Multi-modal imaging of small vessel disease

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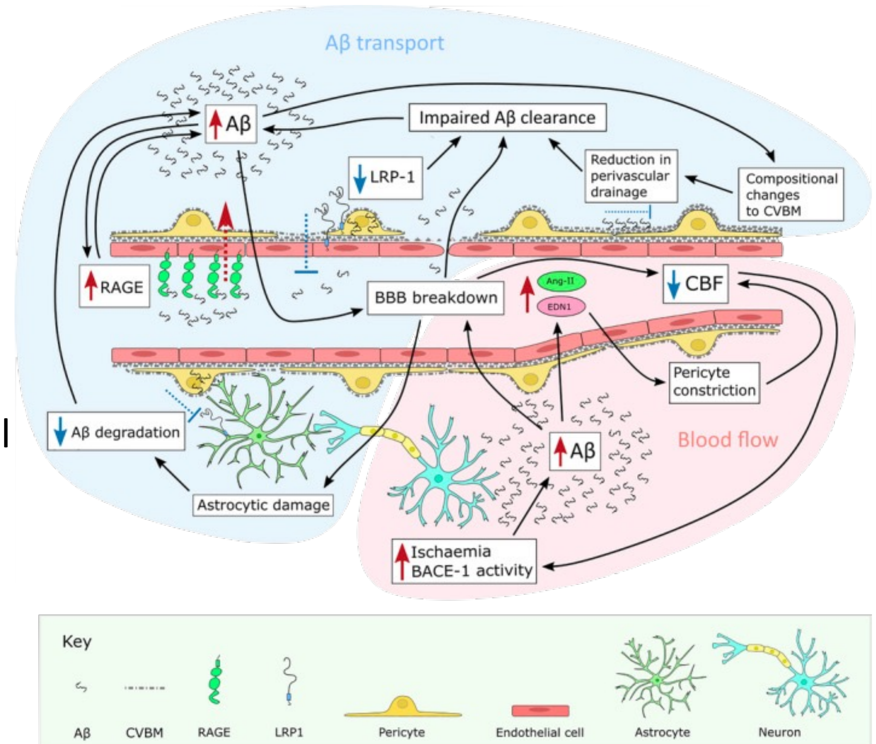
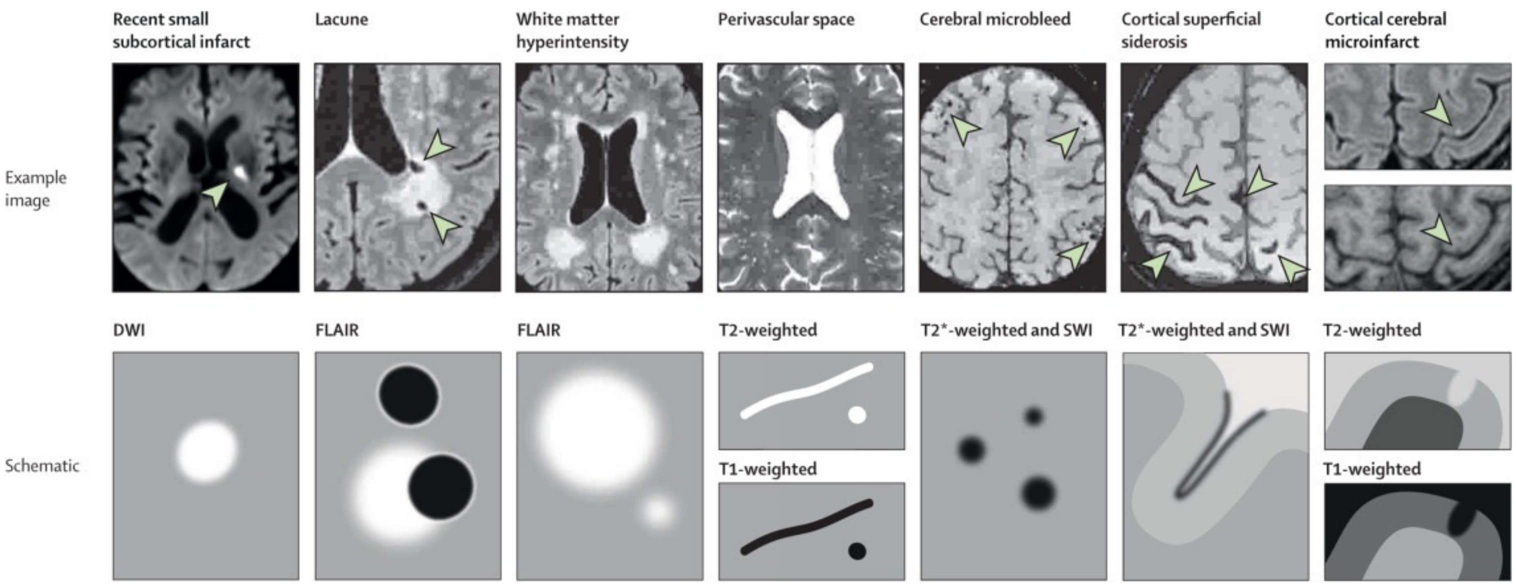
Clinical Relevance of Small Vessel Disease (SVD)

- SVD plays an important role in many conditions such as aging, stroke, cognitive impairment, motor and gait impairment, and mood disorders
- Majority dementia cases have mixed pathologies that primarily includes cerebrovascular small disease
- While amyloid accumulation, a hallmark of AD, causes small vessel pathology, non-amyloid-related small vessel pathology is also abundant and may increase risk of AD
- Vascular cognitive impairment and AD both have common risk factors: diet, physical activity, midlife hypertension, diabetes, inflammation, chronic kidney disease
- No good biomarker for assessing SVD



Love S, Miners JS. Cerebrovascular disease in ageing and Alzheimer's disease. Acta Neuropathol. 2016 May;131(5):645-58. doi: 10.1007/s00401-015-1522-0. Epub 2015 Dec 28. PMID: 26711459; PMCID: PMC4835514.
Wardlaw JM, Valdés Hernández MC, Muñoz-Maniega S. What are white matter hyperintensities made of? Relevance to vascular cognitive impairment. J Am Heart Assoc. 2015 Jun 23;4(6):001140. doi: 10.1161/JAHA.114.001140. Erratum in: J Am Heart Assoc. 2016 Jan 13;5(1):e002006. PMID: 26104658; PMCID: PMC4599520.
Arvanitakis Z, Capuano AW, Leurgans SE, Bennett DA, Schneider JA. Relation of cerebral vessel disease to Alzheimer's disease dementia and cognitive function in elderly people: a cross-sectional study. Lancet Neurol. 2016 5(9):934-943. doi: 10.1016/S1474-4422(16)30029-1. Epub 2016 Jun 14. PMID: 27312738; PMCID: PMC4969105.
Iturria-Medina Y, Sotero RC, Toussaint PJ, Mateos-Pérez JM, Evans AC; Alzheimer's Disease Neuroimaging Initiative. Early role of vascular dysregulation on late-onset Alzheimer's disease based on multifactorial data-driven analysis. Nat Commun. 2016 Jun 21;7:11934. doi: 10.1038/ncomms11934. PMID: 27327500; PMCID: PMC4919512.

