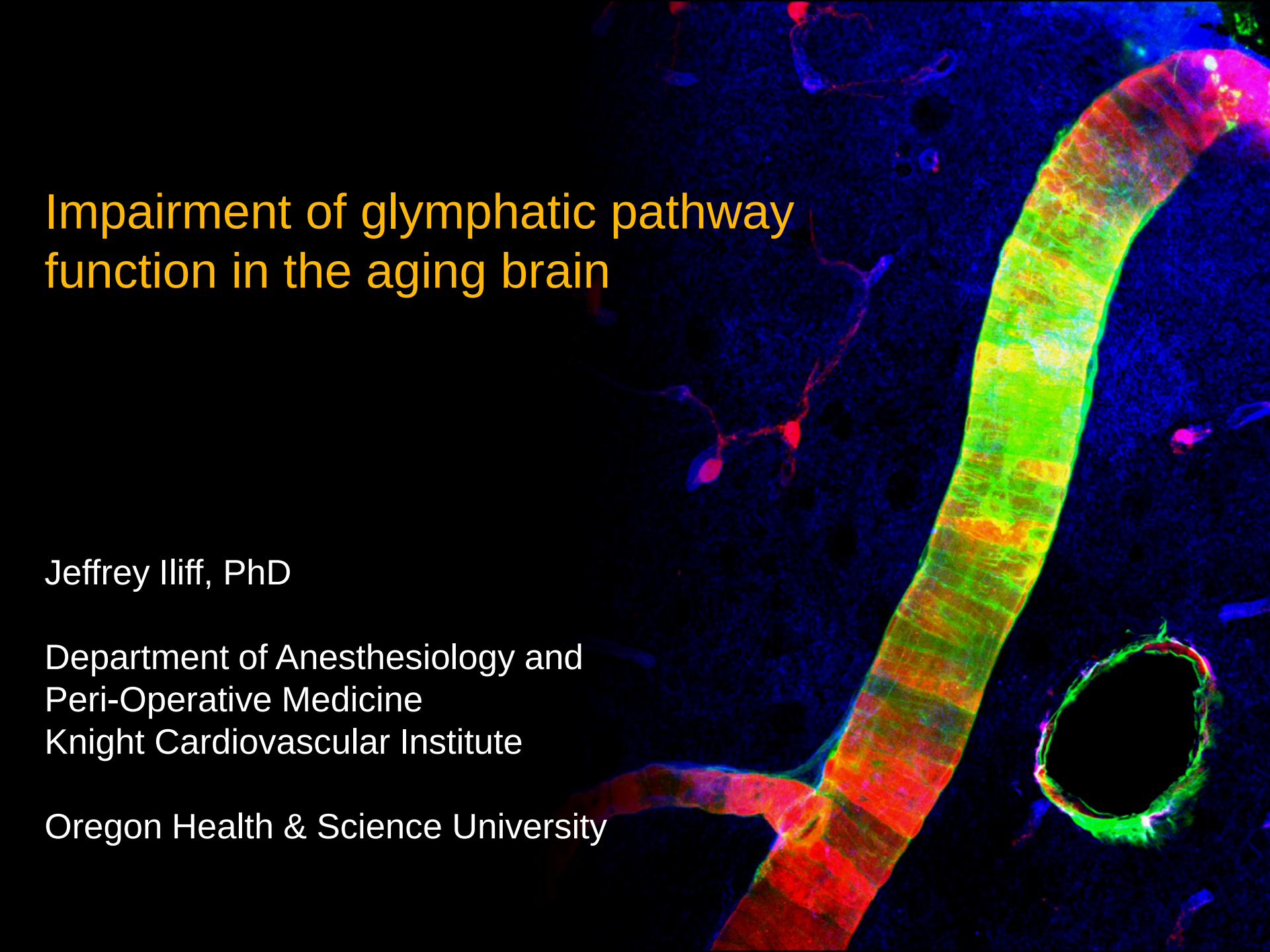
Impairment of glymphatic pathway function in the aging brain



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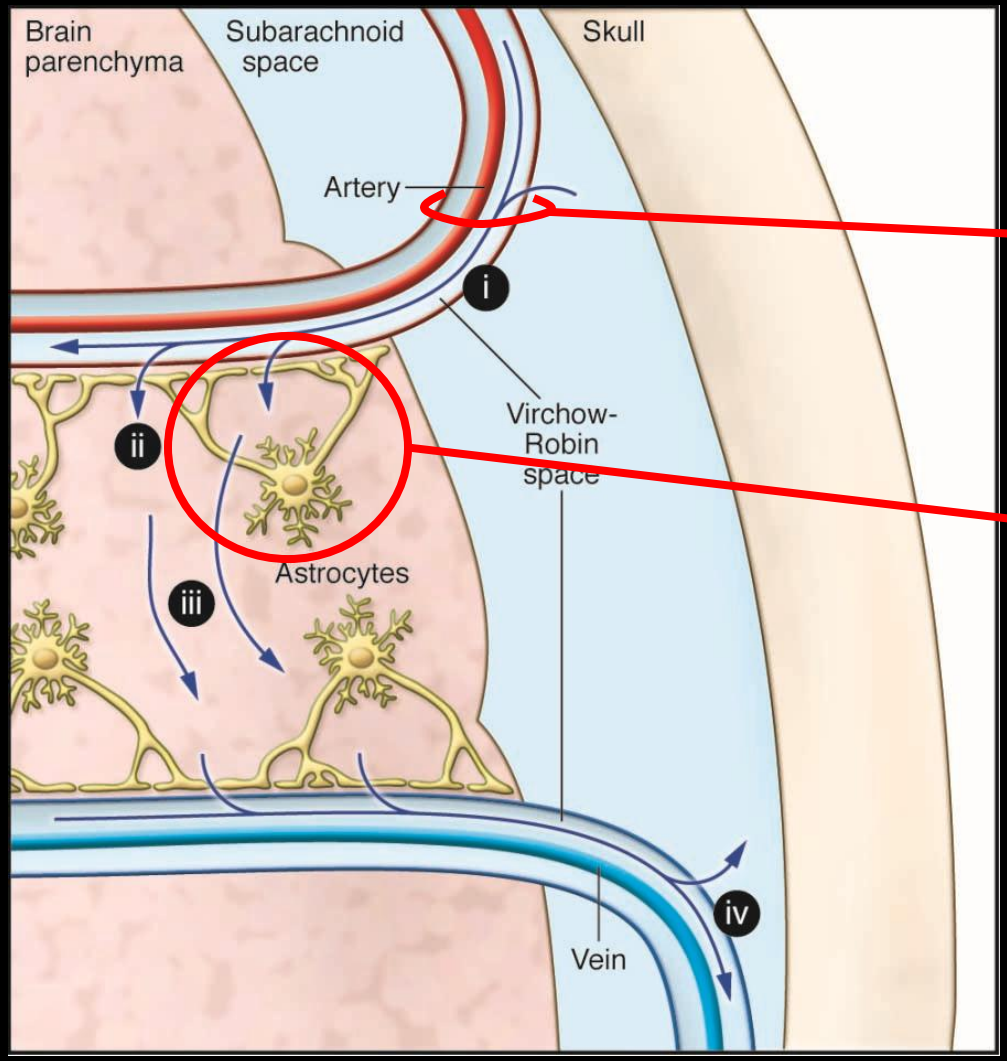
Oregon Health & Science University

