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Amyloid independent effects of vascular health on brain

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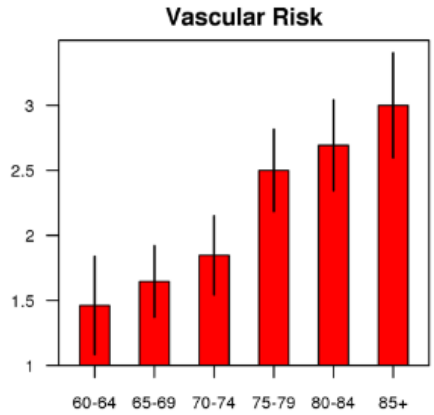
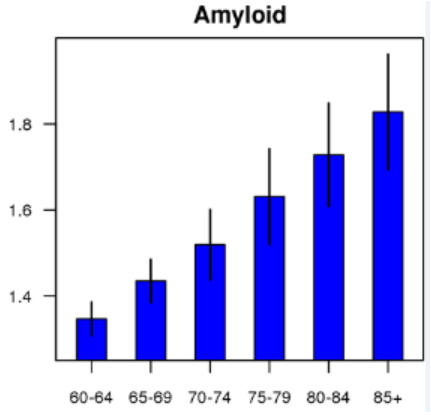
MCI Symposium 2019
Miami, FL





Age

Vascular Disease

Alzheimer's (Aβ and tau)

Neurodegeneration

Cognitive Decline

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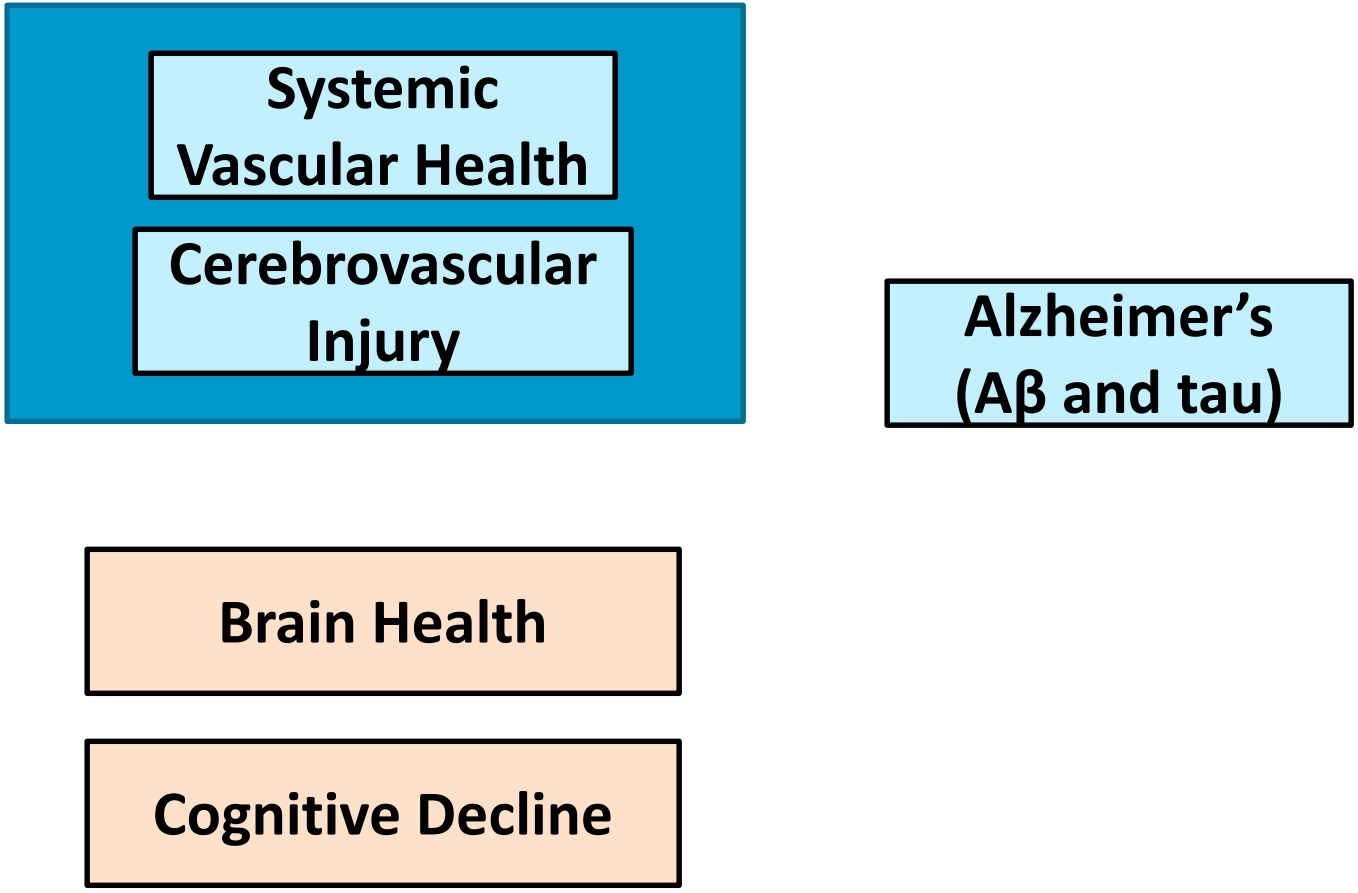

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The role of cerebrovascular disease in the elderly both as a stand-alone etiology and as a co-existing pathology along with other dementias

Overview

- Evidence for amyloid negative cerebrovascular brain injury
- Systemic vascular health and AD biomarkers
- Systemic vascular health and brain health
  - Prodromal cerebrovascular disease marker

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Mayo Clinic Study of Aging

Olmsted County, MN, USA
PI: Walter Rocca, M.D.

MCSA - Mayo Clinic Study of Aging
PI: Ron Petersen M.D., Ph.D.

