

Impact of Microglia in Neurodevelopmental Disorders: A Review

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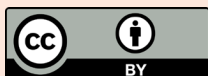
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ABSTRACT

OBJECTIVE Microglia, immune cells that dwell in the brain, have essential functions in neurodevelopment and are responsible for synaptic pruning, neuronal circuit creation, and inflammatory responses. Disrupted microglial activity can contribute to conditions such as autism spectrum disorders, schizophrenia, and ADHD by impacting the health and connections of neurons through the production of pro-inflammatory cytokines. These cells, which arise during central nervous system (CNS) development and have the ability to regenerate themselves throughout an individual's lifespan, display considerable functional variation. Microglia, which have traditionally been known for their immunological functions, also play a role in regulating neurodevelopmental processes such as programmed synaptogenesis, synaptic pruning and cell death. Recent genetic and pre-clinical research indicates that abnormalities in microglial activity can result in a range of neurological health, varying in intensity from moderate to severe. The critical function of microglia in the development of the CNS is determined by their interactions with neurons and other glial cells, that have an impact on the structure of synapses and on the formation of new neurons. This review aims to fill gaps in earlier research by examining the diverse nature of microglial cells and their crucial functions in the development of the nervous system. It specifically focuses on current discoveries related to the rearrangement of synapses, the regeneration of neurons, and the impact of environmental stimuli. Comprehending these interactions is essential for creating precise treatments for neurodevelopmental diseases, emphasizing the necessity for ongoing investigation into microglial processes and measures to reduce their negative impact on brain development.

KEYWORDS microglia in synaptic; neural regeneration, neurodevelopmental disorders, environmental changes and brain development

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INTRODUCTION

Microglia, which are highly motile and attentive macrophages located in the brain, constitute a substantial percentage of neuroglia in the central nervous system (CNS). These cells, which are

created during the formation of the CNS, have the ability to renew themselves throughout an animal's lifespan, therefore sustaining their numbers in healthy tissues (1). Microglia are primarily recognized for their immunological tasks, including

the removal of pathogens and debris by phagocytosis, as well as their involvement in inflammatory responses during neurodegenerative illnesses. However, they also have essential roles in the formation, maintenance, and restoration of the CNS (2). Microglia, which are important regulators of the brain's microenvironment, display molecular and state-specific functional diversity across the CNS. Our comprehension of this variability is now in its nascent phase. The lack of healthy microglia can lead to a variety of repercussions, ranging from minor dysregulation of microglial status to severe pediatric-onset leukoencephalopathy, as shown by recent findings from human genetic studies and preclinical (3). During steady conditions, microglia serve as the main immune cells in the CNS. These myeloid cells, known as macrophages, have a role in several processes inside the CNS, such as regulating inflammation, combating infections, and eliminating cellular waste through phagocytosis (4). In addition to their conventional functions, current studies have emphasized the significance of microglia in intricate neurodevelopmental processes. Throughout these processes, their phagocytic and signalling functions play a crucial role in 1) controlling programmed cell death to determine the destiny of neurons, 2), stimulating the growth of neurites, the formation of synapses, and the bundling of axons, and 3) removing surplus synapses from developing neurons to facilitate the creation of functional neural circuits. Microglia originate uniquely, enabling them to occupy a specific niche as resident macrophages in an area that is usually considered immune-privileged. Research on the origins of microglia has demonstrated that they mostly come from yolk-sac erythromyeloid progenitors (5). These progenitors migrate to the developing neuroepithelium and settle in the CNS. Despite the prior assumption that macrophages may change their gene expression in response to their surroundings, bone marrow-derived macrophages (BMDMs) do not acquire the same gene expression profile as microglia when they enter the brain tissue (6). In mice, microglia have been eliminated by using diphtheria toxin under the CX3CR1 promoter and by blocking the CSF-1 receptor, which is necessary for microglial survival and is also found in other macrophages (7). Manipulating microglia makes them a great target for studying

