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Excellence is just the beginning.

Rush University Medical Center

New Insights into Small Vessel Disease in Aging and Alzheimer's Disease

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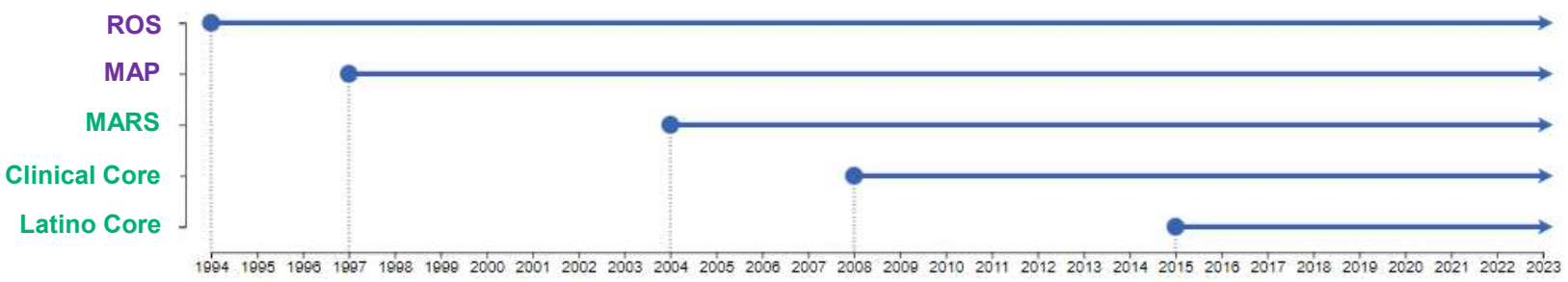
April 29th, 2026

Why did the small vessel break up with the neuron?

Because every time things got stressful, it said:
“I need space… preferably *perivascular* space.

RADC cohort studies of aging and dementia



Brain donation required

Brain donation optional

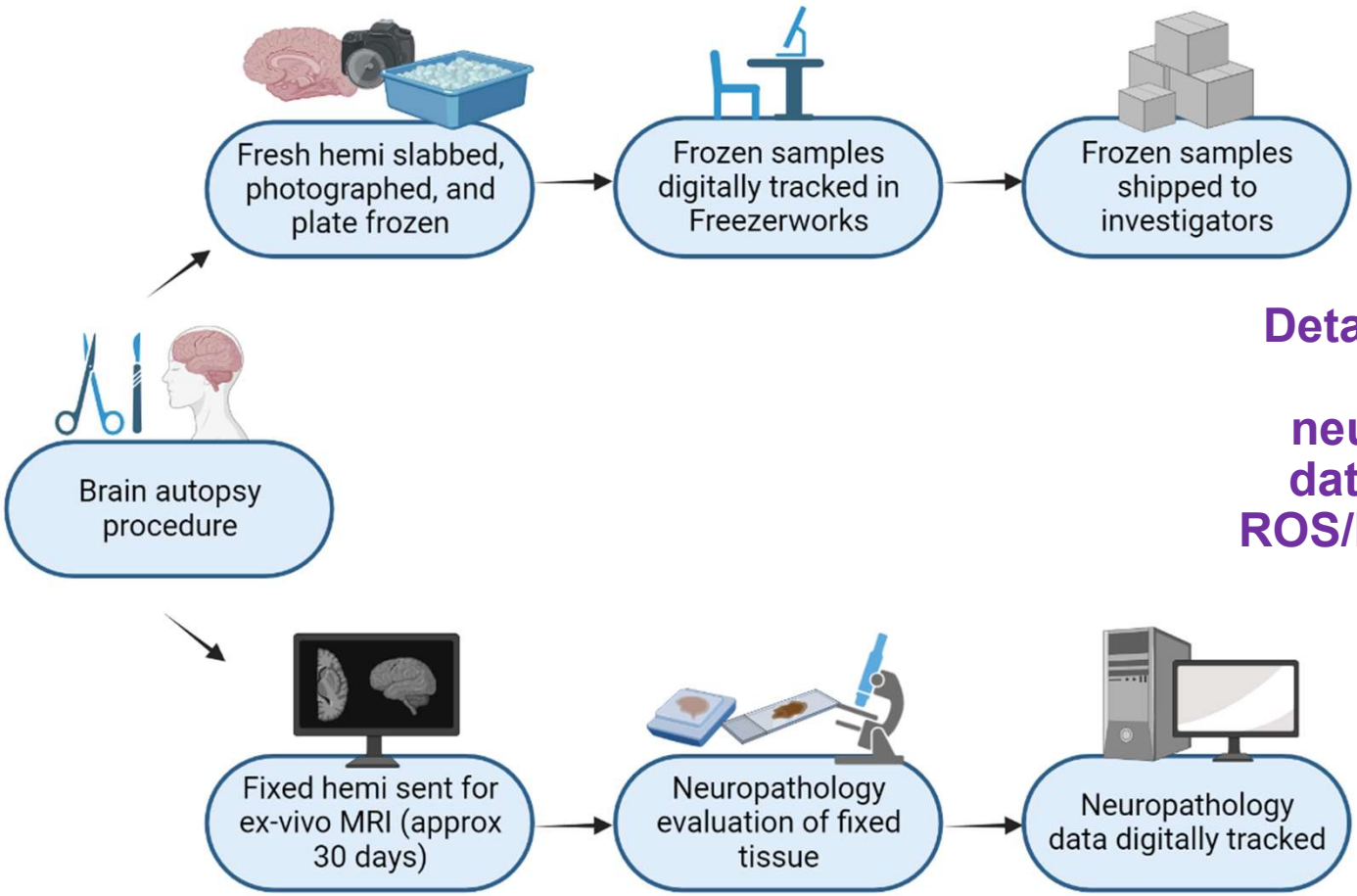
Participant outreach and building relations with the community

Annual neurologic, cognitive, behavioral, and physical evaluations

Brain donation and neuropathologic evaluations

65+ enroll persons without dementia

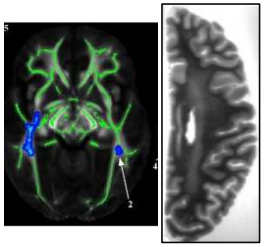
Brain tissue procedures for research studies

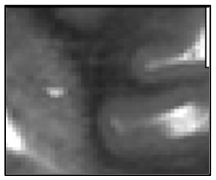


Detailed longitudinal clinical and neuropathological data on over 1,500 ROS/MAP participants.

