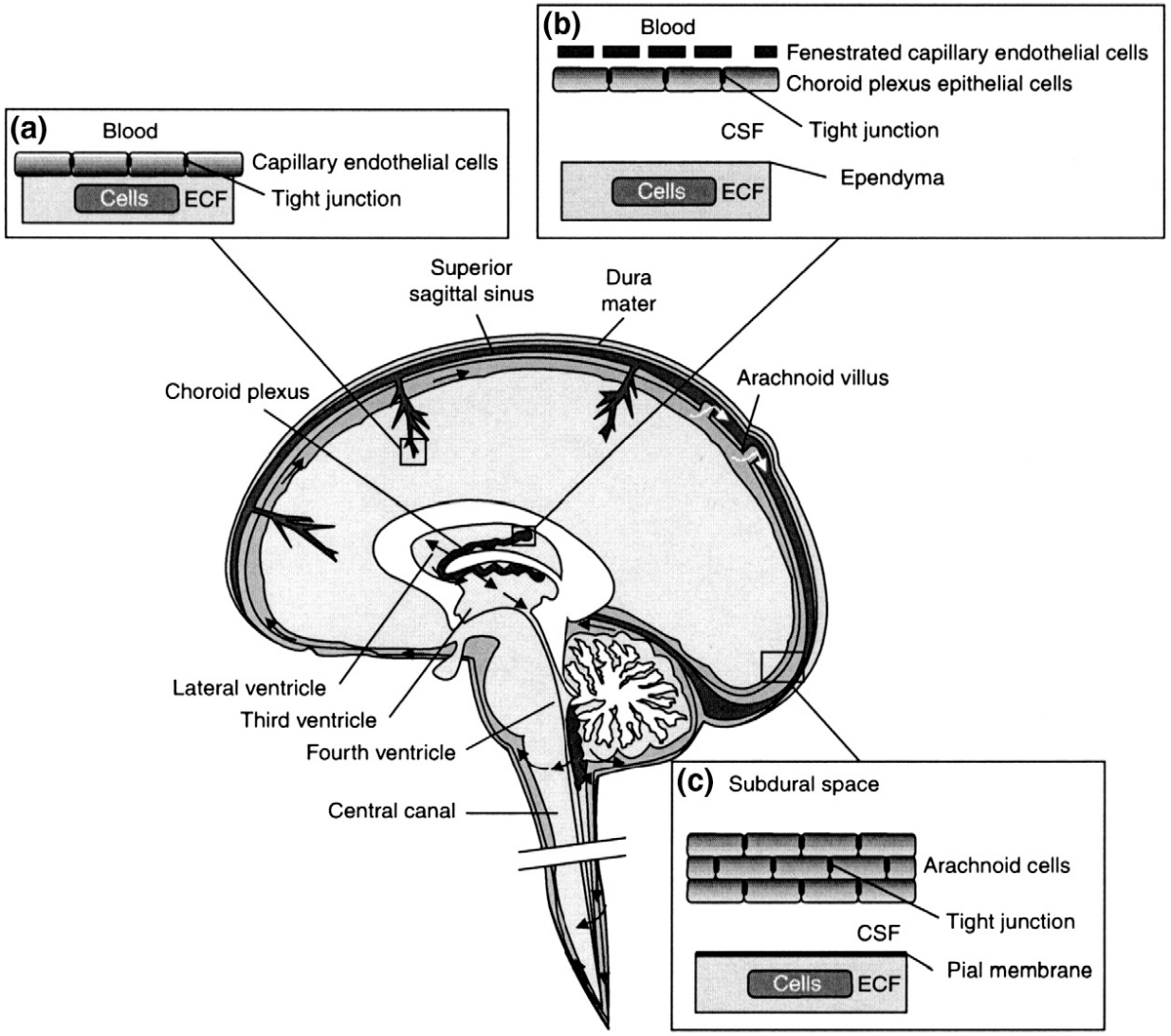
Blood-Brain Barrier Breakdown in the Aging Human Hippocampus

Montagne et al., 2015, Neuron 85, 296–302

Vorgetragen im JC – Applied Immunology 2019 – Daniel Bormann

Introduction – Brief notes on the blood brain barrier (BBB)



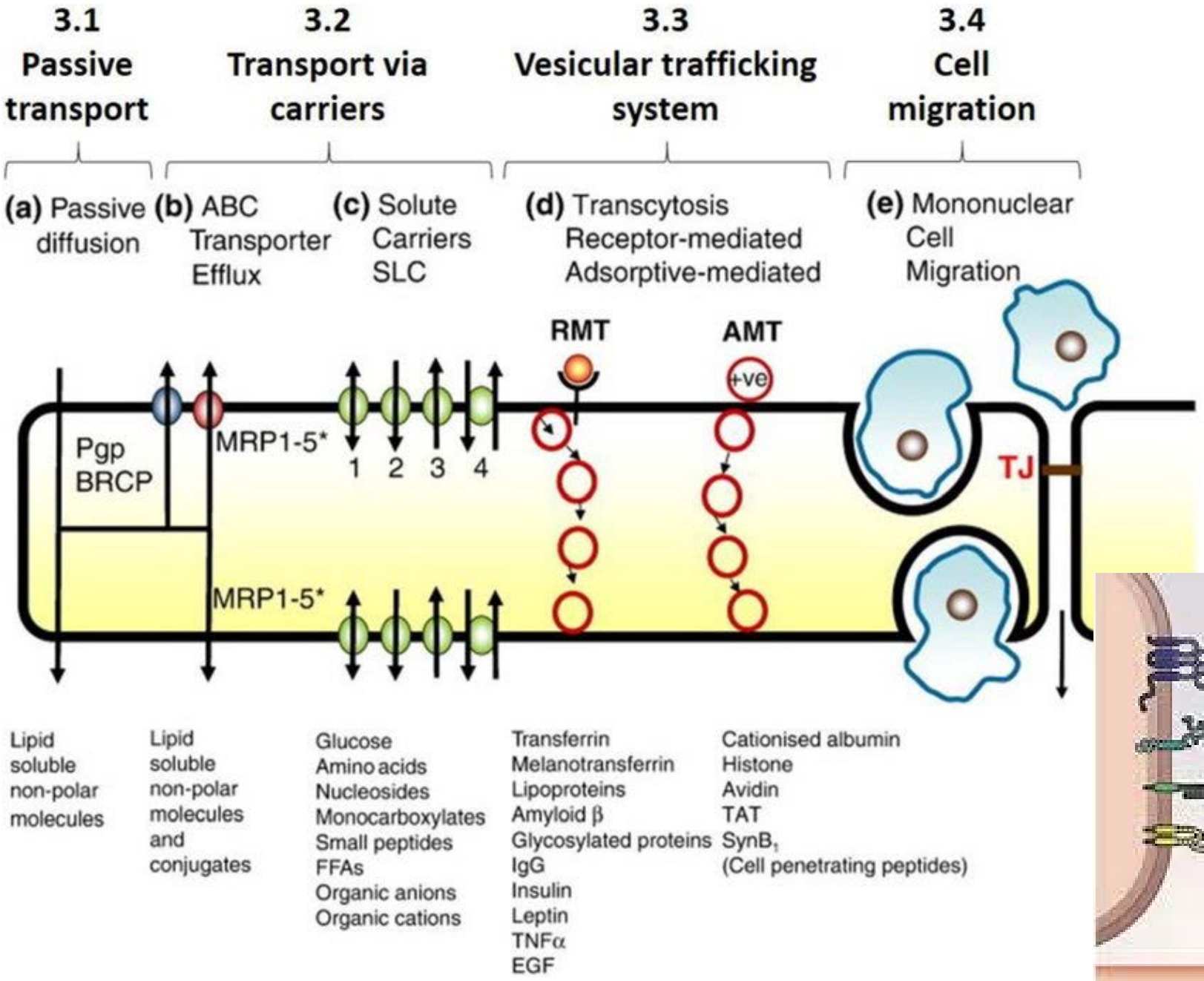
- **The „BBB proper“:** Tight junction formations of the brain capillary endothelial cells

(Surface-Area: 12-18 m2! No neuron in the brain is away further from an endotehlial cell than 25 mikrometers!)

