

INSIGHTS

Parkinson's at the brain border

Henry Kim^{1,2} , Tsogt-Ilgel Munkhbat^{1,2} , and Max A. Tischfield^{1,2} 

Parkinson's disease is increasingly recognized as a disorder that extends beyond neurons. In this issue of *JEM*, Stevenson et al. (<https://doi.org/10.1084/jem.20251245>) highlight the functional consequence of α -synuclein aggregates at the brain border, uncovering their active role in reshaping lymphatic integrity and the neuroimmune macroenvironment.

Our understanding of Parkinson's disease (PD), a debilitating neurological disorder characterized by a progressive loss of motor function, has been centered on the brain parenchyma—the site of selective neurodegeneration of dopaminergic neurons and accumulation of pathological forms of α -synuclein (α -syn). Although neurons lie at the heart of PD pathology, they do not exist in isolation. Instead, neurons interact with a host of other central nervous system (CNS) components, including cerebrospinal fluid (CSF), which assists in the clearance of metabolic waste and macromolecules to meningeal lymphatic vessels (mLVs) that drain into cervical lymph nodes (Zhang et al., 2025). This process, localized to CNS border tissues, has emerged as a key regulator of waste clearance and communication between the brain and peripheral immune system. However, whether CSF clearance deficits and mLV dysfunction may play a direct role in PD pathogenesis has remained elusive thus far. In this issue, Stevenson et al. shed new light on the pathophysiology of PD, moving beyond the neuron and expanding to meningeal lymphatics at the brain border. Their results indicate that α -syn accumulation within CNS border tissues is sufficient to elicit an innate inflammatory response that disrupts both CNS waste clearance and the structural integrity of mLVs, suggesting these may be early indicators of disease progression (Stevenson et al., 2026).

The (re)discovery of mLVs has reshaped our understanding of CNS homeostasis.

Situated adjacent to the dural venous sinuses, mLVs actively shuttle CNS proteins, waste products, and immune cells from CSF to the cervical lymph nodes, highlighting their central role in waste clearance and immune surveillance (Louveau et al., 2015). It is well recognized that mLV dysfunction is associated with numerous neurological conditions, from neurodegenerative diseases to aging (Zhang et al., 2025). In addition, neuroimaging studies have shown that mLV drainage is impaired in PD (Ding et al., 2021). Consistent with these findings, deficits in mLV drainage have been shown to exacerbate α -syn pathology and promote a neuroinflammatory response (Zou et al., 2019). However, the question remains of how the lymphatic system is functionally impacted in PD. Does pathological α -syn in CSF contribute directly to meningeal lymphatic drainage deficits or are observed perturbations merely a downstream consequence of neurodegeneration?

To address this question, Stevenson et al. begin with an intriguing clinical observation: pathological α -syn accumulates in extracellular compartments beyond the neuron. Consistent with previous reports, the authors detect α -syn in CSF from PD patients. α -Syn also localizes to the dura mater adjacent to the superior sagittal sinus. These findings are important in light of the expanding appreciation that the dura mater is not simply a covering of the brain but a dynamic neuroimmune interface between the CNS and the peripheral immune system, which also facilitates waste clearance



Henry Kim, Tsogt-Ilgel Munkhbat, and Max A. Tischfield.

