v2: 17 July 2026

Review Article

Infectious vs. Sterile Neuroinflammation: Differential Consequences on Neuronal Circuitry

Preprinted: 4 February 2026
Peer-approved: 31 May 2026

Qeios, Vol. 8 (2026)
ISSN: 2632-3834

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Introduction: Neuroinflammation modulates synaptic function and neuronal network organization, influencing cognition, emotion, and behavior. However, how infectious versus sterile inflammatory stimuli—and particularly their temporal dynamics—shape distinct circuit-level outcomes remains unclear. To address this, we propose the Circuit-level Neuroinflammatory Dynamics Framework (CNDF), which emphasizes functional network output and identifies the resolution threshold as a key determinant between reversible perturbation and persistent circuit dysfunction.
Methods: A structured narrative review was conducted across PubMed, Web of Science, Scopus, and Europe PMC {m/2009-2026/}. After screening 2,404 records, 142 experimental, translational, and human studies with circuit-level relevance were included.
Results: Infectious and sterile neuroinflammation engage overlapping neuroimmune pathways but differ in the persistence of their functional effects. Infectious stimuli generally induce acute and predominantly reversible disruptions in excitation–inhibition balance and network oscillations, whereas sterile neuroinflammation is associated with sustained glial activation, synaptic remodeling, and progressive functional disconnection. Across both contexts, inflammatory persistence—rather than stimulus origin—emerged as the principal determinant of long-term circuit dysfunction. Failure of pro-resolving mechanisms during the subacute phase promotes glial priming and maladaptive plasticity, defining the resolution threshold as a critical regulator of neuroimmune outcomes.
Conclusion: Neuroinflammatory outcomes depend less on whether the trigger is infectious or sterile than on inflammatory persistence and resolution capacity. These findings support a circuit-level interpretation of neuroinflammation and identify the resolution threshold as a potentially modifiable determinant of chronic brain dysfunction and neurodegenerative vulnerability.

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 doi.org/10.32388/1H63QT.3

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—such as the acute blood–brain barrier (BBB) breakdown observed in systemic sepsis [1][2][3], ischemic stroke [4][5][6], and traumatic brain injury [7]—by infiltrating peripheral immune cells, notably Ly6C-high monocytes and T-lymphocyte subsets. [5][7][8][9] This coordinated immune activity is characterized by the production of inflammatory mediators that can modulate neuronal and synaptic function. [10][11][12][13]

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 resident immune populations at CNS borders has redefined immune privilege as a state of active regulation and specialized brain-immune crosstalk. [14][15][16][17] Within this framework, immune signaling is recognized as an integral component of brain physiology, supporting neural development, synaptic pruning, and the maintenance of functional circuits. [10][14][16] However, a critical distinction is required: the term 'neuroinflammation' should be reserved for contexts where multiple inflammatory hallmarks converge to disrupt homeostasis, avoiding the misclassification of basal or adaptive immune processes as pathological. [17][18] Consequently, circuit dysfunction emerges not from the presence of immune signals per se, but from a failure in this regulated crosstalk. [17]

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. [10][11][12][13] 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. [10][11][15][16]

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. [19][20] 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. [19][20]

Within this circuit-based framework, both infectious and sterile neuroinflammation activate largely overlapping molecular repertoires, despite being initiated by distinct stimuli. However, this distinction should be understood as a pragmatic analytic framework rather than a strict biological boundary; rather, it represents a spectrum of temporal trajectories. While infectious neuroinflammation—driven by PAMPs—is typically associated with rapid, transient responses, and sterile neuroinflammation—triggered by DAMPs—often involves sustained glial activation, significant exceptions exist. Persistent infectious states, such as viral reservoirs, can lead to chronic dysfunction, while sterile events like mild traumatic brain injury or post-surgical inflammation may resolve acutely. [11][20] Consequently, although both contexts disrupt synaptic plasticity and E/I balance, evidence suggests that the persistence of the inflammatory state, rather than the stimulus origin alone, is preferentially associated with chronic circuit impairment and long-term functional deficits. [19][20] To address this, a 'Circuit-level Neuroinflammatory Dynamics Framework' is proposed, shifting the focus from cellular morphology toward functional network output. This framework defines neuroinflammation as a dynamic modulator where stimulus temporality and glial immune memory (priming) dictate the transition from transient network 'noise' to chronic synaptic disconnection and E/I imbalance.

By critically integrating experimental and clinical evidence, this review aims to bridge the current fragmentation in the literature, examining how infectious and sterile contexts converge or diverge at the circuit level. Ultimately, the resolution threshold is identified as the primary boundary between reversible behavioral adaptation and permanent neurological impairment, providing a novel synthesis of how neuroimmune signaling redefines long-term circuit stability.

Methods

A structured, integrative literature search was conducted to identify and synthesize evidence on the effects of neuroinflammation on synaptic function and neural circuit dynamics, with a particular focus on the comparison between infectious and sterile inflammatory contexts. The search was limited to articles published between 2009 and 2026 to ensure a comprehensive overview of modern neuroimmunological advances.

The search was performed across multiple databases, including PubMed, Web of Science, Scopus, and Europe PMC. A combination of Boolean operators and thematic keyword clusters was used to capture distinct dimensions of the topic, including: [1] neuroinflammation (“neuroinflammation”, “CNS inflammation”), [2] etiological context (“infectious”, “viral”, “bacterial”, “parasitic”, “fungal”, “mycotic”, “encephalitis”, “sterile inflammation”, “aseptic”), [3] functional outcomes (“synaptic plasticity”, “neuronal circuits”, “network activity”, “functional connectivity”, “excitation–inhibition balance”), and [4] temporal dynamics (“acute”, “chronic”, “persistent”, “resolution”). Additional targeted queries incorporated mechanistic terms such as “microglia”, “astrocytes”, “cytokines”, and “immune signaling”, as well as exclusion operators to refine infectious and sterile models independently.

The search yielded a total of 2,404 records across databases (PubMed, n = 299; Web of Science, n = 363; Scopus, n = 655; Europe PMC, n = 1,087). (Figure 1) Europe PMC returned a higher number of records, likely reflecting its broader indexing scope, including preprints and non-peer-reviewed content.

Following database export and consolidation, duplicate records were removed. The remaining studies were screened by title and abstract based on conceptual relevance to central nervous system inflammation and its impact on neuronal or circuit-level function. Articles were excluded if they focused exclusively on peripheral inflammation, lacked functional or synaptic outcomes, or addressed neuroinflammation only tangentially without mechanistic or systems-level analysis. (Figure 1)

Full-text articles were subsequently assessed for eligibility. Selection was guided by relevance to the central aims of the review, prioritizing studies that examined the interaction between immune signaling and neural function across multiple levels of analysis. Experimental studies (in vitro and in vivo), human studies, narrative and systematic reviews, as well as selected case reports and reference texts or book chapters relevant to neuroimmune mechanisms were considered.

