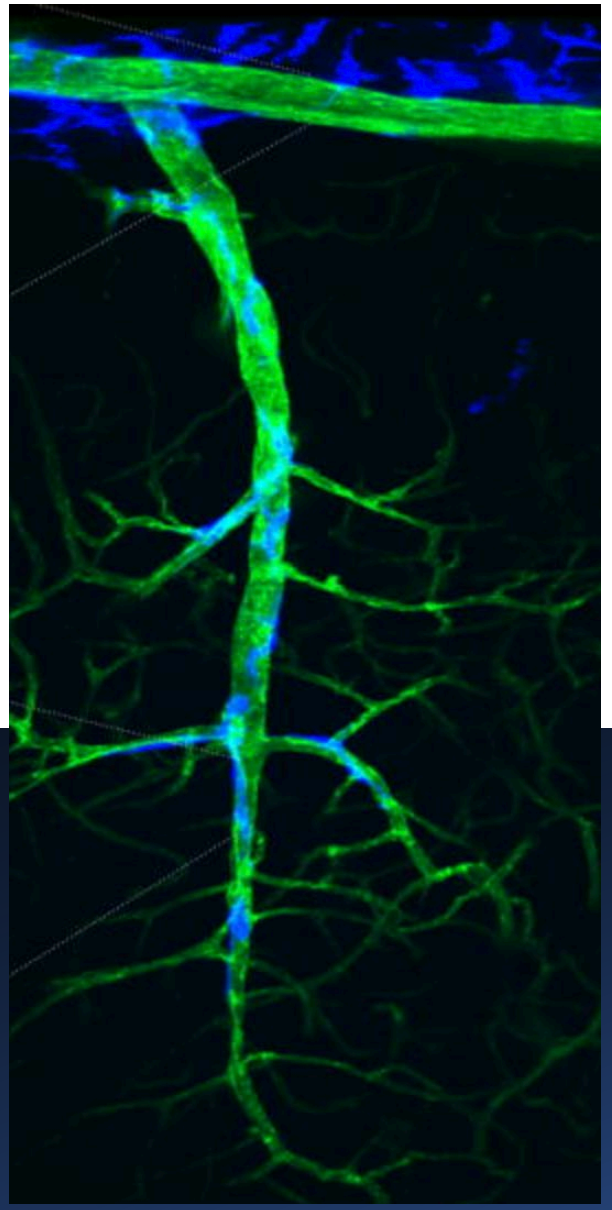
Il sistema glinfatico:

l'interesse della neuropatologia allo studio

della complessa struttura anatomo-funzionale

di pulizia del Sistema Nervoso Centrale



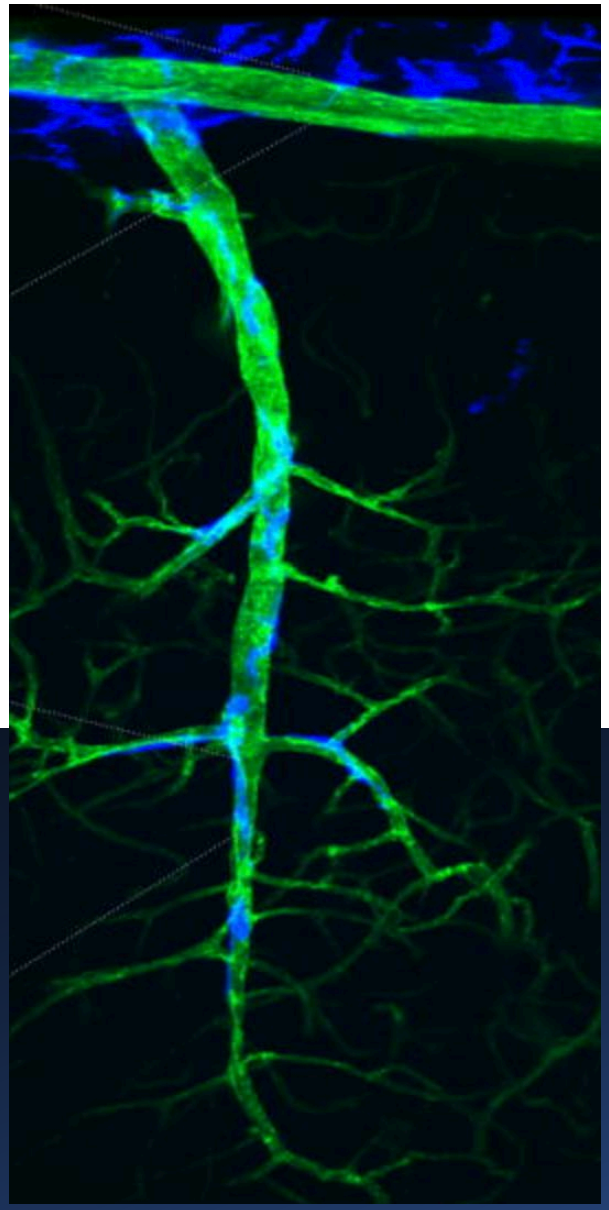
Carla Uggetti
MILANO

Glymphatic system

OUTLINE

- ”Glymphatic system”
- Study methods
- Related diseases
- Future outlook

THE GLYMPHATIC SYSTEM



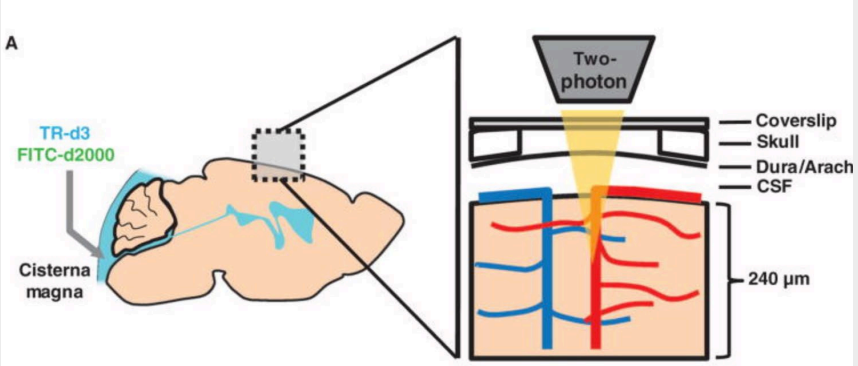
(G)-lymphatic

A Paravascular Pathway Facilitates CSF Flow Through the Brain Parenchyma and the Clearance of Interstitial Solutes, Including Amyloid β

Sci Transl Med 2012

Jeffrey J. Iliff[1,*], **Minghuan Wang**[1,2], **Yonghong Liao**[1], **Benjamin A. Plogg**[1], **Weiguo Peng**[1], **Georg A. Gundersen**[3,4], **Helene Benveniste**[5,6], **G. Edward Vates**[1], **Rashid Deane**[1], **Steven A. Goldman**[1,7], **Erlend A. Nagelhus**[3,4], and **Maiken Nedergaard**[1,*]

Glymphatic



A Paravascular Pathway Facilitates CSF Flow Through the Brain Parenchyma and the Clearance of Interstitial Solutes, Including Amyloid β

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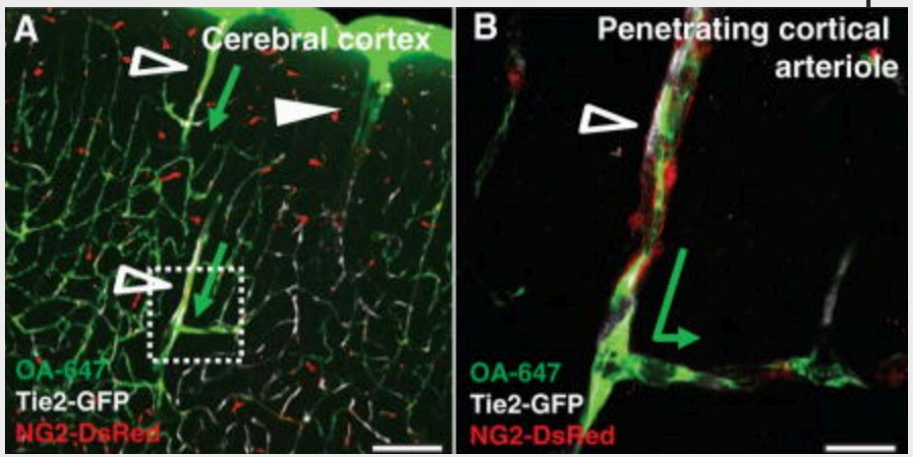
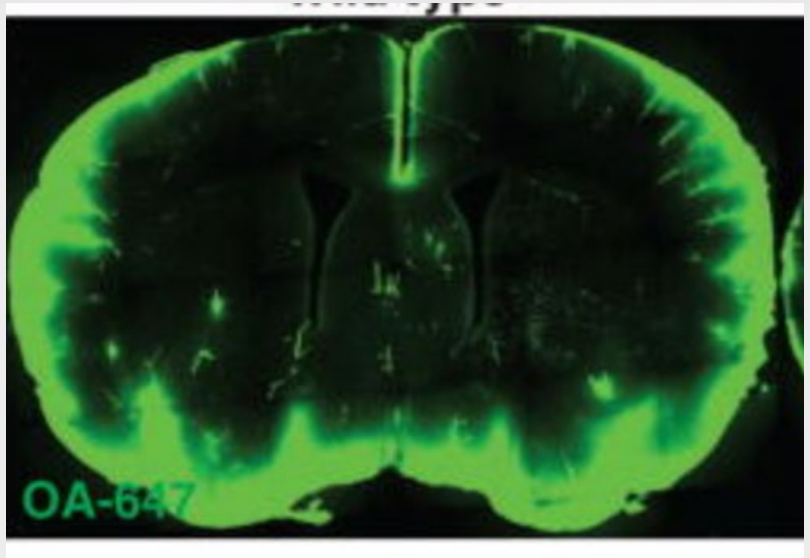
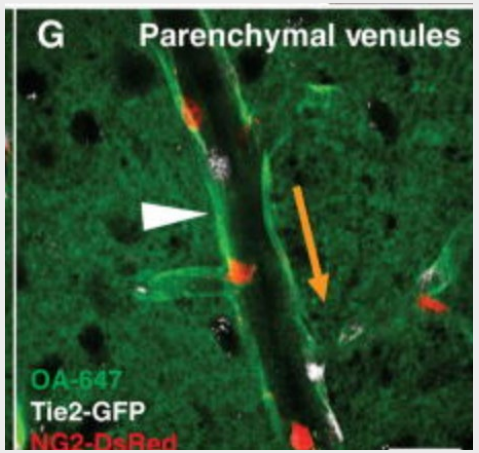
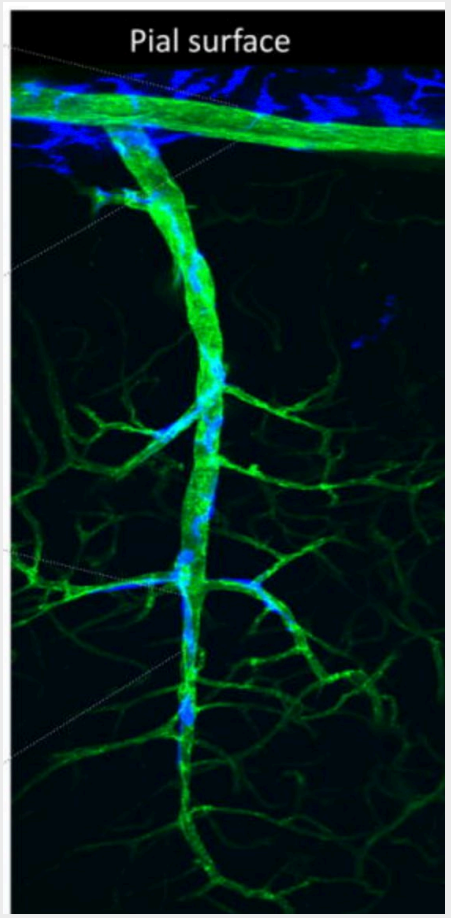
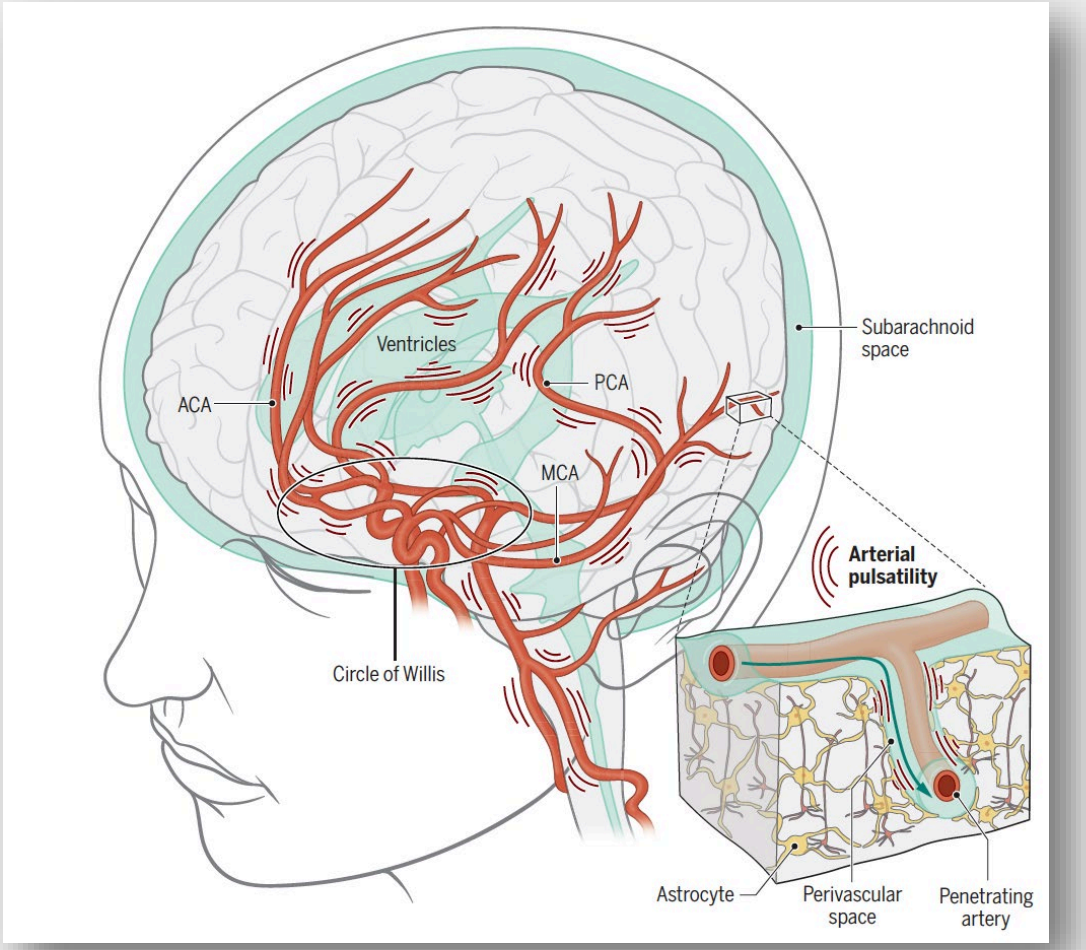




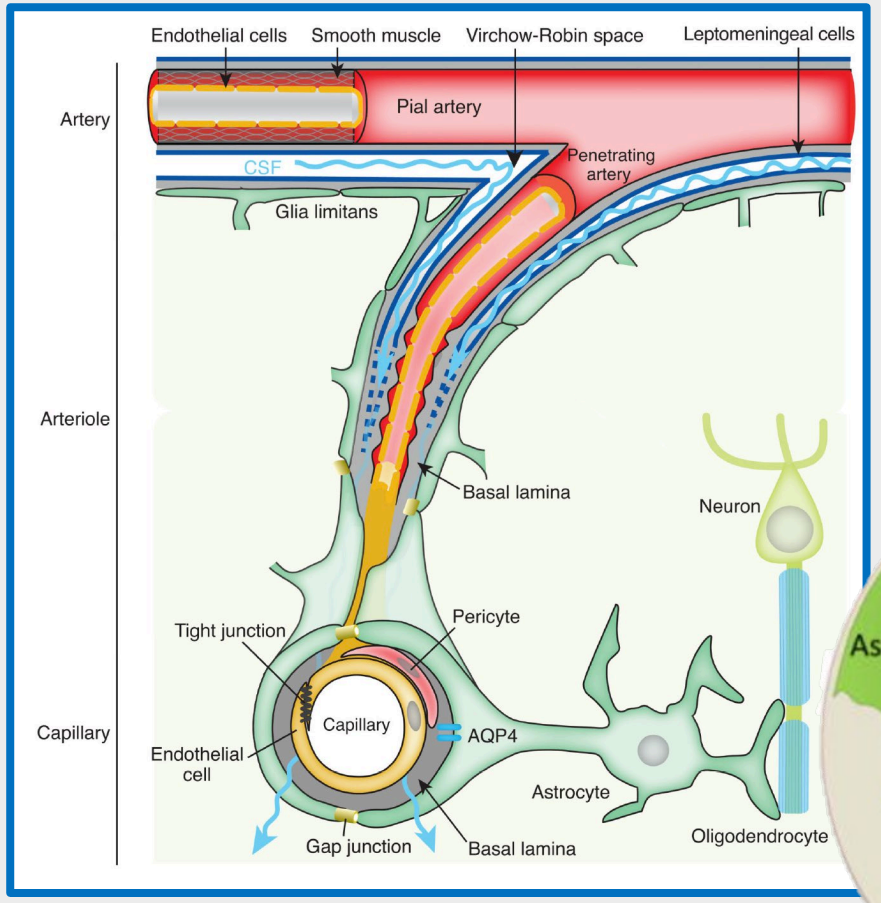


Glymphatic

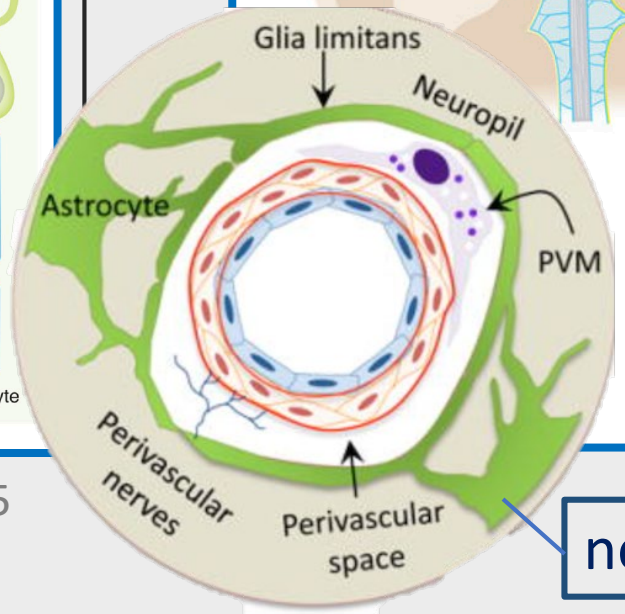

Pial surface


Ventricles
ACA
PCA
MCA
Subarachnoid space
Circle of Willis
Arterial pulsatility
Astrocyte
Perivascular space
Penetrating artery

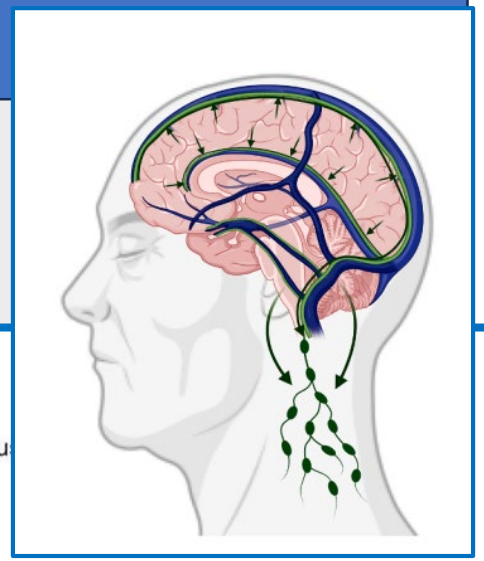
Glymphatic = *glial-lymphatic*

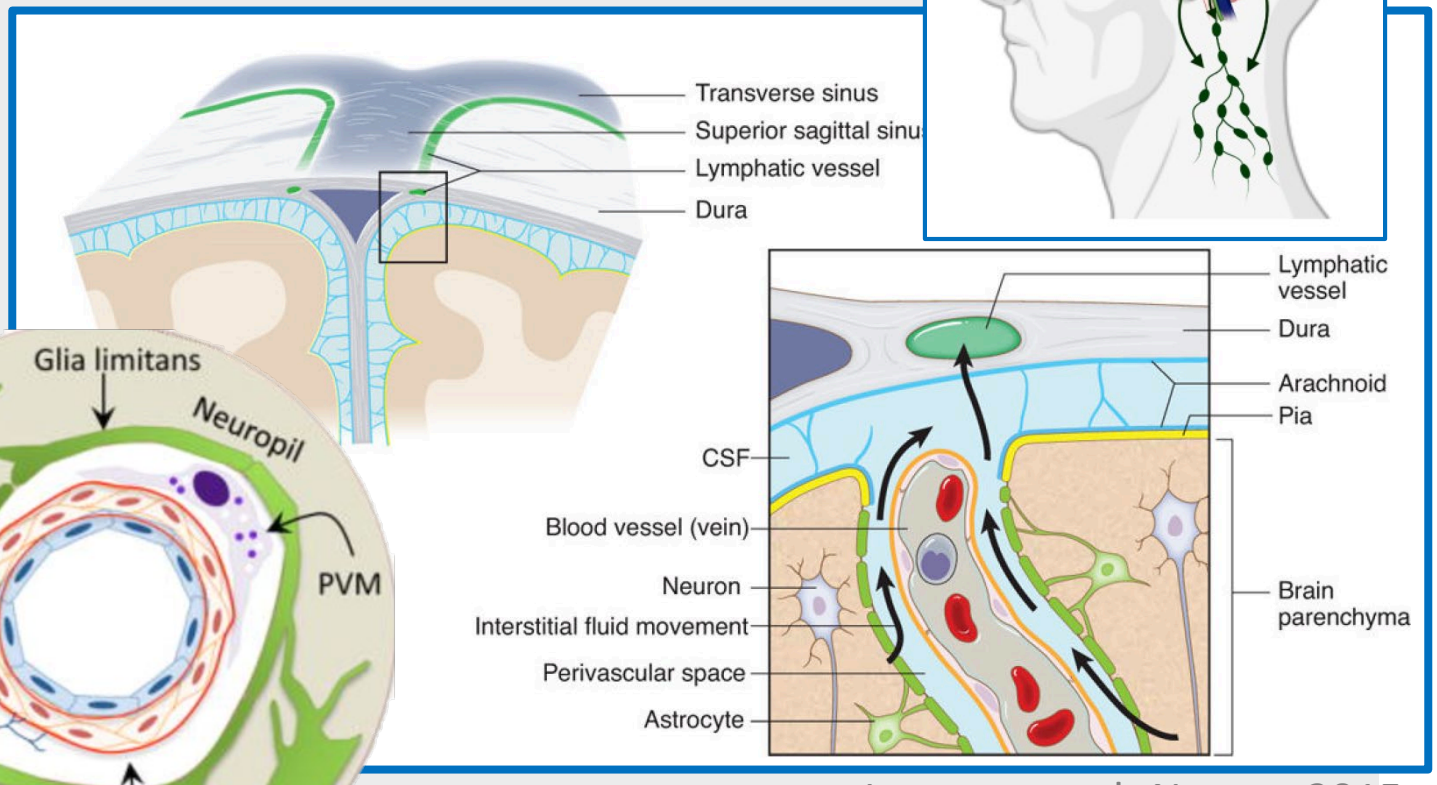


Nedergaard et al, *Neurochem Res*, 2015



neuro-vascular unit





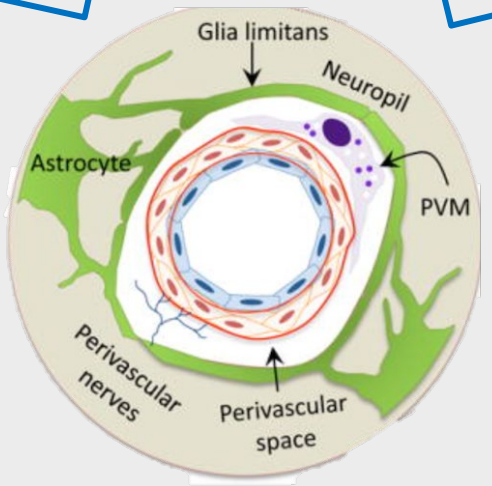
Louveau et al, *Nature*, 2015

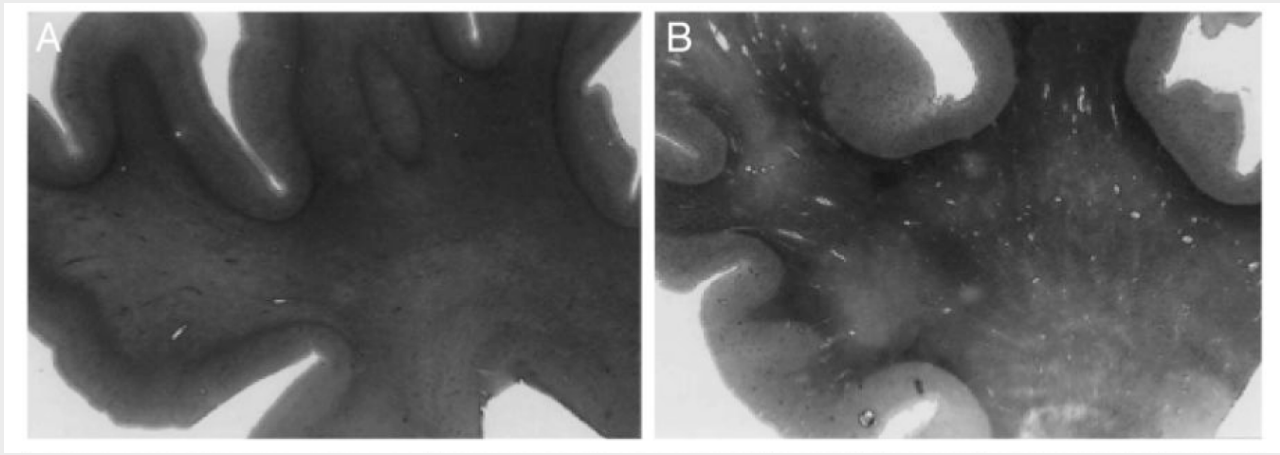
Perivascular spaces

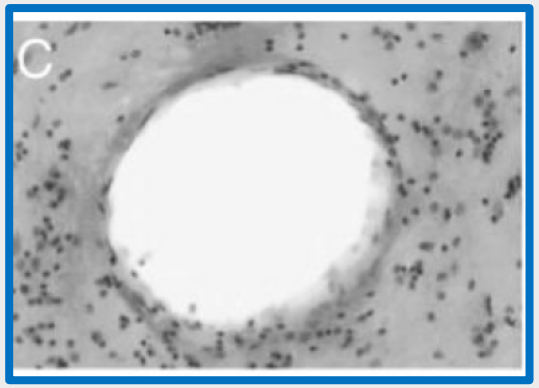
Perivascular spaces ''Virchow-Robin''

