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Incorporating VCID imaging biomarkers in AD/ADRD studies

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10th ISNVD annual meeting, NYC

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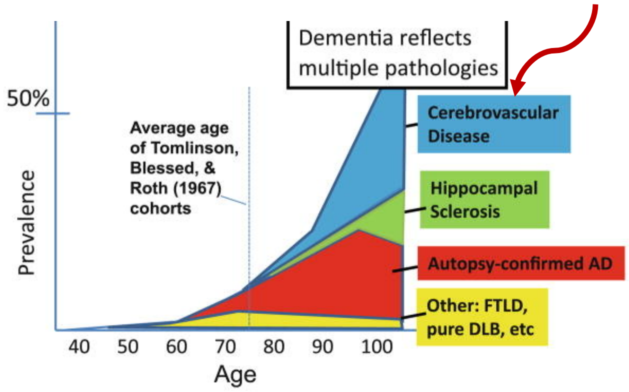
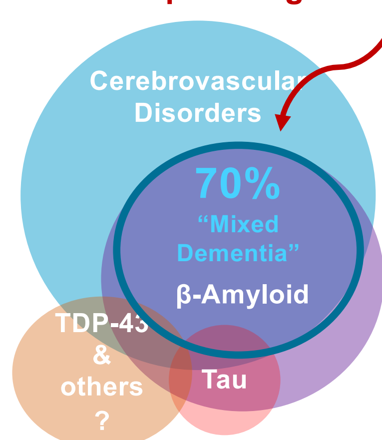
VCID is common

Very Common



Nelson PT et. al. Acta Neuropathol. 2011

Co-exists with other neurodegenerative pathologies



Data from Kapasi et. al. Acta Neuropathol. 2017
Venn Diagram Courtesy: Timothy Hughes, PhD

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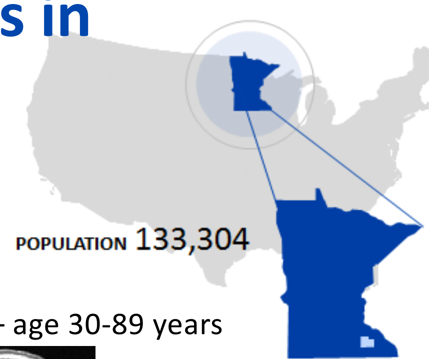
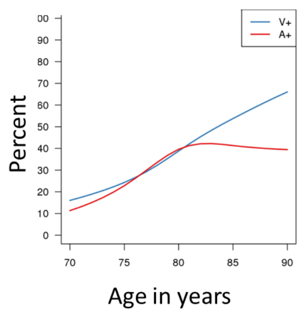
Searching for VCID biomarkers in Mayo Clinic Study of Aging

STUDY OF AGING

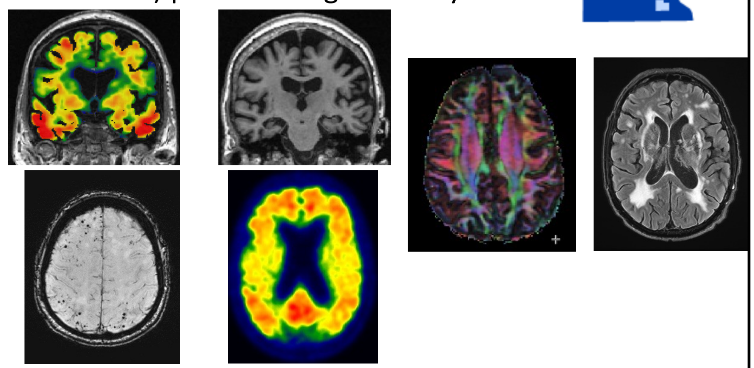


Funded by National Institute of Health, GHR Foundation, Alexander Family Foundation

Population-based study of 5000+ (3200 active) persons – age 30-89 years



Full Spectrum of CVD and AD



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VCID Biomarkers in AD/ADRD studies

- What is available?
- What criteria can be used to narrow the focus?
- Are we there yet ?

