White matter hyperintensities are a core feature of Alzheimer's disease:

Evidence from late onset and genetic forms

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Disclosure

- Consultant/Scientific advising:
  - Keystone Heart, Ltd
  - Cognition Therapeutics, Inc
  - F. Hoffmann-La Roche, Ltd
  - Regeneron Pharmaceuticals, Inc
  - CogState
- Equity:
  - Venus MedTech (via Mars Holding Company)
- Funding:
  - National Institutes of Health (NIH)/National Institute on Aging (NIA)
  - Alzheimer's Association
  - Columbia University
  - Mars Symbioscience

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Agenda

- Alzheimer's disease classification and some caveats
- Vascular brain injury (white matter hyperintensities--WMH) in dementia and Alzheimer's disease
- Is vascular brain injury a “core feature” of Alzheimer’s disease?

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Alzheimer’s disease: Probabilistic diagnosis

Clinical diagnosis of Alzheimer’s disease:
Report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer’s Disease

Guy McKhann, MD; David Drachman, MD; Marshall Folstein, MD; Robert Katzman, MD; Donald Price, MD; and Emanuel M. Stadlan, MD

McKhann et al., 1984 Neurology

Table 1. Criteria for clinical diagnosis of Alzheimer's disease

I. The criteria for the clinical diagnosis of PROBABLE Alzheimer's disease include:

dementia established by clinical examination and documented by the Mini-Mental Test,[1] Blessed Dementia Scale,[2] or some similar examination, and confirmed by neuropsychological tests;

deficits in two or more areas of cognition;

progressive worsening of memory and other cognitive functions;

no disturbance of consciousness;

onset between ages 40 and 90, most often after age 65; and

absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.

II. The diagnosis of PROBABLE Alzheimer's disease is supported by:

progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia);

impaired activities of daily living and altered patterns of behavior;

family history of similar disorders, particularly if confirmed neuropathologically; and

laboratory results of:

normal lumbar puncture as evaluated by standard techniques,

normal pattern or nonspecific changes in EEG, such as increased slow-wave activity, and

evidence of cerebral atrophy on CT with progression documented by serial observation.

III. Other clinical features consistent with the diagnosis of PROBABLE Alzheimer's disease, after exclusion of causes of dementia other than Alzheimer's disease, include:

plateaus in the course of progression of the illness;

associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional, or physical outbursts, sexual disorders, and weight loss;

other neurologic abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder;

seizures in advanced disease; and

CT normal for age.

IV. Features that make the diagnosis of PROBABLE Alzheimer's disease uncertain or unlikely include:

sudden, apoplectic onset;

focal neurologic findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness; and

seizures or gait disturbances at the onset or very early in the course of the illness.

V. Clinical diagnosis of POSSIBLE Alzheimer's disease:

may be made on the basis of the dementia syndrome, in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, in the presentation, or in the clinical course;

may be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be *the* cause of the dementia; and

should be used in research studies when a single, gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause.

VI. Criteria for diagnosis of DEFINITE Alzheimer's disease are:

the clinical criteria for probable Alzheimer's disease and

histopathologic evidence obtained from a biopsy or autopsy.

VII. Classification of Alzheimer's disease for research purposes should specify features that may differentiate subtypes of the disorder, such as:

familial occurrence;

onset before age of 65;

presence of trisomy-21; and

coexistence of other relevant conditions such as Parkinson's disease.

Probabilistic diagnosis

- Probable AD: Dementia syndrome, rule out of any other potential cause of dementia
- Possible AD: Dementia syndrome, some question about onset and course, and may be present in the context of other causes of dementia that are not considered primary
- Definite AD: Probable AD + histological confirmation from biopsy or autopsy (only after death)

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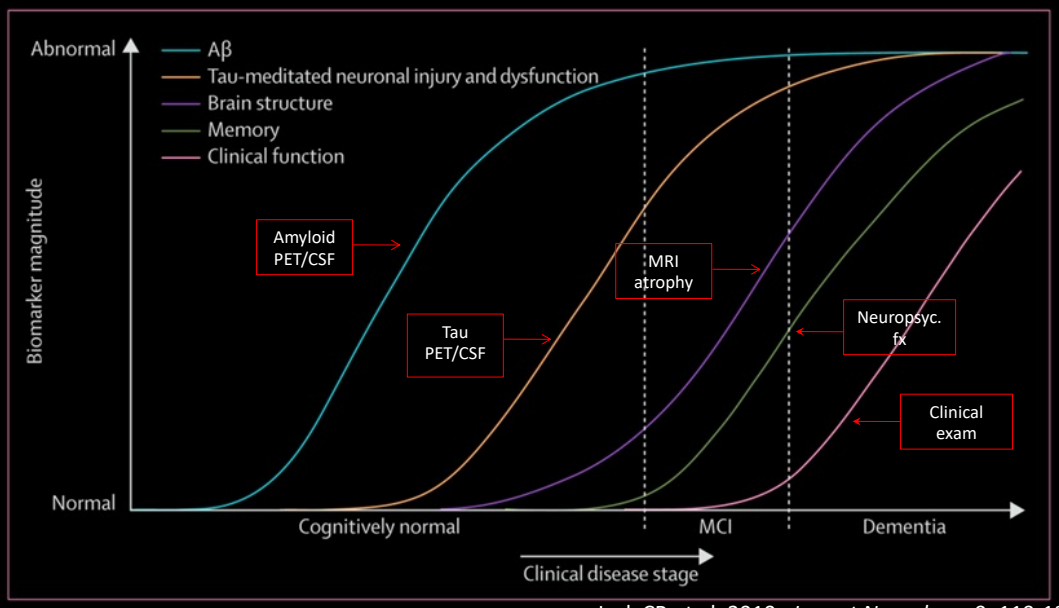
AD: Age of biomarkers



Jack CR et al, 2010. *Lancet Neurology*, 9, 119-128

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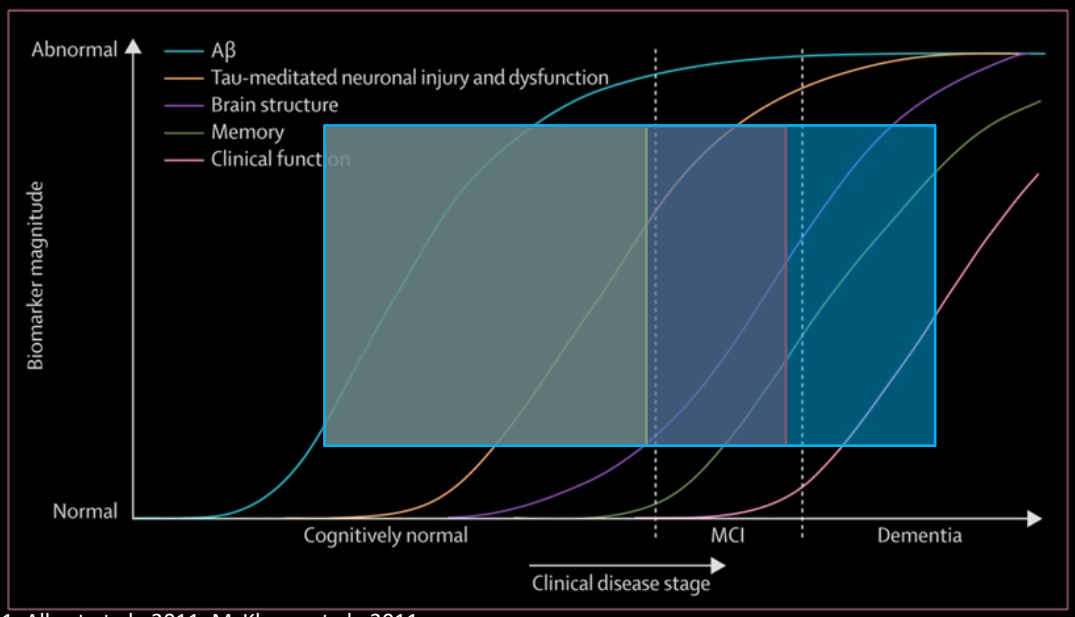
Diagnosing based on putative etiology



Sperling et al., 2011; Albert et al., 2011; McKhann et al., 2011

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Diagnosing based only on biomarker status without consideration of symptoms

ELSEVIER

CrossMark

Alzheimer's & Dementia 14 (2018) 535-562

Alzheimer's & Dementia

2018 National Institute on Aging—Alzheimer's Association (NIA-AA) Research Framework

NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease

Clifford R. Jack, Jr.,[a,*], David A. Bennett[b], Kaj Blennow[c], Maria C. Carrillo[d], Billy Dunn[e], Samantha Budd Haeberlein[f], David M. Holtzman[g], William Jagust[h], Frank Jessen[i], Jason Karlawish[j], Enchi Liu[k], Jose Luis Molinuevo[l], Thomas Montine[m], Creighton Phelps[n], Katherine P. Rankin[o], Christopher C. Rowe[p], Philip Scheltens[q], Eric Siemers[r], Heather M. Snyder[d], Reisa Sperling[s]

Contributors[†]: Cerise Elliott, Eliezer Masliah, Laurie Ryan, and Nina Silverberg

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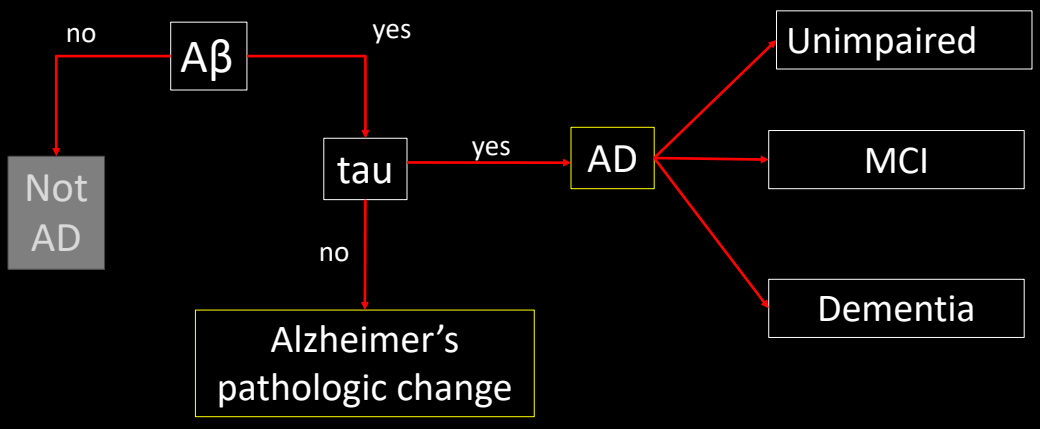
Biomarker diagnosis: AT(N)~~C~~

Clinical Staging



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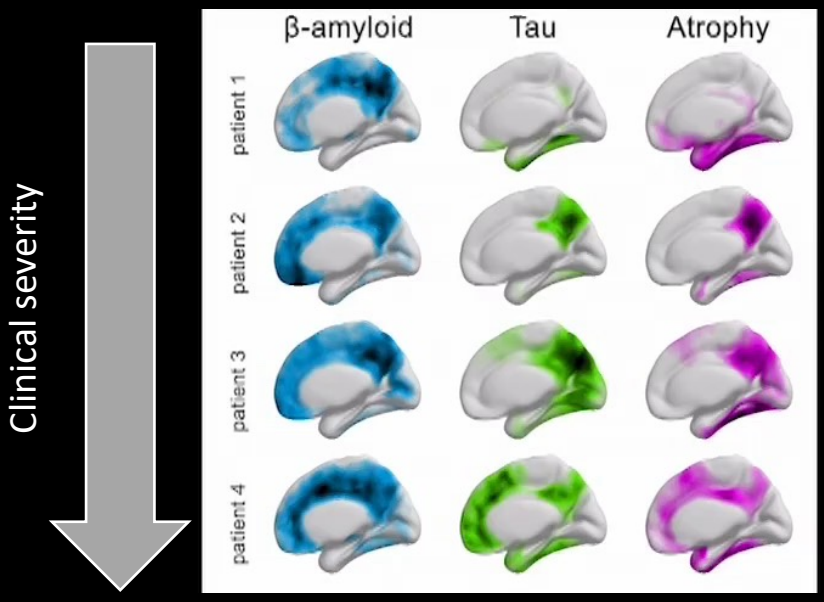
Biomarker diagnosis: Accumulating evidence



La Joie et al., 2020. *STM*

Slide courtesy of Renaud La Joie

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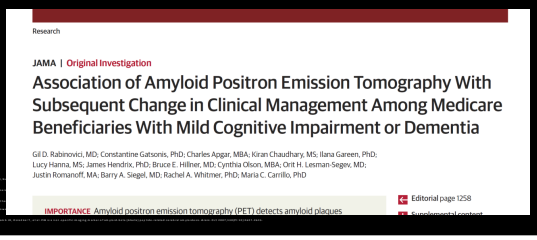
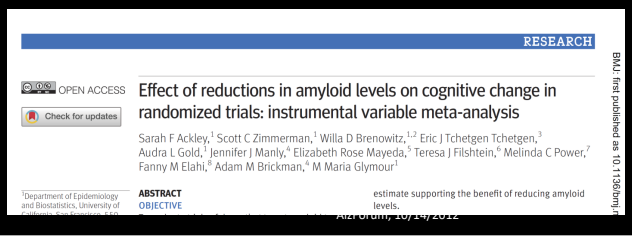
Caveats

- ~30+% of older adults without dementia have significant amyloid deposition detected with PET or at autopsy without any apparent cognitive impairment.
- IDEAS study: about 30-50% of patients diagnosed with MCI/AD by dementia experts were amyloid negative (Rabinovici et al.)
- Successful amyloid reduction in clinical trials has nominal (if any) effect on cognition (Ackley et al., 2019)
- Tau appears more linked to cognition, even independent of or in the absence of amyloid
- Individual risk: Given a specific biomarker profile, we still don't know what the risk of AD is in a given period of time for a single individual and there is tremendous variability (40% PPV over a 5-year period in Aβ+ individuals)


Research

JAMA | Original Investigation

Association of Amyloid Positron Emission Tomography With Subsequent Change in Clinical Management Among Medicare Beneficiaries With Mild Cognitive Impairment or Dementia


RESEARCH

OPEN ACCESS

Effect of reductions in amyloid levels on cognitive change in randomized trials: instrumental variable meta-analysis

Check for updates

BMJ: first published as 10.1136/bmj.

