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Three's Company: Neuroimmune activation, sex, and memory at the tripartite synapse

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ABSTRACT

The neuroimmune system is required for normal cognitive functions such as learning and memory in addition to its critical role in detecting and responding to invading pathogens and injury. Understanding the functional convergence of neurons, astrocytes, and microglia at the synapse, particularly in the hippocampus, is key to understanding the nuances of such diverse roles. In the healthy brain, communication between all three cells is important for regulating neuronal activation and synaptic plasticity mechanisms, and during neuroinflammation, the activity and functions of all three cells can produce and be modulated by inflammatory cytokines. An important remaining component to this system is the conclusive evidence of sex differences in hippocampal plasticity mechanisms, hormone modulation of synaptic plasticity, functional properties of hippocampal neurons, and in neuroimmune activation. Sex as a biological variable here is necessary to consider given sex differences in the prevalence of memory-related disorders such as Alzheimer's disease and Post-Traumatic Stress disorder, both of which present with neuroimmune dysregulation. To make meaningful progress towards a deeper understanding of sex biases in memory-related disease prevalence, I propose that the next chapter of psychoneuroimmune research must focus on the signal integration and transduction at the synapse between experience-dependent plasticity mechanisms, neuroimmune activation, and the influence of biological sex.

1. WELCOME TO THE JUNGLE: introduction

The neuroimmune system is a specialized immune system in the brain critical for both regulating normal neural function and behavior as well as responding to illness and injury (Marin and Kipnis, 2013). This distinct set of functions is due to the precise extracellular location of two innate immune cells, astrocytes and microglia, at neuronal synapses. The presynaptic neuron, postsynaptic neuron, and surrounding astrocytes comprise what is known as the tripartite synapse (Araque et al., 1999). Microglia also play a crucial role in regulating synaptic activity *via* communication with both astrocytes and neurons. In this review, I will describe the key mechanisms involved specifically in synaptic plasticity and memory in both healthy, normal conditions in the brain as well as under activation of the neuroimmune system. (see Fig. 1)

According to the synaptic plasticity hypothesis of memory, physical and measurable changes to specific synapses are necessary for memory formation and depend on the neuronal activity induced by the experience (Kandel and Schwartz, 1982). This hypothesis is largely supported by studies reviewed by others (Martin et al., 2000). This review will focus on mechanisms by which synaptic plasticity can be modulated by the neuroimmune system and subsequently affect learning and memory. To this end, I will first characterize the communication between neurons, astrocytes, and microglia at the synapse. Next, I will layer mechanisms of neuroimmune activation and the influence of biological sex to this framework. Ultimately, I propose that investigating the *integration* of these complex layers in the modulation of synaptic plasticity is the next ideal step towards our understanding of memory in health and disease in all individuals.

2. REMEMBER THE TRIPARTITE SYNAPSE: regulation of activity at the tripartite synapse is important for learning and memory

Experience-dependent synaptic plasticity in the hippocampus is a core feature of mechanisms of learning and memory. At the tripartite synapse, communication between neurons is regulated and modulated by the activity and bidirectional communication with astrocytes (Anderson and Swanson, 2000; Haydon, 2001; Noriega-Prieto and Araque, 2021). Here, I will highlight key components and the role of the tripartite synapse in learning and memory.

Glutamatergic signaling is necessary for initiation and maintenance of

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Fig. 1. Caitlin Posillico. Caitlin has been working in the field of behavioral neuroimmunology since 2013 and found her research home in the Psychoneuroimmunology Research Society while attending their annual meeting in 2015. She is primarily interested in the interaction and communication of neurons, astrocytes, and microglia in the context of neuroimmune activation and memory dysfunction and in characterizing any sex-specific processes in these systems. Caitlin is a Ph.D. candidate in Dr. Natalie Tronson's lab in the Biopsychology area of Psychology at the University of Michigan and expects to defend her dissertation studying the interaction of neuroimmune and memory mechanisms in male and female mice in 2022. Caitlin received a master's degree in Neuroscience from the University of Delaware in 2015 where she worked with Dr. Jaclyn Schwarz studying the psychoneuroimmunology of pregnancy and risk factors for developing postpartum depression-like behaviors in rat dams. Outside of the lab, Caitlin has strong passions for teaching and science outreach. She enjoys teaching introductory neuroscience and neuroimmunology to undergraduates and doing outreach for students of all ages to inform, encourage, and support those interested in STEM fields and laboratory research. She is a founding mentor of the Students Tackling Advanced Research (STAR) Scholars program in the Psychology department at the University of Michigan – a program designed to help break down barriers to entering and remaining in research and academia for students from first-generation, underrepresented, and low-income groups. Additionally, she has worked as an advisor for the Psychology department where she meets with prospective and current Psychology or Biopsychology, Cognition, and Neuroscience (BCN) majors to help with course planning, getting involved in research, and preparing for graduate school and future careers. Ultimately, Caitlin hopes her own career will continue to welcome and support future generations of neuroscientists and researchers in higher education and beyond.

