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Review Article

Infectious vs. Sterile Neuroinflammation: Differential Consequences on Neuronal Circuitry

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Neuroinflammation constitutes a key modulator of synaptic function and neuronal network organization, with direct implications for cognition, emotion, and behavior. However, a conceptual gap persists in understanding how the origin of the inflammatory stimulus—infectious or sterile—and, in particular, the temporal trajectory of the neuroimmune response determine divergent functional outcomes at the circuit level. In this narrative review, evidence from experimental models and translational studies is integrated to analyze the mechanisms through which neuroinflammation modulates synaptic plasticity, excitation–inhibition balance, and network efficiency. The reviewed data indicate that neuroinflammation induced by infectious stimuli is typically characterized by acute glial activation, intense but predominantly reversible network dysfunction, and transient functional alterations, mediated by proinflammatory cytokines and dynamic changes in neuronal excitability. In contrast, sterile neuroinflammation and unresolved inflammatory states are associated with sustained glial activation, complement-dependent synaptic remodeling, microglial priming, and persistent circuit dysfunction, with long-lasting effects on plasticity and cognitive performance. Prolonged microglia–astrocyte interactions emerge as a critical determinant in the transition from reversible functional alterations to states of chronic circuit disconnection. Taken together, this review proposes that the functional outcome of neuroinflammation depends less on the initial origin of the stimulus than on the duration, resolution, and inflammatory memory of the neuronal circuit. These findings underscore the need for experimental approaches that integrate temporal and circuit-level dimensions to understand the contribution of neuroinflammation to persistent brain dysfunction and neurodegenerative vulnerability.

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Introduction

Neuroinflammation refers to the context-dependent immune response that arises within the central nervous system (CNS) in response to disturbances of homeostasis, including infection, trauma, ischemia, or neurodegeneration. This response is primarily mediated by resident immunocompetent cells, such as

microglia and astrocytes, and, under specific conditions, by infiltrating peripheral immune cells, and is characterized by the production of inflammatory mediators that can modulate neuronal and synaptic function. [1][2][3][4]

The classical conception of the CNS as a strictly immune-privileged compartment has been substantially revised. Although access of peripheral immune cells remains highly regulated, the discovery of meningeal lymphatic vessels and resident immune cell populations at the CNS borders has redefined immune privilege as a state of active regulation rather than an absence of immune activity. [5][6][7] Within this framework, immune signaling is now recognized as an integral component of brain physiology, with functions that extend beyond host defense to include neural development, synaptic pruning, and the maintenance of functional neuronal circuits. [1][5][7]

Neuroinflammation is neither a uniform nor a static process. Its functional consequences depend on the nature, intensity, and duration of the initiating stimulus, as well as on the balance between proinflammatory and regulatory mechanisms. Acute neuroinflammatory responses may promote repair and restoration of homeostasis, whereas persistent or dysregulated inflammation can lead to long-lasting functional alterations and, in certain contexts, neurodegeneration. [1][2][3][4] At the mechanistic level, these responses are initiated through the recognition of pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) by pattern recognition receptors (PRRs) expressed on glial cells, particularly microglia, thereby triggering inflammatory cascades that may resolve or persist depending on the context. [1][2][6][7]

Critically, the functional impact of neuroinflammation cannot be adequately understood at the level of individual cells. Brain function emerges from highly interconnected neuronal circuits whose stability and flexibility depend on finely regulated synaptic plasticity and excitation–inhibition balance (E/I balance). These processes are increasingly recognized as being sensitive to signals derived from the immune system. [8][9] Through bidirectional communication, neurons, glial cells, and immune elements form functional neuroimmune circuits in which inflammatory mediators modulate synaptic function and neuronal activity, while neuronal signaling can, in turn, shape immune responses within the CNS. [8][9]

Within this circuit-based framework, both infectious and sterile neuroinflammation activate largely overlapping cellular and molecular repertoires, despite being initiated by distinct stimuli. Infectious neuroinflammation, driven by the recognition of PAMPs, is typically associated with rapid and transient immune responses, whereas sterile neuroinflammation, triggered by DAMPs released following stress or tissue injury, tends to involve sustained glial activation in the absence of pathogens. Although both contexts can disrupt synaptic plasticity and circuit connectivity, accumulating evidence suggests that sterile and persistent inflammatory states are preferentially associated with chronic circuit dysfunction and long-term functional impairment, even in the absence of overt neuronal loss. [8][9] However, the mechanisms through which distinct neuroinflammatory contexts converge or diverge at the level of neuronal circuits remain fragmented in the literature. This review aims to critically integrate the available experimental and clinical evidence to examine neuroinflammation—infectious and sterile—as a dynamic

modulator of neuronal circuit function, emphasizing temporality, persistence, and resolution capacity as key determinants of functional outcome.

