Complex Neuroimmune Involvement in Neurodevelopment: A Mini-Review

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Abstract: It is increasingly evident that cells and molecules of the immune system play significant roles in neurodevelopment. As perinatal infection is associated with the development of neurodevelopmental disorders, previous research has focused on demonstrating that the induction of neuroinflammation in the developing brain is capable of causing neuropathology and behavioral changes. Recent studies, however, have revealed that immune cells and molecules in the brain can influence neurodevelopment without the induction of overt inflammation, identifying neuroimmune activities as integral parts of normal neurodevelopment. This mini-review describes the shift in literature that has moved from emphasizing the intrusion of inflammatory events as a main culprit of neurodevelopmental disorders to evaluating the deviation of the normal neuroimmune activities in neurodevelopment as a potential pathogenic mechanism.

Keywords: cytokine, glia, neuroinflammation, neurodevelopmental disorders

Introduction

Mammalian neurodevelopment is a complex and intricately regulated process that allows the formation of the mature central nervous system (CNS) that dictates the autonomic life-sustaining functions of the internal organs, controls motor activities of the muscles, performs cognitive assessments of the environment, and produces affective responses to emotional stimuli. This process involves the production1 and migration of neurons,2 elimination of unwanted neurons,3 formation and reshaping of neurocircuits,4 interaction and integration of glial cells,5-7 and incorporation of early life experiences into the maturation processes of the CNS.8,9 During neurodevelopment, both intrinsic and extrinsic factors could derail its proper course. Thus, perinatal injury or infection are well-known extrinsic risk factors that are associated with the development of psychiatric or psychological disorders later in life.10-12 These risk factors could produce significant pathology if they are combined with genetic mutations (intrinsic risk factors) that predispose the individuals to developmental mental disorders.13-16 A critical facilitator of neurodevelopmental diseases that has been spotlighted by recent research is neuroinflammation.17-21 Obviously, injury and infection of the CNS are likely to trigger neuroinflammation as part of the immune reaction to wounding and invading pathogens. The potential bystander damage a neuroinflammatory reaction might inflict upon the developing nervous tissue was thought to be an important pathogenic mechanism of neurodevelopmental diseases.22,23 Although this thesis was initially supported by animal models of relatively severe perinatal injury or infection/inflammation and by those of CNS inflammatory cytokine over-expression,24-27 frank inflammation in the CNS is not common in most neurodevelopmental diseases. Therefore, the influence of less blatant “neuroinflammatory” activities may be more important in causing most of the aberrant neurodevelopmental changes. New discoveries have now identified non-inflammatory neuroimmune activities in the regulation of physiological processes of the nervous system, suggesting that immune cells in the CNS, eg, microglia5 and T cells,28 and immune signal molecules, eg, cytokines,29-31 chemokines32,33 and complements34,35 are capable of modulating neuronal function and neuronal connectivity without eliciting the attendant traditional immunological or
inflammatory activities these factors were previously known for. In this mini-review, we will briefly summarize the history of research that has implicated neuroinflammation in neurodevelopmental diseases and discuss how current research has shifted its focus to a broader context that encompasses the impact of non-inflammatory neuroimmune activities on neurodevelopment.

**Origin of Immune-Driven Neurodevelopmental Diseases Theory**

The impact of immune activity on mental health might first have been deduced from historical observations that almost every form of CNS disease may follow an infectious epidemic. For example, various neuropsychiatric symptoms were noted as early as the years following the 1385 German Flu. Similar observations were made after the Russian Flu of 1889 and the Spanish Flu of 1918. Mental illnesses also appeared after infectious diseases caused by other viruses and bacteria such as HIV, Zika virus, and Group B streptococcus. Currently, the COVID-19 pandemic is well-known to cause long COVID symptoms which include many psychiatric comorbidities. As infections inevitably stimulate the immune system, an immune-driven pathogenic mechanism for CNS diseases may be surmised.

Not only may adults display psychopathic sequelae from infectious diseases, but their offspring also show higher rates of developing mental or neurological disorders. In addition, perinatal infection and childhood infection have been found to increase the risk of developing mental illness later in life. These findings point to the possibility that immune activation in the developing nervous system during the perinatal period or in early childhood could significantly influence neurodevelopment, thereby causing behavioral aberrations later in life.