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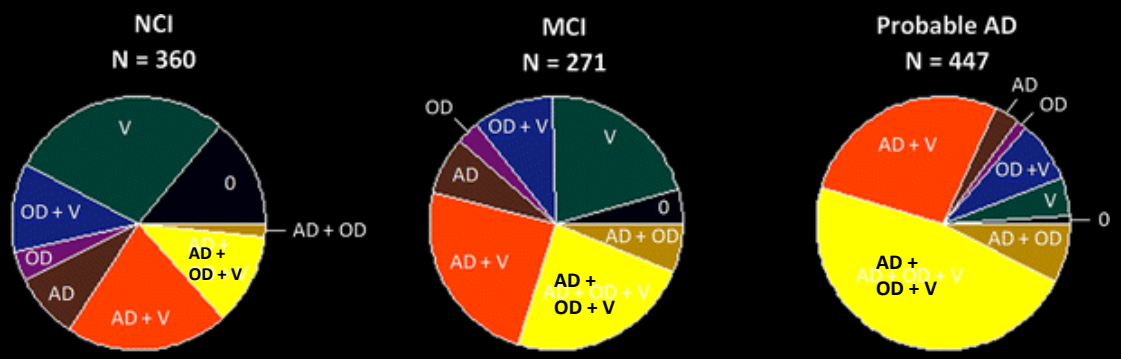
Does pure Alzheimer's disease exist?



Kapasi, DeCarli, & Schneider, 2017 *Acta Neuropathol*

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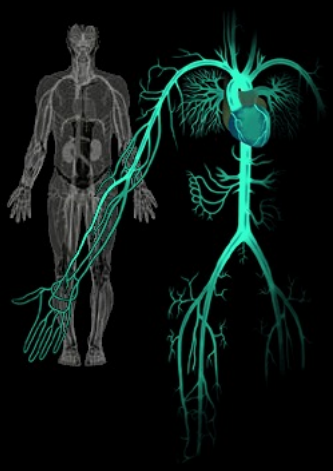
Does pure Alzheimer's disease exist?

- Diabetes
- Insulin resistance
- High blood pressure and hypertension
- Atrial fibrillation
- Hypercholesterolemia
- Midlife central obesity
- APOE
- Presumably, increase risk for AD is due to proximal vascular damage in the brain
- Cumulative vascular burden may put the brain's white matter at particular risk of injury



www.graphicshunt.com

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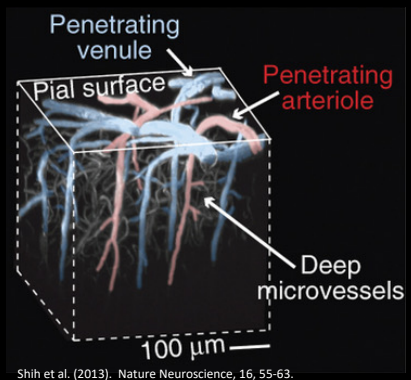
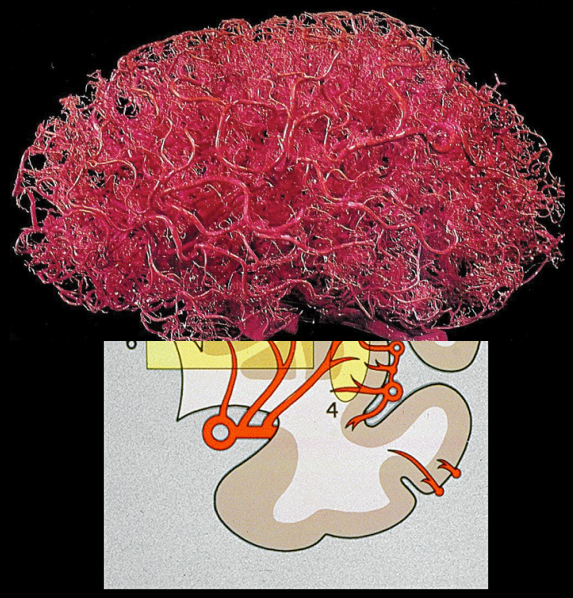
Why might white matter be particularly vulnerable?



Shih et al. (2013). Nature Neuroscience, 16, 55-63.



Fotuhi (2009), Nature Rev, Neurol; Moody et al (1990). AJNR, 11, 431-439

- Vascular supply throughout the brain is not uniform.
- WM is perfused mostly by delicate arterioles that are quite vulnerable to damage or pathology

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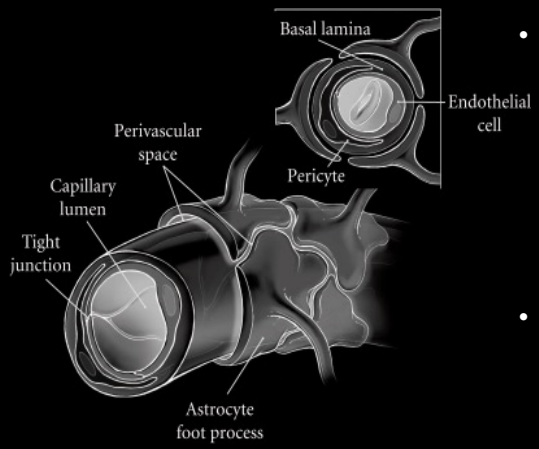
Why might white matter be particularly vulnerable?

BBB breakdown



Anderson VC et al. (2011). Cardiovasc Psychiatry Neurol

- Arterioles/capillaries in WM are particularly delicate and leaky
- Astrocytes form tight junctions with the capillaries (BBB)
- Damage to the capillaries and/or astrocytes can make vessels more leaky, allowing toxic materials to enter and reducing blood flow, nutrient delivery, and the ability to clear toxic material, increasing risk of neuronal damage
- Damage can be caused by factors that accumulate across the lifespan (genetic, HTN, inflammation, mechanical injury, oxidative stress, etc) and/or by frank pathology (Aβ)

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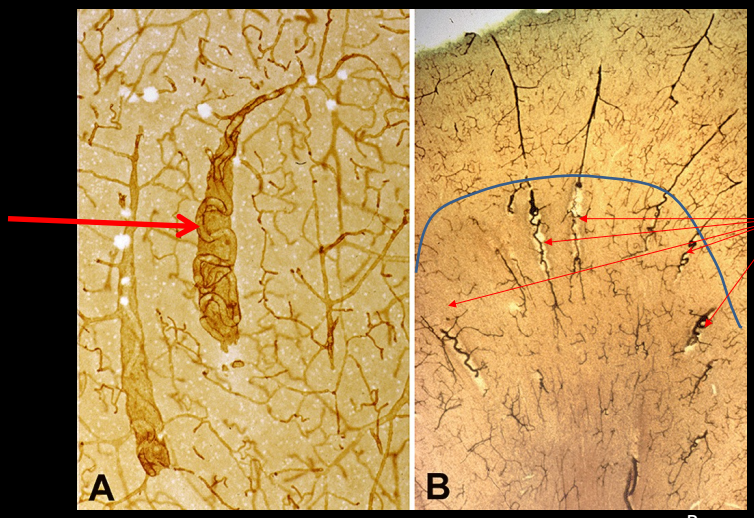
Why might white matter be particularly vulnerable?

Tortuous arterioles



Brown WR et al., 2002, J Neurol Sci

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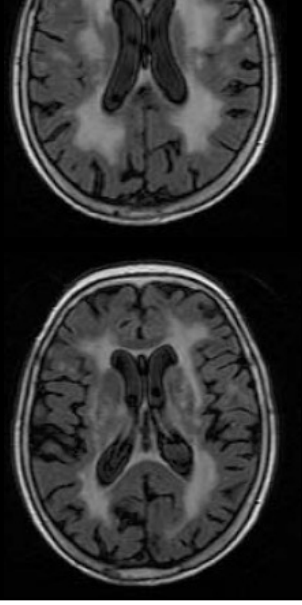
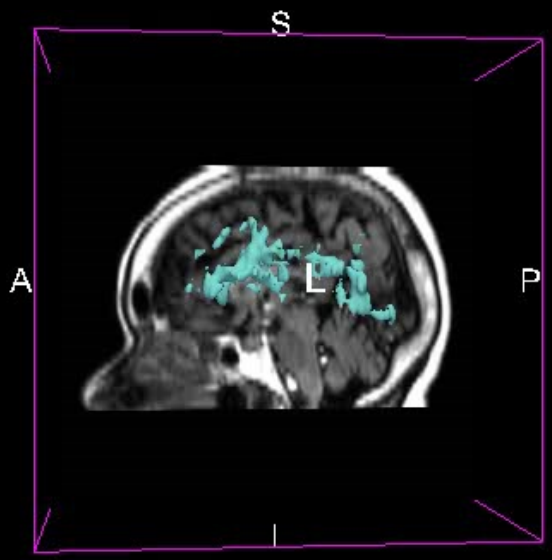
WMH





With Frank Provenzano, Jordan Muraskin, Atul Narkhede, and Kay Igwe

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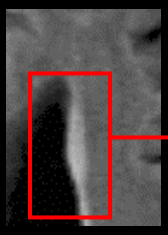
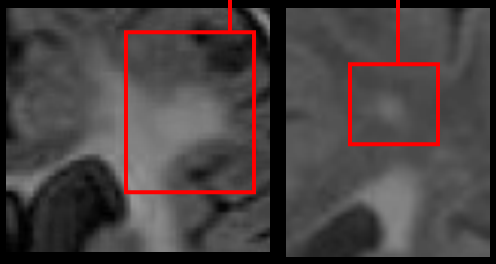
Pathology



Non-ischemic, demylenation secondary to ependymal gliosis, WM rarefaction



Ischemic in nature, perivascular reduction in lining, rarefaction of myelin, fiber loss, arteriolar sclerosis, etc. Pathogenic mechanisms?

Most consider WMH to reflect rarefaction of white matter secondary to small-vessel occlusive disease*

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Overall questions

- Are white matter hyperintensities, as a marker of small vessel disease, a core feature of AD and involved with the pathogenesis and/or clinical presentation of AD?
- Do WMH interact with other biological markers of AD and what drives that interaction?
- Can we leverage neuroimaging to inform our conceptualization of AD and identify potential treatment targets?

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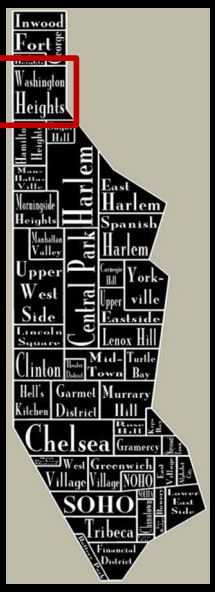
WHICAP & Offspring: Imaging

The Offspring Study
BRAIN HEALTH MATTERS
LA SALUD CEREBRAL IMPORTA

		OFFSPRING	WHICAP
N		~550	~1800
Age		55±10	73±5
Sex/Gender, % women		65%	61%
Race/ethnicity, %	Non-Latinx White	7%	25%
	Black/African American	24%	35%
	Latinx	69%	40%



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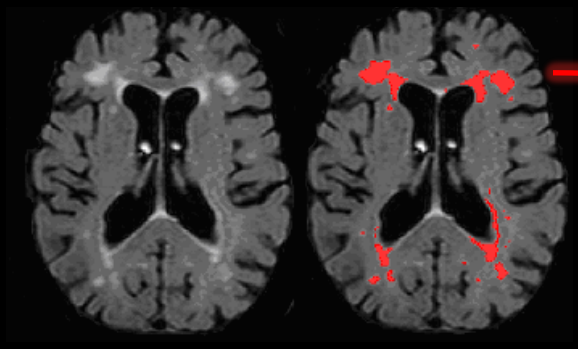
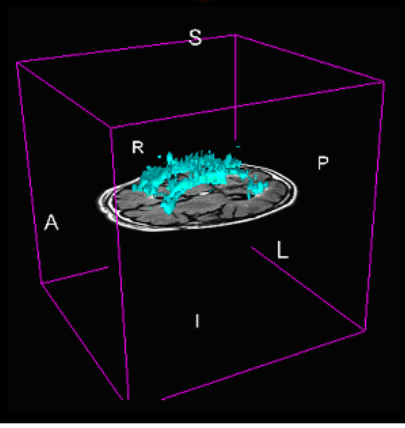
WHICAP imaging





- Standard T2-weighted FLAIR images.
- WMH volume calculated with intensity-driven algorithm.

