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CAI²R Center for Advanced Imaging Innovation and Research

New perspectives on age-related white matter hyperintensities of VCID research

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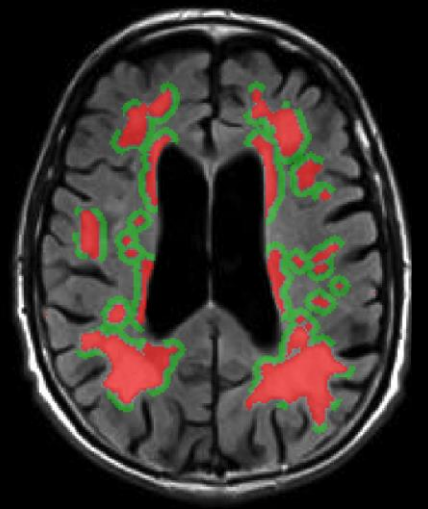
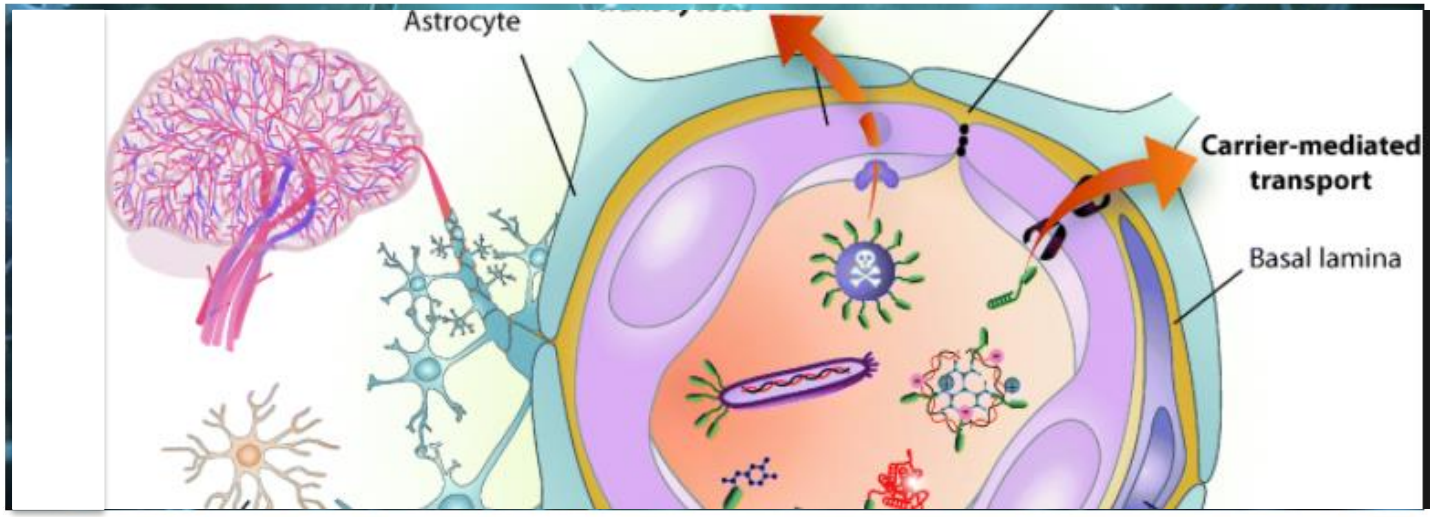


VCID

- Vascular abnormalities play a crucial role in aging, cognitive impairment & dementia
- An old topic with new perspectives on dementia
  - Conditions arising from vascular injuries (e.g., stroke) can cause significant changes to memory, thinking and behavior

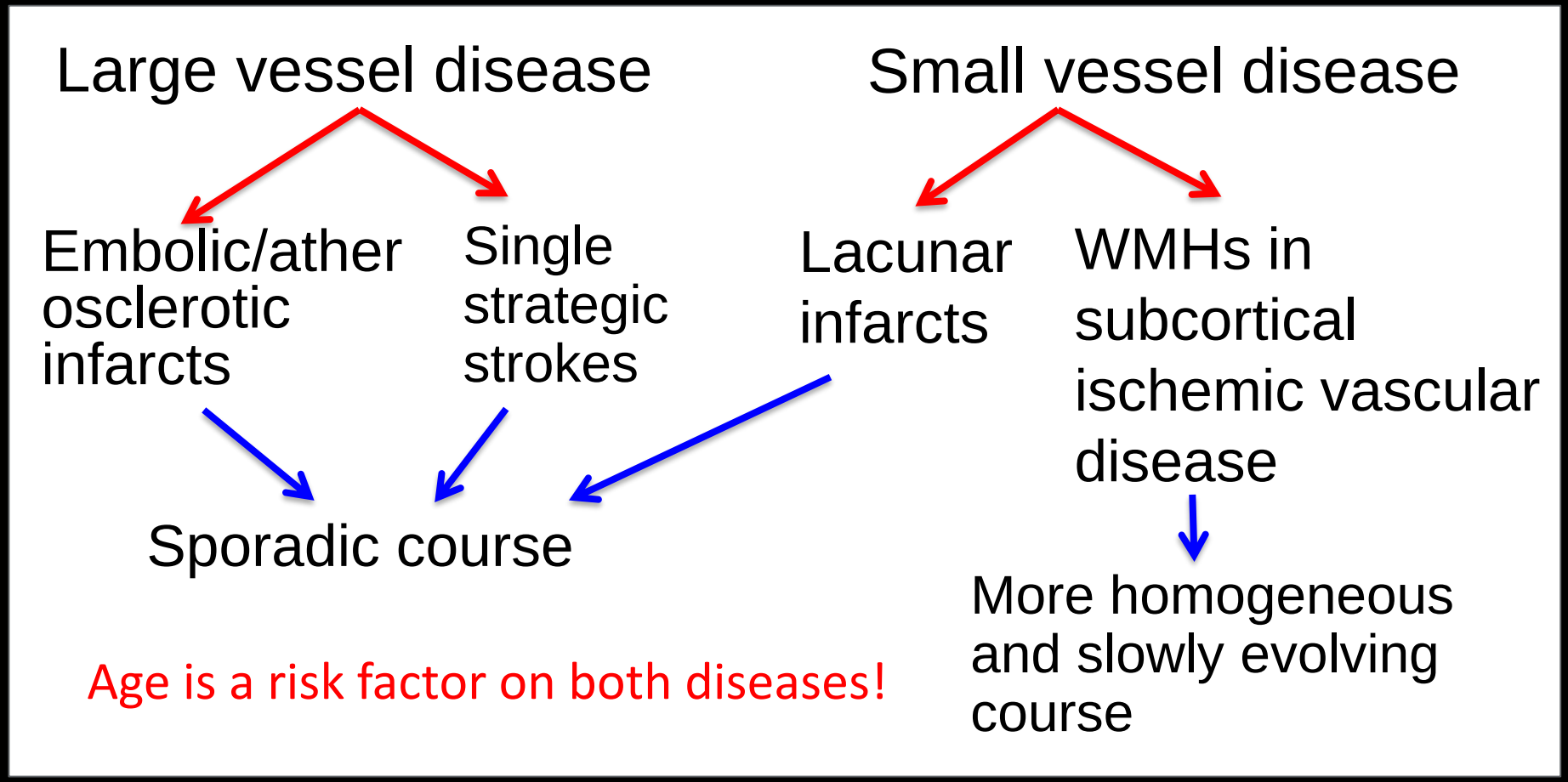
Focus On Vascular Contributions to Cognitive Impairment & Dementia (VCID) Research



NINDS Program Description

Decades of research have shown a strong link between cardiovascular and cerebrovascular disease, including stroke, and subsequent cognitive impairment and dementia. Moreover, cerebrovascular disease is exceedingly common in the elderly diagnosed with Alzheimer's disease. Vascular contributions to cognitive impairment & dementia (VCID) encompasses all types of cerebrovascular cardiovascular disease-related cognitive decline. Because of the proven ability to prevent and treat cardiovascular disease and hypertension, the NIH has designated VCID as a critical research area. To learn more read: Science of Vascular Contributions to Cognitive Impairment and Dementia (VCID): A Famework for Advancing Research Priorities in the Cerebrovascular Biology of Cognitive Decline.