Imaging markers of SVD



	Recent small subcortical infarct	Lacune	White matter hyperintensity	Perivascular space	Cerebral microbleed	Cortical superficial siderosis	Cortical cerebral microinfarct
Usual diameter	≤20 mm	3–15 mm	Variable	≤2 mm	≤10 mm	Variable	<4 mm
DWI	↑	↔ (↓)	↔	↔	↔	↔	↔/↑ (acute)
FLAIR	↑	↓	↑	↓/↔	↔	↔	↑/↓
T2-weighted	↑	↑	↑	↑	↔	↔	↑
T1-weighted	↓	↓	↔ (↓)	↓	↔	↔	↓
T2*-weighted	↔	↔	↑	↔	↓↓	↓↓	↔

↑ Increased signal ↓ Decreased signal ↔ Isointense signal

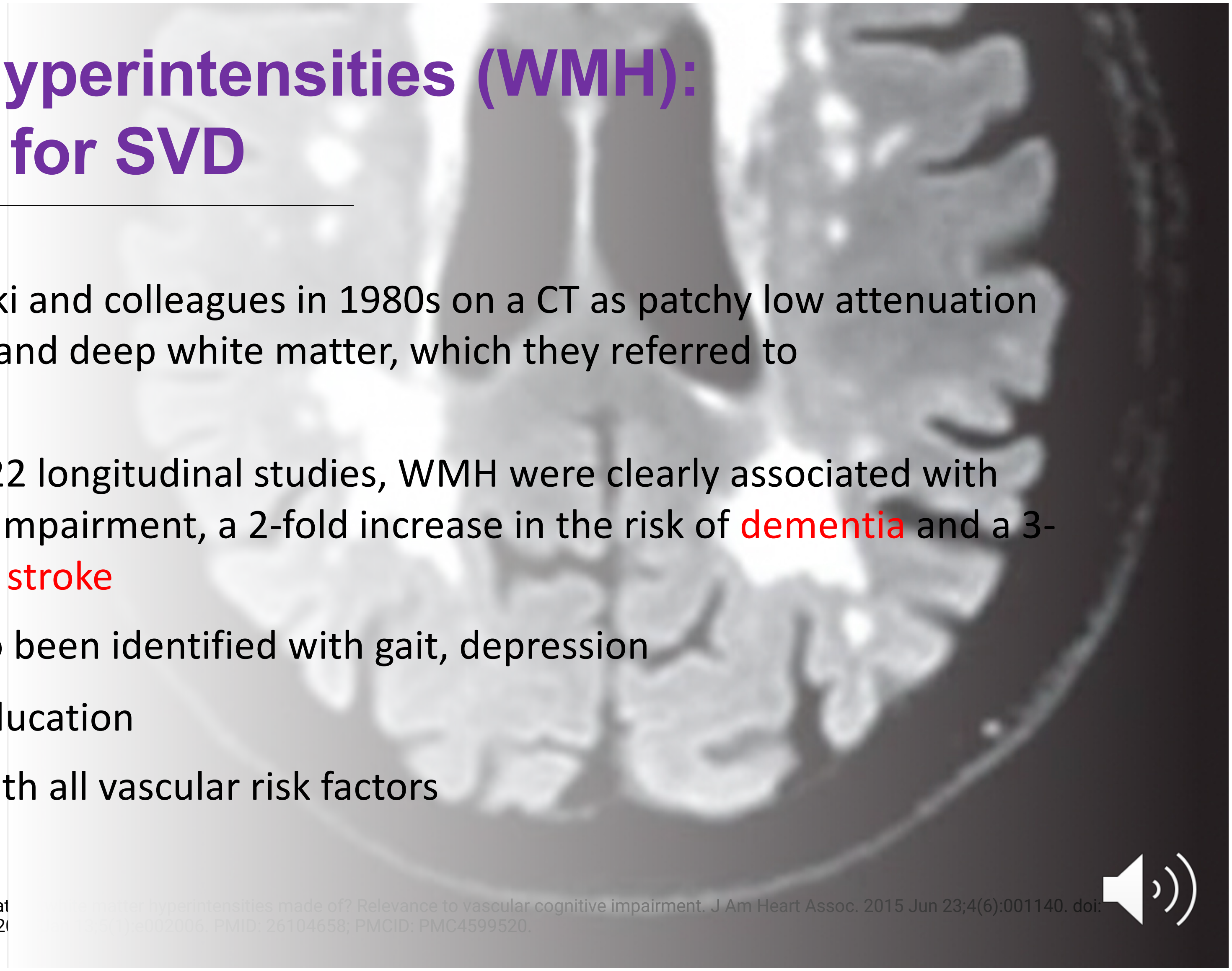
Wardlaw, Joanna M et al. "Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration." *The Lancet. Neurology* vol. 12,8 (2013): 822-38.

Revised ATN(/V/I/S) classification

Table 2. Intended uses for imaging and fluid biomarker assays

Intended Use	CSF	Plasma	Imaging
Diagnosis			
A: (Aβ proteinopathy)			Amyloid PET
T_1: (phosphorylated and secreted AD tau)		p-tau 217	
Hybrid ratios	p-tau181/Aβ42, t-tau/Aβ42, Aβ42/40	p-tau217/np-tau 217	
Staging, prognosis, as an indicator of biological treatment effect			
A: (Aβ proteinopathy)			Amyloid PET
T_1: (phosphorylated and secreted AD tau)		p-tau 217	
Hybrid ratios	p-tau181/Aβ42, t-tau/Aβ42, Aβ42/40	p-tau217/np-tau 217	
T_2: (AD tau proteinopathy)	pT205, MTBR-243, non-phosphorylated tau fragments	pT205	Tau PET
N (injury to or degeneration of neuropil)	NfL	NfL	Anatomic MR, FDG PET
I (inflammation) Astrocytic activation	GFAP	GFAP	
Identification of co-pathology			
N (injury, dysfunction, or degeneration of neuropil)	NfL	NfL	Anatomic MR, FDG PET
V vascular brain injury	?	?	Anatomic infarction, WMH, abundant dilated perivascular spaces
S α-synuclein	αSyn-SAA *		

https://aaic.alz.org/diagnostic-criteria.asp#drafts



White matter hyperintensities (WMH): Gold standard for SVD

- Described by Hachinski and colleagues in 1980s on a CT as patchy low attenuation in the periventricular and deep white matter, which they referred to as *leukoaraiosis*
- In a meta-analysis of 22 longitudinal studies, WMH were clearly associated with progressive cognitive impairment, a 2-fold increase in the risk of dementia and a 3-fold increase in risk of stroke
- Associations have also been identified with gait, depression
- Inversely related to education
- Strongly associated with all vascular risk factors

