UNIVERSITÀ DEGLI STUDI
DI GENOVA

BLOOD-BRAIN BARRIER BREAKDOWN IN AGING HUMAN HIPPOCAMPUS

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Report

Blood-Brain Barrier Breakdown in the Aging Human Hippocampus

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BLOOD-BRAIN BARRIER BREAKDOWN IN AGING HUMAN HIPPOCAMPUS

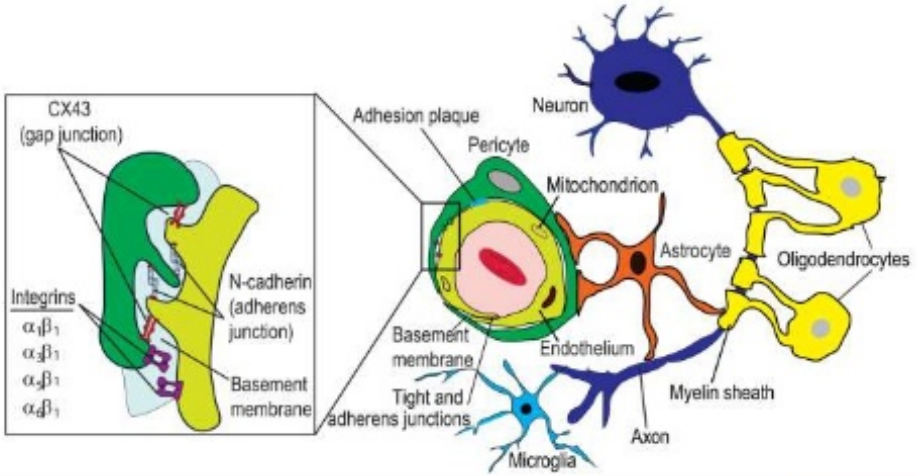
- The blood-brain barrier (BBB) limits entry of blood-derived products, pathogens, and cells into the brain that is essential for normal neuronal functioning and information processing

- Post-mortem tissue analysis indicates BBB damage in Alzheimer's disease (AD). The timing of BBB breakdown remains, however, elusive

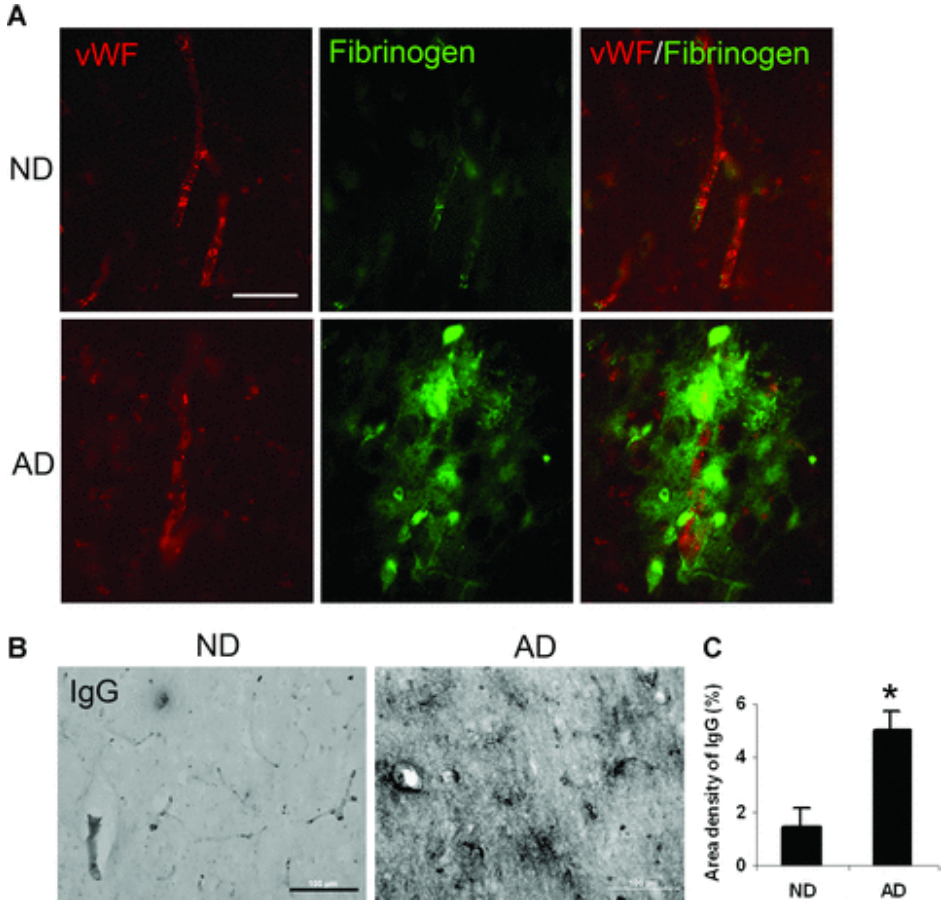
- Authors use an advanced dynamic contrast-enhanced MRI protocol with high spatial and temporal resolutions to quantify regional BBB permeability in the living human brain, aiming at exploring age-dependent BBB breakdown in the hippocampus, a region critical for learning and memory that is affected early in AD

Some studies of BBB in aging and dementia relied on autopsy material to detect extravasation of plasma proteins such as fibrinogen

These approaches are not ideal since in post-mortem brains tissue degradation, advanced disease and coexisting pathologies complicate establishing cause effect relationships

