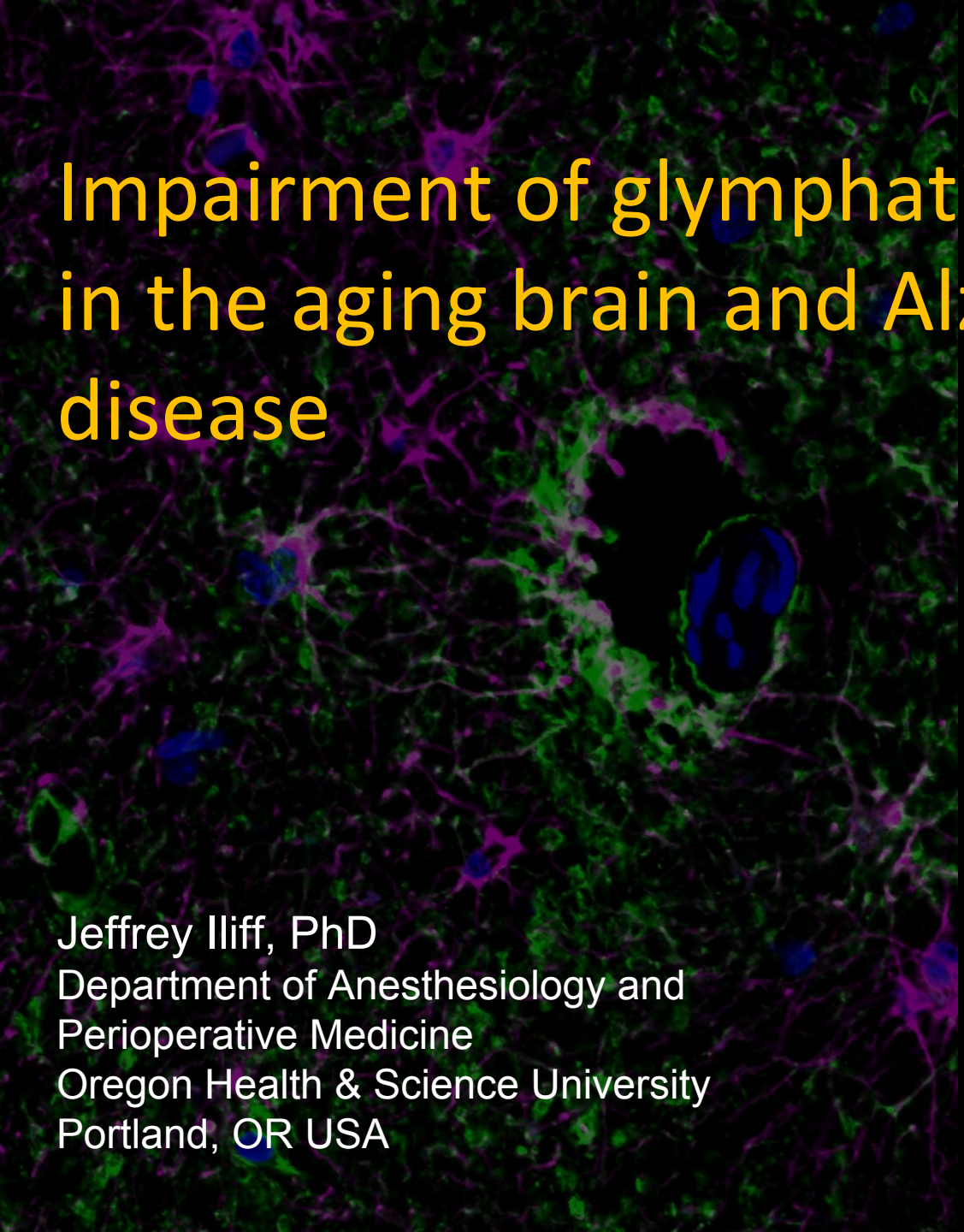
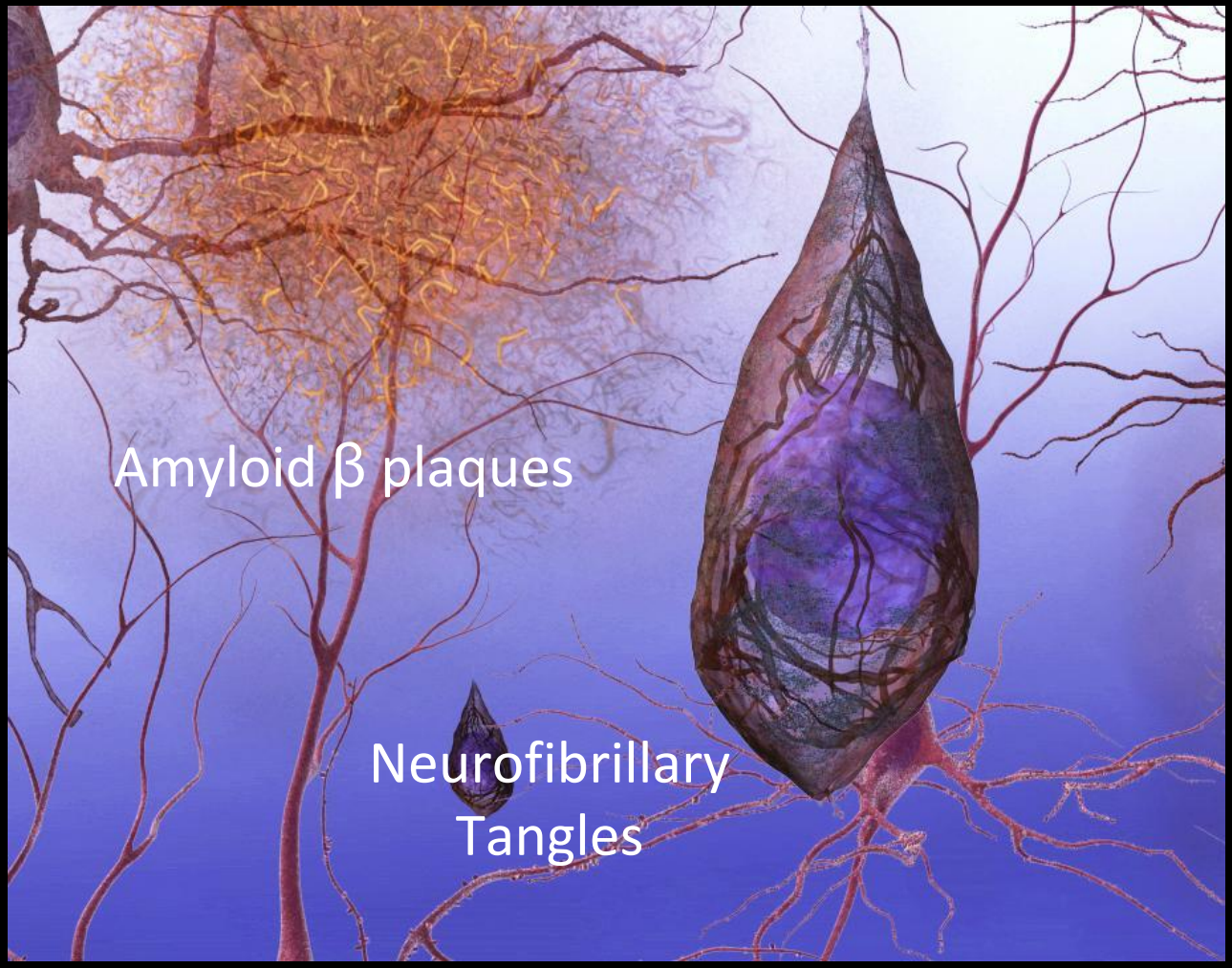
Impairment of glymphatic function in the aging brain and Alzheimer's disease



Jeffrey Iliff, PhD
Department of Anesthesiology and Perioperative Medicine
Oregon Health & Science University
Portland, OR USA



Aging is inseparably tied to Alzheimer's disease

- Risk doubles every 5 years over age 65.
- Incidence approaches 40% among subjects >85 years of age.

The cerebrospinal fluid (CSF) circulation

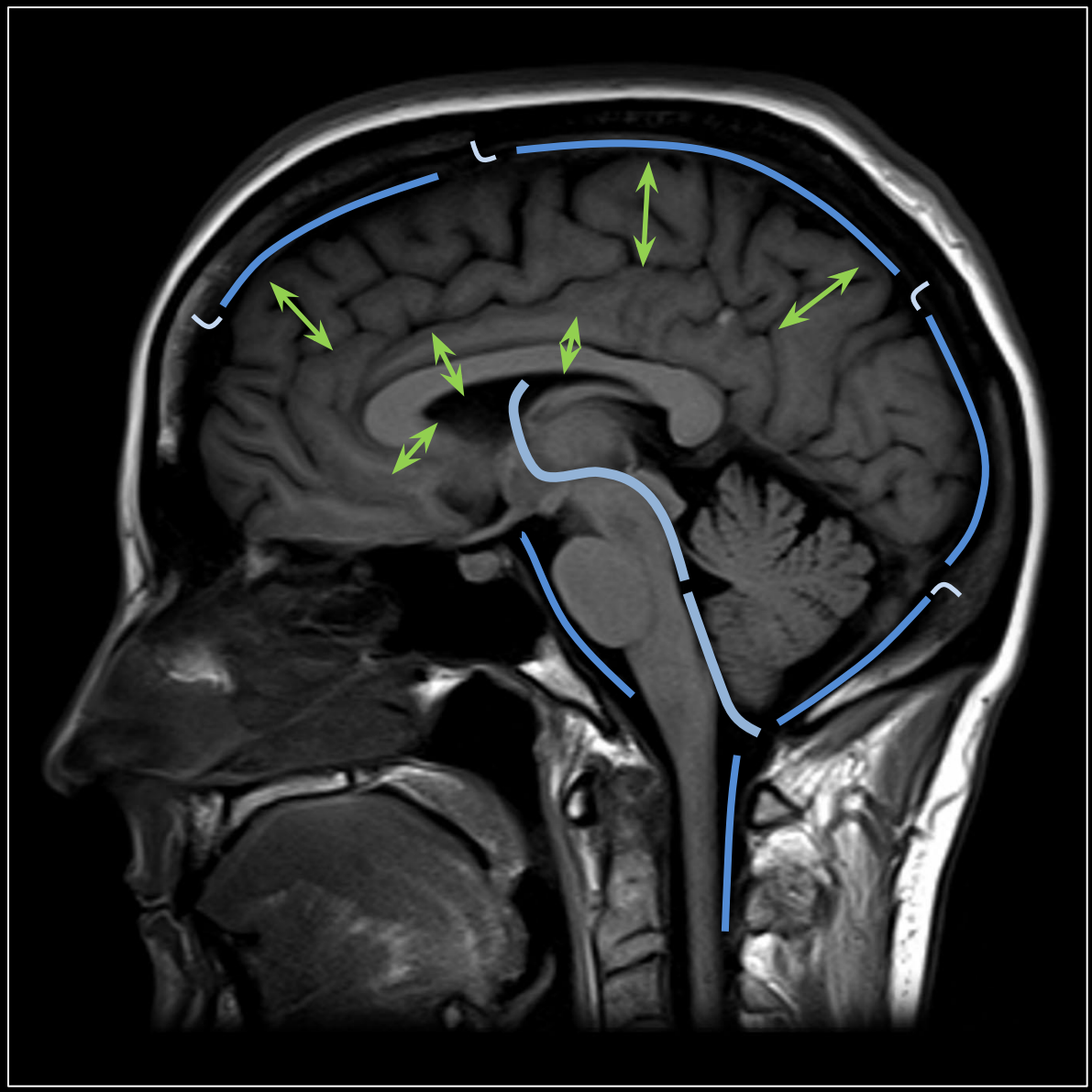
No lymphatic vessels in the CNS

CSF is secreted at the choroid plexuses within the cerebral ventricles

CSF serves as a ‘sink’ for CNS waste products

Diffuse bulk flow facilitates exchange of CSF and ISF

Reabsorption at arachnoid villi



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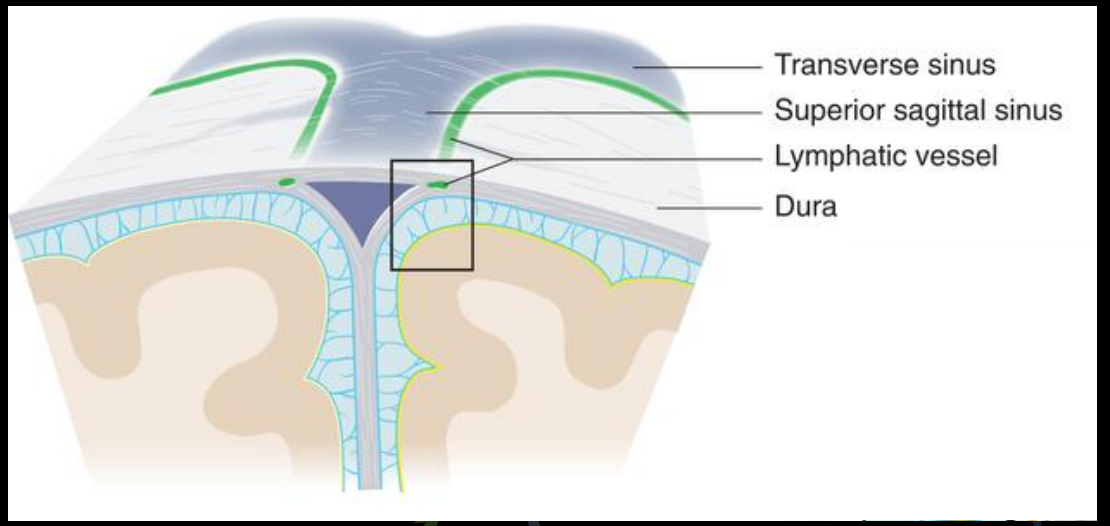
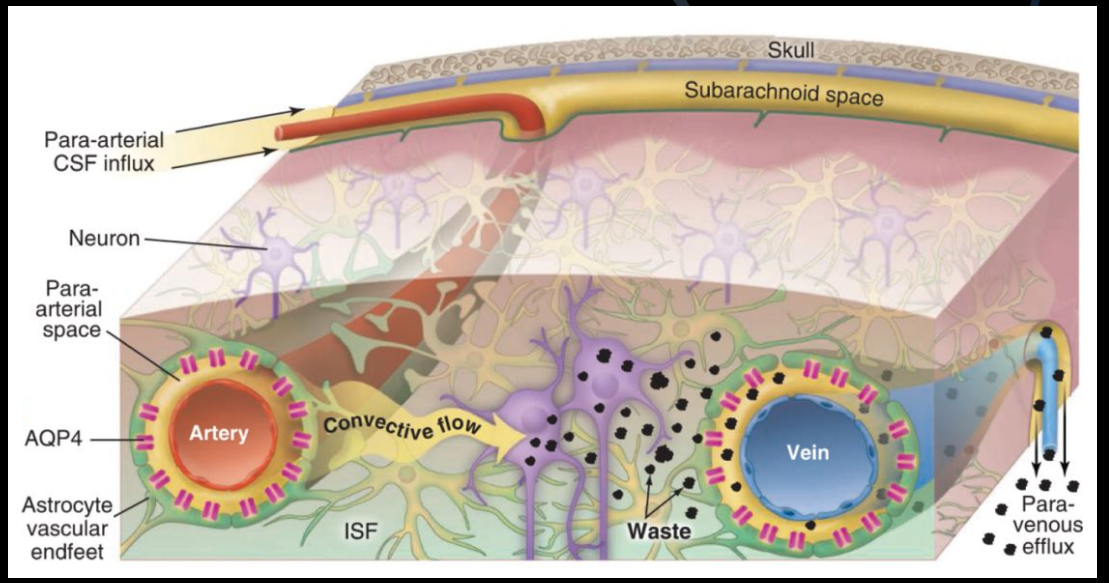
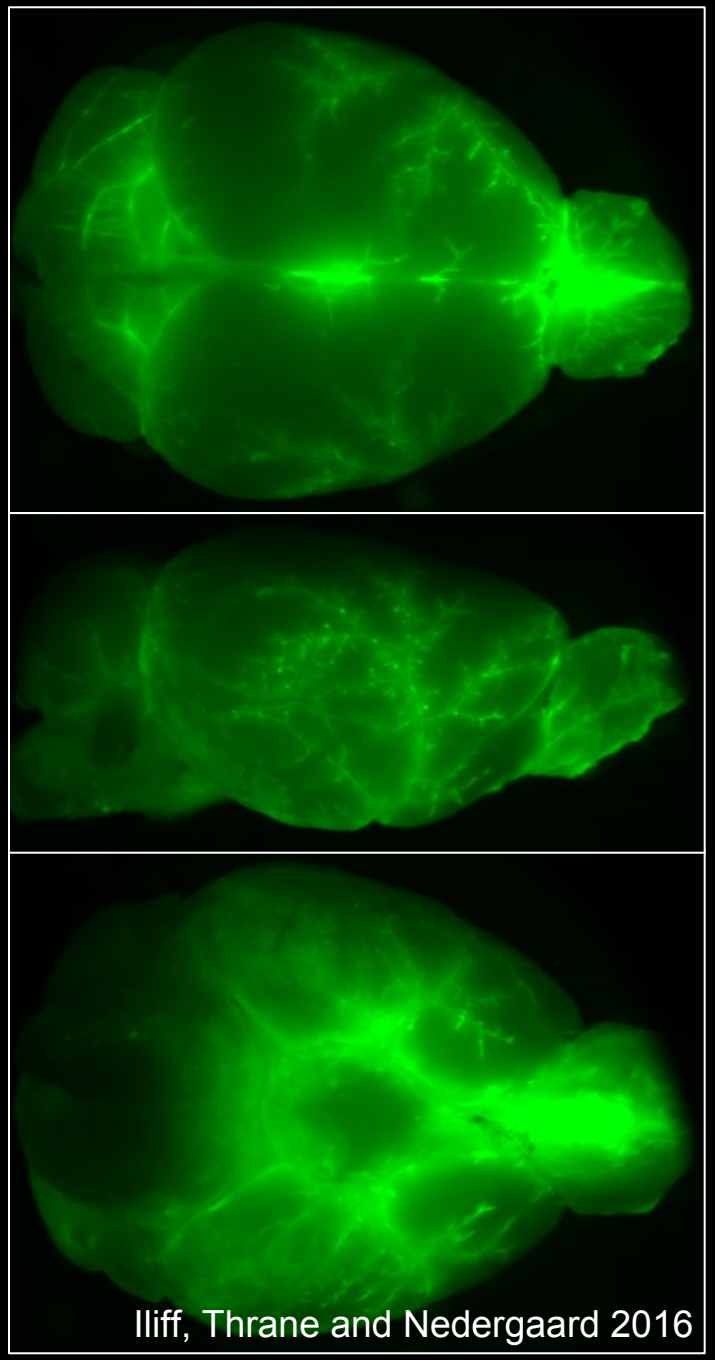


