Reconsidering the role of vascular disease in Alzheimer's disease pathogenesis

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Disclosure

- Consultant and Scientific Advisory Board: Keystone Heart, LLC
- Consultant and Scientific Advisory Board: ProPhase, LLC

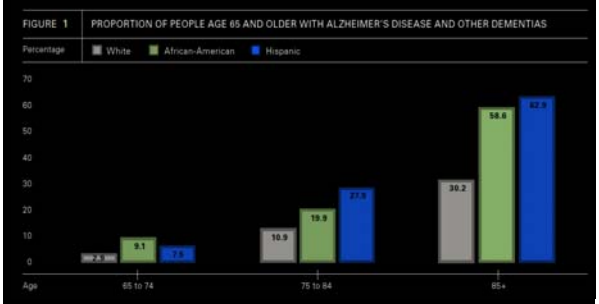
Disclosure

- I have either too many slides or too few slides.
- I am biased.

Agenda

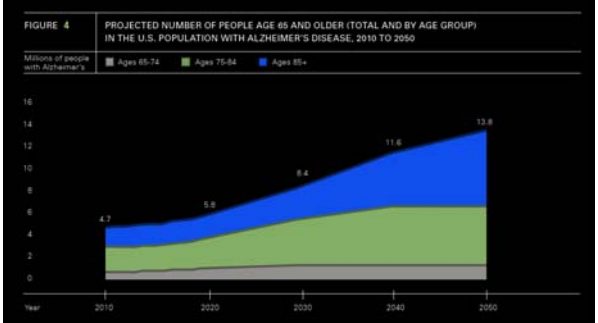
- Facts and figures
- Current hypothetical pathogenic models of AD?
  - Support
  - Caveats
- Epidemiological evidence linking vascular factors to AD.
- What are the possible mechanisms linking vascular disease to AD?
- Is there a special role of white matter damage in AD?
  - Why might white matter be particularly vulnerable and underlie cognitive aging?
  - Is there a special role of white matter disease in cognitive aging and AD?
  - Summary/conclusions

Alzheimer's disease



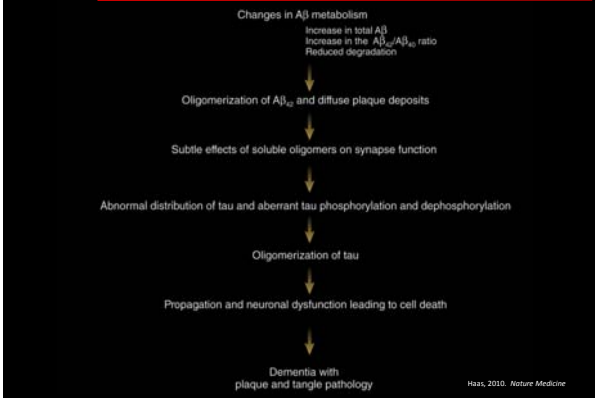
Alzheimer's Association, 2013. Facts and Figures.

Alzheimer's disease

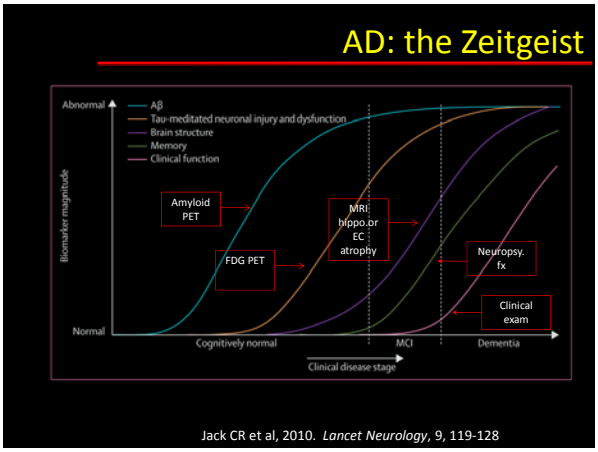


Alzheimer's Association, 2013. Facts and Figures.

Amyloid cascasde hypothesis

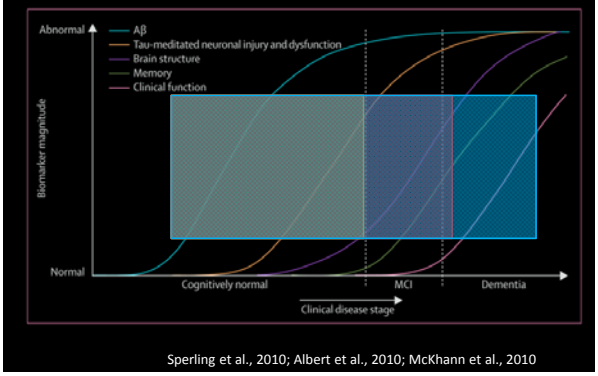


AD: the Zeitgeist



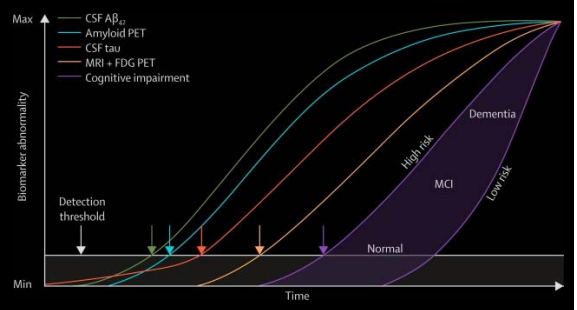
Jack CR et al, 2010. *Lancet Neurology*, 9, 119-128

Diagnosing based on putative etiology



Sperling et al., 2010; Albert et al., 2010; McKhann et al., 2010

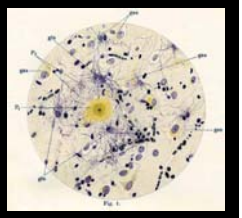
A (slightly) updated model



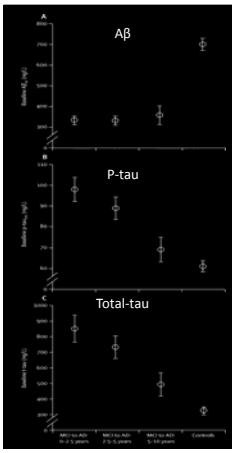
Jack et al., 2013, *Lancet Neurology*

Evidence for pathology

- Amyloid plaques and neurofibrillary tangles have been observed in the brains of AD patients since the beginning.
- Over 18,000 articles on the association between beta amyloid and AD.
- Autosomal dominant forms of AD and Down's are associated with genetic mutations that either encode APP or alter AB generation (PS1 and PS2).
- Mouse models that overproduce beta amyloid sort of look like dementia.
- Removal of amyloid from AD mice improves their symptoms.
- CSF measures of tau and postmortem measures of neurofibrillary tangle burden correlate moderately with severity of cognitive symptoms



Evidence for ordering



- Some cross-sectional evidence that biomarker change in beta amyloid precedes biomarker change in tau.
- Beta amyloid changes appear early, but not in a "dose-dependent" fashion.

Jack et al., 2013, *Lancet Neurology*

But does Aβ cause AD?

- Genetic mutations that cause amyloid overproduction produce an early-onset syndrome similar to AD, but it is it the same as the much more typical "sporadic" or "late-onset" form of the disease?
- Amyloid plaques do not initially form close to where we see the earliest damage in AD (frontal lobe vs. hippocampus/entorhinal cortex)
- No "dose effect" of beta amyloid.
- So many unsymptomatic older adults have huge amounts of amyloid in their brains.
- Very old people (90s-100s) can develop dementia similar to the one seen in younger adults with AD, but have very few plaques at autopsy
- Some have argued that it is the soluble forms of beta amyloid (oligomers) that are more toxic, but the amount needed to produce a toxic effect is physiologically unlikely
- Transgenic mouse models of beta amyloid do not produce tangles
- All beta amyloid reducing trials have failed or are harmful to patients

Drachman, 2014, *Alzheimer's & Dementia*

Caveats: pathological features

- ~30% of non-demented older adults have significant amyloid deposition detected with PET or at autopsy without any apparent cognitive impairment.
- "Both Phase 3 programs await numerous further analyses. For example, the ApoE4 non-carrier bapineuzumab trial, startlingly, turned out to have included 36.1 percent of participants who were amyloid-negative on PIB PET. Was this a technical error with PET or a clinical misdiagnosis?"
- Tau-related changes can be non-specific markers of neuronal damage and frequently occur before or in the absence of beta 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

AlzForum, 10/14/2012

Caveats: Other factors?

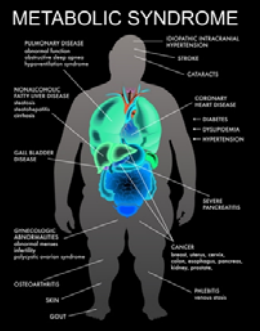
- Diabetes (Luchsinger et al., 2001; Ott et al., 1999; Peila et al., 2002)
- Insulin resistance (Craft, 2005)
- High blood pressure and hypertension (Skoog et al., 1996)
- Atrial fibrillation (Ott et al., 1997)
- Hypercholesterolemia (Kivipelto et al., 2002)
- Midlife central obesity (Whitmer et al., 2008)
- 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

Vascular risk factors: Metabolic syndrome, diabetes, and obesity

METABOLIC SYNDROME

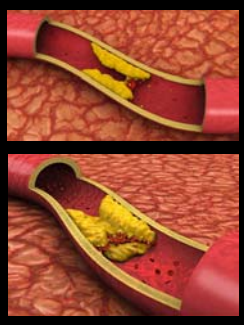
- Central obesity
- Dyslipidemia (↑TG and/or ↑ HDL-C)
- High blood pressure
- Diabetes or pre-diabetes (↑ fasting glucose)



http://www.hollandclinic.com/science-of-weight-loss/obesity-basics/risks-of-obesity/obesity-syndromes/metabolic-syndrome

Vascular risk factors : Hypercholesterolemia

- Serum cholesterol levels have been shown to be higher in middle age among individuals who develop AD in the Seven Countries Study (Finland) and WHICAP.
- Cholesterol levels tend to decrease close to incidence.
- Prevalence of AD among older adults taking statins is 60%-70% lower than those not taking statins.



Notkola et al., 1998; Romas et al., 1999; Wolozin et al., 2000; Kivipelto et al., 2001

http://www.truemedcost.com/something-high-cholesterol-late/

Vascular risk factors : Hypertension

- Framingham: high blood pressure and chronicity of hypertension in 1702 55-88 year-olds inversely related to attention and memory.
- Midlife HTN predicted impairment on MMSE and Trails 20 years later in 999 Swedish men (OR 1.45).
- Midlife HTN associated with 2.5-fold increase in risk for AD in 1,449 Swedes age 65-79.
- Epi studies in Japan, Hawaii, China, Canada, etc. have had similar observations.
- Barnes & Yaffe estimated that 5% (1.7 million) of the current 34 mill. AD cases are attributable to midlife HTN. A reduction of 35% BP would result in 400,000 fewer cases of AD.

