Stony Brook Medicine

The Glymphatic System, Sleep & other states of unconsciousness

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Disclosures

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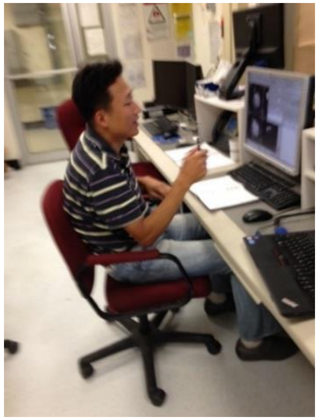
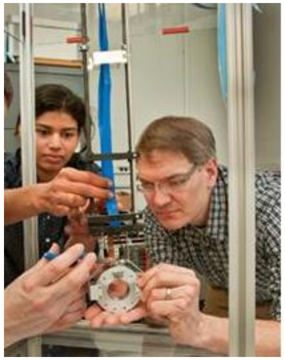
- Dinko Franceschi, MD (Stony Brook Medicine)
- Jean Logan, PhD (NYU)
- Vadim Ratner, PhD (Stony Brook Medicine)
- Allan Tannenbaum (Stony Brook Medicine)
- Mark Schweitzer, MD (Stony Brook Medicine)
- John Danias, MD, PhD (SUNY-Downstate, NY)

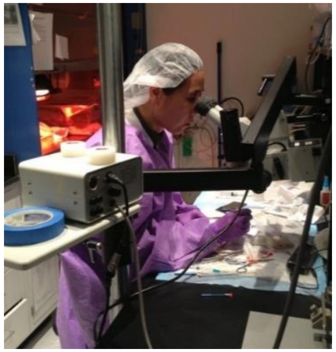


Dr. Hedok Lee

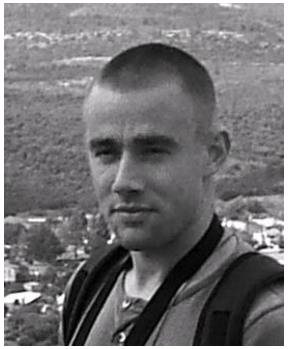
Dr. Maiken Nedergaard



Dr. Paul Vaska



Mei Yu



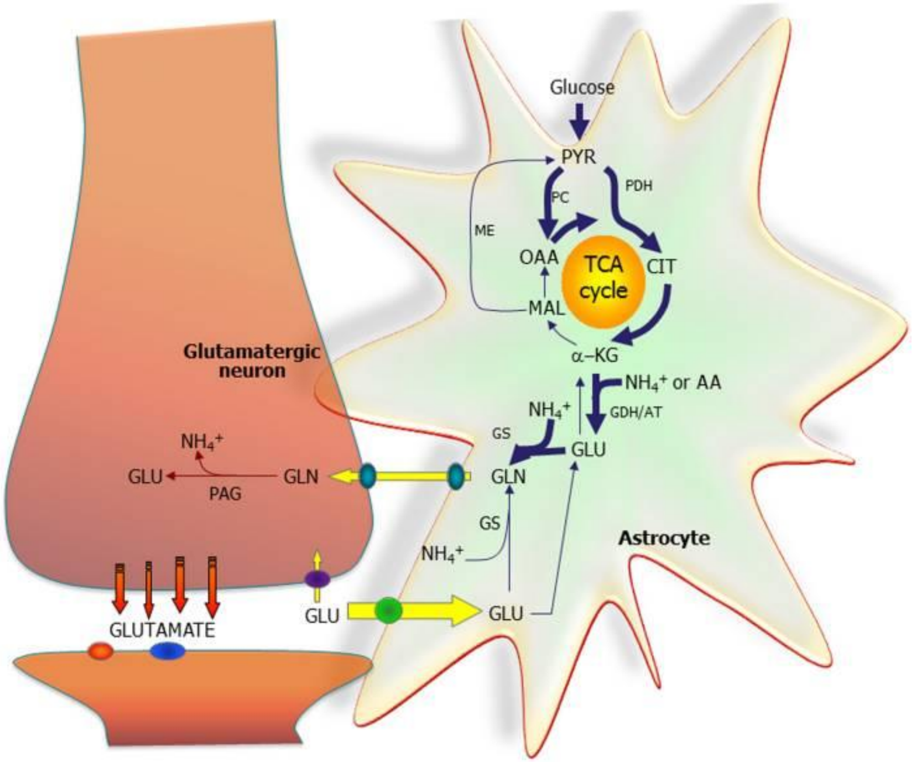
Dr. Vadim Ratner

Dr. S. David Smith

Significance

- The brain is one of the most metabolically active organs in the body
- Removal of excess fluids and waste products is critical for normal brain function
- The brain parenchyma has no authentic lymphatic vessels for detoxification

The brain & metabolic waste: Example - Ammonia (NH_3)



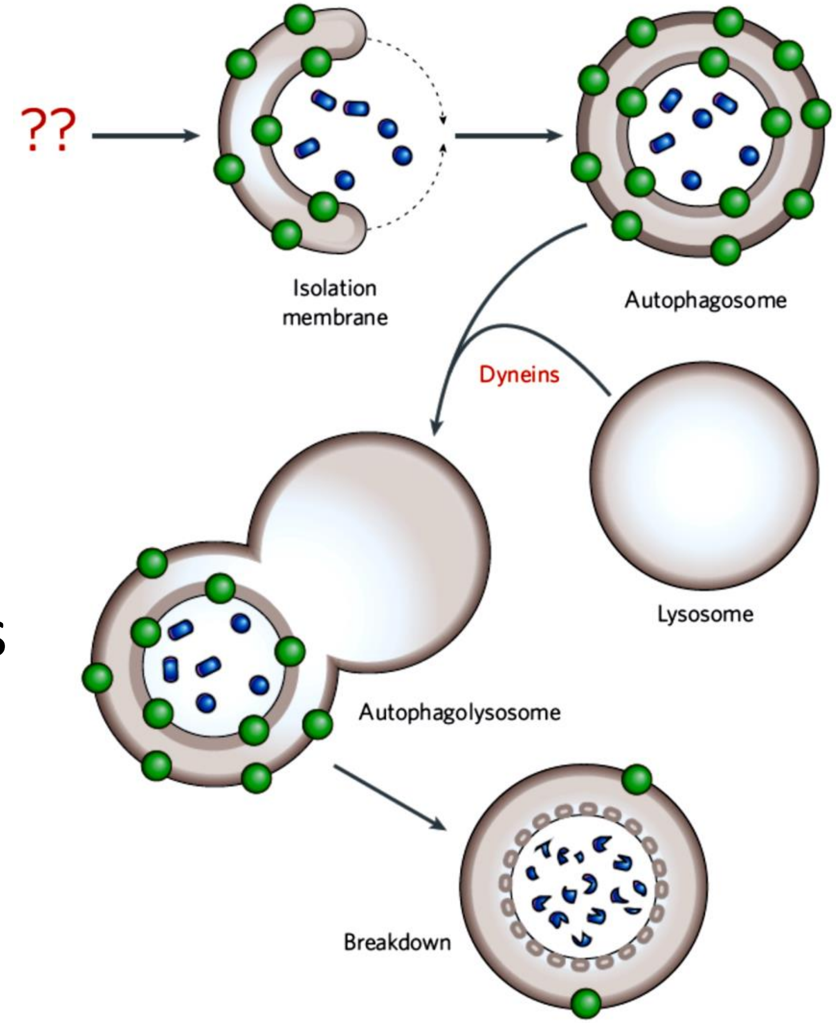
The glutamate-glutamine cycle leads to production of ammonia (NH_3)….at the same time ammonia is needed in astrocytes for the synthesis of glutamine from glutamate.