Small *vs* large vessel disease



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In vivo insights of small vessel changes with age using USPIO-enhanced MRI (Ge, Haacke)

- To develop USPIO^{+}-MRAV imaging in order to visualize and quantify micro-angioarchitecture changes with age.
- To see the “unseen”
- To provide the insights of in vivo microvascular changes across the adult life span (18-85 yrs).

Face changes with age, what about brain, vessel?

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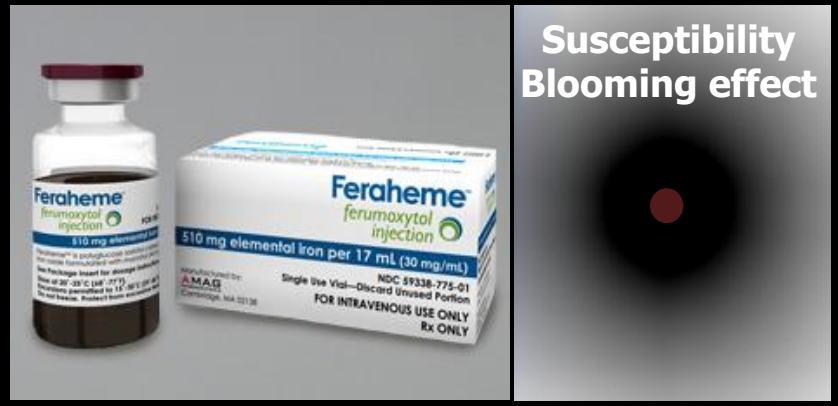
Ultrasmall super-paramagnetic iron oxide (USPIO)

- Ferumoxytol – FDA approved USPIO for human use to treat iron deficiency anemia; off-label contrast agent
- Blood pool agent with half-life of 15h
- Strong T2* shortening effect, ideal for SWI at higher resolution for MRAV
- Strong blooming effects for detection of small vessels (eg arteries), where vascular pathology often initiated



Has a superparamagnetic iron particle core

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Hypotheses

Age-related micro-vascular system changes can be detected using double-echo USPIO-enhanced SWI

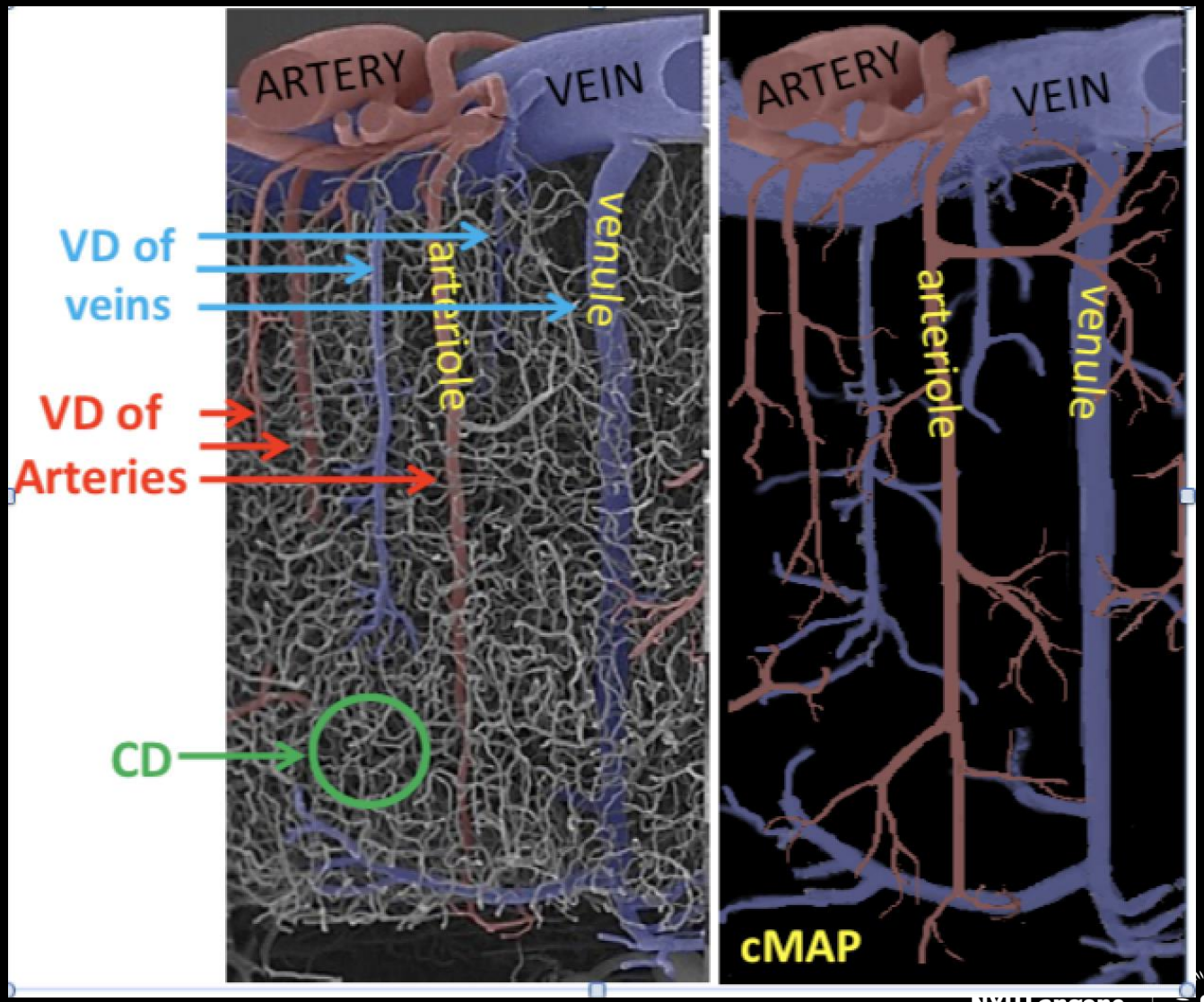
Visual inspection

- Small vessel (e.g., arteriole) morphological changes on cerebral micro-vascular architecture print (cMAP)