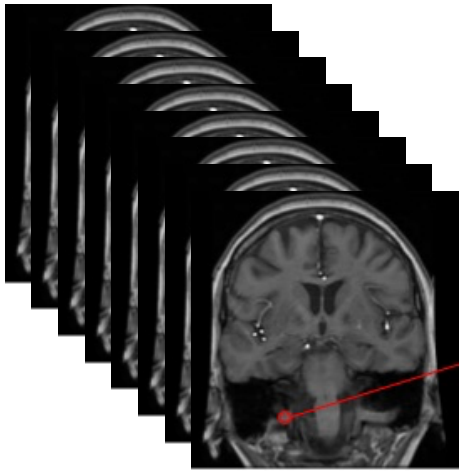


A leaky BBB fibrinogen infiltration and microglial reactivity in inflamed AD brain

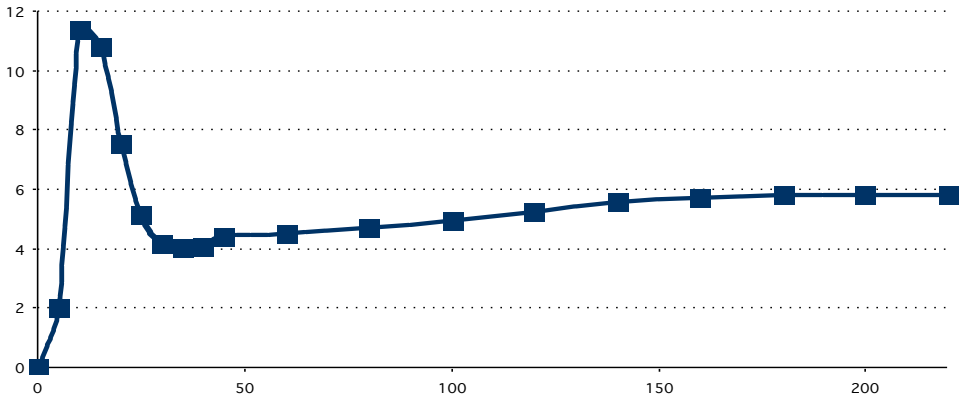


Journal of Cellular and Molecular Medicine

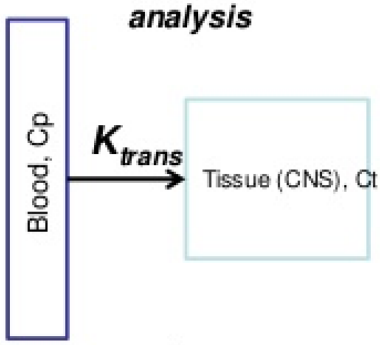
Advanced dynamic contrast-enhanced MRI protocol



Time



Patlak unidirectional linear analysis



$$C_t(t) = K_{trans} \int_0^t C_p(u)du + v_p C_p(t)$$

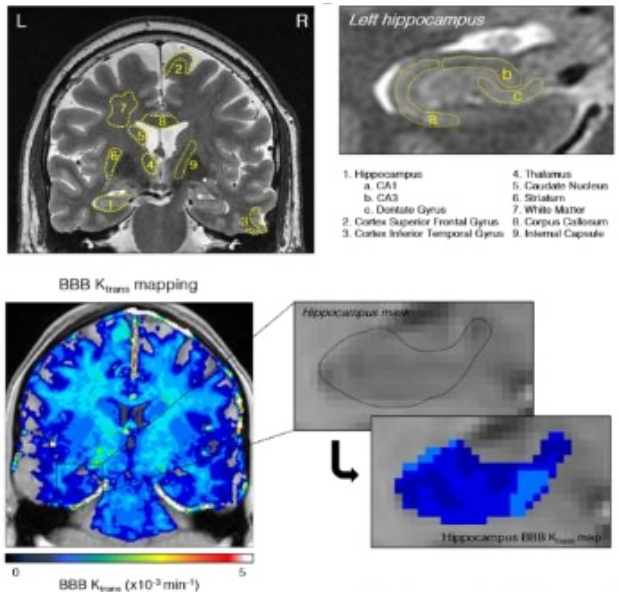


Table 1. Participants' Demographic Information

	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.

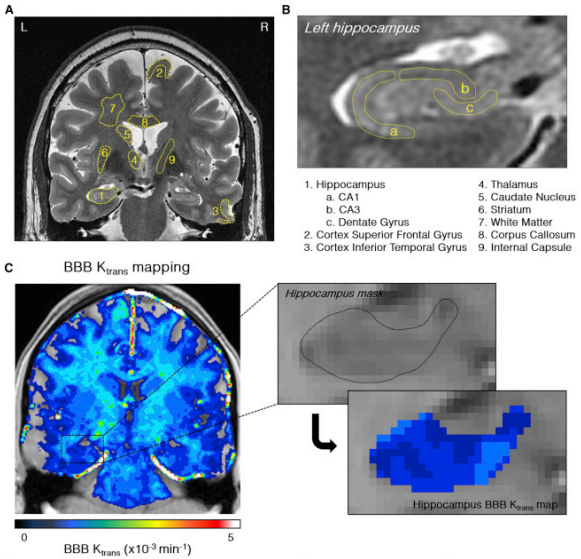
Neuropsychological Evaluations

Older NCI and MCI participants were evaluated using the Uniform Data Set (UDS) (Morris et al., 2006; Weintraub et al., 2009).

In addition California Verbal Learning Test, block design, letter-number sequencing, letter fluency, and token test.

Cognitively intact NCI participants were defined by CDR=0 and neuropsychological test scores within normal limits.

MCI participants were defined by CDR=0.5 and impairment in neuropsychological test scores in one or more cognitive domains.