Ammonia is rapidly eliminated by the brain

From: Schousboe et al. Frontiers in Endocrinology, 2013

The brain & metabolic waste: Proteins

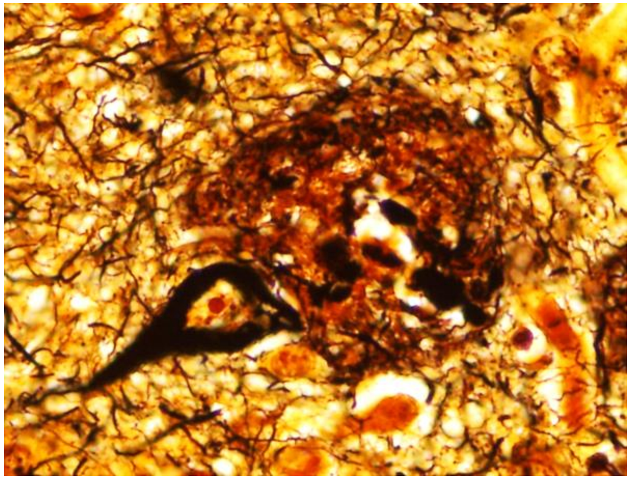
- Cytosolic proteins are constantly renewed
- Proteins incorporated in the cytoskeleton and membranes are constantly renewed
- Lack of specialized BBB transporters for most peptides and protein
- Recycling/degradation of protein: ubiquitination and autophagy



Schematic overview of autophagy
Rubinzstein, NATURE, Vol 443; 206

Significance

- Age-related decline in the efficiency of protein degradation has been implicated in pathological protein aggregation
- Neurodegenerative diseases, are characterized by accumulation of aggregation-prone mutated, misfolded or hyperphosphorylated proteins
- These proteins are present intracellular and extracellular



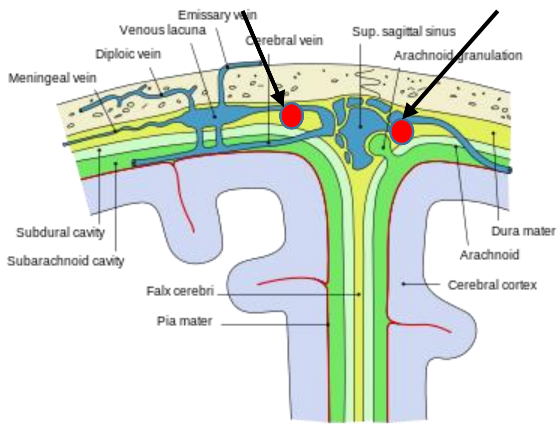
Neurofibrillary tangle and amyloid plaque

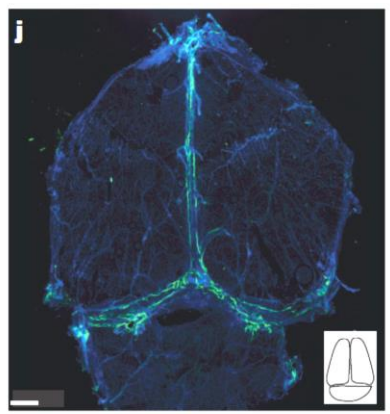
http://neuropathology-web.org/

Alternative waste removal pathway from CNS: CSF-ISF exchange

New discovery (mouse), 2015

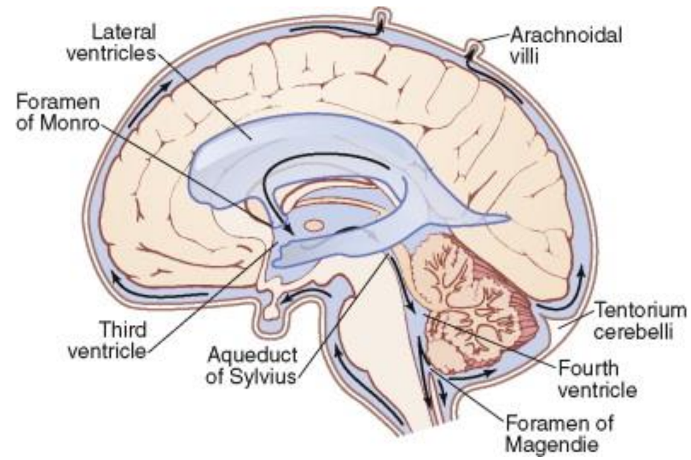
Brain parenchyma lacks a lymphatic system ?





Louveau et al., Nature 2015

CSF has been proposed as a sink for waste removal from brain



Authentic Lymphatic Vessels

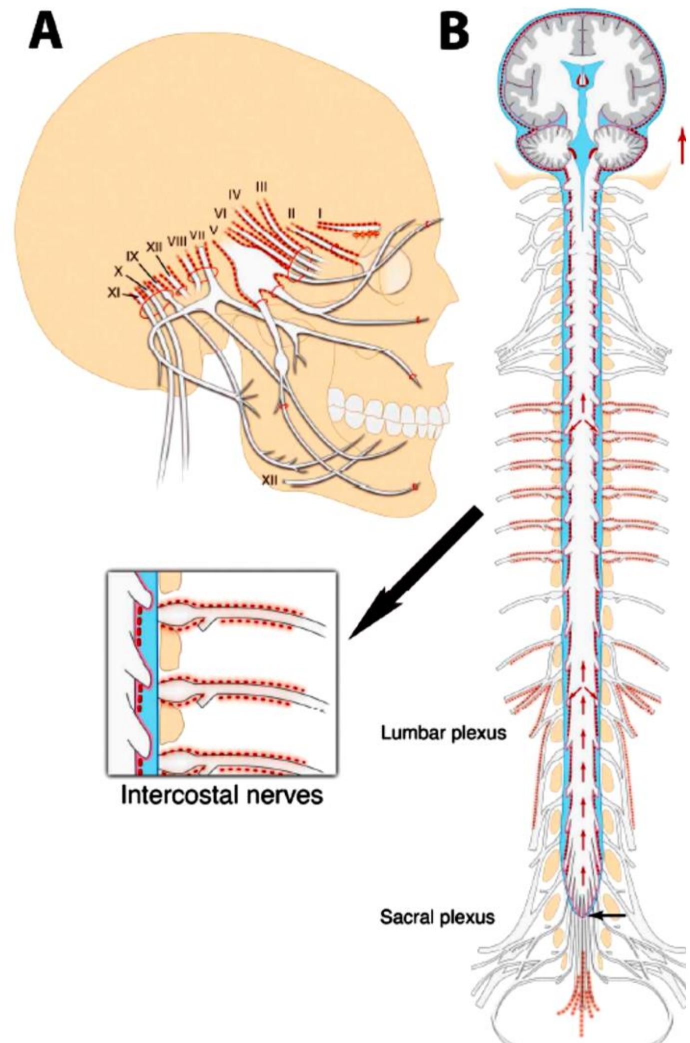
CSF is produced by the choroid plexus in the ventricles from where it flows through foramen magendi and eventually leaves via the arachnoid villi, the olfactory bulb, or cranial nerves….

Waste removal via CSF characterized by Heinrich Quincke in 1872

Quincke injected cinnabar granules into CSF of anim
(dogs, cats, rabbits)

1 mm

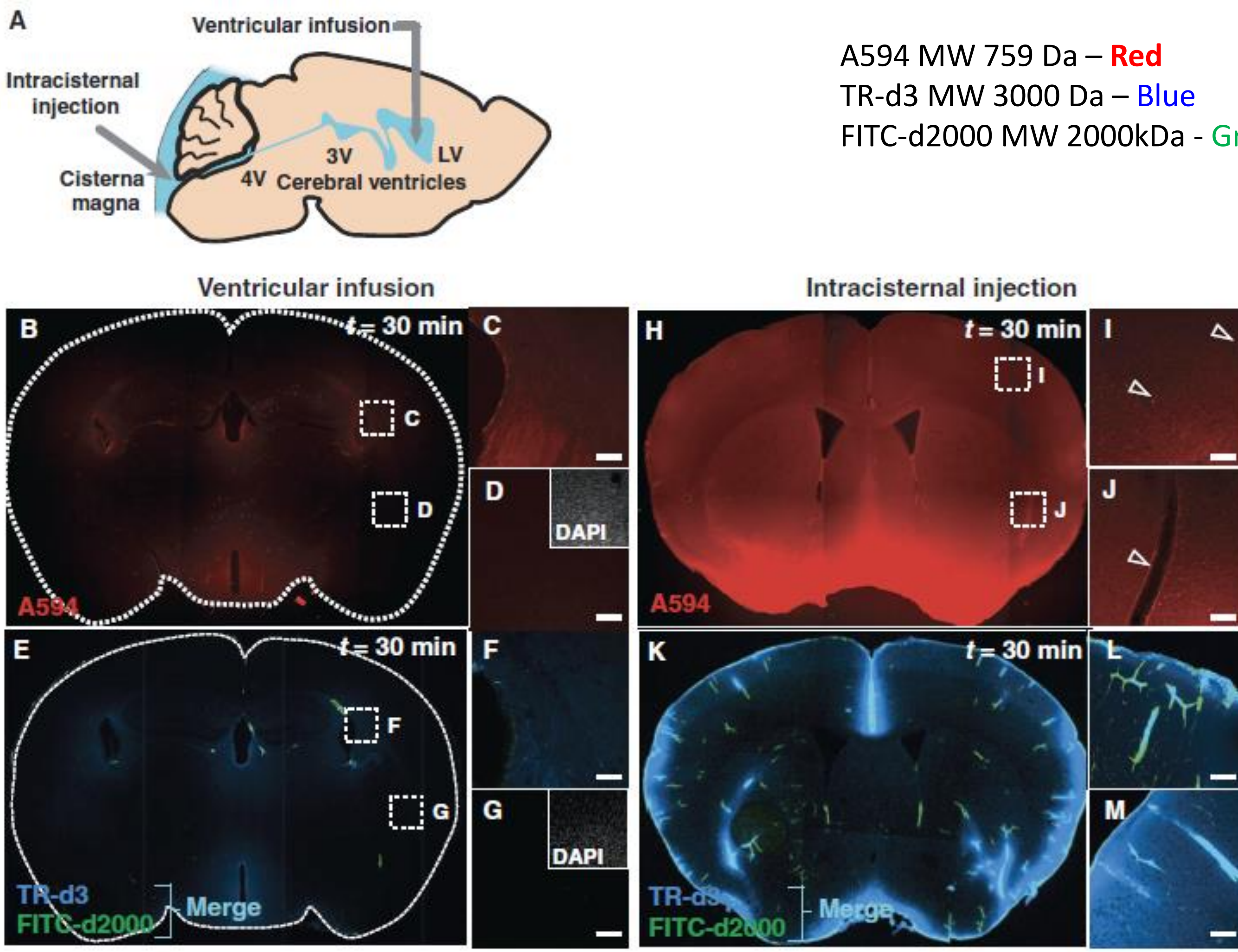
Cinnabar is a large molecule and while it is transported in CSF it does not go into parenchyma….