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

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

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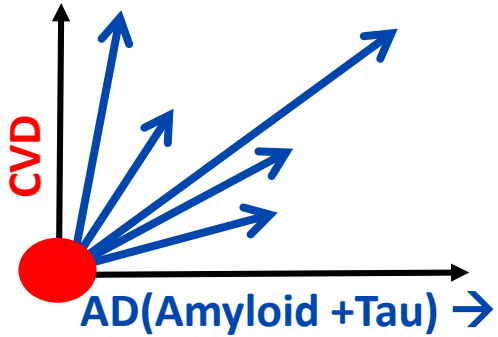
Systemic Vascular Health

1. Heterogeneity in Cognitive Aging



2. U.S. Department of Health and Human Services 2010 Chronic Conditions Definitions – 7 cardiovascular and metabolic conditions (CMC)

Hypertension, hyperlipidemia, cardiac arrhythmias, coronary artery disease, congestive heart failure, diabetes mellitus, and stroke

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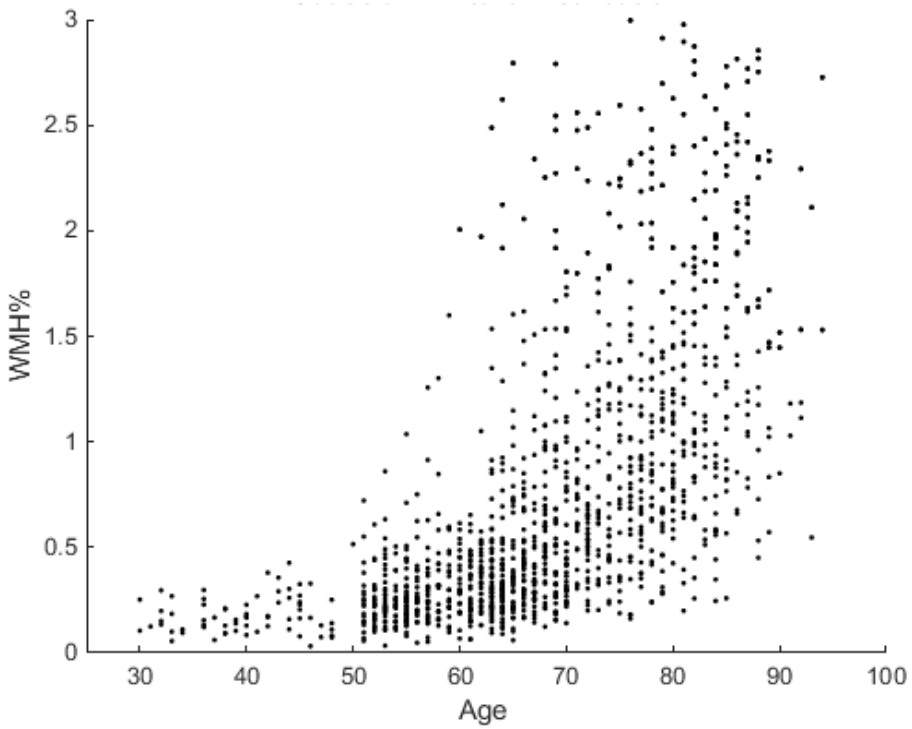
Cerebrovascular Injury: FLAIR images



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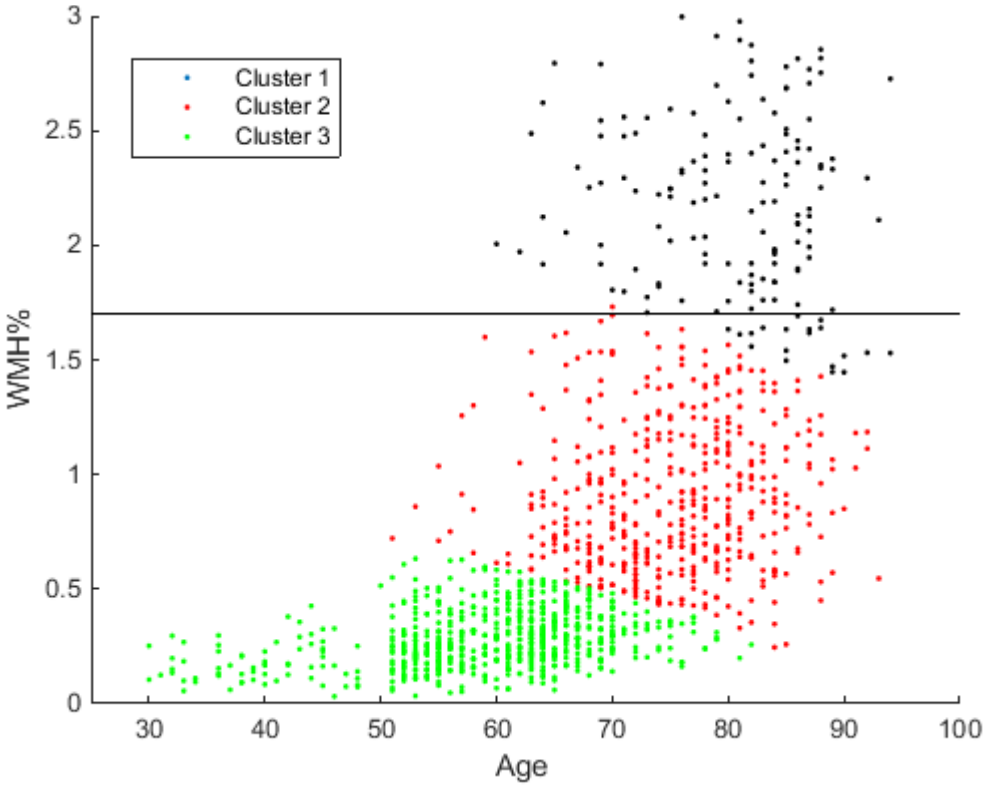

