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Peer Review

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

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Peer Review Report

Manuscript title: Infectious vs. Sterile Neuroinflammation: Differential Consequences on Neuronal Circuitry

Manuscript type: Narrative Review (Preprint v1, 4 Feb 2026)

Reviewer report prepared for editor and authors

Overall recommendation

Major revision (publishable in principle, but requires substantial strengthening of scholarship, citation accuracy, and conceptual rigor before it can serve as a reliable reference for specialists).

Summary of the work

This narrative review contrasts infectious versus sterile neuroinflammation and discusses how inflammatory signals affect synaptic plasticity, excitation–inhibition balance, and circuit-level network efficiency. A central claim is that long-term functional outcomes depend less on whether the trigger is infectious or sterile and more on the duration/resolution of the inflammatory state and the emergence of glial priming ("inflammatory memory"). The manuscript includes two conceptual figures: Figure 1 (shared versus divergent signaling routes) and Figure 2 (a time/persistence model linking inflammatory resolution to circuit outcomes).

Strengths

- Timely topic: neuroimmune modulation of synapses and circuits is of broad interest to neuroimmunology, systems neuroscience, and neurology.

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- Circuit-level framing is valuable and helps bridge cellular immunology with functional outcomes (oscillations, E/I balance, network efficiency).
- Figures are clear and pedagogical; Figure 2 usefully emphasizes temporal resolution thresholds and glial priming as a pivot for persistent dysfunction.
- The reference list contains several relevant recent reviews and primary studies (including 2019–2025 coverage in multiple areas).

Major concerns (must be addressed)

1) Citation accuracy and DOI integrity

The reference list contains at least one incorrect DOI-journal mismatch. For example, the manuscript lists Barajas et al. (2026) as International Journal of Molecular Sciences but assigns a DOI starting with 10.1016 (Elsevier), which is inconsistent with IJMS/MDPI DOIs. The correct DOI appears to be 10.3390/ijms27010546. Because the review may be used as a reference source, DOI correctness must be systematically audited and corrected (authors, journal, year, volume/issue, pages/article number, and DOI should be mutually consistent).

2) Methodological transparency for a narrative review

The manuscript states it is a narrative review, but it does not provide a minimal description of how the literature was identified and selected (databases, time window, key terms, inclusion/exclusion rationale, and how preclinical vs. clinical evidence was weighted). Even for a narrative review, a short "Search strategy and scope" paragraph would increase credibility and reduce perceived selection bias.

3) Conceptual novelty requires clearer positioning versus existing frameworks

The thesis that 'persistence/resolution' and 'immune memory/priming' dominate long-term outcomes is plausible, but similar ideas exist in prior conceptual work on neuroinflammation trajectories and neurodegenerative vulnerability. The manuscript should explicitly state what is new: e.g., (i) a circuit-centric operationalization of outcomes (E/I balance, oscillations, network efficiency), (ii) testable predictions, or (iii) a specific model for why infectious inflammation is often reversible while sterile inflammation more often becomes unresolved. Without this, the work reads as a synthesis rather than a distinctly novel framework.

4) The infectious–sterile dichotomy should be refined to avoid oversimplification

Infectious neuroinflammation is often framed as 'acute and reversible,' while sterile is framed as 'persistent.' However, infections can be persistent or relapsing (including viral reservoirs, post-infectious

neuroimmune syndromes, and chronic immune activation), and sterile drivers can be acute and resolving. The manuscript should incorporate a clear taxonomy: acute-resolving vs. chronic-nonresolving states can arise in both infectious and sterile contexts. This aligns with the manuscript's conclusion that time-course matters more than initial origin.

5) Mechanistic depth and causal language

Several sections imply causal chains (e.g., cytokines → synaptic remodeling → circuit dysfunction) based on heterogeneous models. The manuscript appropriately acknowledges limitations, but it should tighten causal language and explicitly flag which statements are supported by direct manipulations (e.g., complement inhibition preventing synapse loss) versus correlative readouts (cytokine elevations associated with cognitive symptoms).

