also Andreano and Cahill, 2009; Galea et al., 2013). Sex differences are also evident across the cognitive strategies used to learn a task (Grissom et al., 2013; Shah et al., 2013), neural circuits recruited for memory (Gruene et al., 2014), the molecular mechanisms of memory (Keiser and Tronson, 2016), and the modulation of memory by stress (Waddell et al., 2008). Many disorders of memory, including Alzheimer's disease (Seshadri et al., 1997) and posttraumatic stress disorder (Kessler et al., 2012), are more prevalent in women than in men (Sohrabji et al., 2016). Determining sex-specific mechanisms of memory formation and its dysregulation is of high importance for developing novel preventive and treatment strategies for both men and women.

There is growing evidence for a central role of immune cells and signaling in memory formation and its modulation (Donzis and Tronson, 2014; Haydon and Nedergaard, 2015; Wu et al., 2015). Immune proteins are required for normal synaptic plasticity (O'Connor and Coogan, 1999; del Rey et al., 2013), and stress may influence memory via interactions with immune signaling (Deak et al., 2015; Vecchiarelli et al., 2015). Furthermore, activation of the peripheral immune system during illness or injury, and the resulting neuroimmune response (Fig. 1), dramatically alters memory processes. In patients of major surgery or illness, persistent cognitive deficits are

SIGNIFICANCE

Inflammatory events such as illness or injury alter cognition, emotion, and memory via activation of the immune system in the brain. Recent studies have demonstrated that the immune system activates different mechanisms in male vs. female brains. This suggests that the immune system may have different impacts on memory in males and females. In this review, we discuss ongoing research in the modification of memory by immune responses. We propose potential ways in which the neuroimmune activity can affect memory and contribute to differential prevalence of disorders of memory in men and women.

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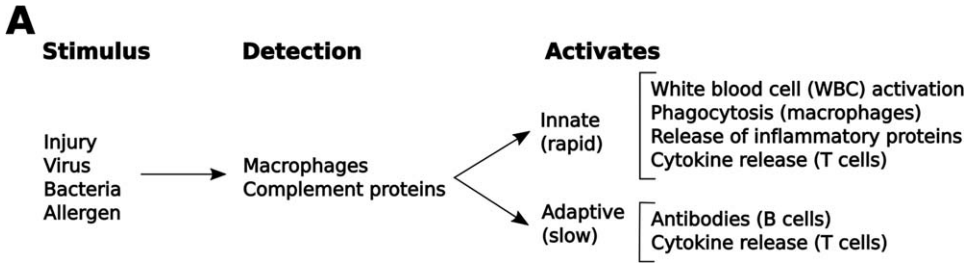


Fig. 1. A brief overview of innate and adaptive immune responses. Potentially dangerous "nonself" stimuli are detected by macrophage cells via toll-like receptors and by complement via antibody binding. These, in turn, release cytokines that activate both innate and adaptive immune responses. The innate immune system acts via cytokine release and cell-based mechanisms to quickly eliminate these stimuli. The adaptive immune system works more slowly and produces antibodies to fight infections that cannot be removed by the innate system.

common and correlate with levels of inflammatory signaling (Hovens et al., 2014; Petrovitch et al., 1998; Hudetz et al., 2009; Girard et al., 2010). Dysregulated immune activity contributes to neurological and psychiatric disorders of memory, including Alzheimer's disease and posttraumatic stress disorder (Azizi et al., 2014; Wieck et al., 2014; Dzamba et al., 2016). Immune-related signaling is an important mechanism for synaptic plasticity and memory, as well as persistent cognitive dysregulation, after major illness and in psychiatric and neurological diseases.

Given sex differences in mechanisms of memory, activation of immune signaling, and memory-related neurological and psychiatric disorders, it is likely that neuroimmune modulation of memory differs in males and females. If so, differential targeting of neuroimmune cells or immune signaling in males and females may provide novel, sex-specific pathways for intervening in disorders of memory. Here we will review the current literature on neuroimmune influences on memory with an emphasis on sex differences in memory modulation by cytokine signaling, activation of immune cells in the brain, and immune-related regulation of adult neurogenesis.

## THE NEUROIMMUNE SYSTEM

The neuroimmune system and its role in neural processes is a relatively new area of study. In the 1980s, it was postulated that fever was caused by actions of "pyrogenic cytokines," in particular interleukin-1 (IL-1), on the hypothalamus (Atkins, 1985). In contrast, other sickness behaviors, including increased sleep, decreased grooming, and anorexic effects, were believed to be caused by peripheral effects of inflammation (Hart, 1988). This discrepancy was clarified with the demonstration that IL-1 in the brain, and not peripheral immune signaling, directly mediates sickness behaviors (Nakamura et al., 1988), demonstrating for the first time a critical role for immune signaling in the brain on behavioral regulation. Subsequent evidence for immune-driven impairments in cognition (Gibertini et al., 1995), together with the correlation between immune changes and depression (Anisman et al., 2002; Dantzer et al., 2008; Capuron and Miller, 2011), additionally demonstrated a central role for neuroimmune signaling in complex neural functions.