Quantitative analysis

- VD – vascular density
- CD – capillary density

Cerebral vascular system



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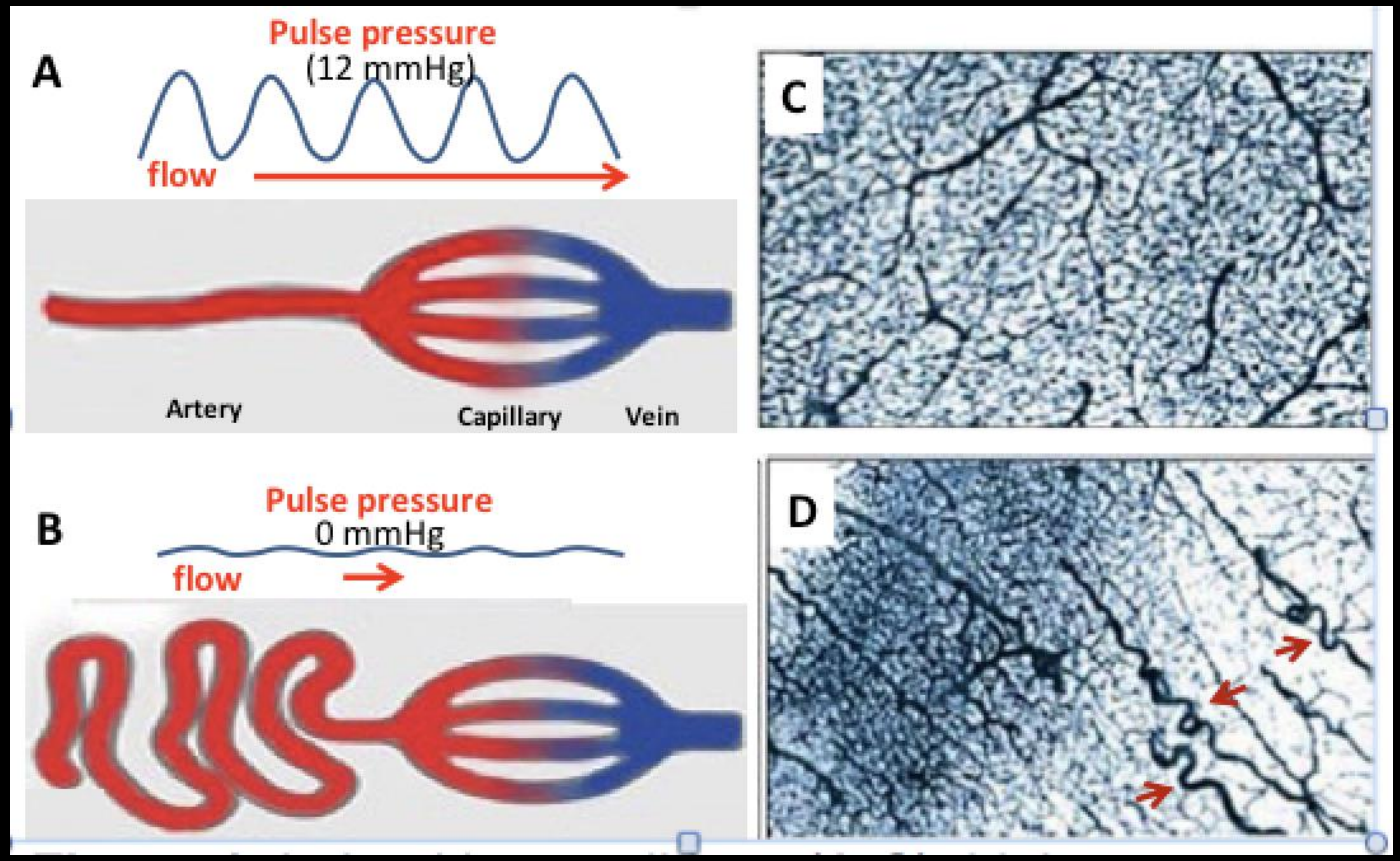
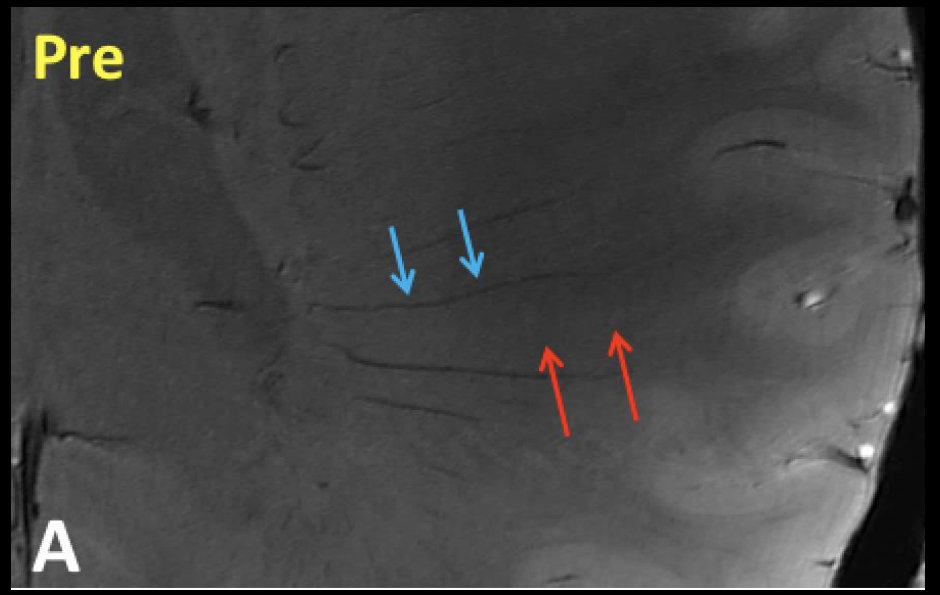
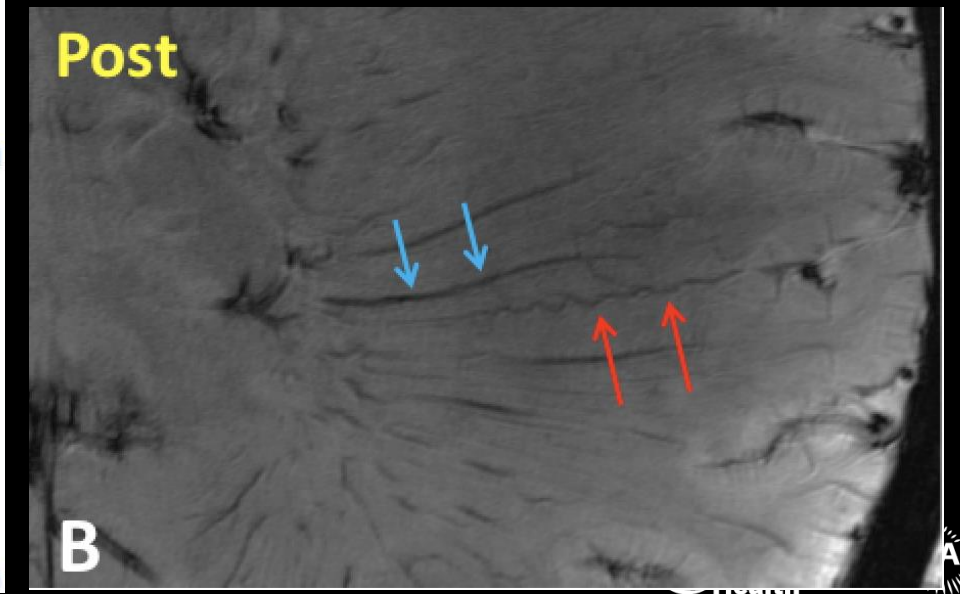
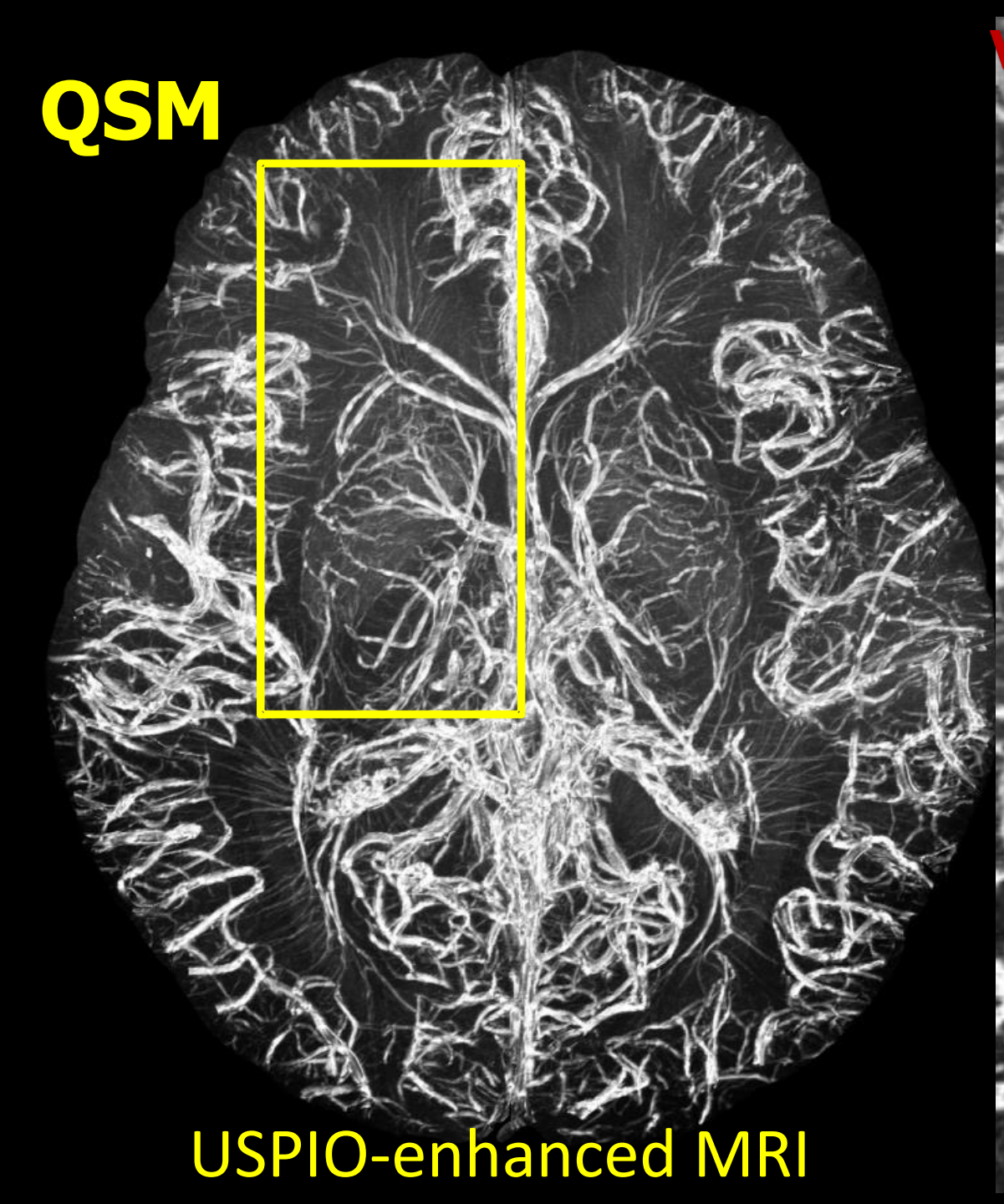
Small vessel disease