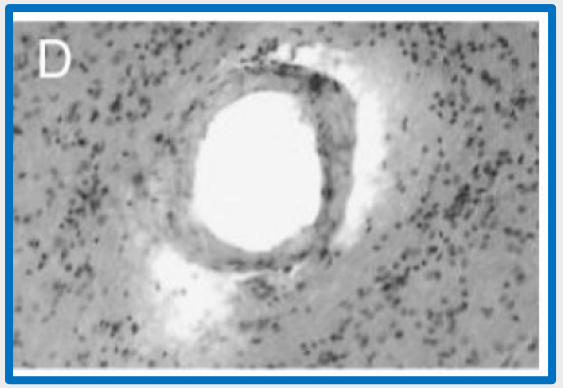
1851

1859

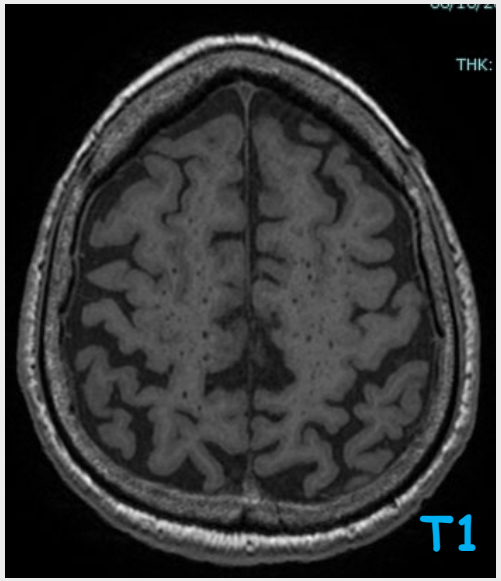


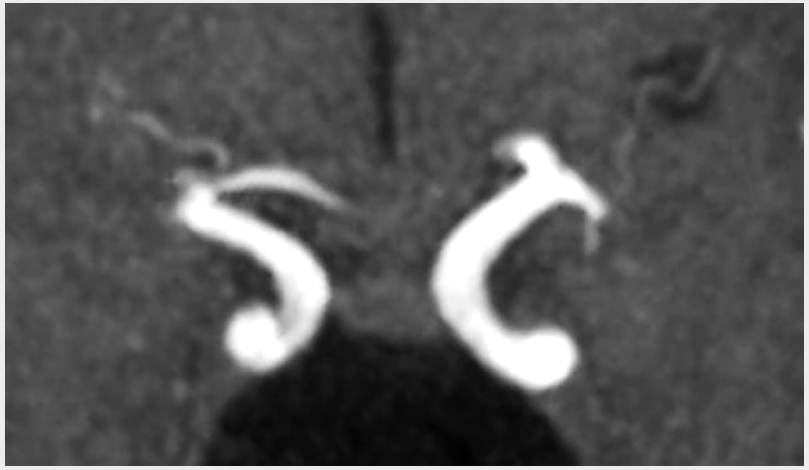


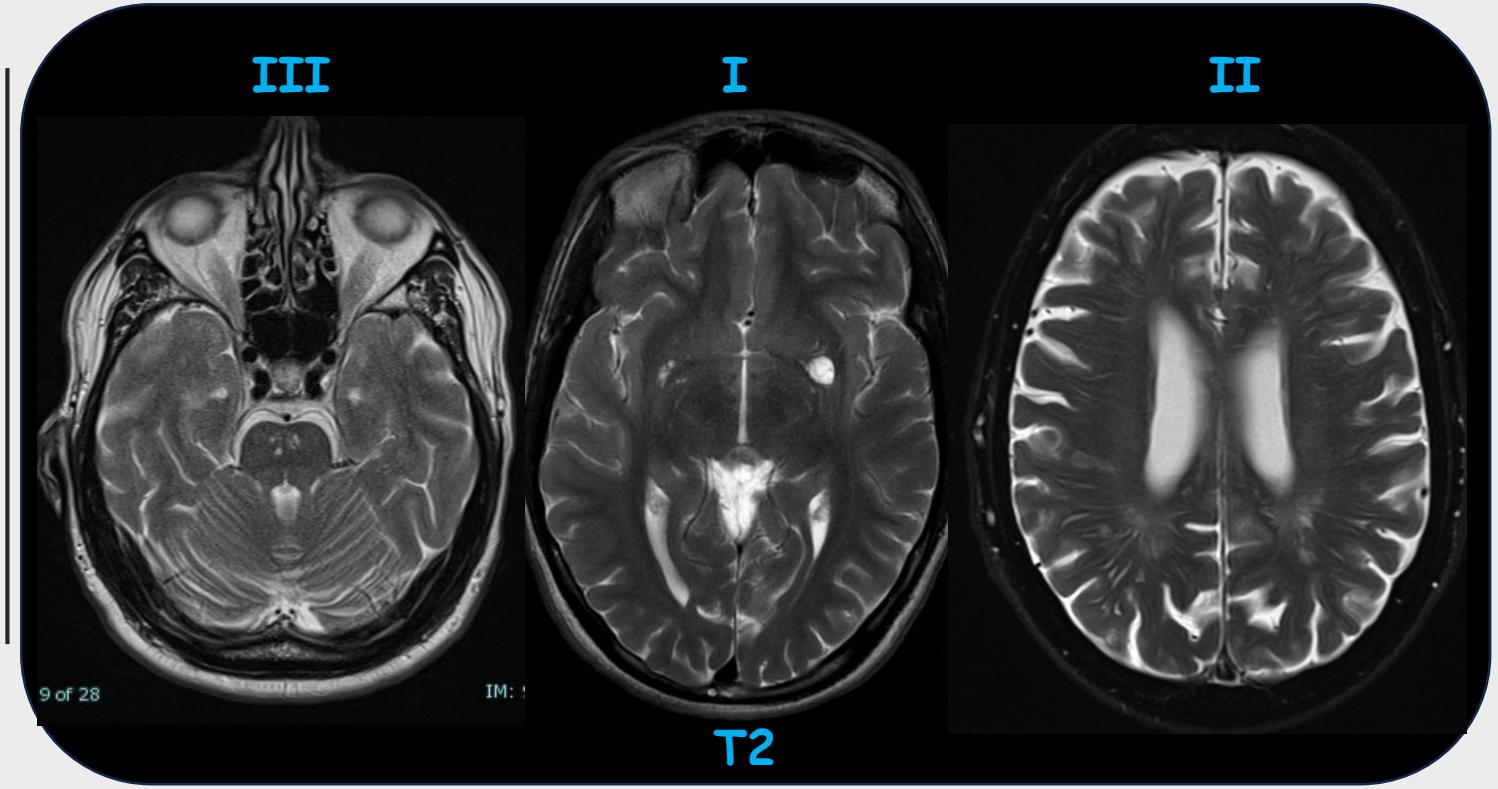




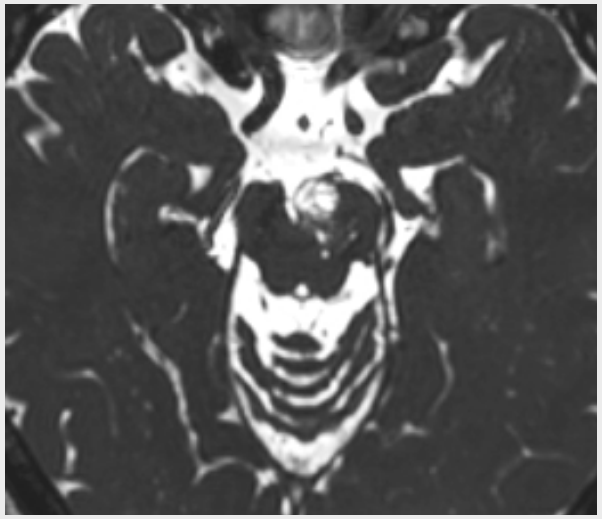
Perivascular spaces: MRI

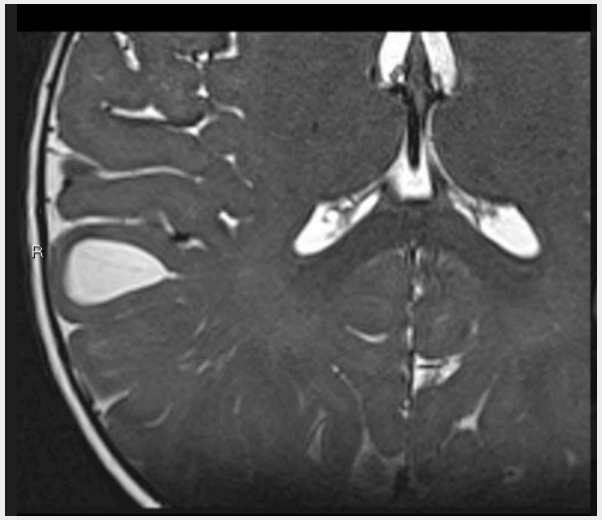


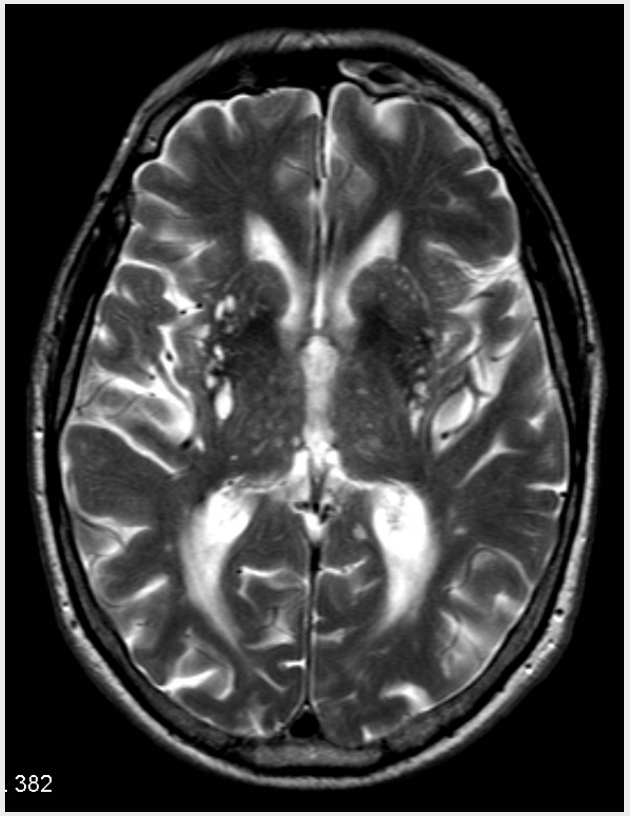




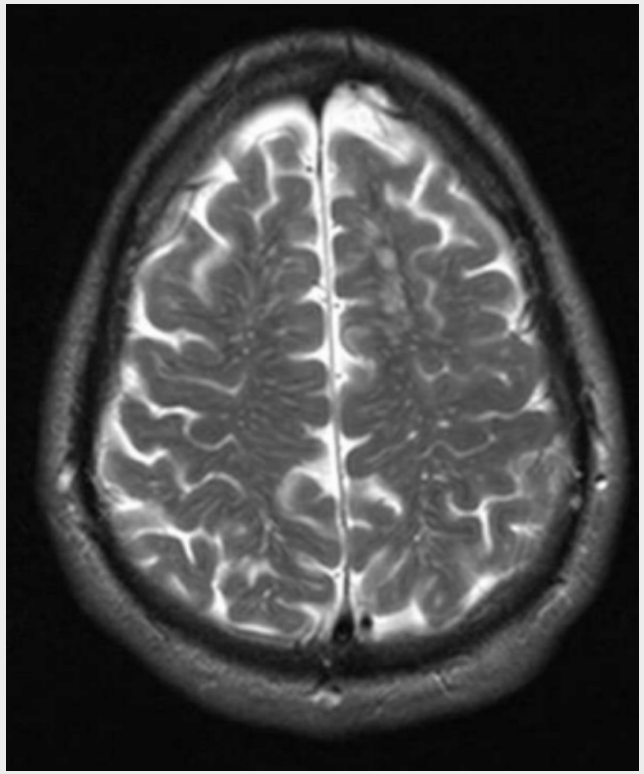
Widened perivascular spaces: MRI







''état cribré''



Widened perivascular spaces

Original Paper

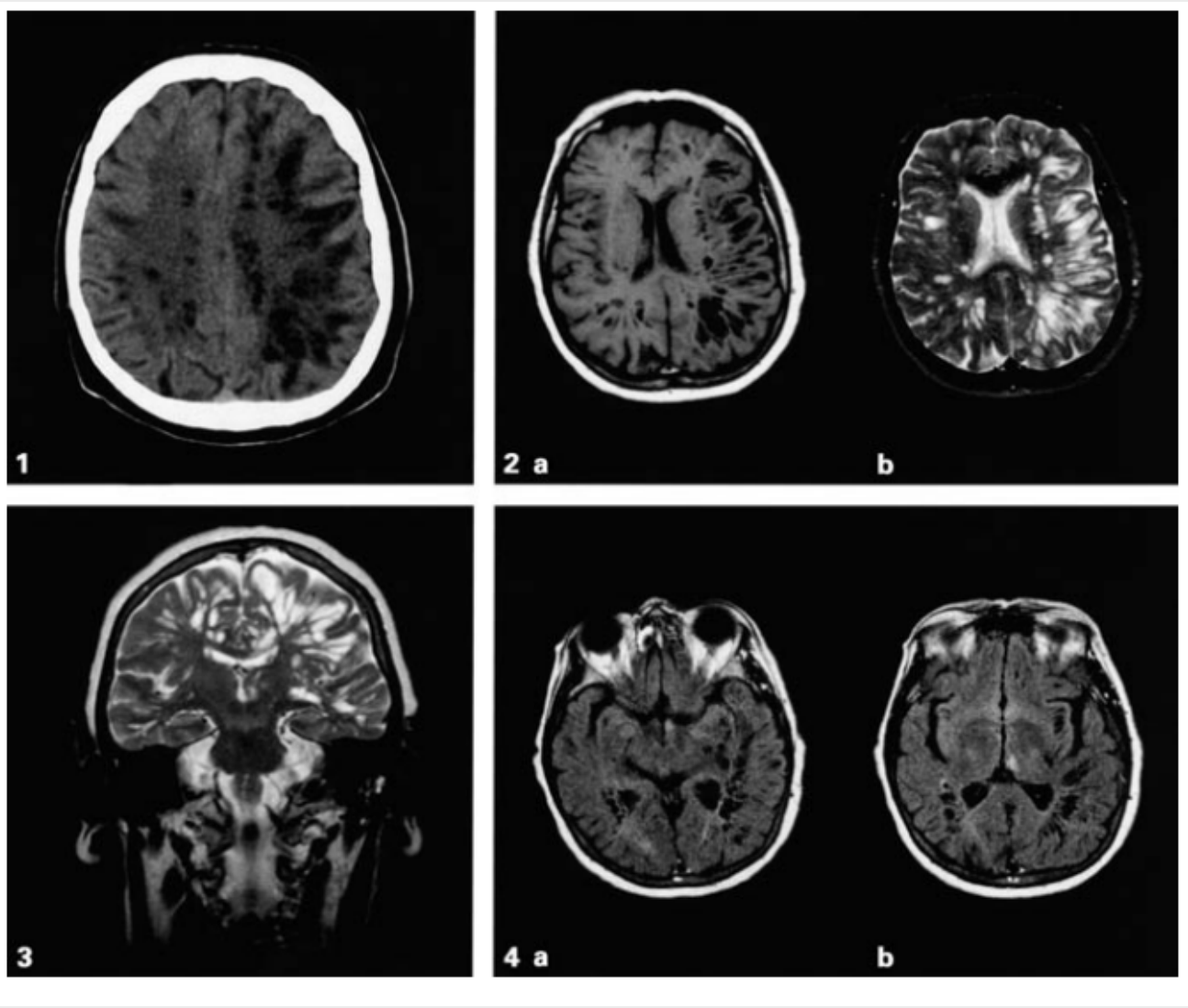
Cerebrovascular Diseases

Cerebrovasc Dis 2001;12:287–290

2001

Subcortical Dementia Associated with Striking Enlargement of the Virchow-Robin Spaces and Transneural Degeneration of the Left Mammillo-Thalamic Tract

Carla Uggetti[a] Maria Grazia Egitto[a] Anna Pichiecchio[a] Elena Sinforiani[b]
Maria Stella Bevilacqua[b] Anna Cavallini[c] Giuseppe Micieli[c]

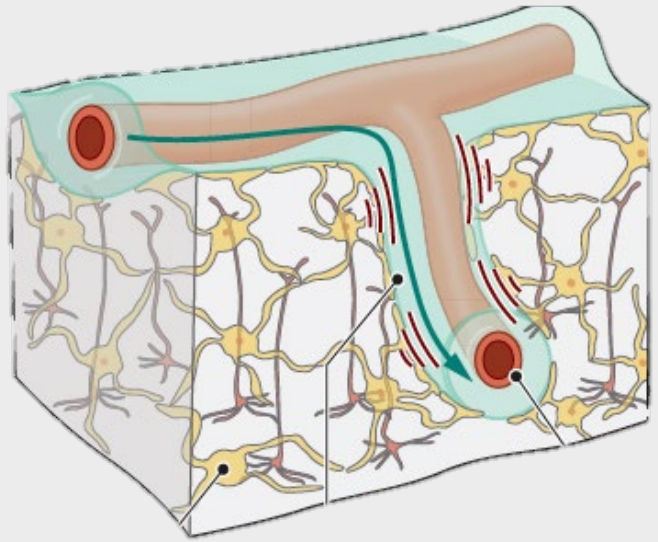


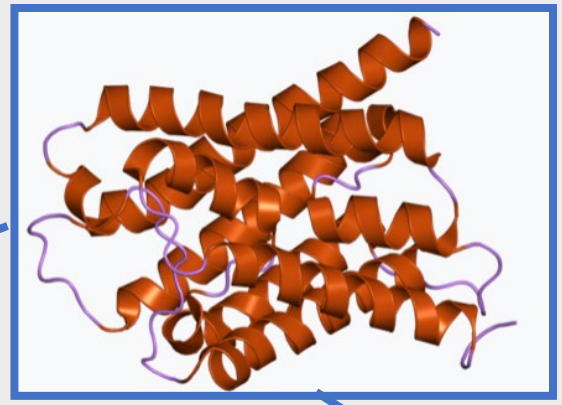
Glymphatic system: functional features

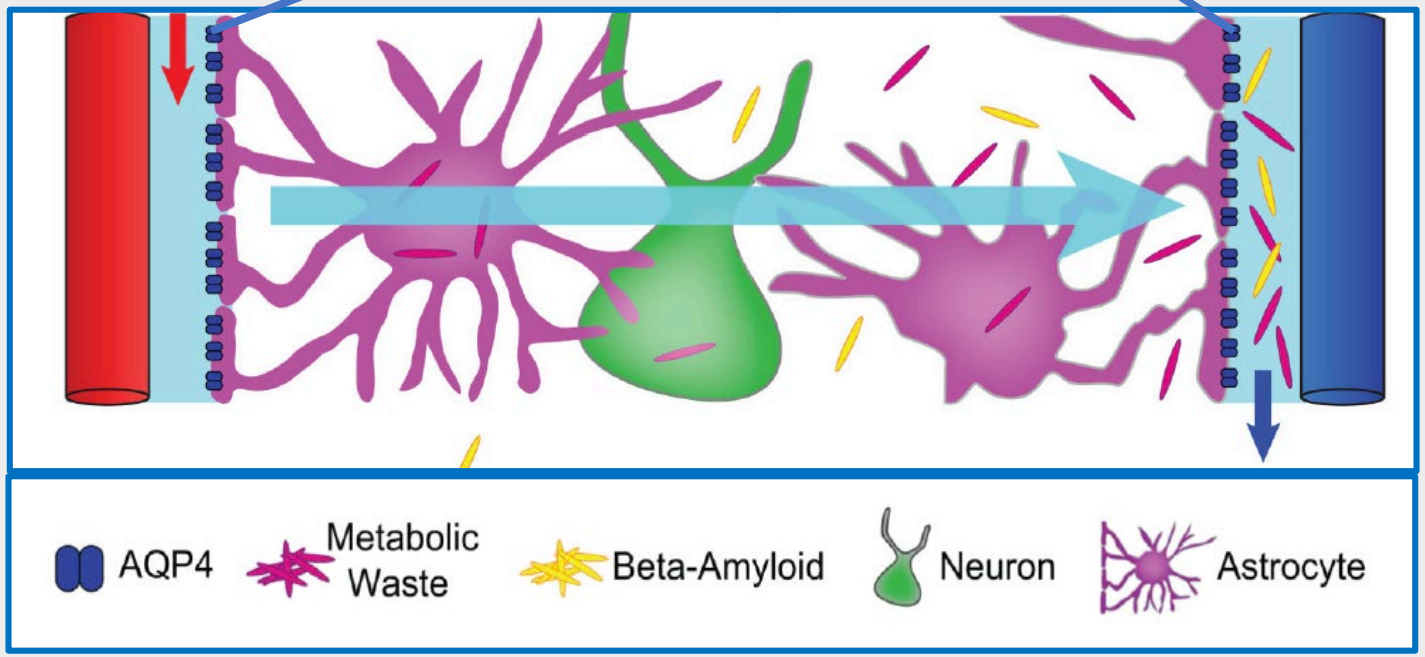
Neurochem Res, 2015

The Glymphatic System – A Beginner's Guide

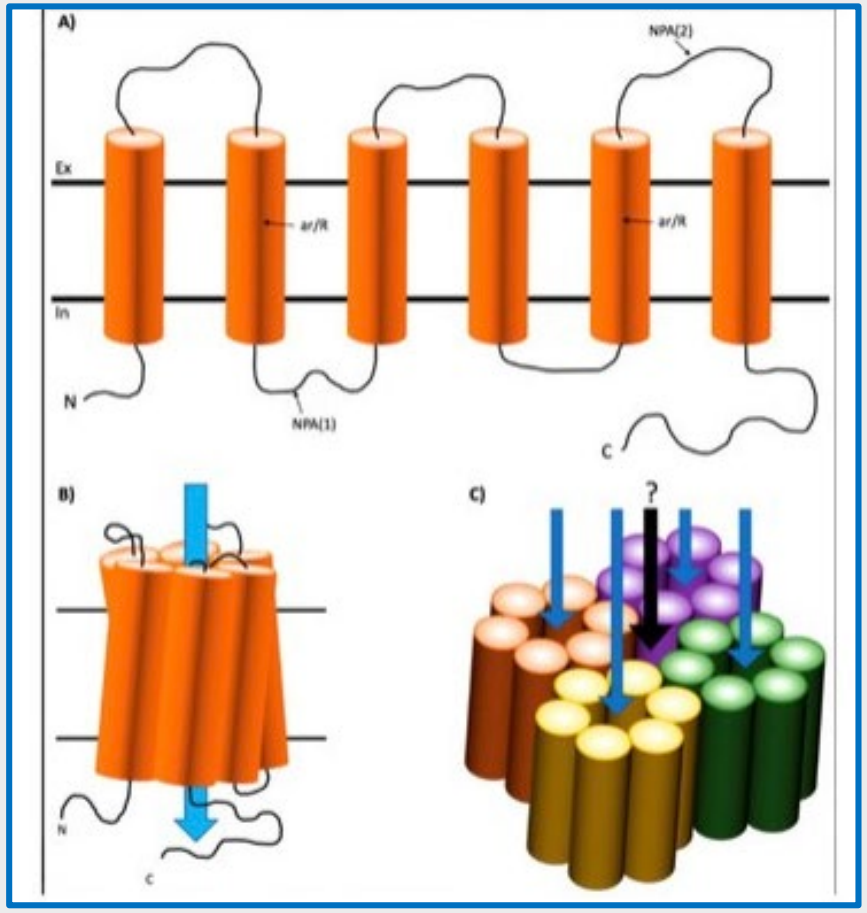
Nadia Aalling Jessen[1], **Anne Sofie Finmann Munk**[1], **Iben Lundgaard**[1], and **Maiken Nedergaard**

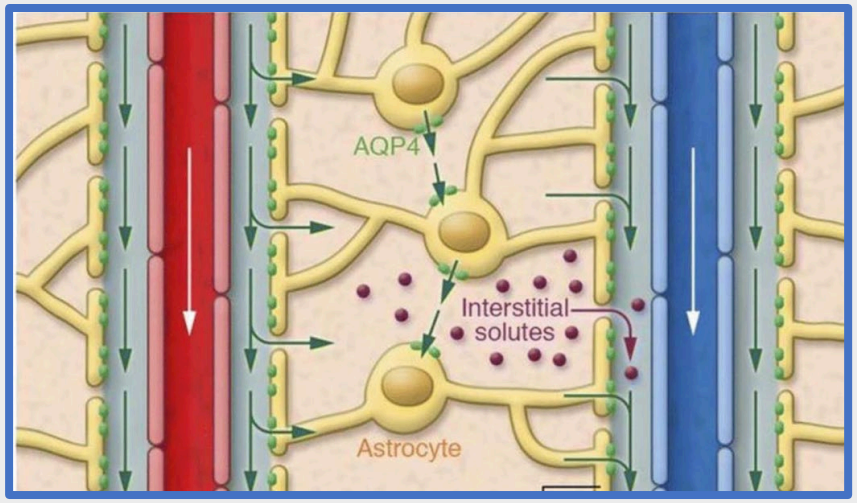


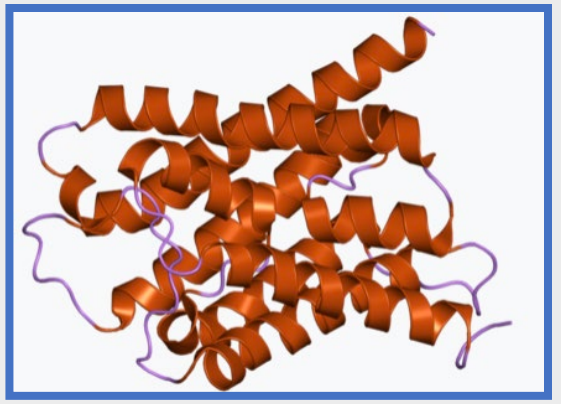


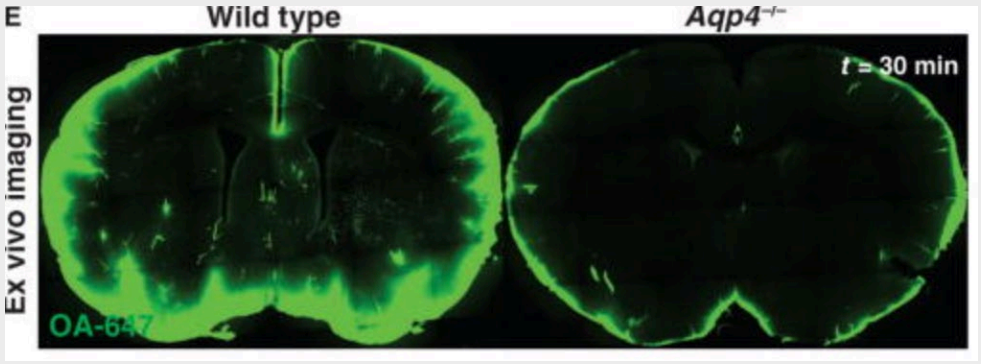


AQP4

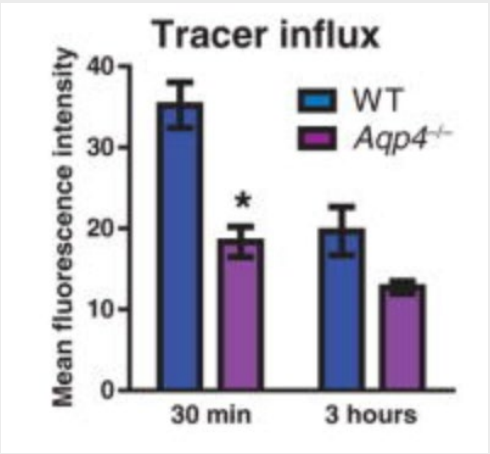








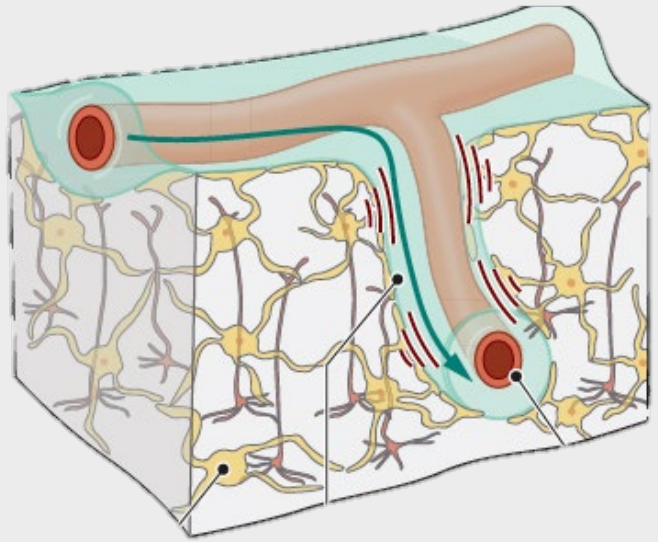
Clearance of fluorescent-tagged soluble ß-A

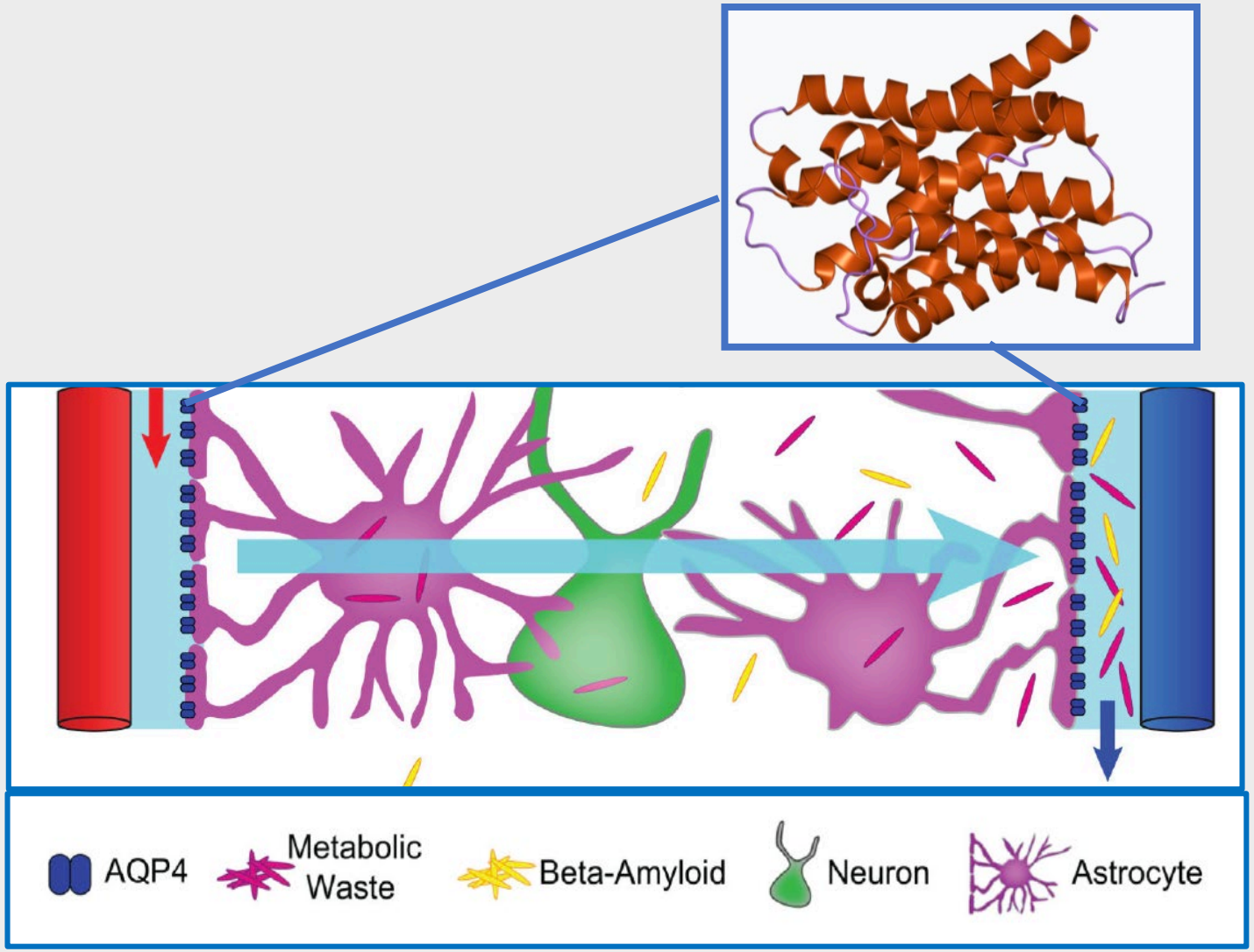


Glymphatic system: functional features

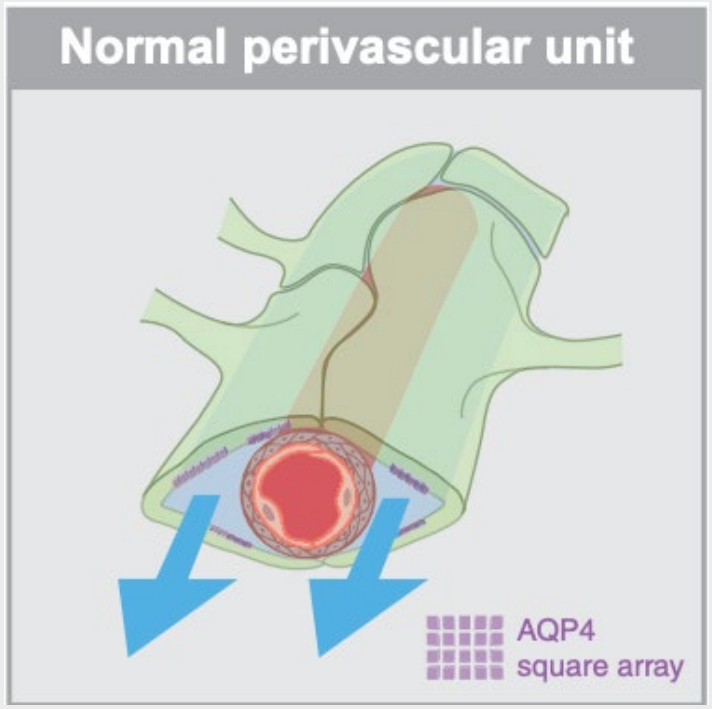
A → V

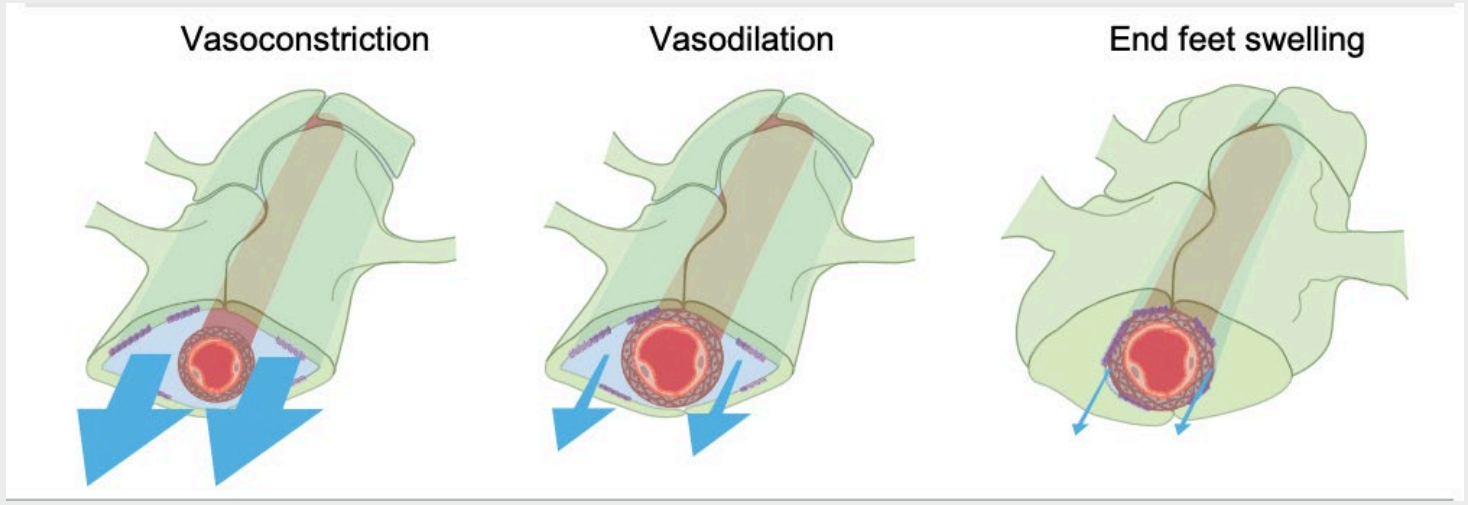
- AQP4 (>>50%)
- Arterial pulsation
- Breathing
- CSF production
- Intracranic pressure