This notion has been extensively tested in animal models of maternal immune activation (MIA) or perinatal immune activation (PIA). The majority of these studies used E. coli, lipopolysaccharide (LPS), or polyIC to stimulate immune activity in the fetal brain or in the postnatal CNS. LPS is a component of the bacterial cell wall and polyIC is a synthetic analog of viral double-stranded RNA. LPS and polyIC do not cause infection; rather, they induce immune activation, mimicking those induced by bacterial or viral infection, respectively. These studies clearly show that activation of the immune system without a true infection can alter neurodevelopment and produce behavioral phenotypes that resemble various neurological and psychological disorders. A common consequence of immune activation is the induction of cytokines. Cytokines are the communication molecules of the immune system that stimulate immune cell proliferation and the production of effector molecules designed to destroy and clear invading pathogens. Not surprisingly, MIA and PIA can drive increased expression of inflammatory cytokines in the developing brain. Further, the expression levels of inflammatory cytokines in these models often correlate with behavioral outcomes, and brain specific transgenic over-expression of inflammatory cytokines during development results in significant neurological pathologies. In addition, blockade of activities of inflammatory cytokines with their specific inhibitors can alleviate MIA- or PIA-induced neurological and behavioral changes. Thus, increased inflammatory cytokine expression in the perinatal brain has been considered a critical mediating event that derails neurodevelopment.

**Bystander Damage Hypothesis**

The mechanisms by which neuroinflammatory activities alter neurodevelopment remain poorly understood, although an obvious postulation is bystander damage. A full-blown inflammatory response should induce heightened expression of inflammatory cytokines, infiltration of immune cells to the infected or injured tissue, and the production of reactive oxygen species (ROS). Therefore, bystander damage to the developing brain from immune activation could occur if: (1) inflammatory cytokines at high levels are neurotoxic by themselves, (2) the recruited peripheral leukocytes can cause neuronal injury, and (3) ROS causes neurotoxicity. These three mechanisms may not be mutually exclusive. In in vitro culture systems, adding inflammatory cytokines, especially TNFa, were shown to cause neuronal death, sometimes via induction of ROS in glial cells. In addition, infiltrating neutrophils can cause neuronal death through the release of extracellular proteases. In vivo, these mechanisms are probably the cause of neuropathology found in transgenic animals with brain-specific over-expression of inflammatory cytokines. It should be noted that, while there is no doubt that bystander damage following frank CNS inflammation in the developing brain can cause neurological and psychiatric pathologies, it is often associated with gross structural changes in the brain, eg, enlargement of cerebral ventricles and reduced hippocampal volume. Although gross structural abnormalities have indeed been associated with
neurodevelopmental diseases,70,71 these changes are not obligatory for these disorders, suggesting that subtler immune-driven pathogenic mechanisms need to be investigated.

One important conceptual advance is the “two-hit” or “multiple-hit” theory. According to this theory, perinatal immune activation causes subtle changes in development, which prime the system such that, upon receiving a second “hit” simultaneously or later in life, pathological behaviors are finally elicited. An excellent example here is a body of work from Bilbo et al showing that neonatal infection with E. coli primed infected rats such that later a low dose LPS challenge induced memory deficit only in rats with the prior neonatal infection.72 They were also able to demonstrate that neonatal infection caused long-lasting re-programming of microglial cells in the brain that allows the second hit of a low dose of LPS to induce high levels of brain IL-1β that is required for the manifestation of memory impairment. A shortcoming of this specific two-hit theory is that the impact of the first hit directly on neural circuit development was not addressed. Other two-hit models exist. For example, transient blockade of glutamate neurotransmission together with early life social isolation (which could cause neuroimmune activation in the brain) can produce schizophrenia-like behaviors later in life.72 In addition, MIA cooperates with neonatal hypoxia ischemia to promote autism-like behaviors in offspring.73 These multiple-hit theories are also supported by clinical evidence showing that genetic risk factors and early life neuroimmune disturbances can combine to produce developmental psychiatric diseases.74-76 These studies also revealed that different risk factors (genetic, inflammatory, stress, nutritional) may combine at different time points of neurodevelopment to cause mental health disorders. A corollary challenge, however, is that there are a very high number of combinatorial possibilities for these “hits” and each type of “combinatorial multiple-hit” could represent a different pathogenic mechanism for a given disease, rendering discovering common underlining mechanisms difficult.