the etiology of neurodevelopmental diseases. Microglia, the macrophages that live in the CNS, are recognized for their functions in combating infection, eliminating cellular waste, and preserving tissue equilibrium. In addition to their conventional immune roles, microglia also participate in complex neurodevelopmental processes, including neurogenesis and synaptic pruning (8). During these activities, glial cells engage in interactions with neurons and other glial cells offer nourishing support, react to cytokine and metabolic signals from the nearby neural environment, and assist in refining functioning neuronal circuits. Microglia, the immune cells that live in the CNS, which includes the brain, spinal cord, and retina, were initially identified as innate immune cells responsible for protecting against bacterial and viral invasions inside the CNS (9). Microglia were initially believed to predominantly participate in pathological circumstances such as aging, chronic stress, and Alzheimer's disease by facilitating neuroinflammatory processes. Although several activities of microglia in the adult brain have been identified, there has been very limited study on their roles in the embryonic brain (10). These cells move around a lot in the developing brain wall and interact with nearby neural lineage cells (neural progenitors and mature neurons) and vascular endothelial cells. Microglia engage in extensive patrolling to carry out many activities during the processes of neurogenesis and vascular formation in development (11).

THE ROLE OF MICROGLIA IN SYNAPTIC RECONFIGURATION

Microglia have a crucial role in building functioning neuronal circuits by exerting influence on synaptogenesis, synapse development, and synaptic activity. Recent research has shown novel ways in which microglia influence the functioning of synapses in different cellular, geographical, and temporal situations. For instance, in prenatal animals lacking microglia, certain neocortical Lhx6+ inhibitory interneurons may not be appropriately situated in the lamina, which is essential for the functioning of the circuit (12). Microglia have the ability to directly contact the dendrites of pyramidal neurons in the somatosensory cortex. This interaction leads to the deposition of actin and an increase in calcium ion transients. As a

result, it promotes the production of filopodia and spines (13). The number of spines and the development of excitatory synapses are reduced by pharmacologically inhibiting microglia. In addition to this intricate nature, the reduction of microglia in adult mice results in a rise in the quantity of synapses and intensifies the functioning of both excitatory neurons and inhibitory parvalbumin interneurons in the visual cortex (14). The apparent inconsistencies in these findings highlight the significance of examining the variations in time and space of microglia during their maturation. The reciprocal interplay between microglia and neurons is an additional key element in regulating synaptic activity. Adolescent mice have hippocampal neurons that become active and release IL33 (15). This IL33 then causes microglial cells to change the structure of their spines and engulf the extracellular matrix. As a result, the frequency of excitatory postsynaptic currents increases. Further research, utilizing different genetically modified mouse models to disturb the balance of microglial cells throughout the development of the CNS, has shown that microglia have a crucial function in inhibiting neuronal activity in a way that is reliant on ATP to prevent excessive activation and seizures (16). These investigations indicate that the process of synaptic pruning by microglia has a function in protecting the neurons. Reactive microglia in adult mice physically damage inhibitory presynaptic terminals in the somata of cortical neurons. Microglia controls the formation and modification of synapses in both normal and diseased conditions through several processes, which are determined by their specific cellular, geographical, and temporal contexts. Glial biologists have shown that microglia have important functions in the development of the brain, especially at the key periods when synaptic pruning occurs in areas like the retinogeniculate system and the hippocampus (17). Studies on microglia in the retinogeniculate system have resulted in the formulation of a "punishment model." This model proposes that neuronal synapses that are weaker or less functioning do not provide a defensive chemical signal, rendering them vulnerable to being swallowed by microglia. Phagocytic cells eliminate less robust synapses in order to build efficient synaptic circuits. Through ongoing improvements, this model has become more precise.