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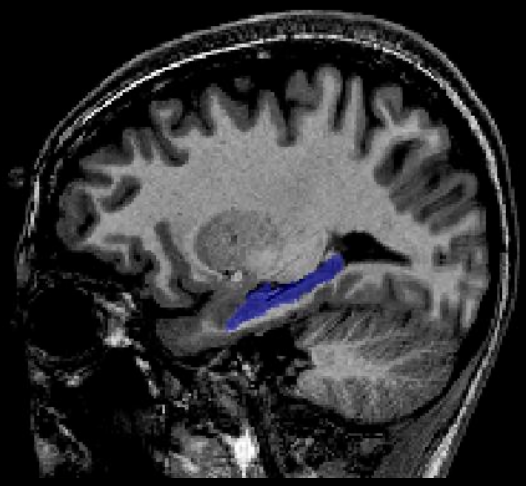
WHICAP imaging



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MCI

- Neuropsychological battery:
  - Memory
  - Language
  - Processing speed/ Executive function
  - Visuospatial abilities

- Cognitively normal (n=508)
- Amnestic MCI (n=97): Impairment in memory function
- Non-amnestic MCI (n=74): Impairment in non-memory domains
- Alzheimer's disease (n=52)

Luchsinger, Brickman, et al., 2009, Neurology

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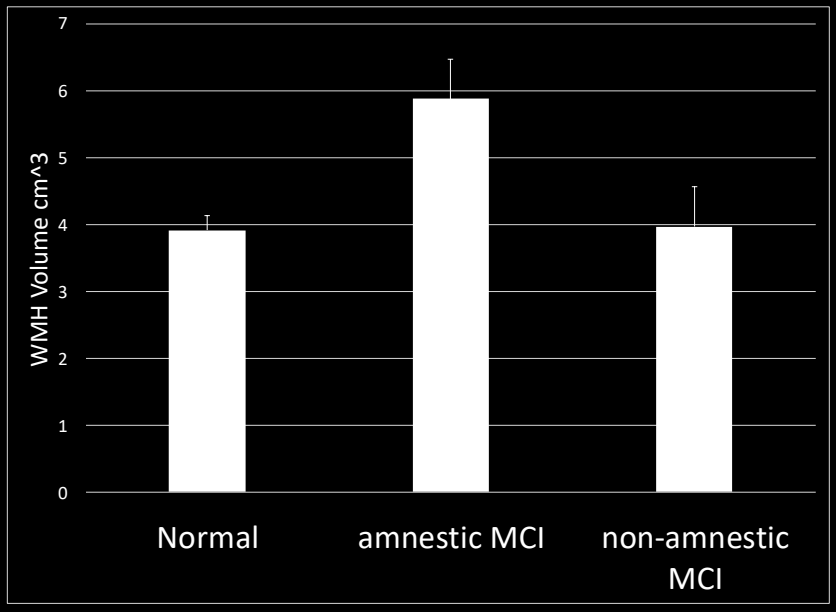
MCI



Adapted from Luchsinger, Brickman, et al., 2009, Neurology, 11;73(6):450-6

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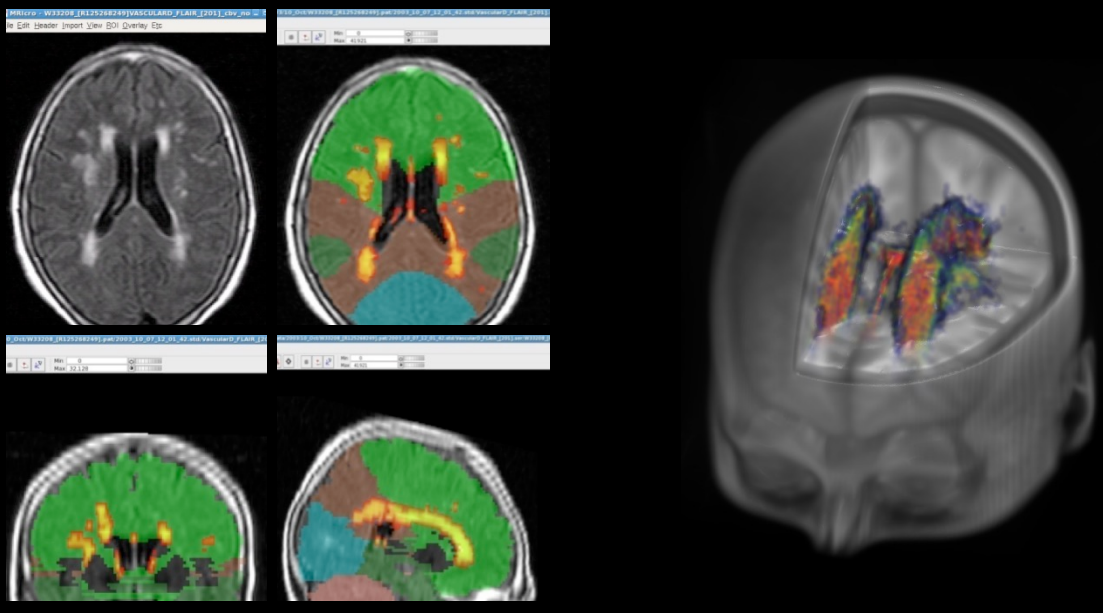
Regional specificity



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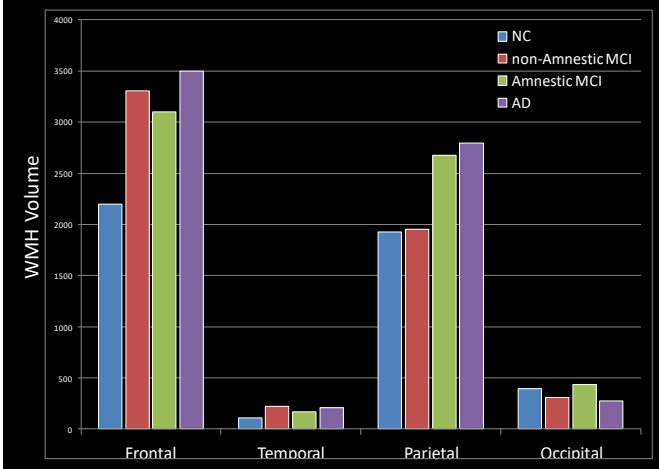
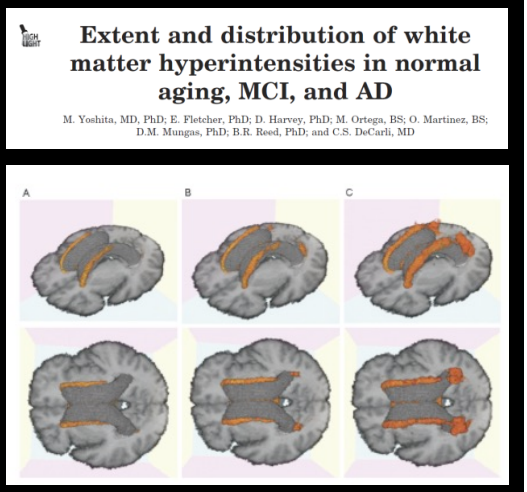
AD: Regional specificity





Extent and distribution of white matter hyperintensities in normal aging, MCI, and AD

M. Yoshita, MD, PhD; E. Fletcher, PhD; D. Harvey, PhD; M. Ortega, BS; O. Martinez, BS; D.M. Mungas, PhD; B.R. Reed, PhD; and C.S. DeCarli, MD

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Regional specificity: predicting AD (future decline)

	HR	P
Age	1.075	0.032
Frontal WMH	0.949	0.424
Temporal WMH	1.116	0.903
Parietal WMH	1.197	0.049
Occipital WMH	0.221	0.156
Hippocampal volume	0.302	0.701

Controlling for APOE e4, education*, sex, ethnicity

Brickman, et al, 2012

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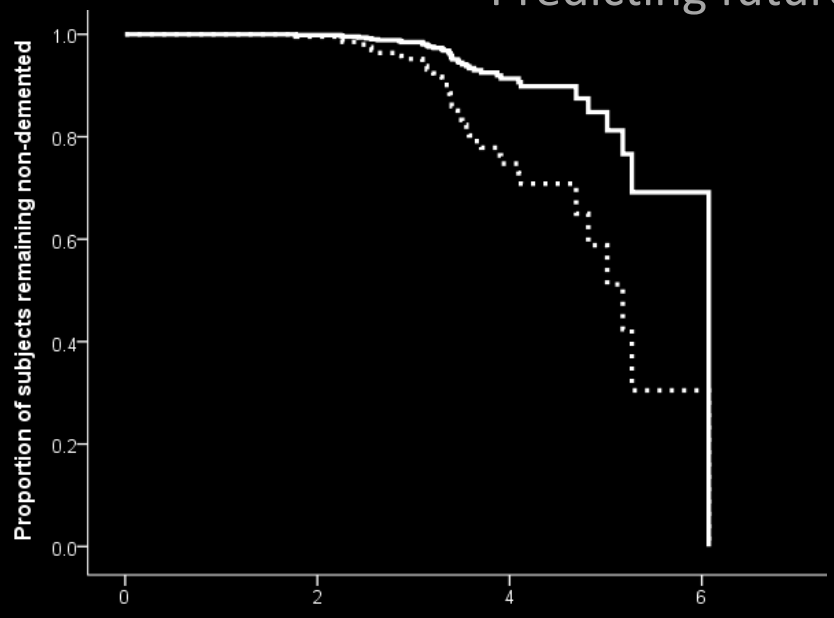
Predicting future decline



Brickman, et al., 2012

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DO WMH AND AD RISK HANG TOGETHER?

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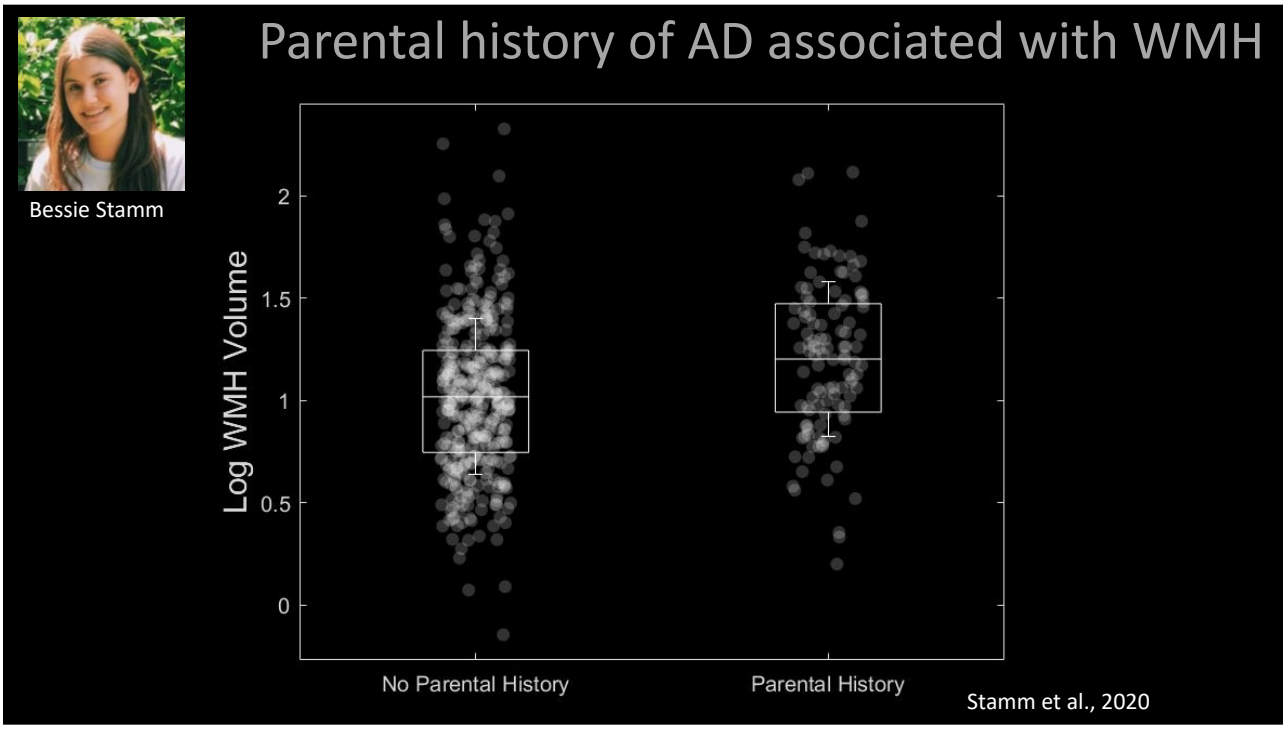
Parental history of AD associated with WMH
Bessie Stamm
Log WMH Volume
2
1.5
1
0.5
0
No Parental History
Parental History
Stamm et al., 2020