Glymphatic system: functional changes



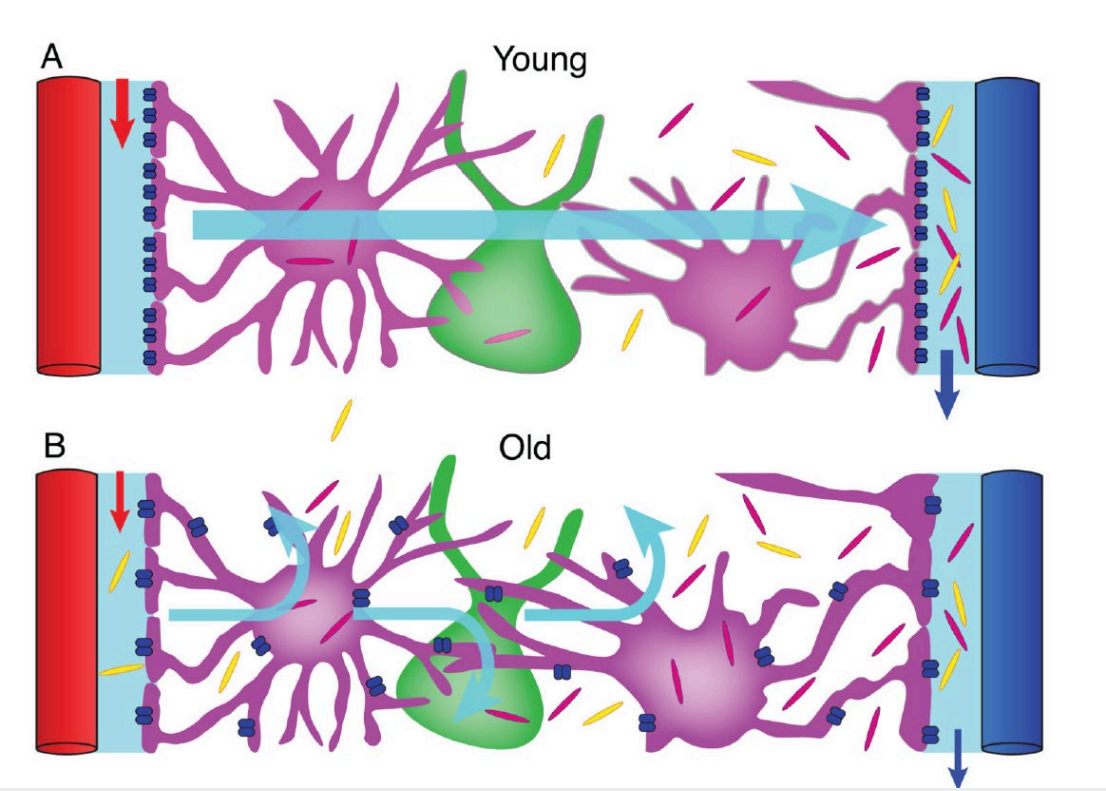


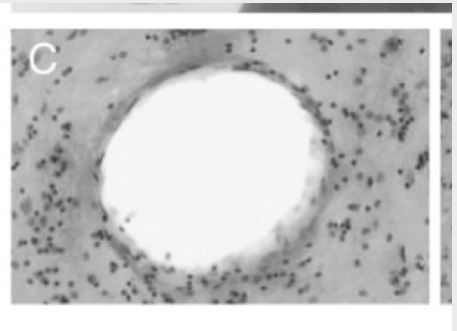
Hablitz & Nedergaard
J Neurosci 2021

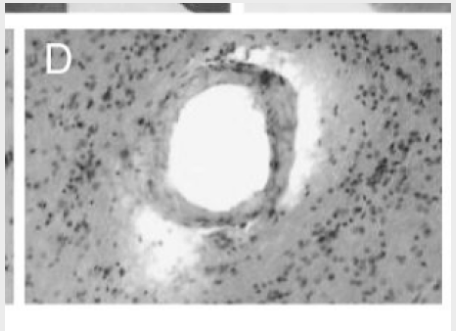
Glymphatic system: age

	Beginning of development	Maturation
Ventricles	IV week GA	birth
AQP4 polarization	XXIV week GA	birth
Aracnoid granulation	Birth	18 months
Glymphatic function	Birth	30-40 years

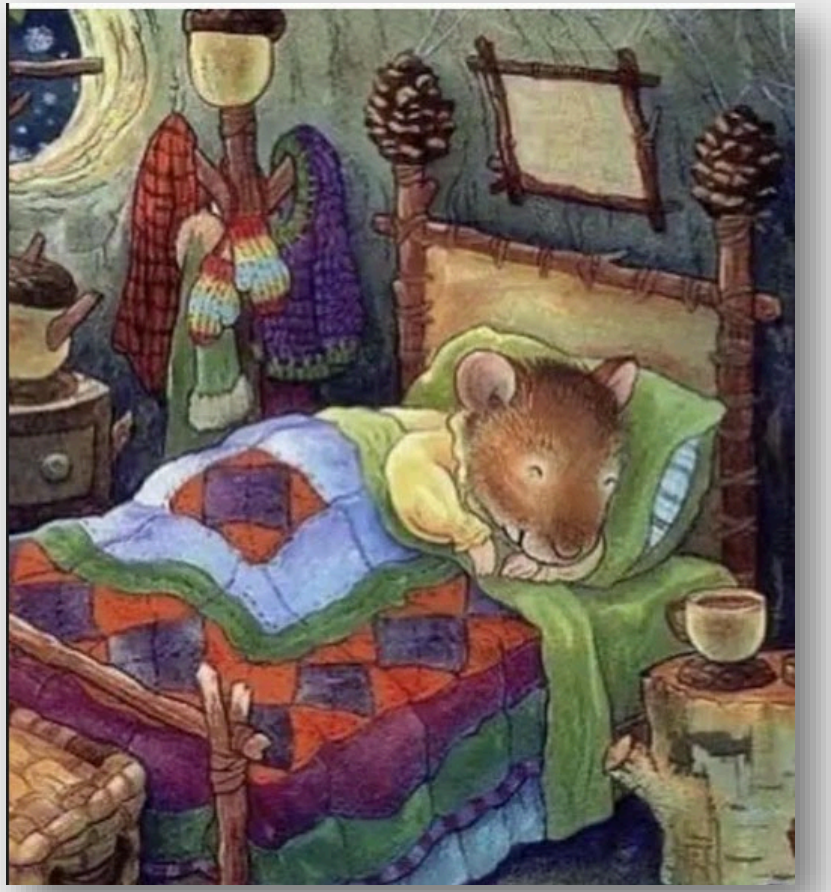
Glymphatic system: aging







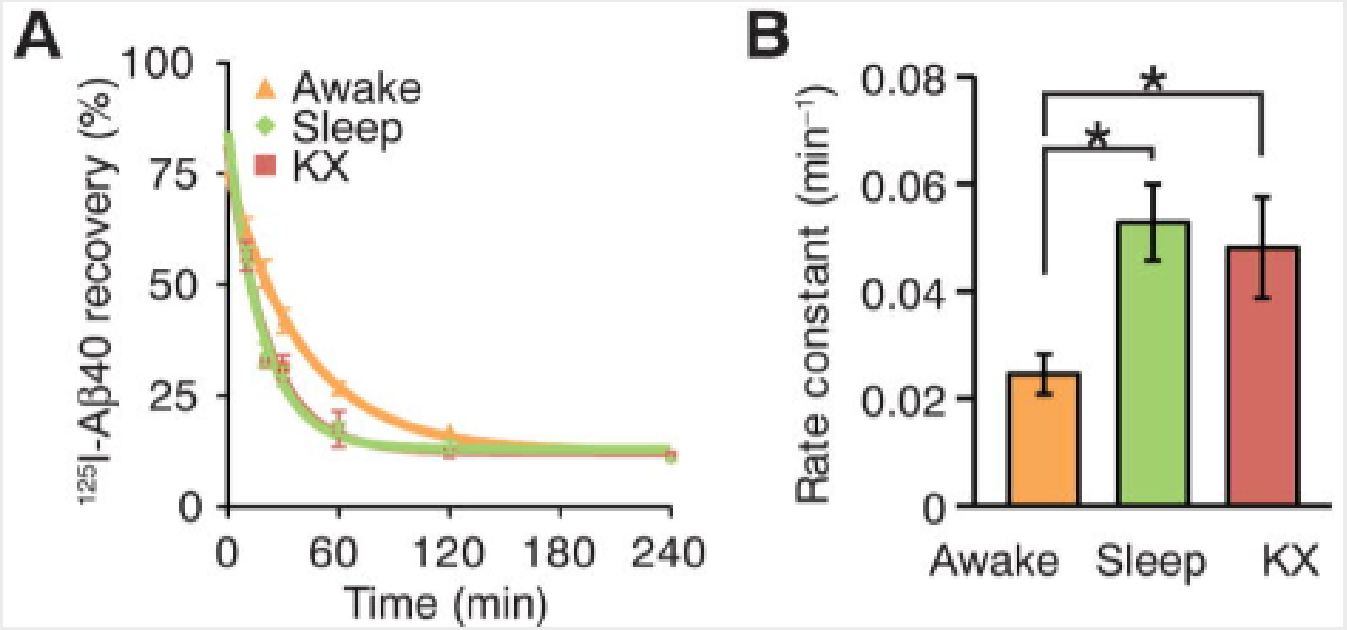
Glymphatic system: sleep



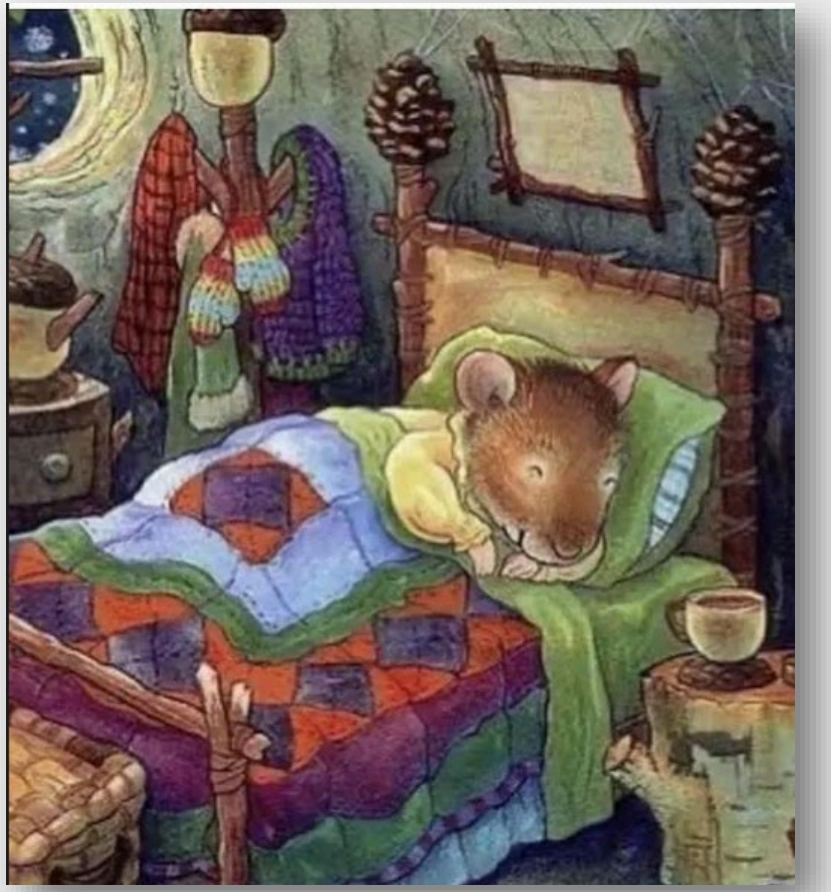
Science, 2013

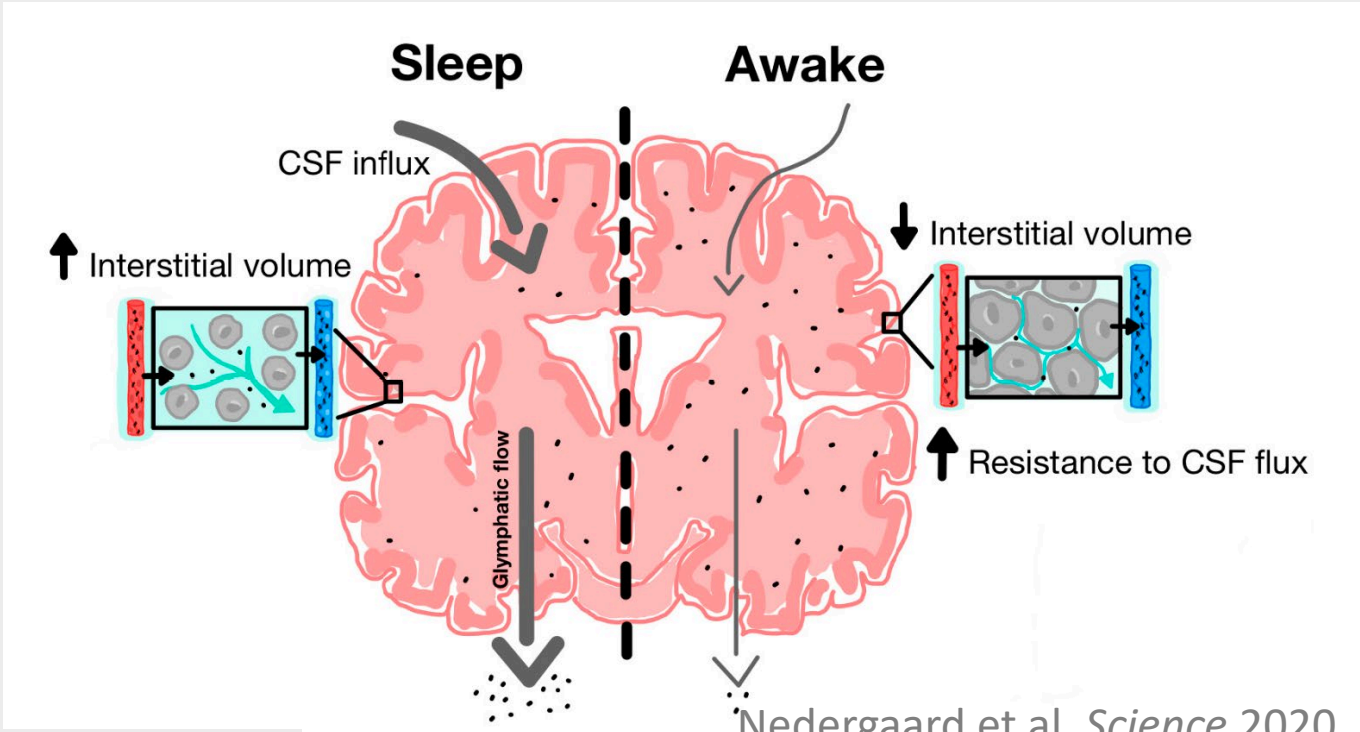
Sleep Drives Metabolite Clearance from the Adult Brain

Lulu Xie[1,*], Hongyi Kang[1,*], Qiwu Xu[1], Michael J. Chen[1], Yonghong Liao[1], Meenakshisundaram Thiyagarajan[1], John O'Donnell[1], Daniel J. Christensen[1], Charles Nicholson[2], Jeffrey J. Iliff[1], Takahiro Takano[1], Rashid Deane[1], and Maiken Nedergaard[1,†]



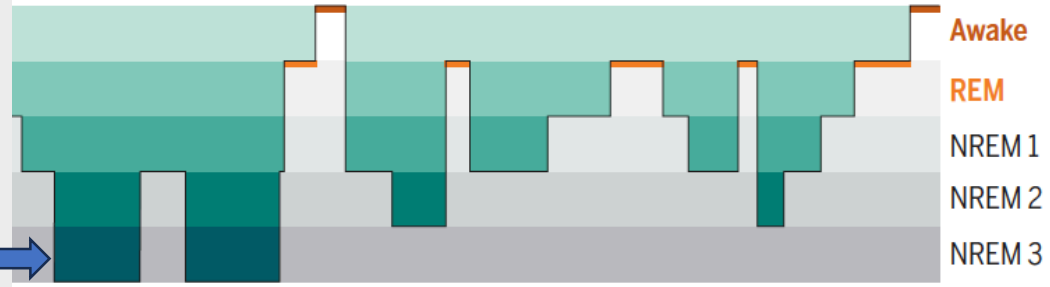
Glymphatic system: sleep



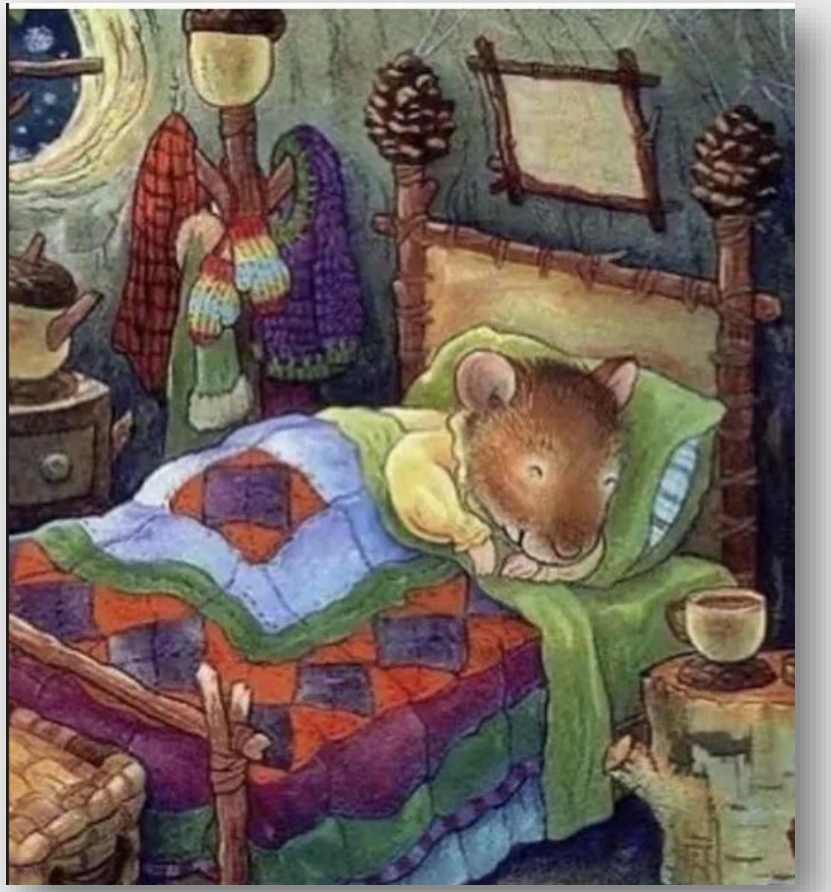


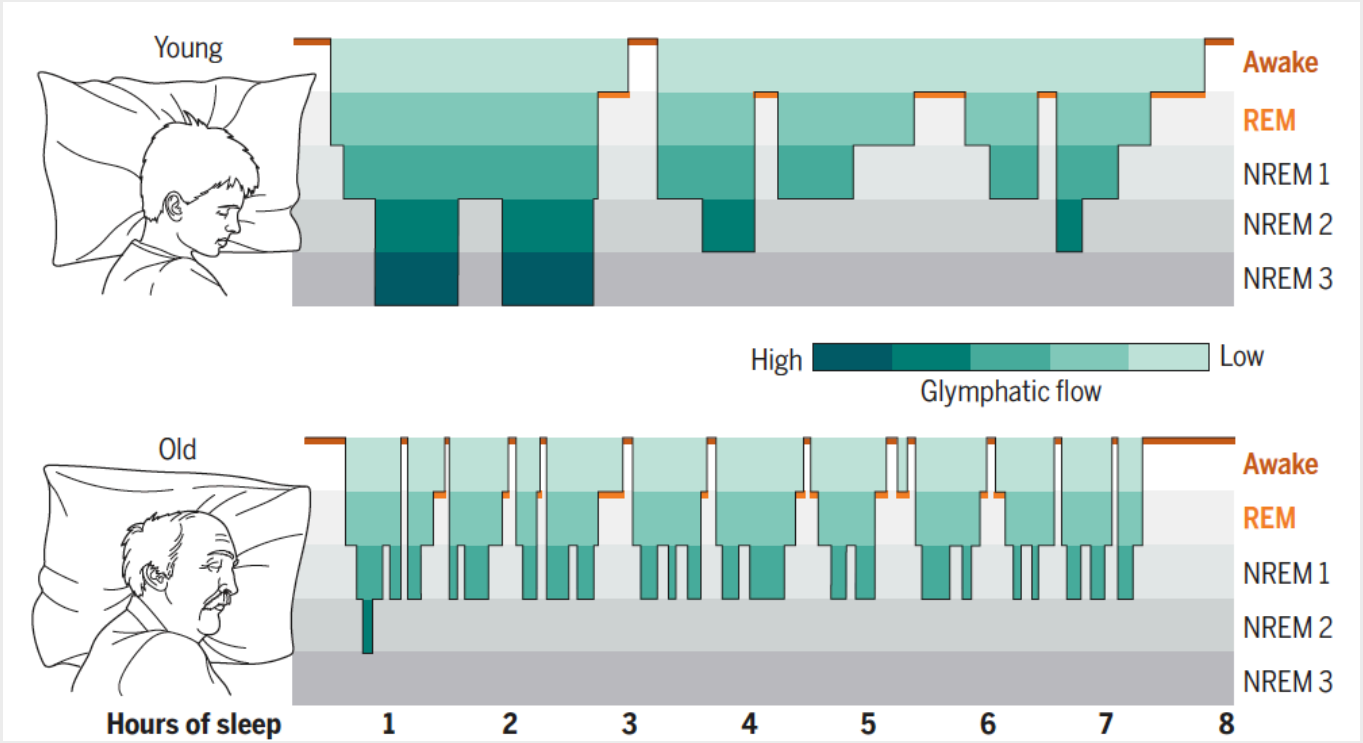
Nedergaard et al, *Science* 2020

Delta waves
1-4 Hz



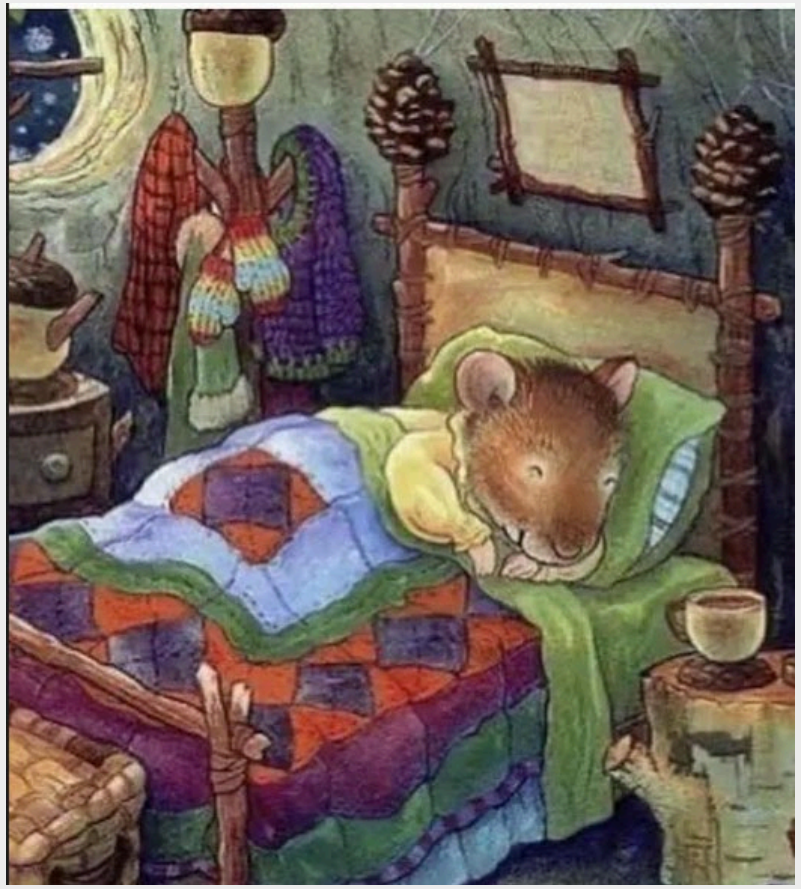
Glymphatic system: sleep





Nedergaard et al, *Science* 2020

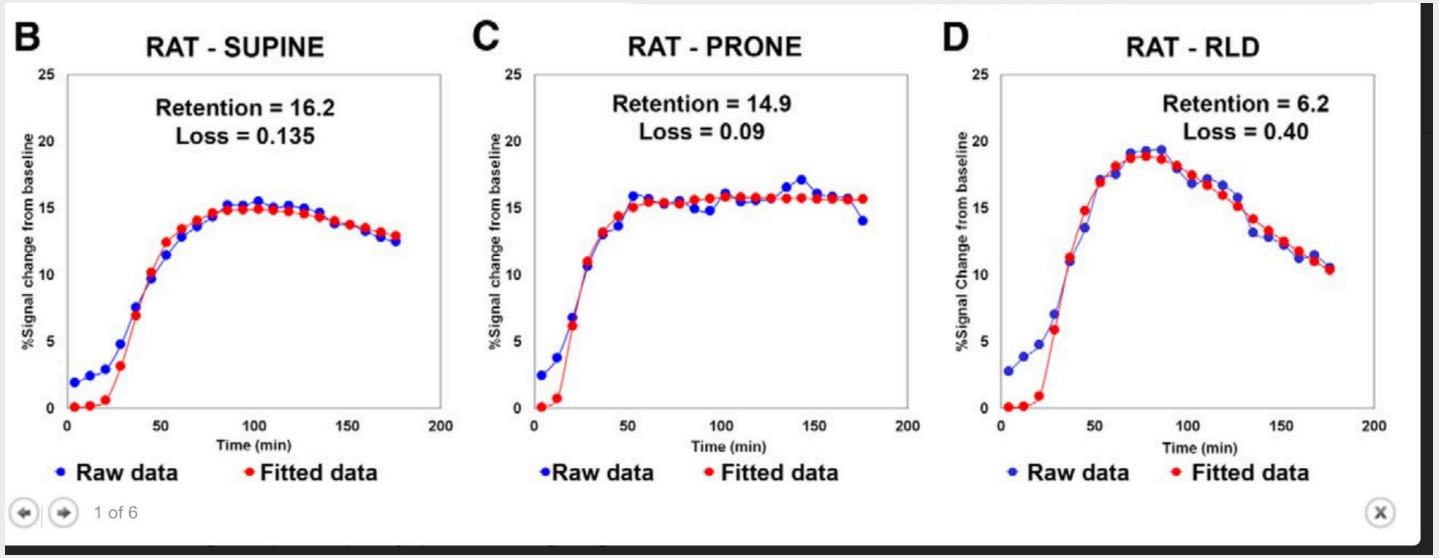
Glymphatic system: posture



J Neurosci. 2015 Aug 5;35(31):11034-44. doi: 10.1523/JNEUROSCI.1625-15.2015.