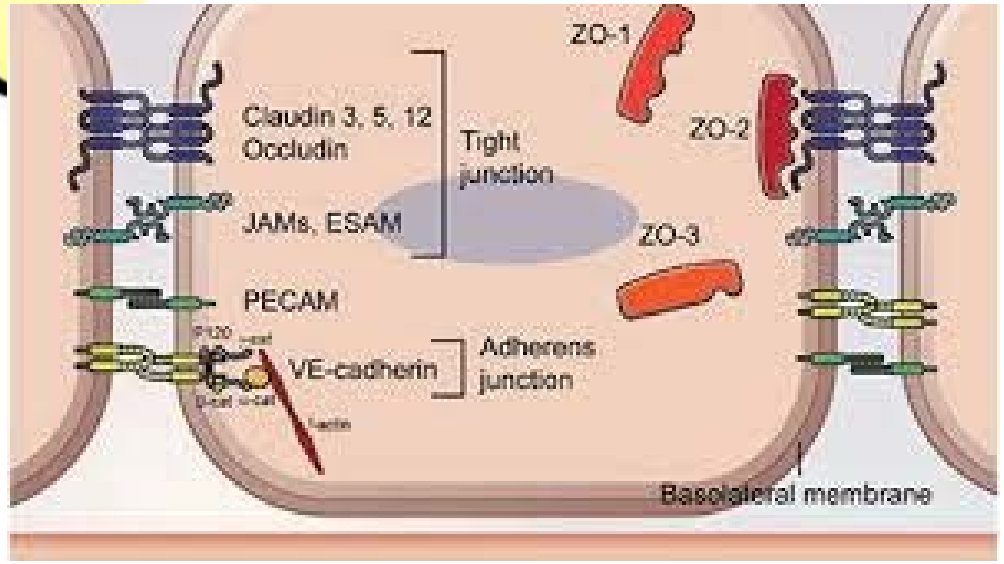
- **The Blood-CSF-barrier:** Fenestrated capillaries, tight junctions between single layered choroid plexus epithelial cells

- **The Arachnoid-barrier:** Multilayered tight junction rich epithelial cells.

1. Abbott NJ, Patabendige AA, Dolman DE, Yusof SR, Begley DJ. Structure and function of the blood-brain barrier. Neurobiol Dis. 2010;37(1):13-25.



As the term suggests transport across the BBB is tightly regulated



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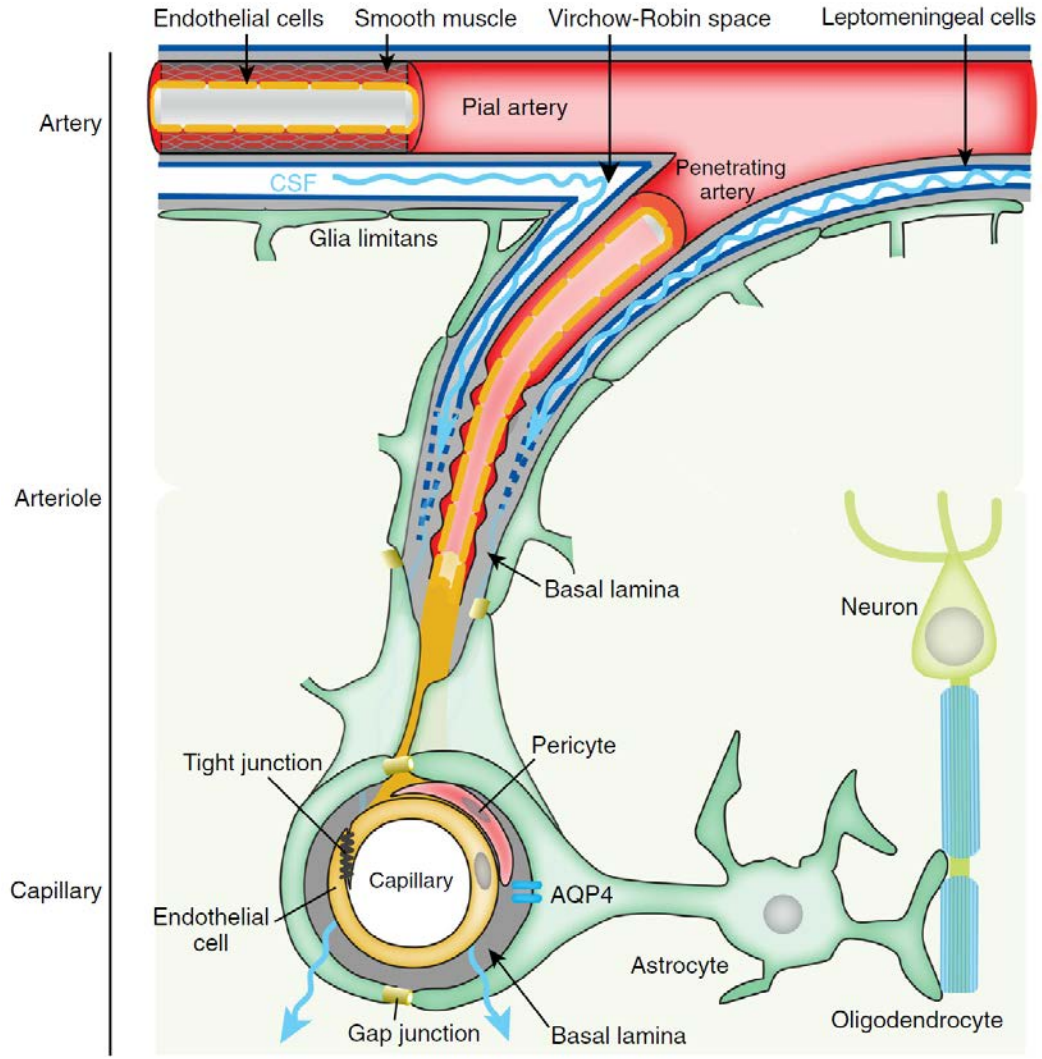
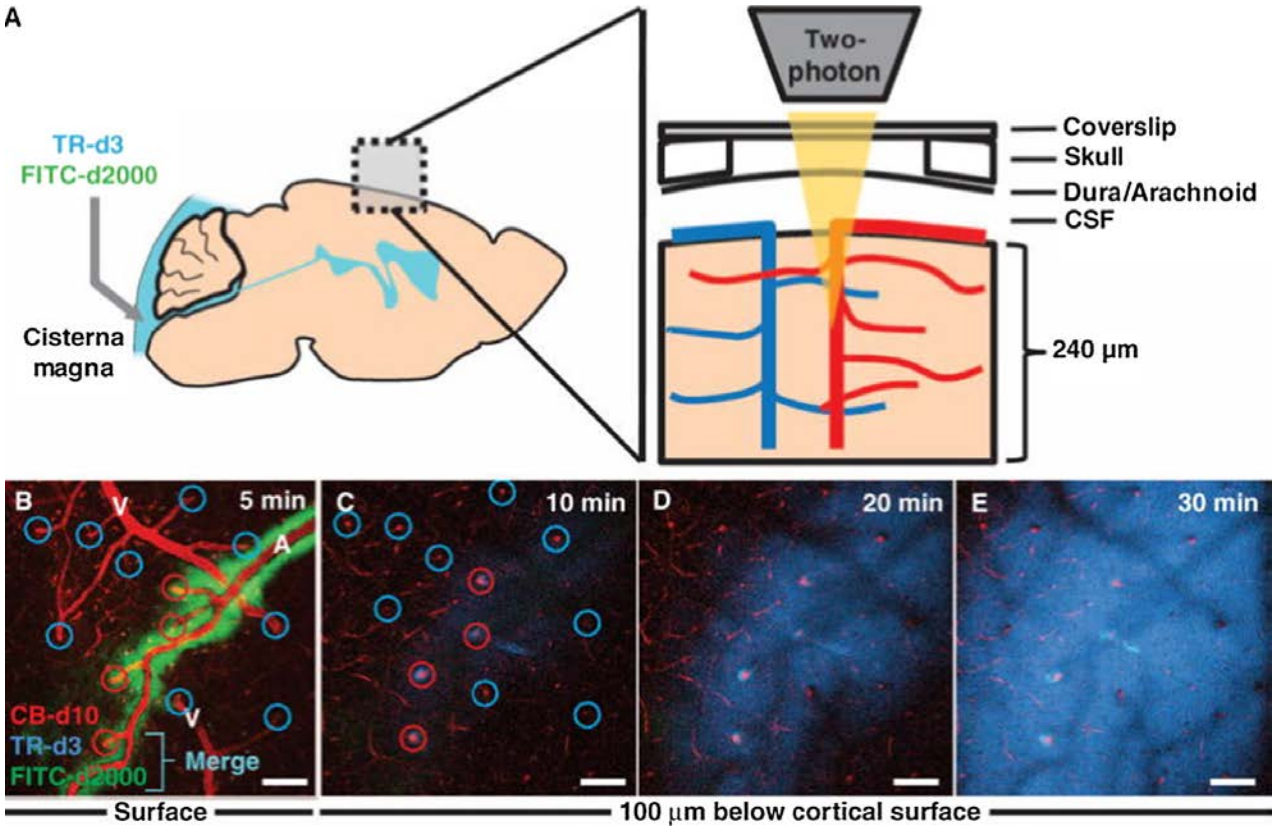
The „Neurovascular Unit“

