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Review Article

From Immune Sanctuary to Neurological Battlefield: The Role of Neuroimmune Cells

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Abstract

The brain, traditionally regarded as immune-privileged due to the blood-brain barrier, harbors a sophisticated immune system crucial for maintaining neural health and resilience against various challenges. Microglia, the resident immune cells of the central nervous system, actively monitor their environment, participating in immune surveillance, synaptic pruning, and neuroprotection. Astrocytes also play vital roles by regulating neurotransmitter levels, supporting metabolism, and maintaining the blood-brain barrier integrity. Recent research underscores the involvement of T cells and monocytes in modulating neuroinflammation and immune responses within the brain. Neurological disorders such as Alzheimer's and Parkinson's disease highlight the brain's vulnerability to immune dysregulation. This review aimed to elucidate the role of neuroimmune cells in brain health and the progression of neurological diseases. It aimed to identify critical mechanisms to enhance therapeutic strategies and improve outcomes. Understanding these interactions is essential for developing targeted therapies to mitigate neuroinflammation and preserve cognitive functions. This review critically examines neuroinflammation related to aging and disease, with a focus on neuroimmune cells and their underlying mechanisms. It highlights how chronic inflammation, driven by activated microglia and astrocytes, exacerbates neuronal damage, synaptic dysfunction, and cognitive decline. The disruption of immune privilege in these conditions involves complex pathways that trigger inflammatory responses, impairing essential neural functions. Despite its immune-privileged status, the brain's immune system, primarily involving microglia and astrocytes, is crucial for maintaining homeostasis and managing illness. Our review strongly suggests that neurological diseases, influenced by genetic, environmental, and aging factors, often involve heightened neuroinflammation. Targeted therapies are needed to address infections, chronic inflammation, and environmental impacts. Additionally, research into mental health disorders and advancements in imaging techniques are critical for understanding immune dysfunction and enhancing treatment strategies.

Introduction

The brain is a marvel of complexity, with its functions governed by intricate networks of cells and molecules. At its core lies a unique immune system that safeguards the central nervous system (CNS) from external threats. Central to this defense are microglia, specialized immune cells strategically positioned within the CNS, acting as vigilant sentinels that swiftly detect and eliminate abnormal cells or pathogens.[1–4] This ability is crucial for maintaining the brain's immune privilege—a phenomenon where tissue transplanted into the brain parenchyma can persist without eliciting the immune responses seen in peripheral tissues.[5,6]

This immune privilege is further reinforced by the blood-brain barrier (BBB), a robust barrier formed by endothelial and glial cells that selectively permits the passage of essential nutrients and molecules while rigorously excluding toxins and pathogens.[7–9] Unlike many other organs, the brain has a limited lymphatic system, reducing its exposure to circulating immune cells and antigens that could trigger immune responses.[10–12]

However, despite these formidable defenses, the narrative of the brain's immune response is evolving. Alzheimer's diseases (AD) and Parkinson's diseases (PD), characterized by progressive neuronal dysfunction and cognitive decline, challenge the brain's immune privilege.[12–14] Similarly, autoimmune disorders such as multiple sclerosis (MS), driven by immune attacks against self-antigens within the CNS, lead to significant neurological impair-

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ment.[15–17] Additionally, infectious agents capable of breaching immune barriers can provoke inflammatory responses, resulting in a spectrum of neurological complications, from acute encephalitis to chronic neurodegeneration.[18–20]

This evolving understanding challenges the traditional view of the brain as an immune-privileged organ, highlighting the dynamic role of the immune system in both brain health and disease. In essence, the immune system is both the brain's best ally and its adversary, embodying a double-edged sword. While it protects the brain from infections and aids in tissue repair, it can also trigger autoimmune diseases and cause inflammation that drives neurodegeneration.

Thus, the once tranquil concept of immune privilege gives way to a vivid portrayal of conflict—a battleground within the intricate landscape of the nervous system. This shift prompts deeper exploration into the enigmatic interplay between the brain and the immune system, aiming to unravel the complex mechanisms underlying the development of neurological disorders.

The changing landscape of brain diseases underscores a significant shift in our understanding of their immune implications. Once viewed as an immune-privileged domain, the brain and its complex neural networks now emerge as dynamic arenas where the immune system plays a crucial role. This transformative paradigm challenges conventional viewpoints while presenting new avenues for research and therapeutic strategies.

By embracing this new understanding, we can unlock deeper insights into neurological disorders and pave the way for more effective treatments, offering hope to millions affected by these complex conditions.

Building on this foundation, this article explores the brain's immune system, illustrating how its dysregulation can lead to neurological disorders, autoimmune diseases, and brain infections. By examining the underlying immune mechanisms, we aimed to provide a comprehensive understanding of these complex interactions and their implications for brain health.

Neuroimmune cells and their roles in brain health

The brain, traditionally viewed as "immune-privileged" due to the BBB and lack of conventional lymphatic drainage, actually hosts a diverse array of immune cells that are crucial for maintaining homeostasis, responding to injury, and defending against pathogens.[1–6] These immune cells include microglia, astrocytes, perivascular macrophages, dendritic cells, and, under specific conditions, infiltrating peripheral immune cells such as T cells and B cells.[21–25]

Microglia, which originate from yolk sac progenitors during embryonic development, are the primary resident immune cells in the CNS, comprising about 80% of the brain's immune cells. They continuously survey the brain parenchyma through highly motile processes, monitoring for signs of damage, infection, or abnormalities.[21–25] Upon detecting such threats, microglia become activated, transitioning through various activation states (from M1-like to M2-like) and releasing pro-inflammatory cytokines to mount an immune response. Beyond immune defense, microglia play a critical role in synaptic pruning during brain development, refining neural circuits by eliminating excess synapses and optimizing connectivity.[26–28]

In addition to their role in synaptic pruning, microglia are now recognized for their involvement in modulating neurogenesis and maintaining brain plasticity throughout life.[29,30] Recent research has shown that microglia influence the generation of new neurons in the hippocampus, a key region for learning and memory, by interacting with neural stem cells and regulating the microenvironment necessary for neurogenesis.[31,32]

Moreover, microglia contribute to brain plasticity by responding to and shaping experiences and learning processes, ensuring that neural circuits adapt to new information and experiences. This dynamic role in supporting brain plasticity underscores the importance of microglia not only during development but also throughout adulthood.[29–32]

Astrocytes, derived from neural progenitor cells, are another predominant CNS cell type. They provide metabolic support to neurons, maintain BBB integrity, regulate neurotransmitter levels, and modulate immune responses by producing cytokines and chemokines. This multifunctional role positions astrocytes as integral players in brain homeostasis and immune regulation.[33–36]

Recent research has advanced our understanding of astrocyte differentiation into two distinct reactive forms: A1 and A2 astrocytes. A1 astrocytes, which arise in response to severe or chronic brain damage, release a range of cytotoxic substances, including inflammatory cytokines and reactive oxygen species (ROS).[37,38] These harmful factors can lead to the death of neurons and oligodendrocytes, exacerbating neurodegenerative conditions and contributing to disease progression.[39,40] The detrimental effects of A1 astrocytes underscore their role in promoting inflammation and neuronal damage in various neurodegenerative diseases (NDs).[41,42]