The ‘Glymphatic’ Pathway



Paravascular CSF-ISF exchange is a feature of the sleeping brain

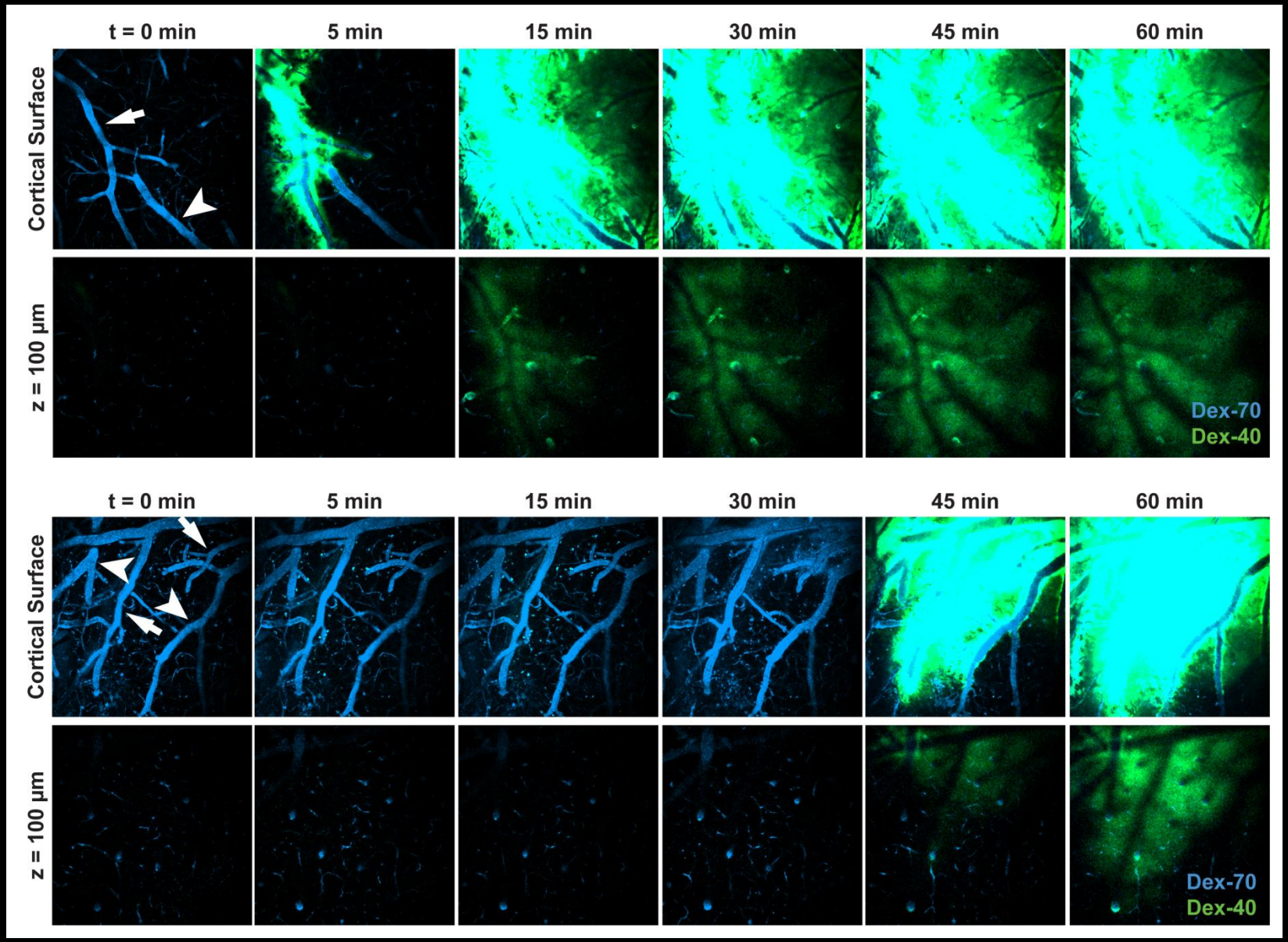
Para-arterial CSF influx driven by arterial pulsatility

Key role of astrocytes
- Perivascular AQP4
- Regulation of extracellular volume

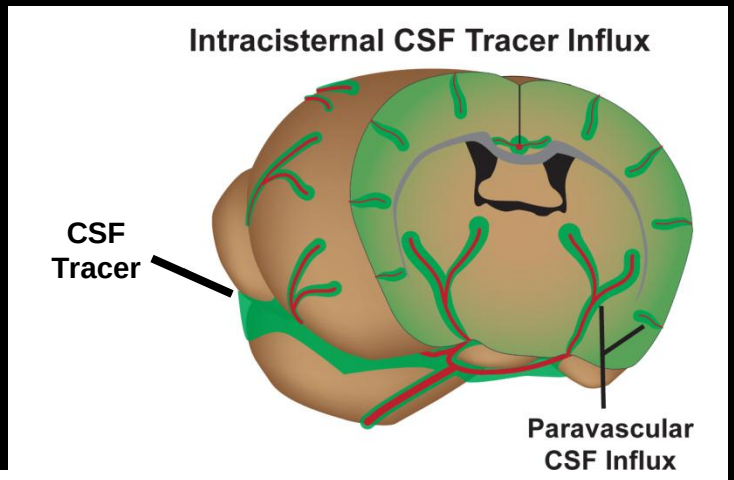
Is glymphatic pathway function compromised in the aging brain?

