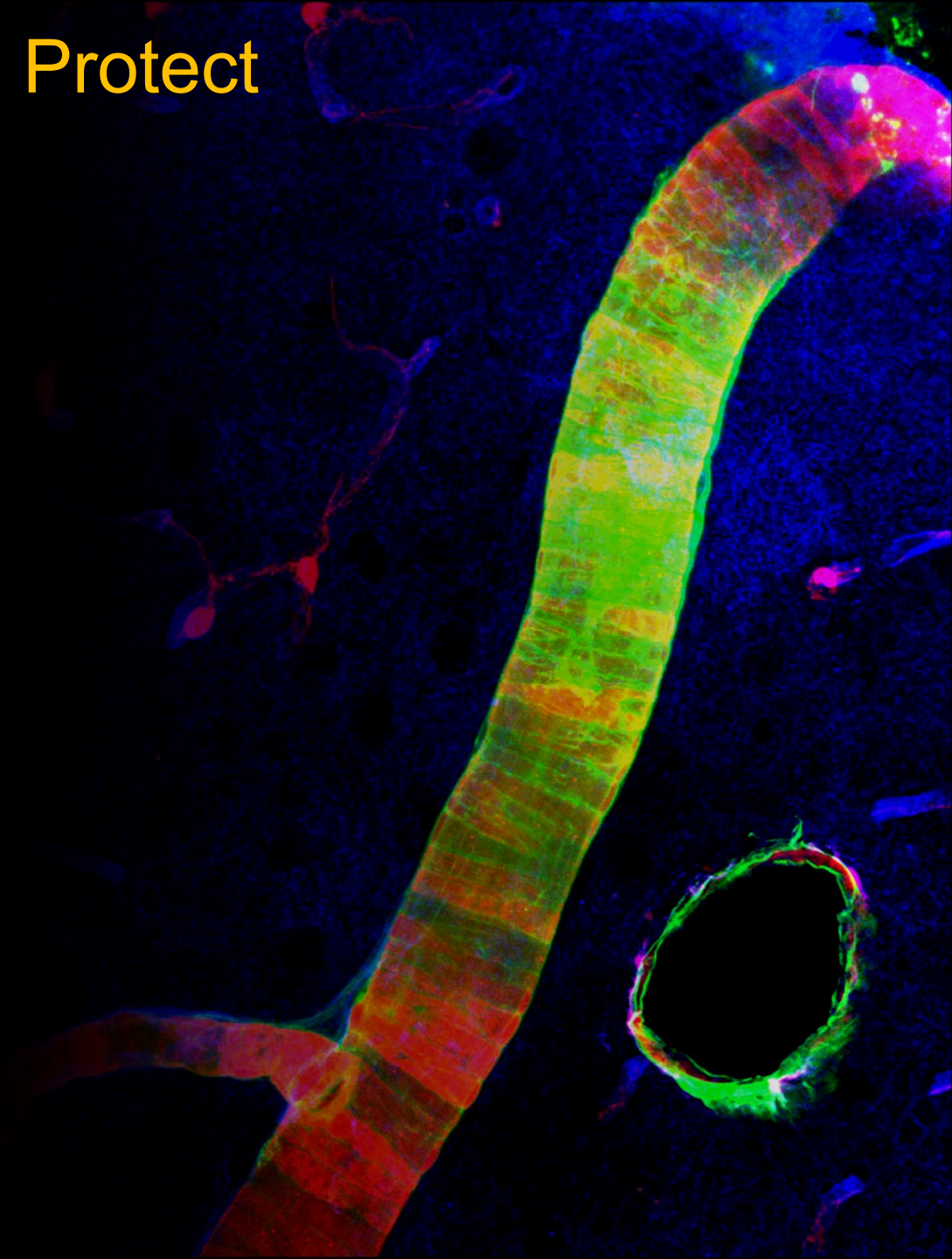


How Sleep and Brain Waste Removal Protect Against Neurodegeneration

Jeffrey Iliff, PhD

VISN 20 Mental Illness Research, Education and Clinical Center (MIRECC)
VA Puget Sound Health Care

Department of Psychiatry and Behavioral Sciences
Department of Neurology
University of Washington School of Medicine

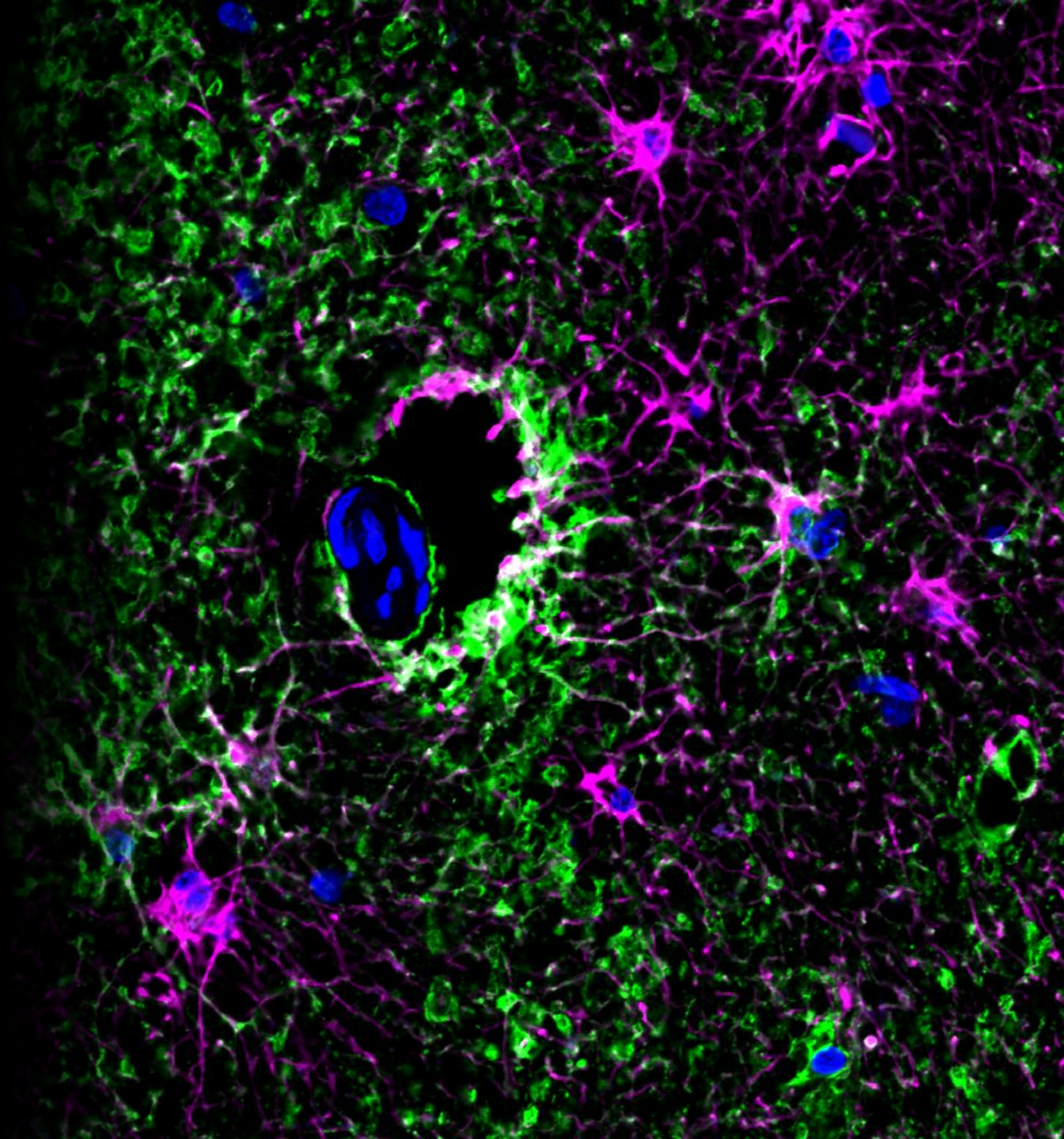


Disclosures

Work in the Iliff lab is funded by the US National Institutes of Health, the US Department of Defense, the US Department of Veterans Affairs, and the University of Washington School of Medicine.

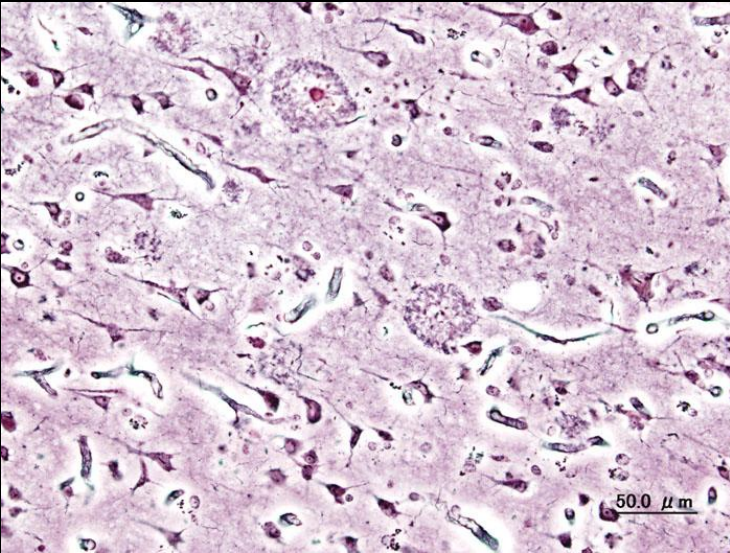
Dr. Iliff serves as the Chair of the Scientific Advisory Board for the company Applied Cognition, from which he receives compensation and in which he holds an equity stake.

The views expressed in this talk do not reflect those of the US Government.

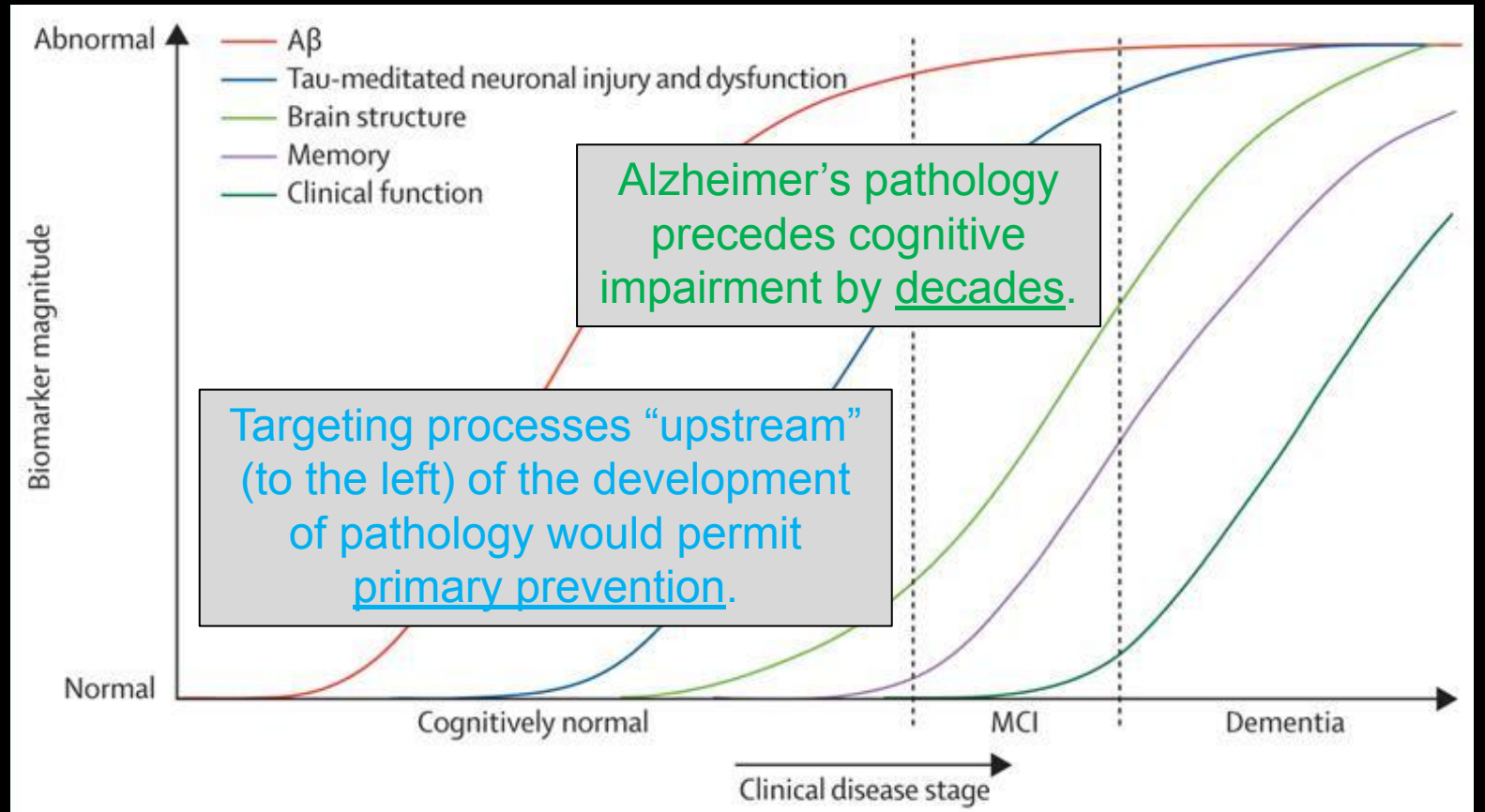


The long road to Alzheimer's disease

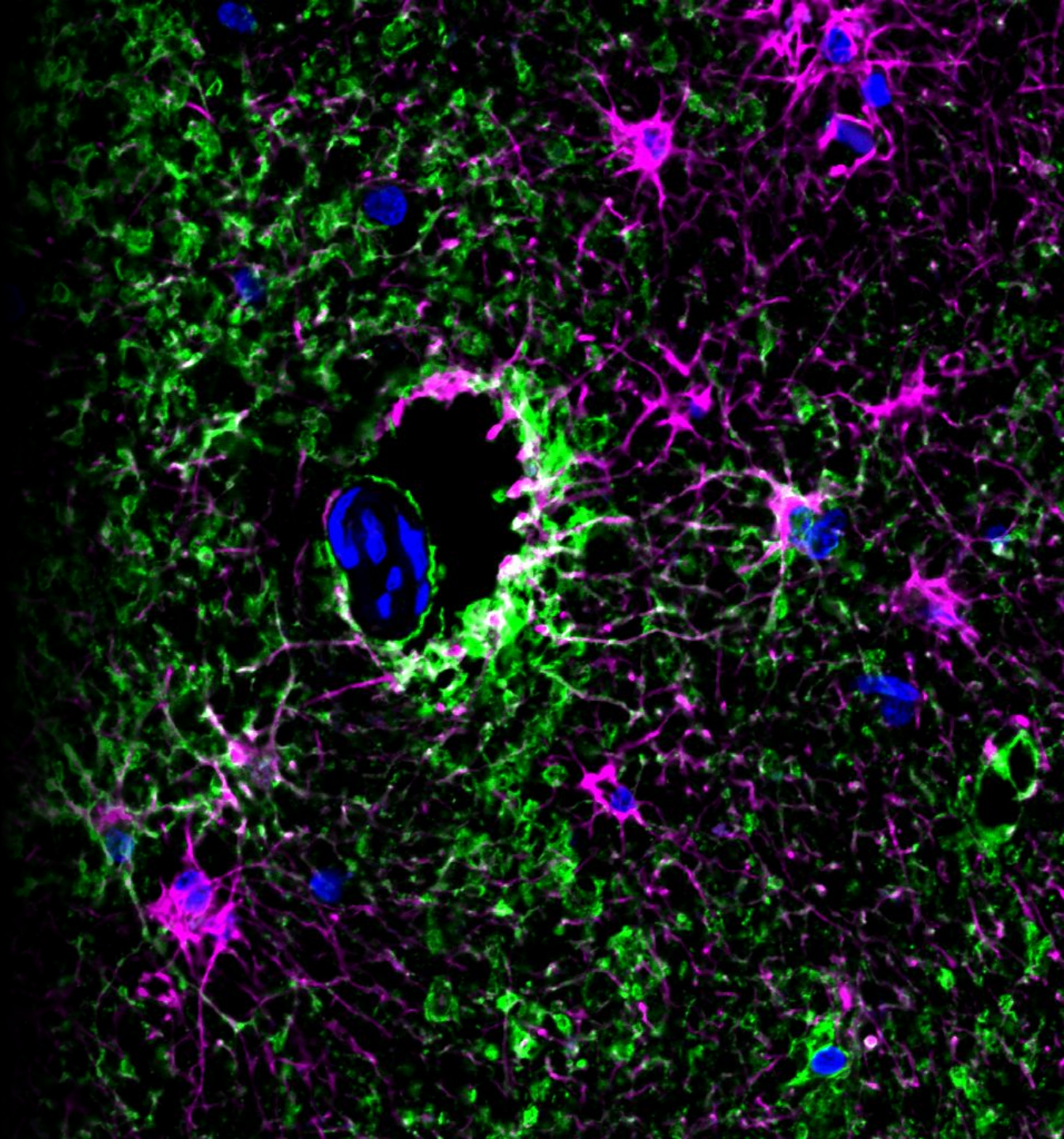
Alzheimer's disease pathology:
Amyloid plaques
Neurofibrillary tangles



Sequential progression of Alzheimer's pathology and cognitive/functional impairment



Sleep disruption and
neurodegeneration.
A two-way street?



