

Deep Learning-Based Clinical T2-Weighted Image To Whole Brain Voxel Level Glymphatic Fluid Mapping: A Multi-Cohort Study

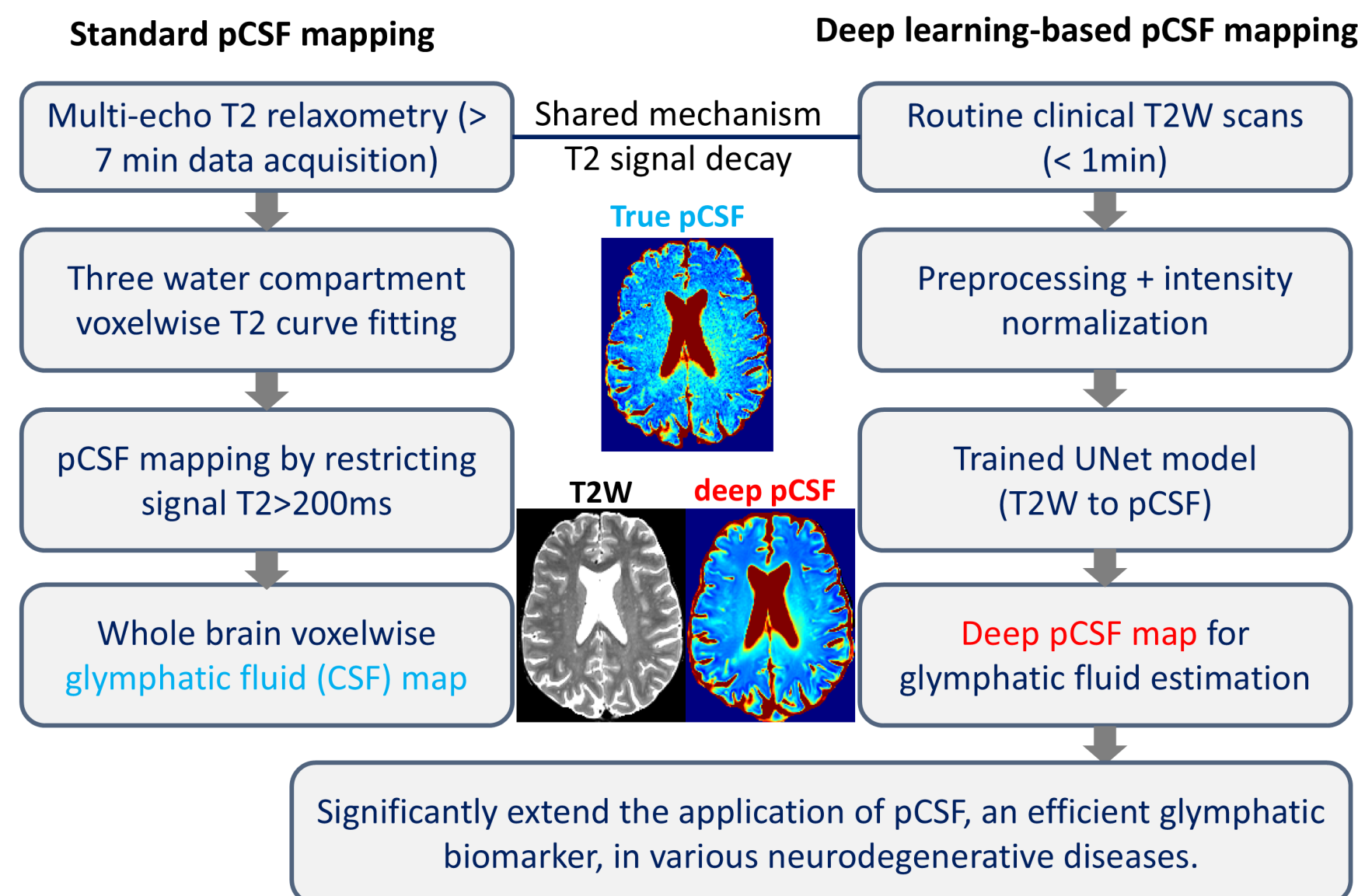
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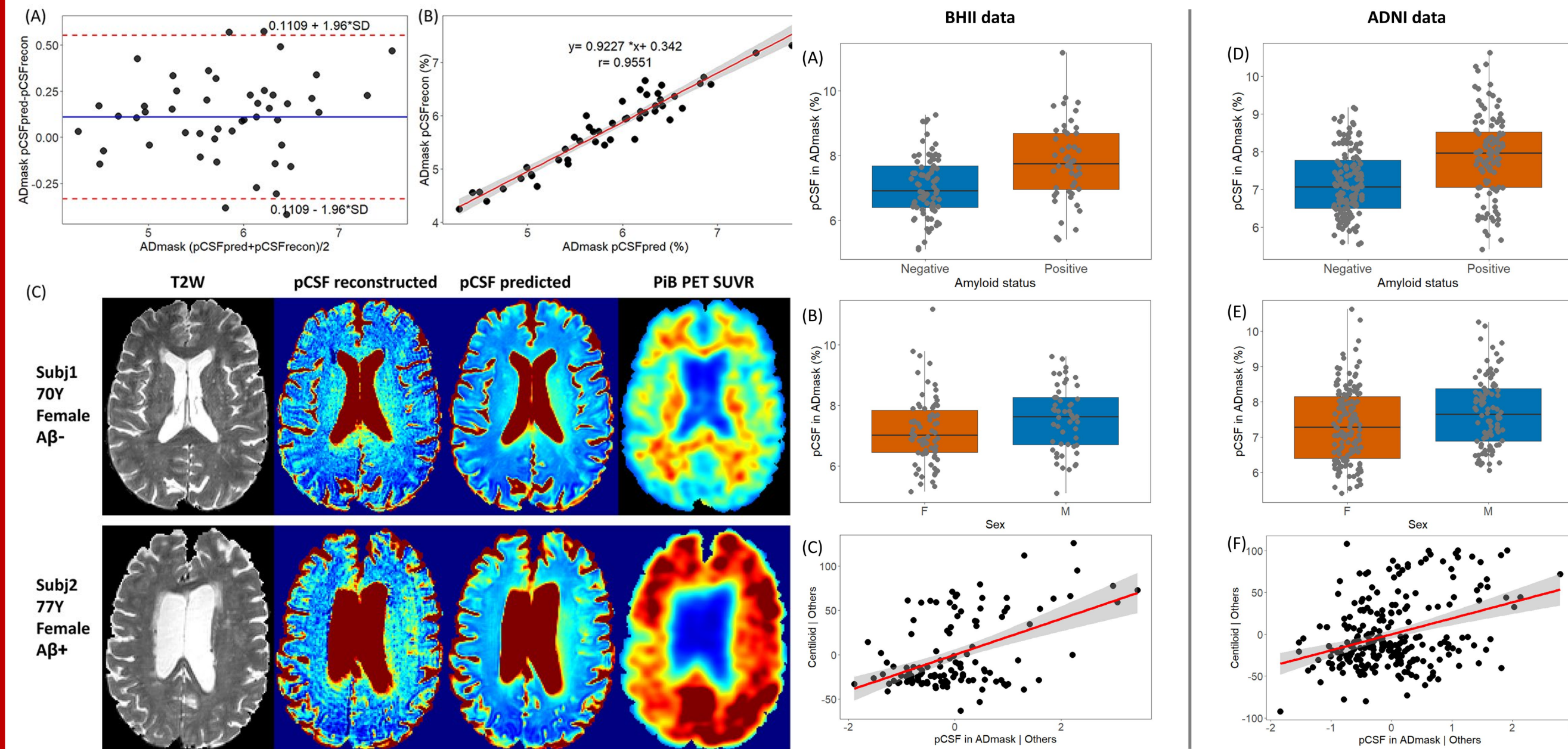
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Introduction: We recently developed parenchymal CSF (pCSF) mapping, a voxel-wise MRI T2-relaxometry technique that quantifies whole-brain glymphatic fluid distribution; higher pCSF is interpreted as impaired glymphatic clearance. Prior work shows pCSF increases with normal aging¹, is elevated in A β + individuals and A β + voxels in AD², tracks A β burden more sensitively than PVS segmentation or DTI free-water metrics³, and normalized with CPAP therapy for OSA patients⁴. Despite these advantages, pCSF currently requires multi-echo T2 relaxometry with acquisition times >7 minutes, limiting routine clinical deployment.