**Brave Neuroimmune World**

Recent advances in biotechnology have significantly improved our ability to observe and manipulate genes, proteins, cells and neural circuits. As a result, an unexpected revelation is that immune cells and immune molecules were found to have normal functions in the CNS outside of the context of immune stimulation. Rather than using the word neuroinflammatory to describe something associated with or evolved from injurious or infectious stimulations, the word neuroimmune is now employed to encompass entities and events related to non-inflammatory CNS functions executed by cells and molecules previously believed to belong to the immune system. In this new world of the neuroimmune system, microglia, astrocytes, mast cells, and T cells are recognized to modulate numerous aspects of neurodevelopment, whereas cytokines, chemokines, complements, and MHC molecules are found to participate in the homeostatic and circuit-organizing activities of the CNS. This broader perspective of neuroimmune integration invites a rethinking of how the immune system might impact neurodevelopment and related mental health disorders. Whereas the previous paradigms would primarily see increased neuroinflammatory activity as a risk, the current paradigm would also examine the deleterious effects of inappropriate down-regulation of neuroimmune activity. Further, low-level increase of neuroimmune activity, which does not result in frank inflammatory responses in the brain and is not caused by infection and injury, has been analyzed to uncover how deviation from homeostatic neuroimmune activities can produce significant neurodevelopmental deficits.

**Present but Different**

The CNS has long been considered a site of immunological privilege.77 Physically, most immune cells and immune signal molecules are prevented from entering the CNS by the blood–brain barrier (BBB).78 functionally, transplanted tissue that is rejected in the periphery may survive in the CNS, indicating a muted environment for immune activation.79 The notion of brain immunological privilege, however, does not translate to the absence of an immune system in the CNS.

The most abundant CNS immune cells are the microglia. These cells are closely related to peripheral macrophages and monocytes. They were initially considered to be derived from bone marrow hematopoiesis, similar to their peripheral counterparts. It is now established that most microglia originate in the yolk sac early in embryonic development.80 They then populate the primitive brain and co-evolve with the developing nervous system to adapt to this unique environment. A small percentage of microglia may still be derived from peripheral monocytes, especially when significant neurodegeneration is present in the brain.81,82 Furthermore, monocyte-derived microglia may produce higher amounts of
inflammatory cytokines and contribute more to the pathogenesis of neurodevelopmental diseases. Most of the CNS microglia display distinct phenotypes compared to peripheral monocytes. For example, microglia express low levels of the cell surface marker CD45, such that immunohistochemical labeling of CD45 generally stains infiltrating leukocytes but not microglia. In addition, although microglia are the primary producer of the inflammatory cytokine interleukin-1 (IL-1), they do not express the receptor for IL-1 (IL-1R) in the unstimulated brain, thus preventing autocrine amplification of inflammatory reaction that can be induced in the peripheral monocytes. Further, microglia may even mediate anti-inflammatory activities induced by peripheral LPS preconditioning. These findings suggest that microglia may perform similar inflammatory functions as peripheral macrophages, but at a somewhat temperate level. On the other hand, microglia are now discovered to modulate neural networks without the presence of inflammation.

The function of microglia in the normal brain was suggested by the finding that “resting microglia” are highly mobile; that is, their processes are constantly in motion to surveil the CNS environment. During development, neurons produced in excess undergo apoptosis and produce “find-me” signals to guide microglia to remove them. Interestingly, after phagocytosing dead neurons, microglia can also secrete factors to promote the genesis of new neurons, thereby modulating both life and death of neurons. In addition, developmental imbalance of excitatory/inhibitory circuit activity can lead to apoptosis of just the excitatory dendritic spines which are then deleted by activated microglia. An even finer modulatory modality is microglial synaptic pruning. An excellent body of recent work has established that microglia prune less efficient synapses in an activity-dependent manner. This process is guided by a specific synaptic “eat-me” signal, fine-tuned by inhibitory pathways to prevent inappropriate pruning, and mediated by opsonization of activated complement molecules. In the absence of neuroinflammation, such microglial synaptic pruning is an integral part of normal brain development and deficiency in neuron–microglia signaling in this process impairs neural connectivity and social behavior. Different from inflammation-triggered phagocytosis of the whole dead cell body, ultrastructural analysis found that microglia can focus their phagocytic activity just on the synapse by nibbling on the presynaptic structure and enveloping the postsynaptic spine head with filopodia. Even more exquisite is the phenomenon that under certain conditions microglia can displace inhibitory presynaptic terminals on neuronal cell bodies, thereby altering the functional characteristics of neurocircuits. Further, microglia-derived BDNF can play a role in promoting synaptogenesis, thus allowing microglia to modulate both the initiation and elimination of synaptic structures. Another way in which microglia influence neural function is that they can guide the migration of CNS precursor cells by secreting chemotactic factors for neural stem cells. These new findings demonstrate that these professional CNS immune cells have a gentler side: in addition to destroying invading pathogens and clearing debris and waste materials, they modulate neurotransmission and neural connectivity during development and in adult homeostasis. It is these non-inflammatory functions that are beginning to be recognized as critical activities that might be involved in the pathogenesis of neurodevelopmental diseases.