MRI complements neuropathology

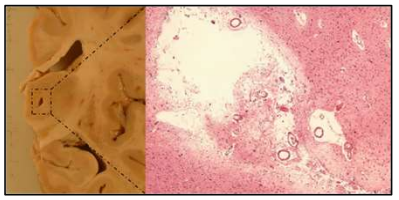
MRI TECHNIQUES



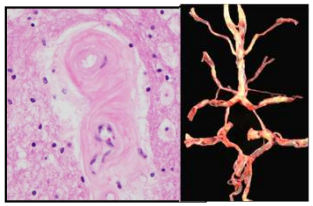


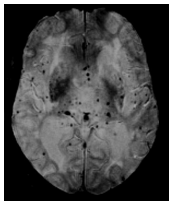
WMH
WM Integrity

Infarcts and Microinfarcts



Arteriolosclerosis
Atherosclerosis

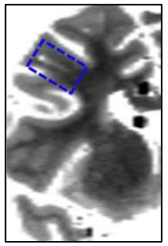




Microbleeds

Cognitive Impairment

Cerebral Amyloid Angiopathy

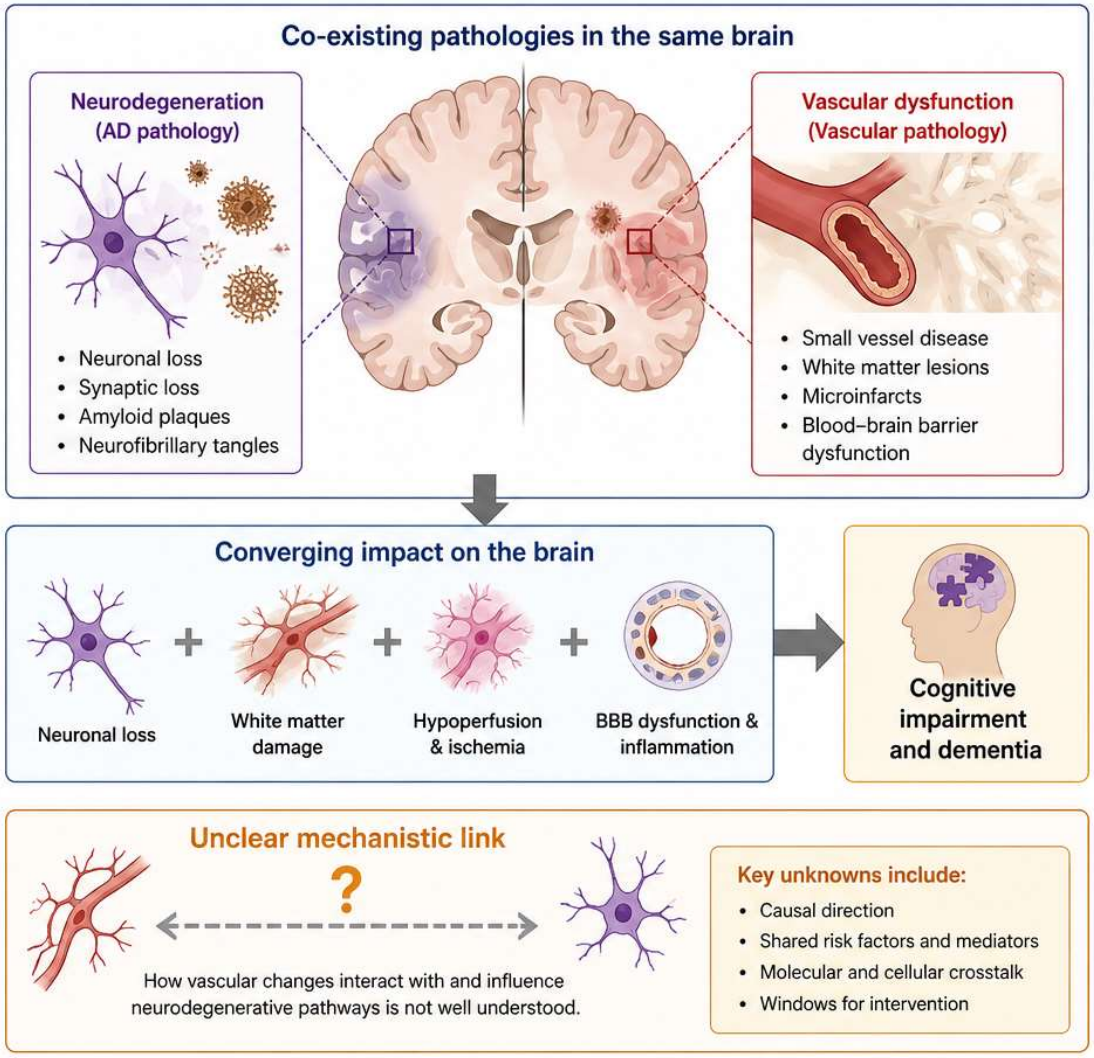


Enlarged Perivascular Spaces

- Limited by restricted brain coverage, <0.01%

NEUROPATHOLOGY

Intersection between AD-related neurodegeneration and cerebrovascular pathologies



Arteriolosclerosis affects small arteries and arterioles

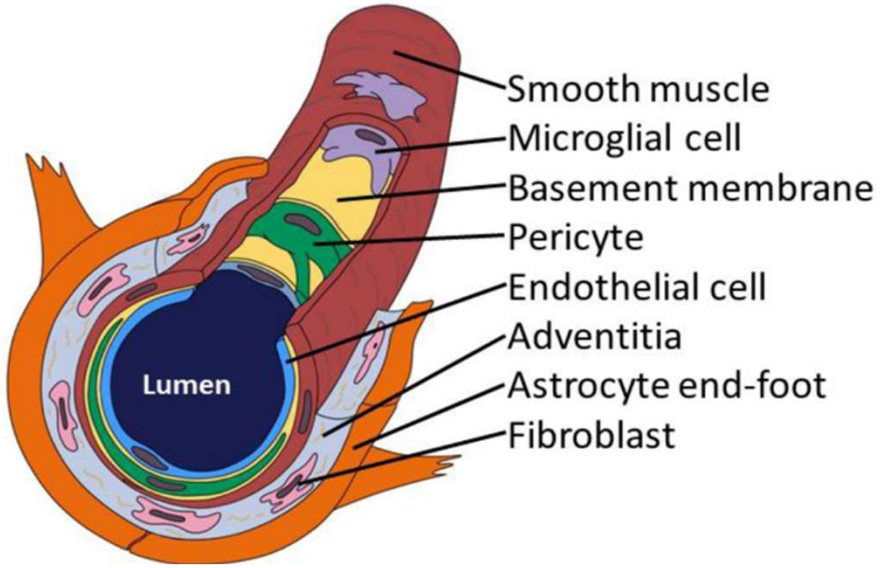
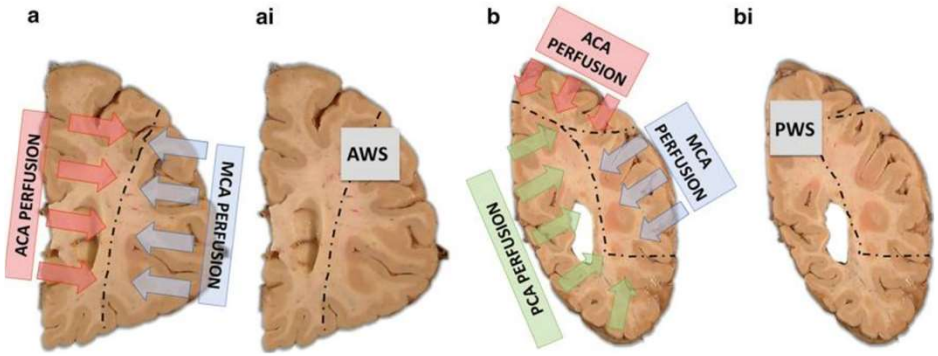
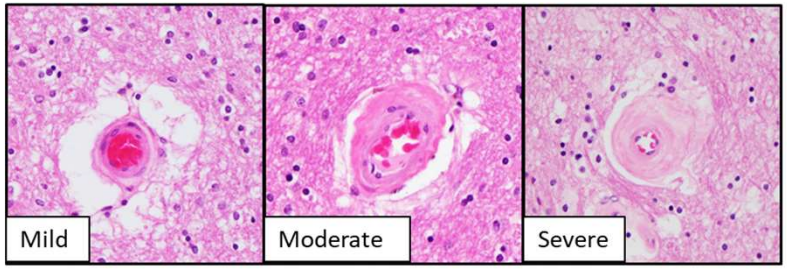


Image from Blevins et al., Acta Neuropathol (2020)

- ❑ Vessel wall thickening and luminal narrowing
- ❑ Loss of arterial elasticity = arterial stiffness
- ❑ Damage to the most inner endothelial cell layer marks the beginning of the process
- ❑ Very common; present in 35% of older participants
- ❑ Often noted in subcortical/periventricular white matter and deep gray nuclei
- ❑ Associated with hypertension and diabetes

