



Amyloid and deoxyglucose PET Imaging in Alzheimer's Disease and Vascular Cognitive Impairment patients with significant White Matter Disease



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on behalf of the
MITNEC-C6 project group



Disclosure of Potential Conflict of Interest

Clinical Trial Contract Research:

Pfizer, Novartis, Roche, Lundbeck, Lilly-Avid,
GE Healthcare,

CME Lecturer: Novartis, Eisai

Ad hoc Consultant: GE Healthcare,
Lilly-Avid, Boehringer Ingelheim

No stock or equity interests

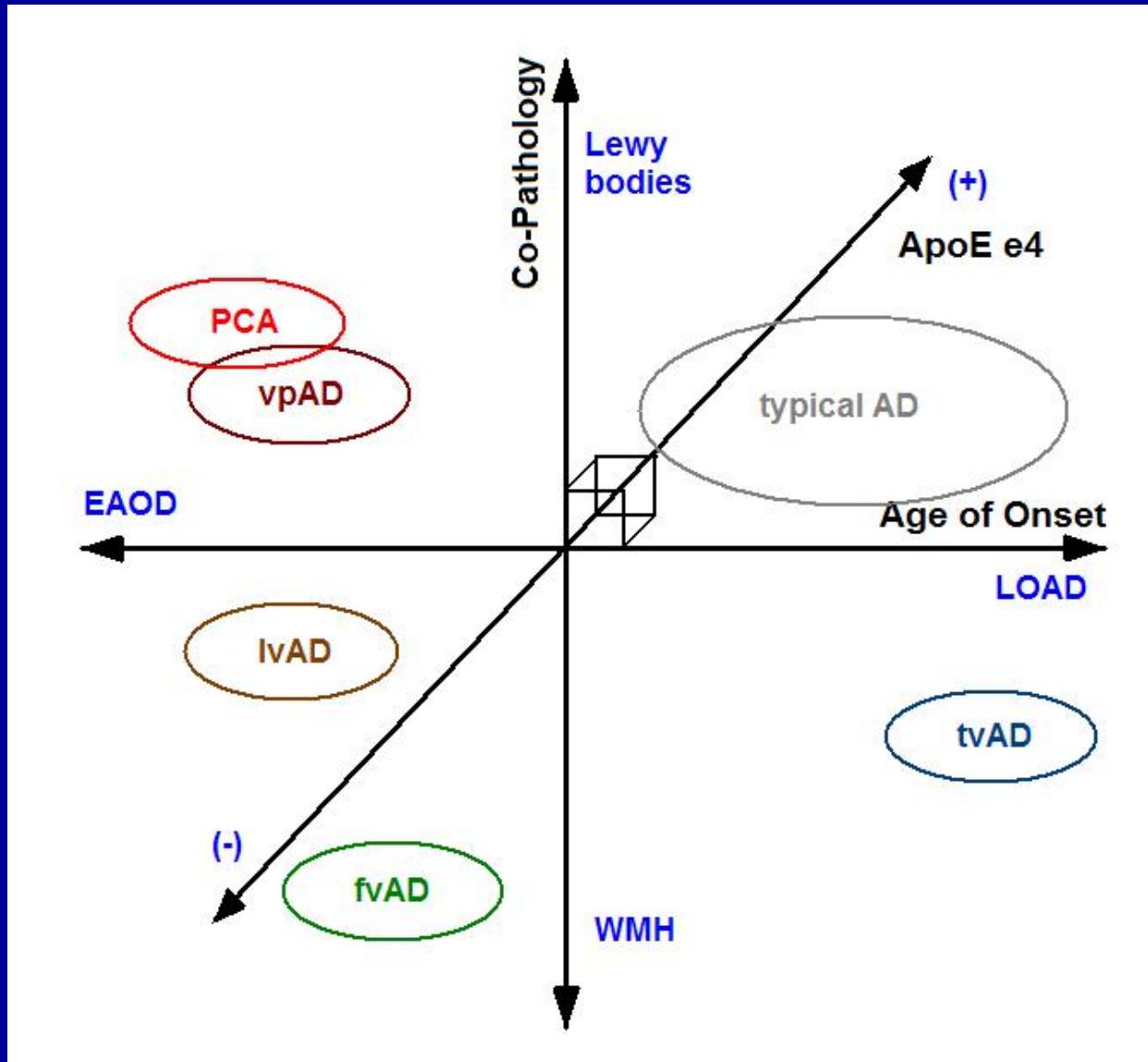
Medical Imaging Trials NEtwork of Canada (MITNEC) CIHR-funded network

- A national medical imaging clinical trials network established to provide a clinical platform for imaging research in Canada to move innovations in imaging to facilitate the uptake of research outcomes into clinical practice and improved patient care.
 - Theme A – Imaging Trials in Oncology
 - Theme B – Imaging Trials in Cardiology
 - Theme C – Imaging Trials in Neurology
 - Theme D - Clinical validation of non-reactor-based source of ^{99m}Tc

Rationale

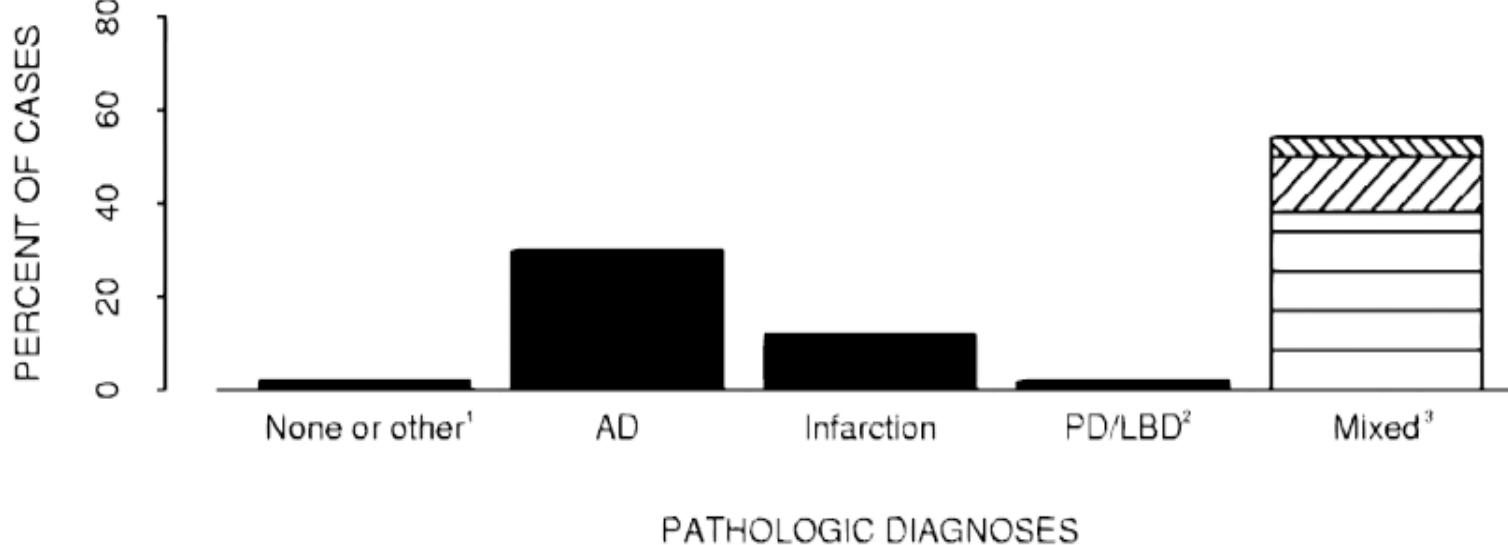
- Small vessel disease often coexists with Alzheimer's disease (AD) and can contribute to cognitive decline and progression to dementia.
- Longitudinal imaging using cerebral amyloid labeling is needed to understand the additive/interactive effects of small vessel disease and AD.
- Elders with extensive periventricular White Matter Disease may represent an at-risk group for amyloid deposition and could be an important target group for dementia prevention.
- Progression to dementia could be averted in at-risk groups through aggressive vascular risk factor management and potentially anti-amyloid agents.