Magnetic Resonance Imaging

Images were obtained on a GE 3T HDXT MR scanner.

Gd-based contrast agent was administered intravenously.

Coronal DCE-MRI scans were acquired using a T1-weighted 3D SPGR pulse sequence repeated for 16 minutes with 15.4 seconds temporal resolution per image. Voxel size was 0.625 x 0.625 x 5 mm.

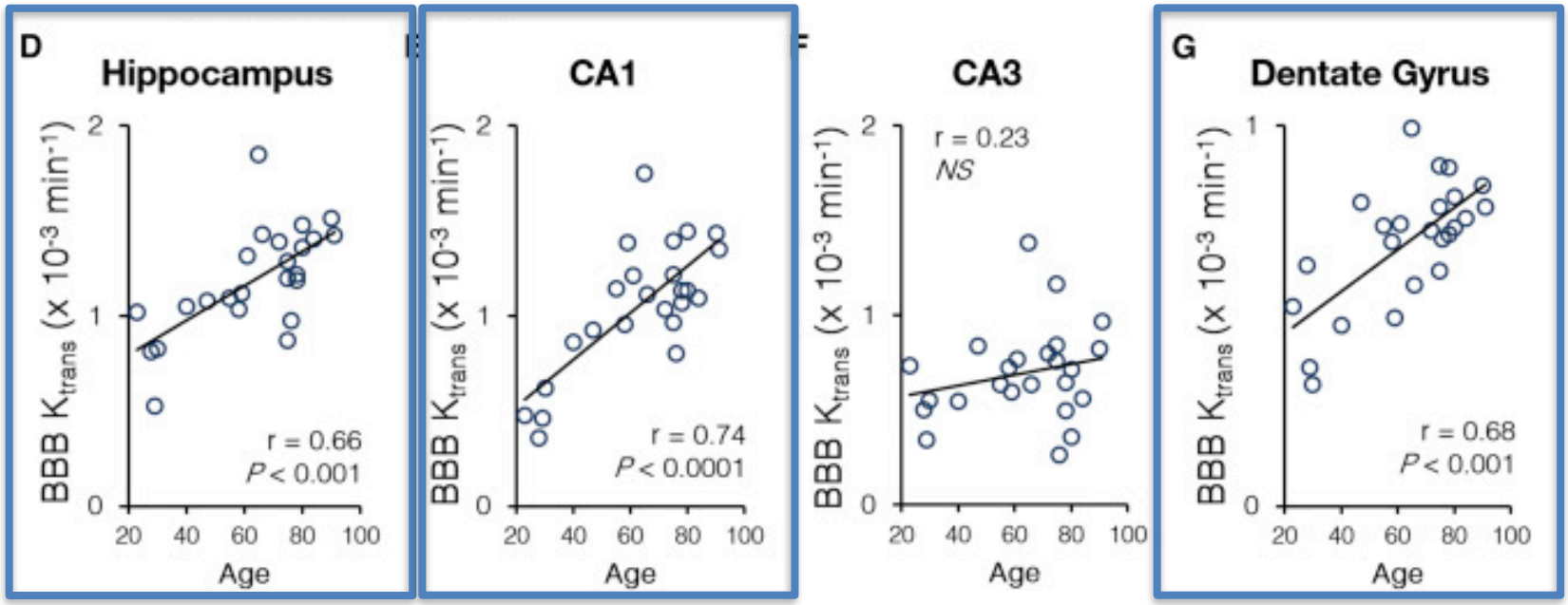
Quantification of the Blood-Brain Barrier Permeability

Post-processing analysis was performed using in-house scripts. The Patlak linearized regression mathematical analysis (Patlak and Blasberg, 1985; Taheri et al., 2011, 2013) was modified to generate the BBB permeability K_{trans} maps with high spatial and temporal resolutions

K_{trans} represents the flow from the intravascular to the extravascular space using equation

$$C_t(t)=K_{trans}\int^{t} C_p(u)du + v_p C_p(t)$$

BLOOD-BRAIN BARRIER BREAKDOWN IN AGING HUMAN HIPPOCAMPUS



Dynamic contrast enhanced MRI was used to quantify the blood-brain barrier (BBB) regional permeability K_{trans} constant in 12 regions of interest in the gray and white matter in the living human brain

Age-dependent increase in the BBB permeability K_{trans} constant in the entire hippocampus, its CA1 region, and dentate gyrus, but not CA3 region. Single data points for the K_{trans} constant from 24 individuals with no cognitive impairment (both genders, ages 23–91) were plotted against age

