NACC New Investigator Project

The intersection of amyloid and cerebrovascular pathology: the perivascular space

Erin Boespflug, Ph.D.

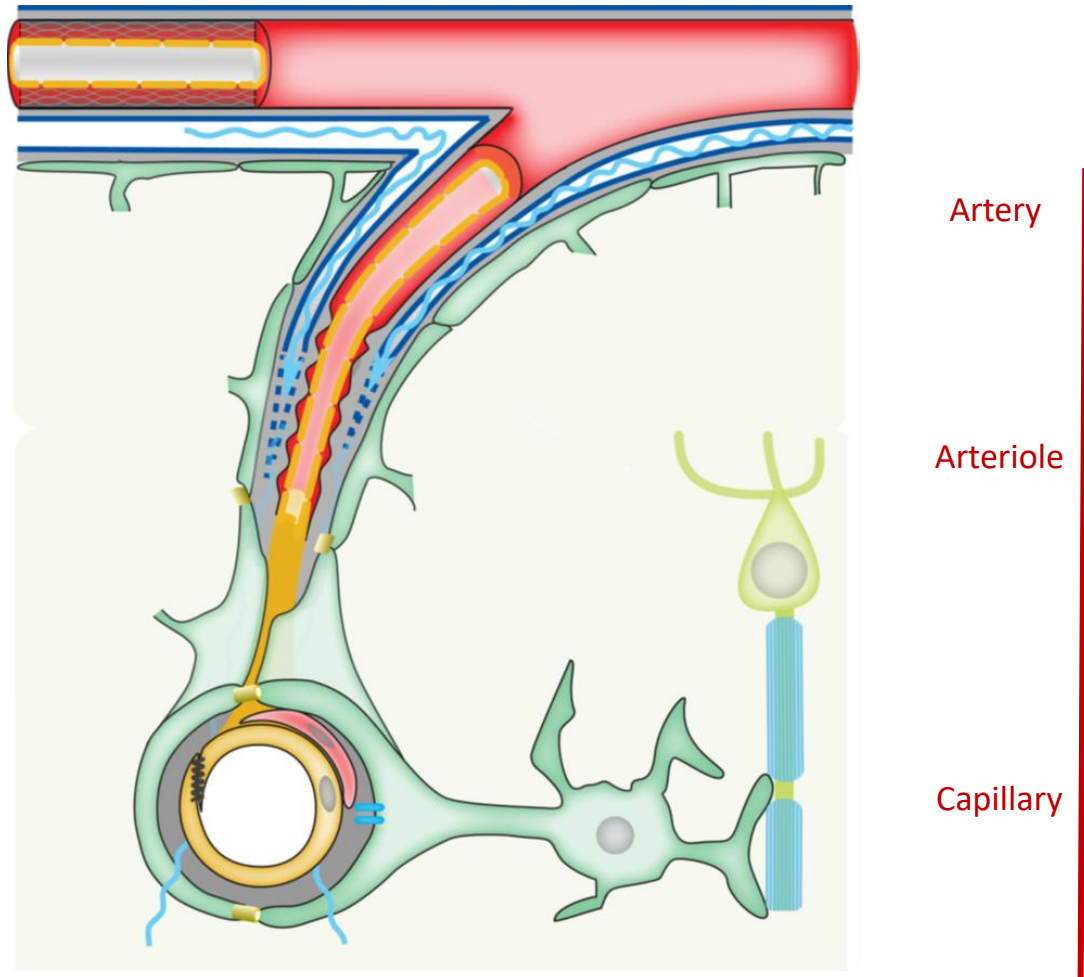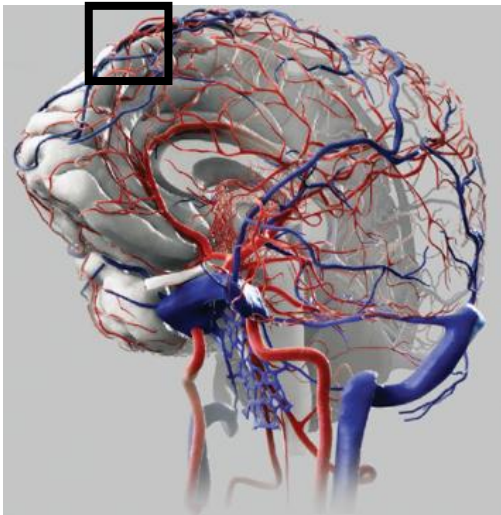boespfle@ohsu.edu

Assistant Professor, Neurology
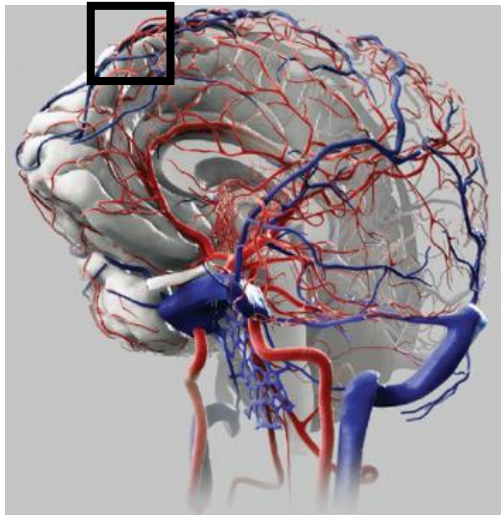
Oregon Aging and Alzheimer's Disease Center