5 cannonical components:
Endothelial cells, Pericytes, Astrocytes, Smooth muscle cells, Neurons



- Pial arteries -> penetrating arteriols
- Virchow-Robin-Space -> perivascular space -> continious with the Basallamina
- Endothelia, pericytes and Astrocyte all reside on, or contact the Basallamina

The Virchow-Robin Spaces
Constitue the highway by which CSF enters the brain parenchyma



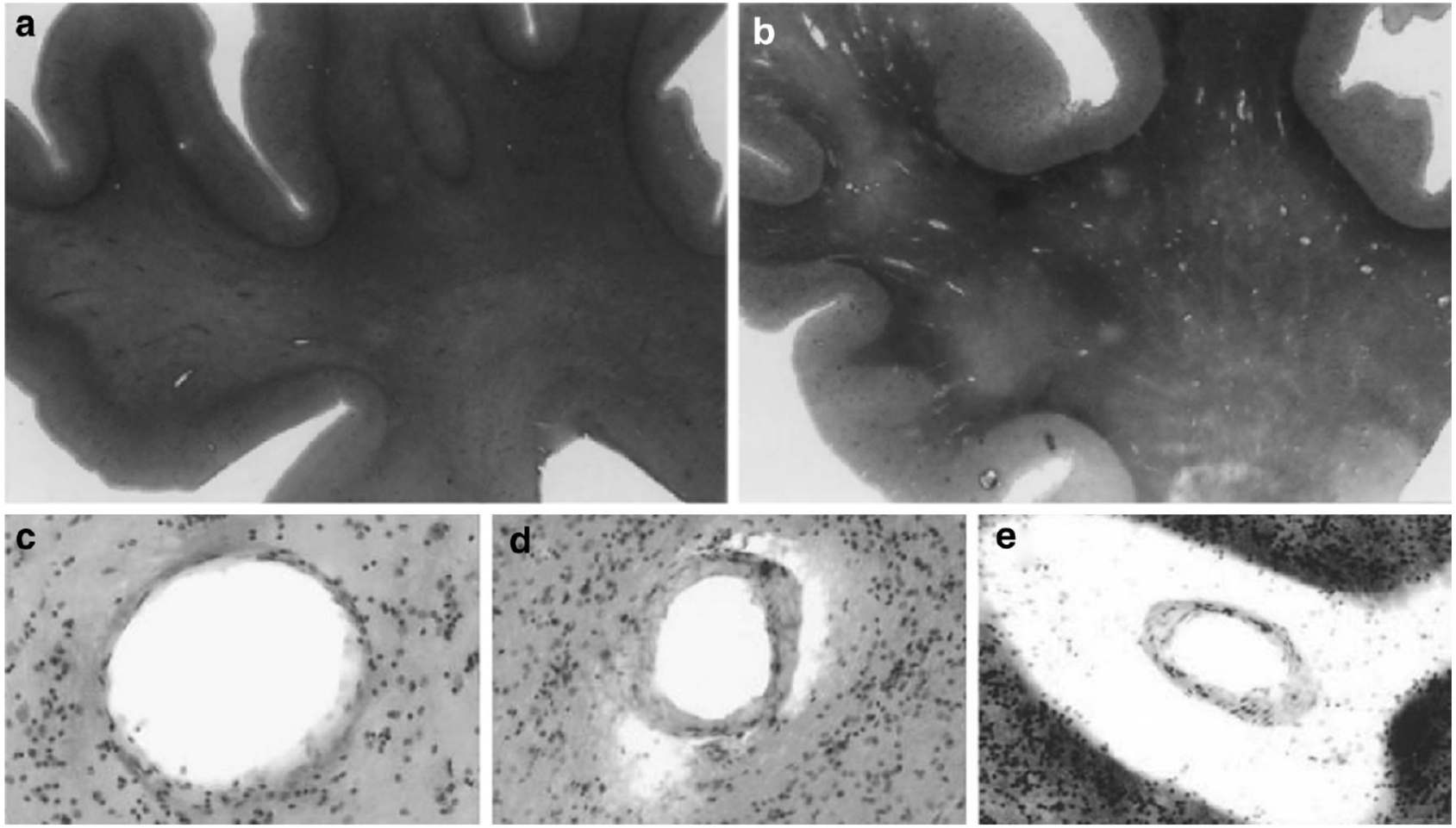
Jessen NA, Munk AS, Lundgaard I, Nedergaard M.
The Glymphatic System: A Beginner's Guide. Neurochem Res. 2015;40(12):2583-99.

Briefly: Important characteristics of BBB pathology for this paper

- Essential to create a distinct compartment with a well defined micromillieu
- Tight regulation of what may enter or leave the „immunopriviliged“ CNS-compartment
- Breakdown/Dysregulation associated with the entry of blood-derived neurotoxic proteins to the CNS: fibrin, thrombin, hemoglobin, iron-containing hemosiderin, free iron, plasmin, cytokines,…

→ Associated to primary and secondary neurotoxic effects (e.g. oxidative stress, excitotoxicity, detachment, extracellular millieu dysregulation,…)

BBB-Breakdown and „Glymphatic System“ Dysfunction are strongly associated to the pathology of Alzheimer´s disease



HE-Stainings of postmortem brains

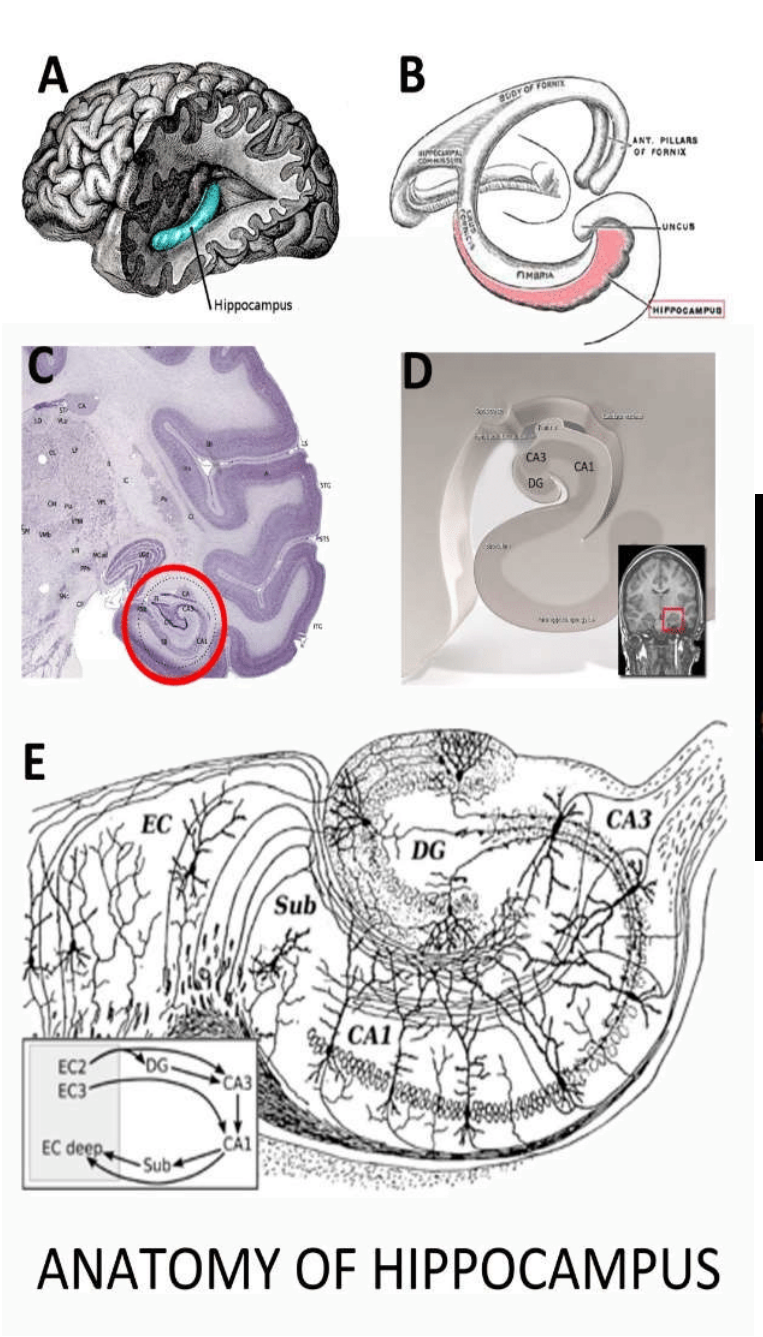
a.) 74a, male, neurotypic,
no AD history, homogenous staining of white matter tracts, tight perivascular spaces c.)