Elias et al., 1993; Kilander et al., 1998; Kivipelo et al., 2001; Barnes & Yaffe, 2011

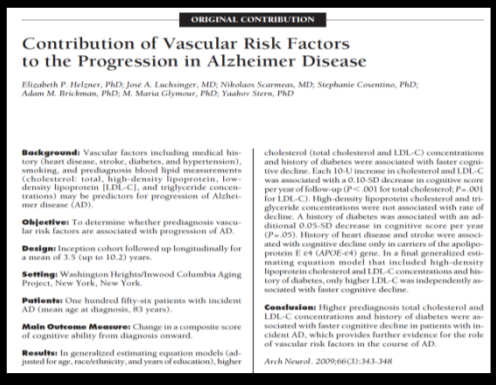
Vascular risk factors and AD: (pre-) Diabetes

- Several studies have shown a link between diabetes and AD.
- Risk of developing clinical AD in the Rotterdam study was 2X higher among individuals with diabetes than among those without.
- According to Barnes and Yaffe, 2% of cases of AD in the world is attributable to diabetes; a 10% lower prevalence of diabetes would lead to 81,000 fewer cases of AD.

www.graphicshunt.com

Ott, et al., 1996; Luchsinger et al., 2010; Barnes & Yaffe, 2011

Vascular risk factors and AD



ORIGINAL CONTRIBUTION

Contribution of Vascular Risk Factors to the Progression in Alzheimer Disease

Elizabeth P. Helzner, PhD; José A. Luchsinger, MD; Nikolaos Scarmeas, MD; Stephanie Cosentino, PhD; Adam M. Brickman, PhD; M. Maria Glymour, PhD; Yaakov Stern, PhD

Background: Vascular factors including medical history (heart disease, stroke, diabetes, and hypertension), smoking, and prediagnosis blood lipid measurements (cholesterol: total, high-density lipoprotein, low-density lipoprotein [LDL-C], and triglyceride concentrations) may be predictors for progression of Alzheimer disease (AD).

Objective: To determine whether prediagnosis vascular risk factors are associated with progression of AD.

Design: Inception cohort followed up longitudinally for a mean of 3.5 (up to 10.2) years.

Setting: Washington Heights/Inwood Columbia Aging Project, New York, New York.

Patients: One hundred fifty-six patients with incident AD (mean age at diagnosis, 83 years).

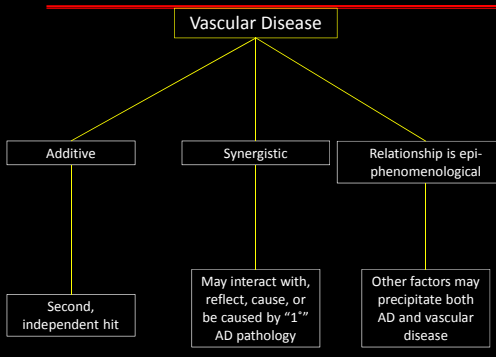
Main Outcome Measure: Change in a composite score of cognitive ability from diagnosis onward.

Results: In generalized estimating equation models (adjusted for age, race/ethnicity, and years of education), higher cholesterol (total cholesterol and LDL-C) concentrations and history of diabetes were associated with faster cognitive decline. Each 10-U increase in cholesterol and LDL-C was associated with a 0.10-SD decrease in cognitive score per year of follow-up ($P < .001$ for total cholesterol; $P = .001$ for LDL-C). High-density lipoprotein cholesterol and triglyceride concentrations were not associated with rate of decline. A history of diabetes was associated with an additional 0.05-SD decrease in cognitive score per year ($P = .05$). History of heart disease and stroke were associated with cognitive decline only in carriers of the apolipoprotein E ε4 (APOE-ε4) gene. In a final generalized estimating equation model that included high-density lipoprotein cholesterol and LDL-C concentrations and history of diabetes, only higher LDL-C was independently associated with faster cognitive decline.

Conclusion: Higher prediagnosis total cholesterol and LDL-C concentrations and history of diabetes were associated with faster cognitive decline in patients with incident AD, which provides further evidence for the role of vascular risk factors in the course of AD.

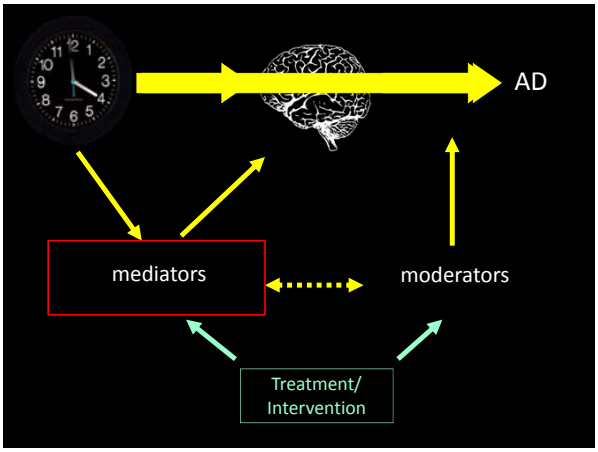
Arch Neurol. 2009;66(3):343-348

Why might vascular risk and AD be linked?



Why might vascular risk and AD be linked?

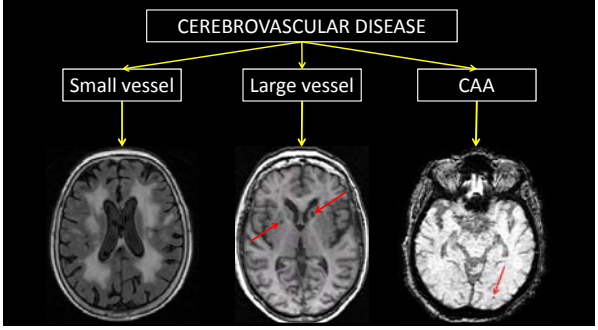
- If we define Alzheimer's disease only by plaques and tangles, then the question is whether vascular disease is independent of plaques and tangles or somehow promotes plaques and/or tangles (or results from them).
- If we define Alzheimer's disease as a mixed pathology disorder, then does it matter if the pathologies are independent of each other?
- Indeed, cerebrovascular disease occurs in patients with clinical AD more often than it does not.



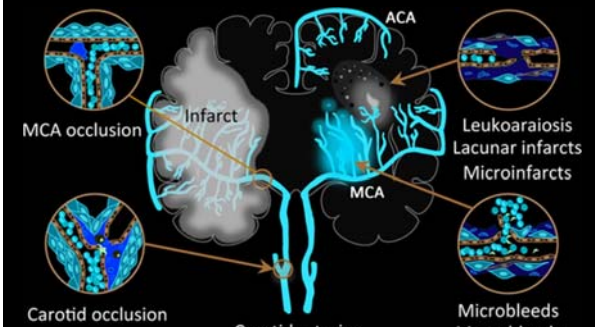
Why might vascular risk and AD be linked?

Additive

- Vascular risk factors are risk factors for small and large cerebrovascular disease.



Why might vascular risk and AD be linked?
Additive



Faraco & Iadecola, 2013

Why might vascular risk and AD be linked?
Additive

- Small and large cerebrovascular disease increase the risk for clinical AD and (or?) the clinical expression of the disease.


ARTICLES

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

Julie A. Schneider, MD
Zoe Arvanitakis, MD
Woojeong Bang, MS
David A. Bennett, MD

ABSTRACT

Objective: To examine the spectrum of neuropathology in persons from the Rush Memory and Aging Project, a longitudinal community-based clinical-pathologic cohort study.

Methods: The study includes older persons who agreed to annual clinical evaluation and brain donation. We examined the neuropathologic diagnoses, including Alzheimer disease (AD) (NIA-Reagan Criteria), cerebral infarctions, and Parkinson disease/Lewy body disease (PD/LBD), in the first 141 autopsies. We calculated the frequency of each diagnosis alone and mixed diagnoses. We used logistic regression to compare one to multiple diagnoses on the odds of dementia.

Results: Twenty persons (14.2%) had no acute or chronic brain abnormalities. The most common chronic neuropathologic diagnoses were AD (n = 80), cerebral infarctions (n = 52), and PD/LBD (n

Why might vascular risk and AD be linked?
Additive


ORIGINAL CONTRIBUTION

Stroke and the Risk of Alzheimer Disease

Lawrence S. Honig, MD, PhD; Ming-Xin Tang, PhD; Steven Albert, PhD, MSc; Rosanne Costa, MA; Jose Luchsinger, MD; Jennifer Manly, PhD; Yaakov Stern, PhD; Richard Mayeux, MD, MSc

Background: Alzheimer disease (AD) and stroke are common in elderly individuals, but the relation between these 2 disorders remains uncertain.

Objective: To investigate the association between a clinical history of stroke and subsequent risk of AD.

Design: A cohort of 1766 Medicare recipients without dementia participated in a longitudinal follow-up study from 1992 through 1999 in upper Manhattan, New York, NY. History of stroke and presence of cardiovascular risk factors were ascertained at the onset of the study. Incidence rates for AD among those with and without stroke were calculated; proportional hazards ratios were computed using age at onset of the disease as the time-to-event variable.

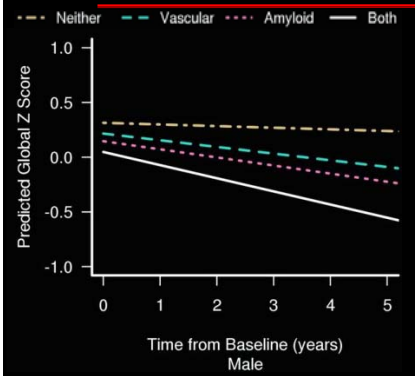
Results: The annual incidence for AD was 5.2% among individuals with stroke vs 4% for those without stroke. The hazards ratio for AD among those with a history of stroke was 1.6 (95% confidence interval, 1.0-2.4) compared with those without stroke. Of the vascular risk factors, hypertension, diabetes, and heart disease, only diabetes related to risk of AD in the absence of stroke. Stroke remained weakly associated with AD in the absence of these factors, but risk significantly increased with the additional factors of hypertension (relative risk, 2.3; 95% confidence interval, 1.4-3.6), diabetes (relative risk, 4.6; 95% confidence interval, 2.2-9.5), or heart disease (relative risk, 2.0; 95% confidence interval, 1.2-3.2).

Conclusions: Stroke is associated with AD among elderly individuals. The relation is strongest in the presence of known vascular risk factors. The observed association between stroke and AD might relate to an underlying systemic vascular disease process, or alternatively, to the additive effects of stroke and AD pathologic features, leading to an earlier age at onset of disease.

