The glymphatic system in Alzheimer's disease

Some things we know and many things we don't

Jeffrey Iliff, PhD
Department of Anesthesiology and Perioperative Medicine
Knight Cardiovascular Institute
Oregon Health & Science University

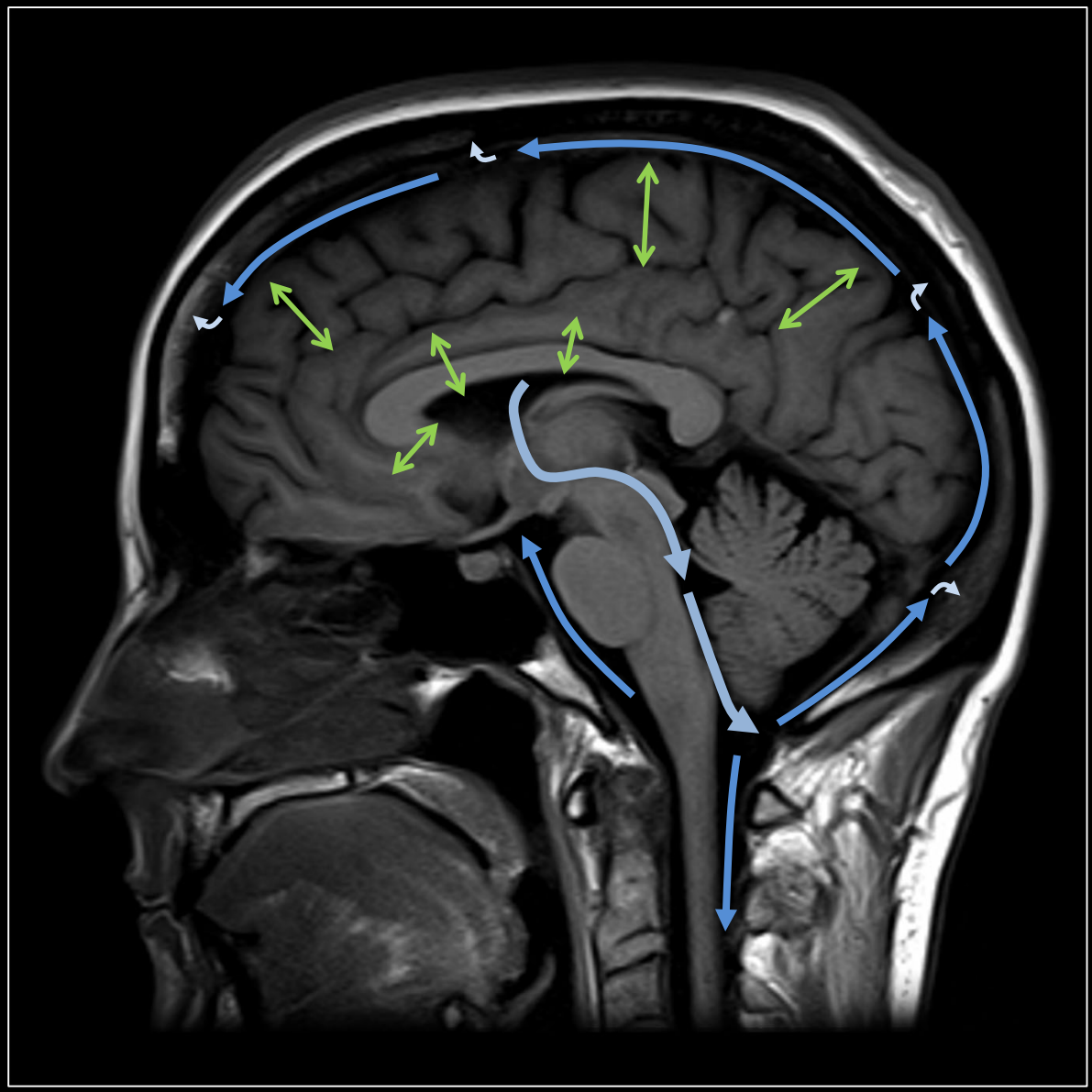
The cerebrospinal fluid (CSF) circulation

No lymphatic vessels in the CNS

CSF serves as a ‘sink’ for CNS waste products

Reabsorption at arachnoid villi

Diffuse bulk flow facilitates exchange of CSF and ISF



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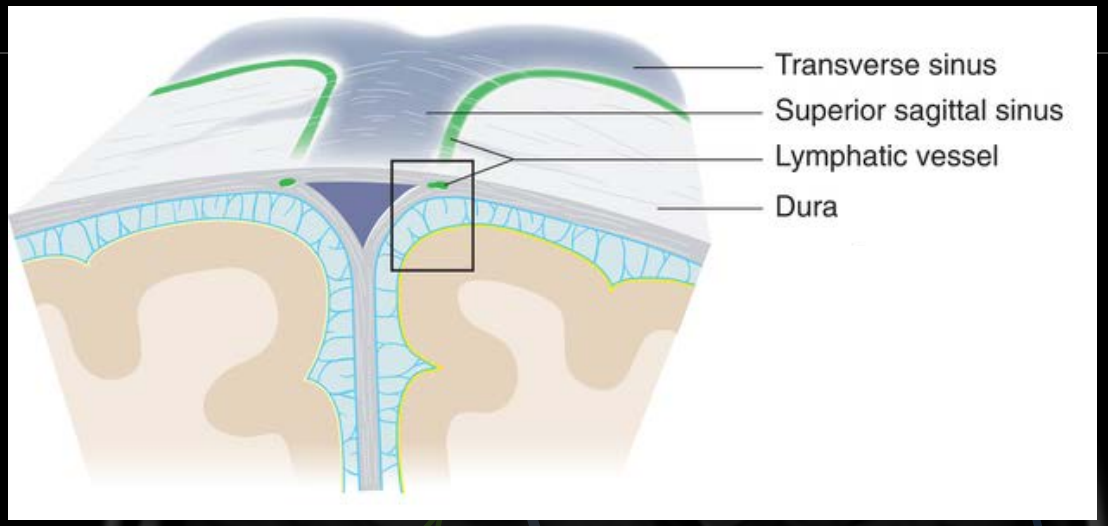

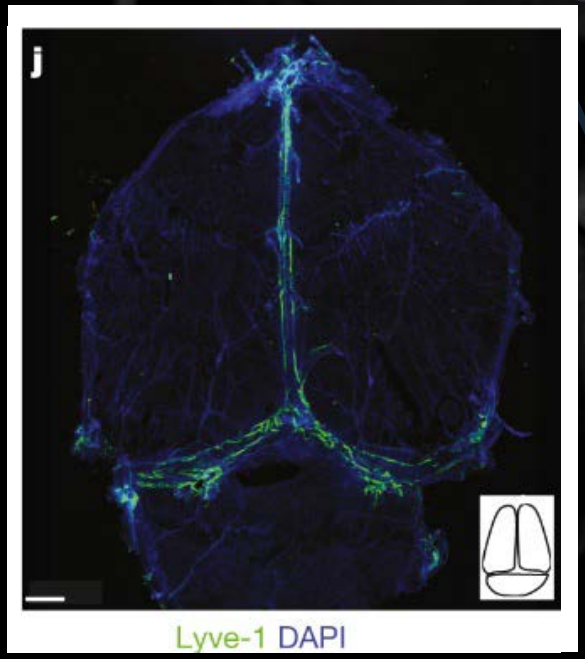

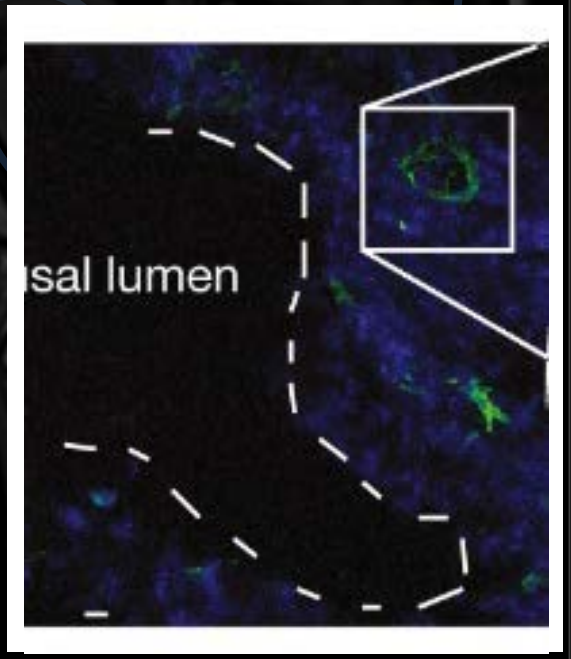

From Louveau et al. *Nature* 2015

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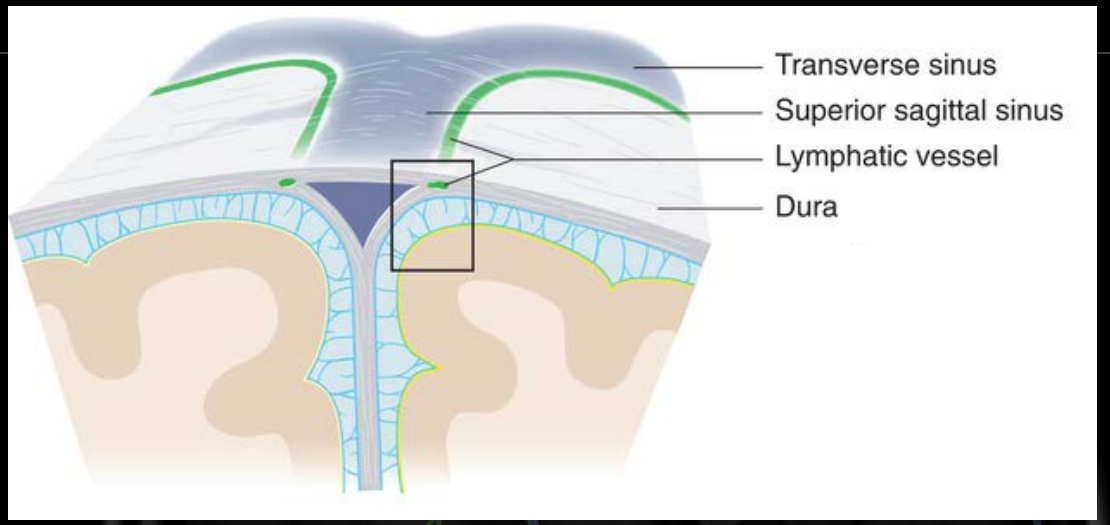
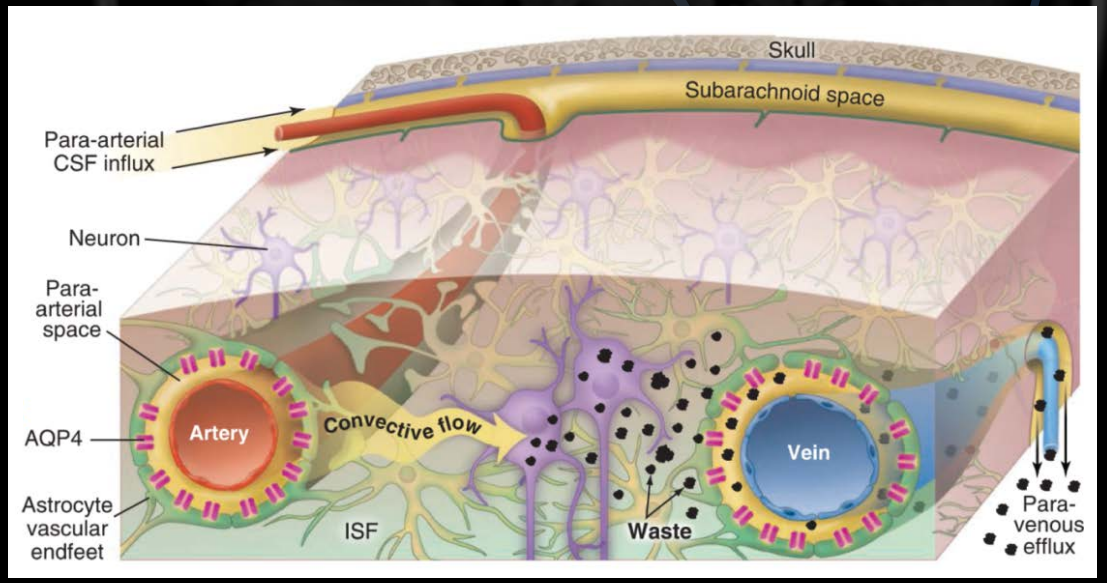
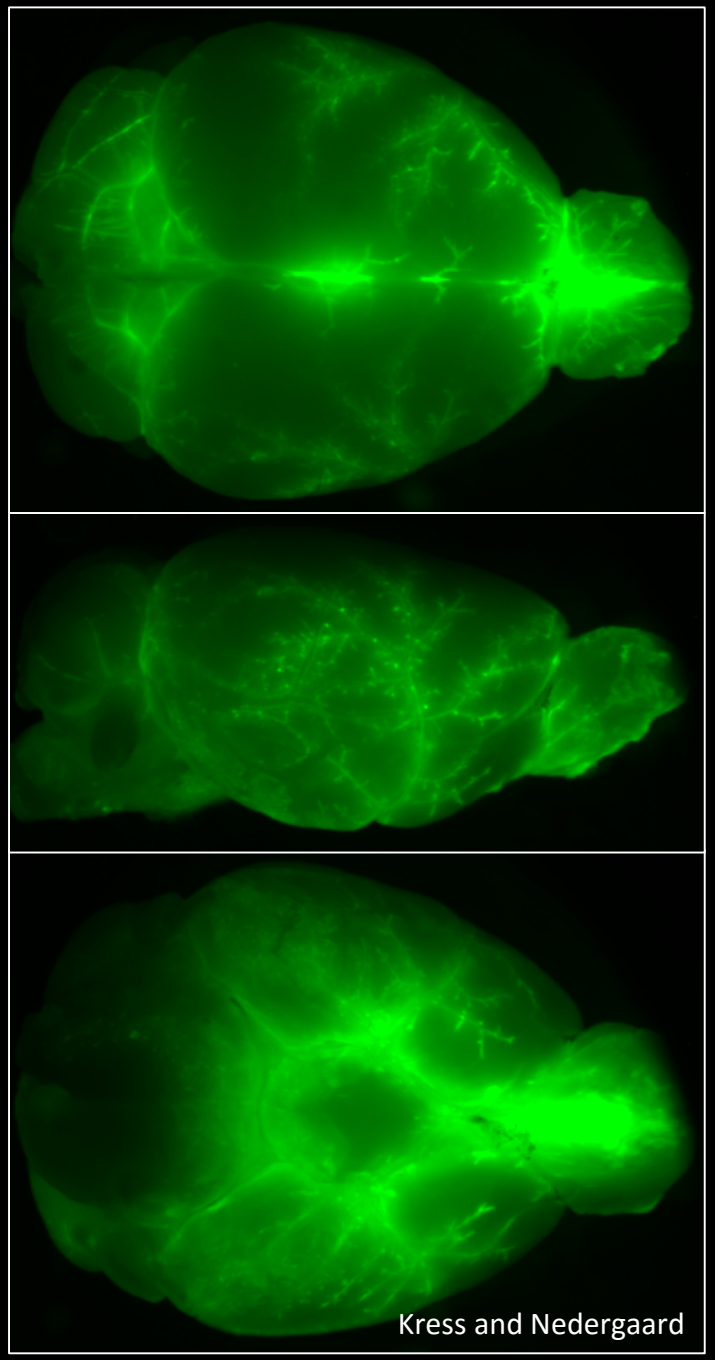