This new understanding has begun to be applied to studies investigating animal models of neurodevelopmental disorders. For example, Lebovitz et al used a mouse model of maternal microbiome dysbiosis (MMD) to cause social behavior deficits in offspring. These offspring also showed microglial dystrophy and increased Cx3cr1, a microglia-specific receptor, expressed in the prefrontal cortex, suggesting microglial dysfunction and altered microglia–neuron interaction. Treating the MMD dams with the probiotic Lactobacillus attenuated the MMD-induced social deficits in offspring and prevented microglial morphological dystrophy and the over-expression of Cx3cr1. In addition, Cx3cr1 knockout prevented MMD-induced social deficits in the offspring. No frank neuroinflammation was observed in this study, demonstrating in this model that altered non-inflammatory microglial function is the cause of neurodevelopment psychopathology. On the other hand, deletion of Cx3cr1 during the early postnatal period by itself resulted in deficient synaptic pruning, weak synaptic neurotransmission, and autism-like behaviors. Thus, changes in Cx3cr1 in either direction could result in developmental abnormalities, indicating that the neurophysiological functions of microglia, not just the neuroinflammatory activities of microglia, can be involved in the pathogenesis of developmental disorders.

**Other Neuroimmune Actors in Neurodevelopment**

While the neuroimmune functions of microglia are gaining prominence, other cells and microglia-interacting molecules are also emerging as critical neuroimmune influencers of neurodevelopment.

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**Citation:**


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**Additional Resources:**

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Astrocytes are the other major glial cells in the CNS. After CNS injury or infection, astrocytes are activated by inflammatory cytokines. In response, astrocytes can exacerbate or inhibit neuroinflammation depending on specific circumstances. For example, stimulation of the receptor of interleukin-1 (IL-1) on astrocytes could result in an inhibition of microglial production of inflammatory cytokines and reduce excitotoxic-induced neuronal apoptosis. On the other hand, during epilepsy, astrocyte activation can augment inflammation and increase neural damage. In homeostasis of the adult CNS, astrocytes regulate interaction between neuronal activity and brain microcirculation, neurotransmitter levels in synaptic clefts, extracellular K+ concentration, CNS water content, synaptogenesis and synaptic pruning. It is perceivable that these neuromodulatory functions of astrocytes could be altered by neuroimmune factors during neurodevelopment, thereby contributing to the pathogenesis of neurodevelopmental disorders.

Indeed, initial studies discovered that developmental astrocytes promote efficient synaptogenesis. Later, synaptogenic molecules produced from developing astrocytes such as thrombospondins (TSP1 and 2) and hevin were identified. Interestingly, TSP plays important roles in peripheral inflammation and injury, and hevin is involved in tissue remodeling, adding these molecules to the list of neuroimmune factors. In addition, transcriptomic analysis revealed that astrocytes express phagocytic pathway proteins and the two phagocytic receptors, Megf10 and Mertk, were found to mediate astrocytic synaptic pruning during development. Outside the context of normal neurodevelopment, astrocytic phagocytosis through these receptors is involved in the clearance of apoptotic neurons and debris during CNS tissue injury. Thus, astrocytic phagocytosis may also straddle two kingdoms: inflammatory astrocyte phagocytosis is part of post-injury tissue repair, whereas non-inflammatory astrocyte phagocytosis participates in neurodevelopmental synaptic structuring.