Arch Neurol. 2003;60:1707-1712

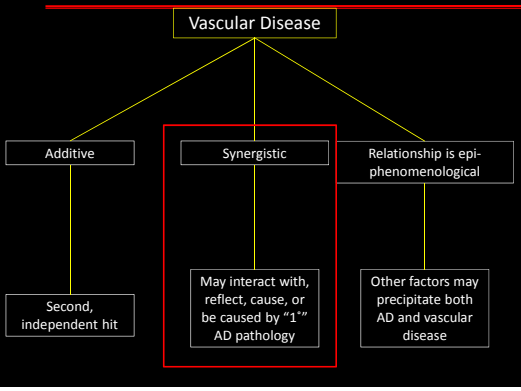
Why might vascular risk and AD be linked?
Additive

Why might vascular risk and AD be linked?
Additive



- Additive not synergistic effect
- Vascular and AD markers not related to each other
- Vascular disease contributed EQUALLY to cognitive decline as AD pathology

Why might vascular risk and AD be linked?



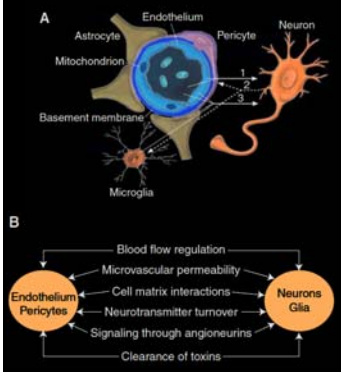
Why might vascular risk and AD be linked? *Synergistic*

Little to some evidence from autopsy studies

- Diabetes associated with infarcts but not with NPs or NFTs (Peila et al., 2002)
- In BLSA, quantitative measures of atheroscleroiss in the aorta, heart, and intracranial vessels not associated with AD pathology (Dolan et al., 2010)
- CF. Other groups have shown a modest relationship between atherosclerosis and AD pathology (Roher et al., 2004; Beeri et al., 2006)

Chui et al., 2012

Why might vascular risk and AD be linked? *Synergistic*

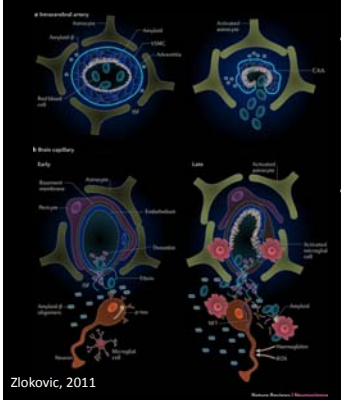


Microcirculation

- Neurovascular unit (capillary)
- Endothelial cells and pericytes form the BBB (ion channels, permeability, and transporters)
- These cells regulate multiple neurovascular functions

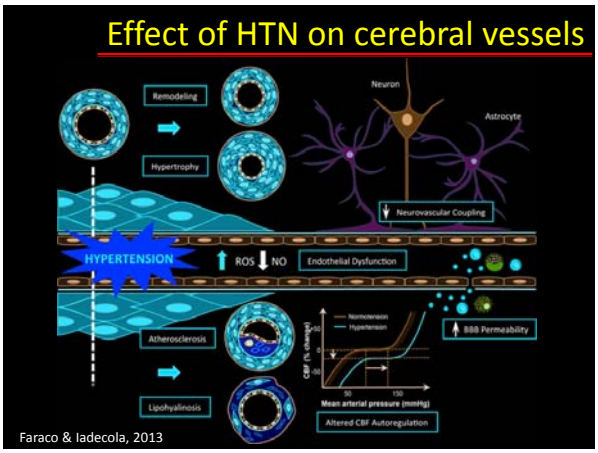
Sagare , Bell, & Zlokovic, 2012

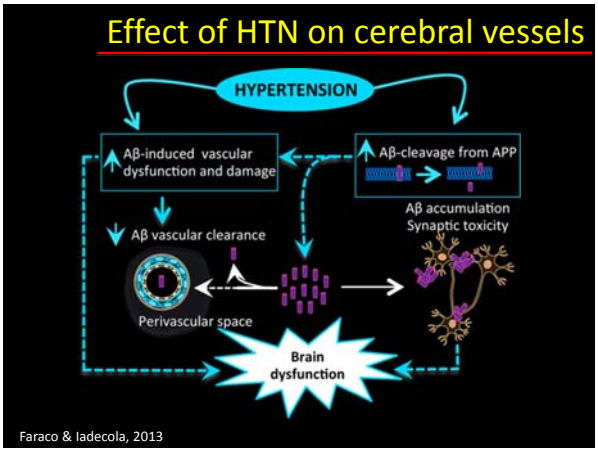
Why might vascular risk and AD be linked? *Synergistic*

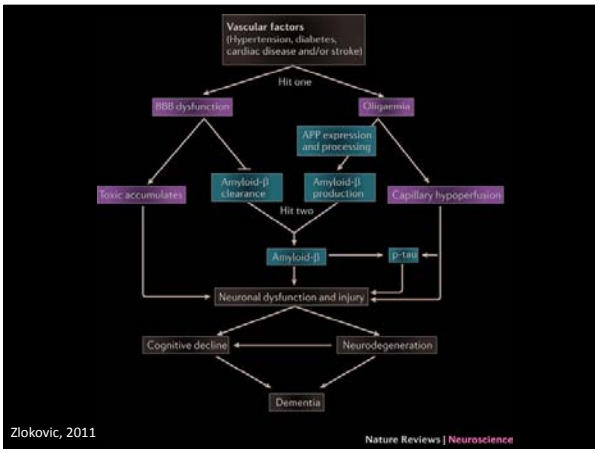


- A. In the arteries, dyregulated CBF in early stages of AD is associated with diminished A-beta clearance by smooth muscle cells. Later stags, CAA causes microbleeds.
- B. In the capillaries, BBB dysfunction leads to diminished A-beta clearance and accumulation of toxic bi-products (AB?). P-tau accumulates in response to injury or AB toxicity. Increased microglia activation and other inflammatory processes in response.

Zlokovic, 2011


Effect of HTN on cerebral vessels
Remodeling
Hypertrophy
Neuron
Astrocyte
Neurovascular Coupling
HYPERTENSION
ROS
NO
Endothelial Dysfunction
Atherosclerosis
Lipohyalinosis
BBB Permeability
Normotension
Hypertension
CBF (% change)
50
150
Mean arterial pressure (mmHg)
Altered CBF Autoregulation
Faraco & Iadecola, 2013


Effect of HTN on cerebral vessels
HYPERTENSION
Aβ-induced vascular dysfunction and damage
Aβ-cleavage from APP
Aβ accumulation
Synaptic toxicity
Aβ vascular clearance
Perivascular space
Brain dysfunction
Faraco & Iadecola, 2013


Vascular factors
(Hypertension, diabetes, cardiac disease and/or stroke)
Hit one
BBB dysfunction
Oligaemia
APP expression and processing
Toxic accumulates
Amyloid-β clearance
Amyloid-β production
Capillary hypoperfusion
Hit two
Amyloid-β
p-tau
Neuronal dysfunction and injury
Cognitive decline
Neurodegeneration
Dementia
Zlokovic, 2011
Nature Reviews | Neuroscience

Three non-mutually exclusive paths

- Blood brain barrier breakdown
- Hypoperfusion and hypoxemia
- Endothelial neurotoxic and inflammatory processes

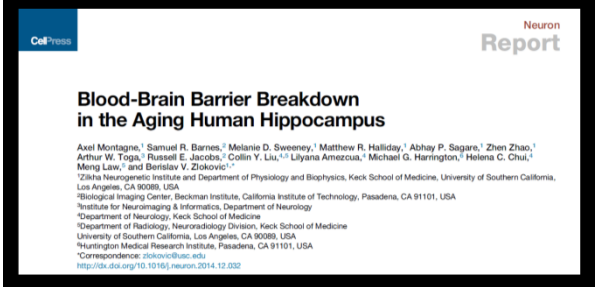
Zlokovic 2011

BBB breakdown

- Typically leads to accumulation of various molecules in the brain
  - Serum proteins can cause edema and suppression of capillary flow
  - Increased RBCs deposits other toxic products like iron, which generate neurotoxic reactive oxygen species (ROS)

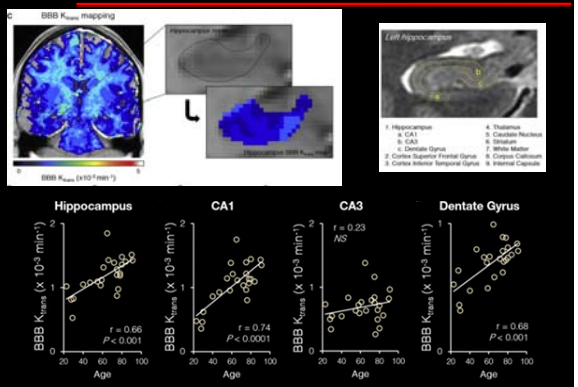
Zlokovic 2011

BBB breakdown



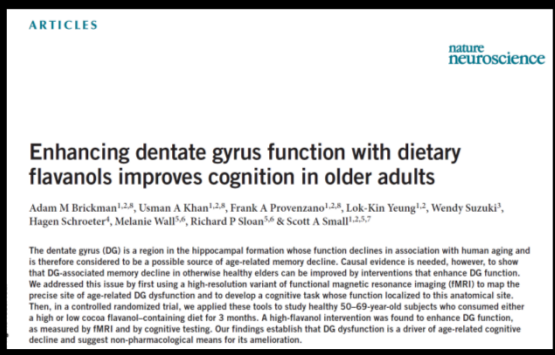
Montagne et al., 2015

BBB breakdown



Montagne et al., 2015

BBB breakdown vs. CBV (parenthetical)



ARTICLES

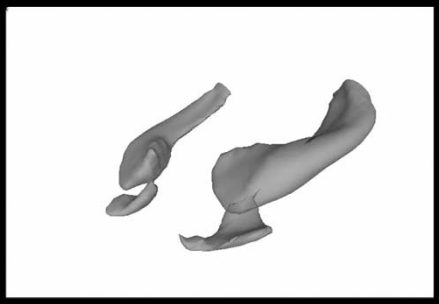
nature neuroscience

Enhancing dentate gyrus function with dietary flavanols improves cognition in older adults

Adam M Brickman[1,2,8], Usman A Khan[1,2,8], Frank A Provenzano[1,2,8], Lok-Kin Yeung[1,2], Wendy Suzuki[3], Hagen Schroeter[4], Melanie Wall[5,6], Richard P Sloan[5,6] & Scott A Small[1,2,3,7]

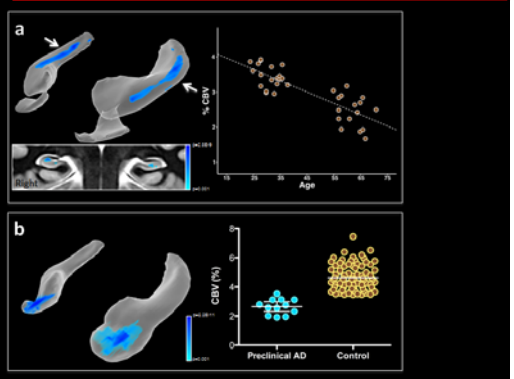
The dentate gyrus (DG) is a region in the hippocampal formation whose function declines in association with human aging and is therefore considered to be a possible source of age-related memory decline. Causal evidence is needed, however, to show that DG-associated memory decline in otherwise healthy elders can be improved by interventions that enhance DG function. We addressed this issue by first using a high-resolution variant of functional magnetic resonance imaging (fMRI) to map the precise site of age-related DG dysfunction and to develop a cognitive task whose function localized to this anatomical site. Then, in a controlled randomized trial, we applied these tools to study healthy 50–69-year-old subjects who consumed either a high or low cocoa flavanol–containing diet for 3 months. A high-flavanol intervention was found to enhance DG function, as measured by fMRI and by cognitive testing. Our findings establish that DG dysfunction is a driver of age-related cognitive decline and suggest non-pharmacological means for its amelioration.