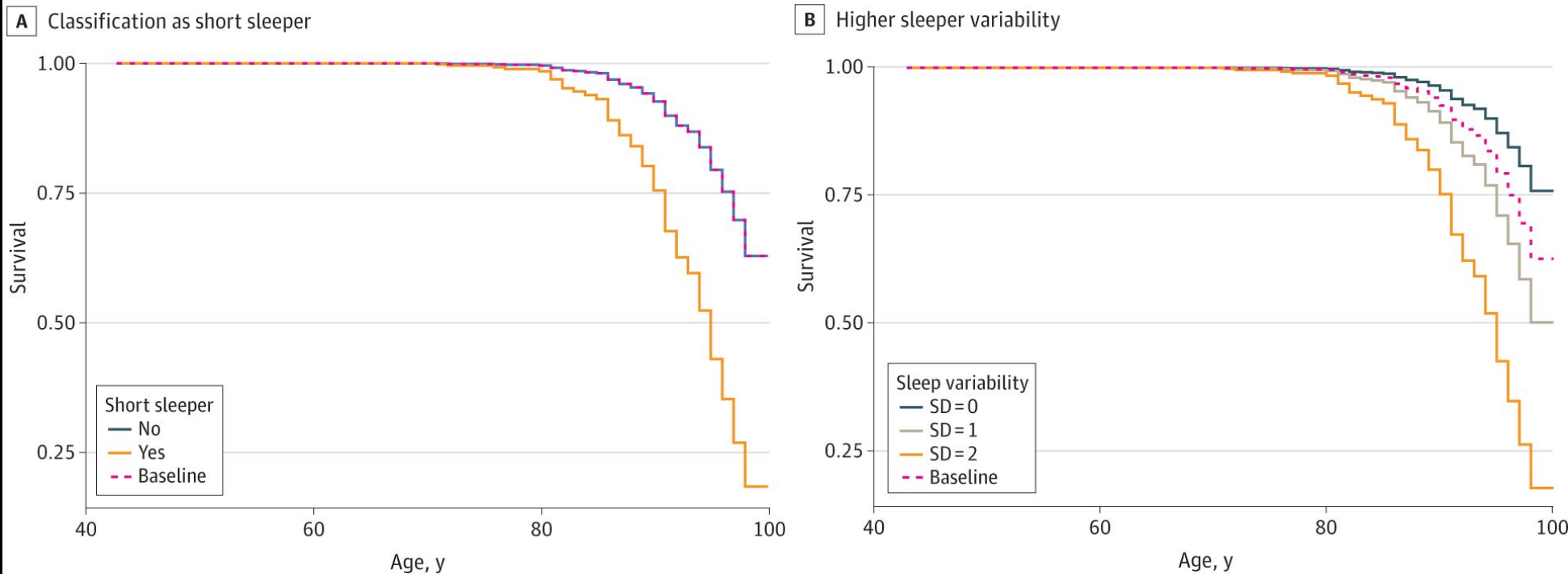
The clinical association between poor sleep and cognitive impairment

Original Investigation | Neurology

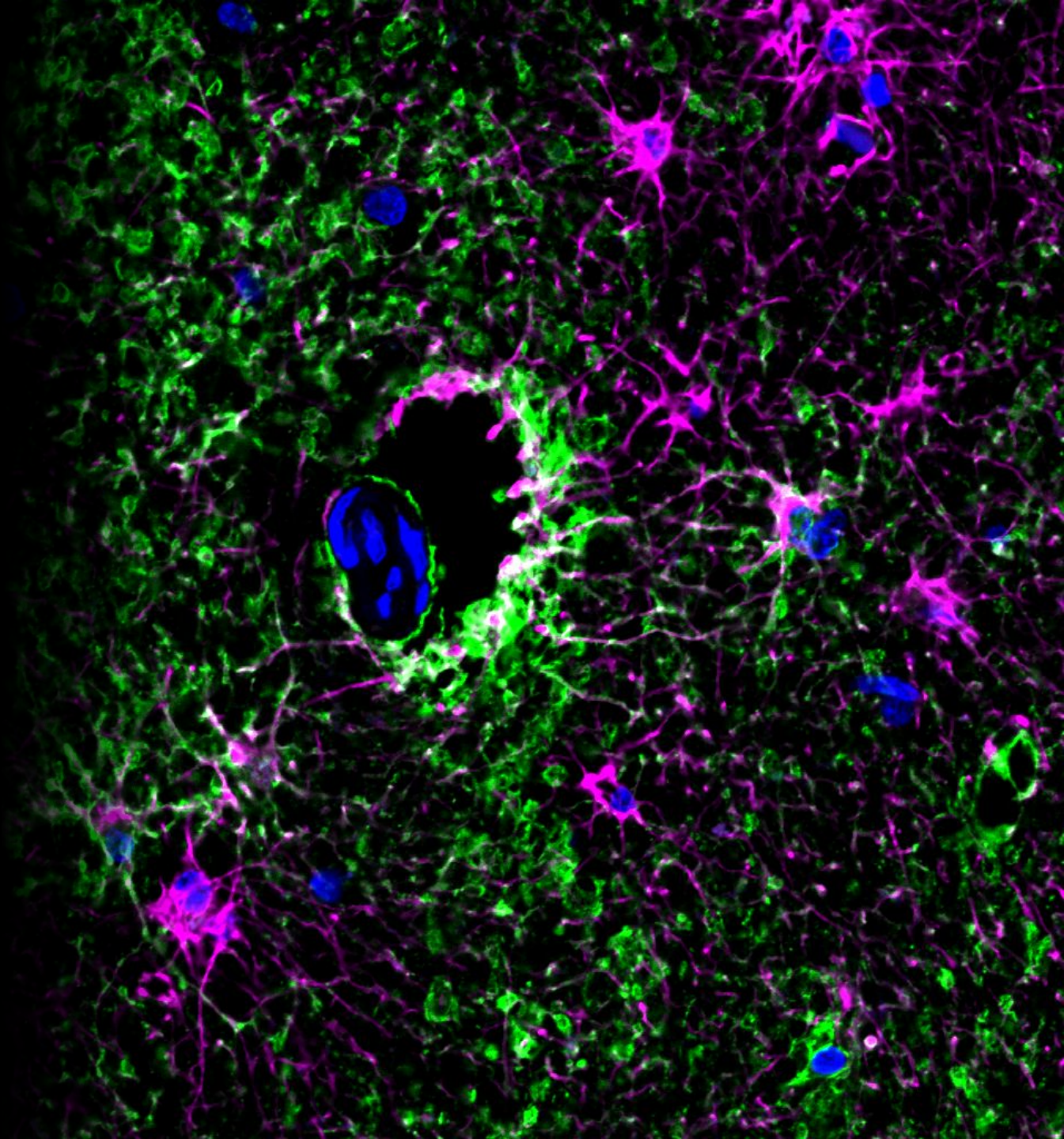
Longitudinal Sleep Patterns and Cognitive Impairment in Older Adults

Samantha A. Keil, PhD; Abigail G. Schindler, PhD; Marie X. Wang, PhD; Juan Piantino, MD; Lisa C. Silbert, MD; Jonathan E. Elliott, PhD; Madeleine L. Werhane, PhD, MPH; Ronald G. Thomas, PhD; Sherry Willis, PhD; Miranda M. Lim, MD, PhD; Jeffrey J. Iliff, PhD

In 614 participants 40-100 years of age evaluated over 10-20 years, short sleep duration (< 7hrs) or variable sleep were associated with incident cognitive impairment.

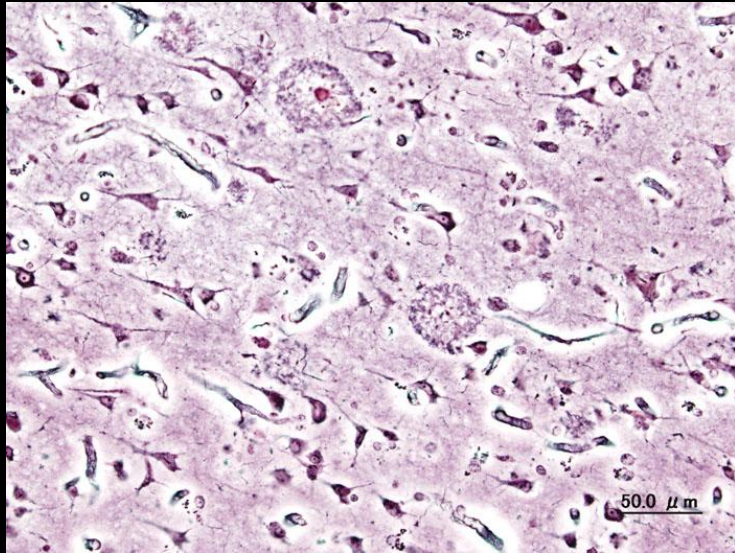


QUESTION 1



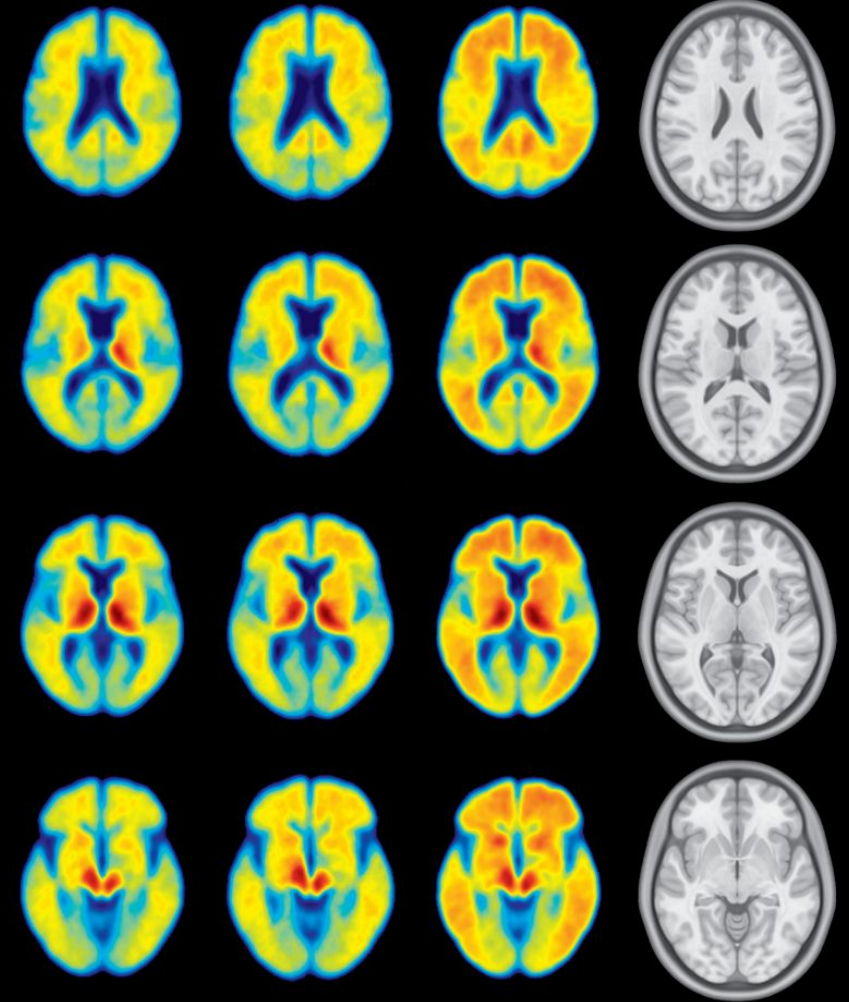
Short sleep duration is associated with increased of Alzheimer's pathology

Alzheimer's disease pathology:
Amyloid plaques
Neurofibrillary tangles



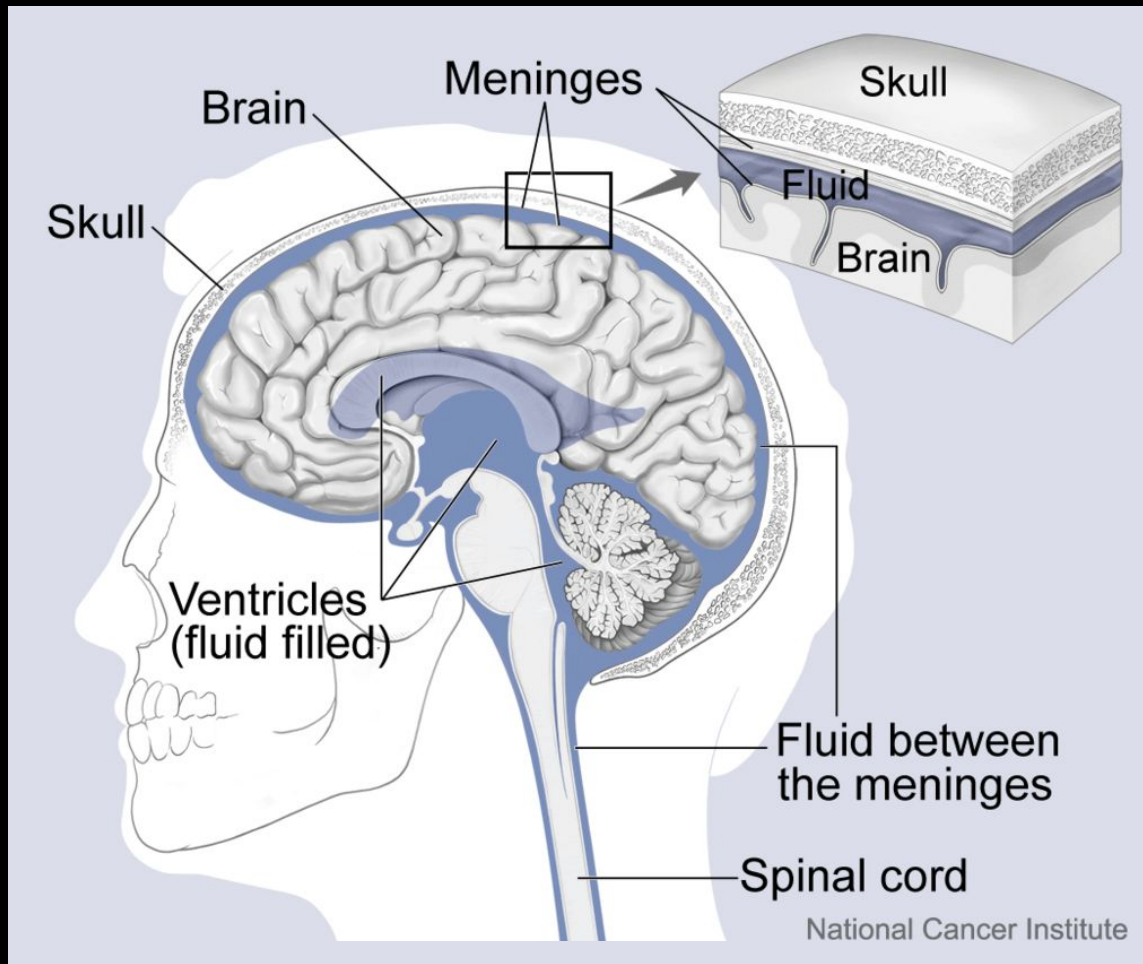
Self-reported sleep duration

>7h 6 - 7 h <6 h

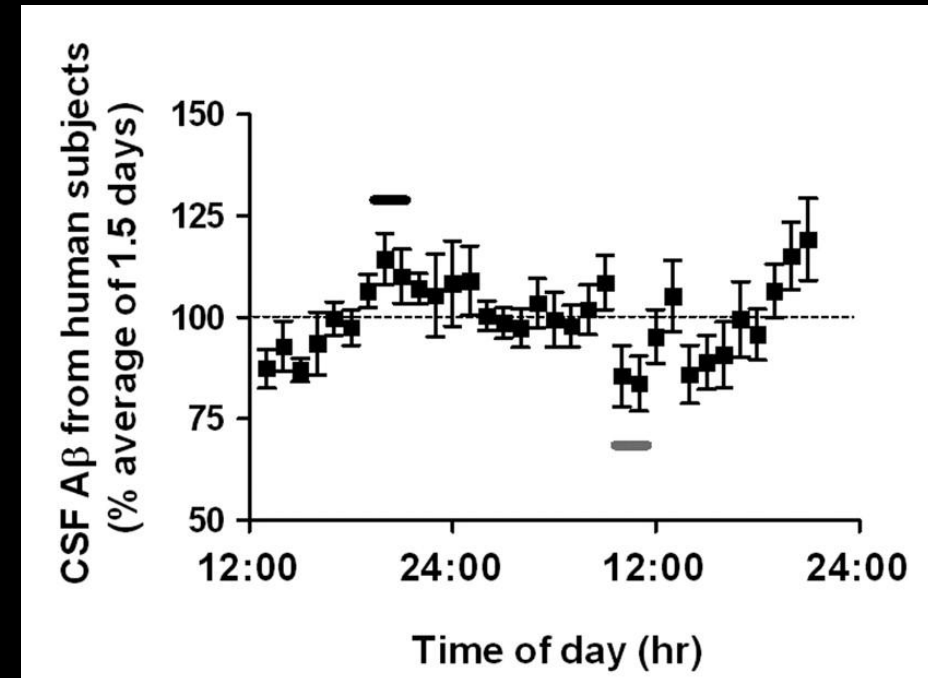


Spira et al. *JAMA Neurology* 2013

Levels of Alzheimer's-related proteins in the brain are acutely regulated by sleep