From Louveau et al. *Nature* 2015



From Nedergaard *Science* 2014

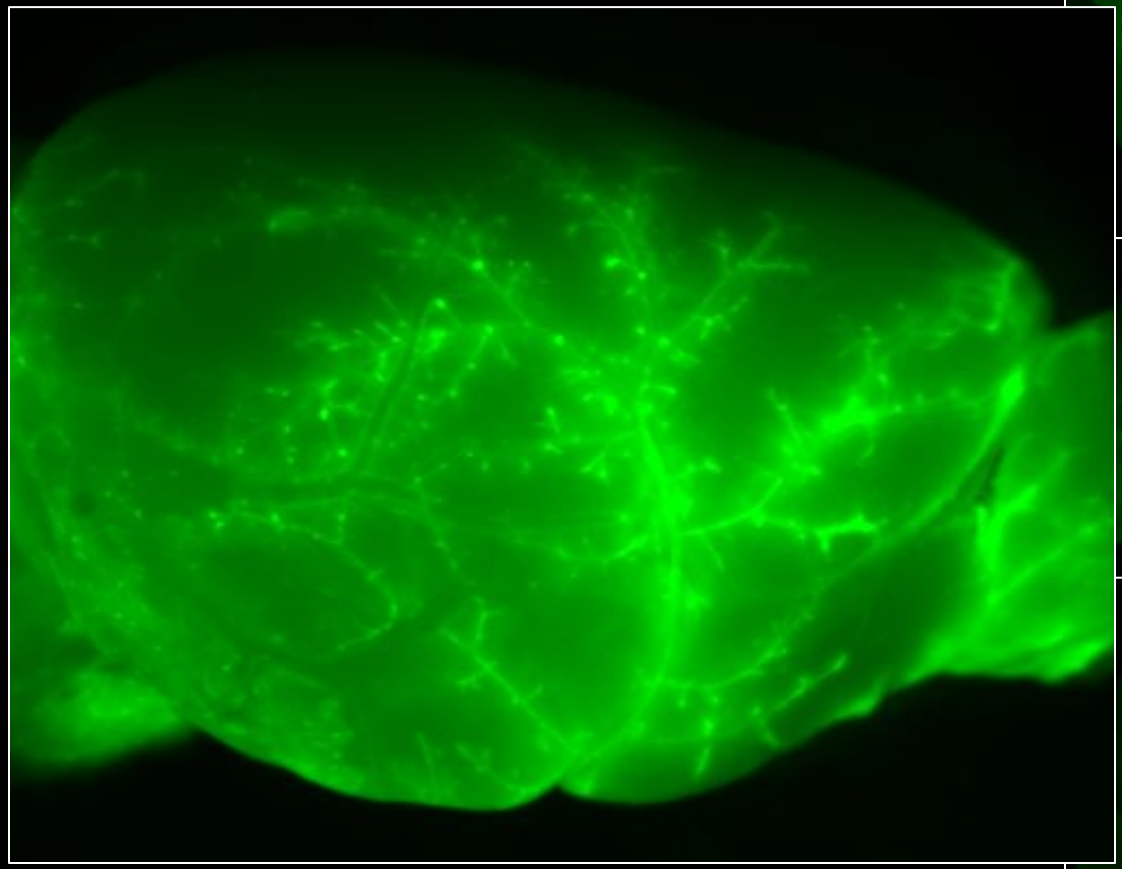
A brain-wide perivascular pathway for CSF-ISF exchange

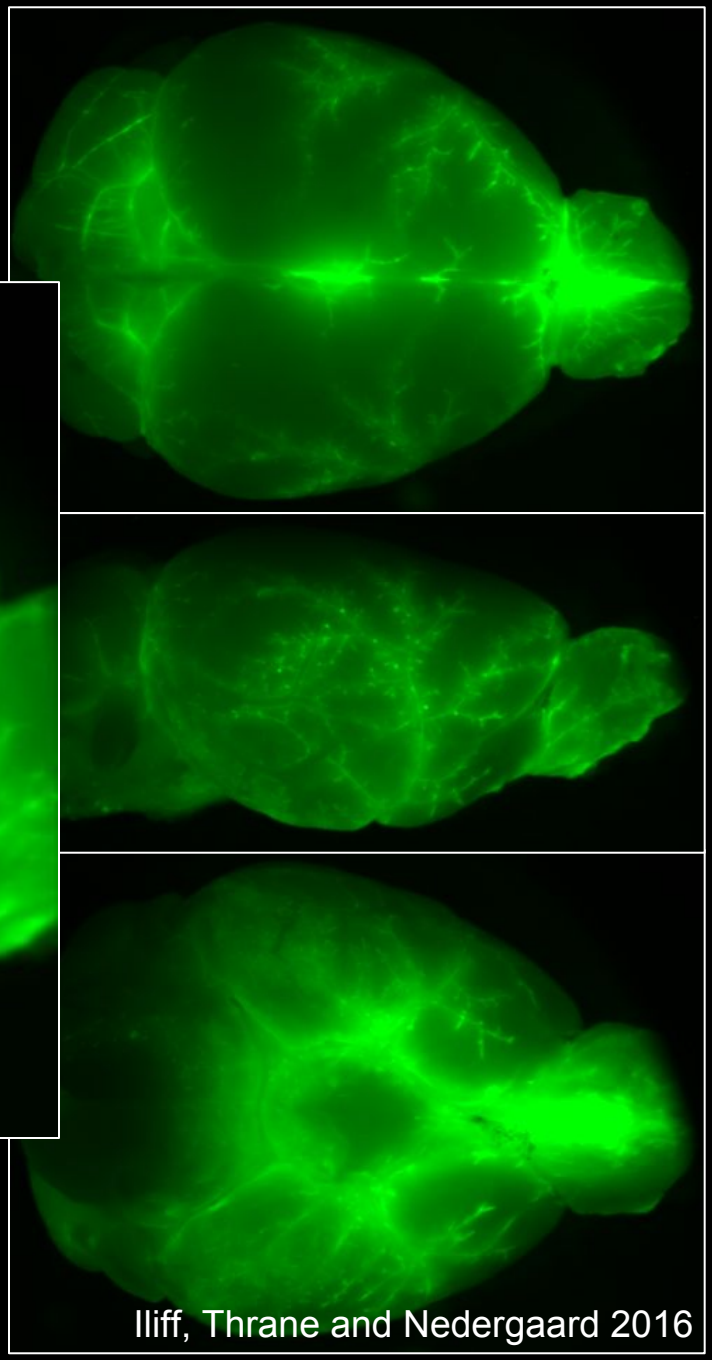


CSF Tracer (BSA-488)
30min post-injection

Iliff, Thrane and Nedergaard 2016

A brain-wide perivascular pathway for CSF-ISF exchange



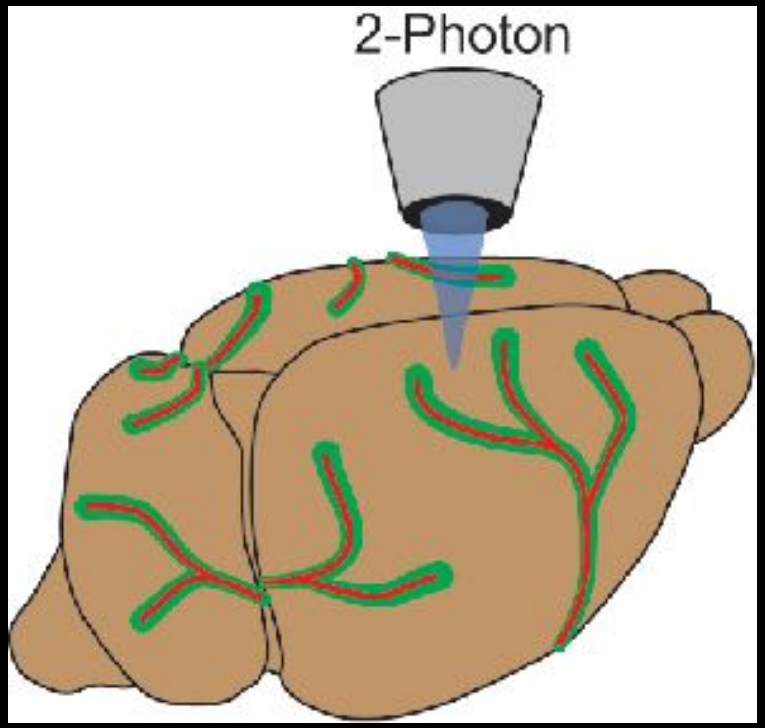


CSF Tracer (BSA-488)
30min post-injection

Iliff, Thrane and Nedergaard 2016

A brain-wide perivascular pathway for CSF-ISF exchange

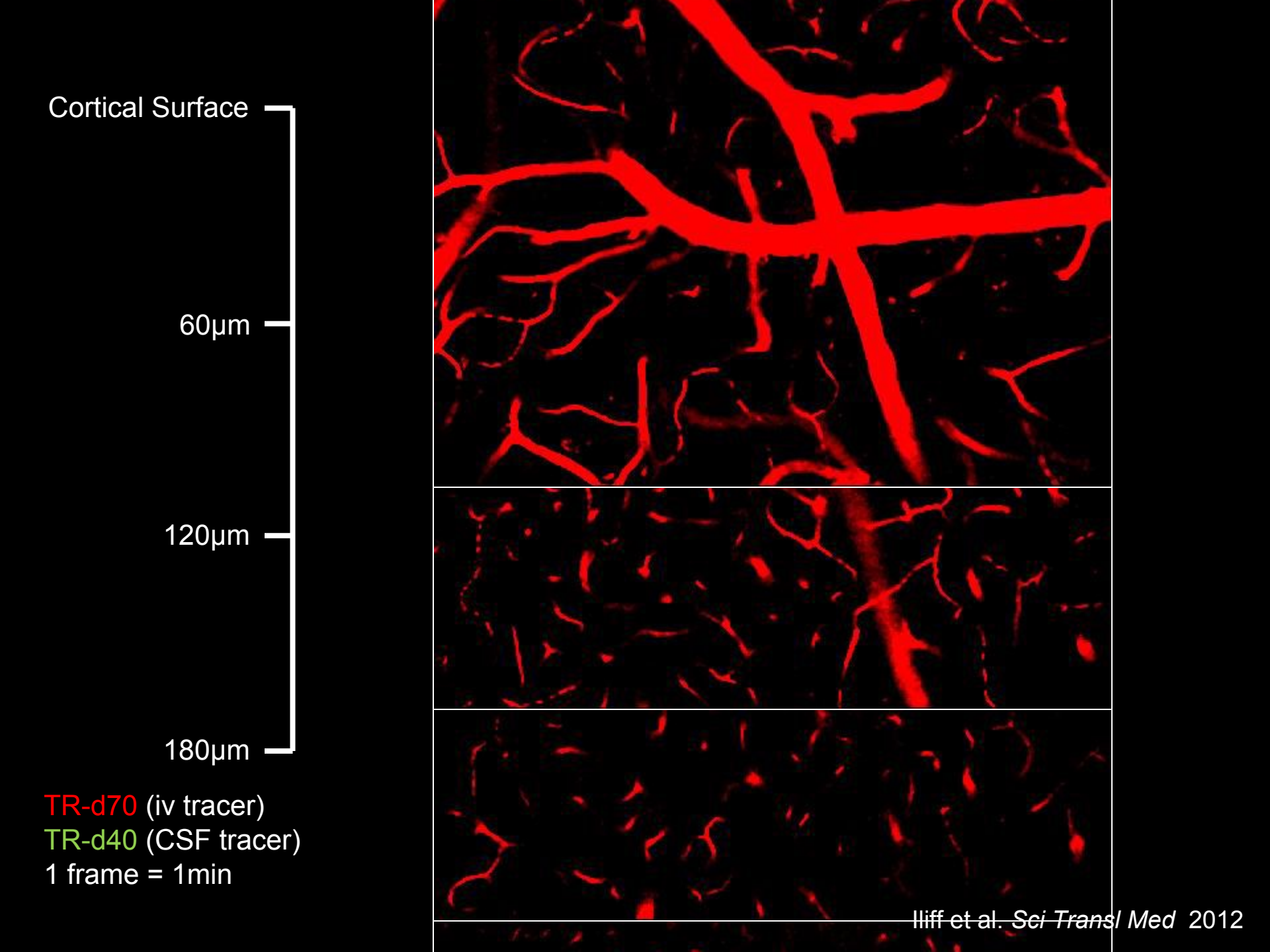
In vivo 2-photon microcopy



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

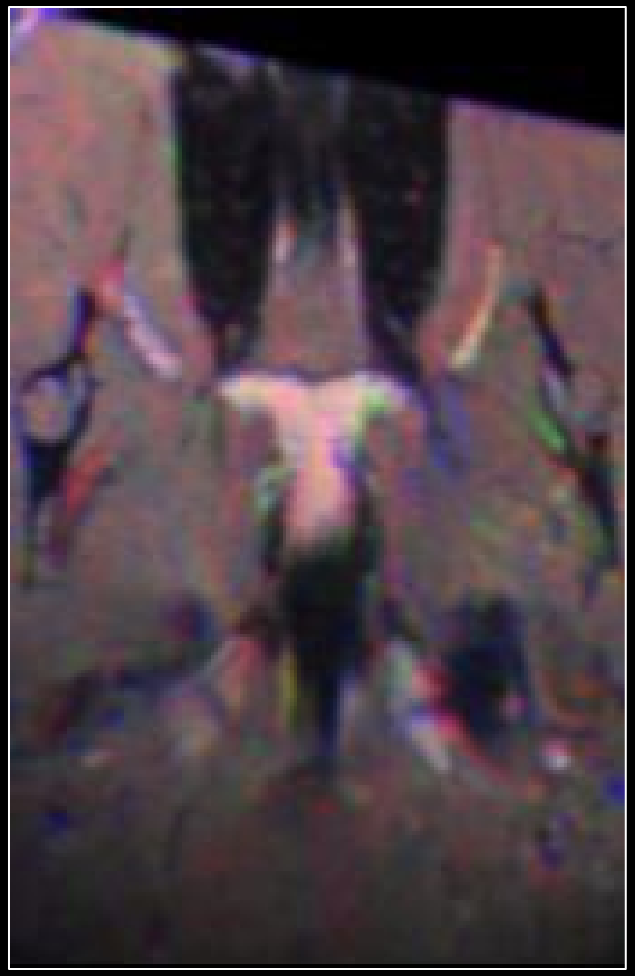
Cortical Surface

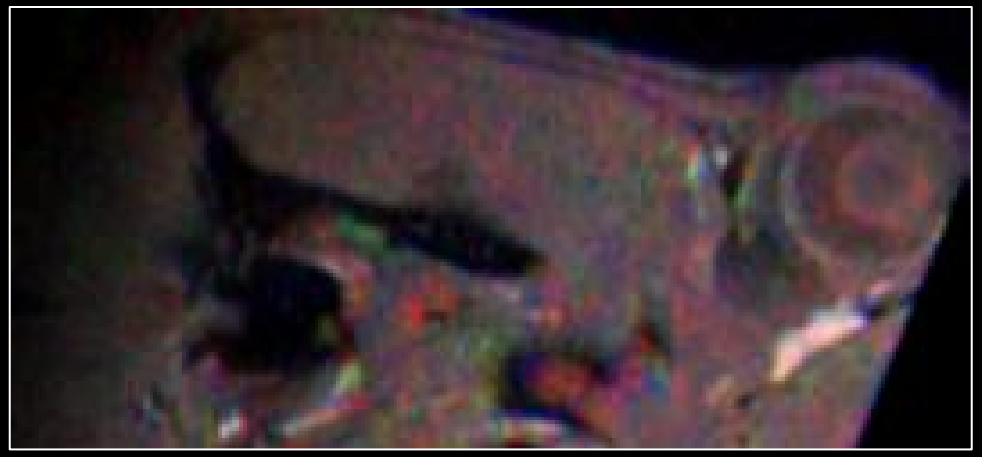
Iliff et al. *Sci Transl Med* 2012

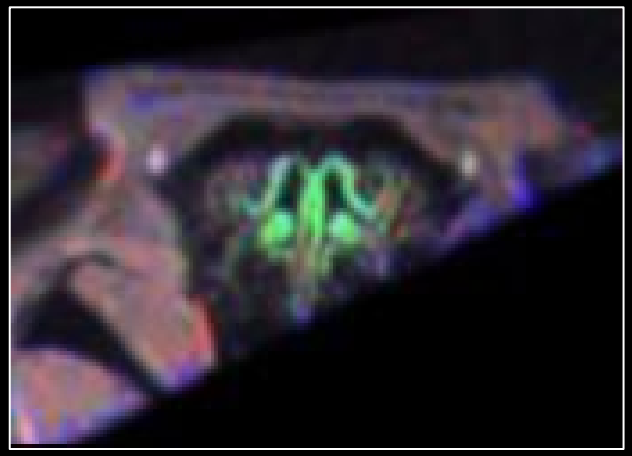


Iliff et al. *Sci Transl Med* 2012

Imaging brain-wide glymphatic function by dynamic contrast-enhanced (DCE)-MRI



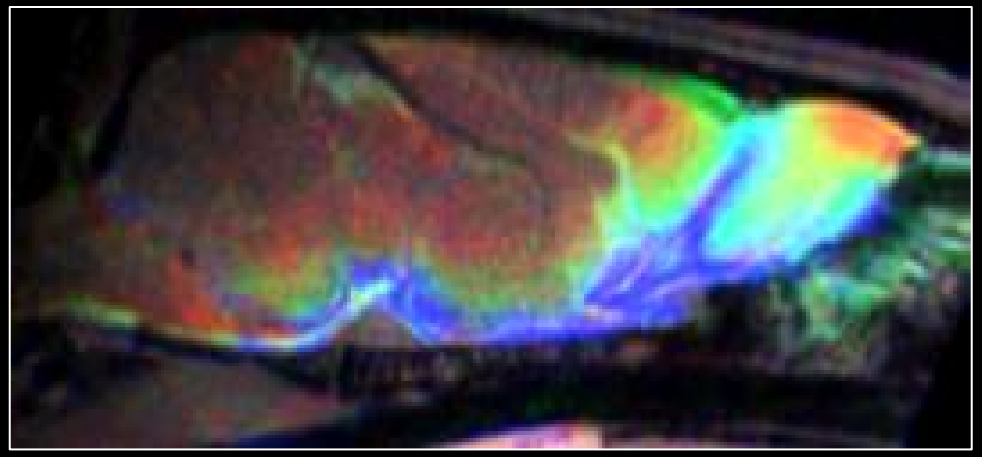


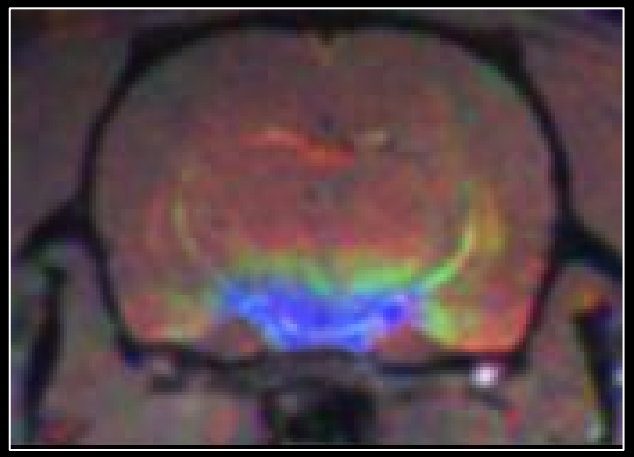


- Adult Male SD Rats
- DCE-MRI (11.7T)
- Intracisternal gadoteridol infusion
- Time Post-Injection:
  - 0-60 min
  - 60-120 min
  - 120-180 min