BBB breakdown vs. CBV (parenthetical)



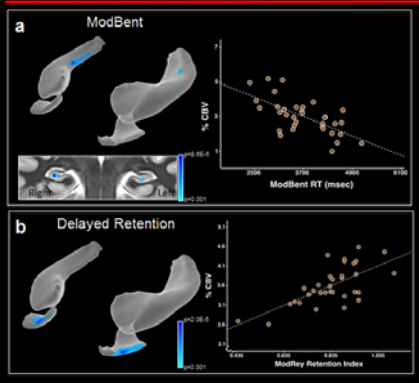
Brickman et al., 2014

BBB breakdown vs. CBV (parenthetical)



Brickman et al., 2014

BBB breakdown vs. CBV (parenthetical)



Brickman et al., 2014

Hypoperfusion and hypoxemia

- CBF is regulated locally (neurovascular coupling)
- Hypoperfusion can affect protein synthesis and ATP synthesis
- Reduced CBF occurs in older adults at risk for AD before onset of cognitive symptoms or measurable neurodegenerative changees
- Hypoperfusion causes oligomerization of beta amyloid in animal models
- Ischemia leads to accumulation of hyperphosphorylated tau
- Hypoxemia causes mitochondria to release factors that mediate oxidative damage to the endothelium

Zlokovic 2011

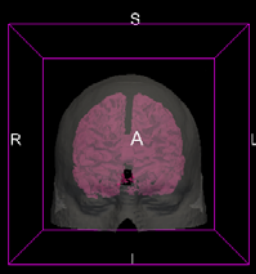
Endothelial neurotoxic and inflammation

- Microvessels in AD brains secrete multiple inflammatory mediators
- Cause or effect?

Zlokovic 2011

Is there a special role of white matter damage in cognitive aging and AD?

White matter

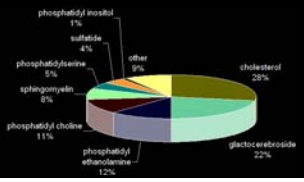


- Emerging literature suggests that lifespan development changes in white matter properties may mediate much of the cognitive change we see with age
- Takes up a large proportion of the brain, but has been understudied.
- Plays an important role in cognition across various stages of development and neuropsychological disorders.

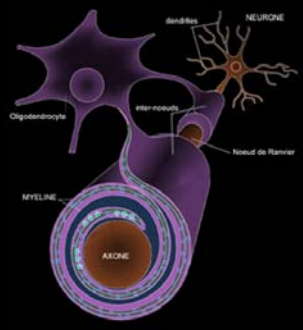
White matter

- White matter is white because of myelin.
- 80% lipid fat and 20% protein
- Increases the speed at which electrical impulses propogate along the axon, facilitating *fast* and *efficient* neural transmission.
- Damage to myelin can have obvious consequences to neural transmission, affecting basic perceptual, motoric, and cognitive processes.

Figure source: Wikimedia



White matter

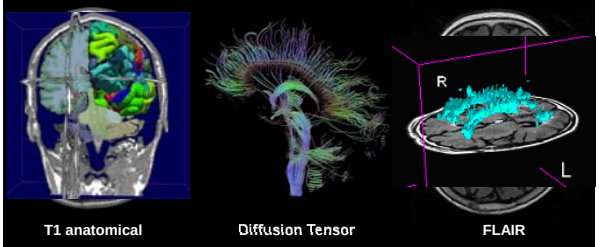


Measuring various aspects of WM with MRI

- Macrostructure
- Microstructure
- Pathology

- REMEMBER: MRI scans do not provide a photograph of the brain; they provide reconstructed representations of tissue types that roughly reflect various aspects of the underlying tissue. Diffusion tensor measures, for example, may reflect myelination, density of the fibers, and gross organization of fibers.

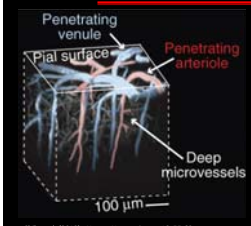
Measuring various aspects of WM with MRI



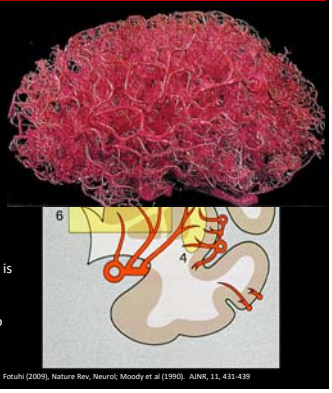
T1 anatomical | Diffusion Tensor | FLAIR

- Recent advances in acquisition and analysis of structural neuroimaging allow for greater visualization of normal and abnormal white matter.

Why might white matter be particularly vulnerable?



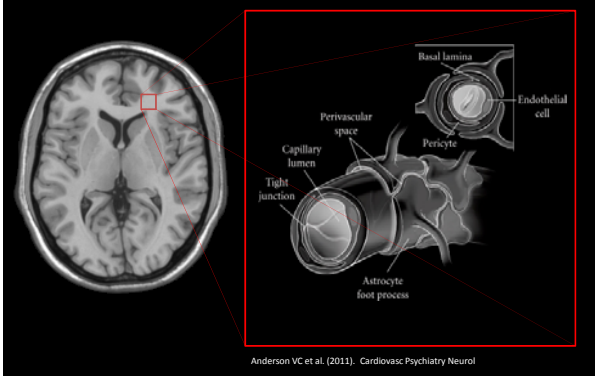
Shih et al. (2013). Nature Neuroscience, 16, 55-63.



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

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

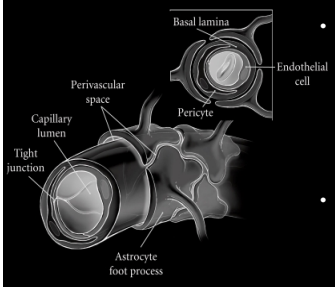
Why might white matter be particularly vulnerable?



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

Why might white matter be particularly vulnerable?

BBB breakdown

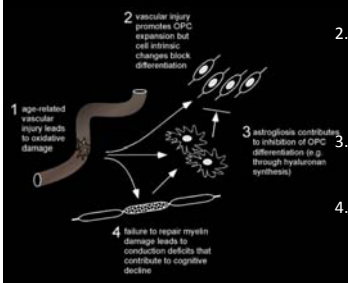


Anderson VC et al. (2011). Cardiovasc Psychiatry Neurol

- 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 a variety of factors that accumulate across the lifespan (HTN, inflammation, mechanical injury, oxidative stress, etc) and/or by frank pathology (Aβ)

Why might white matter be particularly vulnerable?

Lack of myelin repair

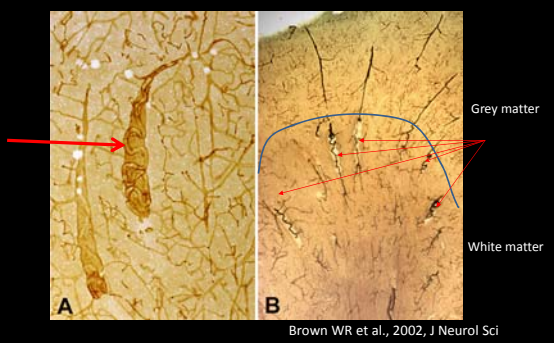


Kohama SG et al., 2012. AGE.

1. Age-related vascular injury leads to oxidative damage
2. Vascular injury promotes oligodendrocyte progenitor cell expansion but cell intrinsic changes block differentiation
3. Astrogliosis contributes to inhibition of OPC differentiation
4. Failure to repair myelin damage leads to conduction deficits that contribute to cognitive decline

Why might white matter be particularly vulnerable?

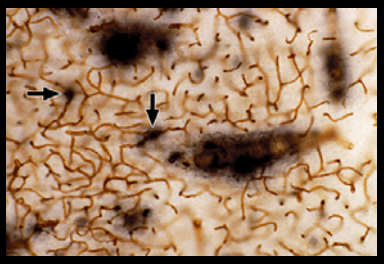
Tortuous arterioles



Brown WR et al., 2002, J Neurol Sci

Why might white matter be particularly vulnerable?

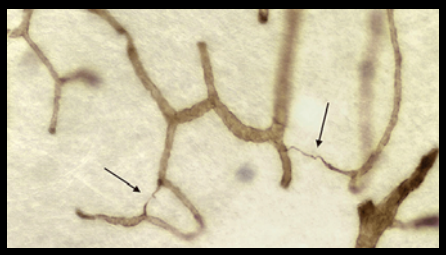
Pathology accumulation



Brown WR et al., 2000, Ann NY Acad Sci

Why might white matter be particularly vulnerable?

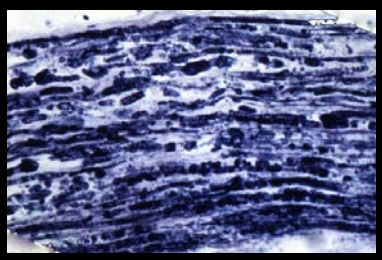
String vessels



Brown WR & Thore CR, 2011, Neuropathology & Applied Neurobiology

Why might white matter be particularly vulnerable?

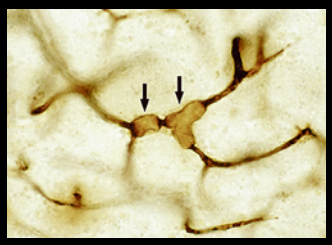
Wallerian degeneration



http://neuropathology-web.org/chapter12/chapter12Neuropathy.html

Why might white matter be particularly vulnerable?