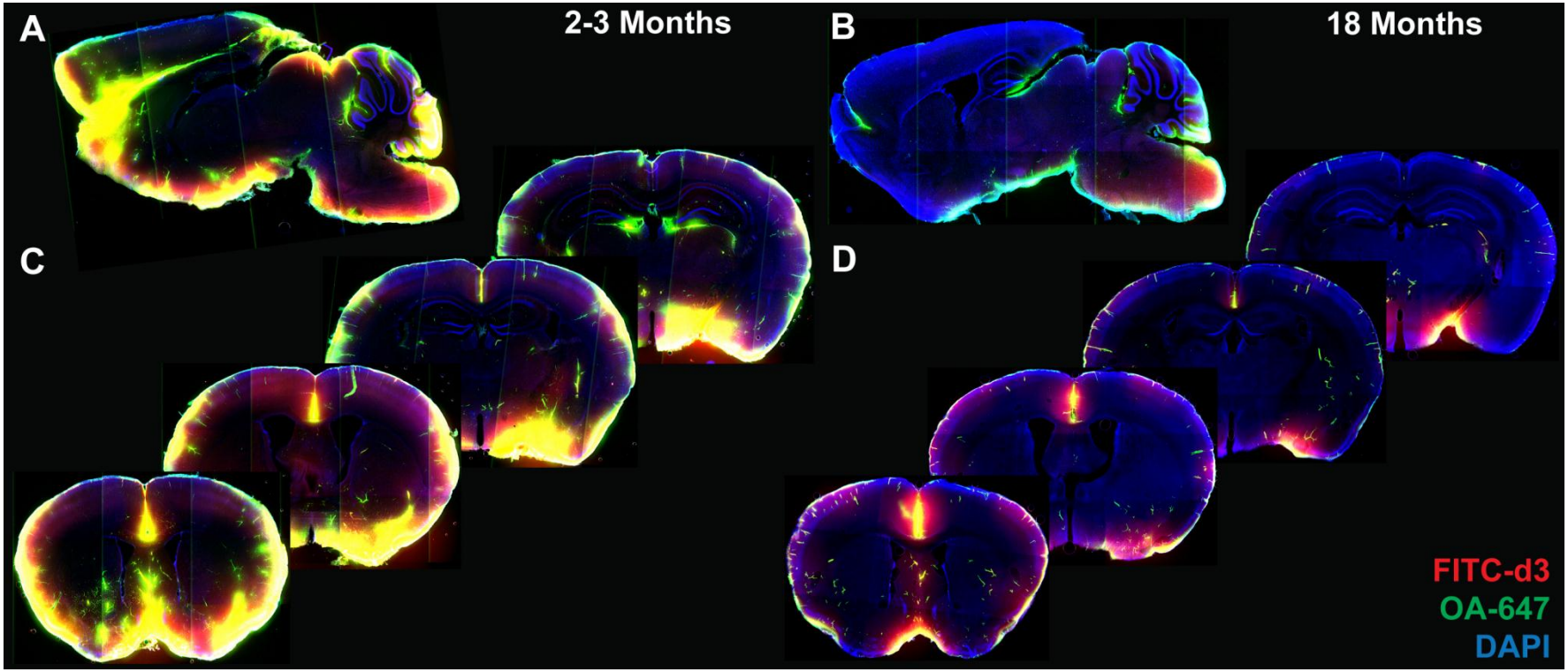
Strittmatter *J Clin Invest* 2013

Paravascular influx is impaired in the aging brain

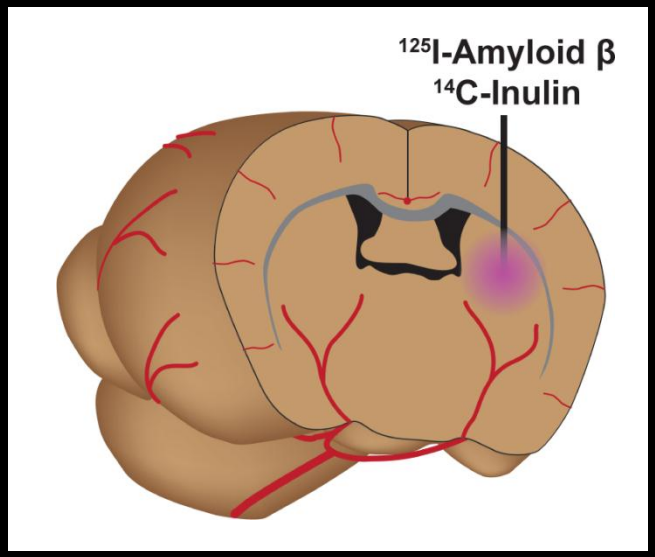


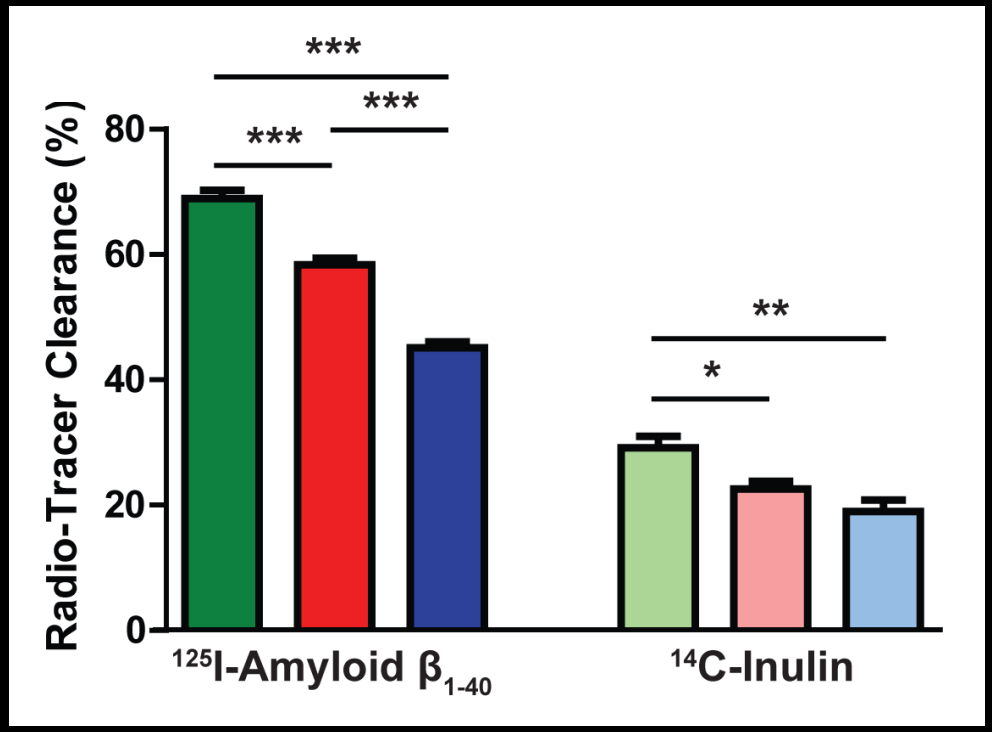
Paravascular influx is impaired in the aging brain