Axis of pathological heterogeneity



A Demented

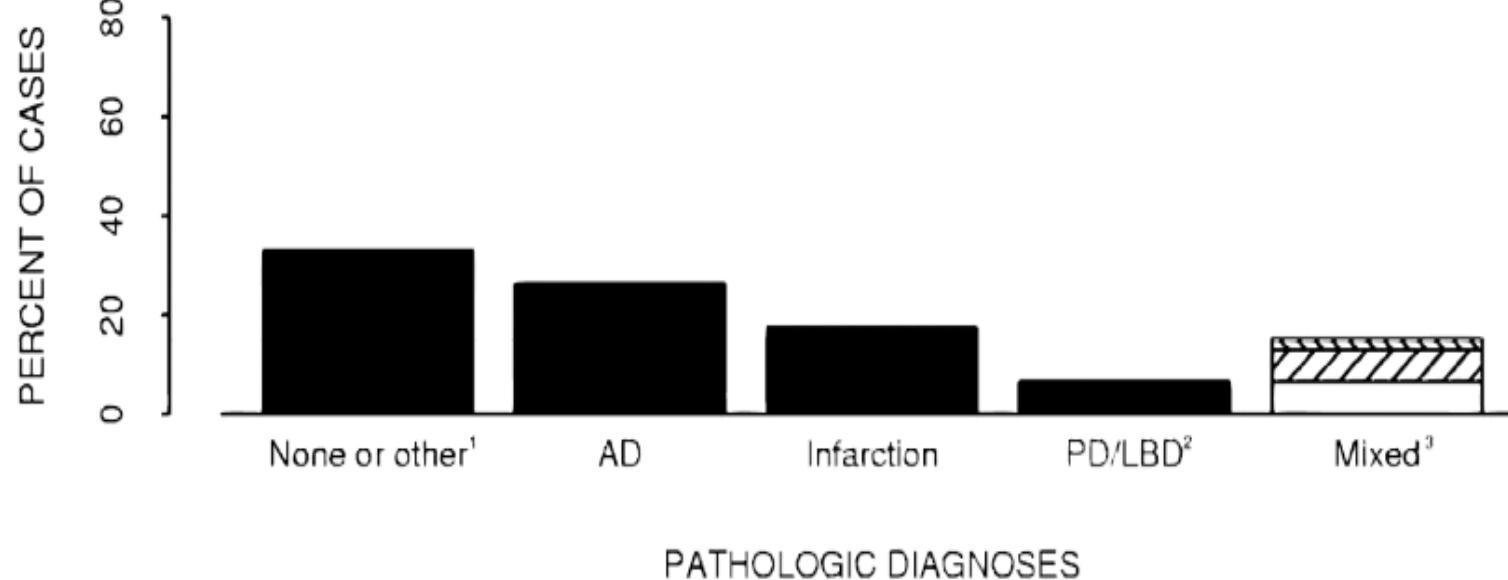
148 Community Autopsies



In Autopsy Series
Dementia is usually a Co-morbid disease, especially with vascular lesions

B

Not demented



Schneider et al
Neurology
2007

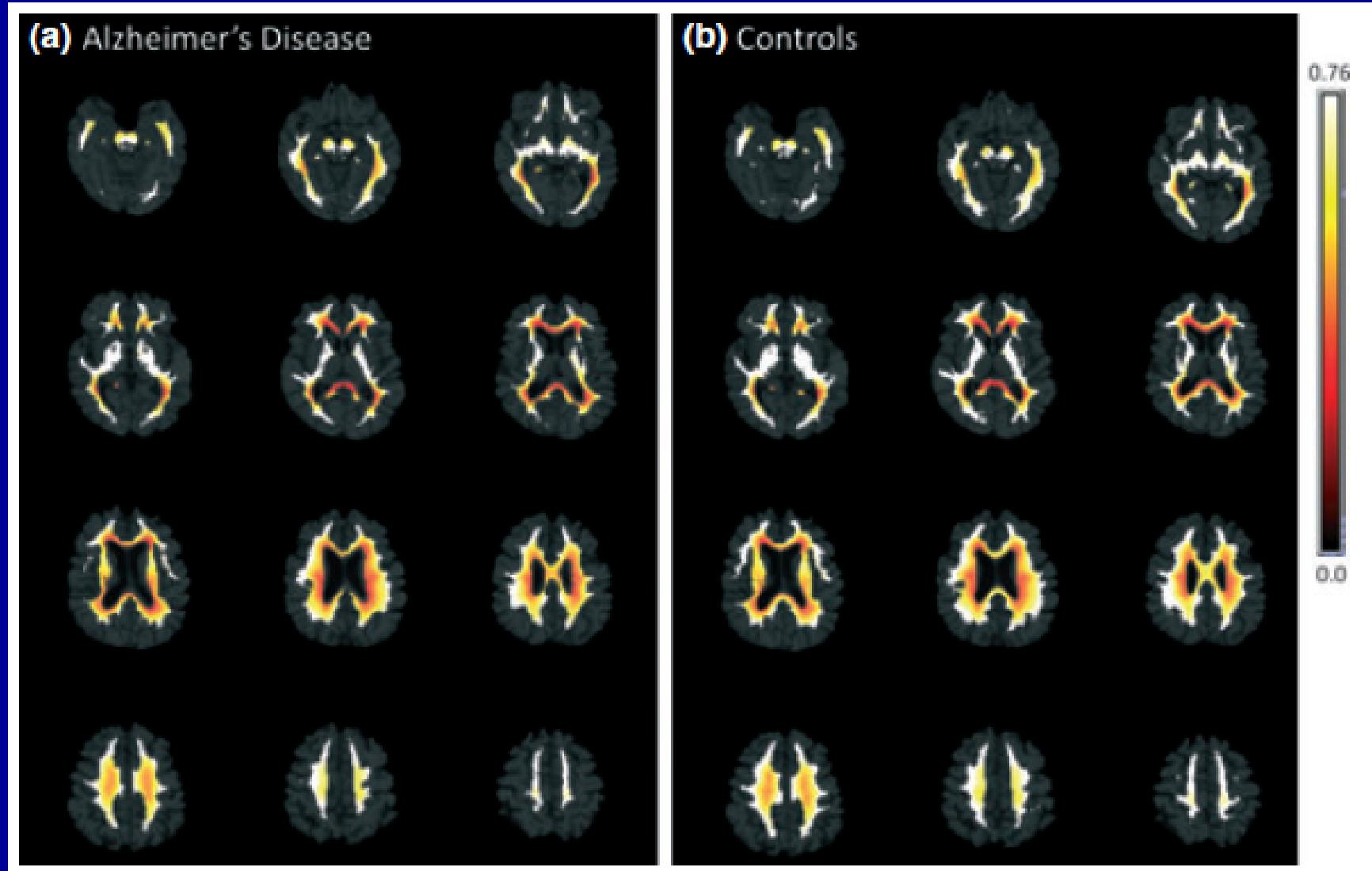
Prevalence of amyloid positivity in Subcortical VaD