Microembolic lesions

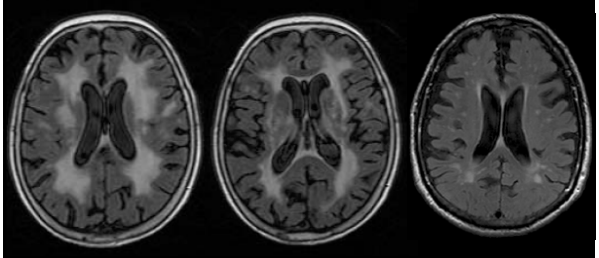


Brown WR et al., 1996, Echocariography

Caveats: Other factors?

- Diabetes (Luchsinger et al., 2001; Ott et al., 1999; Peila et al., 2002)
- Insulin resistance (Craft, 2005)
- High blood pressure and hypertension (Skoog et al., 1996)
- Atrial fibrillation (Ott et al., 1997)
- Hypercholesterolemia (Kivipelto et al., 2002)
- Midlife central obesity (Whitmer et al., 2008)
- 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

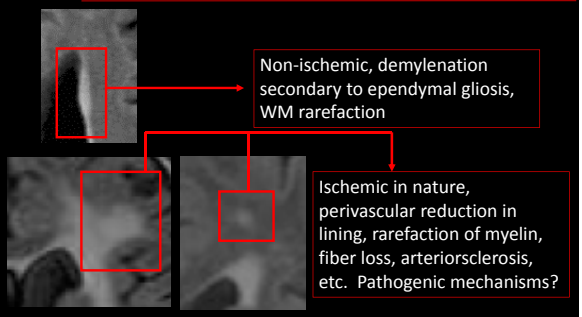
White matter hyperintensities



WMH what we know

- White matter hyperintensities are bad.
- White matter hyperintensities are not good.
- Most older adults have some degree of WM change (normal vs. healthy?)
- Overall burden accounts for a lot of variance in cognitive performance in normal aging, esp working memory and executive functioning (Raz et al)
- If you have white matter hyperintensities now, you used to not have them.
- In the context of aging, once you have them, they tend get worse. They rarely get better.
- WMH burden (severity) is a measurable reflection of brain pathology, whereas many other MRI markers may reflect pathology or may reflect lifelong individual differences

Pathology



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

WMH risk factors

- Age, stroke, diastolic blood pressure, diuretic use, internal carotid artery thickness (Monolio Kronmal et al., 1994)
- HTN, elevated cholesterol, myocardial infarction, carotid atheroscleroiss (de Leeuw et al., 2000, Rotterdam)
- Prior h/o HTN, being African American (accounted for mostly by HTN) (Liao et al., 1996, 1997, ARIC)
- Association between middle life systolic BP and later life WMH volume (DeCarli et al., 1999, NHLBI twin study)
- Carotid artery atherosclerosis (Romero et al., 2009, FHS)

Overall questions

- Are white matter hyperintensities, "normal aging" pathology, involved with the pathogenesis and/or clinical presentation of AD?
- Do WMH help explain what we see in the trajectories of cognitive aging above and beyond (or interacting with) putative AD biomarkers?
- Can we leverage neuroimaging to identify targets for group or personalized intervention, prevention, or maintenance strategies?

Quantification: Scheltens Scale

Scan Date: __/__/____

CHS study #: _____ Examiner: _____

SCHELTENS VISUAL RATING OF HYPERINTENSITIES

PERIVENTRICULAR HYPERINTENSITIES

Note: Report the largest dimension if spots are asymmetrical.

		Grade (0,1,2)
caps:	Frontal	____
	Occipital	____
bands:	Lat. Ventricles	____

Overall PVH ____ (0-6)

KEY: *Periventricular Hyperintensities*

0 = Absent
1 = ≤ 5 mm
2 = > 5 mm and < 10 mm

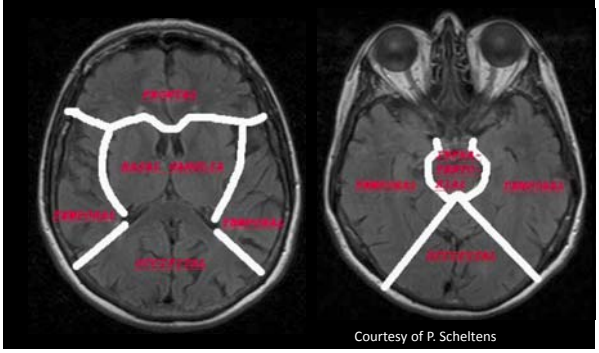
WHITE MATTER HYPERINTENSITIES

	Grade (0–6)
Frontal	____
Temporal	____
Parietal	____
Occipital	____

Overall WMH ____ (0-24)

0 = N/A
1 = < 3 mm n ≤ 5
2 = < 3 mm n ≥ 6
3 = 4-10 mm n ≤ 5
4 = 4-10 mm n > 6
5 = > 11 mm n > 1
6 = confluent

Quantification: Scheltens Scale



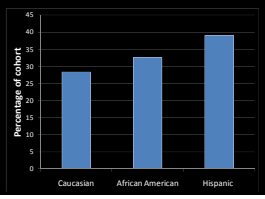
Courtesy of P. Scheltens

Washington Heights Inwood Columbia Aging Program

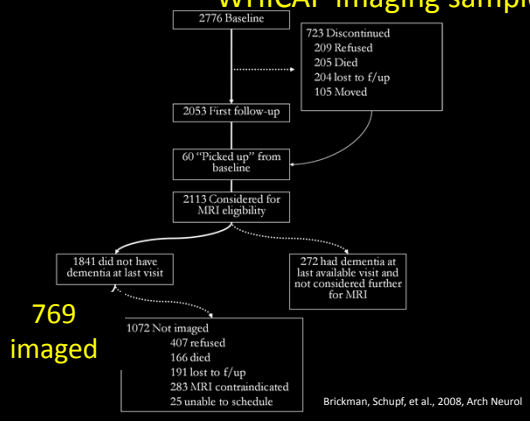
WHICAP

INWOOD
WASHINGTON HEIGHTS
HAMILTON HEIGHTS

- N = 2125 in 1992
- Added 2174 in 1999 to total 2801
- Age 65 and older
- Spanish or English speaking
- Seen in home at 18 – 24 month intervals
- Dx based on neuropsychological test battery, medical & functional interview



WHICAP imaging sample



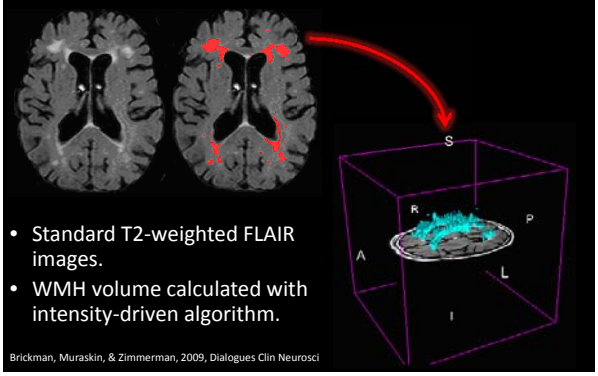
Brickman, Schupf, et al., 2008, Arch Neurol

WHICAP imaging sample

	AGE	EDUCATION	VASCULAR (Σ: HTN, DM, CAD, stroke)
CAUCASIANS (n = 203)	80.25	13.73	1.29
AFRICAN AMERICANS (n = 243)	79.71	12.31	1.92
HISPANICS (n = 256)	80.27	6.86	1.96
TOTAL SAMPLE (N nondemented = 717) (N AD = 52)	80.07	10.73	1.69

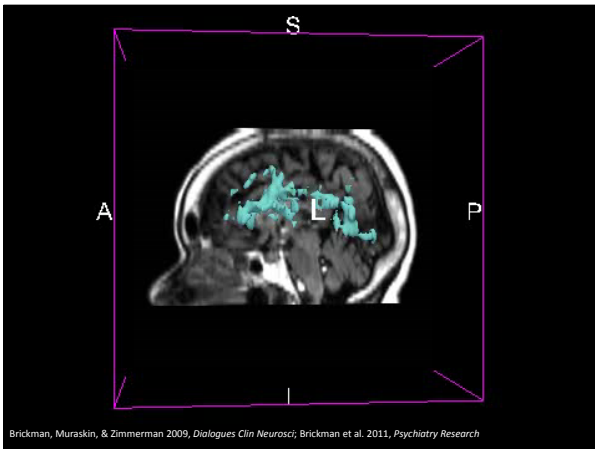
Brickman, Schupf, et al., 2008, Arch Neurol

Quantification of WMH



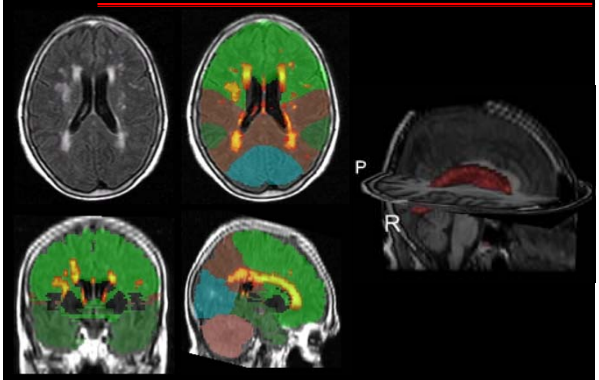
- Standard T2-weighted FLAIR images.
- WMH volume calculated with intensity-driven algorithm.