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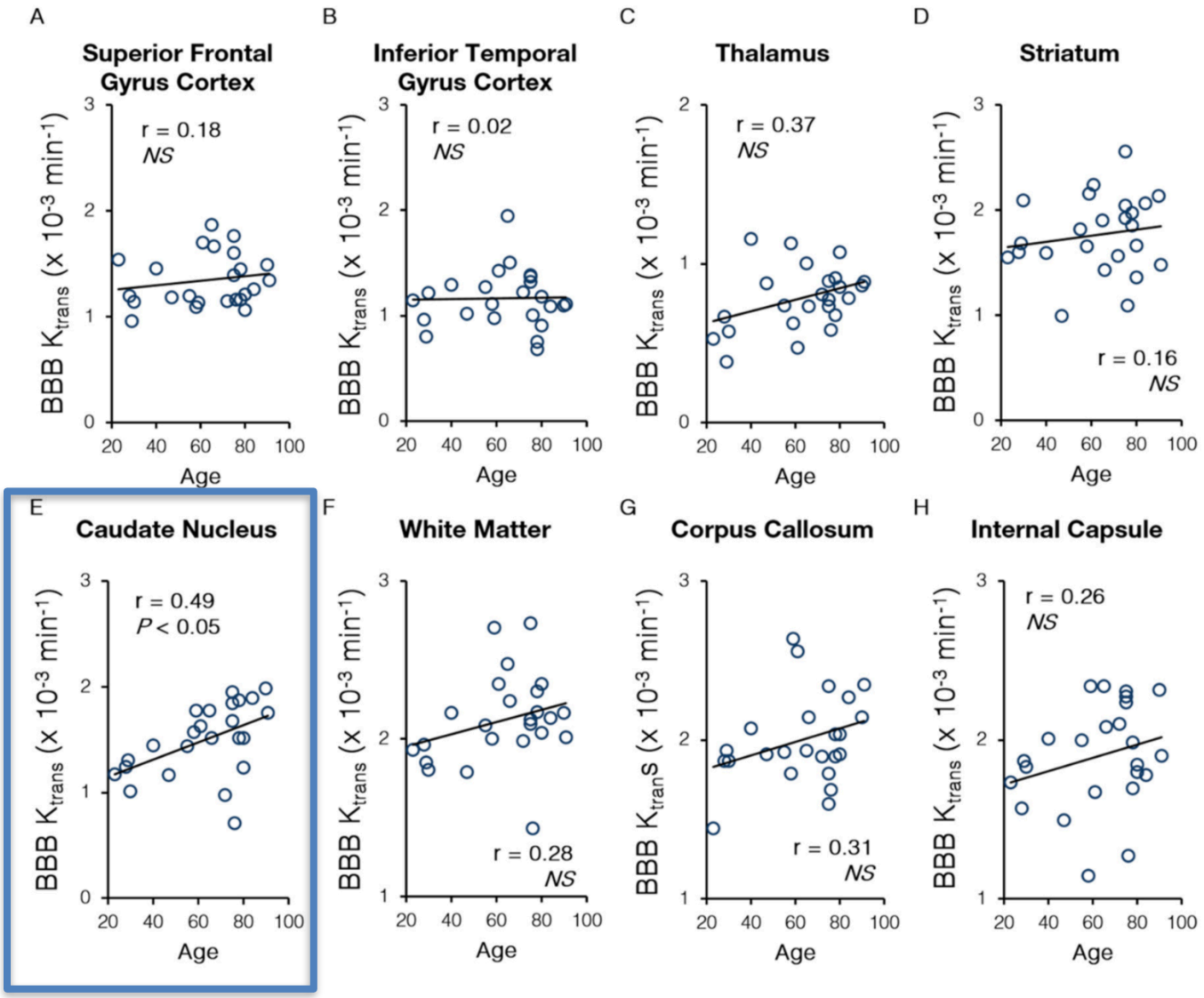
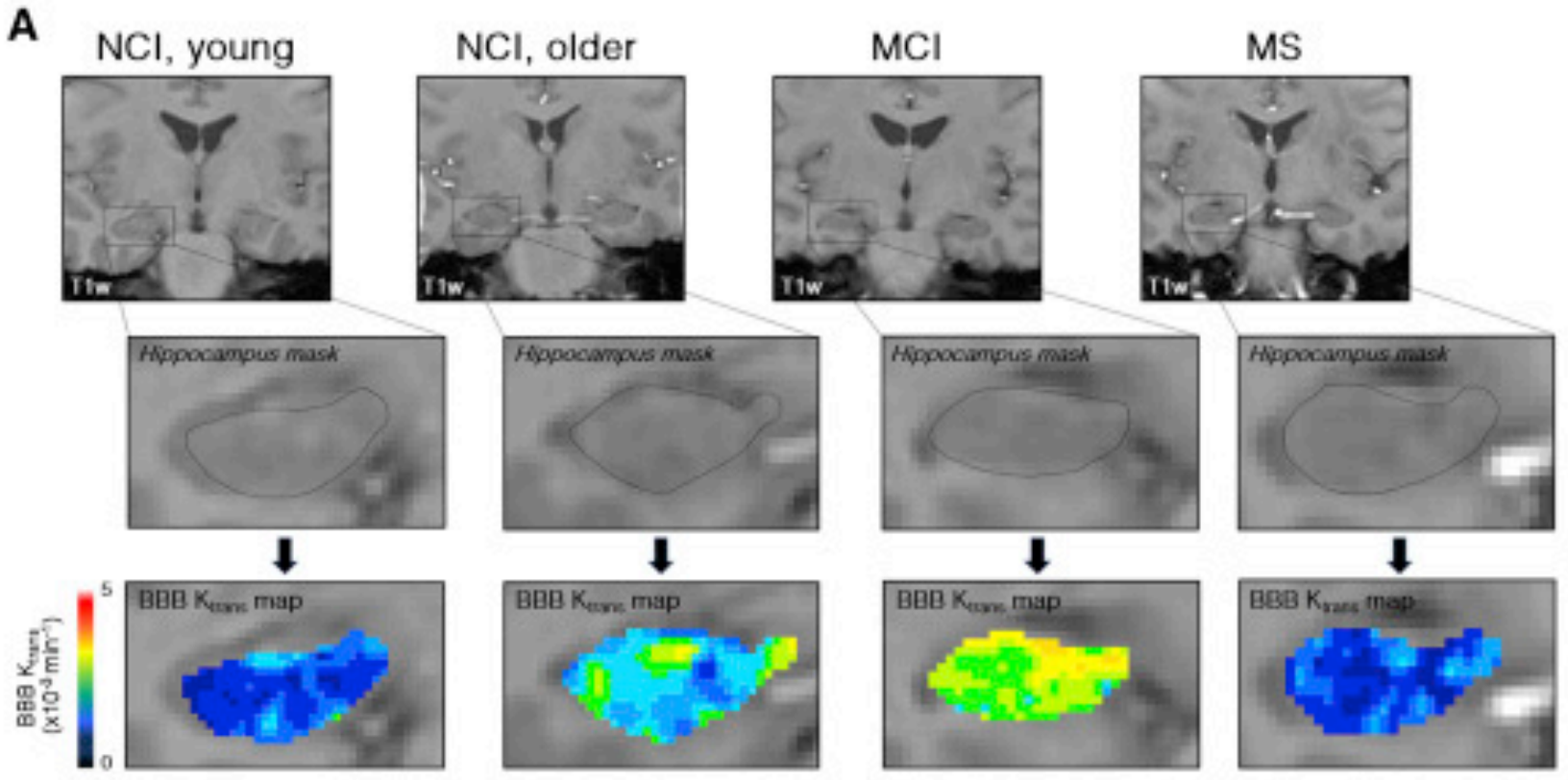