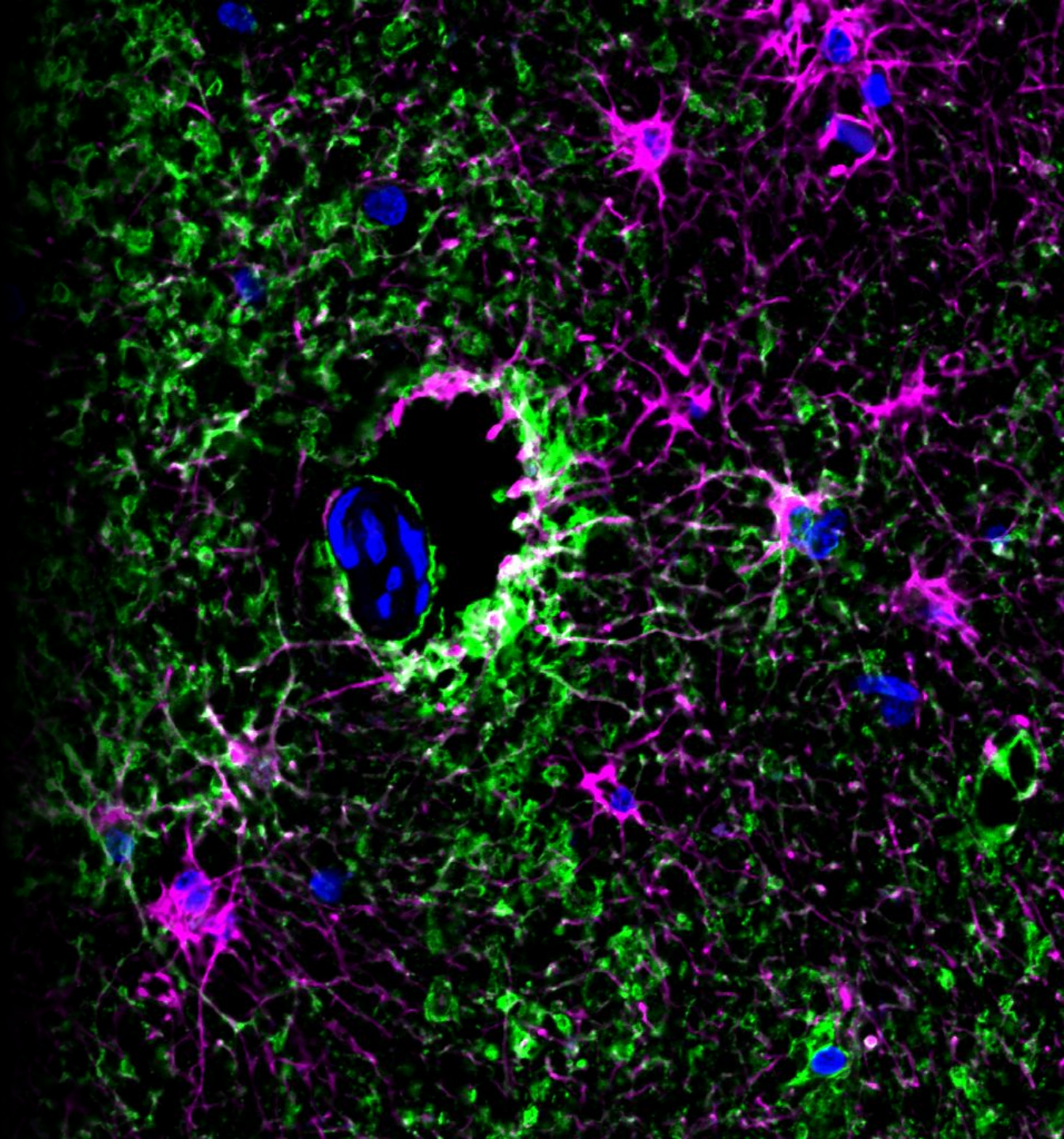


Sleep-wake regulation of amyloid levels in humans

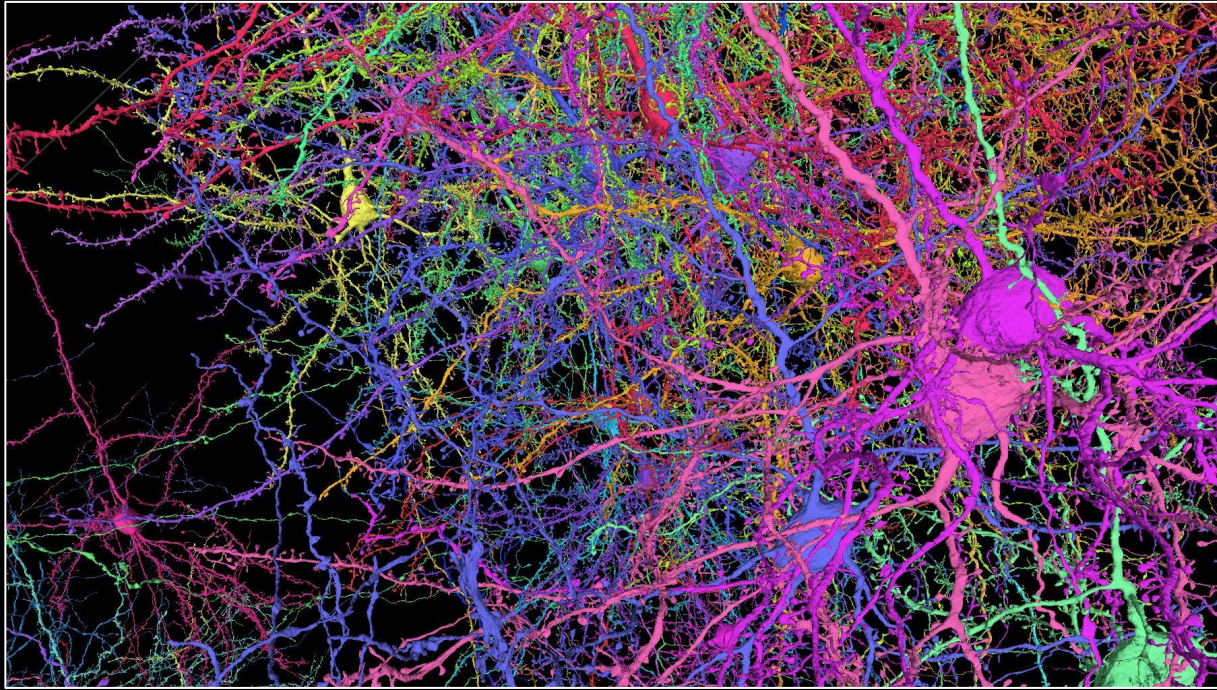


Kang et al. *Science* 2009

Brainwashing.
The good kind



The brain is a high-performance machine

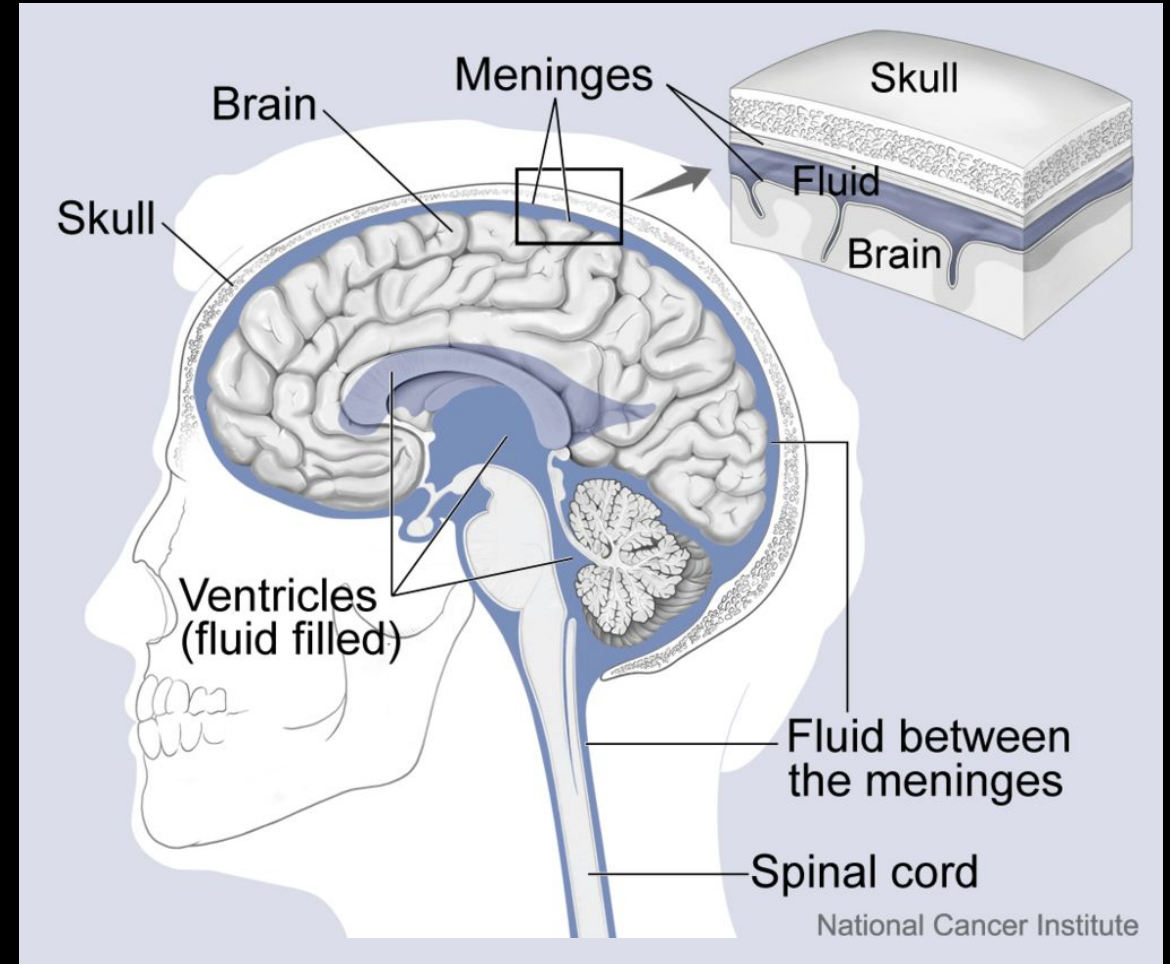


The human brain

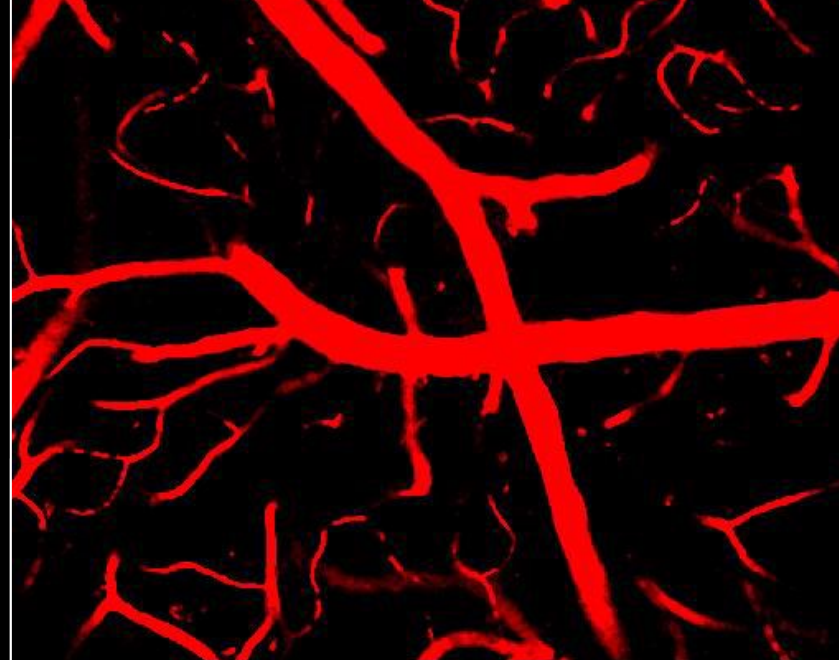
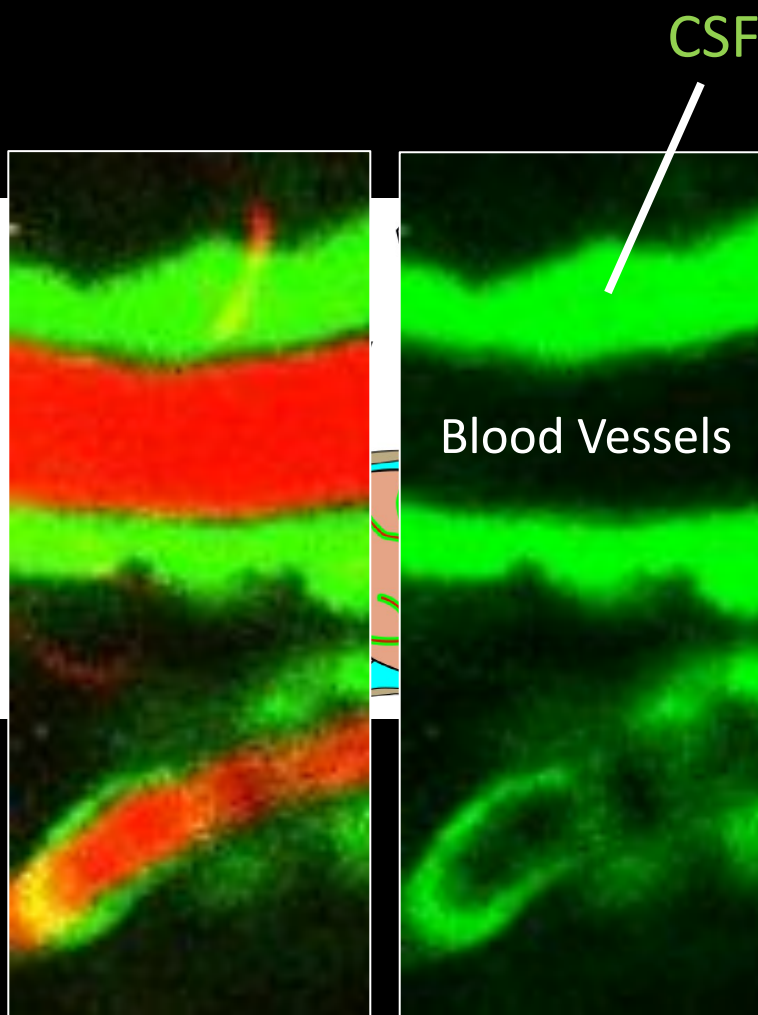
- 86 billion neurons
- 125 trillion synapses
- billions-trillions of action potentials per second

From the Allen Brain Institute

Brain waste clearance

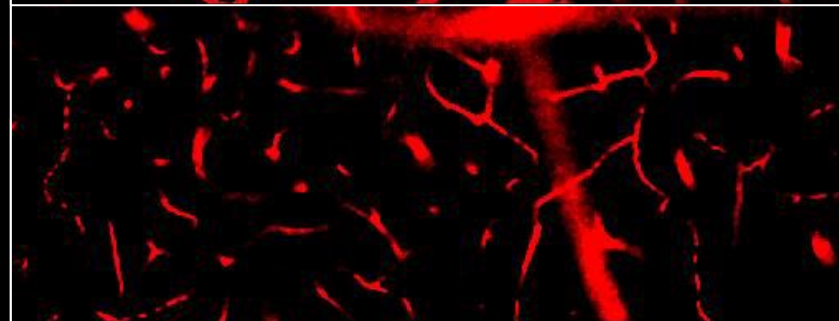


More than a cushion

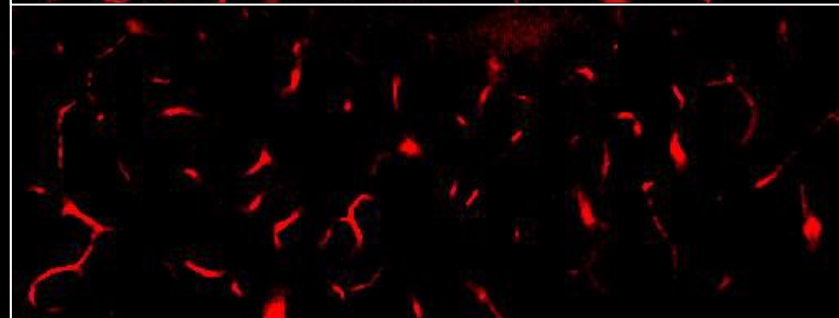


Cortic
al
Surfac
e

60 μ
m

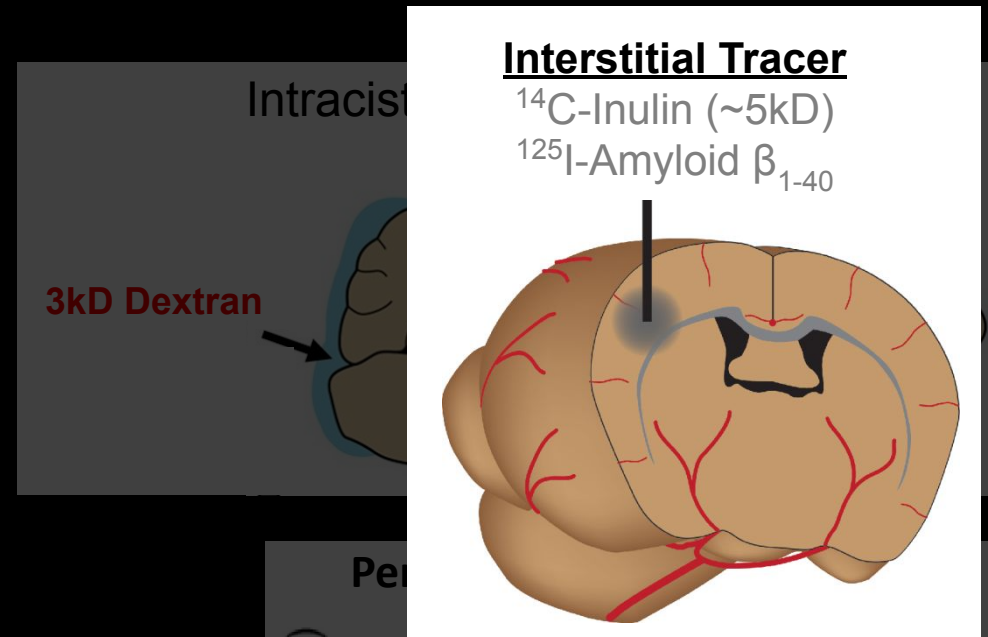
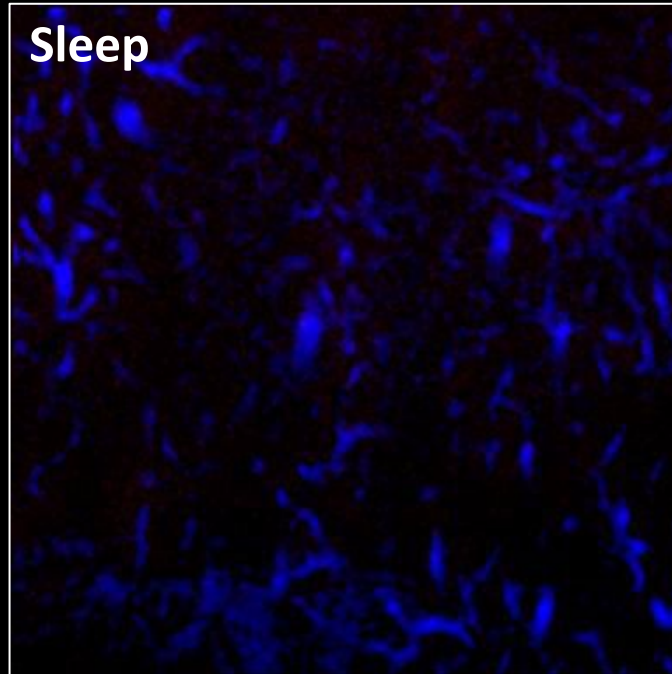
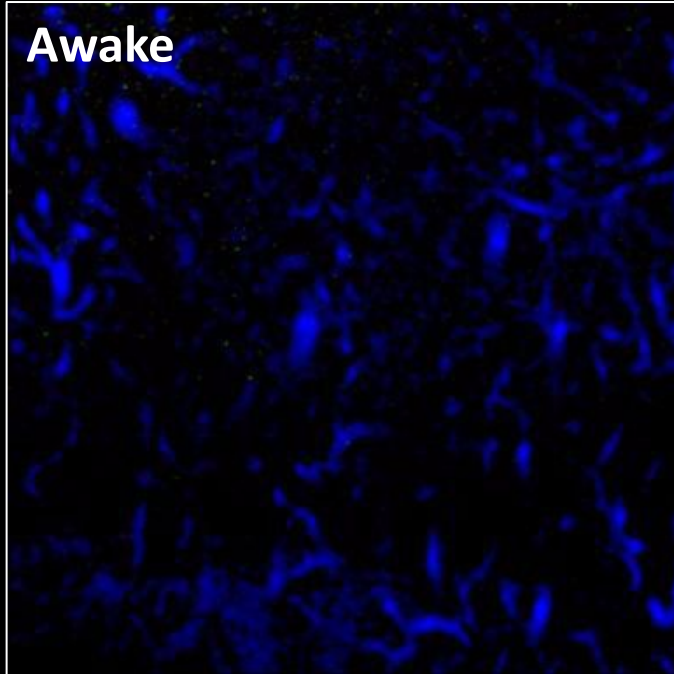


120 μ
m

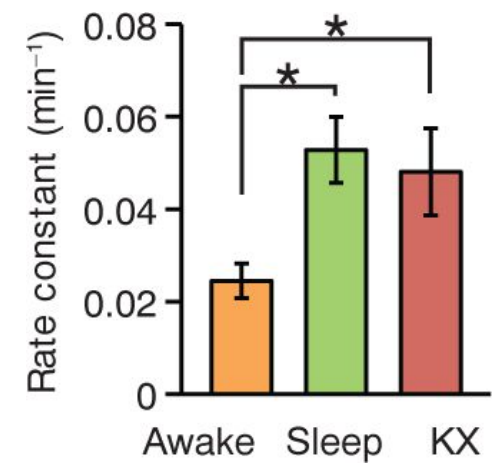
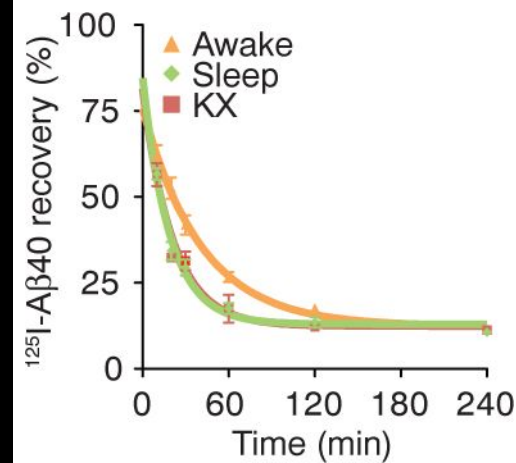