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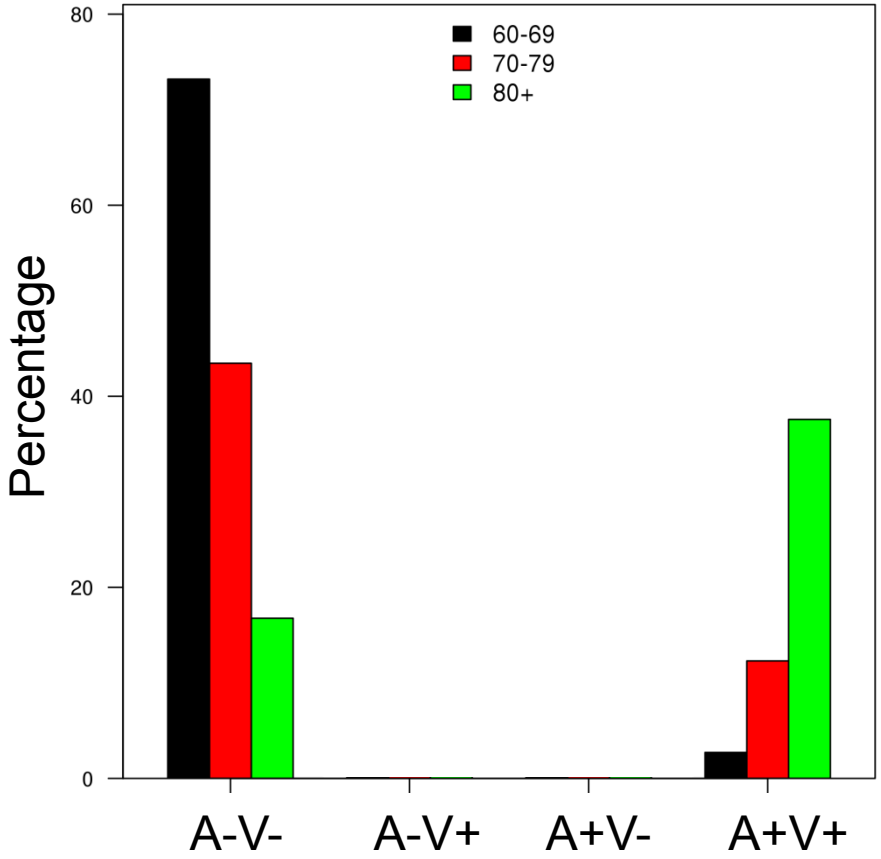
Frequency of Cerebrovascular Disease

60-69 (n = 515)
70-79 (n = 382)
80+ (n = 322)



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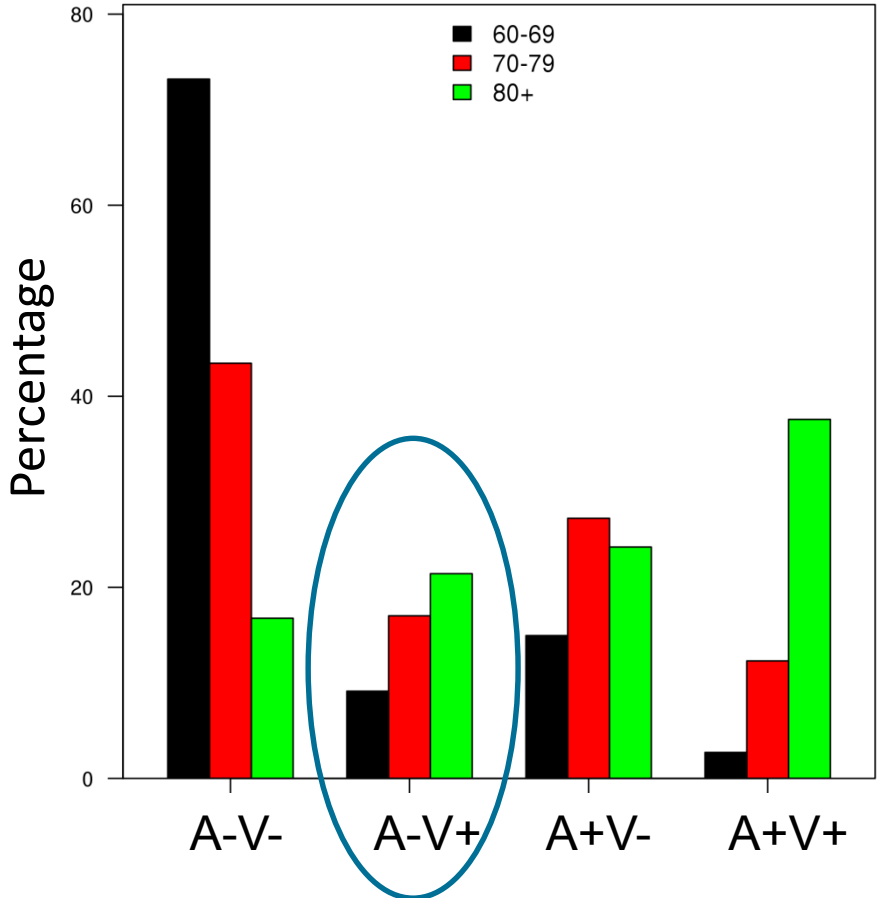

Evidence for cerebrovascular injury in the absence of amyloidosis

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Overview

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Vascular Health and Amyloid
(n=942 and ages 70-90+)

	P-values	AMYLOID EFFECTS		NEURODEGENERATION	
Midlife risk factors					
Physical inactivity	.13	−0.004 (0.01)	.58	−0.01 (0.01)	.04
Obesity	<.001	−0.03 (0.07)	.66	−0.27 (0.06)	<.001
Ever smoked	.01	0.05 (0.06)	.40	−0.15 (0.06)	.01
Diabetes	.01	0.17 (0.13)	.17	−0.28 (0.12)	.02
Hypertension	.11	−0.01 (0.07)	.87	−0.13 (0.06)	.04
Dyslipidemia	.01	−0.18 (0.07)	.01	−0.12 (0.06)	.06
Late life chronic conditions					
Cardiovascular and metabolic conditions	<.001	0.01 (0.02)	.79	−0.09 (0.02)	<.001

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Vascular Health and ATN Framework
(n=340 and ages ≥ 60 years)

	Biomarker	CMC -	CMC +	P-value	Cohen's D
A	PIB Ratio, SUVr	1.47 (0.32)	1.60 (0.45)	0.71	0.048
T	TAU ERC Ratio, SUVr	1.08 (0.12)	1.14 (0.18)	0.36	0.12
N	FDG PET, SUVr	1.61 (0.18)	1.51 (0.14)	0.002	0.46
N	MRI (AD Sig), mm	2.92 (0.14)	2.81 (0.19)	0.050	0.256