Roese and Pike 2016

Imaging brain-wide glymphatic function by dynamic contrast-enhanced (DCE)-MRI





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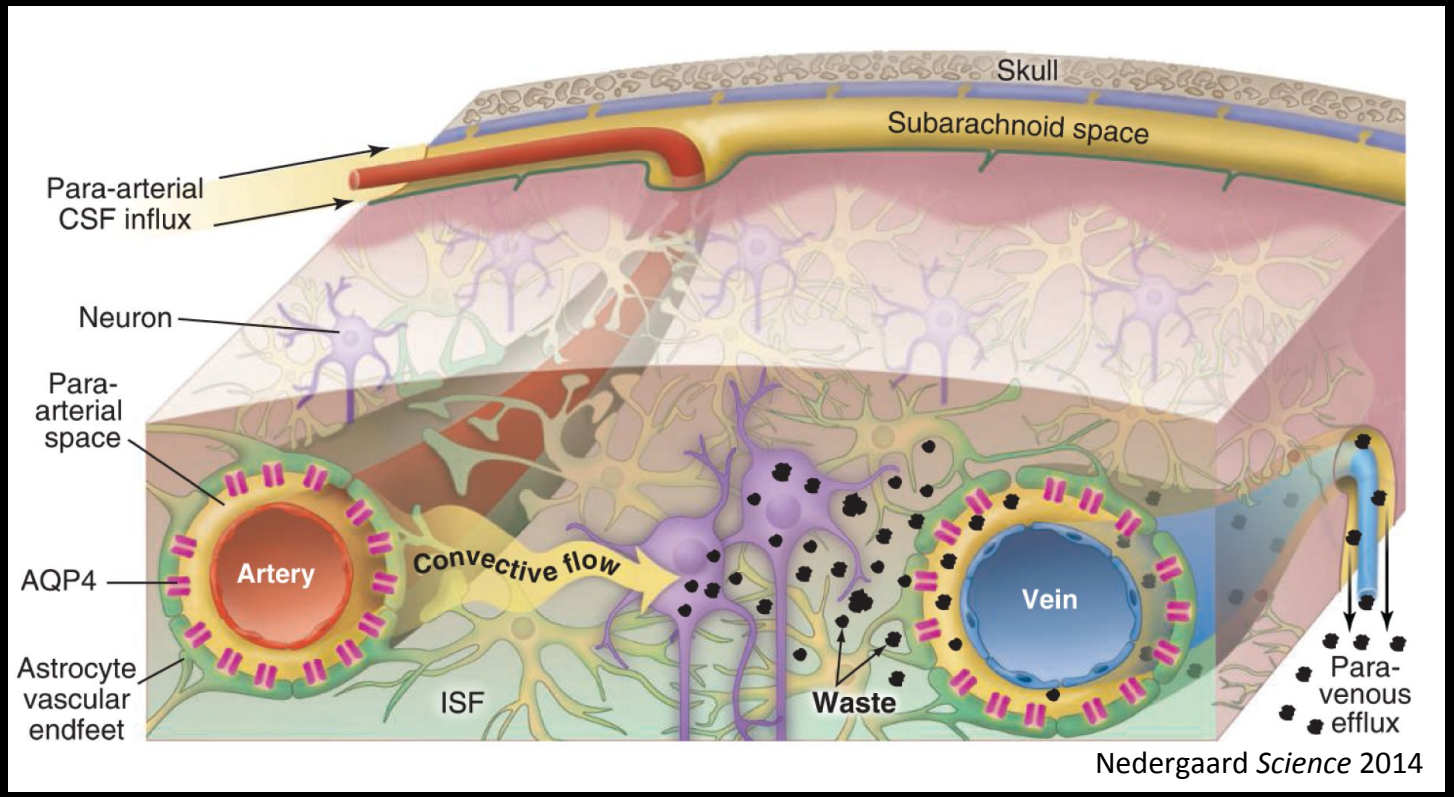
Roese and Pike 2016

A perivascular pathway for CSF-interstitial fluid exchange --- the "glymphatic" system



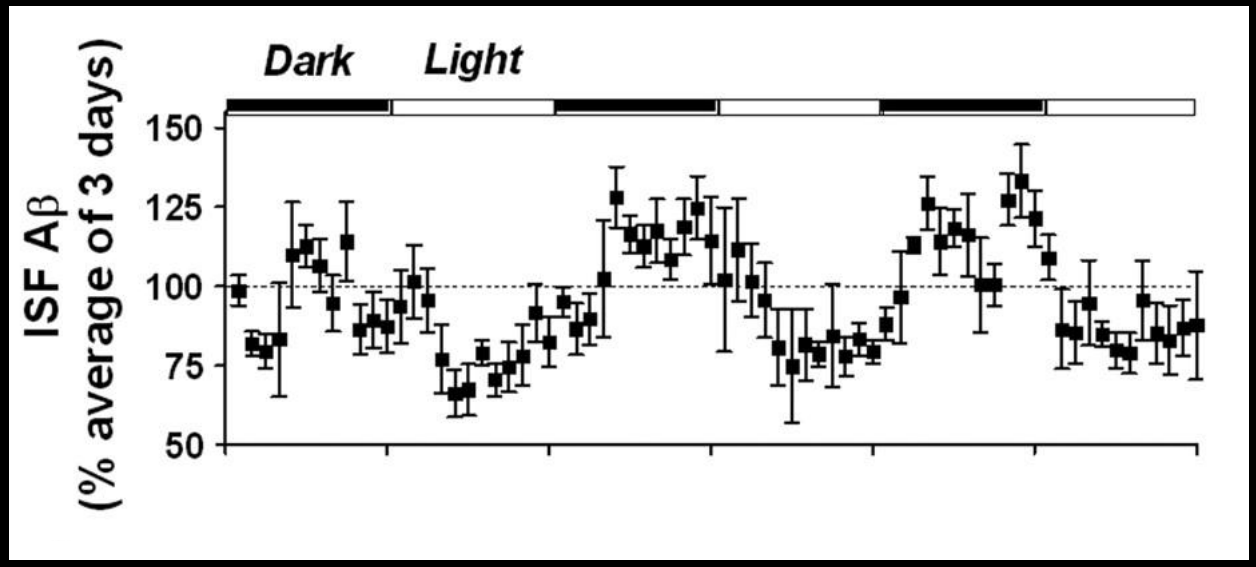
Nedergaard *Science* 2014

- CSF re-circulates along perivascular spaces surrounding arteries.
- Interstitial solutes are cleared along perivascular spaces surrounding large draining veins.
- Soluble amyloid β and tau are cleared along this paravascular pathway.

A word about amyloid β and sleep

Sleep modulates interstitial amyloid β levels

Mouse ISF



Kang et al. *Science* 2009

Sleep modulates interstitial amyloid β levels

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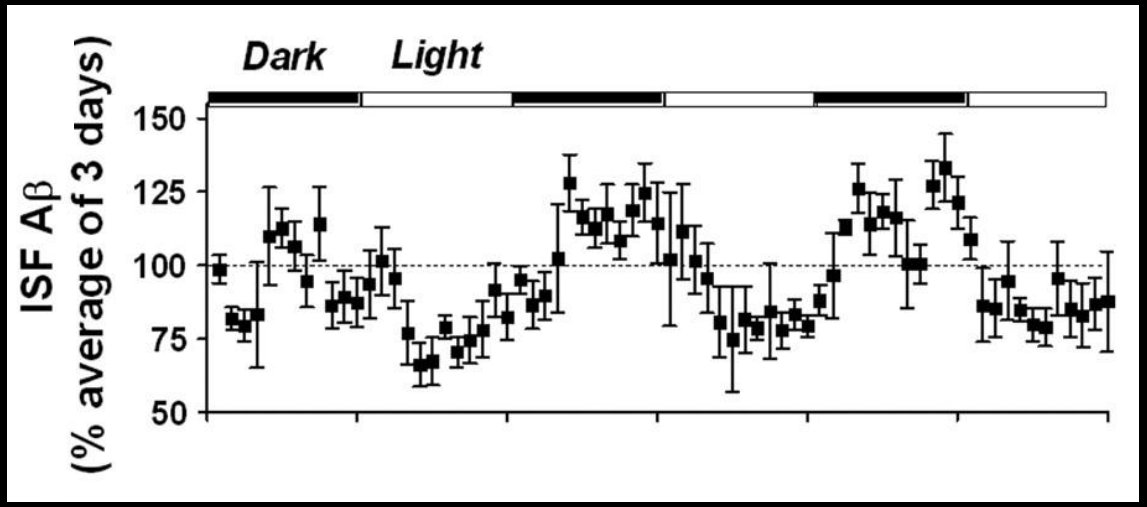
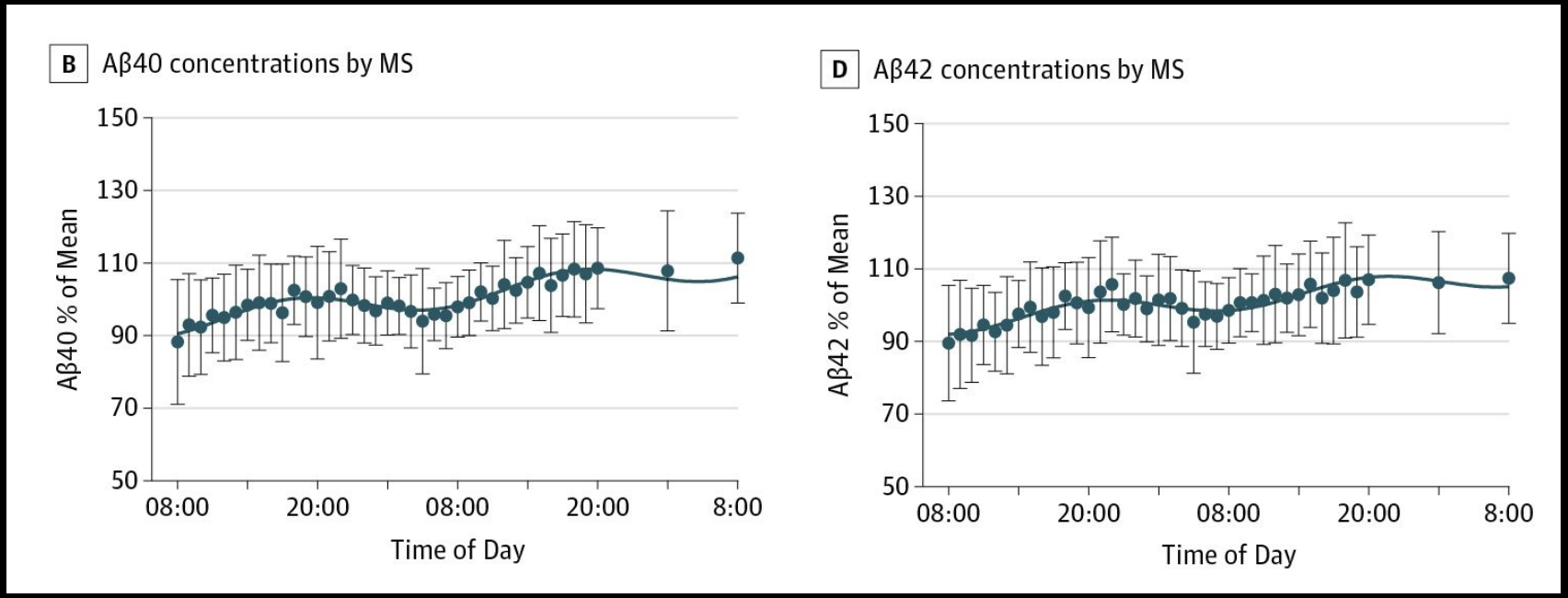


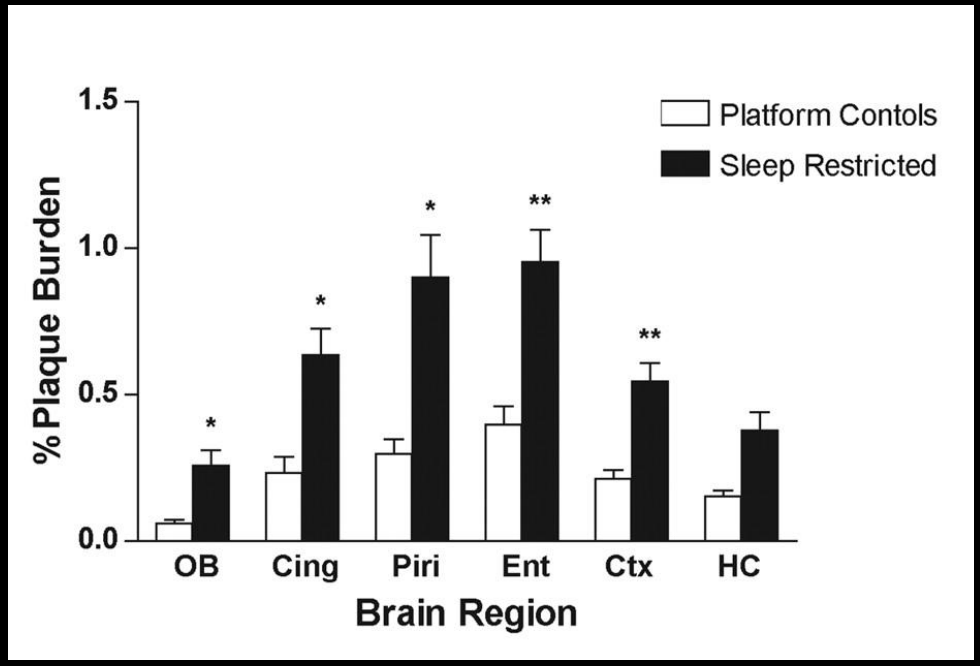
Kang et al. *Science* 2009

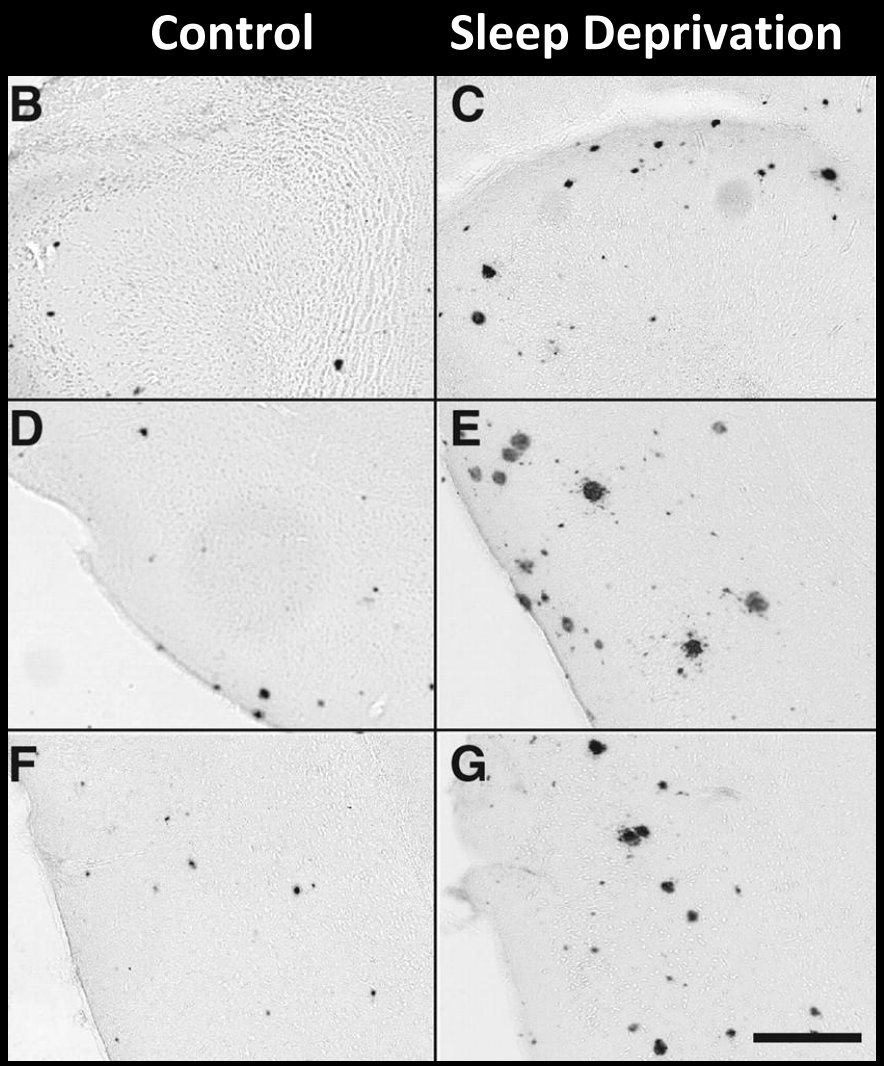
Human CSF



Lucey et al. *JAMA Neurol* 2016

Sleep modulates interstitial Aβ levels and Aβ aggregation



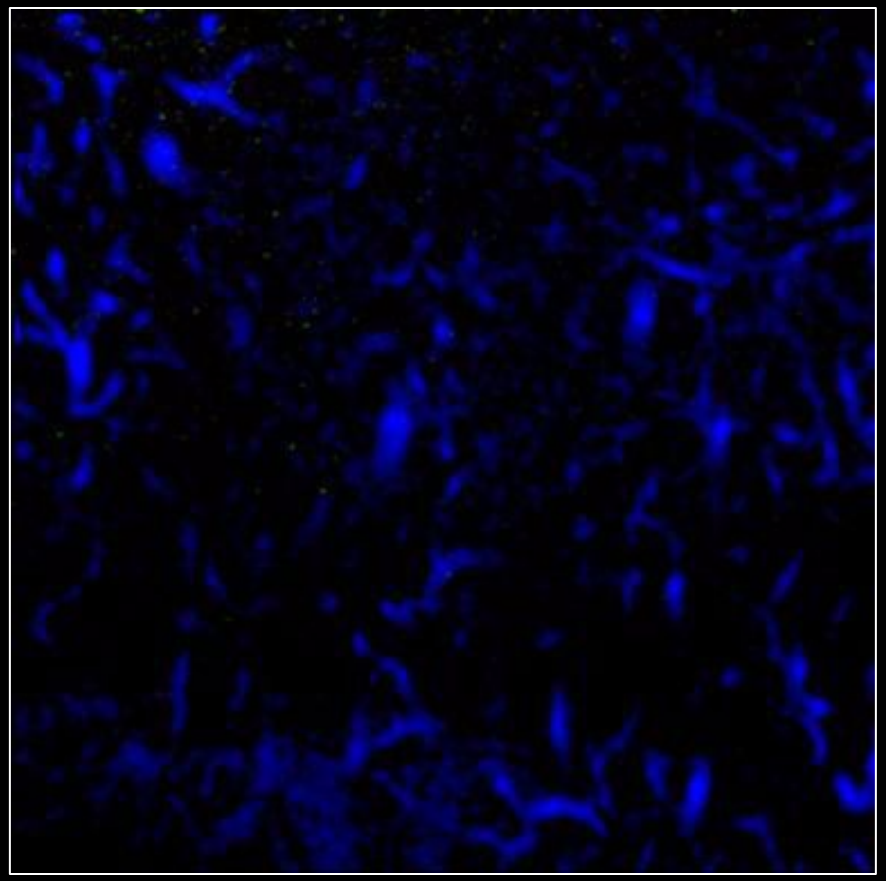


Kang et al. *Science* 2009

Does perivascular CSF-ISF exchange differ between sleeping and waking?