A total of 142 studies were included in the final synthesis. These were critically analyzed with attention to their methodological approach, model system, and relevance to the central research questions, allowing for a coherent integration of findings across different levels of evidence. Given the conceptual scope of the review, individual studies were considered in relation to multiple mechanisms when applicable. Additional references were incorporated to support conceptual definitions, historical context, introductory framework, and broader mechanistic background relevant to the interpretation of neuroimmune circuit dysfunction.

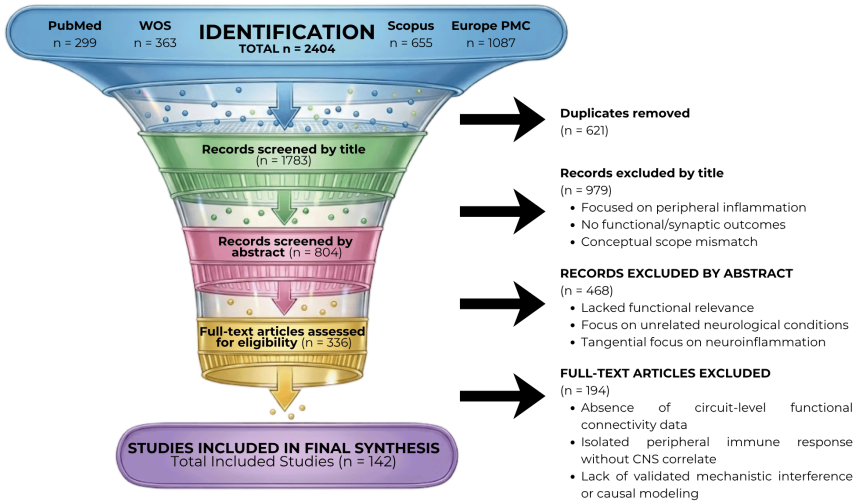

Figure 1. Literature Search and Study Selection Process. Overview of the literature search, screening, eligibility assessment, and study selection process used for the final evidence synthesis. A total of 2,404 records were identified across databases, and 142 studies were included in the final review.

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

The following sections operationalize the Circuit-level Neuroinflammatory Dynamics Framework (CNDF) introduced above. Consistent with its core premise —that functional network output, rather than cellular morphology, constitutes the relevant unit of analysis—the mechanistic evidence reviewed here is

doi.org/10.32388/1H63QT.3

organized around three interacting determinants: [1] the functional architecture of circuits sensitive to immune signals, [2] the glial interface that translates inflammatory inputs into synaptic and network-level changes, and [3] the cytokine-mediated mechanisms that define the resolution threshold separating transient network perturbation from consolidated circuit dysfunction.

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 the isolated properties of individual neurons or discrete anatomical regions. [21][22][23][24] 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. [21][22][23][24][25]

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. [24][25] 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. [26][27] Operationally, this dysfunction manifests as a quantifiable deviation from homeostatic synaptic weights—evidenced by impaired long-term potentiation (LTP) or long-term depression (LTD) [28][29][30]—and the desynchronization of network oscillations. In preclinical experimental models, inflammatory cytokines such as IL-1β and TNFα disrupt the E/I ratio by altering GABAergic interneuron signaling [31] [32] and hyperpolarization-activated cyclic nucleotide-gated channel 1 (HCN1)-mediated dendritic currents [33], leading to measurable declines in gamma and theta band power, as demonstrated in rodent in vivo and acute slice preparations. [34][35][36] 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. [26][27] Experimental models assessed using positron emission tomography (PET) and resting-state functional magnetic resonance imaging (rs-fMRI) indicate that this paradox is driven by a degradation of network efficiency; specifically, neuroinflammation disrupts "small-world" topology and nodal centrality independently of macroscopic atrophy. [28][37] [38] In clinical studies of patients with multiple sclerosis, disability correlates more closely with increased path length for information transfer and network noise than with visible lesion volume. [26][27] Consistent with this, preclinical studies show that experimental neuroinflammation impairs LTP and synaptic synchrony without necessarily inducing structural damage. [29][31] [39] Electrophysiological and functional neuroimaging studies in patients with multiple sclerosis and Alzheimer's disease have demonstrated aberrant patterns of synchronization, hyperexcitability, or network inefficiency even at early stages or in the presence of minimal atrophy [26][27][40]; complementary findings

in rodent aging models further confirm the structural–functional dissociation. [41]

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 act as non-canonical regulatory cues that alter neuronal excitability, synaptic transmission, and plasticity without necessarily inducing cell death. [21][23][26][40][42] Proinflammatory cytokines such as interleukin-1 beta (IL-1β) and tumor necrosis factor alpha (TNF-α) fine-tune the gain of synaptic receptors and neurotransmission, redefining the operational state of the network through the disruption of homeostatic plasticity. [26][40][42][43][44] While these mediators frequently coexist within inflammatory microenvironments, their effects are not entirely overlapping: IL-1β has been linked predominantly to the modulation of inhibitory neurotransmission and NMDA receptor–dependent excitability, whereas TNF-α more strongly regulates AMPA receptor trafficking and excitatory/inhibitory synaptic scaling, suggesting partially distinct mechanistic and temporal contributions to circuit dysfunction. [44]

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. [23][26][43] 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. [45][46]

Under the proposed framework, neuroinflammatory outcomes are defined by a shift from transient fluctuations in neuronal excitability to the consolidation of maladaptive plasticity and network reorganization. [26][40][41][44][47] In rodent experimental models of traumatic brain injury and lipopolysaccharide (LPS)-induced neuroinflammation, functional changes are considered reversible when electrophysiological and behavioral baselines are restored within a 7-to-14-day window [48][49][50], though whether this temporal boundary translates directly to human neuroinflammatory conditions remains to be established. This period serves as a critical boundary: while a human clinical study of sport-related concussion documents biomarker normalization within approximately one week post-injury [51], and rodent LPS models show comparable electroencephalography (EEG) recovery timelines [52], the failure to engage resolution programs by day 14—as demonstrated in rodent models of traumatic brain injury [48][53][54]—facilitates the persistence of aberrant circuit configurations. Consequently, the persistence of inflammation beyond this 14-day threshold—rather than the stimulus origin—is the primary driver of chronic circuit impairment, fueled by sustained microglial priming and permanent synaptic recalibration. [55][56][57] This transition is further reinforced by the sustained engagement of intracellular pathways—specifically NF-κB and PI3K–Akt–mTOR—which, alongside glial priming, facilitates the stabilization of pathological circuit architectures. [42][44][47] This mechanistic transition is consistent with clinical observations in neurodevelopmental, movement, and oculomotor disorders, as well as epilepsy, where functional circuit inefficiency

and E/I imbalance predominate over focal structural damage [58][59][60], though the mechanistic link between neuroimmune signaling and these clinical presentations remains largely inferred from preclinical models.