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Criteria

1. Ease of acquisition in AD/ADRD studies

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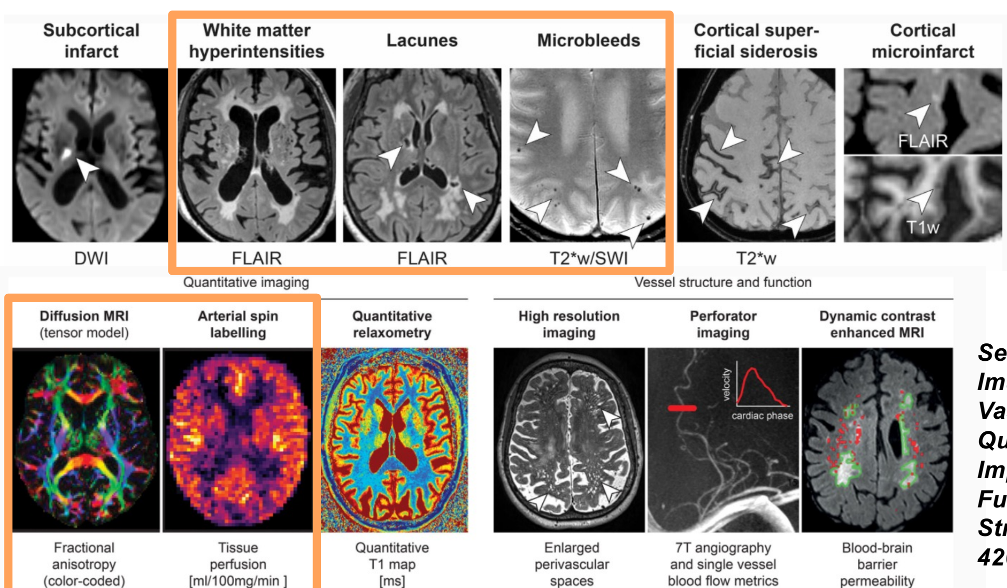
Imaging Markers of VCID



See Review: Imaging Markers of Vascular Brain Health: Quantification, Clinical Implications, and Future Directions; Stroke: 2022;53:416–426.

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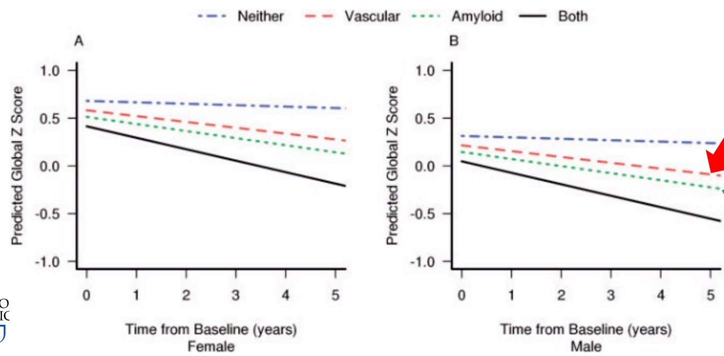
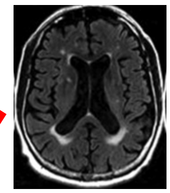
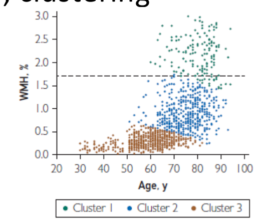
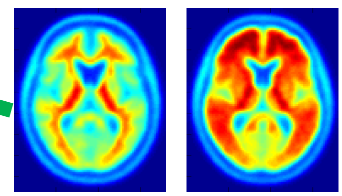
FLAIR MRI Sequence – Starting point

- FLAIR MRI = High WMH and/or infarction (Marchant et. al. NBA 2011)
- Operationalizing a cutoff for white matter hyperintensity burden based on (1) pathological criteria; (2) degree of cognitive impairment; (3) recently, clustering









Vemuri P et. al. Brain 2015

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Criteria

1. Ease of acquisition in AD/ADRD studies
2. Early changes
   - Vascular risk causes brain changes (Werden et. al. Neurology 2017)
   - Structural MRI, Diffusion MRI, ASL acquisitions