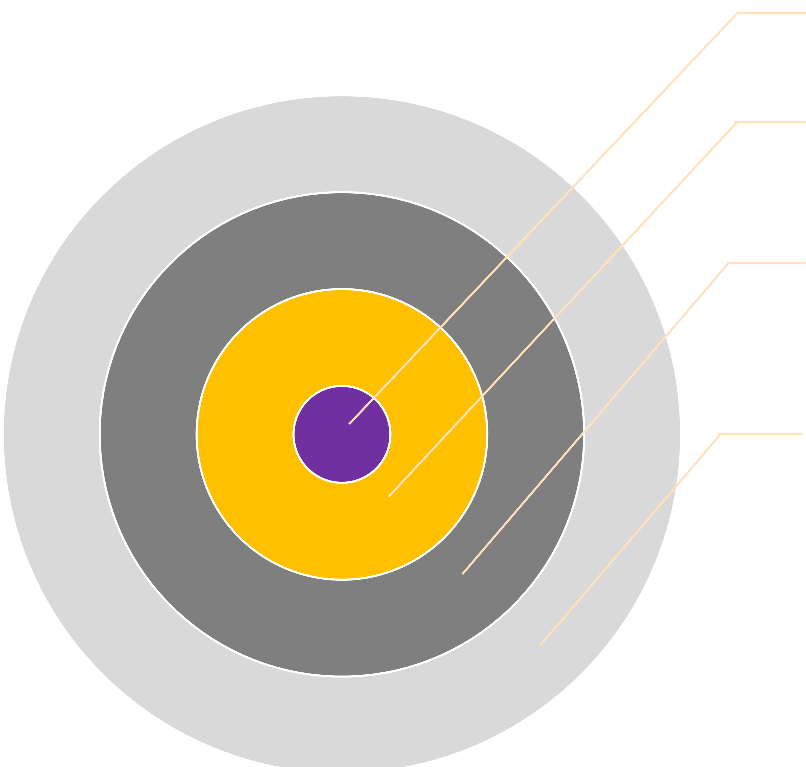
Wardlaw JM, Valdés Hernández MC, Muñoz-Maniega S. What [illegible] white matter hyperintensities made of? Relevance to vascular cognitive impairment. J Am Heart Assoc. 2015 Jun 23;4(6):001140. doi: 10.1161/JAHA.114.001140. Erratum in: J Am Heart Assoc. 20[illegible] Jan 13;5(1):e002006. PMID: 26104658; PMCID: PMC4599520.

White matter hyperintensities (WMH): But still, just the tip of the iceberg

- Remain radiologic features on a T2 FLAIR MRI
- Multiple pathological mechanisms are hypothesized to underlie WMH
  - Vascular (elevated ICAM, BMP, enlarged perivascular spaces, CSF:plasma albumin, APP)
  - Neuronal (demyelination/lower LFB signal)
  - Inflammatory (gliosis, increased CD68, HIFs, MMP)
- Single snap-shot imaging, the temporal evolution of pathology is difficult. Not all are studied at the same time and not in many individuals

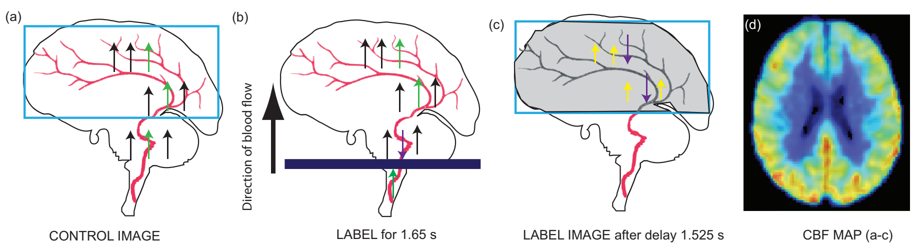
Fernando, Malee S et al. "White matter lesions in an unselected cohort of the elderly: molecular pathology suggests origin from chronic hypoperfusion injury." *Stroke* vol. 37,6 (2006): 1391-8.

Goal: To identify specific WMH pathology to target and reduce the cognitive sequelae of WMH



Cerebrovascular imaging methods

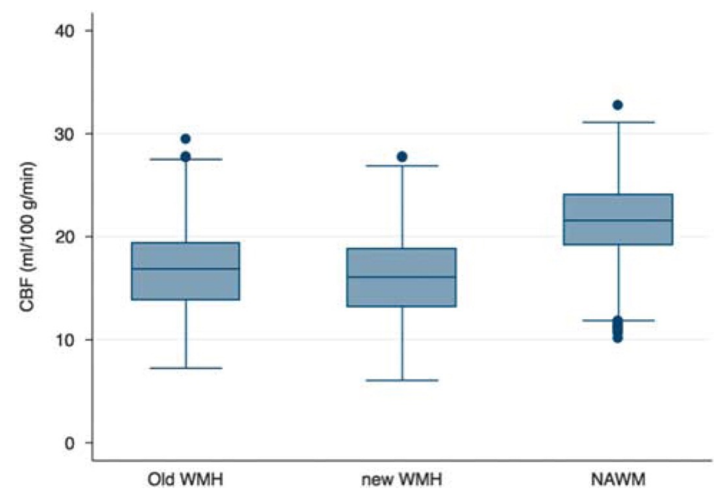
Arterial spin labeling



- Quantitative measurement of cerebral blood flow (CBF) in ml/100g/min
- Rigorously tested imaging protocol and analyses pipeline (Reproducibility ICC = 0.81) and QA

Bernbaum, Manya et al. "Reduced blood flow in normal white matter predicts development of leukoaraiosis." *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism* vol. 35,10 (2015): 1610-5

- WMH burden is associated with poor perfusion in WMH, normal appearing white matter and gray matter