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. [61][62][63][64][65][66][67] Crucially, this activation induces immune memory, or "trained immunity," where sustained epigenetic and metabolic reprogramming [68][69][70] lowers the reactivity threshold. [71][72] This state dictates the glial system's long-term modulatory capacity, potentially perpetuating neuropathology long after the initial stimulus. [73][74]

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 [64][65][66][67], as demonstrated in rodent developmental and inflammatory models. [75][76][77] This interaction is synapse-type specific: microglial subpopulations can selectively modulate inhibitory synapses via GABAergic signaling, sculpting inhibitory connectivity without affecting excitatory synapses. [78] (Figure 2A) In pathological contexts, these same mechanisms may become maladaptive; for example, in rodent epilepsy models, with supporting validation in human epileptic tissue, microglial activation induced by hyperactive inhibitory neurons promotes the selective elimination of inhibitory synapses and amplifies network hyperexcitability through complement-dependent feedback circuits. [64][79]

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. [62][80] Evidence from rodent studies indicates that 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. [81] Neuroinflammation disrupts these functions, reducing glutamatergic uptake and promoting states of hyperexcitability and E/I imbalance. [62][80]

Bidirectional communication between microglia and astrocytes integrates these responses at the circuit level. In ex vivo slice preparations and rodent in vivo models, 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. [80][82] 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. [63][64][77]

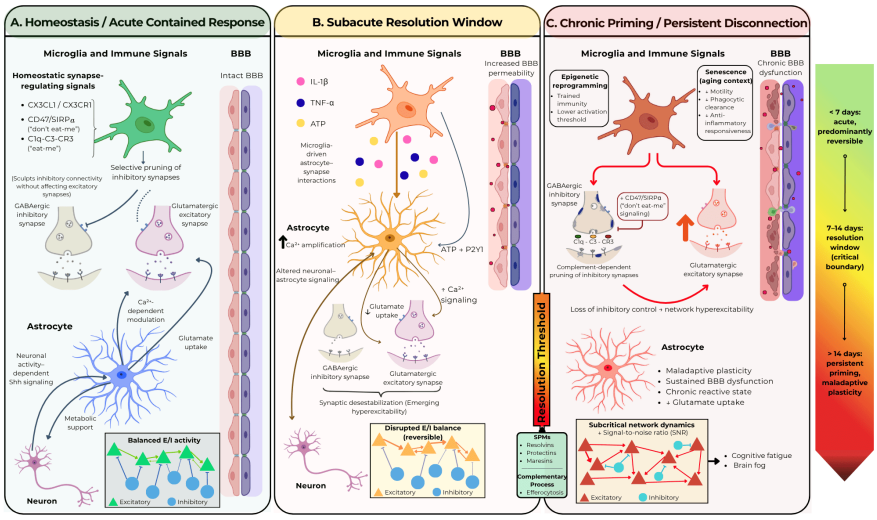

Figure 2. Sequential states of neuroimmune-circuit interaction: from homeostatic synaptic pruning to maladaptive glial priming and chronic disconnection. This figure presents a mechanistic, temporally organized model of the cellular and intercellular transitions that determine circuit-level functional outcomes during neuroinflammation. Three sequential states are depicted across panels A–C, with a right-lateral timeline indicating the temporal boundaries associated with each phase. **(A)** Under physiological conditions, microglia engage in activity-dependent synaptic pruning governed by homeostatic molecular signals, including CX3CL1/CX3CR1, CD47/SIRPα, and C1q–C3–CR3. This process is synapse-type specific and contributes to the maintenance of balanced excitation–inhibition (E/I) activity. Astrocytes support circuit stability through glutamate uptake, Ca^{2+}-dependent signaling, metabolic support, and neuronal activity-dependent transcriptional programs. **(B)** Neuroinflammatory activation promotes microglia–astrocyte crosstalk through the release of IL-1β, TNF-α, and ATP, leading to amplified astrocytic Ca^{2+} signaling, reduced glutamate uptake, increased BBB permeability, and emerging E/I imbalance. The Resolution Threshold represents the critical boundary at which specialized pro-resolving mediators (SPMs; resolvins, protectins, and maresins) together with efferocytosis can restore homeostatic programs and prevent progression toward chronic dysfunction. **(C)** Failure of resolution promotes glial priming characterized by trained immunity, epigenetic reprogramming, and lowered activation thresholds. Complement-dependent elimination of inhibitory synapses, accompanied by reduced CD47/SIRPα-mediated protection, favors sustained network hyperexcitability and chronic circuit dysfunction. Concurrently, astrocytes adopt a persistent reactive phenotype associated with maladaptive plasticity, reduced glutamate uptake, and ongoing BBB dysfunction. Collectively, these processes shift network dynamics toward a subcritical state characterized by a reduced signal-to-noise ratio, impaired information processing, and clinical manifestations such as cognitive fatigue and brain fog. Additional mechanisms implicated in chronic neuroinflammation, including cGAS–STING signaling and type I interferon-mediated disruption of synaptic homeostasis, are not shown.

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

doi.org/10.32388/1H63QT.3

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][37][61][63][83][84][85][86]

IL-1β regulates synaptic plasticity in a concentration-dependent manner, suppressing 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. [28][37][38][83][87] 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. [43]

In rodent and in vitro models, TNF-α modulates plasticity through synaptic scaling mechanisms that adjust surface expression of AMPA receptors and bidirectionally regulate E/I balance [63][64]; IL-6 contributes similarly to synaptic dysfunction in states of persistent neuroinflammation, as demonstrated in preclinical paradigms. [28][37][83] In contrast, cytokines such as IL-13 may exert modulatory and neuroprotective effects by enhancing phosphorylation of glutamatergic receptors and activating cAMP response element-binding protein (CREB)-dependent transcriptional programs. [88]

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. [38][58][63][87] Sustained dysregulation of these pathways promotes excessive synaptic pruning, loss of plasticity, and persistent network alterations. [58][64]

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. [28][37][44][63][87]