- Thirty-one (**68.9%**) of 45 patients with SVaD were negative for cortical PiB binding
- Significant differences between PiB-positive and PiB-negative groups in:
 - Age- older(**79.5 vs 71.9 years**)
 - MMSE lower (**18.6 vs 22.6**)
 - Number of lacunes fewer (**3.9 vs 9.0**)
 - Visual rating scale-more hippocampal atrophy **h(3.1 vs 2.3)**
- PiB-negative SVaD performed better on delayed recall of both verbal and visual memory tests than the PiB-positive

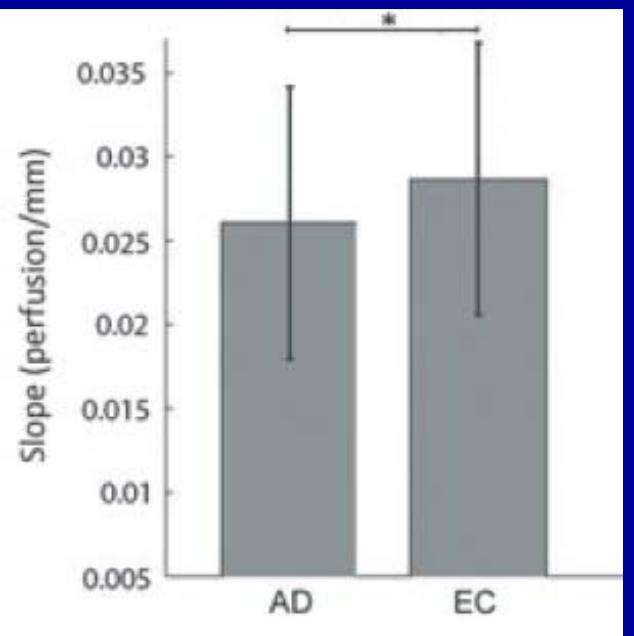
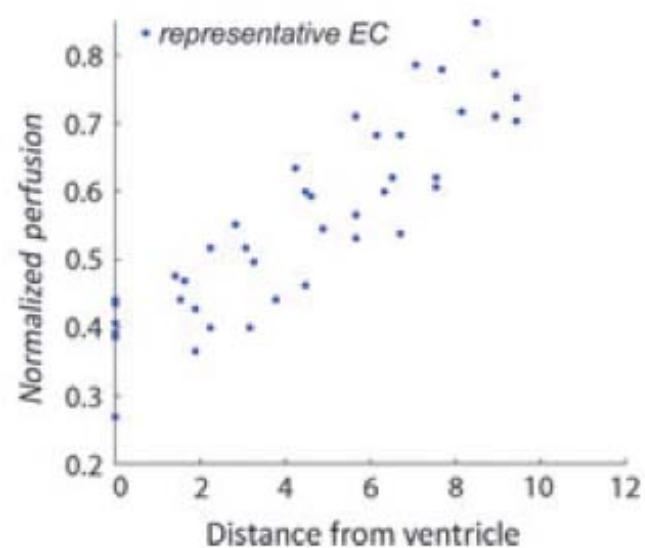
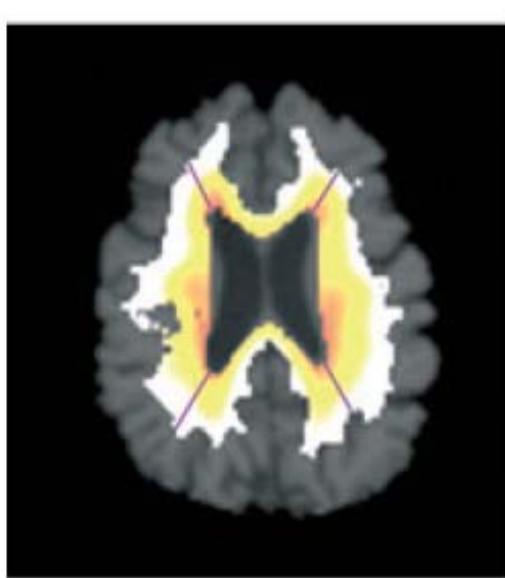
Prevalence of amyloid positivity in Subcortical Vascular Dementia

- Thirty-one (**31%**) with SVaD had cortical PiB binding
- Significant differences between PiB-positive and PiB-negative groups in:
 - Age (**79.5** vs 71.9 years)
 - Mini-Mental State Examination score (**18.6** vs 22.6)
 - Number of lacunes (**3.9** vs 9.0)
 - Visual rating scale of hippocampal atrophy (**3.1** vs 2.3)
- PiB-negative SVaD patients performed better on delayed recall of both the verbal and visual memory test than PiB-positive patients