Perivascular CSF recirculation is modulated by sleep state

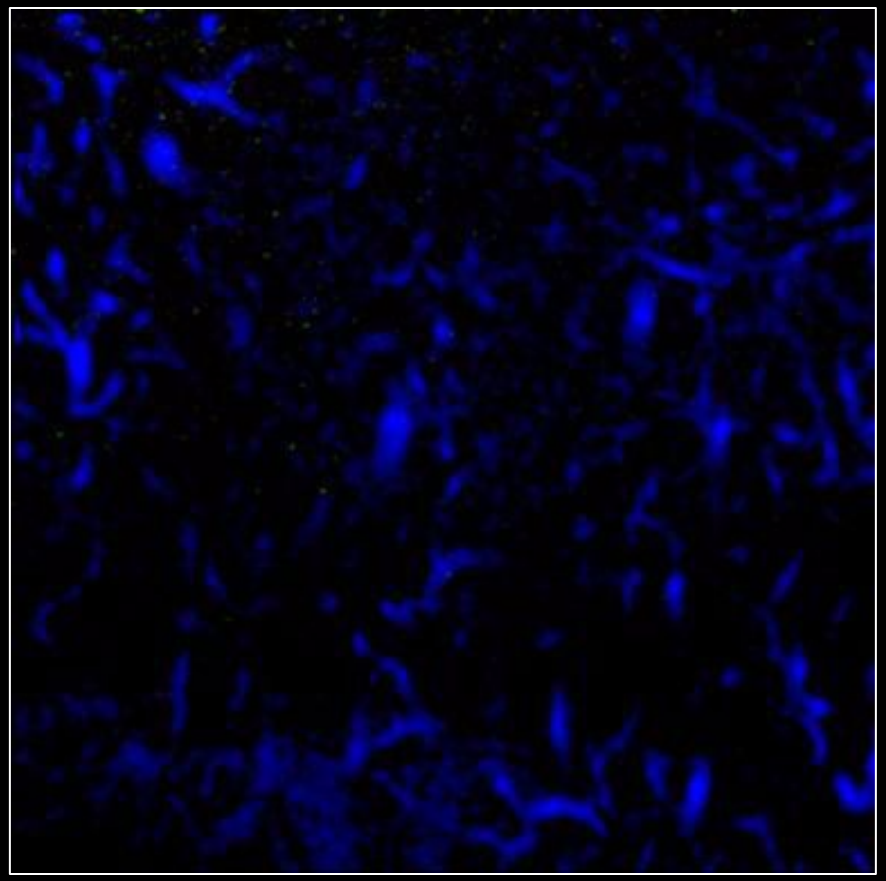
Awake



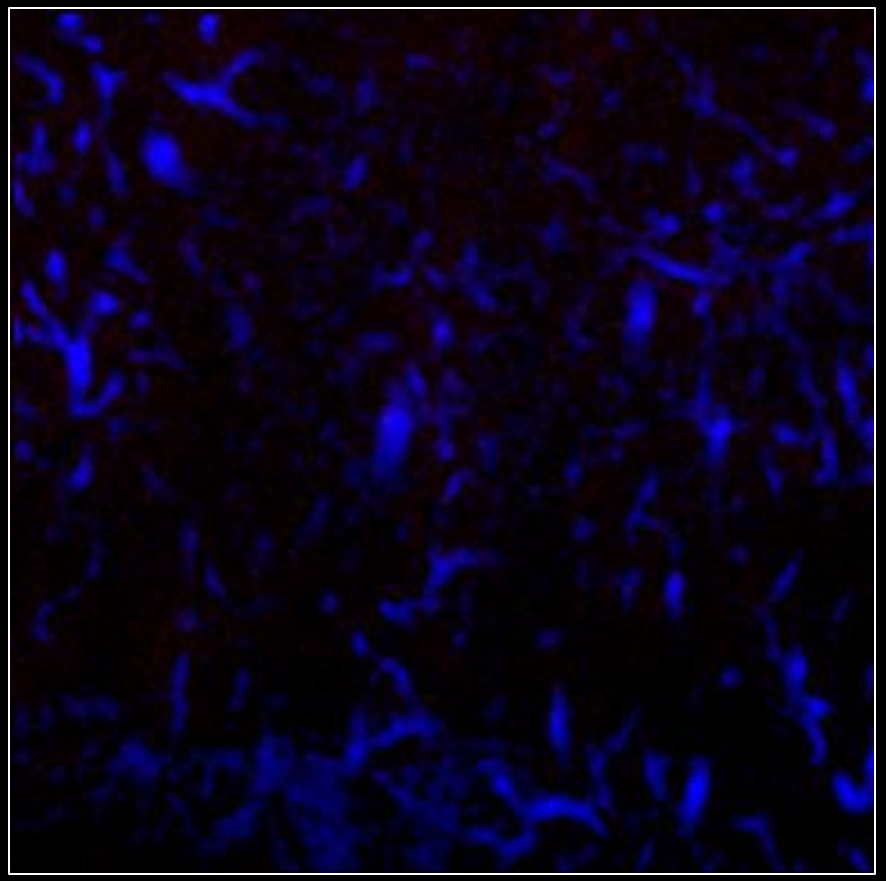
Xie et al. *Science* 2013

Perivascular CSF recirculation is modulated by sleep state

Awake

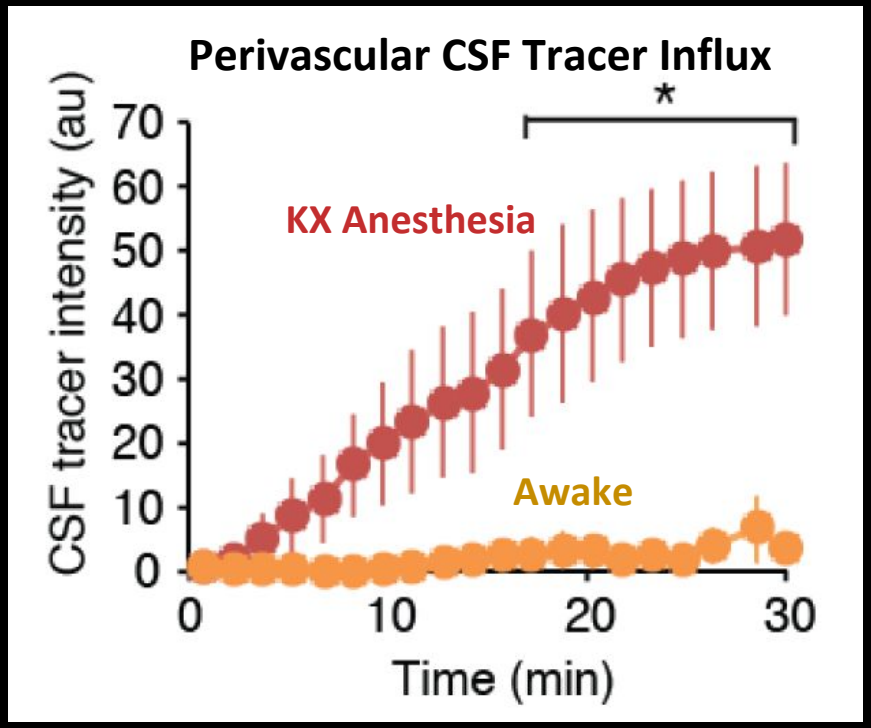


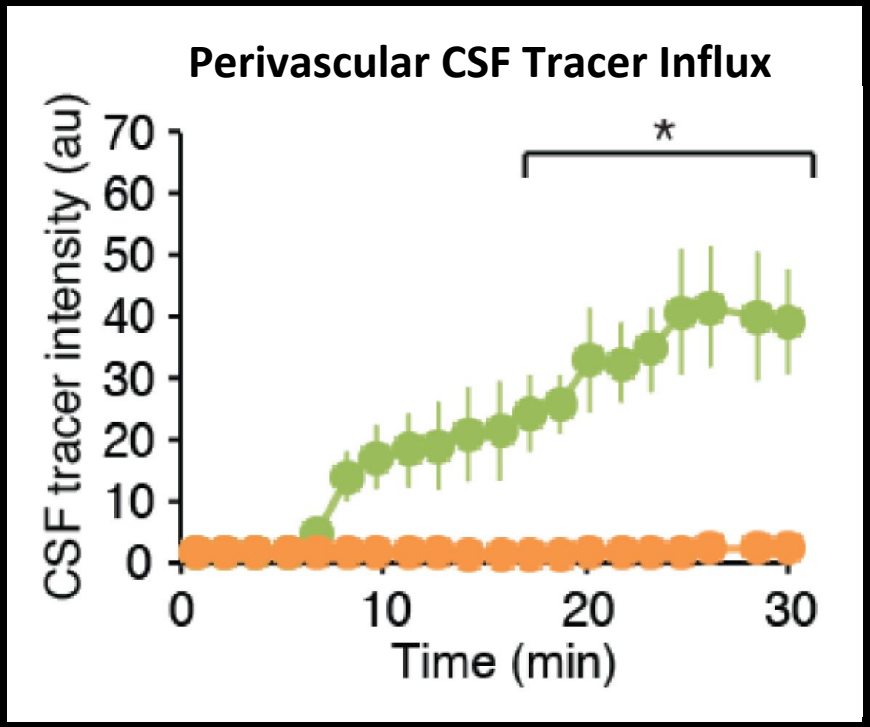
Anesthetized



Xie et al. *Science* 2013

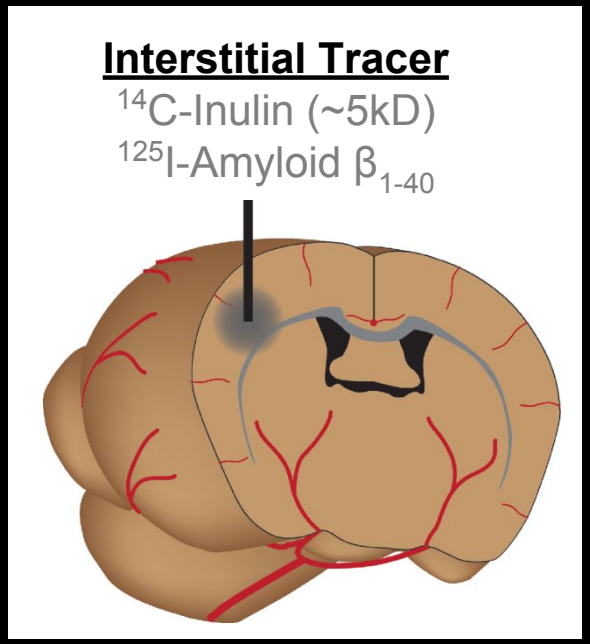
Perivascular CSF influx is a feature of the sleeping brain



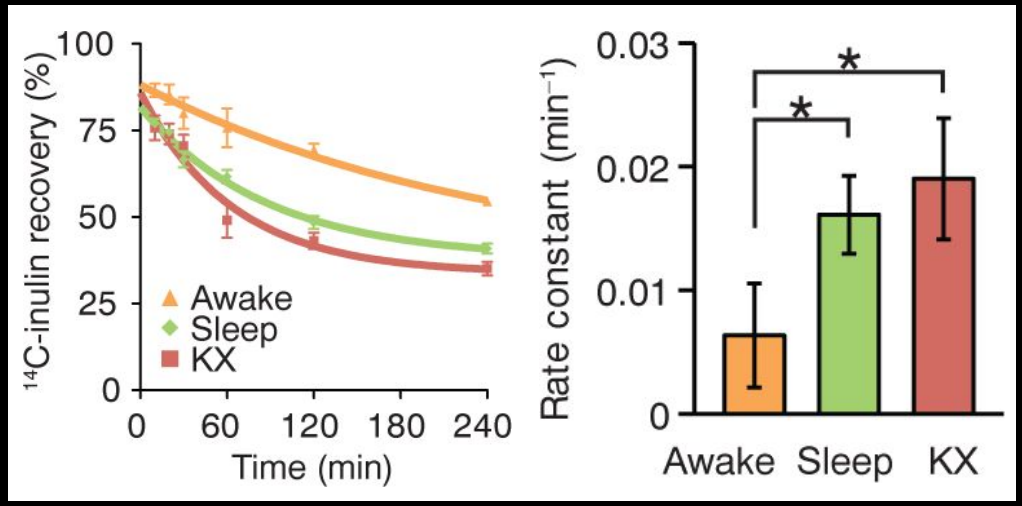


Xie et al. *Science* 2013

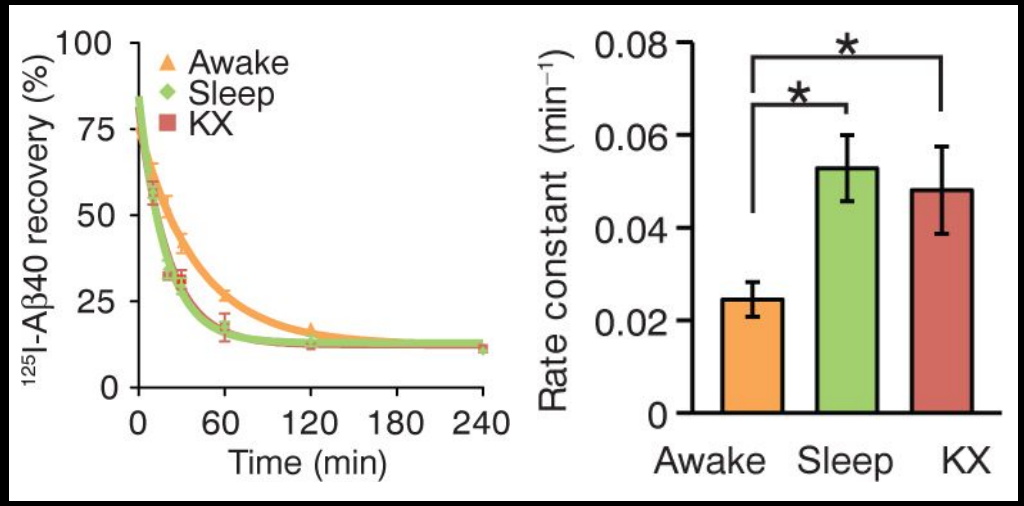
Amyloid β is cleared more rapidly from the sleeping brain



Interstitial ^{14}C-Inulin clearance



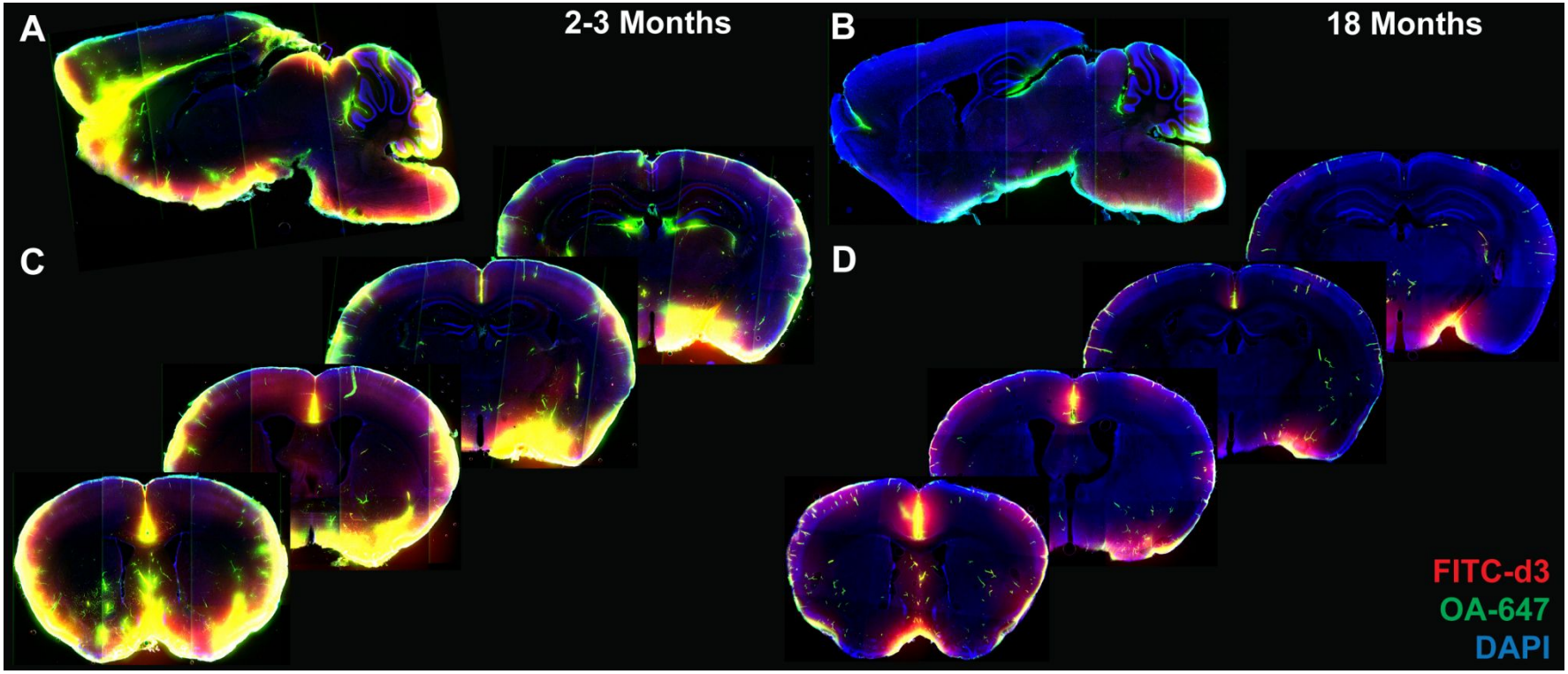
Interstitial ^{125}I-Amyloid β_{1-40} clearanece



Xie et al. *Science* 2013

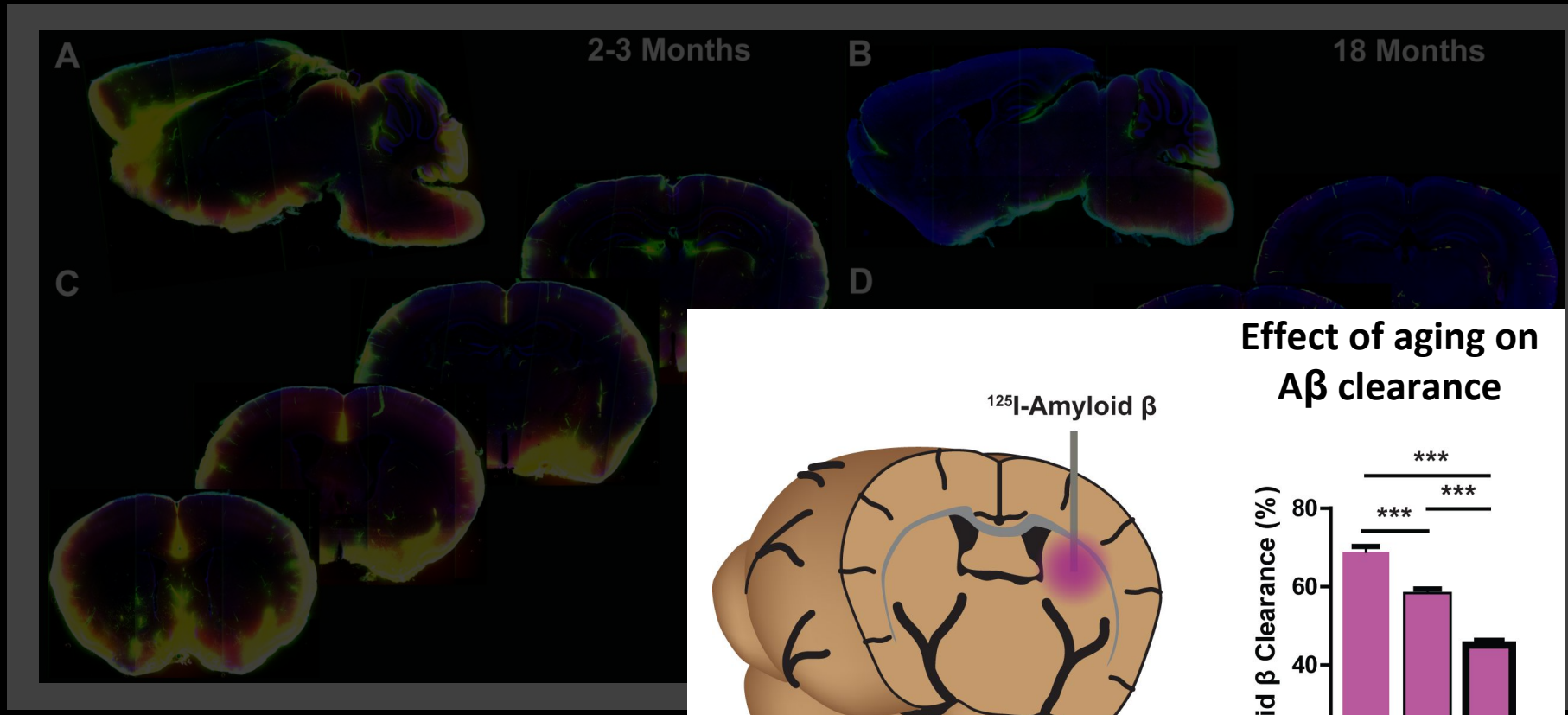
Is perivascular CSF-ISF exchange impaired in the aging brain?