Functional Framework: Neuroinflammation, Glia, and Modulation of Neuronal Circuits

Neuroinflammation and Neuroimmunity as Functional Modulators of Neuronal Circuits

Brain function emerges from dynamic neuronal circuits organized through the coordinated interaction of excitatory and inhibitory neurons, glial cells, and immune signals, rather than from isolated properties of individual neurons or discrete anatomical regions. [10][11][12][13] The stability and flexibility of these circuits depend on E/I balance, which is regulated by synaptic and homeostatic plasticity mechanisms that adjust connectivity and network gain in response to changes in activity and context. [10][11][12][13][14]

From this perspective, synaptic plasticity constitutes a circuit-level phenomenon, in which coordinated modifications of excitatory and inhibitory synapses remodel entire networks, regulate neuronal synchrony, and support processes such as learning, memory, and contextual adaptation. [13][14] Circuit dysfunction is therefore defined as alterations in the activity, connectivity, and information processing of neuronal networks in the absence of overt structural damage, such as neuronal loss or macroscopic lesions. [15][16] This dissociation between structure and function explains why cognitive, sensory, or behavioral deficits do not necessarily correlate with structural lesion burden, a phenomenon classically described as the clinicoradiological paradox in multiple sclerosis and also observed in other neurological disorders. [15][16] Electrophysiological and functional neuroimaging studies have demonstrated aberrant patterns of synchronization, hyperexcitability, or network inefficiency in neurodegenerative and autoimmune diseases, as well as during aging, even at early stages or in the presence of minimal atrophy. [15][16][17][18]

Within this framework, neuroinflammation emerges as a central modulator of circuit-level functional dysfunction. Immune signals derived from microglia, astrocytes, and, in certain contexts, peripheral immune cells alter neuronal excitability, synaptic transmission, and plasticity without necessarily inducing cell death. [10][12][15][17][19] Proinflammatory cytokines such as interleukin-1 beta (IL-1β) and tumor necrosis factor alpha (TNF-α) modulate synaptic receptors, glutamatergic and GABAergic neurotransmission, and mechanisms of long-term potentiation (LTP), thereby disrupting E/I balance at the circuit level. [15][17][19][20][21]

The existence of neuronal circuits sensitive to immune signals is supported by the identification of neuronal populations that express specific receptors, such as IL-1R1, enabling them to respond to cytokines through non–cell-autonomous transcriptional programs. [12][15][20] These circuits constitute the neural substrate of sensory, affective, and cognitive symptoms induced by immune activation, even in the absence of central structural damage, and are integrated into specific functional neuroimmune axes—such as brain–skin circuits in

atopic dermatitis and psoriasis—that can perpetuate pathological states through circuit–immunity feedback loops. [22][23]

The functional impact of neuroinflammation depends critically on its temporality and context. Acute inflammatory states typically induce reversible circuit dysfunction through rapid changes in excitability and synaptic transmission, whereas chronic inflammation promotes maladaptive plasticity, persistent network reorganization, and progressive loss of functional efficiency. [15][17][18][21][24] Microglial activation and priming, together with sustained engagement of pathways such as NF-κB and PI3K–Akt–mTOR, contribute to the stabilization of pathological network states and to clinical vulnerability, as observed in epilepsy, movement and oculomotor disorders, and neurodevelopmental disorders, in which circuit dysfunction predominates over focal structural damage. [19][21][24][25][26][27]

Glia as an Active Interface Between Immunity and Neuronal Circuits

Microglia and astrocytes form an integrated glial system that detects infectious and sterile signals and translates them into functional changes at synapses and within neuronal circuits. Both populations express PRRs, including toll-like receptors (TLRs), complement receptors, and chemokine–receptor axes, enabling them to respond to both PAMPs and DAMPs and to directly modulate synaptic function. [28][29][30][31][32][33][34]

Under physiological conditions, microglia regulate circuit organization and refinement through activity-dependent synaptic pruning, a highly selective process mediated by “find-me,” “eat-me,” and “don’t eat-me” signals, such as the C1q–C3–CR3, CX3CL1/CX3CR1, and CD47/SIRPα axes. [31][32][33][34][35][36][37] This interaction is synapse-type specific: microglial subpopulations can selectively modulate inhibitory synapses via GABAergic signaling, sculpting inhibitory connectivity without affecting excitatory synapses. [38] In pathological contexts, these same mechanisms may become maladaptive; for example, in epilepsy, microglial activation induced by hyperactive inhibitory neurons promotes the selective elimination of inhibitory synapses and amplifies network hyperexcitability through complement-dependent feedback circuits. [31][39]

Astrocytes regulate the synaptic microenvironment through glutamate uptake, metabolic support, and Ca^{2+}-dependent signaling, actively participating in the modulation of synaptic transmission and plasticity. [29][40] Neuronal activity controls astrocytic transcriptional programs through pathways such as Sonic hedgehog (Shh), which regulate the expression of synaptic modulators critical for experience-dependent plasticity. [41] Neuroinflammation disrupts these functions, reducing glutamatergic uptake and promoting states of hyperexcitability and E/I imbalance. [29][40]