From Louveau et al. *Nature* 2015



From Nedergaard *Science* 2014

A brain-wide perivascular pathway for CSF-ISF exchange



CSF Tracer (BSA-488)
30min post-injection

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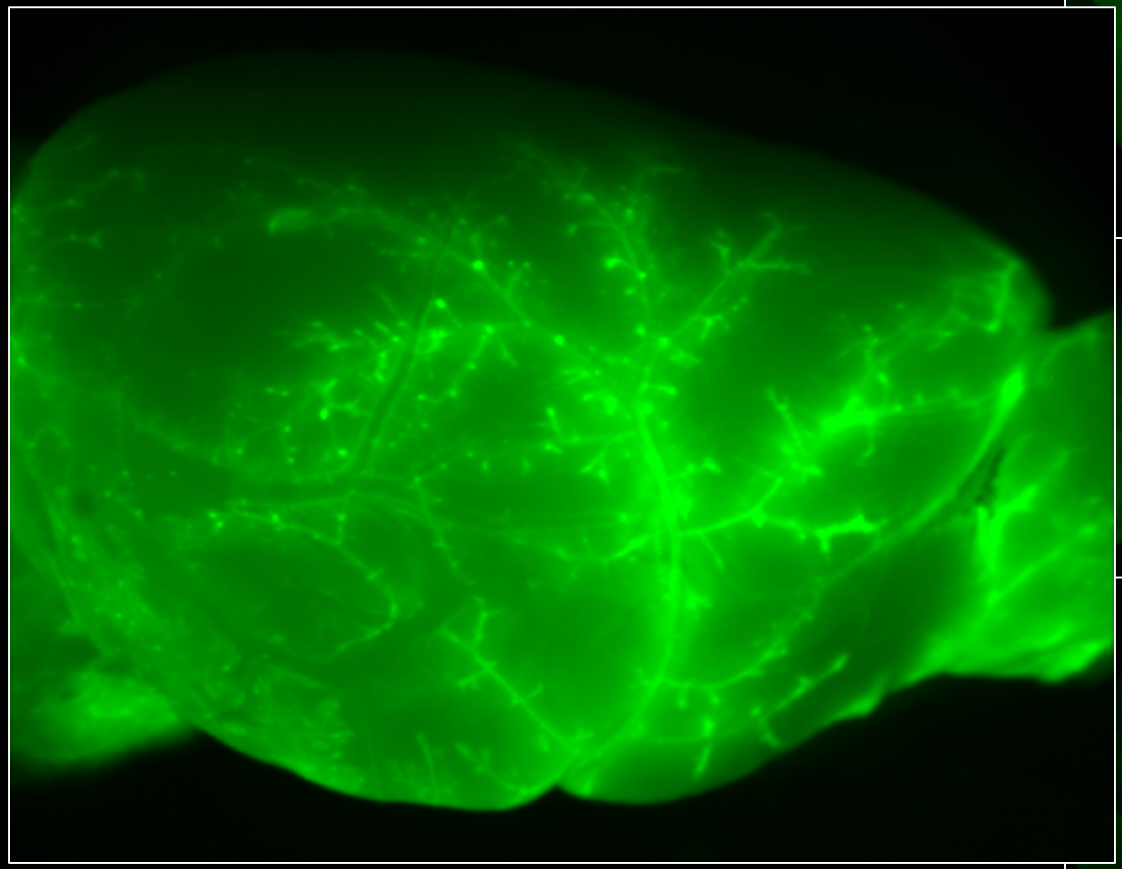

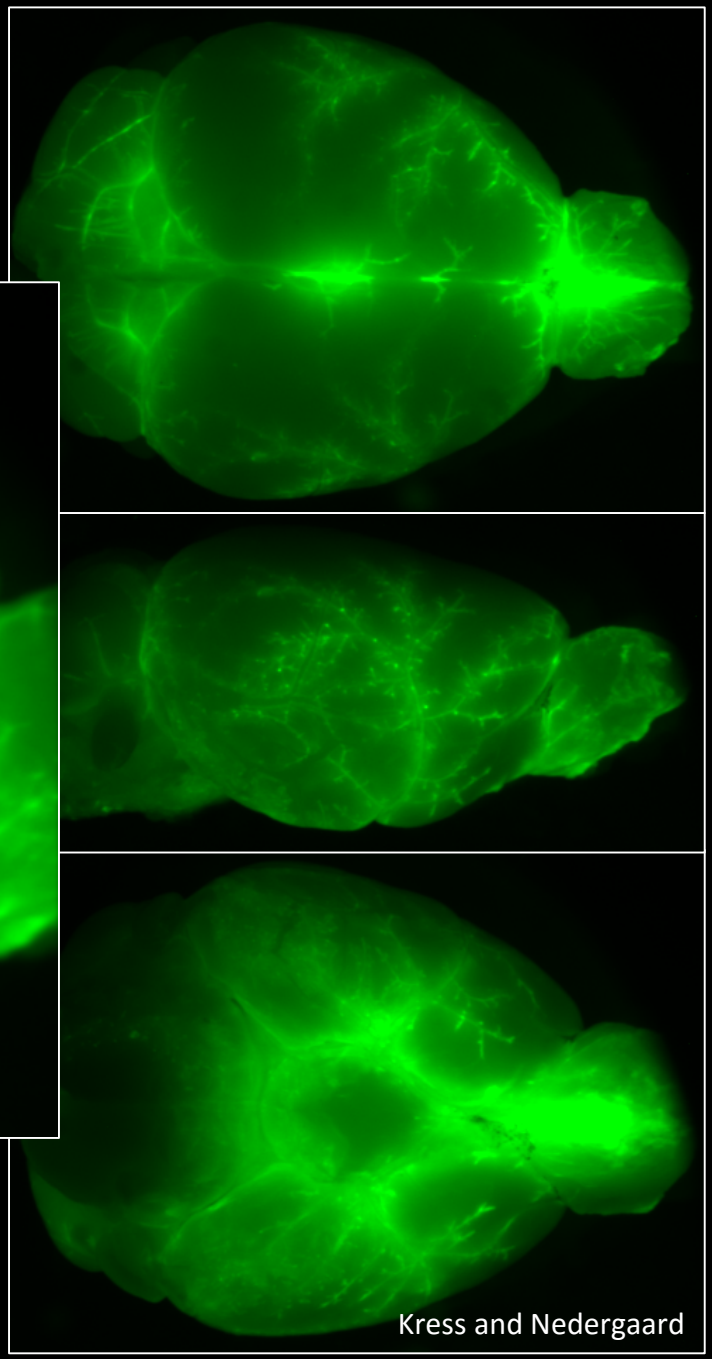

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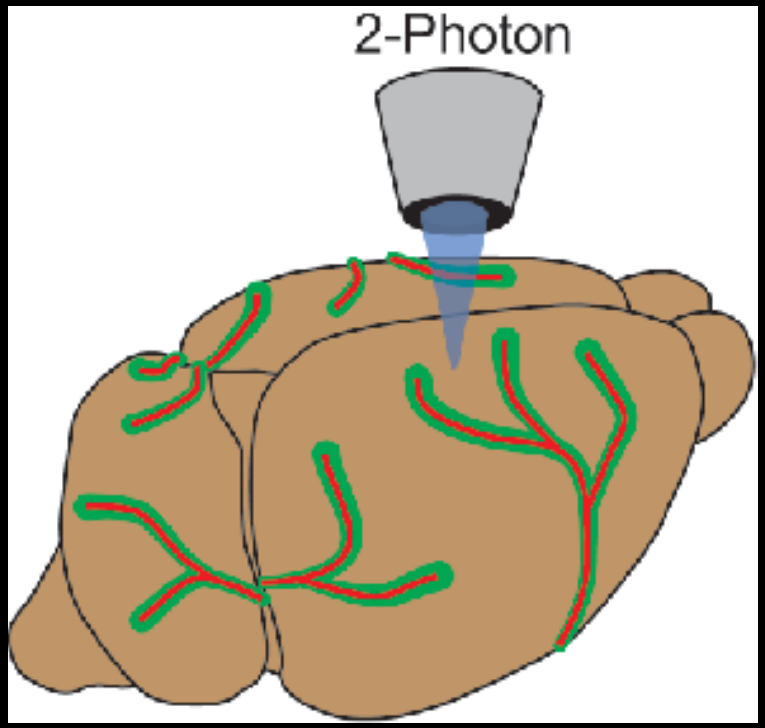
Kress and Nedergaard

In vivo 2-photon microcopy

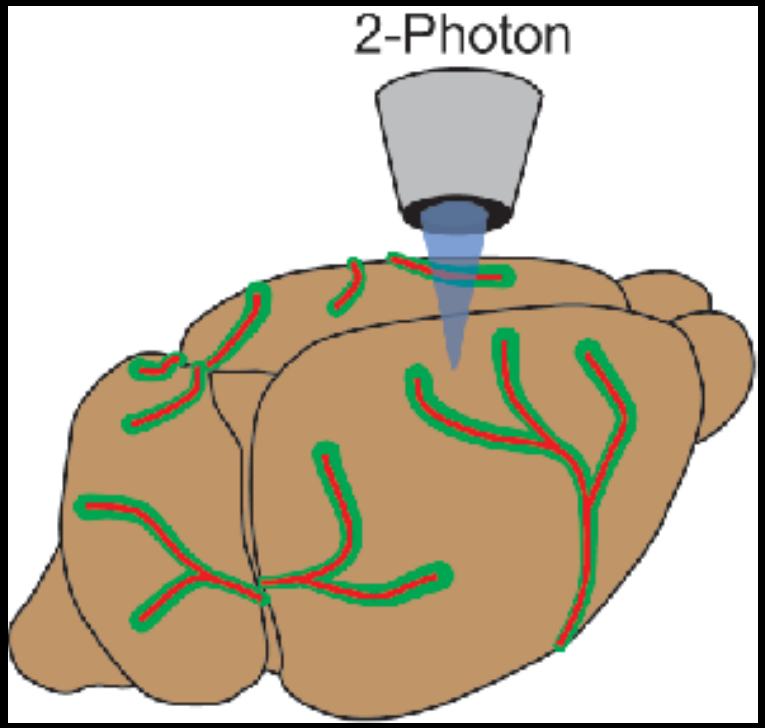


Cortical Surface

TR-d70 (iv tracer)
FITC-d40 (CSF tracer)
1 frame = 1min

Iliff et al. *Sci Transl Med* 2012

In vivo 2-photon microcopy



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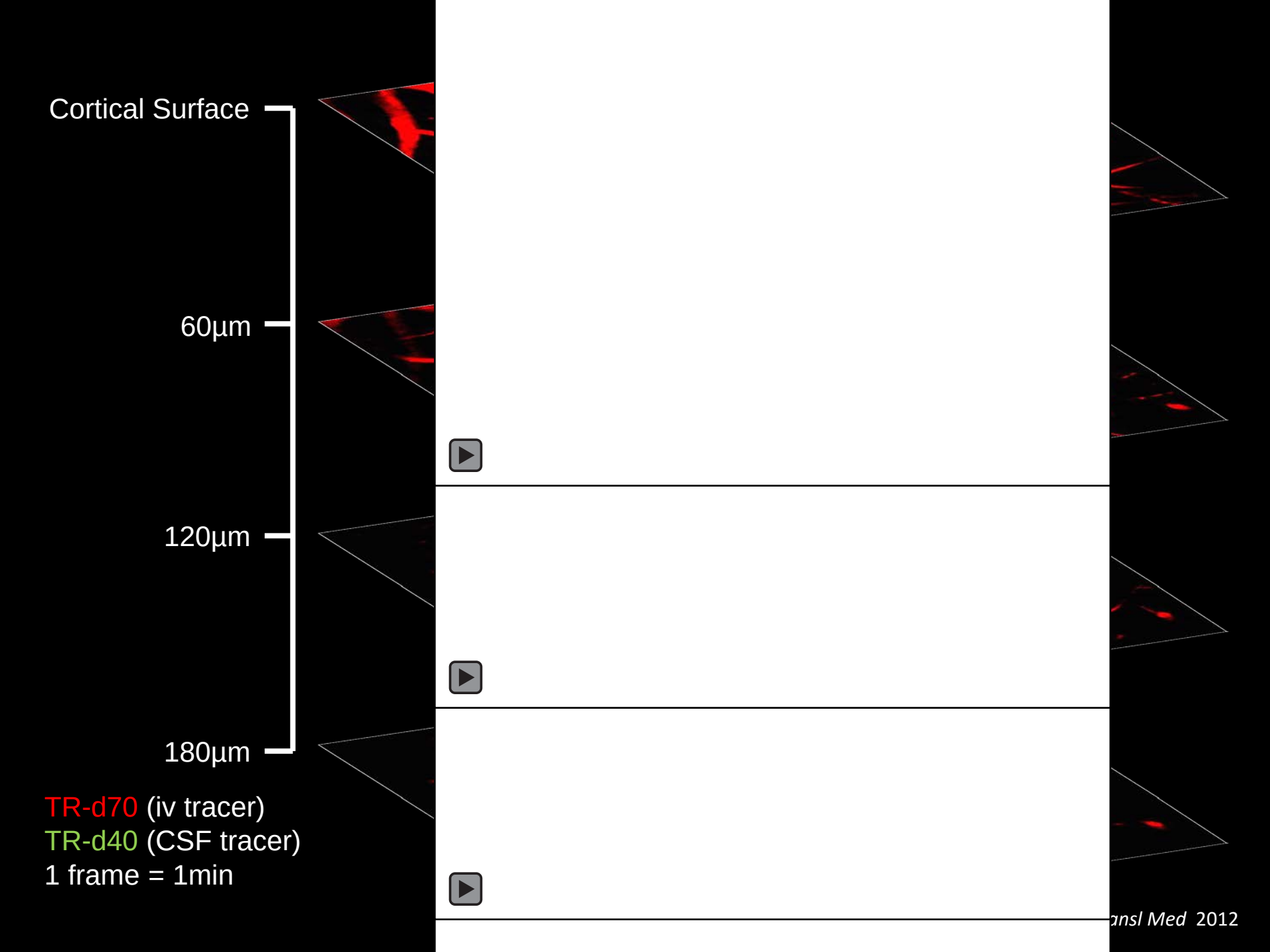
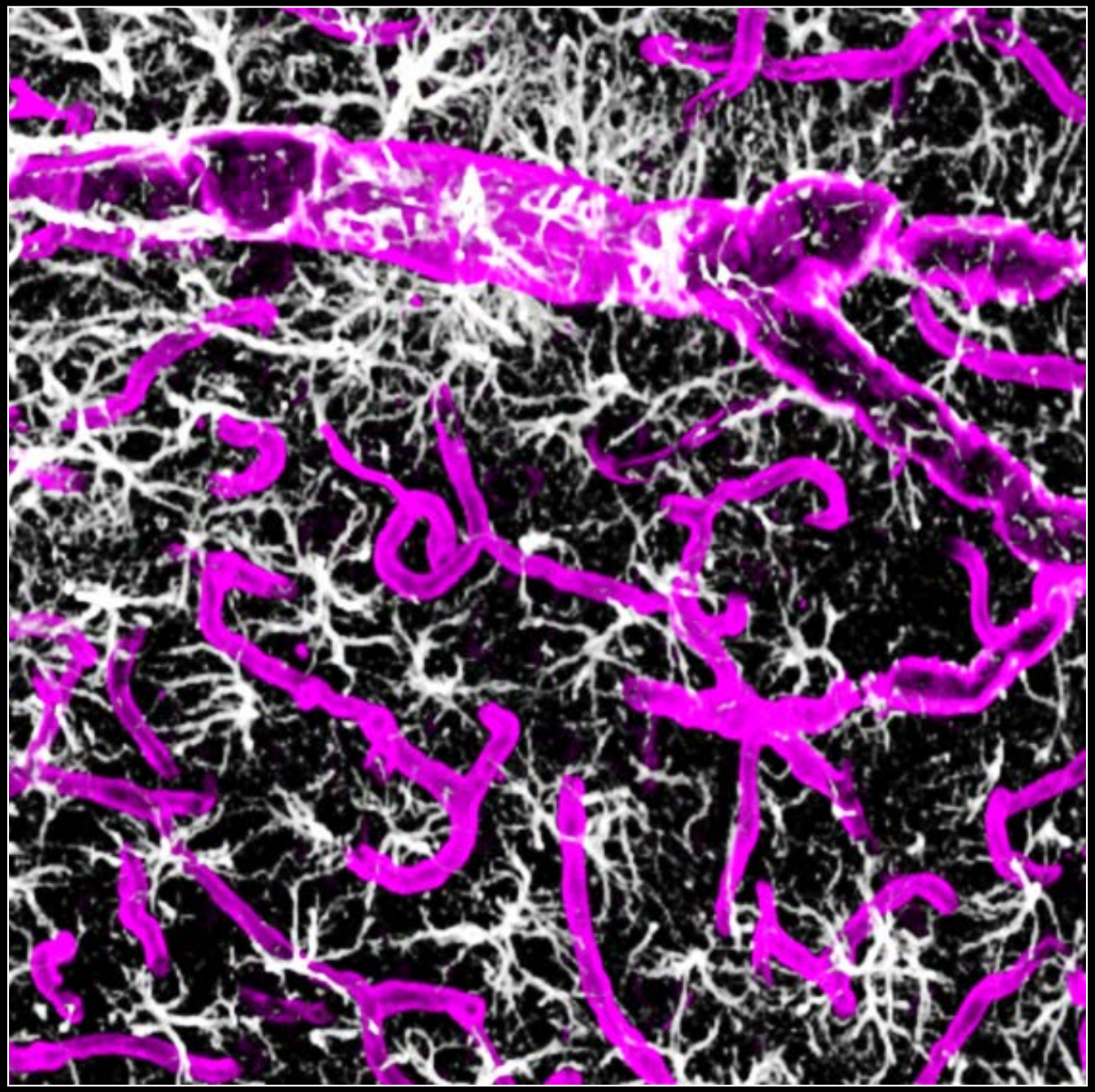
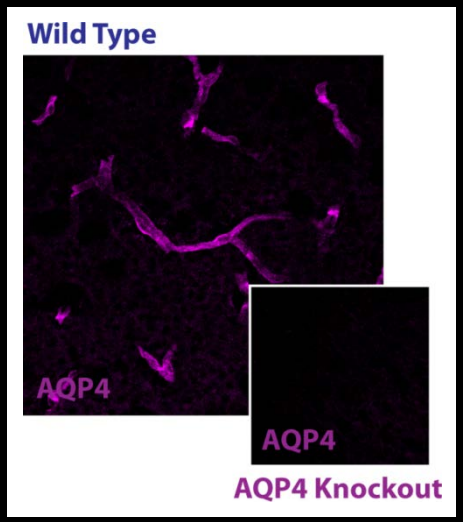


