Imaging BBB Water Exchange with Diffusion Weighted Arterial Spin Labeling

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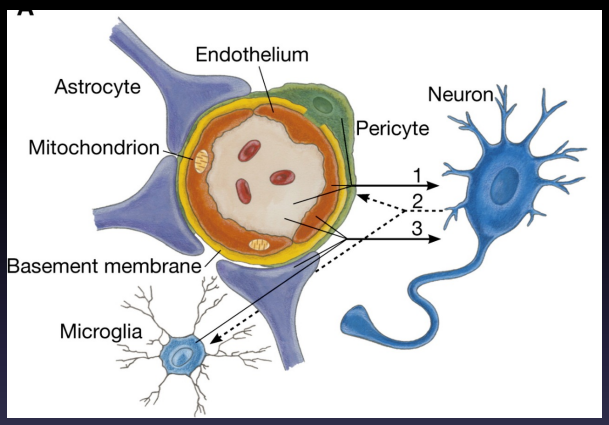
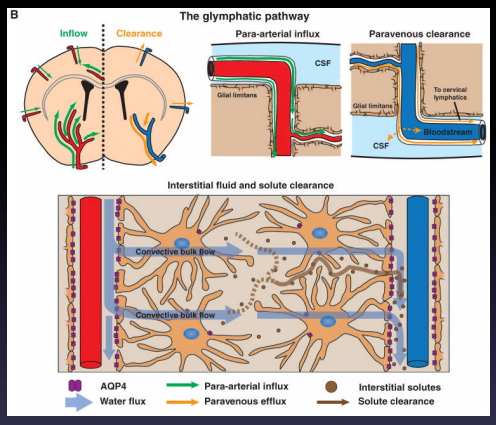
BBB and Glymphatic System





- BBB plays important roles in the exchange of substances between blood and brain parenchyma, and protecting the CNS from neurotoxic substances circulating in the blood
- BBB water exchange hypothesized as driver of glymphatic flow and waste clearance

Zlokovic *Neuron* 2008 Iliff, J. *Sci Transl Med*. 2012 Aug 15; 4(147): 147ra111

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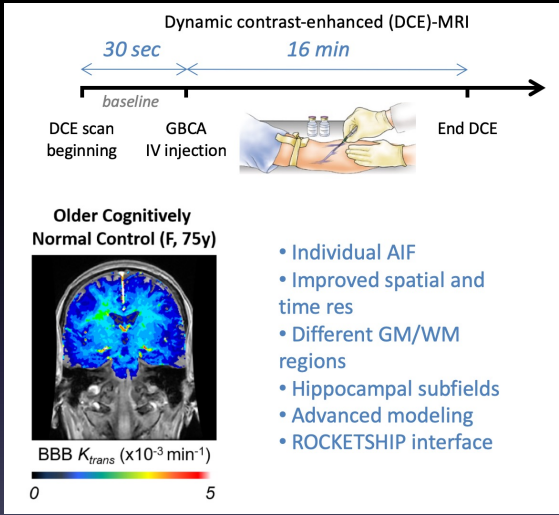
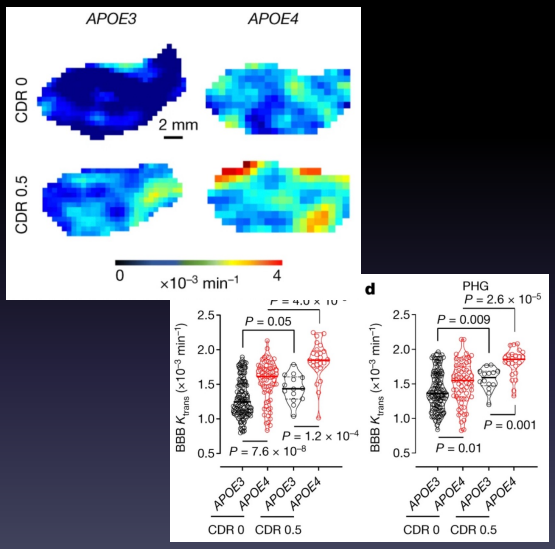
DCE MRI for BBB Permeability – USC Method





Montagne et al., *Neuron* 2015; Barnes et al., *BMC Med Imaging* 2015; Barnes et al., *Mag Reson Med* 2016 ; Montagne et al., *Acta Neuropathol* 2016; Nation*, Sweeney*, Montagne* et al., *Nat Med* 2019; Montagne et al., *Nature* 2021

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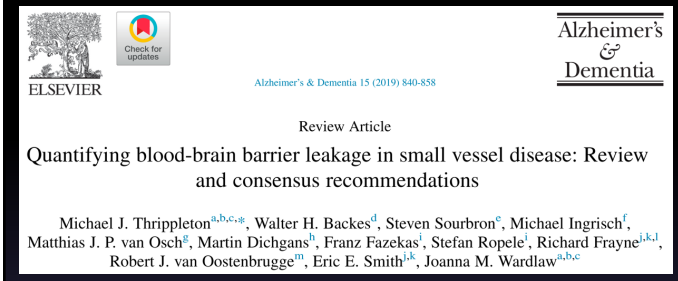
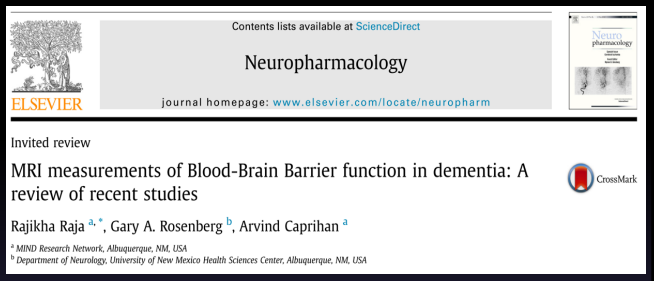
DCE MRI of Subtle BBB Permeability Changes