Regional blood-brain barrier integrity in the living human brain during normal aging

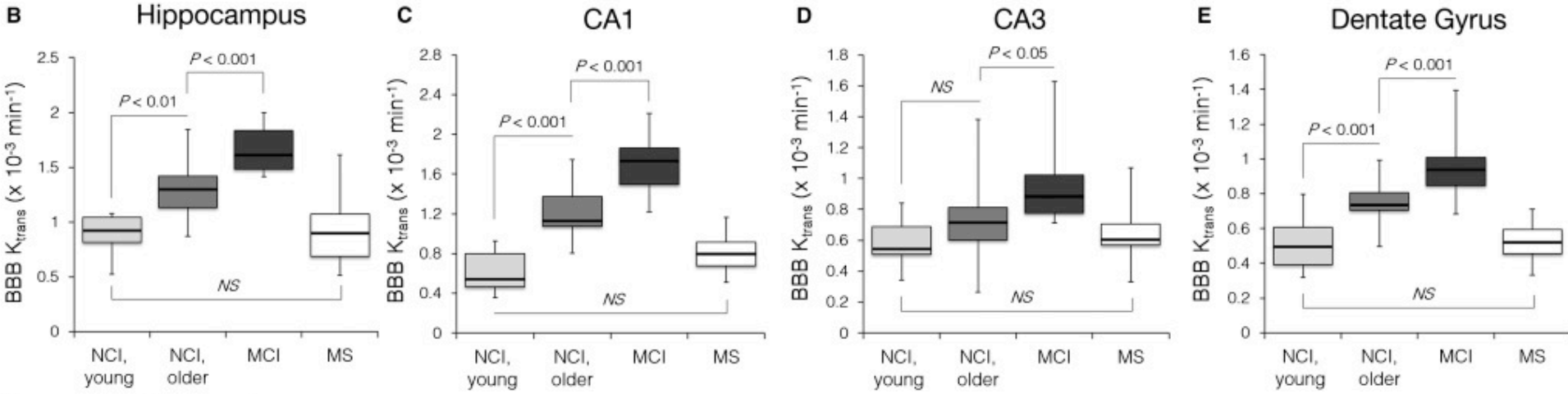
Normal aging did not result in an increase in the BBB permeability Ktrans constant in multiple gray matter regions and/or in the white matter areas except for the ***hippocampus*** and the ***caudate nucleus***

BLOOD-BRAIN BARRIER BREAKDOWN IN AGING HUMAN HIPPOCAMPUS



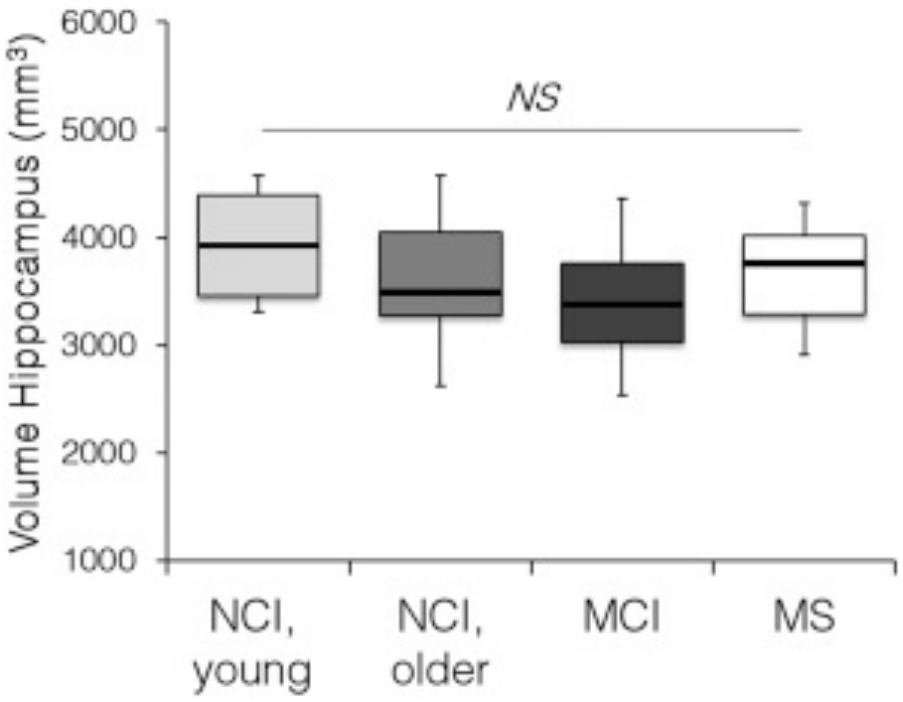
Representative K_{trans} maps within the hippocampus in young and older individuals with no cognitive impairment (NCI) and mild cognitive impairment (MCI). MS, a multiple sclerosis case with no cognitive impairment

Age dependent BBB breakdown in hippocampus and its CA1 region and DG



A progressive significant increase in the BBB permeability constant K_{trans} in older compared young NCI group and MCI compared to older NCI group in the entire hippocampus, CA1 region, and dentate gyrus. MS group was compared with age-matched young NCI group.