Impairment of CSF recirculation in the aging brain



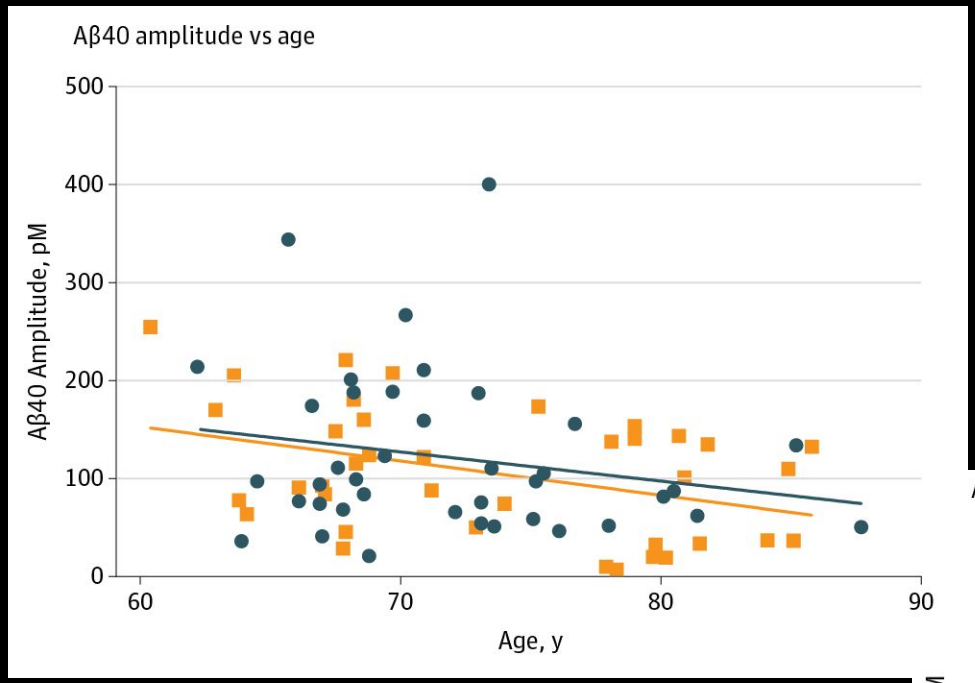
Kress, Iliff et al. *Annals Neurol* 2014

Impairment of CSF recirculation in the aging brain

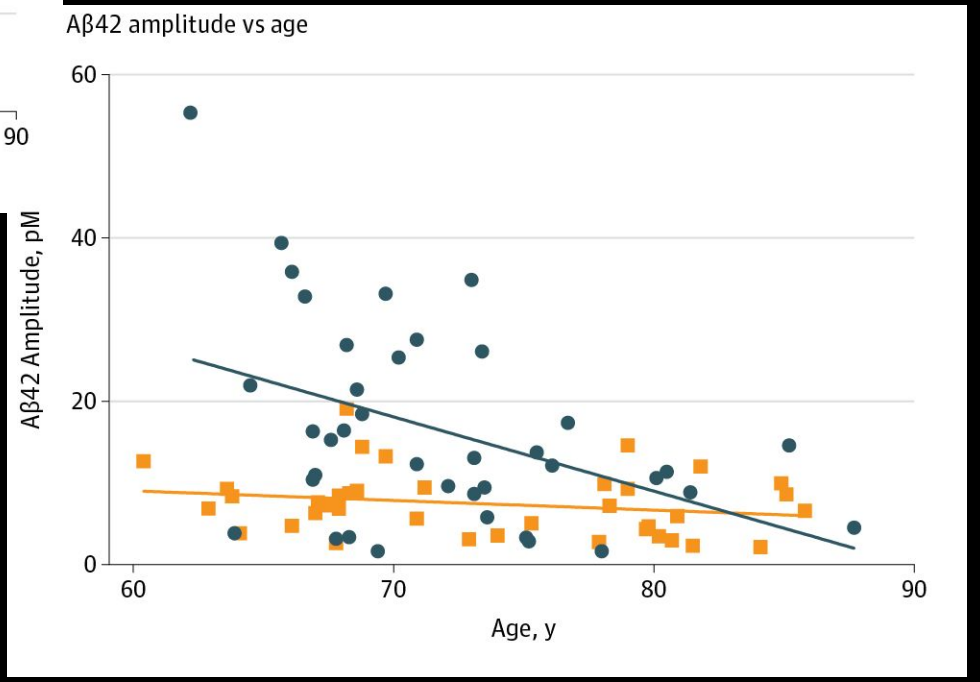


Kress, Iliff et al. *Annals Neurol* 2014

Reduced diurnal fluctuation in CSF Aβ in the aging human CNS

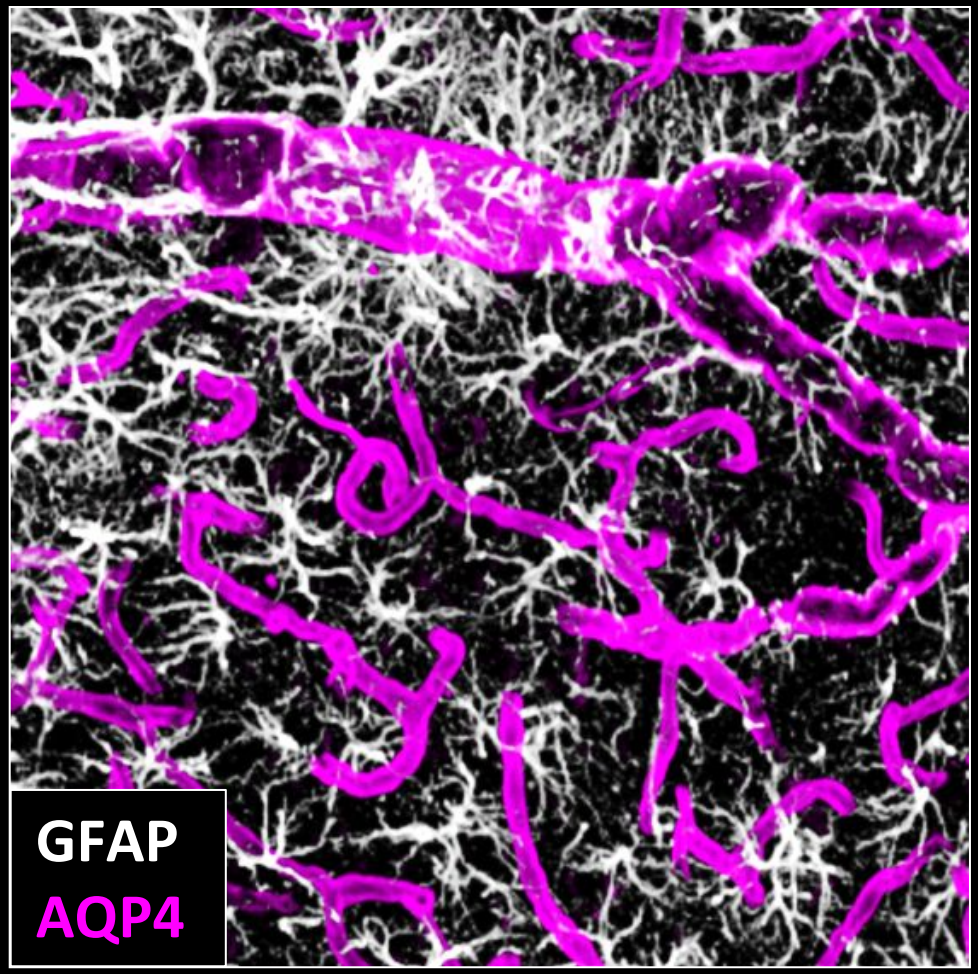


Lucey et al. *JAMA Neurol* 2016

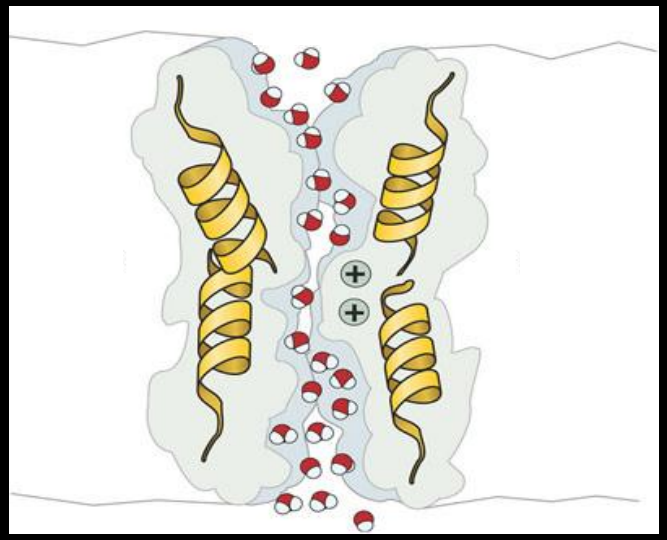


What factors are changing in the aging brain that may underlie these effects?

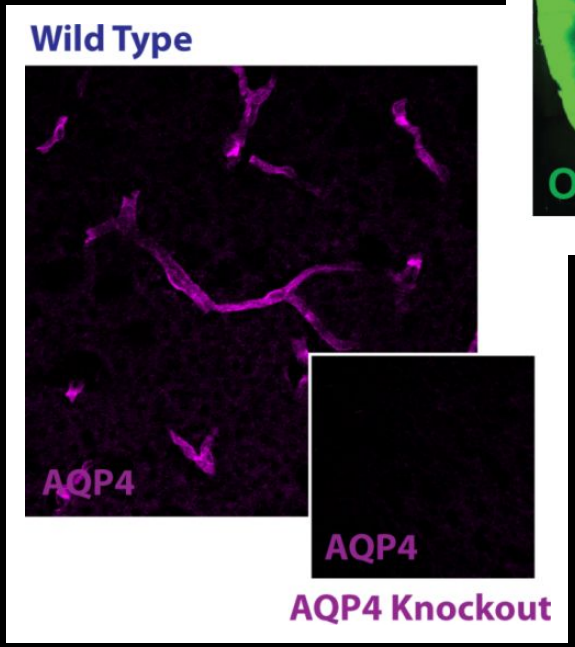
Aquaporin-4 (AQP4) organizes water movement throughout the brain

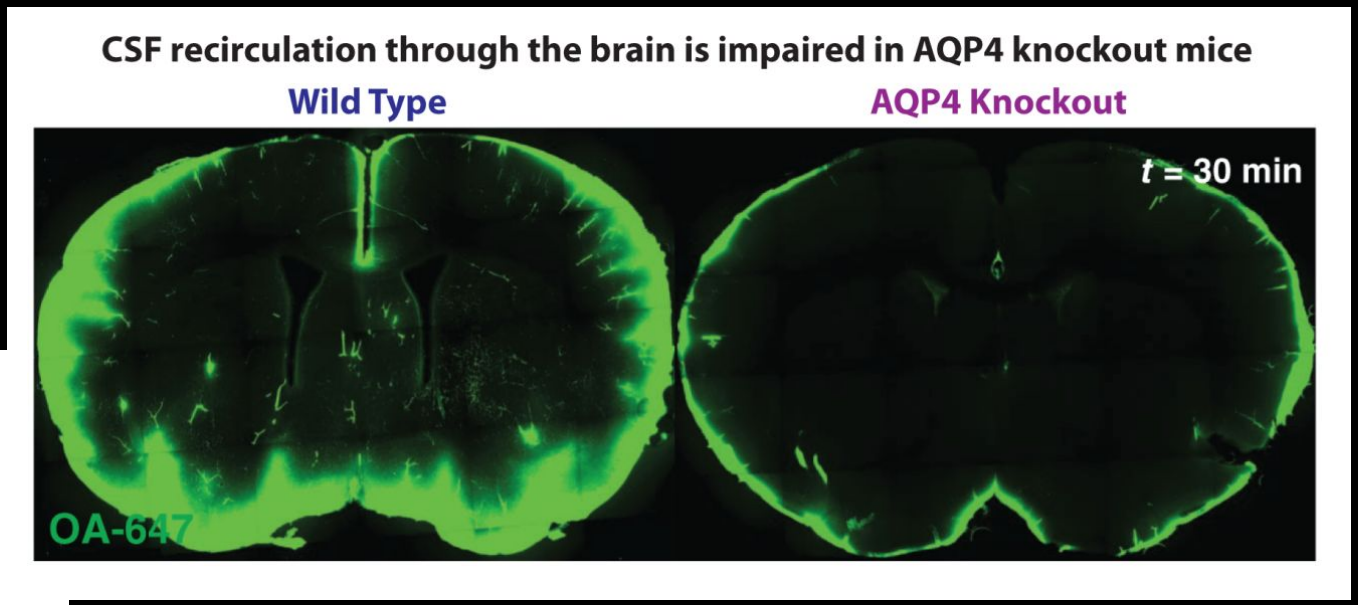


Adapted from Simard et al. *J Neurosci* 2003



AQP4 supports perivascular CSF recirculation and amyloid β clearance





Iliff et al. *Sci Translat Med* 2012

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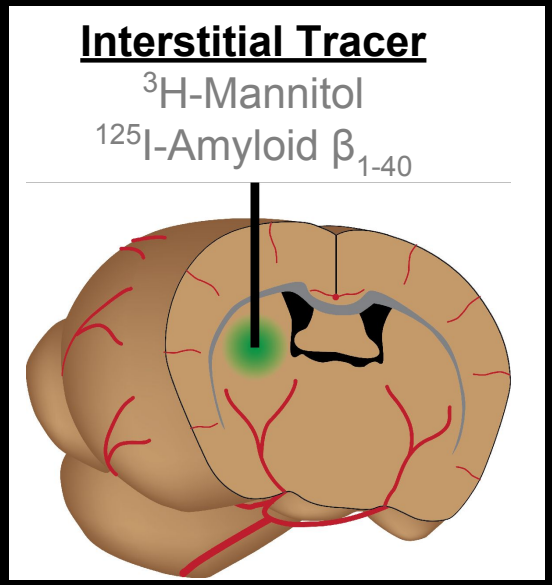
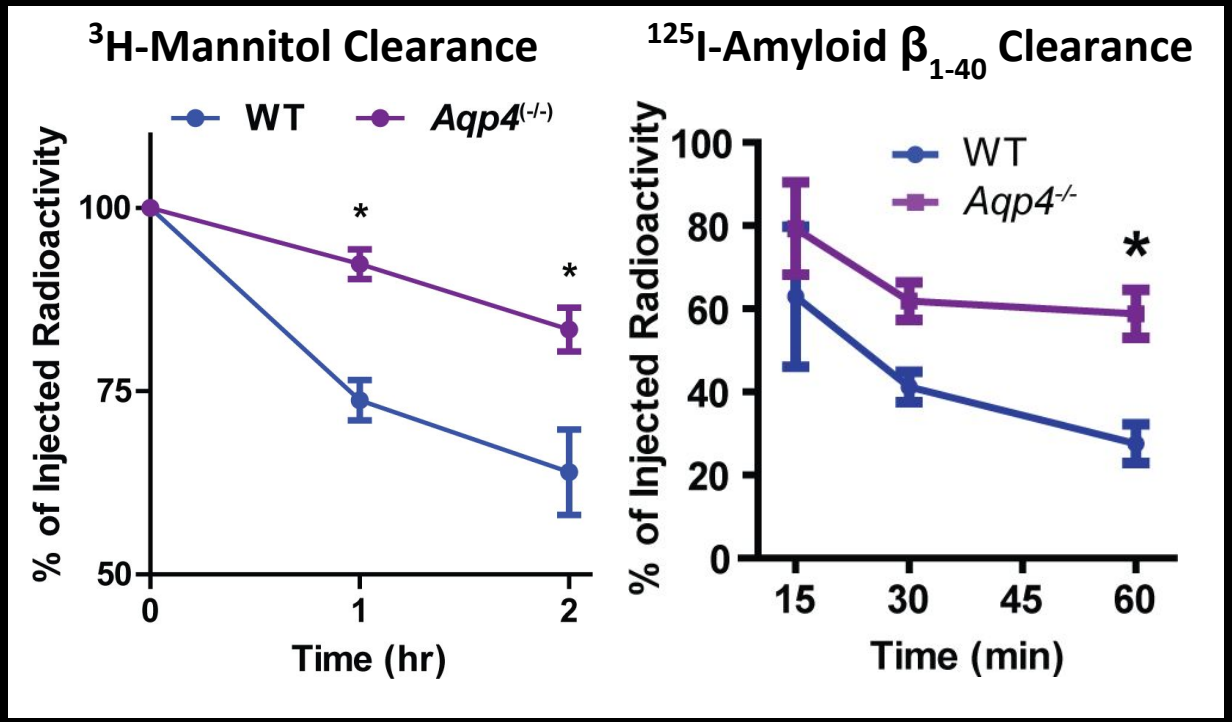
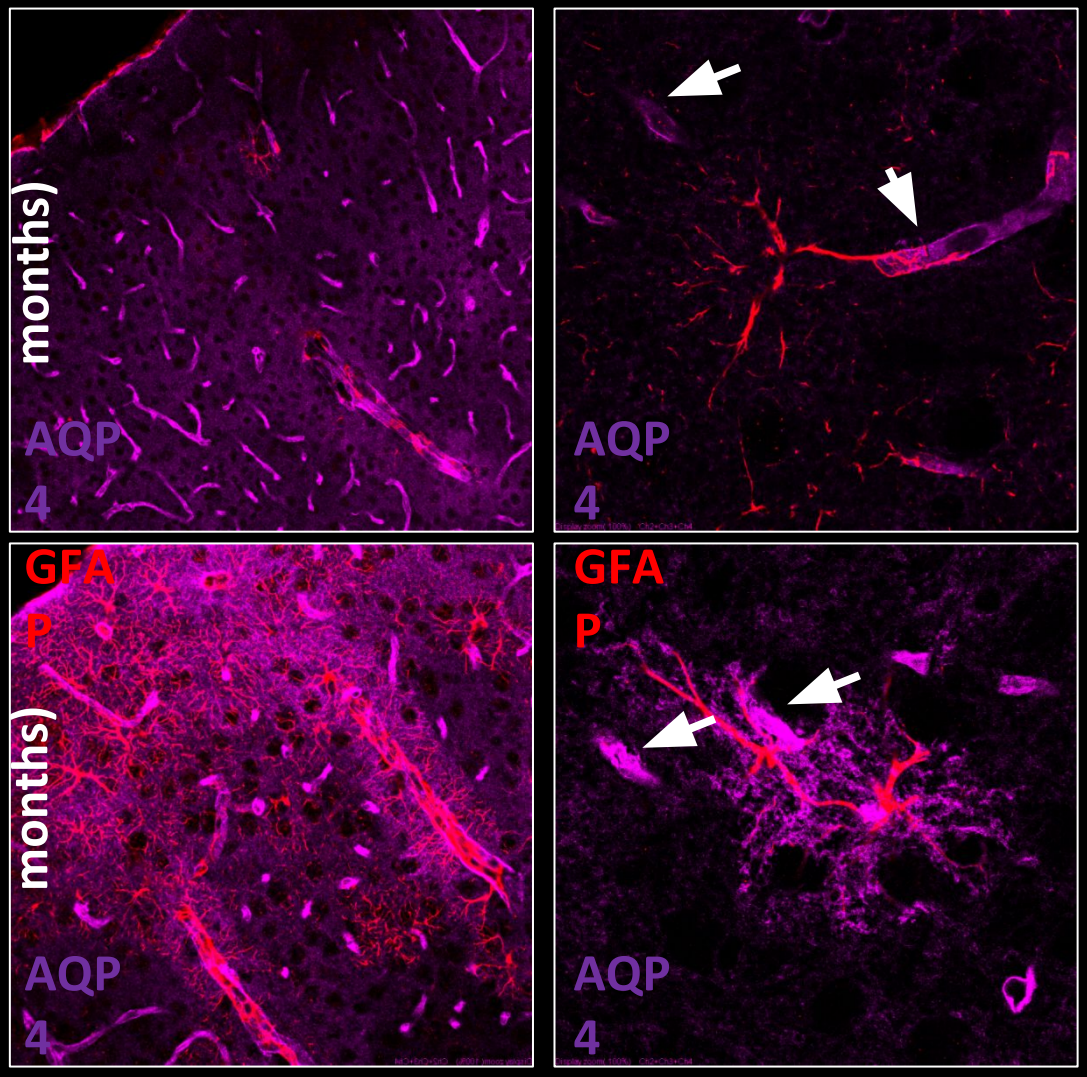