Bidirectional communication between microglia and astrocytes integrates these responses at the circuit level. During inflammation, microglial release of ATP activates P2Y1 receptors on astrocytes, amplifying Ca^{2+} signals and modulating excitatory transmission, while microglia can dynamically instruct astrocyte–synapse interactions and facilitate activity-dependent synaptic elimination. [40][42] This integrated glial system enables rapid and context-dependent modulation of neuronal circuits, with effects—adaptive or maladaptive—critically determined by the intensity, duration, and timing of the immune stimulus. [30][31][37]

Cytokines and Immune Mediators as Direct Modulators of Plasticity and Excitability

Proinflammatory cytokines, particularly IL-1β, TNF-α, and IL-6, act as direct modulators of synaptic transmission and neuronal circuit plasticity, without requiring structural damage or neuronal death. Primarily released by activated microglia and astrocytes, these molecules alter neuronal excitability, receptor trafficking, and synaptic organization, thereby redefining network function in a manner dependent on the inflammatory context. [28][30][43][44][45][46][47][48]

IL-1β regulates synaptic plasticity in a concentration-dependent manner, suppressing long-term potentiation (LTP) at elevated levels and impairing learning and memory processes. These effects are mediated through activation of p38 MAPK, interference with brain-derived neurotrophic factor (BDNF) signaling, and epigenetic mechanisms that repress gene programs associated with plasticity. [43][44][48][49][50] Neuronal expression of IL-1R1 delineates circuits that are specifically sensitive to immune signals, providing a direct link between inflammation and cognitive, affective, and sensory alterations. [20]

TNF-α modulates plasticity through synaptic scaling mechanisms that adjust the surface expression of AMPA receptors and bidirectionally regulate the excitation–inhibition balance, while IL-6 contributes to synaptic dysfunction in states of persistent neuroinflammation, acting synergistically with other proinflammatory cytokines. [30][31][43][44][48] In contrast, cytokines such as IL-13 may exert modulatory and neuroprotective effects by enhancing the phosphorylation of glutamatergic receptors and activating CREB-dependent transcriptional programs. [51]

These effects converge on the activation of shared intracellular pathways—including p38 MAPK, NF-κB, JAK/STAT, and PI3K–Akt–mTOR—that regulate receptor trafficking, synaptic organization, and gene expression. [25][30][49][50] Sustained dysregulation of these pathways promotes excessive synaptic pruning, loss of plasticity, and persistent network alterations. [25][31]

Both acute and chronic exposure to cytokines can disrupt E/I balance and synaptic plasticity in the absence of structural neurodegeneration. Whereas acute inflammation typically induces reversible functional changes, chronic inflammation stabilizes maladaptive plasticity states through transcriptional and epigenetic modifications, perpetuating circuit dysfunction even after the resolution of the initial stimulus. [21][30][44][48][50]

Infectious vs. Sterile Neuroinflammation: Functional Convergence and Contextual Divergence

Shared Sensors, Signal Integration, and Functional Trajectories

Activation of PRRs by infectious stimuli—through PAMPs—or by sterile stimuli—via DAMPs derived from tissue injury or protein aggregation—leads to alterations in synaptic function and neuronal circuitry within the CNS. However, the functional differences between these contexts do not arise from the engagement of entirely distinct molecular repertoires but rather from how these signals are integrated and translated into temporal and persistent effects on excitatory and inhibitory synapses.

Both PAMPs and DAMPs activate a largely overlapping set of PRRs expressed by microglia and astrocytes, including TLRs, NOD-like receptors (NLRs), inflammasome components, and complement receptors. Among TLRs, TLR2, TLR3, TLR4, and TLR9 recognize specific bacterial or viral motifs, whereas some of these receptors—particularly TLR4—also respond to endogenous signals and noninfectious stress stimuli, acting as contextual sensors rather than exclusively pathogen-specific detectors. [29][52][53][54][55] Complementarily, NLRs such as NLRP3 can be activated by both microbial products and endogenous damage signals, promoting inflammasome assembly and caspase-1–dependent cytokine maturation. [56] Likewise, activation of the complement cascade (C1q–C3) and its receptor CR3 mediates synaptic pruning processes induced by both infectious and sterile insults. [56] (Figure 1A)

Although the repertoire of activated PRRs is largely shared, the functional integration of these signals differs substantially between infectious and sterile neuroinflammation. In both contexts, PRR activation converges on common intracellular cascades—including NF-κB, p38 MAPK, JAK/STAT, and PI3K–Akt–mTOR—but the intensity, kinetics, and molecular context of pathway activation vary depending on the origin and persistence of the stimulus. [56][57] (Figure 1A) Additional modulatory signals, such as canonical and noncanonical WNT pathways, can bias glial responses toward pro-resolutive or proinflammatory programs, determining whether these shared cascades support transient responses oriented toward defense and repair or, conversely, persistent inflammatory states associated with synaptic dysfunction and neurodegeneration. [58][59][60]