NCI, young (n = 6, ages 23–47, both genders); NCI, older (n = 18, ages 55–91, both genders); MCI (n = 20, ages 55–85, both genders); MS (n = 19, ages 26-53, both genders).



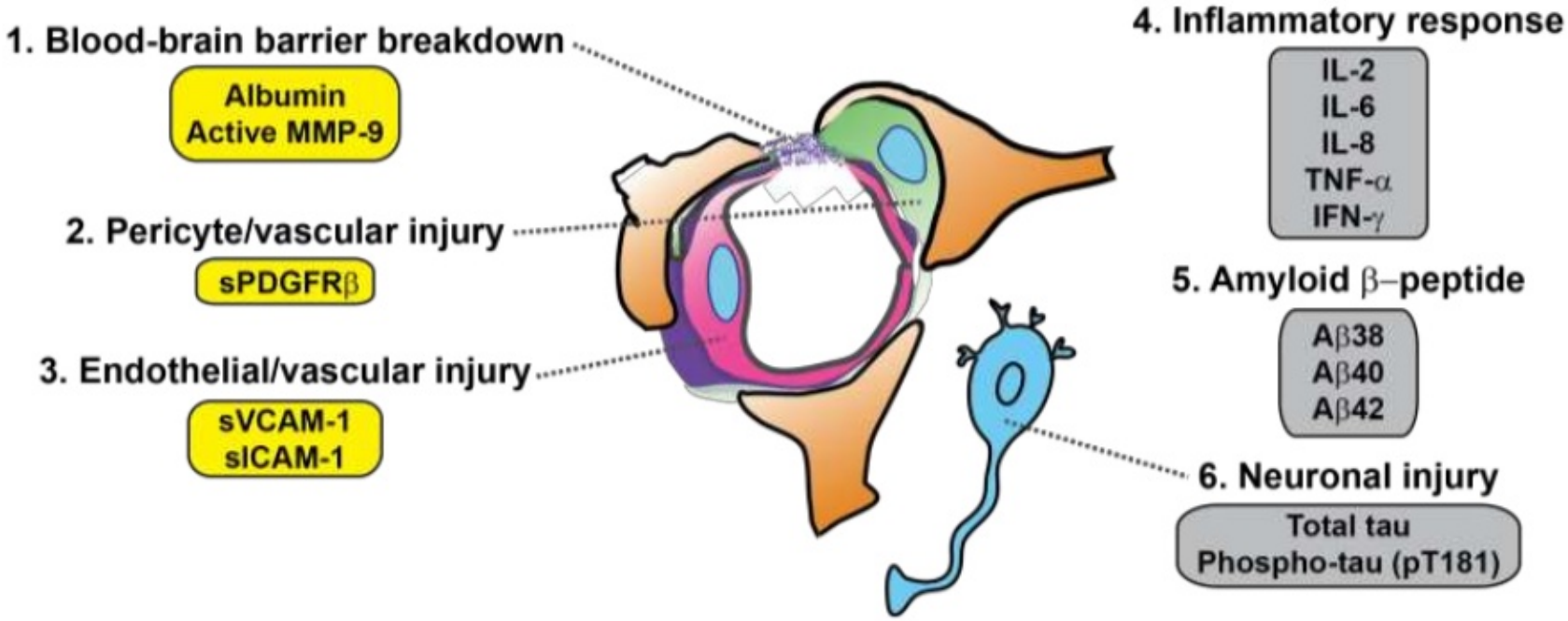
Hippocampus Volume in the Studied Groups

Hippocampus volume was determined on T2-weighted images in individuals with no cognitive impairment (NCI), with mild cognitive impairment (MCI), and multiple sclerosis (MS) cases with no cognitive impairment.

NCI, young (n = 6, ages 23–47, both genders); NCI older (n = 18, ages 55–91, both genders); MCI (n = 20, ages 55–85, both genders); MS (n = 19, ages 26–53, both genders).

Increase in permeability not associated with decreased hippocampal volume suggesting that these changes precede atrophy