Method: We propose a deep learning framework to generate synthetic whole-brain pCSF maps from standard clinical T2W images, leveraging shared T2 signal-decay-related contrast. The model was trained in 75 older adults (CN, MCI, AD) and validated in 15 participants, using multi-echo FAST-T2-derived pCSF as ground truth. In an independent test set of 50 previously unseen participants, the model achieved a mean bias of less than 1% relative to ground truth. We then applied the model to two external cohorts, Brain Health Imaging Institute from WCM-BHII and ADNI4, to derive pCSF from routine T2W scans.



Results: The predicted pCSF matched well with the ground truth as shown in Bland-Altman plot. Across both cohorts, synthetic pCSF reproduced established biological and clinical associations: higher pCSF in males and A β + participants (both $p < 0.001$), increasing pCSF with age ($p < 0.001$), and a positive association between pCSF and amyloid burden (Centiloid) controlling for age and sex (BHII: $n = 125$, $R^2 = 0.275$, $p < 0.001$; ADNI4: $n = 238$, $R^2 = 0.223$, $p < 0.001$).



Conclusion: These findings support deep learning-derived pCSF from routine T2W, a non-invasive, voxelwise, whole brain map of glymphatic fluid distribution, as a scalable biomarker of glymphatic function for large clinical and research studies for neurodegenerative diseases.

References: 1. L Zhou, Front Aging Neurosci. 2023; 2. L Zhou, Alzheimers Dement. 2024; 3. L Zhou, Brain Commun. 2025; 4. S Keil, Neurobiol Dis. 2026.