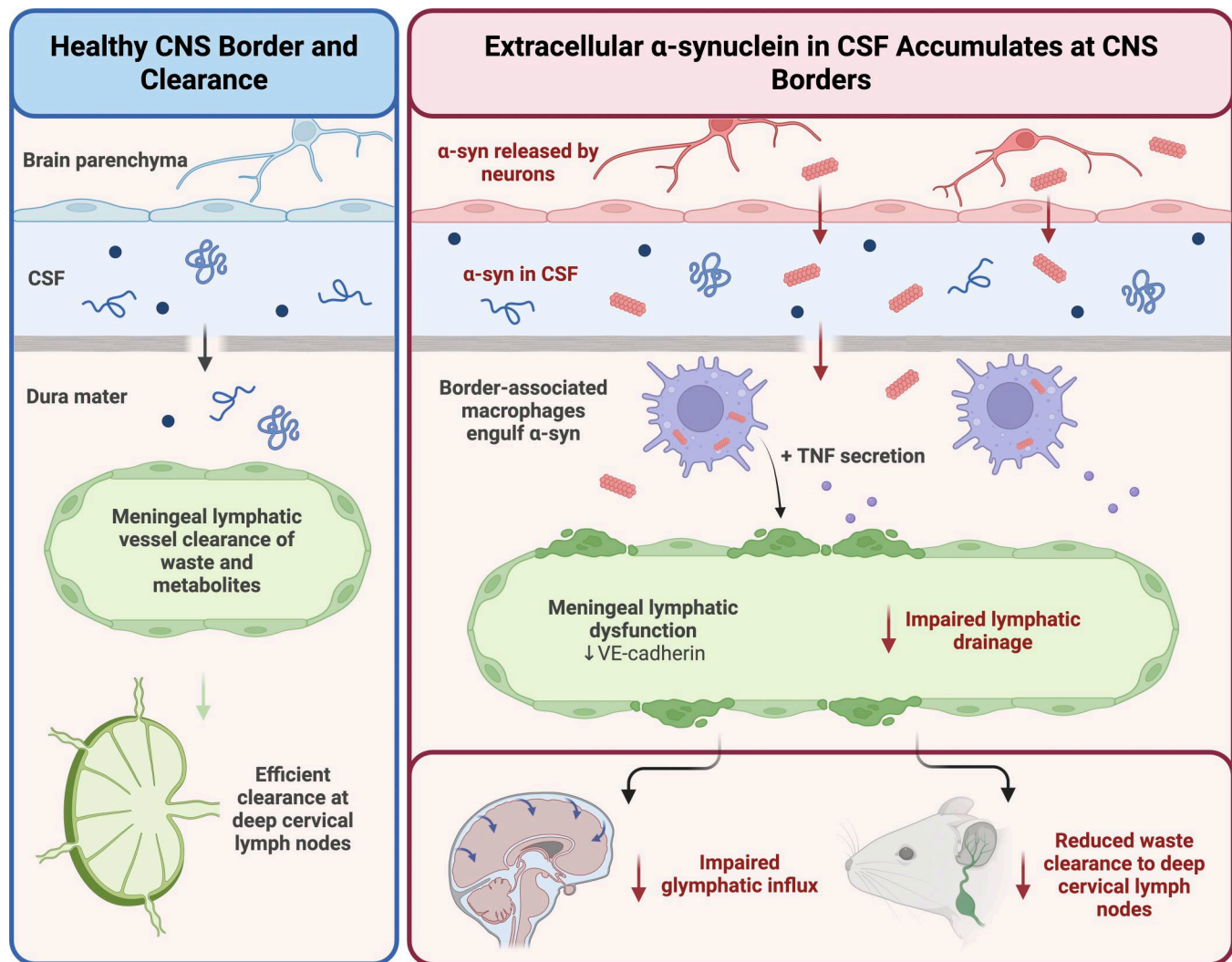
(Smyth et al., 2024). Thus, the localization of α -syn to this CNS border niche suggests that it has direct engagement with the dura and mLVs, raising the question of whether α -syn may affect brain homeostasis and neurological functions independent of its effects on neurons and glia.

To test this idea, the authors established complementary acute and chronic models of extracellular α -syn exposure in mice. To this end, α -syn preformed fibrils (PFFs) were injected into CSF via the cisterna magna to allow direct access to CNS border tissue. α -Syn PFFs were internalized by monocytes, macrophages, and dendritic cells at both dura and arachnoid cuff exits, specialized breaks in the arachnoid barrier that permit the efflux of CSF to dura (Smyth et al., 2024). In this acute phase of α -syn exposure, mice demonstrated altered mLV junctional organization, local expansion of macrophages, and impaired drainage of CSF tracer solutes. Similar observations were seen when using viral transduction to produce a dural environment that was under continuous exposure to α -syn over several months. These changes were detected in the absence of

¹Division of Life Sciences Center for Collaborative Neuroscience, Rutgers University, School of Arts and Sciences, Piscataway, NJ, USA; ²Department of Cell Biology and Neuroscience, Rutgers University, School of Arts and Sciences, Piscataway, NJ, USA.