Recent research suggests that microglia, under the influence of interleukin-33 (IL-33) released by astrocytes, also play a role in synaptic pruning in the reticular thalamic nucleus and in the hippocampus (18). Microglia can be considered a heterogeneous population *in vivo* due to the impact of environmental signals on macrophage activity and the distinct molecular environments of various areas within the CNS. Hence, a comprehensive method for comprehending glial-glial and neuronal-glial communication is insufficient. Microglial traits, including their morphological complexity, motility, electrical properties, and transcriptional profiles, differ depending on their location. It is hypothesized that deficiencies in synaptic pruning have a role in illnesses such as autism spectrum disorder (ASD) and schizophrenia (19). These disorders are characterized by either excessive or insufficient connections in areas such as the amygdala, prefrontal cortex, and components of the default mode network. Neuronal dopaminergic signalling plays a crucial role in reward-seeking and social behavior. In adolescent male rats, a lack of microglial clearance of (Dopamine Receptor D1 has been associated with decreased social play and exploration. This suggests that microglia are involved in behavioral outcomes via refining synaptic connections.

MICROGLIA'S ROLE IN NEURAL REGENERATION PROCESSES

Microglia are thought to have a vital role in neurogenesis, which encompasses the process of precursor cells transforming and developing into neurons. These cells play a crucial role in removing waste material, which is important because of the programmed cell death that occurs during the formation of new neurons (20). Studies investigating the involvement of microglia in the process of neurogenesis commonly utilize laboratory techniques conducted outside of a living organism or focus on the development of new neurons in adult organisms. This is due to the challenges associated with researching embryonic systems. Published reports have shown that microglia play a crucial role in important elements of neurogenesis by engaging in phagocytosis and signalling activities, as well as by regulating inflammation within the central nervous system. It is postulated that disturbances to the microglial transcriptome,

particularly decreased phagocytic activity, may impede synaptic refinement or support for neurogenesis, perhaps resulting in aberrant synaptic connections or alterations in the survival of migratory neuroblasts (21). Recent research has emphasized important connections between microglia and (Neural precursor cells) NPCs, which have a considerable impact on neurogenesis and the general development of the brain in vertebrates. Microglia control the process of generating new neurons during brain growth in different parts of the brain by engulfing and digesting cellular debris. Microglia in the subgranular zone engulf apoptotic neuroblasts during the early postnatal period in order to regulate their incorporation into hippocampal circuits. While the specific processes behind microglial selection of NPC phagocytosis remain unclear, a growing amount of data suggests that microglial released substances have a role in controlling NPCs and neurogenesis to facilitate brain growth. When murine NPCs are cultivated in isolation, they lose the capacity to generate specialized neuroblasts (22). However, this ability is regained when they are cultured along with microglia or are exposed to a medium conditioned by microglia. These findings demonstrate how microglia regulate the formation of NPCs and neurogenesis through both phagocytic and secretory processes. Further investigation into the reciprocal communication mechanisms, whether by secretion or other means, that are involved in phagocytosis will provide a clearer understanding of the intricate connections between NPCs and microglia throughout the development of the nervous system. Reactivating microglia in the retina has been shown to result in a limited recovery of neurogenesis. Recent research has

demonstrated that microglial processes form distinct connections with the cell bodies of growing neurons during the embryonic, early postnatal, and adult phases of neurogenesis (23). The interaction between microglia and immature neurons in the growing brain and the impact of these interactions on the complexity of neural networks in the adult brain exists. Additional investigation is required to elucidate the exact cellular communication channels by which microglia influence neuronal growth and the establishment of neural networks. (Figure 1)

MICROGLIA AND THEIR CONTRIBUTION TO NEURODEVELOPMENTAL DISORDERS

Although there is evidence of sexual dimorphism in adult microglia and variations in microglial activity depending on sex, it is still unclear whether genetic sex differences or sex hormones have an impact on microglial specifications. Studying the impact of gender on microglia is essential for comprehending the gender-related prejudices that play a role in different neurodevelopmental and neurodegenerative illnesses (24). External variables can have a substantial impact on the maintenance of microglial homeostasis. Gut-brain interactions have an impact on the states and activities of microglia. Prenatal mice that are reared in germ-free surroundings exhibit changes in the growth and maturation of microglia which differ depending on the sex and brain area (25). The ingestion of omega-3 fatty acids by the mother is crucial for the development of the hippocampus in children. This growth is aided by the process of microglial phagocytosis. A new study has discovered a distinct subgroup of microglia in mice called capillary-associated microglia.