Infectious Neuroinflammation: Rapid Glial Activation and Predominantly Reversible Network Dysfunction

Infectious stimuli, through PAMPs, directly and potently activate TLRs and NLRs via recognition of microbial motifs, triggering robust and typically acute glial activation. This pattern is characterized by the rapid release of cytokines and chemokines, production of nitric oxide, and strong induction of antiviral and antibacterial programs. [29][52][53][57] At the molecular level, for example, LPS efficiently activates TLR4 and downstream MAPKs in microglia, promoting marked expression of TNF-α and reactive nitrogen species. [56][57] In viral infections, coupled activation of NMDA glutamatergic receptors in microglia has also been described, with Ca^{2+} mobilization, activation of CaMKII, NF-κB, and AP-1, increased oxidative and endoplasmic reticulum stress, and the emergence of a highly reactive and neurotoxic microglial phenotype. [61] In contrast, sterile stimuli—such as extracellular ATP, HMGB1, misfolded proteins (β-amyloid), or extracellular matrix fragments—activate the same PRRs but tend to induce more gradual and context-dependent responses, with preferential engagement of reparative or neurodegenerative programs, including chronic NF-κB or JAK/STAT3 signaling in astrocytes. [29][56] In these scenarios, sustained activation of axes such as PI3K/Akt can alter receptor trafficking, synaptic plasticity, and neuronal metabolic homeostasis. [62] (Figure 1B)

These differences in signal integration are reflected in the hierarchical organization of the glial response. During infectious neuroinflammation, microglia act as primary sensors, rapidly detecting PAMPs and releasing proinflammatory cytokines such as IL-1β and TNF-α, which secondarily induce reactive astrocyte activation. [63][64][65][66] Activated astrocytes amplify and

modulate the inflammatory response, disrupt blood–brain barrier integrity, and directly affect synaptic transmission through changes in glutamate uptake and gliotransmitter release. [65][67][68] Bidirectional microglia–astrocyte crosstalk can escalate neuroinflammation, perturb synaptic homeostasis, and generate acute changes in network excitability and functional connectivity. [63][64][69] (Figure 1B) In this context, astrocytes may also act as viral reservoirs, contributing to the persistence and dissemination of infection within the CNS. [65]

Sterile Neuroinflammation: Sustained Activation and Persistent Circuit Dysfunction

In sterile neuroinflammation, although microglia continue to act as the initial sensors, activation is predominantly driven by DAMPs and is associated with more persistent functional trajectories. Microglia mediate synaptic pruning and remodeling processes, often through complement-dependent mechanisms, and release cytokines that induce astrocytes to transition toward neurotoxic or neuroprotective states. [1][43][66][70] Endogenous DAMPs, such as HSP60 released by stressed neurons, can activate TLR4 and promote NLRP3 inflammasome activation in microglia, inducing sustained IL-1β release and reinforcing chronic, infection-independent inflammatory circuits. [71] In this context, microglial activation does not adopt a rigid binary phenotype but rather dynamic mixed states modulated by local and systemic signals. [59][71] Astrocytes assume a more prominent role in the long-term modulation of synaptic plasticity, metabolic support, and maintenance of the extracellular environment, contributing to chronic, low-grade circuit dysfunction rather than acute excitotoxicity. [1][43][72] This contribution increases progressively, particularly in chronic neurodegenerative conditions, where astrocytes sustain maladaptive plasticity states and functional network disconnection. [1][43] (Figure 1C)

Consistent with these prolonged kinetics, sterile neuroinflammation induced by traumatic injury or protein aggregation (for example, tauopathies or Alzheimer's disease extracts) generates gradual and persistent changes in synaptic structure and function. In vivo imaging studies show that both systemic LPS-induced inflammation and tauopathy models prolong microglial contacts and promote excessive synaptic remodeling, with increased microglial phagocytosis of dendritic spines and filopodia. [35] This process is complement-dependent, with upregulation of the C1q–C3–CR3 pathways, and is exacerbated in pathological contexts. [53] In Alzheimer's disease, sustained microglial activation may fail to efficiently clear Aβ, favoring non-resolving inflammation that accelerates synaptic loss and cognitive decline. [73] In models of direct central inflammation, such as experimental autoimmune encephalomyelitis (EAE), selective impairment of hippocampal LTP, reduction of NR2B subunits of the NMDA receptor, and increased IL-1β are observed, indicating a specific alteration in the composition and function of excitatory synapses. [74] Although both central and peripheral inflammation can affect LTP, only sterile central inflammation is associated with these particular molecular changes. [74]