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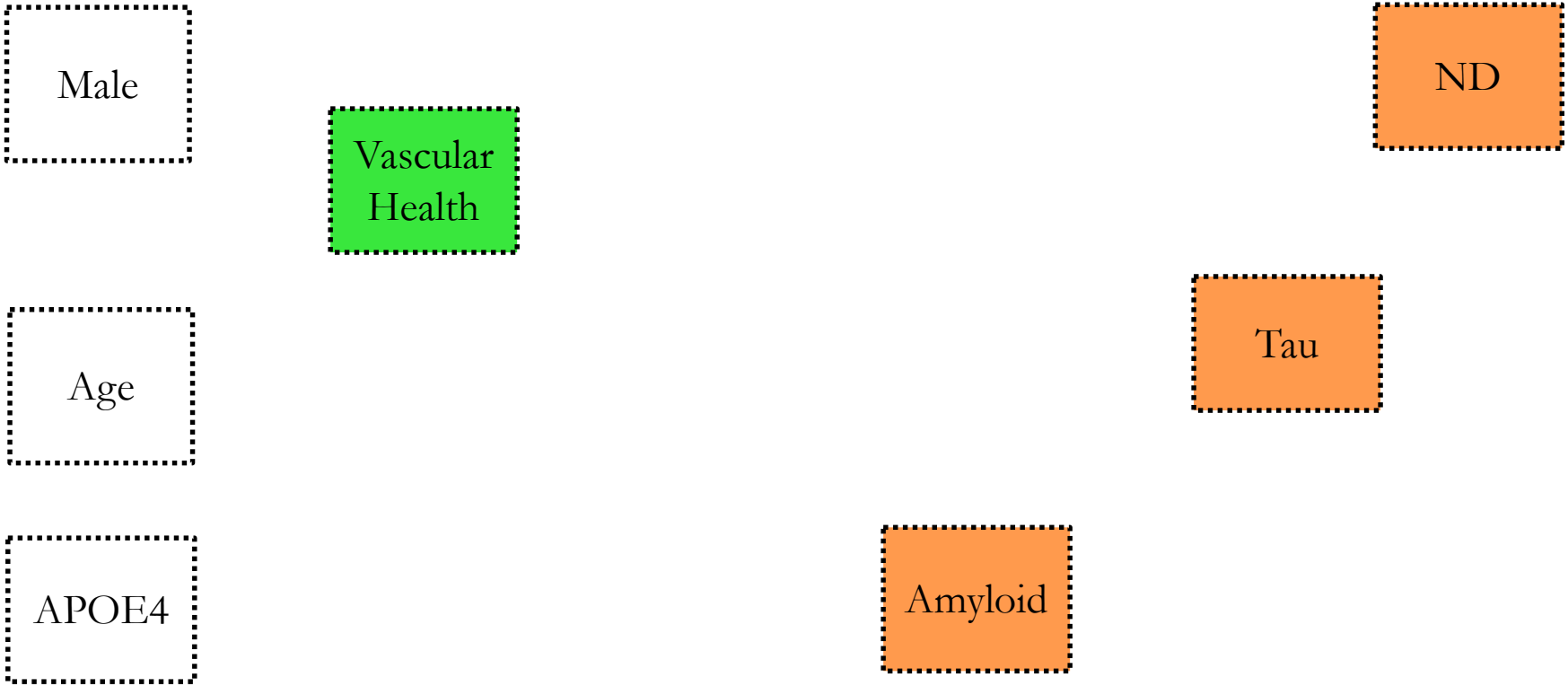
Vascular Health and ATN Framework
(n=340 and ages ≥ 60 years)



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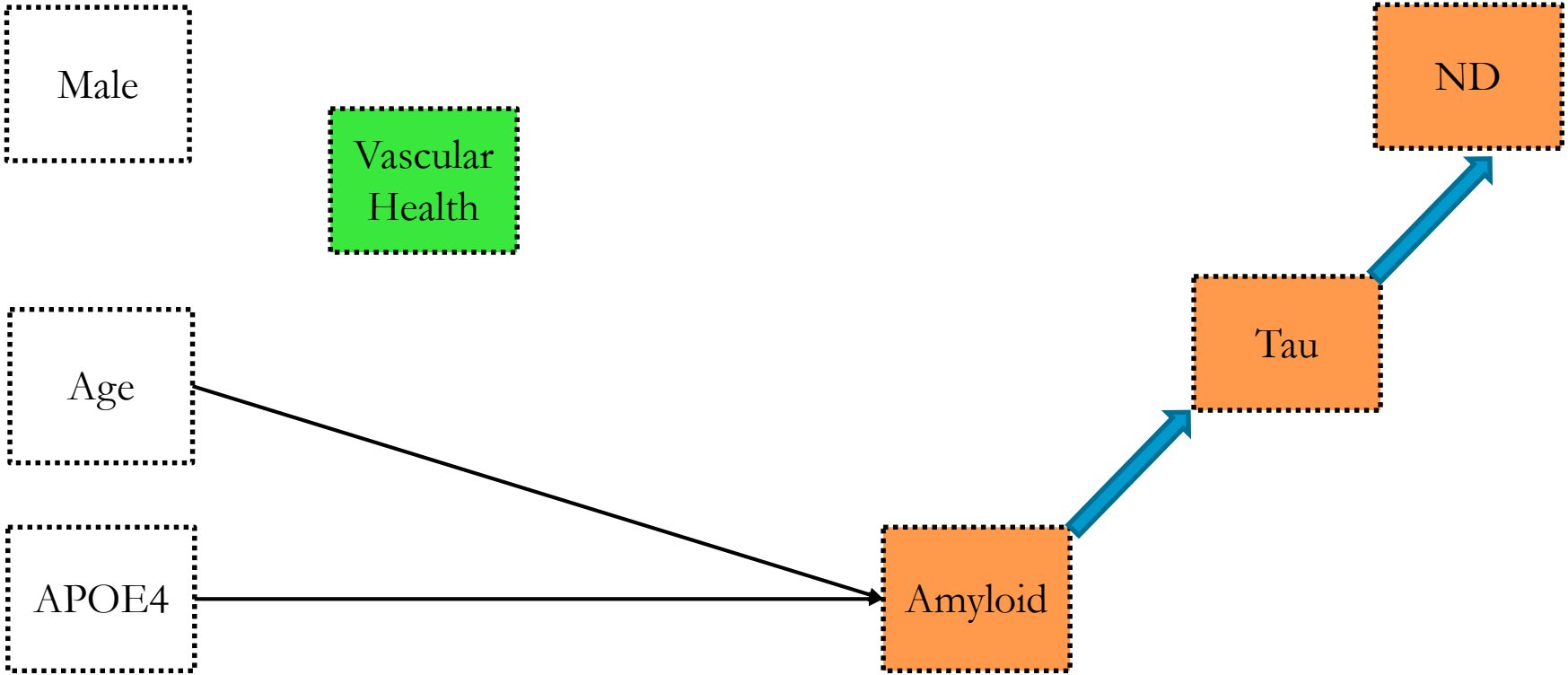
Vascular Health and ATN Framework