180 μ
m

Perivascular exchange is regulated by sleep state

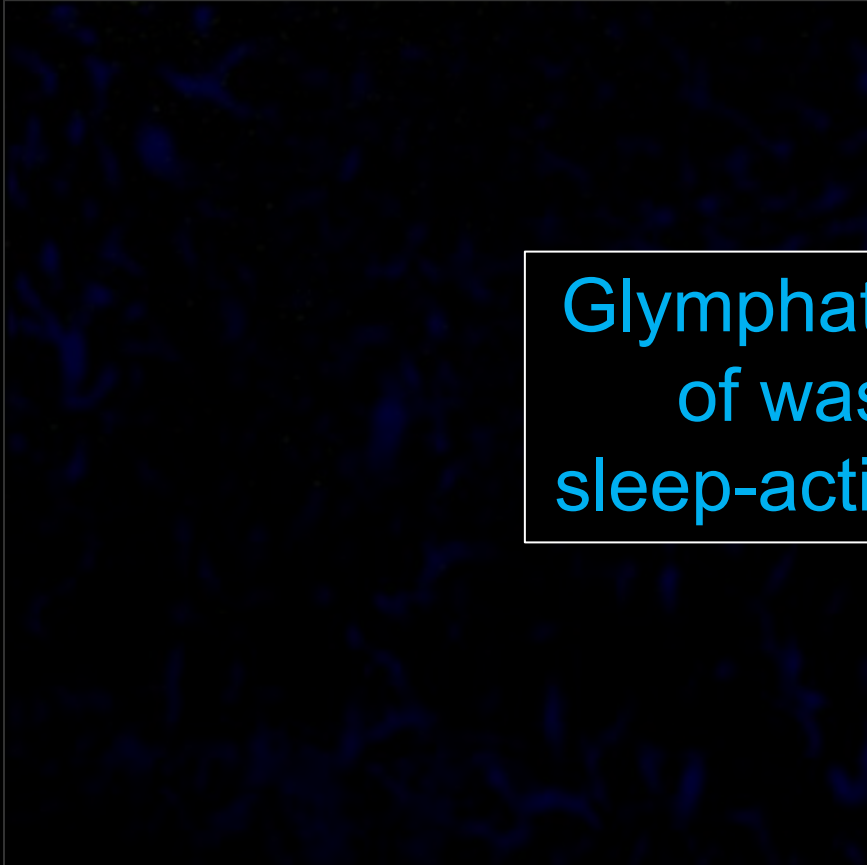


Interstitial ^{125}I -Amyloid β_{1-40} clearance

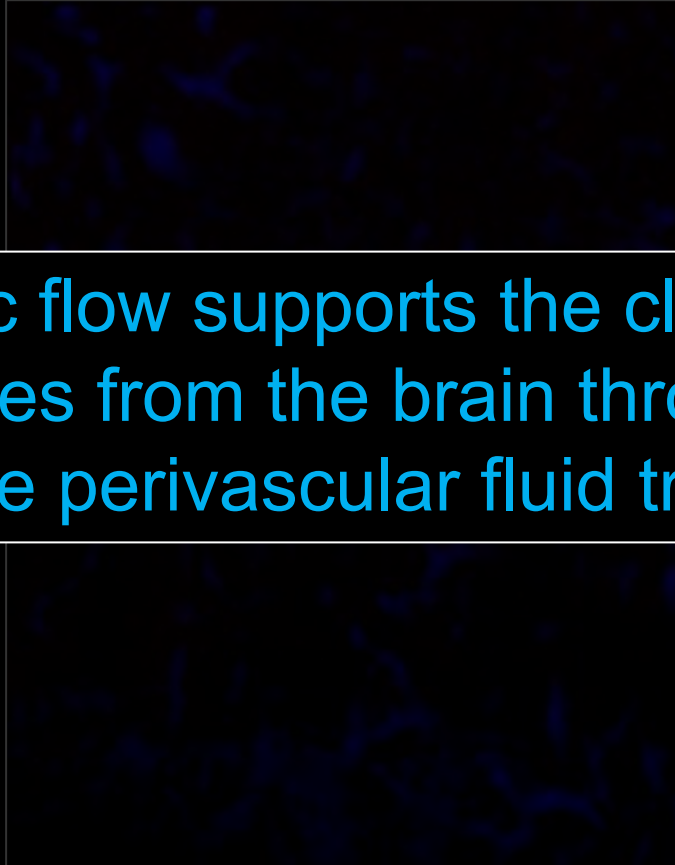


More than a cushion

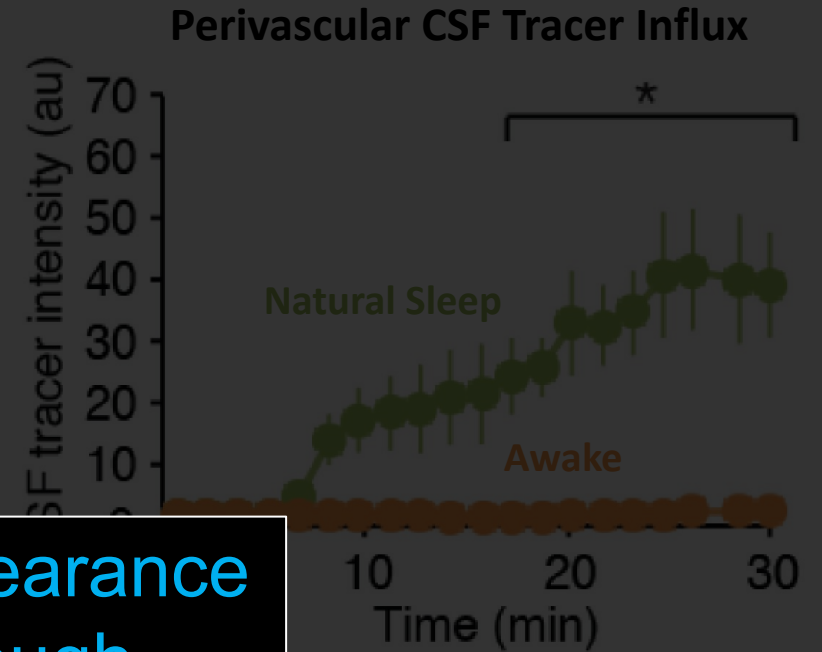
Awake



Sleeping

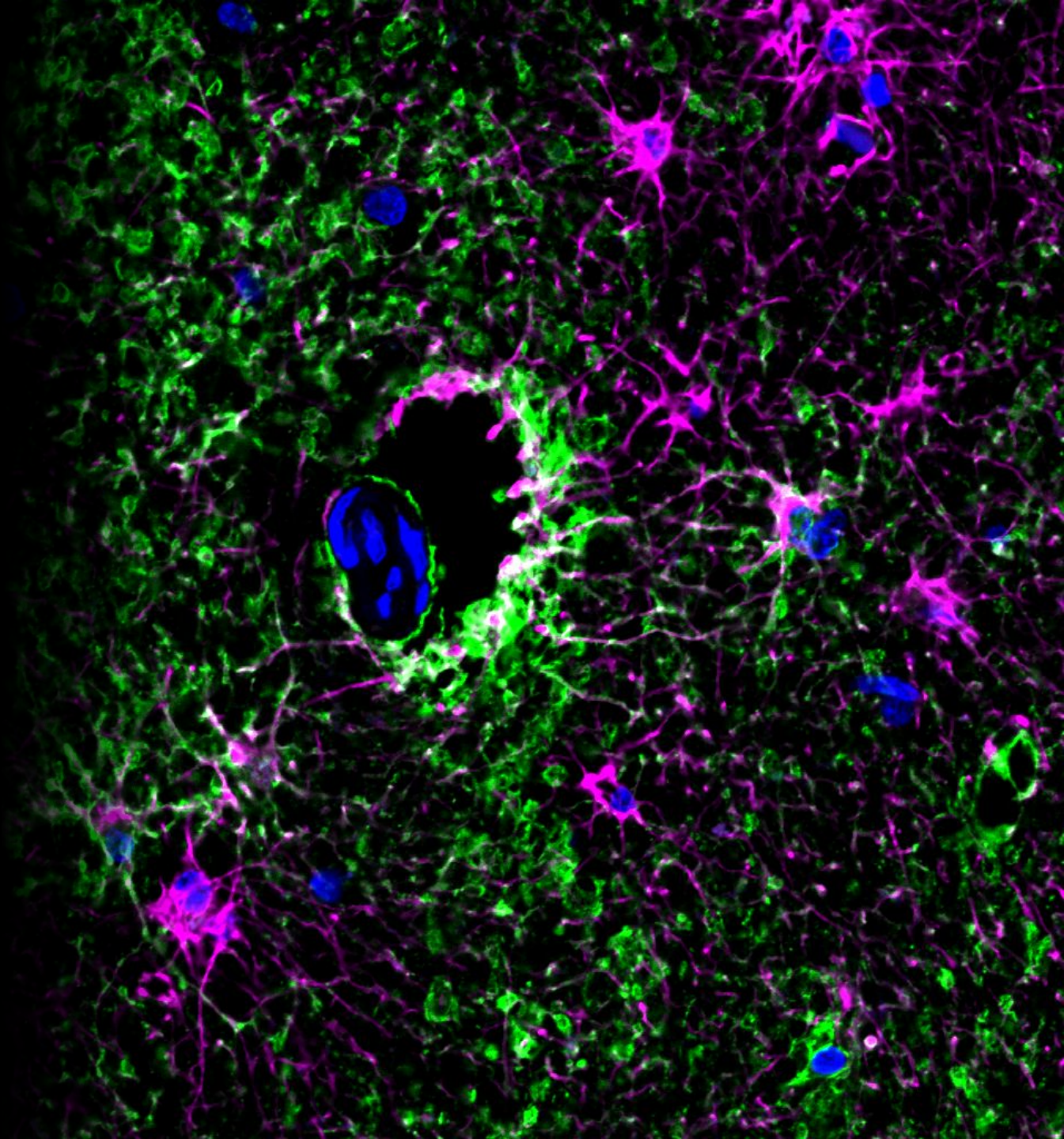


Glymphatic flow supports the clearance of wastes from the brain through sleep-active perivascular fluid transport.

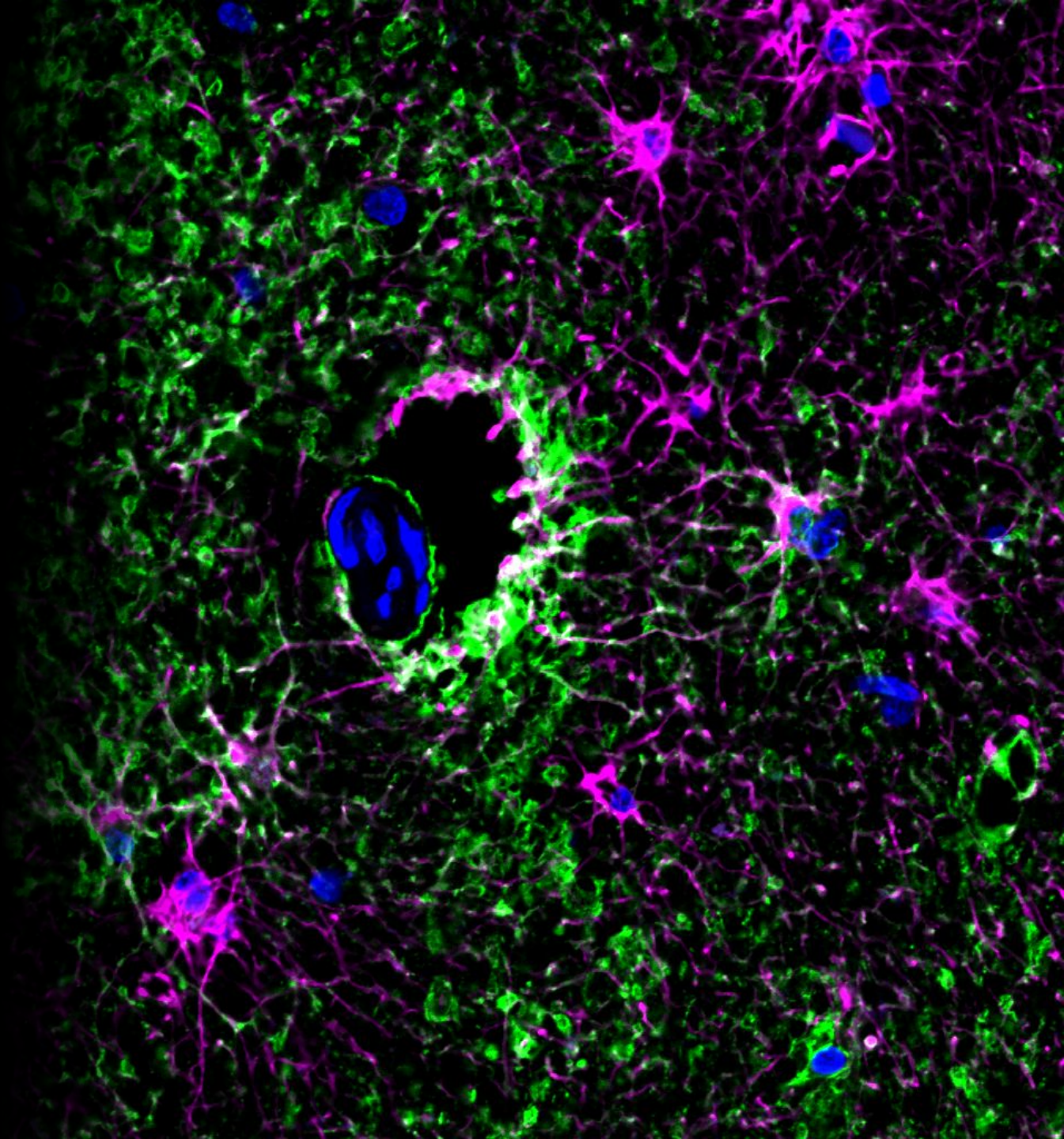


Xie et al. *Science* 2013
Thomas *FBCNS* 2022

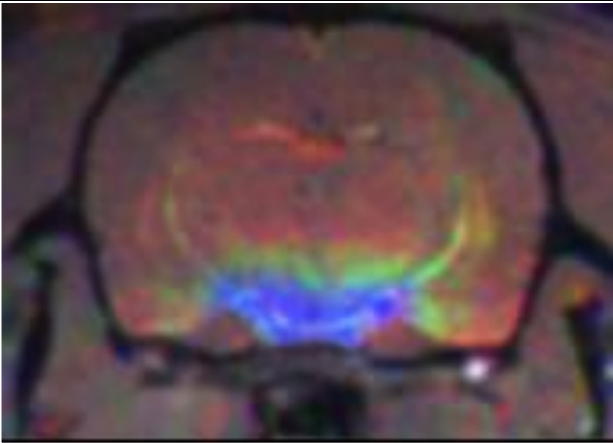
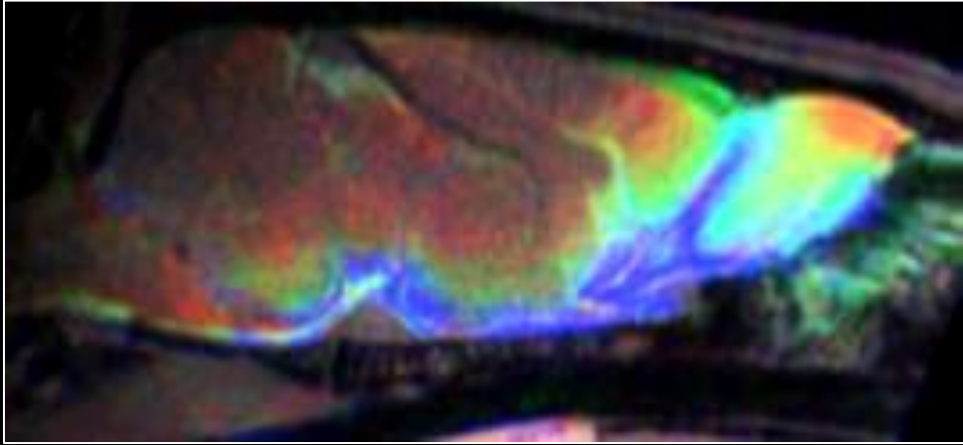
QUESTION 2



More than mice?
Imaging glymphatic function in
the human brain



Imaging glymphatic clearance in the human brain



Roese, Pike, Iliff (unpublished)

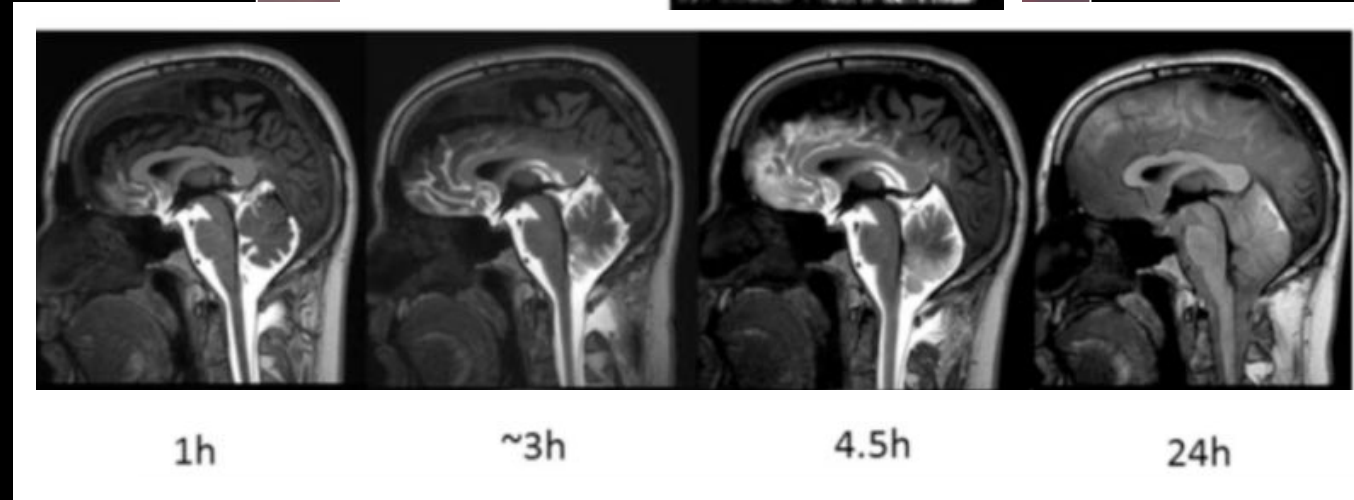
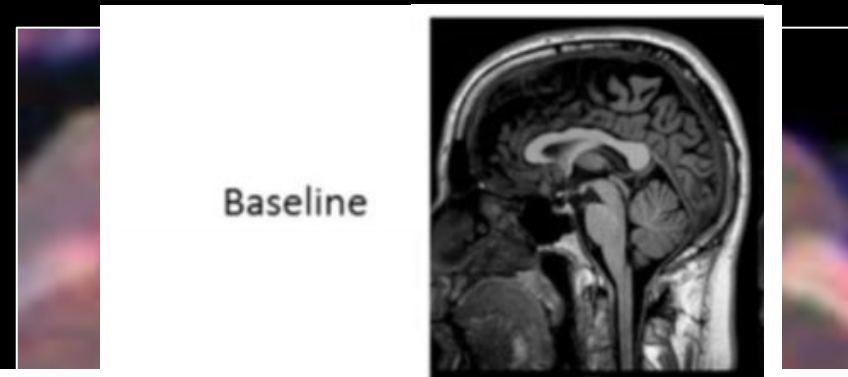
Measuring glymphatic function in rats by MRI after contrast agent injection.