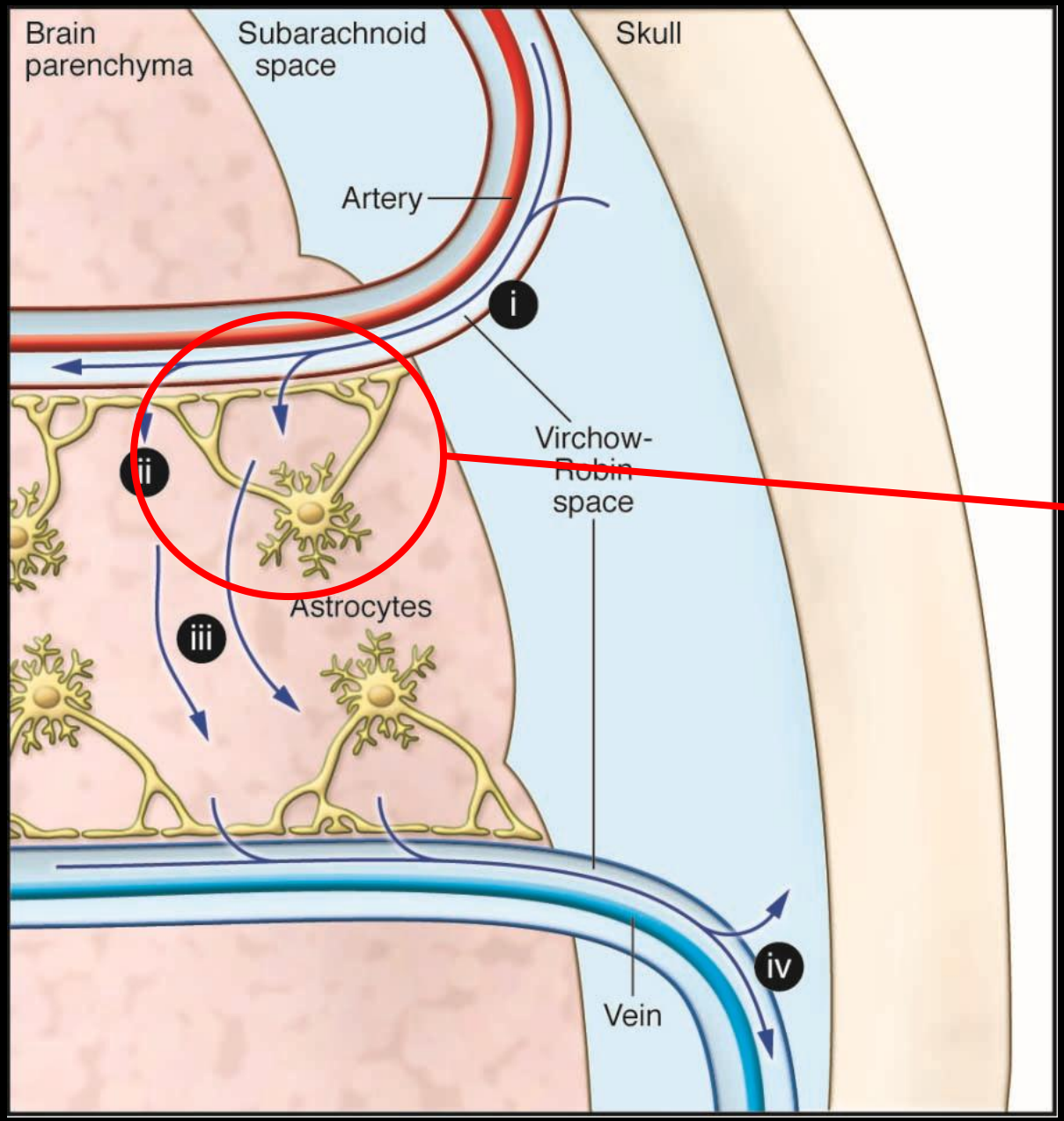


Interstitial solute clearance is impaired in the aging brain



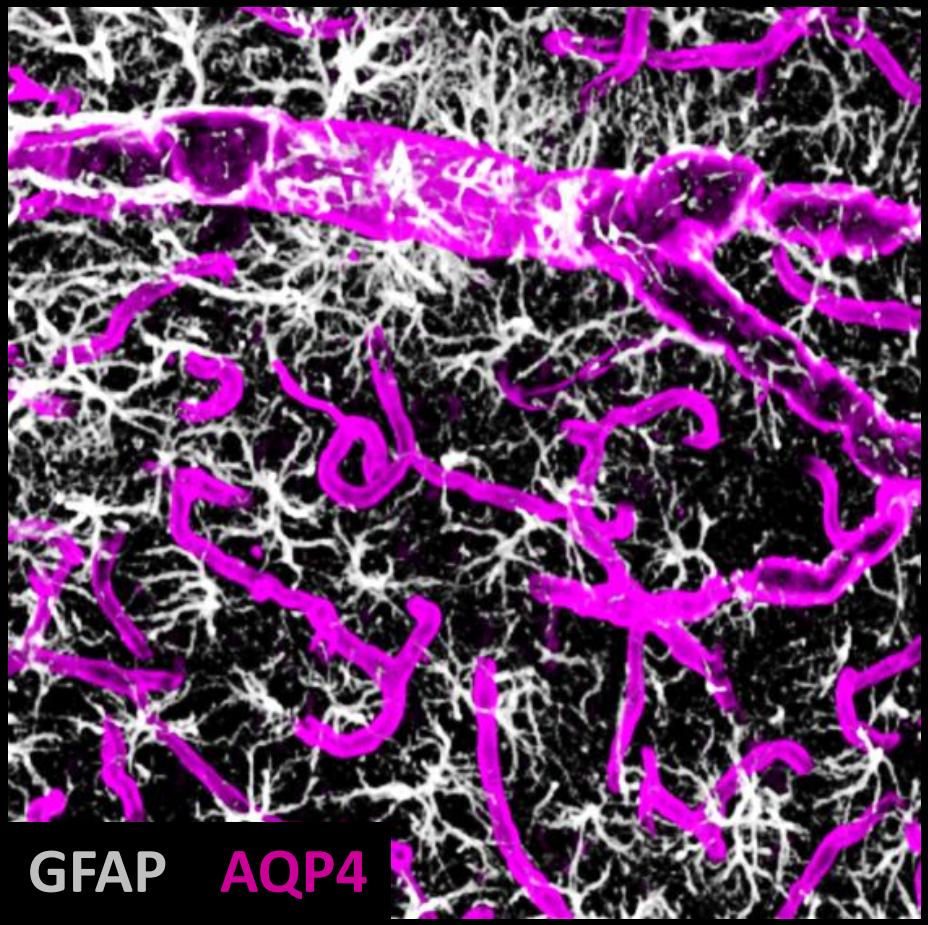


What is the mechanism for impaired para-vascular clearance in the aging brain?