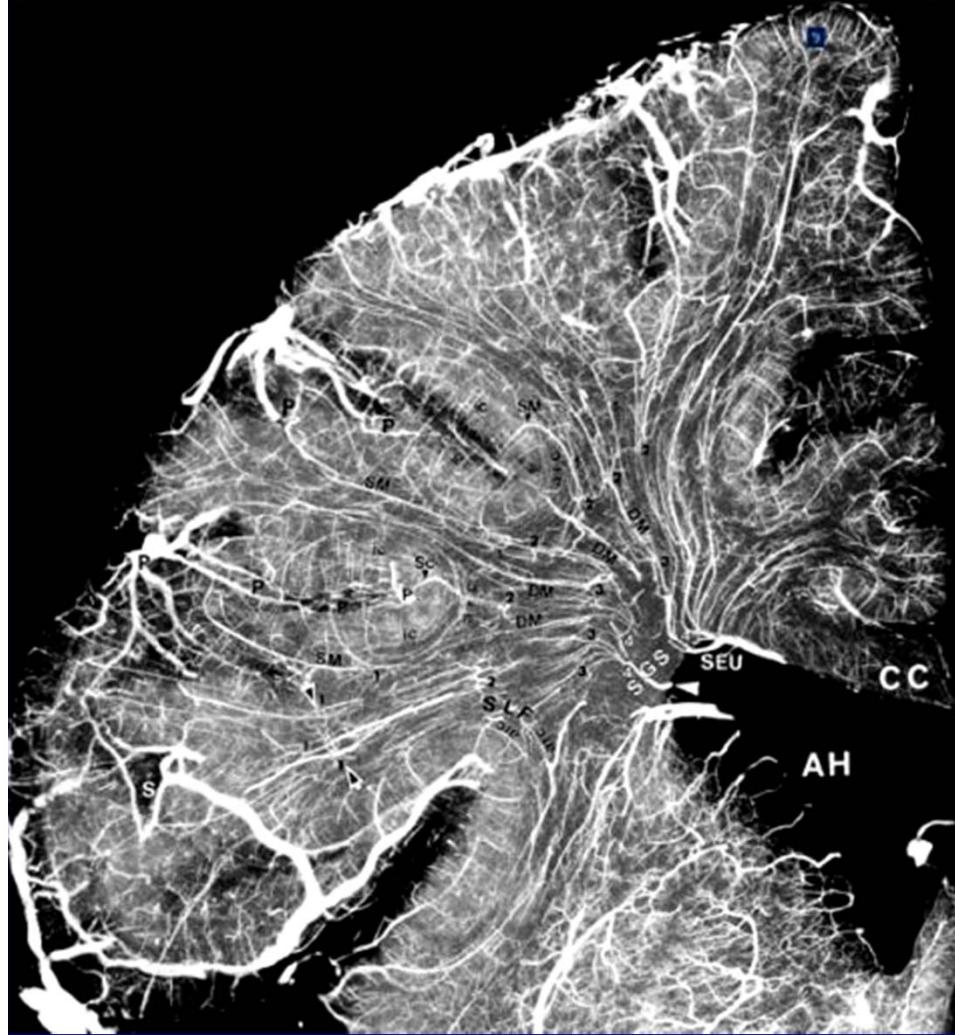
AD and Control Perfusion Maps



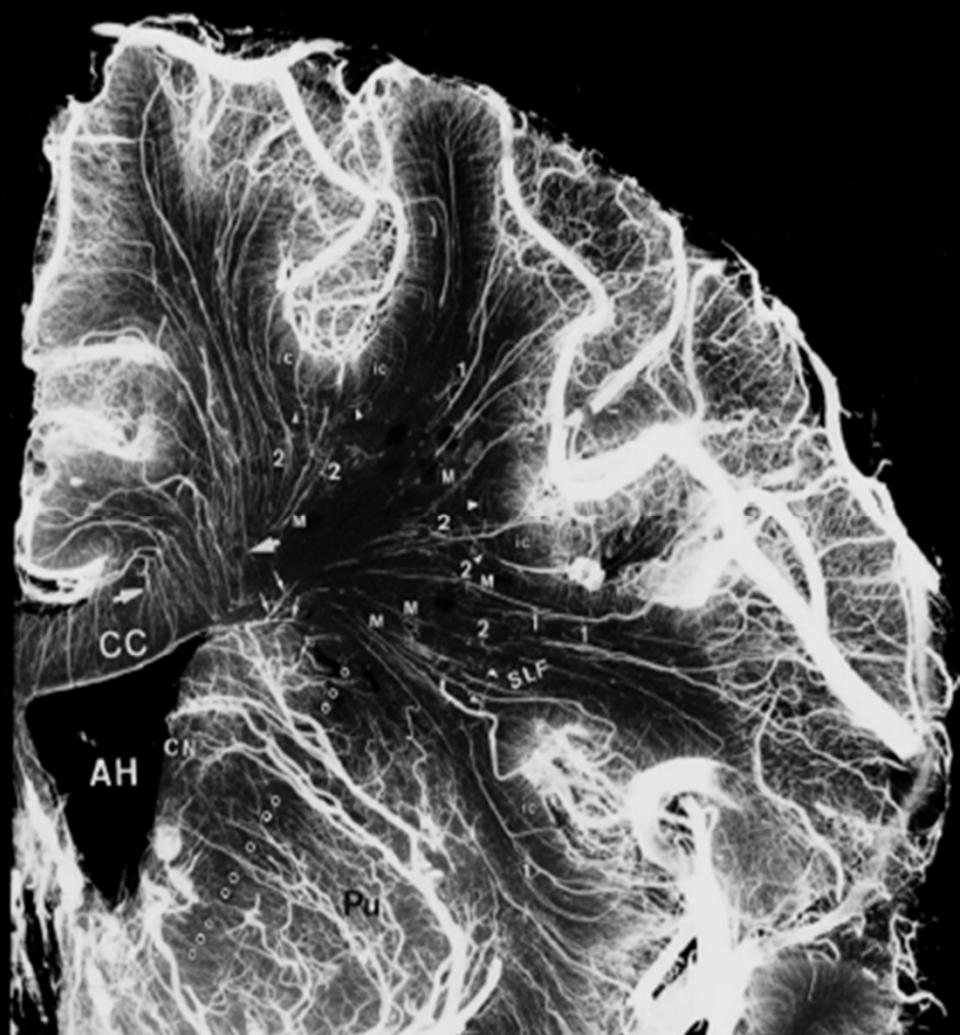
Watershed Areas, Perfusion and Group Comparison