The Effect of Body Posture on Brain Glymphatic Transport

Hedok Lee [1], Lulu Xie [2], Mei Yu [3], Hongyi Kang [2], Tian Feng [4], Rashid Deane [2], Jean Logan [5], Maiken Nedergaard [2], Helene Benveniste [6]



Glymphatic system: *«need to sleep?»*

Gly and Sleep:

- Phase (NREM3)
- Young age
- Lateral posture
- AQP4

Glymphatic system: definition

Glial-lymphatic

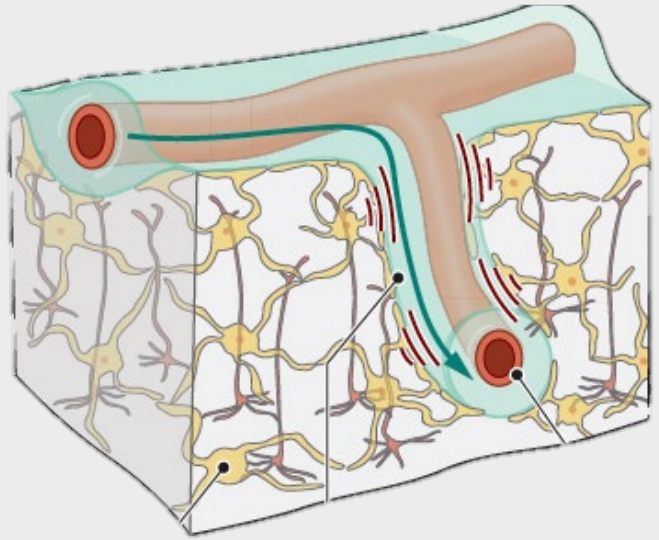
process that serves as a pseudo-lymphatic function in the CNS

Astrocyte-mediated transport of CSF and ISF

that clears metabolic waste from the interstitial space of the brain parenchyma

primarily during non-REM sleep and states of high slow wave activity.

Glymphatic system



STUDY METHODS

Glymphatic system : study methods

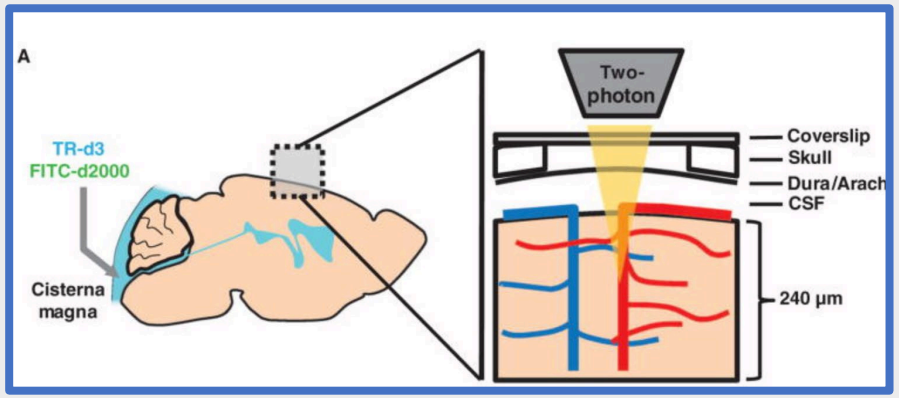
IMAGING

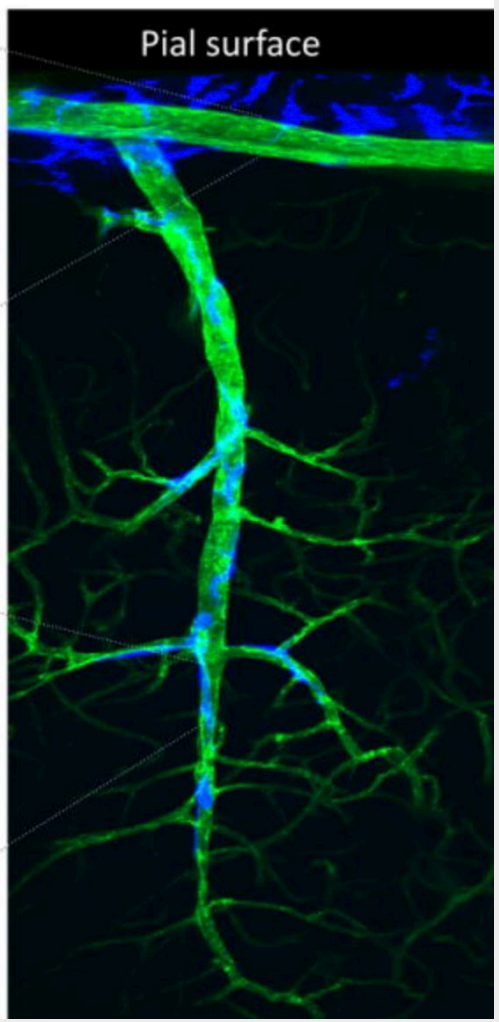
- Two-photon imaging
- PET
- Conventional MR (CT)
- MRI by advanced techniques

Glymphatic system : study methods

Tracers

In vivo two-photon imaging

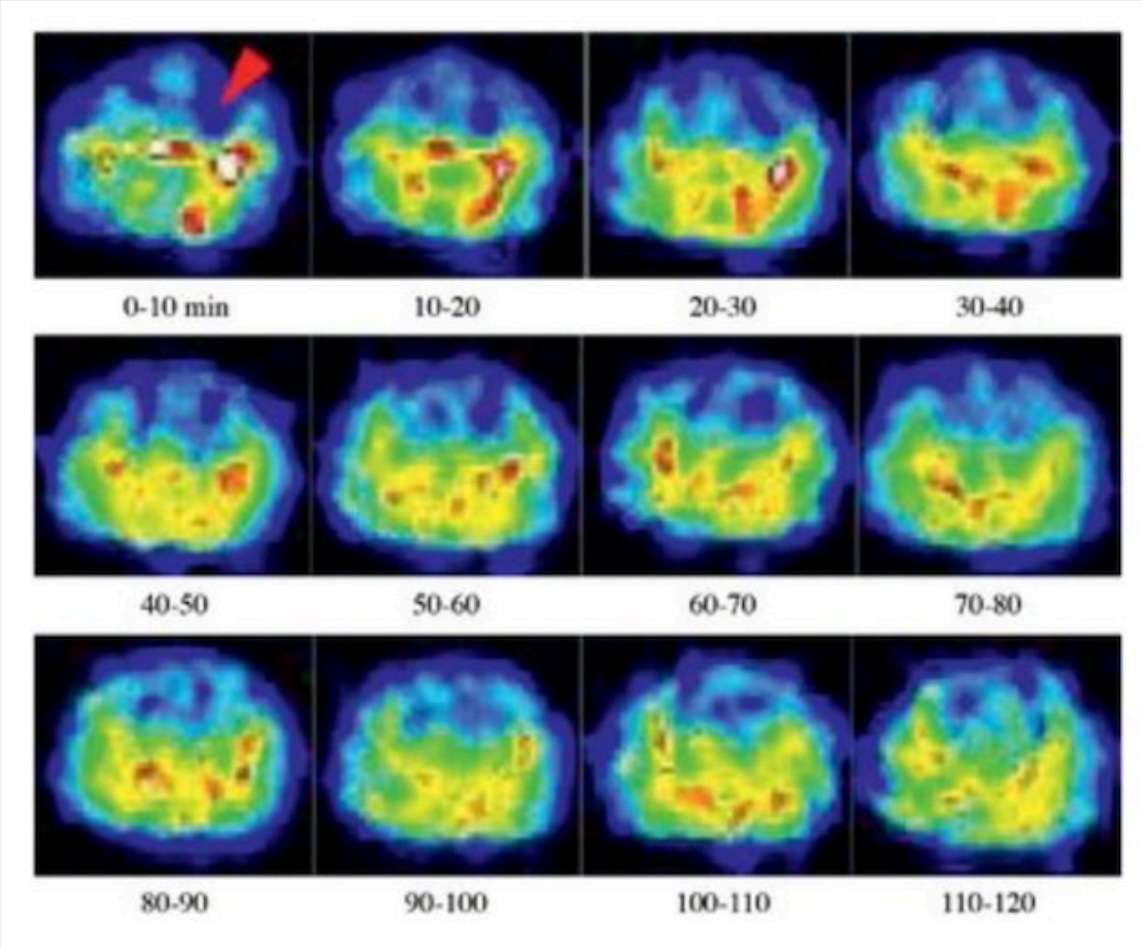




Glymphatic system: PET imaging

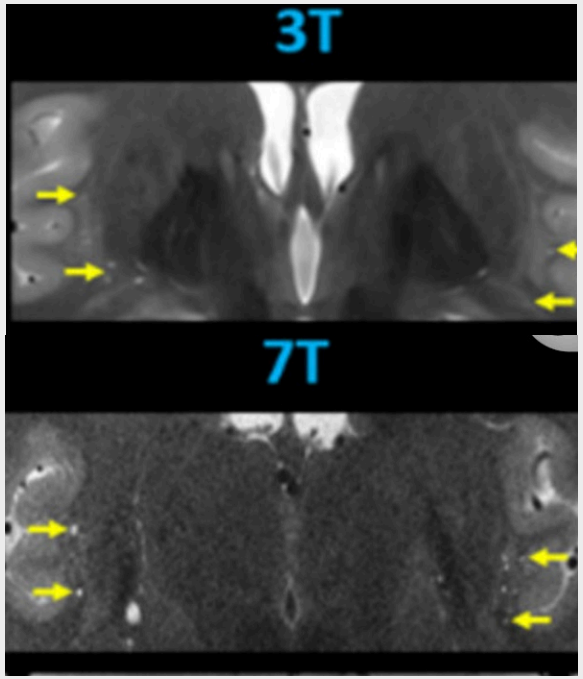
PET

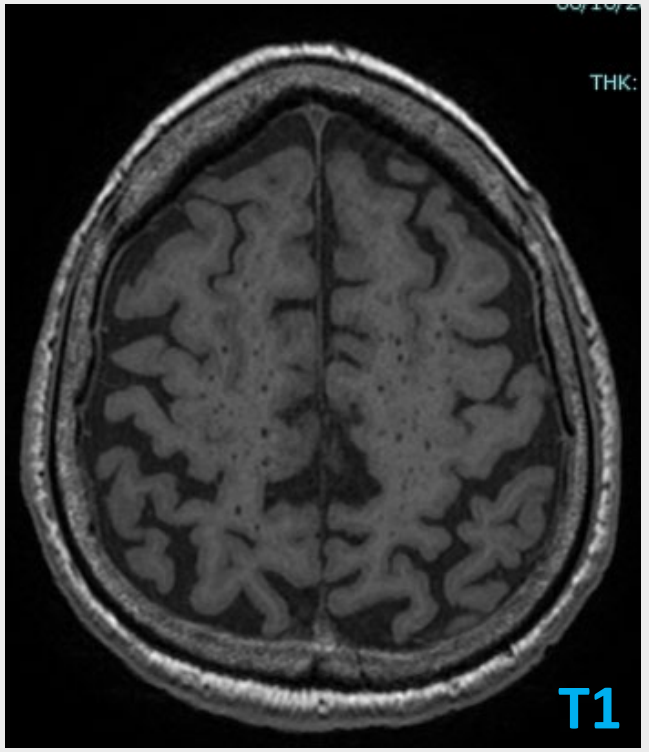
sperimental studies by [^{18}F]-labeled PEG-liposomes

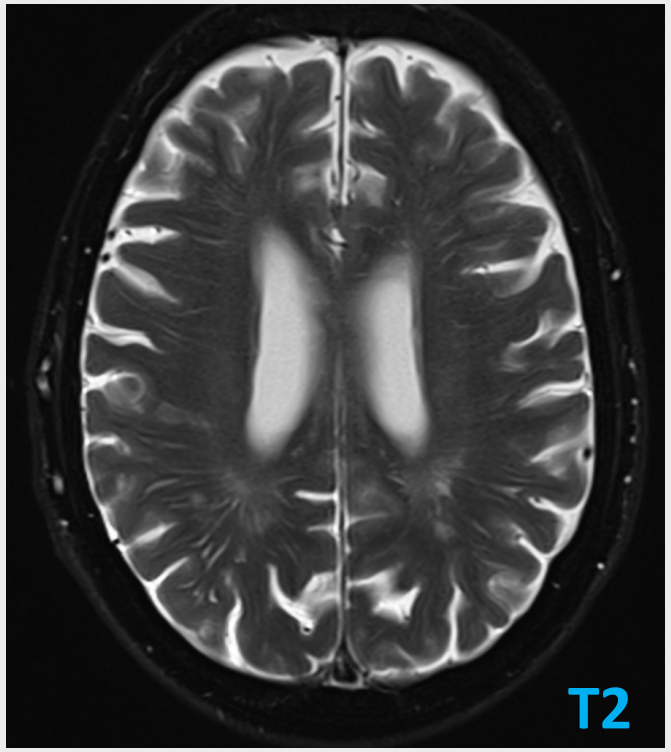


MRI

PVS



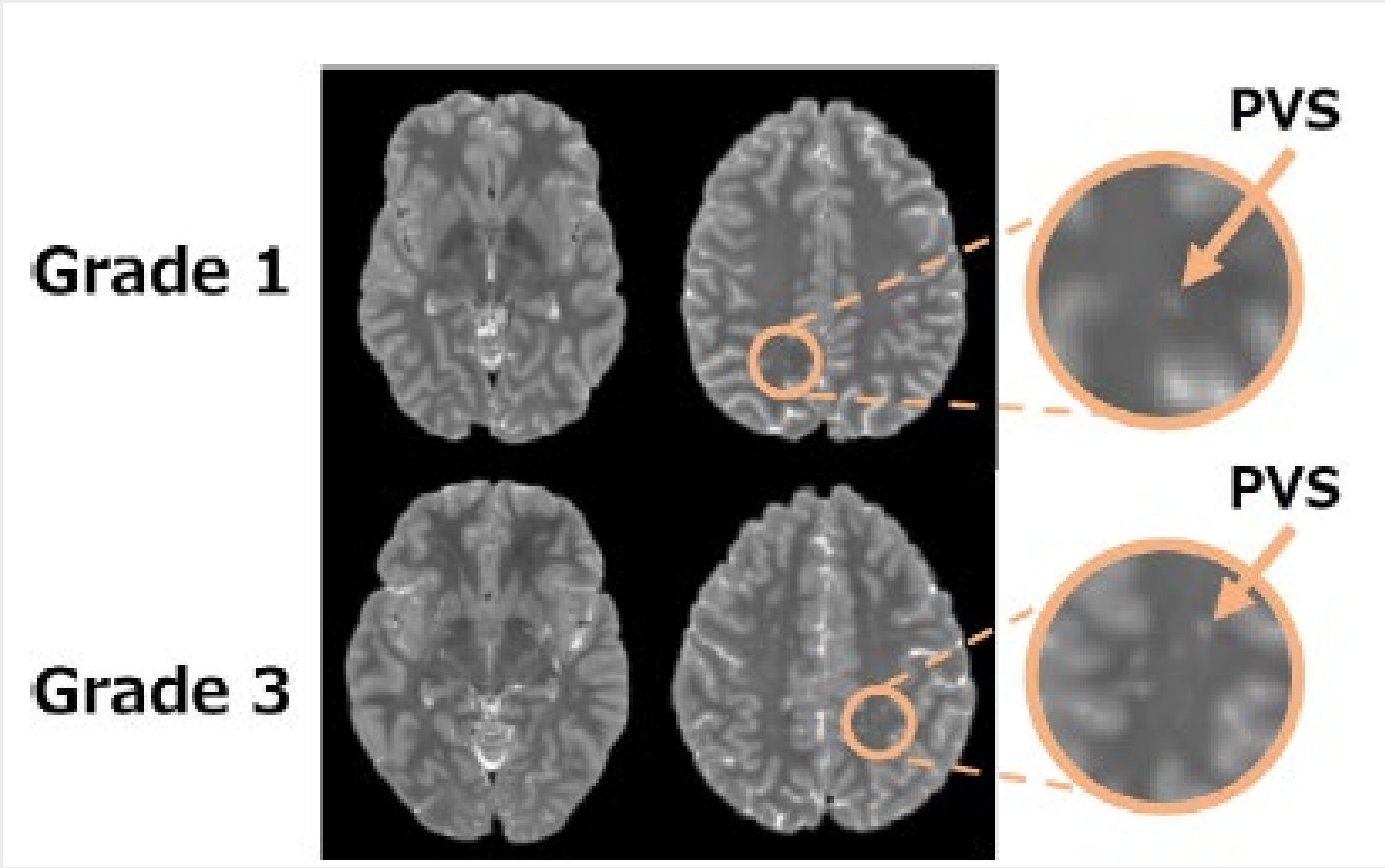




MRI: PVS

Potter scoring

grade	0:	0
grade	1:	1-10
grade	2:	11-20
grade	3:	21-40
grade	4:	> 40



Potter *et al*, Cerebrovasc Dis 2015

MRI: PVS

computerized systems

A critical guide to the automated quantification of perivascular spaces in magnetic resonance imaging

William Pham[1*], Miranda Lynch[1], Gershon Spitz[1,2], Terence O'Brien[1,3,4,5], Lucy Vivash[1,3,4,5], Benjamin Sinclair[1,3,4*] and Meng Law[1,6,7]

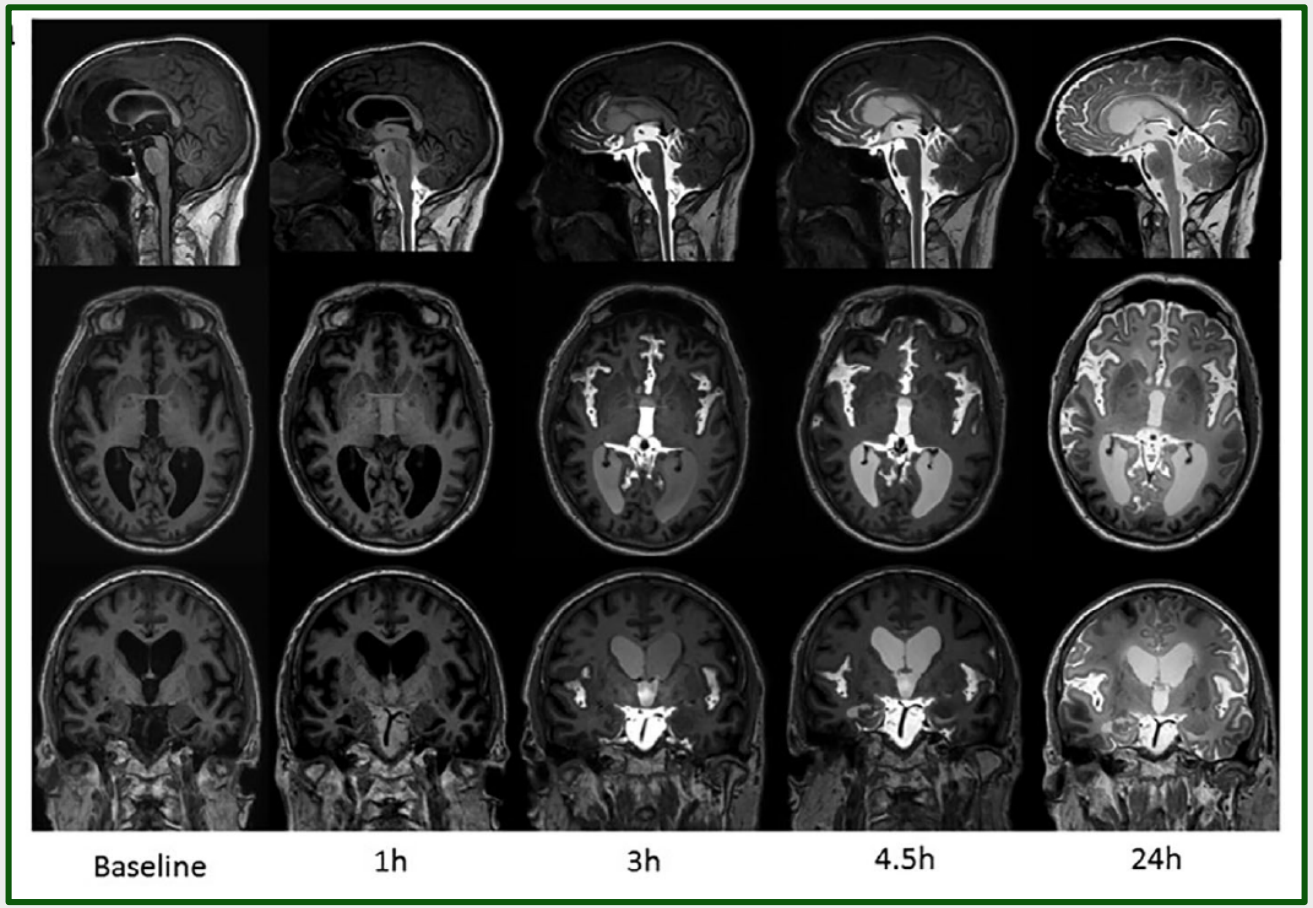
Front Neurosci 2022

Number and volume of perivascular spaces

- -> riproducibility
- excellent correlation with biological variables and pathology

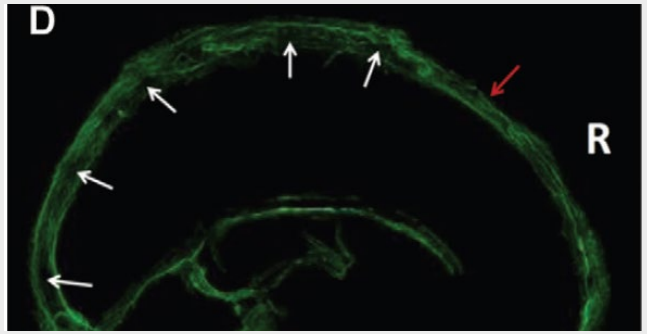
c.e. MRI (Gd)

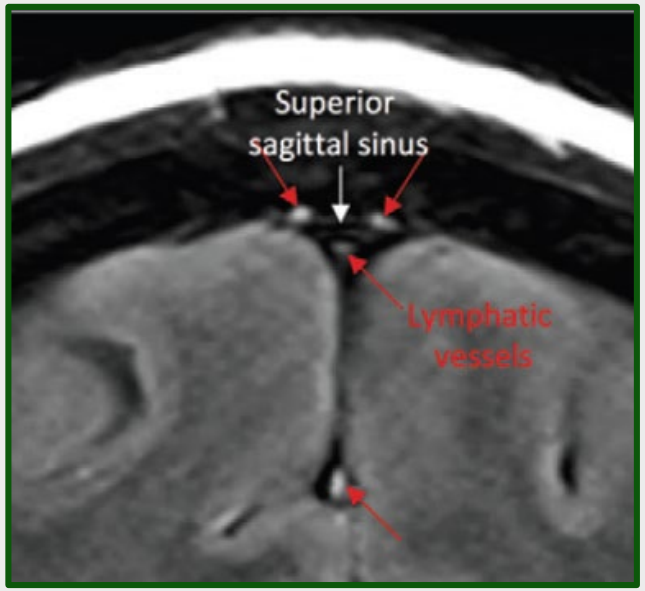
Cisternography

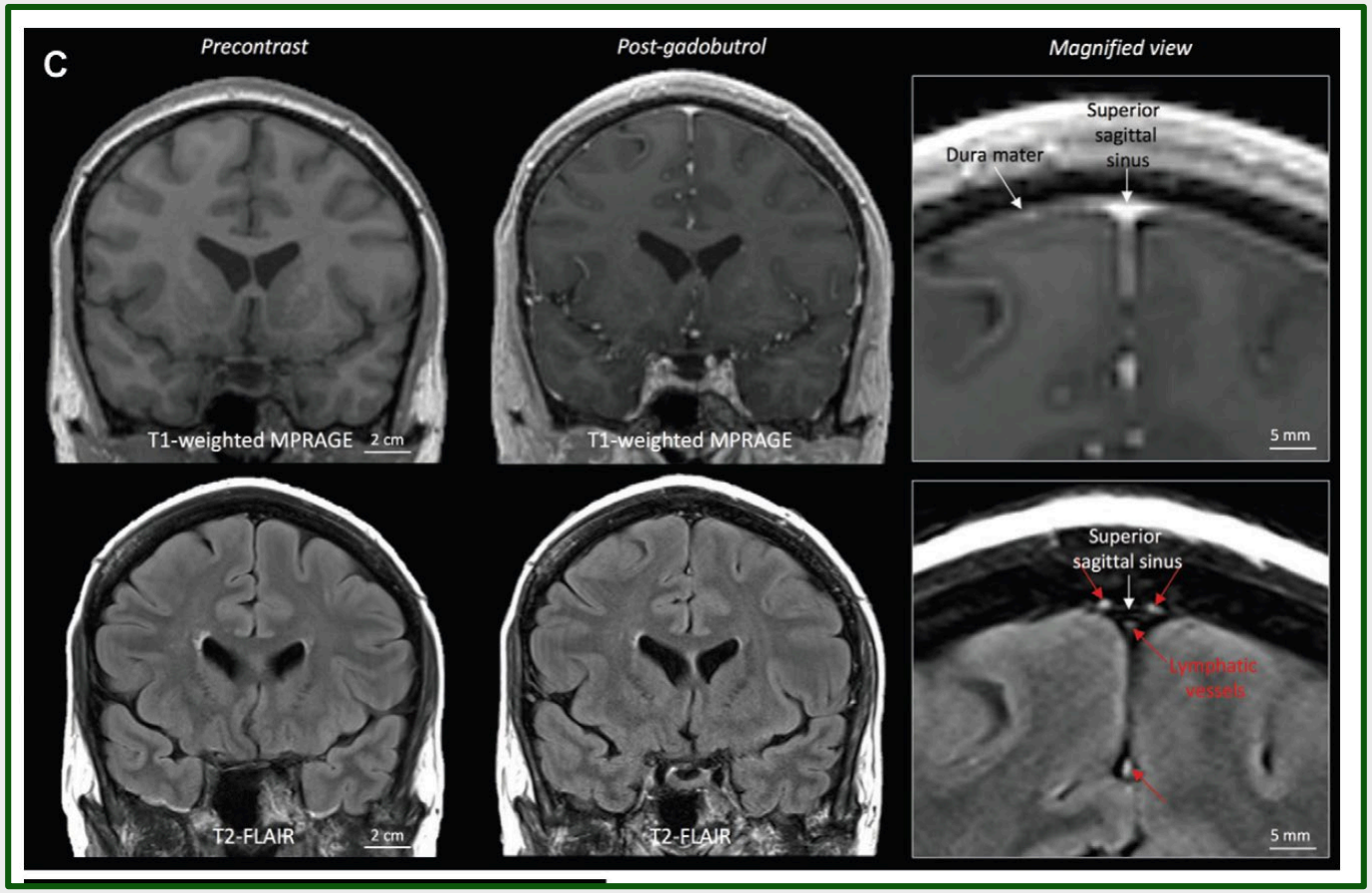


Taoka et al, 2020

c.e. MRI (Gd)







Ringstad et al, 2018

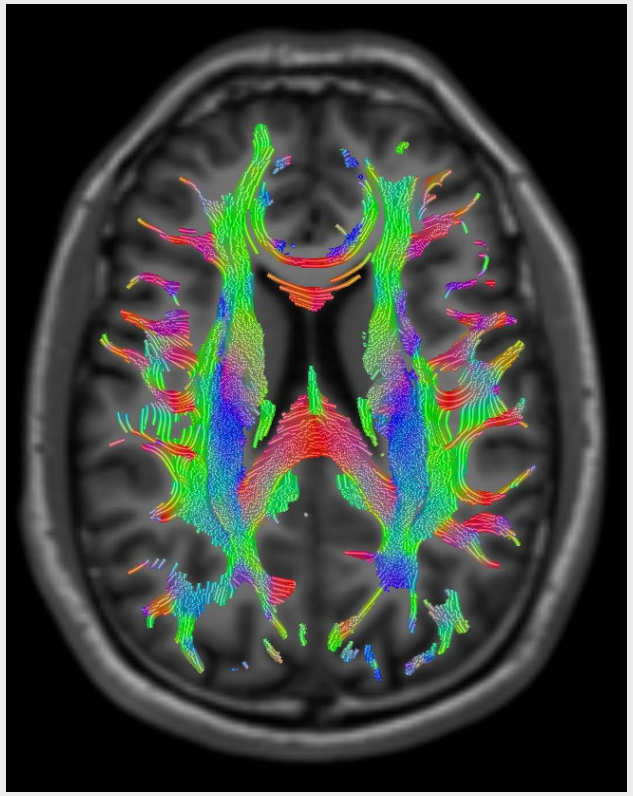
MRI: advanced techniques

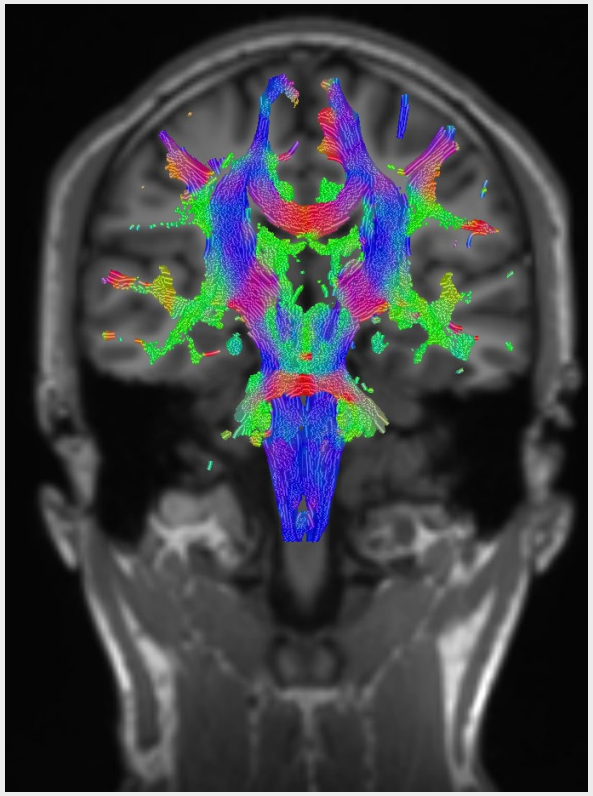
Spectroscopy	**CEST** *chemical exchange saturation transfer*
Perfusion	**ASL** *arterial spin labelling*
Diffusion/Perfusion	**IVIM** *intraxoxel incoherent motion*
Activation	**BOLD** *blood oxygen dependent level*