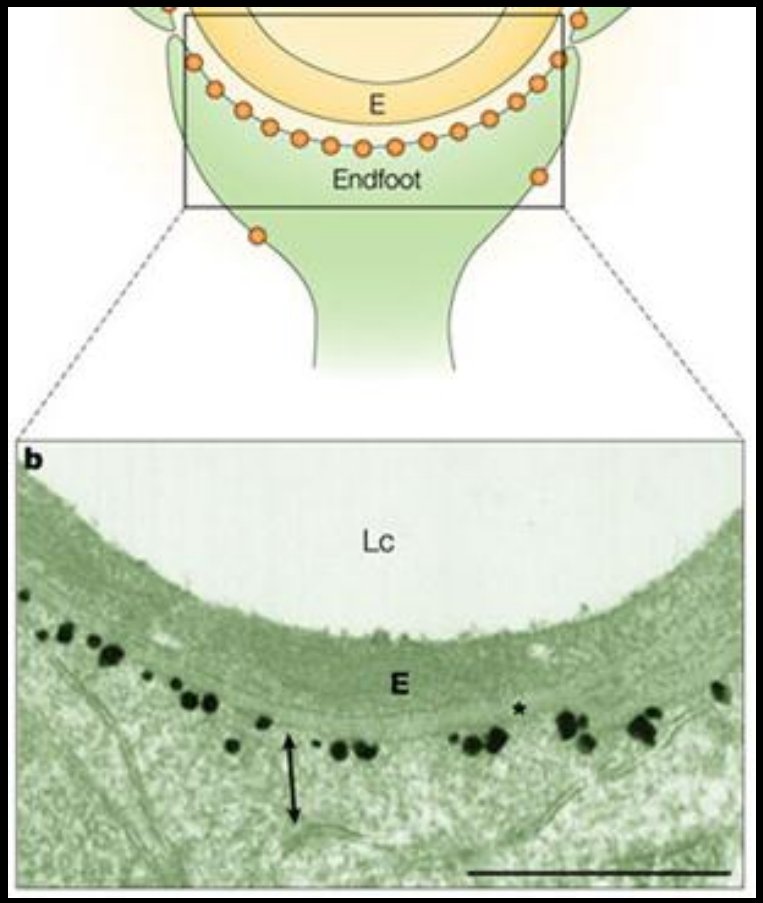
Astrocytes are positioned as gatekeepers to the paravascular spaces

Strittmatter *J Clin Invest* 2013



Aquaporin-4
A perivascular astrocytic water channel

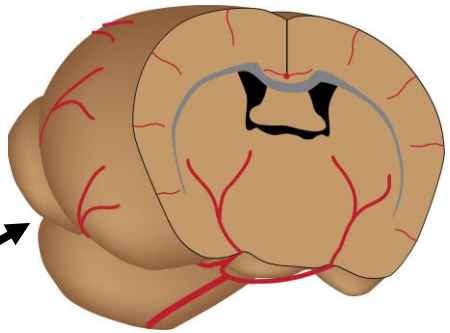
From Amiry-Moghaddam and Ottersen *Nat Rev Neurosci* 2003.

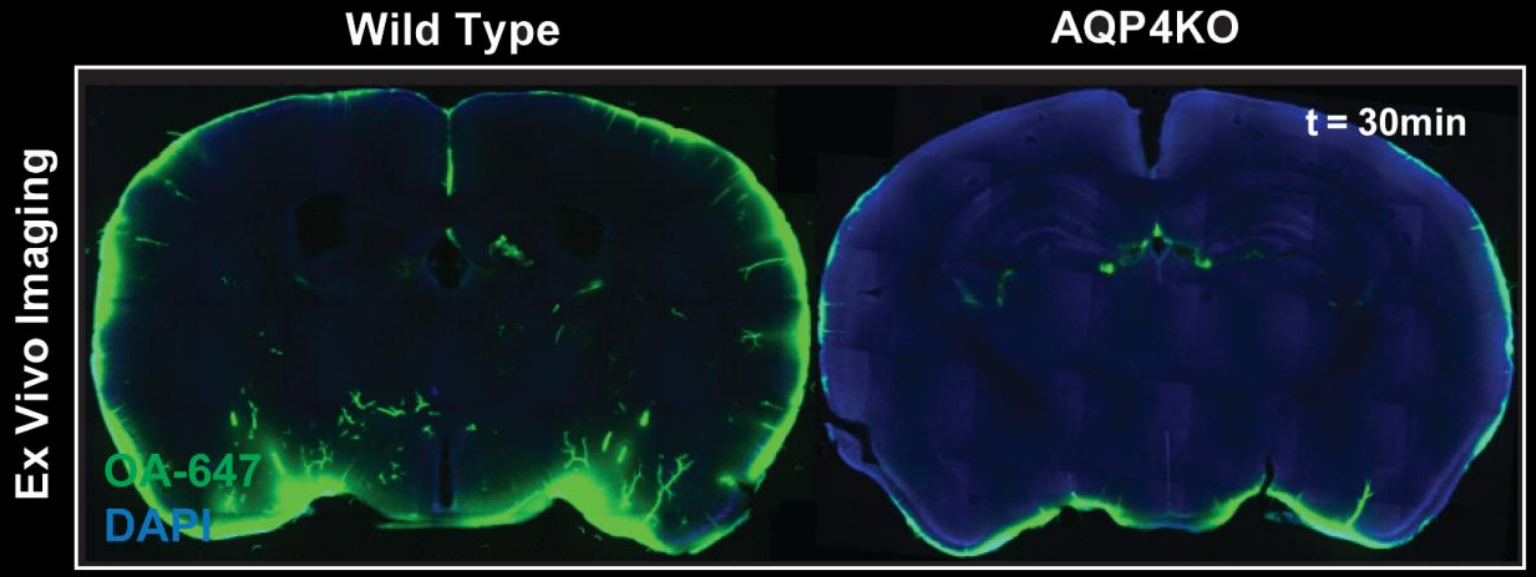


Aqp4 gene deletion reduces CSF influx into the brain parenchyma

CSF Tracers
Ovalbumin-ALEXA647
(45kD)