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OHSU
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The Neurovascular Unit
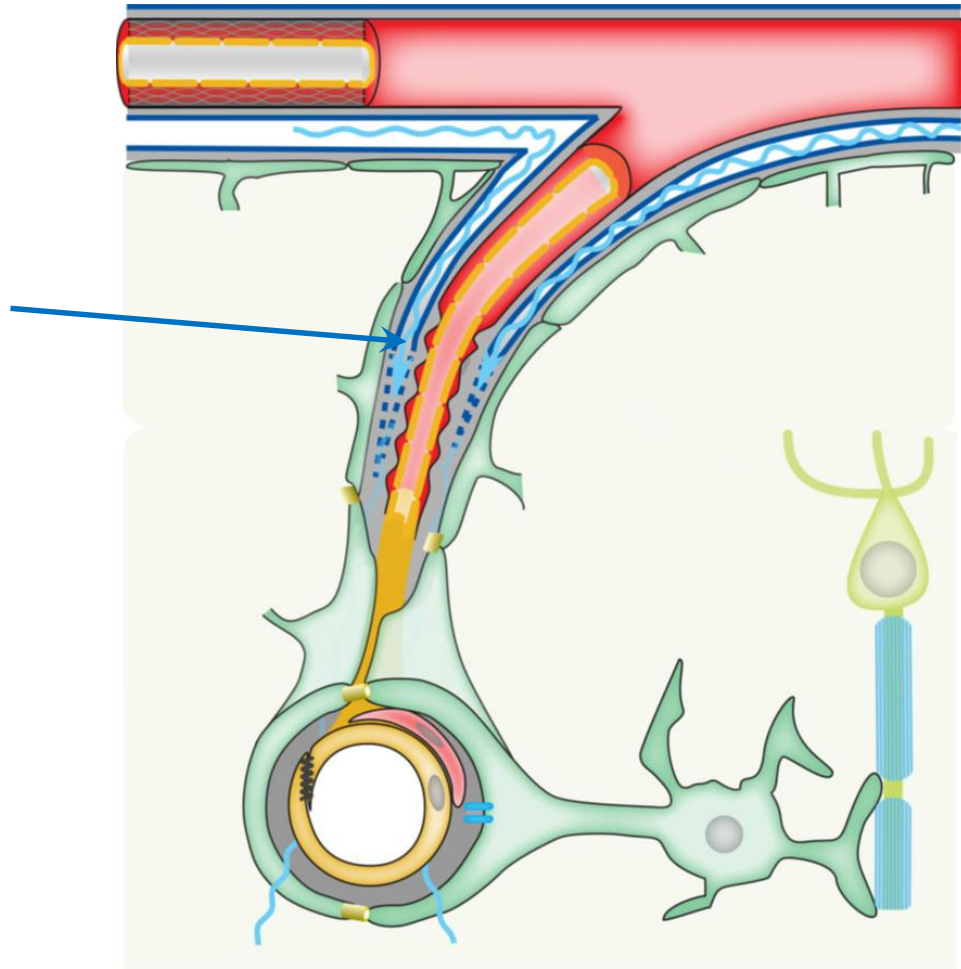

Artery

Arteriole

Capillary

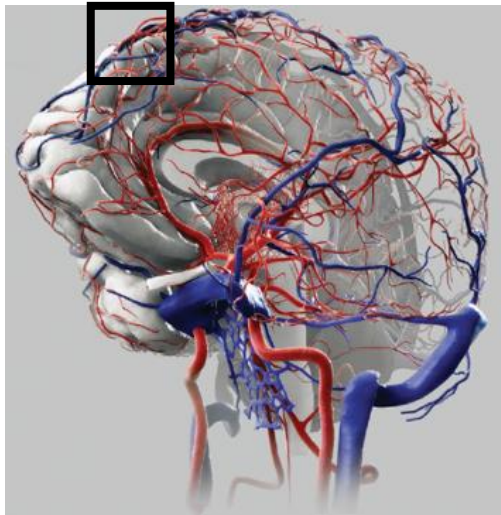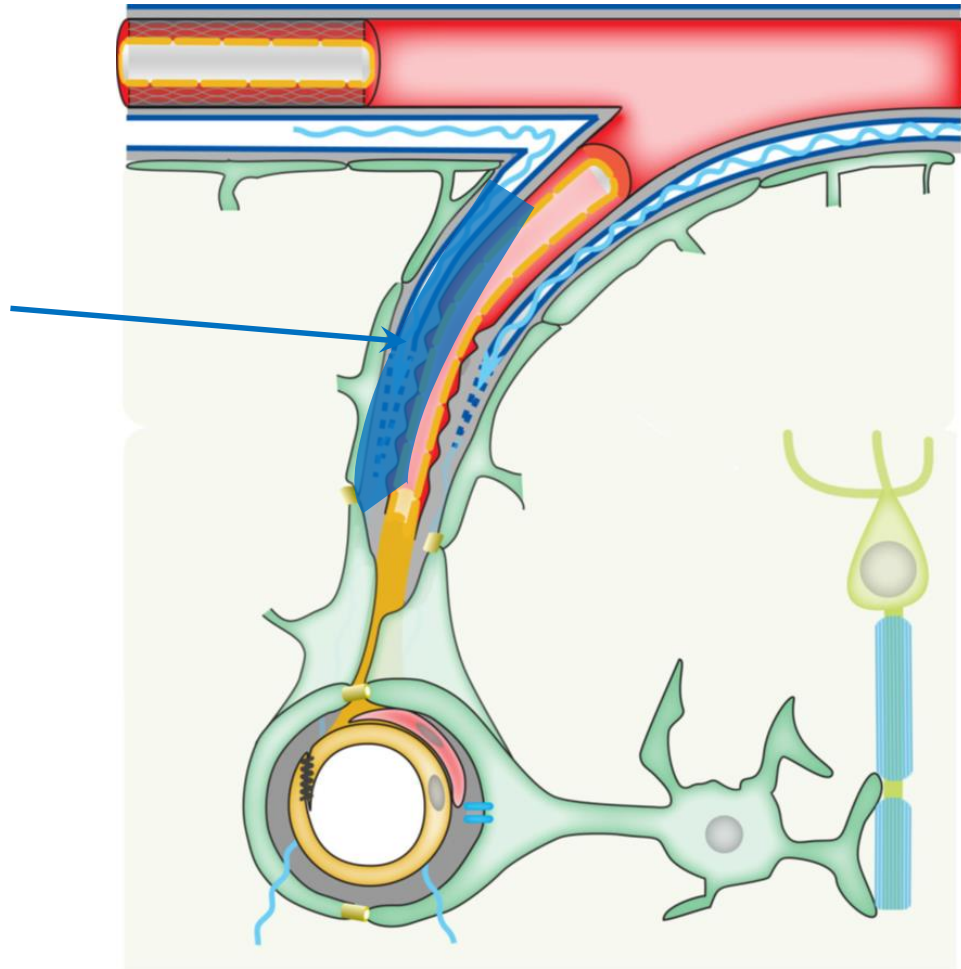Modified from Jessen et al., *Neurochem Res.* 2015

The perivascular space

Perivascular space

enlarged perivascular space (ePVS)