Time after contrast injection:

60 min

120 min

180 min



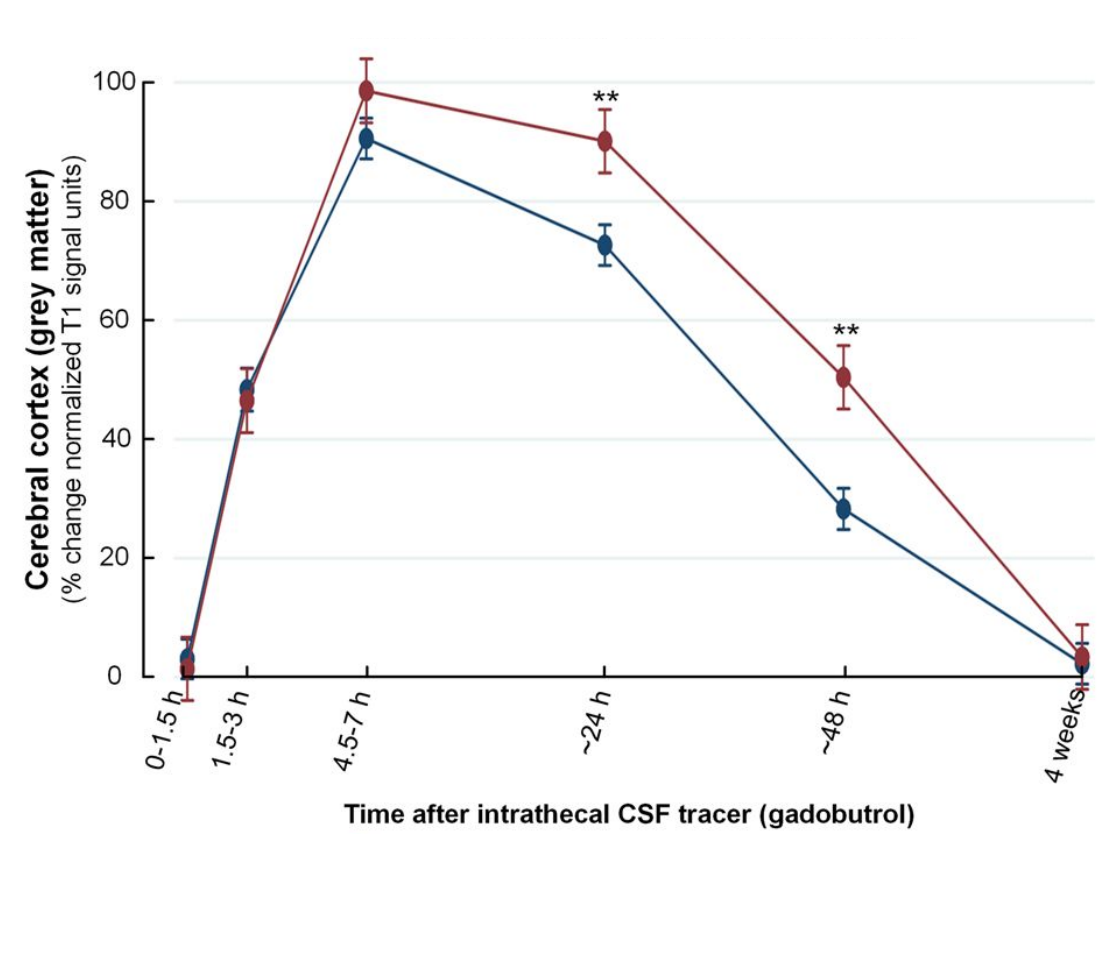
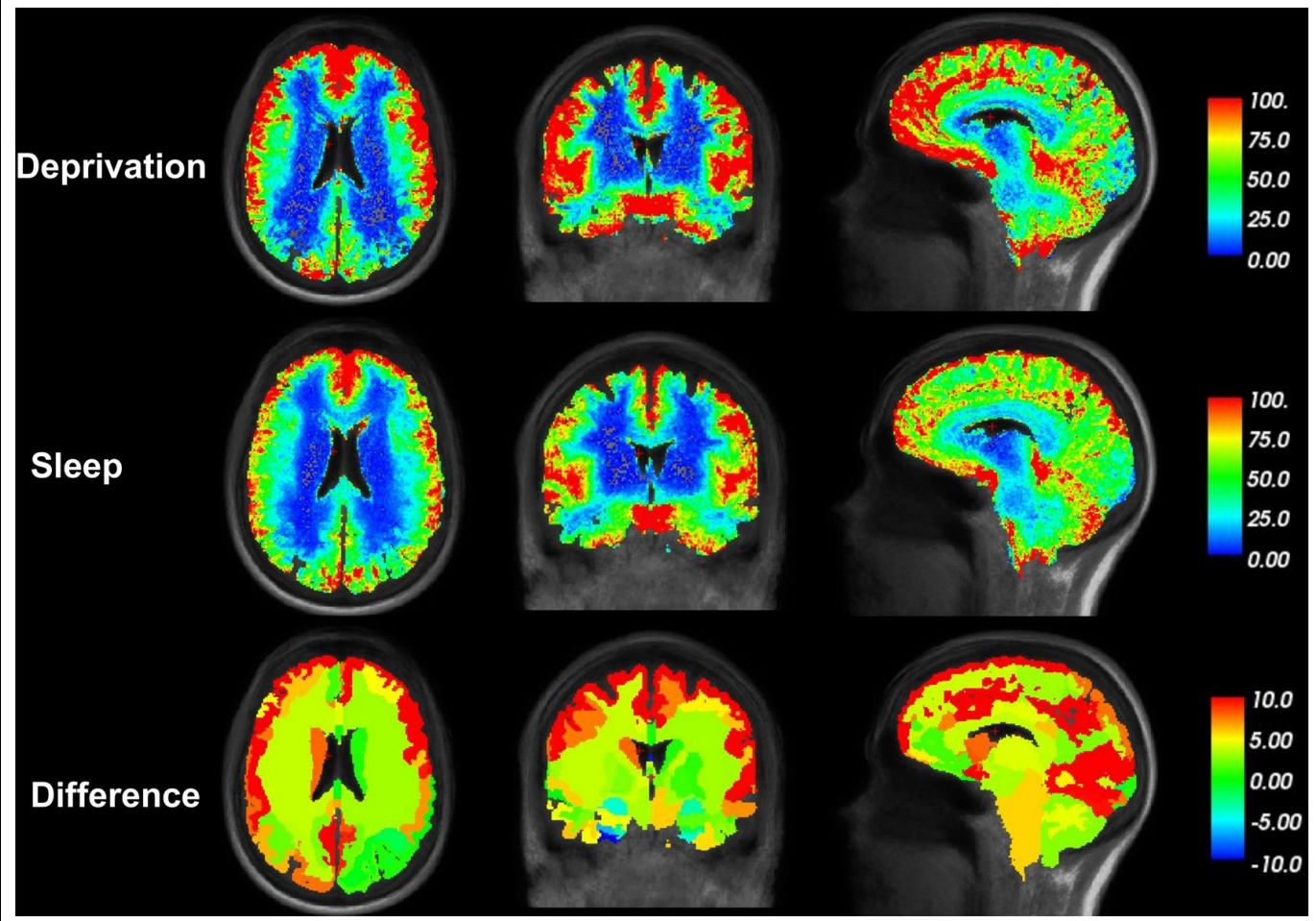
Ringstad et al. *Brain* 2017

Measuring glymphatic function in humans by MRI after contrast agent injection.

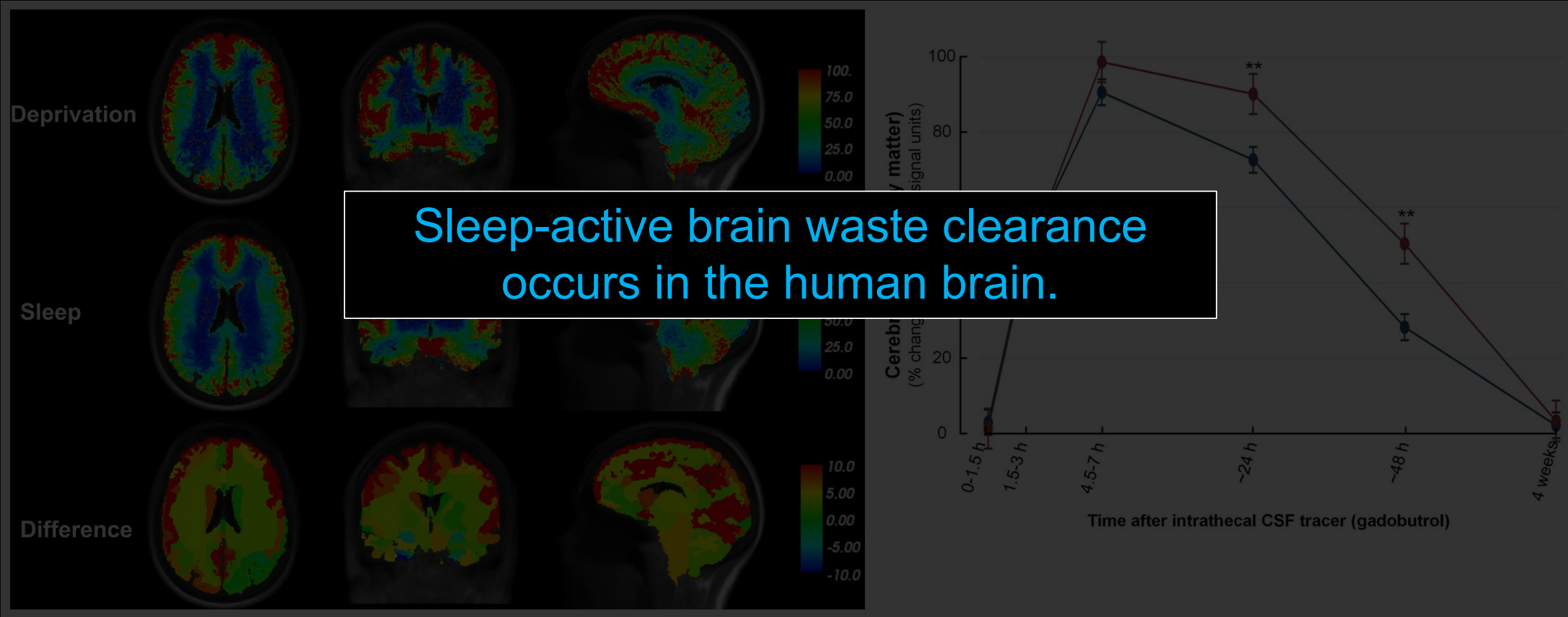
n = 8 reference subjects, 41.1 +/- 13.0 yrs

Scans at t = 0, 1, 3, 4.5 and 24 hrs

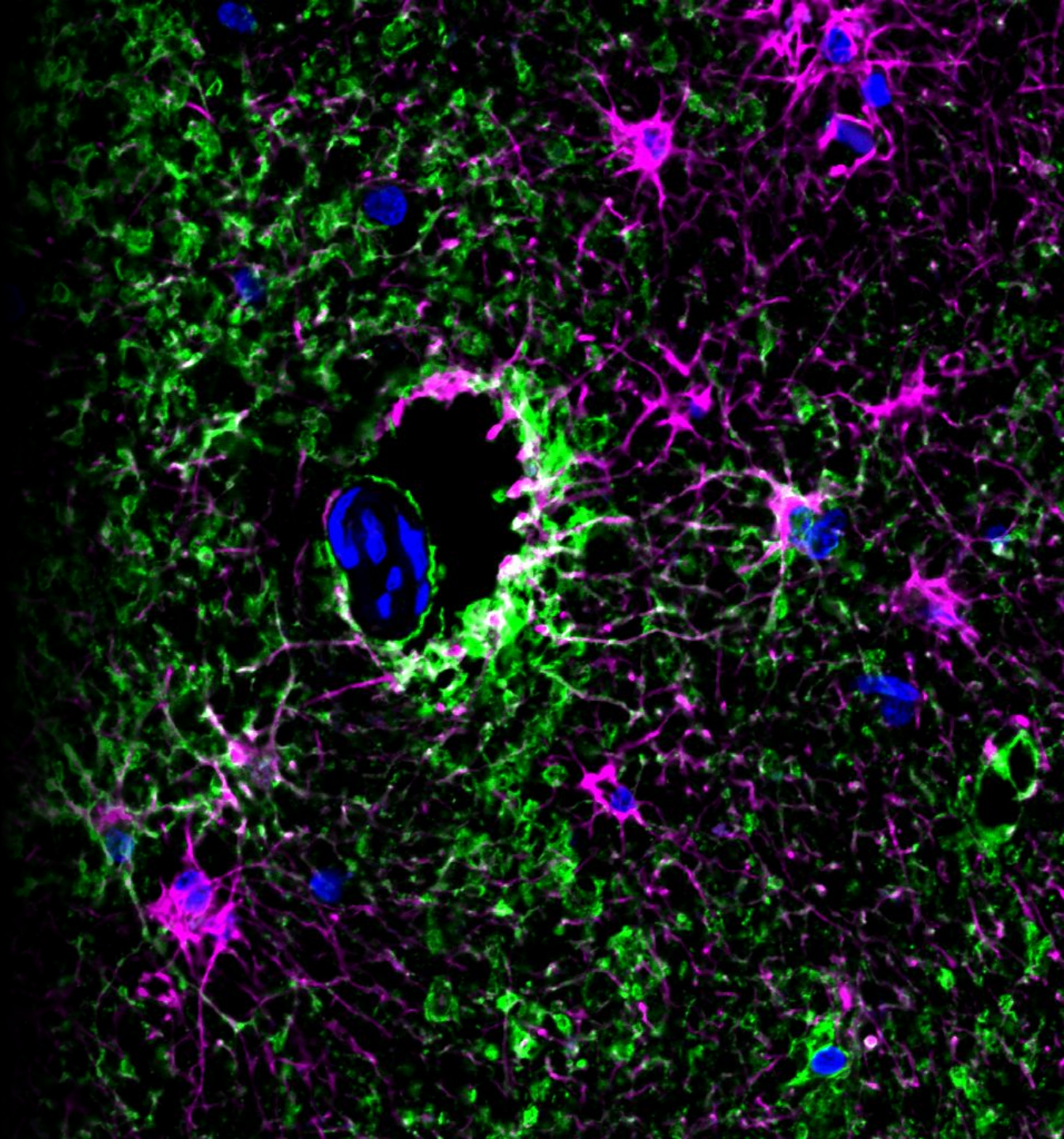
Imaging glymphatic clearance in the human brain



Imaging glymphatic clearance in the human brain

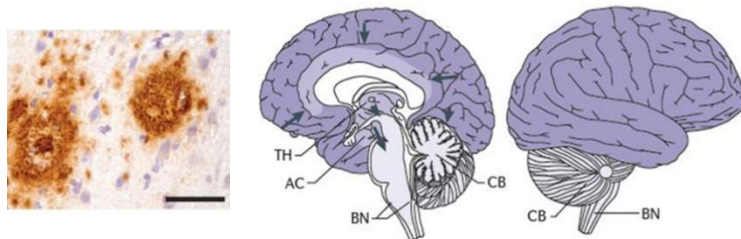


Getting old is a dirty business.
Does slowing brain waste
clearance contribute to
Alzheimer's disease?

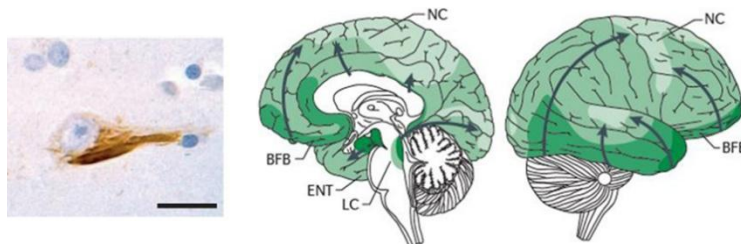


Slowed brain waste clearance promotes the development of Alzheimer's-related pathology

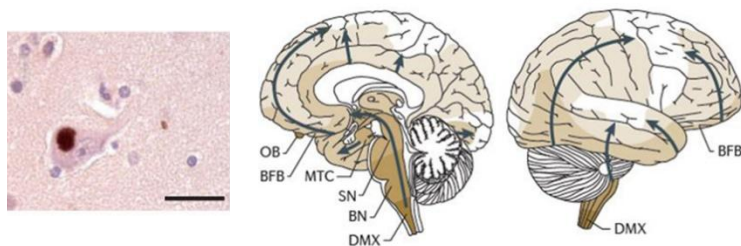
Alzheimer's: amyloid β



Alzheimer's: tau



Parkinson's and LBD: α -synuclein



Adapted from Jucker and Walker *Nature* 2013

In human populations, neurodegenerative conditions are...

...associated with aggregation of $A\beta$, tau, α synuclein.

In animal models, glymphatic function...

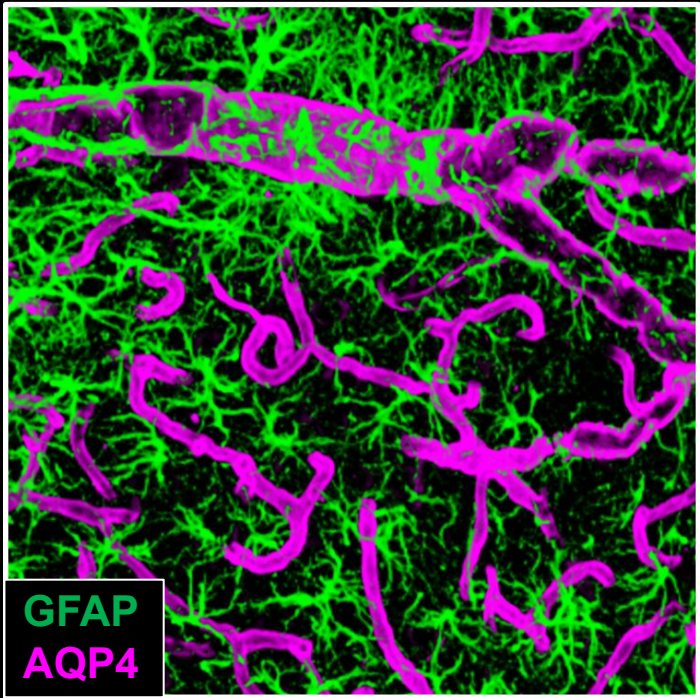
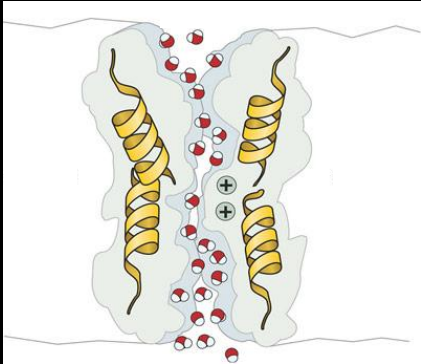
...contributes to the clearance of soluble $A\beta$, tau, α synuclein.