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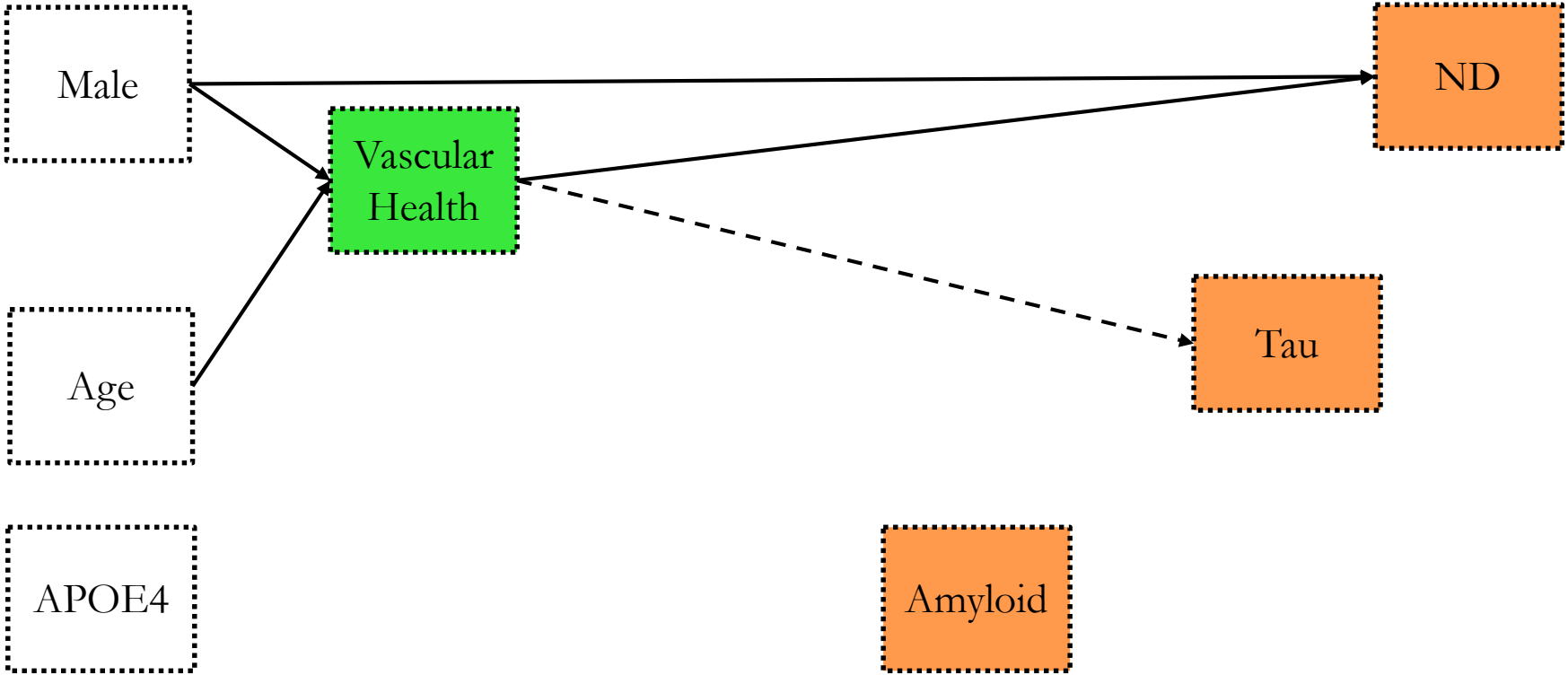
Vascular Health and ATN Framework



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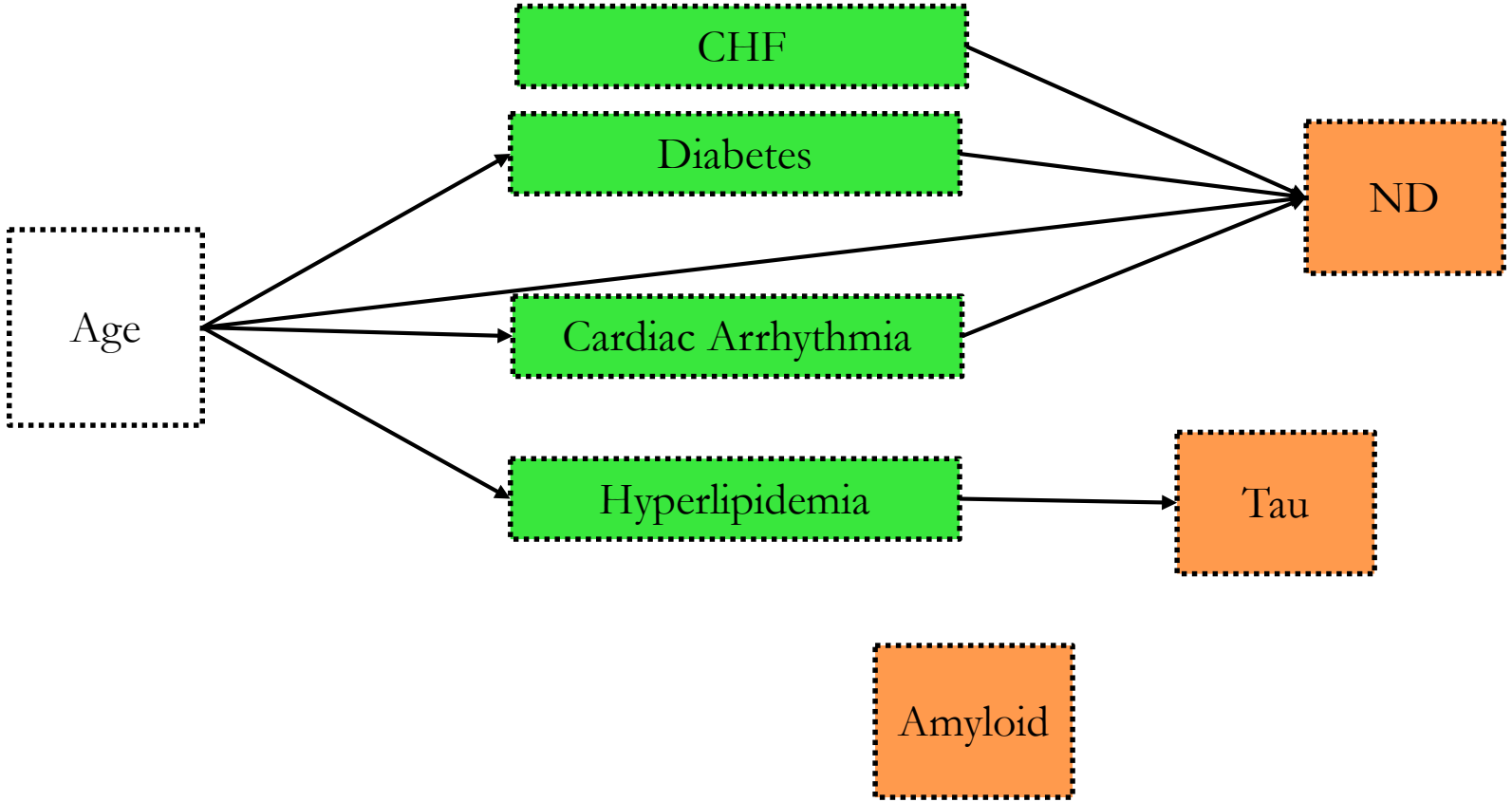
Vascular Health and ATN Framework