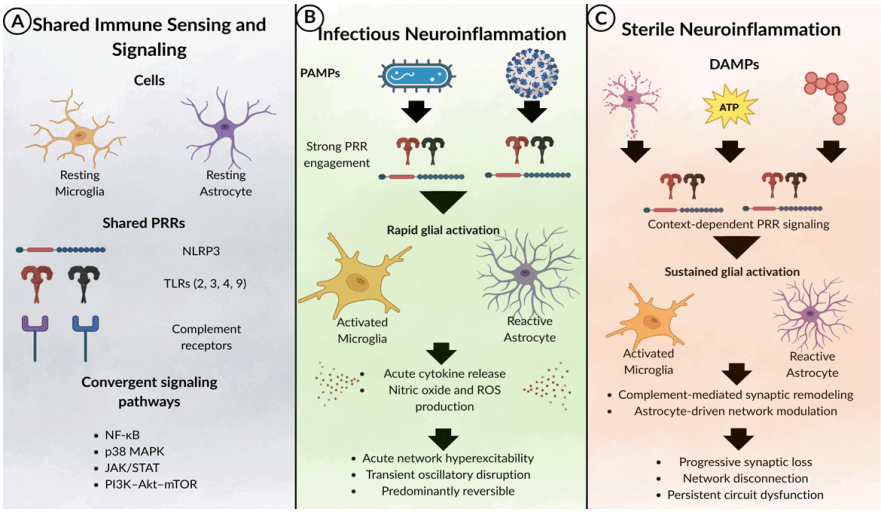

Figure 1. Shared and divergent immune signaling pathways in infectious and sterile neuroinflammation. This figure illustrates the shared immune-sensing architecture and the divergent downstream consequences of infectious and sterile neuroinflammation at the circuit level. **(A)** Both infectious and sterile inflammatory stimuli engage overlapping sets of pattern-recognition receptors (PRRs), including Toll-like receptors (TLRs), NLRP3 inflammasome components, and complement receptors, which converge on common intracellular signaling pathways such as NF-κB, p38 MAPK, JAK/STAT, and PI3K–Akt–mTOR. These pathways are expressed across multiple glial cell types and constitute a shared molecular framework for neuroimmune activation, regardless of the inflammatory origin. **(B)** In infectious neuroinflammation, pathogen-associated molecular patterns (PAMPs) induce robust PRR engagement, leading to rapid glial activation, transient cytokine release, and production of nitric oxide and reactive oxygen species. This response is typically associated with acute network hyperexcitability and oscillatory disruption that is largely reversible following effective inflammatory resolution. **(C)** In sterile neuroinflammation, damage-associated molecular patterns (DAMPs) elicit context-dependent PRR signaling that favors sustained glial activation, complement-mediated synaptic remodeling, and astrocyte-driven network modulation, ultimately promoting progressive synaptic loss, functional disconnection, and persistent circuit dysfunction.

Network Functional Patterns Induced by Infectious and Sterile Neuroinflammation

Differences in PRR activation and signal integration during infectious versus sterile neuroinflammation translate into distinct functional patterns of neuronal network excitability, synchronization, and disconnection. In infectious contexts, immune activation typically induces acute and intense network dysfunction, characterized by rapid changes in neuronal activity and transient alterations in oscillatory dynamics; in contrast, sterile neuroinflammation follows slower and more persistent trajectories that culminate in chronic, low-grade circuit dysfunction. [1][52][53][75][76] Experimental exposure to TLR ligands such as LPS, peptidoglycan, or poly(I:C), recognized by TLR4, TLR2, and TLR3 respectively, triggers acute microglial activation with the release of proinflammatory cytokines (TNF-α, IL-6) and reactive oxygen and nitrogen species, producing immediate effects on network dynamics. [52] These alterations include slowing of gamma oscillations, emergence of beta-band activity, and episodes of

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neuronal hyperexcitability, even in the absence of neuronal death. [52] [53] Repeated or combined PRR activation exacerbates these effects, with nitric oxide and microglial-derived oxidants acting as central mediators of more severe network dysfunction. [52] In models of peripheral viral challenge with poly(I:C), acute-phase cytokines such as CXCL10 increase seizure susceptibility by enhancing excitatory transmission and suppressing inhibitory signaling. [77] Nevertheless, these responses may be attenuated after repeated stimulation through tolerance and negative regulatory mechanisms, such as induction of A20 or IRAK3, reflecting processes of functional microglial reprogramming. [78]

In contrast, sterile neuroinflammation is associated with sustained activation of microglia and astrocytes, prolonged release of inflammatory mediators, and progressive impairment of synaptic plasticity, including reduced LTP, neuronal morphological changes, and cognitive decline. [1][75][76][79] In this context, chronic activation of pathways such as PI3K/Akt, NF-κB, or cGAS–STING sustains persistent production of type I interferons and proinflammatory cytokines, promoting synaptic loss and neurodegeneration. [60][62][75][79] Recent evidence indicates that sustained type I interferon signaling directly disrupts synaptic homeostasis and activity-dependent plasticity, favoring states of functional disconnection in cortical and hippocampal networks. [75][79][80] Consistently, comparative studies show that although infectious and sterile stimuli activate overlapping inflammatory pathways, they differ in their functional consequences: the former induce predominantly acute network hyperexcitability, whereas the latter are associated with complement-mediated persistent synaptic loss and chronic circuit dysfunction. [69][81][82]