Brickman, Muraskin, & Zimmerman, 2009, Dialogues Clin Neurosci



Brickman, Muraskin, & Zimmerman 2009, *Dialogues Clin Neurosci*; Brickman et al. 2011, *Psychiatry Research*

Quantification of WMH



Brickman, Muraskin, & Zimmerman 2009; Brickman et al. 2011

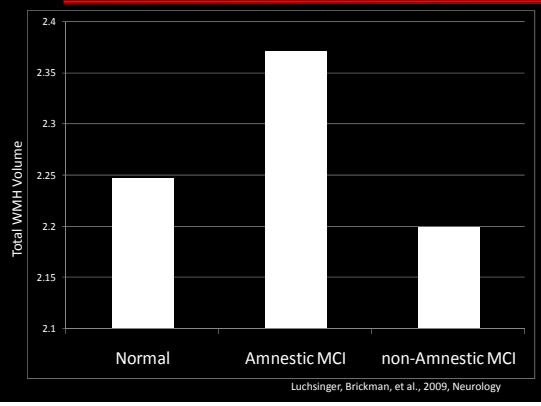
MCI

- 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)

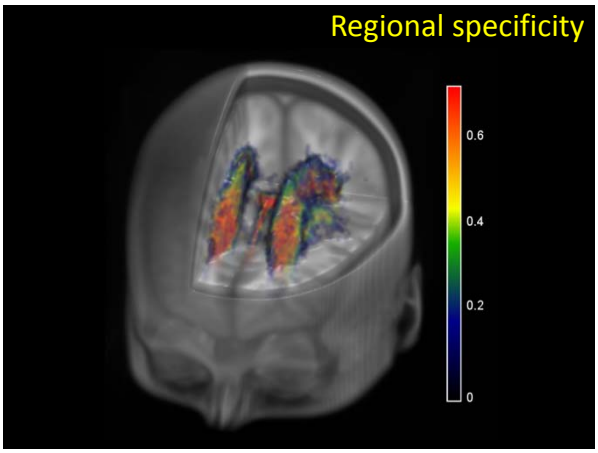
Luchsinger, Brickman, et al., 2009, Neurology

MCI

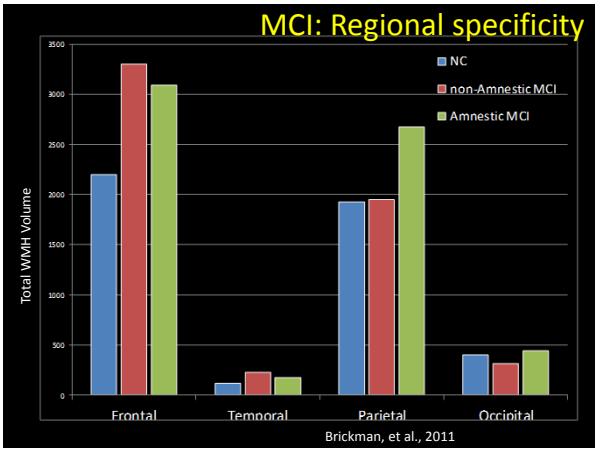


Luchsinger, Brickman, et al., 2009, Neurology

Regional specificity

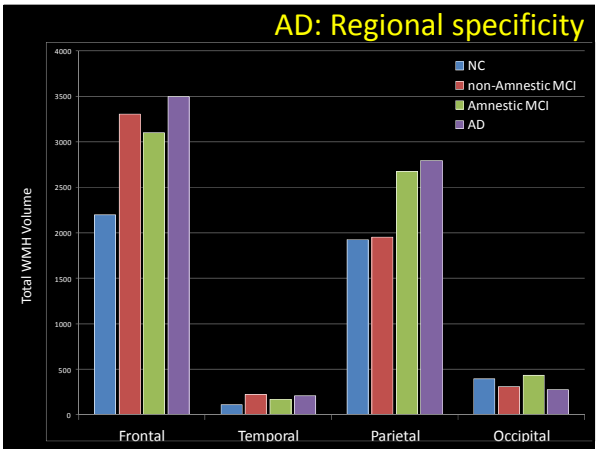


MCI: Regional specificity

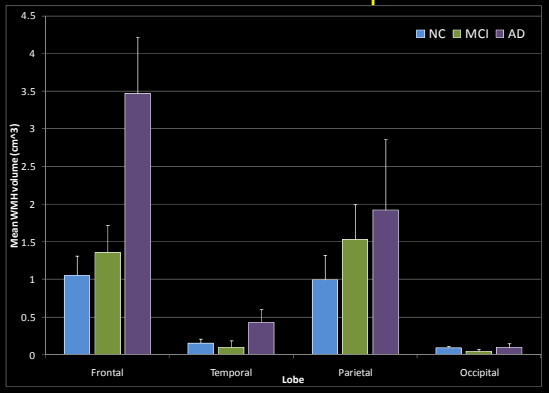


Brickman, et al., 2011

AD: Regional specificity

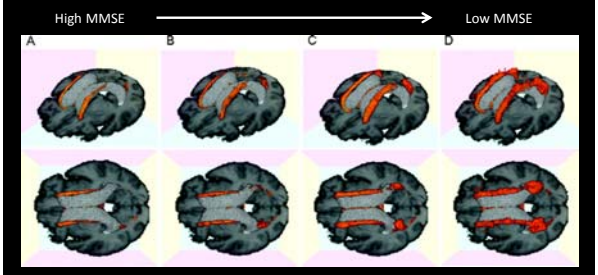


Replication: AAG



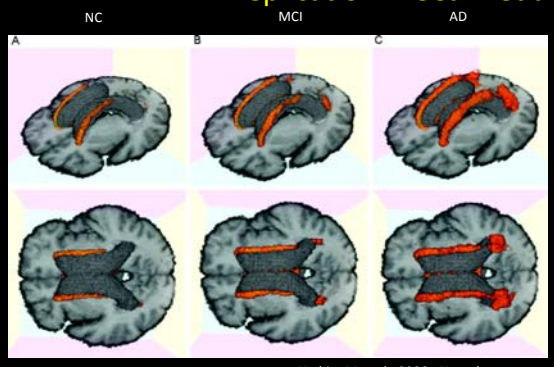
Meier et al., 2012, *JINS*

Replication: DeCarli et al.



Yoshita M et al., 2006. *Neurology*

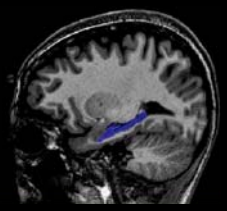
Replication: DeCarli et al.



Yoshita M et al., 2006. *Neurology*

See also: Scheltens et al., 1992; Kalaria, 2000; Rezek et al., 1987

Hippocampus volume

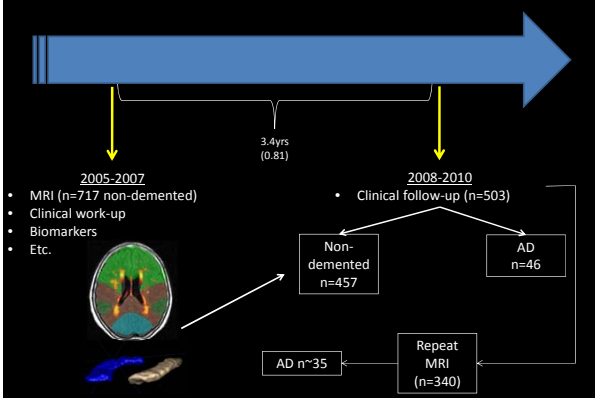


Regional specificity: predicting aMCI (x-sectional)

	β	p
Parietal lobe WMH volume	0.195	0.020
Hippocampus volume	-0.080	0.672
Age	0.040	0.058

Results from logistic regression analysis predicting aMCI vs. NC. Additional covariates: sex, TCV (both non-significant).

Future decline



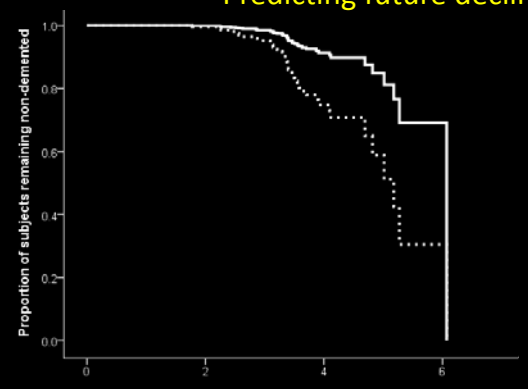
Regional specificity: predicting AD (future decline)

	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

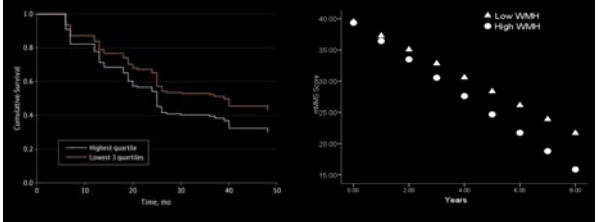
Brickman, et al, 2012

Predicting future decline



Brickman, et al., 2012

WMH predicts cognitive decline



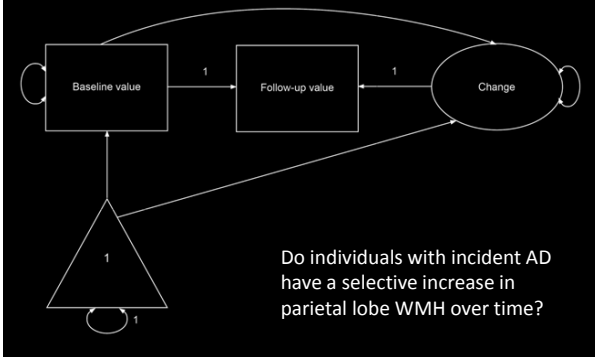
Brickman, et al., 2008, Arch Neurol; Tosto et al., 2014

Longitudinal analysis with latent difference scores

- Do individuals who "convert" from 'normal' to AD have a selective increase in parietal lobe WMH over time?
- Rather than calculating difference scores in raw data, latent difference scores define a latent variable as the portion of the time 2 value that is not identical to the initial value and models
- We modeled the latent change in parietal lobe WMH vs. all other WMH as a function of incident AD status, controlling for baseline values, change scores of hippocampus volume, and relevant demographic covariates.

Brickman et al., 2014

Latent Difference Score model

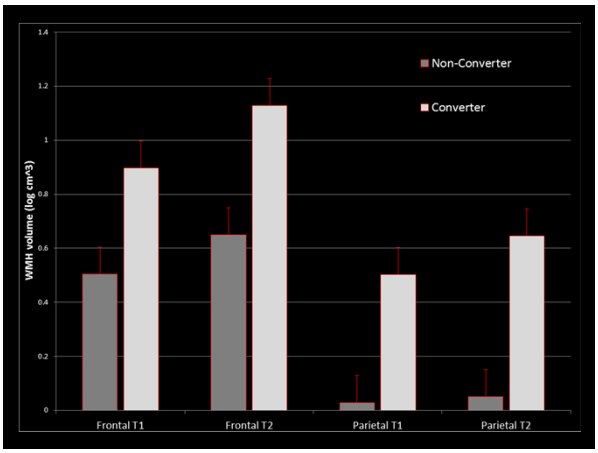


Do individuals with incident AD have a selective increase in parietal lobe WMH over time?