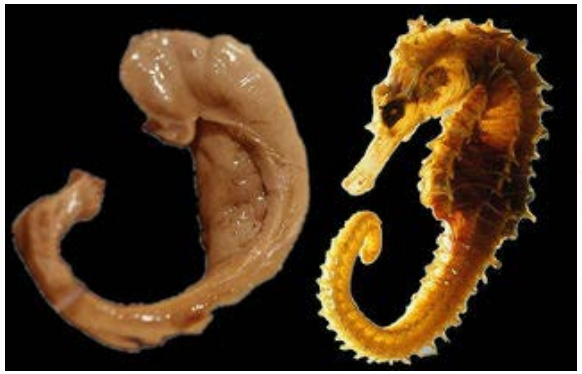
b.)d.)e.) Specimen from AD patients: Note the enlarged disfigured perivascular spaces.

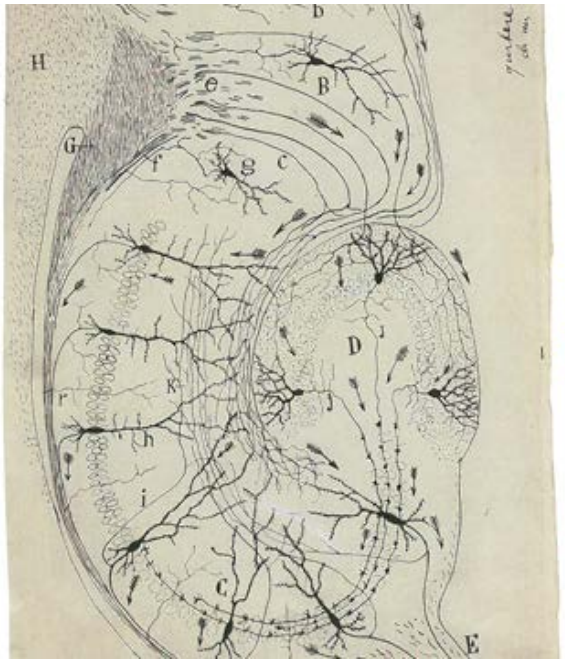
Jessen NA, Munk AS, Lundgaard I, Nedergaard M. The Glymphatic System: A Beginner's Guide. Neurochem Res. 2015;40(12):2583-99.

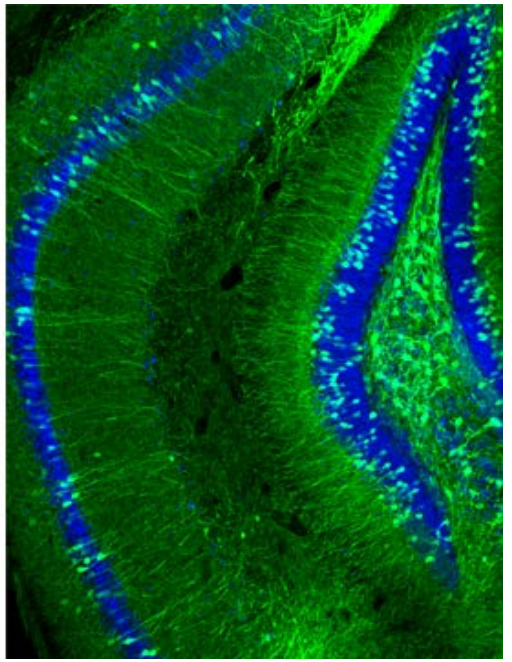
Interlude: A CNS region of particular interest for this paper:

The hippocampal formation – highly aesthetic, highly important



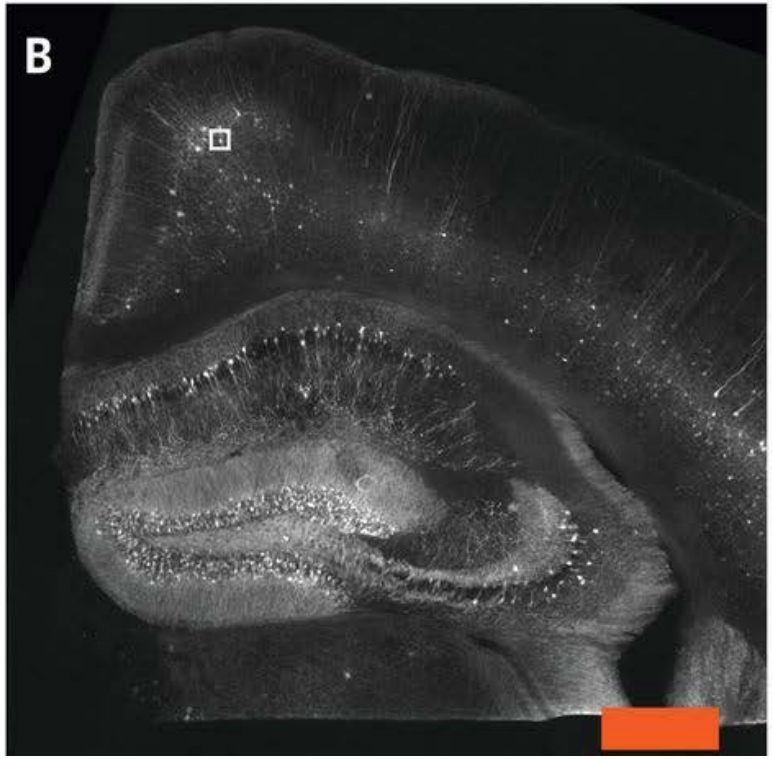






Left: drawing of the trisynaptic pathway by Ramon y Cajal
Right: High res. Immunoflurescence
From:
https://mcgovern.mit.edu/2018/01/17/the-beautiful-brain/

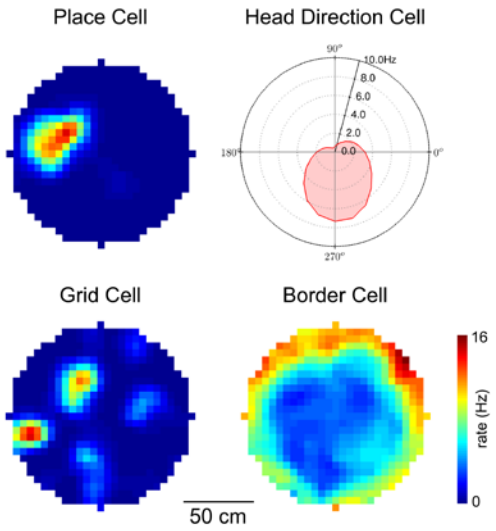
https://www.researchgate.net/publication/315696579_A_Bio-Electrical_Tornado_in_The_Hippocampus_Mechanisms_of_Temporal_Lobe_Epilepsy



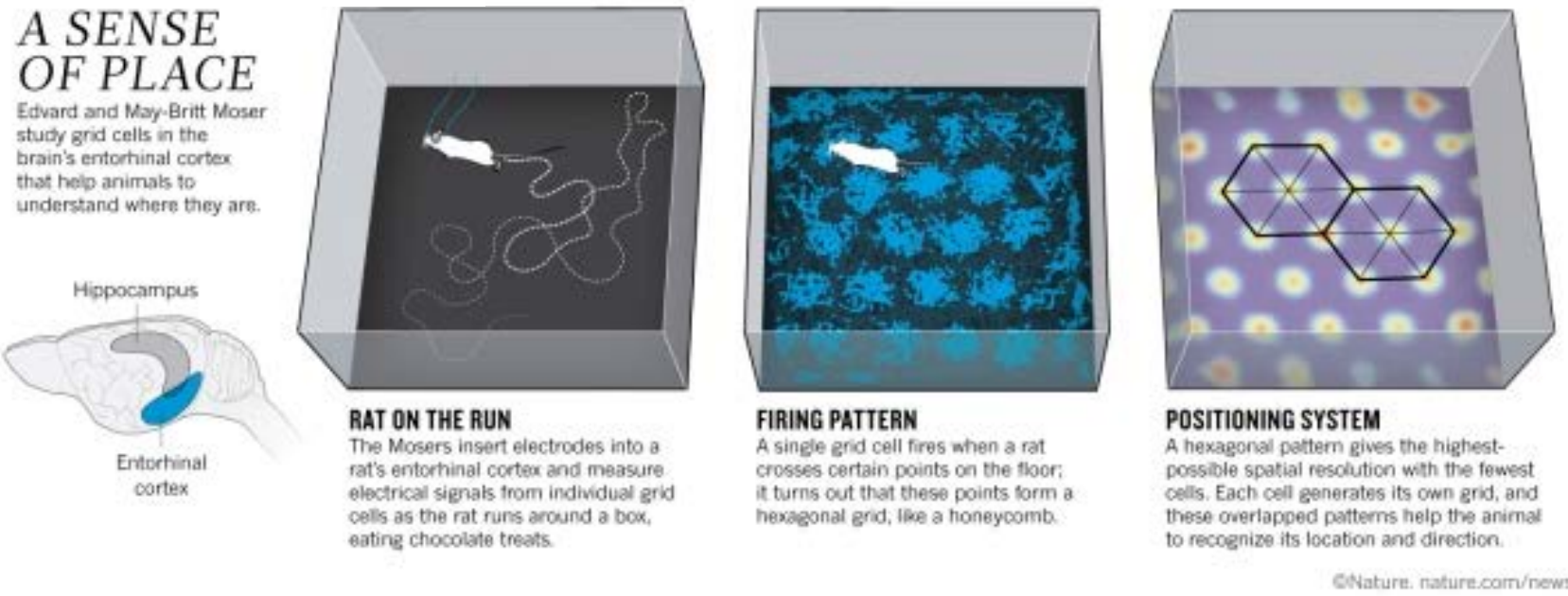
Chen F, Tillberg PW, Boyden ES. Expansion microscopy. Science. 2015;347(6221):543-8.