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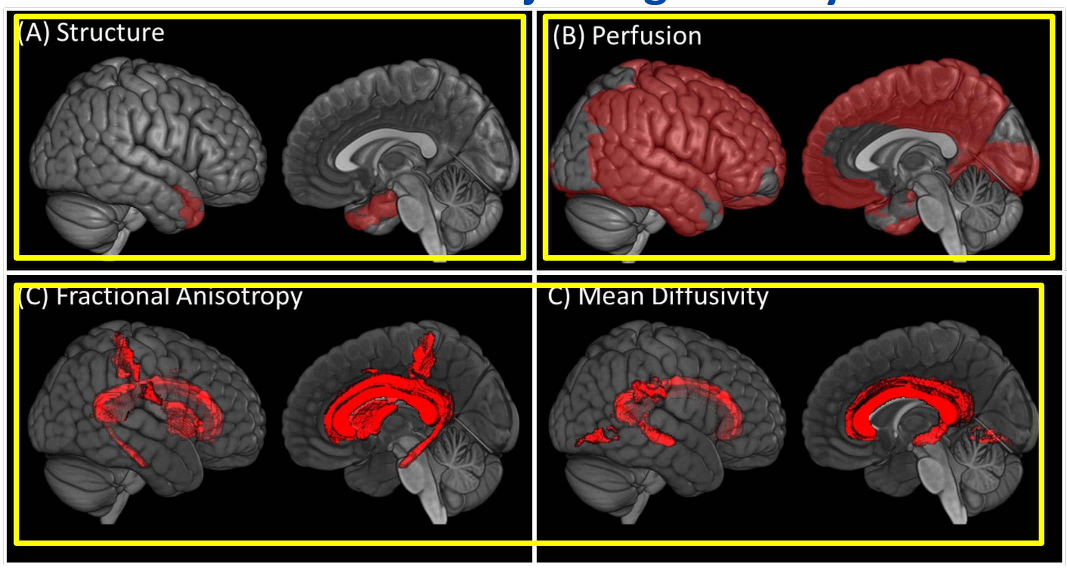
Vascular Risk Factors and Brain

..after adjusting for amyloid and tau



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Vemuri et. al. Annals of Neurology 2018

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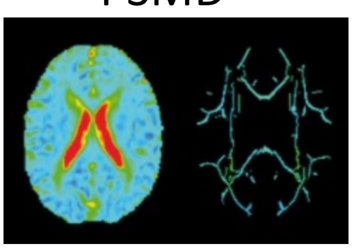
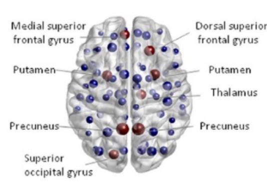
Diffusion MRI: What do we measure ?

PSMD



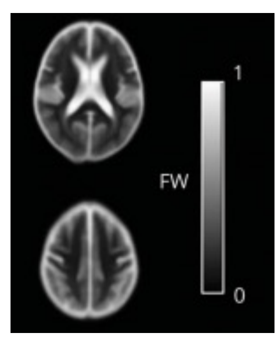
Baykara et. al. 2016

Connectivity



Tuladhar et. al. 2017

Free water



Maillard et. al. 2019

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Criteria

1. Ease of acquisition in AD/ADRD studies
2. Early changes
3. Specific changes (to VCID)

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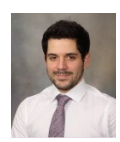
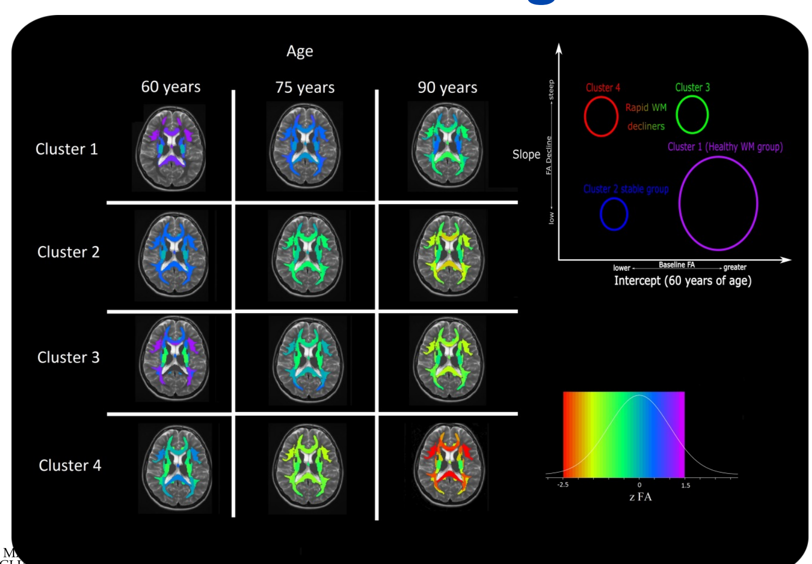
Are all WM changes the same