In the brain, as in the periphery, cytokines are the major chemical cell-to-cell signaling proteins. The superfamily of cytokines includes interferons (e.g., IFN$\gamma$), interleukins (IL-1$\beta$, IL-4, IL-10), chemokines (e.g., CCL2, CXCL10, CX3CL1), tumor necrosis factors (e.g., TNF$\alpha$), and some growth factors (insulin-related growth factor [IGF], brain-derived neurotrophic factor [BDNF]), among others (Dinarello, 2007). Microglia, astrocytes, and neurons all secrete and express receptors for cytokines (Galic et al., 2012). Like other cell-to-cell signaling proteins, many cytokines act as a ligand, binding to their receptor and initiating second messengers, signal transduction, and transcription, often resulting in the production or suppression of additional cytokines (Greenhalgh and Hilton, 2001; Qiao et al., 2013). Others act as receptor antagonists (e.g., IL-1ra blocks the IL-1 receptor, preventing IL-1 binding) (Spulber et al., 2009) or adhesion proteins (e.g., CX3CL1 [fractalkine]) (Sheridan and Murphy, 2013). Cytokines are therefore well placed to mediate interactions between immune cells and neurons, acting as a major communication system in the brain (Adler et al., 2005).

The role of immune signaling in normal and dysregulated brain function is a growing focus of research. There are at least three distinct roles of the immune system in the brain. First, resident neuroimmune cells, including microglia and astrocytes (Fig. 2), have important functions in the absence of central or peripheral immune system activity. Without immune stimulation, glial-derived cytokines including IL-1 (Goshen et al., 2007) and CX3CL1 (Sheridan and Murphy, 2013), among others (Gadani et al., 2012), regulate normal neural functions and plasticity. Second, there is a classic immune role of increased neuroimmune signaling during inflammatory events such as stroke, brain infection, or

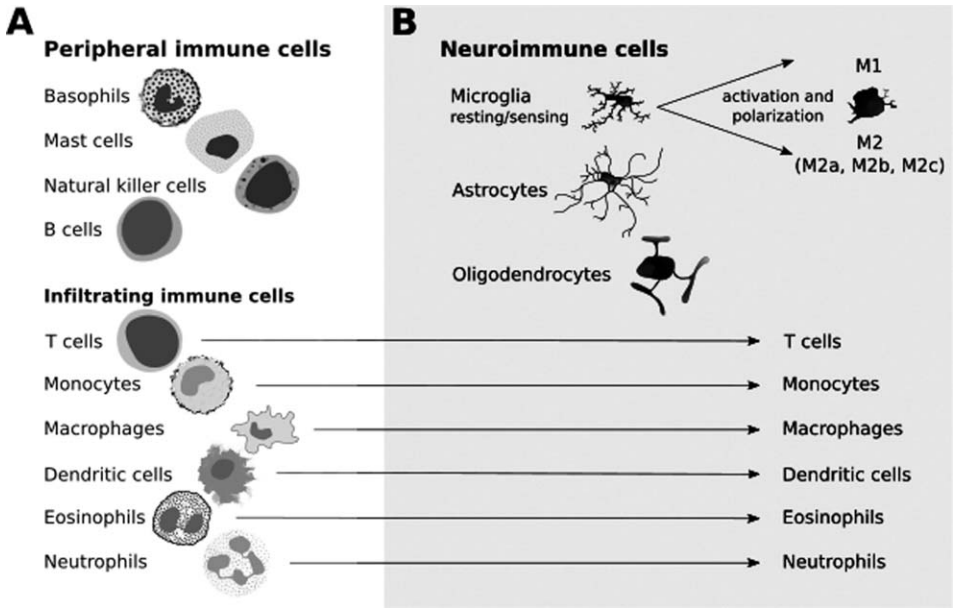


Fig. 2. Immune cells in the periphery and in the brain. **A**: Cells of the peripheral immune system. Peripheral immune cells are predominantly white blood cells. *Basophils* and *mast cells* release cytokines and activate the innate immune system (Stone et al., 2010). *Natural killer* cells attack "nonself" invaders as part of the innate immune system (Mandal and Viswanathan, 2015). *B cells* produce antibodies and are a critical part of the adaptive immune system (den Haan et al., 2014). Many of these white blood cells also infiltrate into the central nervous system after immune challenge and contribute to the neuroimmune response (Weber et al., 2016). *T cells* (T-helper, cytotoxic, and memory cells) are critical for the adaptive immune response, and sex-biased activation of T-helper cells contributes to differences between males and females in the adaptive immune response. *Monocytes* rapidly release cytokines during inflammation and stress (Xiong and Pamer, 2015). Monocytes can differentiate into macrophages and dendritic cells. *Macrophages* have two activation states, M1 and M2, and are important for phagocytosis of invading cells and cytokine release (Italiani and Boraschi, 2014). Peripheral *dendritic cells* stimulate antibody production by T cells and B cells (Bieber and Autenrieth, 2015). *Eosinophils* (Stone et al., 2010) and *neutrophils* (Kruger et al., 2015) are innate immune response cells activated during infections and migrate to the brain during infection or injury. **B**: Cells of the neuroimmune system. Central nervous system–specific immune cells include microglia, astrocytes, and oligodendrocytes. In a resting state, characterized by highly branched processes, *microglia* are important for surveillance of the brain (Casano and Peri, 2015). Once activated by immune signaling, microglia form an amoeboid shape and release different cytokines based on their activation state: M1, M2a, M2b, or M2c (Crain et al., 2013). *Astrocytes* maintain the tripartite synapse and release cytokines to modulate neuronal functions (Jensen et al., 2013). *Oligodendrocytes* release neurotrophins and repair myelin (Acosta et al., 2013).

traumatic brain injury, which mediates both neurotoxicity and neuroprotection (Pickering and O'Connor, 2007; Jha et al., 2015). Third, there is a strong role of signaling between the peripheral immune system and central nervous system (CNS) that influences behavioral states. Sickness behavior, in particular, has been well studied (Dantzer et al., 2008), which has led to a broader investigation of the role of immune modulation in emotional and behavioral states (and vice versa). Together, these findings suggest a critical role of neuroimmune signaling in normal neural functions, as well as modulation by peripheral or central immune activation.