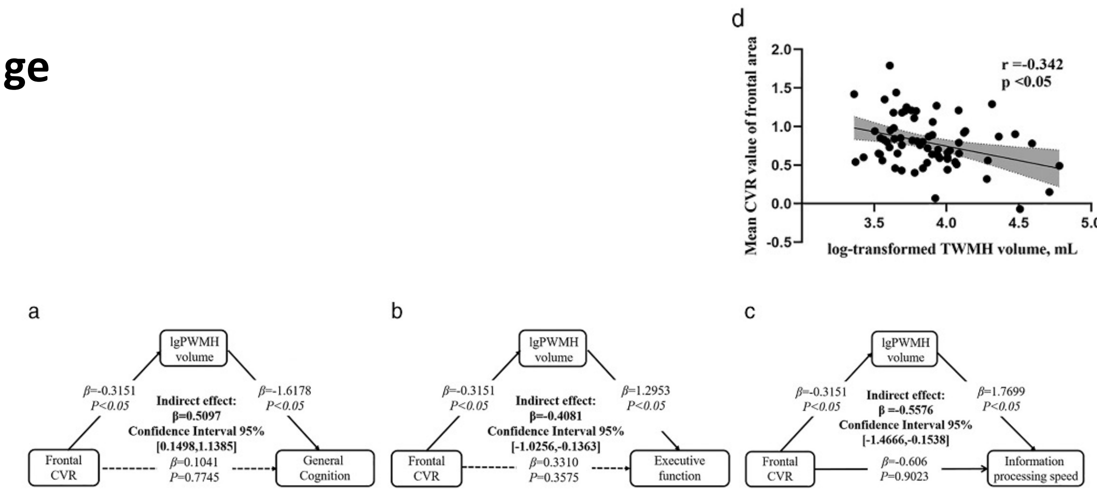


- Perfusion deficit could be more focal but is yet unexplored

Low cerebrovascular reactivity (CVR) is associated with greater WMH burden

BOLD fMRI + breathhold/gas challenge

- Breathhold experiment
- Simple design
- Easy to implement in impaired individuals
- 1-3 mm Hg change in $EtCO_2$ as opposed to a hypercapnia challenge >5 mm Hg
- Modest signal change but a whole brain signal, also called cerebrovascular reactivity (CVR)

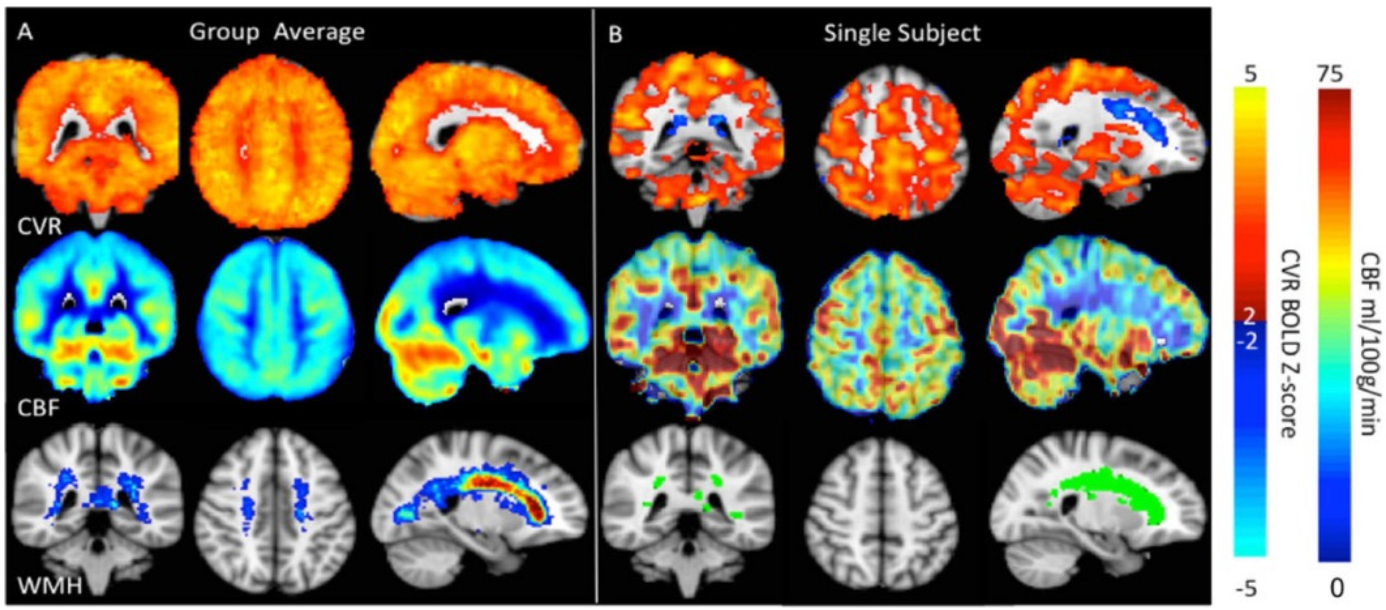


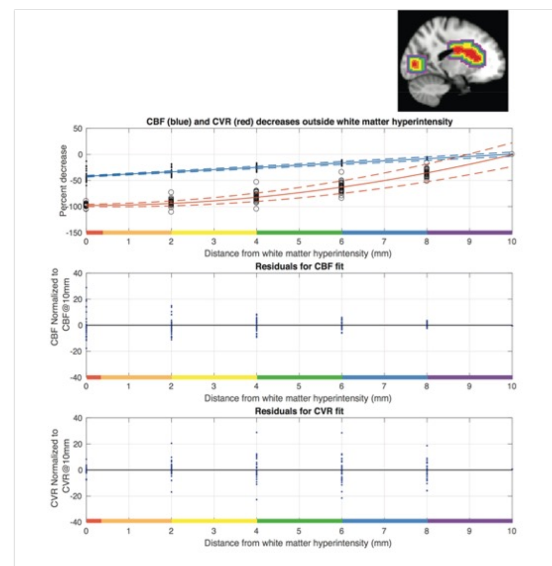
MarkVCID: CVR adds to the predictive power to evaluate cognition after controlling for age, sex, education, and site.

Ni, Ling et al. "Lower Cerebrovascular Reactivity Contributed to White Matter Hyperintensity-Related Cognitive Impairm A Resting-State Functional MRI Study." *Journal of magnetic resonance imaging : JMRI* vol. 53,3 (2021): 703-711.

Liu, Peiying et al. "Multi-vendor and multisite evaluation of cerebrovascular reactivity mapping using hypercapnia challenge." *NeuroImage* vol. 245 (2021): 118754.