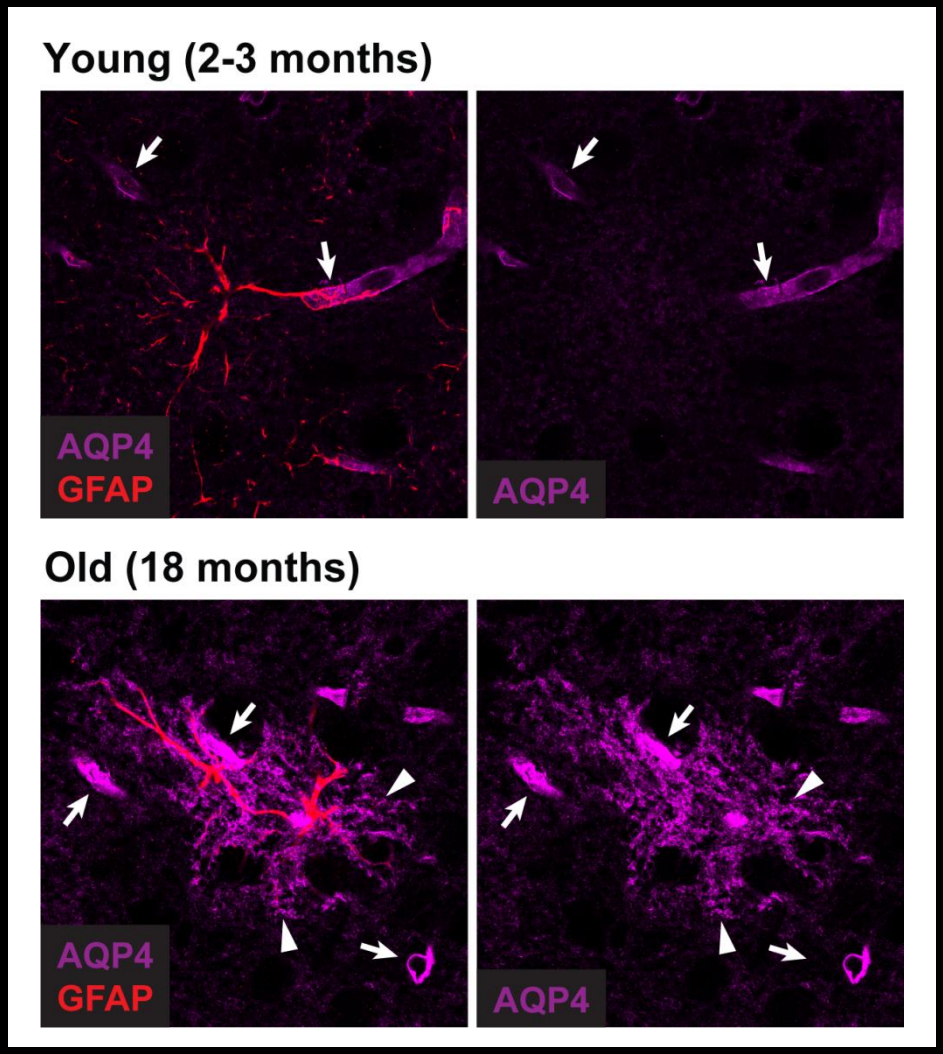
Intracisternal Injection
(Subarachnoid Space)

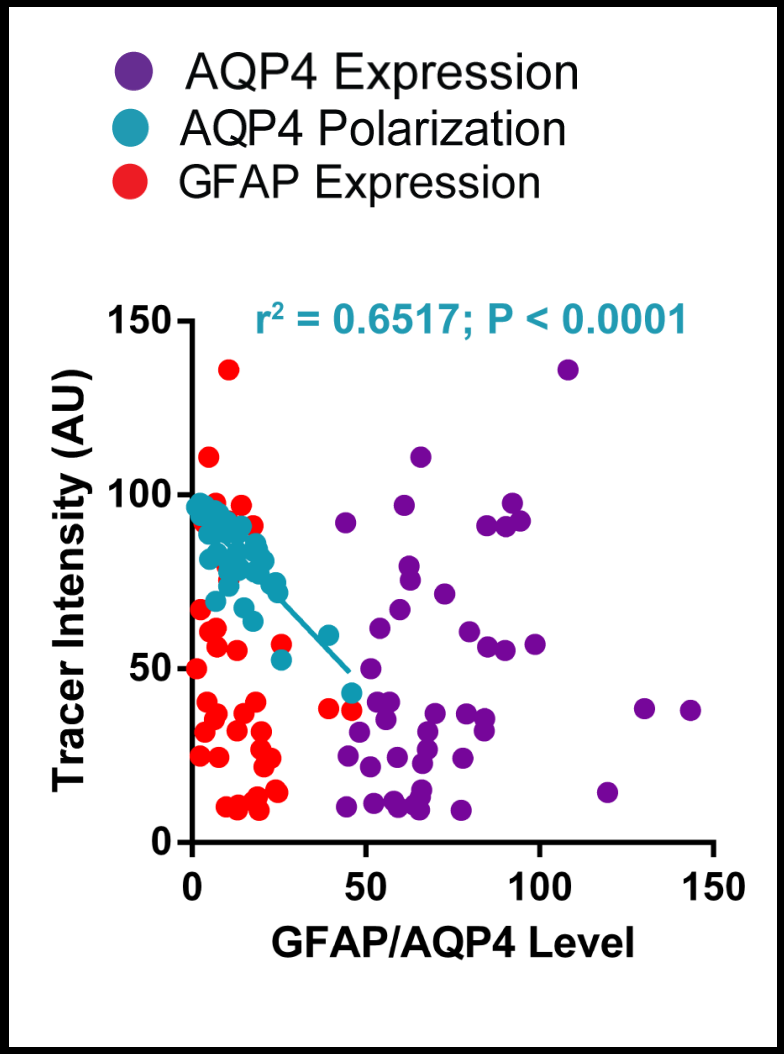




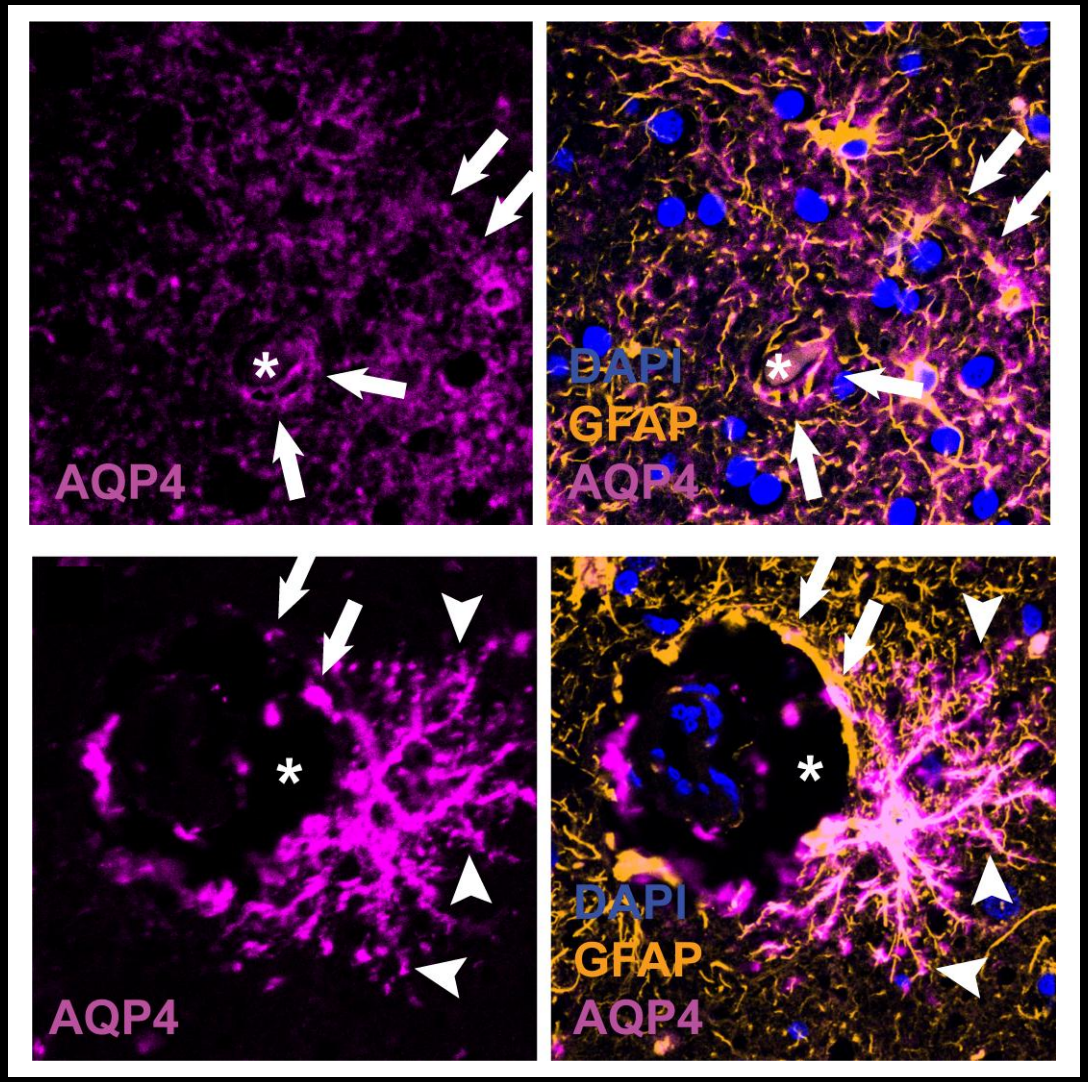
Iliff et al. *Sci Transl Med* 2012.