In contrast, A2 astrocytes emerge in response to less severe damage or within regenerative contexts.[39] These cells are characterized by their production of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and insulin-like growth factor 1, which are crucial for supporting neuronal survival, promoting repair, and enhancing synaptic plasticity. The presence of these factors helps counteract neuronal damage and facilitates recovery and repair processes in the brain.[43–45]

Recent insights have revealed that the transition between A1 and A2 states is regulated by specific molecular signals in the brain's microenvironment.[46] These signals, including various cytokines, growth factors, and signaling pathways, determine whether astrocytes adopt a neurotoxic or neuroprotective phenotype. Manipulating these signals could potentially shift astrocyte behavior from harmful A1 states to protective A2 states.[47–50]

This evolving understanding points to the potential for targeted therapeutic interventions aimed at modulating astrocyte reactivity. Strategies that inhibit the detrimental effects of A1 astrocytes or enhance the beneficial functions of A2 astrocytes are currently being explored. Such approaches hold promise for improving outcomes in NDs, brain injuries, and neuroinflammatory disorders by fostering a more favorable environment for neural repair and recovery.[51,52]

Perivascular macrophages, derived from bone marrow progenitors, surround blood vessels in the brain and act as sentinels, monitoring pathogens or debris entering the brain via the bloodstream. Dendritic cells, although less abundant in the brain compared to other tissues, are present in specialized regions like the meninges and choroid plexus, where they capture antigens and initiate adaptive immune responses by presenting them to T cells.[53–55]

Importantly, distinguishing between resident microglia, perivascular macrophages, and infiltrating monocytes involves analyzing their specific markers, locations, and functions.[56–58] Infiltrating monocytes are immune cells that enter the brain from the bloodstream in response to inflammation or injury, migrating into the brain to influence immune responses and contribute to tissue repair or inflammation.[59,60] Resident microglia are identified by markers such as P2RY12 (purigenic 2Y type 12 receptor) and Iba1

(ionized calcium binding adaptor molecule 1). They are distributed throughout the brain parenchyma, playing a key role in maintaining brain homeostasis and responding to injury.[61,62] Perivascular macrophages, marked by cluster of differentiation (CD) 163 and CD14, are located around blood vessels in the perivascular spaces and are involved in local immune responses.[58,63,64]

In contrast, infiltrating monocytes, characterized by markers like Ly6C and CCR2(C-C chemokine receptor type 2), originate from the bloodstream and enter the brain during inflammation, where they may differentiate into macrophage-like cells.[60,65,66] Techniques such as immunohistochemistry, flow cytometry, and single-cell RNA sequencing are used to accurately identify and differentiate these cell types based on their unique markers and roles.[67–69]

Additionally, T cells play diverse roles in brain function beyond traditional immune responses. They influence processes such as spatial learning, memory, emotional behavior, and stress responsiveness through cytokine signaling and immune modulation. For instance, $CD4^+$ T cells release interleukin (IL)-4, promoting an anti-inflammatory M2 phenotype in microglia and stimulating astrocytes to produce BDNF, which is crucial for synaptic plasticity and cognitive function.[70–73]

Regulatory T cells (Tregs) are essential for maintaining the brain's immune-privileged environment by modulating immune responses and controlling inflammation, thus protecting neurons from collateral damage during immune activation.[74–76] Recent research has emphasized the role of Tregs, including specialized brain-resident subsets adapted to the unique CNS environment, in sustaining immune tolerance.[77] These Tregs produce anti-inflammatory cytokines, such as IL-10 and transforming growth factor-beta, which help suppress excessive immune reactions. Additionally, Tregs play a role in preserving the integrity of the BBB, regulating immune cell entry into the CNS, and preventing unwanted neuroinflammation. By balancing immune activity and supporting neuronal health, Tregs are crucial for maintaining the brain's delicate immune equilibrium and ensuring long-term neuroprotection.[78,79]

During pathological conditions, peripheral T cells, including cytotoxic $CD8^+$ T cells and helper $CD4^+$ T cells, can infiltrate the brain. They eliminate infected or damaged cells and modulate the local immune environment through cytokine release, influencing disease progression in NDs like AD and PD.[80–82]

Natural killer cells, another type of immune cell, contribute to neuroprotection by regulating immune responses, suppressing inflammation, and promoting neuronal recovery following CNS damage. Their ability to modulate T-cell responses highlights their potential therapeutic role in neurological conditions.[83–85]

Additionally, B cells are crucial for antibody production against pathogens and play a pivotal role in antigen presentation to T cells within the brain. This interaction shapes the local immune environment and is essential for defending against neurological threats. Regulatory B cells further modulate immune responses, preventing excessive inflammation and contributing to immune tolerance in the CNS.[86–89]

Moreover, B cells have been implicated in oligodendrogenesis, the process of generating oligodendrocytes responsible for myelin sheath formation in the CNS. This interaction underscores the broader impact of B cells on neural function and suggests potential therapeutic avenues for enhancing remyelination in neurodegenerative conditions.[90–92]

In summary, immune cells within the brain intricately regulate neural function, immune responses, and disease processes. Understanding their roles and interactions provides insights into neuroimmune mechanisms and reveals potential targets for therapeutic interventions aimed at preserving brain health and combating NDs.

Breach of the brain's sanctuary: Unveiling the causes and mechanisms of neurological disorders

The human brain, often regarded as a sanctuary of cognitive and neural function, is remarkably resilient yet extraordinarily vulnerable. Neurological diseases, spanning a broad spectrum of disorders, disrupt this delicate sanctuary, leading to significant cognitive and motor deficits.[93,94] The underlying mechanisms contributing to these conditions are complex and multifaceted, involving an interplay of genetic predispositions, environmental factors, and systemic physiological processes.[95] Recent research has underscored the pivotal role of immune system dysregulation, neuroinflammation, and the breach of the BBB in the development of neurological diseases and aging-related cognitive decline.[96,97] Hence, this section aims to elucidate the intricate biological pathways, particularly those involving various types of brain immune cells, that lead to the breach of brain health and contribute to the onset of neurological diseases.