Arteriolosclerosis pathology in posterior brain regions and tau pathology



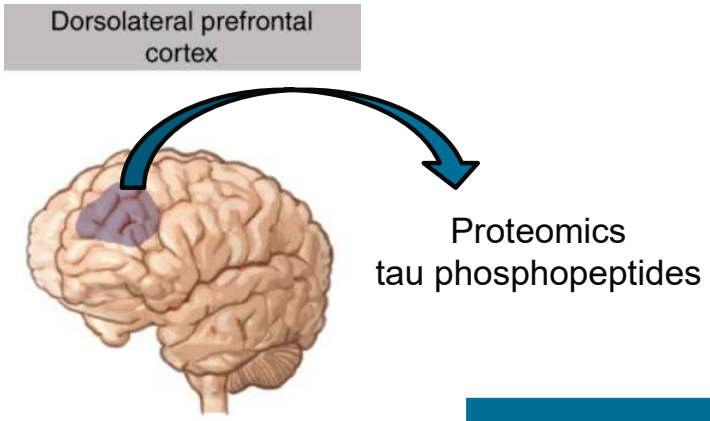


Kapasi et al., Acta Neuropathol (2022)

	Overall Amyloid	Mesial Temporal β-Amyloid	Neocortical β-Amyloid	Overall Tangles	Mesial Temporal Tangles	Neocortical Tangles
AWS Arteriolosclerosis	0.06 (0.04,0.13)	0.03 (0.03,0.32)	0.06 (0.04,0.12)	0.005 (0.04,0.91)	-0.01 (0.06,0.87)	0.01 (0.05,0.67)
PWS Arteriolosclerosis	-0.04 (0.04, 0.29)	-0.02 (0.03,0.59)	-0.04 (0.04,0.28)	**0.10 (0.04, 0.01)**	0.09 (0.06,0.14)	**0.11 (0.04,0.008)**

Linear regression models adjusted for demographics and all common age-related pathologies (N = 982)

Arteriolosclerosis pathology and tau phosphopeptides



Arteriolosclerosis pathology is associated with higher abundance of phosphorylated tau peptides

	AT8(^{S202})	AT100(^{T217})	12E8(^{S262})	PHF-1(^{S404})	77G7(^{S305})
AWS Arteriolosclerosis	0.01 (0.02, 0.71)	0.01 (0.03, 0.71)	**0.12 (0.06, 0.05)**	-0.01 (0.03, 0.78)	-0.01 (0.05, 0.78)
PWS Arteriolosclerosis	**0.05 (0.02,0.02)**	**0.07 (0.03,0.03)**	**0.15 (0.06,0.02)**	**0.06 (0.03, 0.03)**	**0.13 (0.05,0.006)**

Linear regression models adjusted for demographics and PMI (N=654)

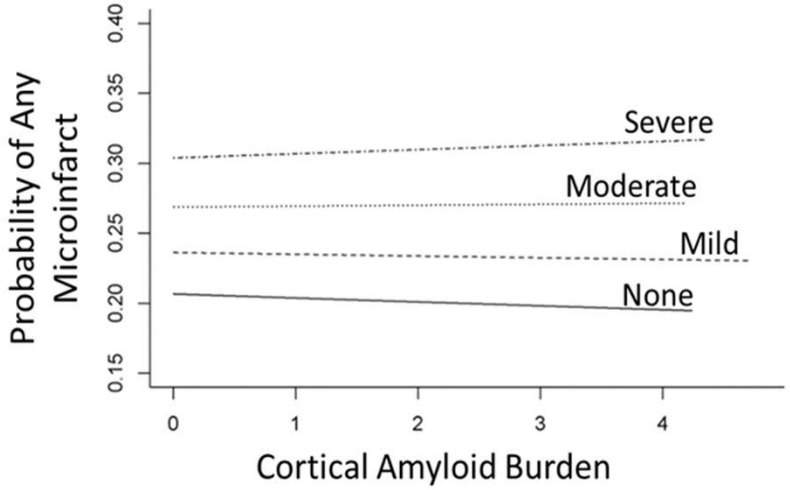
Kapasi et al., Acta Neuropathol (2022)

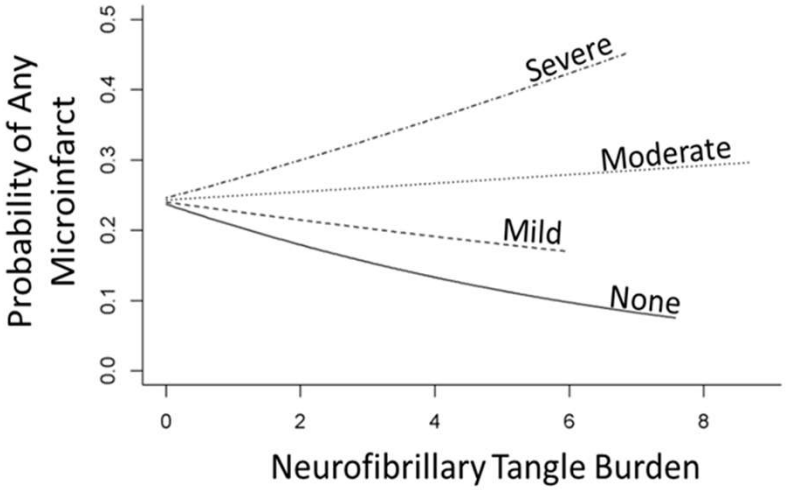
Interplay between vessel pathology, tau, and tissue injury

Vessel pathology → Tissue injury (microinfarcts)

AD pathology?

Does the relationship between vessel pathology and tissue injury differ by AD burden?





Kapasi et al., Stroke (2021)

Intriguing link between vasculature and tau

Image from Kovacs et al., Acta Neuropath (2016)

Proc Natl Acad Sci U S A. 2018 Feb 6;115(6):E1289-E1298. doi: 10.1073/pnas.1710329115. Epub 2018 Jan 22.

Tau induces blood vessel abnormalities and angiogenesis-related gene expression in P301L transgenic mice and human Alzheimer's disease.

Bennett RE[1], Robbins AB[1], Hu M[1], Cao X[2], Betensky RA[2], Clark T[1], Das S[1], Hyman BT[3].

⊕ Author information

Acta Neuropathol. 2016; 131: 737–752. PMCID: PMC4835519
Published online 2016 Mar 17. doi: 10.1007/s00401-016-1560-2 PMID: 26988843

Tau pathology-dependent remodelling of cerebral arteries precedes Alzheimer's disease-related microvascular cerebral amyloid angiopathy

Mario Merlini, Debora Wanner, and Roger M. Nitsch

▸ Acta Neuropathol. 2024 Jun 17;147(1):101. doi: 10.1007/s00401-024-02751-9

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RESEARCH ARTICLE | Open Access

Fibrillar tau alters cerebral endothelial cell metabolism, vascular inflammatory activation, and barrier function in vitro and in vivo

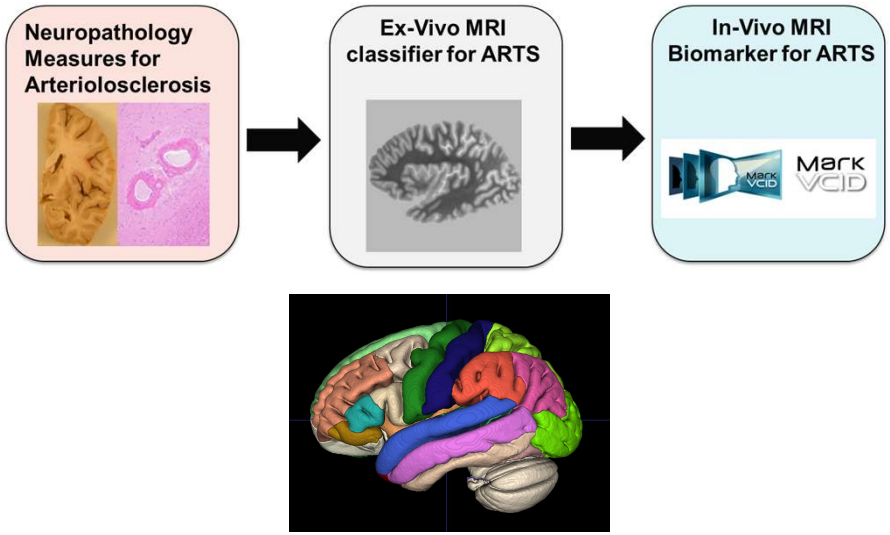
Roberto Guzmán-Hernández, Silvia Fossati

First published: 20 March 2025 | https://doi.org/10.1002/alz.70077 | VIEW METRICS