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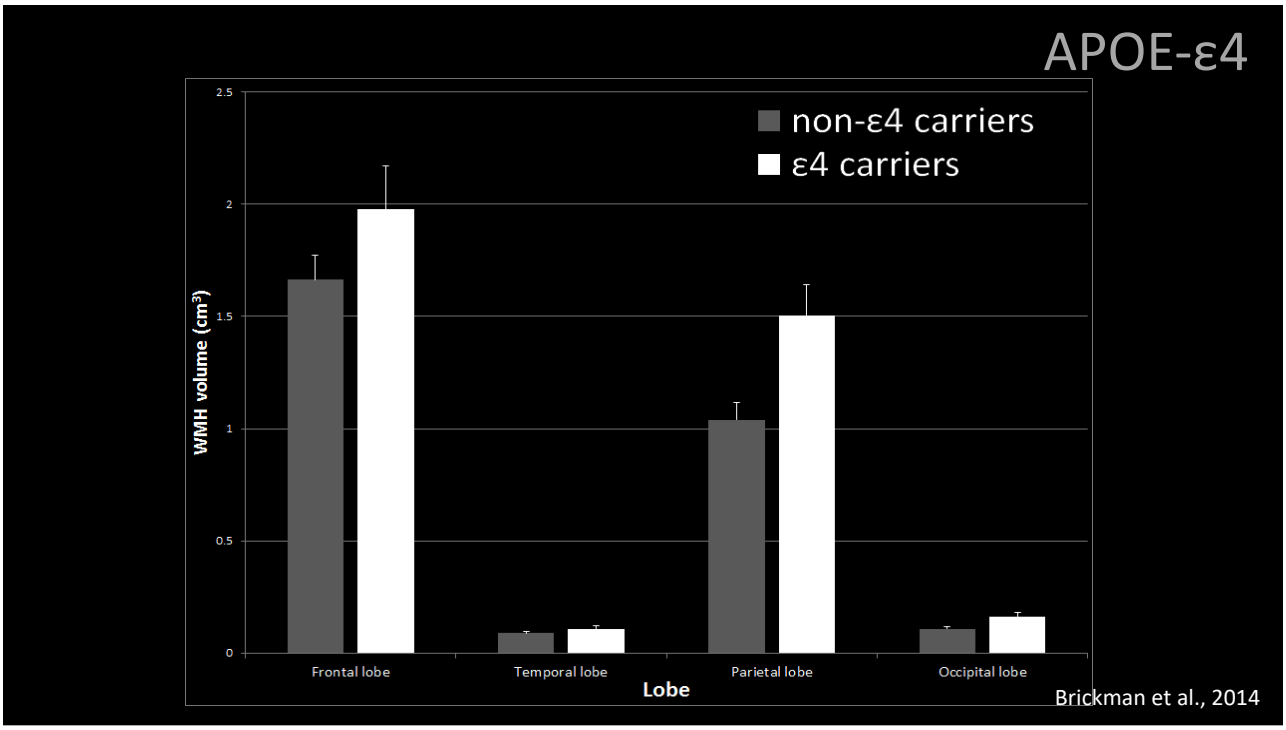
APOE-ε4
non-ε4 carriers
ε4 carriers
WMH volume (cm³)
2.5
2
1.5
1
0.5
0
Frontal lobe
Temporal lobe
Parietal lobe
Occipital lobe
Lobe
Brickman et al., 2014

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Can genetic forms of AD inform the question?

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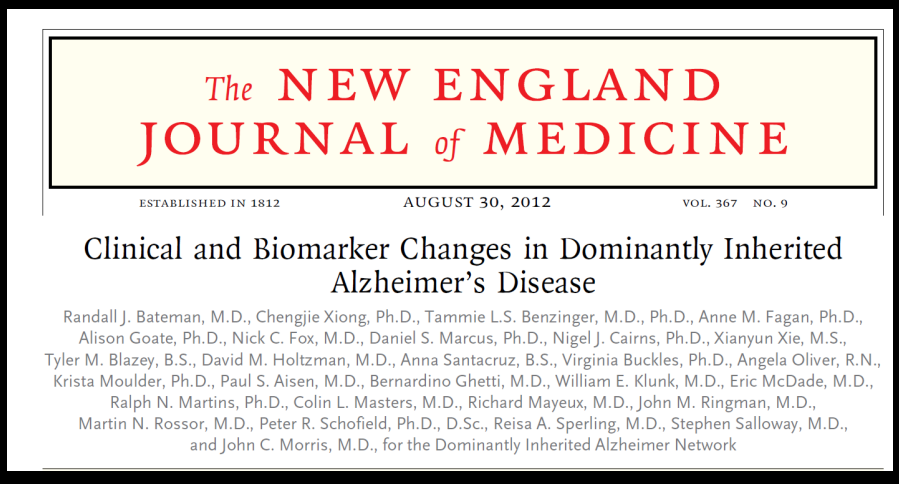
DIAN Study: Genetically-determined AD



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 30, 2012 VOL. 367 NO. 9

Clinical and Biomarker Changes in Dominantly Inherited Alzheimer's Disease

Randall J. Bateman, M.D., Chengjie Xiong, Ph.D., Tammie L.S. Benzinger, M.D., Ph.D., Anne M. Fagan, Ph.D., Alison Goate, Ph.D., Nick C. Fox, M.D., Daniel S. Marcus, Ph.D., Nigel J. Cairns, Ph.D., Xianyun Xie, M.S., Tyler M. Blazey, B.S., David M. Holtzman, M.D., Anna Santacruz, B.S., Virginia Buckles, Ph.D., Angela Oliver, R.N., Krista Moulder, Ph.D., Paul S. Aisen, M.D., Bernardino Ghetti, M.D., William E. Klunk, M.D., Eric McDade, M.D., Ralph N. Martins, Ph.D., Colin L. Masters, M.D., Richard Mayeux, M.D., John M. Ringman, M.D., Martin N. Rossor, M.D., Peter R. Schofield, Ph.D., D.Sc., Reisa A. Sperling, M.D., Stephen Salloway, M.D., and John C. Morris, M.D., for the Dominantly Inherited Alzheimer Network

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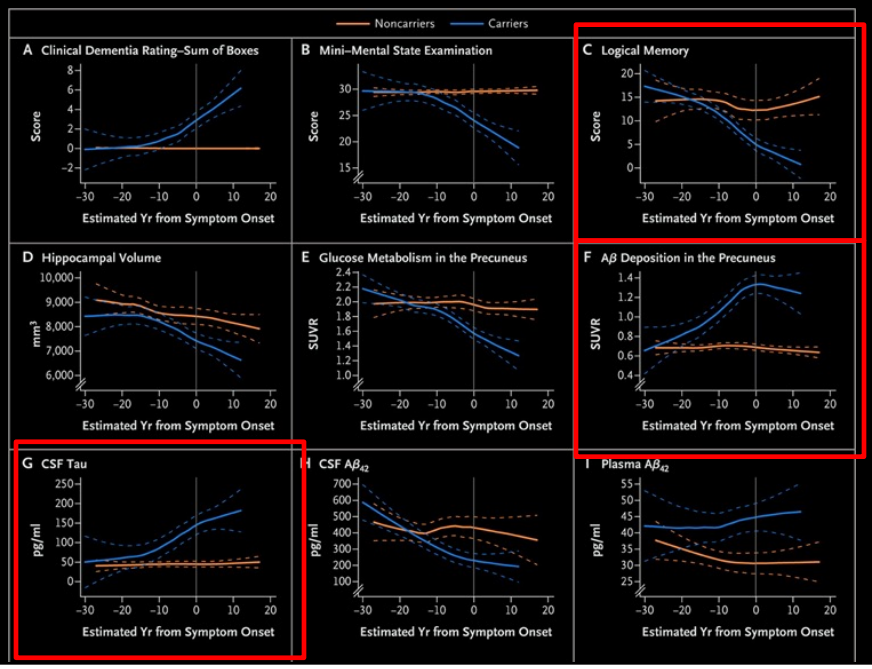
DIAN Study



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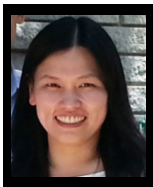
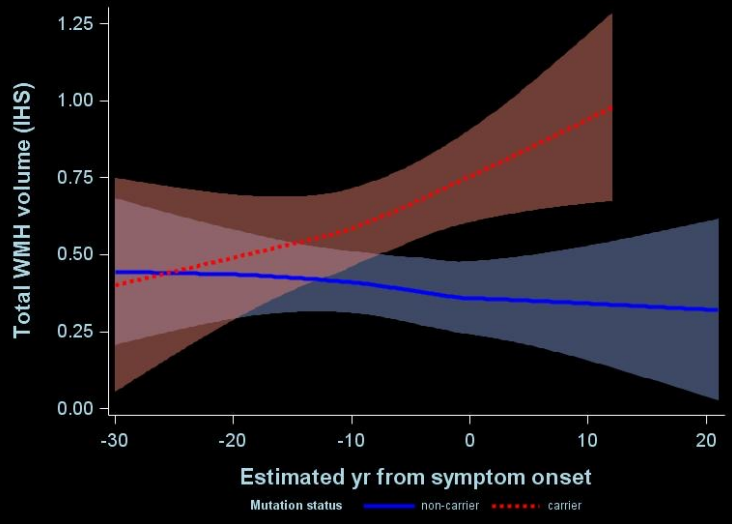
DIAN Study: Total WMH



Seonjoo Lee



Inflection point = 6 years prior to expected symptom onset

Seonjoo Lee et al 2016

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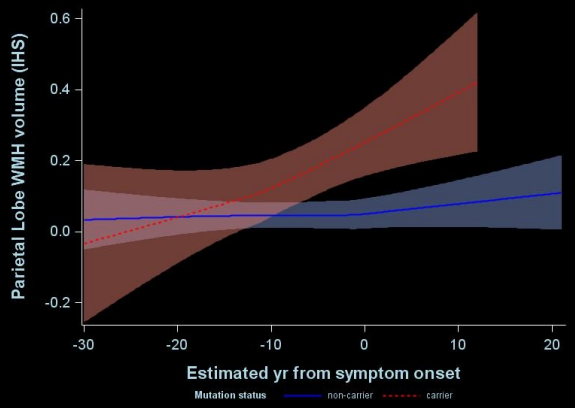
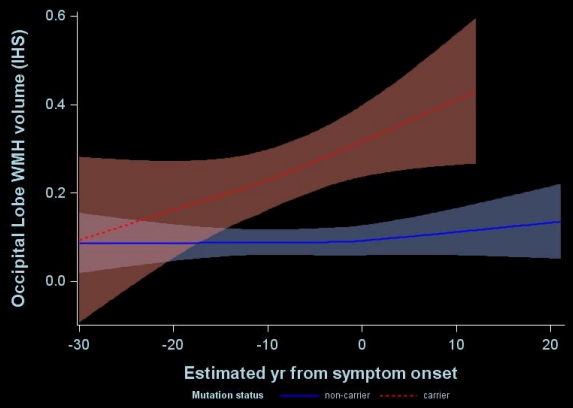
DIAN Study: WMH



Inflection point = 7 years prior to expected symptom onset



Inflection point = 22 years prior to expected symptom onset

Seonjoo Lee et al 2016

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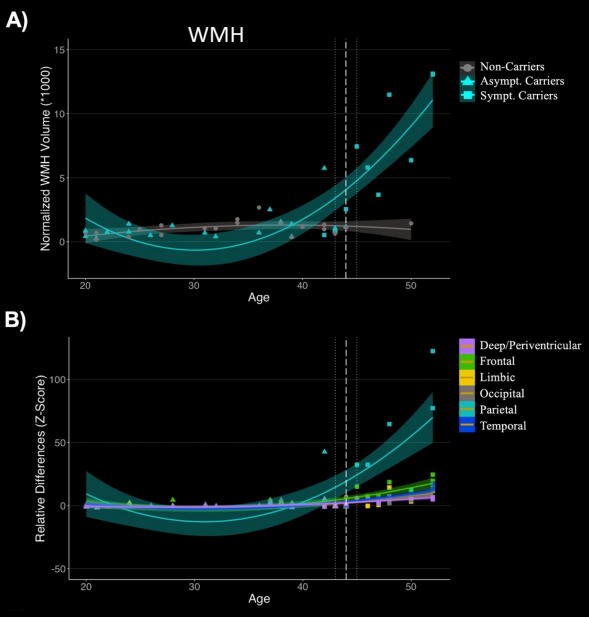
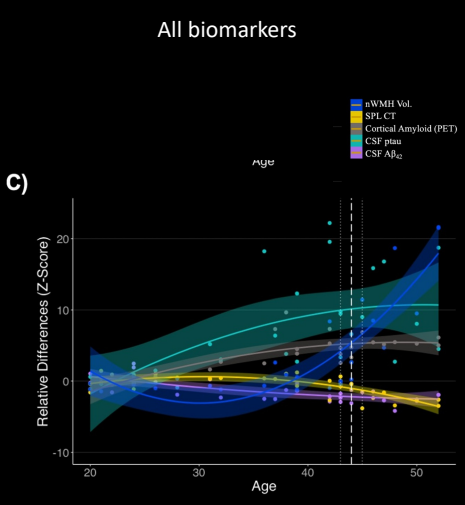
Colombia-Boston Biomarker Study of ADAD