The central role of immune cells and signaling proteins in complex neural functions, from behavioral regulation and affective processes to cognition and synaptic plasticity, makes neuroimmune function an important target for research. Given sex differences in memory processes, as well as in prevalence of psychiatric and neurological disorders (Seshadri et al., 1997; Kessler et al., 2012; Sohrabji et al., 2016), understanding the contribution of immune signaling in the brain is not complete without consideration of sex.

## SEX DIFFERENCES IN THE PERIPHERAL IMMUNE SYSTEM

It is well established that the peripheral immune system has differential activity in males and females. The sex differences are both *quantitative*, with greater immune activity in females compared with males, and *qualitative*, with differences in which cells and pathways are triggered after stimulation. Specifically, females have greater adaptive immune responses (i.e., stronger antibody production; Fig. 1) than males (Klein et al., 2015). Innate immune responses also differ qualitatively between sexes with peripheral immune cells (Fig. 2) producing different patterns of cytokines in males than in females (Moxley et al., 2002; Klein et al., 2015).

Sex differences in activation of immune cells and signaling start at the level of pathogen detection via toll-

like receptors (TLRs) and their subsequent cytokine response (Scotland et al., 2011; vom Steeg and Klein, 2016). Whereas males show higher numbers of TLR4 receptors (Roberts et al., 2013), females show stronger activation of intracellular signaling pathways (Zheng et al., 2006) and stronger cytokine response after TLR7 stimulation (Berghöfer et al., 2006), potentially mediating divergent responses of males and females. Strikingly, there are consistent sex differences in T-cell activation following an immune response. T-helper (Th) cells have multiple activation states, including "classic" Th1 and "alternative" Th2 states. These have different cytokine triggers, cytokine release profiles, and different functional consequences. Men show more Th1 cell activity, together with higher levels of Th1-associated cytokines including IFNγ and IL-2 after an immune challenge, and women show more "alternative" Th2 cells and associated cytokines IL-4 and IL-10 (Giron-Gonzalez et al., 2000; Engler et al., 2016). Mice also show this sex-dependent effect, with males showing stronger Th1 and females showing stronger Th2 responses (Huber and Pfaeffle, 1994). Macrophages can be similarly classified as M1 and M2 activation, based on cytokine responses, and, like Th cells, there is a bias towards M1 macrophage polarization in males and M2 polarization in females during immune activation (Martinez and Gordon, 2014). Sex differences across all levels of the immune system demonstrate that males and females differ in both the strength as well as the type of immune response.

Differences in immune activity correlate with higher susceptibility to infection in men than women (Furman et al., 2014; Giefing-Kröll et al., 2015). Similarly, women show stronger immune responses to vaccines, with greater antibody production and more adverse effects compared with men (Klein et al., 2010; Furman, 2015). Autoimmune disorders are also more prevalent in women, who compose more than 80% of affected patients (Fairweather et al., 2008). Specifically, women are more susceptible to autoimmune disorders with antibody-mediated pathology including the most common autoimmune disorders: multiple sclerosis and lupus, among others (Fairweather et al., 2008). In contrast, males are more likely to develop disorders with cell-mediated pathophysiology, such as acute myocarditis (Fairweather et al., 2008).

Both sex hormones (Lang, 2004; Lai et al., 2012; Furman et al., 2014) and chromosomes (Smith-Bouvier et al., 2008; Klein et al., 2010; Bianchi et al., 2012; Case et al., 2013) contribute to sex differences in immune activation. Circulating estrogens generally act to increase immune function in both male and female mice and may dose-dependently shift T cells toward a Th2 phenotype (Huber and Pfaeffle, 1994; Lang, 2004; Salem, 2004). Conversely, testosterone suppresses immune function in both sexes (Rantala et al., 2012; Furman et al., 2014). The chromosomal contribution is due to the high number of immune genes clustered on the X chromosome (Libert et al., 2010), the X complement (Smith-Bouvier et al., 2008), and the number of genes that escape from X-inactivation (XCI) (Bianchi et al., 2012). For example, several autoimmune disorders, including arthritis and thyroid diseases, are correlated with "skewed" XCI and higher expression of immune-related genes in females (Uz et al., 2009; Ishido et al., 2015). The immune system is strongly influenced by sex hormones and sex chromosomes, resulting in sex differences across many measures of immune function. Whether—and how—sex differences in the immune system translate into differential influences on neural function is less well established.

## SEX DIFFERENCES IN THE NEUROIMMUNE SYSTEM

Sex differences in the peripheral immune system cross over to the neuroimmune system, which is also regulated by both sex hormones (Mor et al., 1999; Czlonkowska et al., 2005) and chromosomal factors (Stamova et al., 2012). In the brain, differential microglial migration and immune-related gene expression in males and females (Schwarz et al., 2012) emerge early in development. Differences in neuroimmune cells persist throughout the life span, with sex-dependent activation of astrocytes (Santos-Galindo et al., 2011; Acaz-Fonseca et al., 2015), microglia (Crain et al., 2013), and cytokine release (Speirs and Tronson, in review) in response to immune challenge. Individual cytokines have sex-specific functions in the brain. For example, IL-2 impairs adult neurogenesis only in males (Beck et al., 2005), and IL-13 has a female-specific role in symptoms of experimental autoimmune encephalitis (Sinha et al., 2008). Sex differences in the neuroimmune system thus have important functional consequences.