MRI: advanced techniques

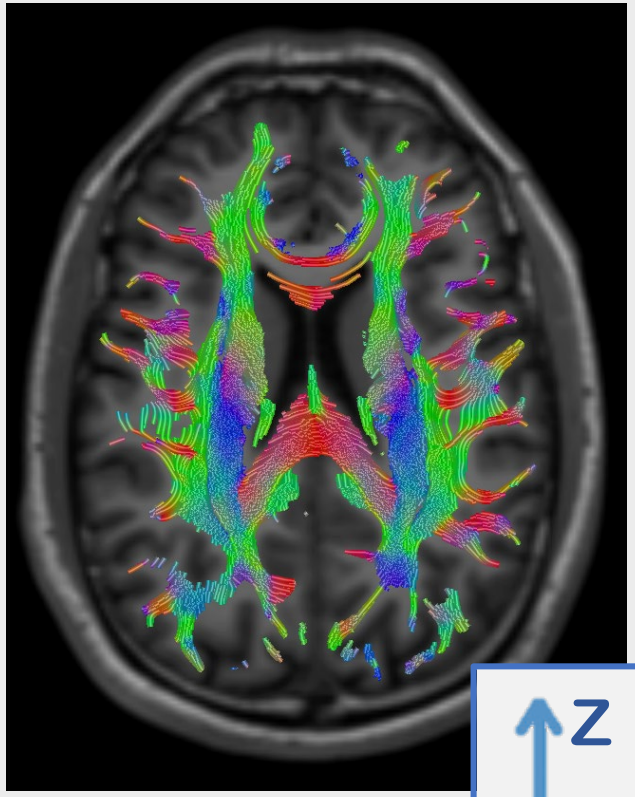
DTI

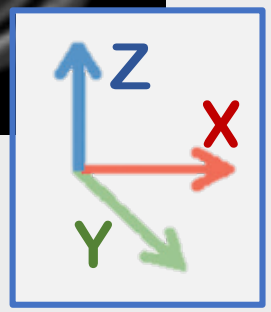
diffusion tensor imaging

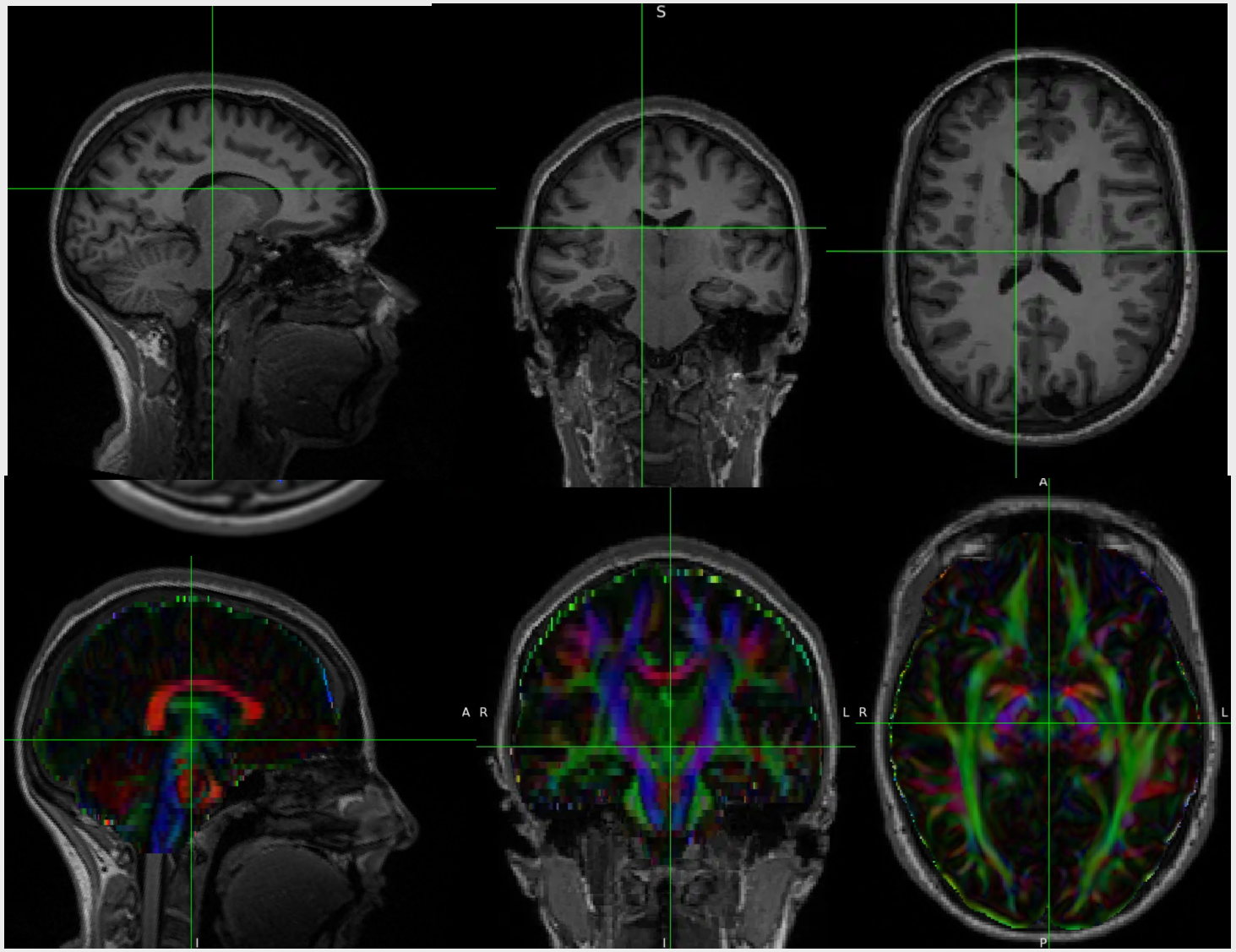




DTI







DTI ALPS

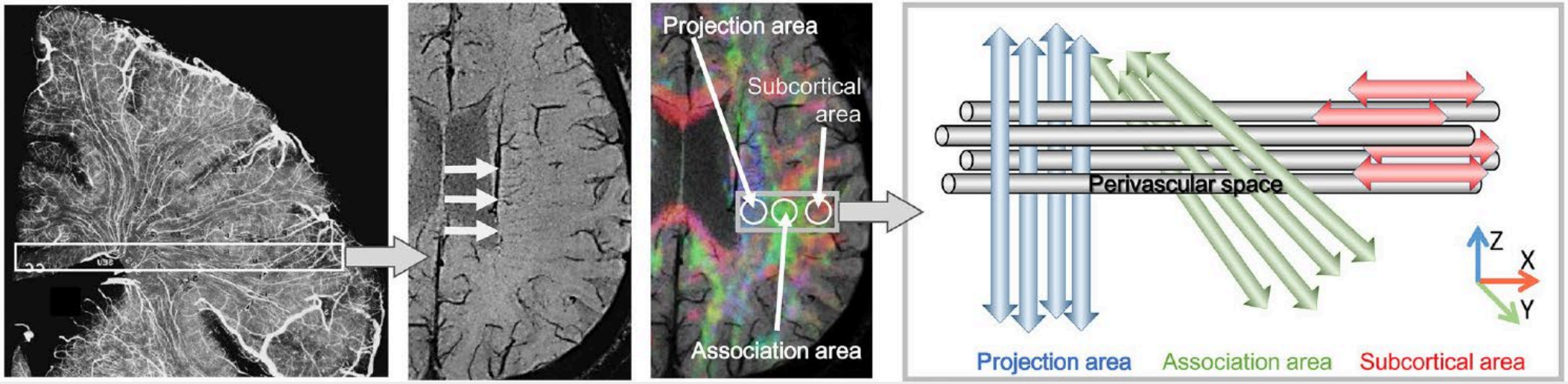
Diffusion Tensor Imaging ALong Perivascular Spaces

ORIGINAL ARTICLE

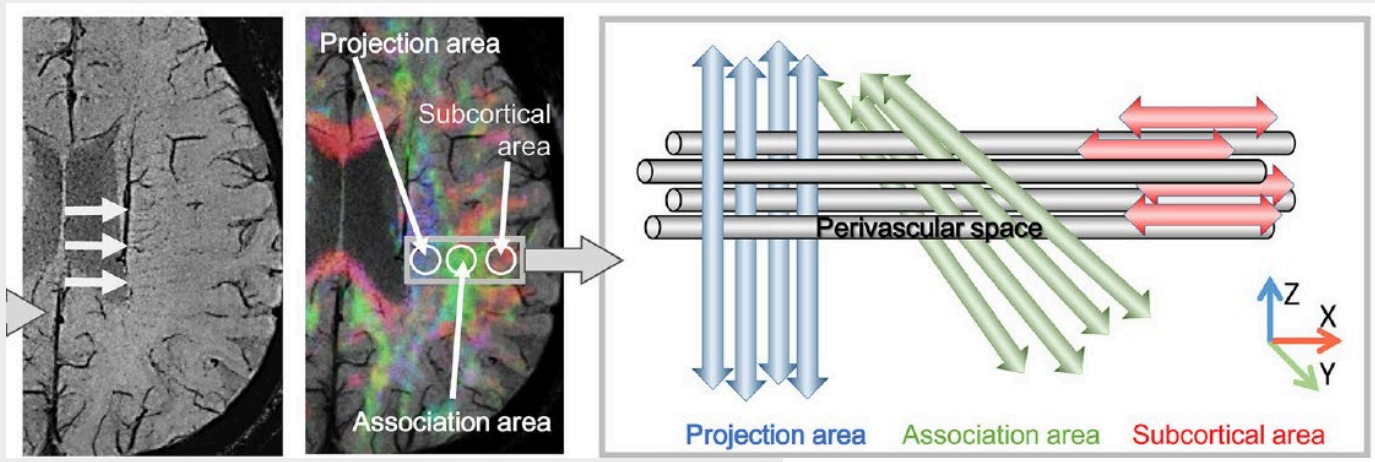
Jpn J Radiol 2017

Evaluation of glymphatic system activity with the diffusion MR technique: diffusion tensor image analysis along the perivascular space (DTI-ALPS) in Alzheimer's disease cases

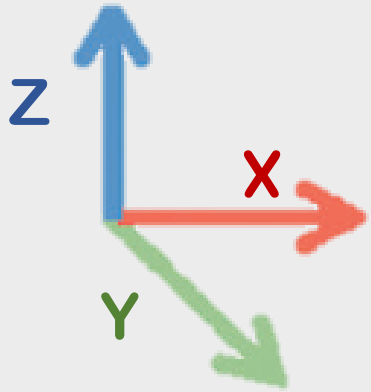
Toshiaki Taoka[1] · Yoshitaka Masutani[2] · Hisashi Kawai[1] · Toshiki Nakane[1] · Kiwamu Matsuoka[3] · Fumihiko Yasuno[3] · Toshifumi Kishimoto[3] · Shinji Naganawa[1]



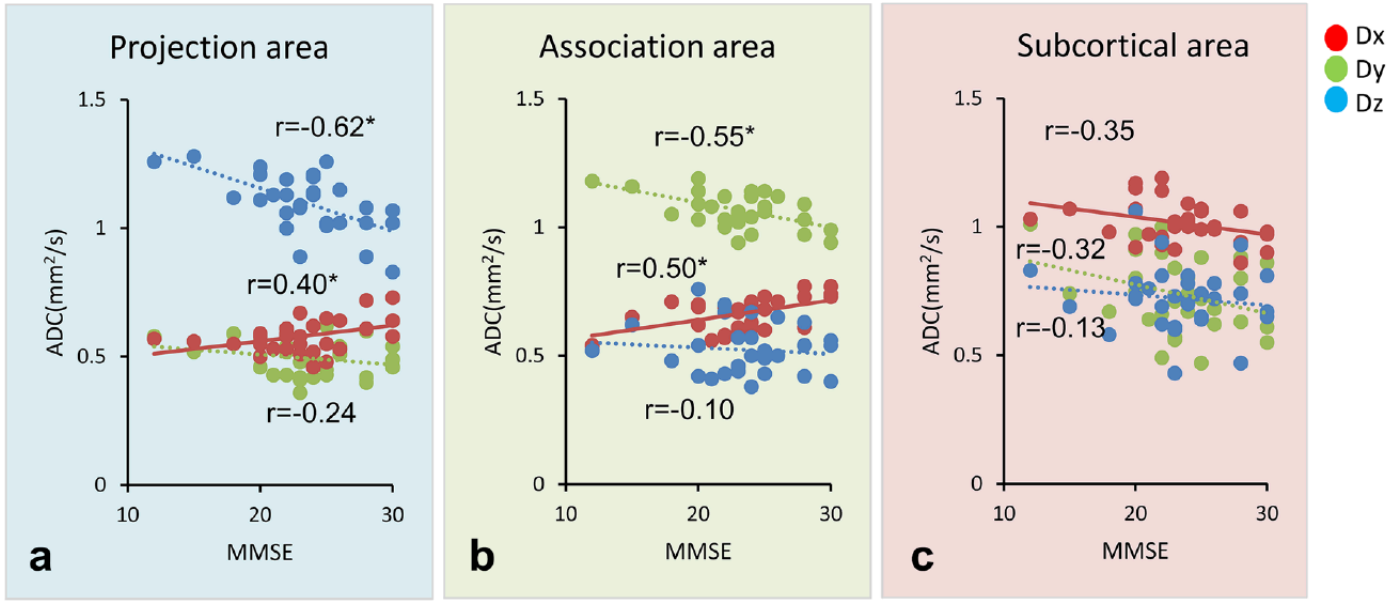
ADC



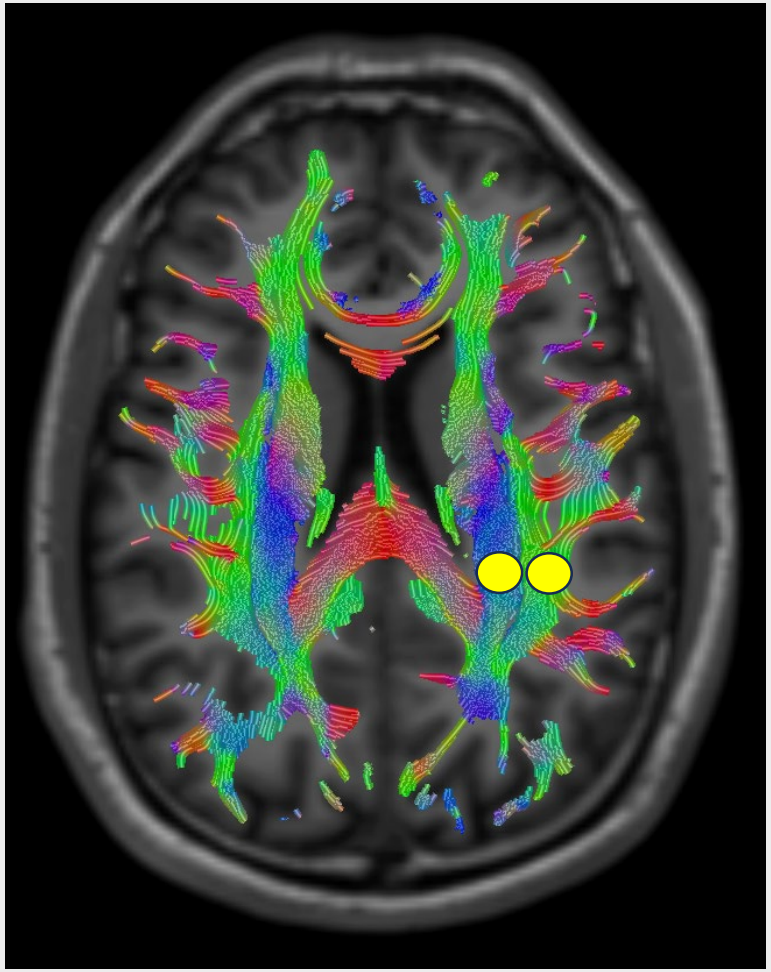
ADC → mm^2/s



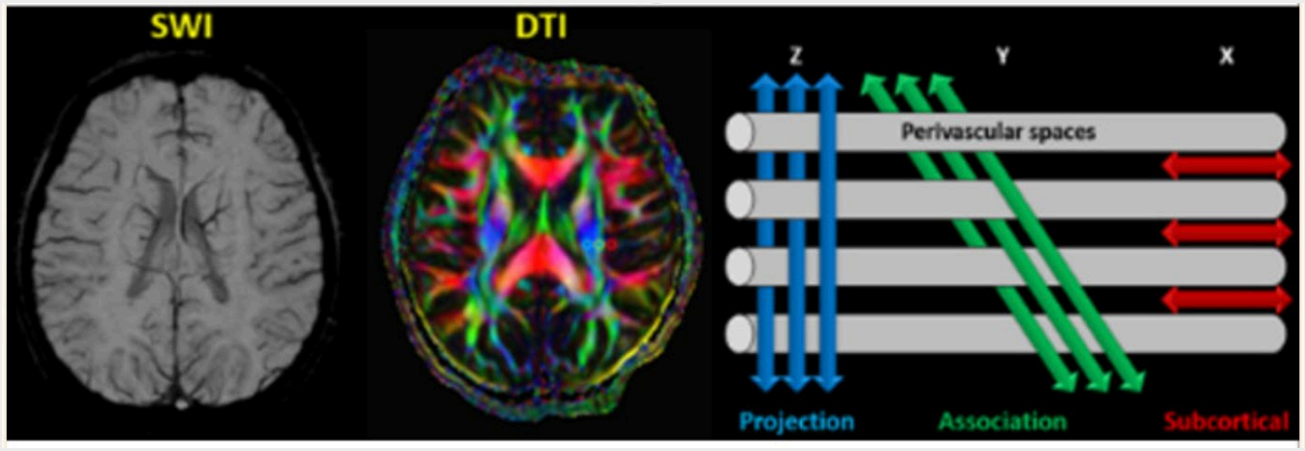
b=1000s/mm²



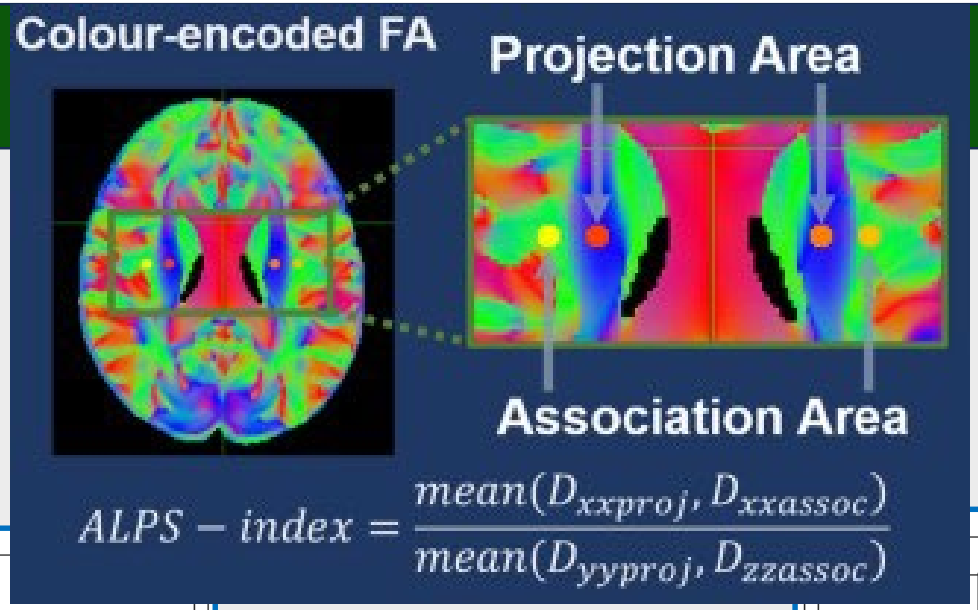
DTI-ALPS index

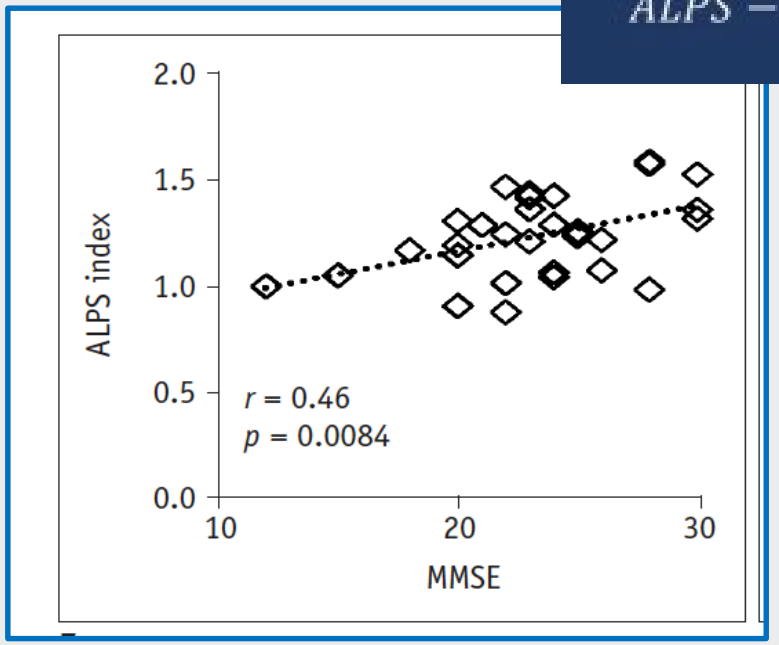


$$\text{DTI-ALPS index} = \frac{mean(Dx\ proj, Dx\ assoc)}{mean\ (Dy\ proj, Dz\ assoc)}$$

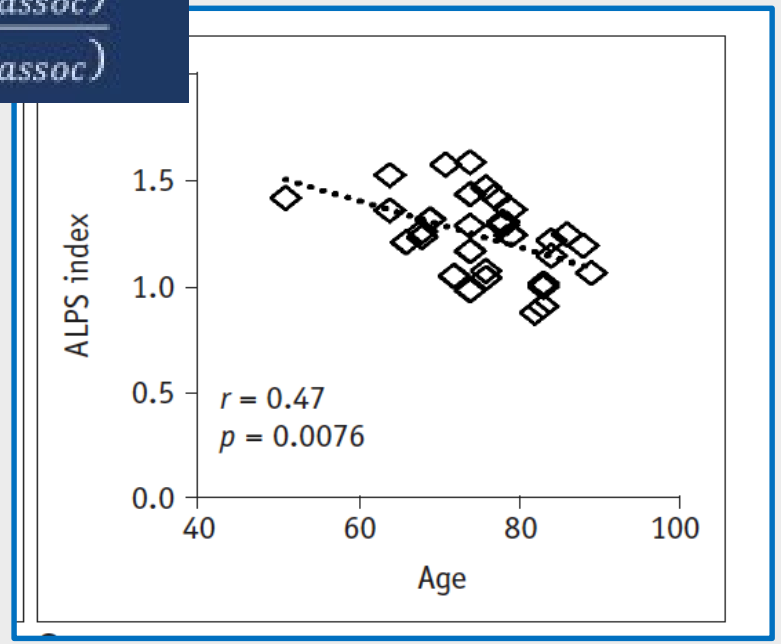


DTI-ALPS index



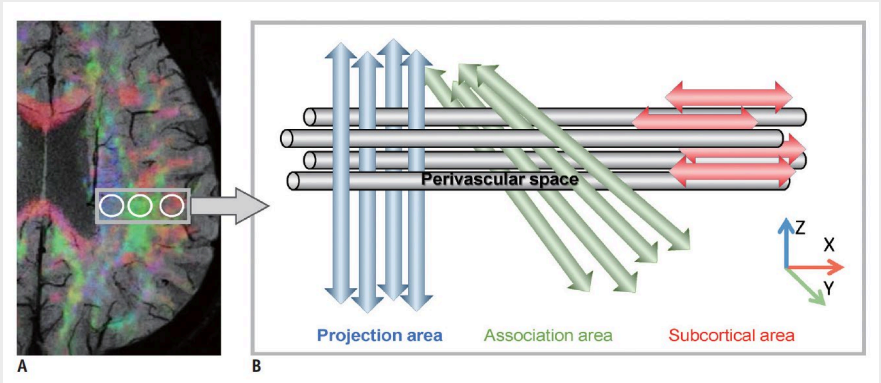


DEMENTIA



AGING

DTI-ALPS index: reflects Glymphatic function or not?



$$DTI-ALPS = \frac{mean(Dx\ proj, Dx\ assoc)}{mean(Dy\ proj,\ Dz\ assoc)}$$

Magn Reson Med Sci. 2024 Apr 2. doi: 10.2463/mrms.rev.2023-0175. Online ahead of

Diffusion Tensor Image Analysis ALong the Perivascular Space (DTI-ALPS): Revisiting the Meaning and Significance of the Method

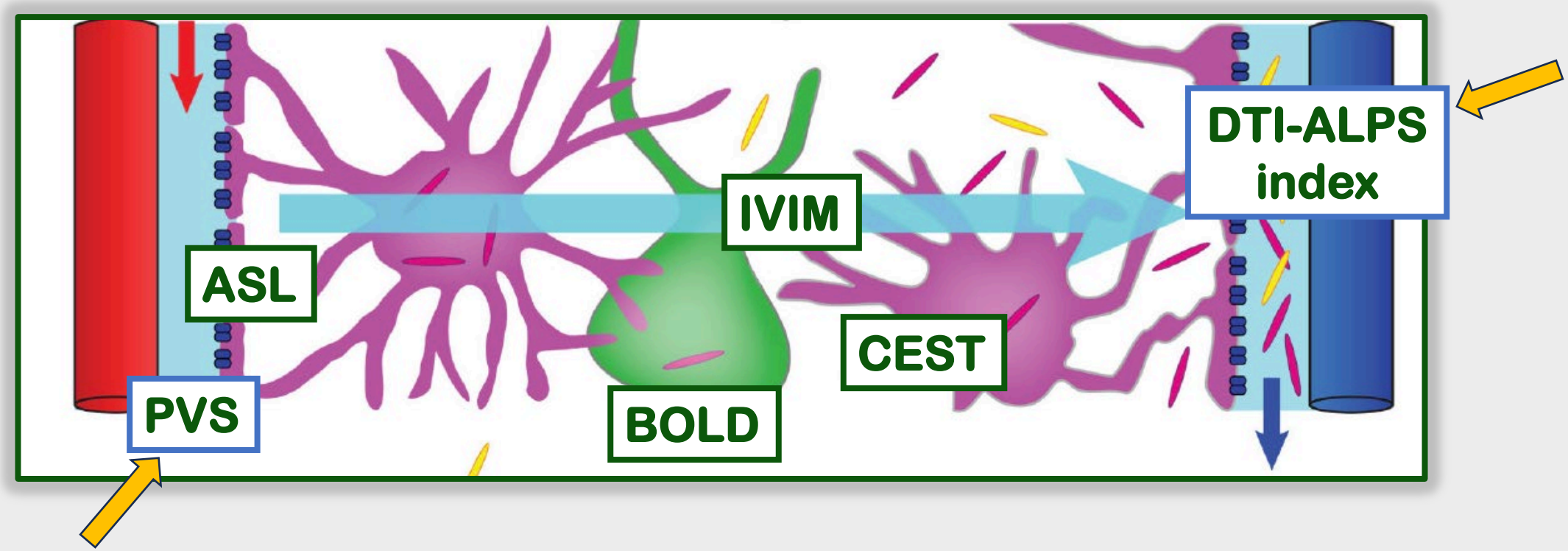
Toshiaki Taoka [1,2], Rintaro Ito [1,2], Rei Nakamichi [2], Toshiki Nakane [2], Hisashi Kawai [3], Shinji Naganawa [2]