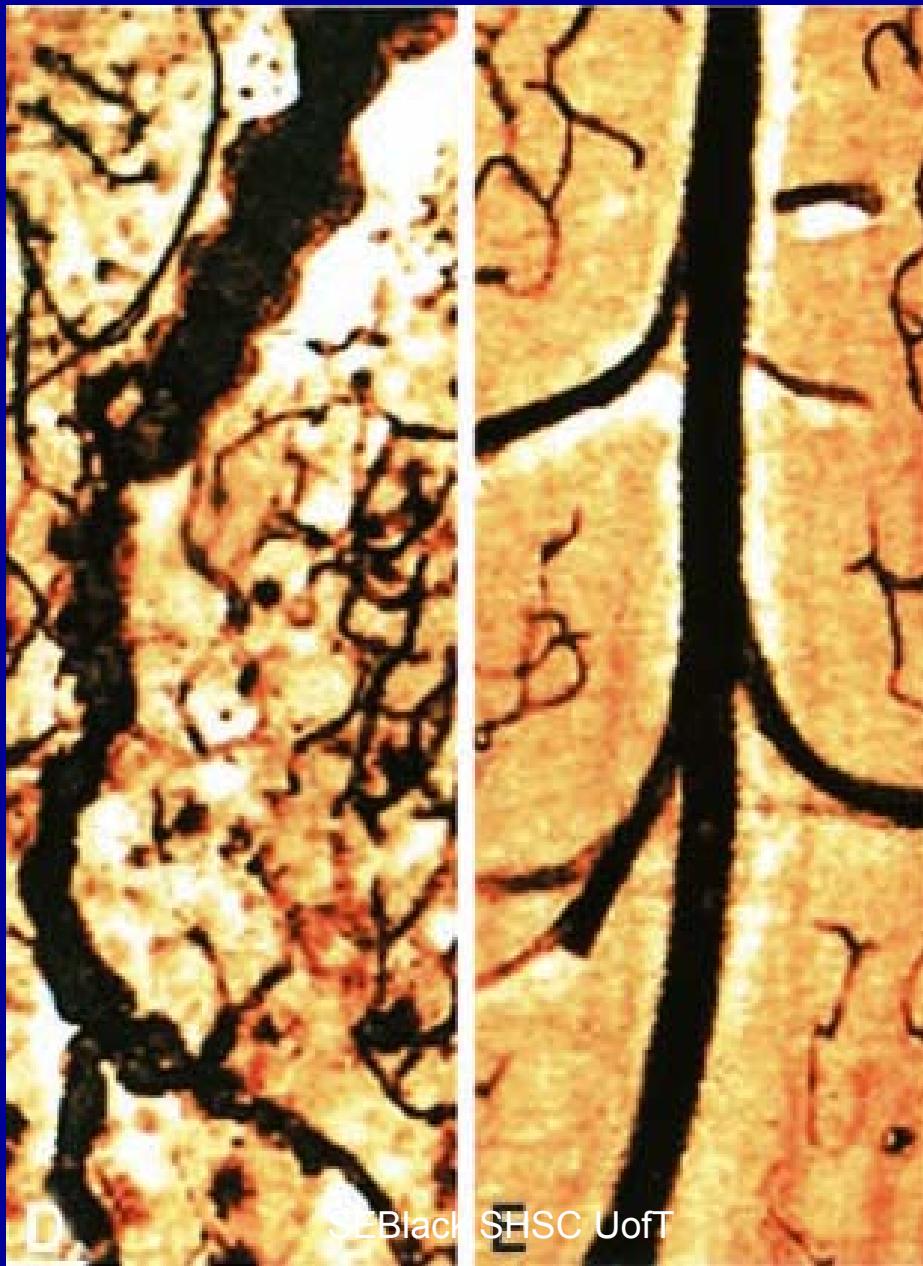
Medullary veins



Penetrating arteries

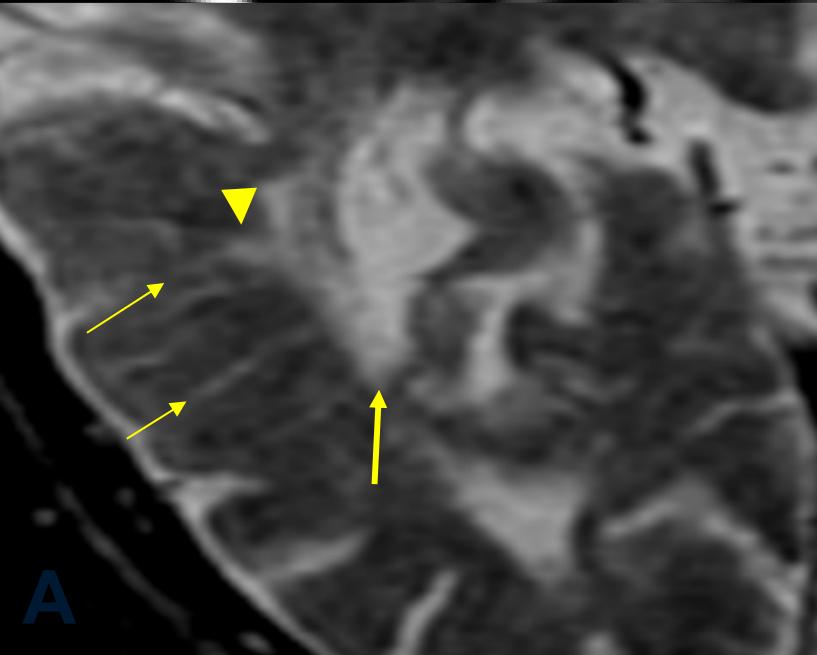
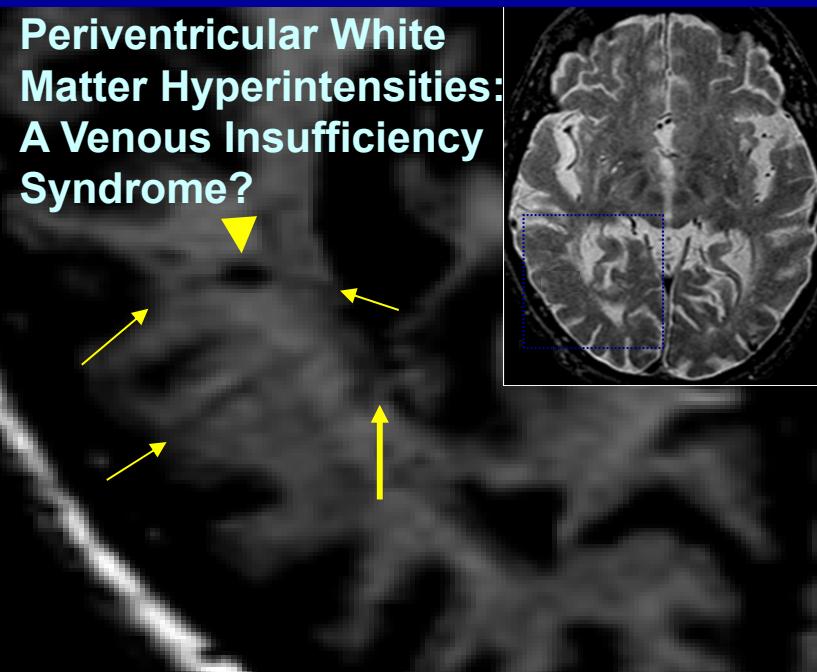