A striking recent finding highlights qualitative sex differences in the neuroimmune system—namely, that males and females have unique immune–neuron interactions in the spinal cord mediating persistent pain. In males, inflammatory pain models result in microglia-mediated persistent neuropathic pain. In contrast, T-cell–mediated mechanisms via peroxisome proliferator–activated receptors mediate persistent pain in females (Sorge et al., 2015). These sex-specific mechanisms of pain, with different cell interactions and signaling pathways recruited in males and females, are important for development of effective treatments of pain in both sexes. Furthermore, these findings illustrate that divergent mechanisms in males and females are often different ways to achieve the same outcome (de Vries, 2004).

It is noteworthy that the male phenotype—TLR4 activation of microglia-to-neuron signaling (Sorge et al., 2011, 2015)—has long been considered *the* mechanism for neuropathic pain (Sorge et al., 2011). Because of the dominance of males in neuroscience research, whether females rely on different mechanisms than males is yet to be examined for most neuroimmune functions. Sex differences in cells, cytokines, and function of the neuroimmune system nevertheless suggest broader implications for fundamental neural functions.

Sex differences in behavioral effects of neuroimmune stimulation are also evident in fever and sickness

behavior after peripheral immune activation. After vaccination, women show stronger febrile responses (Klein et al., 2015) suggesting differential activation of hypothalamic pathways (Spinedi et al., 2002). In rodent models, females also show greater behavioral and autonomic responses to immune challenges (Lipton and Ticknor, 1979; Yee and Prendergast, 2010; Engeland et al., 2003). Women show greater socioemotional responses (Moieni et al., 2015) and depressed mood (Eisenberger et al., 2009) in response to lipopolysaccharide (LPS) injection compared with men, and rodent models show similar effects (Avitsur and Yirmiya, 1999; Yee and Prendergast, 2010). These findings suggest that not only does the peripheral immune system initiate neuroimmune signaling and modulate affective and physiological processes, it does so in sex-specific ways.

Sex differences in neuroimmune function span across cell types and cytokine responses (Santos-Galindo et al., 2011; Crain et al., 2013; Acaz-Fonseca et al., 2015), through development into adulthood (Schwarz et al., 2012; Tay et al., 2016), and from physiological responses to cognitive and affective processes (Lipton and Ticknor, 1979; Tonelli et al., 2008). These observations strongly implicate the neuroimmune system as a critical mediator of neural functions. Given the roles of microglia (Morris et al., 2013; Wu et al., 2015), astrocytes (Ben Achour and Pascual, 2010; Papa et al., 2014; Haydon and Nedergaard, 2015), cytokines (Goshen et al., 2007; Gadani et al., 2012; Donzis and Tronson, 2014), and growth factors (Peters et al., 2010; Chen et al., 2011) in learning and memory, we anticipate that differences in the neuroimmune system drive sex differences in memory and its modulation.

## NEUROIMMUNE MODULATION OF MEMORY: AVENUES FOR INVESTIGATING SEX DIFFERENCES

Many aspects of neuroimmune signaling are required for neural plasticity during development (Williamson et al., 2011; Wu et al., 2015), and similar mechanisms are involved in synaptic plasticity and memory formation in adults (Donzis and Tronson, 2014). Given the known sex differences in neuroimmune function, it is likely that memory regulation differs between males and females. Few studies have directly examined this question, yet there is substantial indirect evidence supporting the likelihood of sex differences in immune modulation of memory.

### Neuroimmune Signaling and Plasticity

Cytokines, including growth factors and chemokines, are critical for memory and synaptic plasticity (Donzis and Tronson, 2014). Induction of long-term potentiation (LTP) induces expression of a number of cytokines including IL-1β, IL-6, and TNFα (del Rey et al., 2013), and several of these play important roles in plasticity and memory. IL-1β is required for synaptic plasticity under normal conditions, and either decreases or increases of this cytokine impair memory (Balschun et al., 2003; Goshen et al., 2007; Spulber et al., 2009). IL-6 plays a negative regulatory role in memory and LTP (Balschun et al., 2004; Braida et al., 2004; Hao et al., 2014), likely via JAK-STAT signaling (Hao et al., 2014). TNFα increases glutamatergic and decreases GABAergic receptor trafficking (Beattie et al., 2002; Stellwagen, 2005), thereby impairing plasticity. Furthermore, during aging, decreases of IL-4 contribute to memory impairments (Maher et al., 2005; Gadani et al., 2012). Chemokines also play important regulatory roles. For example, CCL2 and CCL3 impair memory and synaptic plasticity (Belarbi et al., 2013; Marciniak et al., 2015), whereas CX3CL1 is required for memory formation, possibly via glial–neuron interactions (Rogers et al., 2011; Sheridan and Murphy, 2013). Immune challenges such as LPS administration trigger cytokine elevations and impair memory consolidation (Pugh et al., 1998; Cunningham and Sanderson, 2008), memory retrieval (Czerniawski et al., 2015), and discriminative memory (Czerniawski and Guzowski, 2014). Cytokines are therefore important contributors to plasticity in normal conditions and in dysregulation of memory processes after an immune challenge.