From: “Modern CSF Research and Heinrich Quincke’s Seminal Paper on the Distribution of Cinnabar in Freely Moving Animals. Benveniste et al., JCN 2015

State-of-the-art knowledge of the glymphatic pathway

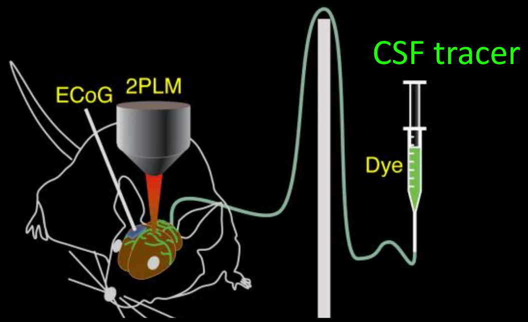
State-of-the art knowledge of the ISF-CSF exchange process

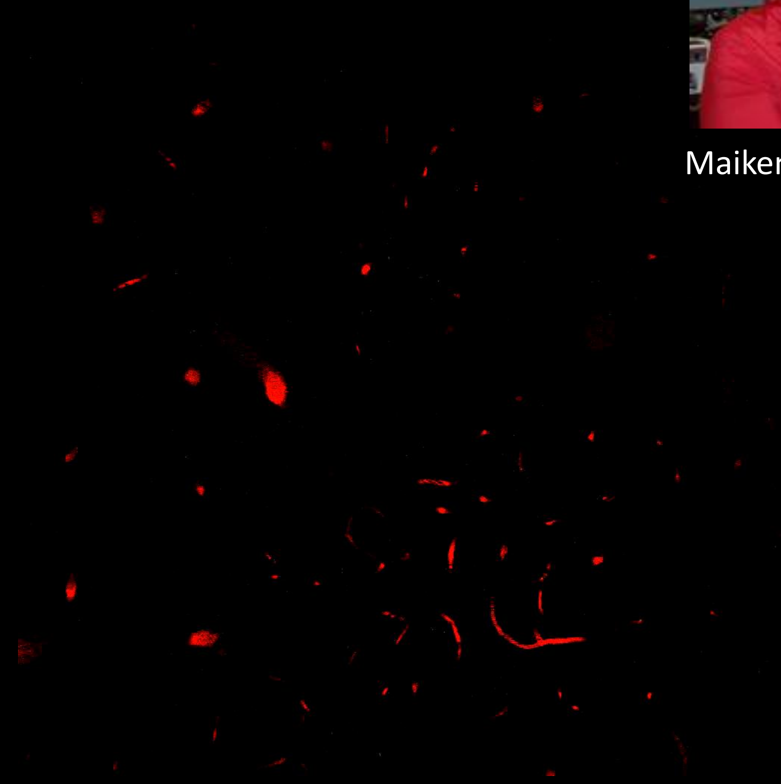


A594 MW 759 Da – Red
TR-d3 MW 3000 Da – Blue
FITC-d2000 MW 2000kDa - Green

Illif et al., Science Translational Medicine, 2012

In vivo imaging of CSF tracers: Discovering the glymphatic pathway





Vasculature
● CSF tracer
180 µm below the surface

5-10 min

Maiken Nedergaard

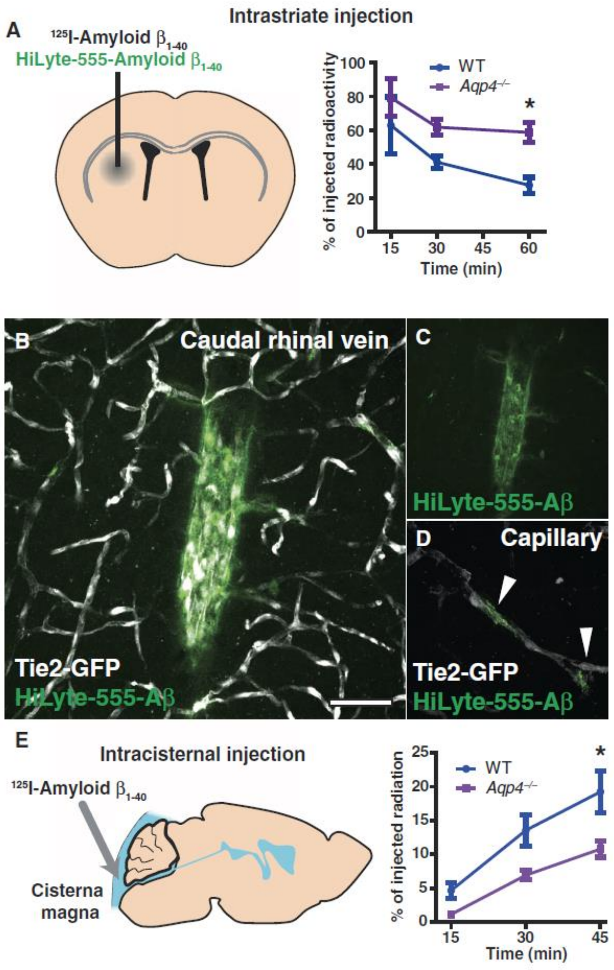
Jeff Iliff

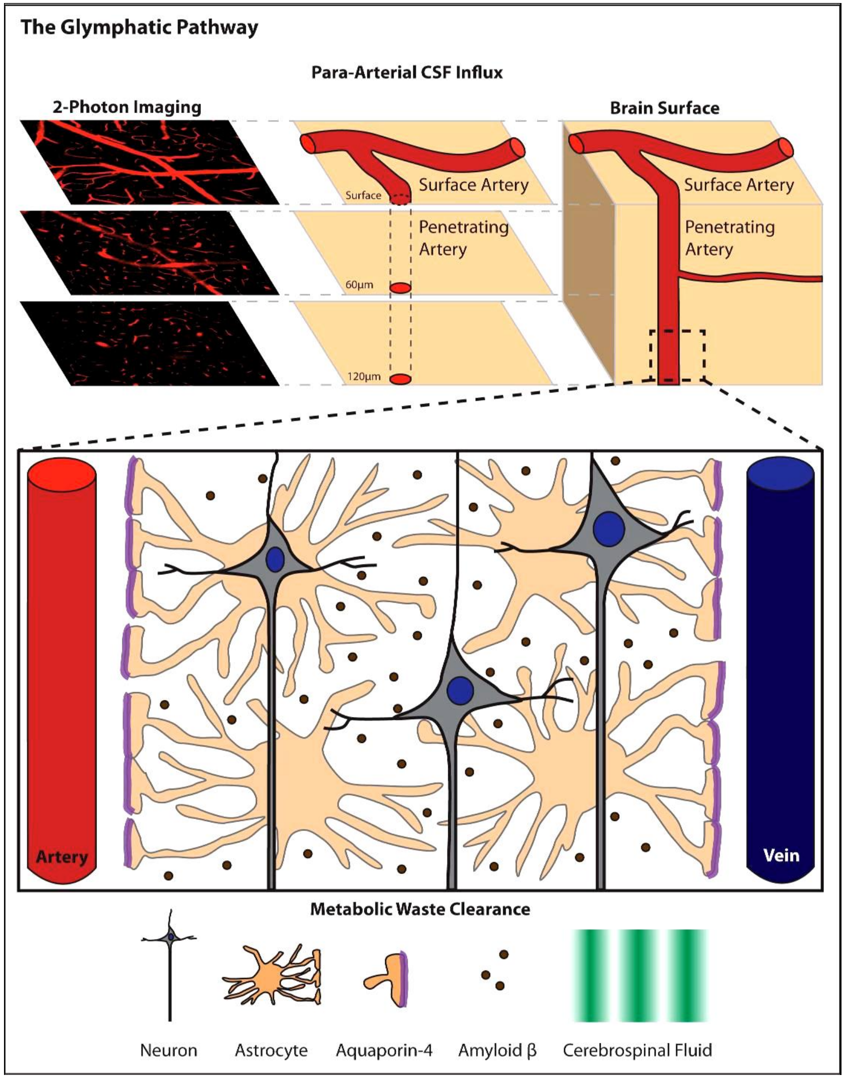
Rashid Deane

Steve Goldman

Iliff – Nedergaard (et al.), Science Translational Medicine, 2012

How do we know that this system removes waste products?



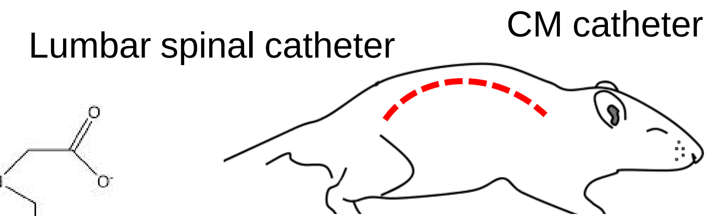


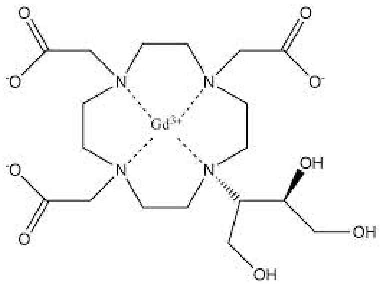
Iliff et al., Science Translational Medicine, 2012

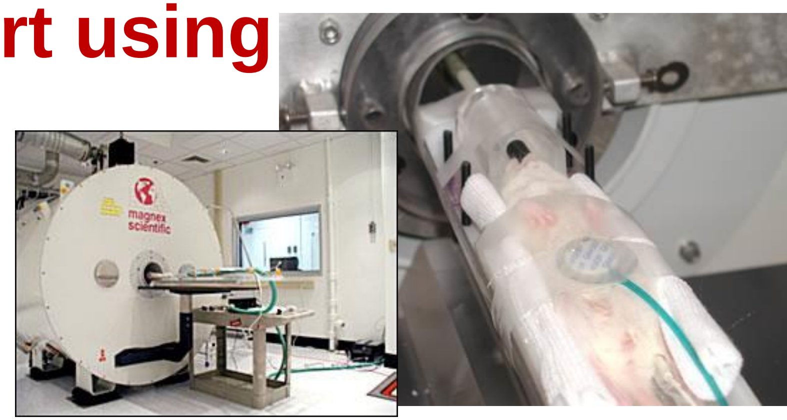
State-of-the-art-knowledge:

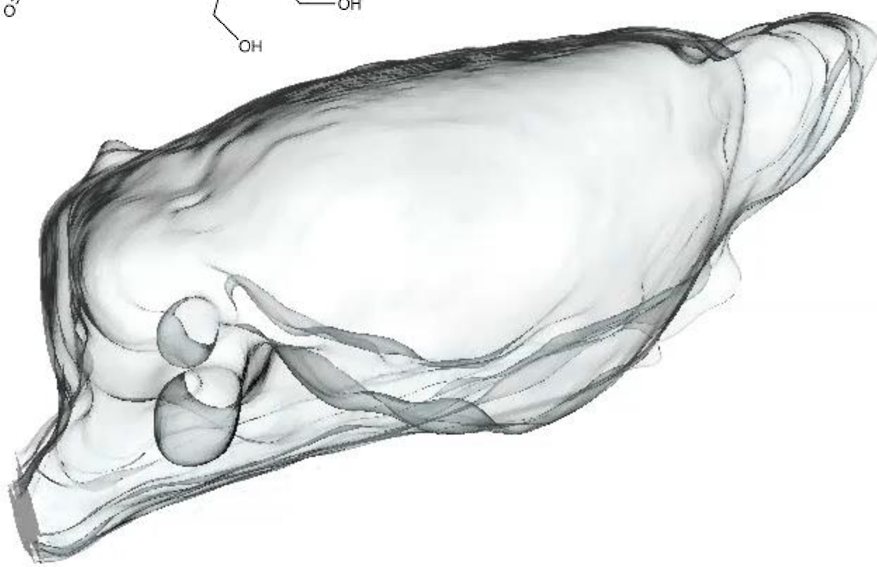
Visualizing glymphatic transport in real time using MRI