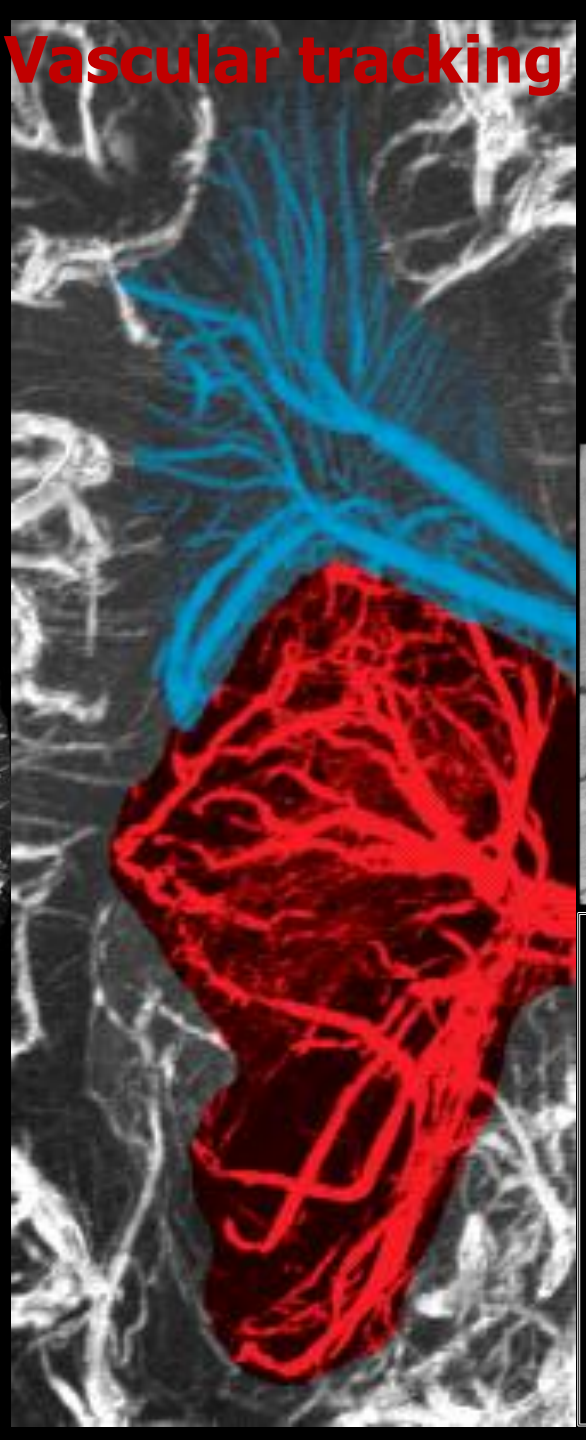
With age, small arteries can become torturous that leads to significantly reduced blood flow



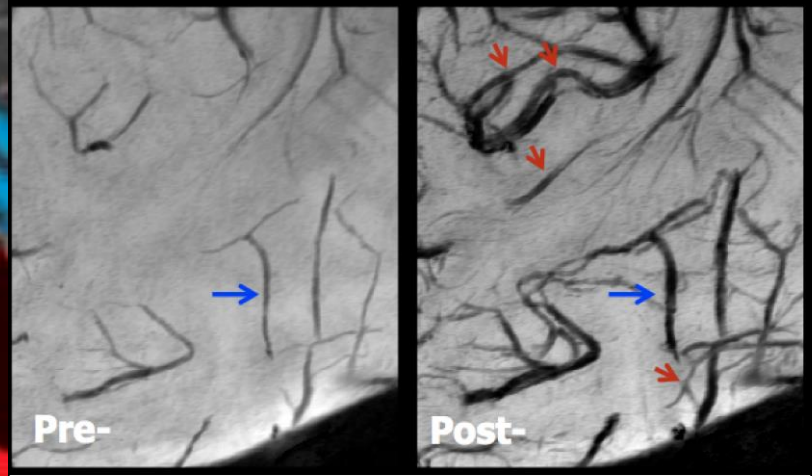


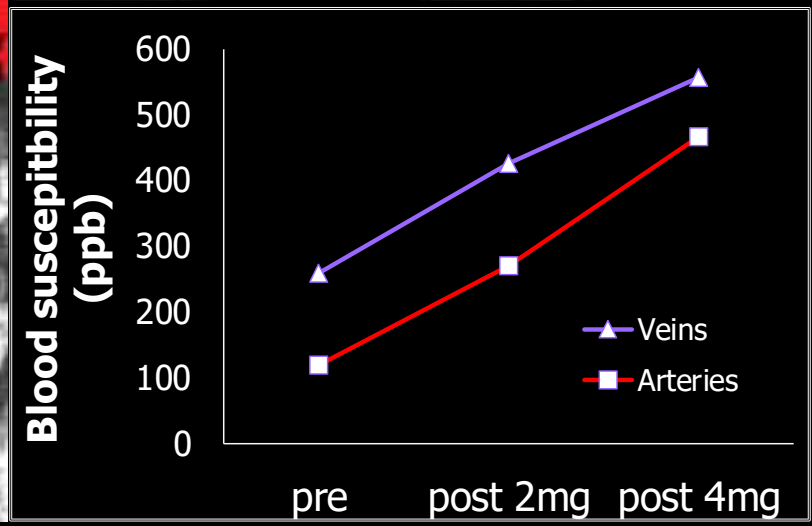






Introducing USPIO into the blood





Mechanisms of age-related white matter hyperintensities: insights from advanced MRI

Yulin Ge (NYU), Hanzhang Lu (JHU)

Lesions are only the tip of iceberg in aging

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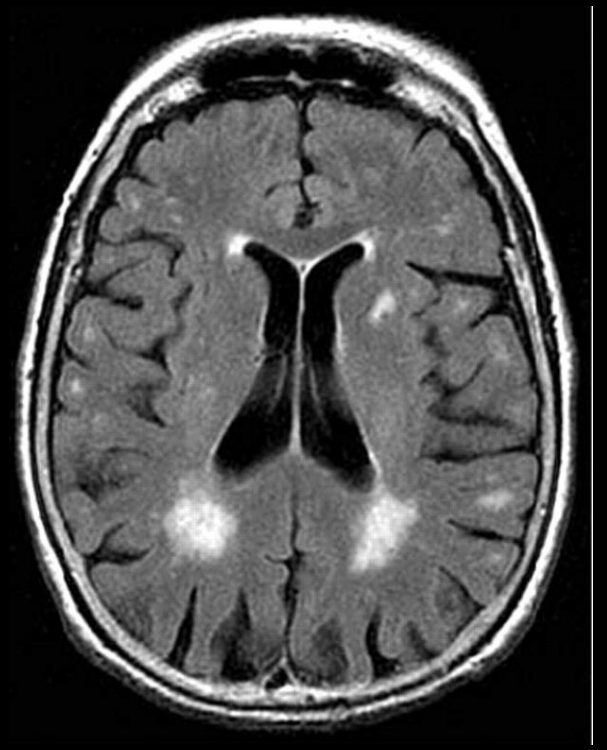
White matter hyperintensities (WMHs)

- Age-related WMHs or leukoaraiosis is considered a small vessel disease (SVD), which is common in the elderly on MRI.