hippocampal long-term potentiation and depression *in vitro* (Katagiri et al., 2001; Neyman and Manahan-Vaughan, 2008), *in vivo* (Heynen et al., 2000; Naie and Manahan-Vaughan, 2004; Stäubli et al., 1994), and for learning and memory in both rodent models (Aultman and Moghaddam, 2001) and humans (Stanley et al., 2017). Insufficient stimulation of glutamatergic N-Methyl-D-aspartic acid (NMDA) receptors in the rodent hippocampus can be insufficient to induce long-lasting synaptic plasticity *in vitro* (Bliss and Collingridge, 2013; Fox et al., 2006; Lu et al., 2001), while too much glutamate can result in seizure activity and cell death due to excitotoxicity *in vivo* (Petr et al., 2015; Tanaka et al., 1997). As such, it is extremely important that levels of glutamatergic activity are tightly regulated in the synapse. Glutamate transporter 1 (GLT-1) is a high-affinity glutamate transporter and accounts for more than 95% of excess hippocampal glutamate uptake (Tanaka et al., 1997). While many cell types express glutamate transporters, astrocyte-specific expression makes up approximately 80% of total GLT-1 expression (Furness et al., 2008; Petr et al., 2015). Studies using a single-prolonged stress model of Post-Traumatic Stress disorder (PTSD) in male rodents found increased glutamate concentrations and decreased expression of astrocytic glutamate transporters coupled with enhanced fear memory expression and impaired fear memory extinction (Feng et al., 2015; Yamamoto et al., 2009). Administration of fibroblast growth factor 2, a mitogen produced by astrocytes and important for hippocampal neurogenesis and neuronal activation (Kirby et al., 2013), alleviated memory impairments by restoring function in astrocytic glutamate transporters (Feng et al., 2015; Xia et al., 2013). Astrocytic control of glutamate has also been implicated in Alzheimer's disease (Vincent et al., 2010). Taken together, astrocytic control of glutamate has important implications for fine-tuning mechanisms of experience-dependent synaptic plasticity and memory in health and disease.

In addition to glutamate uptake, astrocytes also release glutamate and other neurotransmitters crucial for synaptic plasticity in a process known as gliotransmission (Hamilton and Attwell, 2010). These actions augment long-lasting synaptic plasticity between pre- and post-synaptic rodent neurons in addition to increasing neuronal synchrony *in vitro* (Angulo et al., 2004; Carmignoto and Fellin, 2006; Fellin et al., 2004). For example, changes to intracellular calcium levels in astrocytes stimulate the release of glutamate, D-serine, and adenosine 5′-triphosphate (ATP), among others (Montana et al., 2006; Parpura et al., 1994). Both D-serine and glutamate are required for NMDA receptor activation, and astrocytic contributions of both ligands have been shown to bind to postsynaptic neuronal NMDA receptors as well as extra-synaptic NMDA receptors in rat slice preparations (Fellin et al., 2004; Yang et al., 2003). Importantly, dysregulation of astrocytic calcium in male mice was found to reduce astrocytic coverage of neuronal synapses and subsequently impair both spatial and contextual fear memory (Tanaka et al., 2013). Astrocytes, therefore, are critical for synaptic plasticity, and dysregulation of astrocyte functions can have a detrimental impact on learning and memory.

3. DON'T YOU (FORGET ABOUT MICROGLIA): microglia supplement regulation of the tripartite synapse

Microglia are the resident immune cells of the brain and, like astrocytes, also play important roles in neuronal communication, synaptic plasticity, and memory mechanisms. Like astrocytes, microglia receive signals from activated nearby neurons as a supplement member of the tripartite synapse. Microglia express a chemokine receptor, CX3CR1 that binds to fractalkine CX3CL1 released by neurons (Hughes et al., 2002). Several *in vitro* rodent studies show that this communication acts to inhibit microglia activation and maintain microglia in a surveying state (Biber et al., 2007; Ransohoff et al., 2007) as well as suppress inflammatory cytokine production (Zujovic et al, 2000, 2001). Interestingly, disruption of CX3CL1-CX3CR1 communication can either improve (Maggi et al., 2011; Reshef et al., 2014) or impair (Bachstetter et al., 2011; Rogers et al., 2011) synaptic plasticity and memory in rodents, highlighting the importance of tightly regulating this communication at the synapse.