Yakeel Quiroz

Dorothee Schoemaker





Shoemaker et al., 2022

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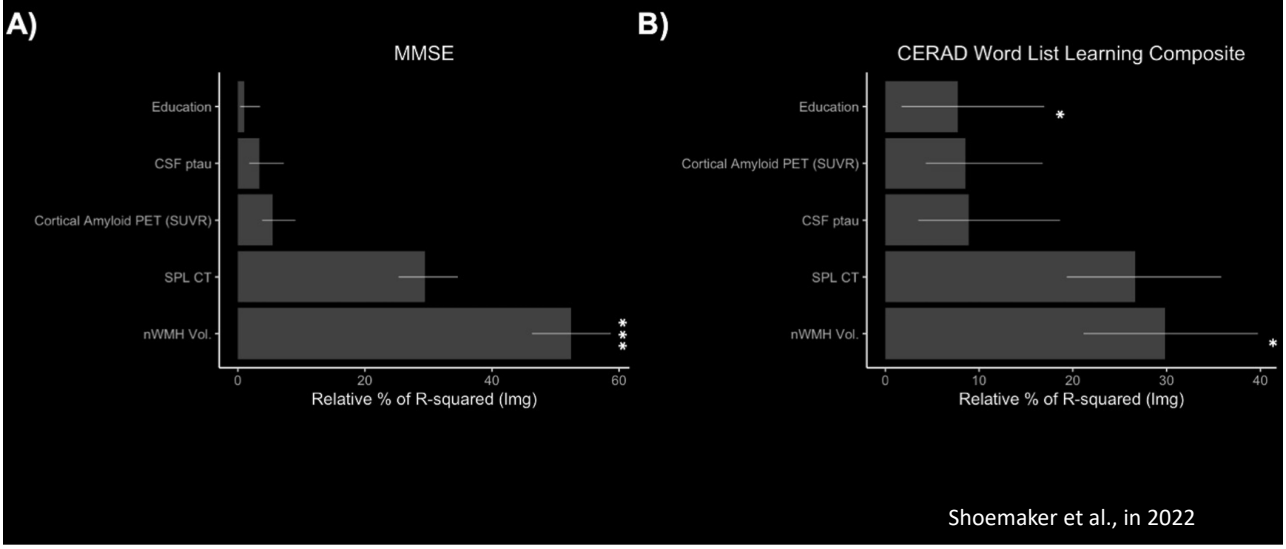
Colombia-Boston Biomarker Study of ADAD



Shoemaker et al., in 2022

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NIH National Institute on Aging

Alzheimer's Biomarkers Consortium — Down Syndrome (ABC-DS)

ADDS STUDY; https://www.nia.nih.gov/research/abc-ds

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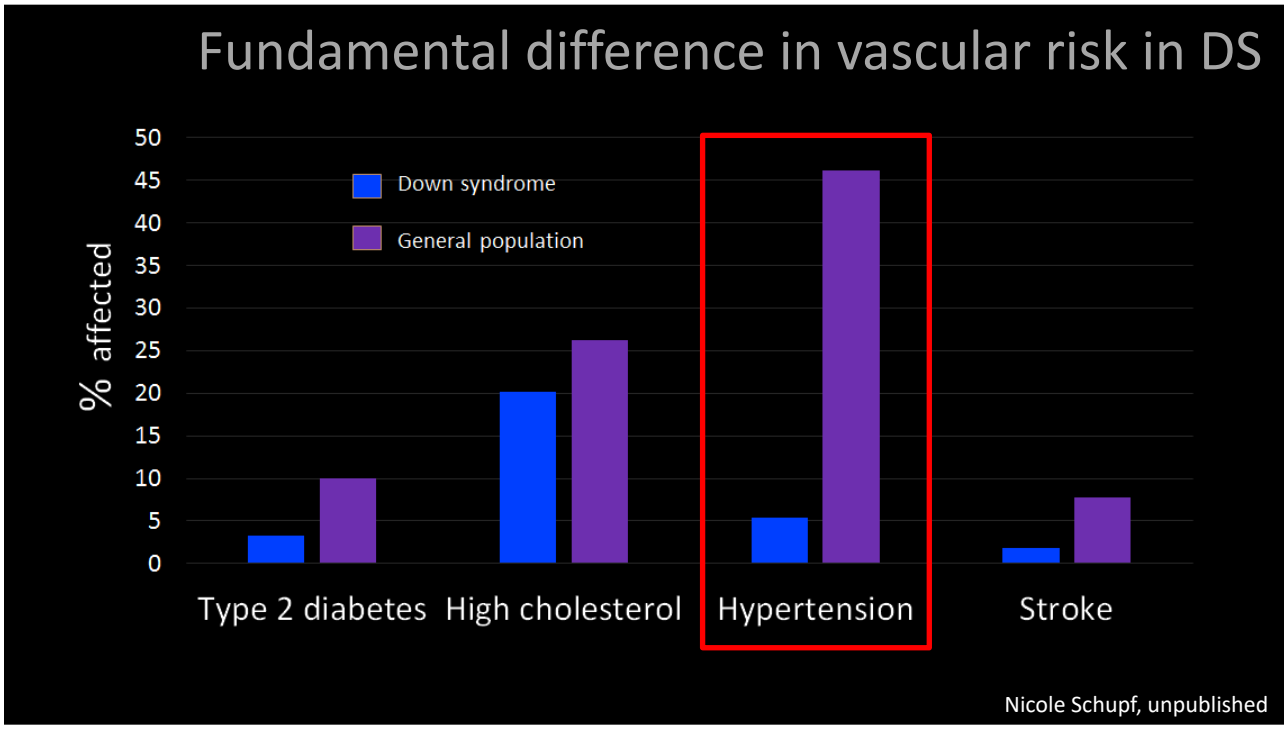
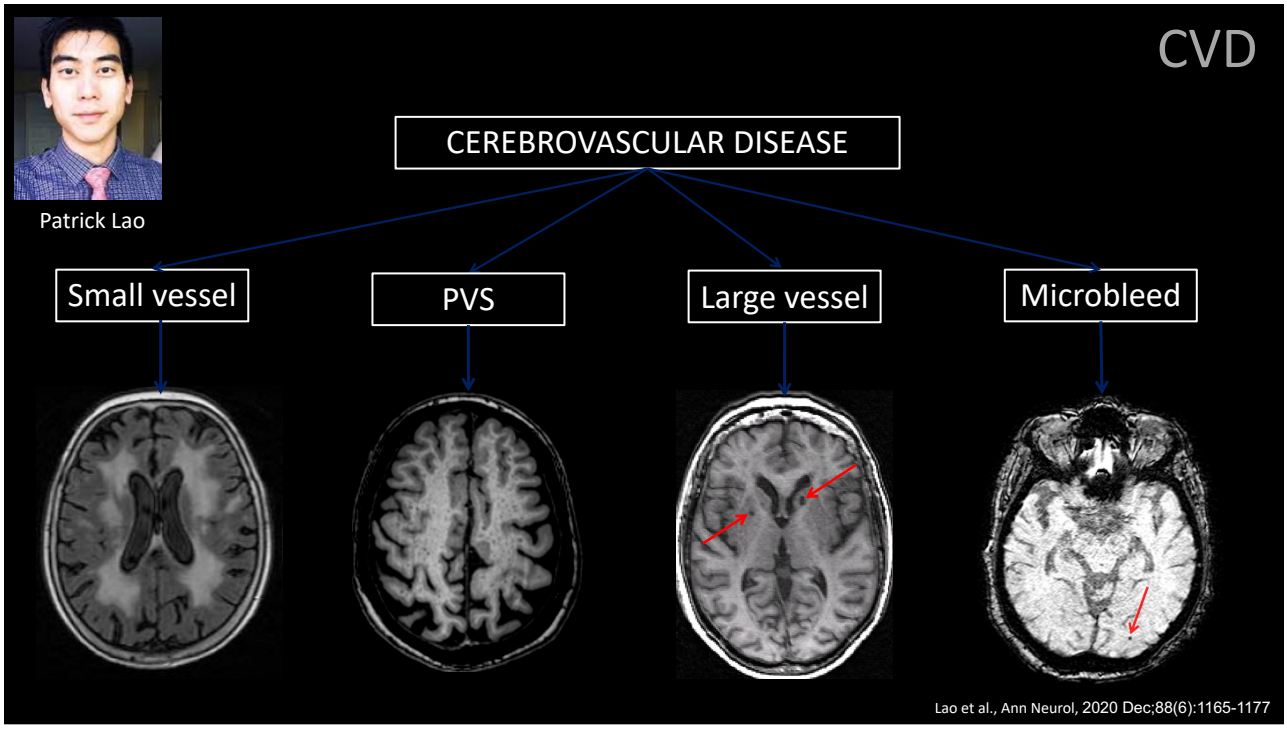

Fundamental difference in vascular risk in DS
% affected
50
45
40
35
30
25
20
15
10
5
0
Down syndrome
General population
Type 2 diabetes
High cholesterol
Hypertension
Stroke
Nicole Schupf, unpublished

40


CVD
Patrick Lao
CEREBROVASCULAR DISEASE
Small vessel
PVS
Large vessel
Microbleed
Lao et al., Ann Neurol, 2020 Dec;88(6):1165-1177

41

MRI participants

		Cognitively Normative	MCI	Possible AD dementia	Probable AD dementia	Total
MRI subset	N	79	24	7	11	121
	Age [yrs]	49 ± 6	53 ± 6*	55 ± 8*	56 ± 7*	51 ± 7
	% Women	44	25	57	45	40
PET subset	N	57	16	5	7	85
	Age [yrs]	49 ± 6	54 ± 6*	55 ± 8*	52 ± 6	50 ± 7
	% Women†	40	6	60	43	35

Table 1. Demographic characteristics of the MRI and PET subsets. * $p<0.05$ compared to Cognitively Normative. † $p<0.05$ across cognitive stage groups.

Lao et al., Ann Neurol, 2020 Dec;88(6):1165-1177

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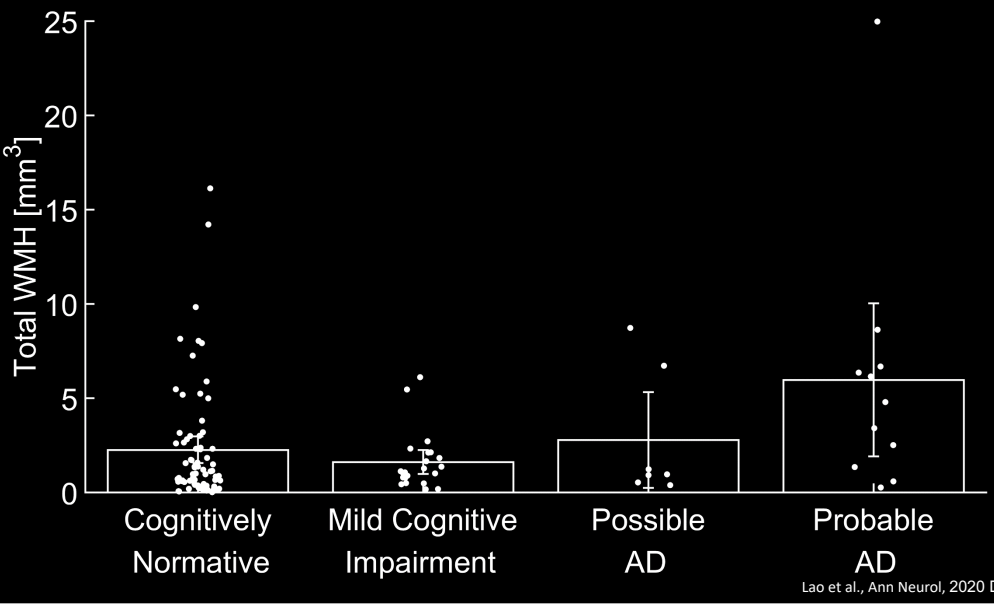
Total WMH volume