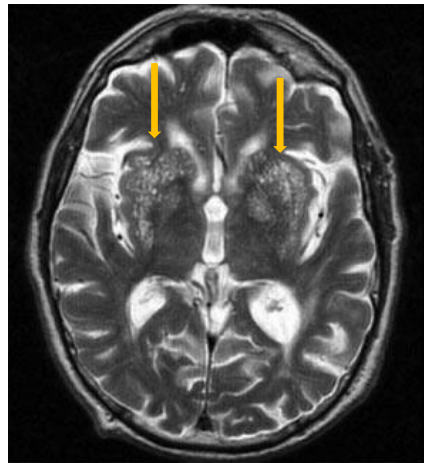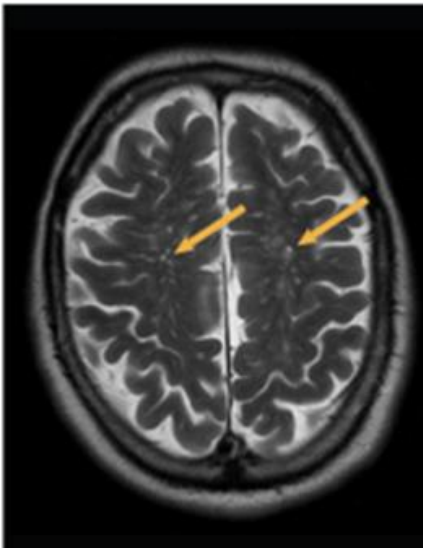Perivascular space

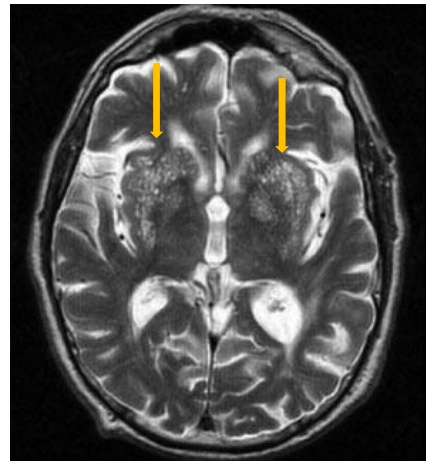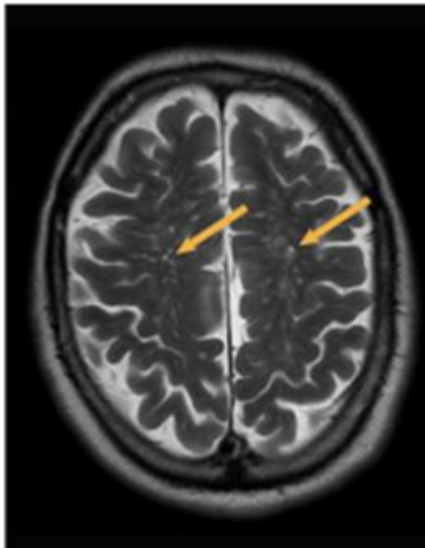Modified from Jessen et al., *Neurochem Res.* 2015

ePVS were previously considered

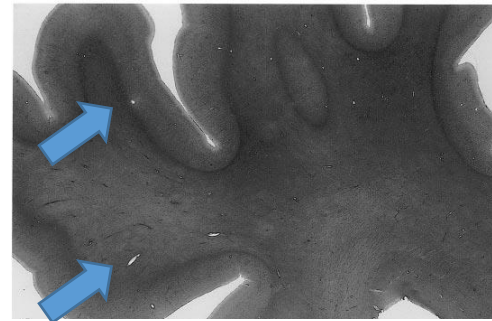...a benign clinical finding

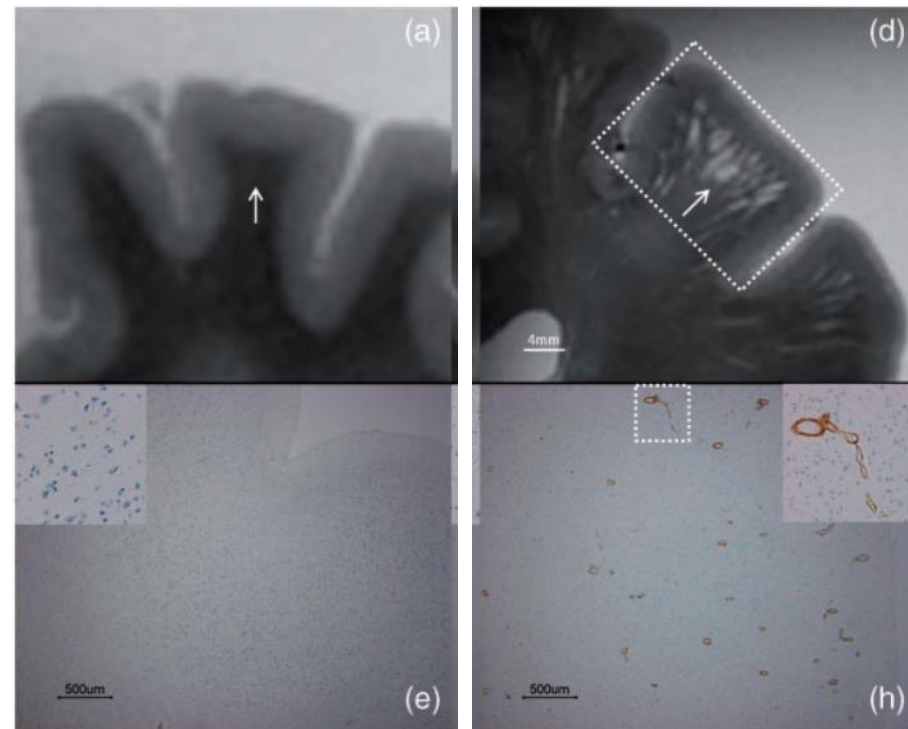# ePVS were previously considered

...a benign clinical finding

....or an artifact of tissue fixation

ePVS : Clinical Relevance

ePVS burden is associated with:

- cerebral small vessel disease
  Patankar 2005, Potter 2015, Bouvy 2016
- vascular disease risk factors: lacunar stroke, hypertension, WMH Yakushiji 2014
- CAA Charidimou 2014, vanVeluw 2016
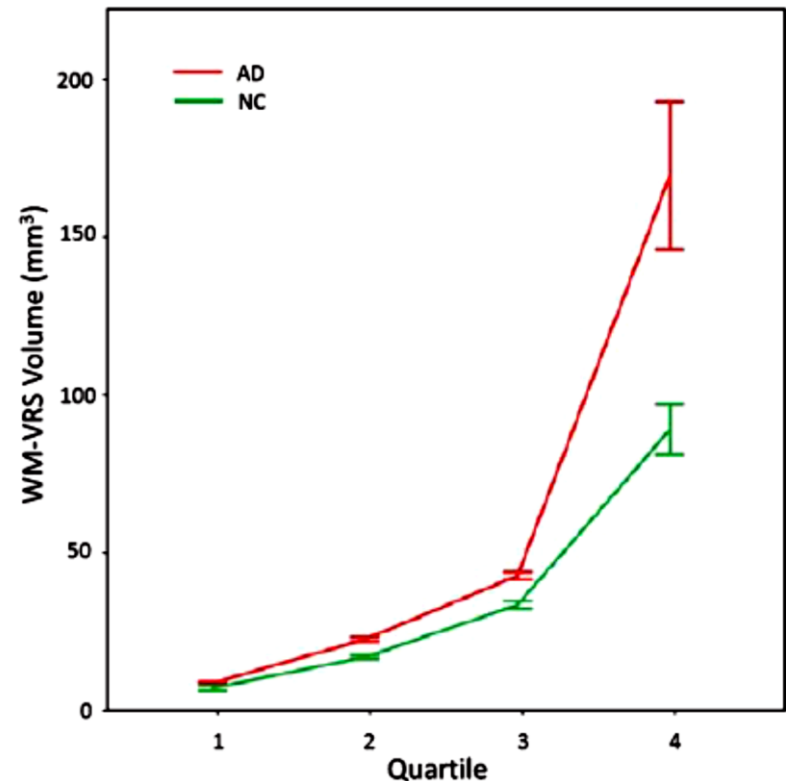
vanVeluw, JCBFM, 2016

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- vascular disease risk factors: lacunar stroke, hypertension, WMH Yakushiji 2014
- CAA Charidimou 2014, vanVeluw 2016
- APOE4 status, cortical Aβ
  Roher 2003
- Alzheimer's disease status
  Ramirez 2015

Ramirez., *JAD,* 2015

Clinical and Pathology correlates of ePVS

Perivascular
Diameter:
54.328 µm

Parenchymal

PV

Vessel
Diameter:
31.534 µm

GFAP
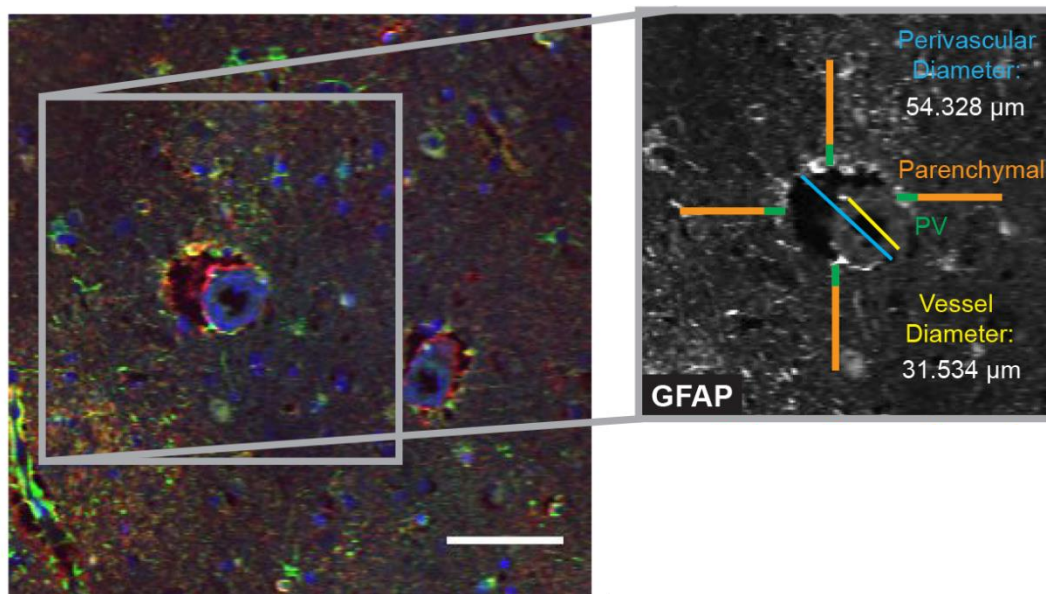
328 large (mean 16, SD 5.8 µm)
vessels from:

Alzheimer's disease (N=10)
mixed dementia (N=7)
control (N=16)

Boespflug et al*., Journal of Alzheimer's Disease, 2018*

ePVS in AD and mixed dementia
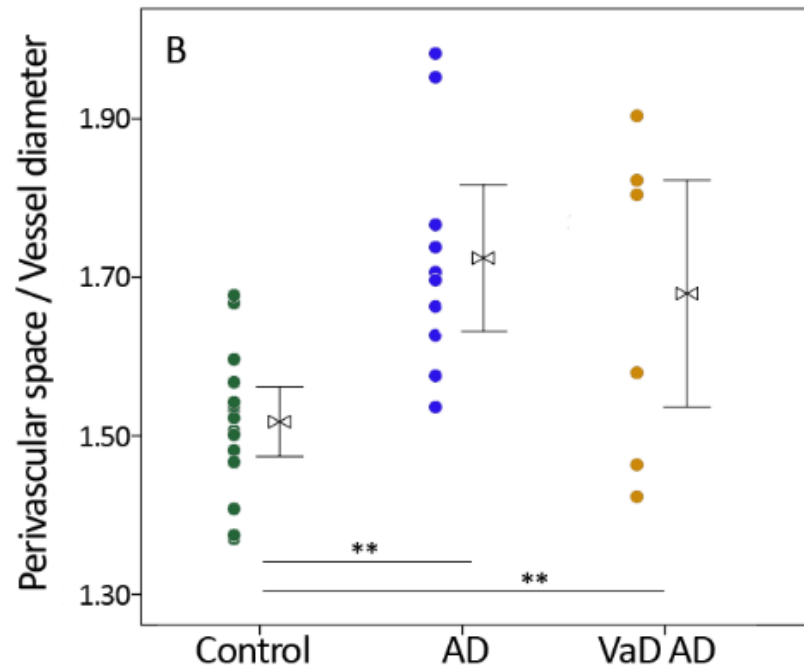
Cases with Alzheimer's disease and with cerebrovascular disease have higher dilation of the perivascular space than do control cases.