(www.harness-neuroimaging.org)

- Subtle permeability: K_{trans} in the range of 10^{-3} to 10^{-4} min^{-1}
- DCE MRI most widely used with diverse acquisition and analysis methods
- Long scan time (15-20min) (motion, scanner drift)
- Patlak model commonly used (negligible back-flux)
- Lack of test-retest, only one study (Wong et al JMRI 2017 reported CoV of 11.6 and 14.4% in WM and GM)

Thrippleton et al. Alzheimer's and Dementia 2019: 1-19; Raja et al. Neuropharmacology 2018 134: 259-271

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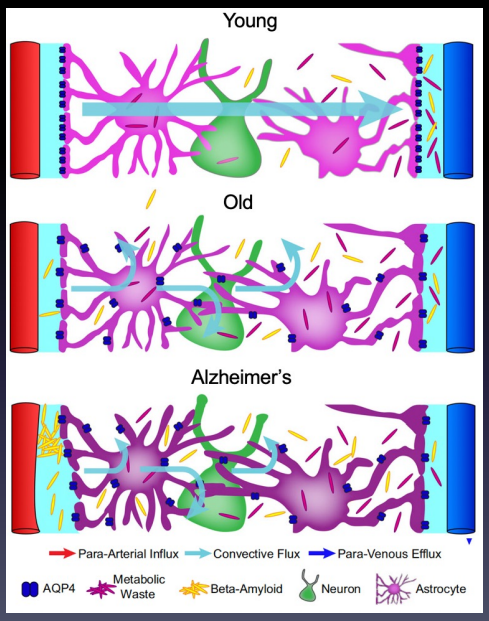
Assessing water exchange across BBB



Possible early marker of BBB dysfunction:

1) Small size relative to contrast agents

2) Related to aquaporin-4 function:
   - Plays a key role in astrocytic water transport
   - Linked to the glymphatic system

Molecule	Molecular Weight g/mole
Water	18
Glucose	180
Magnevist	938
Albumin	66500

Jessen *Neurochem Res* 2015

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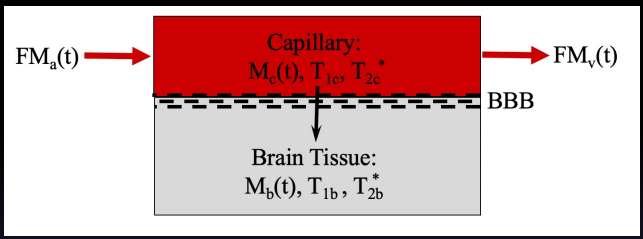
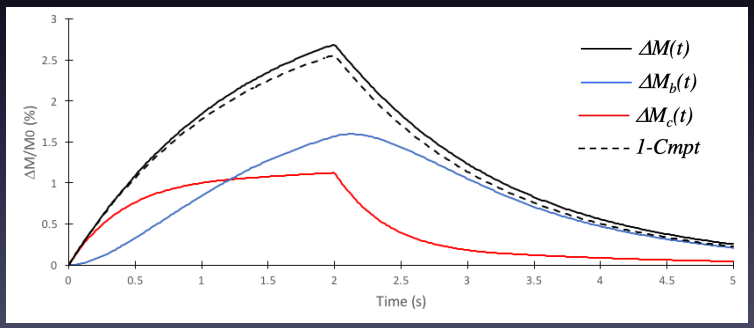
Two Compartment ASL Modeling



$$\Delta M(t) = \Delta M_b(t) + \Delta M_c(t)$$

- ASL signal is sum of capillary and tissue components
- Exchange across the BBB depends on PS_w (~100 min^{-1})



St Lawrence et al., *MRM* 2000;44:440; Ewing et al., *MRM* 2001;46:465; Parkes and Tofts *MRM* 2002;48;27

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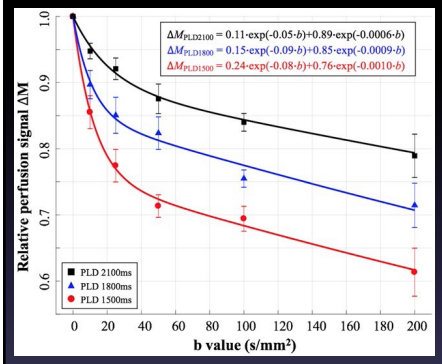
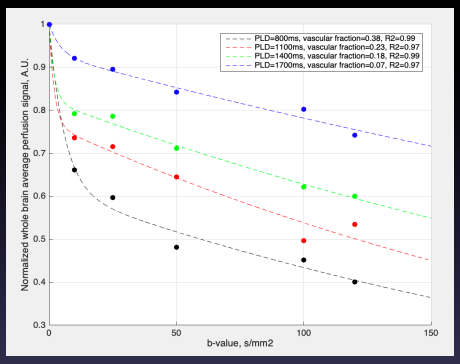
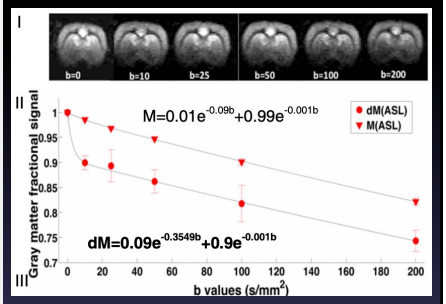
In vivo imaging of water exchange across BBB (Kw) using diffusion weighted-ASL