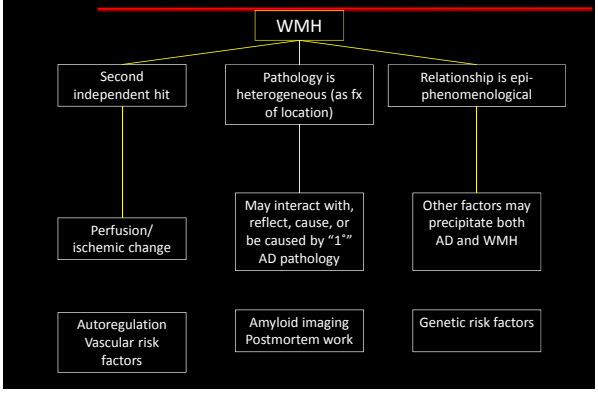
Latent Difference Score model

	Estimate	SE	Z	P
Change in parietal WMH	0.39	0.16	2.40	0.02
Change in all other WMH	0.03	0.09	0.39	0.70
Change in hipp volume	0.70	0.18	-3.83	<0.01
Age	0.05	0.03	1.66	0.10

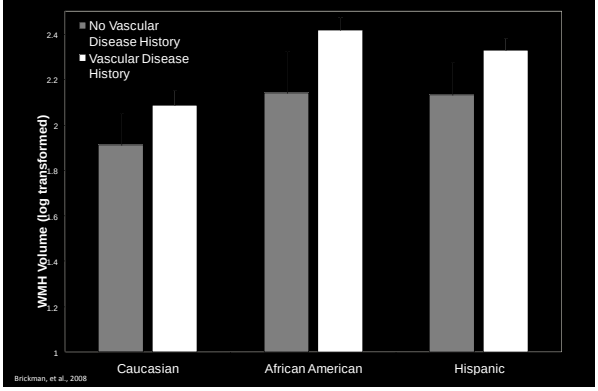
Covariates: baseline WMH and hipp, age, education, ethnicity, sex, total cranial volume APOE



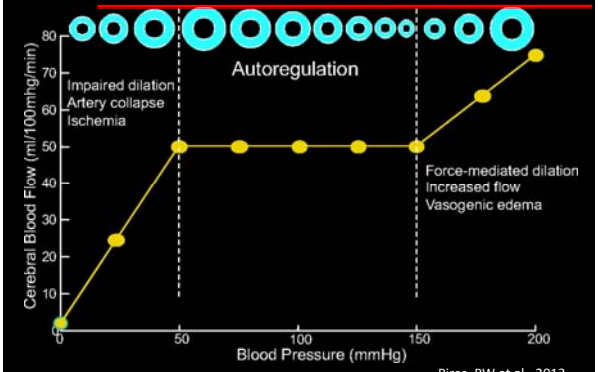
Why would WMH and AD be linked?



Perfusion: Vascular disease history

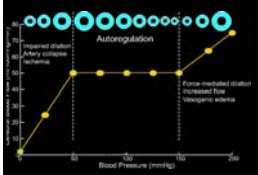


Perfusion: Autoregulatory dysfunction



Pires, PW et al., 2013

Perfusion: Autoregulatory dysfunction



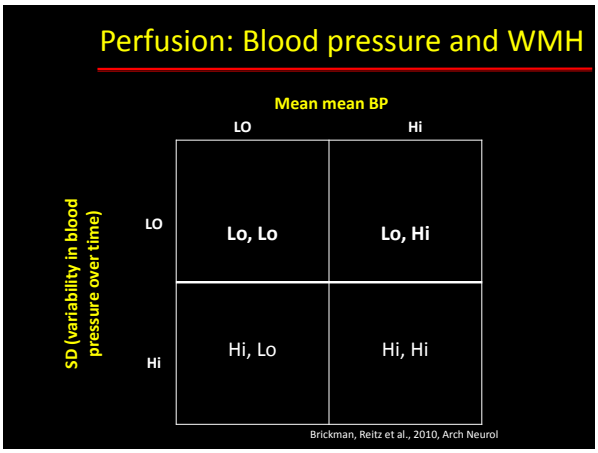
- Cerebrovascular disease via hypoperfusion and oxidative stress may modulate neuronal overproduction of beta amyloid
- Beta amyloid may exert deterimental effects on cerebrovascular function
- AD amyloid mice have reduced CBF, endothelium-dependent vasdilation is impared, and vasoconstrictor responses are impaired.
- Never shown in humans….

Claasen & Zang, 2011

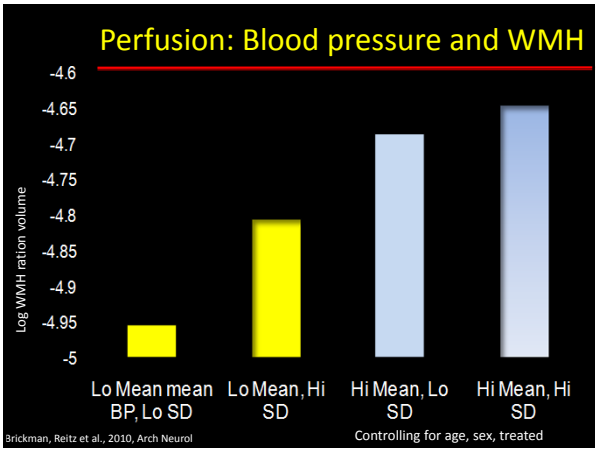
Perfusion: Autoregulatory dysfunction

- Autoregulatory dysfunction could promote small vessel disease, which in turn can promote the deposition or inhibit the clearance of amyloid pathology
- Alternatively, it is possible that amyloid pathology itself leads to vascular disease, via vessel deposition of beta amyloid pathology (i.e., cerebral amyloid angiopathy), and subsequently result in autoregulatory dysfunction
- Transgenic amyloid mice have severely impaired autoregulation *prior* to deposition of amyloid pathology
- In humans, the relationship between autoregulatory dysfunction and AD has not been shown definitively.

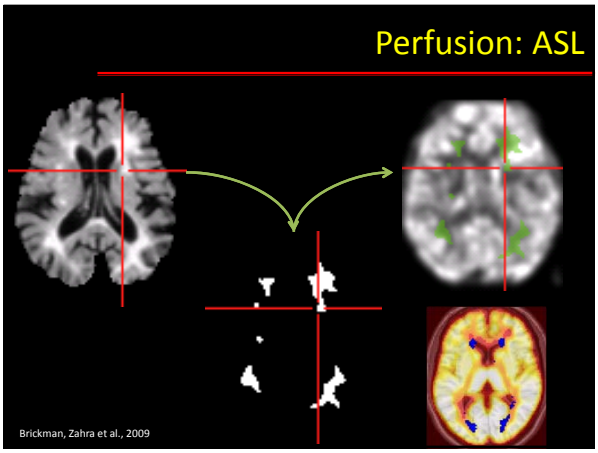
Perfusion: Blood pressure and WMH



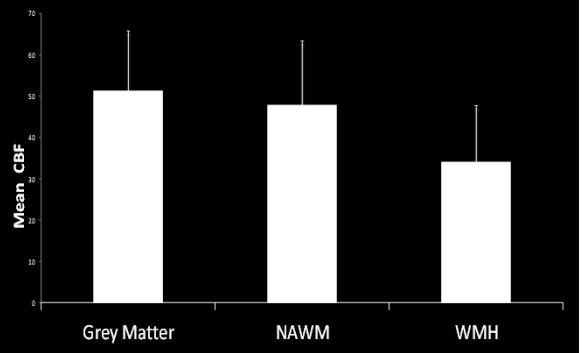
Perfusion: Blood pressure and WMH



Perfusion: ASL

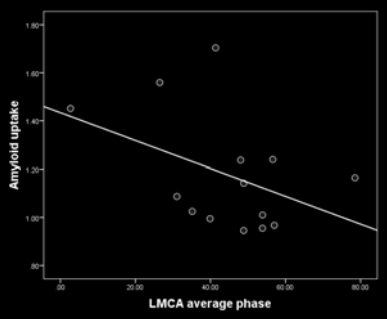


Perfusion: ASL



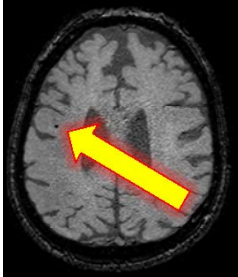
Brickman, Zahra et al., 2009

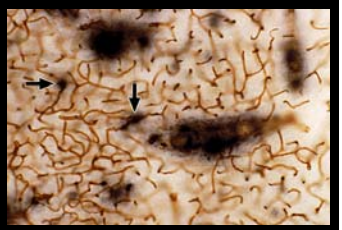
Perfusion: Autoregulatory dysfunction



Brickman et al., under review

WMH x AD pathology



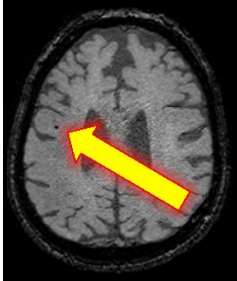


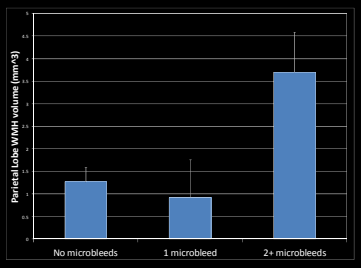
Brown WR et al., 2000, Ann NY Acad Sci

Cerebral Amyloid Angiopathy

Meier et al

Heterogeneous pathology: CAA



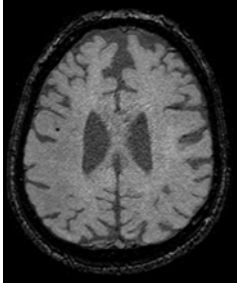


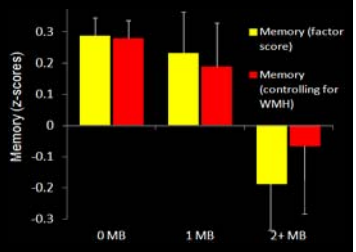
Cerebral Amyloid Angiopathy

More parietal lobe WMH in people with 2+ microbleeds

Meier et al., 2012 (INS)

Heterogeneous pathology: CAA

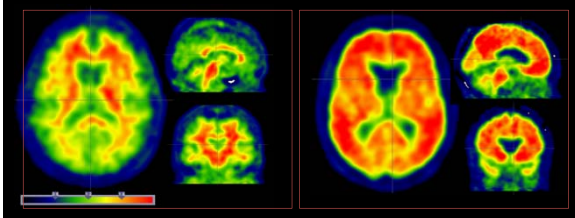




Cerebral Amyloid Angiopathy

2+ microbleeds, worse memory, due to WMH?