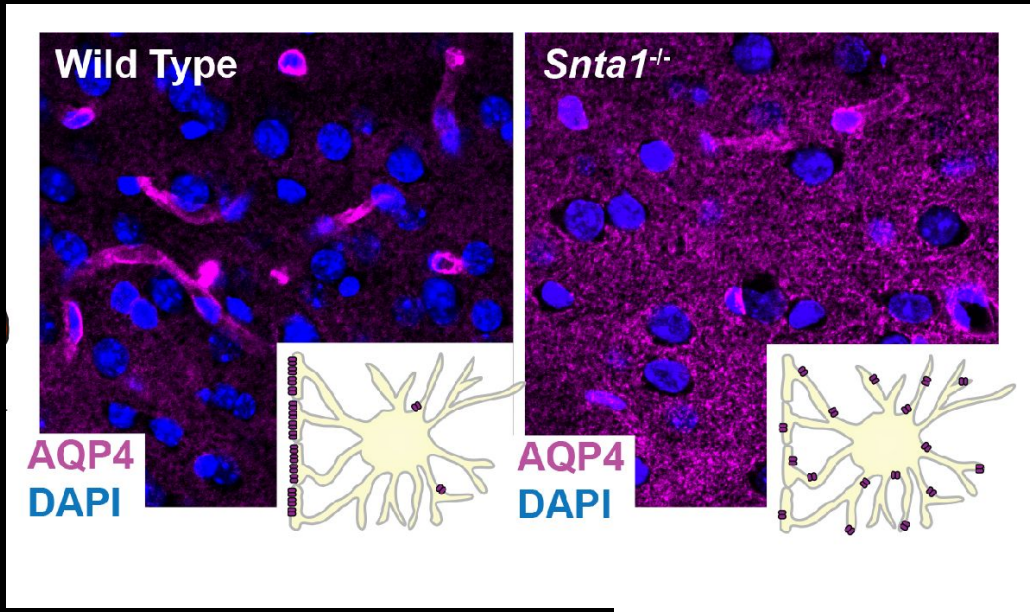
Iliff et al. *Sci Translat Med* 2012

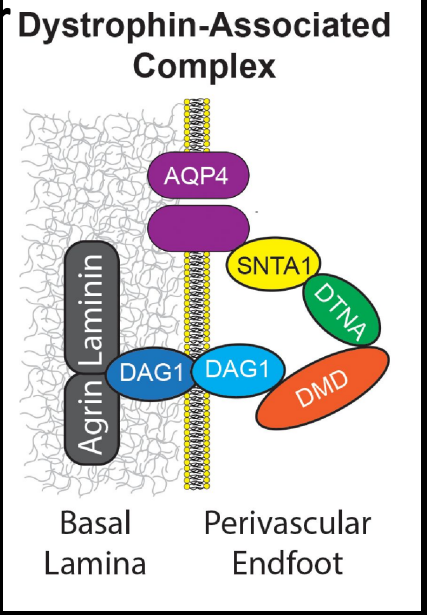
Perivascular AQP4 localization is lost in the aging brain



Kress, Iliff et al. *Annals Neurol* 2014

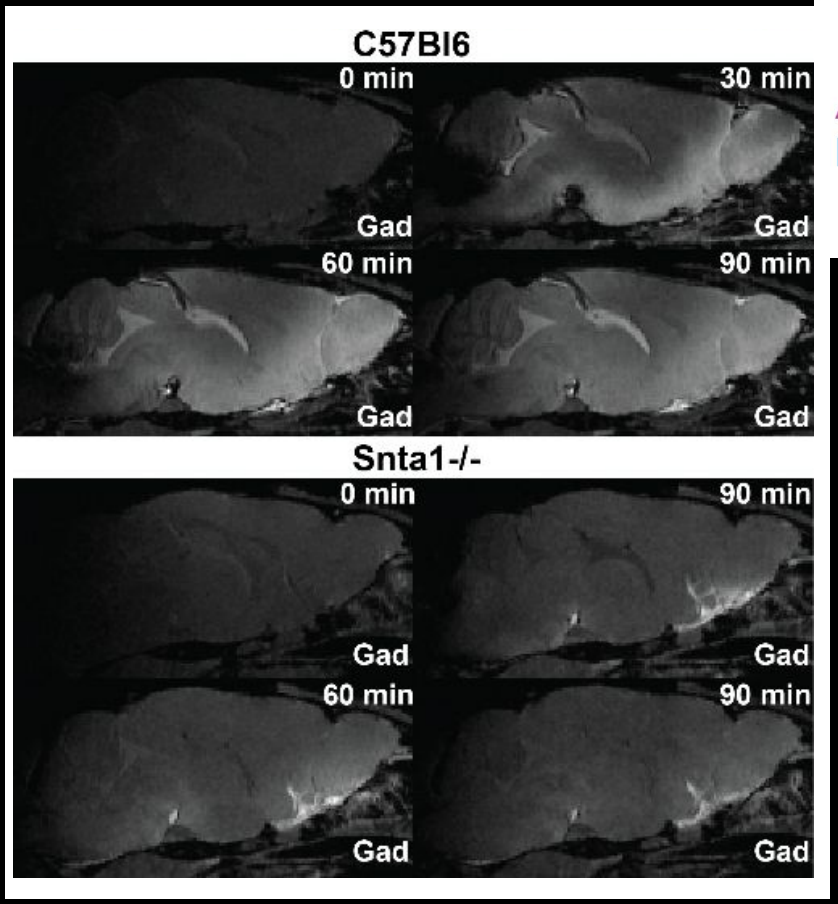
AQP4 polarization supports perivascular CSF-ISF exchange

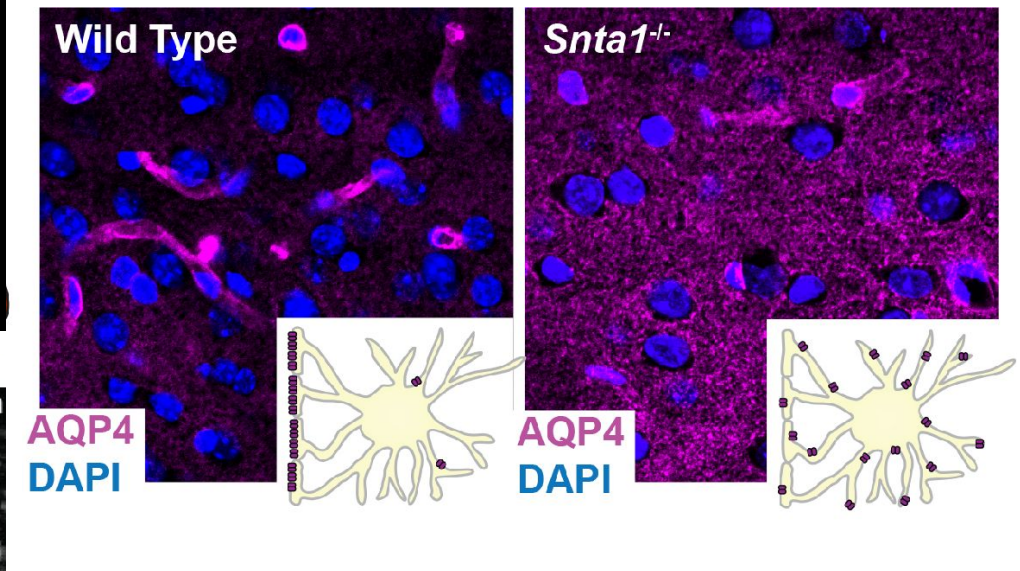


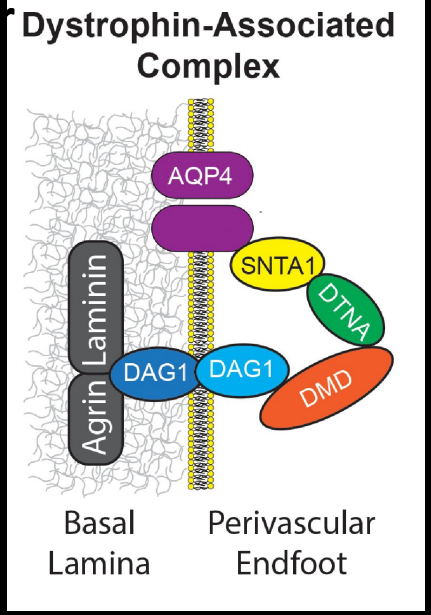


Simon, Zeppenfeld 2016

AQP4 polarization supports perivascular CSF-ISF exchange



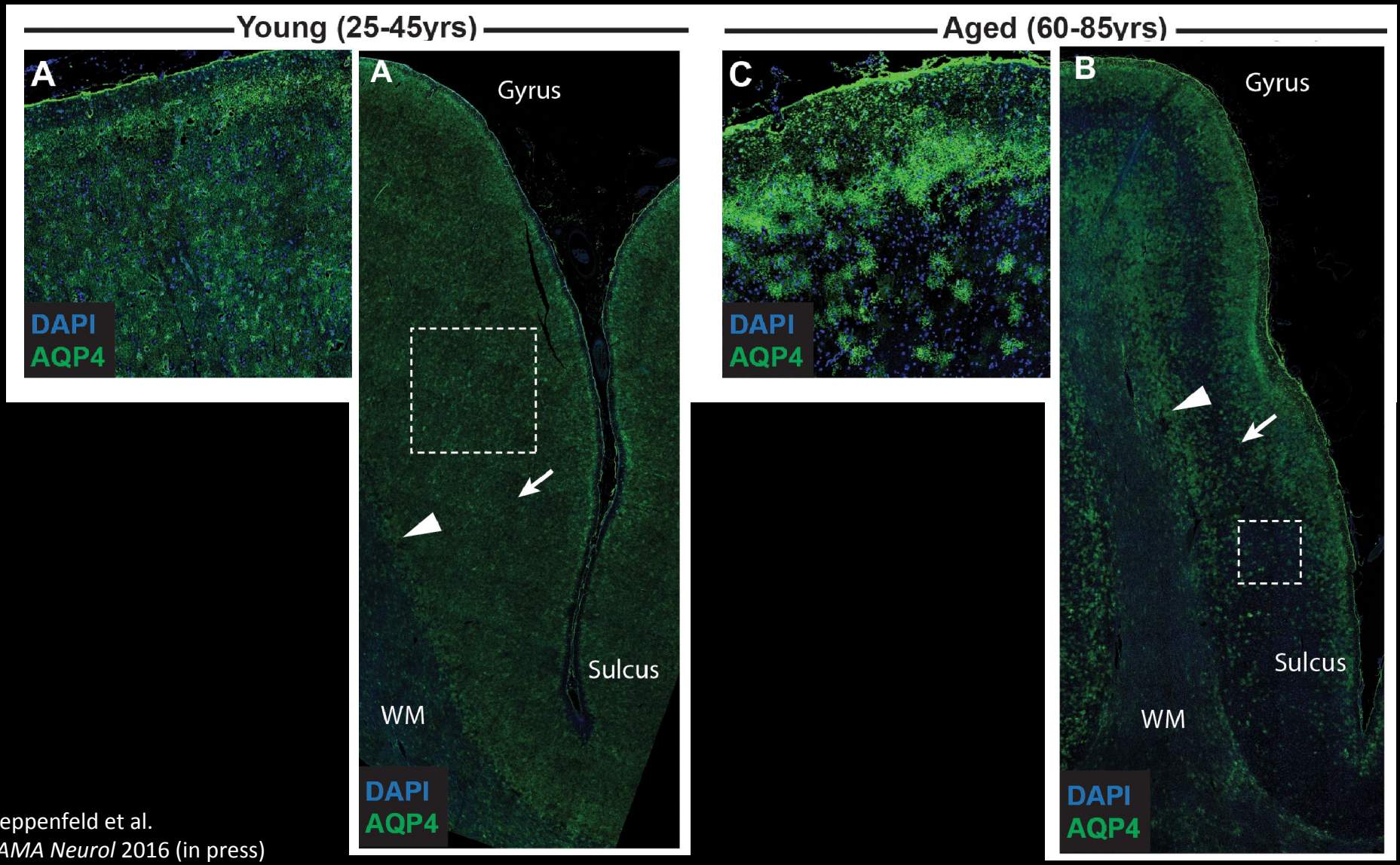




Simon, Zeppenfeld 2016

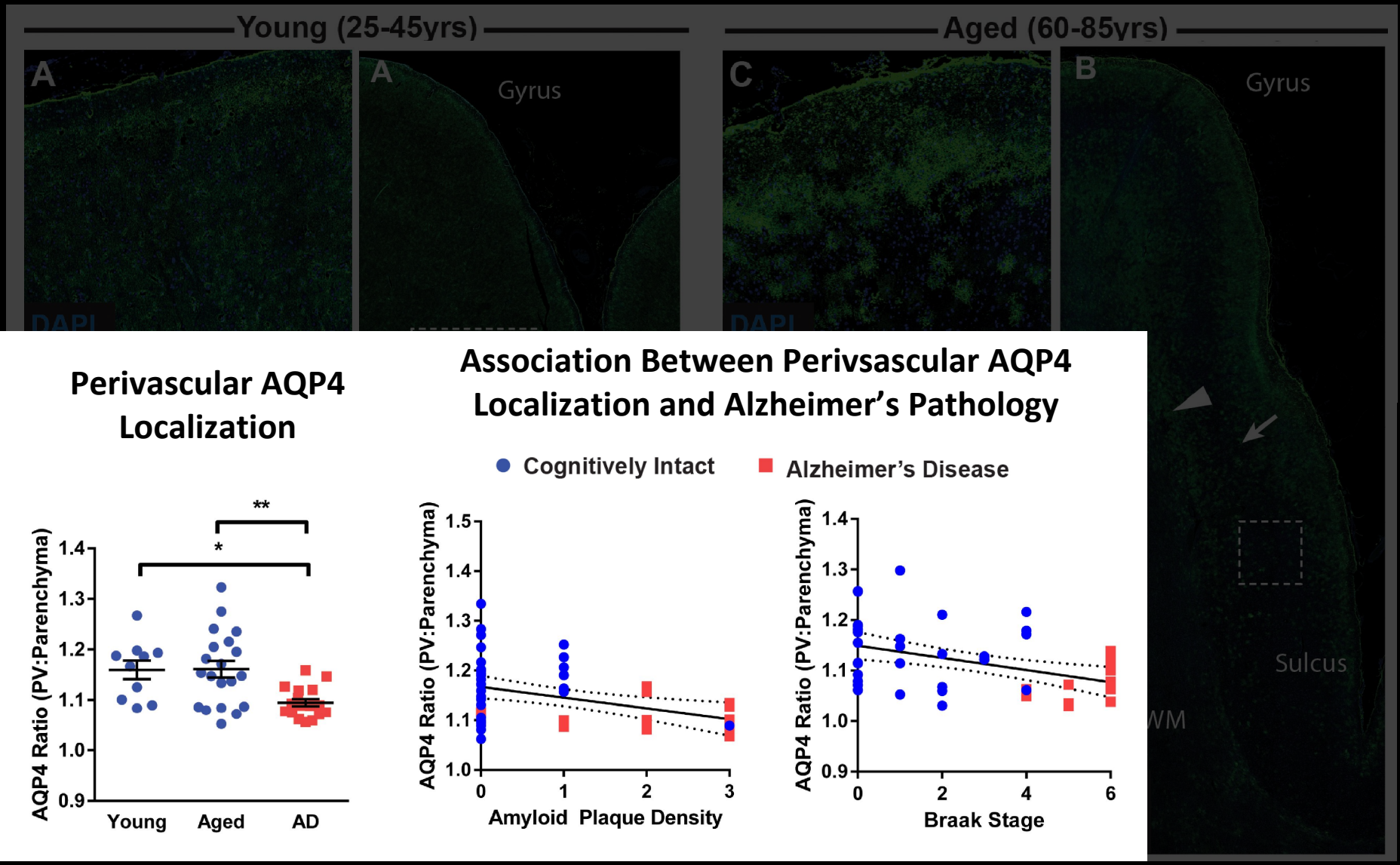
Are changes in AQP4 localization associated with Alzheimer's pathology?

Patterns of AQP4 localization are altered in the aging human cortex



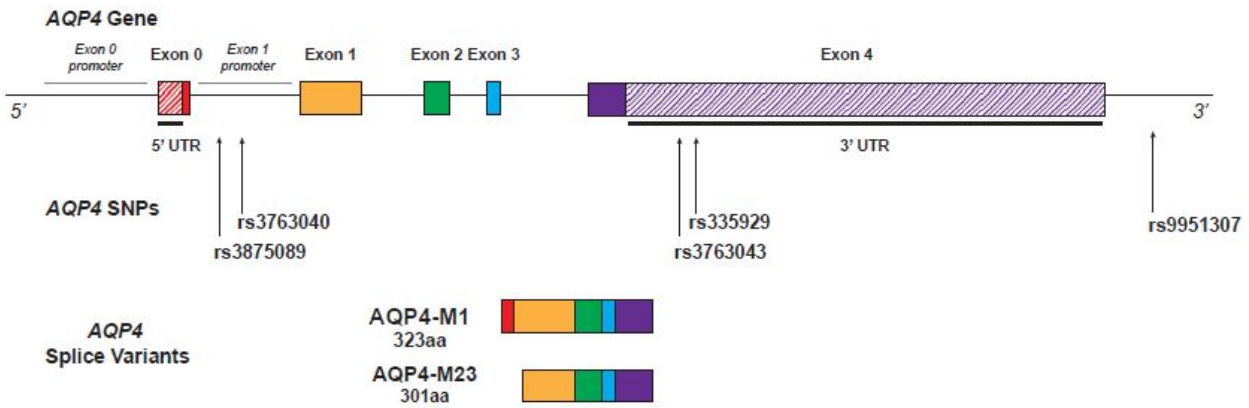
Zeppenfeld et al.
JAMA Neurol 2016 (in press)

Patterns of AQP4 localization are altered in the aging human cortex



Are naturally-occurring variants in the human *AQP4* gene associated with cognitive decline?