In animal models, impairment of glymphatic function...

...promotes $A\beta$ pathology.
...promotes tau pathology.
...promotes α synuclein pathology.



Aquaporin-4 (AQP4) supports perivascular glymphatic exchange and amyloid β clearance

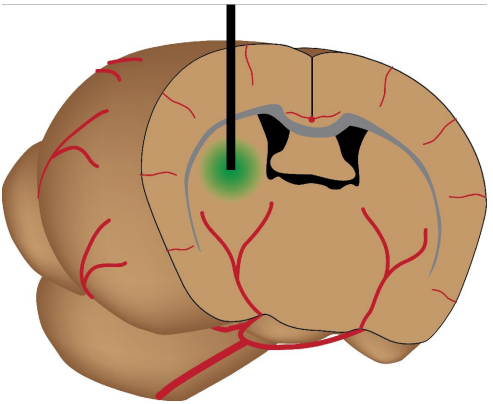


GFAP
AQP4

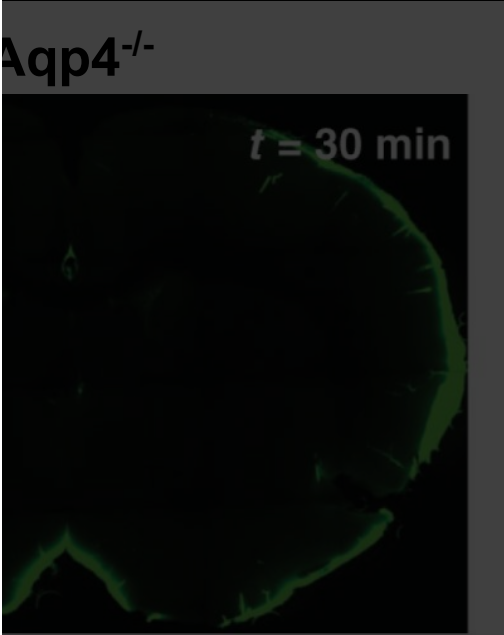
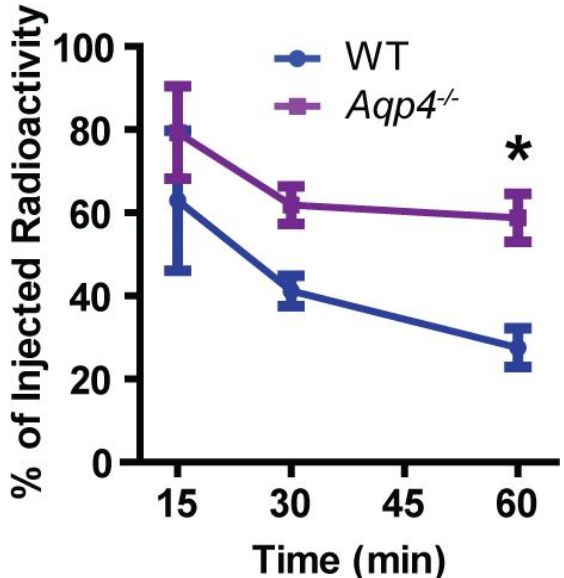
Adapted from Simard et al. *J Neurosci* 2003

Interstitial Tracer

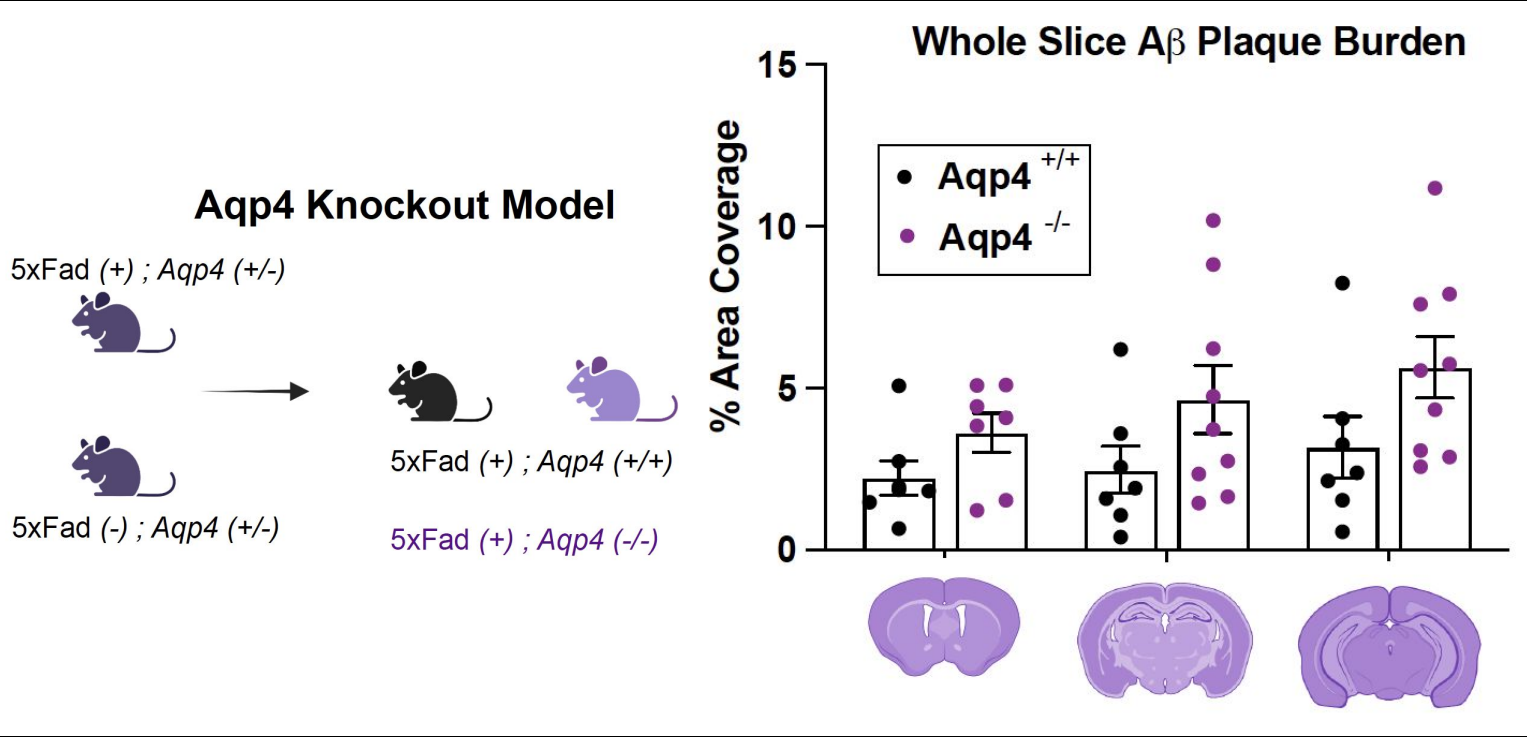
^3H -Mannitol
 ^{125}I -Amyloid β_{1-40}



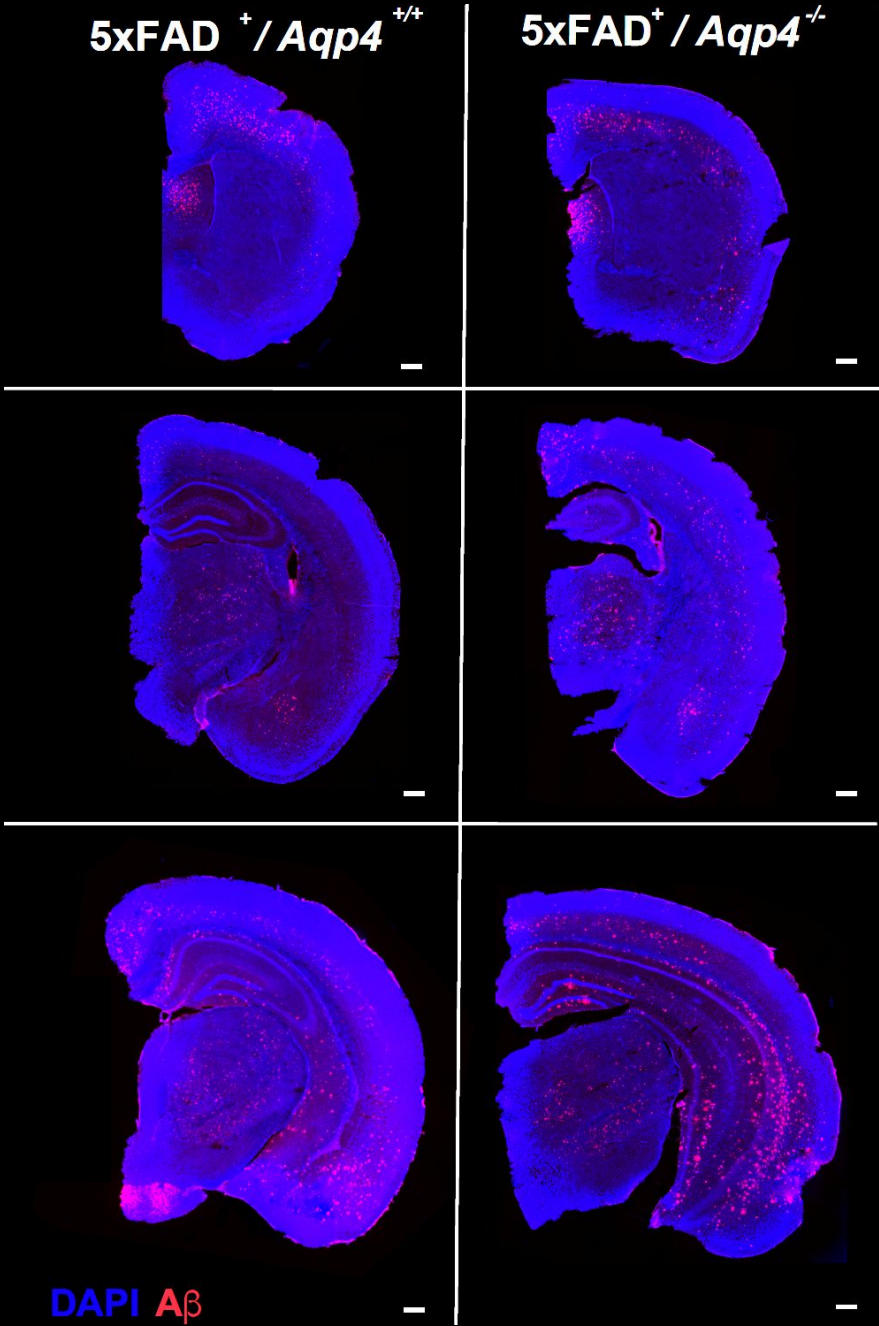
^{125}I -Amyloid β_{1-40} Clearance



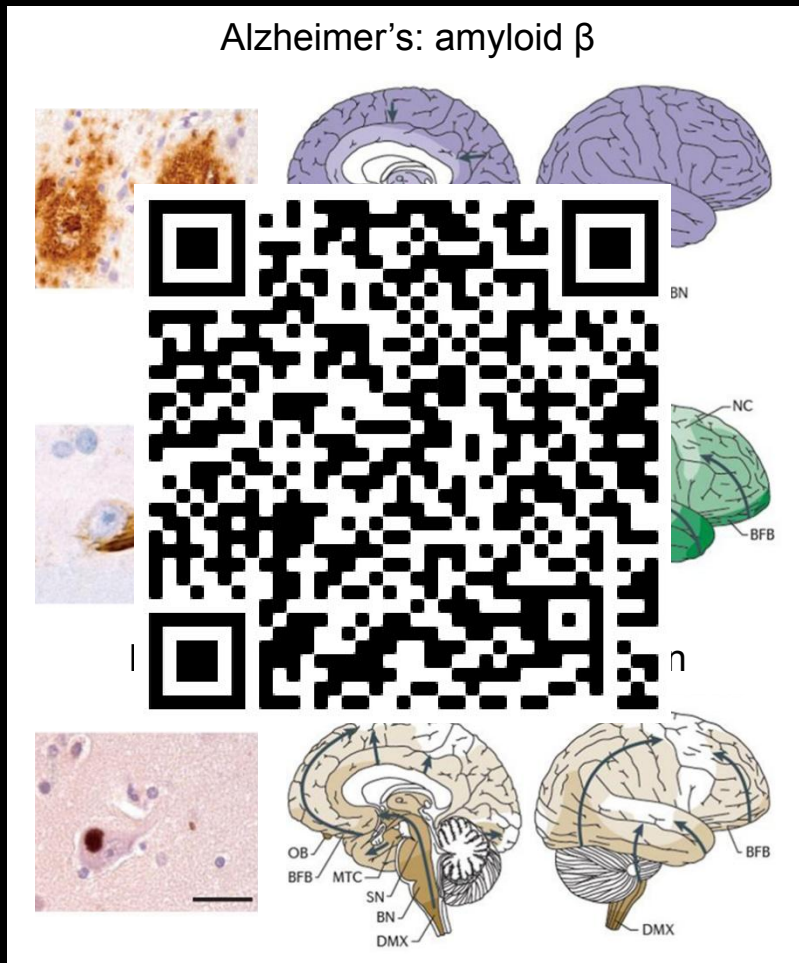
Aqp4 gene deletion exacerbates Aβ pathology in mouse models of Alzheimer's



Pedersen et al. *Neurobiol Dis* 2023



Non-genetic risk factors of Alzheimer's disease impair glymphatic brain waste clearance



Adapted from Jucker and Walker *Nature* 2013

Neurodegenerative conditions are...

...associated with protein mis-aggregation.

...influenced by non-genetic risk factors:

- Aging
- Cerebrovascular disease
- Traumatic brain injury
- Chronic sleep disruption

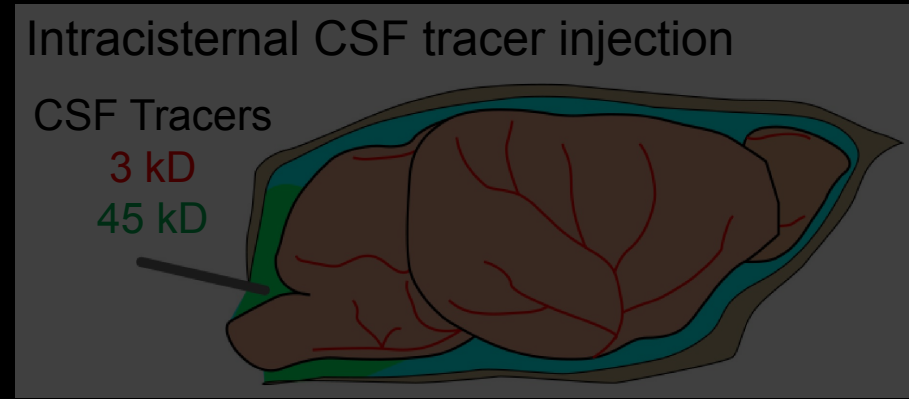
Glymphatic dysfunction...

...promotes amyloid β , tau and synuclein pathology (in animal models).

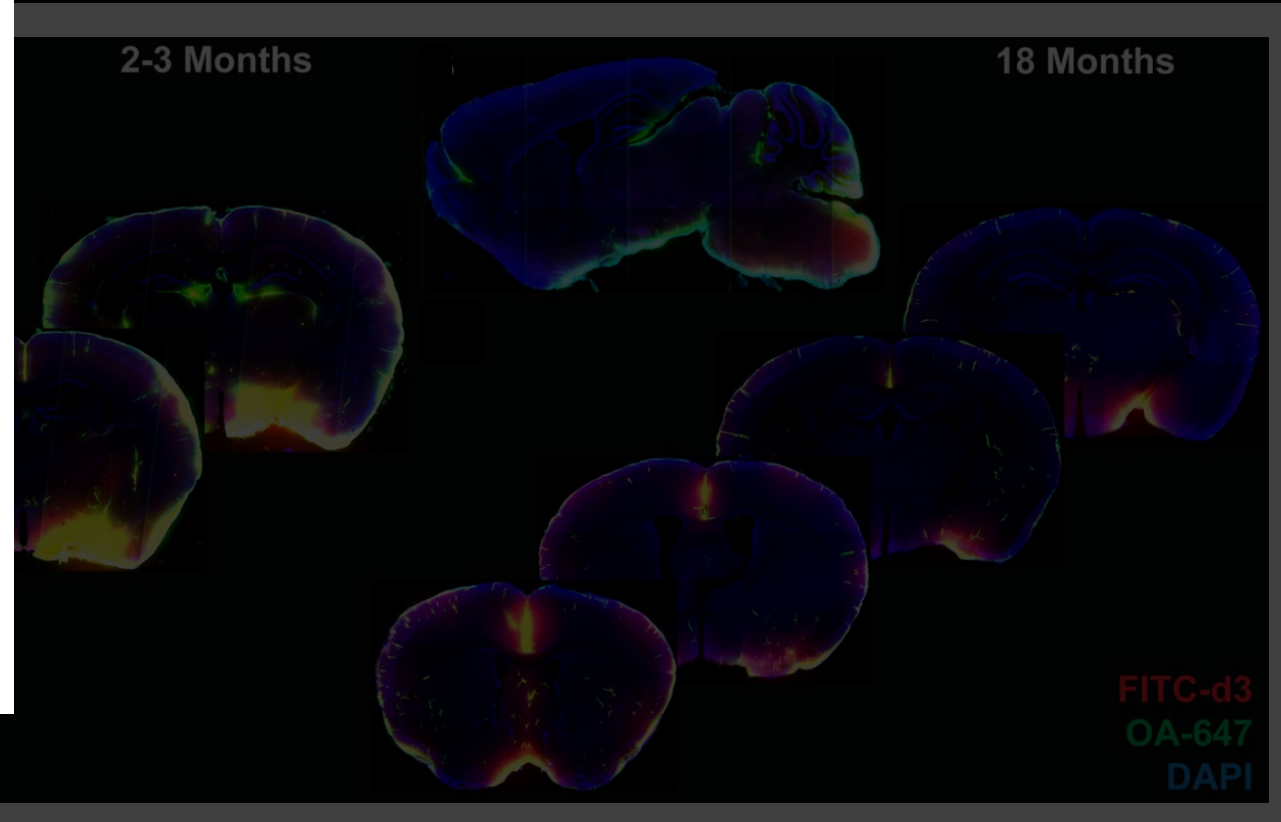
...is impaired in animal models of:

- Aging
- Cerebrovascular injury
- Traumatic brain injury
- Acute sleep deprivation