When a decreased ALPS-index is observed,

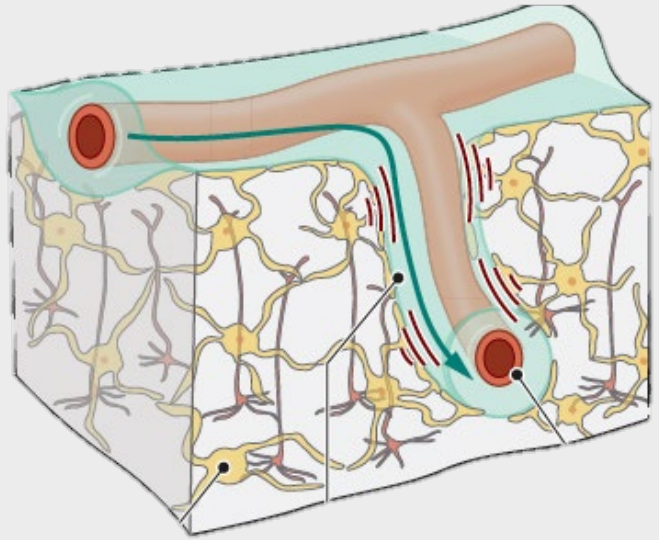
it should be expressed as ***"decreased ALPS-ind***

and **not** directly as ***"glymphatic dysfunction"***

Study methods: MRI



Glymphatic system

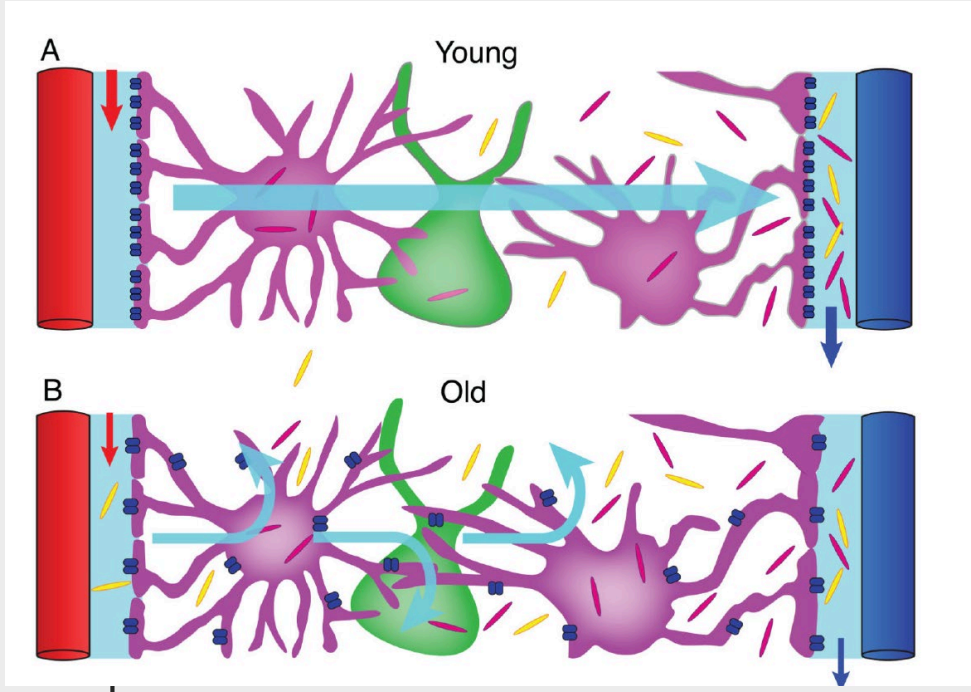


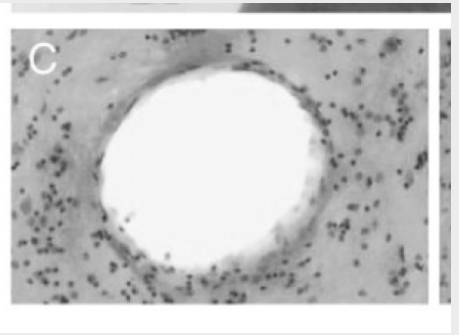
RELATED DISEASES

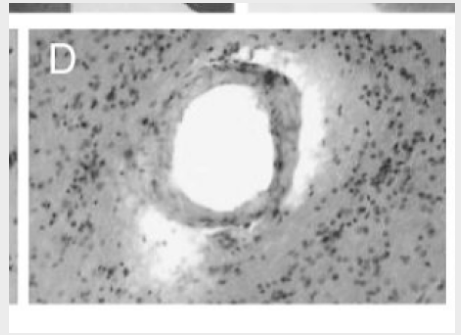
Glymphatic system

Youth

Aging





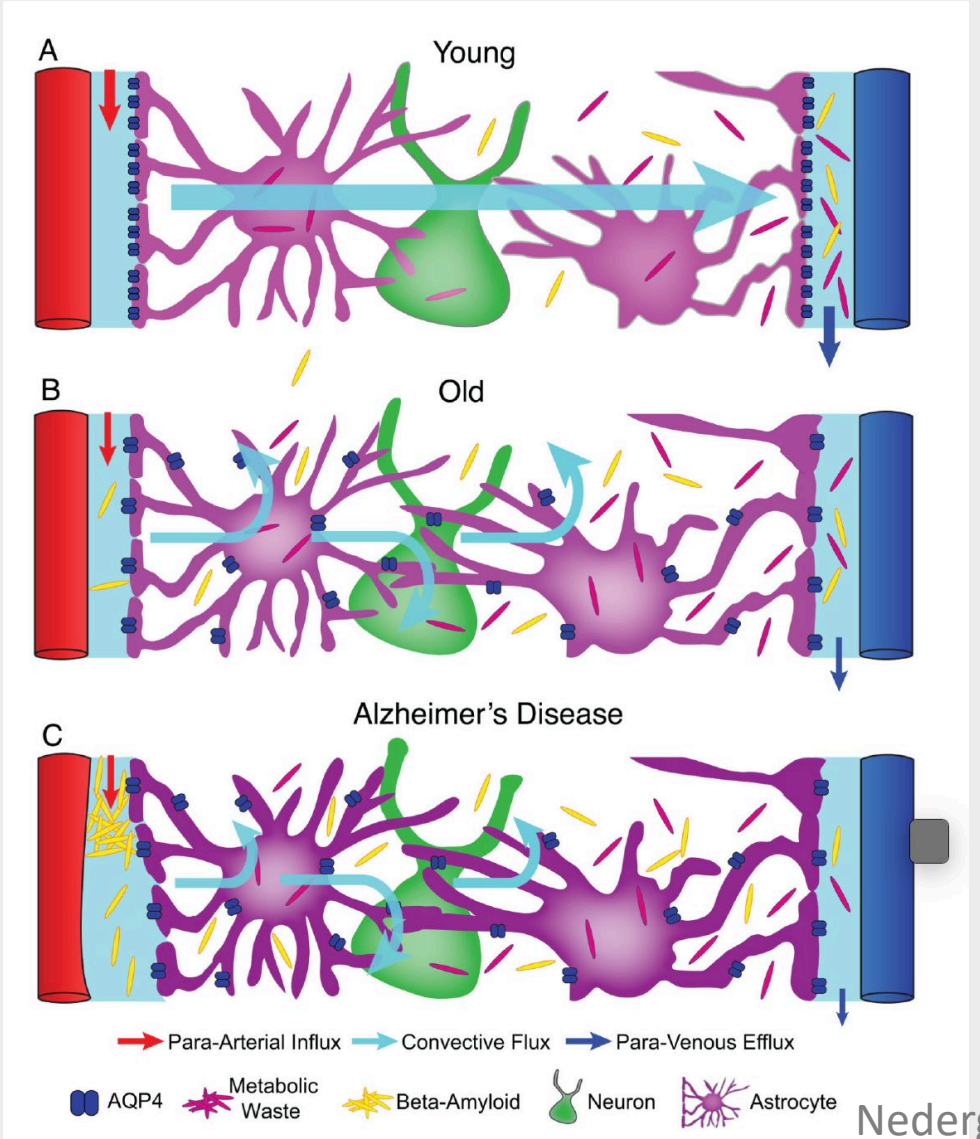


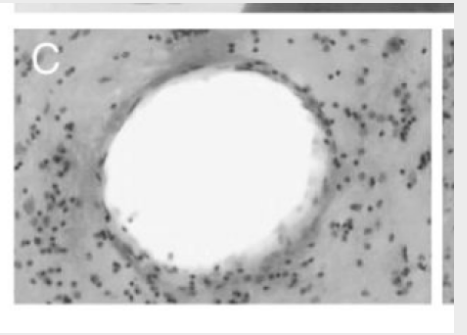
Glymphatic system

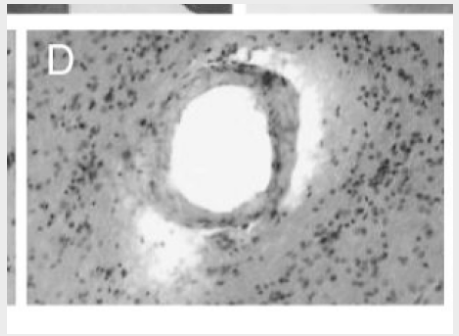
Youth

Aging

Pathological aging

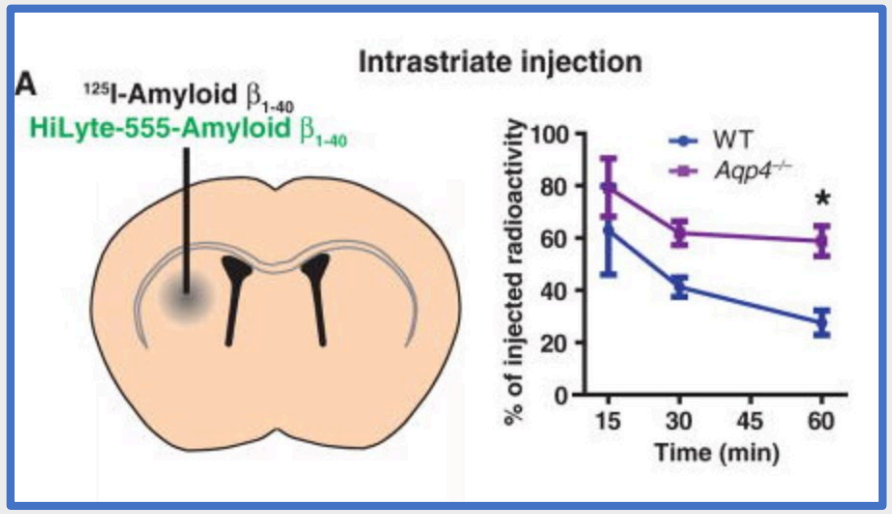






Nedergaard et al, *Neurochem Res*, 2015

Alzheimer disease



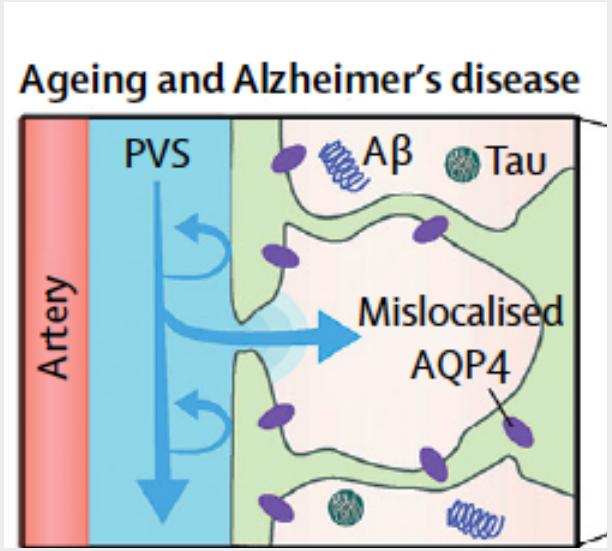
A Paravascular Pathway Facilitates CSF Flow Through the Brain Parenchyma and the Clearance of Interstitial Solutes, Including Amyloid β

Sci Transl Med 2012

Jeffrey J. Iliff[1,*], **Minghuan Wang**[1,2], **Yonghong Liao**[1], **Benjamin A. Plogg**[1], **Weiguo Peng**[1], **Georg A. Gundersen**[3,4], **Helene Benveniste**[5,6], **G. Edward Vates**[1], **Rashid Deane**[1], **Steven A. Goldman**[1,7], **Erlend A. Nagelhus**[3,4], and **Maiken Nedergaard**[1,*]

It has been estimated that 55%-65% of extracellular β-Amyloid is eliminated via the glymphatic pathway

Alzheimer disease



Nedergaard M et al, Lancet Neurol, 2018

proteinopathy

- ↓ glymphatic system

-> extracell accumulation of toxic β-amyloid

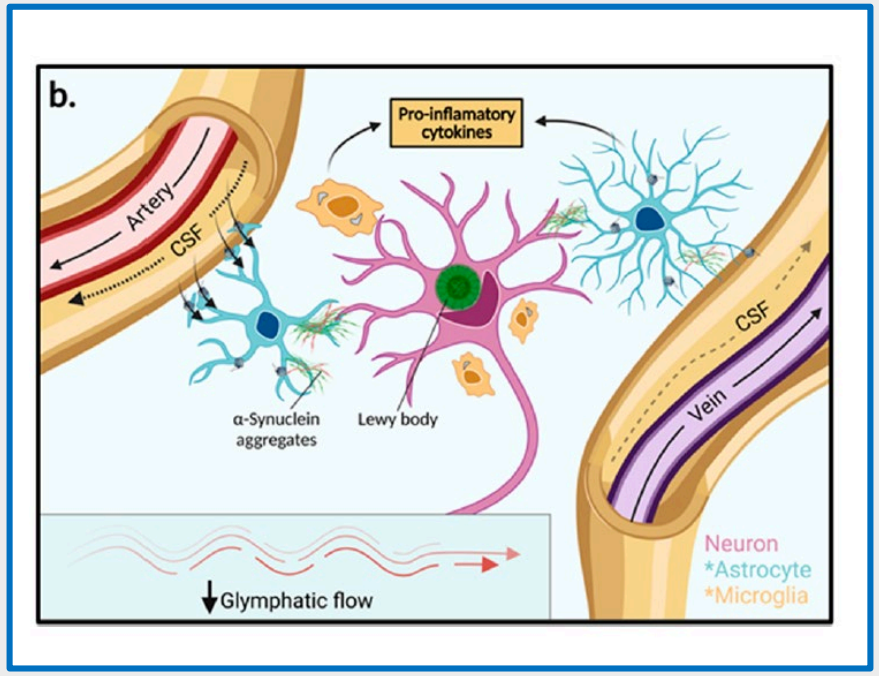
-> intracell accumulation of C-tau proteins

-> neuritic plaques

-> microglial activation

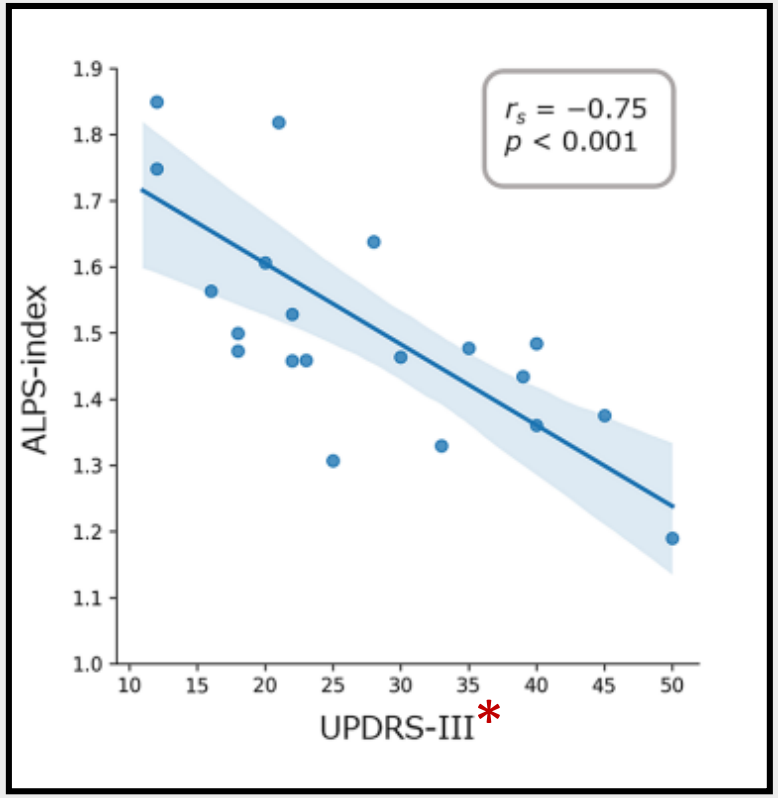
- ↓ AQP4 -> AD progression

Parkinson disease



Massey *et al*, **Int J Mol Sci** 2022

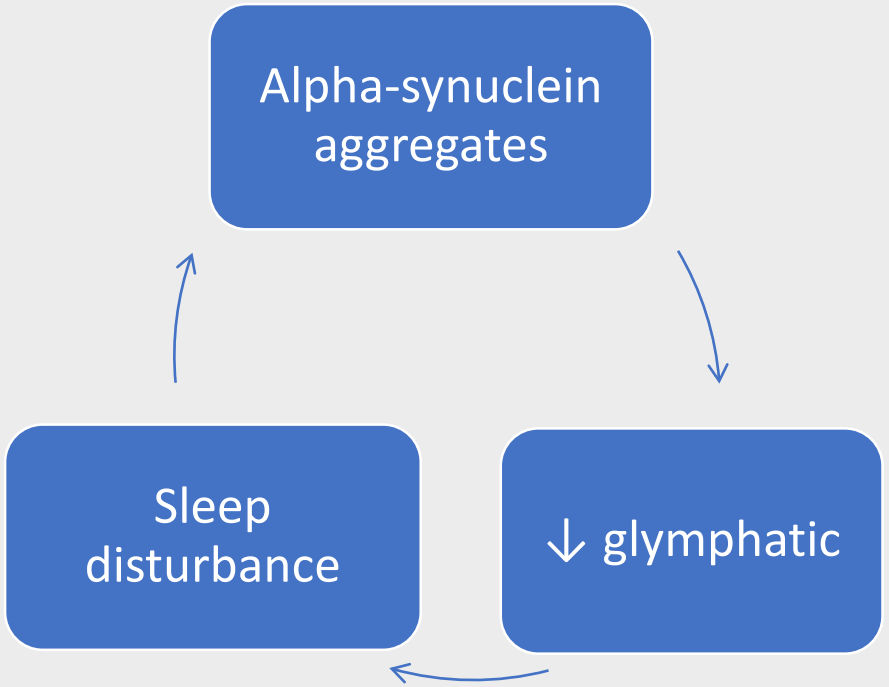
’’Proteinopathy’’ with α-synuclein aggregations



Saito Y *et al*, Jap J Radiol 2023

*Unifed PD’s Rating Scale III

Parkinson disease: sleep disturbance



International Journal of
Molecular Sciences

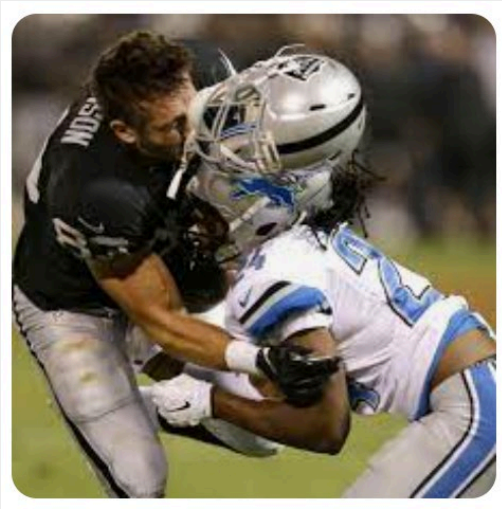
Review

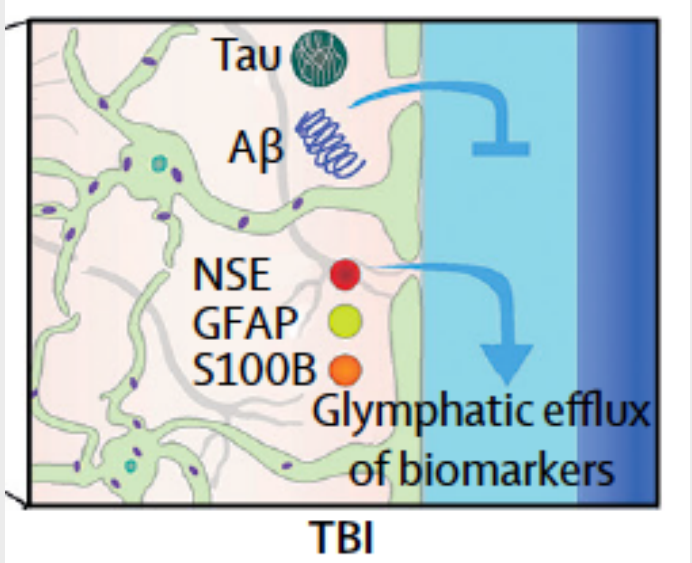
Glymphatic System Dysfunction and Sleep Disturbance May Contribute to the Pathogenesis and Progression of Parkinson's Disease

Andie Massey [1], Matthew K. Boag [1], Annie Magnier [1], Dharah P. C. F. Bispo [1], Tien K. Khoo [2,3] and Dean L. Pountney [1,*]

Intimate link exists
between sleep disturbance and PD

Chronic traumatic brain injury





Nedergaard M et al, Lancet Neurol, 2018

Impairment of Glymphatic Pathway Function Promotes Tau Pathology after Traumatic Brain Injury *J Neurosc*, 2014

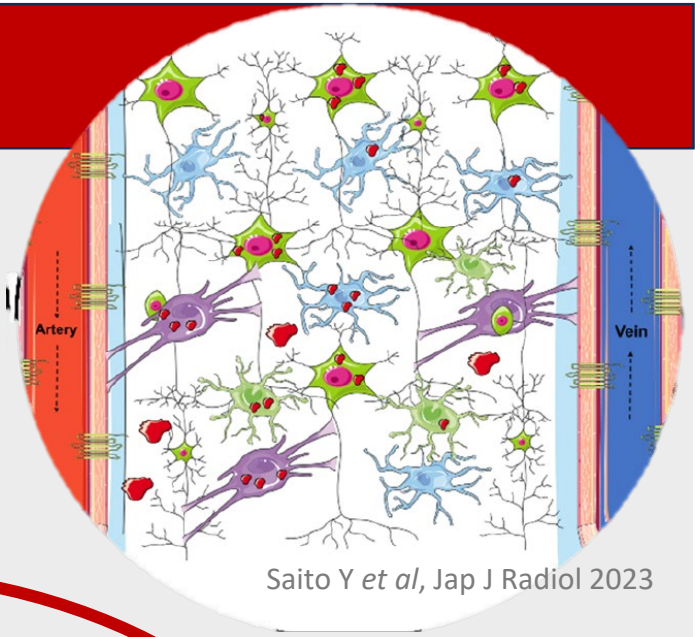
Jeffrey J. Iliff,[1,2,3] Michael J. Chen,[1] Benjamin A. Plog,[1] Douglas M. Zeppenfeld,[2,3] Melissa Soltero,[2] Lijun Yang,[1] Itender Singh,[1] Rashid Deane,[1] and Maiken Nedergaard[1]

Decreased of glymphatic influx persisting for more than 24 days after the injury

- ✓β-amyloid and C-tau proteins-> neuritic plaques
- ✓glyal scars -> neuroinflammation
- ✓AQP4 channels disruption
- ✓haematic debris

↓GLYMPHATIC ➡ DEMENTIA

fluidopathy



Saito Y *et al*, Jap J Radiol 2023

aging

neuroinflammation

↓GLYMPHATIC

↑aggregates

neurodegeneration

DEMENTIA

sleep

vascular pathology

neuroinflammation

Neuroinflammation

International Journal of *Molecular Sciences*

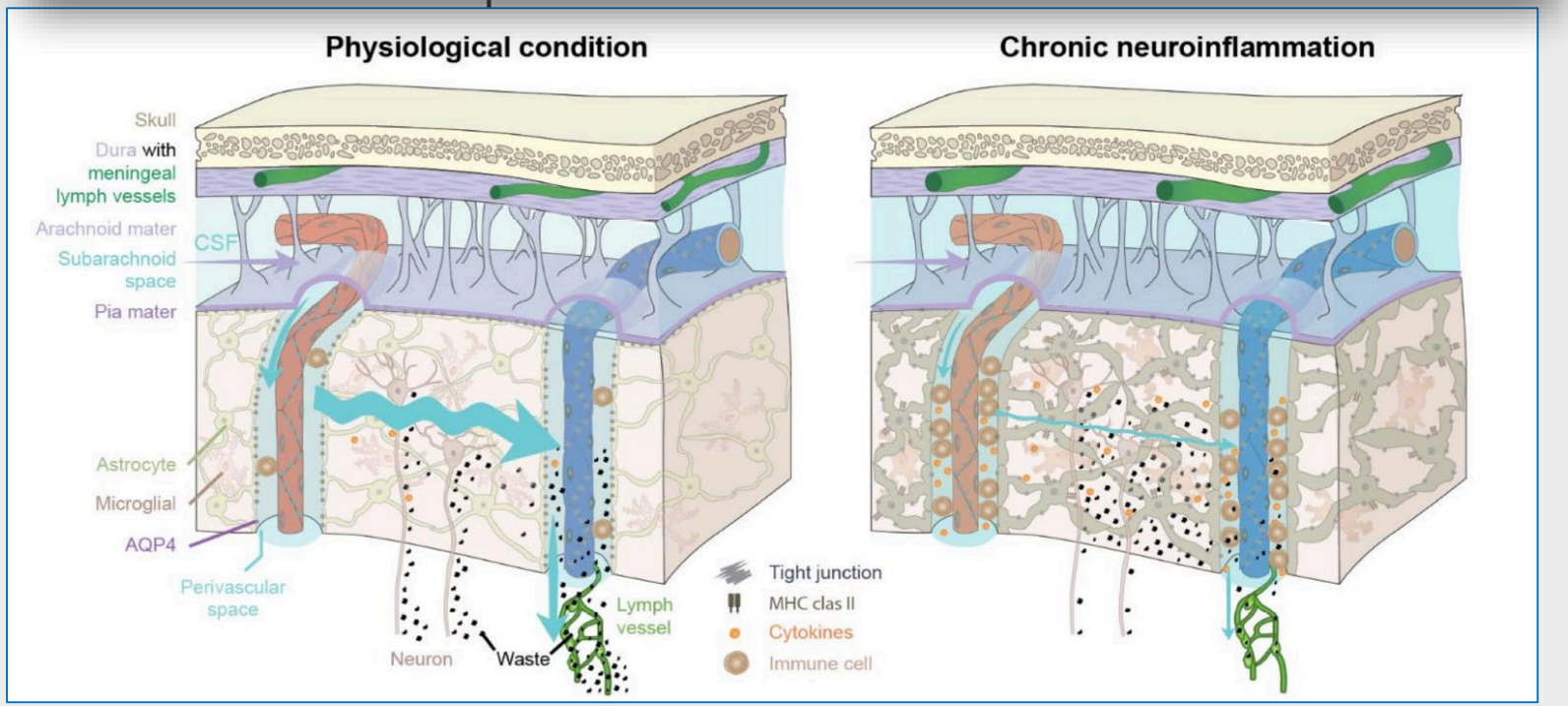
MDPI

Review

The Glymphatic System (En)during Inflammation

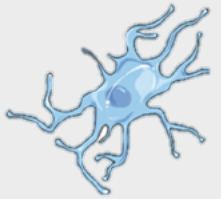
2021

Frida Lind-Holm Mogensen [1,†], Christine Delle [1,†] and Maiken Nedergaard [1,2,*]

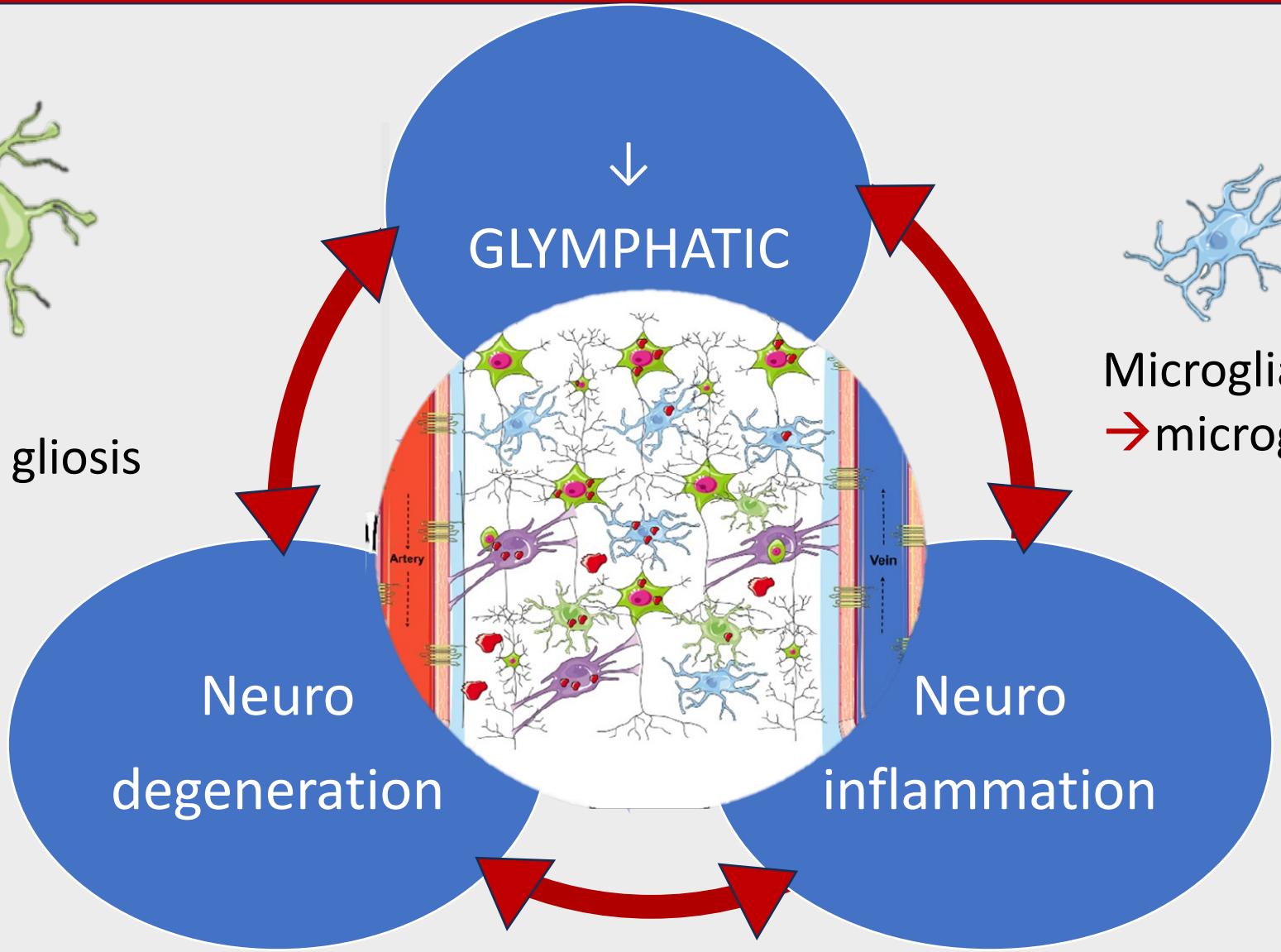


↓GLYMPHATIC → VICIOUS CIRCLE

Astrocytes
→ ↓AQP4, gliosis



Microglia
→microglial activation



Dementia ⟷ DTI ALPS

DTI-ALPS index AD, MCI e VCI < NC
p<0.001

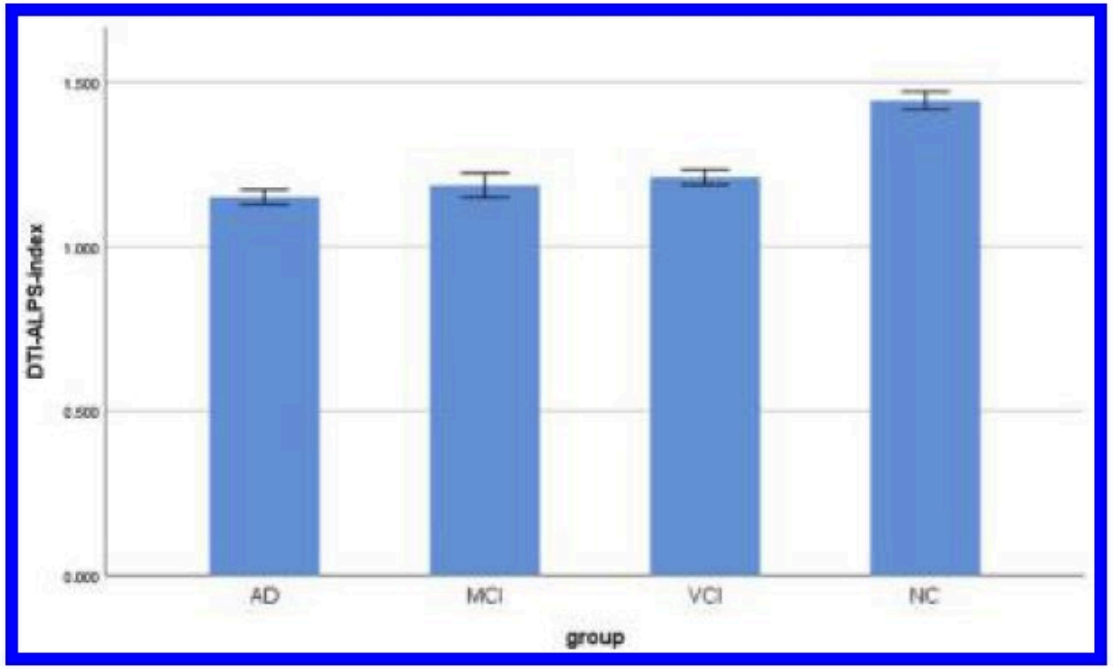
DTI-ALPS index AD < VCI
p<0.007

FULL PAPER

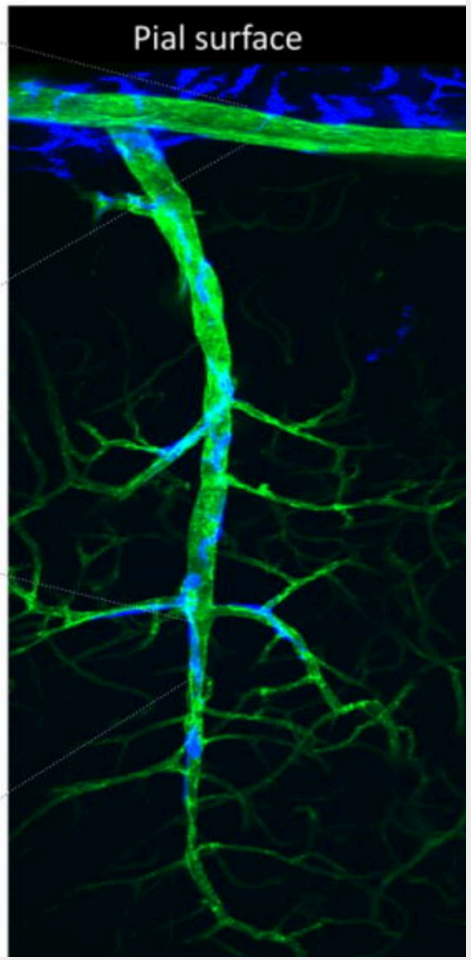
BJR, 2023

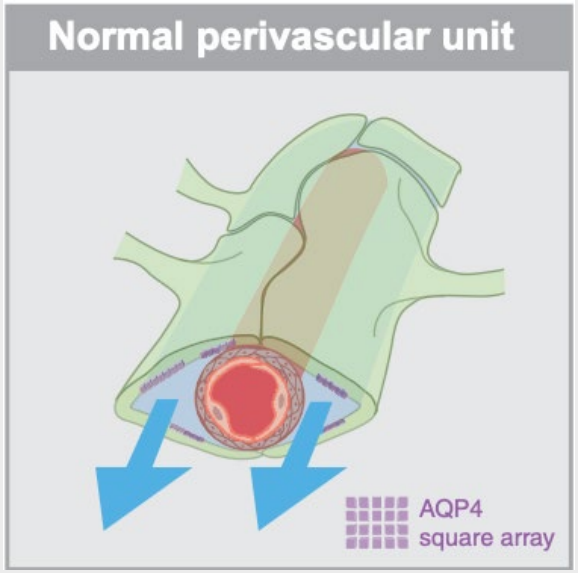
Evaluation of glymphatic system activity by diffusion tensor image analysis along the perivascular space (DTI-ALPS) in dementia patients