- Different clusters (healthy WM, fast WM decliners, and intermediate WM group)
- Commissural fibres > association/brainstem fibres
- Three fibres important for cluster assignments
  - genu of corpus callosum, posterior corona radiata and anterior internal capsule

Poulakis, Reid et. al Brain Communications 2020

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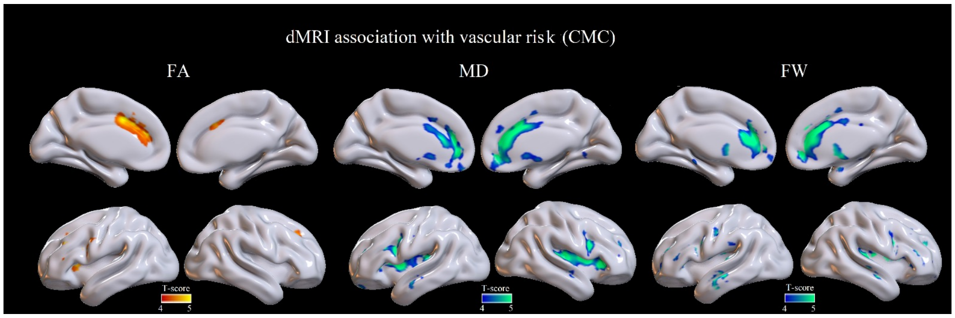
Genu of the Corpus Callosum



Raghavan et. al. To be submitted

- Greater sclerotic changes in the arteries (frontal lobes)
- Late myelinating genu (structure)
- Reproducibility and quantification
- Usefulness in capturing cognitive decline in the population

Vemuri et. al. Annals of Neurology 2018, 2019, Raghavan et. al, NBA 2021

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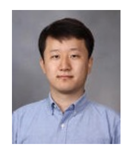
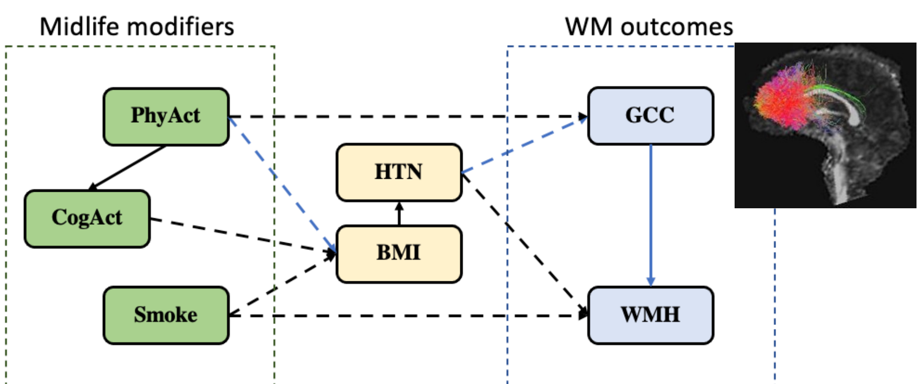
Is it early enough ?



WMH and Intensive blood pressure control intervention ACCORD MIND (de Havenon et. al. Neurology 2019) and SPRINT-MIND Study (JAMA 2019)



Shen et. al. NeuroImage Clinical 2022

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Does it capture CVD pathology?