Alterations of Excitation–Inhibition Balance According to Inflammatory Context

From the perspective of E/I balance, infectious neuroinflammation tends to acutely potentiate excitatory transmission and transiently suppress inhibition, favoring reversible states of synchronization and hyperexcitability. [52][77] In contrast, sterile neuroinflammation is associated with sustained microglia-mediated synaptic pruning and progressive loss of excitatory synapses, contributing to functional disconnection and cognitive decline. [73][74] The relative preservation of inhibitory interneurons during acute infections suggests mechanisms of differential vulnerability and underscores the importance of inflammatory context in determining functional outcome. [52]

Inflammatory Persistence, Glial Priming, and Functional Circuit Outcomes

At the network level, functional outcomes do not depend exclusively on microglial activation but rather on the dynamic interaction between microglia and astrocytes, whose contribution to circuit remodeling varies according to the origin, intensity, and duration of the inflammatory stimulus. In infectious contexts, both glial populations participate in rapid responses aimed at damage containment, whereas in sterile and chronic scenarios, this interaction tends to sustain prolonged inflammatory states that durably disrupt synaptic and metabolic homeostasis. In infectious neuroinflammation, acute and high-intensity glial activation promotes rapid, activity- and complement-dependent

synaptic pruning, associated with severe but potentially reversible network dysfunction. [35][52][53][57][77] In contrast, chronic or repetitive sterile stimuli promote glial priming, sustained phenotypic changes, and chronic complement-dependent synaptic pruning, characterized by prolonged microglial contacts, excessive elimination of dendritic spines, and persistent alterations in phagocytic capacity, contributing to progressive synaptic loss and long-lasting disruption of circuit homeostasis. [35][52][53][56][57][60][78]

Beyond the initial origin of the stimulus, experimental evidence converges on the notion that the duration and persistence of the neuroinflammatory state are the primary determinants of synaptic and network functional outcomes. Episodes of acute, self-limited neuroinflammation—whether infectious or sterile—induce transient alterations in synaptic plasticity, reversible E/I imbalance, and short-term cognitive deficits that tend to resolve following the restoration of glial and neuronal homeostatic programs. [1][43][83][84][85][86][87] In contrast, sustained or unresolved neuroinflammation, whether driven by persistent infection, ongoing sterile injury, or chronic pathology, is associated with long-lasting synaptic dysfunction, maladaptive plasticity, and persistent E/I imbalance that progresses toward circuit disconnection and neurodegeneration. [1][43][83][87] This qualitative shift is linked to prolonged exposure to proinflammatory cytokines such as IL-1β, TNF-α, and IL-6, sustained activation of microglia and astrocytes, and persistent engagement of inflammatory pathways such as the NLRP3 inflammasome. [43][83][87]

A central element in the transition toward persistent inflammatory states is glial priming, or "innate immune memory," whereby microglia acquire a durably sensitized functional state following an initial activation. This phenomenon is supported by epigenetic reprogramming mechanisms, including chromatin modifications, stable changes in gene expression, and metabolic reprogramming, such as sustained upregulation of glycolysis. [88][89][90][91][92] As a result, primed microglia respond disproportionately to secondary stimuli, even of low intensity, with amplified release of inflammatory mediators, increased circuit vulnerability, and persistent synaptic dysfunction. [28][83][88][93][94][95][96][97]

From a functional perspective, this priming translates into a state of persistent circuit sensitization, characterized by sustained impairment of synaptic plasticity, slowing of network oscillations (including gamma activity), reduced efficiency of neuronal processing, and increased vulnerability to functional relapses, even in the absence of overt structural neurodegeneration. [28][94][95][98][99][100] Models of aging, traumatic brain injury, and neurodegenerative diseases show that this sensitized state conditions exaggerated responses to subsequent inflammatory challenges and durably compromises the circuit's capacity for functional recovery. [28][94][96] (Figure 2)

Importance of the Origin of the Inflammatory Stimulus

Comparisons between infectious and sterile models indicate that the origin of the inflammatory stimulus is indeed relevant during early phases, particularly when marked differences exist in the intensity, kinetics, and compartmentalization of the initial immune response. Infectious stimuli typically elicit rapid, high-intensity responses, with acute cytokine peaks and predominantly transient functional alterations, such as reversible cortical

hyperexcitability and brief cognitive deficits. [101][102][103] In contrast, sterile stimuli generate more gradual initial responses but with slower onset and greater persistence, favoring long-lasting alterations in synaptic plasticity and chronic circuit dysfunction. [1][83][86]