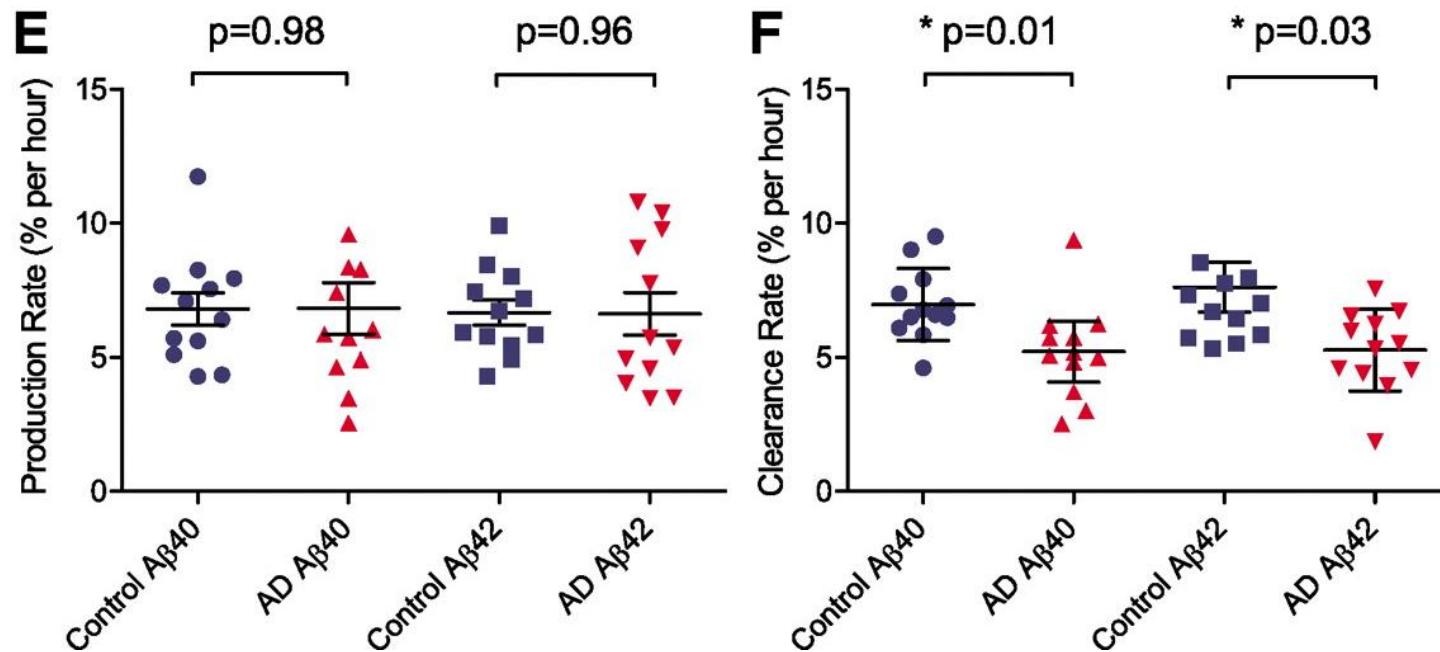Boespflug et al., *Journal of Alzheimer's Disease, 2018*

ePVS : Pathology correlates
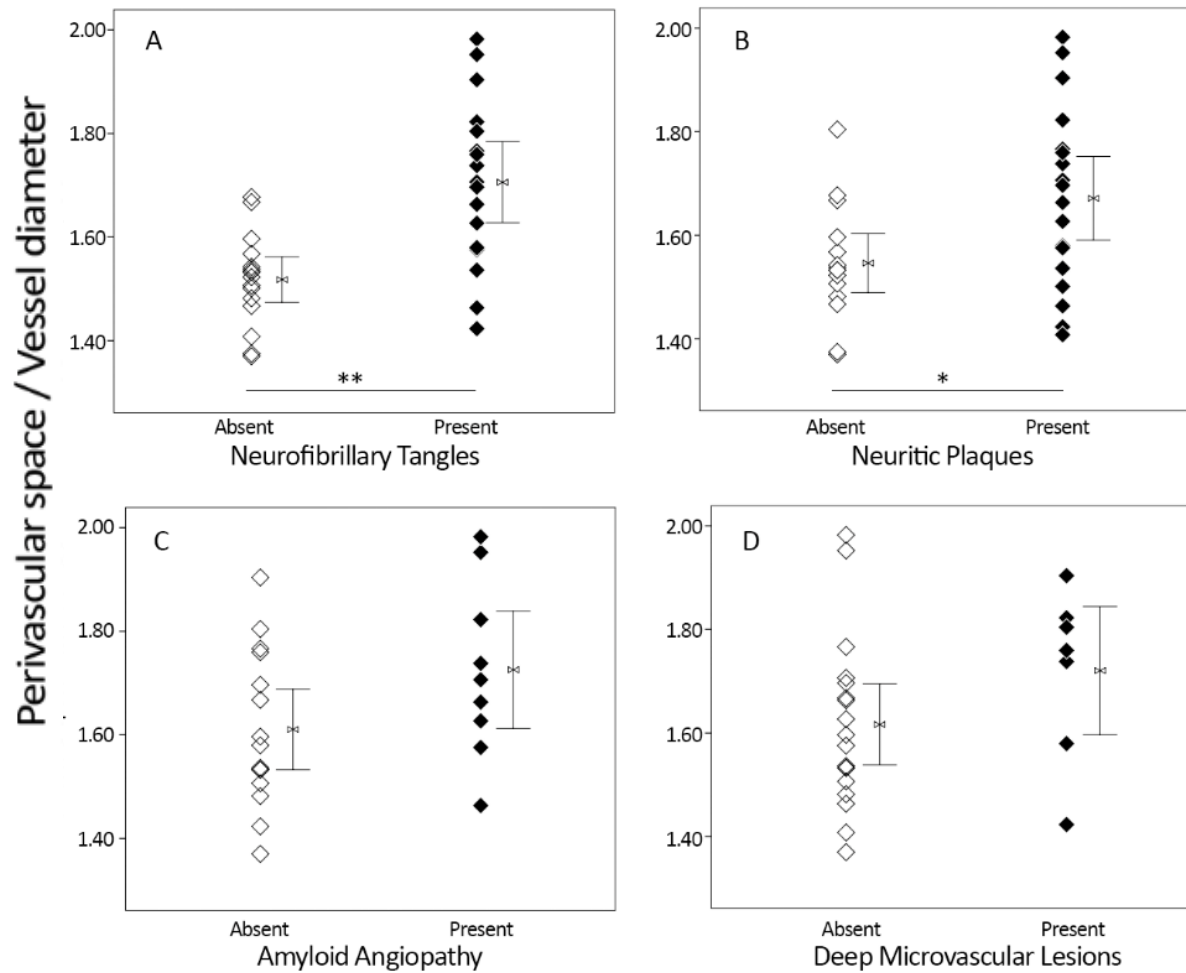
Cases with AD pathology : hTau (A) and amyloid plaque (B) have greater ePVS than do cases without.