Heterogeneous pathology: Amyloid



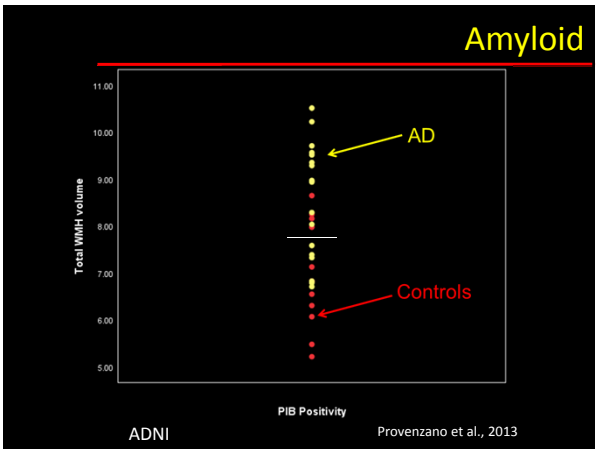
PIB negative

PIB positive

Amyloid imaging

Provenzano et al., 2013

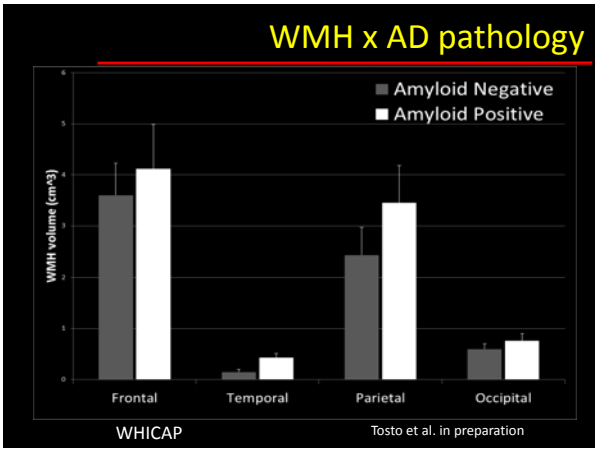
Amyloid



ADNI

Provenzano et al., 2013

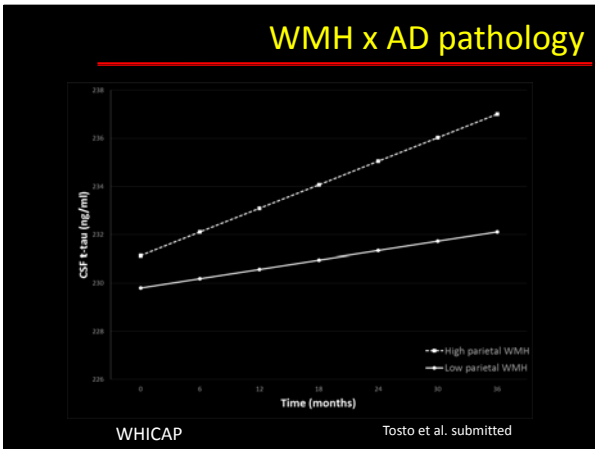
WMH x AD pathology



WHICAP

Tosto et al. in preparation

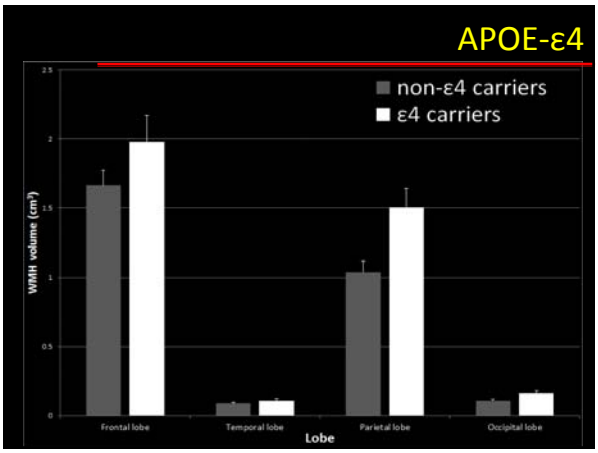
WMH x AD pathology



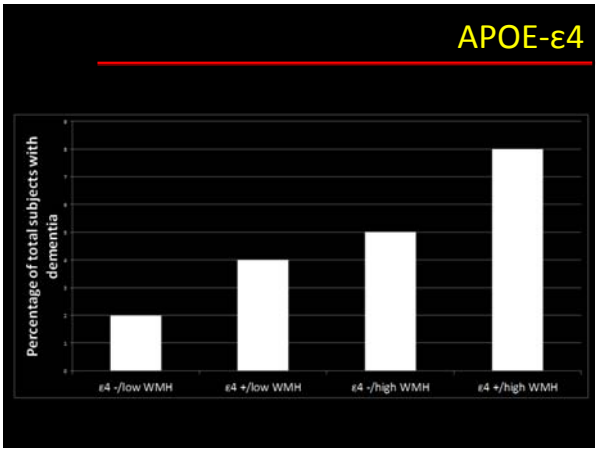
WHICAP

Tosto et al. submitted

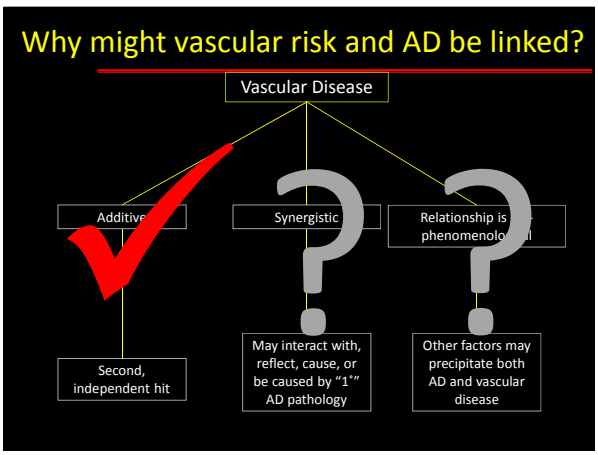
APOE-ε4



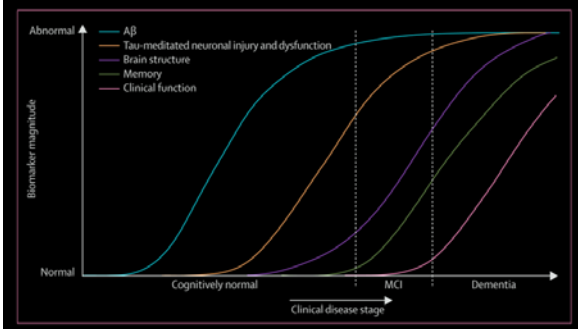
APOE-ε4



Why might vascular risk and AD be linked?

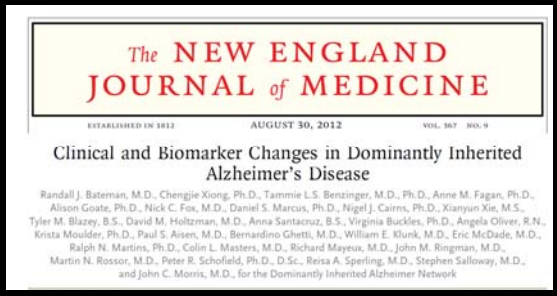


AD: the Zeitgeist



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

DIAN Study



The NEW ENGLAND JOURNAL of MEDICINE

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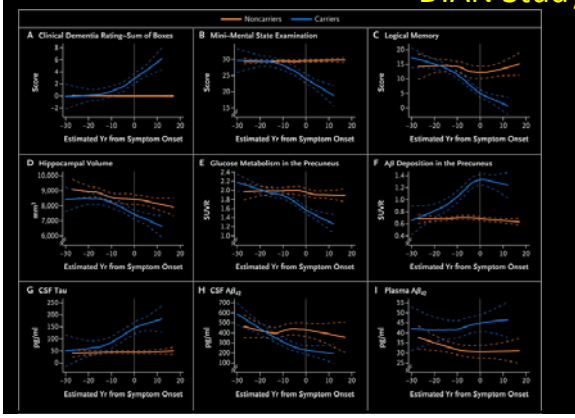
Clinical and Biomarker Changes in Dominantly Inherited Alzheimer's Disease

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

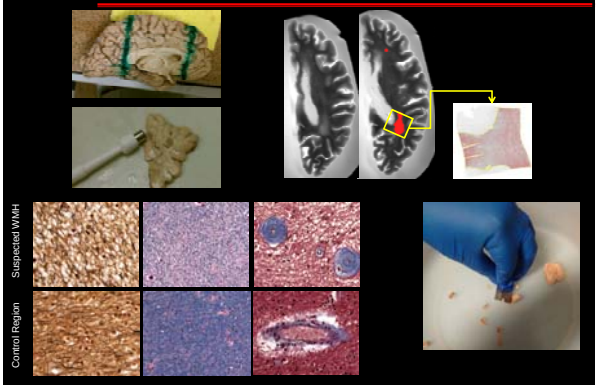
DIAN Study



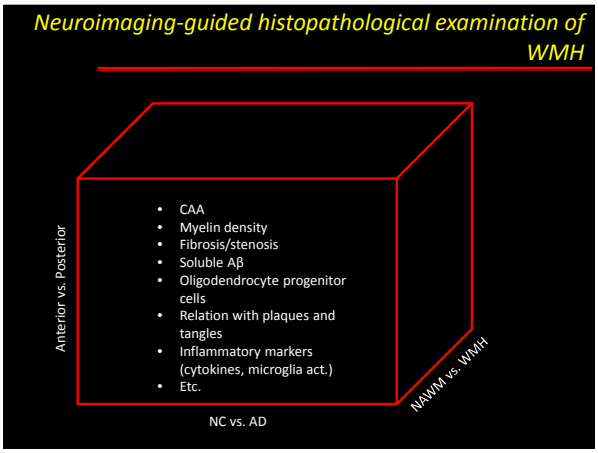
DIAN Study: WMH

UNPUBLISHED DATA

Neuroimaging-guided histopathological examination of WMH



Neuroimaging-guided histopathological examination of WMH



Summary

- Vascular risk factors certainly increase risk for AD and they do so *at least* additively
- Some viable mechanisms that might suggest causal or interactive effects.
- Brain white matter is particularly vulnerable to injury in later life
- White matter injury appears to play a specialized role in AD symptoms onset or pathogenesis

Summary

- Does white matter damage play a particularly specific role in Alzheimer's disease?
  - At least additive
  - Possibly interactive
  - Does it matter?
  - Is it a semantic question?

Is there a role for WMH/vascular disease in disease conceptualization?

- What is normal/healthy and what is not normal/healthy?
- Who are we including in our studies and how is that impacting our conclusions and definitions?
- Are we defining disease by a preconceived notion of the biology of that disease rather than focusing on a behavior and trying to understand the factors that lead to that behavior?
- Diseases like AD occur in the context of (normal?) aging and normal aging sometimes occurs in the context of disease.

Mixed pathology: norm not exception

- Lest we forget, AD has always been a "mixed" pathology (plaques and tangles)

ARTICLES

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

Julie A. Schneider, MD
Zoe Arvanitakis, MD
Woojeong Bang, MS
David A. Bennett, MD

ABSTRACT

Objective: To examine the spectrum of neuropathology in persons from the Rush Memory and Aging Project, a longitudinal community-based clinical-pathologic cohort study.

Methods: The study includes older persons who agreed to annual clinical evaluation and brain donation. We examined the neuropathologic diagnoses, including Alzheimer disease (AD) (NIA-Reagan Criteria), cerebral infarctions, and Parkinson disease/Lewy body disease (PD/LBD), in the first 141 autopsies. We calculated the frequency of each diagnosis alone and mixed diagnoses. We used logistic regression to compare one to multiple diagnoses on the odds of dementia.

Results: Twenty persons (14.2%) had no acute or chronic brain abnormalities. The most common chronic neuropathologic diagnoses were AD (n = 80), cerebral infarctions (n = 52), and PD/LBD (n

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