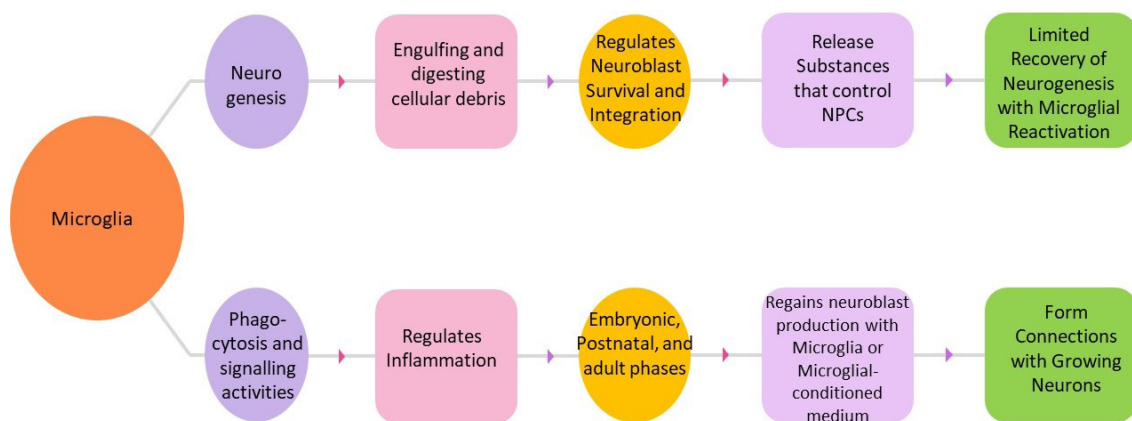


Figure 1. Role of microglia in the neural regeneration processes

These microglia are found along brain capillaries and have a role in controlling vasodilation and blood flow (26). Microglia can enhance vessel sprouting in murine aortic ring cultures by releasing secreted factors. The involvement of microglia in embryonic angiogenesis is intricate and encompasses several processes, presenting numerous opportunities for future exploration of the interactions between microglia and endothelial cells in neurodevelopment. Early-life infections and inflammation can disturb delicate neurodevelopmental processes, leading to developmental impairments seen in neurological illnesses such as autism spectrum disorders (ASD) and schizophrenia (27). Investigations investigating of the function of microglia in neurogenesis frequently depend on *in vitro* techniques or examinations of adult neurogenesis, mostly because of challenges associated with embryonic systems. Research has demonstrated that the pro-inflammatory cytokine IL-6 is significantly involved in causing neurodevelopmental impairments. When IL-6 is administered alone, it can lead to the development of pathological conditions. However, the negative effects of maternal immune activation (MIA) can be reduced by using IL-6 neutralizing antibodies (28). Although MIA has its difficulties and restrictions, it is a valuable tool for investigating the immune-related origins of neurodevelopmental diseases until more efficient developmental neuroimmunological models are established. Recent meta-analyses have demonstrated a male sex bias in both ASD and schizophrenia (29). These conditions can be replicated in rats. Behavioural assessments conducted in these animal models primarily evaluate characteristics associated with ASD or schizophrenia, including ultrasonic vocalizations, social interactions, repetitive behaviors, and anxiety. The diagnostic criteria for schizophrenia are hallucinations, delusions, disordered speech, and catatonia. Although MIA mice have some characteristics associated with autism, such as impairments in social interaction, communication, and repetitive activities, it is difficult to apply these results to more intricate neurological illnesses. However, MIA remains a helpful method for studying the immune-related causes of neurodevelopmental disorders.