  - Although many studies have been performed on WMH and its clinical association, mechanistic understanding of WMH is still incomplete.
  - Much still remains to be explored concerning the in vivo micro-vascular pathophysiology of WMHs.



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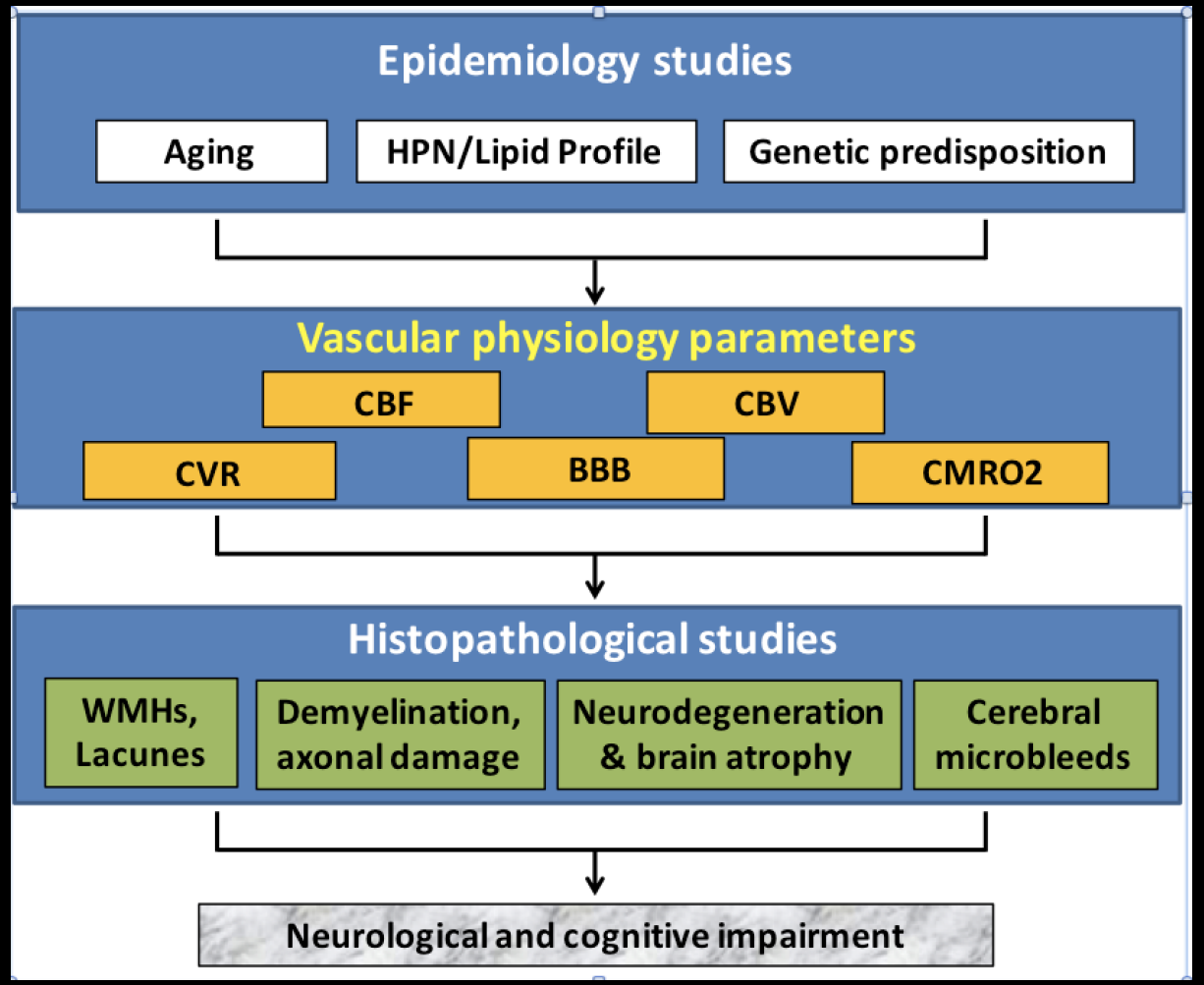
Hypothesis

Microvascular physiology and function changes play a crucial role in age-related small vessel disease or WMHs

- Vascular hemodynamics
  - CBF & CBV
- Vascular functions
  - Cerebrovascular reactivity (CVR) & BBB



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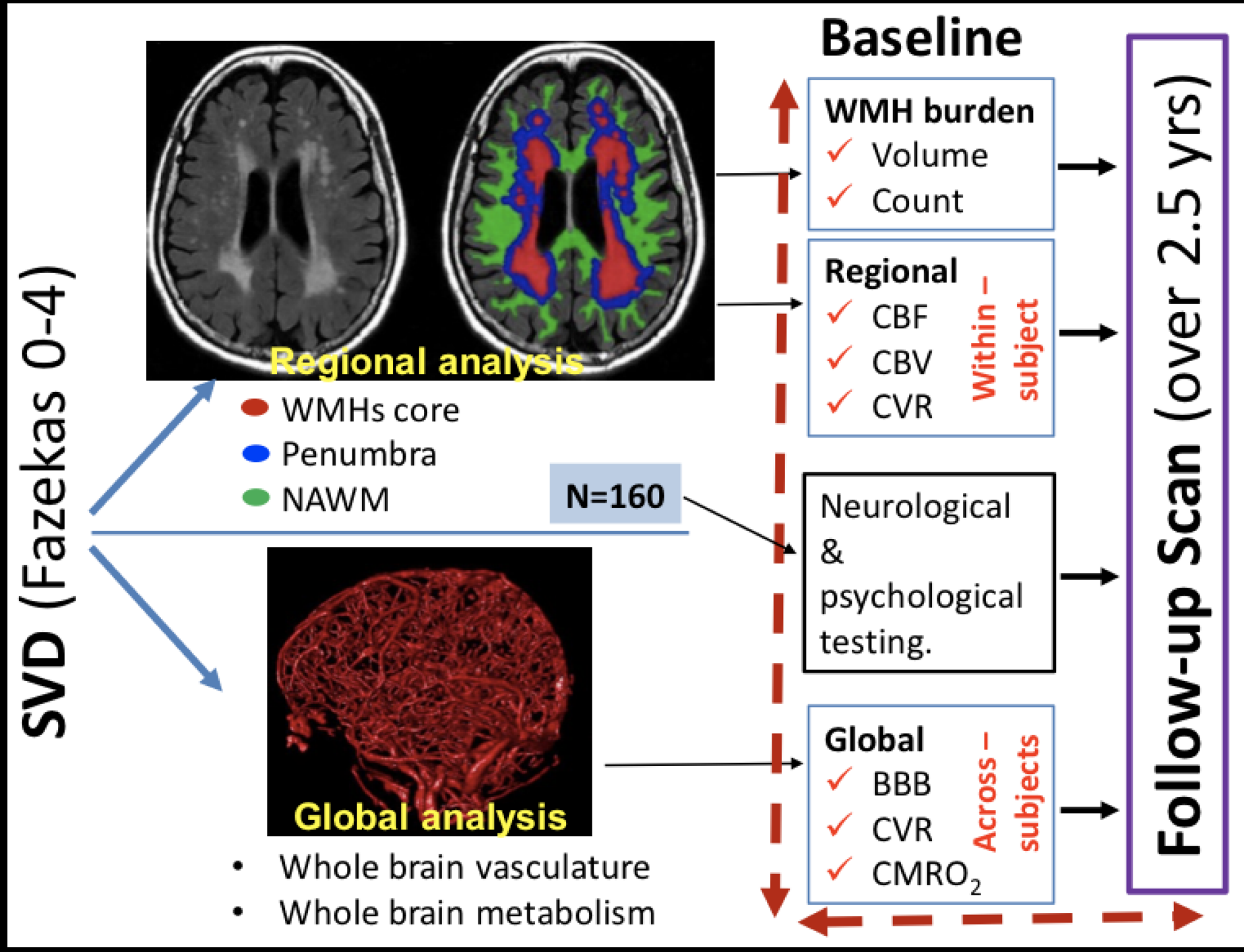
Study design