Severely disturbed cortical vascular network in AD



Suter Stroke 2002

**Periventricular White Matter Hyperintensities:
A Venous Insufficiency Syndrome?**



A

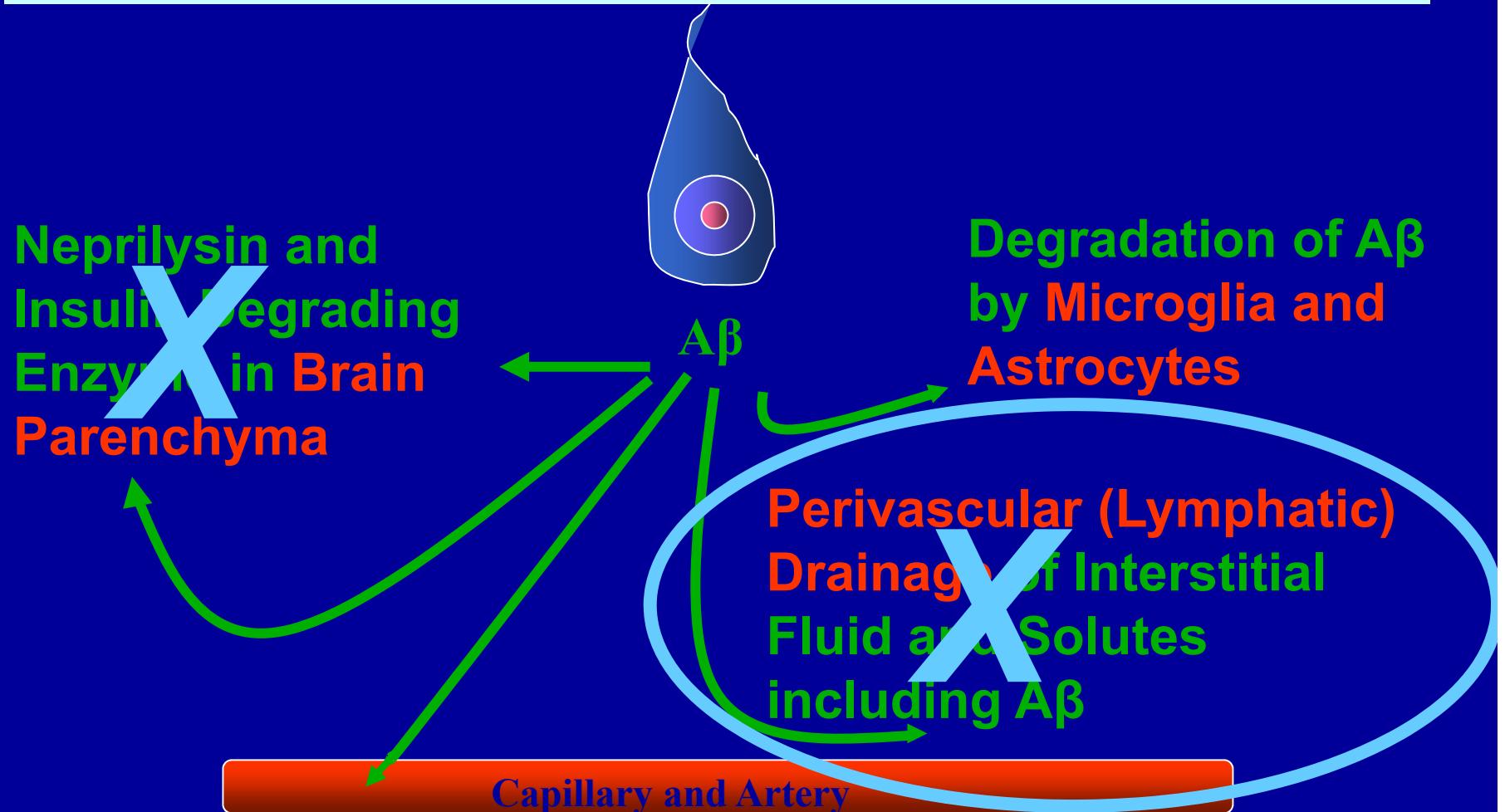
Courtesy of FQ Gao



B

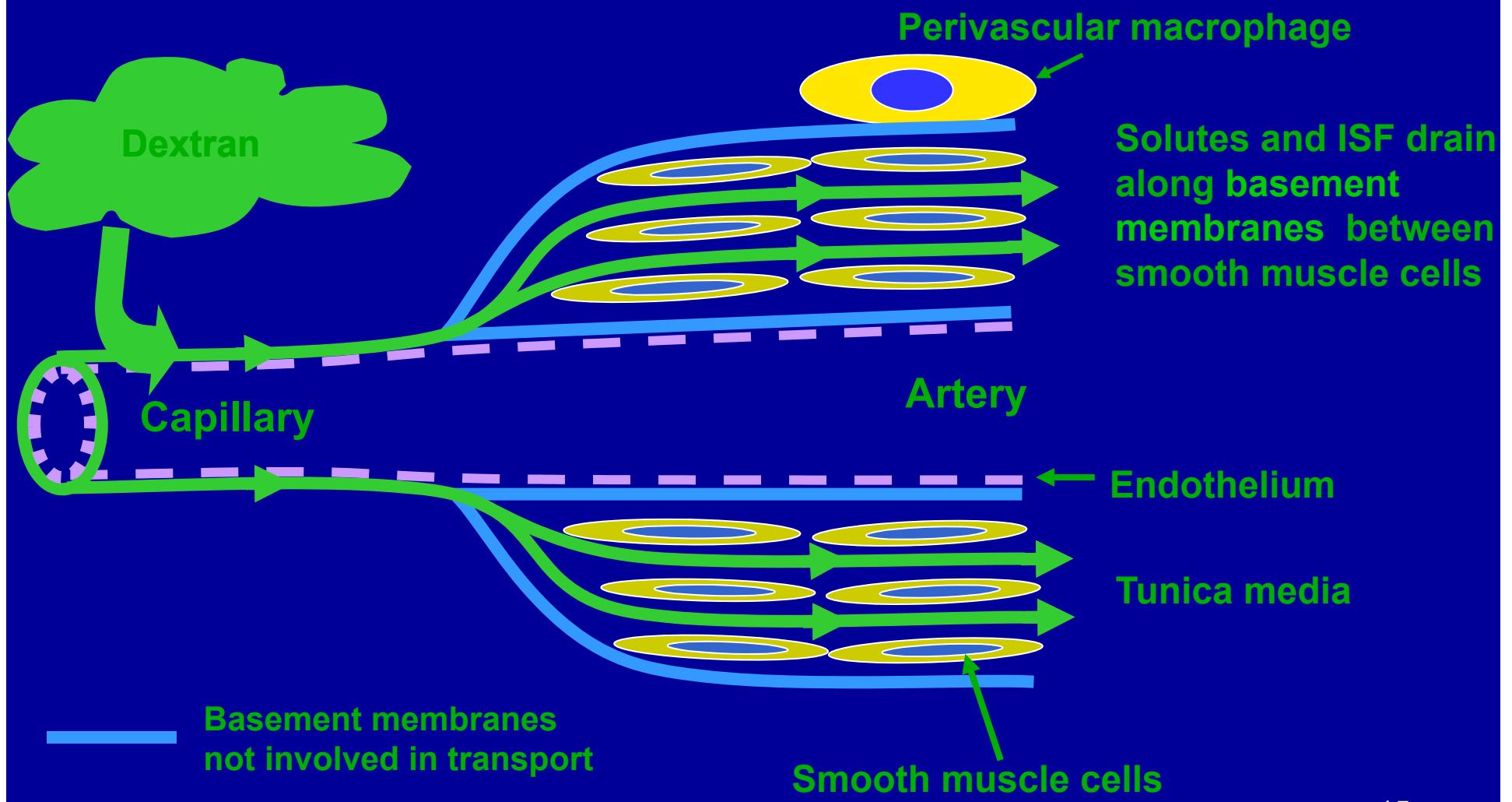
SEBlack SHSC UofT

Mechanisms for elimination of A_β from the brain

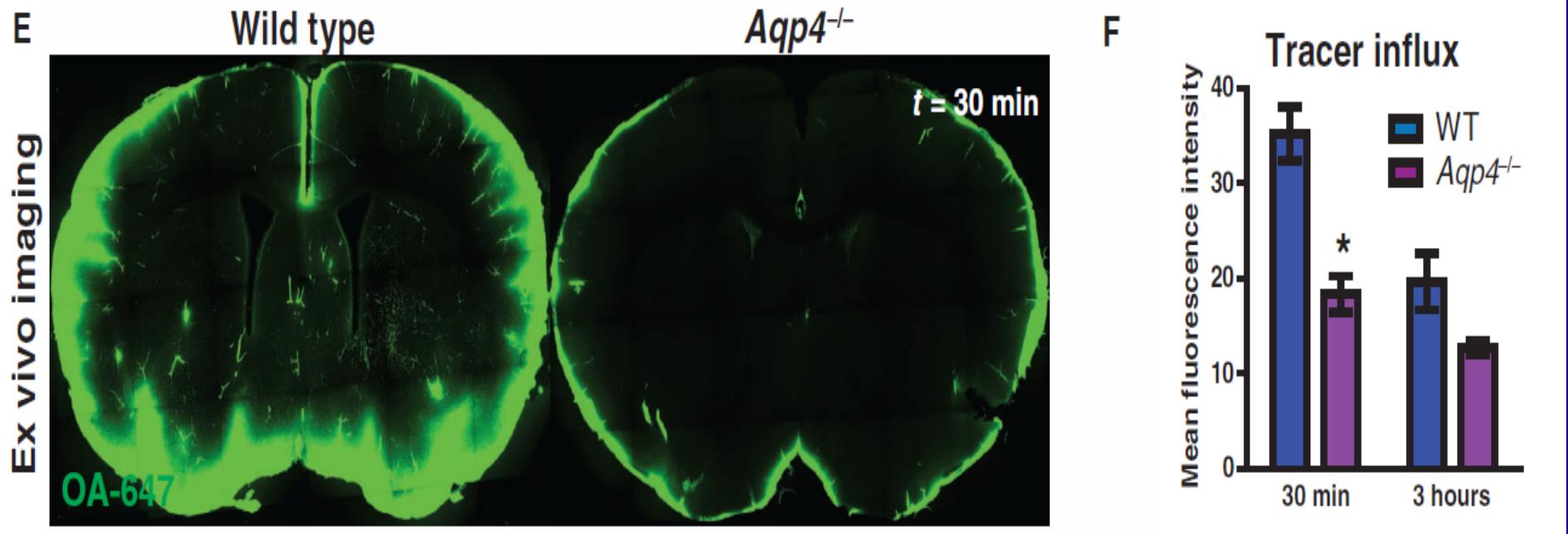


Absorption into blood via Low density lipoprotein receptor-related protein-1 (LRP1) and P-glycoprotein mediated mechanisms ? CSF pathways¹⁴

Perivascular (lymphatic) drainage of interstitial fluid and solutes along basement membranes of capillaries and arteries



CSF Tracer Influx into the Brain Parenchyma in WT Controls vs. *Aqp4*-null Mice



Iliff, *Sci Trans Med*, 2012

Aim

- To determine in patients with significant WMD, stratified by apolipoprotein E e4 status:
 - The baseline prevalence and degree of uptake of amyloid on PET in relation to baseline clinical and multimodal brain imaging measures
 - if baseline white matter disease volume predicts increased amyloid uptake at 1 year
- To evaluate changes, if any, in amyloid uptake in correlation with the changes in clinical and structural and functional brain measures over 1 year

Primary Hypotheses

Patients who have high burden of Periventricular White Matter Hyperintensities (pvWMH) will have a higher likelihood of amyloid positive scans.

The volume of pvWMH will correlate with the standardized measures of florbetapir uptake.

Patients who have high burden of pvWMH volumes will show greater increase in amyloid deposition over one year.

Secondary Hypotheses

Patients with abnormal florbetapir uptake ratios on PET at baseline will have lower cognitive scores, hippocampal and brain volumes, and posterior cingulate-parietal–temporal metabolism on 18-FDG PET, and larger ventricular volumes compared to their subgroup counterparts with amyloid negative PET scans.