Lao et al., Ann Neurol, 2020 Dec;88(6):1165-1177

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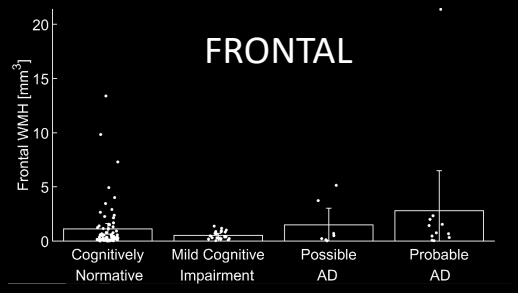
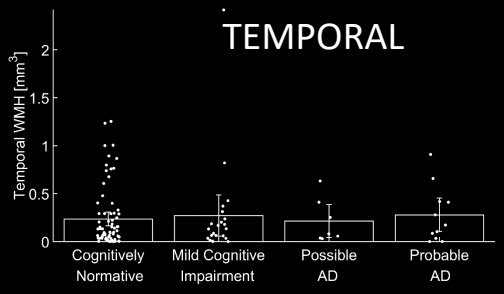
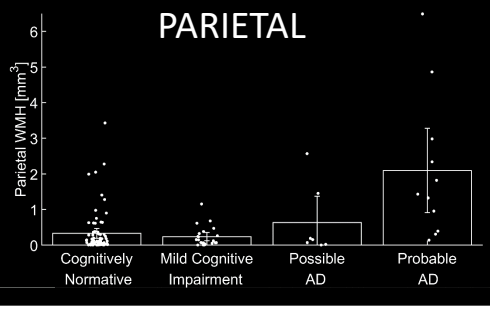
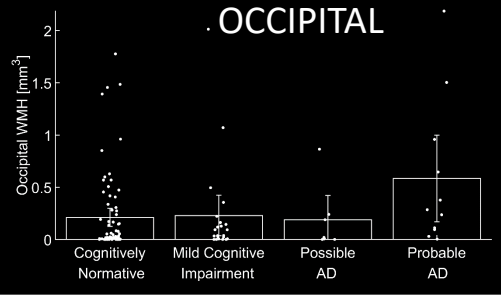
Regional WMH volume









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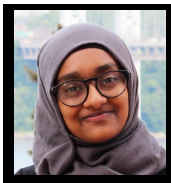
Angiogenesis and inflammation

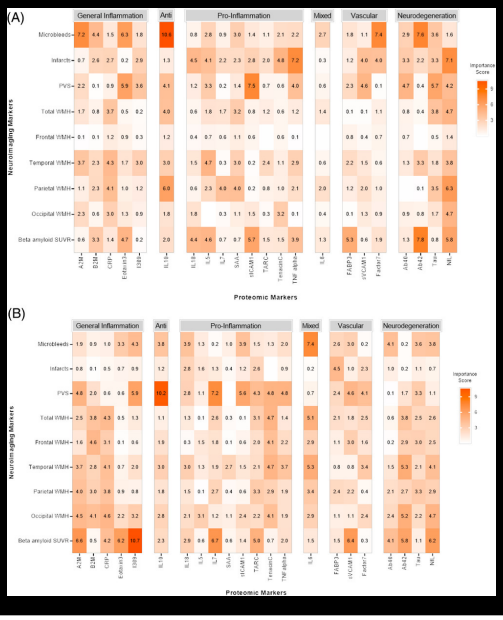


Fahmida Moni

Received: 24 August 2021 | Revised: 16 January 2022 | Accepted: 25 January 2022
DOI: 10.1002/alz.12627
ALTERNATE FORMAT RESEARCH ARTICLE
Alzheimer's & Dementia
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

Probing the proteome to explore potential correlates of increased Alzheimer's-related cerebrovascular disease in adults with Down syndrome

Fahmida Moni[1] | Melissa E. Petersen[2] | Fan Zhang[2] | Patrick J. Lao[1,3] | Molly E. Zimmerman[4] | Yian Gu[1,2,5] | José Gutierrez[3] | Batool Rizvi[1] | Krystal K. Laing[1] | Kay C. Igwe[1] | Mithra Sathishkumar[6,7] | David Keator[7] | Howard Andrews[1] | Sharon Krinsky-McHale[8] | Elizabeth Head[9] | Joseph H. Lee[1,5,10] | Florence Lai[11] | Michael A. Yassa[6,7] | H. Diana Rosas[11,12] | Wayne Silverman[13] | Ira T. Lott[13] | Nicole Schupf[1,3,5,10] | Sid O'Bryant[2] | Adam M. Brickman[1,3,10]



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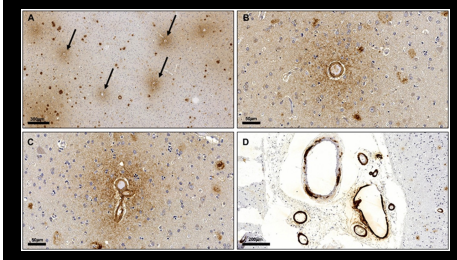
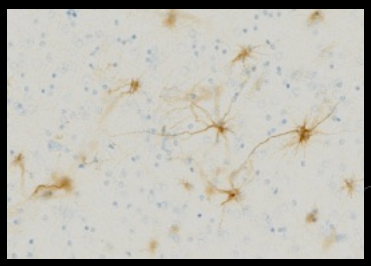
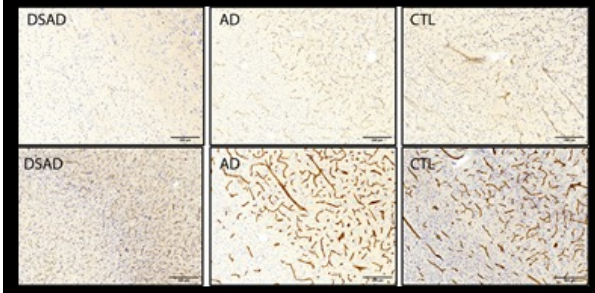
Cerebrovascular contributions to AD in DS



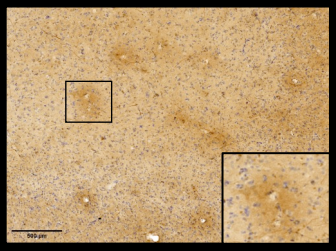
Amyloid angiopathy



Astrocyte phenotypes



Reduced pericytes (CD18)



BBB breakdown (fibrinogen)

Liz Head

46

DO WMH AND Aβ PATHOLOGY INTERACT?

47

Frank Provenzano

WMH x AD pathology (ADNI)

ORIGINAL CONTRIBUTION

White Matter Hyperintensities and Cerebral Amyloidosis

Necessary and Sufficient for Clinical Expression of Alzheimer Disease?

Frank A. Provenzano, MS; Jordan Muraskin, MS; Giuseppe Tosto, MD; Atul Narkhede, MS; Ben T. Wasserman, AB; Erica Y. Griffith, BS; Vanessa A. Guzman, BA; Irene B. Meier, MSc; Molly E. Zimmerman, PhD; Adam M. Brickman, PhD; for the Alzheimer's Disease Neuroimaging Initiative

Importance: Current hypothetical models emphasize the importance of β-amyloid in Alzheimer disease (AD) pathogenesis, although amyloid alone is not sufficient to account for the dementia syndrome. The impact of small-

Setting: The Alzheimer's Disease Neuroimaging Initiative public database.

Participants: The study involved data from 21 normal con-

Provenzano et al., 2013

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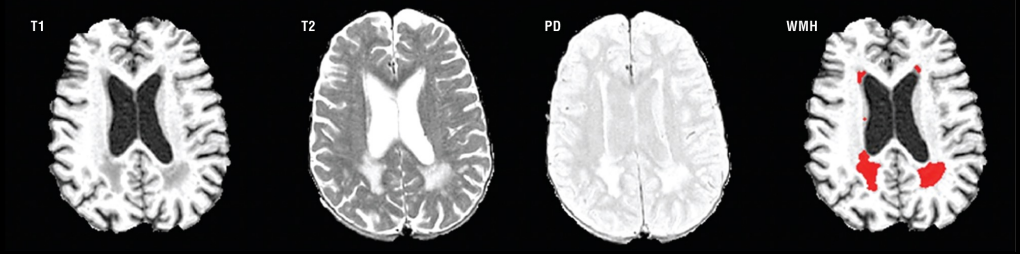
WMH x AD pathology (ADNI)

Table. Characteristics of Study Participants

	Mean (SD)			Statistic		
	NC	MCI	AD	Test	*P* Value	Post Hoc Comparison
No.	21	59	20			
Age, y	76.20 (5.97)	75.72 (7.86)	73.00 (8.55)	$F = 1.90$	.31	
Women, %	38	31	40	$\chi^2 = 0.798$	.67	
MMSE score	28.71 (1.35)	27.22 (1.95)	21.20 (4.28)	$F = 55.87$	<.001	NC>MCI>AD
Modified Hachinski score	0.67 (0.80)	0.67 (0.66)	0.70 (0.57)	$F = 0.020$	.98	
PIB+ individuals, %	52	70	85	$\chi^2 = 5.09$	.02, linear	
Cortical PIB uptake values	1.59 (0.36)	1.81 (0.41)	1.82 (0.35)	$F = 2.87$	.06	
Total WMH volume, cm^3	2.26 (2.80)	4.07 (5.78)	9.34 (9.84)	$F_{2,98} = 7.158$	.001	NC = MCI<AD

Abbreviations: AD, Alzheimer disease; PIB, Pittsburgh Compound B; MCI, mild cognitive impairment; MMSE, Mini Mental State Examination; NC, normal control; WMH, white matter hyperintensity.



Provenzano et al., 2013

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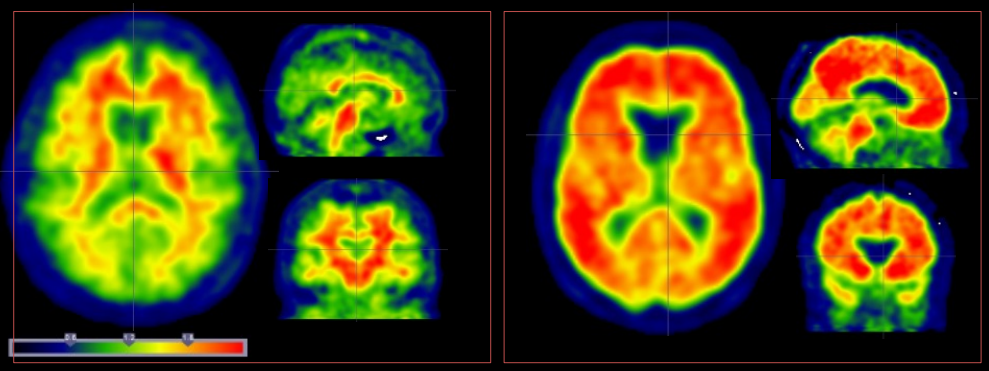
WMH x AD pathology (amyloid)



PIB negative PIB positive

Amyloid imaging

Provenzano et al., 2013

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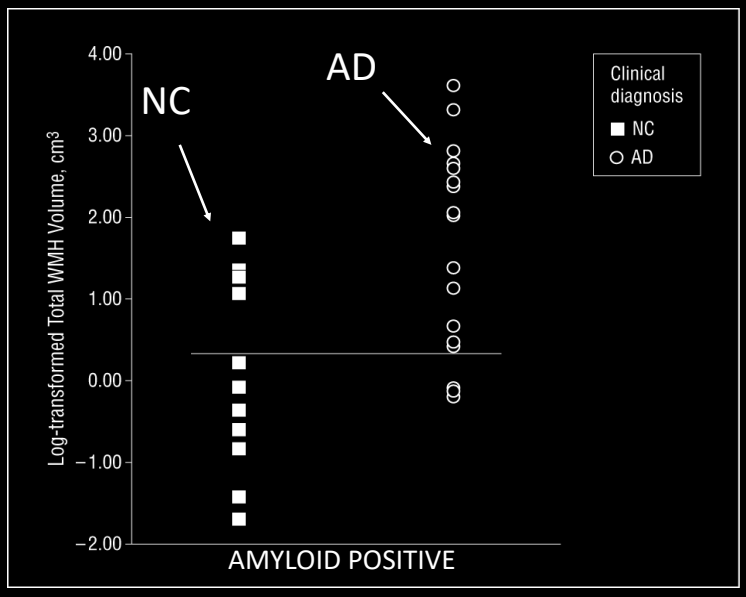
WMH x AD pathology (amyloid)



Among those with amyloidosis, those with clinical symptoms of AD had reliably higher WMH burden (83% sensitivity, 64% specificity).