Brain vasculature accumulates tau and is spatially related to tau tangle pathology in Alzheimer's disease

Zachary Hoglund [1], Nancy Ruiz-Uribe [1,2], Eric del Sastre [1], Benjamin Woost [1], Elizabeth Bader [1], Joshua Bailey [1], Bradley T Hyman [1,2], Theodore Zwang [1,2,✉,#], Rachel E Bennett [1,2,✉,#]

In-vivo MRI measures for arteriolosclerosis with cortical thinning

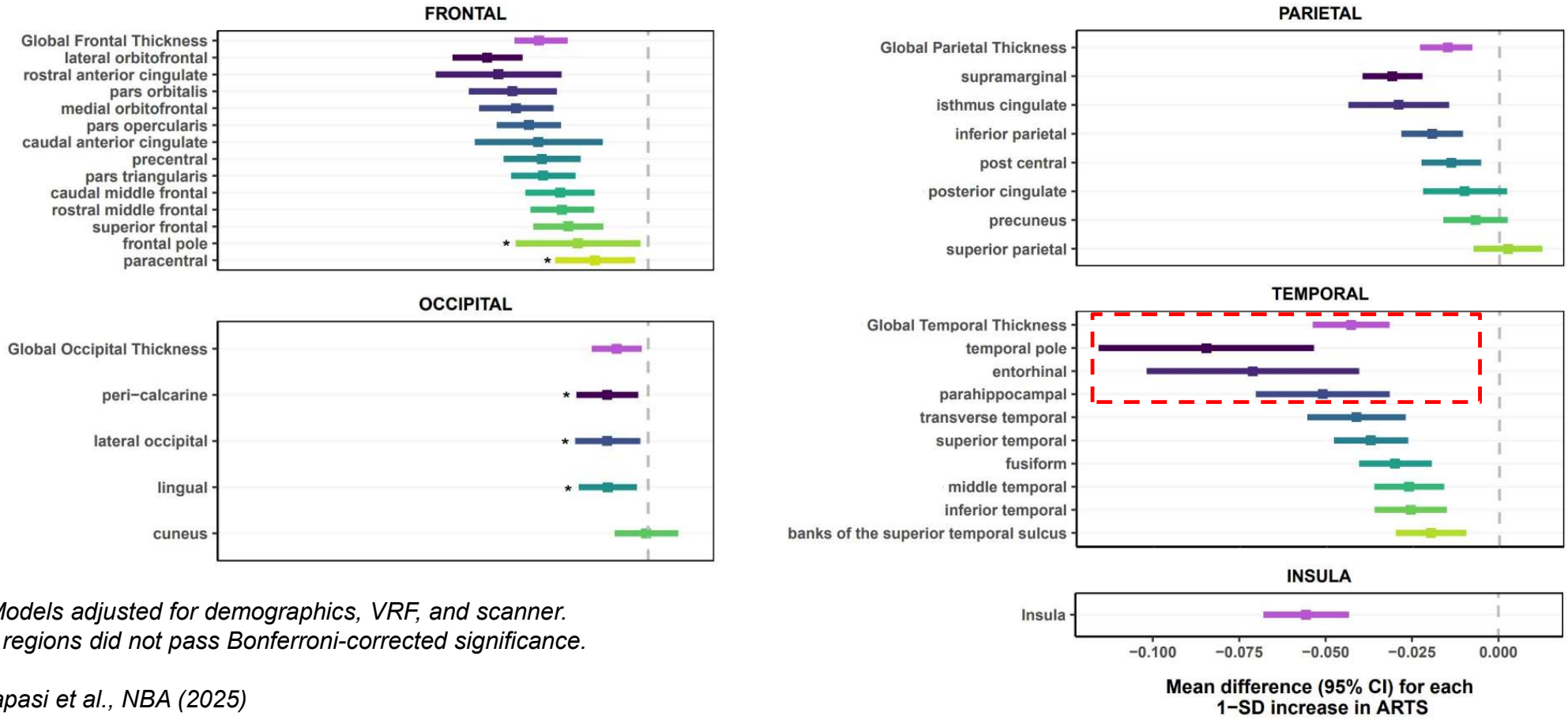


STUDY DESIGN

- ❑ Novel in-vivo MRI classifier for arteriolosclerosis, termed ARTS (Makkinejad et al., 2021)
- ❑ Cortical thickness measures across 34 FreeSurfer ROI's
- ❑ Data included having ARTS and FreeSurfer at the same 3T MRI scan, and completed cognitive eval within a year of MRI
- ❑ Analytic sample – 1,054 participants (mean age at last MRI – 80yrs)

Kapasi et al., NBA (2025)

Association of ARTS with regional cortical thickness

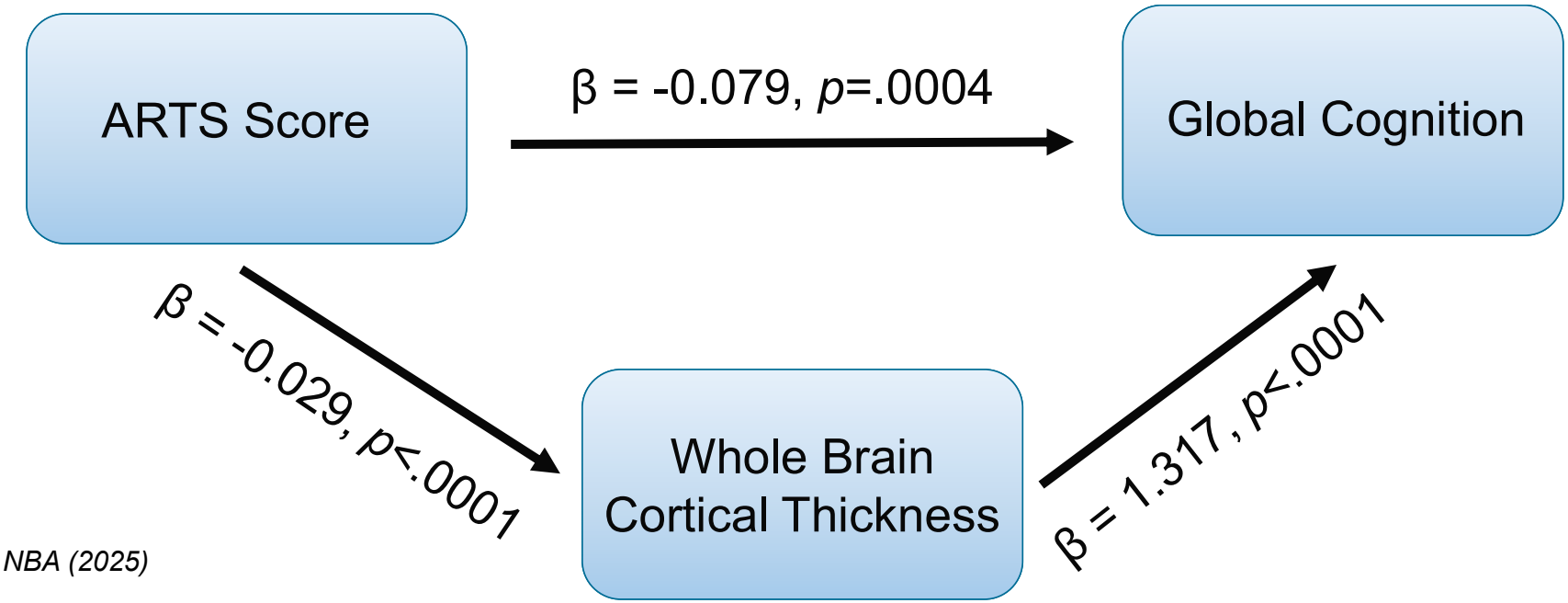


Models adjusted for demographics, VRF, and scanner.
** 5 regions did not pass Bonferroni-corrected significance.*

Kapasi et al., NBA (2025)

ARTS, cortical thickness, and cognition

Cortical thickness accounted for about 32% of the association between ARTS and global cognition



Kapasi et al., NBA (2025)