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Prodromal Cerebrovascular Disease Changes

- Brain changes precede the appearance of overt brain lesions – Prodromal changes

  (Werden, 2017; Maillard, 2013)

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Systemic Vascular Health and Brain Health

..after adjusting for amyloid and tau

Quantify early cerebrovascular health related MRI brain measures (n=390; ages ≥ 60 years) based on associations with vascular health

- Structure (Structural MRI)
- Perfusion (Arterial Spin Labeling)
- Microstructural integrity (Diffusion Tensor Imaging)

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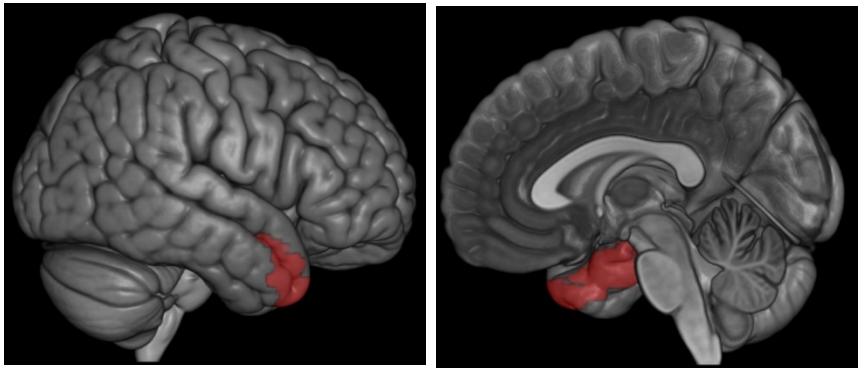
Vascular health and Structural MRI



Specific to vascular health after adjusting for AD as well as A-T- elderly

Worsening vascular health=accelerated aging

(Fjell 2014; Knopman, 2015;Guzman, 2013;Villeneuve, 2014;Werden, 2017)

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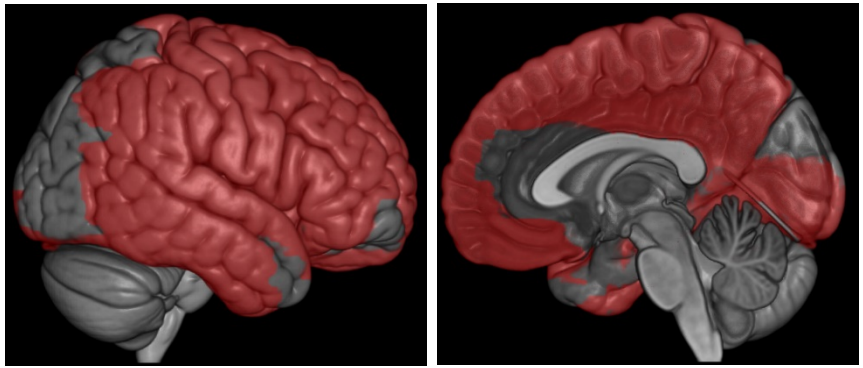
Vascular health and Perfusion



Functional and morphological alterations to the cerebral blood vessels

Widespread cerebral hypoperfusion

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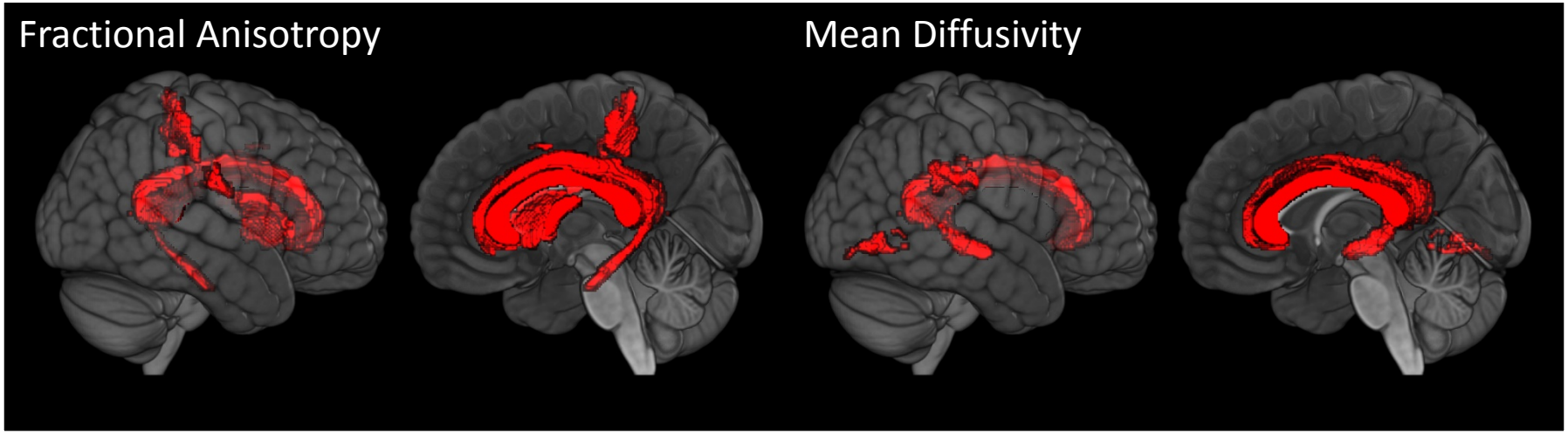
Vascular health and Diffusion