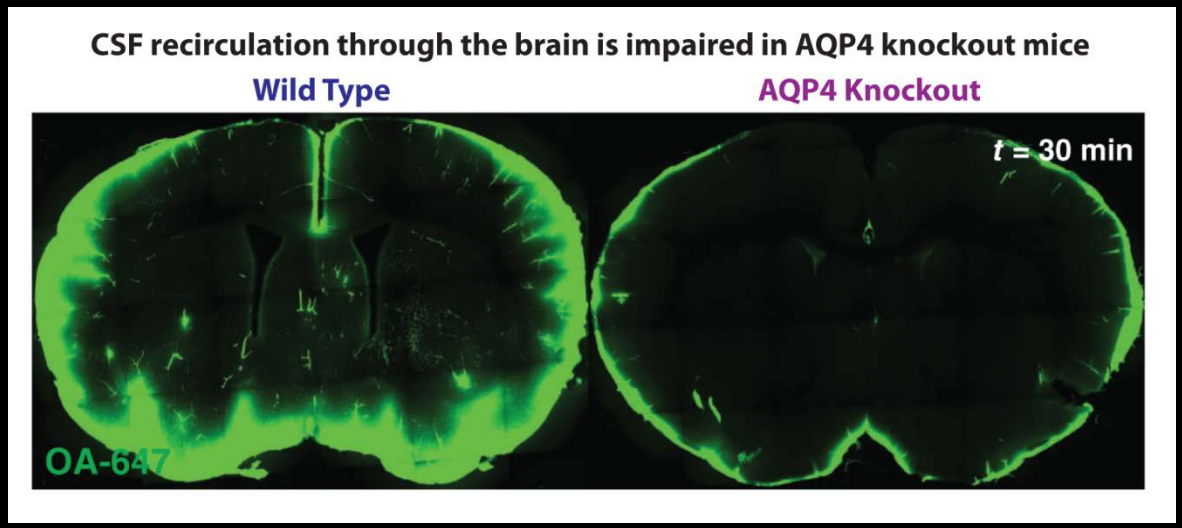
ansl Med 2012

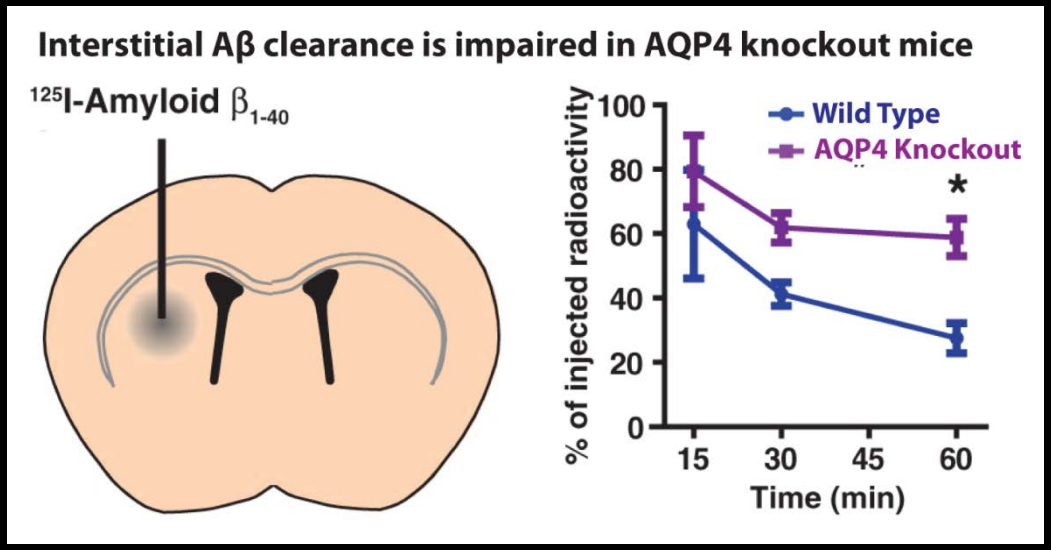
Aquaporin-4 (AQP4)



AQP4 supports perivascular CSF recirculation and amyloid β clearance







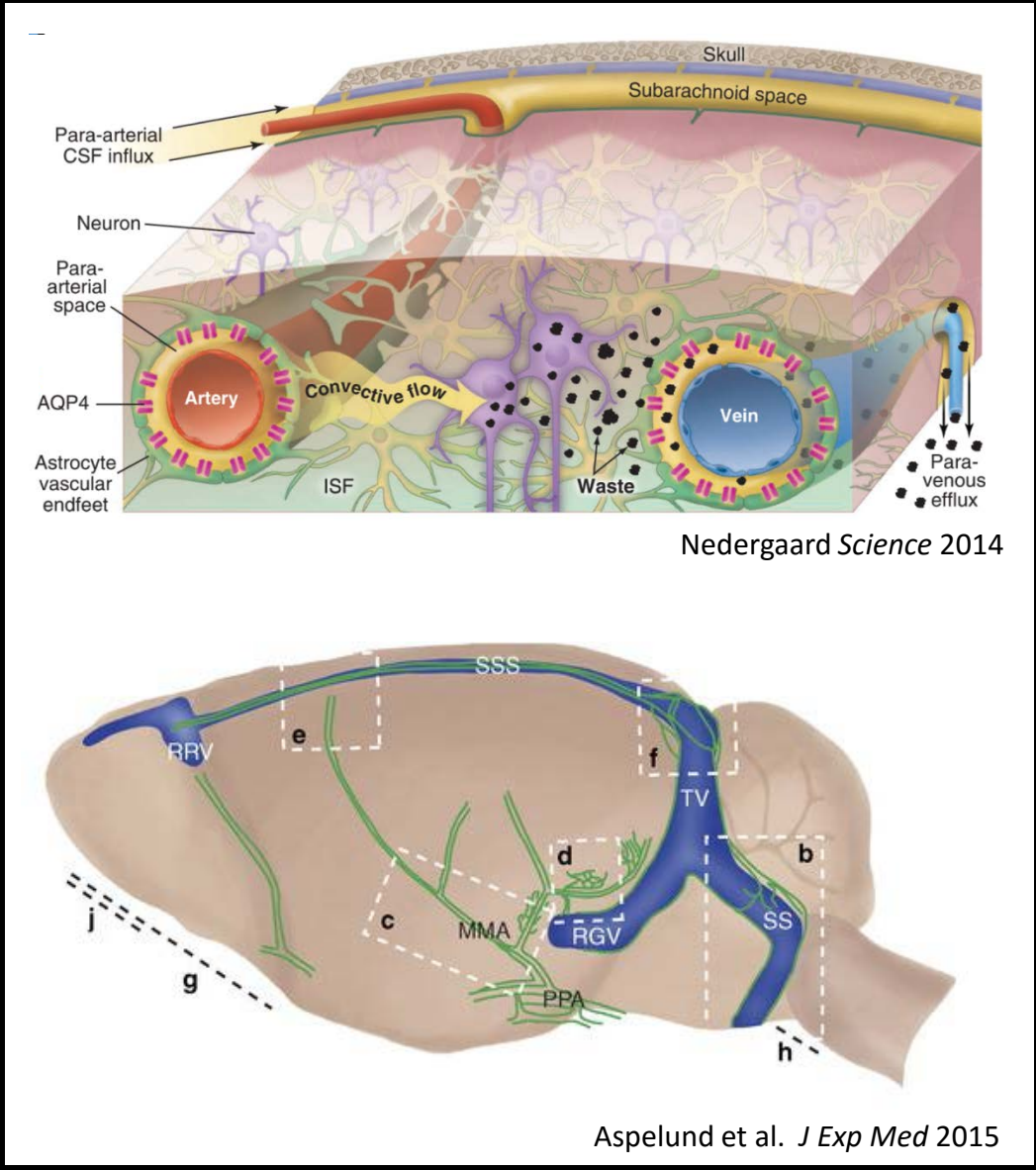
Iliff et al. *Sci Translat Med* 2012

Two recently defined systems

- Perivascular pathways – the 'glymphatic' system
  - -- A feature of the sleeping brain
- Sinus-associated lymphatic vessels

Proposed Functions

- Interstitial solute clearance
- CNS immune surveillance



Nedergaard *Science* 2014

Aspelund et al. *J Exp Med* 2015

The glymphatic system and Alzheimer's

How does it fit in and where are the gaps?