A set of microvascular parameters that are comprehensive and complementary in understanding WMHs in vivo

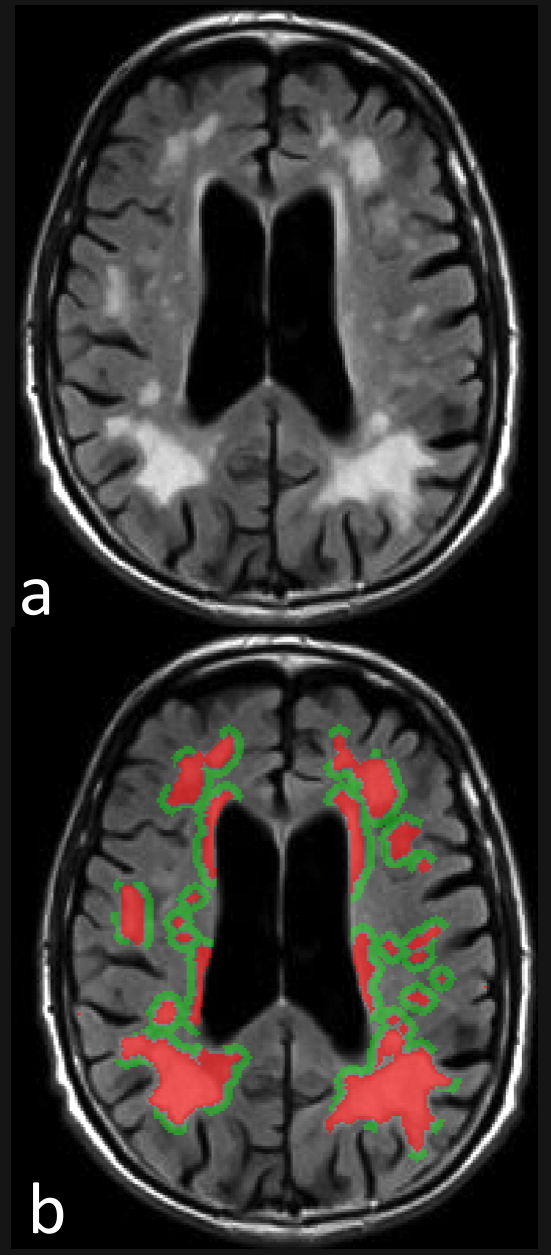
- CBF measured with MR Fingerprinting (MRF) Arterial-Spin-Labeling (ASL), which overcomes the limitation of traditional measures for WM perfusion
- WM cerebrovascular reactivity (CVR) and CBV using concomitant CO2 and O2 gas enhanced BOLD MRI
- BBB permeability for water exchange rate (BBB-x) measured with Water-Extraction-with-Phase-Contrast-Arterial-Spin-Tagging (WEPCAST)

Aims

Aim 1 – use these innovative techniques to understand the hypoperfusion and vessel stiffening associated with WMHs

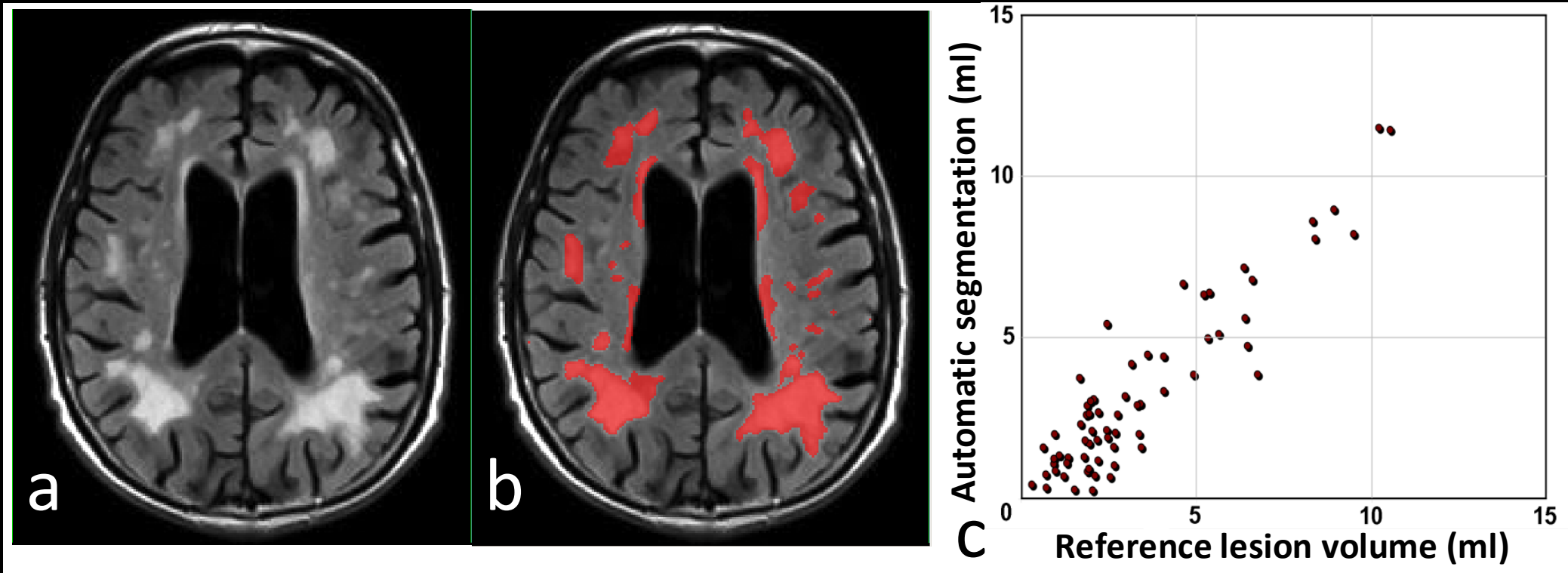
Aim 2 – examine the association between WMH volume and whole-brain measures of BBB and neural function, and their relationship to cognition.

Aim 2 – Followup to demonstrate that baseline BBB-x and CMRO2 are linked to increased WMH burden and worsening of clinical symptoms 2.5 years later.



Preliminary results

- WMHs segmentation



Results of fully automatic lesion segmentation in 73 elderly brains are plotted against the reference volume. Automatic volumes were calibrated to remove a systematic multiplicative bias, yielding an average absolute error of 0.94 ml.