The divergence between these trajectories is dictated by the resolution threshold —the primary boundary between reversible adaptation and permanent impairment. This threshold is operationally defined by the capacity of active resolution programs, specifically specialized pro-resolving mediators (SPMs) such as resolvins and maresins [89][90], to quench glial activation and terminate the NLRP3-IL-1β signaling axis. [91] A failure to engage these programs by the subacute phase allows acute network 'noise' to transition into self-perpetuating chronic inflammatory circuits, as demonstrated in preclinical models [92][93], thereby redefining long-term circuit stability through sustained glial immune memory and permanent synaptic recalibration. [89][92][94][95] (Figure 2B)

Collectively, the mechanistic evidence reviewed in this section establishes the conceptual substrate of the CNDF: neuroinflammation does not act on circuits as a uniform perturbation but rather as a temporally graded modulator whose functional output is determined by the interaction between cytokine kinetics, glial activation states, and the availability of active resolution programs. Under this framework, the infectious or sterile origin of the stimulus defines the initial conditions of this interaction—particularly the intensity and kinetics of PRR engagement—but does not, by itself, determine the circuit-level outcome. The

following sections examine how these CNDF-derived predictions are borne out across infectious and sterile inflammatory contexts.

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. This integration is highly sensitive to the anatomical site of the insult, as the functional response differs significantly between parenchymal microglia and border-associated macrophages. [96]

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. [62][97][98][99][100][101][102][103][104][105] 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. [101] Likewise, activation of the complement cascade (C1q–C3) and its receptor CR3 mediates synaptic pruning processes induced by both infectious and sterile insults. [101] (Figure 3A)

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. [101][102] (Figure 3A) Additional modulatory signals, such as canonical and noncanonical WNT pathways, can bias glial responses toward pro-resolving 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. [103][104][105]

While the following sections contrast the typical trajectories of infectious and sterile neuroinflammation, this distinction is not a rigid dichotomy. The functional outcome is not a binary property of the stimulus origin but a manifestation of a neuroinflammatory spectrum. [106] Within this spectrum, the 'Infectious' and 'Sterile' labels serve as mechanistic archetypes to describe successful resolution versus persistent priming, acknowledging that clinical reality often involves hybrid or atypical trajectories.

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. Under conditions of effective immune clearance, these responses are often associated with predominantly transient network dysfunction, although persistent inflammatory trajectories may also occur. [28][37][44] This pattern is characterized by the rapid release of cytokines and chemokines, production of nitric oxide, and strong induction of antiviral and antibacterial programs. [62][97][98][102] At the molecular level, for example, in primary microglial cell cultures, LPS efficiently activates TLR4 and downstream MAPKs, promoting marked expression of TNF-α and reactive nitrogen species. [101][102] In a murine model of viral encephalitis caused by Japanese encephalitis virus, coupled activation of NMDA glutamatergic receptors in microglia has been associated with Ca^{2+} mobilization, activation of calcium/calmodulin-dependent protein kinase II (CaMKII), NF-κB, and AP-1, increased oxidative and endoplasmic reticulum stress, and the emergence of a highly reactive and neurotoxic microglial phenotype. [107] (Figure 3B)

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. [108][109][110][111] As demonstrated in in vitro human astrocyte cultures and reviewed in the preclinical literature, activated astrocytes amplify and modulate the inflammatory response, disrupt BBB integrity through cytokine-mediated endothelial activation and increased vascular permeability, and directly affect synaptic transmission through changes in glutamate uptake and gliotransmitter release. [110][112][113] Bidirectional microglia–astrocyte crosstalk can escalate neuroinflammation, perturb synaptic homeostasis, and generate acute changes in network excitability and functional connectivity. [108][109][114] (Figure 3B) In this context, astrocytes may also act as viral reservoirs, contributing to the persistence and dissemination of infection within the CNS. [110]

However, the assumption of universal reversibility in infectious contexts has critical exceptions across all major pathogen categories. [115] As reviewed in multiple narrative and translational syntheses, viral infections can establish persistent CNS reservoirs or drive long-term neuroimmune dysregulation and multidimensional neurodegeneration, even after initial pathogen clearance. [108][109][116][117][118][119][120] Based on review-level synthesis of clinical and preclinical data, bacterial infections such as meningitis and CNS tuberculosis frequently trigger destructive glia-neutrophil crosstalk and sustained microglial activation, culminating in irreversible excitotoxicity and neuronal death. [121][122][123][124][125] Evidence from rodent models of parasitic infection indicates that Toxoplasma gondii forms chronic tissue cysts that provoke persistent microvascular dysfunction, sustained BBB disruption, chronic neurovascular inflammation, and long-lasting behavioral alterations [126][127][128], findings further supported by narrative review-level synthesis. [129][130][131] Furthermore, fungal pathogens exemplify chronic trajectories; Candida albicans has been

shown to induce glial granulomas associated with amyloid accumulation in experimental CNS infection studies [132], a phenomenon further discussed in narrative reviews. [133][134] Similarly, other fungal infections, including Talaromyces marneffei, have been implicated in Tau pathology and severe M1-polarized microglial inflammation across both experimental and clinical settings. [135][136] Ultimately, these atypical trajectories demonstrate that infectious stimuli can bypass normal clearance mechanisms, acting as persistent triggers for long-term maladaptive plasticity and neurodegenerative diseases. [115]

In essence, these observations suggest that the long-term impact of infectious neuroinflammation is not merely a product of the pathogen's molecular signature but rather a consequence of whether the immune response escapes homeostatic control, inducing a terminal reconfiguration of the excitatory-inhibitory landscape.

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. [10][83][111][137] Evidence from preclinical subarachnoid hemorrhage models indicates that 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. [138] In this context, microglial activation does not adopt a rigid binary phenotype but rather dynamic mixed states modulated by local and systemic signals. [104][138] Astrocytes assume a more prominent role in the long-term modulation of synaptic plasticity, metabolic support, maintenance of the extracellular environment, and chronic neurovascular regulation, contributing to sustained BBB dysfunction and low-grade circuit instability rather than acute excitotoxicity. [6][10][83][139] This contribution increases progressively, particularly in chronic neurodegenerative conditions, where astrocytes sustain maladaptive plasticity states and functional network disconnection. [10][83] (Figure 3C)

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 in mice 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. [75] This process is complement-dependent, with upregulation of the C1q–C3–CR3 pathways, and is exacerbated in pathological contexts. [98] In Alzheimer's disease, sustained microglial activation may fail to efficiently clear Aβ, favoring non-resolving inflammation that accelerates synaptic loss and cognitive decline. [140] 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. [29] Although both central and peripheral inflammation can affect LTP, only sterile central inflammation is associated with these particular molecular changes. [29]