Correspondence to Max A. Tischfield: max.tischfield@rutgers.edu.

© 2026 Kim et al. This article is distributed under the terms as described at <https://rupress.org/pages/terms102024/>.



JEM | Journal of Experimental Medicine

Extracellular α -syn aggregates impair lymphatic drainage in PD. Under physiological states (left), proteins, metabolites, and immune mediators enter the CSF before being trafficked to mLVs and drained into deep cervical lymph nodes. In PD (right), neurons secrete α -syn into CSF, which then aggregates in dura, proximal to mLVs. Macrophages subsequently engulf α -syn, which results in the elevation of TNF and disruption of mLV junctional integrity. During chronic α -syn exposure, glymphatic influx is impaired in addition to lymphatic drainage, contributing to an overall decrease in waste clearance to the deep cervical lymph nodes. Created in BioRender. Kim, H. (2026) <https://BioRender.com/1tbzxcq>.

neuronal loss and behavioral deficits typically observed in PD mouse models, indicating that lymphatic dysfunction and drainage deficits might be an early biomarker for PD.

Arguably the most compelling findings revolve around the mechanistic underpinnings of α -syn exposure to CNS border tissue. Contributing to their finding that innate immune cells expand during α -syn exposure, Stevenson et al. demonstrate that α -syn selectively increases TNF-dependent expression. Using CSF immunoassay, single-cell transcriptomics, and immunohistochemical analyses of both mouse and human dura, they determined that CNS border-

associated macrophages were the most likely contributor to TNF elevation. Further, both TNF and α -syn treatment were sufficient to induce changes to VE-cadherin junctional organization, reflecting damage to mLVs downstream of α -syn seeding. Together, these findings hint at a dual-hit outcome of pathological α -syn, one which involves both TNF cytokine production and lymphatic dysfunction secondary to the aggregation of α -syn in dura.

Through their work, Stevenson et al. examine a critical shift toward our understanding of PD. Moving beyond the scope of α -syn as a toxic intracellular aggregate, this study highlights the role of extracellular

α -syn as a direct contributor capable of impacting the CNS macroenvironment. α -Syn can not only accumulate within neurons, but also activate a TNF-dependent immune response that disrupts lymphatic drainage beyond the brain border. Under chronic α -syn exposure, these deficits extend beyond lymphatic drainage to include decreased glymphatic influx, which suggests that chronic α -syn compromises a complex network of brain clearance. These changes could presumably contribute to a pathogenic, feed-forward cycle of continued α -syn aggregation in the brain, one where extracellular α -syn impairs clearance of additional toxic α -syn and metabolites.

Moreover, deficiencies in brain-CSF perfusion and glymphatic function could diminish waste exchange between ISF and CSF, further exacerbating a pro-inflammatory environment. This could potentially amplify disease pathogenesis and explain how initial α -syn seeding could propagate large-scale changes across the entire brain parenchyma.

The study also provides a particularly attractive insight into the role of CNS border tissue. Recent advancements in the field have shown that lymphatic endothelial cells and meningeal macrophages respond to and regulate neuroimmune signals (Salvador et al., 2024). The authors offer an additional perspective, suggesting that CNS border tissue may be an integral site where pathological α -syn engage the immune system before neurodegeneration develops. This view comes in light of their observation that robust neurodegeneration and behavioral impairments are not observed alongside lymphatic abnormalities in their mouse models. Thus, a pathogenic mechanism surrounding CSF dynamics and lymphatic dysfunction early in PD provides a novel, understudied view on disease pathology.