Atherosclerosis and MRI marker of hippocampal volume

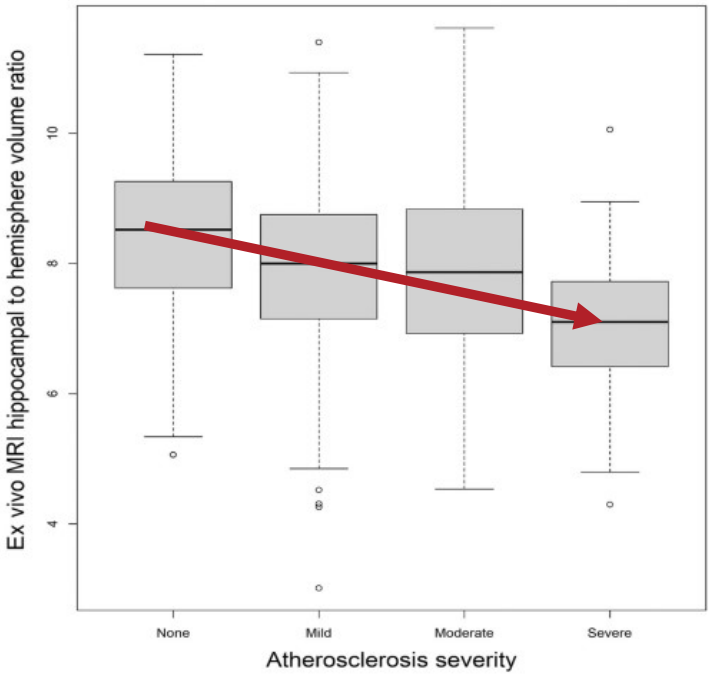


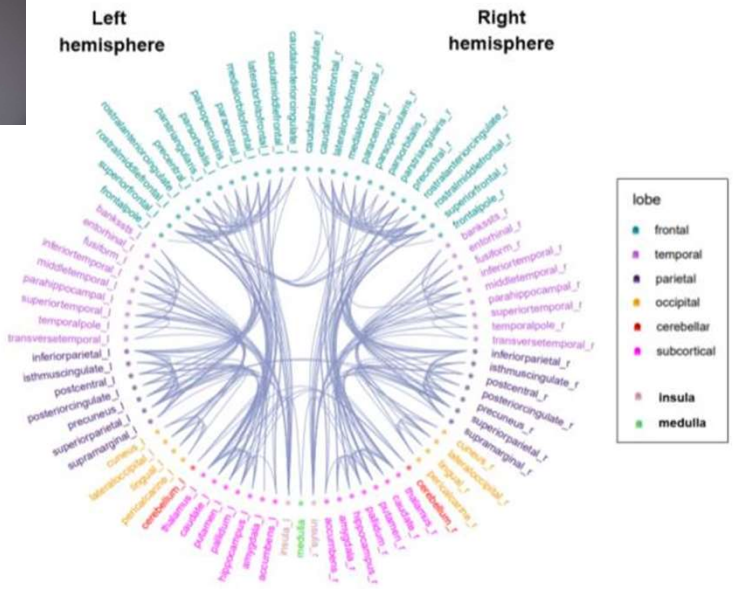
Table 2. Association of Atherosclerosis Pathology With Hippocampal Volume

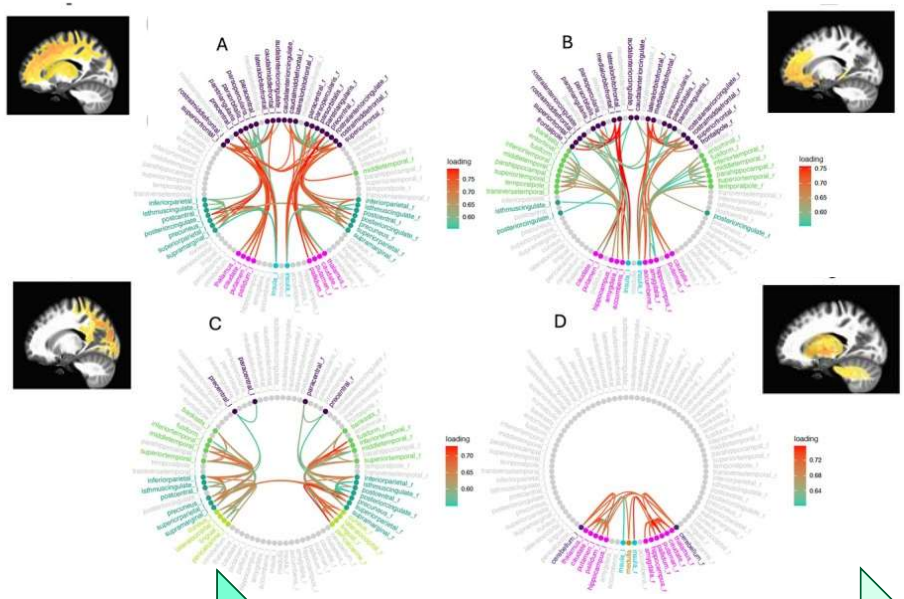
Neuropathologic indices	Hippocampal to hemisphere volume ratio estimate (SE, *P* value)
Atherosclerosis	−0.24 (0.06, 0.001)*
Arteriolosclerosis	0.03 (0.05, 0.53)
Cerebral amyloid angiopathy	−0.06 (0.05, 0.25)
Macroscopic infarcts	0.01 (0.10, 0.93)
Microscopic infarcts	−0.11 (0.10, 0.26)
Alzheimer's disease pathology	−0.27 (0.08, <0.001)*
Limbic predominant age-related transactive response DNA-binding protein 43 encephalopathy neuropathologic changes	−0.26 (0.04, <0.001)*
Lewy bodies	−0.14 (0.10, 0.14)

Kapasi et al., JAHA (2024)

Understanding white matter vulnerability with structural connectome integrity matrices (SCIM)

Lamar et al., Hum Brain Mapp (2026)





Mapped white matter brain connections via a structural connectivity-based atlas

Developed a global SCIM of 308 nodal pair connections, as well as four different patterns of sub-networks

To measure how "healthy" or "unhealthy" connections are, we extract MRI metrics (R_2) from each nodal connection pair

Neuropathologic associations of structural connectome integrity matrices (SCIM)

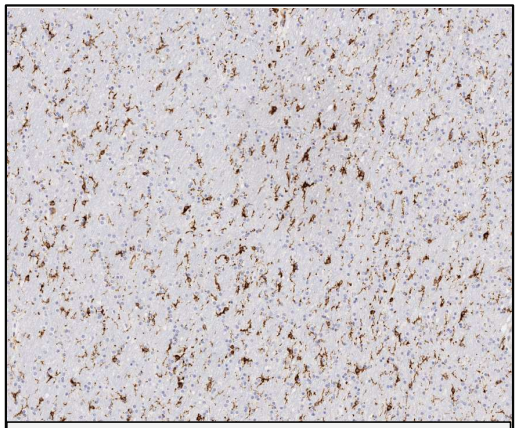
Mayra et al., In preparation

Pathology	Global R_2-SCIM		Sub-Network 1[1]		Sub-Network 2[2]		Sub-Network 3[3]		Sub-Network 4[4]	
	Estimate (SE)	*P*	Estimate (SE)	*P*	Estimate (SE)	*P*	Estimate (SE)	*P*	Estimate (SE)	*P*
Cerebrovascular										
Arteriolosclerosis (moderate-to-severe)	-0.10 (0.12)	0.4	-0.30 (0.15)	0.06	**0.68 (0.14)**	**<0.0001**	-0.02 (0.13)	0.9	**-0.60 (0.14)**	**<0.0001**
Atherosclerosis (moderate-to-severe)	-0.25 (0.14)	0.1	**-0.37 (0.18)**	**0.04**	0.31 (0.16)	0.06	-0.21 (0.15)	0.2	-0.15 (0.16)	0.3
CAA (moderate-to-severe)	0.06 (0.12)	0.7	-0.03 (0.15)	0.9	-0.11 (0.14)	0.4	0.21 (0.13)	0.1	0.16 (0.14)	0.2
Gross infarct present, any chronic	**-0.32 (0.12)**	**0.008**	-0.24 (0.15)	0.1	-0.08 (0.14)	0.6	-0.07 (0.13)	0.6	-0.16 (0.13)	0.2
Microinfarct present, any chronic	0.09 (0.11)	0.4	-0.12 (0.14)	0.4	**0.40 (0.13)**	**0.003**	0.02 (0.12)	0.9	-0.07 (0.13)	0.6
Neurodegenerative										
Global AD burden	-0.13 (0.08)	0.1	0.03 (0.10)	0.8	**-0.23 (0.09)**	**0.01**	0.05 (0.09)	0.6	-0.04 (0.09)	0.7
LATE-NC (stages 2 and 3)	0.06 (0.13)	0.6	0.23 (0.16)	0.2	-0.06 (0.14)	0.7	-0.26 (0.13)	0.05	0.22 (0.14)	0.1
Lewy bodies (presence)	-0.25 (0.13)	0.05	-0.22 (0.16)	0.2	0.06 (0.15)	0.7	0.06 (0.14)	0.7	**-0.37 (0.14)**	**0.01**