Provenzano et al., 2013

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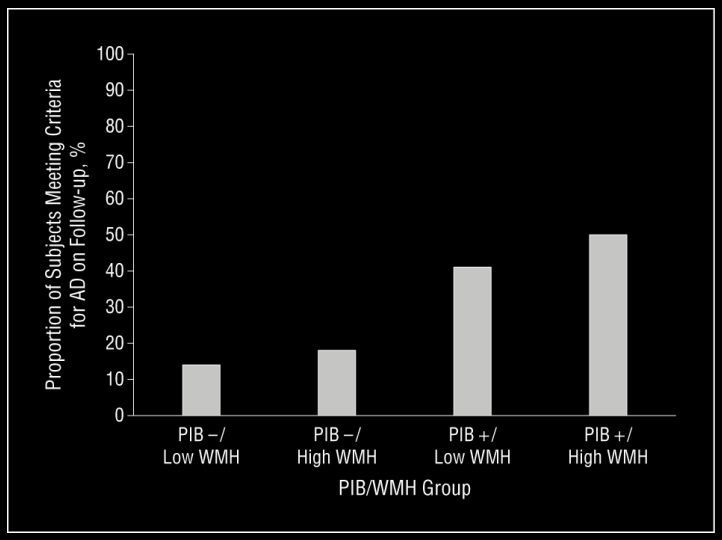
WMH x AD pathology (amyloid)



Both increased WMH and amyloid status predicted risk for future development of clinical AD among patients with MCI

Provenzano et al., 2013

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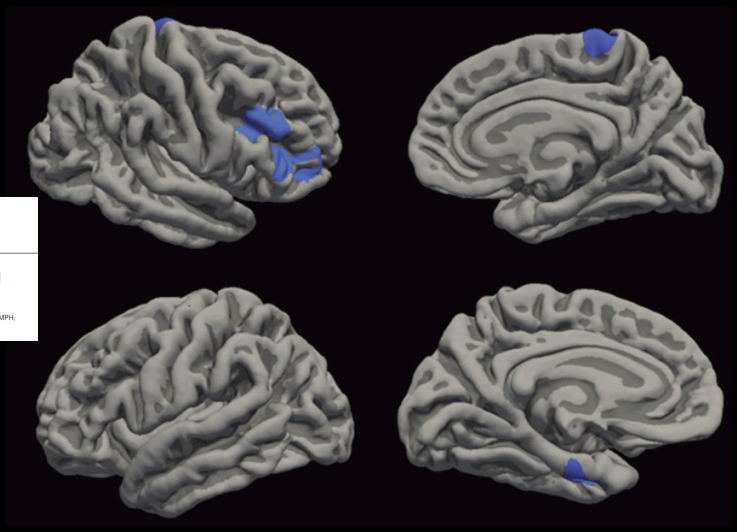
DOES CEREBROVASCULAR DISEASE DRIVE TAU PATHOLOGY?

53

Batool Rizvi

Small vessel CVD promotes neurodegeneration



JAMA Network | Open

Original Investigation | Neurology

Association of Regional White Matter Hyperintensities With Longitudinal Alzheimer-Like Pattern of Neurodegeneration in Older Adults

Batool Rizvi, MS; Patrick J. Lao, PhD; Anthony G. Chesebro, BS; Jordan D. Dworkin, PhD; Erica Amarante, BS; Juliet M. Beato, BA; Jose Gutierrez, MD, MPH; Laura B. Zahodne, PhD; Nicole Schupf, PhD; Jennifer J. Manly, PhD; Richard Mayeux, MD, MS; Adam M. Brickman, PhD

Rizvi et al., 2021

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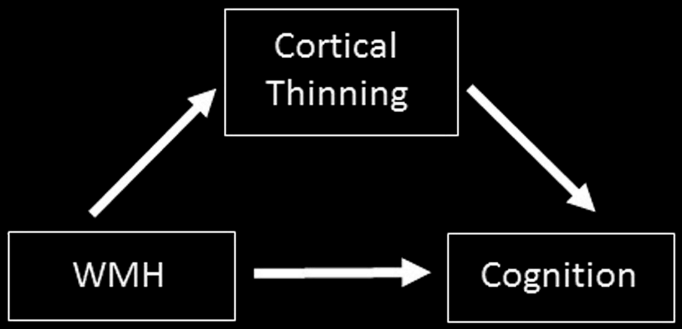
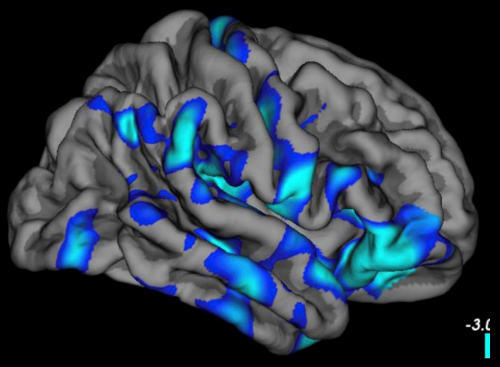
…which mediates cognitive impairment

2. Mediation Model



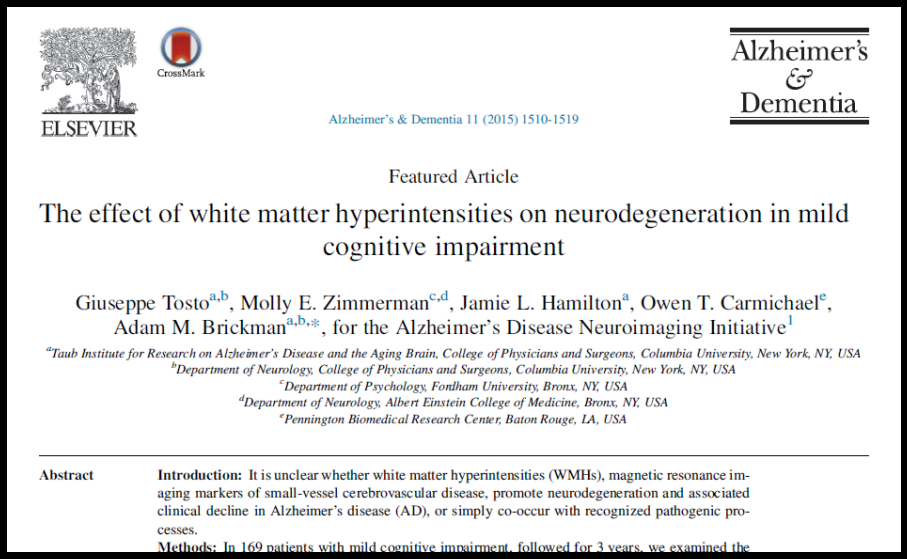


Rizvi et al., 2018

55

Giuseppe Tosto

WMH x AD pathology (tau)



ELSEVIER

CrossMark

Alzheimer's & Dementia 11 (2015) 1510-1519

Alzheimer's & Dementia

Featured Article

The effect of white matter hyperintensities on neurodegeneration in mild cognitive impairment

Giuseppe Tosto[a,b], Molly E. Zimmerman[c,d], Jamie L. Hamilton[a], Owen T. Carmichael[e], Adam M. Brickman[a,b,*], for the Alzheimer's Disease Neuroimaging Initiative[1]

[a]Taub Institute for Research on Alzheimer's Disease and the Aging Brain, College of Physicians and Surgeons, Columbia University, New York, NY, USA
[b]Department of Neurology, College of Physicians and Surgeons, Columbia University, New York, NY, USA
[c]Department of Psychology, Fordham University, Bronx, NY, USA
[d]Department of Neurology, Albert Einstein College of Medicine, Bronx, NY, USA
[e]Pennington Biomedical Research Center, Baton Rouge, LA, USA

Abstract **Introduction:** It is unclear whether white matter hyperintensities (WMHs), magnetic resonance imaging markers of small-vessel cerebrovascular disease, promote neurodegeneration and associated clinical decline in Alzheimer's disease (AD), or simply co-occur with recognized pathogenic processes.

Methods: In 169 patients with mild cognitive impairment, followed for 3 years, we examined the

Tosto et al. 2015

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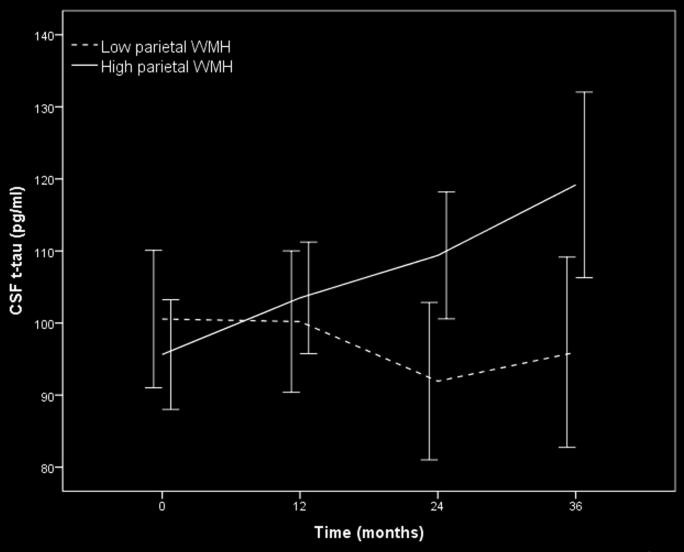
Does small vessel CVD cause neurodegeneration through tau?

More rapid accumulation of CSF tau among individuals with high (parietal lobe) WMH at baseline. Do WMH/ vascular disease potentiate intracellular sequestered tau or propagate the progression of tau pathology?



ADNI

Tosto et al. 2015

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doi:10.1093/braincomms/fcaa132 BRAIN COMMUNICATIONS 2020: Page 1 of 16 | 1

BRAIN COMMUNICATIONS

Cerebrovascular disease promotes tau pathology in Alzheimer's disease

Krystal K. Laing,[1] Sabrina Simoes,[1] Gloria P. Baena-Caldas,[2,3] Patrick J. Lao,[1] Milankumar Kothiya,[1] Kay C. Igwe,[1] Anthony G. Chesebro,[1] Alexander L. Houck,[1] Lina Pedraza,[2] A. Iván Hernández,[4,5] Jie Li,[2] Molly E. Zimmerman,[6] José A. Luchsinger,[7] Frank C. Barone,[2,5] Herman Moreno,[2,5] and Adam M. Brickman[1]; for the Alzheimer's Disease Neuroimaging Initiative*

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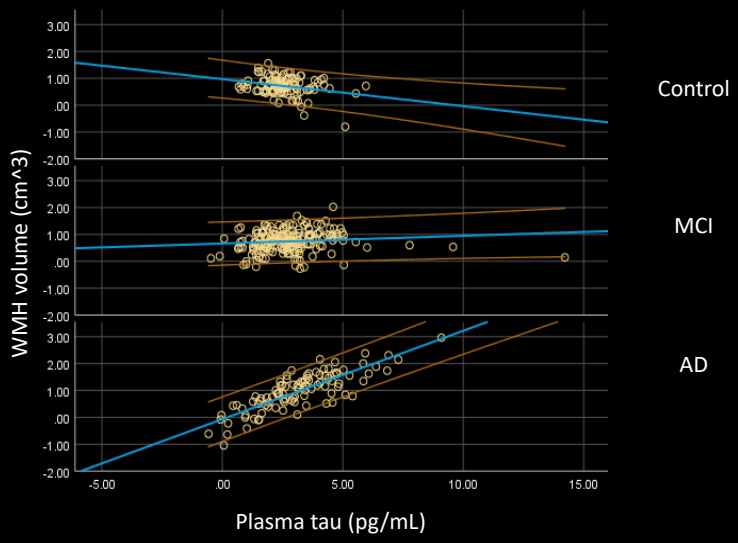
Does small vessel CVD cause neurodegeneration through tau?

Krystal Laing

Increase plasma total tau is associated with WMH volume as a function of diagnostic group.



ADNI

Laing et al., 2020

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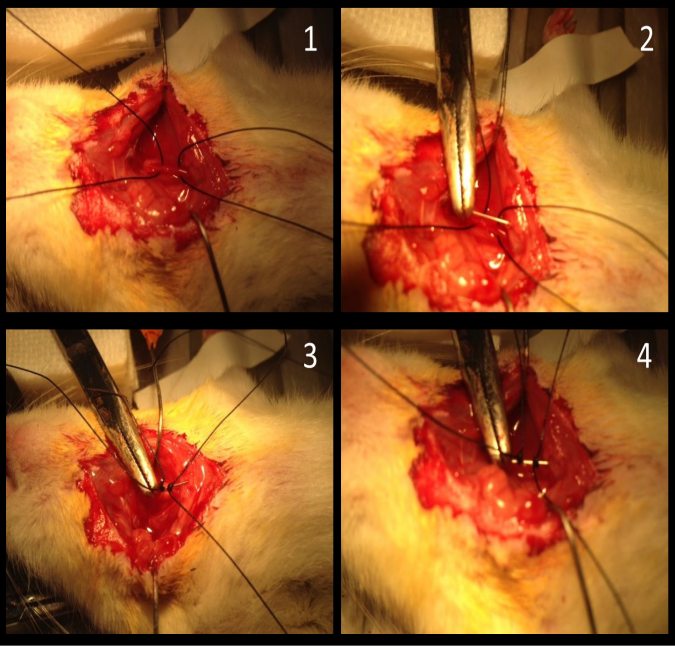
Transient MCA occlusion "WMH" model