Another modality by which neuroimmune activities of the astrocytes can influence neurodevelopment is through cytokines and cytokine receptors. For example, astrocytic TGFβ can promote the formation of inhibitory synapses and astrocytic IL-10 receptor mediates a feedback inhibition of microglial activation, which indirectly impact neurodevelopment. Astrocytes can also produce the alarmin IL-33, which regulates microglial metabolism to facilitate synaptic pruning during development. In addition, astrocyte produced TNFa can mediate synaptic scaling in response to prolonged blockade of neuronal activity by regulating neuronal glutamate and GABA receptor trafficking. Whether this functional modulation of neuronal function by astrocytes is involved in the pathogenesis of neurodevelopmental disorders remains to be determined.

Consistent with the notion that multiple non-inflammatory neuroimmune activities of astrocytes might influence neurodevelopment, associational studies and animal models have now linked astrocyte dysfunction with several developmental disorders including intellectual disability, autism, and schizophrenia. Other immune cell types exist in the brain at extremely low levels. However, recent studies have found powerful influences of these cells on the functions of the brain. For example, antigen-reactive CD4+ T cells was found to support cognitive task performance and meningeal γδ T cells can regulate anxiety-like behavior via its production of IL-17a. The detailed mechanisms regarding how these T cell influences might impact neurodevelopment await further elucidation. Equally intriguing is the finding that mast cells in the developing preoptic area of the hypothalamus (POA) drive masculinization of the brain and inhibition of mast cells in the POA during the critical period for sexual differentiation which blunts neuronal and microglial changes in this region and adult sex behavior. Most likely, these rare immune cells influence the developing brain by releasing neural active immune molecules at low levels that do not result in the frank inflammatory responses that they typically induce in the periphery.

There is also an expanding list of classical immune molecules that are now recognized to participate in the development of the nervous system. For example, chemokines that were traditionally known for their chemotactic activities in leukocytes were found in mothers’ milk to promote postnatal hippocampal neuronal proliferation in offspring and the critical antigen presentation molecule MHC was found to modulate synaptic plasticity during development and its CNS expression to be regulated by neuronal activity. Furthermore, the complement system, which was known to opsonize and destroy invading pathogens or infected cells in an immune response, has now been established to play important roles in mediating synaptic pruning by glial cells. Again, the complement system behaves differently in the non-inflammatory brain from its action in the periphery, which would cause chemotactic effects.
from activated complement fragments and attack a complement-marked whole cell rather than a small portion of a cell (synapse). These neuroimmune molecules have also been identified in human studies as risk factors for the pathogenesis of neurodevelopmental disorders such as schizophrenia and autism.\textsuperscript{134,135}

**Concluding Remarks**

This mini-review is not meant to provide an exhaustive survey of all the neuroimmune elements involved in neurodevelopment. Rather, we wanted to sketch a broad outline of how this field has evolved and point out the important conceptual shift that is occurring in current literature. In contrast to the overt inflammatory activities in the brain, many non-inflammatory neuroimmune modulations of different aspects of neurodevelopment – from neuronal proliferation and migration to synaptogenesis and synaptic pruning – have been discovered (Figure 1). Relevant references are also presented in Table 1 for easy visualization. One emerging salient question is why do these non-inflammatory neuroimmune activities not induce full-blown inflammatory responses as they would in peripheral immune responses? There are several possibilities: (1) neuroimmune cells have different characteristics (eg, microglia are transcriptomically quite different from macrophages\textsuperscript{136}) to their peripheral counterparts or reside outside of brain parenchyma (eg, T cells are mostly found in the glymphatic system in the meninges\textsuperscript{137}); (2) some of the collaborating immune system elements might be missing in the CNS parenchyma (eg, few professional antigen-presenting cells are found in the brain parenchyma, allowing MHC molecules to function outside the context of antigen presentation\textsuperscript{138}); and (3) alternative signaling systems might be deployed in the CNS (eg, alternatively spliced IL-1 receptor accessory protein is expressed in neurons, diverting IL-1 stimulated inflammatory gene expression to neuronal-specific activities\textsuperscript{139}). These possibilities suggest novel mechanisms to explain why neuroimmune activities in the developing brain may not simply cause traditional inflammatory responses but engender CNS-specific roles to influence neurodevelopment too.