Immune cell dynamics in the aging brain: Microglia, astrocytes, and beyond

The aging brain undergoes profound structural and functional changes, particularly affecting its primary immune cells, microglia, and astrocytes.[98–102] Microglia, essential for CNS immune surveillance, become increasingly reactive with age, characterized by heightened pro-inflammatory cytokine expression, reduced phagocytic activity, and impaired resolution of inflammation. These changes contribute to chronic neuroinflammation, a hallmark of age-related NDs.[103–107]

Astrocytes, another critical glial cell type, also undergo significant alterations during aging. Aging astrocytes exhibit dystrophic changes, including a reduction in the size and complexity of their processes, leading to decreased synaptic coverage.[108,109] This astrocytic atrophy, along with reduced expression of glutamate transporters, impairs the clearance of glutamate and potassium buffering. Excessive glutamate accumulation can induce excitotoxicity, contributing to neuronal damage and dysfunction seen in various neurological disorders, including epilepsy and NDs.[110–113]

Additionally, the decline in astrocytic function affects the brain's extracellular environment, which is vital for extrasynaptic signaling and ion balance.[114,115] Astrocytes play a crucial role in clearing neurotransmitters and supporting neuronal metabolism, functions that are compromised with age-related astrocytic hypertrophy, altered gene expression, and increased production of inflammatory mediators. These changes disrupt brain homeostasis and exacerbate neuronal stress, further contributing to neurodegeneration in aging brains.[116–118]

The interplay between aging microglia and astrocytes is pivotal for maintaining brain health. Age-related alterations in microglial function, marked by excessive pro-inflammatory signaling, stimulate astrocytes to release inflammatory mediators, perpetuating a cycle of neuroinflammation. This chronic inflammation significantly contributes to neuronal damage and the progression of NDs. Understanding these intricate interactions offers potential therapeutic avenues to mitigate neuroinflammation and preserve cognitive function in aging individuals.[119–121]

Aging particularly affects microglial and astrocytic functions in PD.[122–124] As people age, microglia, the brain's resident immune cells, become more activated, leading to chronic low-grade

inflammation that exacerbates neurodegeneration. This heightened inflammatory state, driven by increased production of pro-inflammatory cytokines such as IL-1β and tumor necrosis factor-alpha (TNF-α), can further damage dopaminergic neurons, which are already compromised in PD.[125–127]

Furthermore, aging impairs microglial phagocytic activity, reducing the clearance of toxic aggregates such as alpha-synuclein and shifting microglial phenotypes toward a more pro-inflammatory state, amplifying local inflammation.[128,129] Astrocytes, which support neurotransmitter balance and neuronal function, also undergo significant changes with aging. Increased reactive astrogliosis and impaired regulation of neurotransmitters, like dopamine, contribute to heightened neuronal stress and degeneration.[130–132]

Aging disrupts astrocyte-neuron interactions and impairs BBB integrity, further aggravating neuroinflammation and disease progression. The interplay between age-related changes and Parkinson's pathology results in a compounded effect, accelerating the disease and worsening cognitive and motor symptoms.[133,134] Understanding these interactions is crucial for developing effective therapeutic strategies to mitigate the impact of aging on neuroimmune function and PD progression.

Aging also affects the brain's adaptive immune system, particularly T cells and B cells. Thymic involution and reduced production of naïve T cells lead to an accumulation of autoreactive T cells, impaired Treg function, and diminished immune surveillance.[135,136] First, aging impairs negative selection, leading to an accumulation of autoreactive T cells that may target the body's own tissues, increasing the risk of age-related autoimmune disorders. Second, it disrupts the balance of Treg production, impairing immune tolerance and resulting in heightened inflammation and immune dysfunction.[137] Third, the reduction in thymopoiesis decreases the production of new T cells, weakening the immune system's ability to respond to new infections and malignancies, contributing to overall immunosenescence.[138] In the brain, aging T cells contribute to increased neuroinflammation, impair synaptic plasticity, and exacerbate cognitive decline in NDs.[139,140]

Similarly, aging B cells undergo immunosenescence, characterized by reduced diversity in B cell receptors, heightened autoreactivity, and altered cytokine production.[141,142] These changes promote chronic inflammation, or "inflammaging." Age-related alterations in T cells and B cells exacerbate neuroinflammatory conditions and may worsen CNS disorders such as AD and MS.[143–147]

In summary, despite the brain's immune privilege, aging induces significant structural and functional changes in immune cells, particularly microglia and astrocytes. Reactive microglia drive chronic neuroinflammation, while astrocytic dysfunction disrupts neurotransmitter balance and exacerbates neuronal stress. Aging T cells and B cells further contribute to neuroinflammation and neurodegenerative processes. Understanding these immune cell dynamics is critical for developing targeted therapies aimed at reducing neuroinflammation and preserving cognitive health in aging populations.

The impact of infections and pathogens on neurological diseases

Infections and pathogens can lead to neurological diseases through several mechanisms, despite the brain's immune privilege, which typically offers enhanced protection.[148–150] Neurotropic viruses, such as herpes simplex virus, varicella-zoster virus, and enteroviruses, can breach the BBB and infect neural tissues, causing encephalitis or meningitis.[151–154]

Similarly, bacteria such as *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Mycobacterium tuberculosis* can invade the CNS, resulting in bacterial or tuberculous meningitis. The immune response to these infections often involves releasing cytokines and other inflammatory mediators that, while fighting the infection, can also cause neuroinflammation and neuronal damage.[155–158]

In some cases, pathogens carry antigens that resemble host proteins, causing the immune system to mistakenly attack neural tissues, as seen in Guillain-Barré syndrome, which is primarily triggered by *Campylobacter jejuni*.[159–164]

Chronic infections, such as those caused by the human immunodeficiency virus (HIV), can result in continuous neuroinflammation and neurodegeneration. Certain pathogens produce neurotoxins that directly damage neural tissues, like *Clostridium botulinum* and *Clostridium tetani*, which cause botulism and tetanus, respectively.[165–171]

Infections can also disrupt normal brain metabolism, leading to conditions such as hepatic encephalopathy and sepsis-associated encephalopathy. Infections may increase BBB permeability, allowing pathogens and immune cells to infiltrate the brain, and causing cerebral edema and neuronal damage.[172–176]

Post-infectious autoimmune reactions can trigger neurological conditions such as acute disseminated encephalomyelitis and MS.[177,178] Thus, despite the brain's immune privilege, which typically limits immune responses to protect sensitive neural tissues, some pathogens have evolved mechanisms to bypass these defenses.[179–181]

Understanding these mechanisms is essential for developing targeted therapies to prevent and treat infection-induced neurological diseases.

The interplay of genetic and environmental factors in neurological diseases

Neurological diseases arise from a complex interplay between genetic and environmental factors. Inherited and *de novo* mutations, such as those associated with Huntington's disease and autism spectrum disorders, along with genetic predispositions such as apolipoprotein E variations linked to AD, increase the risk of developing neurological disorders.[182–186]

Environmental factors also play a significant role. For example, infections such as the Epstein-Barr virus in MS, exposure to pollutants (e.g., heavy metals and pesticides in PD), nutrient deficiencies (e.g., vitamin B12), and traumatic brain injury (TBI) all contribute to neurological disorders. Lifestyle choices and chronic stress further exacerbate these conditions.[187–191]

The interaction between genetics and the environment is crucial, as genetic vulnerabilities combined with environmental influences increase disease risk.[192] Environmental factors can also induce epigenetic changes, altering gene expression and brain function. Additionally, gut microbiota dysbiosis, influenced by both genetics and environmental factors, has been linked to conditions like PD and MS.[193–196]

Chronic inflammation and its neurological impact

Chronic inflammation, or persistent immune system activation, plays a pivotal role in the development of neurological diseases such as AD, PD, MS, and brain cancer.[197] This sustained inflammatory state often originates from various sources, including chronic infections, exposure to environmental toxins, and autoimmune reactions.[198] Within the brain, this inflammatory environment triggers immune cells to release cytokines and chemokines, which disrupt neural balance and directly harm neurons.[199] Chronic inflammation also contributes to the accumulation of misfolded

proteins, increases oxidative stress, and impairs the brain's mechanisms for clearing toxic protein aggregates.[200,201]