Whether cytokines exert differential effects on memory processes in males and females remains unknown. There is good evidence, however, that males and females show different cytokine activation in the brain following an immune stimulus. After intranasal LPS, female rats show greater expression of IL-6 and TNFα in the brain than males (Tonelli et al., 2008). Furthermore, after systemic LPS injection, males show later, prolonged activation of cytokines in the hippocampus (Speirs and Tronson, in review). Males also show a stronger hippocampal cytokine response after stress, with more TNFα and IL-1β compared with females (Pyter et al., 2013; Hudson et al., 2014). In addition, following ischemic stroke, female mice show increased microglial IL-4 but not IL-10 levels, whereas male mice show the opposite pattern: increased IL-10 but not IL-4 levels (Bodhankar et al., 2015). Given the roles of cytokines in synaptic plasticity and memory, such sex differences in patterns of neuroimmune activity suggest differential modulation of memory by cytokines in males and females.

Downstream of cytokine activation, second messenger signaling and transcription factors also show sex-specific activity. For example, p38MAPK mediates symptoms only in females in a mouse model of multiple sclerosis (Krementsov et al., 2014), and lipocalin-2 is required for increasing body temperature after LPS in females but not males (Hamzic et al., 2013). Furthermore, COX-2 is required for hippocampal memory only in females (Guzmán et al., 2009). Thus, cytokine-dependent signaling has different effects on neural function in males and females, suggesting the possibility of divergent effects of immune signaling on memory between the sexes.

Growth factors, including BDNF, IGF-1, and IGF-2, are important members of the cytokine superfamily. Inflammatory events can decrease neurotrophic factors in the brain; for example, systemic inflammatory challenges

decrease expression of *BDNF* (Lapchak et al., 1993) and other growth factors (Guan and Fang, 2006). Similarly, IGF-1 expression is regulated by cytokines (O'Connor et al., 2008), and conversely, IGF-1 acts to decrease expression of cytokines (Park et al., 2011). These interactions between cytokines and growth factors are critical mechanisms for mediating immune effects in the brain.

BDNF is strongly implicated as a necessary mediator in synaptic plasticity and memory (Andero et al., 2014), and cortical injections of BDNF are sufficient to induce plasticity (Peters et al., 2010). Sex hormones differentially regulate BDNF and its receptors in memory-related brain regions including the hippocampus and amygdala (Spencer-Segal et al., 2011; Luine and Frankfurt, 2013; Scharfman and MacLusky, 2014). In addition, regulation of *BDNF* gene expression during memory processes differs in males and females (Mizuno and Giese, 2012; Harris et al., 2016). Like BDNF, IGFs are important for normal memory processes. IGF-2 plays a critical role in memory consolidation and its enhancement (Chen et al., 2011; Lee et al., 2015), and both IGF-1 and IGF-2 can rescue memory deficits during aging (Deak and Sonntag, 2012; Steinmetz et al., 2016). There is also evidence for sex differences in IGF-1 and memory, where aging-related memory impairments are associated with decreased IGF-1 in men, but not women (Polimanti et al., 2016). Neurotrophins including BDNF and IGF may thereby contribute to sex differences in immune regulation of memory processes.

As the primary cell-to-cell signaling mechanisms in the neuroimmune system, cytokines play important roles in memory and its regulation. Cytokines and their downstream signaling pathways are differentially activated and exert different effects on neural function in males and females. In addition to the direct effects of cytokines and growth factors on receptor trafficking, synaptic regulation, and changes in gene expression, cytokines have a bidirectional relationship with neuroimmune cells. Cytokines are both secreted by and regulate the recruitment, activation, and function of neuroimmune cells that, in turn, are critical mediators of complex neural functions.

## Neuroimmune Cells and Their Activation

Cytokines, chemokines, and growth factors are instrumental in the activation of astrocytes and microglia (Fig. 2). Astrocytes regulate synapse formation and stability (Zorec et al., 2015), and microglia act to continuously monitor or survey the brain and eliminate synapses via synaptic pruning (Wu et al., 2015). Dysregulation of these cells has been strongly implicated in disorders of neurodegenerative memory decline such as Alzheimer's disease (Dzamba et al., 2016) and traumatic brain injury (Sajja et al., 2016). Astrocytes and microglia are critical for normal memory formation (Ben Achour and Pascual, 2010; Ota et al., 2013); however, the precise contribution of glia in memory formation and its modulation, and the sex-specific roles of glial cells, are not known.

Astrocyte processes wrap around neuronal synapses, form a "tripartite synapse," and regulate neurotransmission via calcium-, glutamatergic-, and GABAergic-dependent mechanisms (Perea et al., 2009; Moraga-Amaro et al., 2014). For example, astrocytic TNFα mediates AMPA receptor trafficking in the postsynaptic membrane (Beattie et al., 2002) and GABA receptor trafficking (Pribiag and Stellwagen, 2013) at the synapse. In some models, astrocytic secretion of TNFα resulted in impaired memory (Habbas et al., 2015), demonstrating the importance of astrocytes in the modulation of memory by cytokines. During learning, there is also evidence that astrocytes retract from synapses (Ostroff et al., 2014), suggesting that astrocytes may oppose synaptic plasticity. This implies that mechanisms causing retraction of astroglial processes may be a critical mechanism of memory formation and modulation. In addition to synaptic signaling, astrocytes are required for energy production (Gold, 2014), which, given the high energy requirement of neural plasticity (Steinman et al., 2016), suggests multiple roles of astrocytes in the modulation of memory.