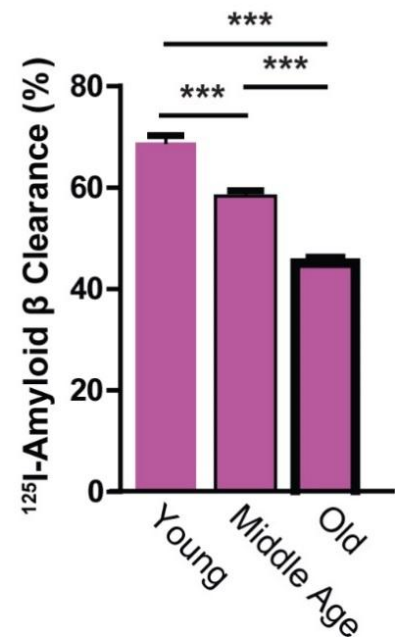
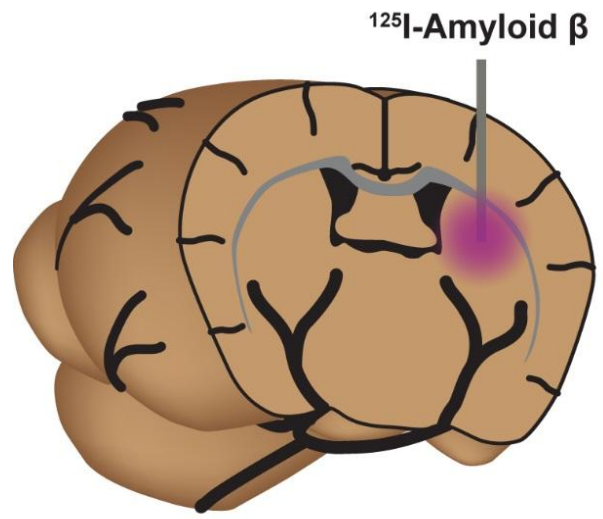
Glymphatic function is impaired in the aging brain



t = 30 min post-injection



Effect of aging on A β clearance



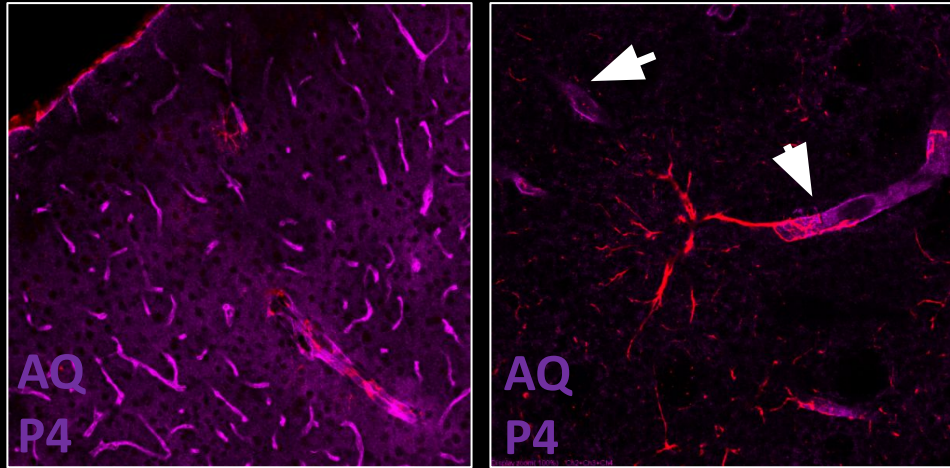
Kress et al. *Annals Neurol* 2014

Kress et al. *Annals Neurol* 2014

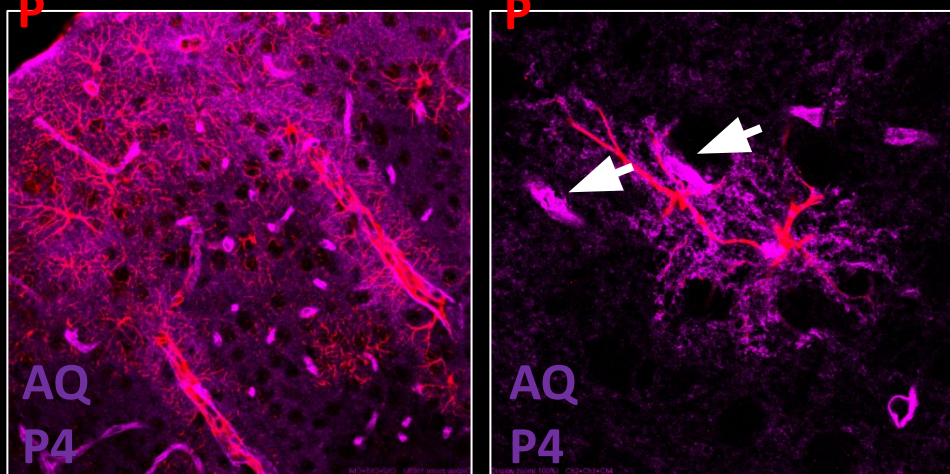
Reduced perivascular AQP4 localization in the aging brain

Mouse Model of Aging

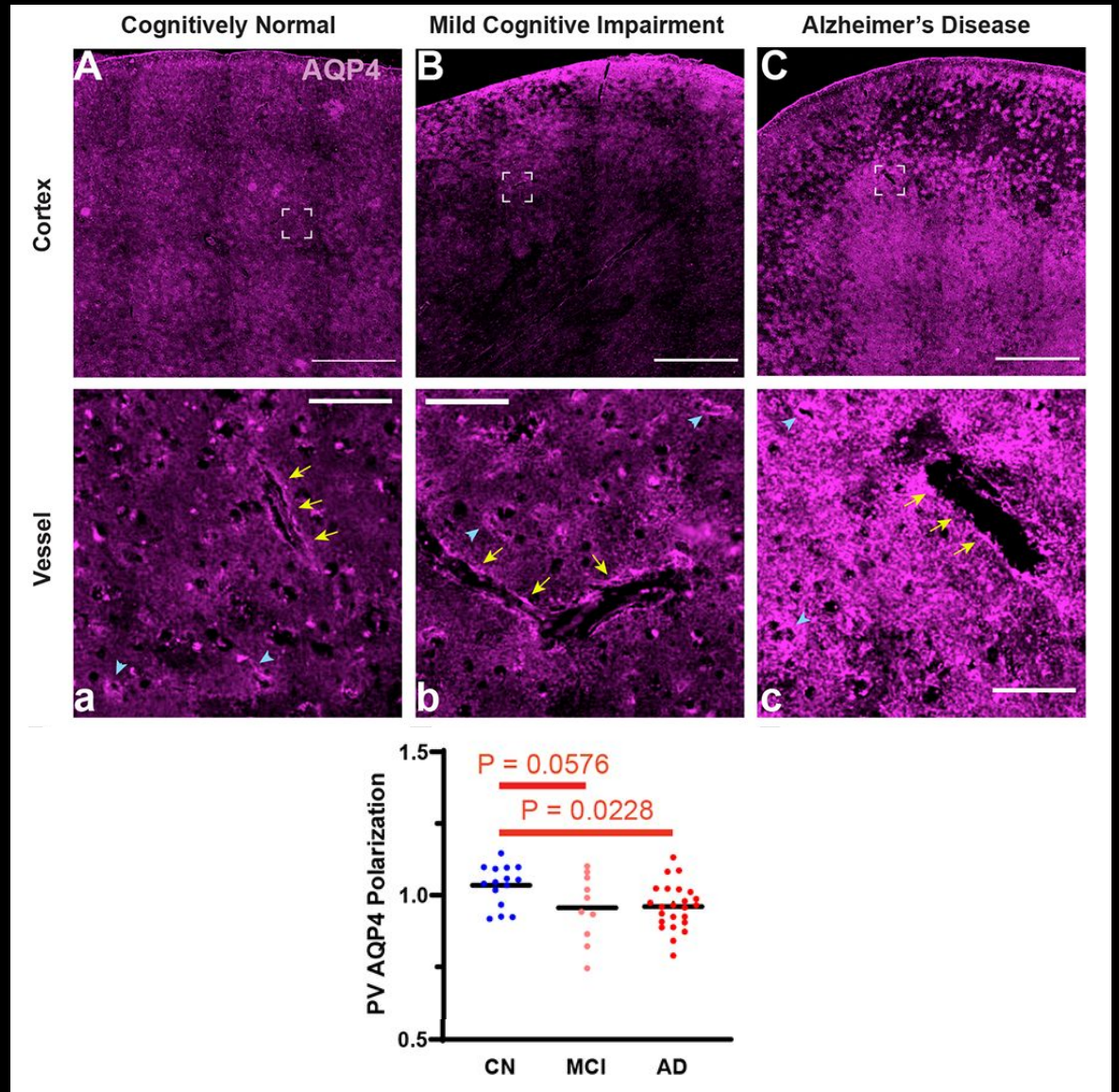
Young (2-3 months)



Aged (18 months)

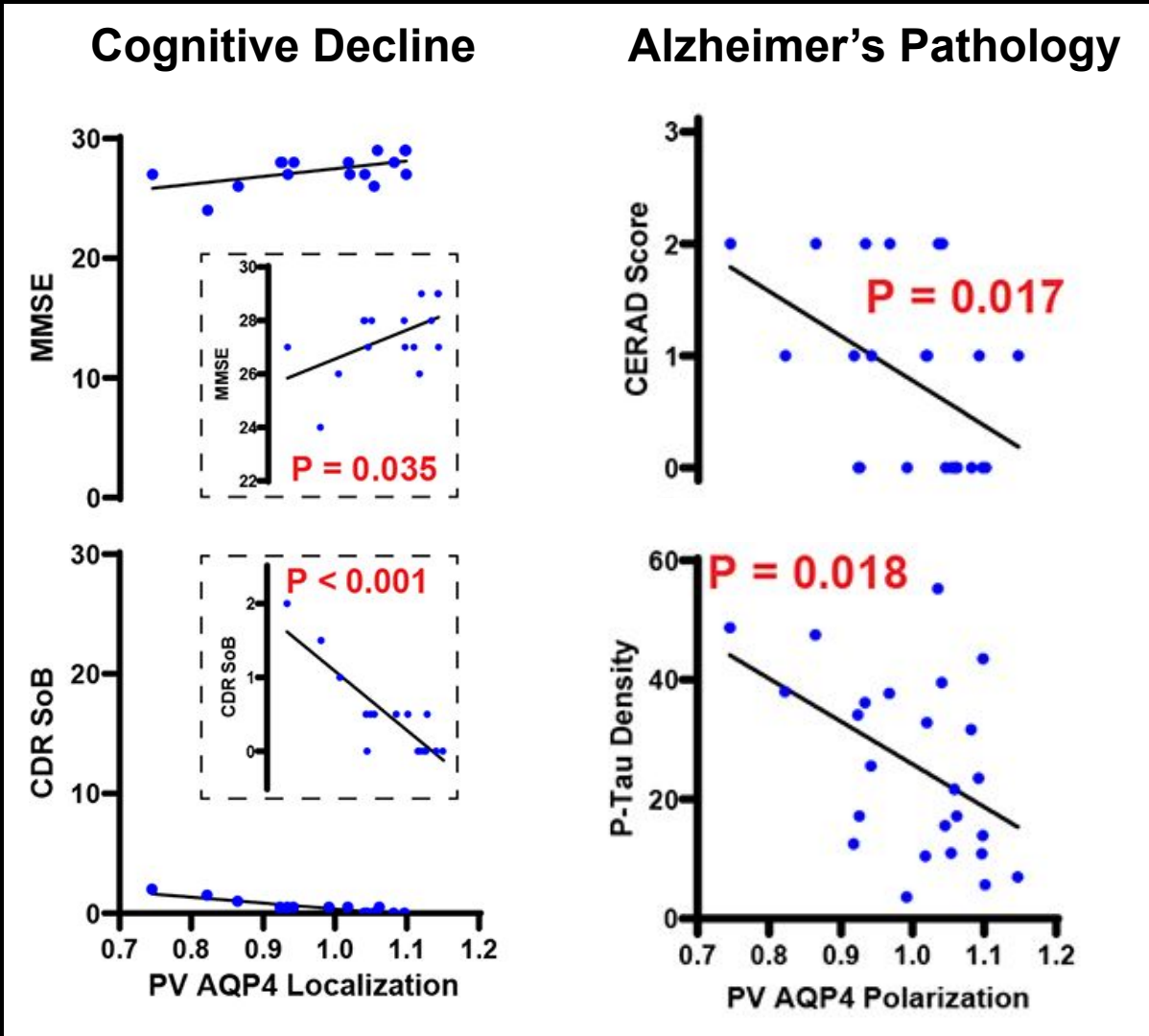


Kress et al. *Annals Neurol* 2014

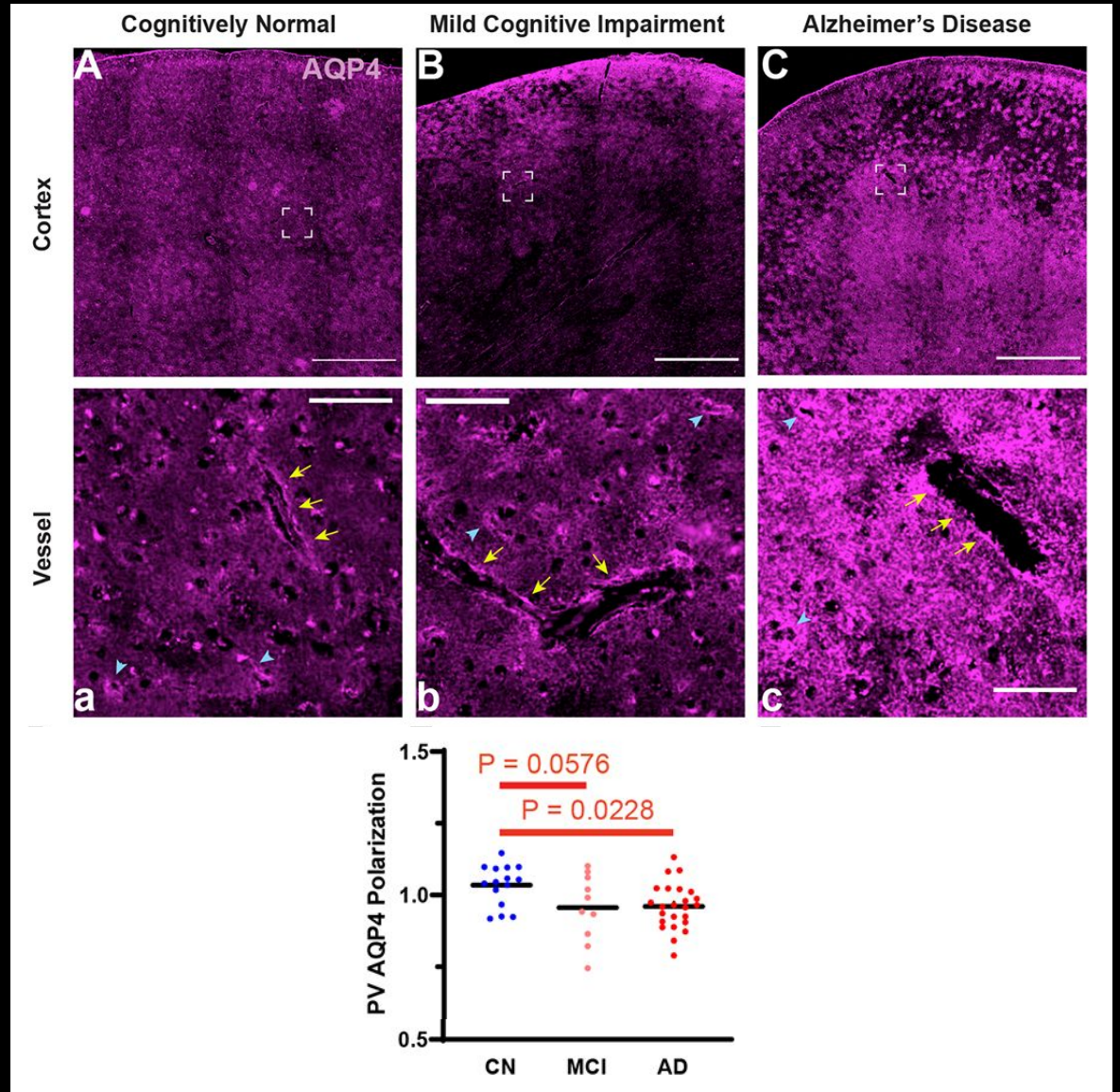


Simon et al. *Alzheimer's Res Ther* 2022

Reduced perivascular AQP4 localization in the aging brain



*In cognitively-intact and MCI individuals



Conclusions

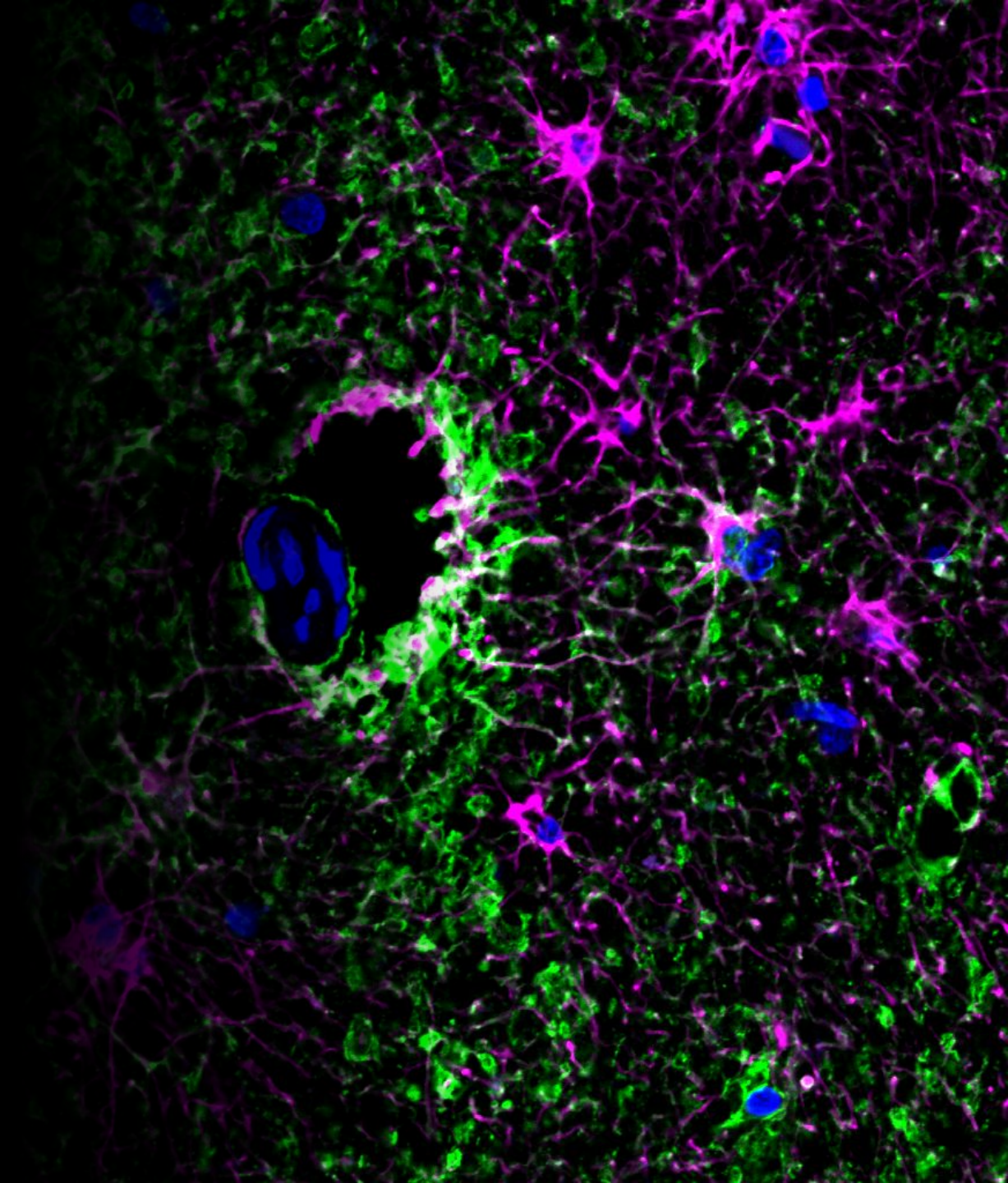
Perivascular glymphatic exchange supports the sleep-active clearance of aggregating proteins including A β , tau, and α synuclein in rodent models.