Human Brain
Shao et al *MRM* (2019)

Primate Brain
(Wey et al ISMRM 2020)

Rat Brain
Tiwari et al *ISMRM* (2015)

$$\frac{\Delta M(b)}{\Delta M(0)} = A_1 e^{-bD_1} + A_2 e^{-bD_2}$$

Bi-exponential diffusion model to differentiate two compartment signals and estimate kw = PSw/Vc

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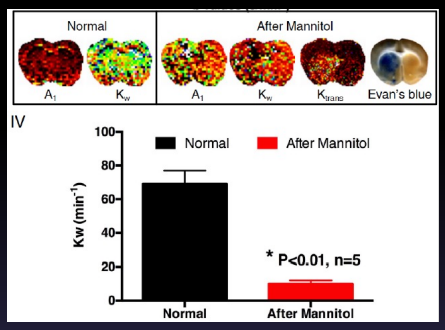
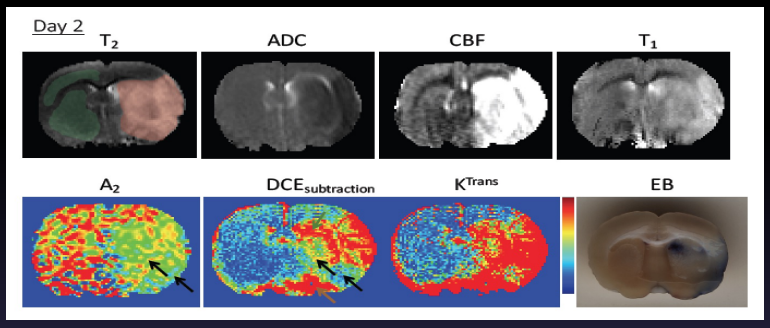
Validation of Kw in Animal Models





- k_w reduces after mannitol injection on the proximal hemisphere

Tiwari et al *ISMRM* 2015

- k_w was lower in infarct zone two days after stroke, reflecting vasogenic edema
- Lower k_w suggestive of AQP4 dysfunction, which is linked to reduced brain water elimination

Tiwari et al *JCBFM* (2017) 37(8): 2706-15

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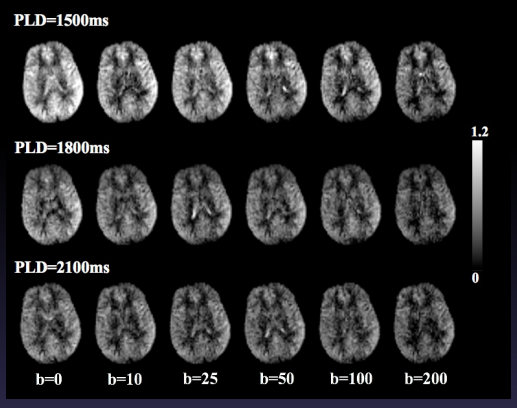
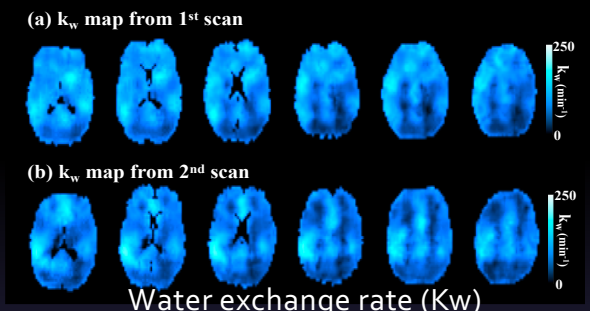
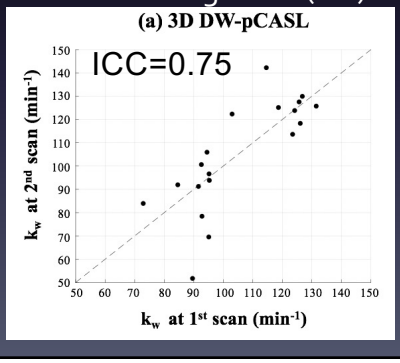
BBB Water Exchange in Small Vessel Disease



DW 3D GRASE pCASL at 3 PLDs



Water exchange rate (Kw)



ICC=0.75 Repeat scans ~6 weeks apart in 19 aged Latino subjects (7M 68.8+/-7.6 Yrs)

Shao et al *MRM* (2019)