In the brain, inflammatory responses involve the activation of microglia and the release of various cytokines and chemokines. For example, cytokines such as TNF-α, IL-1β, and IL-6 are produced, which can disrupt neuronal function by promoting abnormal protein aggregation and altering cellular signaling pathways. Chemokine such as CCL2 (C-C motif chemokine ligand 2) MCP-1 (monocyte chemoattractant protein-1) attract additional immune cells to the site of inflammation, potentially exacerbating the inflammatory response.[202–204]

Similarly, in neuroinflammatory conditions, cytokines such as interferon-gamma and IL-17 contribute to immune cell activation and migration, while chemokines like CCL5 (RANTES) (regulated on activation, normal T cell expressed and secreted)and CXCL10 (C-X-C-motif chemokine ligand 10) (IP-10) (interferon-γ-inducible protein 10) facilitate immune cell movement within the CNS, collectively disrupting neural balance and affecting neuronal health.[205–208]

Chronic neuroinflammation initiates a cascade of detrimental effects in the brain, primarily through the activation of microglia and astrocytes, which release pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. These cytokines interfere with the brain's protein homeostasis by disrupting protein folding processes and enhancing the aggregation of misfolded proteins. Recent research has shown that IL-1β can promote the aggregation of tubulin associated unit (tau) protein, a hallmark of AD.[209] Table S1 provides a list of cytokines and chemokines involved in chronic neuroinflammation.

This inflammatory environment also significantly increases oxidative stress, as activated microglia and astrocytes generate ROS and reactive nitrogen species.[210,211] These oxidative molecules damage proteins, lipids, and DNA, further promoting protein misfolding and aggregation. Studies have demonstrated that increased oxidative markers and weakened antioxidant defenses are prominent in NDs, emphasizing the role of oxidative stress in disease progression, which is linked to chronic neuroinflammation.[212,213]

Chronic inflammation also impairs the brain's ability to clear toxic protein aggregates. The ubiquitin-proteasome system and autophagy, both critical for protein degradation and cellular maintenance, are disrupted by inflammatory cytokines.[214,215] For instance, IL-1β can inhibit the function of the ubiquitin-proteasome system, reducing the degradation of misfolded proteins and worsening their accumulation.[216]

Similarly, inflammation affects autophagic processes by impairing lysosomal function and autophagosome formation, leading to the buildup of amyloid-β plaques and tau tangles in AD.[217,218] Neuroinflammation also compromises BBB integrity, allowing more inflammatory cells and molecules to enter the brain, further intensifying oxidative stress and protein aggregation.[219,220]

Emerging evidence suggests that targeting specific inflammatory cytokines, such as IL-6, could restore cellular protein homeostasis and mitigate the impact of these disruptions.[202,203] Overall, chronic neuroinflammation creates a vicious cycle of protein misfolding, oxidative damage, and impaired clearance, contributing to progressive neuronal damage and functional decline.[204–206]

Chronic inflammation and long-term neurological effects post-COVID-19

Following a COVID-19 infection, the body may experience an intense immune reaction known as a cytokine storm. This response involves the excessive release of inflammatory cytokines and chemokines throughout the body, including the CNS. The resulting widespread inflammation, which affects both systemic and brain functions, contributes to a range of neurological complications, including viral encephalitis, acute disseminated encephalomyelitis, and Guillain-Barré syndrome.[221–223] Notably, the neurological impacts of COVID-19 may arise from direct invasion of the CNS by the virus as well as indirect effects caused by the immune system's response.[224–229]

Recent studies highlight the potential long-term neurological consequences of chronic inflammation following COVID-19. Beyond the acute phase of infection, sustained immune activation and neuroinflammation may lead to persistent cognitive impairment and exacerbate pre-existing neurodegenerative conditions.[230–232] Evidence suggests that the inflammatory response triggered by COVID-19 may further promote neurodegeneration through mechanisms involving neurotoxic cytokines, disruption of BBB integrity, and dysregulation of neuronal function and connectivity.[233–235]

Understanding these complex immunological and pathological processes is crucial for developing targeted therapies to mitigate long-term neurological sequelae in COVID-19 survivors. By identifying the mechanisms that link chronic inflammation to neurological disease progression, researchers can discover potential biomarkers and therapeutic targets to improve clinical outcomes and quality of life for affected individuals.

Chronic neuroinflammation and glioblastoma progression

Chronic neuroinflammation plays a significant role in brain cancer, particularly glioblastoma, through complex mechanisms involving the persistent activation of microglia and astrocytes. In glioblastoma, these activated glial cells secrete pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β.[236,237] These cytokines activate key signaling pathways, including nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and signal transducer and activator of transcription 3 (STAT-3), which enhance tumor cell proliferation and survival by inhibiting apoptosis. For instance, NF-κB activation increases the expression of anti-apoptotic proteins, enabling glioblastoma cells to resist cell death.[238,239]

Furthermore, activated microglia and astrocytes contribute to a tumor-supportive environment by releasing growth factors and extracellular matrix components that promote tumor development and invasion.[240,241] Recent research indicates that glioblastoma cells exploit these inflammatory signals to enhance their own growth and evade treatment. Specifically, glioblastoma cells release factors that attract and activate microglia, which then secrete cytokines that promote tumor proliferation and the formation of new blood vessels.[242,243] Additionally, chronic neuroinflammation triggers the production of ROS, which inflicts DNA damage and accelerates tumor progression.[244,245]

In contrast, astrocytes in glioblastoma often exhibit altered expression of molecules such as fibroblast growth factor and vascular endothelial growth factor, which are crucial for angiogenesis, providing tumors with the necessary nutrients and oxygen for growth.[246,247] Vascular endothelial growth factor, secreted by reactive astrocytes, is particularly important for glioblastoma's ability to develop an extensive and abnormal blood supply.[248] Glioblastoma-associated inflammation also disrupts the BBB through matrix metalloproteinases, facilitating tumor invasion and exacerbating the disease.[249,250] This inflammatory environment not only supports tumor progression but also leads to neurodegeneration and cognitive impairments, complicating treatment and impacting the patient's quality of life.

Recent research into glioblastoma emphasizes the potential of targeting the tumor microenvironment as a therapeutic strat-

egy.[251,252] Efforts are underway to modulate microglial and astrocytic activity to disrupt their roles in tumor growth and improve the efficacy of existing treatments.

Overall, understanding the interplay between chronic neuroinflammation and glioblastoma underscores the need for innovative approaches to managing this aggressive cancer.

Neurological battlefield: Manifestations of brain diseases

The human brain, essential for numerous functions, is increasingly vulnerable to neurological diseases. These conditions present significant clinical challenges, often involving immune mechanisms mediated by brain cells like microglia and astrocytes. The following sections explore the role of these immune cells in the development and progression of selected NDs, highlighting their immune mechanisms.