Microstructural organization of the white matter tracts

Corpus Callosum – Hypertension (Maillard 2012; Gons 2012; McEvoy, 2015), Diabetes (Tan, 2016; Reijmer, 2013), Hyperlipidemia (Maillard, 2015), and Obesity (Stanek, 2011;Bettcher, 2013)

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Ideal Cerebrovascular Disease Biomarker

Regional independence – Capture brain changes that manifest in regions not affected by AD

Low measurement variability – Low measurement variability (acquisition) to enable greater reproducibility

Sensitivity – Even in the absence of infarctions and AD pathologies

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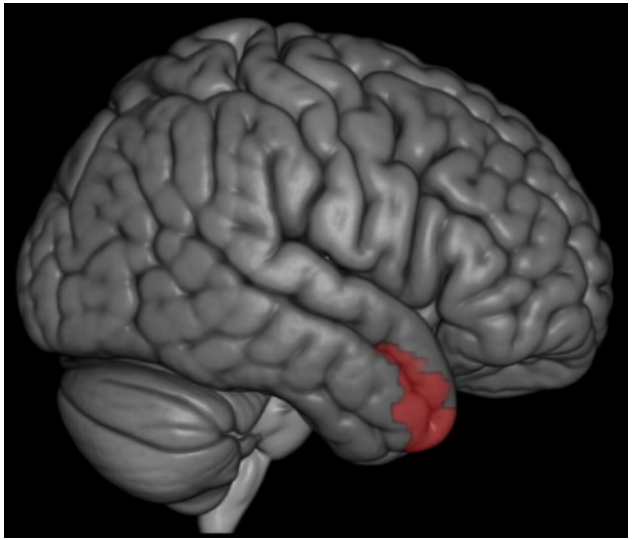
Ideal Cerebrovascular Disease Biomarker

Regional independence and sMRI



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Ideal Cerebrovascular Disease Biomarker

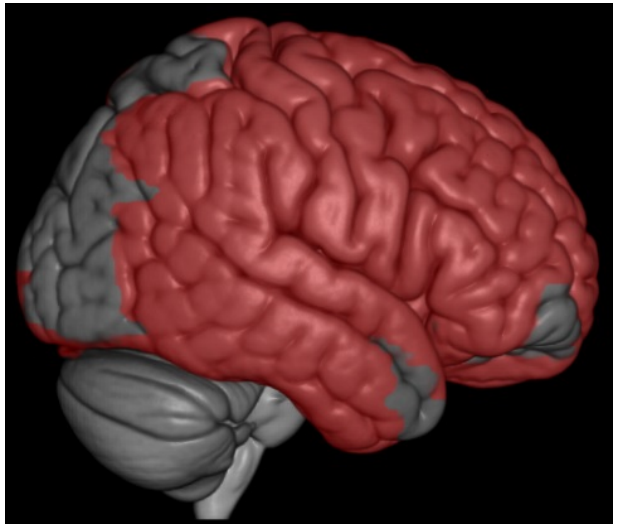
Measurement variability and ASL

Low acquisition SNR

Prolonged transit times

CV of perfusion measure was 0.130 vs.

CV of DTI measure was 0.062



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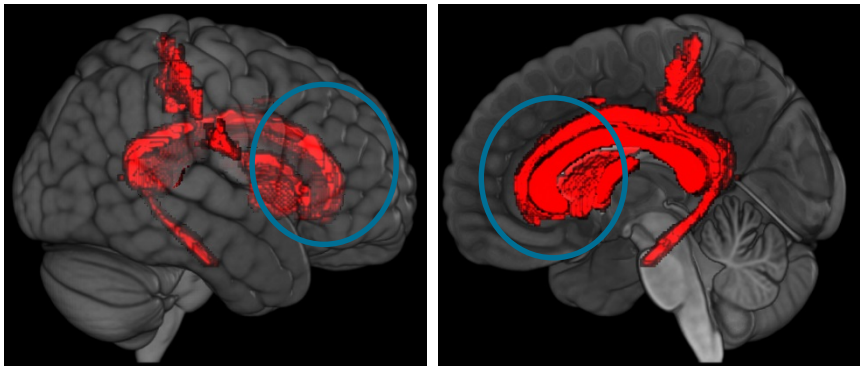
Ideal Cerebrovascular Disease Biomarker

DTI properties

Low measurement variability

Regional independence

Sensitivity of the marker in A-T-



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Cerebrovascular Disease Biomarker

Anterior part (genu) of the corpus callosum

- small diameter or thin fibers
- frontal lobes – greater susceptibility to age and cerebrovascular disease changes
- convergence point