Strozyk Scale Rubric	
Large infarct	
None	0
1 large infarct	1
>2 large infarcts	2
Lacunar/Cystic infarcts	
None	0
1 lacunar infarct	1
>2 large infarcts	2
Leukoencephalopathy	
None	0
Mild	1
Moderate-to-Severe	2
Total vascular score	(out of 6)

Kalaria cerebrovascular disease scale [5-6]	
Cerebral Cortex (select highest that applies)	
0 Normal appearance of brain, vessels, white matter, and cortex	
1 Mild modification of vessel walls, perivascular spaces, or white matter	
2 Moderate to severe but isolated modification of the vessel (arteriolosclerosis or amyloid angiopathy), usually associated with hemosiderin deposits in the perivascular spaces; and/or Moderate to severe cerebral amyloid angiopathy involving parenchyma	
3 Moderate to severe perivascular space dilatations either in the deep or the juxtacortical white matter	
4 Moderate to severe myelin loss; and/or White matter infarct	
5 Presence of cortical microinfarcts	
6 Presence of large infarcts and/or cystic infarcts	
Basal ganglia (select highest that applies)	
0 Normal appearance	
1 Mild modification of vessel walls or perivascular spaces (or if PVS not noted, but isolated moderate to severe arteriolosclerosis)	
2 Moderate to severe perivascular space dilatations	
3 Presence of microinfarcts	
4 Presence of large infarcts; and/or lacunar infarct	
Kalaria score (Total of cortex and basal ganglia)	(out of 10)

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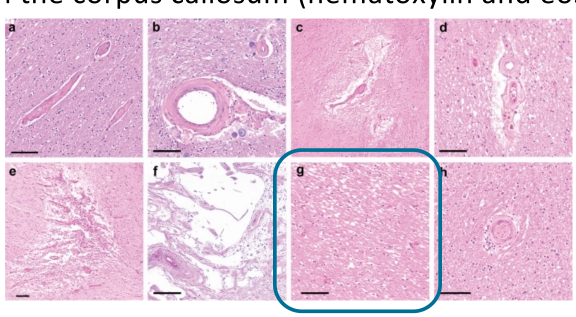
Pathological confirmation

- Genu FA outperformed microbleed counts, infarctions, WMH in predicting CVD neuropathological scales
- Performed slightly better than other global diffusion MRI measures or posterior WM (Cingulum bundle FA)
- Vacuolation in the corpus callosum (hematoxylin and eosin)



Ngyuen et. al. Acta Neuropathologic 2022

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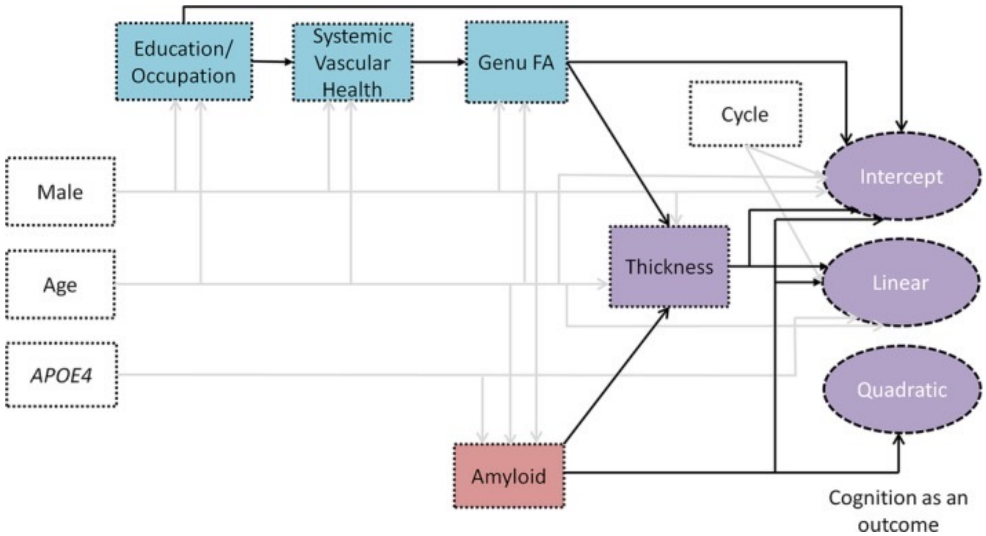
Modeling the multifactorial process – predicting future brain atrophy and cognitive impairment