Immune responses in neurodegenerative diseases

Brain diseases such as NDs involve complex immune responses within the CNS, driven by cortical atrophy and abnormal protein accumulation that stress neurons and lead to their degeneration. This neuronal damage triggers an innate immune response, with microglia and astrocytes undergoing reactive changes to manage diseased neurons and contain abnormal proteins.[253,254] Additionally, adaptive immune cells, such as $CD8^+$ T cells, $CD4^+$ T cells, and B cells, are recruited, shaping the neuroinflammatory environment to either support neuronal health or exacerbate disease progression.[255–257]

In AD, characterized by amyloid-β plaques and neurofibrillary tangles, microglia initially attempt to clear Aβ plaques but become chronically activated, leading to sustained inflammation, neurotoxicity, and synapse loss.[258] This persistent activation not only fails to clear Aβ efficiently but also exacerbates neuronal damage. $CD8^+$ T cells may worsen neurodegeneration by directly interacting with compromised neurons, while $CD4^+$ T cells modulate microglial activity, influencing the balance between neuroprotection and neuroinflammation.[259,260] B cells play a dual role by producing antibodies against abnormal proteins, potentially aiding clearance but also exacerbating inflammation through cytokine release.[260–262]

Microglial cells, the brain's primary immune responders, exhibit distinct activation states known as M1 and M2 phenotypes, which play critical roles in neuroinflammatory diseases such as AD and MS.[3–7] The M1 phenotype, associated with pro-inflammatory responses, is activated by stimuli such as lipopolysaccharides or pro-inflammatory cytokines. M1 microglia release cytokines like TNF-α, IL-1β, and IL-6, along with ROS, which contribute to neurodegeneration. In AD, M1 microglia exacerbate Aβ plaque formation and tau phosphorylation, leading to increased neuronal damage and cognitive decline. Similarly, in MS, M1 microglia promote autoimmune responses and myelin damage, contributing to demyelination and neurodegeneration.[263,264]

In contrast, the M2 phenotype is generally associated with anti-inflammatory and repair functions. Activated by signals such as IL-4 and IL-13, M2 microglia secrete anti-inflammatory cytokines such as IL-10 and transforming growth factor-β (TGF- β) and are involved in tissue repair and debris clearance.[265] In AD, M2 microglia help clear Aβ plaques and promote tissue repair, although their functionality may be impaired during chronic inflammation.[107,108] In MS, M2 microglia contribute to remyelination and repair processes, though their effects are often overshadowed by the dominant M1 response, especially during acute disease phases.[266,267]

Recent insights suggest that modulating the balance between M1 and M2 microglial states could offer therapeutic benefits. Research indicates that shifting the microglial response towards the M2 phenotype may reduce Aβ plaque accumulation in AD and improve cognitive outcomes.[268,269]

Similarly, in MS, targeting pathways that promote M2 polarization or inhibit M1 activation shows promise for slowing disease progression and enhancing repair.[270] Understanding the dynamics of these microglial phenotypes provides potential strategies for managing neuroinflammatory diseases by balancing their roles in inflammation and repair.

On the other hand, astrocytic dysfunction plays a critical role in the progression of brain diseases, particularly in AD. Astrocytes are essential for maintaining brain homeostasis, including the clearance of Aβ through processes such as phagocytosis and the release of Aβ-degrading enzymes. In AD, astrocytes often exhibit impaired functionality, leading to a failure to clear Aβ. This accumulation of Aβ contributes to the formation of neurotoxic plaques and disrupts neuronal function.[113,116]

Recent research has uncovered several mechanisms underlying astrocytic dysfunction in AD. Studies have shown that astrocytes in AD brains exhibit reduced expression of key receptors and transporters involved in Aβ clearance, such as low-density lipoprotein receptor-related protein 1 and aquaporin-4 channels, which are part of the glymphatic system.[271,272] This impairment compromises their ability to effectively remove Aβ from the extracellular space. Additionally, oxidative stress and chronic inflammation further exacerbate astrocytic dysfunction by damaging cellular components and impairing their ability to maintain neurovascular integrity.[273,274]

Research has also explored the impact of impaired astrocytic clearance on disease progression. For example, studies have demonstrated that genetic or pharmacological restoration of astrocytic function can reduce Aβ levels and alleviate cognitive deficits in animal models of AD.[275,276] Activation of astrocytic signaling pathways, such as NF-κB and peroxisome proliferator-activated receptor-γ (PPAR-γ), has been shown to enhance Aβ clearance and reduce plaque burden.[38–44]

Furthermore, research into the role of the glymphatic system has revealed that disruptions in cerebrospinal fluid (CSF) flow and waste clearance, due to dysfunctional astrocytes, significantly contribute to disease progression.[277]

Overall, the dysfunction of astrocytes in AD, particularly their failure to clear Aβ, is a key driver of disease progression. Recent research underscores the importance of restoring astrocytic function as a potential therapeutic strategy, aiming to enhance Aβ clearance and mitigate the neurodegenerative processes associated with AD.

Interestingly, research has revealed significant sex-based differences in the structure and function of microglia. These variations can affect how microglia respond to injuries, diseases, and changes in brain function. Male and female microglia may differ in terms of density, shape, and activity levels, which impacts their susceptibility to neurological disorders and influences the overall immune response in the brain.[278–280] Gaining insights into these sex-specific differences is essential for developing more tailored and effective treatments for neurological conditions.

The higher incidence of AD in women compared to men is strongly associated with sex-specific differences in microglia, the brain's primary immune cells. Studies show that microglia in females and males react differently to the pathological changes seen

in AD.[281–283]

One key factor is the inflammatory response. Research suggests that female microglia may exhibit more pronounced inflammatory reactions than their male counterparts. This heightened response could accelerate neurodegeneration and contribute to the higher incidence of Alzheimer's in women.[284]

Hormonal influences also play a significant role. Estrogen, more prevalent in females, can affect microglial function and inflammation. Fluctuations in estrogen levels, especially during menopause, may impact how microglia interact with Aβ plaques and tau tangles, both of which are central to Alzheimer's pathology.[285,286]

Genetic and epigenetic factors also contribute to these differences. Changes in genes associated with immune responses and neuroinflammation can alter microglial function, resulting in varied susceptibilities to AD between genders. Additionally, differences in microglial density and activity between males and females impact the efficiency of Aβ plaque clearance and the handling of neurotoxic conditions. These differences may help explain the increased vulnerability to AD observed in women.[287,288]

Understanding these sex-dependent differences in microglial structure and function is crucial for developing more targeted and effective approaches to prevent and treat AD in both men and women.[32]

Recent studies have shown that microglia play dual roles in AD.[64,67] While traditionally viewed as contributors to neuroinflammation and plaque accumulation, recent evidence suggests that microglia are also crucial for clearing Aβ plaques and supporting neuronal health. New research using advanced imaging and genetic tools has revealed that microglial depletion can lead to increased Aβ plaque buildup and worsening cognitive deficits, but it may also alleviate inflammation in some contexts.[202–204] This reflects the complex balance between the beneficial and detrimental aspects of microglial activity, which must be carefully considered.[208,211]

On the other hand, emerging data suggest that peripheral immune cells, such as T cells and monocytes, play a significant role in Alzheimer's pathology. Studies have found that depleting peripheral immune cells can reduce systemic inflammation and alleviate some aspects of disease progression.[289,290] However, the overall impact can be mixed, as removing these cells might disrupt essential immune functions and impair the brain's ability to respond effectively to injury.