Tracking glymphatic transport using contrast-enhanced MRI

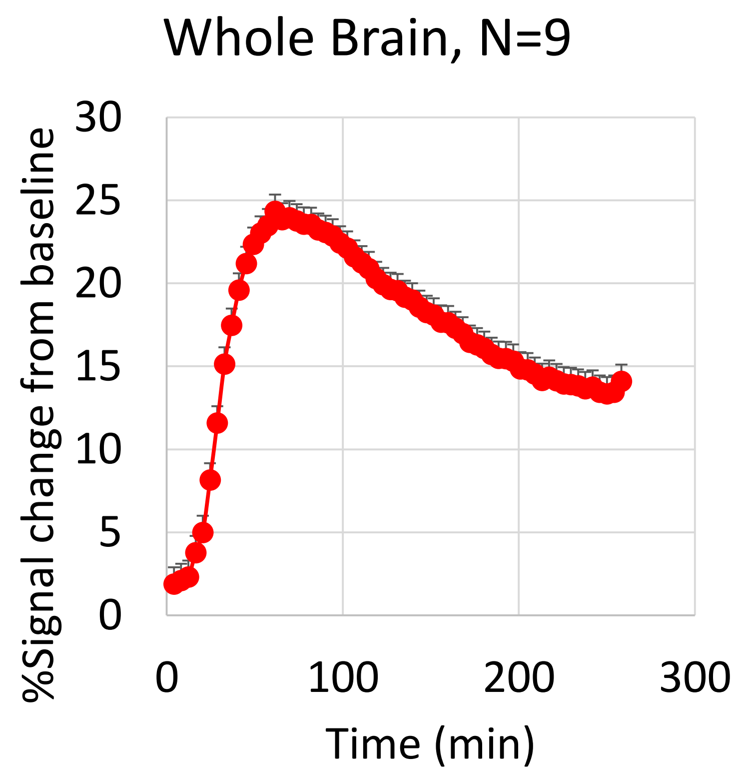






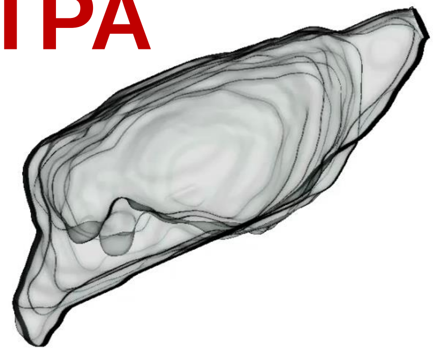


3D FLASH sequence (T1-weighted); each scan acquired over 4 min

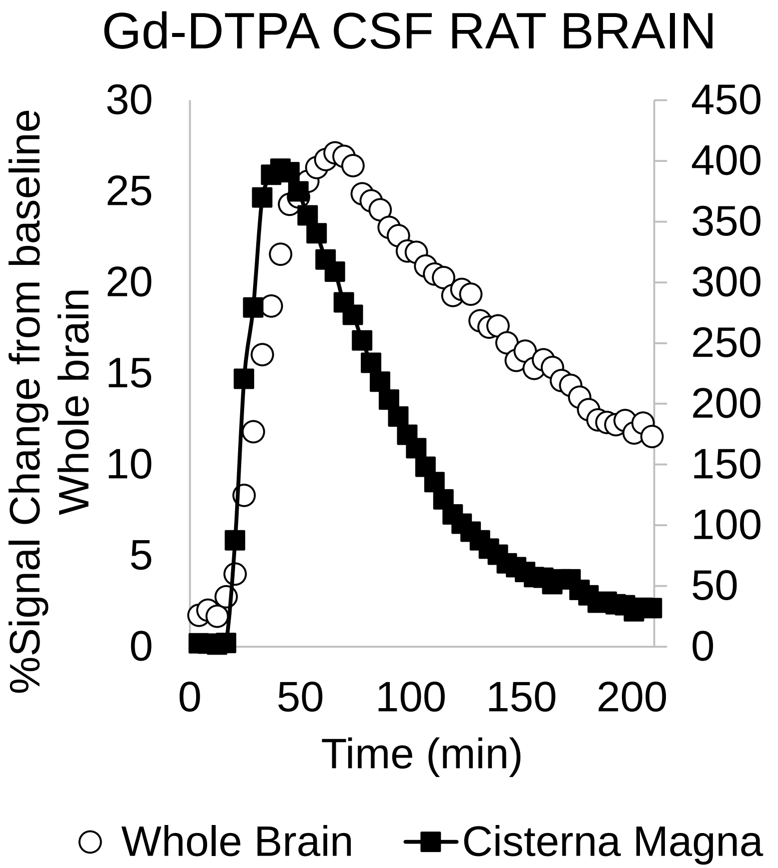


Iliff, Nedergaard, Benveniste; J Clin Invest. 2013 Mar 1;123(3):1299-309

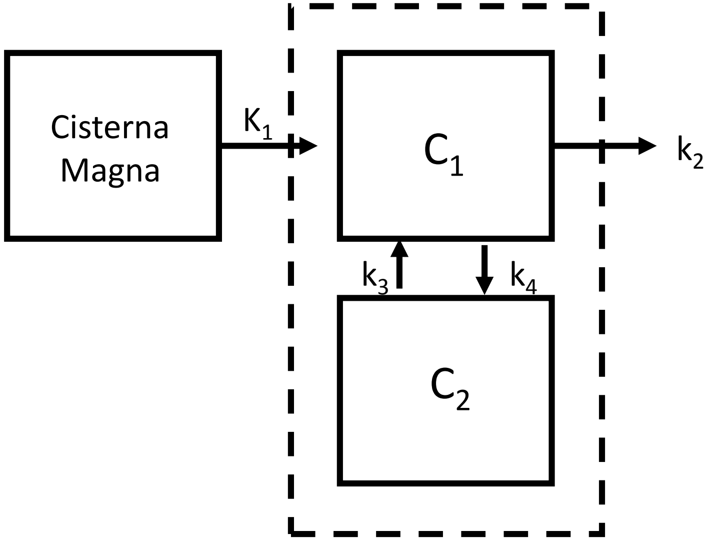
Quantification of Gd-DTPA brain-wide transport



Dr. Jean Logan, NYU



2-Compartment Model

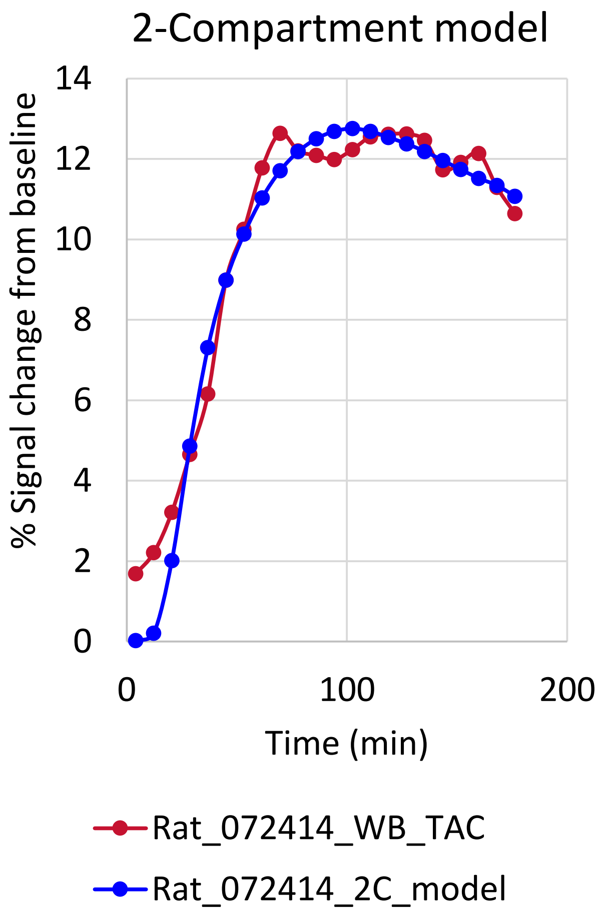


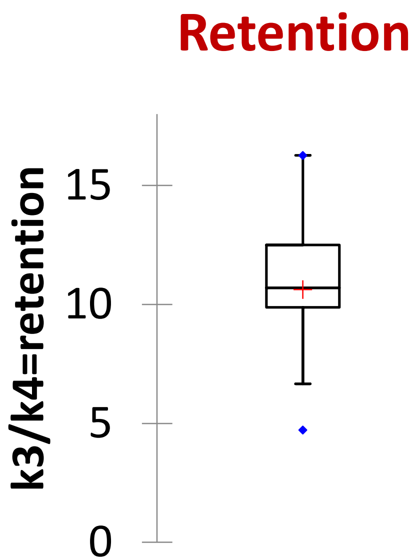
"Retention" = k_3/k_4

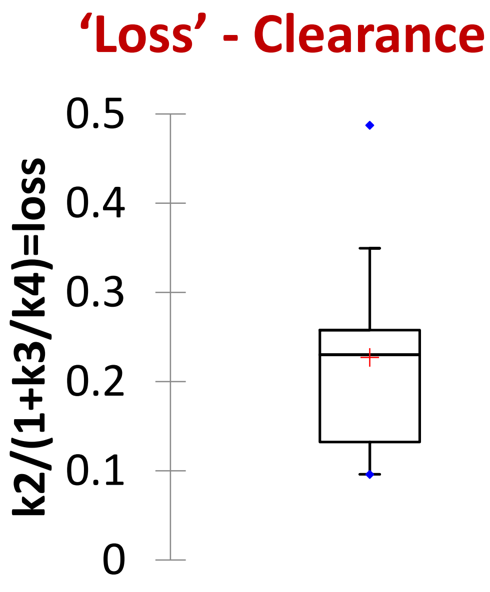
"loss" = $k_2/(1+k_3/k_4)$

Lee et al., J Neuroscience. 2015

Brain loss (clearance) and 'retention' of Gd-DTPA after CSF administration in rodent whole brain