However, accumulating evidence shows that the origin of the stimulus ceases to be the determining factor once a state of persistent neuroinflammation and glial priming has been established. Under these conditions, the duration of the inflammatory state, the circuit's prior inflammatory history, the degree of resolution achieved, and the basal state of the neuronal network predict functional outcomes more accurately than the infectious or sterile nature of the initial insult. [83][88][93][94][100]

Thus, although both types of stimuli activate largely overlapping molecular repertoires, it is the temporal trajectory of the inflammatory response—and not exclusively its origin—that determines whether the circuit returns to a reversible functional state or progresses toward persistent dysfunction. Within this framework, neuroinflammation becomes an emergent property of the circuit, shaped by its inflammatory history and its capacity for resolution.

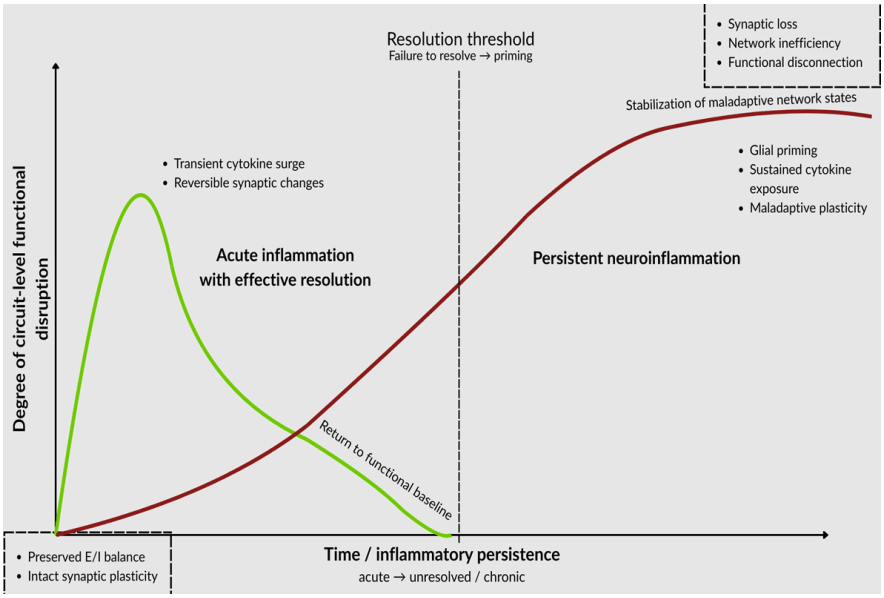

Figure 2. Inflammatory persistence, glial priming, and circuit-level functional outcomes. This conceptual model illustrates how the temporal persistence of neuroinflammatory signaling shapes circuit-level functional outcomes, independently of the initial inflammatory origin. The x-axis represents time and inflammatory persistence, ranging from acute, self-limited responses to unresolved or chronic inflammation, while the y-axis reflects the degree of functional circuit disruption. Acute inflammatory responses with effective resolution (green trajectory) are characterized by transient cytokine surges and reversible synaptic alterations, allowing restoration of excitatory–inhibitory balance and a return to baseline network function. In contrast, failure to resolve inflammation beyond a critical resolution threshold (dashed line) promotes sustained cytokine exposure, glial priming, and maladaptive plasticity (red trajectory). Over time, these processes stabilize dysfunctional network states, leading to synaptic loss, network inefficiency, and functional disconnection. The figure emphasizes inflammatory duration and resolution capacity, rather than inflammatory origin per se, as key determinants of long-term circuit integrity.

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Descending Autonomic Modulation of Neuroinflammation

Autonomic circuits, particularly vagal and cholinergic pathways of the brainstem, exert a context-dependent descending modulation of the immune response during neuroinflammation. Through the inflammatory reflex, afferent signals derived from infection or tissue damage are integrated at the brainstem level and translated into a cholinergic efferent output that suppresses peripheral cytokine release via activation of α7 nicotinic receptors on immune cells. [104][105][106]

During PAMP-induced infectious neuroinflammation, such as that triggered by LPS or viral stimuli, these pathways are robustly engaged and contribute to the efficient resolution of acute inflammation, in part through acetylcholine production by T lymphocytes and adrenergic mechanisms associated with vagal afferent signaling. [107][108] In contrast, in sterile neuroinflammatory contexts, activation of these reflexes is less effective, favoring the persistence of low-grade inflammatory states. [1][109]

Consistently, vagal stimulation effectively suppresses LPS-induced inflammation in acute models but shows limited efficacy in scenarios of chronic sterile neuroinflammation, where glial priming and sustained cytokine production constrain resolution mechanisms. [84][107][110] Thus, the activity of autonomic, limbic, and brainstem circuits differentially modulates glial inflammatory states: whereas acute infectious inflammation is associated with anti-inflammatory feedback loops, chronic sterile inflammation tends to sustain persistent glial activation and impaired resolution. [1][70][84][110] Taken together, these data indicate that the efficacy of autonomic modulation depends primarily on the duration and context of the neuroimmune state, rather than on the infectious or sterile origin of the initial stimulus.