Understanding of the role of astrocytes in cognitive processes is still in its infancy (Haydon and Nedergaard, 2015), and, with no studies directly comparing males and females, there is no direct evidence for sex differences in astrocytic contribution to memory. There are, however, several reasons to believe that such differences exist. First, astrocytes are sex-dependently activated as a consequence of ischemia (Chisholm and Sohrabji, 2016). Second, the release of cytokines by astrocytes differs markedly in males and females (Santos-Galindo et al., 2011; Loram et al., 2012; Acaz-Fonseca et al., 2015). Together, these points suggest that sex differences in cytokines after immune challenge are mediated, in part, by astrocyte activation.

Astrocytes are unlikely to modulate memory in isolation. Rather, interactions with other immune cells, including microglia, are likely necessary for this process. For example, astrocyte-derived IL-10 causes both altered microglia activation and impaired LTP (Almolda et al., 2015). Conversely, microglial activation can result in astrocyte-mediated modulation of synaptic function, resulting in rapid increases of astrocytic glutamate release (Pascual et al., 2012). These findings suggest that astrocytes may mediate neural plasticity either by direct effects on synapses or via activation of microglial cells.

Microglia are also important regulators of synapses and memory. In a resting state, microglia extend and retract their processes to monitor synapse function (Nimmerjahn et al., 2005). These interactions can enhance or eliminate (prune) neuronal connections and circuits in an activity-dependent manner (Tremblay et al., 2011). Bidirectional communication between neurons and microglia is critical for regulation of synapses and plasticity throughout the life span (see also Wu et al., 2015).

Neuron–microglial interactions via chemokine CX3CL1 (Milior et al., 2016) play a critical role in memory processes (Sheridan and Murphy, 2013). CX3CL1 acts, in part, as an adhesion protein anchored to the neuronal membrane and interacting with its receptor

(CX3CLR) on microglia (Chapman et al., 2000). Interaction of neurons and microglia via this pathway is required for synaptic plasticity and memory (Sheridan and Murphy, 2013), with memory impairments and blunted LTP evident in CX3CL1-deficient mice (Maggi et al., 2011; Rogers et al., 2011). Microglia-specific intracellular signaling and gene expression are also important for memory tasks. For example, IKKβ in microglia, but not neurons, is required for instrumental conditioning (Kyrargyri et al., 2014). Similarly, microglia-specific BDNF signaling is required for spine development and both motor learning and tone-dependent fear conditioning (Parkhurst et al., 2013). Therefore, resting microglia regulate synaptic plasticity and memory.

Microglia are activated by immune stimulation, resulting in amoeba-shaped cells that move to the site of damage or infection (Kettenmann et al., 2011). Activated microglia release cytokines and exert both enhancing (Delpech et al., 2015) and impairing (Tanaka et al., 2006; Vasek et al., 2016) effects on memory. Inhibition of microglia can shift LTP-inducing stimuli to result in long-term depression (LTD) via a TNFα-dependent mechanism (Zhong et al., 2010). Inflammatory signaling may modulate memory via microglia-dependent increases in AMPA and NMDA receptor currents and decreased LTP and LTD (Riazi et al., 2015). Immune challenges may thereby result in modification of memory via activation of microglia. Much of this work, however, has been done only with male animals. Given sex differences in microglia (Schwarz et al., 2012) and their function (Sorge et al., 2015) in the CNS, it remains unclear whether similar modulatory effects on memory would be observed in females.

Like macrophages and Th cells, active microglia have several phenotypes that influence their function, and sex differences in these active states have been described (Bodhankar et al., 2015; Xiong et al., 2015). During activation, microglia are polarized into several different activated phenotypes triggered by different cytokines and other factors. The "classical" activated microglia state is the M1 state, triggered by IFNγ and Th1 cytokines, and produces cytokines including TNFα, IL-1β, and IL-6. The M2 microglial activated states include M2a "alternative activation" triggered by IL-4 and IL-13; M2b "alternative activation type II"; and the M2c "acquired deactivation" state triggered by IL-10 or glucocorticoids (Prinz and Priller, 2014; Walker and Lue, 2015; but see also Ransohoff, 2016). Whereas M1 microglia are important for the initiation of the inflammatory response, M2 microglia are predominantly neuroprotective (Xiong et al., 2016). More specifically, M2a produces neurotrophins (Bodhankar et al., 2015), and M2c is involved in remodeling after resolution of inflammation (Cherry et al., 2014). In this framework, females show a stronger predisposition for M2a polarization compared with males (Bodhankar et al., 2015; Xiong et al., 2015). Differential microglia polarization may explain—or be explained by—sex differences in cytokine levels in males and females.

Our understanding of the contribution of astrocytes and microglia to sex differences in the modulation of memory is constrained by both the newness of the study of these cells in synaptic plasticity and, within that, the lack of studies that include both males and females (see Table I). A recent review by Hoogland and colleagues (2015) highlights how little is known about microglial activation after immune challenge. Of the studies examining microglial activation after systemic LPS administration, for example, only three examined both sexes, and only two more studied females. There are similarly few studies on sex differences in astrocyte function. Nevertheless, the cumulative evidence from other models, including pain (Sorge et al., 2015) and stroke (Bodhankar et al., 2015; Xiong et al., 2015; Chisholm and Sohrabji, 2016), suggests that the activation and function of glial cells are likely to differentially affect synaptic plasticity and memory processes in males and females.

## Neuroimmune Modulation of Adult Neurogenesis

In addition to acute effects on memory, immune signaling affects long-acting modulatory processes including neurogenesis (Monje et al., 2003; Borsini et al., 2015). Adult neurogenesis is the production of new neurons in the adult brain, created through asymmetric division of progenitor cells (proliferation). These cells then differentiate into neurons (50%–60%; Abrous et al., 2005) or glia (gliogenesis, ∼10%; Steiner et al., 2004) before becoming functionally integrated into the dentate gyrus. Integration of new neurons modifies the excitability of neuronal circuits (Song et al., 2012) and supports spatial (Snyder et al., 2005) and contextual fear (Drew et al., 2010) memory formation.