CBF is reduced by 50% in the WMH
CVR is almost (100%) exhausted in the WMH



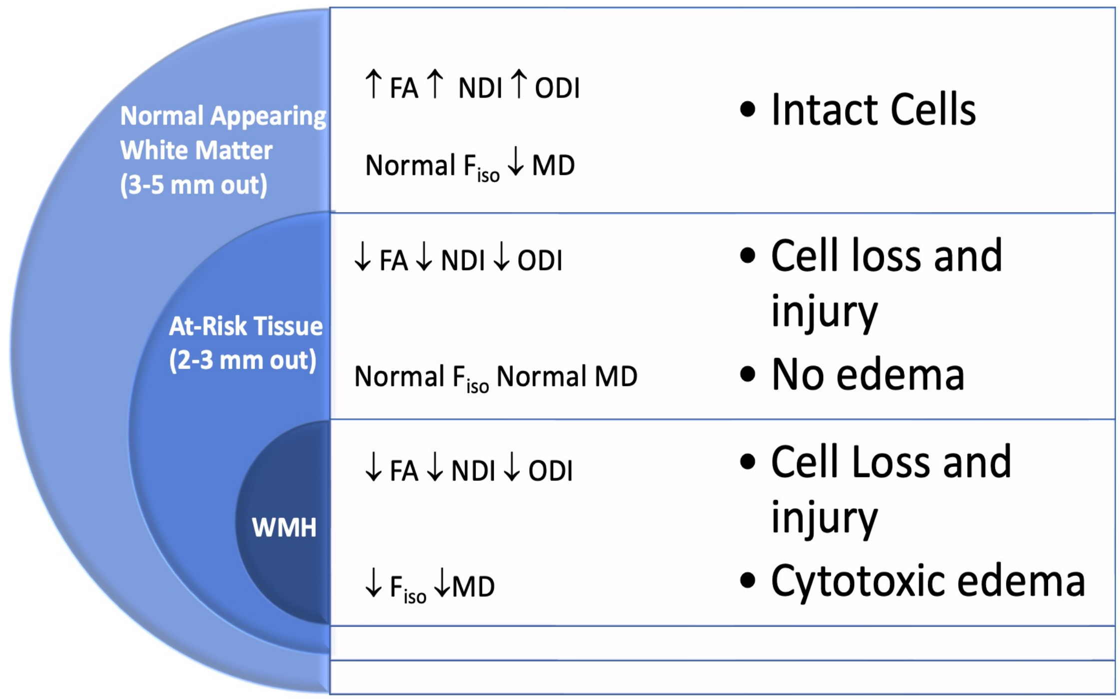


Rane S, Koh N, Boord P, Madhyastha T, Askren MK, Jayadev S, Cholerton B, Larson E, Grabowski TJ. Quantitative cerebrovascular pathology in a community-based cohort of older adults. Neurobiology of aging. 2018 May 1;65:77-85.

Imaging white matter injury and tract disruption

Diffusion tensor imaging

- Understand tissue microstructure
- Parametrized as fractional anisotropy (FA) or apparent diffusion coefficient (ADC)
- Can use multi-shell DTI and biophysical modeling to better characterize tissue (NODDI/DKI/DSI)
- Generic: Could mean demyelination, axon injury/rarefaction, edema,

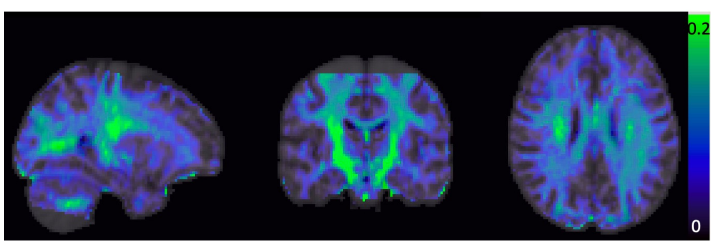


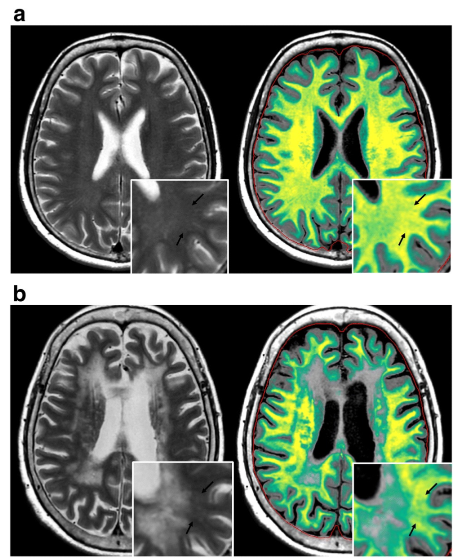
Sudhakar T et al., AAIC 2023

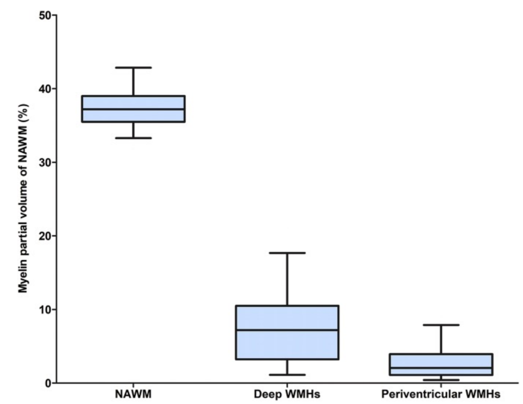
Imaging white matter injury and tract disruption

Myelin water fraction imaging

- Multi-echo acquisition
- Short T2 times (10–40 ms) are correlated with myelin water
- Intermediate T2 times (40–200 ms) as intra- and extracellular water
- longer T2 relaxation times (>1s) as free water