Neurovascular Unit
CSF biomarkers of cell- and system-specific injury



Montagne et al., Neuron 2015

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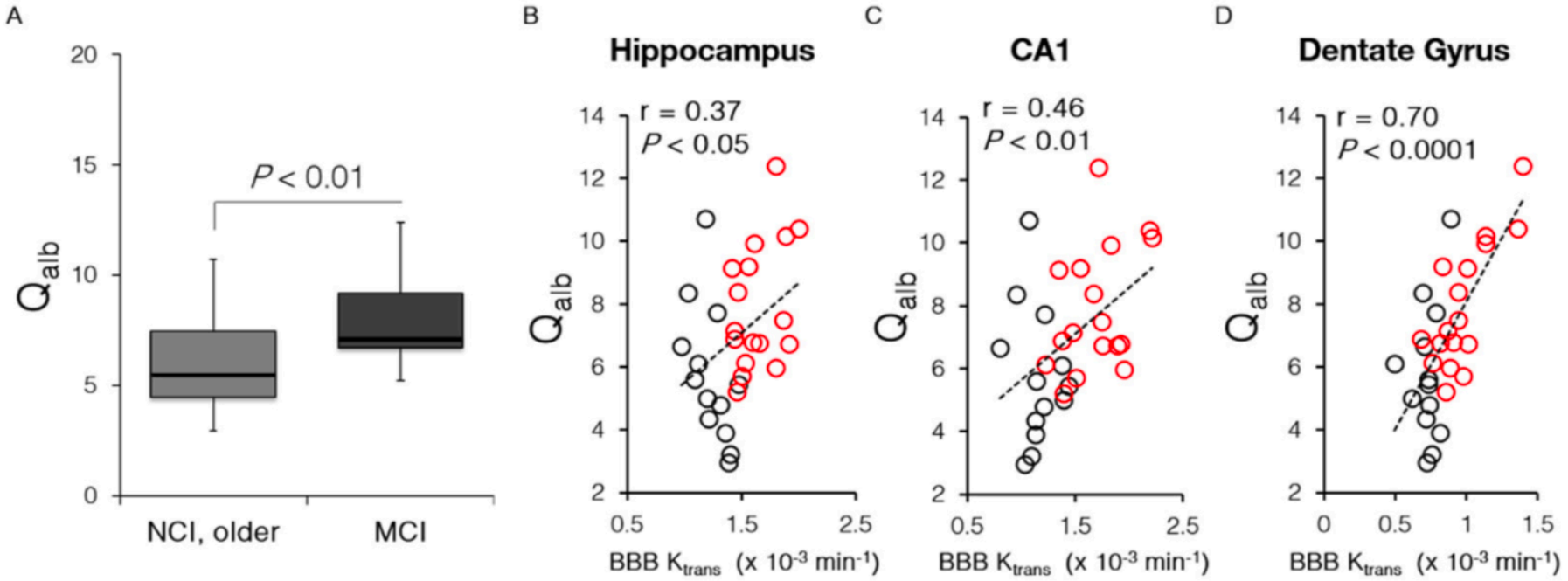
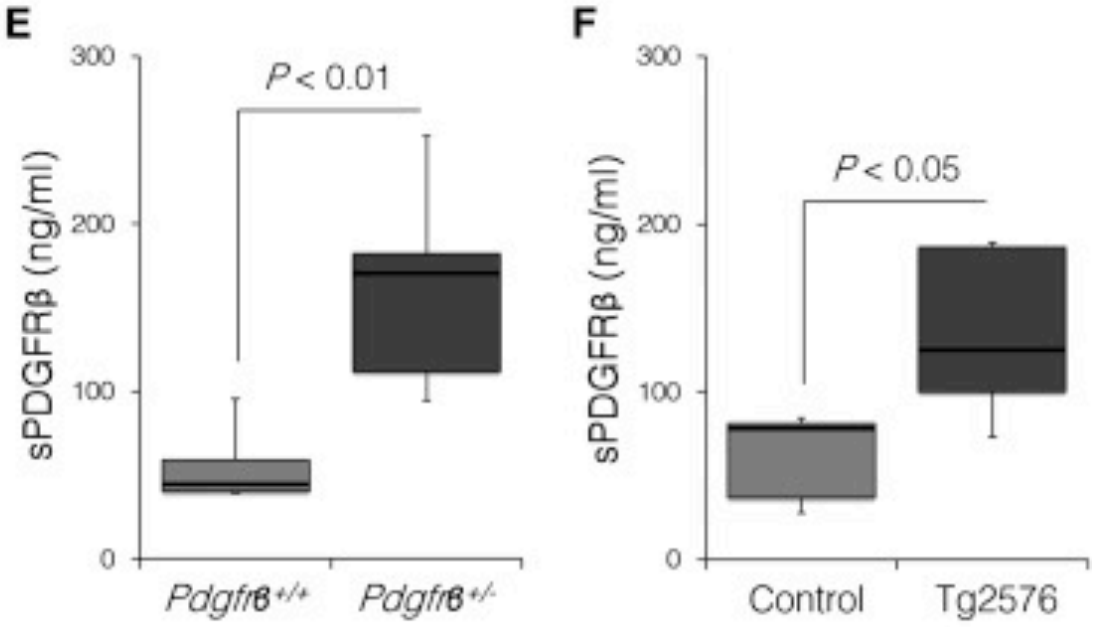


Correlation between albumin cerebrospinal fluid to plasma quotient (Q_{alb}) and the blood-brain barrier K_{trans} values in the hippocampus and its subfields during normal aging and aging associated with mild cognitive impairment

Increase in Q_{alb} in individuals with mild cognitive impairment (MCI; n=17) compared to age-matched individuals with no cognitive impairment (NCI, older; n=14). (**B-D**) Single data points for Q_{alb} from 31 individuals with no cognitive impairment (n=14, black) or mild cognitive impairment (n=17, red) were plotted against the blood-brain barrier (BBB) K_{trans} constant in the entire hippocampus (**B**), its CA1 region (**C**), and dentate gyrus (**D**)