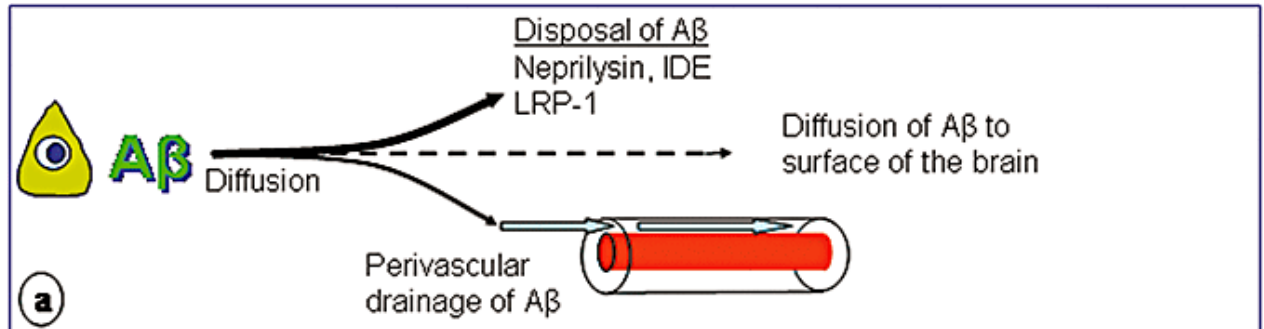A qualitative increase in ePVS is observed in cases with vascular pathology (C, D)

Boespflug et al., *Journal of Alzheimer's Disease, 2018*

Amyloid β clearance, not production is altered in sporadic AD

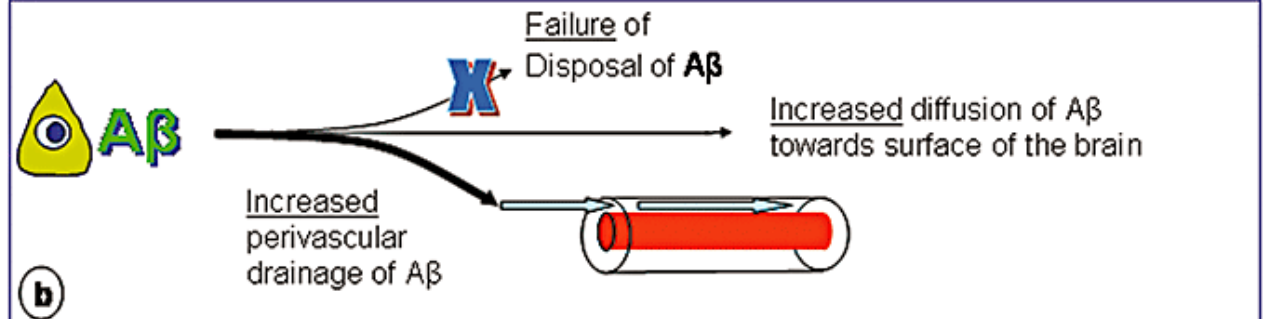Kwasi G. Mawuenyega et al. Science 2010;330:1774

The brain **perivascular space** is a route of fluid flow serving to maintain brain homeostasis, **including clearance of amyloid**
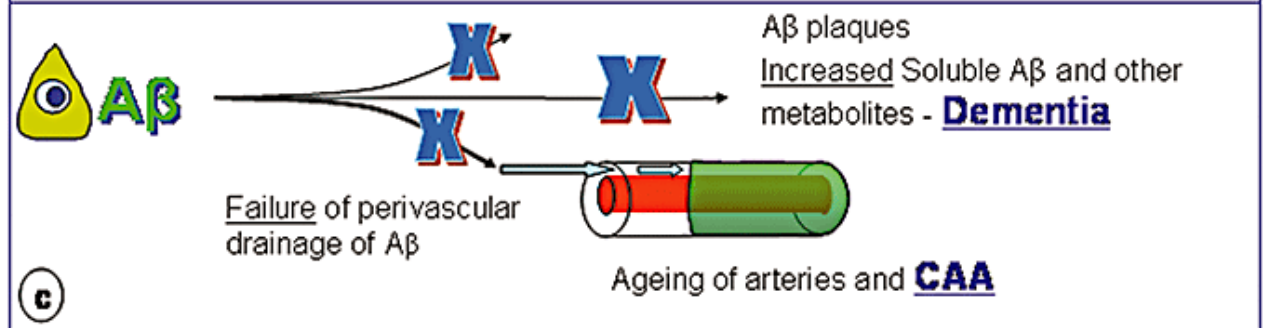

Normal young

Disposal of Aβ
Neprilysin, IDE
LRP-1

Diffusion

Diffusion of Aβ to surface of the brain

Perivascular drainage of Aβ

(a)

Aging

Failure of Disposal of **Aβ**

Increased diffusion of Aβ towards surface of the brain

Increased perivascular drainage of Aβ

(b)

Disease

Aβ plaques
Increased Soluble Aβ and other metabolites - **Dementia**

Failure of perivascular drainage of Aβ

Ageing of arteries and **CAA**

(c)

From Weller et al. *Brain Pathology* 2008

NACC New Investigator Proposal

<u>Goals</u>

1) Understand the extent to which clinical and pathological features of vascular-, amyloid-, and tau-based pathologies are associated with ePVS

2) Begin to test the hypothesis that ePVS are a reflection of impaired waste clearance mechanisms

- Aim 1: **Clinical features**
  - **MRI**, age, cognitive function
- Aim 2: **Neuropathology**
  - amyloid and tau, cerebrovascular disease
- Aim 3: **Amyloid clearance**
  - increased cortical amyloid load (PET)
  - reduced amyloid in the cerebrospinal fluid (CSF)