**Figure 1** Schematic diagram showing neuroimmune activities involved in neurodevelopment. Microglia and astrocytes play a role in appropriate neurodevelopment and contribute to the pathophysiology of neurodevelopmental diseases. In frank inflammation, which is stimulated by perinatal immune activation, astrocytes and microglia are activated by immune stimulus. This activation leads to production of proinflammatory cytokines (TNFα, IL-1β) and damage to the blood-brain barrier. Infiltration of immune cells to the brain parenchyma together with astrocyte and microglial activation results in neuronal damage. Under physiological conditions, astrocytes and microglia play critical roles during neurodevelopment and homeostasis. Astrocyte- and microglia-driven cytokines regulate 5 critical processes of neurodevelopment that are crucial for developing a healthy brain: neuronal proliferation, synaptogenesis, synaptic pruning, neuronal migration, and neural circuitry regulation. Created with BioRender.com.
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<th>References</th>
<th>Finding</th>
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<th>Outcome</th>
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<tr>
<td>Han et al, 2021¹⁷</td>
<td>Astrocyte-derived cytokine expression regulates microglia homeostasis and microglial synaptic pruning</td>
<td>Yes</td>
<td></td>
<td>Neural circuit refinement</td>
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<td>Vainchtein et al, 2018³⁰</td>
<td>Astrocytes regulate microglial metabolism to contribute to synaptic pruning</td>
<td>Yes</td>
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<td>Liu et al, 2019³⁸</td>
<td>Astrocytes can influence microglial activation and production of inflammatory cytokines</td>
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<td>Sokolowski et al, 2014²⁷</td>
<td>Microglial elimination of neurons undergoing apoptosis is guided by “find-me” signals</td>
<td>Yes</td>
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<td>Diaz-Aparicio et al, 2020</td>
<td>Microglia promotes neurogenesis by secreting factors such as BDNF</td>
<td>Yes</td>
<td></td>
<td>Increased neuron production</td>
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<td>Parellada et al, 2021⁹⁰</td>
<td>Microglia is a driver of excessive dendritic pruning and dendritic apoptosis</td>
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<td>Imbalance of excitatory/inhibitory circuit activity</td>
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<td>Schaffer et al, 2012⁹¹; Hong et al, 2016⁹²; Scott-Hewitt et al, 2020⁹³; Lehrman et al, 2018⁹⁴</td>
<td>Microglial synaptic pruning is guided by “eat-me” signals</td>
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<td>Zhan et al, 2014²⁷</td>
<td>A reduction of microglia during the early postnatal period results in a synaptic pruning deficit</td>
<td>Yes</td>
<td></td>
<td>Impaired functional brain connectivity and deficits in social interaction</td>
<td>Deficits in social interaction is a common manifestation of many neurodevelopmental diseases</td>
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<td>Weinhard et al, 2018⁸⁸</td>
<td>Microglia remolds synapses by interfering with pre- and post-synaptic connections</td>
<td>Yes</td>
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<td>Synaptic circuit remodeling and maturation</td>
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<td>Aarum et al, 2003¹⁰²</td>
<td>Microglia can direct migration and differentiation of neural precursor cells</td>
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<td>Directing the replacement of damaged or lost cells in the CNS during neurodevelopment</td>
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<td>Lebovitz et al, 2019¹⁰³</td>
<td>Microglial dysfunction leads to impaired synaptic remodeling</td>
<td>Yes</td>
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<td>Social deficits due to dysfunction of microglia</td>
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<td>Todd et al, 2019¹⁰⁵</td>
<td>Microglia can provide protection to neurons</td>
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Table 1 (Continued).

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<td>Astrocytes regulate the innate immune responses in epilepsy</td>
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<td>Christopherson et al, 2005</td>
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<td>Chung et al, 2013</td>
<td>Astrocytes help mediate synapse elimination</td>
<td>Yes</td>
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<td>Li et al, 2022</td>
<td>Impairment of astrocyte-derived ATP is an etiological factor for neurodevelopmental disorders</td>
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<td>Autism spectrum disorder-like behavior</td>
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<td>Gravina et al, 2022</td>
<td>Impairment of astrocyte-mediated synaptic pruning</td>
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<td>Wang et al, 2022</td>
<td>Astrocytes contribute to intellectual disability via the inflammatory response</td>
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Disclosure
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