Vemuri et. al. Annals of Neurology 2019

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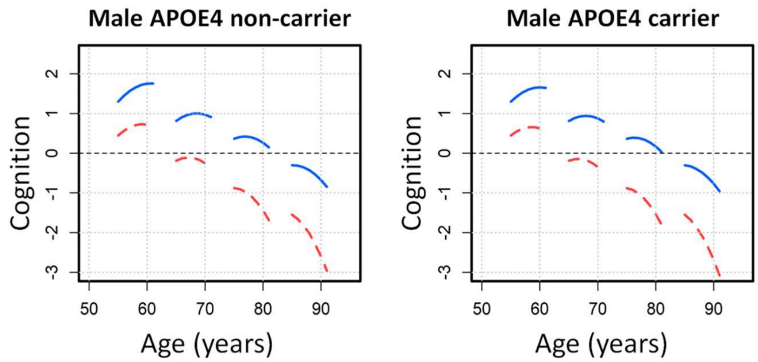
Multiple pathways to cognitive impairment



		Age in years (by decade)			
		50-60	60-70	70-80	80-90
Education/Occupation	Low	11.12	11.08	9.71	9.71
	High	14.63	15.32	15.28	15.32
Amyloid (SUVR)	Low	1.22	1.27	1.30	1.31
	High	1.32	1.42	1.71	2.02
Genu FA	Low	0.60	0.59	0.55	0.52
	High	0.66	0.65	0.63	0.60

Vemuri et. al. Annals of Neurology 2019

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Are we there yet ?

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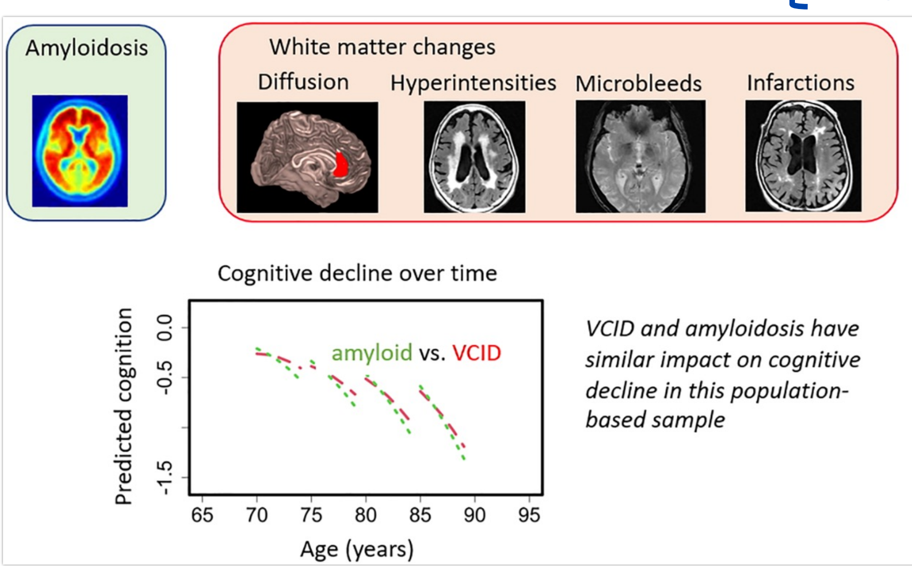
Why not use all information

Diffusion MRI
FLAIR
T2 GRE*



- Primary Principle Component – WMH + Genu FA
- Smaller contribution from microbleeds

Vemuri et. al. Brain Communications 2021

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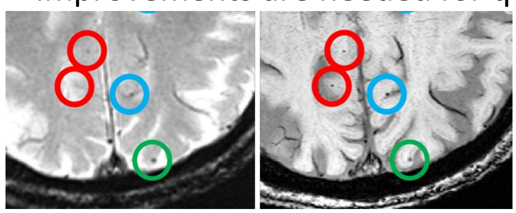
Improving our tool kit

- Genu + WMH – best predictor (early + late)

To be submitted – Raghavan et. al. 2022 – Sample size estimates for a hypothetical VCID trial						
	50% change at 80% power			25% change at 80% power		
	All	Low Vascular Risk	High Vascular Risk	All	Low Vascular Risk	High Vascular Risk
Genu-FA	328	377	298	1308	1504	1187
WMH	209	272	175	830	1085	694
Genu+WMH	169	264	129	672	1053	510