Beyond chronic trajectories, sterile neuroinflammation is not inherently synonymous with irreversible decay. Under specific conditions, acute sterile insults—such as mild traumatic brain injury, transient ischemia, or isolated seizure activity—can follow a self-limiting course that avoids permanent circuit remodeling. [49][141][142][143] Successful recovery in these contexts depends on active, endogenous resolution programs driven by SPMs, including resolvins and protectins, as supported by experimental and review-level evidence across multiple neuroinflammatory settings. [90][144][145][146][147] These lipid mediators, alongside efficient debris clearance via efferocytosis [148][149], orchestrate the dynamic reprogramming of microglia and infiltrating macrophages toward wound-healing, neurotrophic phenotypes, as demonstrated in self-limiting brain inflammation and tissue-repair models. [54][141][150] Evidence from microglial turnover and early monocyte blockade suggests that acute sterile trauma and epileptogenesis can be successfully arrested before irreversible damage occurs. [53][146][151][152][153]

From an integrative perspective, these findings imply that sterile neuroinflammation drives long-term circuit decay primarily when these active resolution pathways fail; an inability to efficiently clear DAMPs prevents the restoration of homeostatic programs, ultimately leading to an insidious network reconfiguration of synaptic weights and the stabilization of a persistently dysfunctional network state.

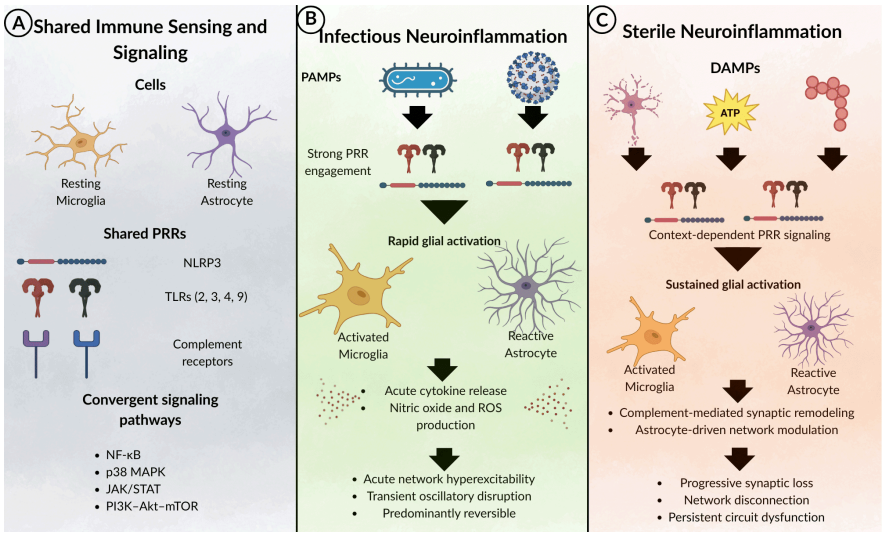

Figure 3. Shared and divergent immune signaling pathways in infectious and sterile neuroinflammation. This figure illustrates the shared immune-sensing architecture and the divergent downstream consequences of infectious and sterile neuroinflammation at the circuit level. **(A)** Both infectious and 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. [10][97][98][154][155]

In acute ex vivo hippocampal slice preparations, experimental exposure to TLR ligands such as LPS, peptidoglycan, or poly(I:C) triggers acute microglial activation with the release of proinflammatory cytokines and reactive oxygen and nitrogen species, producing immediate effects on network

dynamics. [97] These alterations—including slowing of gamma oscillations, emergence of beta-band activity, and episodes of neuronal hyperexcitability—occur even in the absence of neuronal death. [97][98] In controlled experimental endotoxemia studies in healthy human volunteers, acute intravenous LPS administration disrupts resting-state connectivity by reducing functional coupling between the amygdala, insula, and cingulate cortex, while increasing temporal variance in the amygdala. [156][157] Consistent with these human findings, rodent EEG studies demonstrate frequency-specific reductions in alpha and beta-gamma connectivity, reflecting a rapid collapse of high-frequency synchronization. [52] Repeated or combined PRR activation exacerbates these effects, with nitric oxide and microglial-derived oxidants acting as central mediators of more severe network dysfunction. [97]

Experimental studies further indicate that microglial responses to innate immune stimuli are sexually dimorphic, with male microglia generally displaying stronger proinflammatory responses to LPS and higher TLR2-associated inflammatory signaling, whereas estrogen-related pathways in females may favor comparatively less inflammatory activation states. These differences may contribute to variability in susceptibility to neuroinflammatory network dysfunction. [104]

In rodent 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. [158] 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. [159]

In preclinical models and as synthesized in narrative reviews, 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. [10][154][155][160] In this context, chronic activation of pathways such as PI3K/Akt, NF-κB, or cyclic GMP-AMP synthase-Stimulator of Interferon Genes (cGAS–STING) sustains persistent production of type I interferons and proinflammatory cytokines, promoting synaptic loss and neurodegeneration. [105][154][160][161] In rodent models of viral encephalitis and sterile neurodegeneration, sustained type I interferon signaling directly disrupts synaptic homeostasis and activity-dependent plasticity, favoring states of functional disconnection in cortical and hippocampal networks. [154][160][162] In clinical neuroimaging studies of patients with Alzheimer's disease, multimodal studies combining PET and rs-fMRI confirm that persistent neuroinflammation independently correlates with a degradation of network small-worldness and global efficiency. [163][164]

In longitudinal clinical studies of cognitively non-demented older adults and patients along the Alzheimer's disease spectrum, higher baseline peripheral inflammatory markers predict lower connectivity within the Default Mode Network, where an increase in characteristic path length precedes detectable structural damage. [165][166] In line with this, 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, driven by cytokines acting as

neuromodulators that alter action potential thresholds and increase neural stochasticity [167][168], whereas the latter are associated with complement-mediated persistent synaptic loss and chronic circuit dysfunction. [114][169][170] Ultimately, these alterations represent a shift toward subcritical network dynamics, where the reduction in signal-to-noise ratio (SNR) provides a computational basis for the cognitive fatigue and 'brain fog' observed across the neuroinflammatory spectrum. [171][172] (Figure 2C)