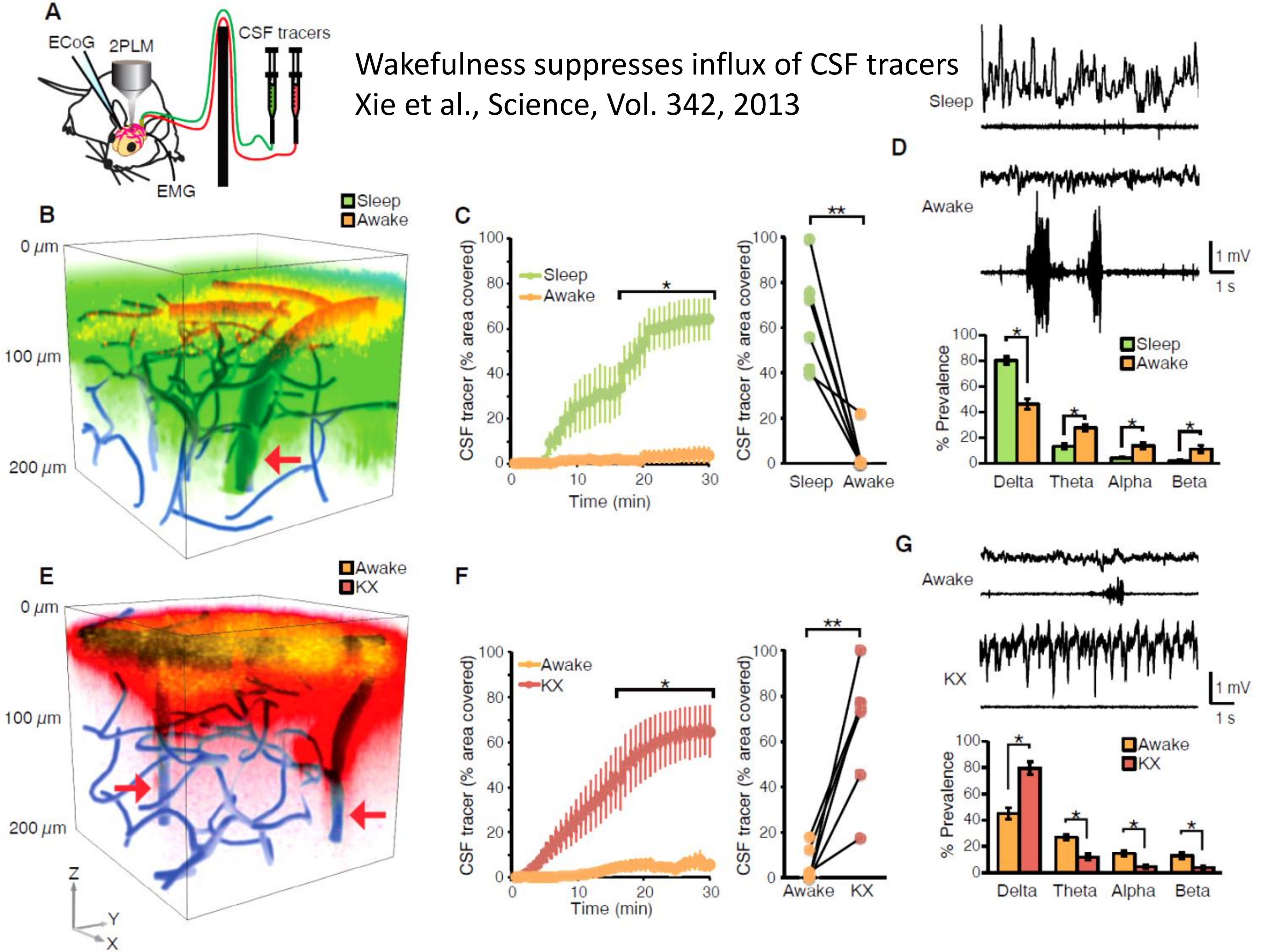


Lee et al., J Neuroscience 2015

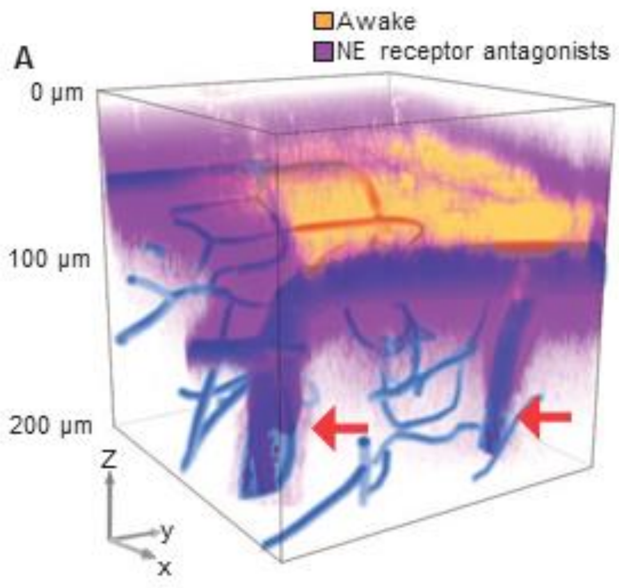
Factors that influence glymphatic pathway function:

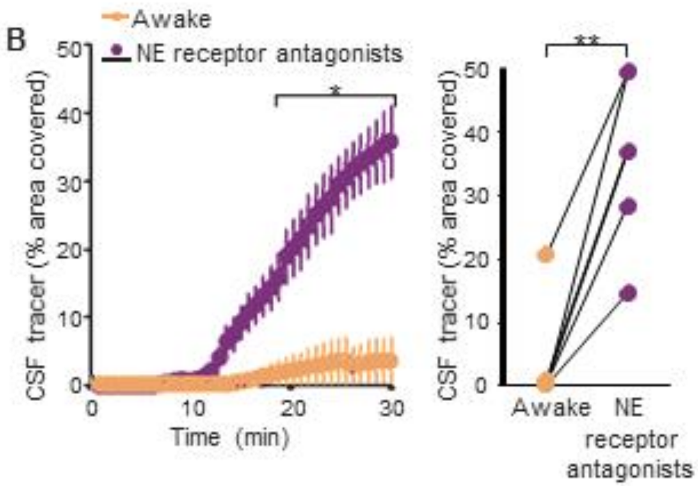
- AQP4
- Adrenergic tone
- Pulsatility
- Sleep / hypnotics

Wakefulness suppresses influx of CSF tracers
Xie et al., Science, Vol. 342, 2013



Importance of Noradrenergic tone





Xie et al., Science, Vol. 342, 2013

..We also see differences in glymphatic transport with use of different anesthetics…

Alpha-2 agonist - dexmedetomidine

Knowledge gap:

If unconsciousness enhance brain waste removal – what about body position during the unconscious state?

How does body position during sleep/anesthesia influence glymphatic transport?

"Consistently, poor sleepers spent more time on their backs with their heads straight" De Koninck et al., Sleep 1983;6 (1):52-9

The most favored position is right lateral decubitus (Sleep 1983;6 (1):52-9)

http://bestadjustablemattress.com/how-to-find-the-best-sleeping-positions/

Results from DeKonick's paper

	Good Sleepers	Poor Sleepers
Body movement/night		
Film records	42.3	50.5
Polygraph records	56.7	77.0
Position changes/night	22.3	35.6
By trunk position (first 3 cycles)		
Stomach	5	3
Back	9	18
Right side	24	17
Left side	15	11

Average body movements and trunk position for good and poor sleepers for both nights (modified Table 4 from (Sleep 1983;6 (1):52-9))

Sleeping gorillas

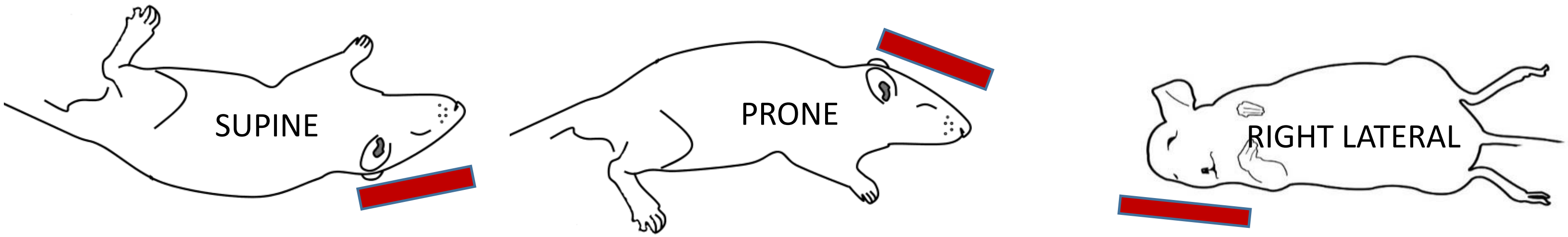
http://www.freepik.com/free-photo/gorilla-sleeping_352304.htm

Sleeping rats

“Slow wave sleep (SWS). During this stage, subjects assumed a reclining posture, sometimes on their abdomen….sometimes curled in a fetal position with eyes closed.” (Hobson; Behavioral Neruoscience; 2000, Vol 114; No. 6, 1239-1244).

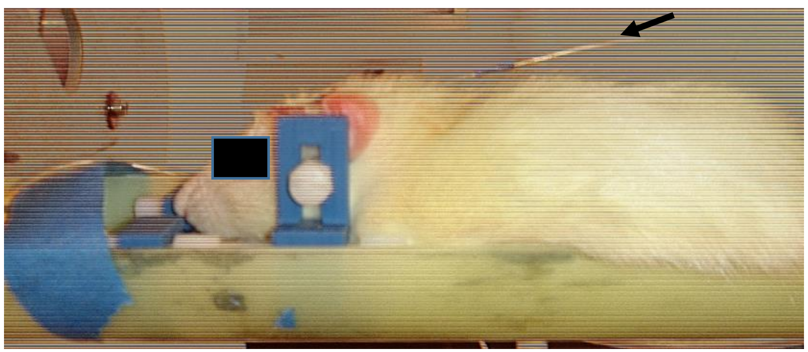
http://blogs.discovermagazine.com/sciencenotfiction/2010/08/10/inception-and-the-neuroscience-of-sleep/#.VLZl0CvF8j4