Both acute (Valero et al., 2014) and chronic (Zonis et al., 2015) inflammation, as well as chronic stressors (McKim et al., 2016), lead to dysregulation of adult neurogenesis. Studies of inflammatory signaling and neurogenesis show conflicting results: immune challenges can increase proliferation (Seguin et al., 2009), decrease proliferation (Islam et al., 2009), maintain neurogenesis by increasing survival of new cells (Ziv et al., 2006), decrease survival of newborn neurons (McKim et al., 2016), or impair integration of new cells into neural circuits (Jakubs et al., 2008).

Hippocampal neurogenesis is strongly influenced by cytokines. Specifically, IL-1 (Koo and Duman, 2008; Ben Menachem-Zidon et al., 2013), IL-2 (Beck et al., 2005), and TNFα (Chen and Palmer, 2013) reduce proliferation. IL-6 decreases multiple stages of neurogenesis including proliferation, differentiation of neural progenitor cells, and survival of new cells (Vallières et al., 2002). These detrimental effects of cytokines on neurogenesis correlate with altered memory processes. For example, LPS-induced decreases in neurogenesis correlate with deficits in spatial memory (Valero et al., 2014). In addition to direct effects of cytokine-dependent signaling on neurogenesis, cytokines have indirect effects via decreased neurotrophic factors. For example, systemic LPS-induced

**TABLE I. Sex of Animals or Humans Used in Studies Cited**

| **The neuroimmune system** | | | |
|---|---|---|---|
| **Male** | **Female** | **Male and female** | **Sex not specified** |
| Goshen et al., 2007 | Gibertini et al., 1995 | | Nakamura et al., 1988 |
| **Sex differences in the immune system** | | | |
| **Male** | **Female** | **Male and female** | **Sex not specified** |
| Lipton and Ticknor, 1979 | Uz et al., 2009† | Moxley et al., 2002† | |
| Rantala et al., 2012† | Ishido et al., 2015† | Scotland et al., 2011 | |
| | | Roberts et al., 2013 | |
| | | Zheng et al., 2006 | |
| | | Berghöfer et al., 2006† | |
| | | Giron-Gonzalez et al., 2000† | |
| | | Engler et al., 2016† | |
| | | Huber and Pfaeffle, 1994 | |
| | | Furman et al., 2014† | |
| | | Smith-Bouvier et al., 2008 | |
| | | Case et al., 2013 | |
| **Sex differences in the neuroimmune system** | | | |
| **Male** | **Female** | **Male and female** | **Sex not specified** |
| Lipton and Ticknor, 1979 | | Stamova et al., 2012★,† | |
| Goshen et al., 2007 | | Schwarz et al., 2012 | |
| Peters et al., 2010 | | Acaz-Fonseca et al., 2015 | |
| | | Sinha et al., 2008 | |
| | | Sorge et al., 2011 | |
| | | Sorge et al., 2015 | |
| | | Moieni et al., 2015† | |
| | | Eisenberger et al., 2009★,† | |
| | | Yee and Prendergast, 2010 | |
| | | Engeland et al., 2003★ | |
| | | Tonelli et al., 2008 | |
| **Neuroimmune modulation of memory: avenues for investigating sex differences** | | | |
| ***Neuroimmune signaling and plasticity*** | | | |
| **Male** | **Female** | **Male and female** | **Sex not specified** |
| del Rey et al., 2013 | Lapchak et al., 1993 | Pugh et al., 1998★ | |
| Balschun et al., 2003 | | Pyter et al., 2013★ | |
| Goshen et al., 2007 | | Hudson et al., 2014 | |
| Spulber et al., 2009 | | Krementsov et al., 2014★ | |
| Balschun et al., 2004 | | Hamzic et al., 2013 | |
| Braida et al., 2004 | | Guzmán et al., 2009 | |
| Hao et al., 2014 | | Spencer-Segal et al., 2011 | |
| Maher et al., 2005 | | Mizuno and Giese, 2012 | |
| Belarbi et al., 2013 | | Harris et al., 2016 | |
| Marciniak et al., 2015 | | Polimanti et al., 2016† | |
| Rogers et al., 2011 | | | |
| Czerniawski et al., 2015 | | | |
| Czerniawski and Guzowski, 2014 | | | |
| Guan and Fang, 2006 | | | |
| Park et al., 2011 | | | |
| Peters et al., 2010 | | | |
| Chen et al., 2011 | | | |
| Lee et al., 2015 | | | |
| Steinmetz et al., 2016 | | | |