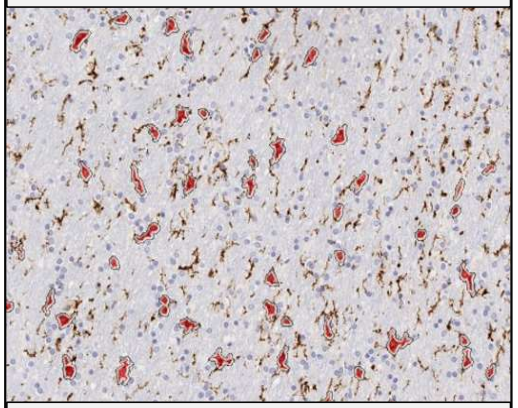
Associations of cerebrovascular and neurodegenerative pathologies with global R_2-SCIM and PCA-derived R_2-SCIM Sub-Networks at last eligible antemortem MRI (N=245).

- Extending this by examining longitudinal change in R2-SCIM with differing mixed pathology profiles

Subcortical White Matter Vulnerability – Microglial Inflammation

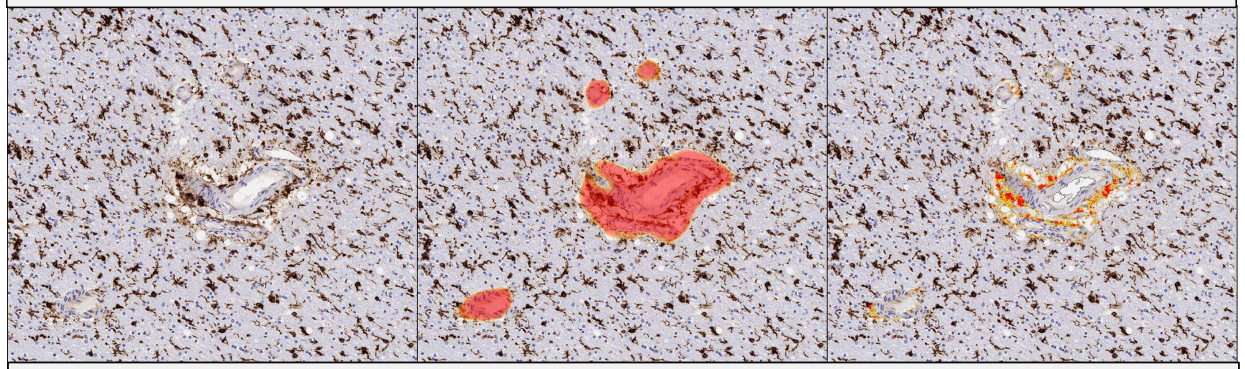


CR3/43-immunostain of subcortical WM

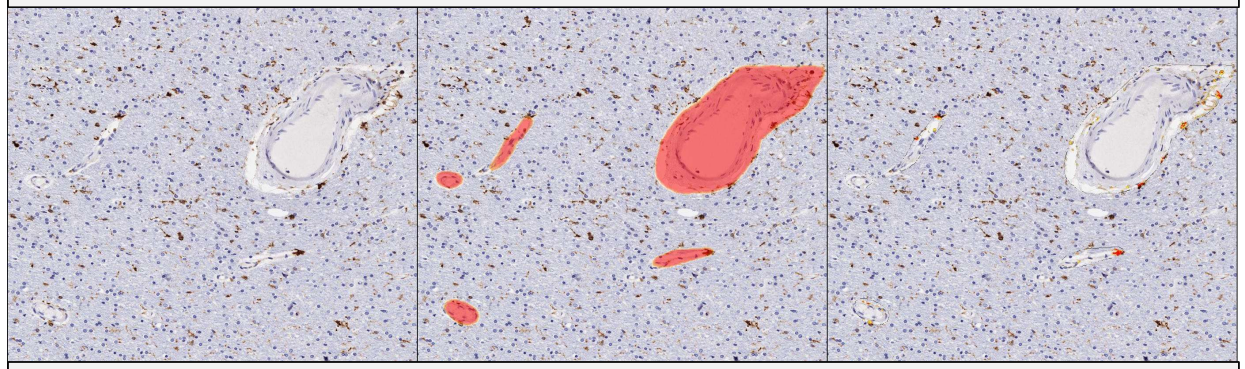


Machine learning-based quantification of total white matter inflammation

Utilizing digital pathology tools to quantify white matter vessel-associated inflammation



Case with high WM vessel inflammation



Case with low WM vessel inflammation

Small Vessel Pathologies and WM Microglial Inflammation

- Examined associations between age-related brain pathologies with subcortical total white matter inflammation in watershed brain regions from 172 postmortem brains.

Predictors	Total Microglia in AWS	Total Microglia in PWS
AD	-9.25 (7.65, 0.23)	-3.93 (6.74 ,0.56)
LATE-NC	1.92 (5.35, 0.72)	-1.75 (4.75, 0.71)
Lewy bodies	-3.80 (13.0, 0.77)	3.64 (11.64, 0.75)
Atherosclerosis	1.42 (8.09, 0.86)	3.00 (7.12, 0.67)
Arteriolosclerosis (AWS)	5.63 (4.86, 0.24)	-
Arteriolosclerosis (PWS)	-	**11.37 (4.58,0.01)**
CAA	**15.89 (6.29, 0.01)**	**12.85 (5.47, 0.02)**
Macroscopic infarcts	-12.93 (12.41, 0.29)	-13.43 (10.95, 0.22)
Microscopic infarcts	-2.65 (12.77, 0.83)	-0.76 (11.34, 0.95)

Linear regression models adjusted for demographics

Kapasi et al., Unpublished Data

Late-Life Blood Pressure and WM Microglial Inflammation

- Examined associations between differing blood pressure metrics with subcortical total white matter inflammation in watershed brain regions from 172 postmortem brains.