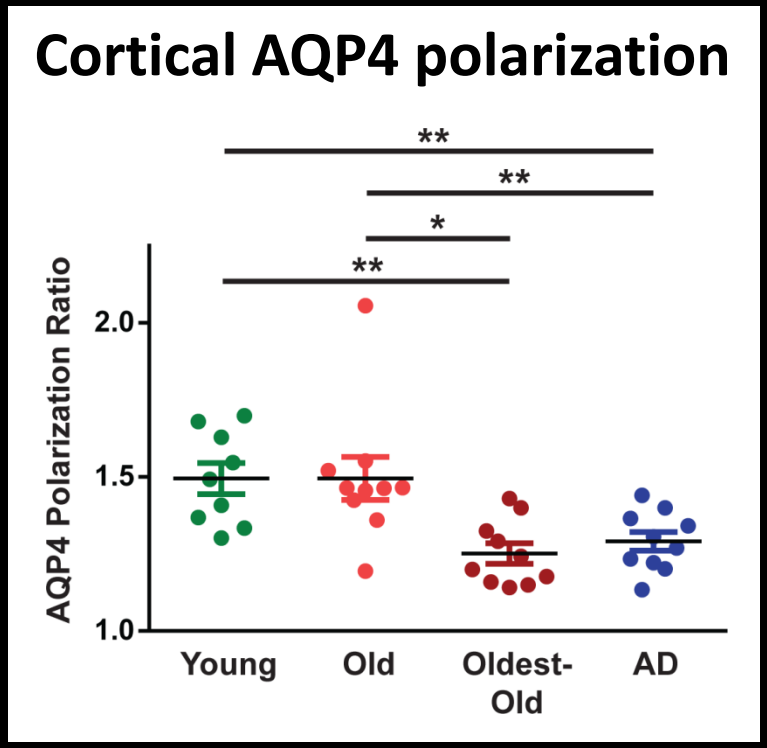
Loss of perivascular AQP4 polarization in the aging mouse brain