Importantly, these new findings can inform novel approaches to PD therapeutics. Historically, treatments have centered on combating dopaminergic neurodegeneration through pharmacologic replacement with exogenous dopamine or dopamine agonists. However, these medications are often limited by their prolonged efficacy and adverse side effects. Thus, this work uncovers several druggable targets for PD, including parenchymal border macrophages and lymphatic endothelial cells. Future studies could explore whether direct lymphatic modulation is able to combat the toxic effects of extracellular α -syn at CNS border tissues. Additional follow-up studies on the effects of TNF-neutralizing antibodies would also provide valuable perspectives on

therapeutic approaches to PD. Beyond pharmacological treatments, this work may be used to inform future diagnostic assessments for PD. Given the proposed early onset of lymphatic dysfunction, evaluating lymphatic health through MRI-based imaging could potentially identify changes suggestive of PD before the hallmark symptoms of the disease emerge (Ding et al., 2021).

Finally, the authors raise a broader question worth exploring: why does α -syn accumulate within CNS border tissues, and is this central to disease pathogenesis? A possibility that emerges from this study is that mLVs function as a complex interface that promotes waste clearance while sampling CSF for immune surveillance. The accumulation of α -syn in dura may highlight how the cerebro-lymphatic system maintains homeostasis, whereby CNS-derived waste is trafficked to lymphatic exit points before draining to deep cervical lymph nodes. Unlike physiologic waste, pathogenic α -syn may divert this process, persistently activating parenchymal border macrophages (or other immune cells) while also impairing lymphatic endothelial cell integrity. This self-amplifying mechanism could continually reduce CNS drainage, increase the accumulation of α -syn at the border, and exacerbate the neuroimmunological response by macrophages. Furthermore, CSF drainage deficits may also reduce the ability of the peripheral nervous system to sense and repair CNS dysfunction. As such, this paradigm implies that the meninges constitute an early checkpoint in PD pathology, whereby efficient clearance and immune activation dictate whether pathological α -syn aggregation is cleared or permitted to accumulate. If true, these findings could extend beyond PD and into numerous neurodegenerative disorders. The accumulation of tau, β -amyloid, and TDP-43 underlies the pathogenesis of Alzheimer's disease (AD)

and amyotrophic lateral sclerosis. Could border tissue protein aggregation, immune response, and mLV dysfunction contribute to pathogenesis in similar proteinopathies, as already postulated for AD (Da Mesquita et al., 2018)? The findings reported by Stevenson et al. highlight these important questions and underscore why future studies should investigate the direct effects of toxic protein aggregation on CSF clearance and drainage pathways at the brain border, independent of their effects on the parenchyma. In doing so, these studies may give rise to a new class of therapeutics that target overlapping and/or distinct mechanisms at the brain-border interface.

Acknowledgments

Author contributions: Henry Kim: visualization and writing—original draft, review, and editing. Tsogt-Itgel Munkhbat: visualization and writing—original draft, review, and editing. Max A. Tischfield: conceptualization, visualization, and writing—original draft, review, and editing.

Disclosures: The authors declare that no competing interests exist.

References

- Da Mesquita, S., et al. 2018. *Nature*. <https://doi.org/10.1038/s41586-018-0368-8>
- Ding, X.B., et al. 2021. *Nat. Med.* <https://doi.org/10.1038/s41591-020-01198-1>
- Louveau, A., et al. 2015. *Nature*. <https://doi.org/10.1038/nature14432>
- Salvador, A.F.M., et al. 2024. *Annu. Rev. Neurosci.* <https://doi.org/10.1146/annurev-neuro-113023-103045>
- Smyth, L.C.D., et al. 2024. *Nature*. <https://doi.org/10.1038/s41586-023-06993-7>
- Stevenson, T.J., et al. 2026. *J. Exp. Med.* <https://doi.org/10.1084/jem.20251245>
- Zhang, Q., et al. 2025. *Signal. Transduct. Target. Ther.* <https://doi.org/10.1038/s41392-025-02177-z>
- Zou, W., et al. 2019. *Transl. Neurodegener.* <https://doi.org/10.1186/s40035-019-0147-y>