6) Internal consistency and text quality issues

There are visible copy-editing problems (double punctuation, occasional duplicated phrases/sentences, and truncated/odd formatting around some references). These issues reduce readability and raise concerns about overall quality control.

Actionable suggestions to strengthen the manuscript

- Add a brief 'Scope and search strategy' subsection (even 5–7 lines) specifying databases, years emphasized, and how the author selected key experimental and translational studies.
- Introduce an explicit conceptual model statement early (end of Introduction) defining testable predictions: e.g., what circuit metrics would indicate 'reversible' vs. 'persistent' dysfunction, and what biomarkers would map onto the resolution threshold in Figure 2.
- Add a dedicated paragraph on chronic/persistent infectious neuroinflammation and post-infectious syndromes (e.g., long COVID, ME/CFS-like phenotypes) to avoid the implicit "infectious = acute" heuristic. Don't give the impression that inflammation caused by infections is always short-lived. Many readers may assume that infectious inflammation (caused by viruses or bacteria) is temporary and goes away quickly. Sterile inflammation (not caused by germs, e.g., injury or degeneration) = long-lasting. But this is not always true.
- Sharpen definitions: provide operational definitions for "circuit dysfunction," "network efficiency," "glial priming," and "resolution," and indicate which are measured by electrophysiology vs. imaging vs. behavior.

- Audit all references and DOIs systematically; correct journal/DOI mismatches; standardize formatting (journal abbreviations, consistent use of article numbers/pages, capitalization).
- Improve figure anchoring: in the main text, explicitly call out where Figure 1A/B/C and Figure 2 are used to support the argument, and briefly describe what empirical evidence most strongly supports each element.

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Minor comments

- Correct typographical issues (e.g., double periods in the Introduction) and scan for duplicated phrases.
- Where possible, specify whether findings are from in vitro, ex vivo slice, or in vivo models; avoid blending without signposting.
- When discussing oscillations (gamma/beta changes), add one sentence clarifying the recording modality and species where key evidence comes from.
- Standardize the use of abbreviations on first use (e.g., PRR, PAMP, DAMP, E/I).

Key seminal and high-impact references recommended for inclusion (with DOIs)

The manuscript already cites key work on complement-dependent pruning (e.g., Schafer et al., Neuron 2012). However, to strengthen the foundational scholarship and astrocyte–microglia interactions, I recommend adding at least the following widely recognized references (and integrating them into the narrative where relevant):

- Stevens B, Allen NJ, Vazquez LE, et al. The classical complement cascade mediates CNS synapse elimination. Cell. 2007;131(6):1164–1178. doi:10.1016/j.cell.2007.10.036.
- Liddelow SA, Guttenplan KA, Clarke LE, et al. Neurotoxic reactive astrocytes are induced by activated microglia. Nature. 2017;541(7638):481–487. doi:10.1038/nature21029.
- Ransohoff RM. How neuroinflammation contributes to neurodegeneration. Science. 2016;353(6301):777–783. doi:10.1126/science.aag2590.

DOI corrections detected (examples)

At minimum, the following DOI mismatch should be corrected; similar issues may exist elsewhere and should be checked systematically:

- Barajas A, Riquelme-Alacid G, Vera-Montecinos A, Ramos B. Cognition, Cytokines, Blood–Brain Barrier, and Beyond in COVID-19: A Narrative Review. Int J Mol Sci. 2026;27(1):546. Correct DOI: 10.3390/ijms27010546 (not an Elsevier 10.1016 DOI).

Final evaluation

This manuscript addresses an important and timely area and contains a helpful circuit-level synthesis and clear conceptual figures. However, before it can be recommended as a citable scholarly resource, it requires (i) a careful audit of reference accuracy (including DOIs), (ii) clearer methodological transparency about literature selection, and (iii) a stronger, more explicitly differentiated statement of novelty relative to existing neuroinflammation trajectory frameworks. With these revisions, the review would be of interest to specialists and could be suitable for publication.

Declarations

Potential competing interests: No potential competing interests to declare.