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Peer Review

Review of: "Reinterpreting Circulating Neuron- and Oligodendrocyte-Derived Extracellular Vesicles for Non-invasive Monitoring of Neonatal Brain Development"

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1. The manuscript presents L1CAM/CD171-based detection of neuron-derived extracellular vesicles as an established analytical foundation without acknowledging the conflicting literature. Norman M, et al. 2021, L1CAM is not associated with extracellular vesicles in human cerebrospinal fluid or plasma. Nat Methods. Jun;18(6):631-634. doi: 10.1038/s41592-021-01174-8. Kadam, V. *et al.* 2025 Most L1CAM Is not Associated with Extracellular Vesicles in Human Biofluids and iPSC–Derived Neurons. *Mol Neurobiol* 62, 10427–10442 . doi.org/10.1007/s12035-025-04909-2
2. CD9 co-detection helps distinguish the assay signal from soluble L1CAM alone, but it does not independently establish that the detected material originates from neonatal brain neurons. For both the L1CAM- and MOG-based assays, please distinguish evidence for vesicular association, cellular origin, and applicability to neonatal samples.
3. A prediction of greater ODE than NDE changes during the first month does not follow from rapid myelination alone. The author acknowledges that this prediction is unvalidated, but should also explain its mechanistic basis and discuss alternative interpretations. The prediction of greater ODE than NDE changes would benefit from a more specific mechanistic rationale. Relevant experimental work links MOG expression to oligodendrocyte maturation (Solly et al., 1996), identifies myelin-associated proteins in oligodendroglial EVs (Krämer-Albers et al., 2007), and demonstrates activity-dependent oligodendroglial EV release (Frühbeis et al., 2013). However, these findings do not establish greater circulating ODE changes during the first neonatal month. Please distinguish

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changes in EV abundance from changes in MOG expression or assay detectability, discuss alternative interpretations, and retain the comparative prediction as an explicitly testable hypothesis.

4. The statement that heel-prick blood is routinely collected around the one-month health check for newborn screening needs a specific healthcare-system reference or correction. Routine newborn blood-spot screening in Europe and the USA is normally performed 24–48 hours after birth, not at one month. Consequently, the proposed second sample cannot generally be assumed to be available without an additional collection. “Minimally invasive” would also be more accurate than “non-invasive” in the title.
5. Please verify reference 2. The listed authors, title, page range, and DOI do not identify a consistent bibliographic record. Please provide the correct details of the intended source and confirm that it supports the statements for which it is cited.

Declarations

Potential competing interests: No potential competing interests to declare.