Baseline positive scans for florbetapir uptake will predict greater cognitive and functional decline at 1 year.

Research Design

- 120 patients (60 from stroke prevention clinics, 60 from memory clinics)
- 250 NC , 400 MCI, and 150 AD from ADNI-GO and ADNI-2 studies will serve as control groups
- Recruitment period: 9 months
- Study Procedures at baseline and one year
 - 3T-MRI
(3DT1/PD/T2/FLAIR/GrEcho/DTI/rsfMRI/(ASL))
 - FDG-PET, Florbetapir Amyloid PET
 - Neuropsychological Testing
 - Blood sampling at baseline for APOE e4, BDNF, other genomics and metabolomics

Inclusion Criteria

- Age \geq 60 years
- WMD score on CT or MRI of 3 on the Fazekas scale, but no cortical infarcts or subcortical >1cm
- Memory clinic patients will meet criteria for amnestic or multi-domain MCI and mild early AD (MMSE \geq 20) using the same criteria as in the ADNI project
- TIA patients from stroke prevention clinics may have MMSE scores between 20 – 30

Exclusion Criteria

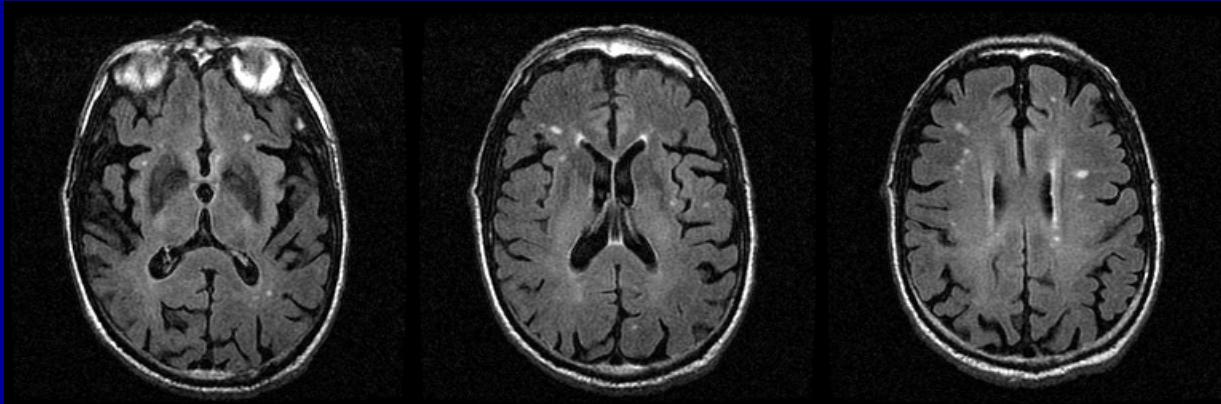
- Unsafe for 3T MRI
- Cortical or non-lacunar infarct
- Major psychiatric disorder during preceding 5 years
- History of substance abuse
- Serious/chronic systemic or neurological illness (other than Alzheimer's disease)

Neuropsychology Protocol

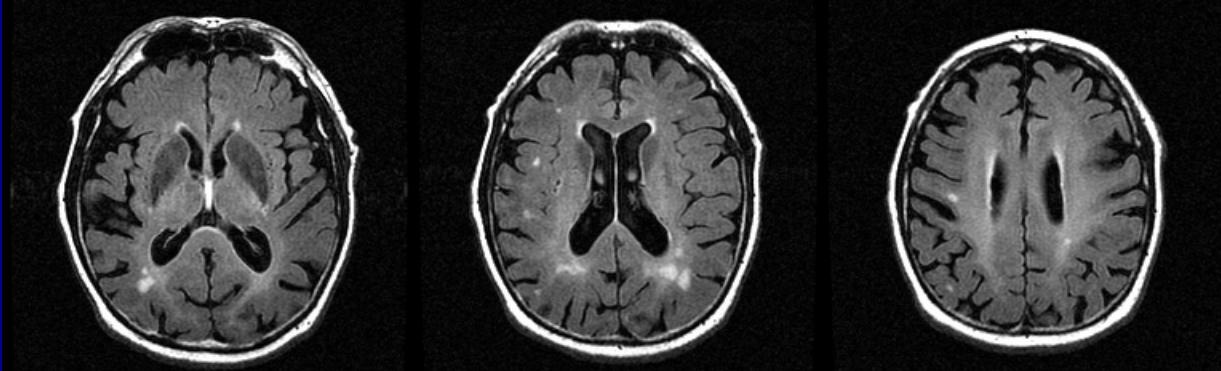
- Mini Mental Status Exam (MMSE)
- Montreal Cognitive Assessment (MoCA)
- Phonemic and Semantic Fluency
- Trails A & B
- Symbol Digit Modalities Test
- The Centre for Epidemiologic Studies Depression scale (CES-D)
- To be added
 - ANART (American National Adult Reading Test)
 - TUG (Timed up and Go)
 - FAQ (Functional Assessment Questionnaire)
 - Other core neuropsychological tests from the ADNI battery