Association with age

Sequence of events

Regional vulnerability

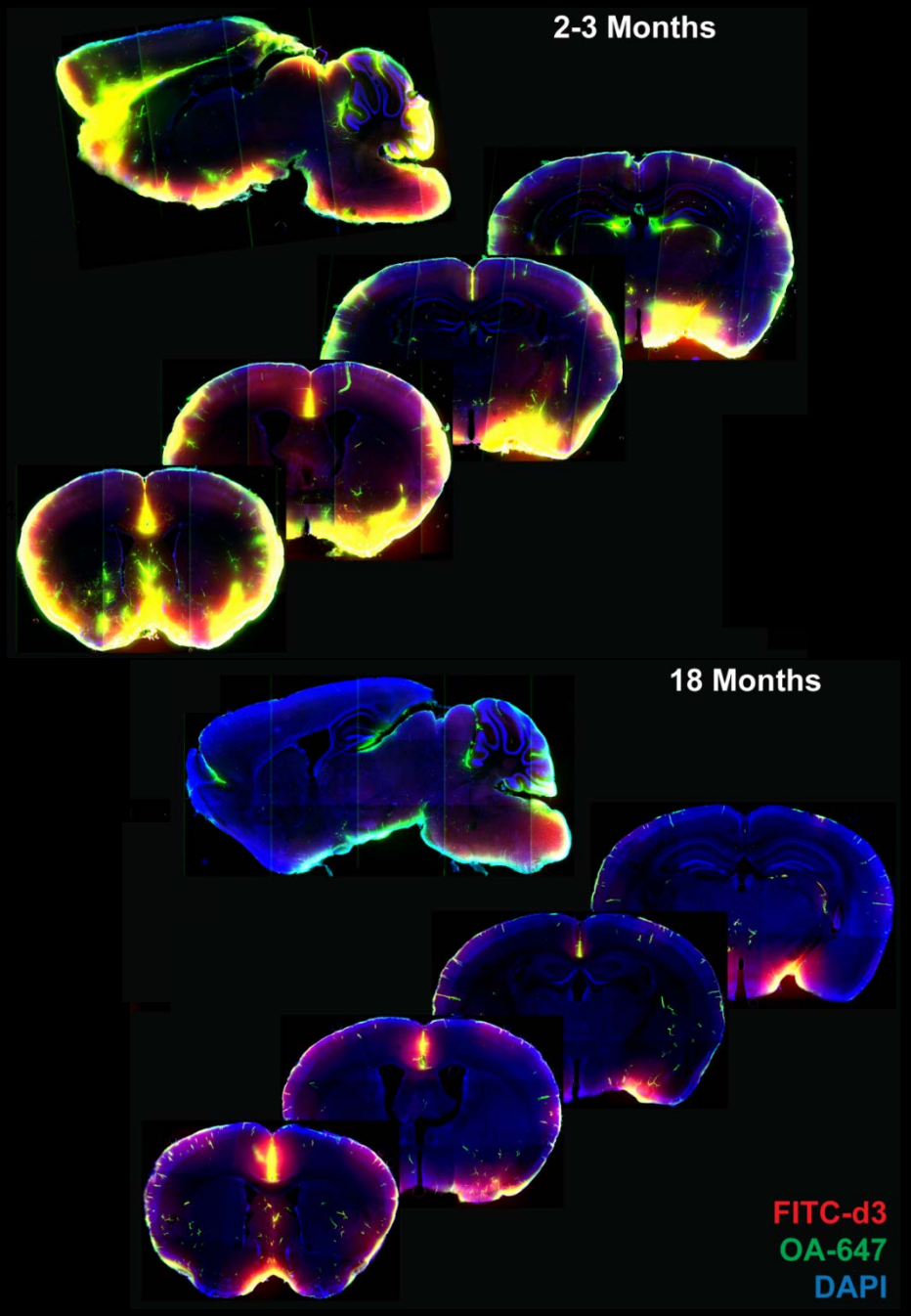
The human brain

Pathogenic interactions

Biomarkers

Translational potential

Association with age



From Kress et al. *Annals Neurol* 2014

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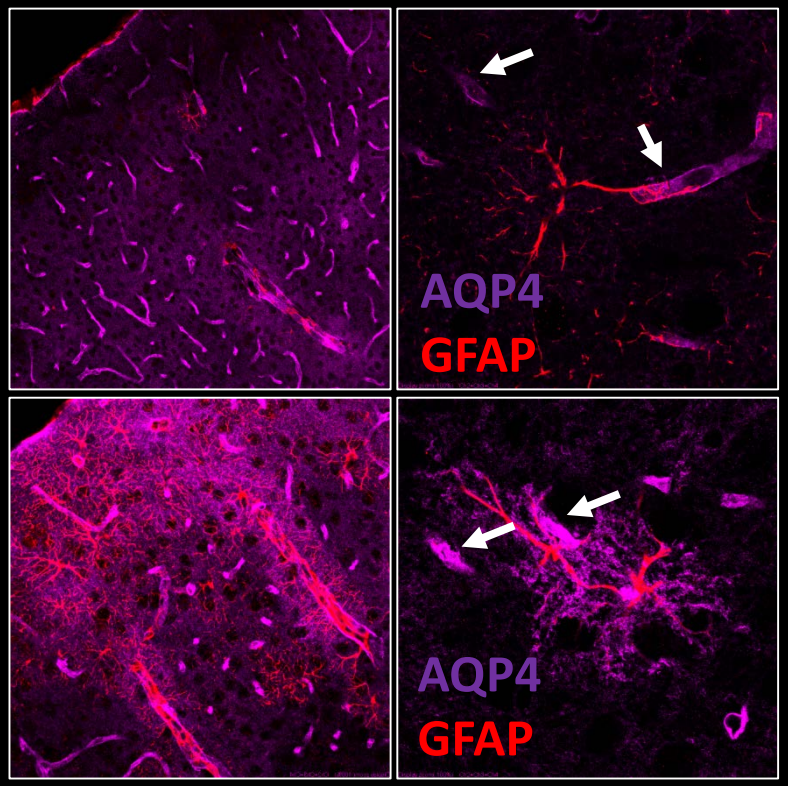

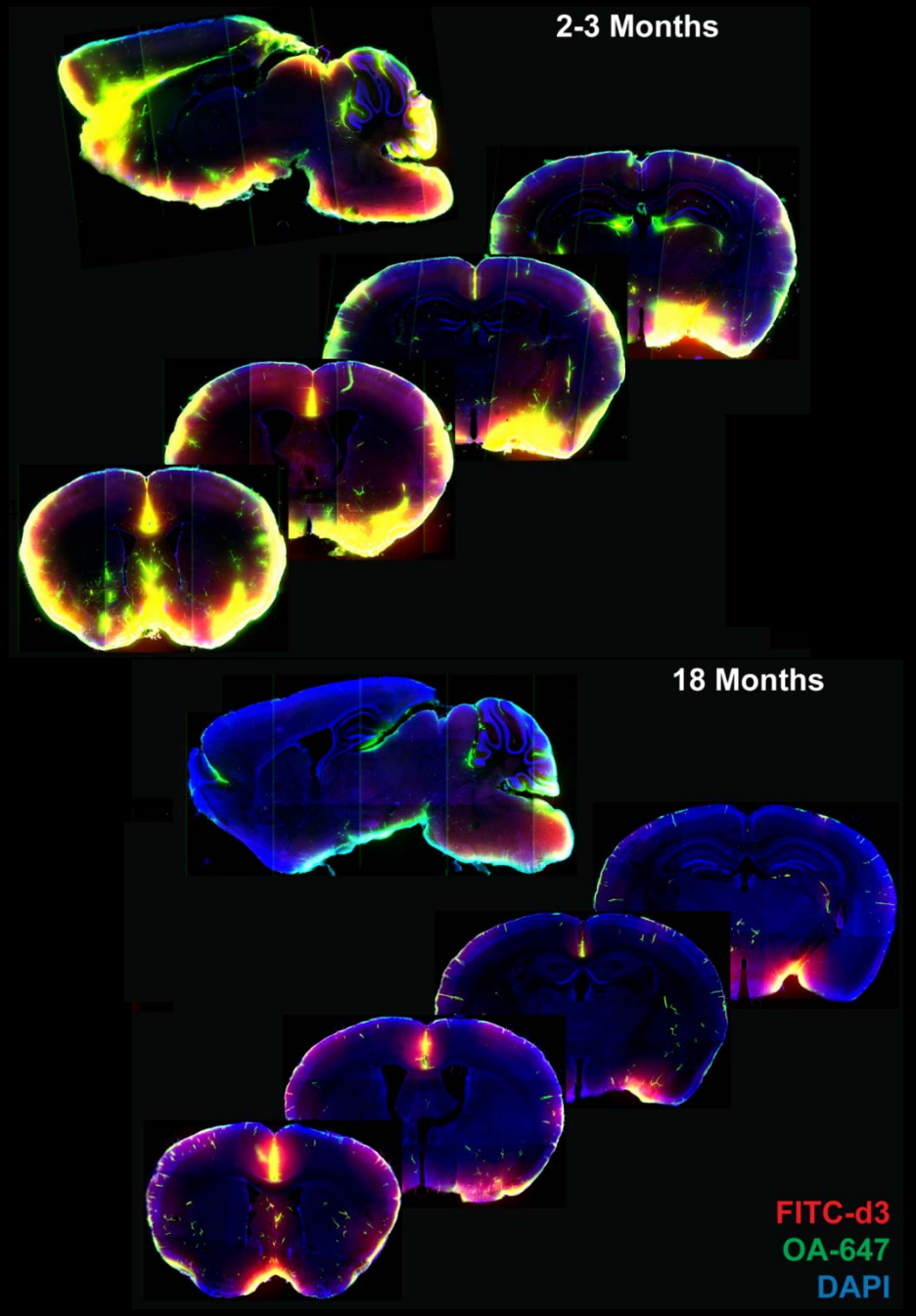

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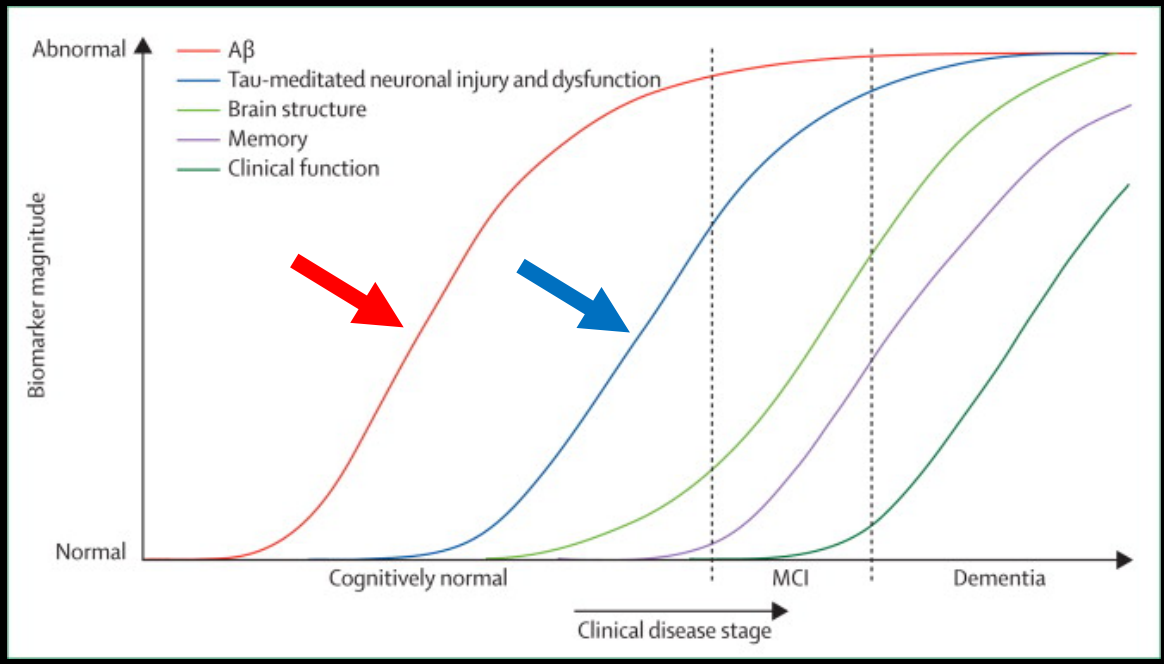
Association with age

Sequence of events

Hypothetical timecourse of AD biomarkers



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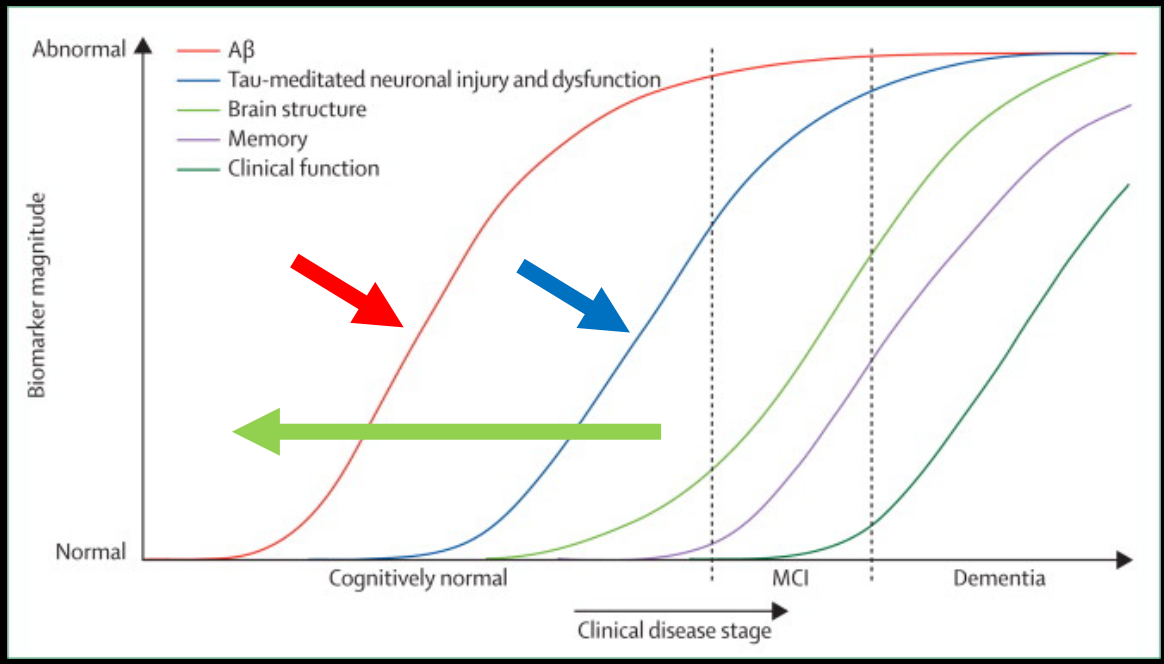

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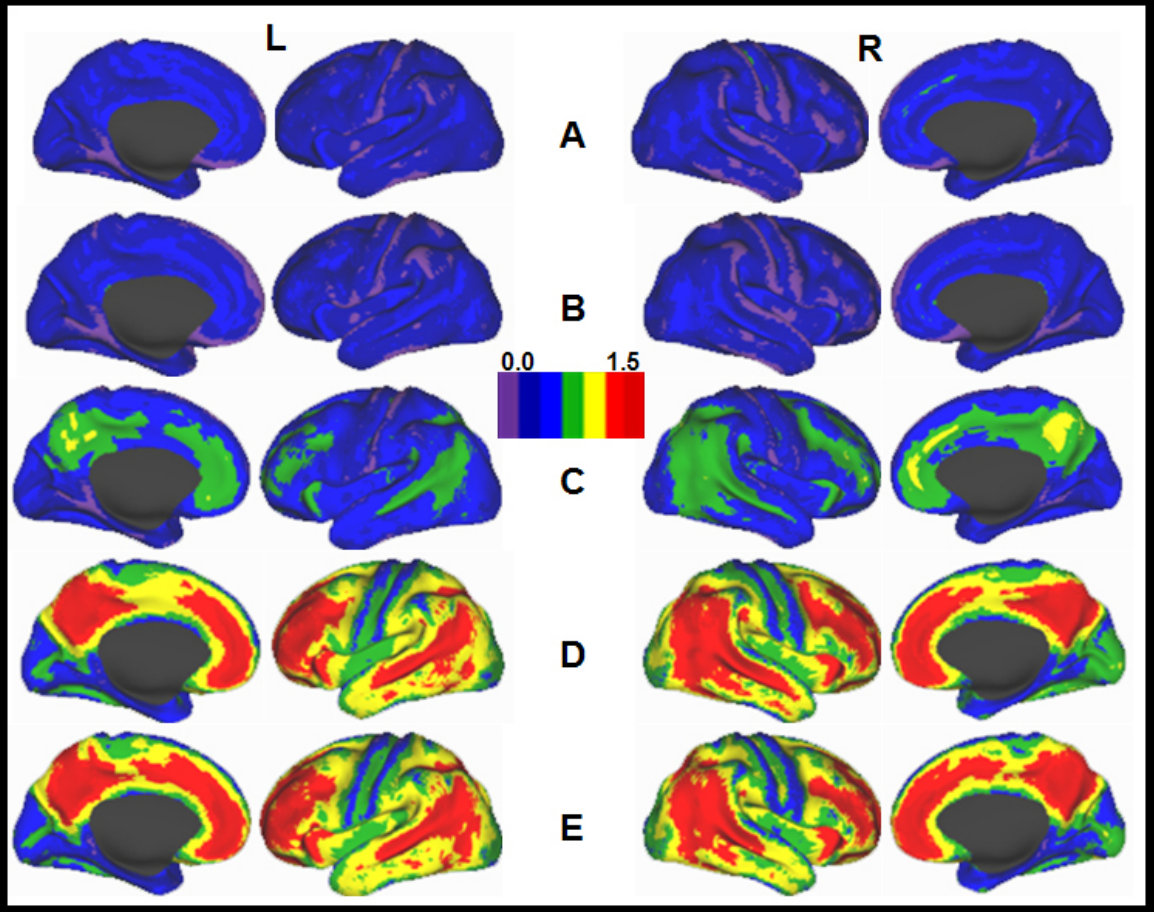