[1]TIAN LIANG, MD, [1]FEIYAN CHANG, MD, [1]ZHENGUO HUANG, MD, [2]DANTAO PENG, MD, [2]XIAO ZHOU, MD and [3]WEIFANG LIU, MD

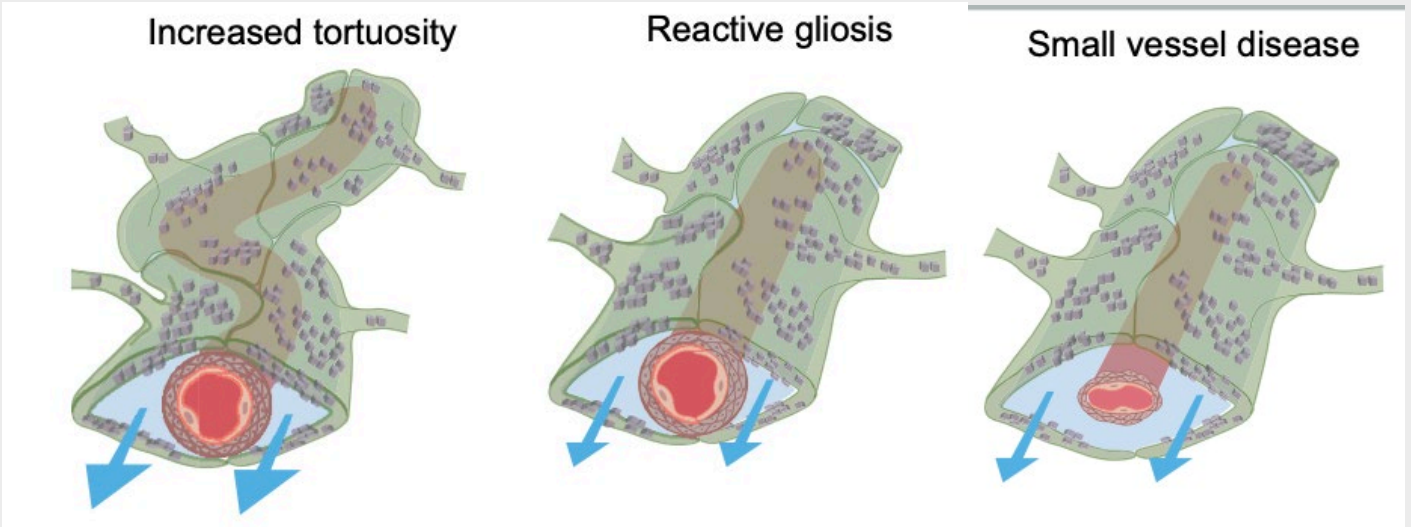


microangiopathy



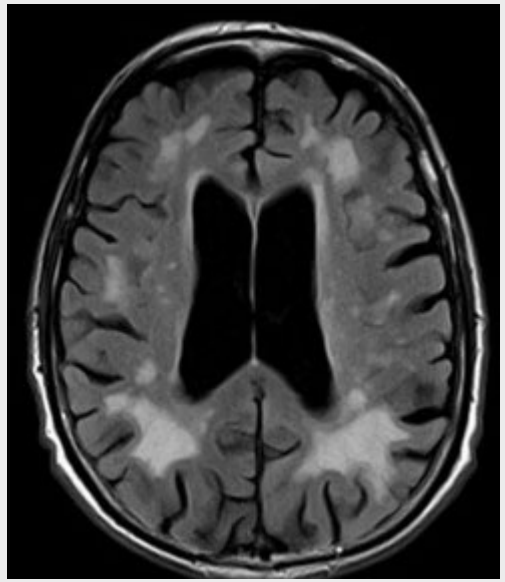


Hablitz & Nedergaard
J Neurosci 2021



Cerebral small vessels disease (CSVD)

CSVD →



AD ←

The glymphatic system and cerebral small vessel disease

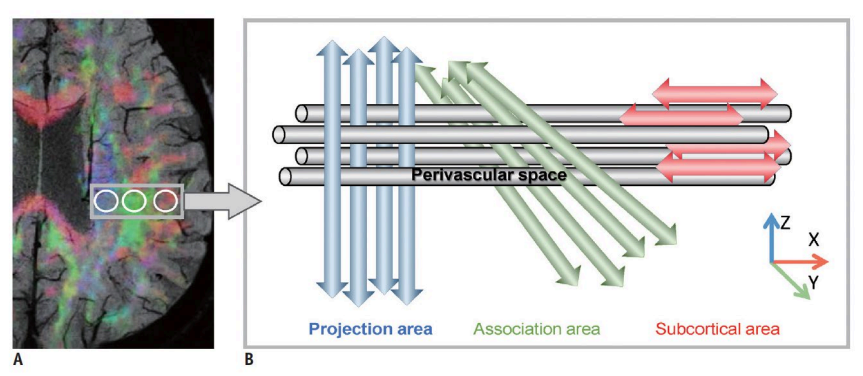
Phillip S. Ang, BA [a], Douglas M. Zhang, BA [a], Saara-Anne Azizi, PhD [a], Salvador A. Norton de Matos, BA [a], James R. Brorson, MD [a,b,*]

Shared risk factors

- Advanced age
- Hypertension
- Type 2 diabetes
- Sleep disruption
- Neuroinflammation

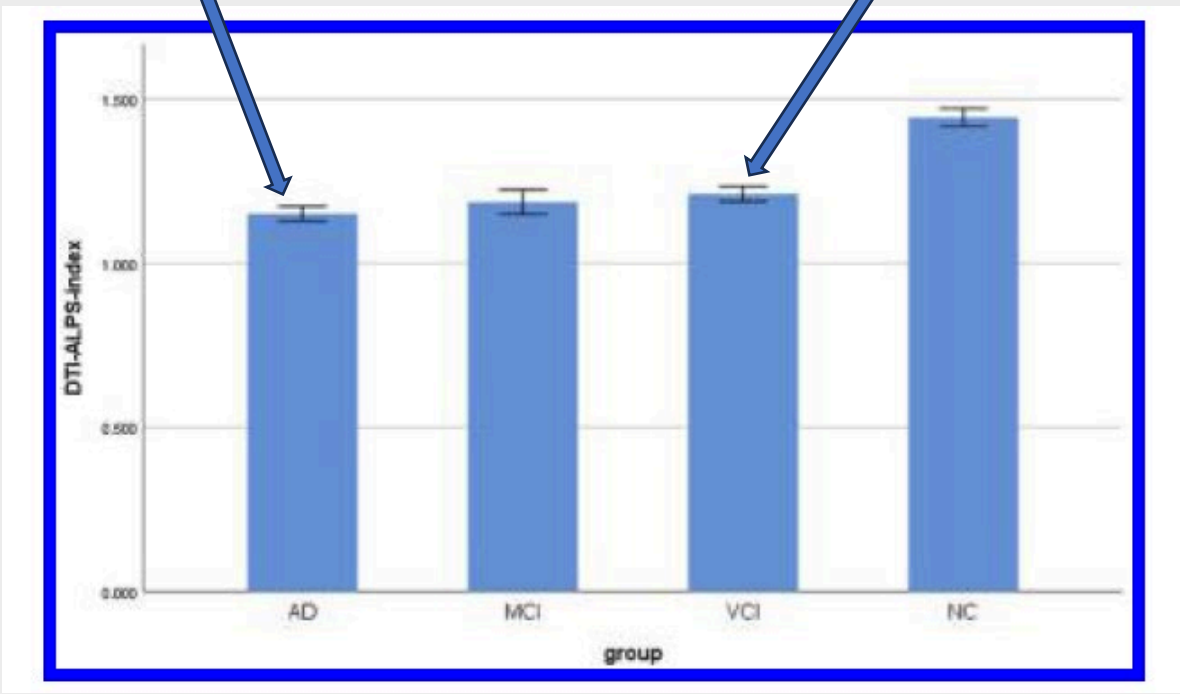
Dementia ⟷ DTI ALPS

$$\text{ALPS index} = \frac{mean\ (Dx\ proj, Dx\ assoc)}{mean\ (Dy\ proj, Dz\ assoc)}$$



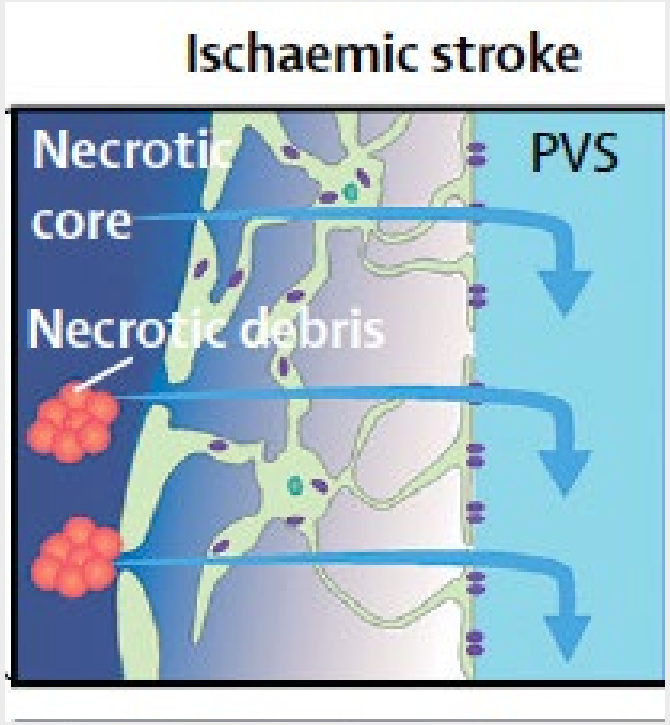
DTI-ALPS-index AD:
↓ Dxassoc

DTI-ALPS-index VCI:
↑ Dzassoc

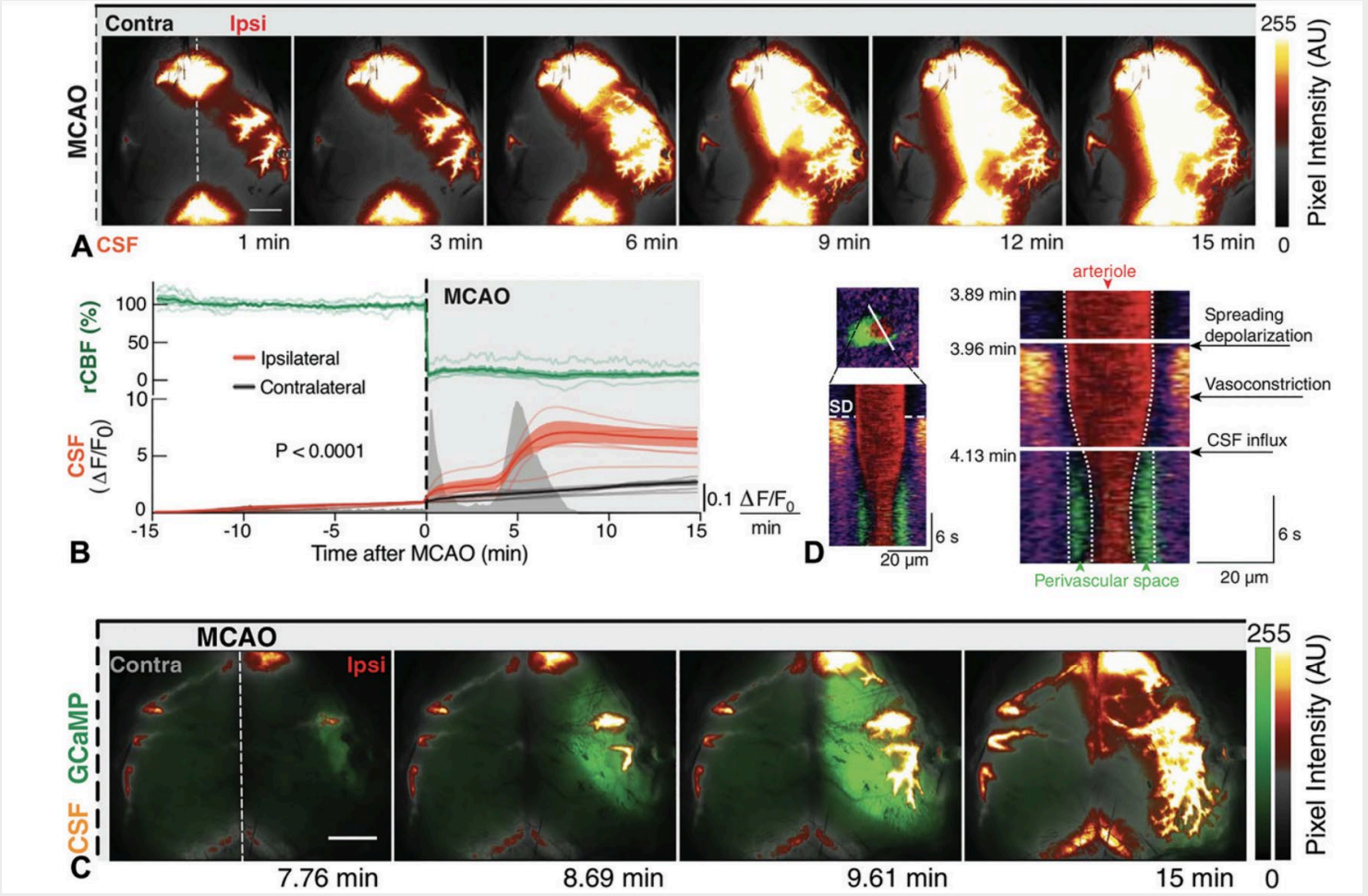


Liang T et al, *Br J Radiol* 2023

Ischaemic stroke

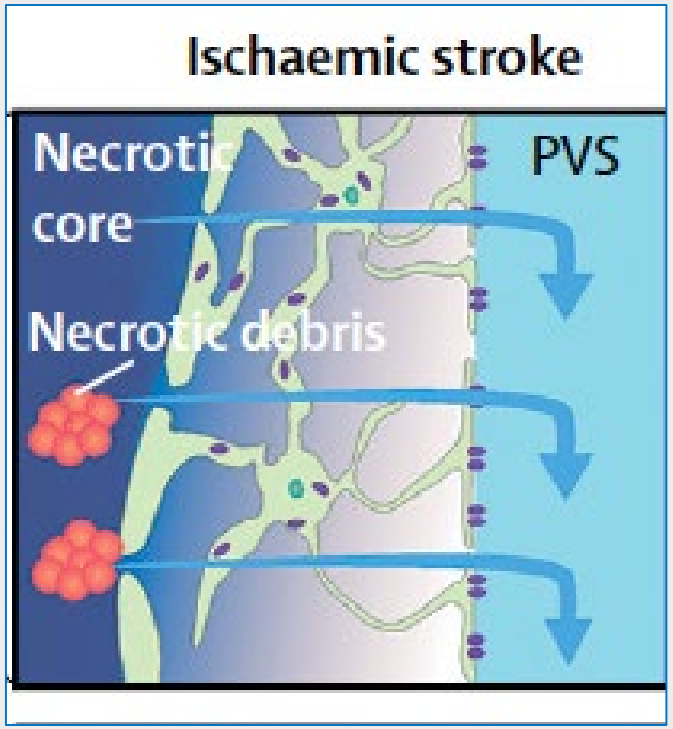


Nedergaard M et al, Lancet Neurol, 2018

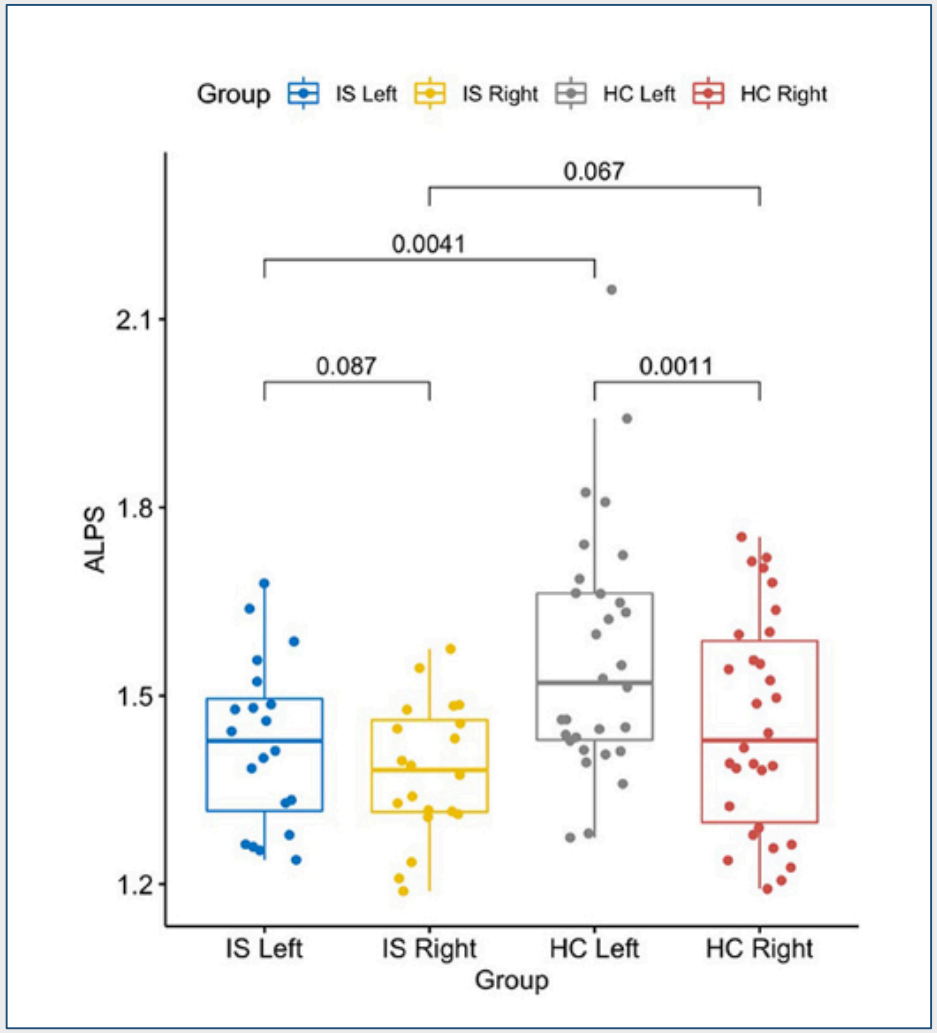


Klostranec et al, Radiology 2021

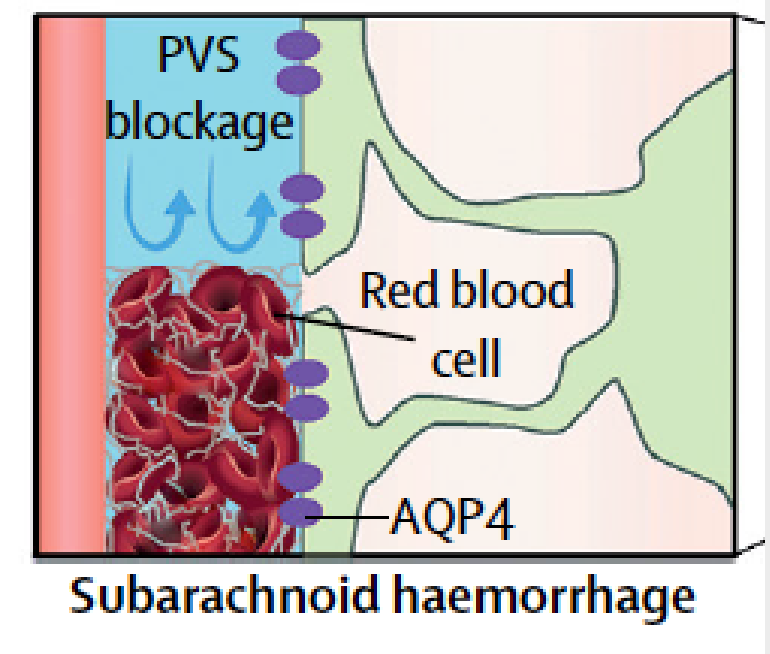
Ischaemic stroke



Nedergaard M et al, Lancet Neurol, 2018



Haemorrhagic stroke

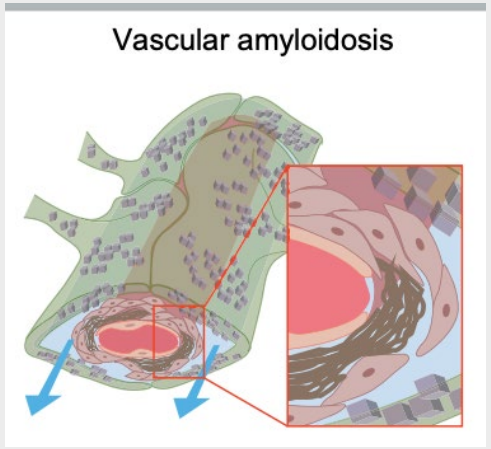


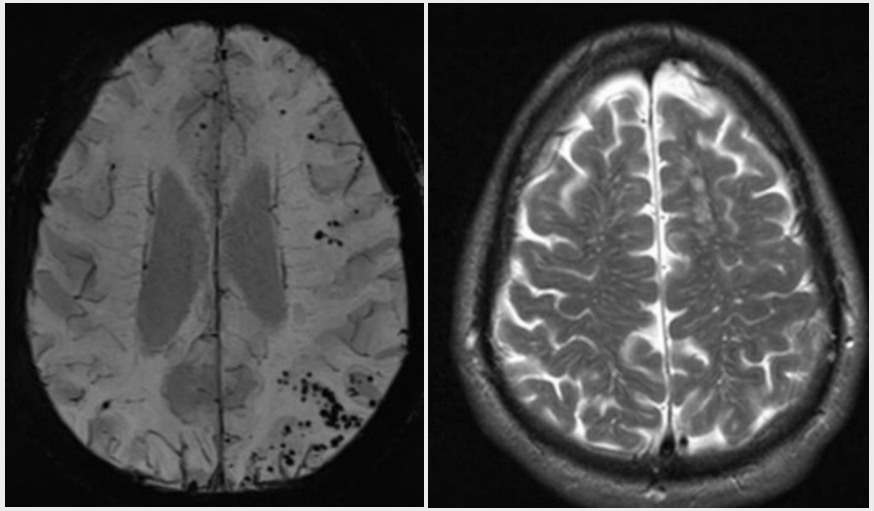
Nedergaard M et al, Lancet Neurol, 2018

Impaired CSF inflow along periarterial influx routes starts at 24 hours after the insult.

Intraventricular delivery of the fibrinolytic plasminogen activator restored CSF flow in rodents.