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. [97][158] In rodent models of acute LPS-induced neuroinflammation, this acute hyperexcitability is closely linked to a disruption of neuronal chloride regulation: peripheral LPS triggers a downregulation of KCC2-mediated chloride extrusion and the emergence of NKCC1-mediated uptake in the dentate gyrus, facilitating a collapse of GABAergic inhibition. [173] Furthermore, glial cells operate as active modulators of this balance; astrocytes detect interneuron activity to upregulate inhibitory tone through purinergic signaling, while microglia provide essential negative feedback by converting ATP to adenosine—a homeostatic loop whose impairment is associated with synchronized hyperactivity and increased seizure susceptibility. [174][175] In rodent models of sterile neuroinflammation and Alzheimer's-related pathology, sustained microglia-mediated synaptic pruning and progressive loss of excitatory synapses contribute to functional disconnection and cognitive decline. [29][140] This synaptic loss is causally linked to the C1q–C3–CR3 complement signaling axis; targeted inhibition of these pathways, or use of IL-1 receptor antagonists, has been shown in rodent models to prevent microglial synaptic engulfment, rescue LTP, and normalize theta oscillations. [176][177][178]

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. [97] Studies using ex vivo hippocampal tissue have shown that early network dysfunction appears to be driven predominantly by microglia-derived reactive oxygen and nitrogen species, which impair gamma oscillatory activity and synaptic synchronization despite preserved structural integrity of parvalbumin- and somatostatin-positive interneurons. [97] This dissociation between functional impairment and overt interneuron degeneration may reflect the initially reversible and metabolically mediated nature of acute inflammatory network disturbances. [97]

Recent transcriptomic studies in experimental models of multiple sclerosis and status epilepticus further reveal that neuroinflammation induces region-specific reconfigurations of receptor subunits and splicing factors. [179][180] In an integrative sense, these alterations shift circuit dynamics toward a subcritical state characterized by impaired 'neuronal avalanches', providing a mechanistic explanation for why restoring neuronal excitability or connectivity can rescue network-level criticality and cognitive performance. [172]

Inflammatory Persistence, Glial Priming, and Functional Circuit Outcomes

Network outcomes are driven by the dynamic interaction between microglia and astrocytes, whose contribution to remodeling depends on the stimulus profile. In infectious contexts, these populations facilitate rapid damage containment; however, sterile and chronic scenarios sustain states that disrupt synaptic and metabolic homeostasis. Specifically, acute, high-intensity activation promotes rapid, complement-dependent synaptic pruning associated with reversible network dysfunction. [75][97][98][102][158] Conversely, chronic sterile stimuli drive sustained phenotypic changes and chronic pruning, characterized by prolonged microglial-synaptic contacts and excessive elimination of dendritic spines. [75][97][98][101][102][105][159]

The duration of the neuroinflammatory state determines the shift from transient alterations to maladaptive plasticity. Self-limited episodes—whether infectious or sterile—induce reversible E/I imbalance and short-term cognitive deficits. [10][54][83][181][182][183][184] In contrast, unresolved neuroinflammation progresses toward circuit disconnection and neurodegeneration through prolonged exposure to IL-1β, TNF-α, and IL-6, alongside the persistent engagement of the NLRP3 inflammasome. [10][83][181][184]

In in vitro microglial preparations and as synthesized in narrative reviews, this transition is mediated by glial priming, or 'innate immune memory,' characterized by epigenetic reprogramming—including chromatin modifications and stable gene expression changes—and metabolic shifts toward glycolysis. [68][69][70][185][186] Consequently, primed microglia exhibit disproportionate responses to secondary, low-intensity stimuli, amplifying mediator release and circuit vulnerability. [61][68][71][72][181][187][188][189] (Figure 2C)

Functionally, priming results in persistent circuit sensitization, impaired synaptic plasticity, and the slowing of network oscillations, such as gamma activity. [34][61][72][187][190][191] Rodent models of aging, traumatic brain injury, and neurodegeneration demonstrate that this sensitized state conditions exaggerated responses to subsequent challenges, durably compromising the circuit's capacity for functional recovery. [61][72][188] Within the aging brain, this primed state also acquires features commonly associated with microglial senescence, including impaired motility, defective phagocytic clearance, reduced responsiveness to anti-inflammatory signaling, and a chronic low-grade inflammatory phenotype that further increases susceptibility to maladaptive neuroinflammatory responses. [72] Within the CNDF, this sensitized state can be conceptualized as a leftward shift of the effective resolution threshold, reducing the circuit's capacity to return to functional homeostasis. (Figure 5A)

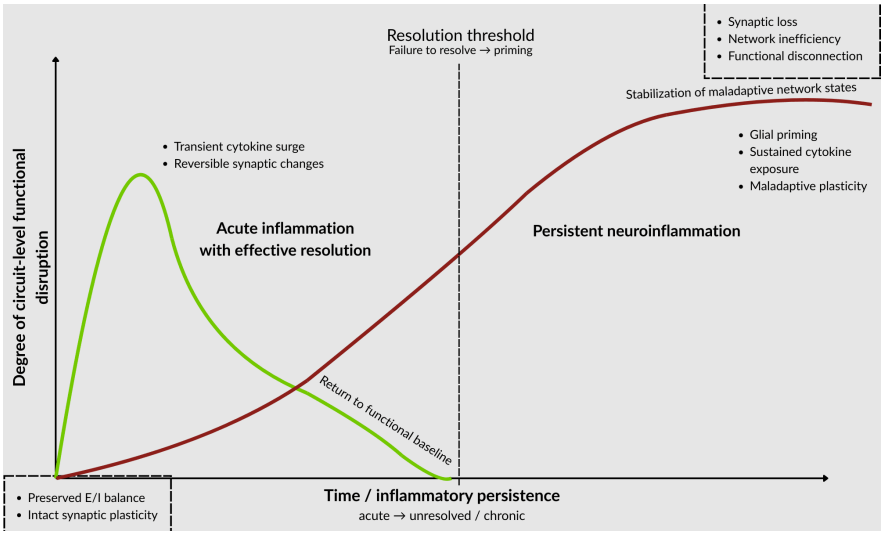

Figure 4. Inflammatory persistence, glial priming, and circuit-level functional outcomes. This conceptual model illustrates how the temporal persistence of neuroinflammatory signaling shapes circuit-level functional outcomes, independently of the initial inflammatory origin. The x-axis represents time 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.

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. [192][193][194] In contrast, sterile stimuli generate more gradual initial responses but with a slower onset and greater persistence, favoring long-lasting alterations in synaptic plasticity and chronic circuit dysfunction. [10][181][183]

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. [68][71][72][181][191] Furthermore, these outcomes are contingent upon regional vulnerability; circuits in the hippocampus and prefrontal cortex exhibit lower thresholds for cytokine-induced E/I collapse compared to brainstem regulatory networks, suggesting that anatomical location is as critical as temporal persistence. [96]

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 the CNDF, this finding is not merely an empirical observation but a structural prediction: once glial priming is established, the circuit's inflammatory history and resolution capacity—rather than the stimulus category—become the primary drivers of the network-level outcome. Neuroinflammation thus emerges as a circuit-emergent property, dynamically shaped by the accumulated interaction between immune signals, glial activation states, and the temporal availability of pro-resolving programs.