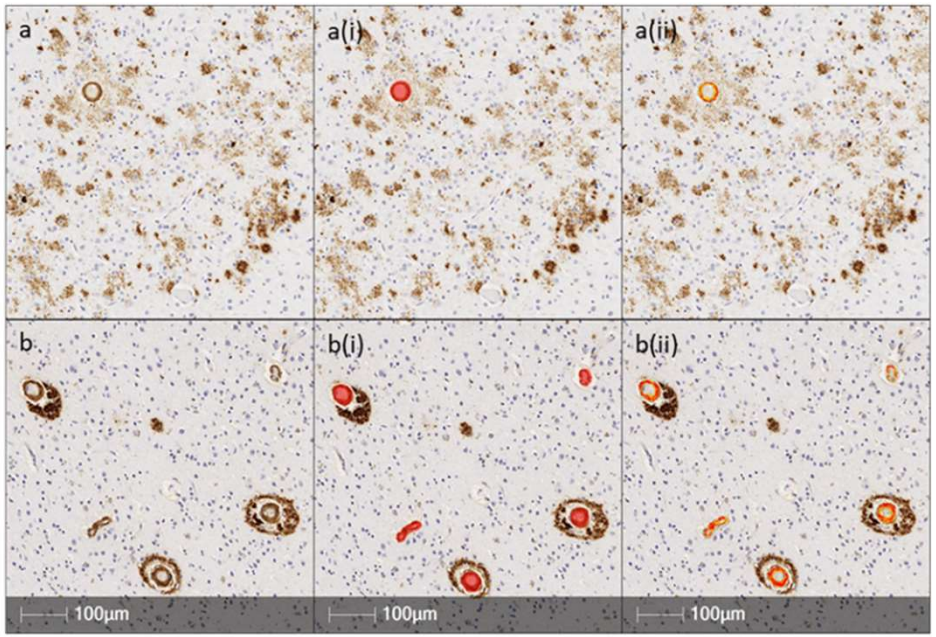
Predictors	Microglia in AWS	Microglia in PWS
Systolic BP slope	**17.29 (6.54, 0.01)**	**11.31 (5.37, 0.03)**
Diastolic BP slope	-0.60 (6.72, 0.92)	-1.74 (5.43, 0.74)
Mean arterial pressure	**1.52 (0.61,0.01)**	**1.10 (0.52, 0.03)**
Pulse pressure	0.07 (0.44, 0.86)	-0.09 (0.37, 0.80)

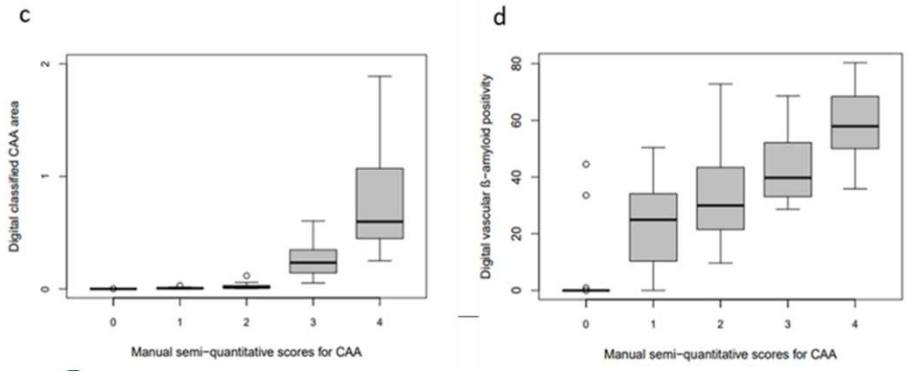
Linear regression models adjusted for demographics

- Extending this work by examining white matter vessel inflammation as well as integrating ex-vivo MRI measures of SVD

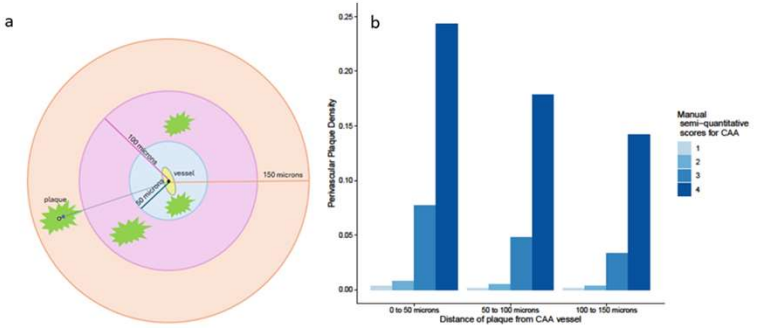
Kapasi et al., Unpublished Data

Quantitative Measures for Cortical Vessels – CAA and Microglial Inflammation

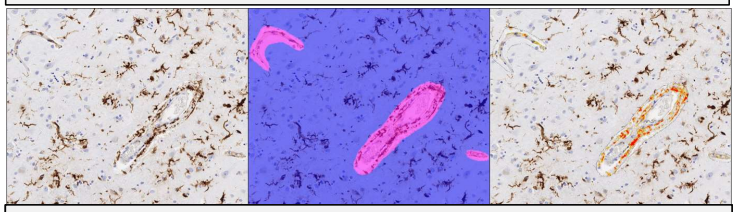




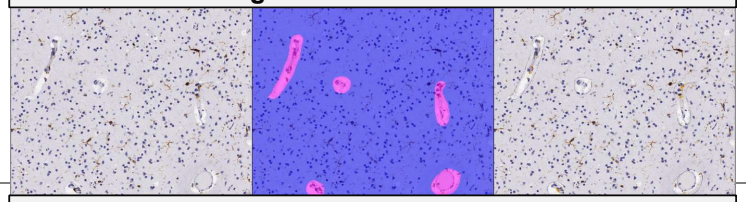
Distance of Aβ plaques from CAA+ vessels



Cortical grey matter vessel-associated inflammation



Case with high cortical vessel inflammation



Case with low cortical vessel inflammation

Mojdeganlou et al., Manuscript in preparation

Summary

- Alzheimer's disease (AD) pathology and vascular brain injury commonly coexist within the same brain, especially in aging populations.

- Link between vascular and degenerative mechanisms is not well understood – some biologic mechanisms have been proposed.
  - Vascular driven inflammation
  - BBB dysfunction
  - Angiogenesis
  - Impaired clearance
  - Chronic hypoperfusion/WM injury

- Integrating neuropathology (+ digital pathology) with MRI provides a powerful approach to study postmortem brain tissue in new ways.

Future Directions

- Defining the cellular basis of vascular–inflammatory associations in vulnerable white matter regions and across AD/CAA pathologic groups.
- Understanding molecular changes that link vascular dysfunction with white matter injury.
- Interested in exploring the role of angiogenesis-factors in small vessel disease.
- Integrate pathology and transcriptomics with in-vivo neuroimaging signatures.
- Blood-based signatures of microvascular and inflammatory brain injury.

Rush Alzheimer's Disease Center: Acknowledgments

Puja Agarwal, PhD
Neelum Aggarwal, MD
Sonal Agrawal, PhD
Konstantinos Arfanakis, PhD
Zoe Arvanitakis, MD
Denis Avey, PhD
Lisa Barnes, PhD
David Bennett, MD
Patricia Boyle, PhD
Aron Buchman, MD
Yi Chen, PhD
Lianlian Du, PhD
Mayra Estrella, PhD
Jose Farfel, MD, PhD
Fran Grodstein, ScD
Bryan James, PhD
Alifiya Kapasi, PhD
Nicola Kearns , PhD
Melissa Lamar, PhD
Brittney Lange-Maia, PhD, MPH
Sue Leurgans, PhD
Katia Lopes, PhD
David X Marquez, PhD *Visiting Appt at Rush
Rupal Mehta, MD
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Bernard Ng, PhD
Shahram Oveisgharan, MD
Victoria Poole, PhD
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NIH National Institute on Aging

NIH National Institute of Neurological Disorders and Stroke

https://www.radc.rush.edu/

Neuropathologic studies confirm majority of brains have mixed pathologies

ARTICLES | June 13, 2007

Mixed brain pathologies account for most dementia cases in community-dwelling older persons

Julie A. Schneider, MD, Zoe Arvanitakis, MD, Woojeong Bang, MS, and David A. Bennett, MD | AUTHORS INFO & AFFILIATIONS

December 11, 2007 issue • 69 (24) 2197-2204 • https://doi.org/10.1212/01.wnl.0000271090.28148.24

Ann Neurol. Author manuscript; available in PMC 2010 Aug 1.
Published in final edited form as:
Ann Neurol. 2009 Aug; 66(2): 200–208.
doi: 10.1002/ana.21706

PMCID: PMC2812870
NIHMSID: NIHMS136027
PMID: 19743450

The Neuropathology of Probable Alzheimer's Disease and Mild Cognitive Impairment

J.A. Schneider, M.D., M.S.,[1,2,3] Z. Arvanitakis, M.D., M.S.,[1,2] S.E. Leurgans, Ph.D.,[1,2] and D.A. Bennett, M.D.[1,2]

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March 12, 1997

Brain Infarction and the Clinical Expression of Alzheimer Disease
The Nun Study

David A. Snowdon, PhD; Lydia H. Greiner, BSN; James A. Mortimer, PhD; et al

› Lancet. 1999 Sep 11;354(9182):919-20. doi: 10.1016/S0140-6736(99)02355-7.