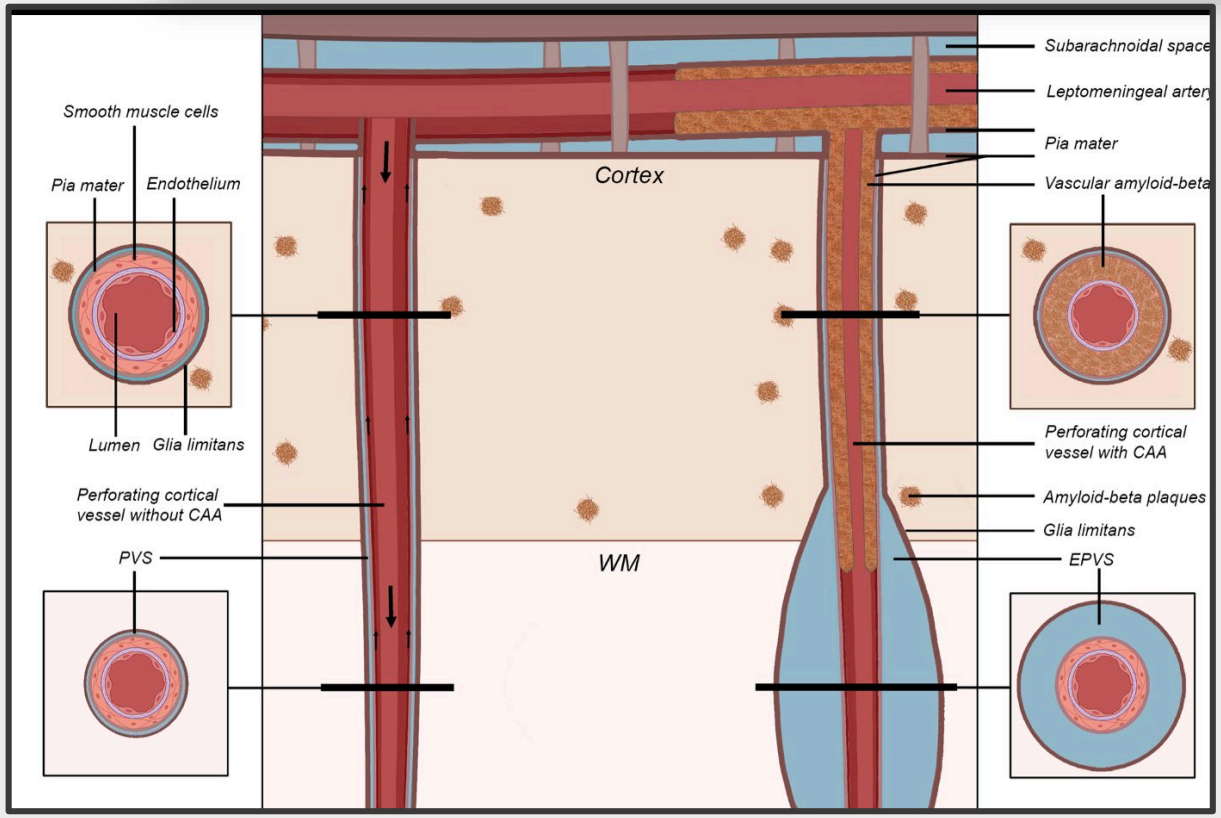
Cerebral amyloid angiopathy



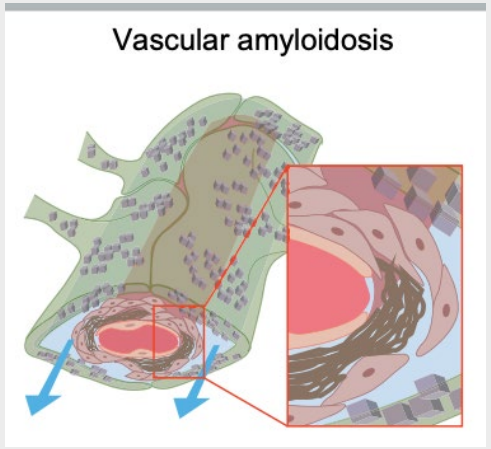


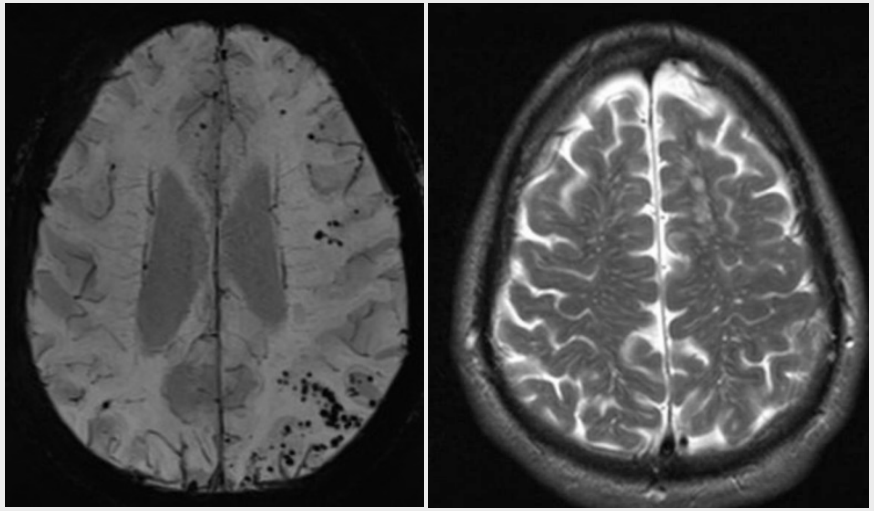
Perivascular space dilation is associated with vascular amyloid-β accumulation in the overlying cortex *Acta Neuropathol* , 2022

Valentina Perosa [1 2 3], Jan Oltmer [4], Leon P Munting [5 6], Whitney M Freeze [6 7], Corinne A Auger [5], Ashley A Scherlek [5 8], Andre J van der Kouwe [4], Juan Eugenio Iglesias [4 9 10], Alessia Atzeni [9], Brian J Bacskai [5], Anand Viswanathan [11], Matthew P Frosch [5 12], Steven M Greenberg [11], Susanne J van Veluw [11 5 6]



Cerebral amyloid angiopathy





Lancet Neurol 2022

The Boston Criteria v2.0 for cerebral amyloid angiopathy: A multicentre MRI-neuropathology diagnostic accuracy study

Probable CAA

- MRI criteria:
  - demonstrates either:
    - at least two of the following strictly lobar hemorrhagic lesions on T2*-weighted MRI, in any combination: intracerebral hemorrhage, cerebral microbleeds, or foci of cortical superficial siderosis (multiple distinct foci are counted as independent hemorrhagic lesions) or convexity subarachnoid hemorrhage (multiple distinct foci are counted as independent hemorrhagic lesions); **or**
    - one lobar hemorrhagic lesion plus one white matter feature (severe perivascular spaces in the centrum semiovale [>20 visible in one hemisphere] or white matter hyperintensities in a multispot pattern)
  - absence of:
    - any deep hemorrhagic lesions on T2*-weighted MRI; **and**
      - hemorrhagic lesion in cerebellum not counted as either lobar or deep hemorrhagic lesion
    - other cause of hemorrhagic lesions*

Dementia

Cerebrovascular Diseases

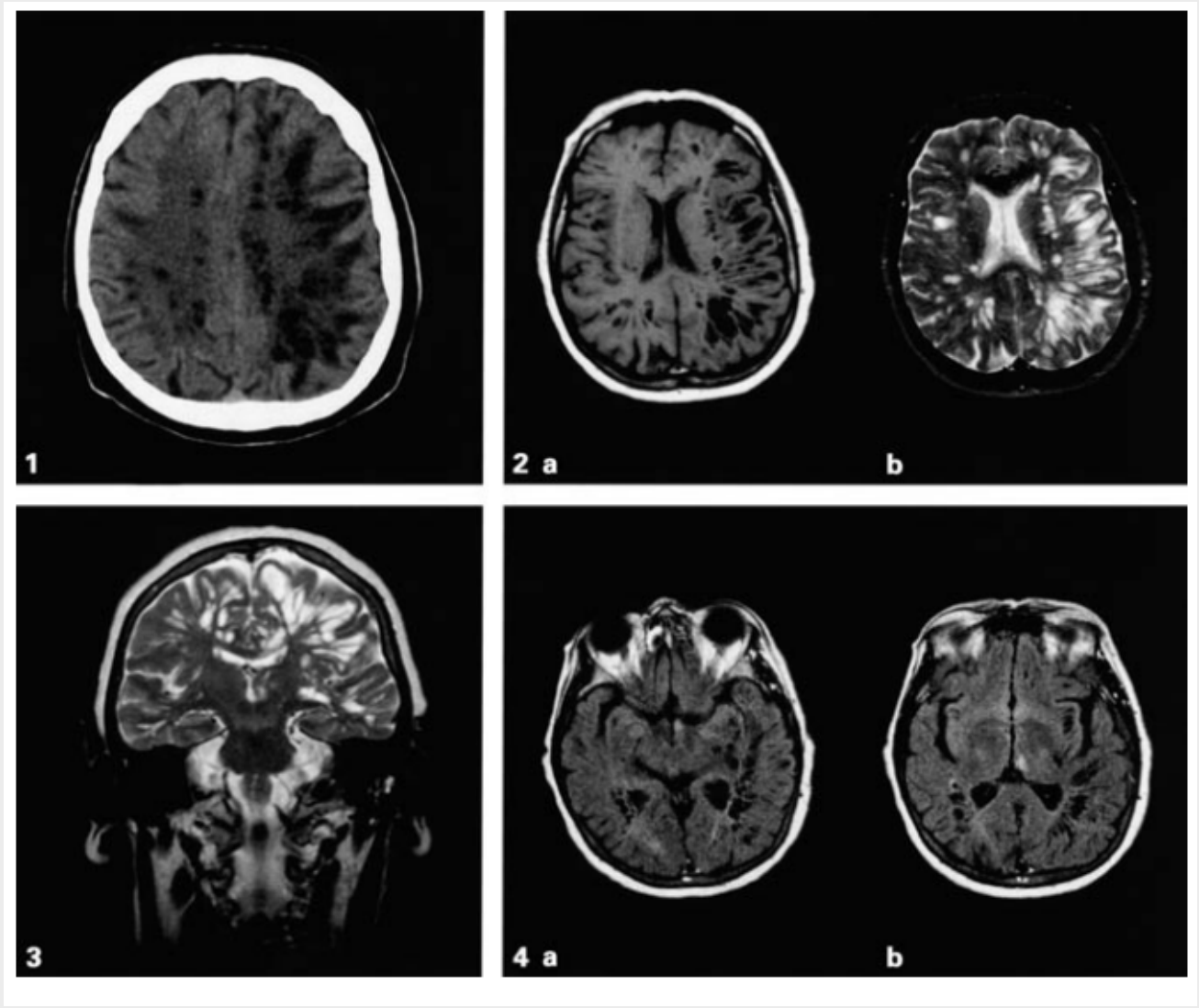
Original Paper

Cerebrovasc Dis 2001;12:287–290

2001

Subcortical Dementia Associated with Striking Enlargement of the Virchow-Robin Spaces and Transneural Degeneration of the Left Mammillo-Thalamic Tract

Carla Uggetti[a] Maria Grazia Egitto[a] Anna Pichiecchio[a] Elena Sinforiani[b]
Maria Stella Bevilacqua[b] Anna Cavallini[c] Giuseppe Micieli[c]



Normal pressure hydrocephalus

Hindawi
Current Gerontology and Geriatrics Research
Volume 2019, Article ID 5675014, 10 pages
https://doi.org/10.1155/2019/5675014

2019

Research Article

Diagnostic Performance of Glymphatic System Evaluation Using Diffusion Tensor Imaging in Idiopathic Normal Pressure Hydrocephalus and Mimickers

Hajime Yokota,[1] Arvind Vijayasarathi,[2] Milos Cekic,[2] Yoko Hirata,[3] Michael Linetsky,[2] Michael Ho,[4] Won Kim,[5] and Noriko Salamon[2]

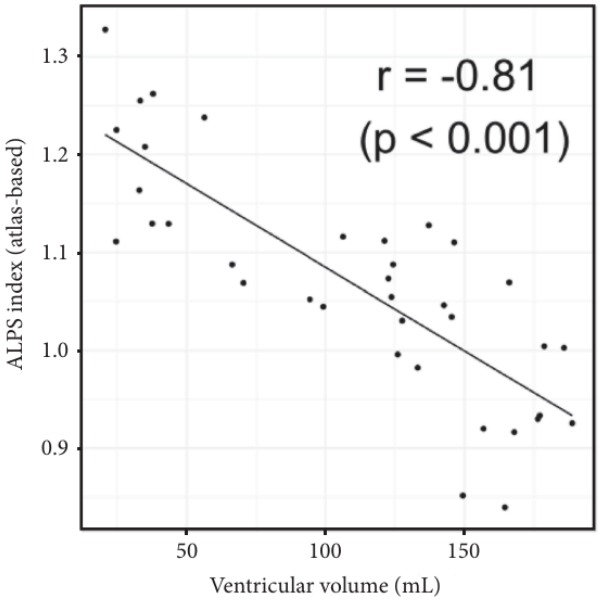
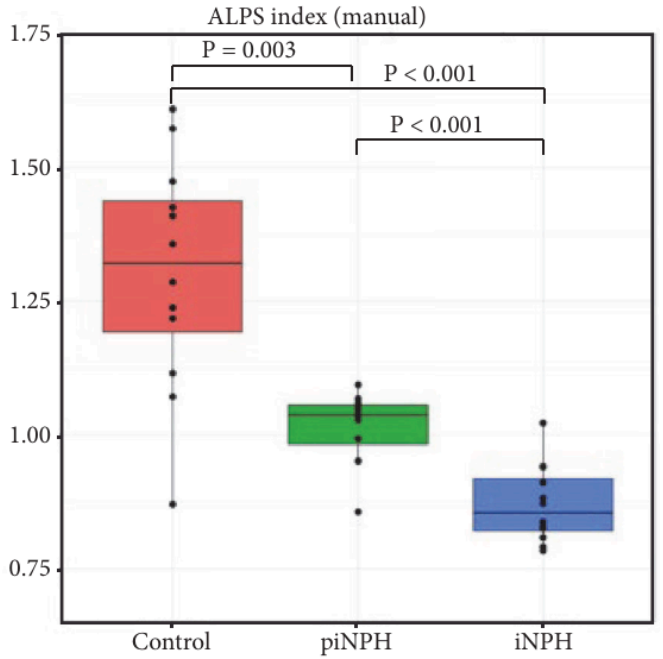


FIGURE 6: Scatter plot shows correlation between atlas-based ALPS index and supratentorial ventricular volume. There was strong correlation between them (r = -0.81, p < 0.001).



(a)

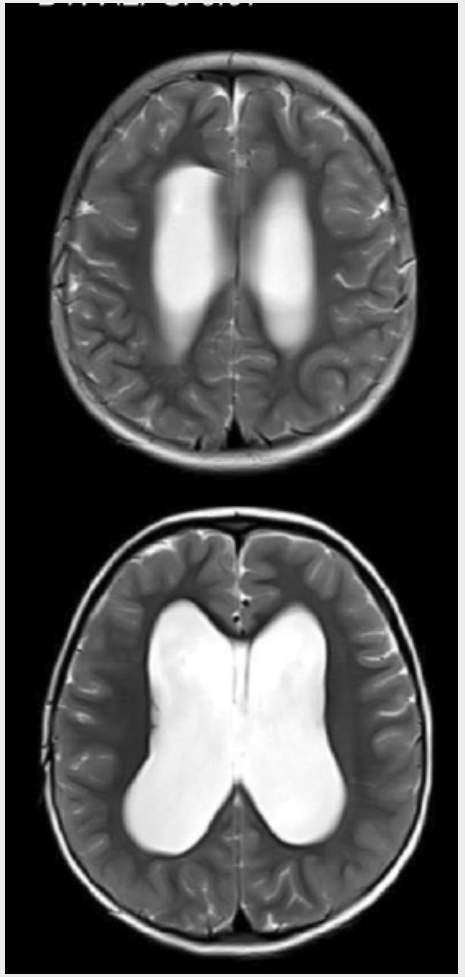
Hydrocephalus

J Magn Res Imaging, 2023

Glymphatic Imaging in Pediatrics

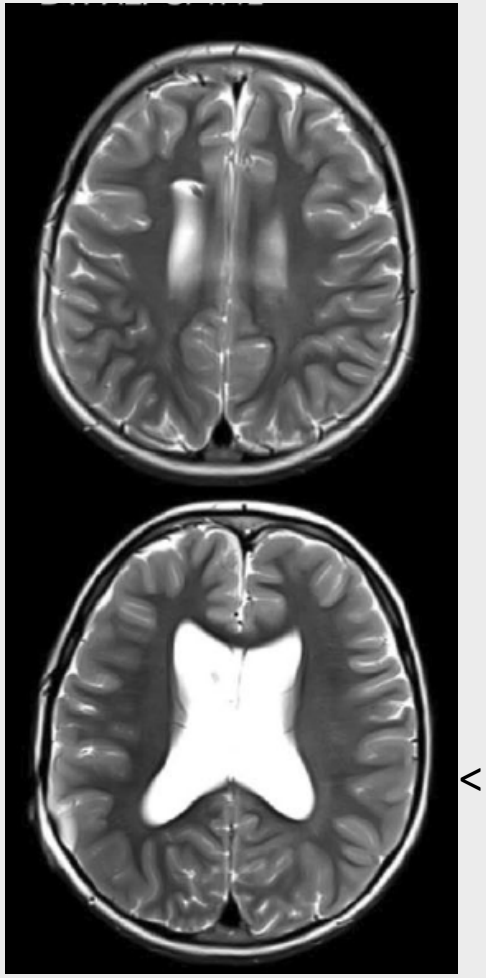
Xianjun Li, PhD,[1] Zixuan Lin, PhD,[2] Congcong Liu, MD,[1] Ruiliang Bai, PhD,[3] Dan Wu, PhD,[2] and Jian Yang, PhD[1,4,5*]

DTI ALPS = 0.97



< Pre-op

DTI ALPS = 1.42



< Post-op
DVP

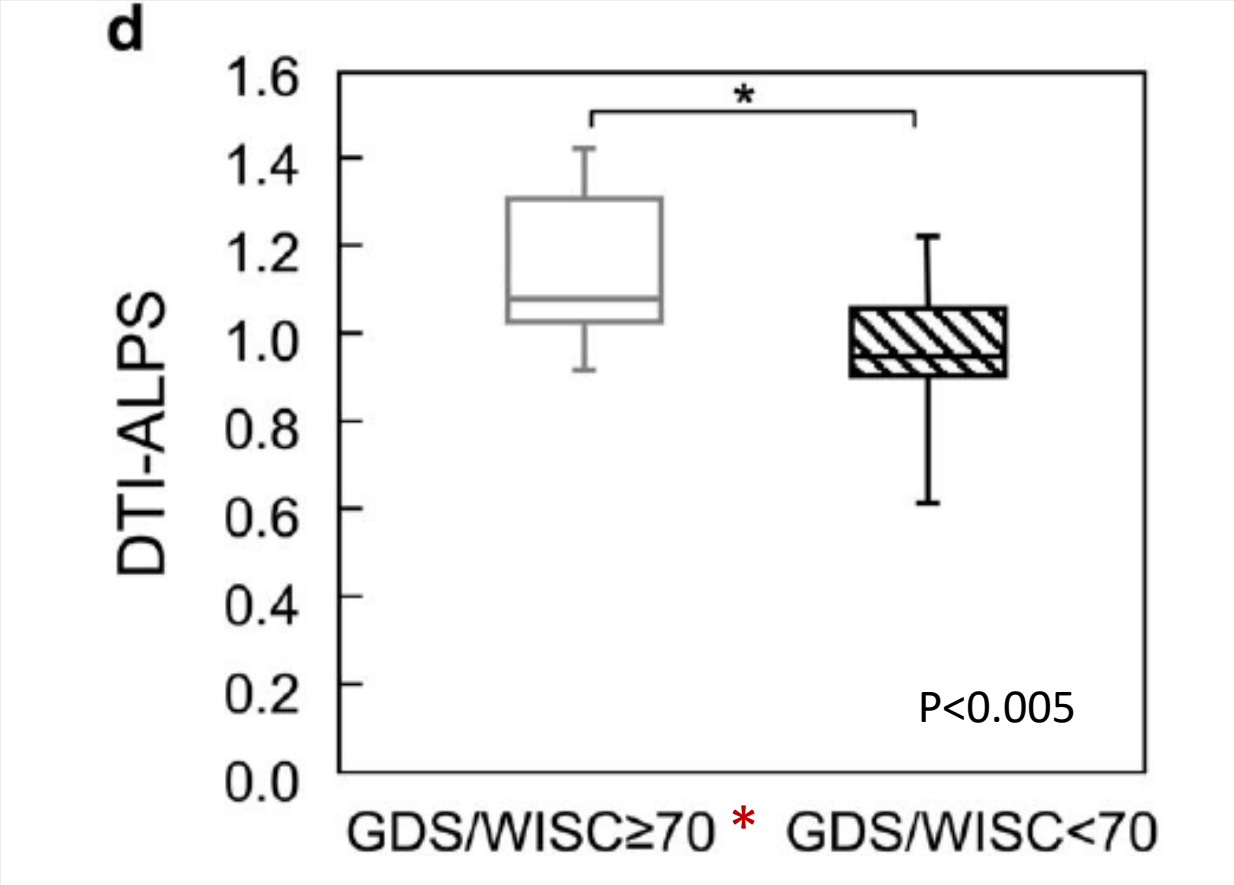
Hydrocephalus

J Magn Res Imaging, 2023

Glymphatic Imaging in Pediatrics

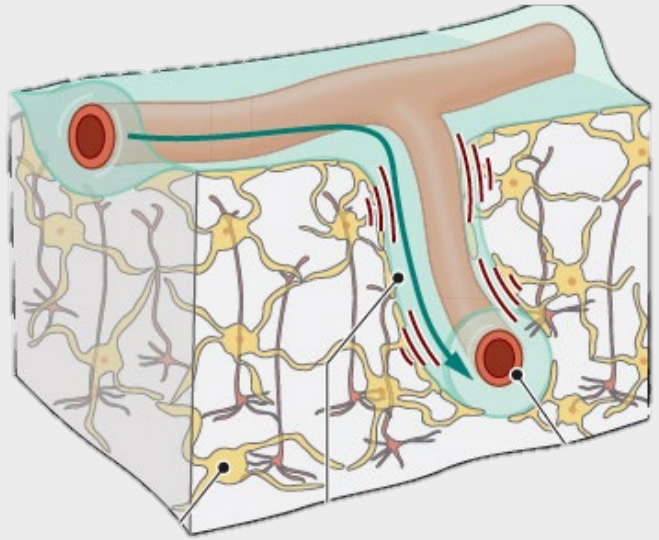
Xianjun Li, PhD,[1] Zixuan Lin, PhD,[2] Congcong Liu, MD,[1] Ruiliang Bai, PhD,[3] Dan Wu, PhD,[2] and Jian Yang, PhD[1,4,5*]

Post-op DVP



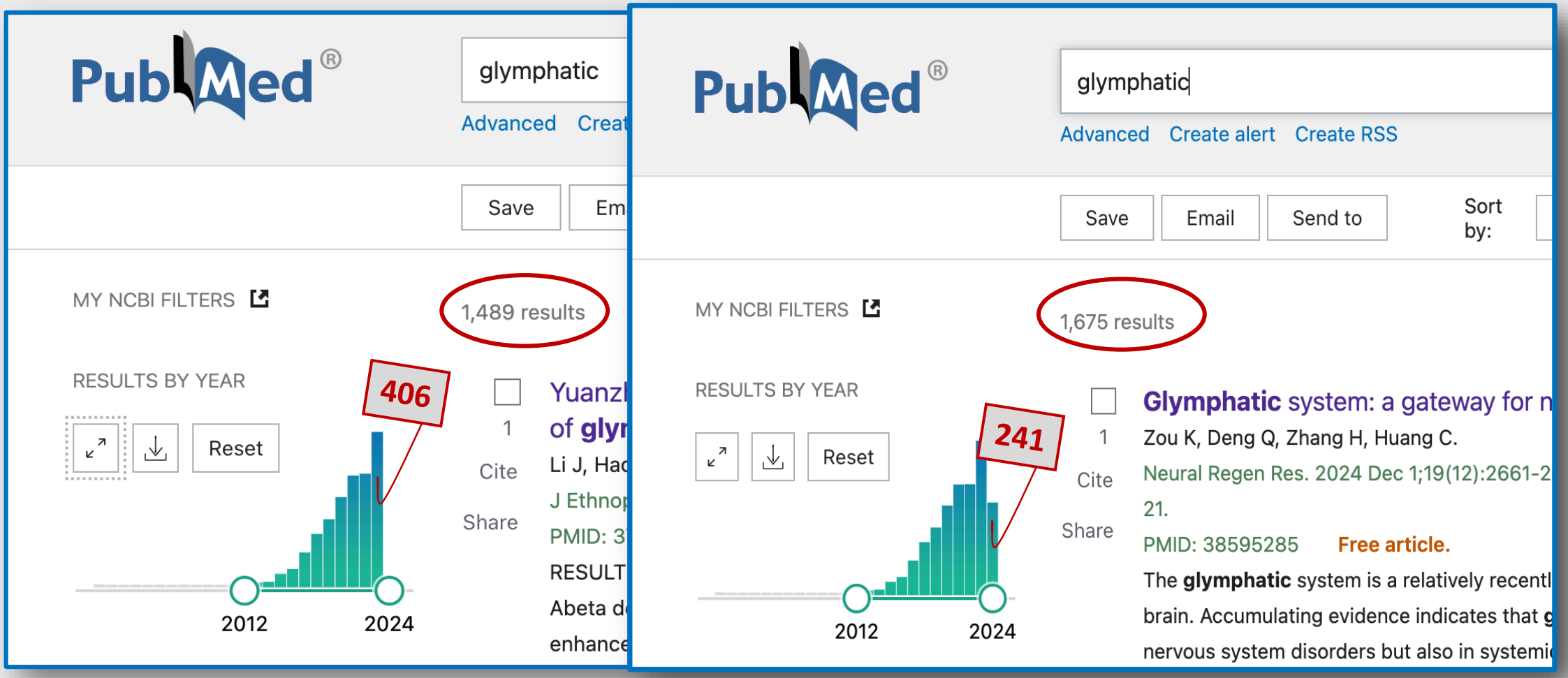
* Gordon Diagnostic System/
Wechsler Intelligent Scale for Children

Glimphatic system

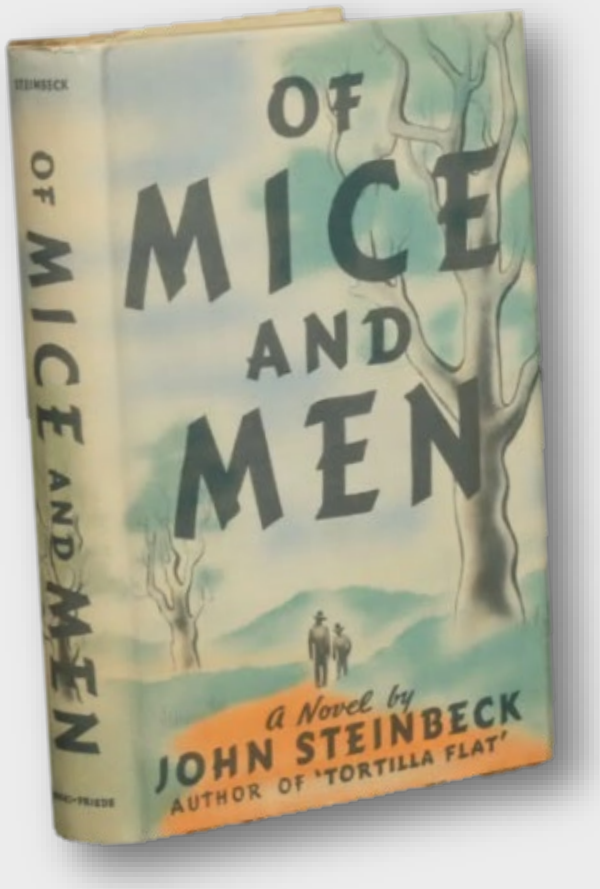


Future outlook

Glymphatic system



Future research is needed



Modifications due to genetics and behavior

Neurodegenerative diseases …
… and beyond: neuroinflammation!

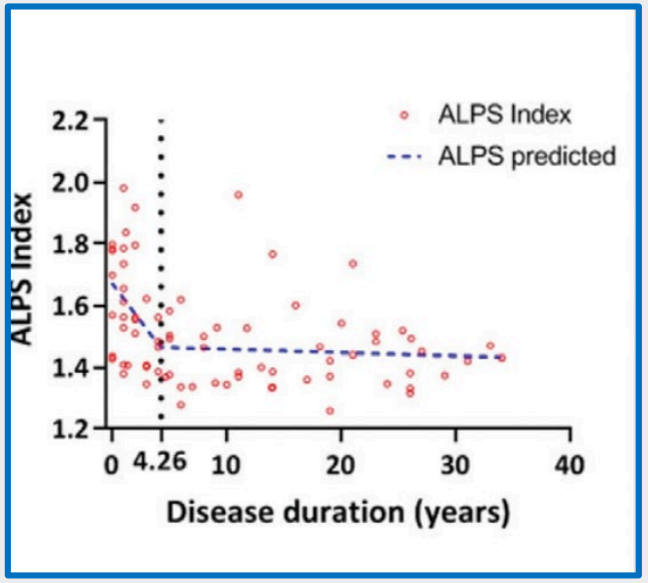
in vivo new diagnostic tools

Novel therapeutic targets

THE GLYMPHATIC PATHWAY

carla.uggetti@gmail.com

Multiple sclerosis



Review > Radiology. 2023 Jun;307(5):e221512. doi: 10.1148/radiol.221512.

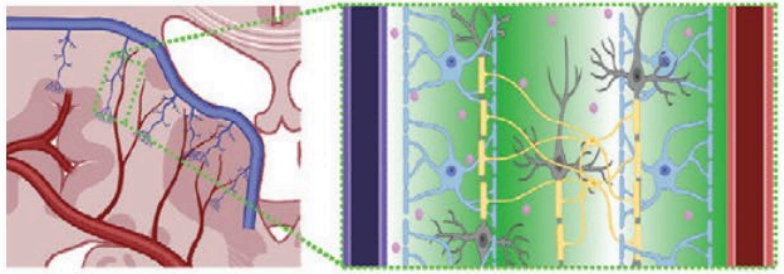
2023

Emerging Perspectives on MRI Application in Multiple Sclerosis: Moving from Pathophysiology to Clinical Practice

Maria Assunta Rocca [1], Monica Margoni [1], Marco Battaglini [1], Arman Eshaghi [1], Jeffrey Iliff [1], Elisabetta Pagani [1], Paolo Preziosa [1], Loredana Storelli [1], Toshiaki Taoka [1], Paola Valsasina [1], Massimo Filippi [1]

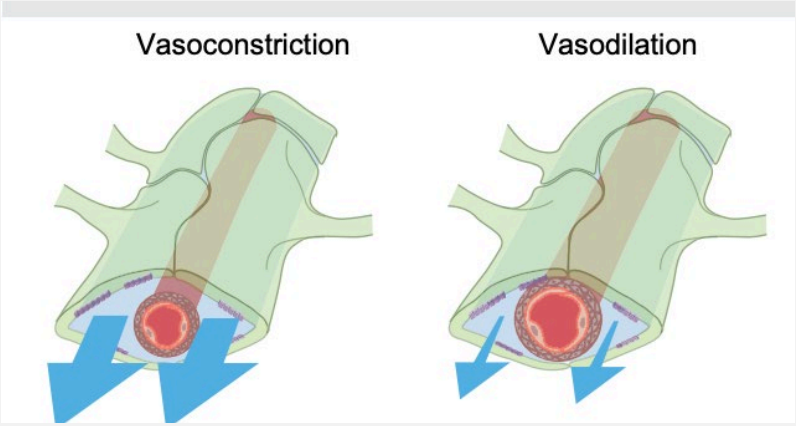
Rocca et al

1) Is noninvasive MRI visualization of the glymphatic system feasible and relevant?



- The appearance of MRI-visible dilated perivascular spaces, visualized on structural MRI scans, is believed to reflect impaired glymphatic exchange.
- A lower DTI-ALPS index was observed in patients with MS compared to HC subjects, even lower in the progressive phase, suggesting an overall glymphatic impairment.
- Non-invasive MRI-based approaches have not yet been validated against reference-standard contrast-based measured of perivascular exchange.

Migraine



J Neurosci. 2017 Mar 15;37(11):2904-2915. doi: 10.1523/JNEUROSCI.3390-16.2017. Epub 2017 Feb 13.

Cortical Spreading Depression Closes Paravascular Space and Impairs Glymphatic Flow: Implications for Migraine Headache

Aaron J Schain [1 2], Agustin Melo-Carrillo [1 2], Andrew M Strassman [1 2], Rami Burstein [3 2]

Zhang *et al.*
The Journal of Headache and Pain (2023) 24:147
https://doi.org/10.1186/s10194-023-01673-3

The Journal of Headache and Pain

RESEARCH Open Access

Increased glymphatic system activity in migraine chronification by diffusion tensor image analysis along the perivascular space

Xue Zhang[1,2,3], Wei Wang[4], Xiaoyan Bai[1,2,3], Xueyan Zhang[5], Ziyu Yuan[4], Bingjie Jiao[6], Yingkui Zhang[1], Zhiye Li[1,2,3], Peng Zhang[4], Hefei Tang[4], Yaqing Zhang[4], Xueying Yu[4], Ruiliang Bai[6,7,8*], Yonggang Wang[4*] and Binbin Sui[1,2*]