# ePVS: Visualization on MRI

- Current gold standard
  - visual rating scales
    - single axial slice
    - category score based on severity (counts)
  - labor and time intensive
 - no volume or morphology information
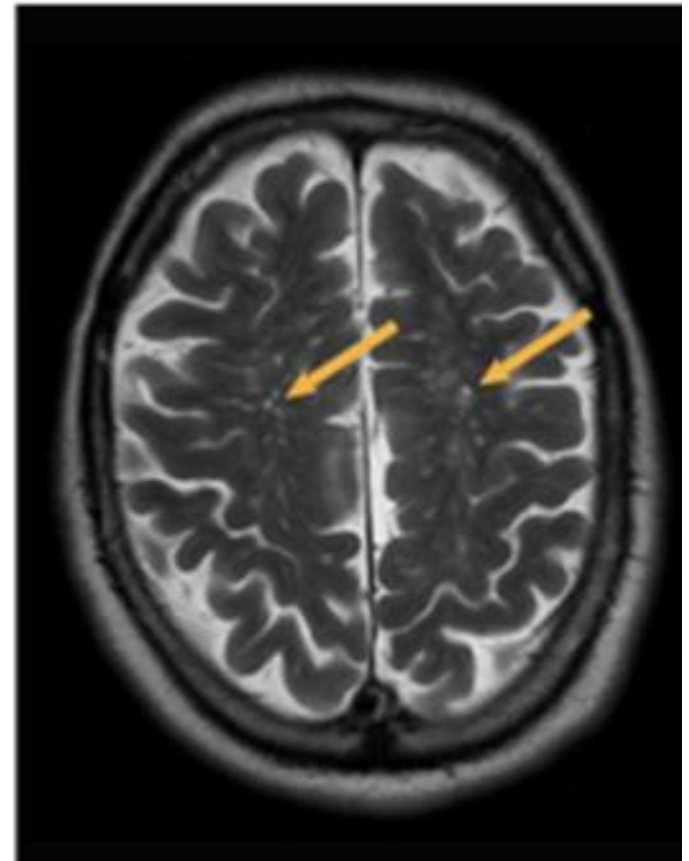
"A major limitation to understanding the etiology and clinical relevance of ePVS is limited reliability in identification on MRI precluding unified research"

Wardlaw, Lancet Neurol. 2013

ePVS detection goal: intensity *and* morphology

Clusters of CSF isointense voxels assessed
on the basis of linear morphology
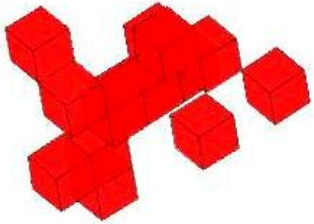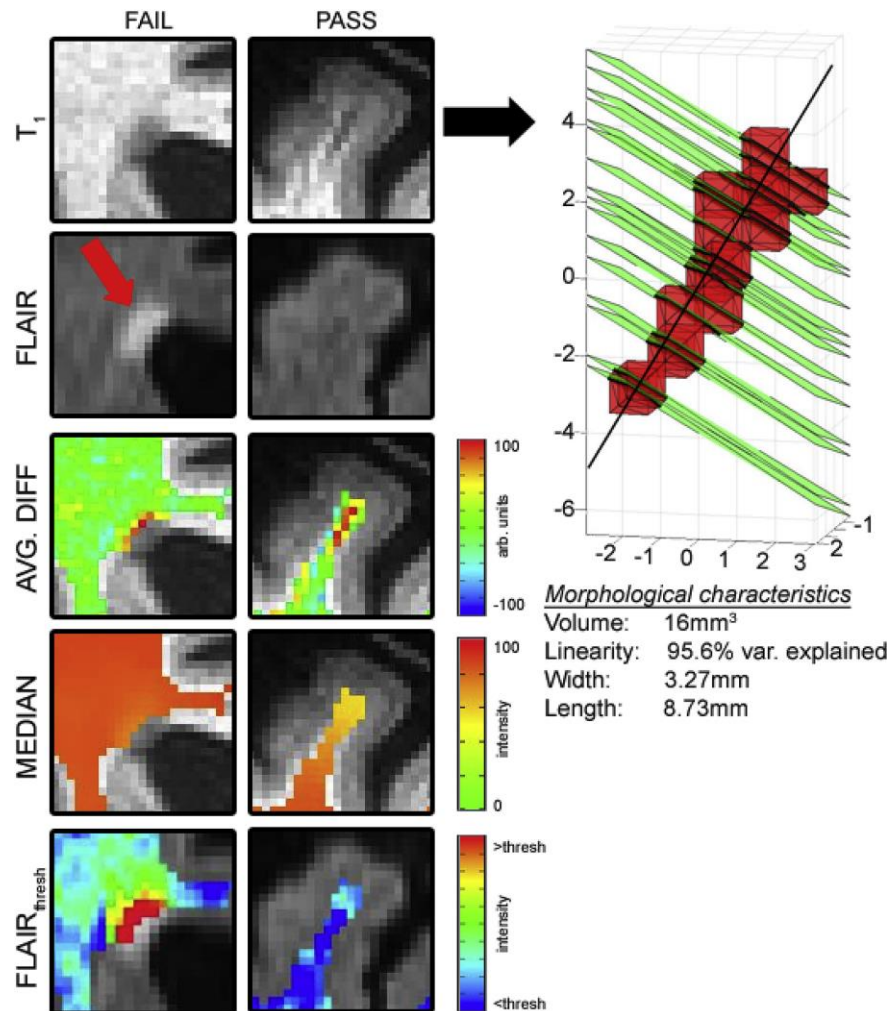
r = 0.66
width = 6.76 mm,
volume = 15 mm^3
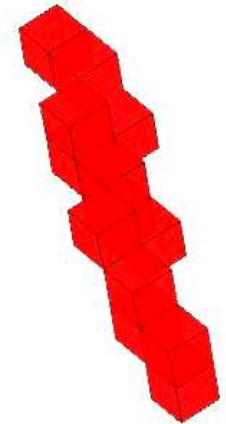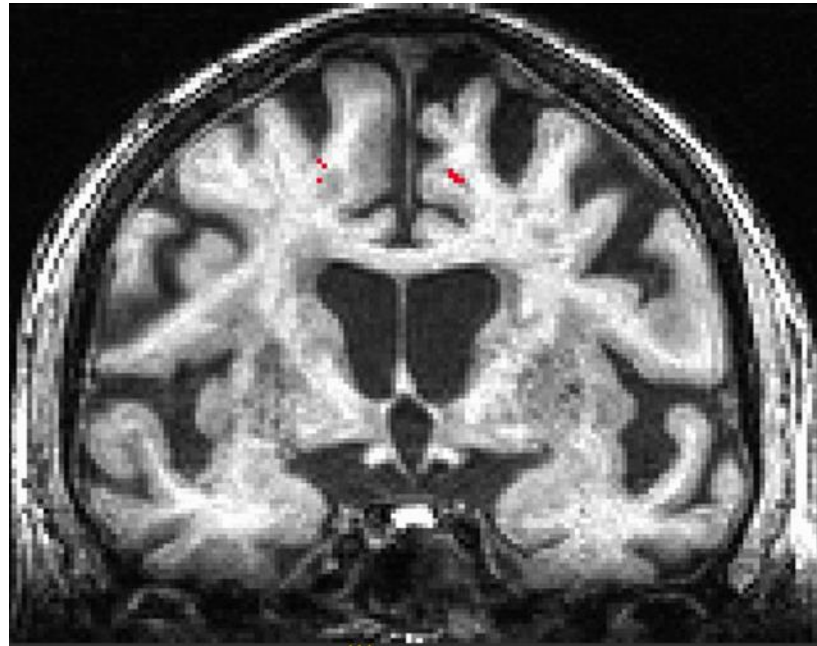
r = 0.84
width = 3.53 mm,
volume = 13 mm^3