Cerebrovascular disease and threshold for dementia in the early stages of Alzheimer's disease

M M Esiri, Z Nagy, M Z Smith, L Barnetson, A D Smith

Review › Acta Neuropathol. 2007 Jan;113(1):1-12. doi: 10.1007/s00401-006-0144-y. Epub 2006 Oct 12.

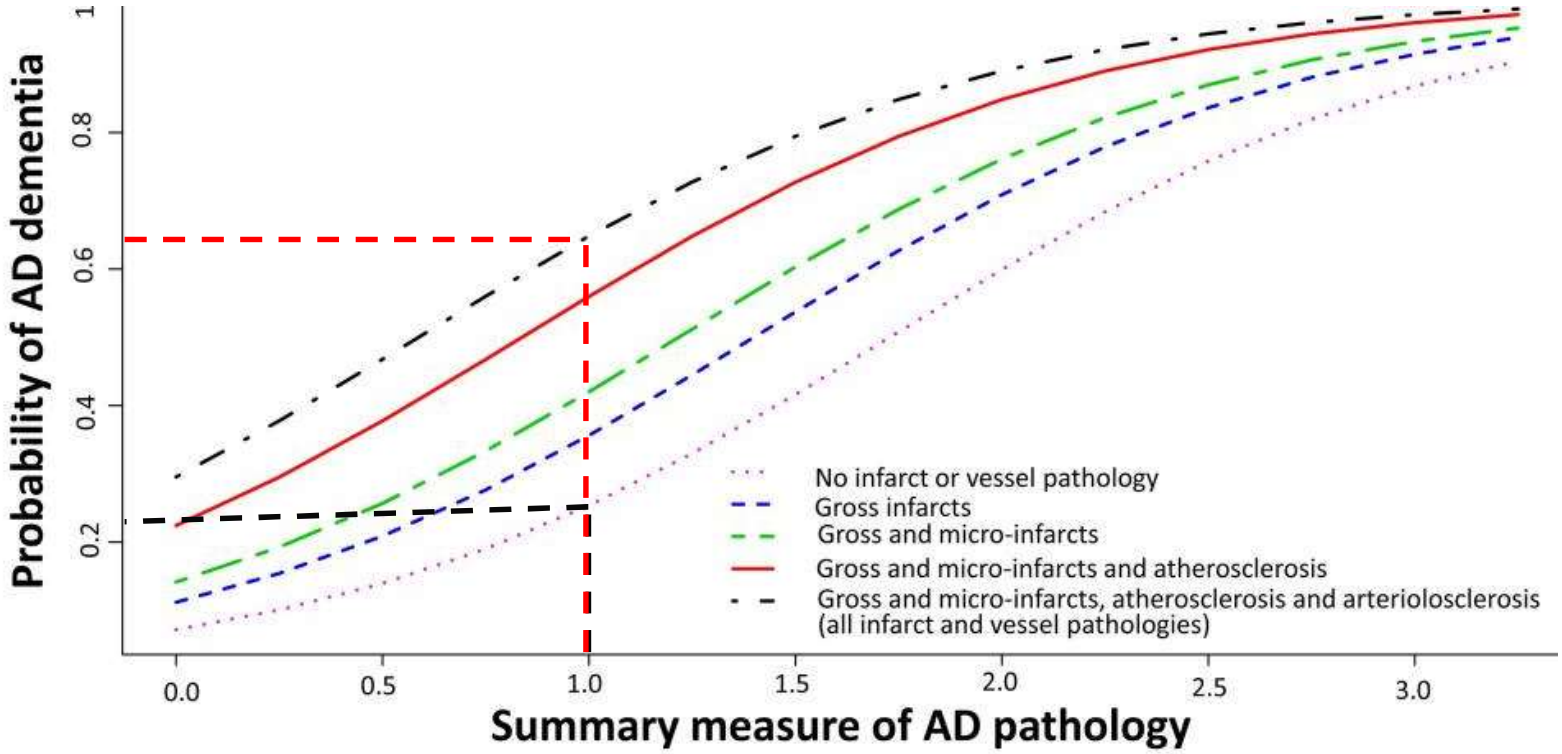
Assessing the cognitive impact of Alzheimer disease pathology and vascular burden in the aging brain: the Geneva experience

Panteleimon Giannakopoulos [1], Gabriel Gold, Enikö Kövari, Armin von Gunten, Anouk Imhof, Constantin Bouras, Patrick R Hof

<u>These studies did not include:</u>

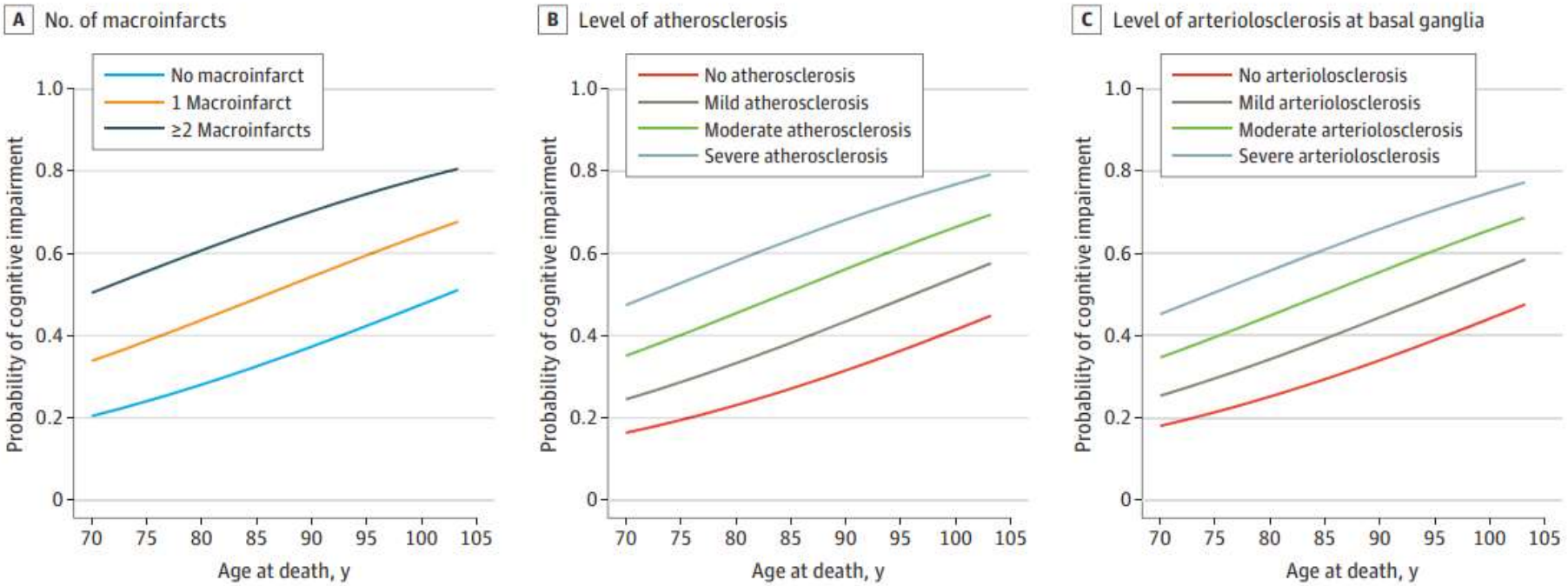
- ❑ Pathologic changes in the vasculature
- ❑ Other non-AD proteinopathy changes (TDP-43)
- ❑ Relatively limited sample size

Multiple vascular brain ‘hits’ increases the likelihood of Alzheimer's dementia



Arvanitakis et al., Lancet Neurol, (2017)

Cognitive impairment in ‘pure’ vascular pathology subgroup



Oveisgharan et al., JAMA Neurol, (2022)