- Microbleeds – improvements are needed for quantification



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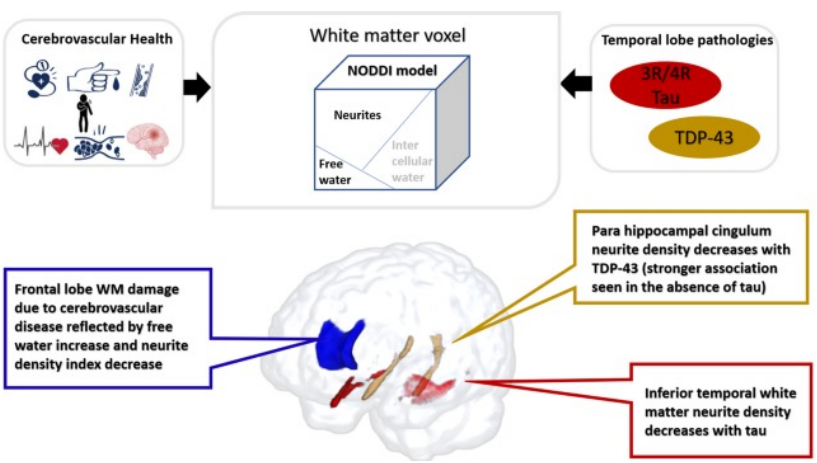
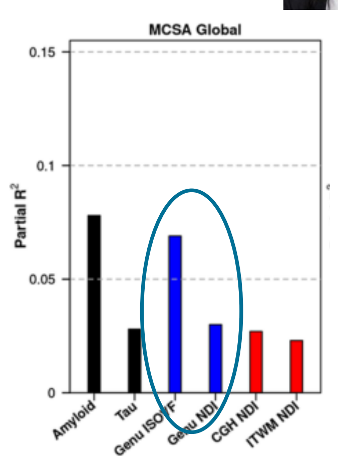
Applying better biophysical models





Raghavan et. al. Brain Comm 2022
Raghavan et. al. Acta Neuropathologica Comm 2022

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Take home points

- Regional dMRI markers capture early systemic vascular risk related changes, specific to CVD, and predictive of future WMH, brain atrophy, cognitive decline
- Combination scores (dMRI + FLAIR) are suitable as VCID biomarkers
- Improving our tool kits to provide repeatable and reproducible VCID marker(s) across different populations

We are almost there !

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Mayo Clinic Study of Aging
Mayo ADRC

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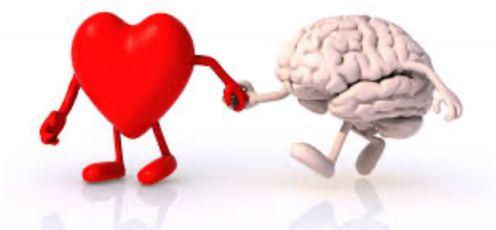
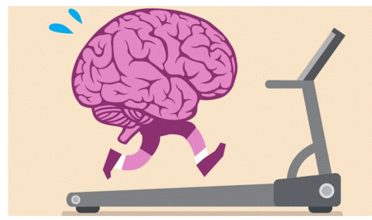
Thank you !





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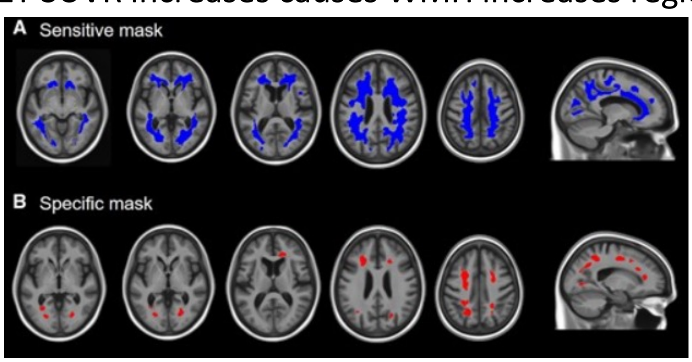
Specificity of WMH

- WMH and AD pathologies (Lee et al. Annals of Neuro 2016, McAleese et. al. 2017 Acta Neuropathol, van Westen et. al. 2016 Scientific Reports)
- Amyloid PET SUVR increases causes WMH increases regionally



Graff-Radford et. al. Brain 2019

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