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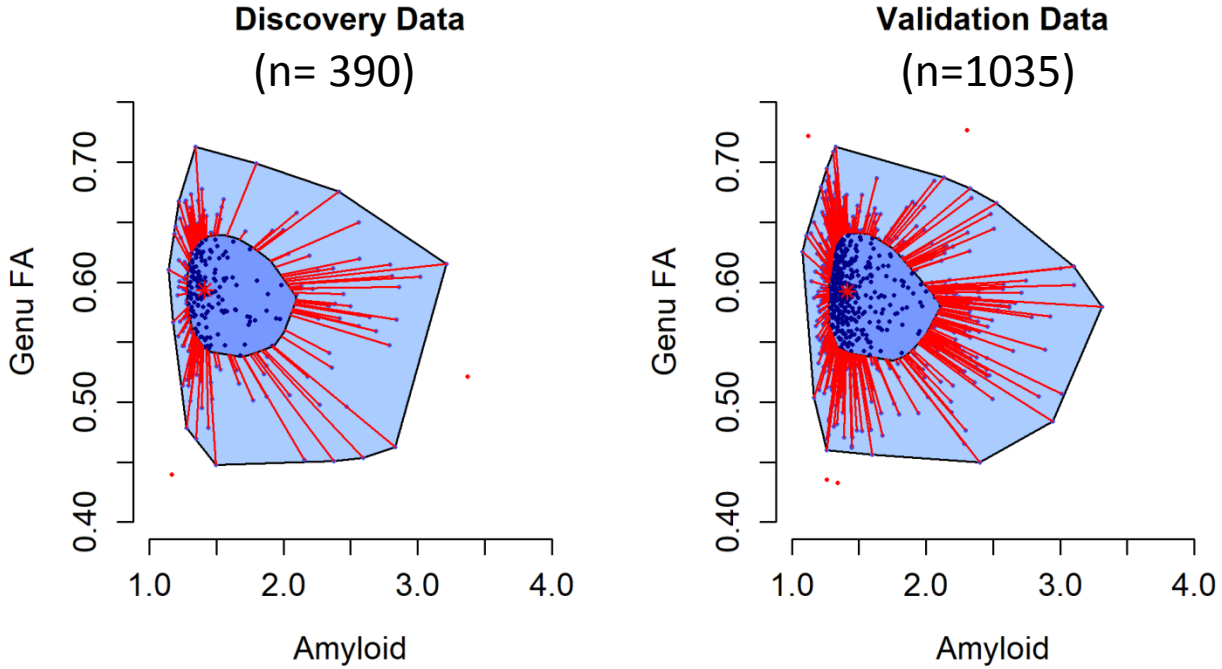
Genu FA as a cerebrovascular biomarker



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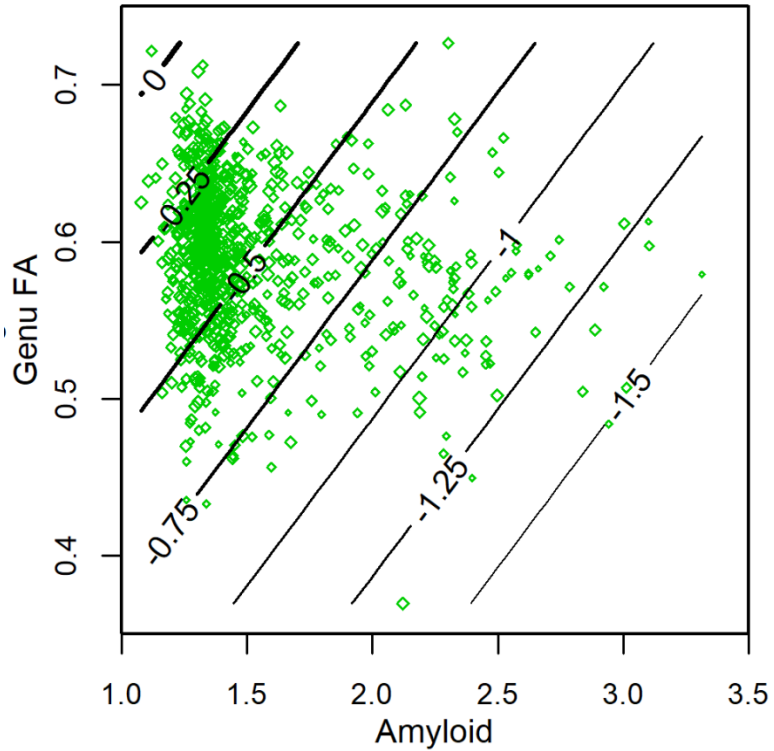
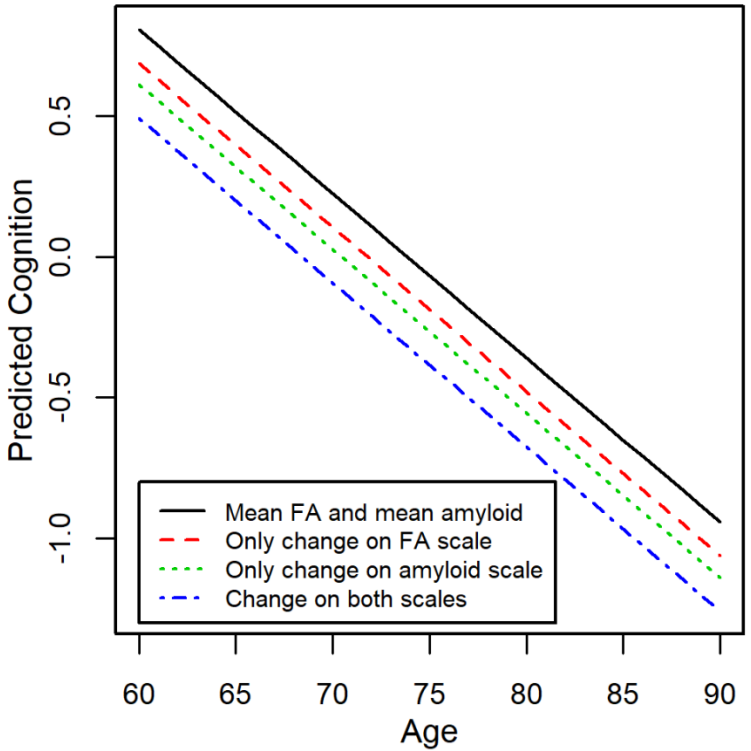
Utility of genu FA as a biomarker





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Summary

- Evidence for amyloid negative cerebrovascular brain injury
  - Amyloid independent effects of vascular health
- Vascular health had quantifiably greater impact on neurodegeneration than on amyloid deposition

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Summary (Contd.)

- Systemic vascular health has significant impact on brain structure and function
- Quantifying prodromal cerebrovascular health related brain measures (independent of AD) - great utility for cognitive aging

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Mayo ADRC
Mayo Clinic Study of Aging

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