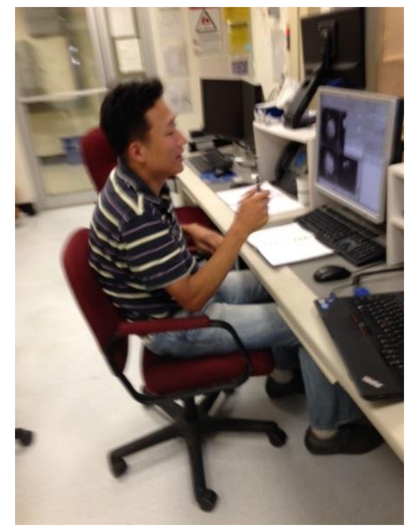
Effect of body position on glymphatic transport



Neck, ears and nose is not affected by the head holder

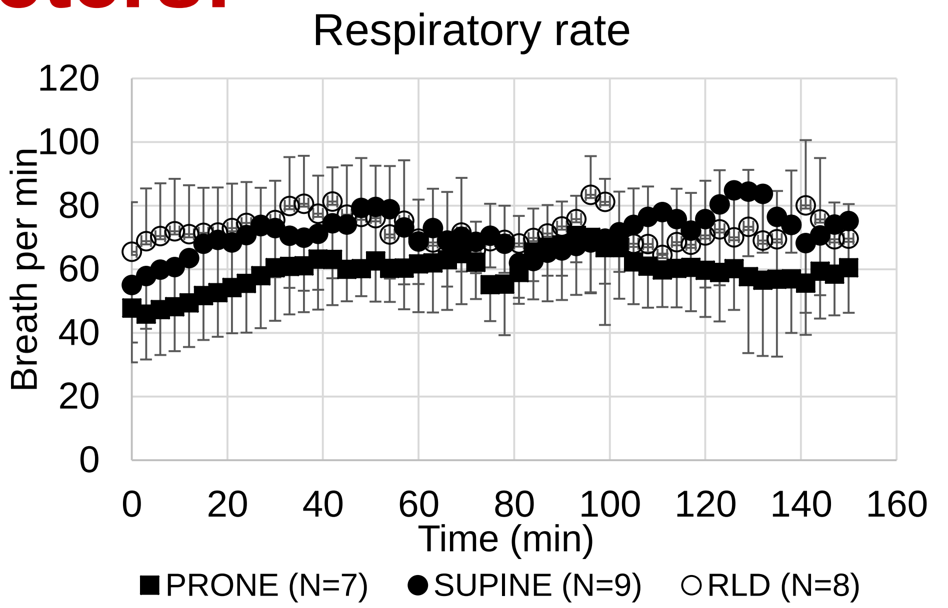
Cisterna Magna Catheter



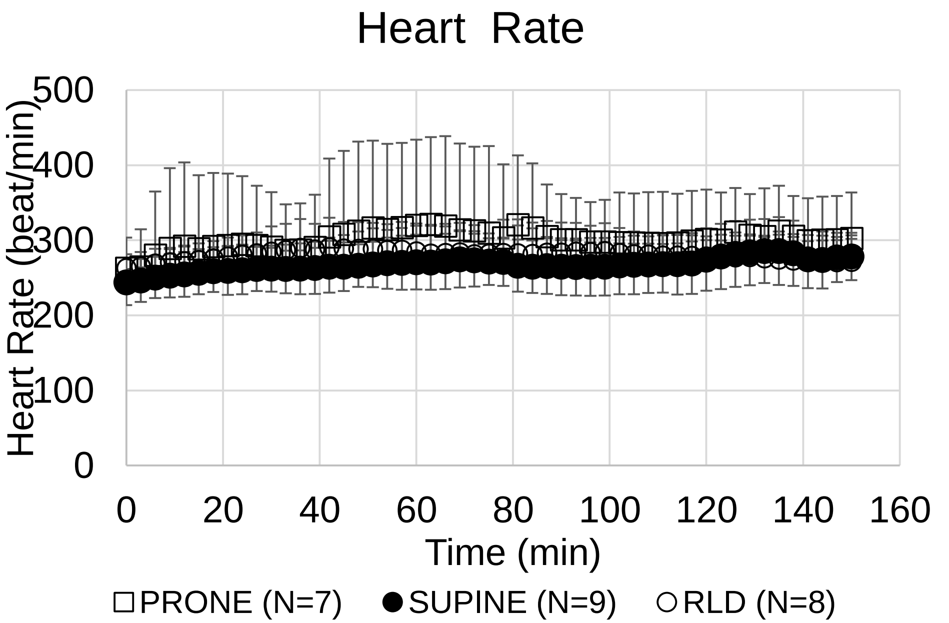


MRI compatible head holder fixing the head of the anesthetized rat in prone position during imaging. There are no ear-bars; the fixation points are at the level of the squamosal bone. Head holder designed by Dr. Hedok Lee.

Physiological parameters:



Anesthetized rat in the SUPINE position being monitored: Respiratory rate, heart rate, Oxygen saturation and body temperature.



All the rats were anesthetized with a mixture of Ketamine:Xylazine i.p.; glycopyrulate 0.01mg/kg i.p was also administered as an anti-sialagogue.
All rats were spontaneously breathing.