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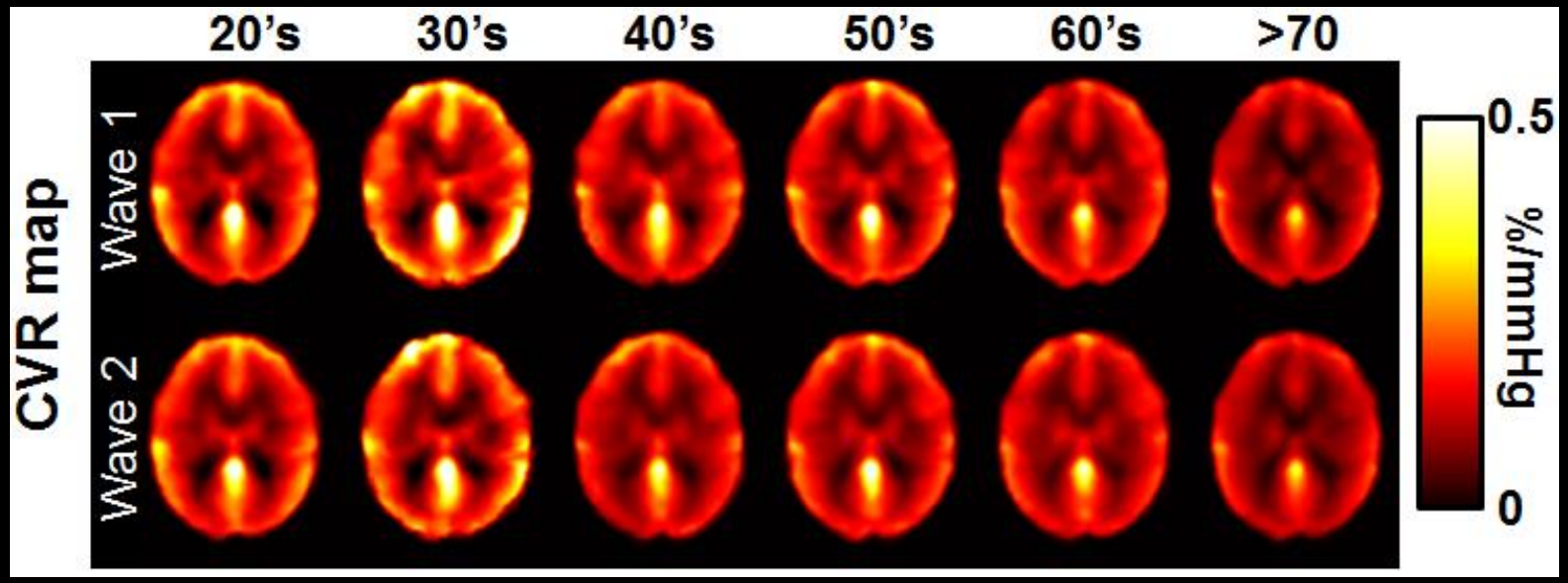
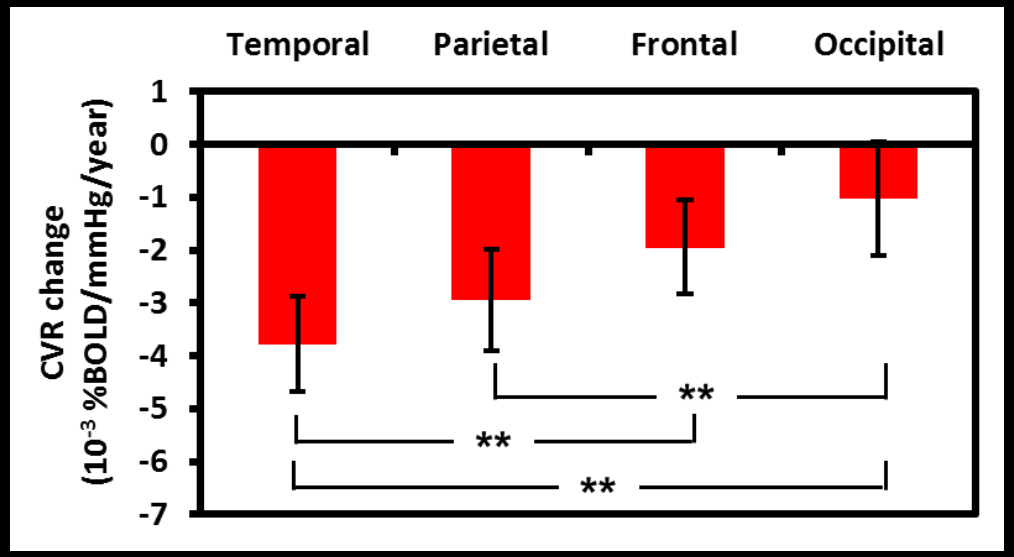
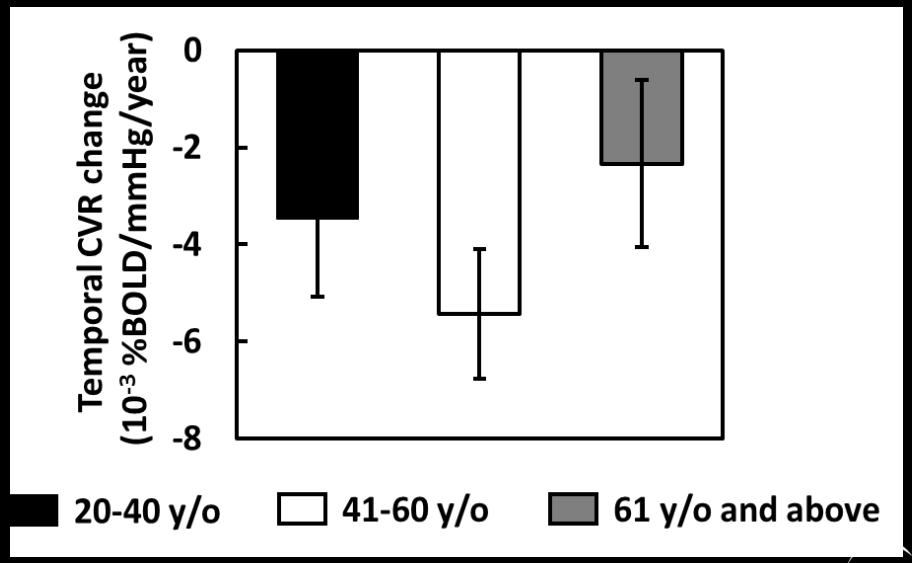
Four-year follow-up study of CVR







Peng et al. Neuroimage, 2018

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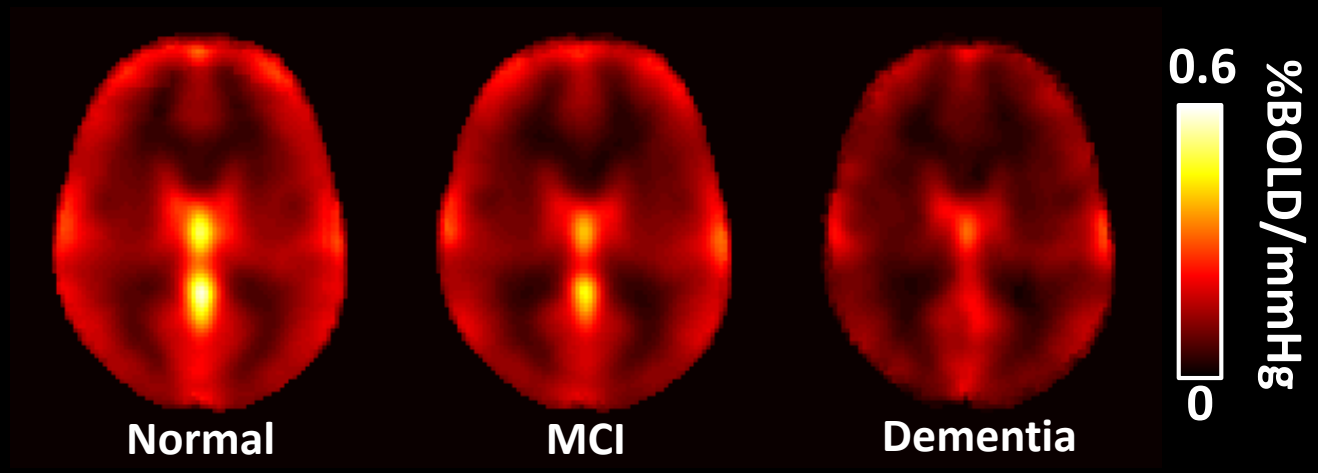
Preliminary results