EFFECTS OF ENVIRONMENTAL CHANGES ON MICROGLIAL ACTIVITY

A recent study suggests that elevated maternal inflammation during pregnancy is associated with diverse psychosocial consequences in children throughout their life. Research using direct measures of inflammatory activation has established a link between maternal infection exposure during pregnancy and an increased likelihood of children having mental disorders, including autism, schizophrenia, bipolar disorder, and major depressive disorder. Mouse models of maternal inflammation generated by LPS treatment was used to uncover alterations in gene expression in newborn microglia in comparison to control groups treated with saline. According to the study conducted on the impact of the presence of harmful substances in the environment and socioeconomic circumstances experienced during pregnancy found that they resulted in long-lasting behavioral problems and alterations in brain network activity associated with social interactions in male offspring (30). These effects were linked to the disrupted process of microglial synapse pruning. Nasu-Hakola disease (NHD), characterized by early-onset cognitive dementia, is associated with the absence of a functioning Trem2 signaling pathway, highlighting the significance of microglial activity in brain development (31). Moreover, new research has linked maternal environmental variables, such as viral or bacterial infections, atypical immunological responses, and dietary circumstances, to anomalous fetal brain development and neurological problems in children. For instance, when pregnant mice were administered poly(I) on day 12.5 of their pregnancy, microglia in the brains of the fetuses from day 16 showed a notably increased production of IL-6 compared to microglia from control mice that were not treated (32). In order to reduce the likelihood of neurological diseases in children that are linked to inflammation in the mother, further investigation is required to comprehend the effects of MIA and environmental elements on fetal microglia. The chromatin alterations and enhancer selections in tissue microenvironments have an impact on the transcriptional control of local microglial phenotypes. Although there is evidence of sexual differences in adult microglia and variations in their behavior depending on sex,

external variables may be important in preserving microglial homeostasis, e.g., the way stomach and brain communication affects the states and activities of microglia. In particular, prenatal mice that are germ-free have compromised growth and maturation of microglia, with variations seen based on sex and brain location. Furthermore, it is crucial for human mothers to consume omega-3 fatty acids in order to promote the growth of the hippocampus in their children. This development is assisted by the process of microglial phagocytosis, as stated. Various studies have examined other environmental elements that may impact microglial homeostasis (33).

MICROGLIAL CONTRIBUTIONS TO BRAIN DEVELOPMENT

Microglia, driven by their geographical and temporal diversity, have a crucial impact on the formation of the developing brain. They promote brain growth and regulate homeostasis by engaging in complex interactions with many types of brain cells, both neuronal and non-neuronal (34). Microglia have a role in several elements of blood vessel generation throughout the development of the CNS. Microglia have been observed in close proximity to recently developed blood vessels in both animal models and people, as shown by initial imaging investigations (35). NPCs play a crucial role in the production of both neurons and several types of glial cells (36). The initial examination of microglia during typical development and their subsequent participation in cell death in mice and birds emphasized their function in molding the developing CNS. Additional investigation employing inducible genetic targeting methods would be beneficial in validating these findings, considering the current limited comprehension of the efficacy and permeation of inhibitory antibodies in brain tissue during embryonic and postnatal periods. While the precise processes behind microglial phagocytosis of NPCs remain incompletely understood, mounting evidence suggests that substances produced by microglia play a vital role in regulating NPCs and neurogenesis, hence promoting brain growth. Murine NPCs undergo a loss of neuroblast production when grown alone. However, this capacity