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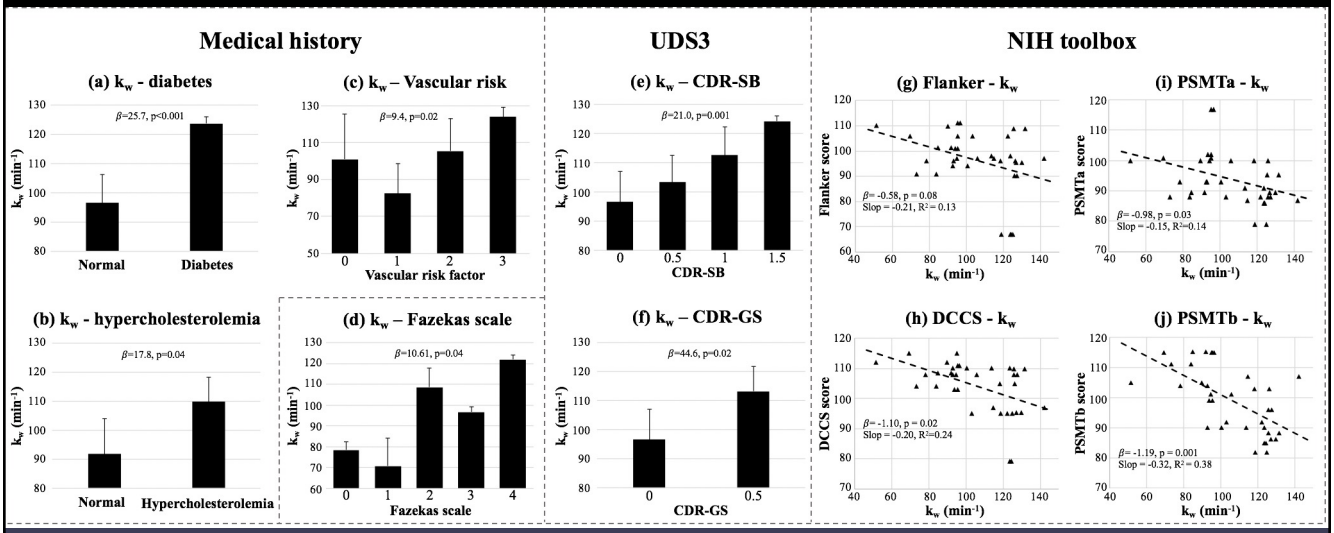
BBB Water Exchange in Small Vessel Disease



Kw correlated with diabetes, high cholesterol, vascular risks, cognitive function, WMH

Shao et al *MRM* (2019)

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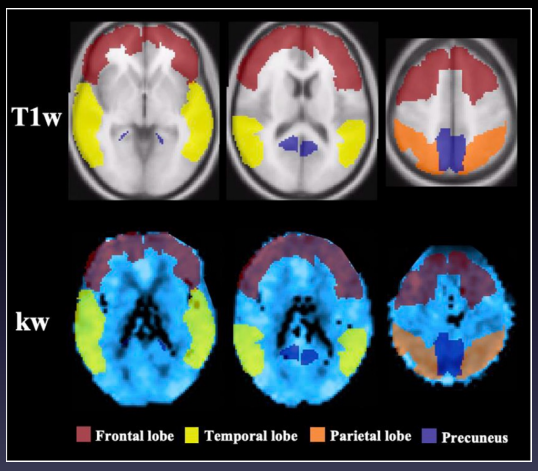
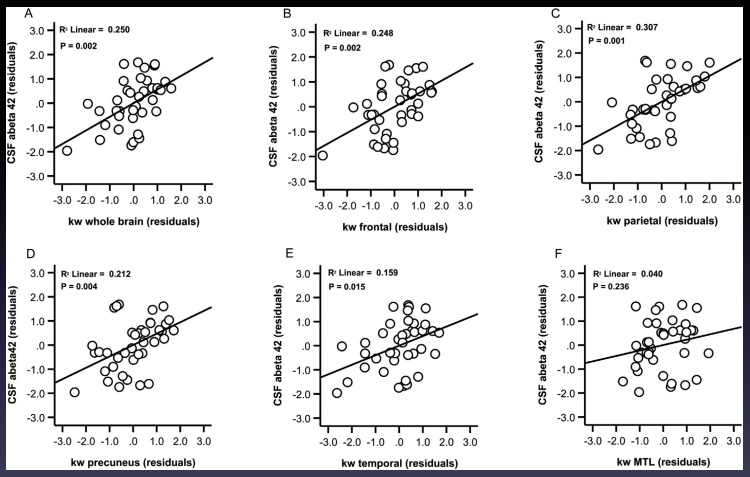
BBB Water Exchange with CSF AD Markers





Kw correlated with CSF Abeta-42 in 38 healthy aged subjects, controlling for age and gender and education

Gold, Shao et al *Alzheimer & Dementia* (2021)

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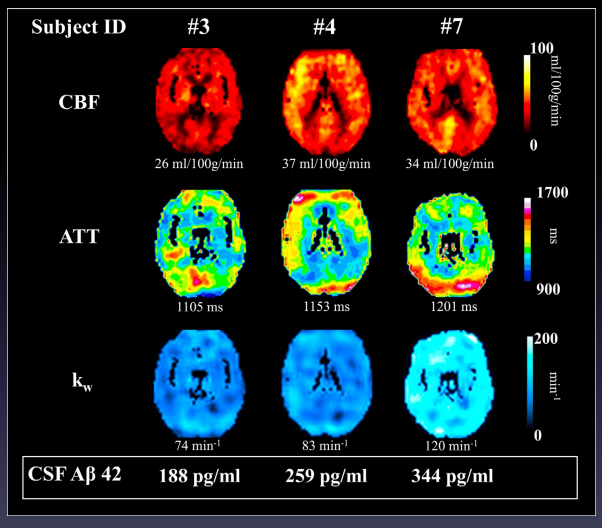
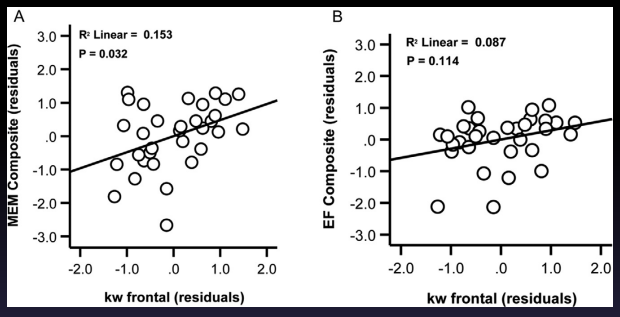
BBB Water Exchange with CSF AD Markers