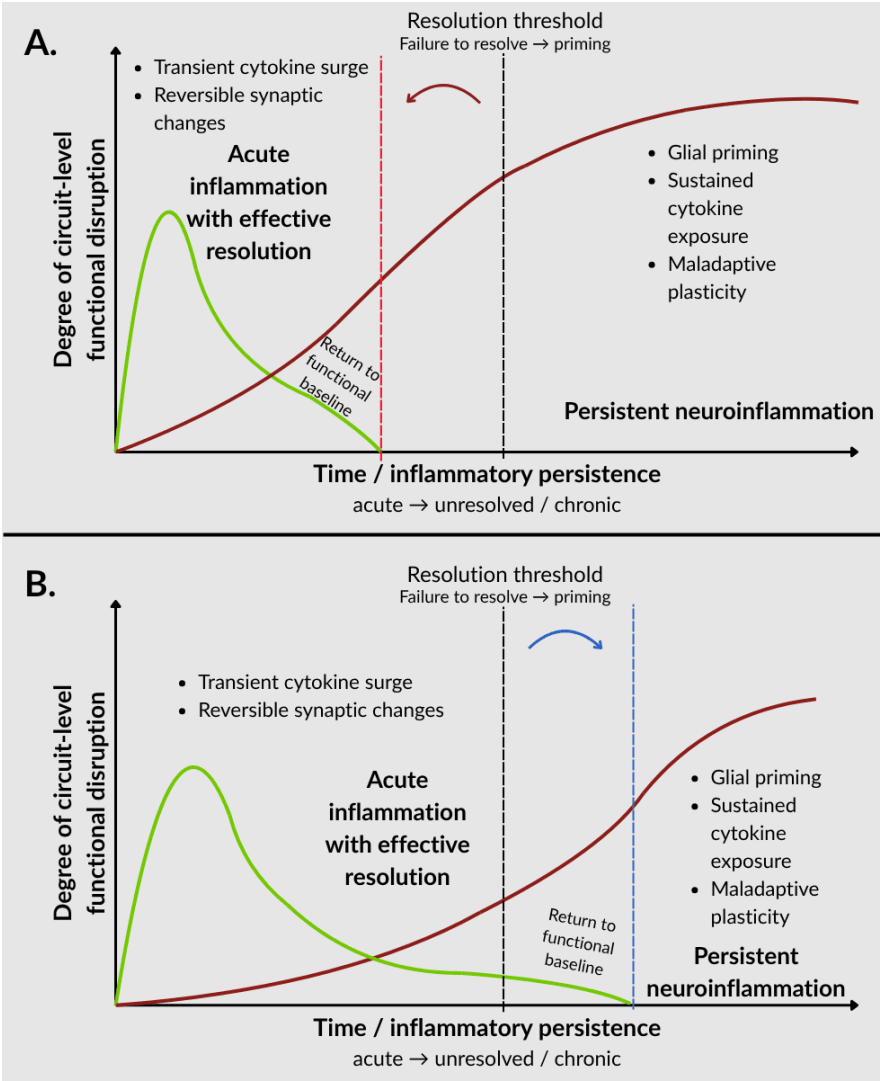

Figure 5. Conceptual modulation of the resolution threshold by glial priming and pro-resolving interventions. (A) Factors associated with glial priming—including innate immune memory, aging-related sensitization, and impaired resolution capacity—may increase circuit vulnerability to subsequent inflammatory challenges, favoring an earlier transition toward persistent neuroinflammation and maladaptive plasticity. This state is represented as a leftward displacement of the resolution threshold. **(B)** Conversely, interventions that promote inflammatory resolution, including specialized pro-resolving mediators (SPMs), vagal anti-inflammatory signaling, and selective modulation of neuroimmune pathways, may preserve recovery capacity and extend the period during which functional homeostasis remains achievable. This state is represented as a rightward displacement of the resolution threshold. The threshold shifts depicted are intended as a conceptual extension of the CNDF and illustrate how factors influencing resolution capacity may alter the trajectory of circuit-level outcomes.

Note: Whereas Figure 4 examines how inflammatory persistence influences circuit-level outcomes under a fixed resolution threshold, the present figure explores the conceptual possibility that biological factors may alter the position of the threshold itself.

doi.org/10.32388/1H63QT.3

Descending Autonomic Modulation of Neuroinflammation

Autonomic circuits, particularly the 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. [195][196][197]

During PAMP-induced infectious neuroinflammation, including experimental LPS-induced inflammation and other infectious contexts discussed in the autonomic neuroimmunology literature, 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. [197][198][199] In contrast, in sterile neuroinflammatory contexts, activation of these reflexes is less effective, favoring the persistence of low-grade inflammatory states. [10][200]

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. [182][198][201] 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. [10][137][182][201] 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. In clinical studies of patients with acute bacterial and viral infections, systemic and central inflammatory activation induces sickness behavior, characterized by fatigue, cognitive slowing, and affective changes, in association with transient elevations of IL-6, TNF-α, and CRP. [202][203][204] 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. [202][203]

In clinical reviews of post-COVID syndrome and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), sterile neuroinflammation and post-infectious states are associated with persistent fatigue, sustained cognitive impairment, and affective disturbances that outlast the initial insult, with durable deficits in attention, memory, and executive functions [205][206]; preclinical rodent models further demonstrate the NLRP3 inflammasome-dependent neuronal changes that may underlie such enduring alterations. [181] Supporting this view, experimental models show that chronic

inflammation compromises synaptic plasticity and network efficiency, thereby promoting persistent cognitive and emotional dysfunction. [171][181][207]

Altogether, 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. [181][202][205] 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. [181][208]

Translational Perspectives: Monitoring and Modulating Persistent Neuroinflammation