Pericyte-deficient mice

Mouse model of AD

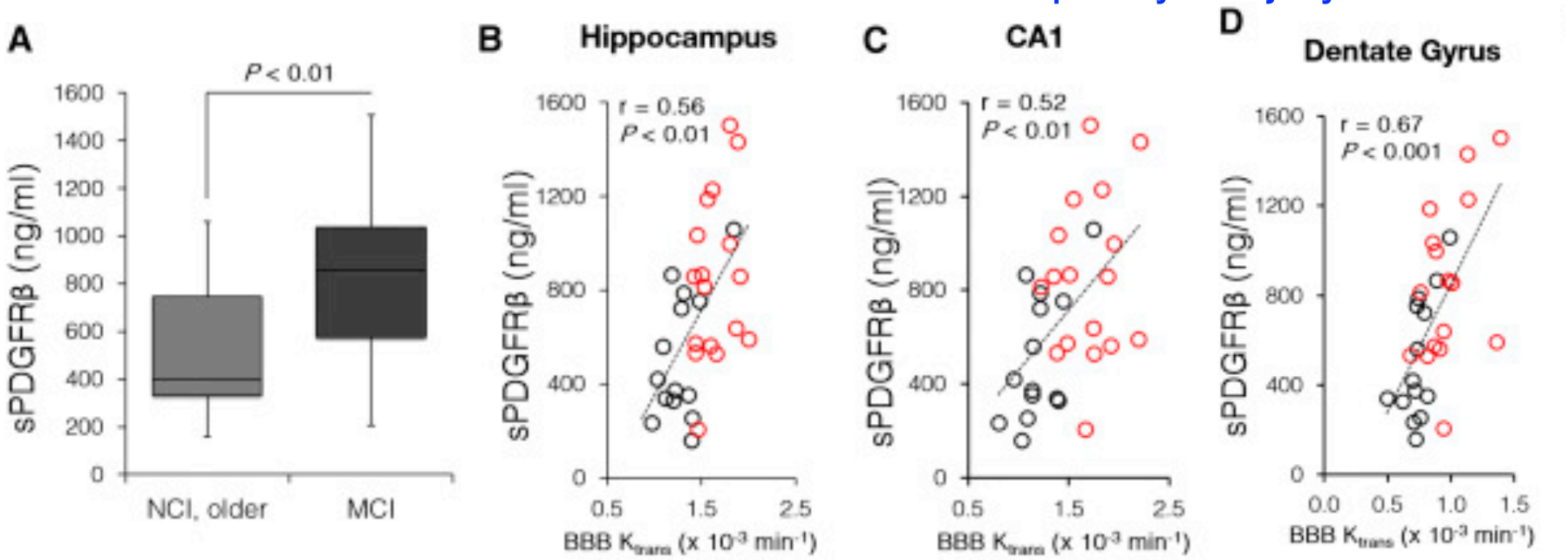


Soluble Platelet-Derived Growth Factor Receptor b in the Cerebrospinal Fluid in Mice

sPDGFRb CSF levels in 16-month-old *Pdgfr*b$^{+/}$ mice and *Pdgfr*b$^{+/+}$ controls

and 16-month-old Tg2576 mice compared to age- matched littermate controls

Soluble PDGFR beta CSF marker of pericyte injury



Soluble Platelet-Derived Growth Factor Receptor b in the Cerebrospinal Fluid in Humans

(A) Elevated sPDGFRb levels in the CSF in individuals with mild cognitive impairment (MCI; n = 17) compared to age-matched group with no cognitive impairment (NCI, older; n = 14).

(B–D) Single data points for sPDGFRb CSF levels from 31 individuals with NCI (n = 14, black) or MCI (n = 17, red) plotted against the K_{trans} constant in the hippocampus (B), its CA1 region (C), and dentate gyrus (D)

- Using an advanced dynamic contrast-enhanced MRI protocol with high spatial and temporal resolutions to quantify regional BBB permeability in the living human brain, authors show an age-dependent BBB breakdown in the hippocampus

- The BBB breakdown in the hippocampus and its CA1 and dentate gyrus subdivisions worsened with mild cognitive impairment and correlated with injury to BBB-associated pericytes, as shown by the cerebrospinal fluid analysis

- These data suggest that BBB breakdown is an early event in the aging human brain that begins in the hippocampus and may contribute to cognitive impairment

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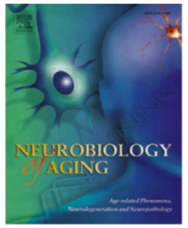

Neurovascular unit impairment in early Alzheimer's disease measured with magnetic resonance imaging

Harm J. van de Haar [a,b,c], Jacobus F.A. Jansen [a,c], Matthias J.P. van Osch [d], Mark A. van Buchem [d], Majon Muller [e], Sau May Wong [a,c], Paul A.M. Hofman [a,c], Saartje Burgmans [b,c], Frans R.J. Verhey [b,c], Walter H. Backes [a,c,*]

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[e] Department of Gerontology and Geriatrics, Leiden University Medical Center, Leiden, The Netherlands

Neurobiology of Aging 45 (2016)

Radiology

Blood-Brain Barrier Leakage in Patients with Early Alzheimer Disease[1]

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Jacobus F. A. Jansen, PhD
Matthias J. P. van Osch, PhD
Mark A. van Buchem, MD
Majon Muller, MD
Paul A. M. Hofman, MD
Frans R. J. Verhey, MD
Walter H. Backes, PhD

Purpose: To investigate whether the blood-brain barrier (BBB) leaks blood-circulating substances in patients with early forms of Alzheimer disease (AD), and if so, to examine the extent and pattern of leakage.

Materials and Methods: This study was approved by the local medical ethical committees of the Maastricht University Medical Center and Leiden University Medical Center, and written informed consent was obtained from all subjects. For this pilot study, 16 patients with early AD and 17 healthy age-matched control subjects underwent dynamic contrast material–en-

Radiology (2016)