From Vlassenko et al. *PNAS* 2010

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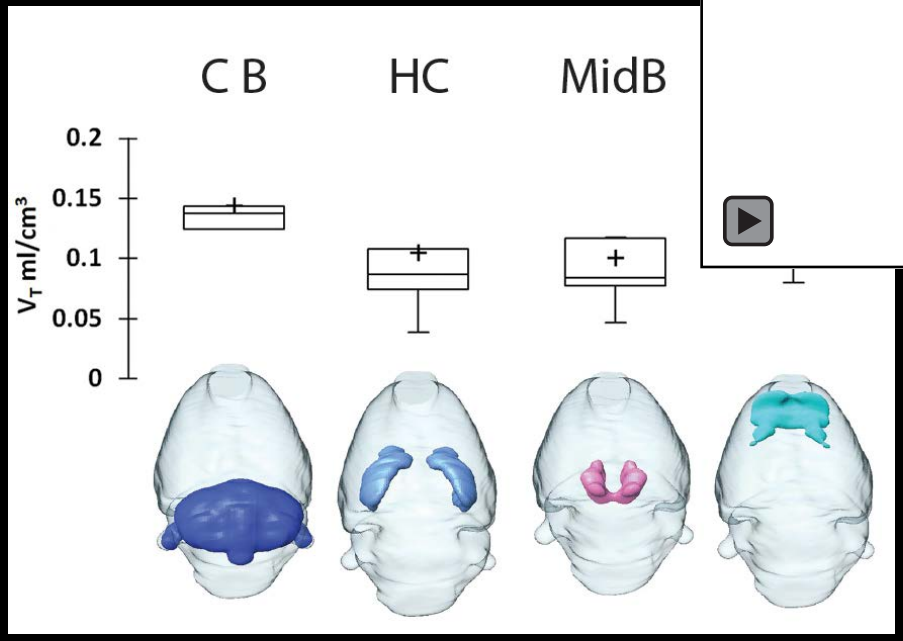

Lee et al. *J Neurosci* 2015

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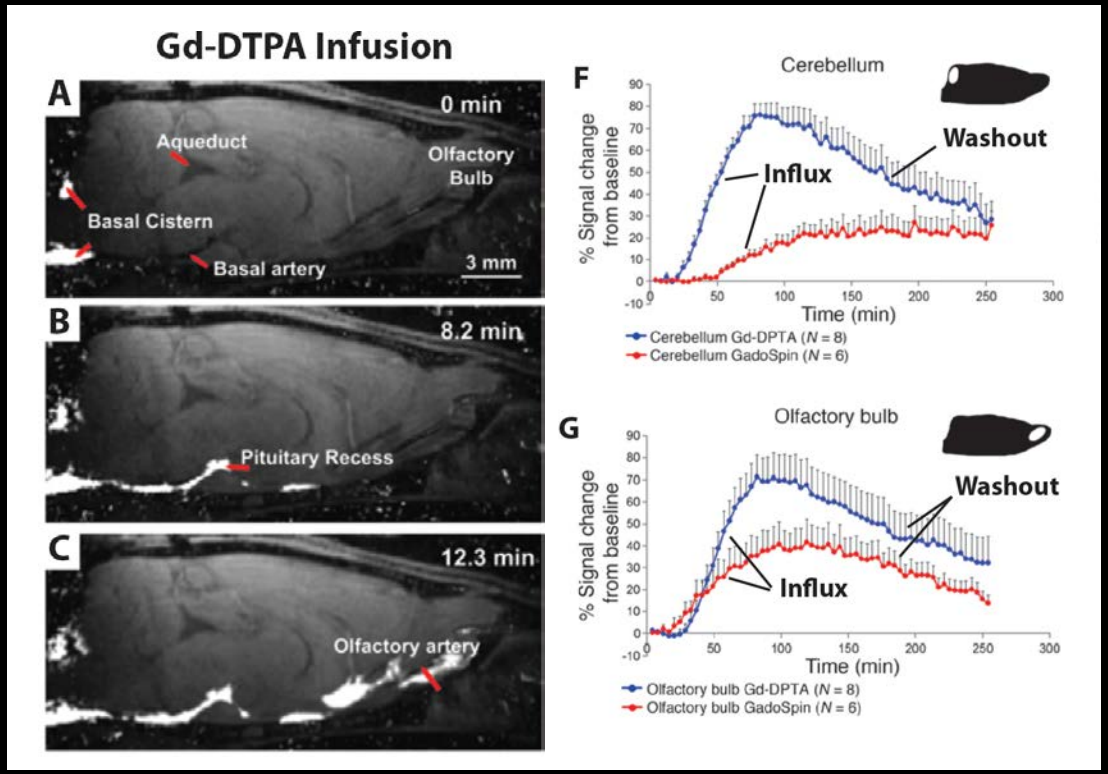
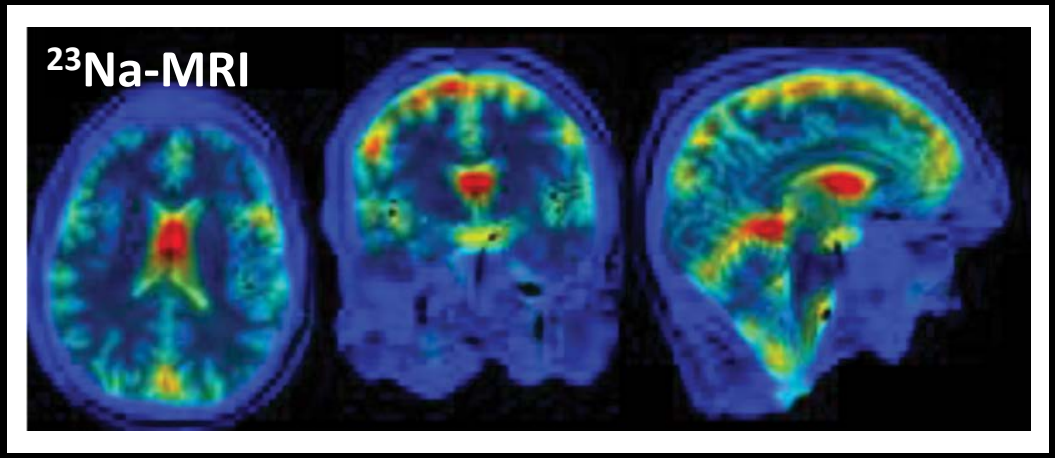


From Iliff et al. *J Clin Invest* 2013



B. Rooney, OHSU AIRC

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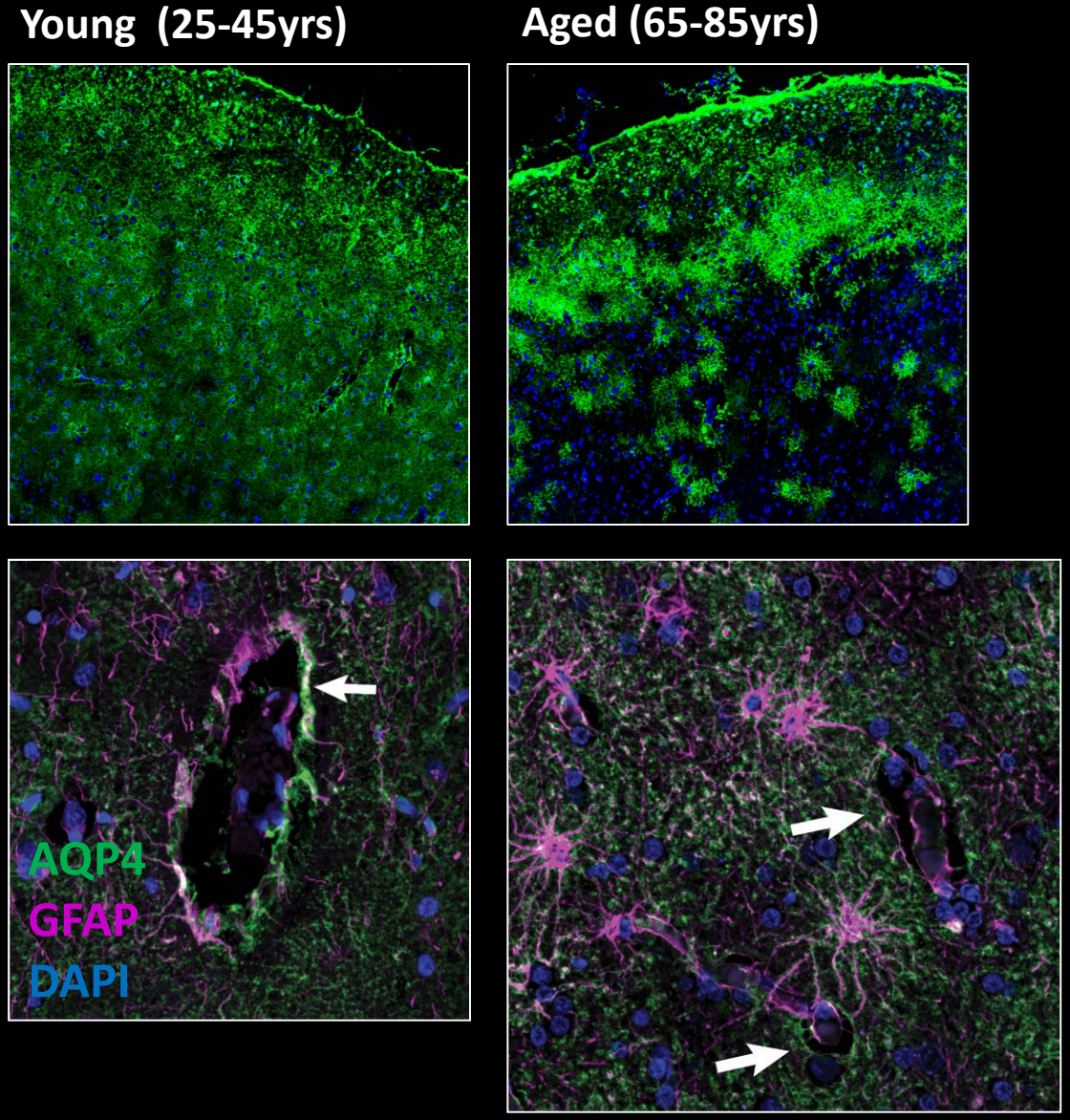

R. Woltjer, OADC Brain Bank

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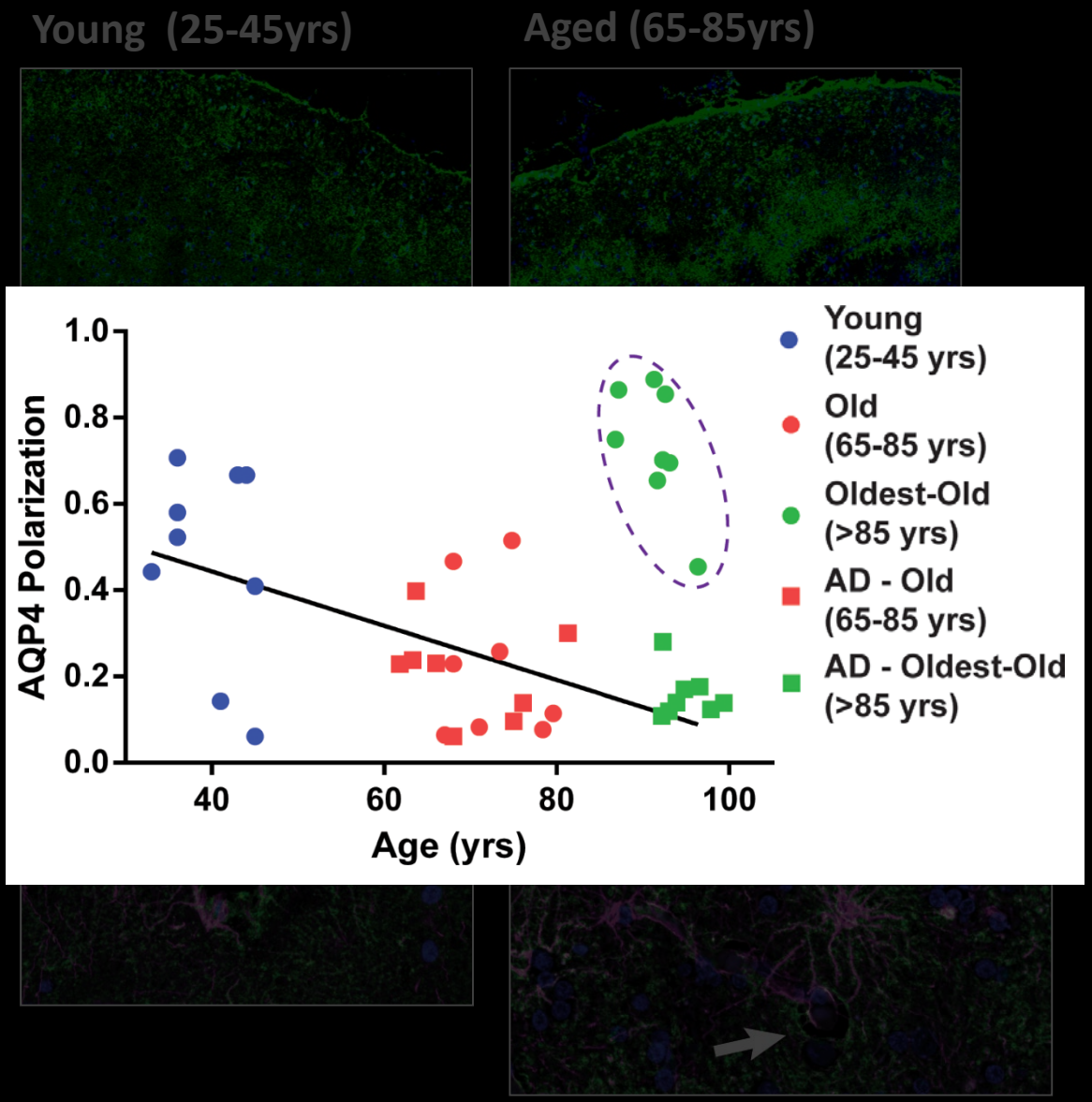