Frontal kw correlation with memory and executive function composite scores

Kw correlated with CSF Abeta-42 in 38 healthy aged subjects, controlling for age and gender and education

Gold, Shao et al *Alzheimer & Dementia* (2021)

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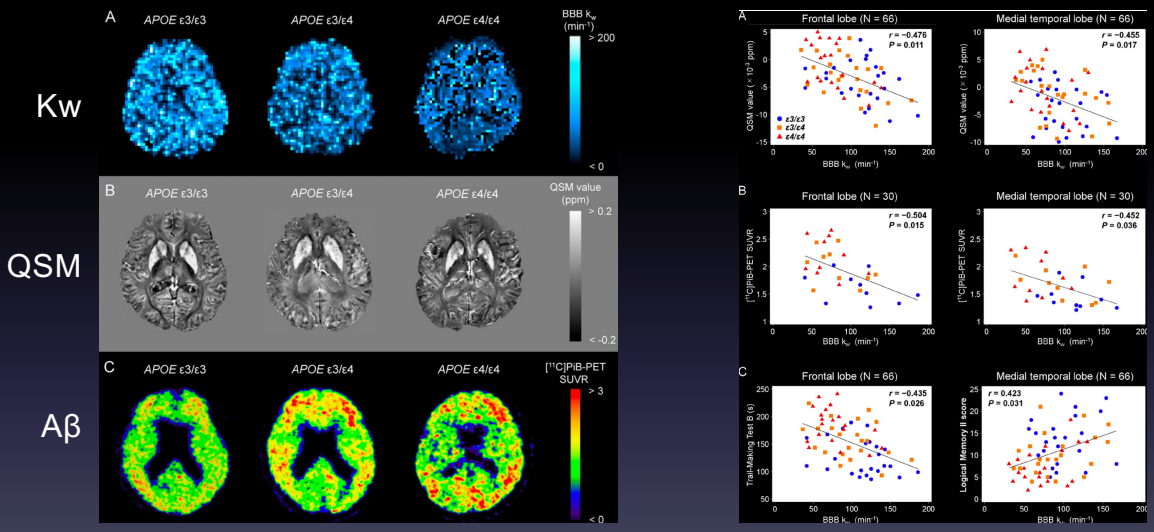
BBB Water Exchange with APOE, Iron, Abeta PET



Kw (APOE ε4 non-carriers> heterozygotes>homozygotes), correlated with brain iron levels, β-amyloid loads and and neuropsychological scores (Philips 3T)

Uchita et al *JNNP* (2022)

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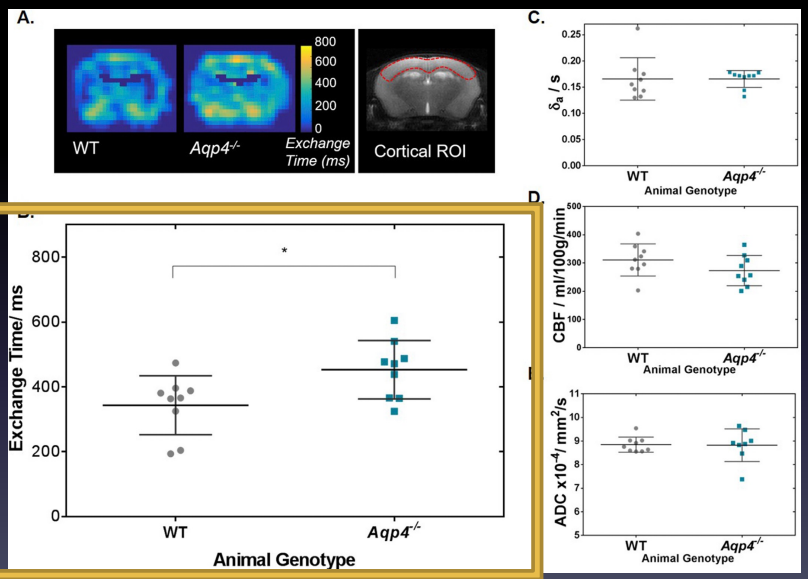
BBB Water Exchange and AQP4

1/kw = water exchange time



Reduced kw in AQP4 knock-out mice

ATT, CBF, ADC not different between WT and AQP4 knock-out mice

Ohene et al *Neuroimage* (2019)

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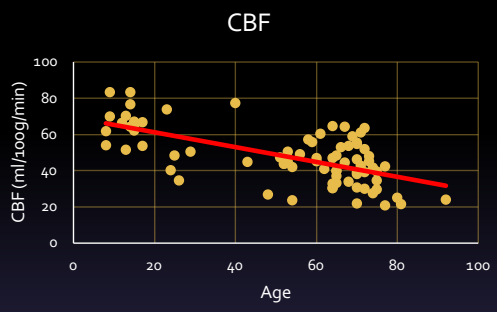
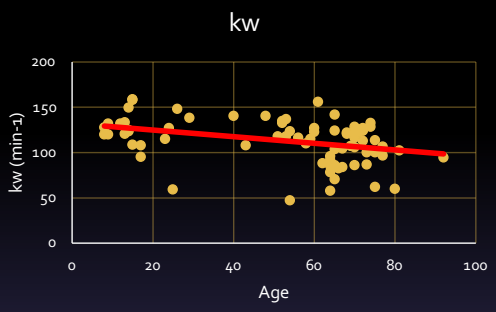
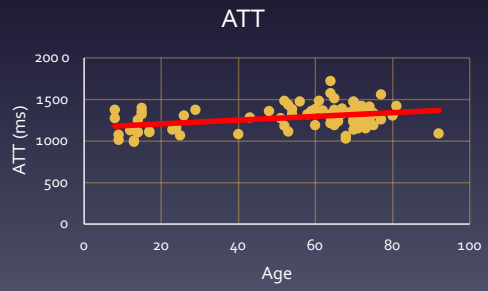
BBB Water Exchange and Age