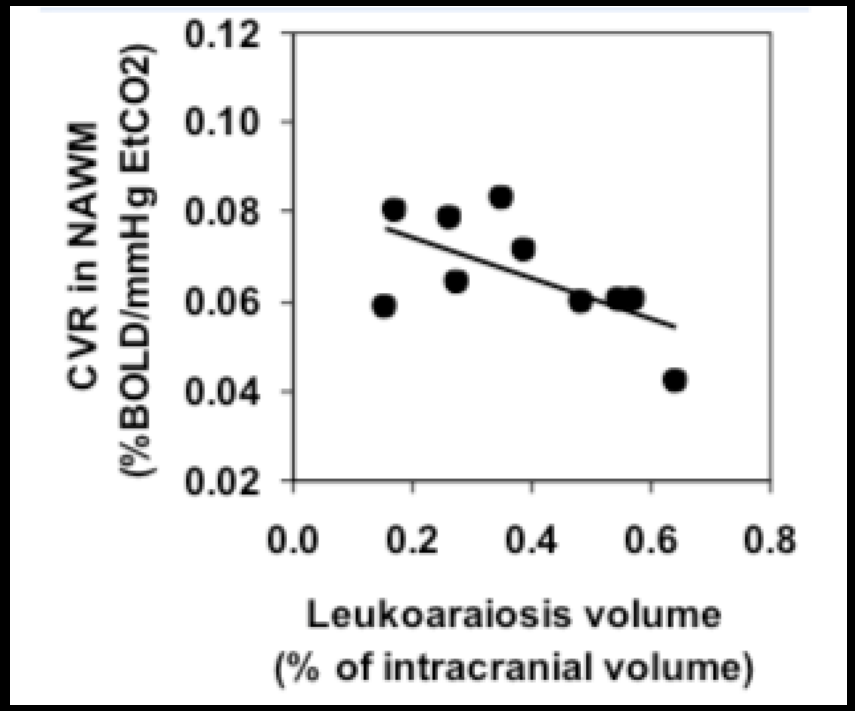


Table 1. Comparison of microvascular parameters between WMHs and NAWM

Parameter	NAWM (mean ± SEM)	WMHs (mean ± SEM)	% change (mean ± SEM)	*P*-value
CBF (ml/min/100 ml brain)	33.5 ± 1.9	13.4 ± 2.0	-60.3 ± 5.2	< 0.001
CVR (%BOLD/mmHg)	0.066 ± 0.004	0.035 ± 0.009	-47.5 ± 11.6	0.005

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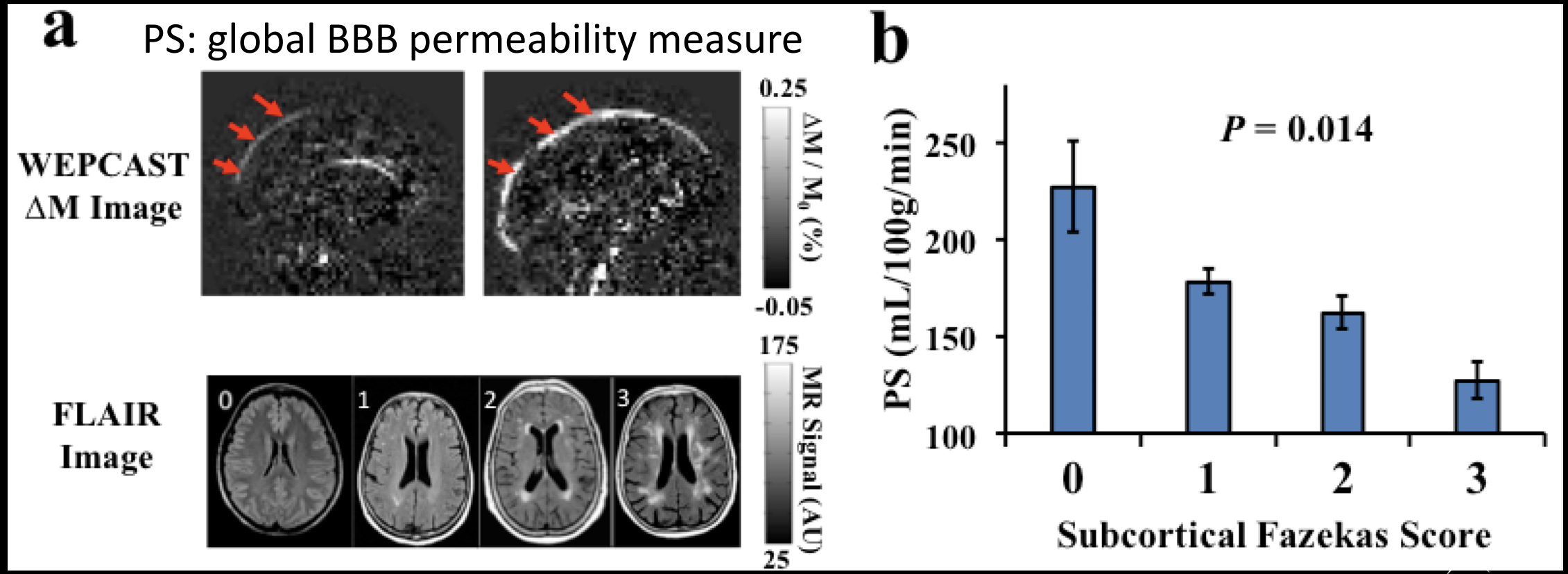
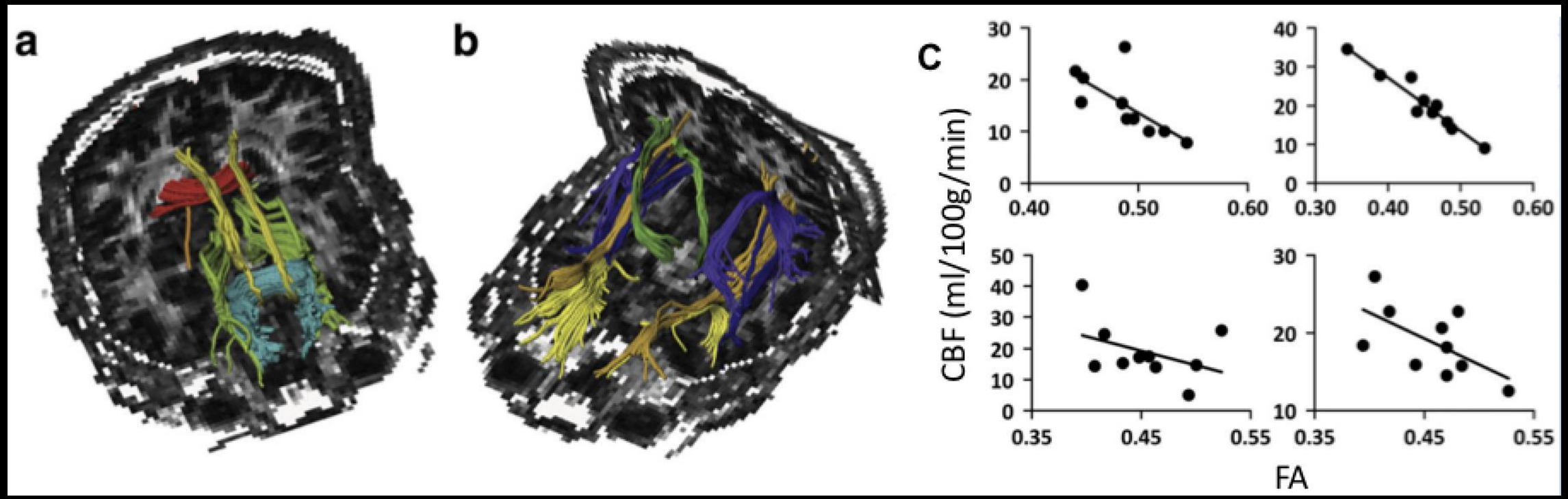
Preliminary results

The relationship between global PS and WMHs in 30 elderly participants (Age: 68.5±7.9 years, Gender: 15F/15M).



Preliminary results

Inverse relationship between tract-specific CBF and FA in 10 healthy volunteers. Illustration of 10 major fiber tracts overlaid on FA maps with five fibers shown in (a) and five in (b). (c) Scatter plots between FA and CBF across all fiber tracts (only four shown here) – <u>higher FA lower CBF</u>



Summary

- *In vivo* mechanistic studies of small vessel disease is crucial in advancing our understanding of vascular health and cognitive impairment.
- In SVD, both inside WMH lesions (i.e. tip of the “iceberg”) and global tissue vascular pathology (i.e. what is hidden underneath the sea-level) should be studied.
- The set of innovative techniques proposed is expected to provide fundamental insights on how age-related microvascular alterations associated with cognitive decline

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Acknowledgement

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- **Collaborators**

  –E Mark Haacke (Wayne State University)

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  –Thomas Wisniewski (Neurology, NYU School of Medicine)

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Emerging research priorities