Microglia and neurons also communicate in the hippocampus *via* the interleukin (IL) cytokine IL-33. In adult male and female mice, Nguyen and colleagues showed that IL-33 is expressed in neurons in an experience-dependent manner, and microglial detection of IL-33 triggers engulfment of the extracellular matrix at the synapse to allow for dendritic spine remodeling, increased synaptic plasticity, and increased memory acuity (Nguyen et al., 2020). Although necessary for bouts of experience-dependent synaptic plasticity, chronic instability of the extracellular matrix is detrimental for homeostatic processes that support neuronal activity and cognition. Specifically, the perineuronal nets that stabilize the extracellular matrix were found to be significantly decreased in both sexes of the 5xFAD mouse model of Alzheimer's disease as well as in the postmortem brain tissue of men and women with Alzheimer's disease relative to controls (Crapser et al., 2020). This study implicated microglial engulfment of the perineuronal nets as a key contributing factor to these findings. Taken together, the ability of microglia to modulate the stability of the synapse is highly important in the context of

both health and disease.

Microglia also detect synaptic ATP, an important modulatory signaling molecule released by both activated neurons and astrocytes. A recent study by Badimon and colleagues showed that microglial processes are directed to activated synapses *via* ATP detection. In response, microglia locally produce adenosine that activates the neuronal A1R adenosine receptor to suppress neuronal excitability (Badimon et al., 2020). Thus, microglia, together with astrocytes, are key players for regulating learning and memory processes due to their extensive abilities to modulate synaptic plasticity through neuronal activity-dependent mechanisms.

4. RING THE NEUROINFLAMMATORY ALARM: inflammatory signaling modulates cellular communication

As innate immune cells of the brain, microglia and astrocytes are crucially involved in the detection of and response to invading pathogens and cellular debris in addition to their discussed roles in mediating neuronal activation and synaptic plasticity in normal, healthy conditions. Both astrocytes and microglia express pattern-recognition receptors (PRRs) that are activated by pathogen- and danger-associated molecular patterns found on bacteria, viruses, and damaged tissue (Kigerl et al., 2014). In response to PRR activation, immune signaling molecules called cytokines are rapidly produced, and receptors for these ligands are expressed on all three cell types, making cytokines another mechanism of communication between neurons, astrocytes, and microglia (Kigerl et al., 2014; Ransohoff and Brown, 2012).

In the periphery, cytokines help to recruit additional immune cells to action in a coordinated response to fight off the invading pathogen or clear up tissue damage and signal to the brain. In the brain, cytokines induce adaptive sickness behaviors, depressive-like behaviors, and disruption of cognitive processes including learning and memory in both rodents and humans (Dantzer et al., 2008; Marin and Kipnis, 2013; Raison et al., 2006; Yirmiya and Goshen, 2011). Interestingly, cytokines such as tumor necrosis factor α (TNFα) (Santello et al., 2011; Stellwagen et al., 2005), interleukins (IL) IL-1β (Huang et al., 2011; Viviani et al., 2003), IL-6 (D'Arcangelo et al., 2000), and IL-33 (Nguyen et al., 2020), and interferons (IFNs) IFNα, IFNβ, and IFNγ (Costello and Lynch, 2013; Mendoza-Fernández et al., 2000; Zhu et al., 2011) can modulate synaptic function by altering membrane receptor trafficking, neuronal signaling, extracellular matrix remodeling, and/or neurotransmitter release at both excitatory and inhibitory synapses (Pribiag and Stellwagen, 2013). For example, manipulation of the interleukin family of cytokines can significantly impair *in vitro* hippocampal long-term potentiation (Ross et al., 2003; Schneider et al., 1998) and memory (Goshen et al., 2007) in rodents. The effects of individual cytokines can be both cell and brain region specific, and it is important to keep this in mind when discussing implications of neuroimmune activation on neuronal functions and mechanisms of synaptic plasticity.