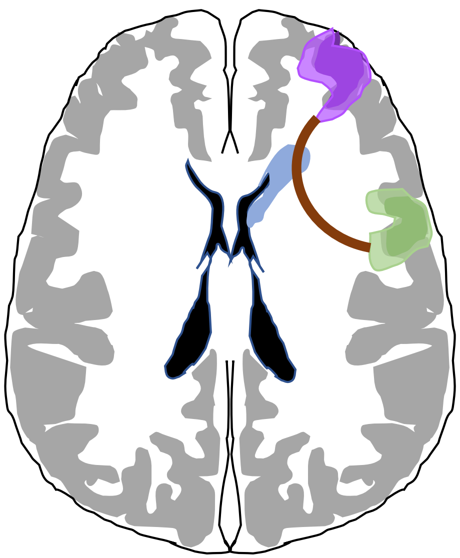


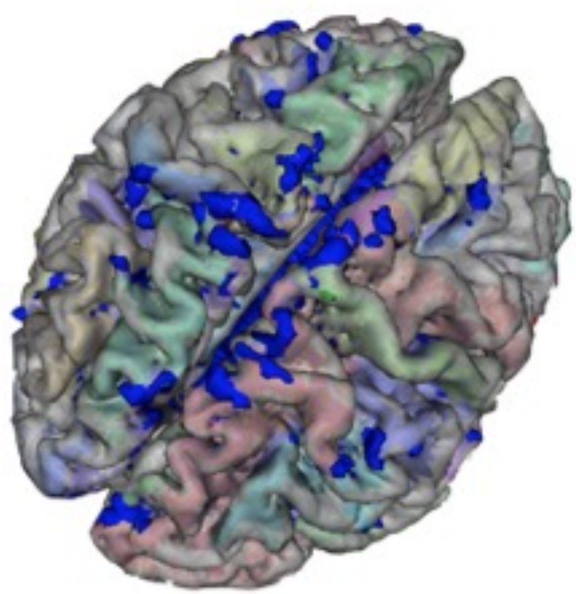


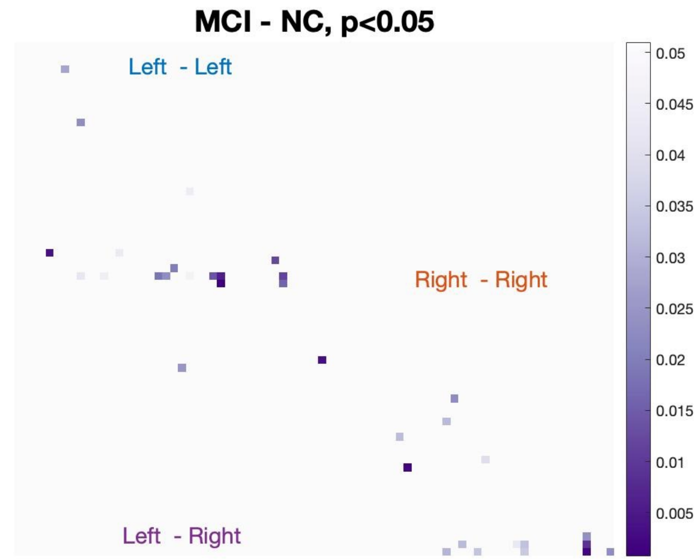
Park, Mina et al. “Myelin loss in white matter hyperintensities and normal-appearing white matter of cognitively impaired patients: a quantitative synthetic magnetic resonance imaging study.” *European radiology* vol. 29,9 (2019): 4914-4921.

Meyers, Sandra M et al. “Simultaneous measurement of total water content and myelin water fraction i[illegible] at 3T using a T_2 relaxation based method.” *Magnetic resonance imaging* vol. 37 (2017): 187-194.

Multi-modal imaging with increased spatial specificity to WMH pathology



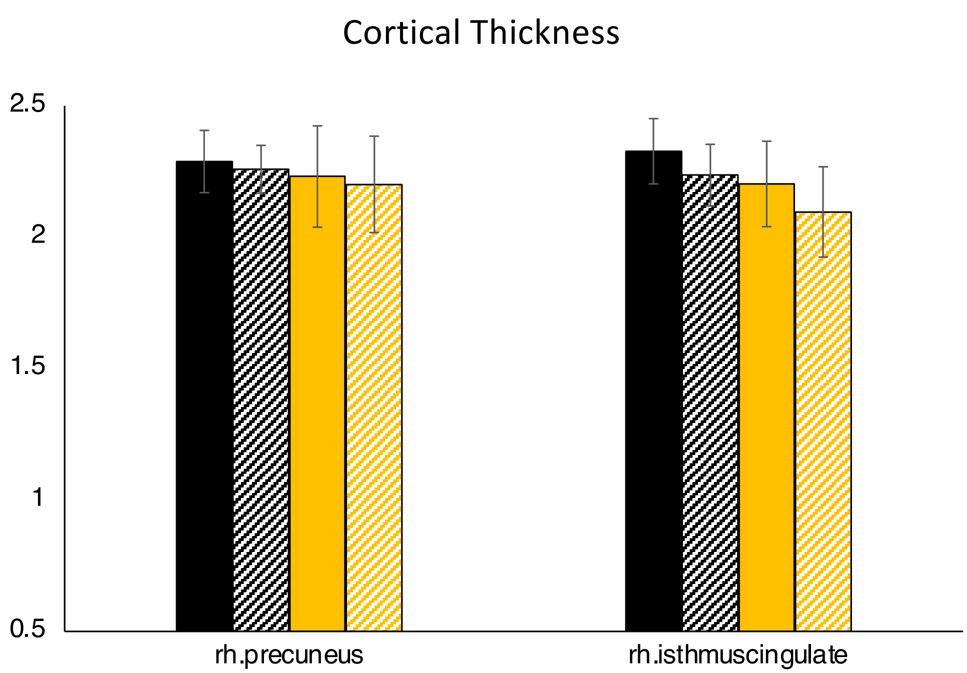


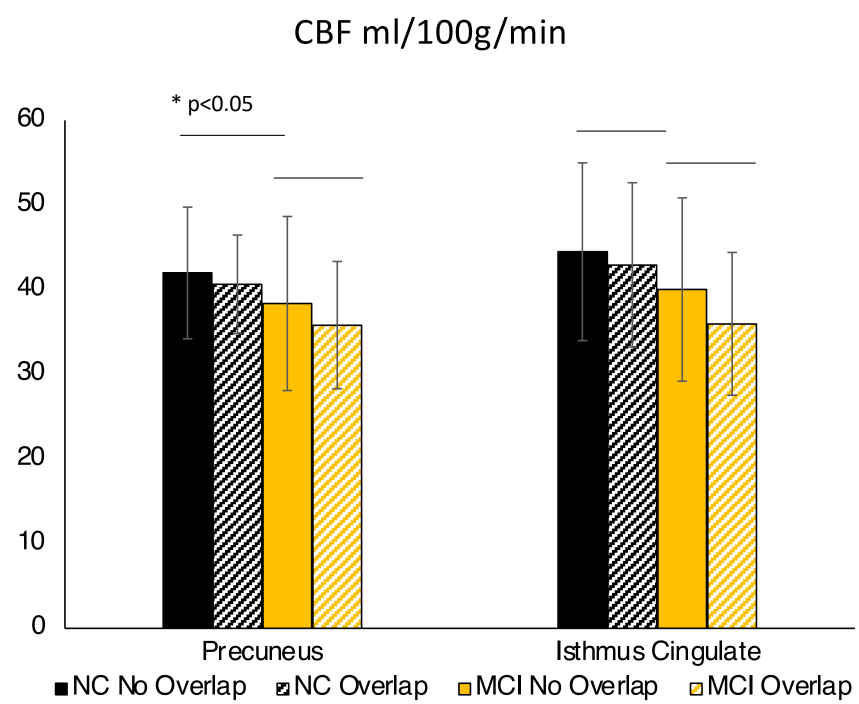


MCI participants showed significantly greater overlap (n = 32, 2.8±1.9%) of these fibers and WMHs than NC (n = 22, 1.1±0.9%).