may be regained by co-culturing the NPCs with microglia or microglial-conditioned medium. Microglial colonization and mobility rely heavily on blood vessels, whereas microglia, in turn, aid in the creation of blood vessels. The proper growth of retinal blood vessels relies on the presence of a substantial number of resident microglia. In mouse models of ischemic retinopathy, a drop in microglia is found along with the typical decline in vasculature throughout the postnatal period (37). Furthermore, research has demonstrated that at the 15th week of gestation, when the development of retinal blood vessels is just commencing from the optic disc, in the human embryonic retina microglia may be found throughout the whole retinal surface (38). Studies of the brain during the neonatal and adult stages have shown that microglia are involved in several aspects of vascular development, such as extending blood vessels, creating branches and regulating their width, promoting blood flow circulation, and maintaining the integrity of the blood-brain barrier. But, there is a scarcity of studies about the role of microglia in the developing brain during the embryonic stage (39). Studying microglial activity during this early period might offer valuable information on the effects of abnormally active microglia on the development and function of blood vessels in the fetal brain (Figure 2). Research on microglia in neurodevelopmental disorders, including ASD and schizophrenia, has increasingly highlighted the therapeutic potential of targeting microglial dysfunction. Studies have revealed that aberrant microglial activity can disrupt synaptic pruning, brain connectivity, and neuroinflammation, all contributing to disease pathology. Clinical trials are currently exploring microglia-modulating drugs, such as minocycline and other anti-inflammatory agents, to address these disruptions. For example, a 2022 pilot study on minocycline in ASD patients showed reduced inflammatory markers and improved behavioral symptoms in 30% of participants (40). Long-term clinical data are needed, but initial results support the viability of precision-targeted therapies in managing symptoms, promoting neuroprotection, and minimizing side effects in neurodevelopmental disorders.

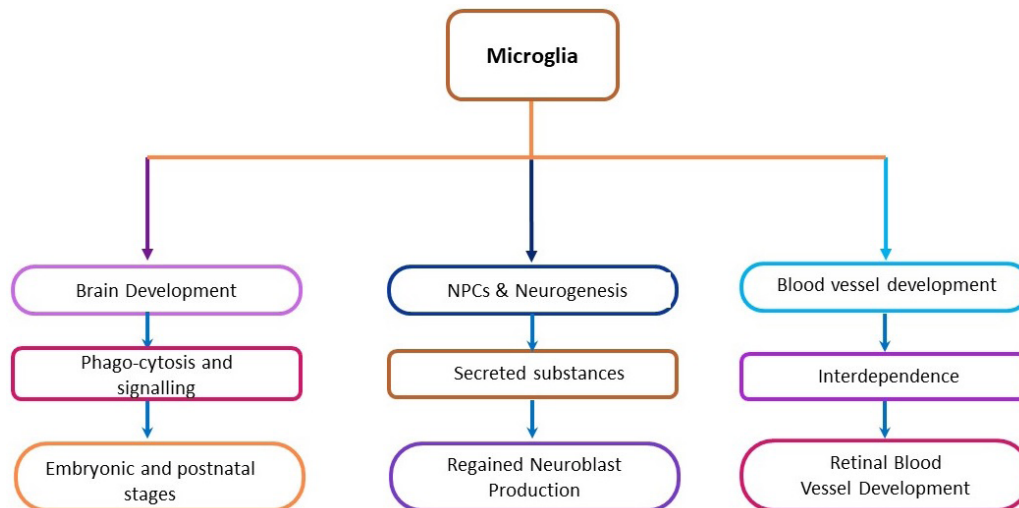


Figure 2. Microglial contributions

CONCLUSIONS

Microglia play a crucial role in the growth, up-keep, and restoration of the CNS. They perform a diverse range of tasks, including immunological responses and the regulation of neurodevelopmental processes. The diverse functionality of microglia, influenced by molecular and environmental variables, highlights the intricate nature of their significance in the CNS. The current review highlights the significant influence of microglial dysregulation on neurological well-being, establishing a connection between it and illnesses such as ASD, schizophrenia, and other neurodevelopmental disorders. Moreover, the interplay between microglia and external stimuli, such as maternal inflammation and nutritional variables, elucidates the wider framework within which these cells function. Future research should prioritize the investigation of the precise processes by which microglial cells function and interact with other cells in the CNS.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

ADDITIONAL INFORMATION

Author contributions

P.L.: conceptualization; D.S.K., P.V.: data curation; S.B.: writing—draft preparation; S.D.: original draft preparation, review and editing; D.S.K.: supervision.

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