An intricate network of excitatory loops, modulated by a diversity of interwoven inhibitory interneurons

→ Prominently associated to memory and learning



https://kloostermanlab.org/research/spatial-code/



Possibly an important neural substrate of how we perceive time and space and are able to navigate and mentaly simulate our sourroundings

-> The Nobel Prize in Physiology or Medicine 2014
John O'Keefe, Edvard Moser, May-Britt Moser

At what stage does BBB-breakdown occur in normal ageing and is this phenomenon associated with cognitive impairment?

- How was this addressed?

I. Advanced dynamic contrast-enhanced MRI (**DCE-MRI**) -> Post-processing -> Quantification of the **BBB regional permeability (K-trans) constant**

   Briefly: Gadolinium (contrast agent) was injected i.v. -> T2 and T1 weighted images were aquired.

   -> In healthy adult CNS tissue: The contrast agent only leaves the vessels in traces!

This data was used to generate BBB permeability Ktrans maps.

Ktrans is a constant that represents the **flow of the contrast agent from the intravascular to the extravascular space.**

Individual Arterial input functions (AIFs) which describe the contrast agent input to the tissue of interest were used.

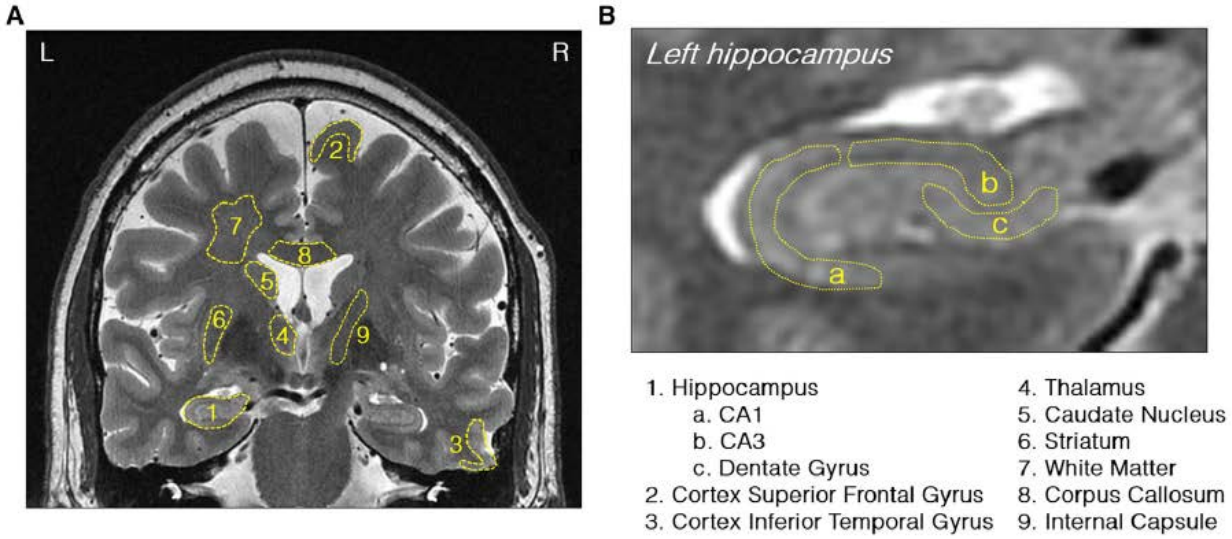
Table 1. Participants' Demographic Information

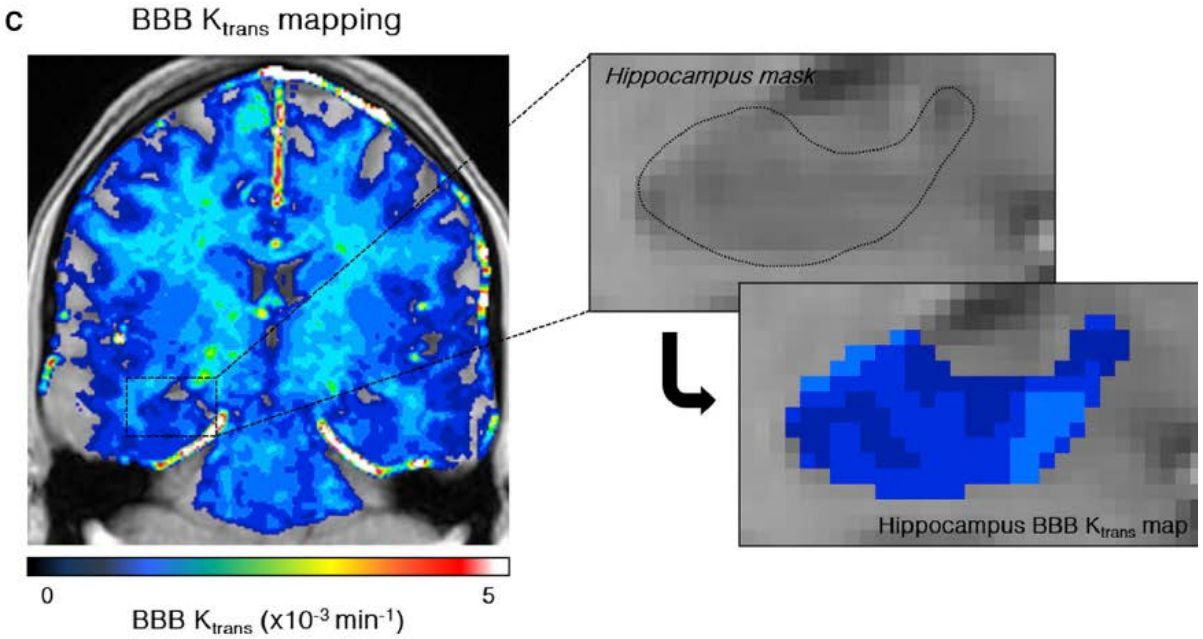
	NCI, Young	NCI, Older	MCI	MS
Clinical Dementia Rating scale	0	0	0.5	0
Number of participants	6	18	21	19
Female	50%	55.6%	52.4%	63.2%
Age range	23–47	55–91	55–85	26–53
DCE-MRI	6/6	18/18	20/21	19/19
Lumbar puncture	0/6	15/18	17/21	0/19
Age at lumbar puncture, Mean (SD)	N/A	73.2 (10.6)	72.0 (8.5)	N/A

NCI, no cognitive impairment; MCI, mild cognitive impairment; MS, multiple sclerosis; DCE-MRI, dynamic contrast-enhanced MRI; SD, standard deviation; N/A, not applicable.