Clusters meet criteria if:
- MRI intensity matches ePVS profile *-and-*
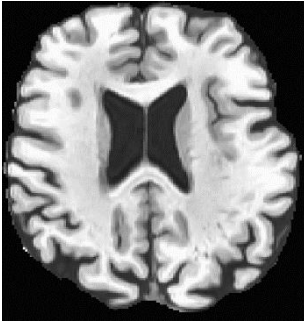- Morphology constraints match ePVS profile

Boespflug, et al., *Radiology*, 2017

Refined segmentation approach : limited sequence MRI

Dataset examples

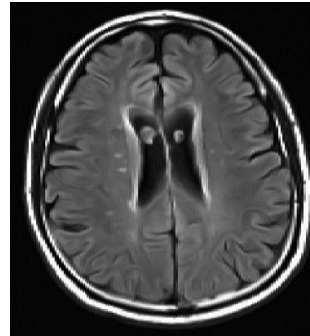**T₁** **FLAIR** **T₁ + PVS overlay**

Low burden volume

Age = 82

WM volume = 489331.08 mm^3

PVS volume = 707 mm^3

PVS : WM volume = 0.14 %

PVS count = 53

Age = 63

WM volume = 454676.46 mm^3

PVS volume = 1048 mm^3

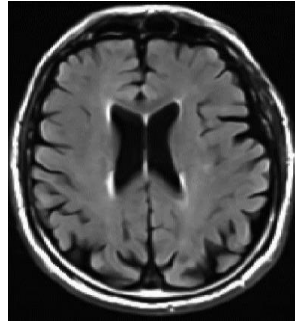PVS : WM volume = 0.23 %

PVS count = 58

High burden volume

Age = 80

WM volume = 452869.55 mm^3

PVS volume = 1716 mm^3

PVS : WM volume = 0.38 %

PVS count = 136

Dataset examples

T$_1$ **FLAIR**   **T$_1$ + PVS overlay**
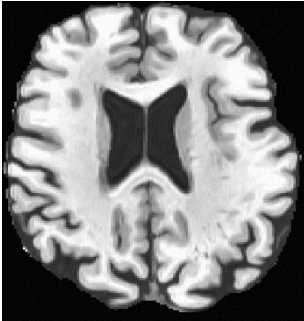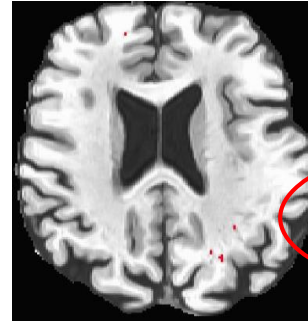
Low burden volume
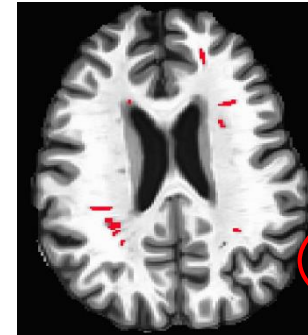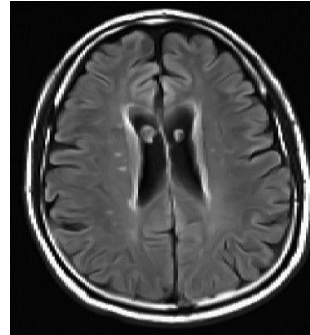
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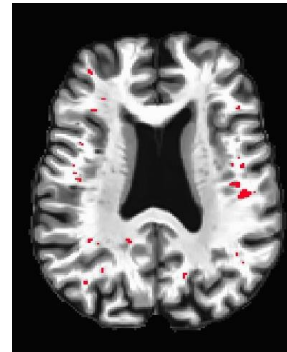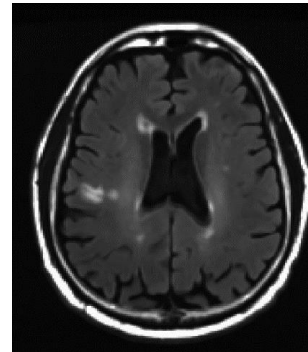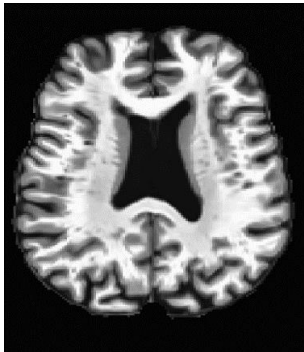PVS : WM volume = 0.14 %

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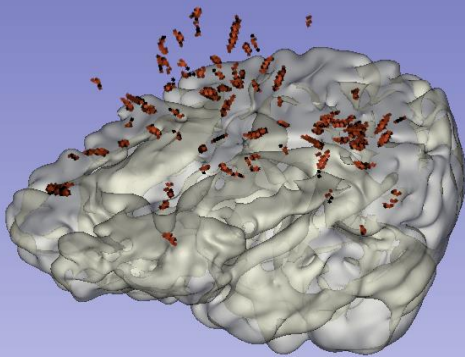WM volume = 452869.55 mm^3

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Dataset examples

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*Additional results slides have been omitted pending publication

Thank you

OHSU Neurology/Layton Aging & Alzheimer's Disease Center
Jeffrey Kaye
*Lisa Silbert
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Matt Simon

UC Davis
Carlie DeCarli
Baljeet Singh

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