Laing et al., 2020

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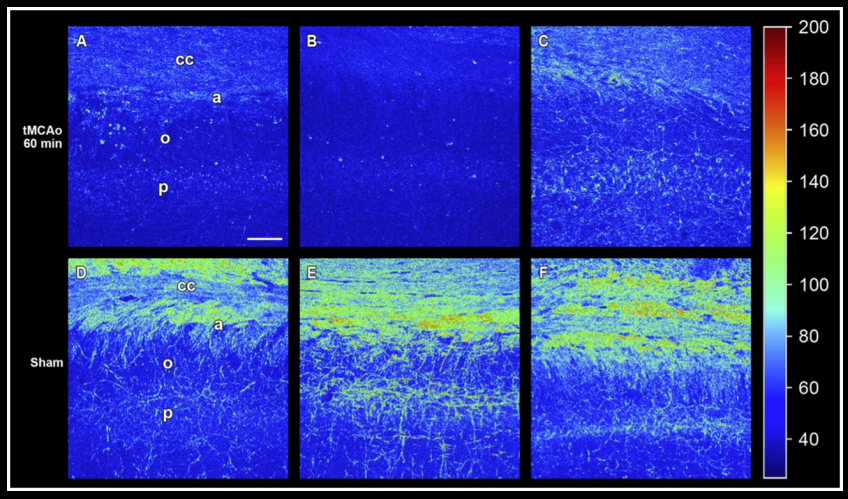
tMCAo induces white matter damage



Transient hypoperfusion induces "white matter hyperintensities" (MBP) in mice

Laing et al., 2020

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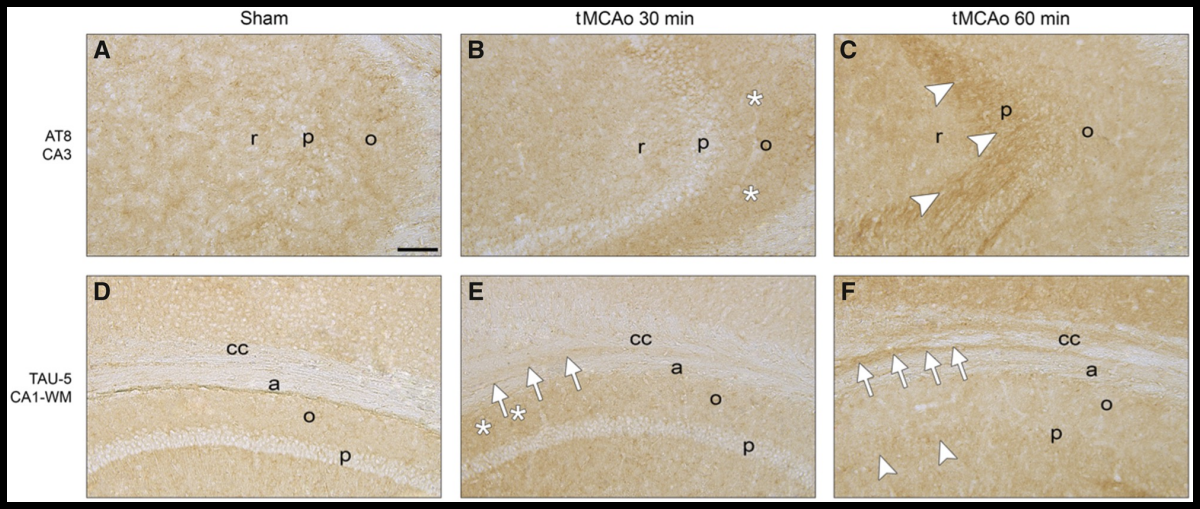
tMCAo induces tau hyperphosphorylation



Phospho tau (upper) and total tau (lower) immunostaining elevated in occluded mice (columns B and C) relative to sham (column A)

Laing et al., 2020

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Jennifer Rabin

Emma Nichols

CAA, tau, and cognition

https://doi.org/10.1093/brain/awac178 BRAIN 2022: 00; 1–11 | 1

BRAIN
ORIGINAL ARTICLE

Cerebral amyloid angiopathy interacts with neuritic amyloid plaques to promote tau and cognitive decline

Jennifer S. Rabin,[1,2,3,†] Emma Nichols,[4,†] Renaud La Joie,[5] Kaitlin B. Casaletto,[5] Priya Palta,[6] Kristen Dams-O'Connor,[7,8] Raj G. Kumar,[7] Kristen M. George,[9] Claudia L. Satizabal,[10,11] Julie A. Schneider,[12] Judy Pa[13] and Adam M. Brickman[14]

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Jennifer Rabin

Emma Nichols

CAA, tau, and cognition

1. CAA and neuritic plaque density share little variance
2. CAA drives tau pathology, which drives cognitive decline (tau mediates the effect of CAA on cognition), particularly among those with high neuritic plaque burden
3. Neuritic plaques drive tau pathology and cognitive decline particularly among those with high levels of CAA

Neuritic plaques and cerebrovascular disease in the form of CAA interact synergistically on tau pathology and cognitive decline

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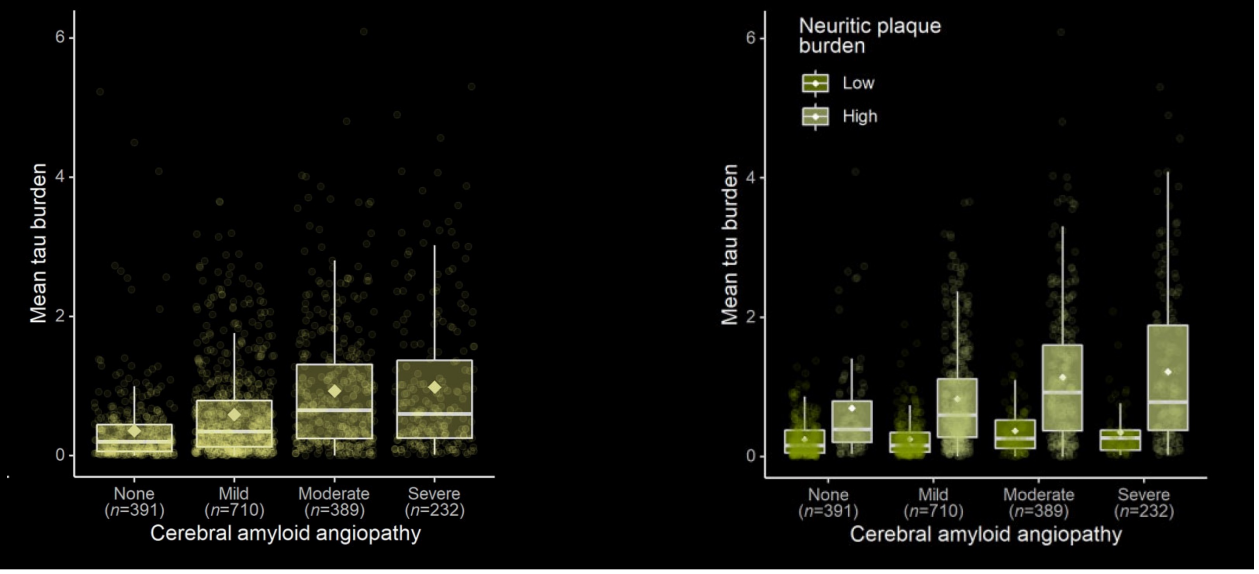
CAA, tau, and cognition



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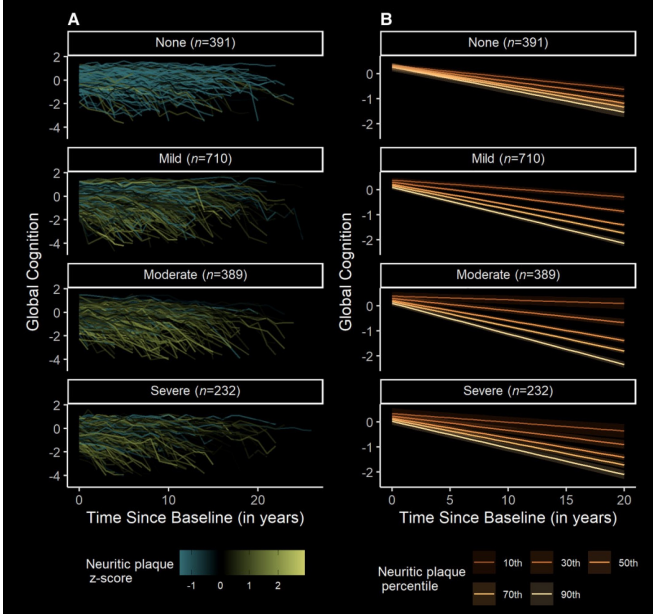
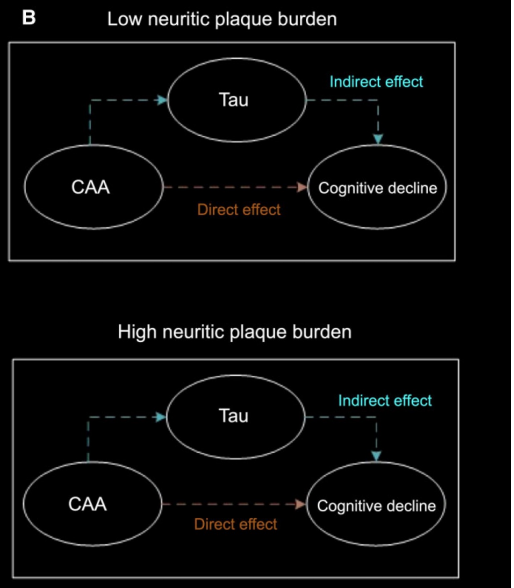
CAA, tau, and cognition





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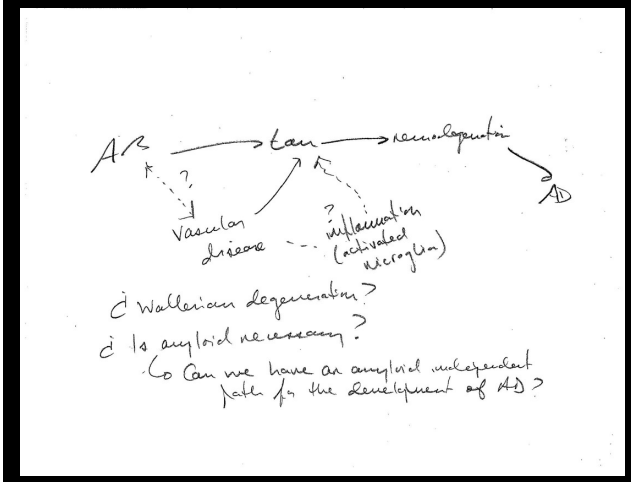
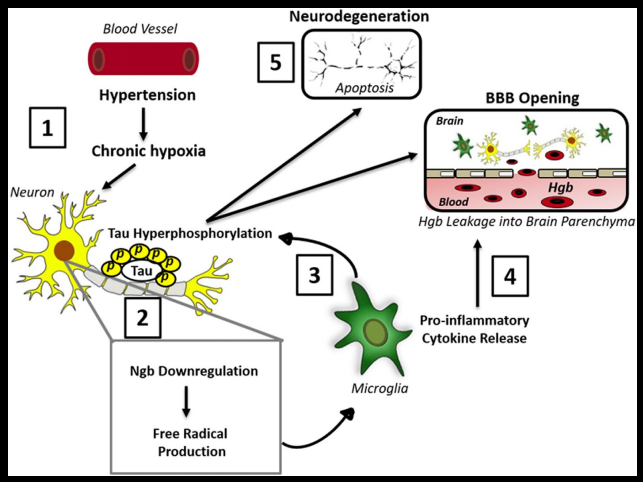
Vascular pathway to AD?



Brickman et al., 3am, sometime in July, 2019 *New York*



Raz, L…Rosenberg, GA., 2019, *Neurobiology of Disease*

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Conclusions

- Current diagnostic models for AD are insufficiently account for the reality of the disease
- Cerebrovascular disease appears to be an important component of the AD syndrome, at least by driving the phenotype and clinical incidence
- Cerebrovascular disease and amyloid pathology may interact in some critical ways to drive disease expression, such that CVD might be a "second hit" necessary for disease expression
- CVD might be contributing to dementia through tau hyperphosphorylation and neurodegeneration
- We can leverage neuroimaging to understand individual differences in sources of cognitive impairment and severity of disease
- Can we start targeting vascular disease and vascular risk to treat or prevent AD?

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What is AD and what isn't?

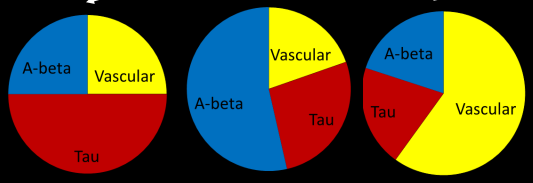
AD = Aβ (+ tau)

↓

With or without symptoms

vs.

Well-defined clinical syndrome with multiple diseases present



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Lab

Current
- Christiane Hale
- Andres Rivera
- Erica Amarante
- Amirreza Sedaghat
- Mohamad Alshikho
- Dejania Cotton-Samuel
- Yina Castillo
- Joncarlos Berroa
- Kelsang Bista
- Heather Shouel
- Rafael Lippert
- Clarissa Morales
- Andrea Benavides
- Jeffrey Pyne
- Indira Turney, PhD
- Lok-Kin Yeung, PhD
- Patrick Lao, PhD

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- Vanessa Guzman
- Erica Griffith
- Ben Wasserman
- Mariana Budge
- Cynthia Abinader
- Atul Narkhede
- Batool Rizvi
- Kay Igwe
- Juliet ColonLinggang Luo
- Alex Houck
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Thank you.

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