The transition from acute to chronic neuroinflammation can be assessed using complementary neuroimaging modalities, with Translocator Protein (TSPO)-PET remaining the most established technique for detecting glial activation in vivo. [209][210] Acute inflammatory states typically show focal increases in TSPO binding, whereas chronic neuroinflammation is associated with more diffuse and persistent signals, although interpretation is limited by reduced cellular specificity and methodological variability. [209][211] Resting-state fMRI further demonstrates that persistent neuroinflammation is linked to disrupted functional connectivity and large-scale network dysfunction, particularly in neurodegenerative and post-inflammatory conditions. [212][213] More recently, Synaptic Vesicle Glycoprotein 2A (SV2A)-PET has emerged as a sensitive marker of synaptic loss secondary to chronic neuroimmune injury, often identifying pathology before structural atrophy becomes evident on conventional MRI. [214] [215] Advanced MRI-based approaches, including diffusion-weighted MR spectroscopy and diffusion imaging, also show promise as noninvasive methods for characterizing microglial and astrocytic activation. [216][217] In parallel, novel non-TSPO PET tracers targeting monoamine oxidase B (MAO-B), Colony Stimulating Factor 1 Receptor (CSF1R), and purinergic receptors are being developed to improve the specificity of neuroinflammation imaging and better distinguish chronic maladaptive inflammation from acute immune activation. [218]

Current therapeutic strategies for chronic neuroinflammation increasingly focus on selective modulation of key inflammatory pathways rather than broad immunosuppression. NLRP3 inflammasome inhibitors, including MCC950, dapansutrile (OLT1177), and newer brain-penetrant compounds such as NT-0796, have shown promising preclinical effects by reducing microglial activation, synaptic dysfunction, and cognitive impairment in neurodegenerative models, potentially favoring a more pro-resolving neuroimmune state and limiting maladaptive synaptic remodeling. [219][220][221][222] Complement-targeted therapies show evidence at multiple levels: C1q blockade has entered a Phase 1b clinical trial in Huntington's disease patients, [223] while C5aR1 antagonism has demonstrated suppression of inflammatory glial responses and synaptic preservation in Alzheimer's mouse models. [224] Within the CNDF, these findings suggest a conceptual rightward displacement of the effective resolution threshold, whereby recovery remains achievable over a longer period before maladaptive states emerge. (Figure 5B) Other emerging approaches include vagus nerve stimulation and SPMs, although these strategies remain in relatively

early translational and clinical stages. [225][226] Notably, vagus nerve stimulation has strong mechanistic support through activation of the cholinergic anti-inflammatory pathway and α7 nicotinic acetylcholine receptor signaling, with additional evidence suggesting promotion of active inflammatory resolution through increased SPM biosynthesis. [225][227][228] However, despite encouraging preclinical findings, current human studies have not consistently demonstrated significant cytokine reduction or reproducible anti-inflammatory effects, highlighting an important translational gap that may depend on stimulation parameters, disease context, and circuit-specific targeting. [229][230][231]

Discussion

The reviewed literature, examined through the lens of the Circuit-level Neuroinflammatory Dynamics Framework, supports its central premise: neuroinflammatory processes induced by infectious and sterile stimuli share a largely overlapping molecular architecture—based on PRR activation, common inflammatory cascades, and bidirectional microglia–astrocyte communication—yet diverge in their functional circuit consequences primarily as a function of stimulus temporality and glial immune memory, rather than of the stimulus origin per se. Specifically, the evidence converges on three CNDF-consistent conclusions: (i) acute, self-limited inflammation—whether infectious or sterile—induces transient network 'noise' that resolves when pro-resolving programs are successfully engaged; (ii) failure to cross the resolution threshold, regardless of stimulus category, promotes glial priming and the stabilization of maladaptive plasticity states; and (iii) the transition from reversible circuit perturbation to persistent functional disconnection is operationally predicted by the duration, resolution capacity, and inflammatory history of the circuit rather than by the nature of the initiating stimulus.

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.

An additional limitation is that a substantial proportion of experimental studies have been conducted predominantly in male rodents. This is particularly relevant given evidence that microglial responses to innate immune stimuli are sexually dimorphic, with differences in inflammatory signaling and activation states that may influence susceptibility to neuroinflammatory network dysfunction. Consequently, current models may not fully capture sex-dependent variability in neuroimmune and circuit-level outcomes.

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.

Conclusion

The evidence synthesized in this review supports a reconceptualization of neuroinflammation as a circuit-emergent, temporally governed process rather

than a stimulus-defined binary state. Formalized through the Circuit-level Neuroinflammatory Dynamics Framework, the central finding is that infectious and sterile stimuli, while engaging largely overlapping molecular architectures, diverge primarily in the kinetics and persistence of their functional consequences at the network level. Across both contexts, the resolution threshold emerges as the critical operational boundary: a subacute window defined by the capacity of specialized pro-resolving mediators (SPMs) and efferocytosis to quench glial activation and terminate the NLRP3–IL-1β signaling axis, beyond which transient network perturbation consolidates into maladaptive plasticity and chronic circuit disconnection. Inflammatory duration and resolution capacity, rather than stimulus origin, are therefore the primary determinants of whether E/I balance is restored or permanently recalibrated, and of whether synaptic weights return to homeostatic baselines or stabilize into a persistently dysfunctional network state.

An important dimension emerging from this synthesis concerns the therapeutic modifiability of the neuroimmune response. The emerging strategies reviewed—including NLRP3 inflammasome inhibitors, complement-targeted therapies, SPM-based approaches, and vagus nerve stimulation—converge mechanistically on pathways that support active inflammatory resolution and limit maladaptive glial remodeling. While their translational validation remains incomplete, their collective mechanistic profile suggests that the transition toward persistent circuit dysfunction is not an inevitable consequence of neuroinflammation, but rather a process that may be amenable to intervention, particularly when targeting the subacute phase during which resolution programs are still inducible. This positions the modulation of glial activation states and resolution biology as a promising frontier in the prevention of neuroinflammation-associated circuit impairment.

From a translational perspective, advancing this field will require experimental designs that integrate temporal and circuit-level dimensions as primary variables, moving beyond categorical comparisons of inflammatory models toward longitudinal approaches that capture the dynamics of glial state transitions, resolution program engagement, and functional network recovery. Characterizing how individual and contextual factors—including age, prior inflammatory history, and regional circuit vulnerability—interact to determine neuroimmune trajectories will enable more precise stratification of neuroinflammatory risk, the identification of individualized intervention windows, and ultimately a more accurate framework for interpreting the transition between reversible adaptation and permanent circuit impairment across the full spectrum of neuroinflammatory disease.

Statements and Declarations

Funding

No specific funding was received for this work.

Potential Competing Interests

No potential competing interests to declare.

Data Availability

Data sharing is not applicable to this article as no new primary data were created or analyzed in this study. All literature synthesized is cited in the reference list.

Author Contributions

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

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Declarations

Funding: No specific funding was received for this work.
Potential competing interests: No potential competing interests to declare.