Qeios

Peer Review

Review of: "Infectious vs. Sterile Neuroinflammation: Differential Consequences on Neuronal Circuitry"

Karen Bohmwald[1]

1. Universidad Autónoma de Chile, Temuco, Chile

The manuscript presents an extensive narrative review addressing the impact of neuroinflammation on neuronal circuit function, with a central emphasis on temporality, persistence, and resolution as primary determinants of functional outcomes. The topic is relevant and conceptually ambitious. The attempt to shift the analytical focus from the infectious versus sterile origin of inflammatory stimuli toward the dynamics of the inflammatory course is intellectually stimulating and potentially valuable for the field. The review is well-referenced and integrates molecular, cellular, and systems-level perspectives. Nevertheless, several conceptual and structural limitations substantially weaken the analytical rigor of the manuscript in its current form.

The central thesis that the duration and resolution of neuroinflammation are more determinant for circuit-level outcomes than the origin of the stimulus is repeatedly asserted but not sufficiently demonstrated through critical comparative analysis. The argument largely relies on parallel interpretations of separate bodies of literature rather than on direct experimental comparisons between infectious and sterile paradigms under controlled conditions. In many sections, mechanistic overlap in PRR signaling is emphasized to support convergence, yet pathogen-specific transcriptional programs, metabolic signatures, and immune compartmentalization are acknowledged only briefly and then downplayed. This produces a conceptual tension: while the manuscript recognizes qualitative differences in innate immune activation depending on stimulus type, it subsequently minimizes their long-term relevance without adequately engaging with contradictory data. A more balanced and critically evaluative approach is necessary to avoid oversimplification.

The review is framed as a critical integration, but in practice, it functions predominantly as an expansive narrative synthesis. The methodological heterogeneity of the cited studies is mentioned but not deeply

 doi.org/10.32388/6G7CRB

examined. For example, LPS and poly(I:C) are repeatedly used as models of infectious neuroinflammation, yet these ligands do not reproduce pathogen replication, cell tropism, or spatiotemporal immune compartmentalization. Similarly, sterile neuroinflammation is often equated with chronic neurodegenerative models or protein aggregation paradigms, which involve complex degenerative cascades not reducible to classical DAMP-driven signaling. The absence of systematic distinctions between acute peripheral immune activation, direct CNS infection, autoimmune inflammation, and chronic neurodegeneration weakens mechanistic precision and risks conflating distinct biological entities under a single conceptual umbrella.

The contrast between “acute and reversible” infectious neuroinflammation and “persistent and maladaptive” sterile inflammation is presented as a recurring pattern. This dichotomy, however, is too schematic. Severe infectious conditions, including viral encephalitis and systemic inflammatory states, can result in enduring cognitive deficits and structural alterations. Conversely, certain sterile inflammatory events can resolve without lasting circuit disruption. The manuscript does not sufficiently define boundary conditions such as stimulus intensity, anatomical localization, developmental stage, systemic immune status, or prior inflammatory history. Without such qualifiers, the proposed framework risks appearing deterministic rather than probabilistic.

The sections on glial priming and innate immune memory are conceptually promising but mechanistically underspecified. The manuscript refers to epigenetic reprogramming, chromatin remodeling, and metabolic shifts, yet it does not clearly differentiate trained immunity, immune tolerance, age-related sensitization, and chronic primed states. These processes are mechanistically distinct and may yield divergent functional consequences at the synaptic and network levels. Moreover, the connection between primed glial phenotypes and specific electrophysiological signatures such as gamma oscillatory slowing, persistent impairment of LTP, or network inefficiency is asserted more strongly than the cited evidence directly supports. The causal chain from molecular reprogramming to measurable circuit dysfunction requires tighter articulation.

Although the manuscript aspires to translational relevance, human data are only superficially incorporated. Circuit-level conclusions are largely extrapolated from rodent models of LTP modulation, synaptic pruning, and microglial morphology. Functional connectivity studies, PET imaging of microglial activation, longitudinal cognitive trajectories following infection or sterile injury, and biomarker-based assessments of inflammatory persistence in patients are not sufficiently integrated. This limits the

translational robustness of the proposed conceptual framework and reinforces the impression that the conclusions are primarily model-derived.

Structurally, the manuscript exhibits substantial redundancy. The emphasis on temporality and resolution appears in the Introduction, is reiterated in the Functional Framework, is elaborated again in the sections on inflammatory persistence, and is restated in the Conclusions with limited incremental refinement. This repetition dilutes argumentative precision. In addition, several key terms such as “circuit dysfunction,” “functional disconnection,” “network inefficiency,” and “resolution capacity” are used conceptually but not operationally defined. Without explicit criteria, these constructs remain descriptive rather than analytically rigorous. Minor textual inconsistencies and duplications also indicate the need for careful editorial revision.

Despite these limitations, the manuscript demonstrates notable strengths. It integrates glial biology with synaptic plasticity and excitation–inhibition balance in a coherent manner. The emphasis on microglia–astrocyte crosstalk as a dynamic interface between immune signaling and circuit modulation is well developed. The inclusion of autonomic and descending regulatory pathways adds mechanistic depth. The breadth of recent literature cited reflects a comprehensive engagement with contemporary research.

However, in its current form, the manuscript requires substantial revision to achieve the level of analytical rigor implied by its ambitions. The argument would be strengthened by explicitly distinguishing between different categories of inflammatory models, clarifying the specific experimental evidence supporting convergence or divergence between infectious and sterile paradigms, and tempering generalizations regarding reversibility versus persistence. Greater integration of human translational data is necessary to substantiate circuit-level claims beyond preclinical models. Conceptual constructs such as priming, resolution threshold, and functional disconnection should be operationally defined and mechanistically anchored. Redundancy should be reduced to sharpen the argumentative trajectory and enhance clarity.

Only after these issues are addressed will the proposed trajectory-based framework convincingly advance understanding of how neuroinflammation shapes neuronal circuit function across pathological contexts.

Declarations

Potential competing interests: No potential competing interests to declare.