- 64 participants
- Cognitive evaluation: Uniform Data Set (UDS), California Verbal Learning Test, block design, letter-number sequencing, letter fluency, and token test
- Patients were categorized as Non-cognitivley impaired or suffering from mild cognitive impairment.
- Patients with severe dementia, trauma, CNS-lesions, etc. were excluded
- Included: diagnosed MS patients to validate the method:
  Expected to have increased WM tract but not GM BBB-permeability

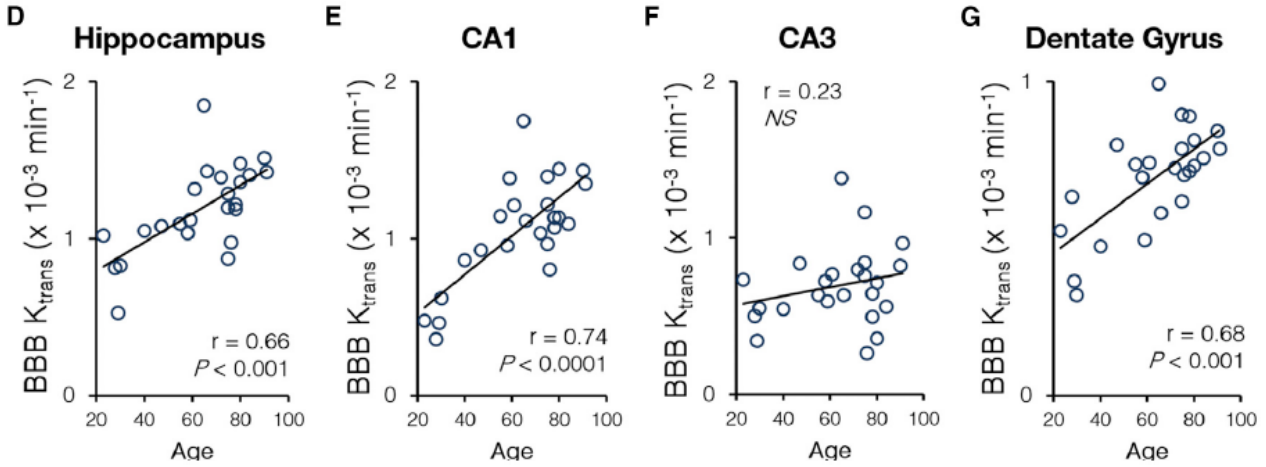
I.



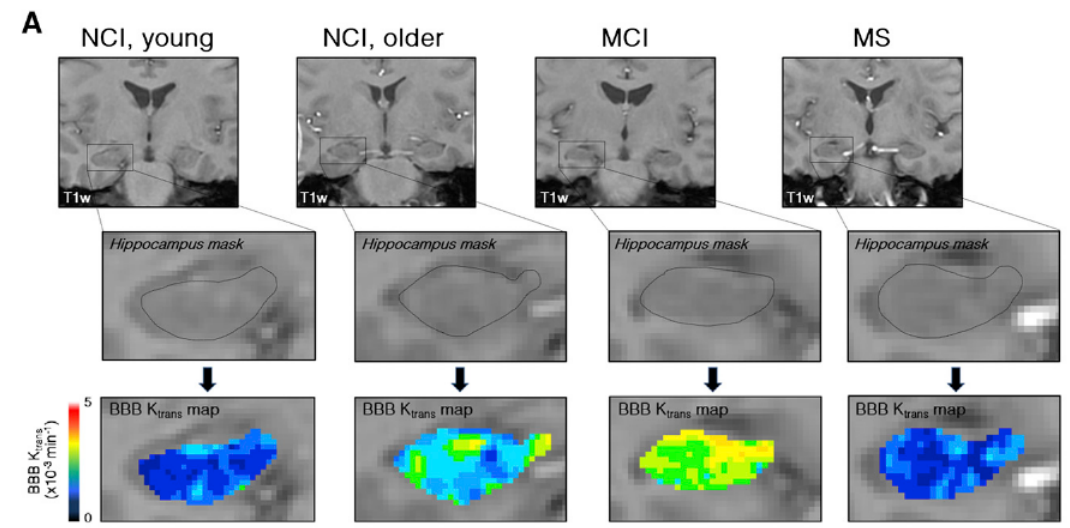


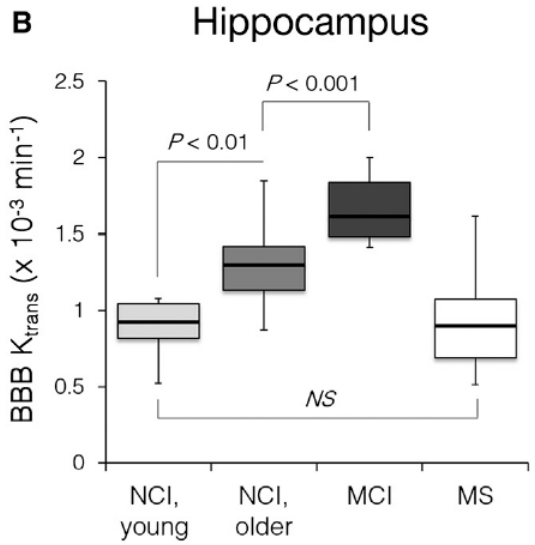
12 distinct brain regions were studied: Main finding -> age-dependent increase of the BBB permeability in the Hippocampus, particularly CA1 and DG!

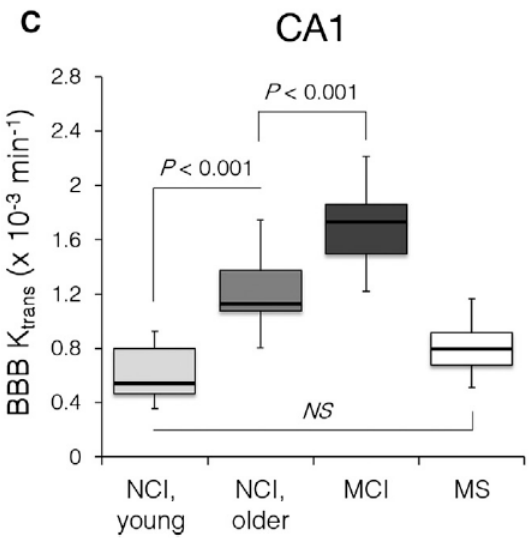
No age-dependent breakdown in any other region, except of the caudate nucleus.

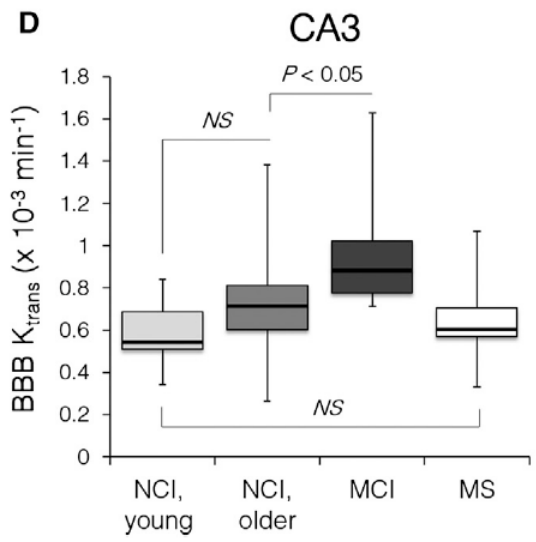


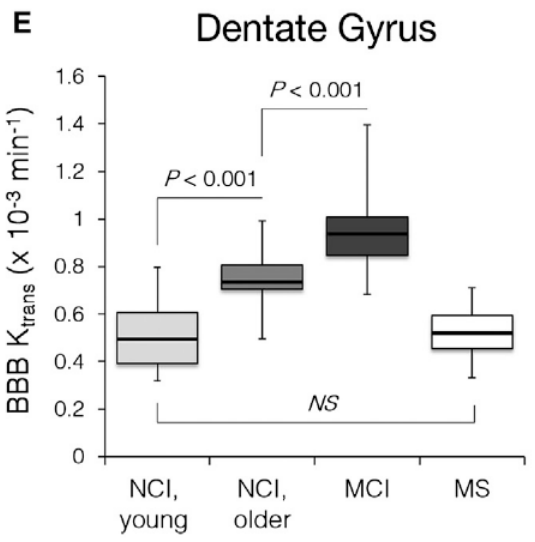
Blood-Brain Barrier Breakdown in the Hippocampus during Normal Aging and Aging Associated with Mild Cognitive Impairment