SNPs in human *AQP4* gene are associated with altered rates of cognitive decline



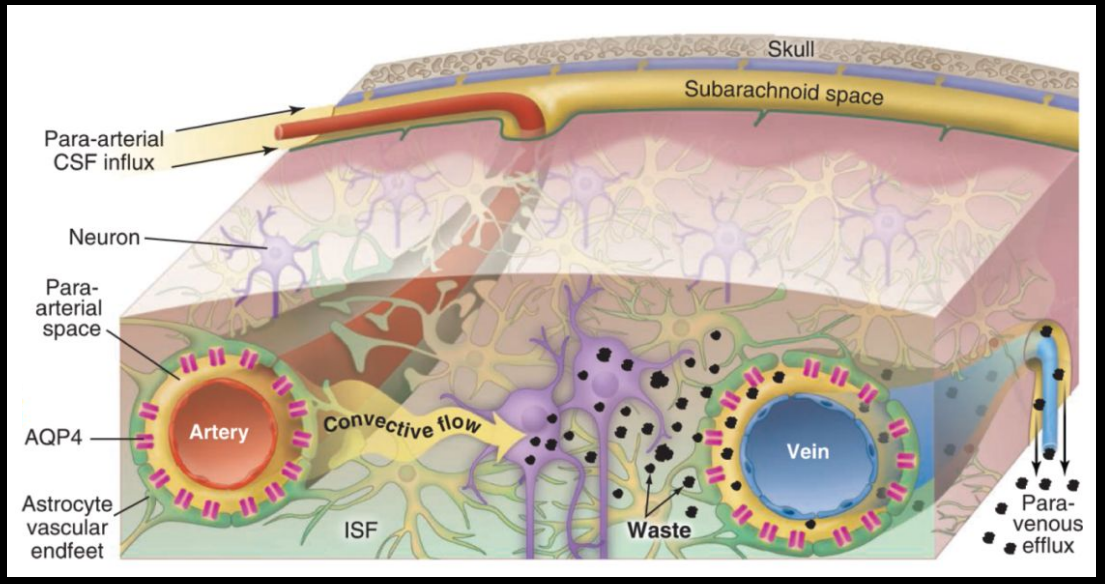
	Name	rs9951307	rs3875089	rs335929	rs3763040	rs3763043
Functional	MMSE	1.10	3.96 ***	-1.35	-3.10 **	-5.63 ***
	CDR	-0.85	6.20 ***	-4.74 ***	-4.43 ***	-0.08
Memory-Based Executive Function	MemoryZ	1.54	0.08	2.59 **	0.31	-0.61
	Logical Memory	3.00 **	-0.37	3.87 ***	-0.34	-3.49 ***
Attention-Based Executive Function	AttentionZ	-0.02	-0.63	2.34 *	-0.70	-0.93
	Digit Symbol	0.45	-0.74	2.56 *	0.36	-2.51 *
Executive	Trails B	2.34 *	-1.84	-1.01	0.55	-1.56

Kevin Burfeind, Chad Murchison 2016

Glymphatic pathway

- Brain-wide perivascular network
- Feature of the sleeping brain
- Dependent upon astroglial water transport
- Impaired in the aging rodent brain
- AQP4 mis-localization associated with Alzheimer's pathology
- Human *AQP4* gene variants modify rate of cognitive decline in Alzheimer's disease.

Glymphatic dysfunction appears to occur in many disease states, including traumatic and spinal cord injury.



From Nedergaard *Science* 2014

The Team

Thierno Madjou Bah
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Carmen Methner
Ali Picnus
Natalie Roese
Matt Simon
Marquitta Smith
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Doug Zeppenfeld

Human Glymphatic Imaging Project

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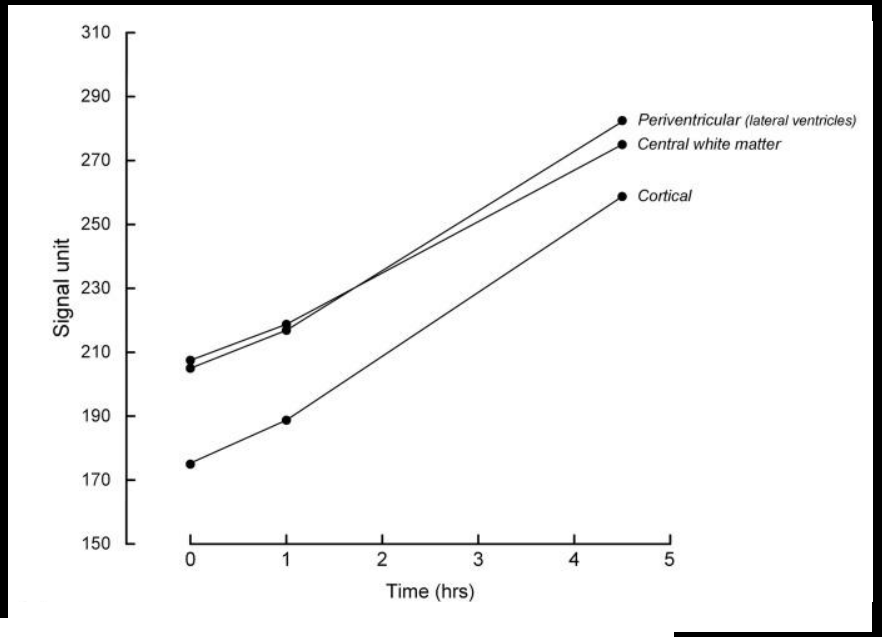
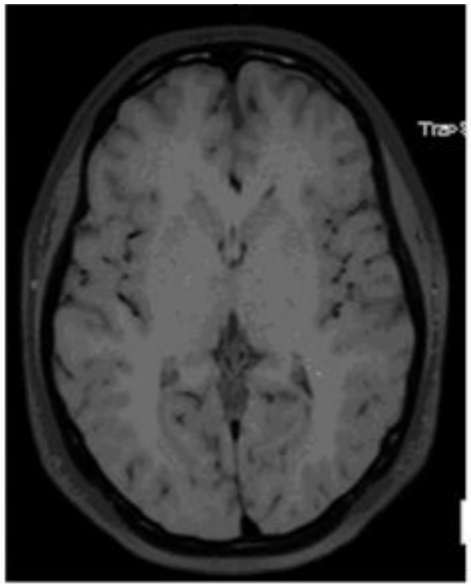
Funding

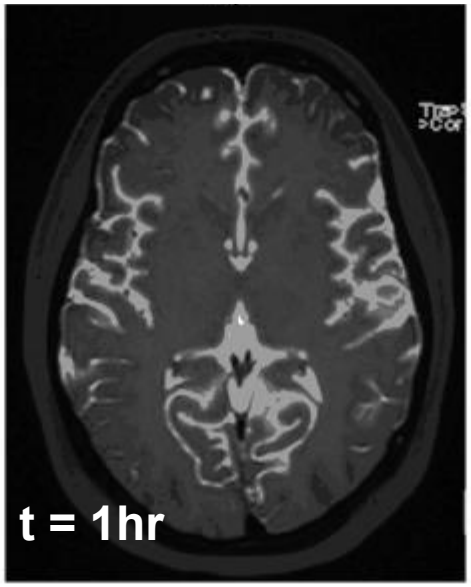
NINDS (JI), NIA (JK), American Heart Association (JI), Oregon Partnership for Alzheimer's Research (JI), Paul G. Allen Family Foundation (JI, BR)

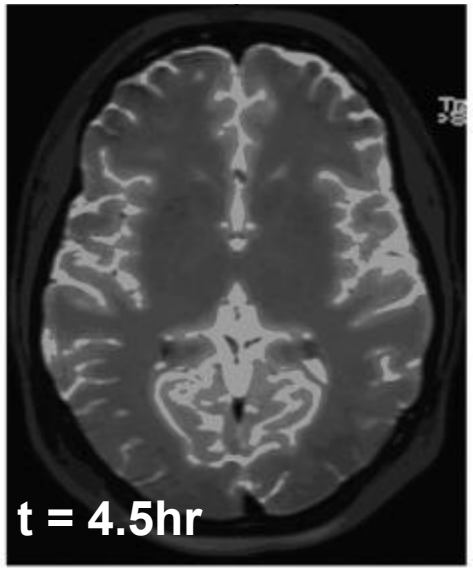
Evaluating glymphatic function in the human brain



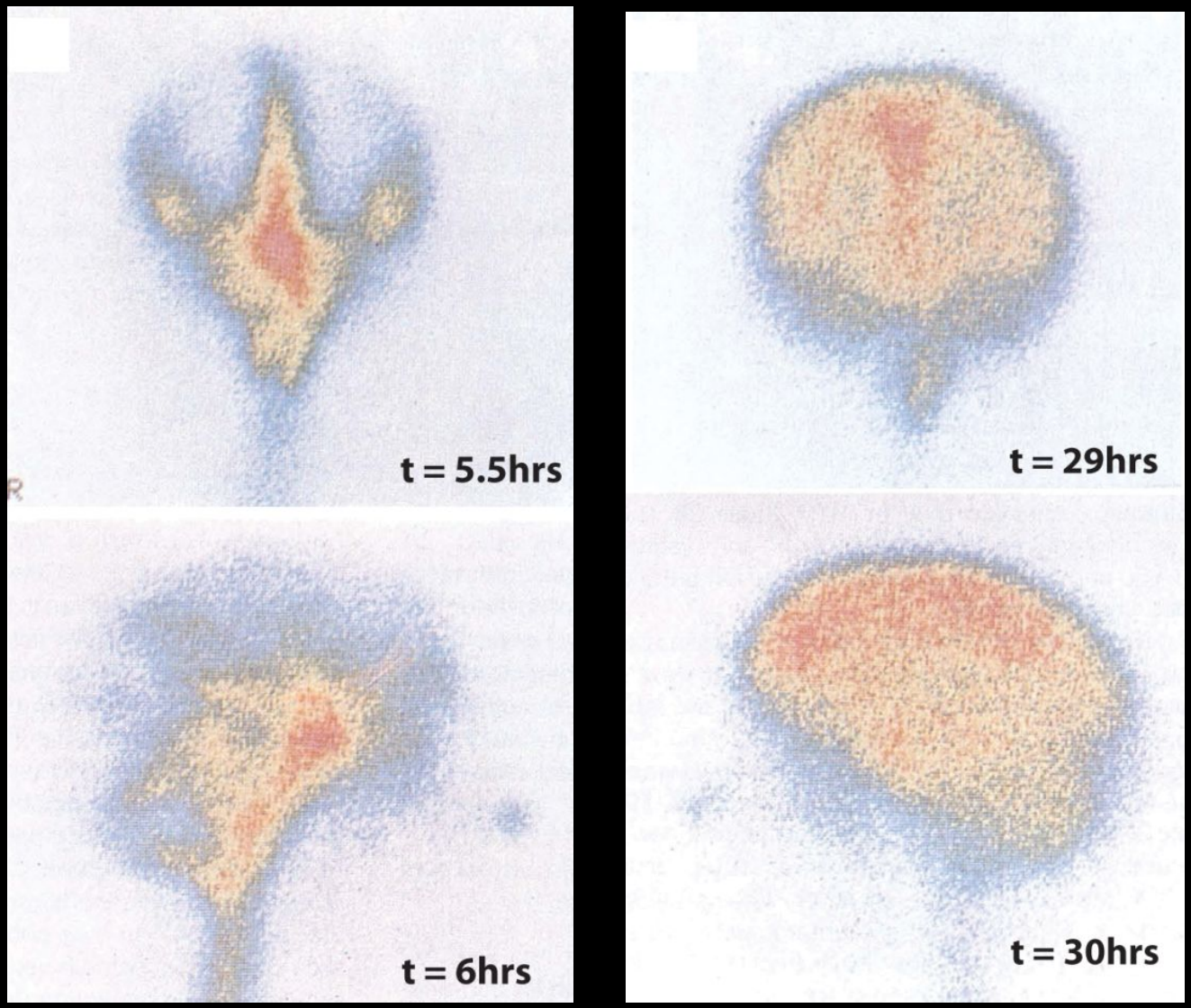
Eide and Ringstad *Acta Radiol Open* 2015





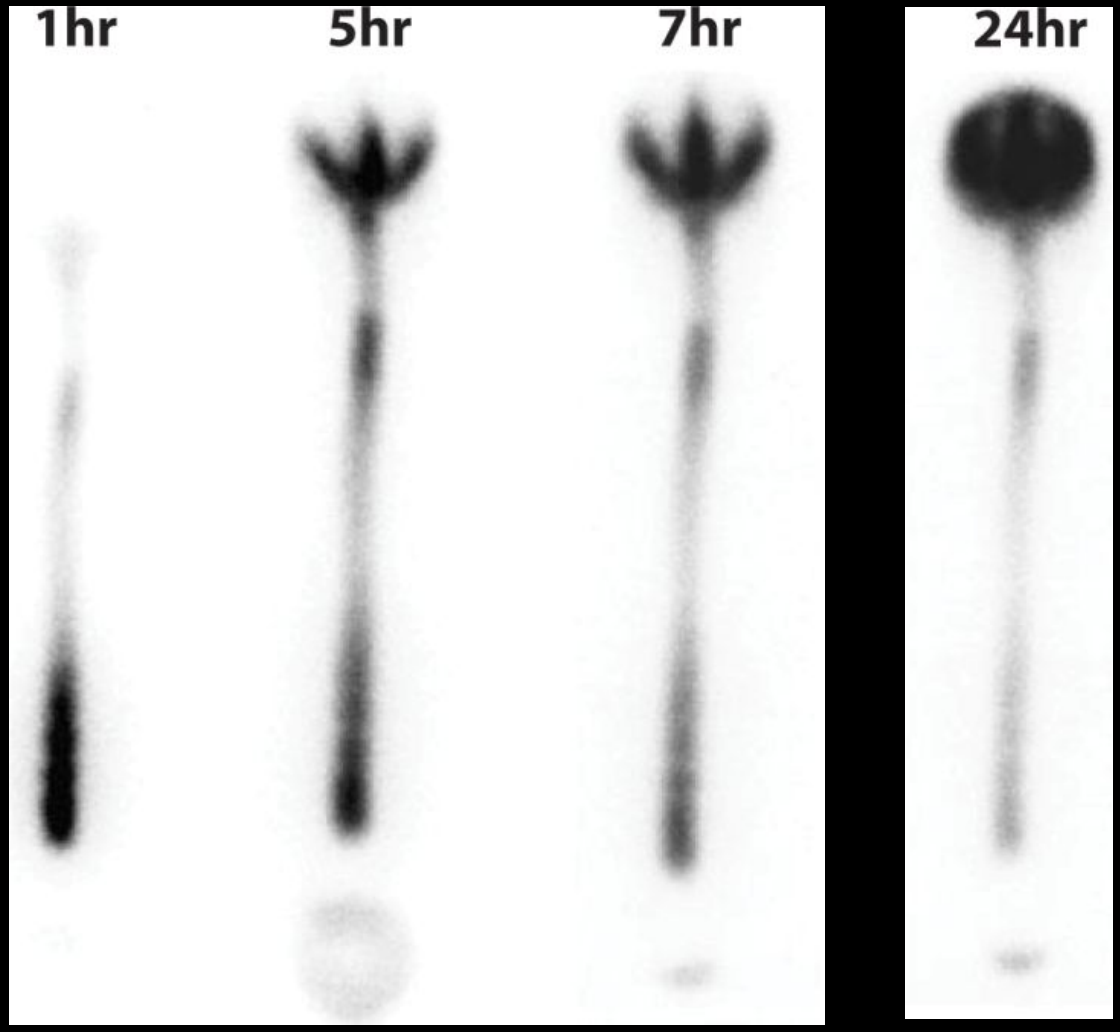


Human ^{111}In-DTPA SPECT imaging suggests role for sleep in IT contrast distribution



From Glaubitt et al. *AJNR* 1983

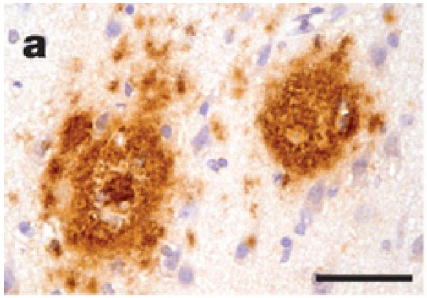
Human ^{111}In-DTPA SPECT imaging suggests role for sleep in IT contrast distribution



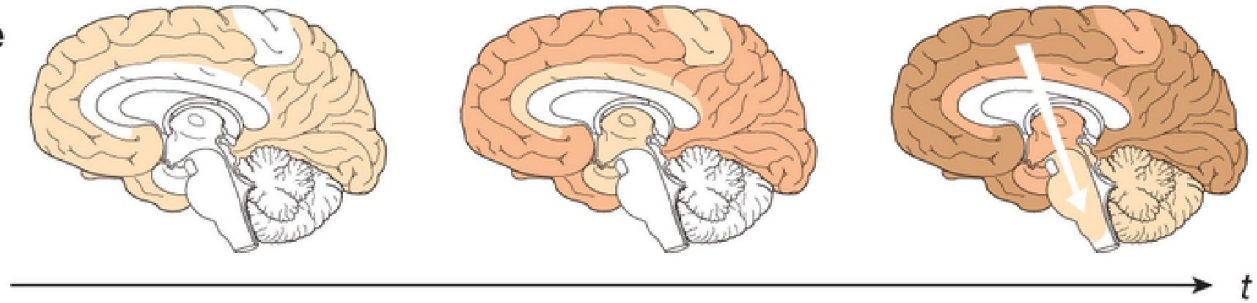
From Horikoshi et al. *Cephalalgia* 2006)

Alzheimer's disease – An age-related disease with characteristic pathology and neuroanatomical spread