In PD, cognitive assessments often show that men perform worse than women.[291] Specifically, males tend to struggle more with verbal fluency, inhibition, and processing speed. This cognitive decline in men is often more pronounced, affecting their ability to generate words, control impulsive responses, and process information quickly. These differences underscore the need for gender-specific approaches to understanding and addressing cognitive impairments in PD.[292]

As previously mentioned, variations in microglial density, morphology, and activity between males and females may influence the progression of NDs. Male microglia, in particular, may show less effective neuroinflammatory responses and compromised synaptic maintenance, which could contribute to the exacerbation of cognitive decline in men. This highlights the importance of considering sex-based differences in neuroinflammatory processes when developing targeted treatments for PD.

Additionally, in PD, there is growing evidence that T cells play a role in driving neuroinflammation and disease progression.[293] T cells influence microglial polarization toward the pro-inflammatory M1 phenotype while suppressing the protective M2 phenotype.[294,295] This dysregulation creates a neurotoxic environment that contributes to the degeneration of dopaminergic neurons, which is central to PD pathology. Understanding the interplay between T cells and microglia reveals potential therapeutic avenues for restoring immune balance and preserving neuronal integrity in PD.[293–296]

Furthermore, evidence suggests that individuals in the prodromal stage of PD, who are at a heightened risk of progressing to the disease, show elevated levels of alpha-synuclein antibodies.[297] This suggests a potential involvement of B lymphocytes in PD progression. Although these antibodies are not found in early PD patients, their presence indicates a potential pathological role for alpha-synuclein antibodies.[298]

There is also speculation that these antibodies could be protective, aiding in the clearance of pathological proteins. Supporting this notion, a study by Li *et al*.[299] demonstrated that certain alpha-synuclein antibodies derived from patients were capable of inhibiting the seeding of alpha-synuclein *in vitro.*

Moreover, B cells perform multiple functions beyond antibody production, including presenting antigens, regulating T cells and innate immune cells, producing cytokines, and maintaining subcapsular sinus macrophages. Considering the significant inflammation observed in both the CNS and the periphery in PD, it is likely that B lymphocytes contribute to the disease. Many of their effects are likely mediated through these various roles. Further research is needed to clarify the specific contributions of B lymphocytes to PD progression.

Additionally, recent research has provided new insights into the role of microglia in PD. While earlier studies suggested that microglial depletion could reduce neuroinflammation and improve motor symptoms, newer research indicates that microglial activity is also essential for responding to neuronal damage and supporting neuronal survival.[300,301] This suggests that complete depletion of microglia might impair the brain's repair mechanisms and exacerbate neurodegeneration. Therefore, targeted modulation of microglial activity, rather than total depletion, may be more beneficial.[302]

On the other hand, recent studies on peripheral immune cell depletion in PD models show that reducing the activity of these cells can decrease systemic inflammation and potentially slow disease progression.[303,304]

However, evidence also suggests that such depletion might disrupt normal immune surveillance and repair processes, potentially leading to adverse outcomes.[305] This highlights the importance of balancing immune responses to support neuronal health while minimizing harmful effects.

These findings emphasize the complex, often context-dependent roles of immune cells in NDs, suggesting that therapeutic strategies must carefully target immune cell functions to balance their protective and harmful effects.

Targeting microglia and astrocytes in AD and PD requires advanced strategies to modulate their complex roles in neurodegeneration and inflammation. Several methods can be used to target microglia. Anti-inflammatory agents and immunomodulatory therapies aim to mitigate the detrimental effects of chronic inflammation by inhibiting the production of pro-inflammatory cytokines and ROS.[306,307]

Additionally, strategies to enhance plaque clearance involve developing pharmaceuticals or employing genetic techniques to boost microglial activity, which is essential for removing Aβ plaques and slowing AD progression. Targeting specific receptors, such as TREM2 (triggering receptor expressed on myeloid cells

2), has also been shown to improve microglial uptake of plaques and enhance neuroprotection. These approaches seek to balance the beneficial and harmful effects of microglial activity to better manage NDs.[308,309]

Similarly, strategies for modulating astrocytes focus on their reactive states. A1 astrocytes, which are neurotoxic, can be shifted toward a more protective A2 state using signaling pathway inhibitors or enhancers. Increasing the production or delivery of neurotrophic factors, such as BDNF and insulin-like growth factor 1, which are produced by A2 astrocytes, supports neuronal survival and repair.[310,311]

Additionally, targeting calcium signaling and astrocytic transport systems helps normalize astrocyte functions critical for maintaining synaptic health and ion balance. Efforts to reduce excessive astrogliosis aim to prevent astrocyte overactivation and scarring, which can further damage neurons.[312,313]

Combining these approaches while ensuring therapeutic specificity and evaluating long-term outcomes is crucial for developing effective treatments. By targeting both microglia and astrocytes, these strategies aim to address the multifaceted nature of neurodegenerative diseases, potentially improving cognitive function and slowing disease progression in AD and PD.

In AD and PD, the roles of immune cells evolve throughout disease progression, necessitating tailored therapeutic approaches at each stage. In the early stages of AD, microglia are initially activated to respond to Aβ plaques and tau pathology. Targeting these cells with anti-inflammatory agents can help manage inflammation and prevent excessive plaque buildup, potentially delaying disease onset.[314]

As AD progresses to the intermediate stage, chronic inflammation becomes more pronounced, and the balance between protective and harmful microglial responses can shift. At this point, therapies should aim to reduce persistent inflammation and promote neuroprotection by modulating both microglial activity and astrocyte states, particularly by shifting neurotoxic A1 astrocytes to a more protective A2 state.

In the late stages of AD, where extensive neuronal loss and severe inflammation are present, treatments may focus on controlling chronic inflammation and preserving the remaining neurons, potentially using advanced immunomodulatory therapies and novel approaches like gene and cell-based therapies.[315,316]

In PD, therapeutic strategies also adapt to the disease stage. During the early stage, localized inflammation in the substantia nigra, where dopaminergic neurons are initially compromised, can be managed by targeting microglial activation with anti-inflammatory drugs to slow neuronal loss.

As the disease progresses to the intermediate stage, inflammation becomes more widespread, involving both central and peripheral immune cells. At this point, combined therapies are necessary to address the contributions of both microglia and astrocytes to neurodegeneration, aiming to reduce sustained inflammation and protect neuronal function.