Sleep-active glymphatic exchange occurs in the human brain.

In animal models, glymphatic impairment is sufficient to promote the development of A β , tau, and α synuclein pathology.

Glymphatic function is impaired in animal models corresponding to non-genetic Alzheimer's risk factors including aging, CV disease, sleep disruption, and TBI.

Initial clinical neuroimaging, histopathological, genetic and transcriptomic studies provide corollary data linking glymphatic dysfunction to Alzheimer's pathology and progression in human populations.



Conclusions

Perivascular glymphatic exchange supports the sleep-active clearance of aggregating proteins including A β , tau, and α synuclein in rodent models.

Sleep-active glymphatic clearance is observed in the human brain.

In animal models, sleep deprivation is sufficient to promote the accumulation of A β and α synuclein.

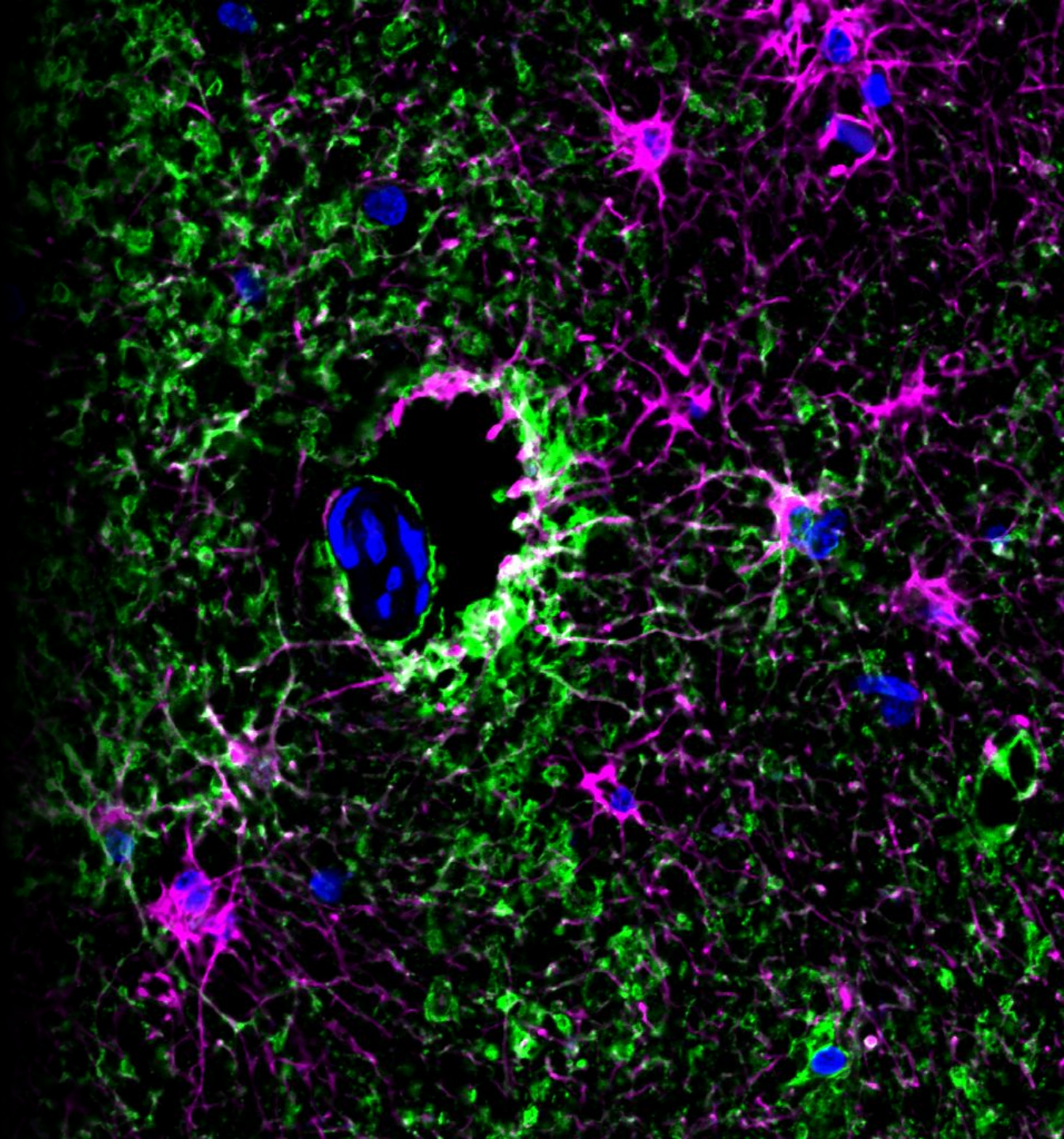
Glymphatic function is regulated by corresponding circadian and sleep factors including melatonin, sleep disruption, and sleep deprivation.

Initial clinical neuroimaging, histopathological, genetic and transcriptomic studies provide corollary data linking glymphatic dysfunction to Alzheimer's pathology and progression in human populations.

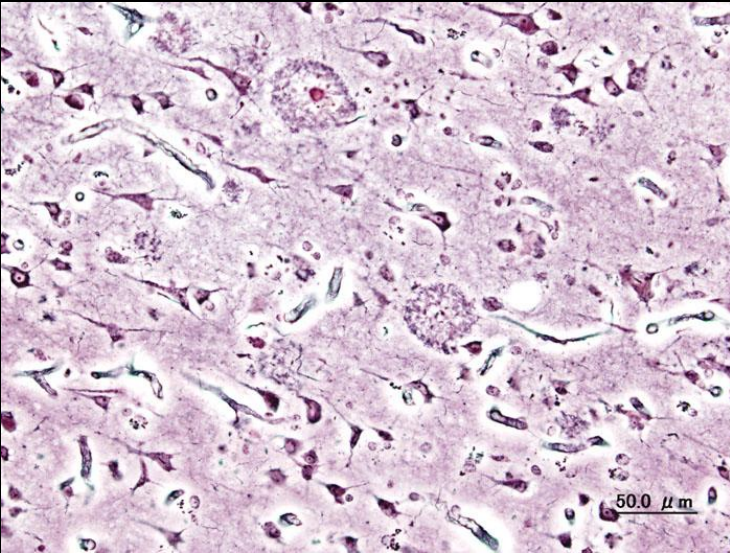
Work over the past 12 years suggests that impairment of brain waste clearance may contribute to the development of Alzheimer's disease and other dementing disorders.

However, a clear causal role has not yet been demonstrated.

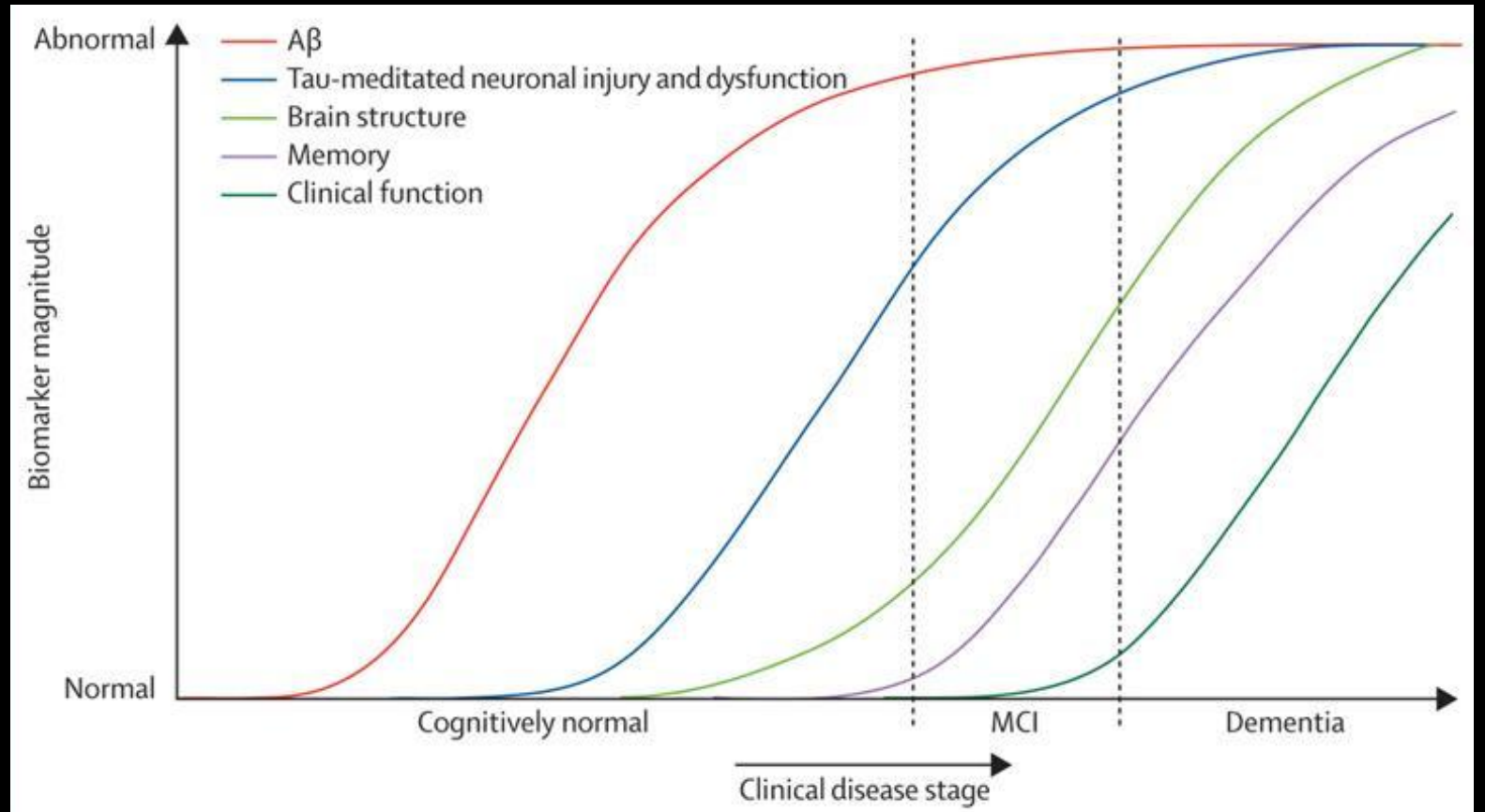
QUESTION 3



Alzheimer's disease pathology:
Amyloid plaques
Neurofibrillary tangles

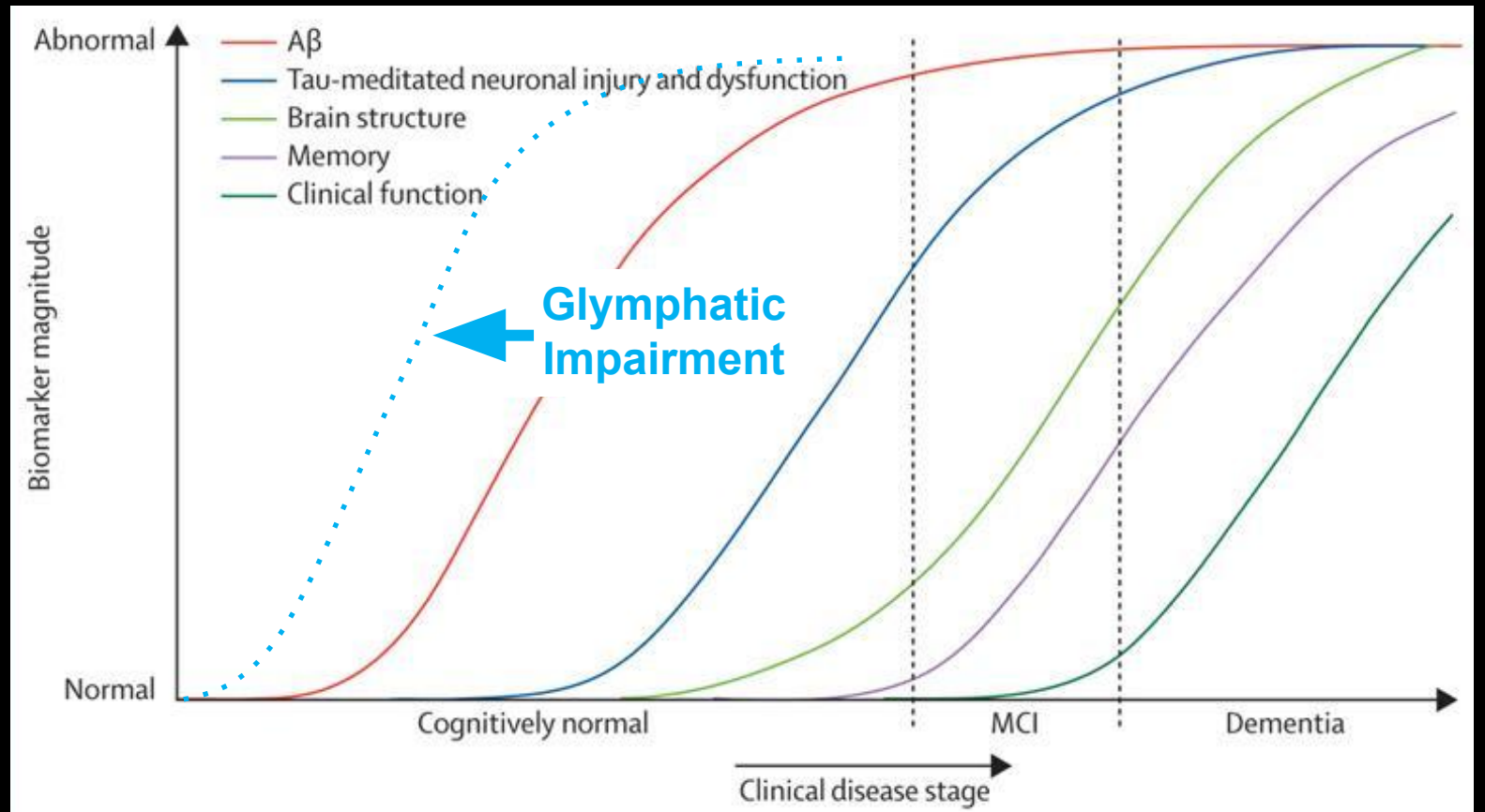


Sequential progression of Alzheimer's pathology and cognitive/functional impairment



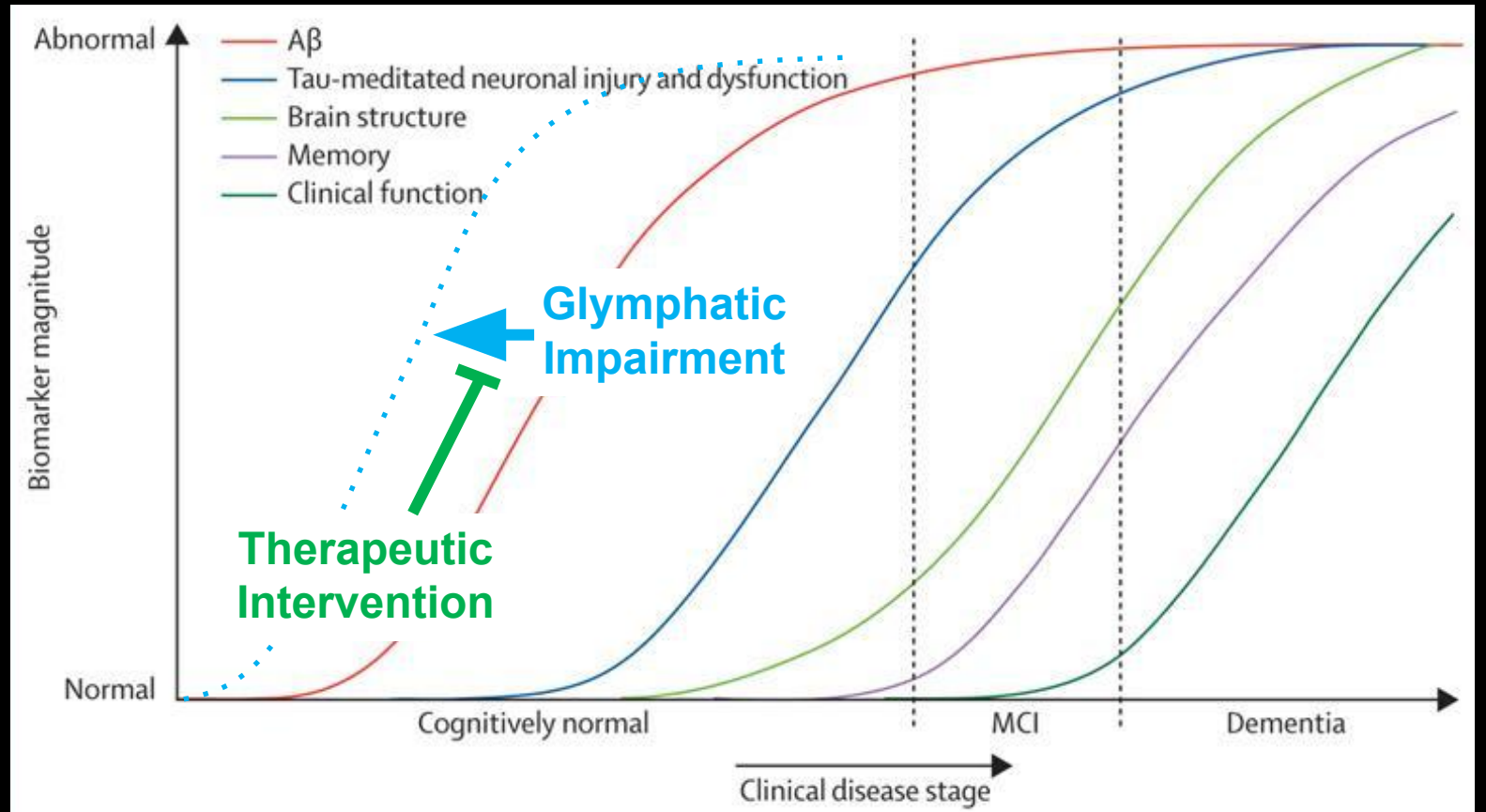
Sequential progression of Alzheimer's pathology and cognitive/functional impairment

Detection of glymphatic impairment may enable the identification of patients at risk for the development of neurodegenerative disease during the long pre-clinical phase of disease.



Sequential progression of Alzheimer's pathology and cognitive/functional impairment

Within these individuals, targeting glymphatic function therapeutically may enable primary prevention of these conditions.



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