Regression model: (gender: F-0,M-1)
CBF = 71.29 – 0.41*age – 3.04*gender
ATT = 1163.9 +2.23*age – 4.85*gender
kw = 129.87 -0.36*age – 3.78*gender

Shao et al *ISNVD* (2022)

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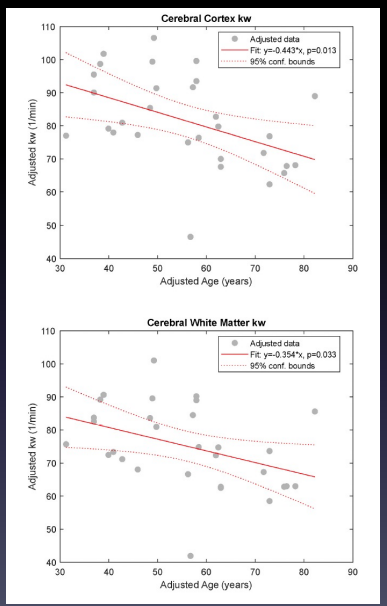
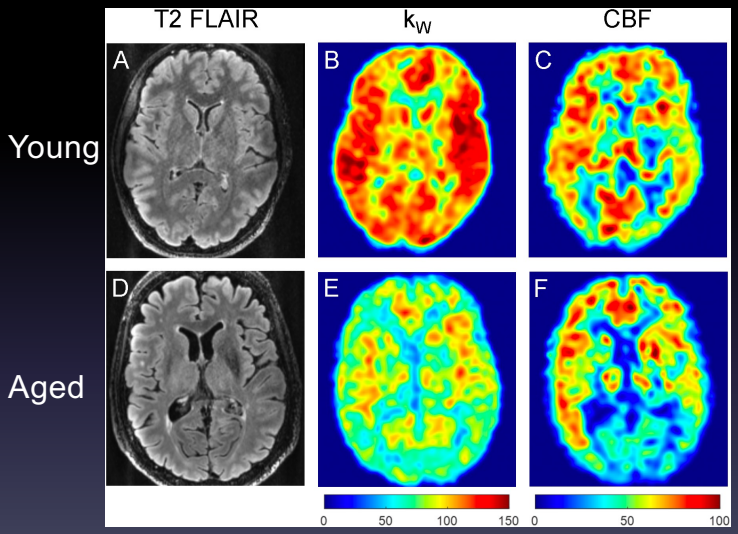
BBB Water Exchange and Age, Vascular Risks and WMH





Kw decreases with aging, vascular risks and WMH (GE 3T)

Ford et al *Frontier Aging Neurosci* (2022)

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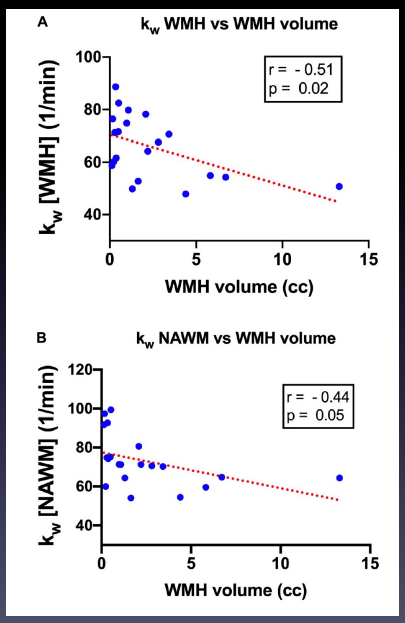
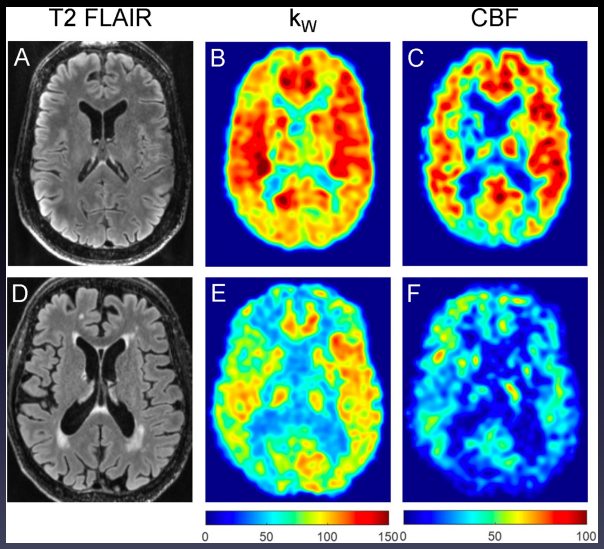
BBB Water Exchange and Age, Vascular Risks and WMH



76yr M
No risk

76yr M
2 risks



Kw decreases with aging, vascular risks and WMH (GE 3T)

Ford et al *Frontier Aging Neurosci* (2022)