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Braak Stage

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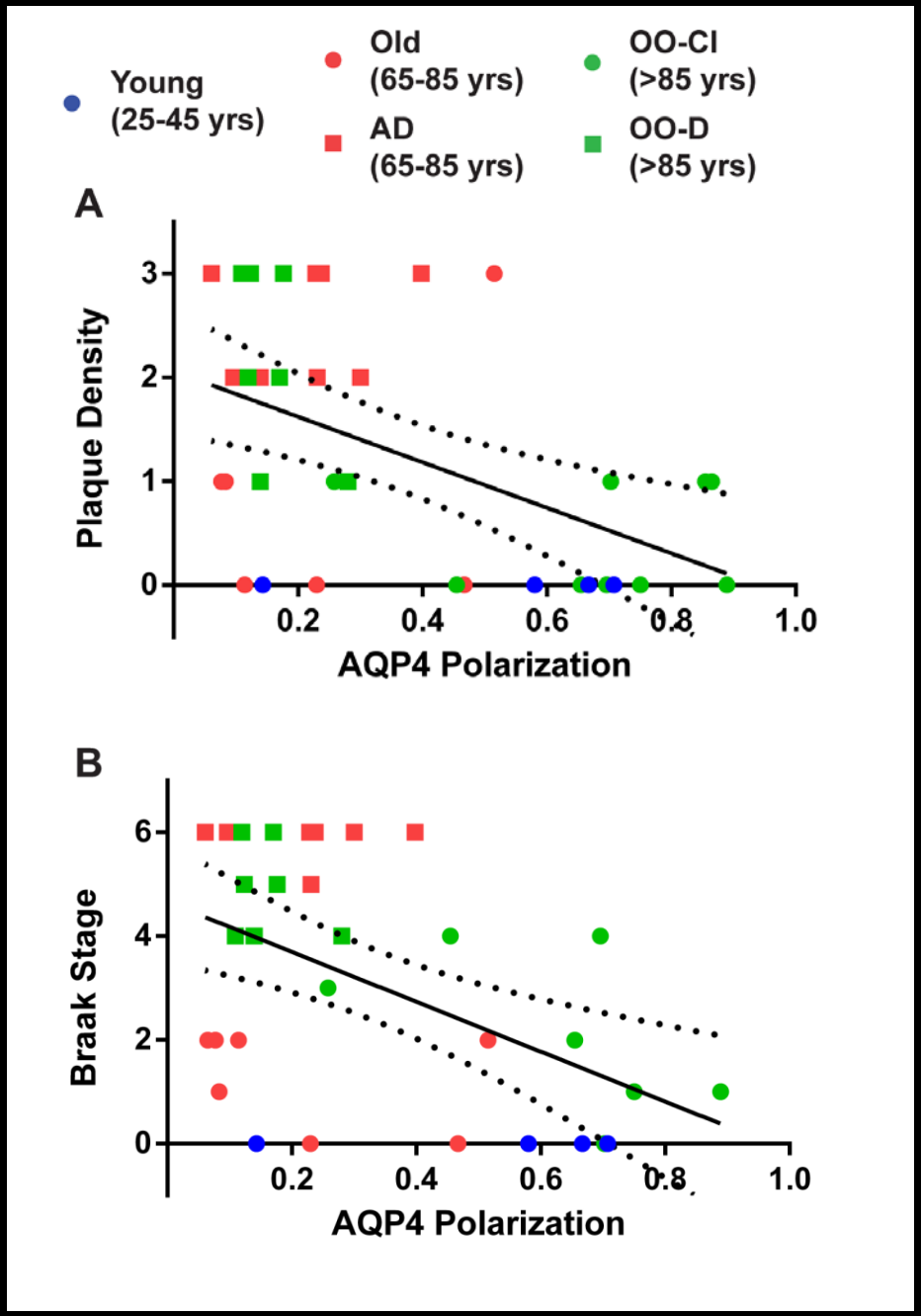
Plaque Burden

- **Polarization (t = -3.38, p=0.0024); Age (t=1.08, p=0.29)**



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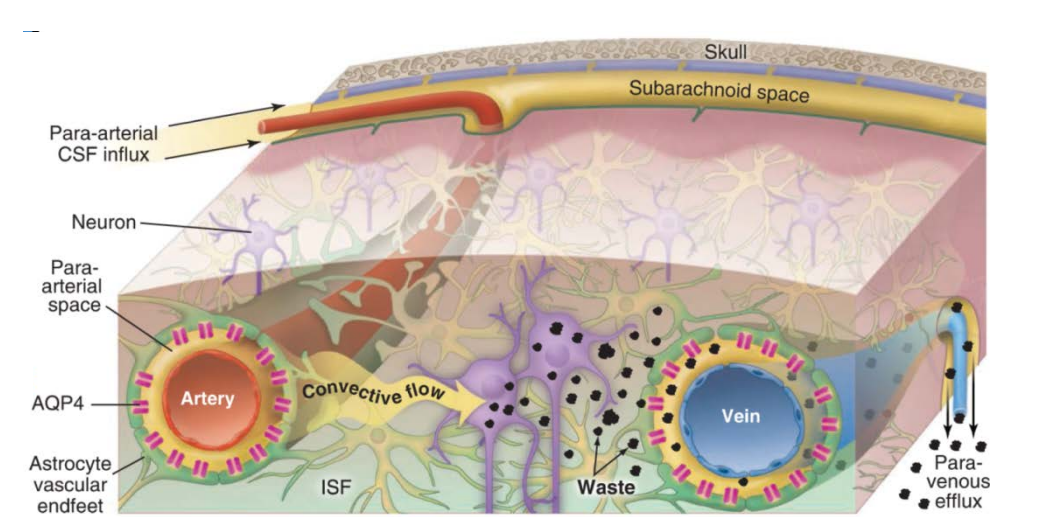
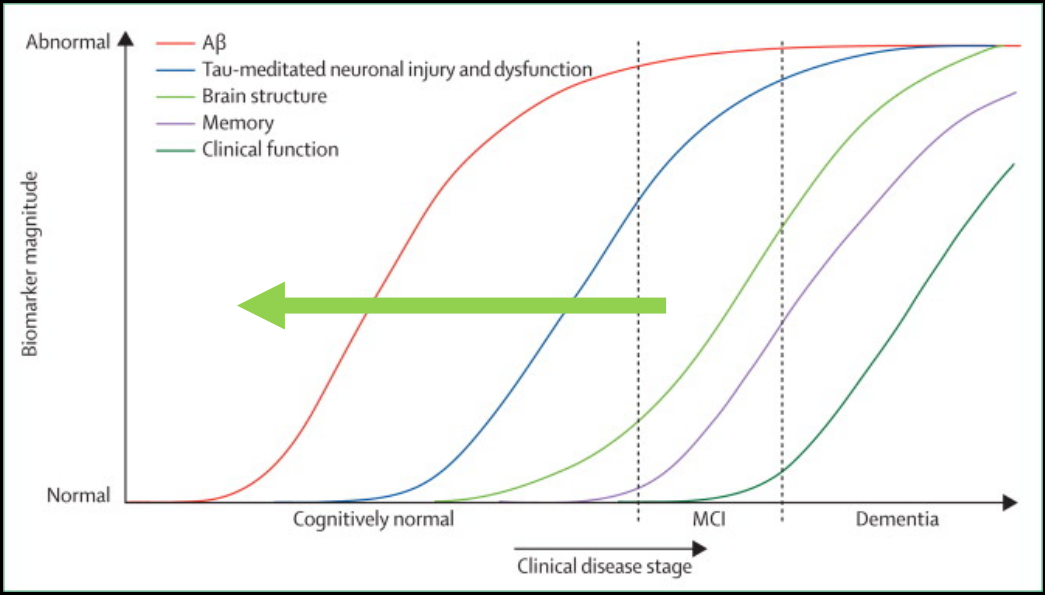


Nedergaard *Science* 2014



From Jack et al. *Lancet Neurol* 2010

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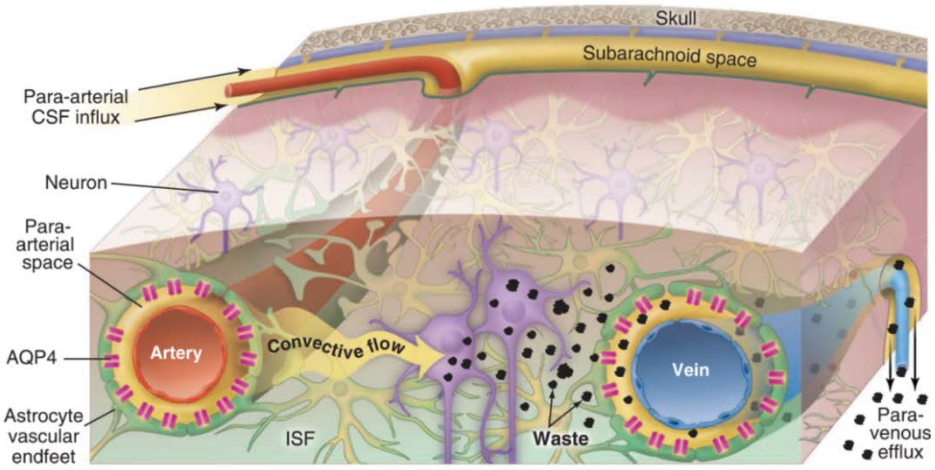

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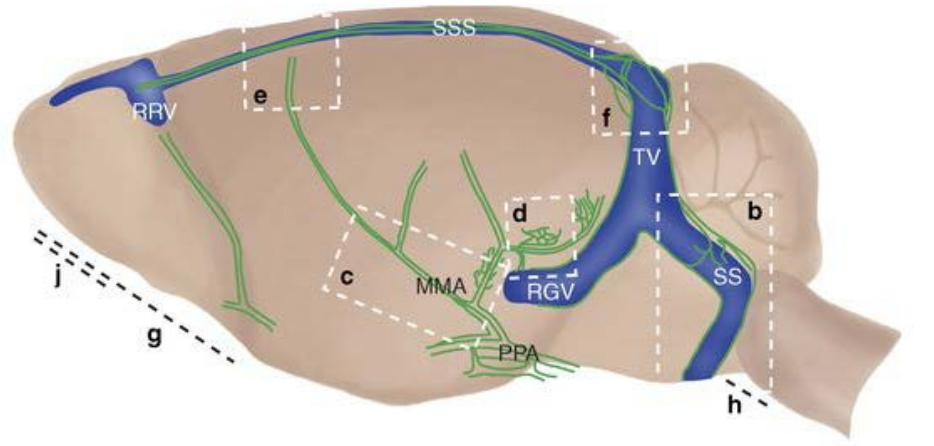

Aspelund et al. *J Exp Med* 2015

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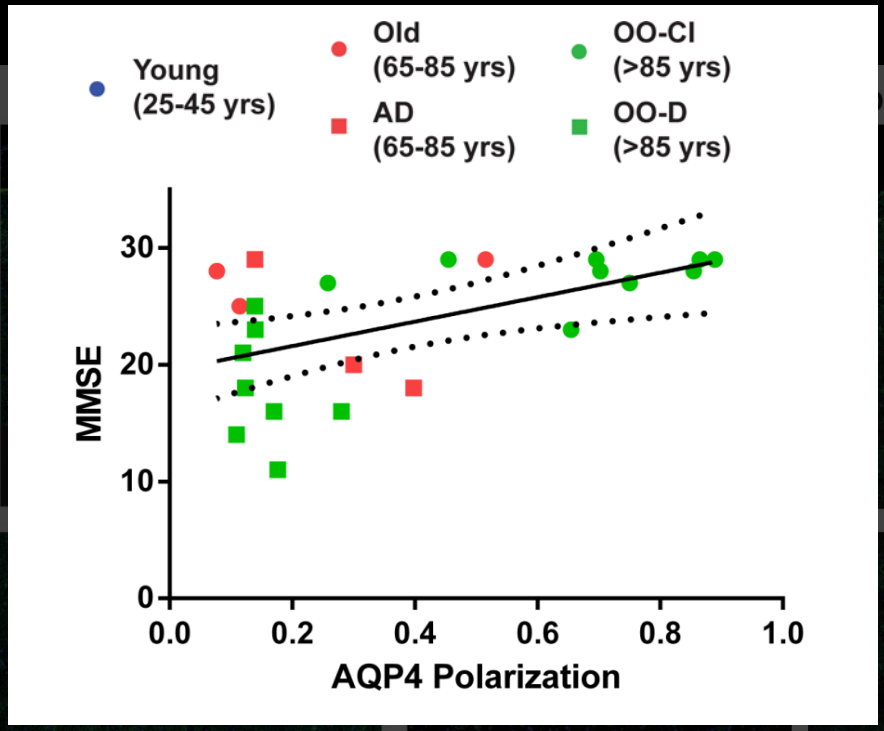
AQP4 mis-localization is associated with worsening Alzheimer's pathology