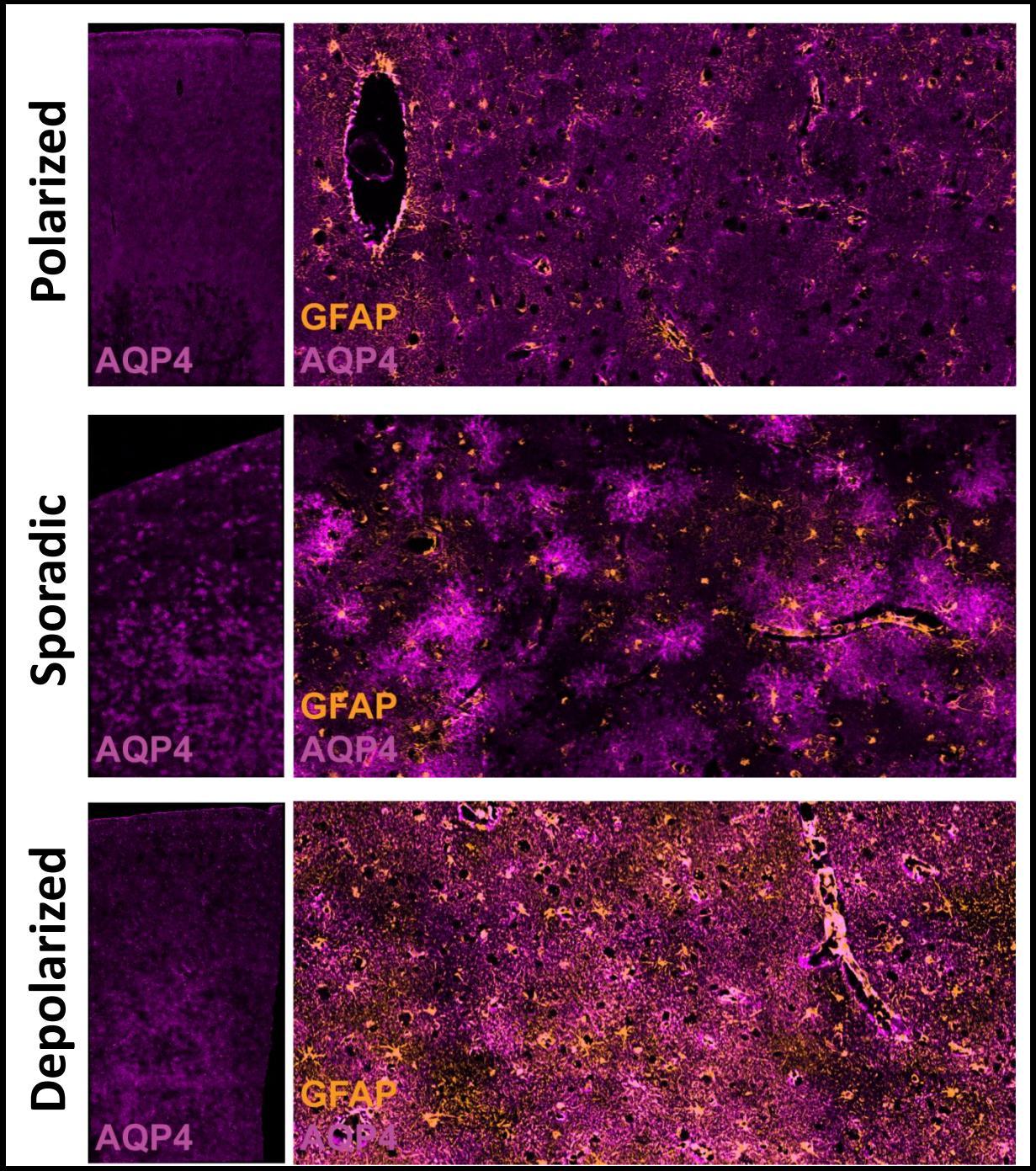


AQP4 polarization is lost in the aging human cortex

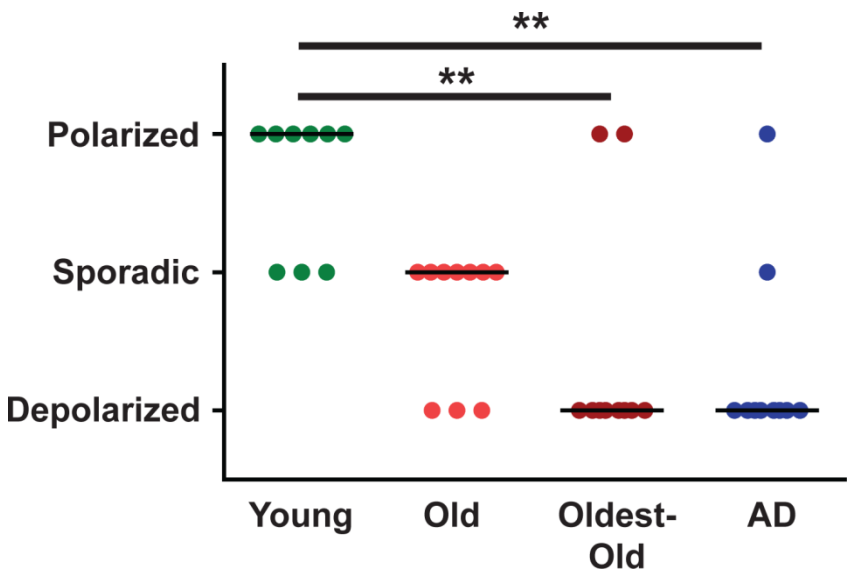




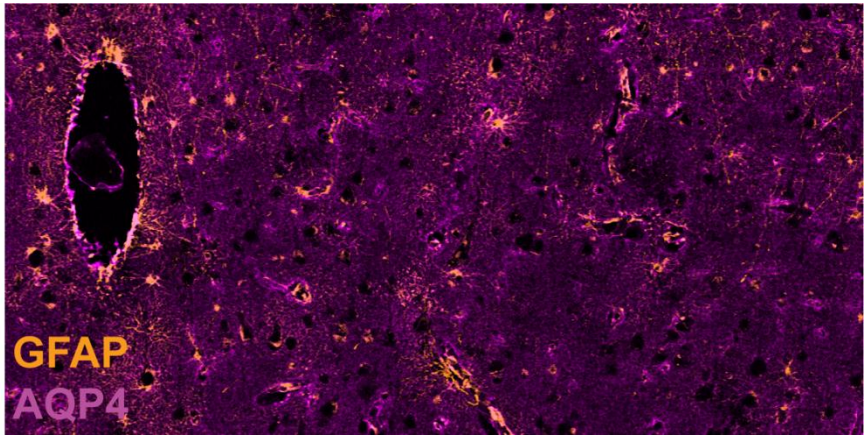
Regional patterns of AQP4 localization in the aging human brain

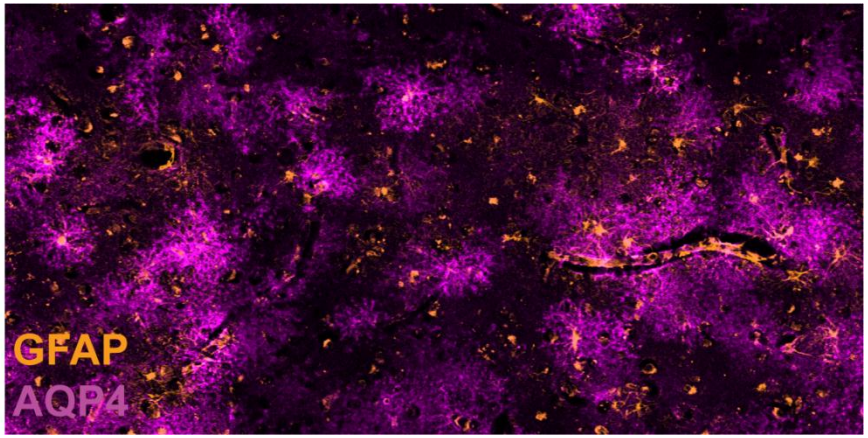


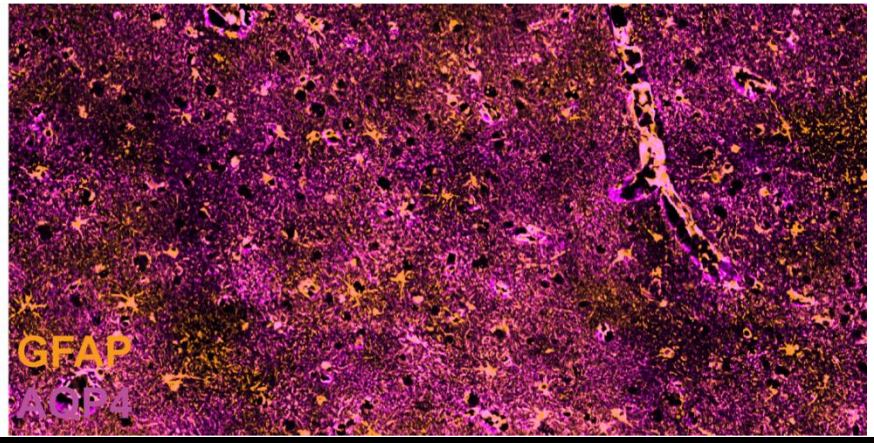
Distribution of AQP4 labeling



AQP4 is mis-localized in the aging human brain and in patients with AD. However patterns of localization are more complex than in rodents.







Things to take away

Paravascular clearance of interstitial solutes

- A feature of the sleeping (and anesthetized) brain
- Key participant in amyloid β clearance
- Driven by arterial pulsation
- Astrocytes are key facilitators (AQP4 and cell volume)

AQP4 localization and glymphatic pathway function are impaired in pathophysiological states

- Aging (slowed amyloid β clearance)
- Traumatic brain injury (slowed tau clearance)
- Diffuse ischemic injury

It seems likely that this contributes to onset and development of pathology in several neurodegenerative states (AD, CTE, others).

Acknowledgements

Oregon Health & Science University
Marjorie Grafe, MD, PhD
Xiao Jing Nie, MS
Lijunan Liu, DVM
Randy Woltjer, MD, PhD
Douglas Zeppenfeld, BS

University of Rochester
Maiken Nedergaard, MD, PhD
Rashid Deane, PhD
Hongyi Kang, BS
Benjamin Kress, BS
Lulu Xie, PhD

University of Oslo
Erlend Nagelhus, MD, PhD
Ole Petter Ottersen, MD, PhD

New York University
Charles Nicholson, PhD