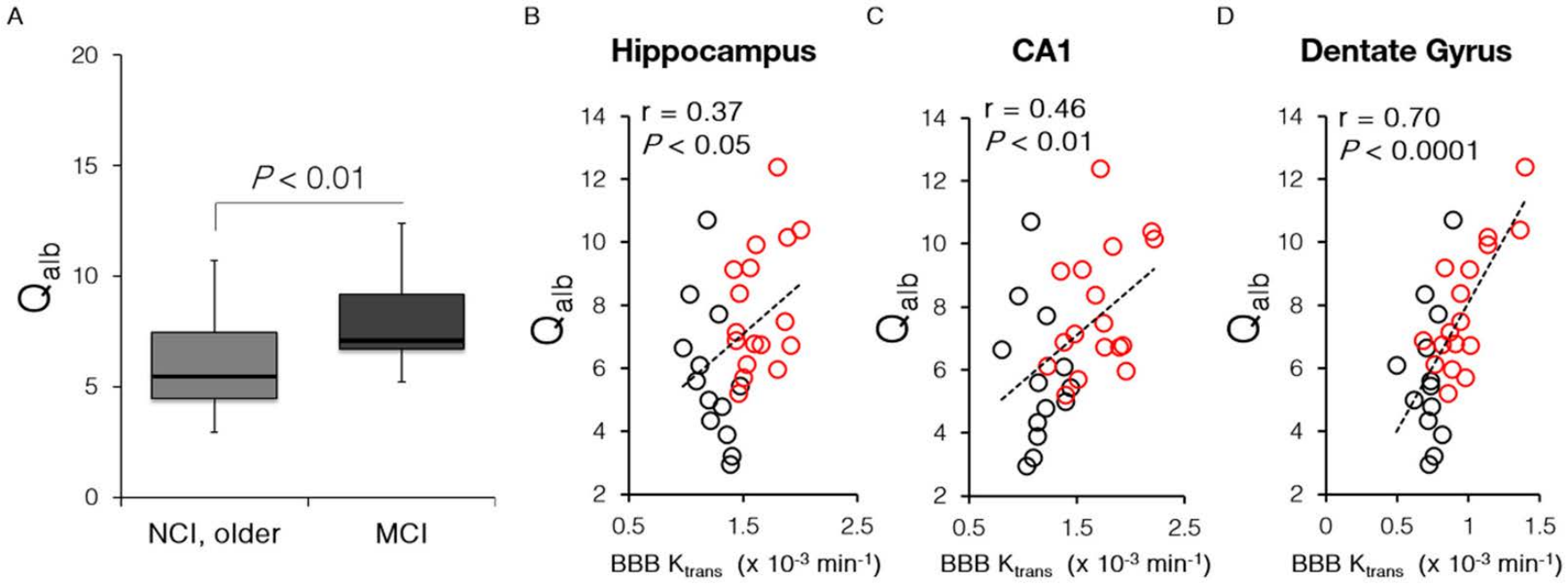


Significant Ktrans increase in the HC, CA1 and DG by 41%, 107% and 48% in older NCI subjects

and

Significant Ktrans increase by 25%, 53% and 27% in MCI subjects compared to age matched NCI controls

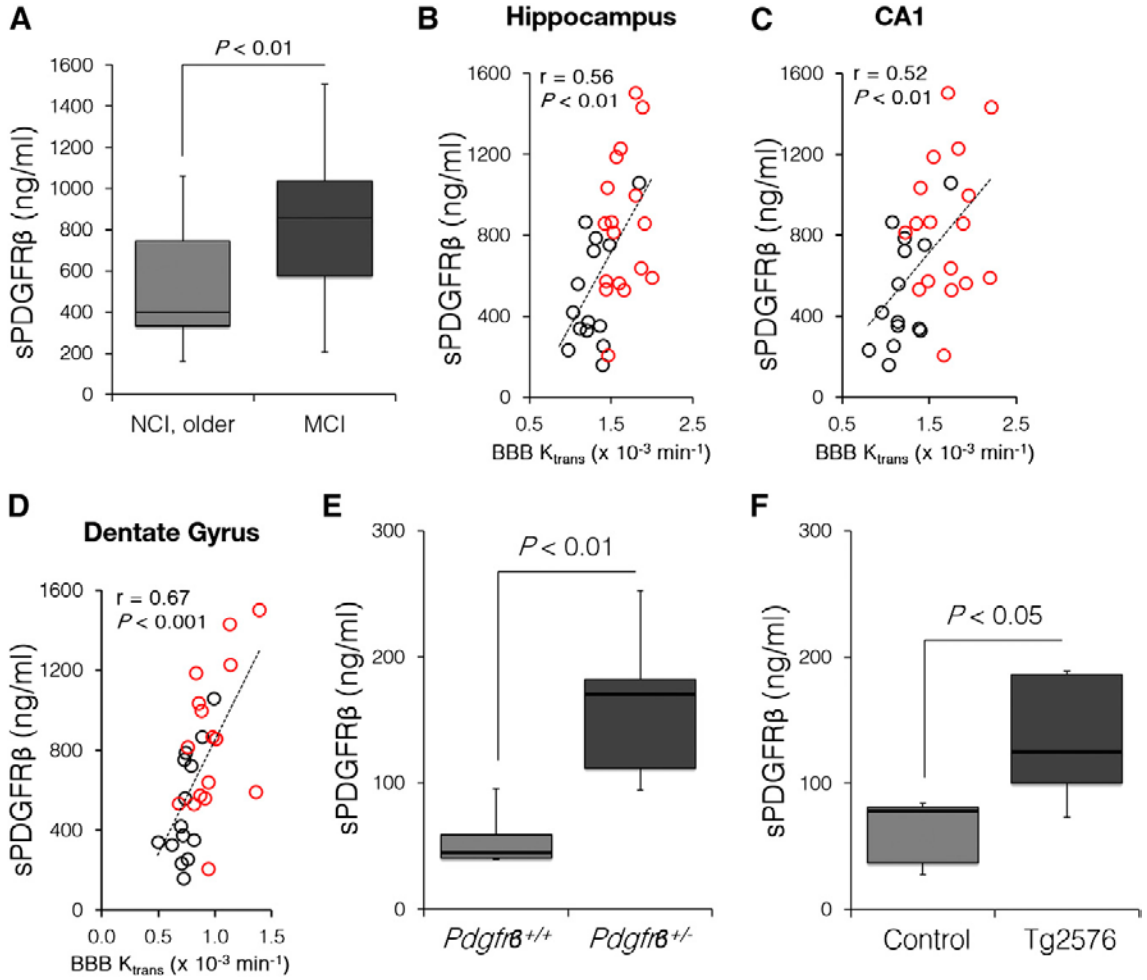
II. Molecular Biomarker CSF Analysis



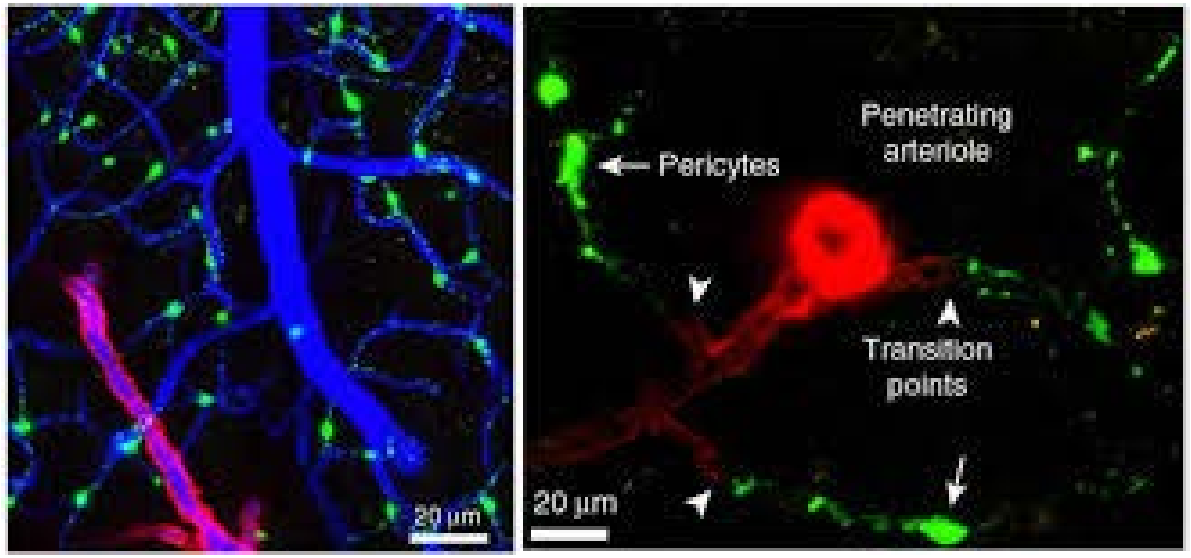
Increase in the CSF/plasma albumin ratio (Qalb) in individuals with mild cognitive impairment (MCI; n=17) compared to age-matched individuals with no cognitive impairment (NCI, older; n=14).

Increase in the CSF/plasma albumin ratio correlated with an increase in the Ktrans values in the hippocampus and its CA1 and DG subregions

Correlations between Ktrans values and CSF levels of soluble platelet-derived growth factor receptor b (sPDGFRb).– a brain pericyte marker(sPDGFRb).