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MMSE

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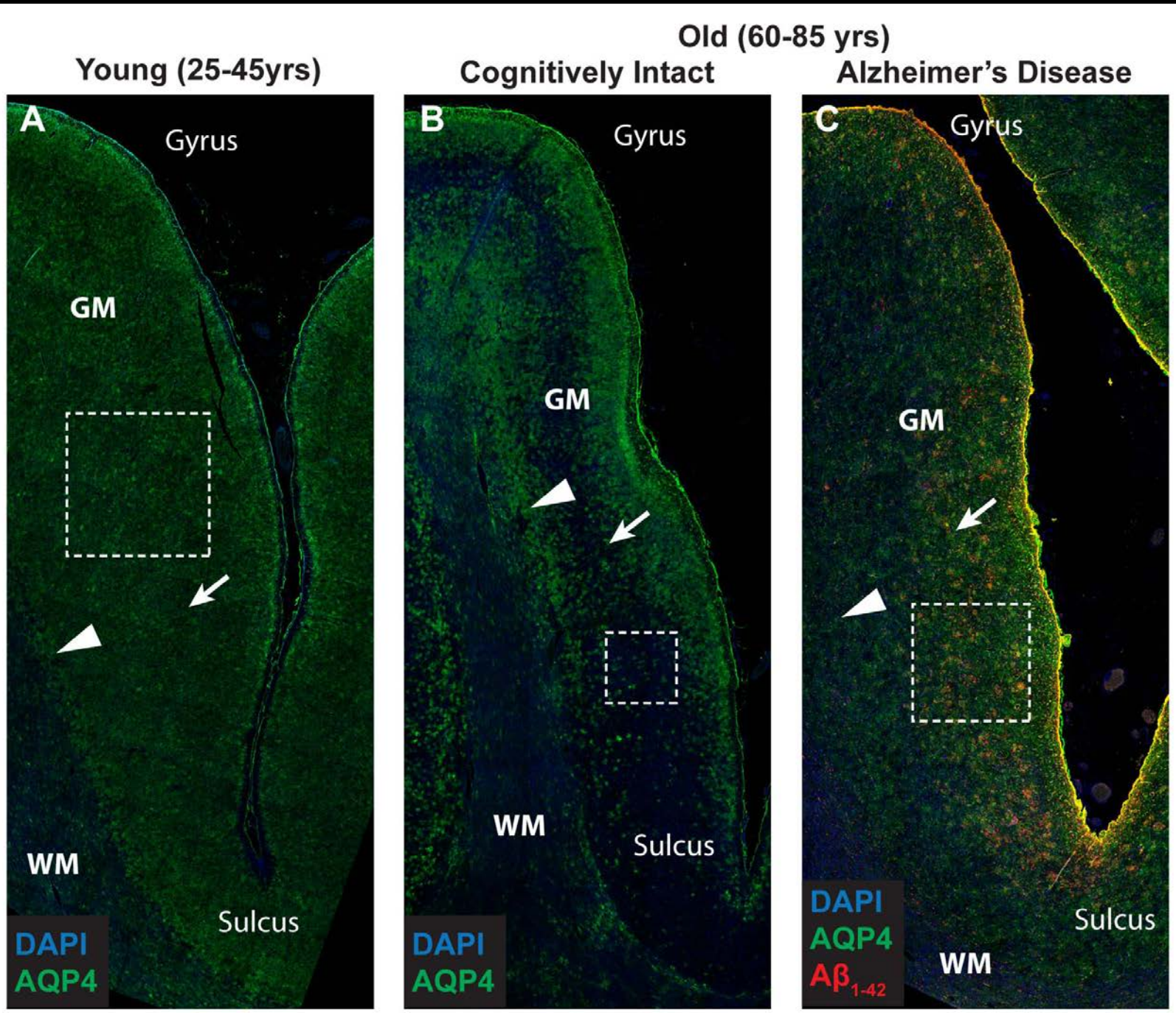
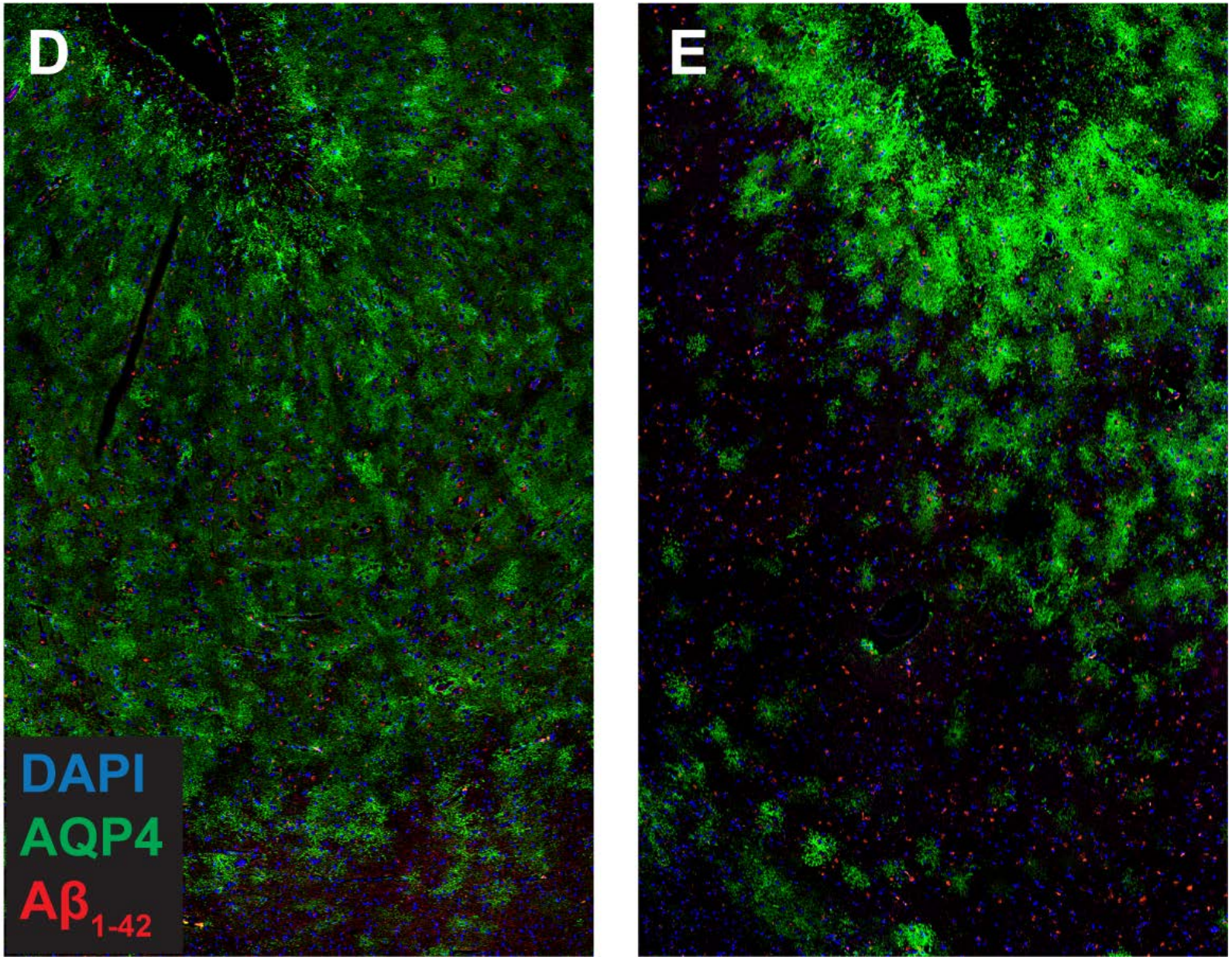
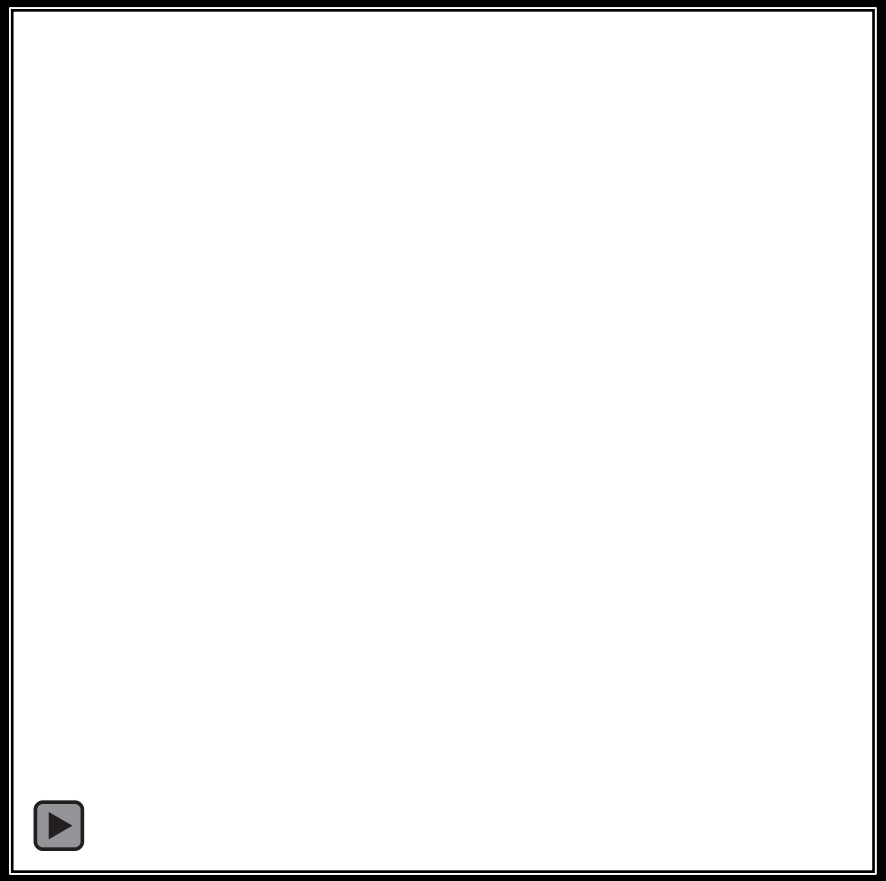

Young (25-45yrs)
Old (60-85 yrs)
Cognitively Intact
Alzheimer's Disease
A
Gyrus
GM
WM
Sulcus
DAPI
AQP4
B
Gyrus
GM
WM
Sulcus
DAPI
AQP4
C
Gyrus
GM
Sulcus
WM
DAPI
AQP4
Aβ1-42


D
E
DAPI
AQP4
Aβ1-42

Paravascular CSF recirculation is modulated by sleep state

Awake



Xie et al. *Science* 2013

Paravascular CSF recirculation is modulated by sleep state

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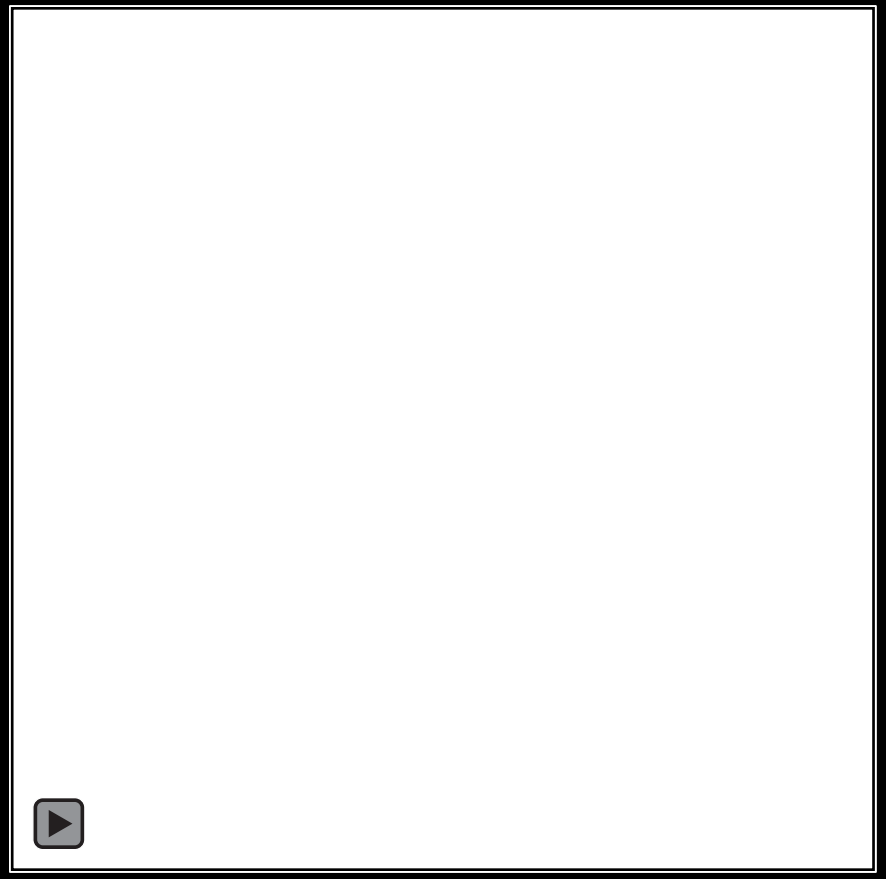
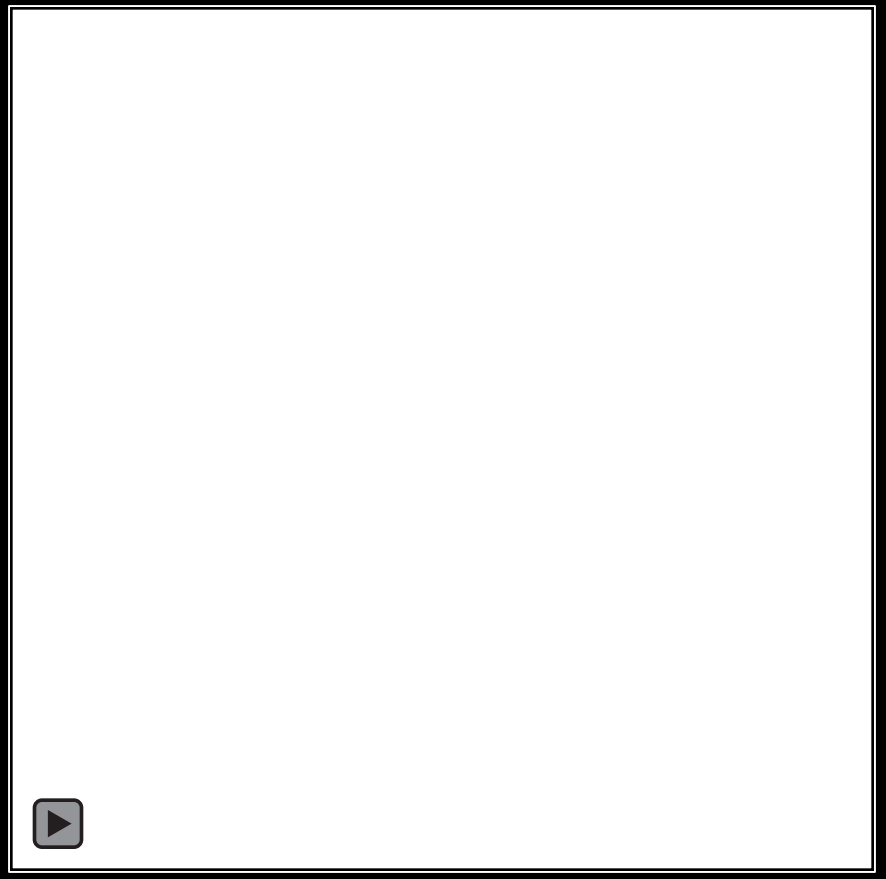
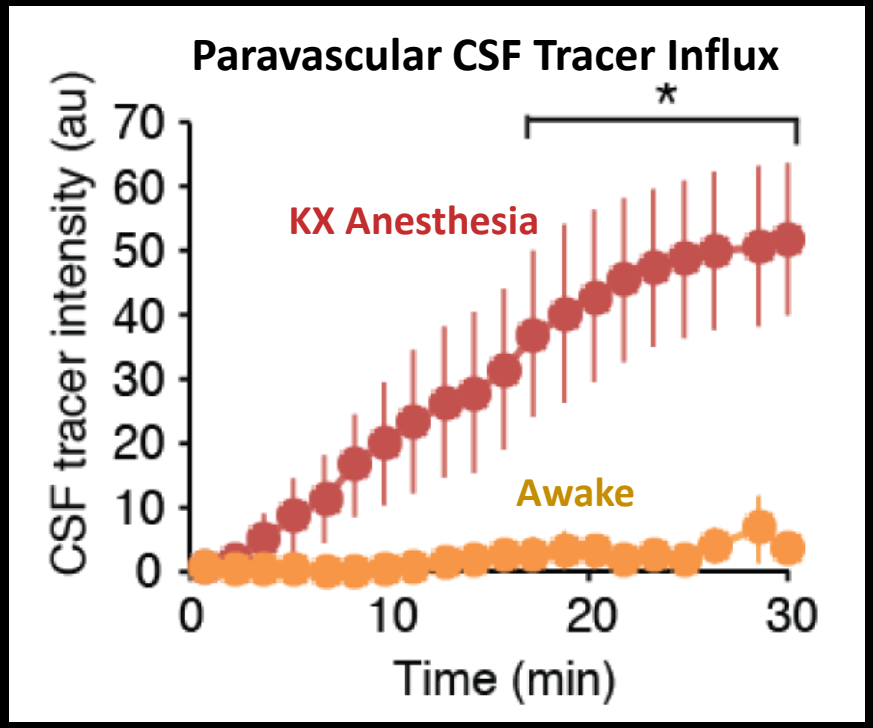