**TABLE I.** *Continued*

| *Neuroimmune cells and their activation* | | | |
|---|---|---|---|
| **Male** | **Female** | **Male and female** | **Sex not specified** |
| Ostroff et al., 2014 | Maggi et al., 2011 | Acaz-Fonseca et al., 2015 | Habbas et al., 2015 |
| Milior et al., 2016 | | Almoda et al., 2015⋆ | Pascual et al., 2012 |
| Rogers et al., 2011 | | Vasek et al., 2016⋆ | Nimmerjahn et al., 2005 |
| Kyrargyri et al., 2014 | | Schwarz et al., 2012 | Parkhurst et al., 2013 |
| Delpech et al., 2015 | | Sorge et al., 2011 | |
| Tanaka et al., 2006 | | Sorge et al., 2015 | |
| Zhong et al., 2010 | | Xiong et al., 2015 | |
| Riazi et al., 2015 | | | |
| *Neuroimmune modulation of adult neurogenesis* | | | |
| **Male** | **Female** | **Male and female** | **Sex not specified** |
| Snyder et al., 2005 | Steiner et al., 2004 | Chow et al., 2013 | Ben Menachem-Zidon et al., 2013 |
| Drew et al., 2010 | Valero et al., 2014 | Vallières et al., 2002⋆ | Kuzumaki et al., 2010 |
| Koo and Duman, 2008 | Monje et al., 2003 | Mitterling et al., 2010 | |
| Chen and Palmer, 2013 | Zonis et al., 2015 | Sorge et al., 2011 | |
| Wu et al., 2007 | | | |
| Ziv et al., 2006 | | | |
| Bachstetter et al., 2011 | | | |
| Ekdahl et al., 2011 | | | |
| McKim et al., 2016 | | | |
| Seguin et al., 2009 | | | |

⋆Did not statistically compare males vs. females.
†Humans.

immune signaling resulted in decreased BDNF and impaired differentiation of new cells into neurons. Here, BNDF levels and proliferation were rescued by wheel running despite persistent high levels of cytokines (Wu et al., 2007).

Immune regulation of neurogenesis also involves neuroimmune cells (Kuzumaki et al., 2010). Microglia, in particular, play a critical role in mediating neurogenesis (Ziv et al., 2006). CX3CL1 modulates activation of microglia in the neurogenic niche (Williams et al., 2014), increasing proliferation and contributing to survival of new cells (Bachstetter et al., 2011). In addition, microglia activated by IFNγ signaling increase survival (Butovsky et al., 2006). As in memory modulation, the polarization of microglia matters. LPS/TLR4 microglia activation (likely M1 microglia) results in reduced survival of new cells (Ekdahl et al., 2011), whereas IL-4–dependent microglia (possibly M2a) activation regulates a switch toward decreased neurogenesis and increased gliogenesis (Butovsky et al., 2006). Cytokine signaling also triggers differentiation of progenitor cells into nonneuronal cell types (Islam et al., 2009; Green et al., 2012), effectively decreasing neurogenesis by increasing gliogenesis.

Despite similar levels of neurogenesis in both sexes, this process is differentially susceptible to modulation in males and females. Estrogens and androgens have sex-specific effects on neurogenesis (Galea et al., 2013), likely through their receptors. Estrogen receptors are located on dividing cells in the neurogenic region of the hippocampus (Mitterling et al., 2010), and androgens mediate neurogenesis through receptors located in other regions of the hippocampus (Galea et al., 2013). Given the sex-biased roles of immune cells in the CNS (e.g., Sorge et al., 2015), sex hormones and neuroimmune signaling may interact during differentiation of precursor cells and thereby alter the proportions of new glial and neuronal cells produced. One of the few studies comparing males and females in immune regulation of neurogenesis (Table I) demonstrated that IL-2 limits neurogenesis only in males (Beck et al., 2005). Thus, immune signaling may act as an intervening variable driving differential roles of new neurons in circuit dynamics of memory in males and females (Chow et al., 2013).

## IMPLICATIONS OF SEX DIFFERENCES IN IMMUNE MODULATION OF MEMORY

It is clear that the immune system plays a critical role in behavioral modification and regulation of neural plasticity throughout the life span. The complexity of interactions between cytokines and neuroimmune cells, between astrocytes, microglia, and neurons, and the roles of the neuroimmune system in normal and dysregulated memory processes, makes understanding the sex-specific roles of each process a daunting task. The task is made more difficult by the lack of studies that directly compare males and females (Table I; Hoogland et al., 2015). Indeed, when males and females are directly compared, it becomes clear that different patterns of cytokines are triggered by an immune challenge (Speirs and Tronson, in review), and these differences are mediated in part by

differential activation of astrocytes (Santos-Galindo et al., 2011; Acaz-Fonseca et al., 2015) and microglia (Schwarz et al., 2012; Bodhankar et al., 2015). The intricacies of neuroimmune signaling, together with the presence of sex differences at every level of analysis, suggest that the role of this system in plasticity is very different in males and females. Here, sex-specific cellular and signaling mechanisms likely result in differential modulation of neurons, spines, and synapses, as well as changes in long-acting processes including neurogenesis.

Identifying similarities and differences in the mechanisms of neuroimmune modulation of memory in males and females is critical for developing targeted treatments for disorders of memory and cognition. Sex differences are particularly important as many of these disorders have sex differences in prevalence (Sohrabji et al., 2016). Women, for example, have higher rates of Alzheimer's disease (Seshadri et al., 1997) and stress-related disorders including posttraumatic stress disorder (Kessler et al., 2012). Inflammatory signaling increases the risk of neurodegenerative disease (e.g., Tan et al., 2007; Azizi et al., 2014) or stress-related disorders (Wieck et al., 2014; Vecchiarelli et al., 2015; McKim et al., 2016). Thus, understanding the similarities and differences in neuroimmune activation in males and females may help identify the specific components of immune signaling that confer higher risk and provide new, sex-specific avenues for prevention and treatment of memory disorders.

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## CONFLICT OF INTEREST

The authors have no conflicts of interest to declare

## ROLE OF AUTHORS

NCT and KMC conceived, designed, wrote, and edited this review. KMC created all figures and illustrations.

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