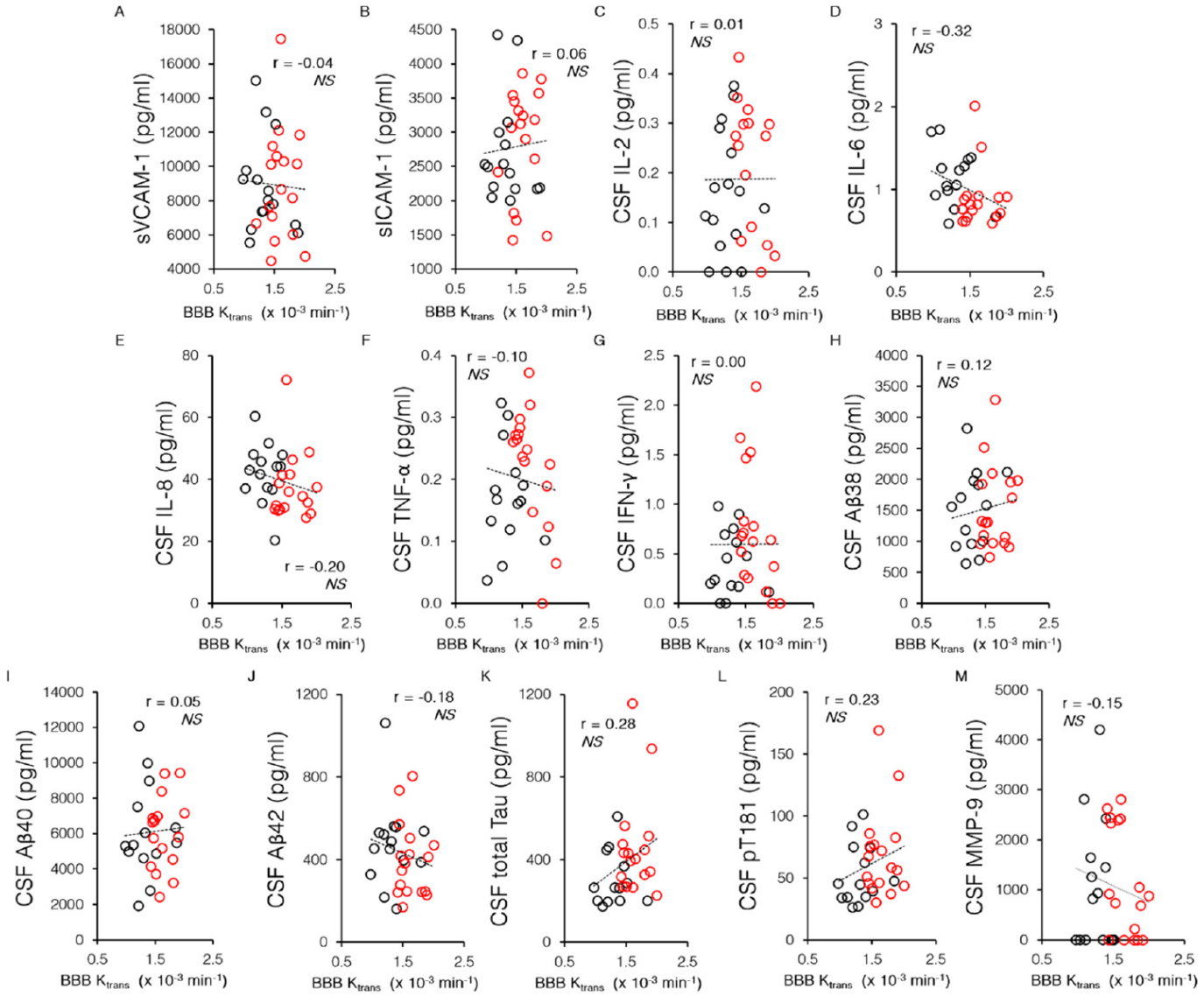


Pericyte dysfunction and loss is implicated in the pathology of AD !



Brain-Capillary-Pericytes: Dyed with Neurotracer green, in blue large vessels, SMA in red – taken from transgenic mice using *in vivo* imaging

Damisah EC, Hill RA, Tong L, Murray KN, Grutzendler J.
A fluoro-Nissl dye identifies pericytes as distinct vascular mural cells during in vivo brain imaging.
Nat Neurosci. 2017;20(7):1023-32.

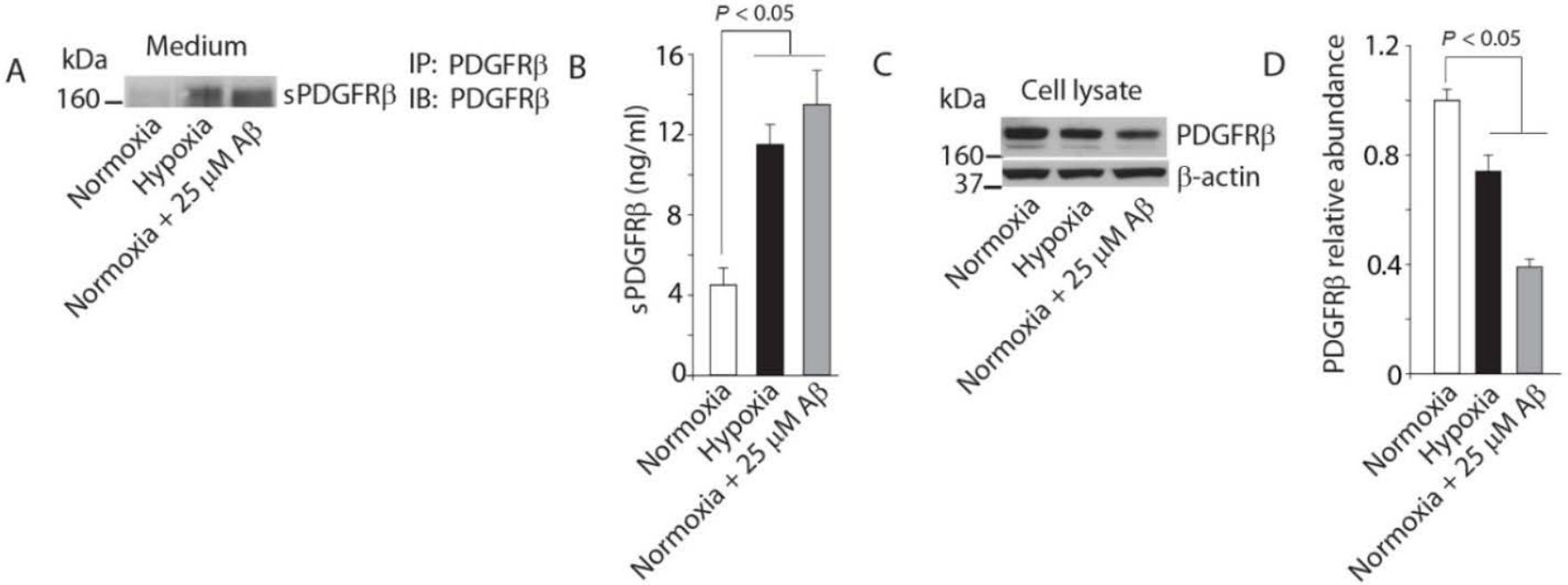


Biomarkers of endothelial cell injury such as soluble intercellular adhesion molecule-1 (sICAM-1) and vascular cell adhesion molecule-1 (sVCAM-1) unchanged

No change in the inflammatory response as shown by unaltered CSF levels of several studied cytokines (e.g., interleukins IL-2, IL-6, and IL-8, tumor necrosis factor-a, and interferon-g);

No change in neuronal injury (e.g., tau and pTau) and Ab (e.g., Ab38, Ab40, and Ab42); and no change in matrix metalloproteinase-9

Immunopercipitation and Westernblots of stressed cultured pericytes



Hypoxia and Amyloid Beta lead to sheeding of soluble PDGFR-Beta in cultured human pericytes

Conclusions and Discussion

- BBB-Breakdown in the CA1 and DG regions of the Hippocampus appears to be an early event in the pathogenesis of Neurodegeneration associated cognitive impairment.

- This inspires further investigations into causal relations in the interplay of BBB-integrity and Neurodegeneration and ist clinical correlates in AD

- sPDGFRb as a screening bio-marker?

- BBB-breakdown as precedeing or even causing inflammatory cascades, intra- and extracellular protein aggregates and damage to brain vascularity and neurodegeneration?

References

1. Abbott NJ, Patabendige AA, Dolman DE, Yusof SR, Begley DJ. Structure and function of the blood-brain barrier. Neurobiol Dis. 2010;37(1):13-25.

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4. Montagne A, Barnes SR, Sweeney MD, Halliday MR, Sagare AP, Zhao Z, et al. Blood-brain barrier breakdown in the aging human hippocampus. Neuron. 2015;85(2):296-302.

5. Chen F, Tillberg PW, Boyden ES. Expansion microscopy. Science. 2015;347(6221):543-8.

Online Resources:

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https://kloostermanlab.org/research/spatial-code/