WMHs affect thirty-five tracts mainly comprising of ipsilateral association, striatal, and thalamic fibers.

Do WMHs represent focal points of Wallerian degeneration along pathways connecting cortical/sub-cortical gray matter?



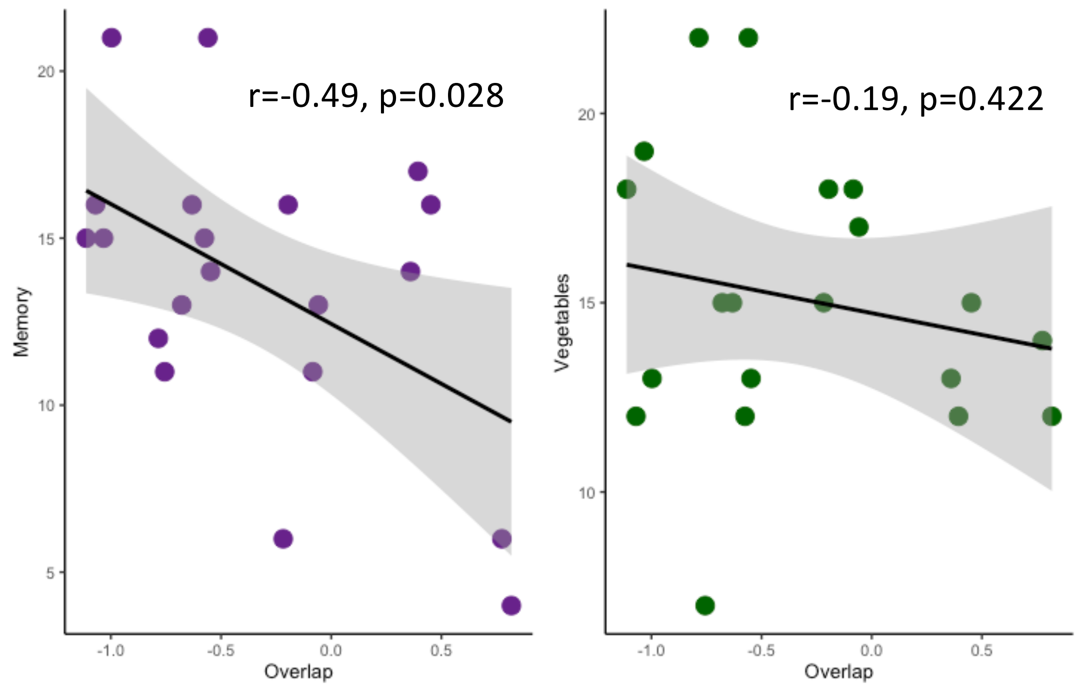


Cortical thickness and perfusion of cortical regions connected with tracts disrupted by WMHs is lower than when the tracts are not disrupted.

WMH tract disruption is associated with specific cognitive symptoms

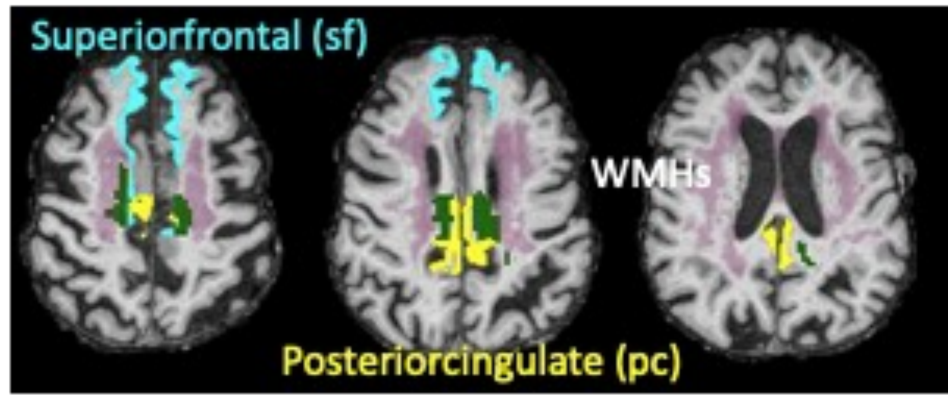
- Precuneus-cingulate track disruption was significantly associated with logical memory scores

- Precuneus-cingulate track disruption was not significantly associated with semantic fluency (vegetables)



WMH tract disruption is associated with specific cognitive symptoms

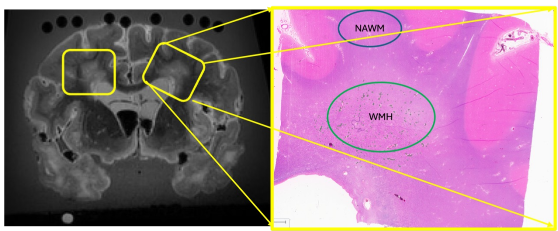
- Anterior-posterior white matter tracts atrophy with age
- More MCI participants have WMHs disruption of this tract
- Target cortical regions have lesser gray matter
- Disruption of this path is associated with lower MMSE score