In the late stage, characterized by significant dopaminergic neuron loss and severe motor symptoms, the focus shifts to managing chronic inflammation and supporting the remaining neurons. Advanced therapies and innovative treatments may be employed to enhance patient quality of life and slow disease progression. Adapting treatments to these stage-specific immune cell dynamics is essential for effective management and improved therapeutic outcomes in PD.[317,318]

Last but not least, emerging evidence suggests a role for B cells in PD, particularly through their potential involvement in alpha-synuclein pathology. Elevated levels of alpha-synuclein antibodies in prodromal PD stages indicate B cell activation, though their exact role—whether protective or pathogenic—remains unclear. B cells contribute to PD pathogenesis through diverse functions beyond antibody production, including antigen presentation, cytokine modulation, and interaction with other immune cells in both CNS and peripheral inflammation contexts.[319–323]

Neuroinflammation and Alzheimer's biomarkers

Recent advances in AD research have enhanced our understanding of how various biomarkers, including MRI (magnetic resonance imaging), fluorodeoxyglucose-positron emission tomography (FDG-PET), tau PET, and CSF levels of amyloid and tau, are linked with immune responses.[324,325] MRI detects brain atrophy, particularly in the hippocampus and cortical regions, which is associated with increased neuroinflammation.[326] Studies have indicated that the activation of microglia and proliferation of astrocytes play a significant role in these structural changes, highlighting that inflammation-driven neuronal loss and synaptic damage are critical contributors to the observed atrophy.[327]

FDG-PET, which measures glucose metabolism, often reveals reduced metabolic activity in areas affected by AD. Recent research indicates that this hypometabolism is not only a result of neuronal loss but also a consequence of neuroinflammation.[328] Activated microglia and astrocytes can disrupt neuronal function and energy metabolism, further contributing to the metabolic declines observed on FDG-PET scans.[329]

Tau PET imaging, which visualizes hyperphosphorylated tau deposits, has shown that tau pathology is closely linked with neuroinflammation.[330] Recent findings suggest that tau deposition can trigger inflammatory responses, with microglial activation potentially exacerbating tau-related damage. This interaction underscores the bidirectional relationship between tau pathology and inflammation, influencing the severity of neurodegeneration.[331]

CSF analysis of amyloid and tau levels reveals that neuroinflammation can affect these biomarkers. Elevated tau levels in CSF often correspond with higher neuroinflammatory activity, as tau release from damaged neurons can stimulate inflammatory responses.[332]

Similarly, reduced amyloid-β levels in CSF may be influenced by impaired clearance due to inflammation. Emerging research is exploring how inflammatory markers in CSF correlate with AD biomarker levels and disease progression, providing insights into the complex interplay between inflammation and AD pathology.[333]

Overall, recent studies highlight that neuroinflammation significantly impacts AD biomarkers, emphasizing the need to consider inflammatory processes when interpreting these biomarkers and developing targeted therapies. This integrated perspective may lead to more effective strategies for diagnosing and treating AD by addressing both pathological and inflammatory aspects of the disease.[117,124,125]

In summary, NDs exhibit complex immune responses triggered by cortical atrophy and protein aggregation in the CNS. AD and PD exemplify distinct patterns of neuroinflammation driven by Aβ and alpha-synuclein, respectively, impacting microglial activation and neuronal health. T cells exacerbate neuroinflammation in PD by skewing microglial responses, while B cells potentially influence disease progression through multiple immune functions. Clarifying these immune dynamics is crucial for developing targeted therapies to mitigate neuroinflammation and preserve neuronal function in NDs.

Therapeutic strategies for combating neuroinflammation

Targeted therapeutic strategies for neuroinflammation are crucial in mitigating the adverse effects of chronic inflammation on brain health and NDs. Current approaches include modulating microglial activity, targeting astrocytes, and employing immunomodulatory and neuroprotective strategies.

Anti-inflammatory agents such as minocycline and pioglitazone are being studied for their potential to reduce microglial activation and inflammation, with minocycline showing promise in preclinical models for PD.[334,335] Small molecules like clopidogrel, a P2Y12 receptor antagonist, are also under investigation for their ability to modulate microglial responses.[336]

In terms of astrocyte targeting, GSK3β inhibitors and adenosine A2A receptor antagonists are being explored for their roles in reducing reactive astrogliosis and inflammatory responses.[337,338] Immunomodulatory approaches include monoclonal antibodies targeting specific cytokines, such as anti-TNF-α and anti-IL-1β antibodies, which are being tested in clinical trials to assess their efficacy in reducing neuroinflammation and improving symptoms in neurodegenerative conditions.[339,340]

Additionally, vaccination approaches designed to elicit an immune response against pathological proteins, like alpha-synuclein in PD, aim to reduce toxic protein accumulation and modulate the neuroimmune response.[341] Nutraceuticals and dietary interventions, including compounds like curcumin and omega-3 fatty acids, are also being investigated for their anti-inflammatory and neuroprotective properties.[342]

Ongoing clinical trials, such as those evaluating minocycline's effects on PD and aducanumab for AD, are crucial for determining the effectiveness of these targeted treatments.[343,344] Another clinical study is investigating how clopidogrel affects neuroinflammation in AD, while an additional study is exploring the effects of the anti-IL-1β antibody canakinumab on various neurodegenerative conditions.[345,346] These strategies and trials provide a comprehensive understanding of how targeted treatments aim to address neuroinflammation and their potential implications for managing NDs. Additional details about the clinical trials are provided in Table 1.

Future directions

Although the brain is considered immune-privileged, its immune system—primarily composed of microglia and astrocytes—is essential for maintaining balance and addressing challenges. During illness, external immune cells can alter the brain's immune dynamics, highlighting a complex relationship with neurological health. The development of neurological diseases is influenced by genetic, environmental, and lifestyle factors, with age-related changes in brain immune cells often leading to increased neuroinflammation.

Infections, pathogens, and chronic inflammation are critical factors that require targeted therapeutic approaches. Recent advancements in neuroimmunology focus on understanding and addressing neuroinflammation, which is a common element in numerous neurological disorders. Nanomedicine shows promise by using engineered nanoparticles to deliver treatments directly to the brain, capable of breaching the BBB.

Precision medicine aims to customize treatments by considering genetic and environmental influences, utilizing biomarkers, and performing genetic screening. Current research explores the communication pathways of immune cells both within the brain and systemically, as well as their dysfunction in neurological disorders, to discover new therapeutic targets.[347] Age-related changes in microglia and astrocytes play a major role in neuroinflammation and neuronal injury, driving efforts to develop strategies that support healthy brain aging.

Studies investigating the influence of environmental factors on the brain's immune system aim to reduce harmful effects. The examination of immune system dysfunction in mental health disorders, including depression, anxiety, and schizophrenia, is a rapidly growing field that presents opportunities for new treatments. Advanced imaging techniques and machine learning play crucial roles in understanding brain immune responses, identifying biomarkers, and predicting disease trajectories.

This review study encounters several limitations. One major challenge is fully clarifying the intricate interactions between brain immune cells, such as microglia and astrocytes, and the overall systemic immune response. The complex and sometimes overlapping functions of these cells make it difficult to pinpoint the exact mechanisms contributing to neuroinflammation and neurological disorders. Additionally, while the review focuses on age-related changes, it may not fully address the variability in individual aging processes, which makes it hard to generalize the findings across different groups.

Furthermore, the varied influence of environmental factors on brain immune systems is not entirely understood, which may limit the review's ability to explore how these exposures affect neuroinflammation and brain health.