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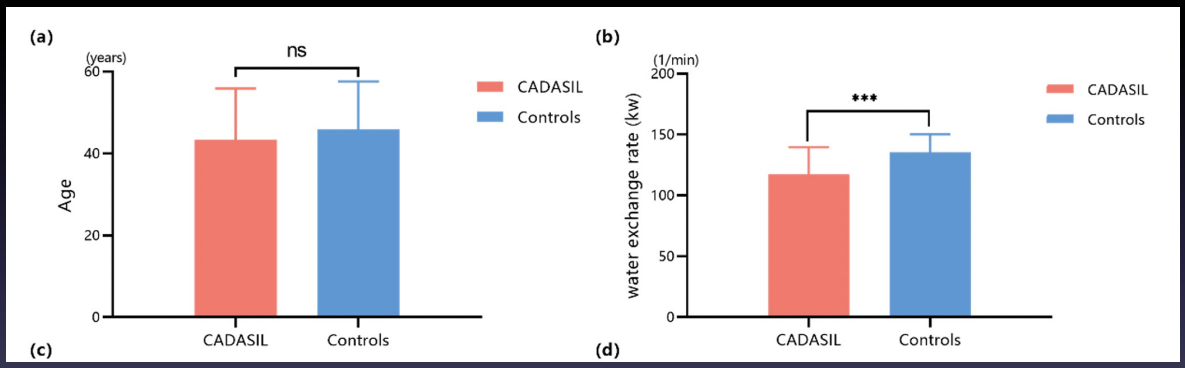
Reduced BBB Water Exchange in CADASIL (NOTCH3)



27 CADASIL patients (45.86±11.72yrs) vs 28 controls (43.26±12.60yrs)

Zhang et al *ISMRM* (2002)

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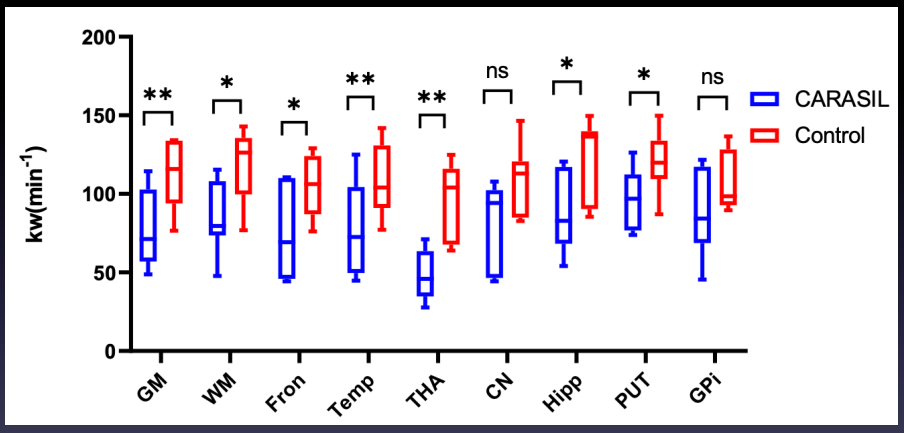
Reduced BBB Water Exchange in CARASIL (*HTRA1)*



10 CARASIL patients (40.7±14.6 yrs) vs 7 controls (46.0±13.6)
Heterozygous *HTRA1* mutations

Pan et al *ISMRM* (2022)

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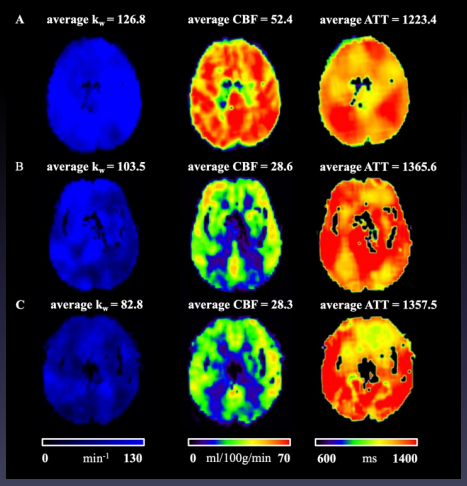
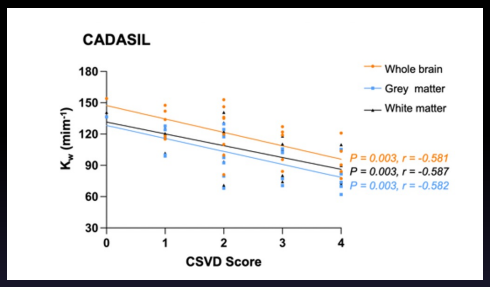
Reduced BBB Water Exchange in CADASIL & CARASIL

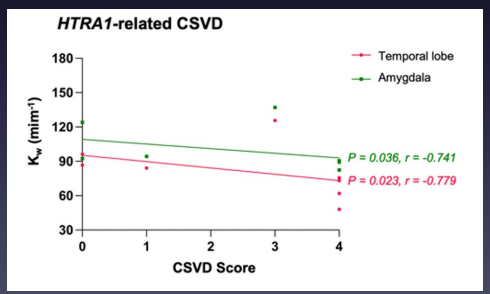
HC

CADASIL

CARASIL







Pan et al (in preparation)