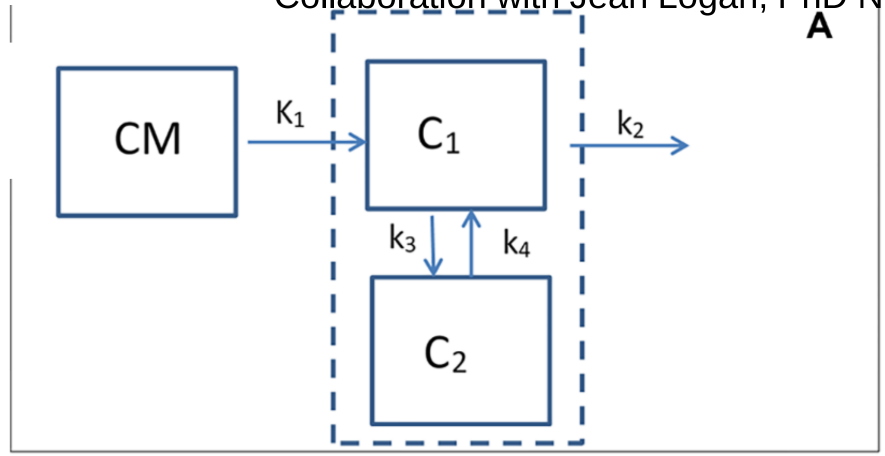
2-compartment model

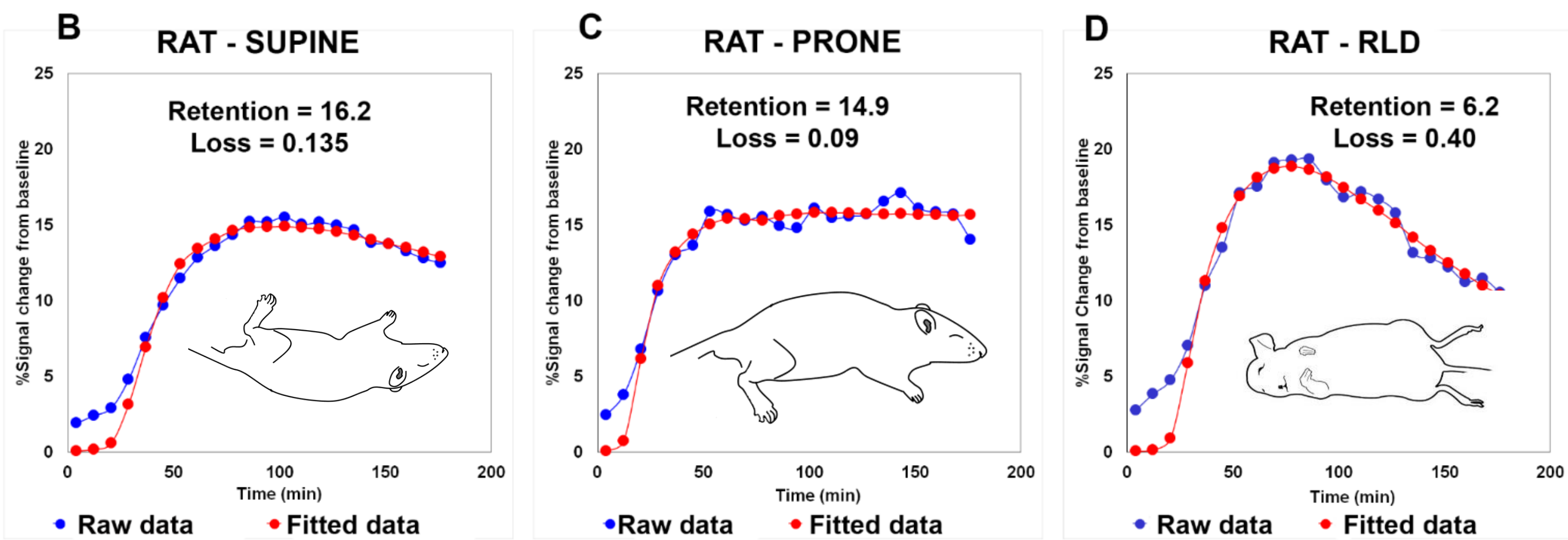
Collaboration with Jean Logan, PhD NYU

Clearance (loss) is greatest in RLD and lowest in prone position…

k3/k4 = Retention

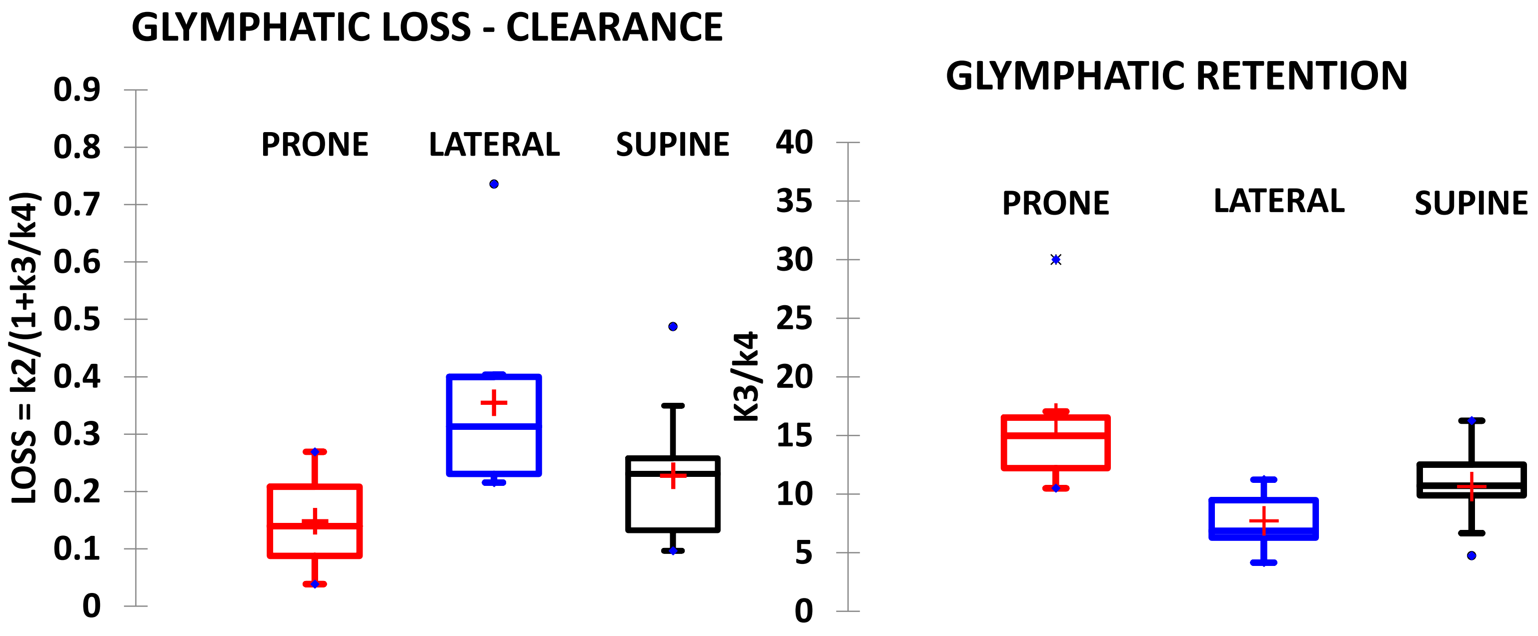
k2/(1+k3/k4) = “loss”





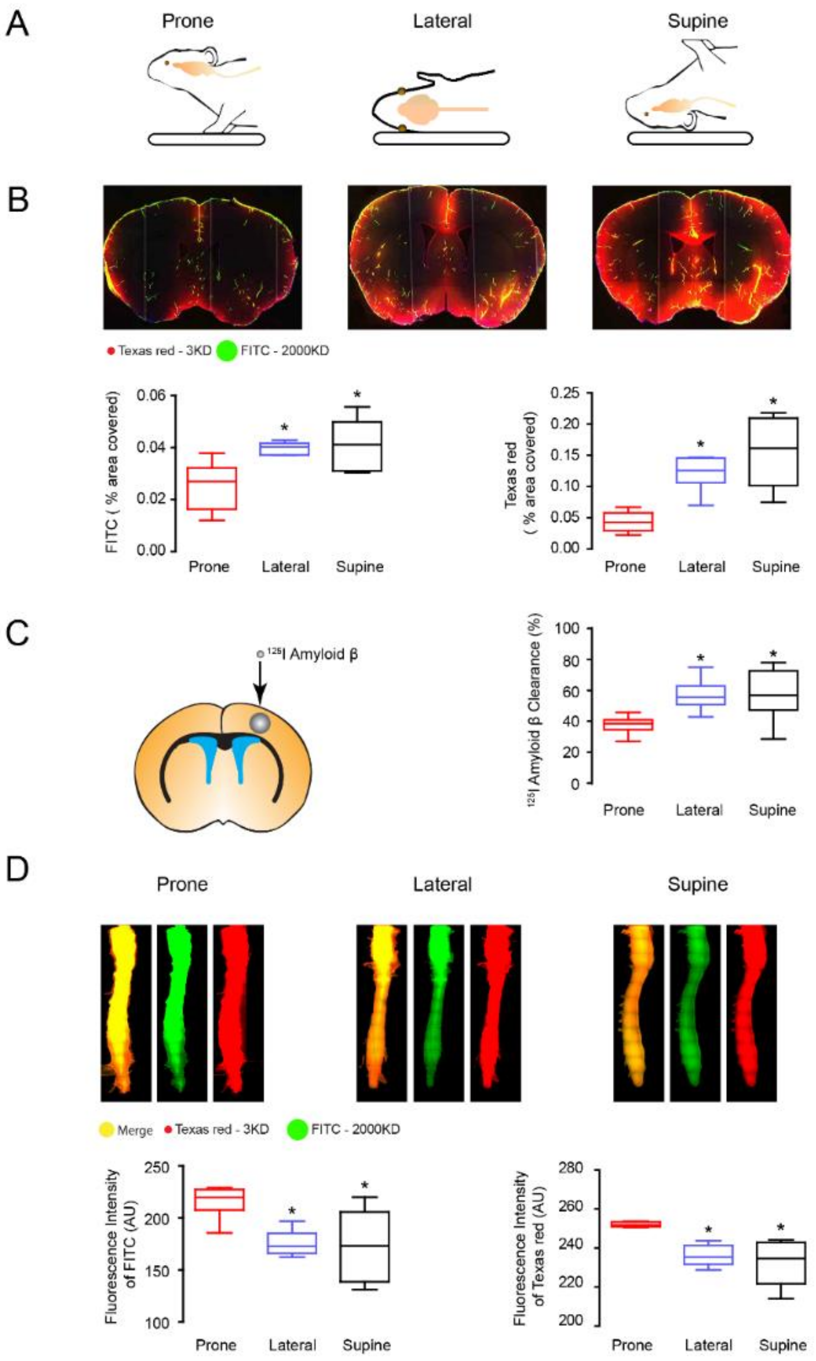
Does body position influence whole brain glymphatic transport of Gd-DTPA

Data are presented as median (1st quartile, 3rd quartile) for each group. *One rat in the PRONE group was excluded from analysis due to 2-compartmental fitting failure.



Kinetic parameter	SUPINE (N=9)	PRONE (N=6*)	RLD (N=8)	P-value
Retention = (k3/k4)	10.70 (9.88, 12.50)	14.98 (12.23, 16.53)	6.86 (6.28, 9.47)	0.008
Loss = k2/(1+k3/k4)	0.23 (0.13, 0.26)	0.14 (0.09, 0.21)	0.31 (0.23, 0.40)	0.021

MRI data validated by optical imaging….and also showing that **Aβ is cleared least efficiently in prone position**



Research opportunities

- Understand how the cardiac sympatho-vagal balance influence central nervous system arousal and glymphatic pathway function in the context of sleep and aging
- Understand how perivascular neurons, gliovascular interactions and intramural vascular signaling change and interferes with glymphatic pathway functioning in normal aging.
- Mapping of the glymphatic, perivascular ‘connectome’; need to understand CSF-ISF streaming pattern in health and disease