Studies in male rats showed that microglia activation contributes to dysregulated synaptic plasticity during inflammatory events, and preventing it ameliorates these effects (Riazi et al., 2015). *In vivo* imaging of neurons in awake male mice showed that microglial contact at neuronal synapses increased synaptic activity and neuronal synchrony important for experience-dependent synaptic plasticity (Akiyoshi et al., 2018). These effects were blocked when microglia were activated by lipopolysaccharide, a bacterial endotoxin. Viruses including West Nile virus and Zika virus have also been shown to cause microglial engulfment of synapses that result in hippocampal-dependent memory impairment in both sexes (Garber et al., 2019; Vasek et al., 2016), and this mechanism of synapse elimination is also postulated in the pathophysiology of PTSD (Enomoto and Kato, 2021). These findings contribute to a growing consensus that mechanisms of synaptic communication and plasticity can be modulated by neuroimmune activation, placing the interaction of neurons, astrocytes, and microglia at the crux of health and disease in the context of learning and memory.

5. LET'S TALK ABOUT SEX: sex differences in synaptic plasticity and neuroimmune mechanisms

Sex differences in mechanisms of hormone modulation of synaptic plasticity, functional properties of hippocampal neurons, and the neuroimmune activation that can modulate neuronal activity highlight how pervasive the effects of biological sex are in the context of learning and memory. As such, sex adds yet another layer of complexity to the function of neurons, astrocytes, and microglia at the tripartite synapse.

Estrogens modulate neuronal activity, long-term synaptic plasticity mechanisms, and learning and memory in both males and females (Frick et al., 2018; Hyer et al., 2018; Woolley, 2007). Despite that females have an additional source of ovarian estrogen, the local production of estrogen by aromatase in both sexes plays a more significant role in these mechanisms of neuronal modulation (Lu et al., 2019; Luine et al., 2018; Wang et al., 2018).

In the hippocampus, both males and females express the estrogen receptors (ER) ERα, ERβ, and G protein-coupled estrogen receptor 1 (GPER1), with greater expression of GPER1 compared with both ERα and ERβ in both sexes (Brailoiu et al., 2007; Hutson et al., 2019). Interestingly, expression of ERα and ERβ is restricted to different subcellular locations of excitatory neurons, and expression levels in both neurons and astrocytes are modulated by levels of hormones, revealing notable sex differences and differences across the estrous cycle (Mitterling et al., 2010). Early rodent studies showed estradiol increased neuronal excitability of hippocampal glutamatergic synapses in both sexes (Teyler et al., 1980; Wong and Moss, 1992), but more recent studies revealed that modulation of pre- and post-synaptic mechanisms is *via* different estrogen receptors in each sex (Oberlander and Woolley, 2016; Wang et al., 2018). Taken together, these findings suggest that sex differences in expression levels of ERα and ERβ, as reported by Mitterling and colleagues, have important functional implications for sex differences in mechanisms of long-lasting synaptic plasticity.

Beyond estrogen receptor activation, there are notable sex differences in hippocampal neurogenesis, intracellular signaling cascades, and transcription during hippocampal-dependent memory formation (Chow et al., 2013; Gresack et al., 2009; Koss and Frick, 2017; Tronson and Keiser, 2019; Yagi and Galea, 2019). While male-specific mechanisms of memory have been identified and characterized, the historical exclusion of females in this research has made female-specific memory mechanisms elusive and not explained by estrogen alone (Tronson, 2018; Tronson and Keiser, 2019). This severe gap in literature has important implications for health and disease, as sex differences in memory are also evident both qualitatively and quantitatively in behavior (Andreano and Cahill, 2009; Loprinzi and Frith, 2018).

Sex differences in neuroimmune function and response to inflammatory triggers may also contribute to differences in memory processes. In the periphery, females have a greater immune response compared to males, as measured by levels of circulating cytokines and chemokines (Klein and Flanagan, 2016). Peripheral immune stimulation using lipopolysaccharide in mice also induces multi-faceted sex differences in the pattern, time course, and magnitude of cytokine levels in the hippocampus, where females show a more rapid onset and resolution of cytokine levels compared to males (Speirs and Tronson, 2018). By contrast, studies on inflammation in the brain show sex differences in the opposite direction. For example, a comprehensive review by Guneykaya and colleagues found that microglia from male mouse brains have a higher capacity and potential to respond to stimuli that would result in a higher magnitude reaction to neuroinflammation in males relative to females (Guneykaya et al., 2018). Microglia from aged male mice are more capable of phagocytosis of neuronal debris under neuroinflammatory conditions relative to aged female microglia (Yanguas-Casás et al., 2020). Similarly, male-derived astrocytes from cortical brain tissue in rodents have a much greater cytokine response to stimulation relative to astrocytes from female tissue (Astiz et al., 2014; Loram et al., 2012; Santos-Galindo et al., 2011). We have also observed