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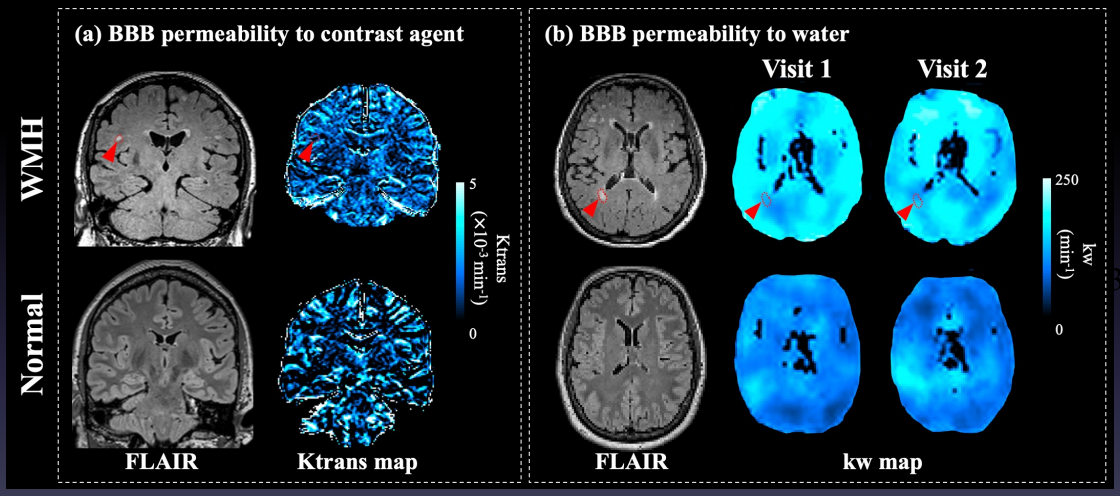
BBB Water Exchange with DCE MRI



Comparison of kw and Ktrans in 16 aged Latinx subjects (3M, age=67.9±3.0 yrs), DW ASL was repeated ~6 weeks apart

Shao et al *Frontier Neurosci* (2020)

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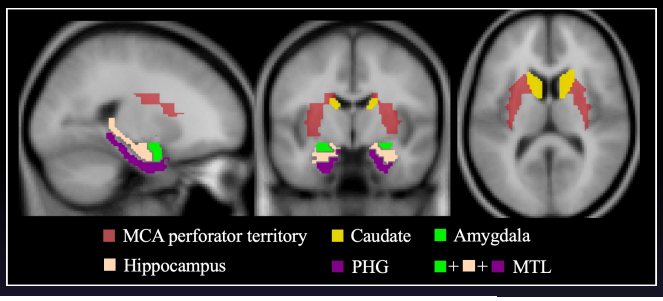
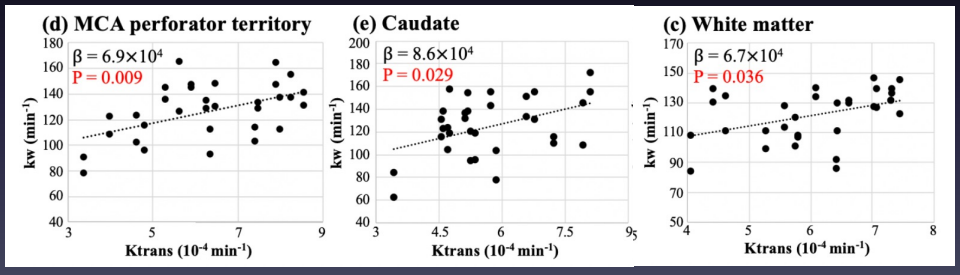
BBB Water Exchange with DCE MRI





Significant correlation was observed in MCA perforator, caudate and WM

Shao et al *Frontier Neurosci* (2020)

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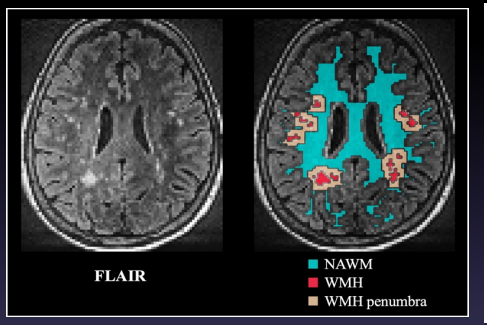
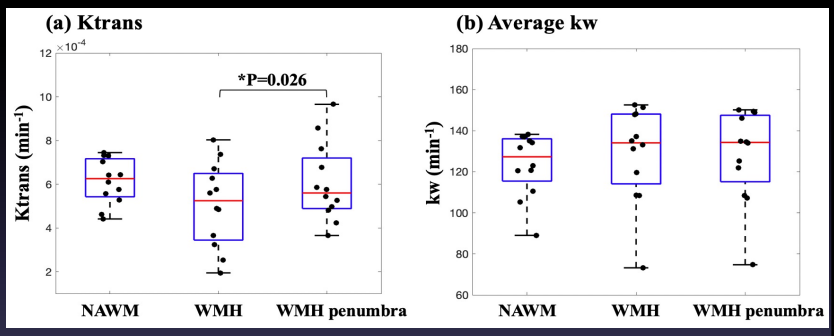
BBB Water Exchange with DCE MRI





Ktrans was significantly higher in WMH penumbra compared to WMH, while kw was not significantly different

Shao et al *Frontier Neurosci* (2020)

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Summary and Discussion

- BBB water exchange imaging is feasible with improved MRI sequences
- Converging evidence suggesting decreasing kw with aging, cognitive decline and cSVD
- Kw may be related to glymphatic flow (AQP4) and waste clearance
- Many potential applications: cSVD, aging and cognitive decline, neurodegeneration, sleep and glymphatic function

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