Although we aimed to provide a comprehensive overview of how neuroimmune cells support health and how their dysfunction contributes to brain disorders, covering every underlying mechanism in detail is challenging. Instead, we have highlighted key mechanisms to emphasize their importance and to provide a clear understanding of their roles.

Future research should focus on elucidating the dynamic interactions between neuroimmune cells and neural circuits in both physiological and pathological contexts. Employing advanced imaging techniques, such as two-photon microscopy and *in vivo* imaging, along with single-cell genomics, could offer unprecedented insights into the behavior and differentiation of resident microglia, perivascular macrophages, and infiltrating monocytes throughout various stages of neurological disorders. Understanding how the roles and functions of these cells evolve over time, particularly during disease progression or resolution, may reveal critical mechanisms driving neuroinflammation and neurodegeneration.

Additionally, investigating the influence of systemic immune signals—such as cytokines and chemokines—on neuroimmune cell function and recruitment could uncover novel therapeutic targets. Insights into how peripheral immune responses affect brain inflammation and pathology could lead to innovative treatment strategies that bridge systemic and central immune interventions.

Moreover, exploring interactions between neuroimmune cells and neuronal populations will deepen our understanding of how immune responses impact cognitive functions and mood, potentially guiding new approaches to address mental health disorders and NDs.

A crucial focus for future research is investigating the impact of neuroinflammation on brain stem cells and neuronal regeneration.[348] Understanding how chronic inflammation disrupts the stem cell microenvironment is essential, as it affects processes such as cell proliferation, differentiation, and survival. Identifying key cytokines, signaling pathways, and sources of oxidative stress involved could provide new targets for counteracting the harmful effects of inflammation.

Table 1. Clinical trials investigating the impact of immunomodulation on neurological disorders

Trial ID	Title	Conditions	Interventions
NCT06177028	MCLENA-2: A Phase II Clinical Trial for the Assessment of Lenalidomide in Patients With Mild Cognitive Impairment Due to Alzheimer's Disease	Alzheimer's disease	Lenalidomide 10 mg
NCT05173701	Effects of Probiotics on Peripheral Immunity in Parkinson's Disease	Parkinson's disease	Probiotics
NCT01545518	IVIG Treatment for Refractory Immune-Related Adult Epilepsy	Epilepsy	Intravenous immunoglobulin (IVIG).
NCT05864534	Phase 2a Immune Modulation With Ultrasound for Newly Diagnosed Glioblastoma	Glioblastoma, gliosarcoma	Balstilimab, botensilimab, liposomal doxorubicin
NCT03879512	Autologous Dendritic Cells, Metronomic Cyclophosphamide and Checkpoint Blockade in Children With Relapsed HGG	Childhood glioblastoma	Drug: Depletion of regulatory T cells; Procedure: Reoperation; Biological: Cancer vaccine
NCT03152318	A Study of the Treatment of Recurrent Malignant Glioma With rQNestin34.5v.2 (rQNestin)	Glioma	Oncolytic virus called rQNestin34.5v.2. Immunomodulation with cyclophosphamide
NCT06146062	Effects of Intravascular Administration of Mesenchymal Stromal Cells Derived From Wharton's Jelly of the Umbilical Cord on Systemic Immunomodulation and Neuroinflammation After Traumatic Brain Injury. (TRAUMACELL)	Traumatic brain injuries (TBI)	Drug: Mesenchymal stromal cells (MSC); Drug: Placebo
NCT04106830	Clinical and Imaging Patterns of Neuroinflammation Diseases in China (CLUE)	Neuroinflammatory and demyelination disease	Drug: Intravenous steroid
NCT05858515	REVERSE-Long COVID-19 With Baricitinib Study (REVERSE-LC)	Neurocognitive impairment, which can manifest as a type of Alzheimer's Disease and Related Dementias (ADRD), or cardiopulmonary symptoms resulting from Long COVID.	Drug: Baricitinib 4 mg; Drug: Placebo
NCT00645749	Helminth-induced Immunomodulation Therapy (HINT) in Relapsing-remitting Multiple Sclerosis (HINT)	Relapsing-remitting multiple sclerosis	Biological: Helminth ova
NCT04106830	Clinical and Imaging Patterns of Neuroinflammation Diseases in China (CLUE)	Neuromyelitis optica spectrum disorder and multiple sclerosis	Drug: Intravenous steroid
NCT05654818	Peripheral Immunological Effects of High-dose Vitamin D Treatment in Healthy Subjects (VDSS)	Multiple sclerosis	Drug: Vitamin D
NCT05080270	Feasibility Study of Tolerogenic Fibroblasts in Patients With Refractory Multiple Sclerosis (MSFibroblast)	Relapsing-remitting multiple sclerosis resistant to interferon.	Biological: Tolerogenic fibroblasts
NCT02983708	Neuroregenerative Potential of Intravenous G-CSF (Granulocyte-Colony Stimulating Factor) and Autologous Peripheral Blood Stem Cells	Neurodegeneration	Biological: Peripheral blood mononuclear cells (mPBMC); Drug: G-CSF; Drug: Placebo

Additionally, studying how neuroinflammation affects the migration and integration of new neurons into existing neural circuits will be critical for developing strategies to promote effective neuronal regeneration. By improving conditions for stem cells through targeted modulation of neuroinflammation, it may be possible to enhance brain repair and recovery, particularly in NDs and brain injuries.

Future research should also focus on elucidating the role of the gut-brain axis in the development and progression of NDs.[349,350] Understanding how dysregulation of the gut microbiota affects neuroinflammation could reveal potential intervention strategies. By investigating the mechanisms through which gut microbial imbalances influence brain inflammation, we may identify novel therapeutic approaches to mitigate neuroinflammatory processes and improve outcomes for individuals with neurodegenerative conditions.

Conclusions

Integrating multi-omics approaches and developing advanced animal models that replicate human disease conditions will be crucial for translating these findings into clinical applications. This approach will enhance our ability to target neuroimmune pathways more effectively, offering hope for novel therapeutic interventions in neurological and psychiatric conditions. Furthermore, research should investigate the potential for targeting neuroimmune cells to counteract cognitive decline, exploring interventions that modulate microglial and astrocytic activity to restore or enhance their beneficial functions in the aging brain. This could involve pharmacological agents, lifestyle changes, or genetic modifications aimed at modifying immune cell behavior. Expanding research into the interactions between neuroimmune cells and other age-related factors, such as vascular health and metabolic changes, will provide new insights into their collective impact on cognitive function. Innovations in imaging technologies and machine learning will be crucial for diagnosing and treating neurological disorders more effectively, enhancing our ability to visualize and analyze complex brain processes and pathology. Interdisciplinary collaboration across neuroscience, immunology, genetics, clinical medicine, nanotechnology, and data science will be essential for advancing treatments and deepening our understanding of the brain's immune system.

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Conflict of interest

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Author contributions

Conceptualization (SKC), data curation (SKC), formal analysis (SKC), investigation (SKC), methodology (SKC), project administration (SKC), supervision (SKC), original draft writing (SKC), review and editing (SKC, DC).

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