that *in vivo*, central immune activation using the viral mimic polyinosinic:polycytidylic acid (poly I:C) causes a greater increase of cytokines and chemokines in the hippocampus of male mice relative to females (Posillico et al., 2021). In this study, we also found sex differences in the expression of anti-viral interferons such that both males and females exhibited increased expression of IFNβ, but only males also showed increased expression of IFNα and IFNγ (Posillico et al., 2021). Given the direct and indirect roles of astrocytes, microglia, and cytokines in modulating neuronal activity and synaptic plasticity mechanisms, sex differences in cytokine responses in the brain likely have important functional consequences on sex-specific immune modulation of learning and memory (Donzis and Tronson, 2014; Tronson and Collette, 2017).

Our recent data provide evidence that sex differences in the magnitude of cytokine response may have functional consequences on neuronal activity and learning and memory mechanisms. Specifically, we observed that central neuroimmune activation by poly I:C disrupts learning in both sexes of mice with preliminary evidence that sex-specific underlying hippocampal mechanisms are at play (Posillico et al., 2021). Given the sex differences in magnitude of cytokine expression in response to poly I:C and the ability for cytokines to modulate neuronal activity in numerous ways, our data implicate sex-specific mechanisms at the tripartite synapse as a root cause.

6. WALK THIS WAY: where do we go from here?

It is crucial that we not only consider, but integrate, the multitude of factors involved in long-lasting plasticity mechanisms in the hippocampus, including functions of astrocytes and microglia at the tripartite synapse during both healthy conditions and neuroinflammation, as well as the sex-specific mechanisms of hippocampal function and influence of locally produced estrogen.

To understand the role of neuroimmune signaling in synaptic plasticity, and modulation of memory during inflammation, there are several questions that need to be answered. Where are the key points of integration in all of these signals at the tripartite synapse? Which mechanisms of modulating neuronal activity described here supersede others during acute or chronic neuroinflammation and thus would dictate the net effects of glutamate transporter trafficking and gliotransmission? In studies of neuroimmune modulation of learning and memory, are the signals that activate astrocytes and microglia from neuronal activation similarly impacting the synapse as activation of astrocytes and microglia from neuroinflammation? How do the signals from acute or chronic neuroinflammation affect the ability of microglia and astrocytes to interpret activity from neurons during experience-dependent plasticity and learning? Since astrocytes are capable of *de novo* synaptic potentiation and enhancement of memory (Adamsky et al., 2018), does activation of astrocytes by neuroinflammation prime neuronal synapses in such a way to uniquely modulate synaptic plasticity during a learning event?

I have observed sex differences in the expression of anti-viral interferons following central administration of a viral mimic in mice (Posillico et al., 2021). Both IFNα and IFNβ have been shown to separately modulate glutamatergic signaling and transporter expression (Costello and Lynch, 2013; Mendoza-Fernández et al., 2000). Thus, sex differences in these cytokines might result in sex-specific changes to glutamatergic signaling that explain, at least in part, why pre-training poly I:C disrupts context fear conditioning in both sexes, but seemingly *via* different hippocampal mechanisms (Posillico et al., 2021). Given the vast evidence of sex differences at all levels from cells to behavior, it is highly possible that this signal transduction of neuroimmune and memory processes happens *via* sex-specific mechanisms, and this question must be at the forefront of our continued research if we hope to make meaningful sense of these multi-faceted complexities.

7. THE BEST IS YET TO COME: conclusion

Neuroimmune activation is known to play a role in cognitive deficits and affective dysregulation in Alzheimer's disease and other dementias (Krstic and Knuesel, 2013), Post-Traumatic Stress disorder (Pace and Heim, 2011; Wang and Young, 2016), depression (Bekhbat and Neigh, 2018; Hodes et al., 2015), and in COVID-19 (Zhou et al., 2020). We also know that there are sex differences in the prevalence, intensity, and/or outcomes of these debilitating disorders and diseases (Laws et al., 2018; Liu et al., 2020; Wan et al., 2020). Public health interest necessitates that we better understand the causes and implications of this so that we can develop novel, effective, and sex-specific treatments to either prevent or ameliorate the devastating consequences of these diseases. To this end, I propose that the future of psychoneuroimmunology research in the context of health and disease lies in understanding the signal integration and transduction between those from neuroimmune activation processes and required learning and memory mechanisms at the tripartite synapse in the hippocampus. Here, the best is yet to come.

Declaration of competing interest

The author, Caitlin Posillico, declares no conflicts of interest in the submission of this article.

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