Amyloid Plaques



Thal Stages



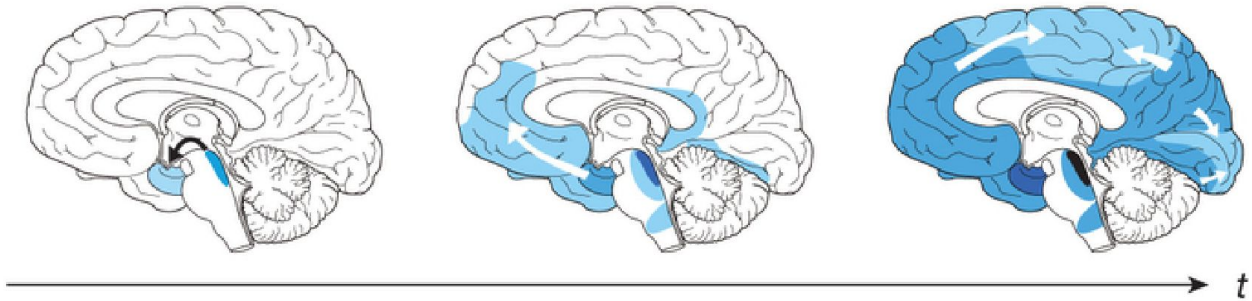
I
Senile Change

II-III
Pathological Aging

IV-V
Alzheimer's Disease

Neurofibrillary Tangles

Braak Stages

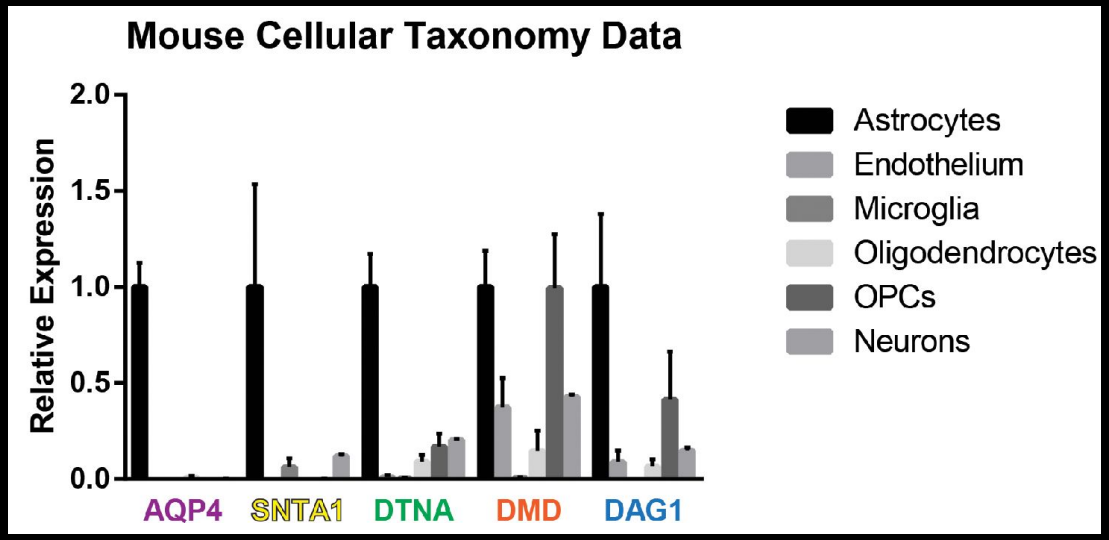


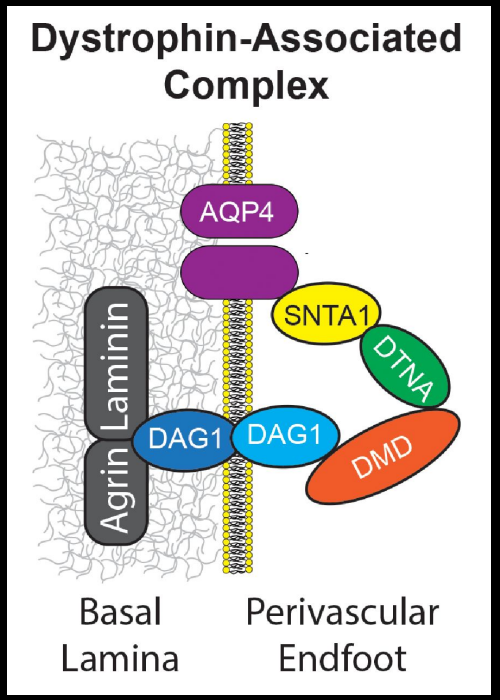
I-II
Prodromal

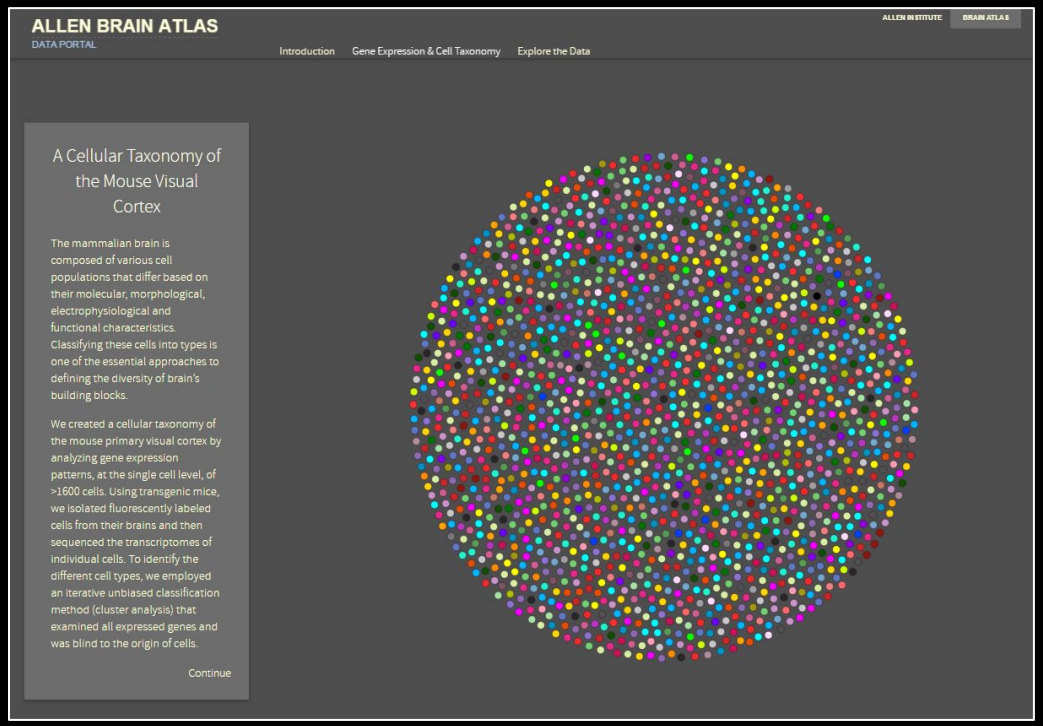
III-IV
Early-Moderate

IV-V
Moderate-Late

Jucker and Walker *Nature* 2013


Mouse Cellular Taxonomy Data
Relative Expression
2.0
1.5
1.0
0.5
0.0
AQP4
SNTA1
DTNA
DMD
DAG1
Astrocytes
Endothelium
Microglia
Oligodendrocytes
OPCs
Neurons


Dystrophin-Associated Complex
AQP4
SNTA1
DTNA
Laminin
DAG1
DAG1
DMD
Agrin
Basal Lamina
Perivascular Endfoot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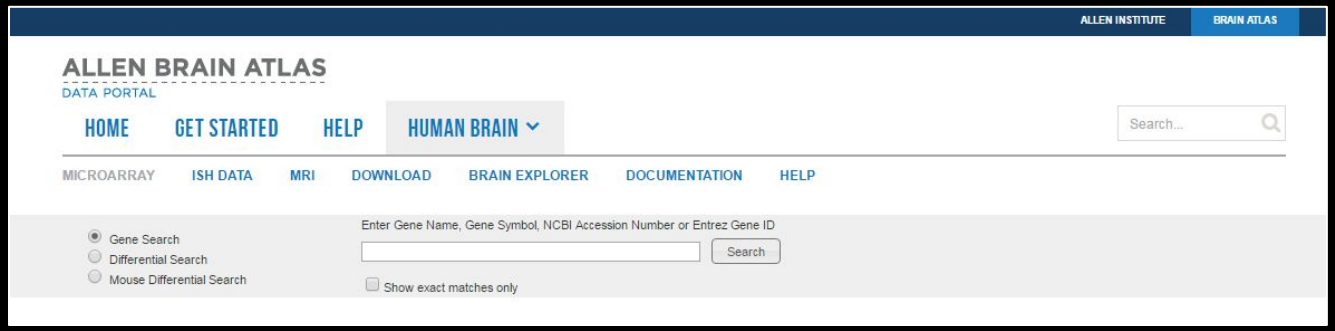
Introduction
Gene Expression & Cell Taxonomy
Explore the Data
A Cellular Taxonomy of the Mouse Visual Cortex
The mammalian brain is composed of various cell populations that differ based on their molecular, morphological, electrophysiological and functional characteristics. Classifying these cells into types is one of the essential approaches to defining the diversity of brain's building blocks.
We created a cellular taxonomy of the mouse primary visual cortex by analyzing gene expression patterns, at the single cell level, of >1600 cells. Using transgenic mice, we isolated fluorescently labeled cells from their brains and then sequenced the transcriptomes of individual cells. To identify the different cell types, we employed an iterative unbiased classification method (cluster analysis) that examined all expressed genes and was blind to the origin of cells.
Continue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HELP
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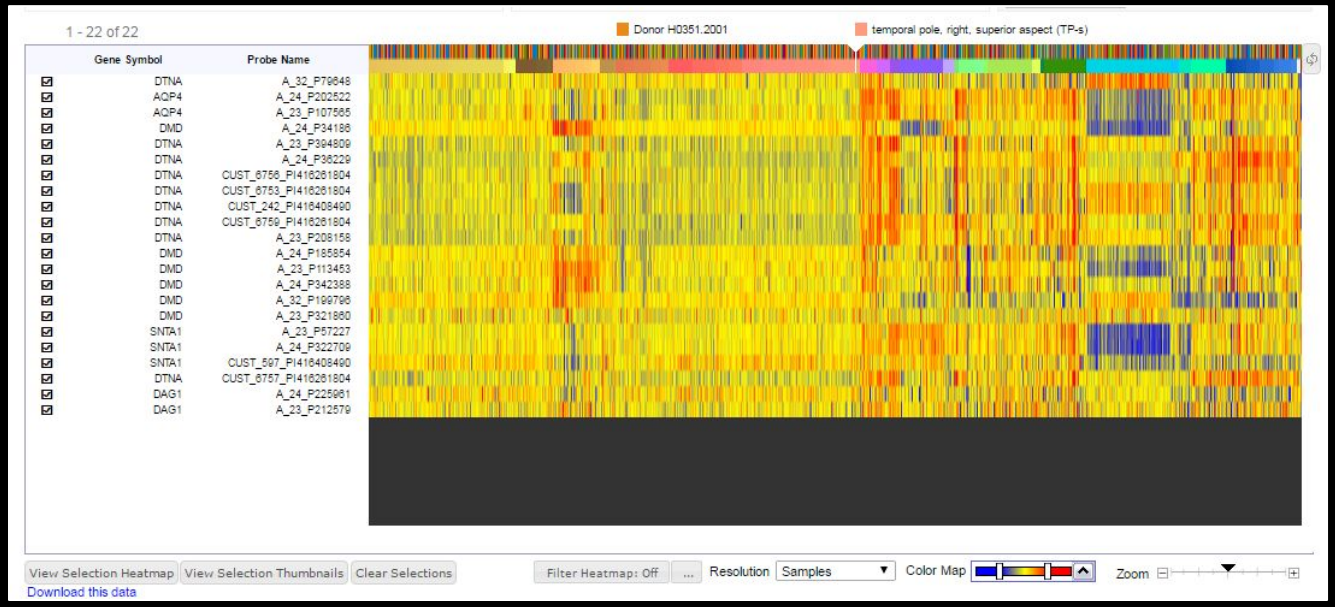
Differential Search
Mouse Differential Search
Enter Gene Name, Gene Symbol, NCBI Accession Number or Entrez Gene ID
Search
Show exact matches only


1 - 22 of 22
Donor H0351.2001
temporal pole, right, superior aspect (TP-s)
Gene Symbol
Probe Name
DTNA A_32_P79648
AQP4 A_24_P202522
AQP4 A_23_P107565
DMD A_24_P34186
DTNA A_23_P394809
DTNA A_24_P36229
DTNA CUST_6756_PI416261804
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DTNA CUST_242_PI416408490
DTNA CUST_6759_PI416261804
DTNA A_23_P208158
DMD A_24_P185854
DMD A_23_P113453
DMD A_24_P342388
DMD A_32_P199796
DMD A_23_P321860
SNTA1 A_23_P57227
SNTA1 A_24_P322709
SNTA1 CUST_597_PI416408490
DTNA CUST_6757_PI416261804
DAG1 A_24_P225961
DAG1 A_23_P212579
View Selection Heatmap
View Selection Thumbnails
Clear Selections
Filter Heatmap: Off
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Resolution
Samples
Color Map
Zoom
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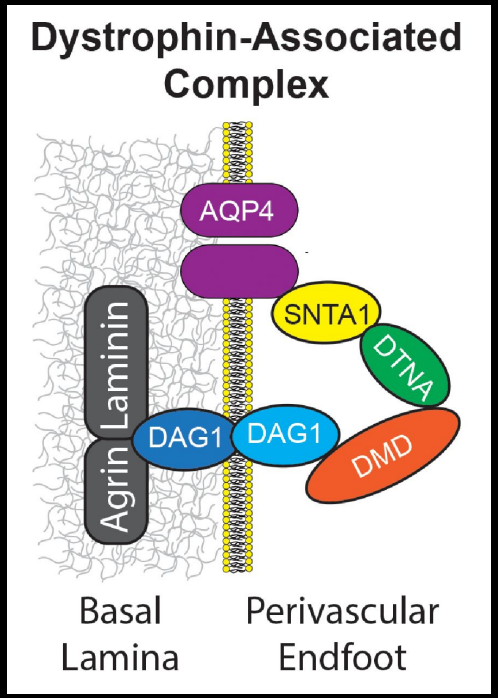
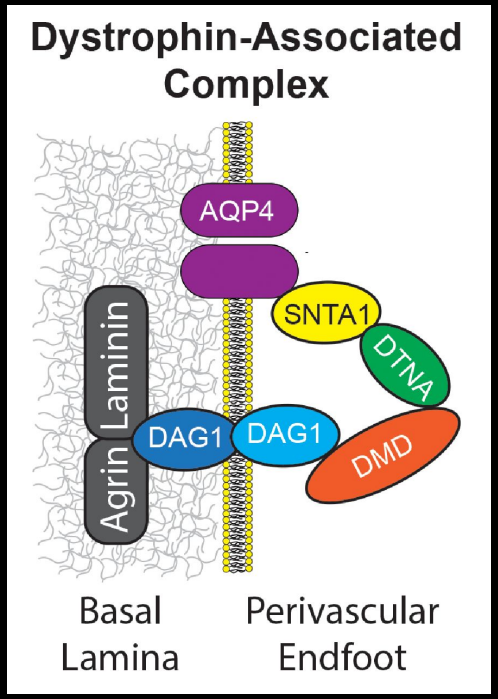
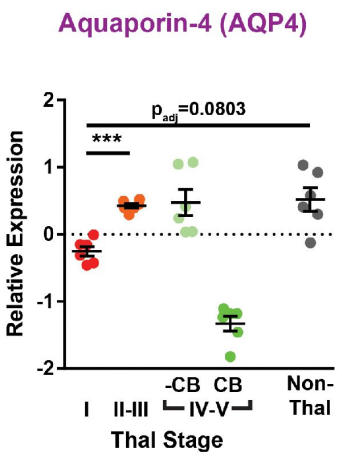
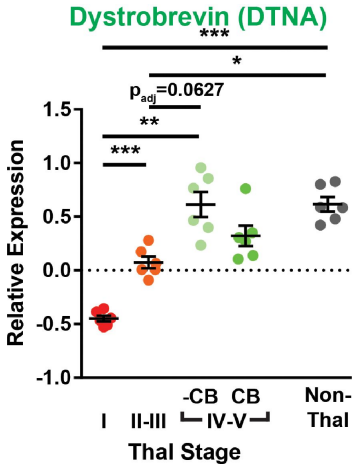
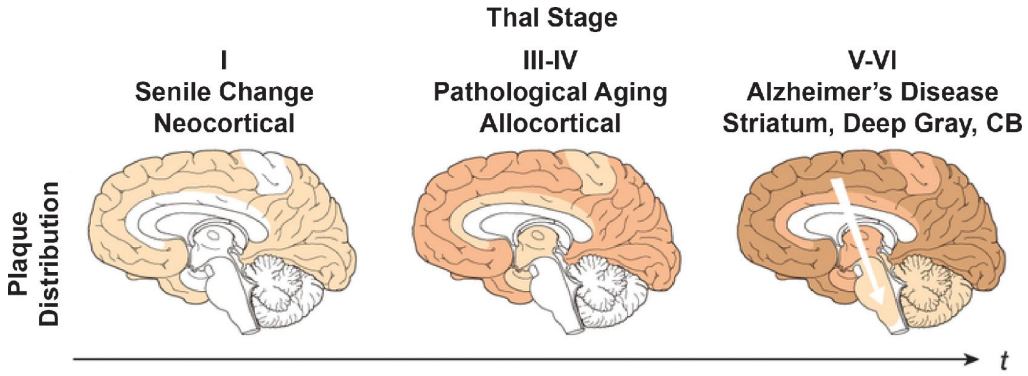

Dystrophin-Associated Complex
AQP4
SNTA1
DTNA
DAG1
DAG1
DMD
Agrin
Laminin
Basal Lamina
Perivascular Endfoot

Altered AQP4 and DAC protein expression in aggregation-prone brain regions



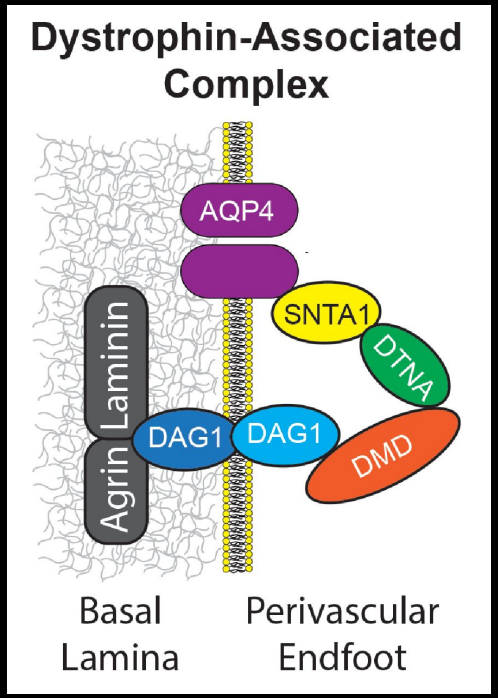


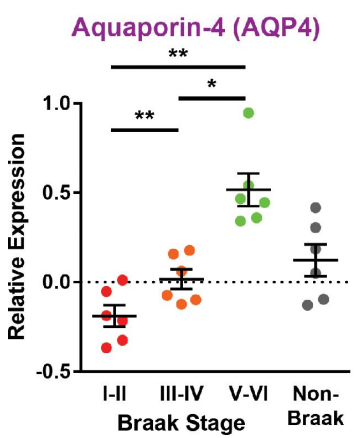


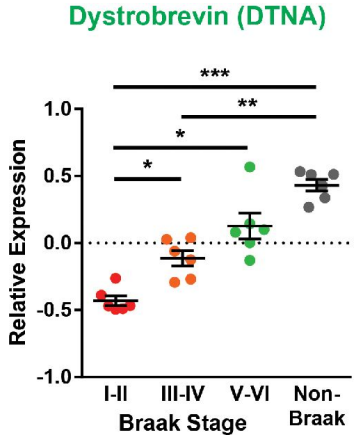


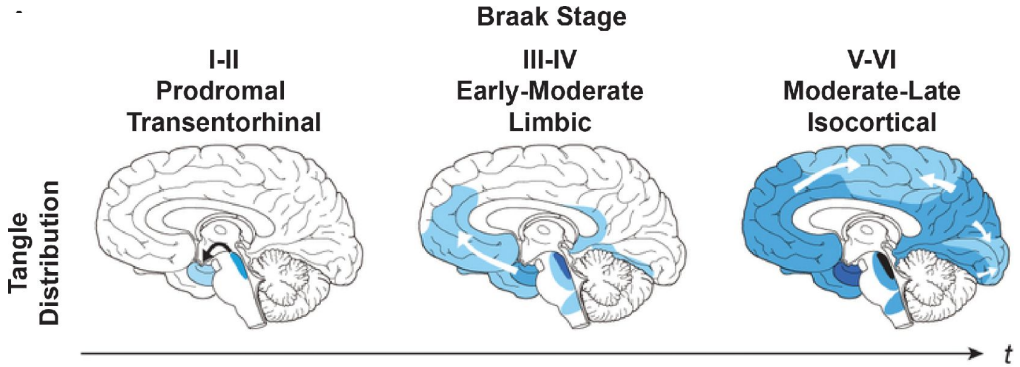
Jucker and Walker *Nature*

Altered AQP4 and DAC protein expression in aggregation-prone brain regions









Jucker and Walker *Nature*