Cognitive, Emotional, and Behavioral Outcomes

Clinical and experimental evidence converges in showing that infectious neuroinflammation is predominantly associated with acute cognitive, emotional, and behavioral alterations that are reversible in a substantial proportion of cases, whereas sterile or chronic inflammatory states tend to produce persistent, multidomain deficits. During bacterial or viral infections, systemic and central inflammatory activation induces so-called sickness behavior, characterized by fatigue, cognitive slowing, and affective changes, in association with transient elevations of cytokines such as IL-6, TNF-α, and CRP. [111][112][113] These changes reflect an adaptive motivational reorganization and typically resolve in parallel with the decline of inflammatory markers, as demonstrated by longitudinal studies documenting cognitive and emotional recovery following infection resolution. [111][112]

In contrast, sterile neuroinflammation and certain post-infectious states are associated with persistent fatigue, sustained cognitive impairment, and affective disturbances that outlast the initial insult. These conditions are linked to ongoing neuroinflammatory signaling, disruption of the blood–brain barrier, and persistent glial activation, resulting in durable deficits in attention, memory, and executive functions. [83][114][115] Consistently, experimental models show that chronic inflammation compromises synaptic plasticity and network efficiency, thereby promoting persistent cognitive and emotional dysfunction. [83][116][117]

Taken together, these data indicate that functional symptoms associated with infectious neuroinflammation display a greater potential for reversibility than those arising from sterile or chronic states, in which long-lasting synaptic and circuit-level alterations predominate. [83][111][114] This distinction supports the concept of inflammation-course-dependent temporal windows, during which early resolution of inflammation is critical to prevent the transition toward persistent circuit dysfunction. [83][118]

Discussion

The reviewed literature suggests that neuroinflammatory processes induced by infectious and sterile stimuli share a largely overlapping molecular architecture, based on the activation of PRRs, common inflammatory cascades, and a close functional interaction between microglia and astrocytes. However, the way these signals are integrated over time—as well as their persistence and degree of resolution—varies considerably across experimental models and pathological contexts.

A central limitation of the available body of evidence is its strong reliance on animal models and on acute or artificial inflammatory paradigms, which do not always capture the temporal and contextual complexity of human neuroinflammation. In addition, methodological heterogeneity—including differences in the type of stimulus, the compartmentalization of inflammation, and the outcomes assessed—hampers the establishment of direct causal relationships between glial activation, synaptic remodeling, and network dysfunction.

These limitations underscore the need to interpret the reported circuit-level outcomes not as inevitable consequences of a given inflammatory stimulus but rather as context-dependent results shaped by experimental conditions, prior inflammatory history, and the resolution capacity of the nervous system.

Conclusions

The evidence synthesized in this review supports a conceptualization of neuroinflammation as a dynamic modulator of brain function, capable of altering synaptic plasticity, excitability, and the organization of neuronal networks without necessarily requiring irreversible structural damage. Infectious and sterile stimuli activate largely overlapping molecular repertoires but differ in the kinetics, persistence, and contextual integration of these signals, resulting in distinct functional trajectories at the circuit level. Within this framework, the distinction between acute, potentially reversible dysfunction and persistent, maladaptive dysfunction emerges as a continuum driven by the inflammatory course rather than as categories strictly defined by the origin of the initial stimulus.

A central theme emerging from the reviewed studies is the role of glial cells—particularly microglia and astrocytes—as an active interface between immunity and neuronal circuits. Through the integration of immune signals, modulation of the synaptic microenvironment, and regulation of activity-dependent pruning and plasticity, these cells largely determine the functional stability of neuronal networks. Persistent glial activation, together with priming phenomena and functional reprogramming, promotes the consolidation of maladaptive plasticity states and circuit disconnection, even in the absence of overt neurodegeneration,

thereby redefining neuroinflammation as an emergent property of the nervous system rather than a transient response to an isolated insult.

From an integrative perspective, this work proposes that the duration, resolution, and prior inflammatory history of a circuit constitute critical determinants of cognitive, emotional, and behavioral outcomes. In this context, a key challenge for future research will be to more precisely characterize how the temporal trajectories of neuroinflammation interact with mechanisms of activity-dependent plasticity and network organization over time. Advancing our understanding of these processes will allow the refinement of current conceptual models and the establishment of a more precise framework to interpret the transition between reversible and persistent dysfunction in neuroinflammatory states, without reducing this complexity to a simple dichotomy between infectious and sterile inflammation.

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Author Contributions

D.T-L. was the sole author and is responsible for all aspects of the manuscript.

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