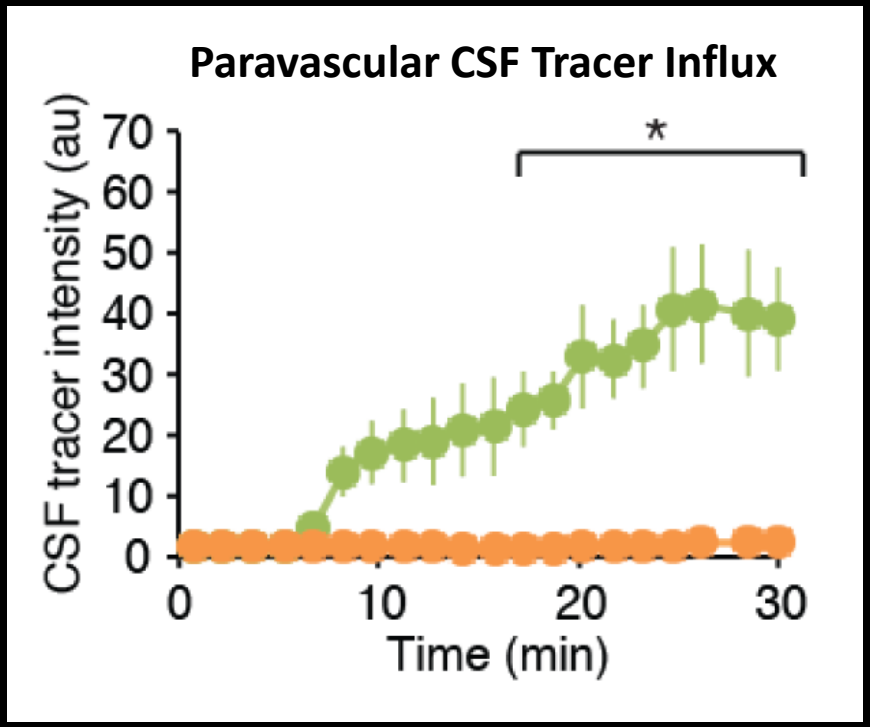
Anesthetized



Xie et al. *Science* 2013

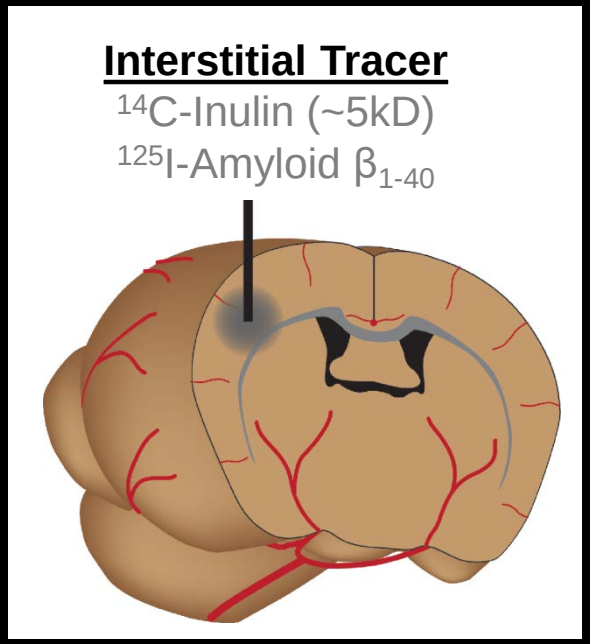
Paravascular CSF influx is a feature of the sleeping brain



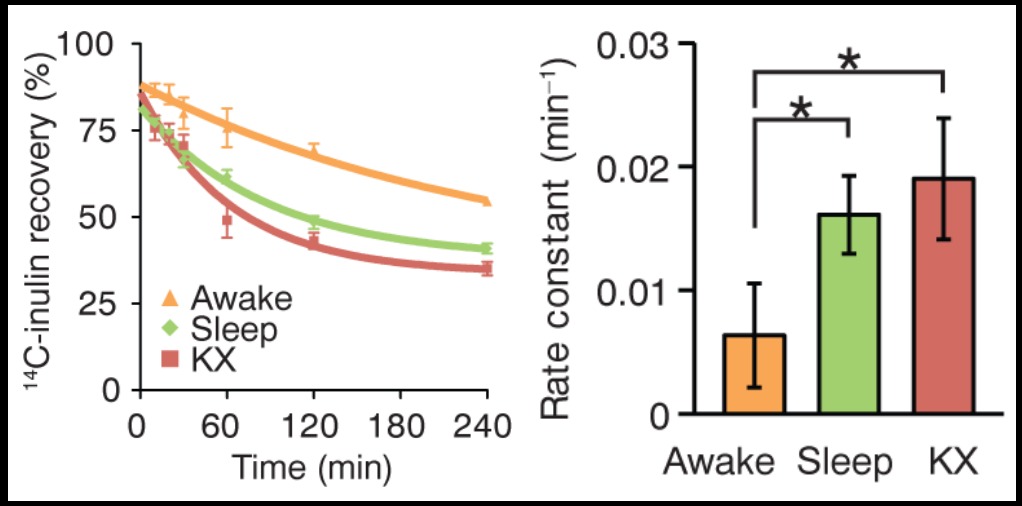


Xie et al. *Science* 2013

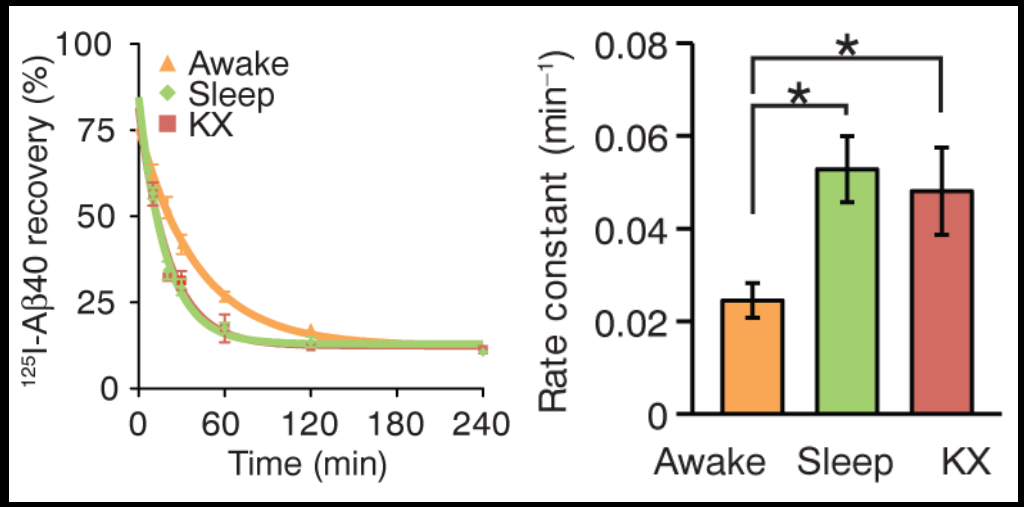
Amyloid β is cleared more rapidly from the sleeping brain



Interstitial ^{14}C-Inulin clearance

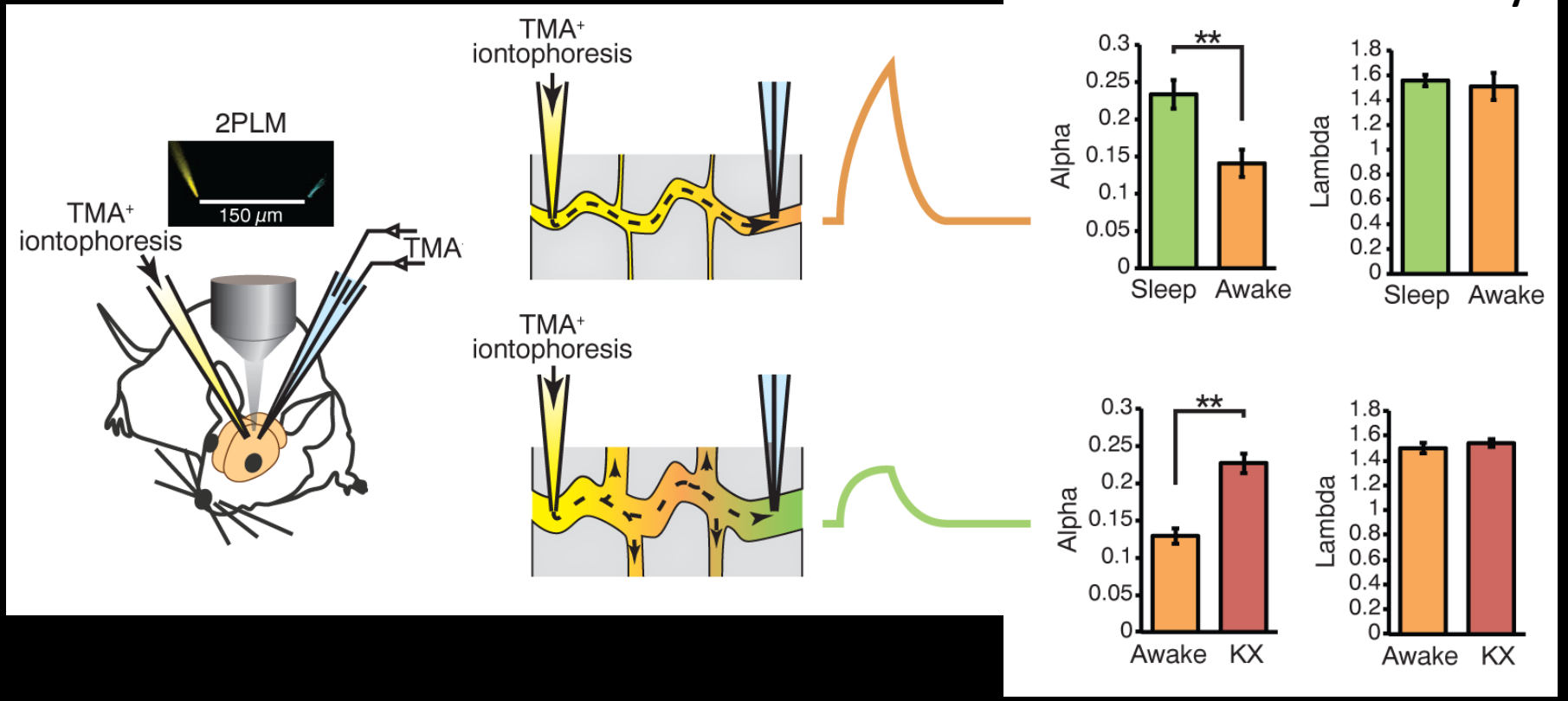


Interstitial ^{125}I-Amyloid β_{1-40} clearanece



Xie et al. *Science* 2013

The brain extracellular volume increases during sleep



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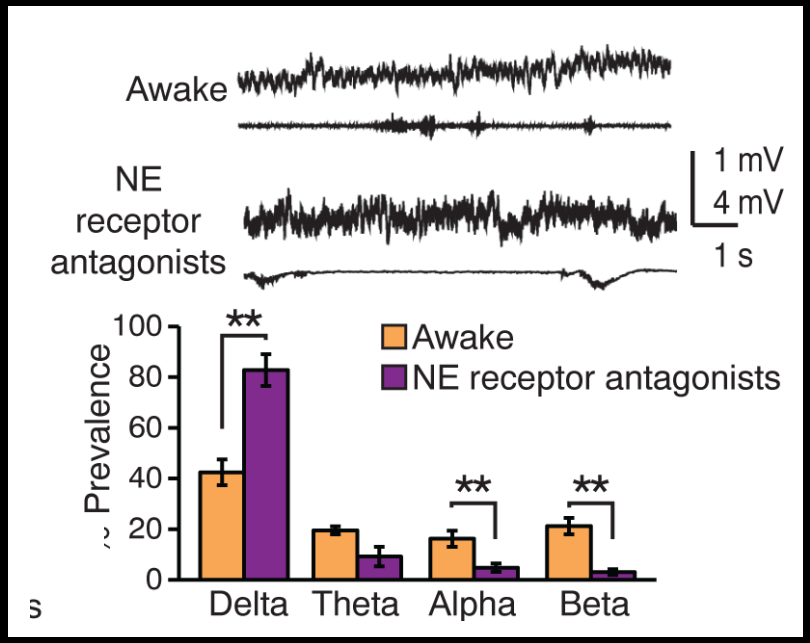
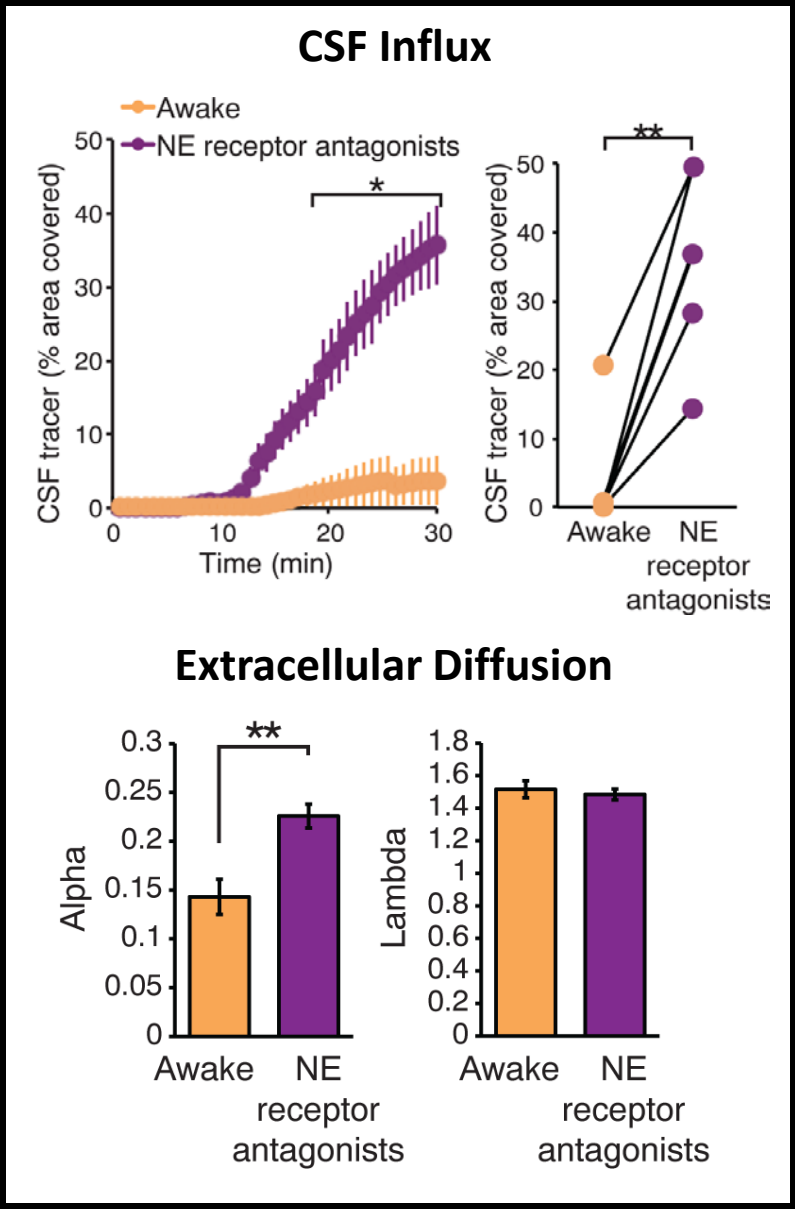
Does arousal state regulate paravascular CSF-ISF exchange?

Cortical noradrenergic blockade activates paravascular CSF circulation





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