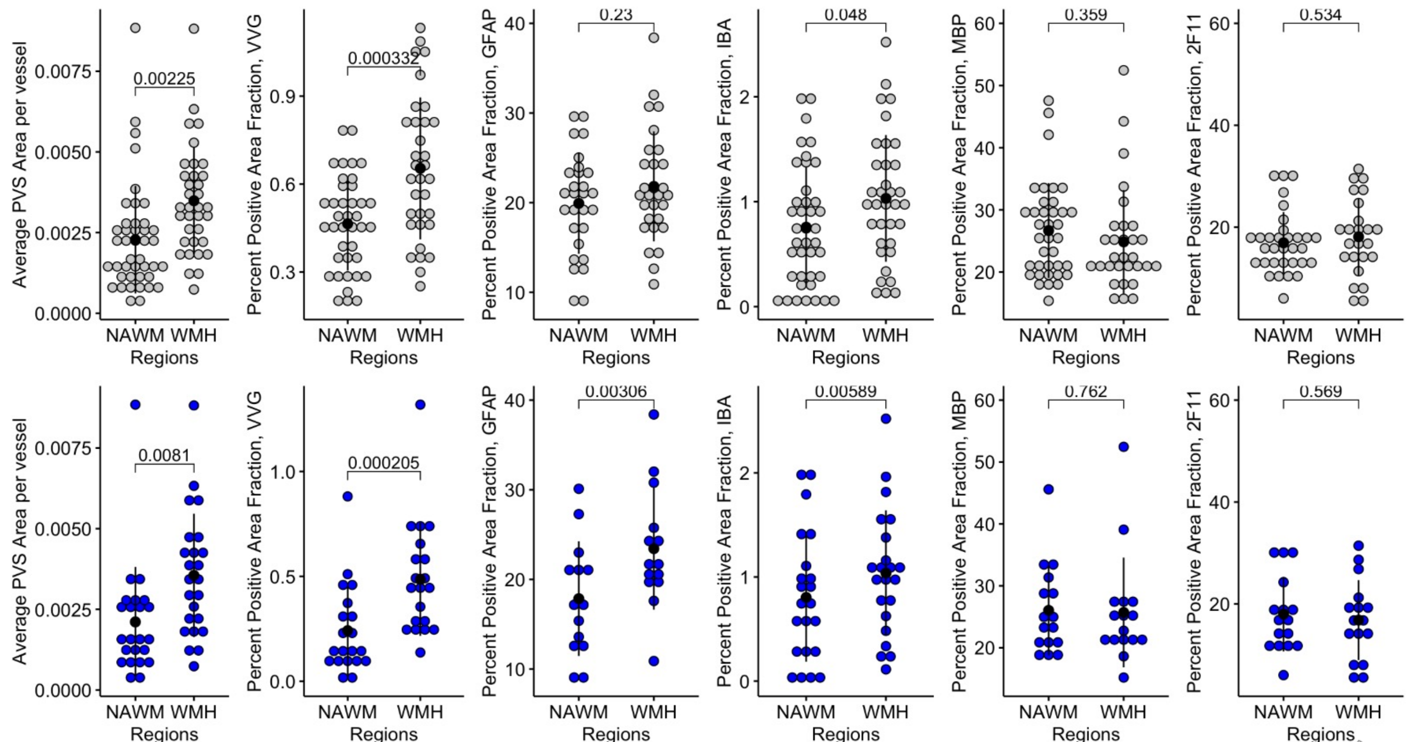


Overlap with WMHs (N)	sf GM%	pc GM%	% MCI	MMSE
No (41)	0.86±0.04	0.89±0.02	36	29±2
Yes (12)	0.84±0.06	0.87±0.05*	58	28±1

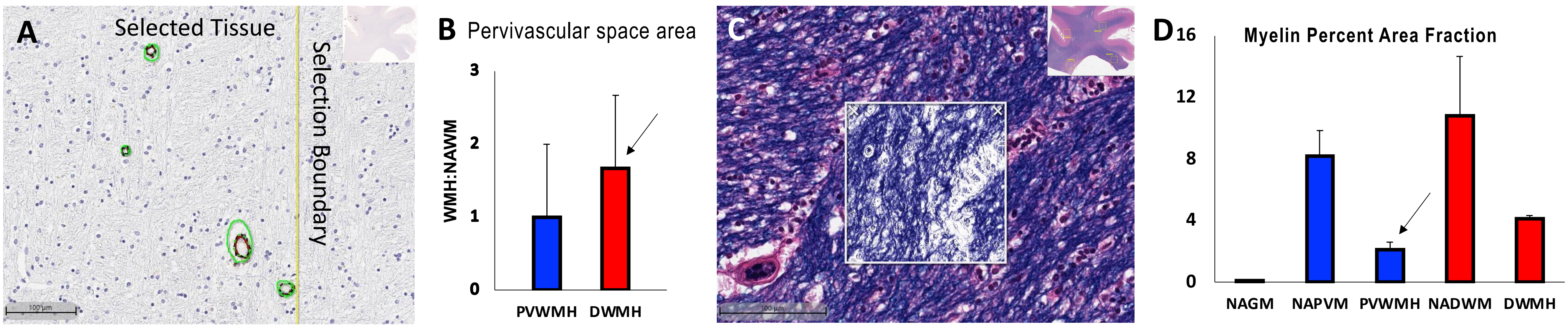
Can we build WMH-based individual cognitive profiles?

Pathological investigations of WMHs





Deep vs. Periventricular WMHs



- Larger enlarged perivascular spaces were observed in deep WMHs than periventricular WMHs
- Greater myelin pallor was observed in periventricular WMHs than deep WMHs

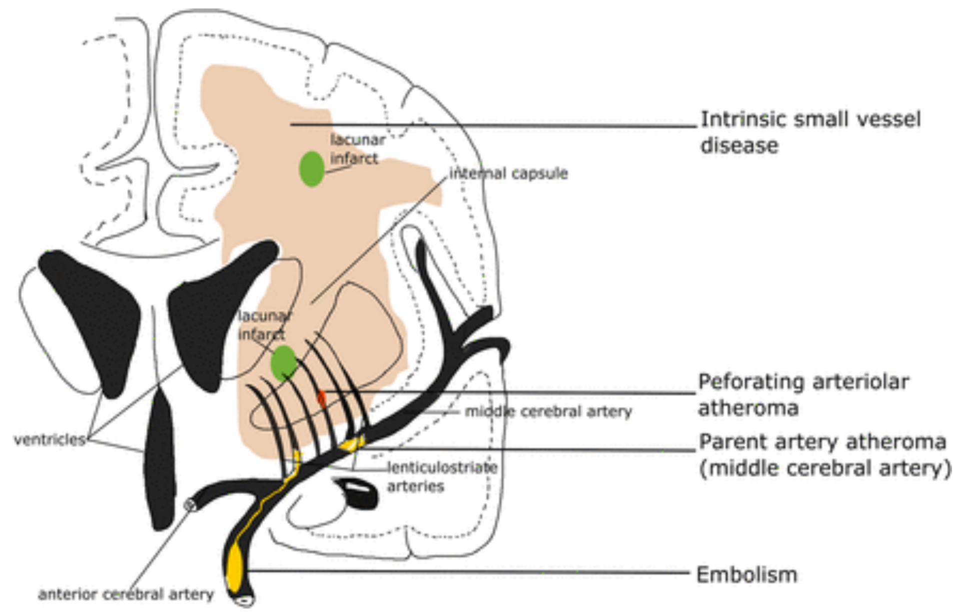

Exciting possibilities

Conclusion

SVD are complex. We need better ways to understand their pathology and their cognitive sequelae

Specifically, we show that

- WMHs overlap with multiple white matter tracts, mostly the ipsilateral association and cortico-striatal tracks
- WMHs could be associated with specific cognitive profiles
- Newer approaches for studying the vasculature have the potential to understand the pathology underlying SVD



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The ACT Study

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