Example of Fazekas Scores

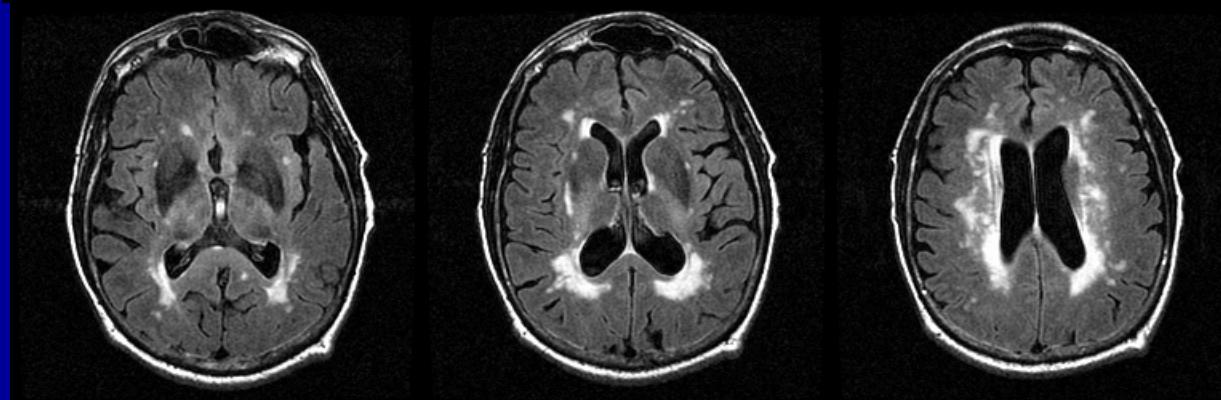
Fazekas 1



Fazekas 2

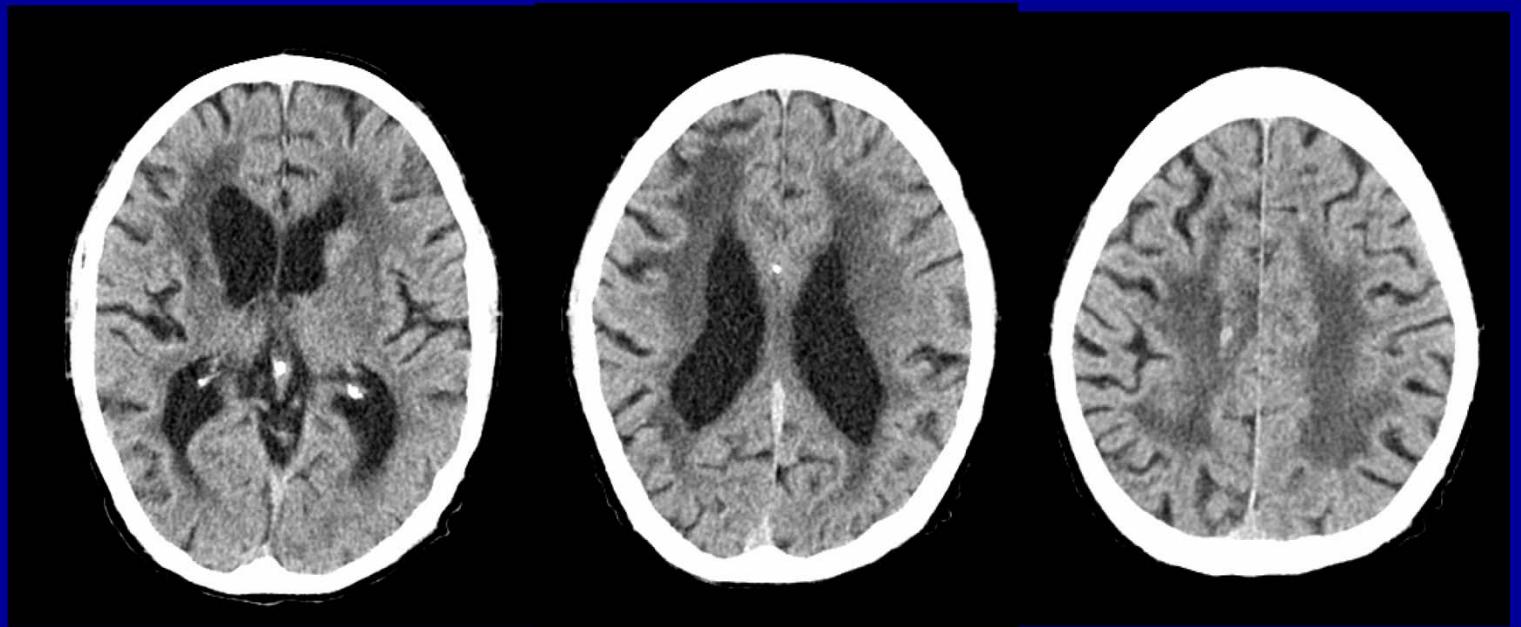


Fazekas 3



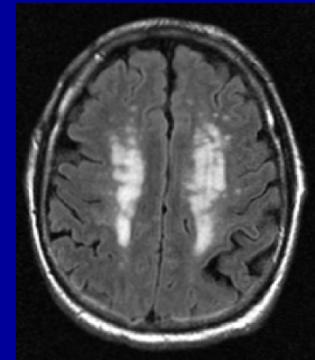
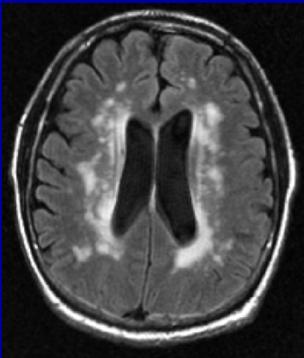
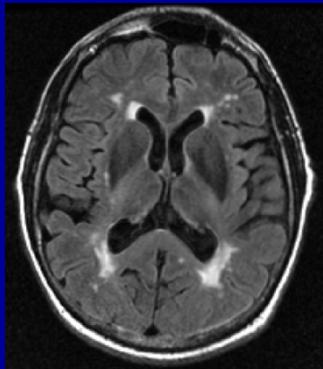
Fazekas 3

CT

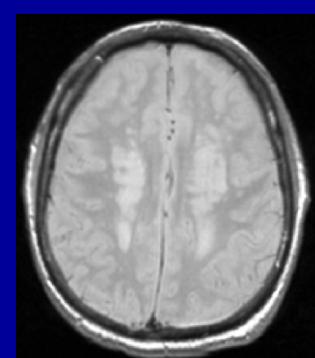
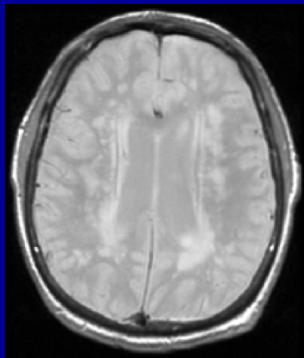
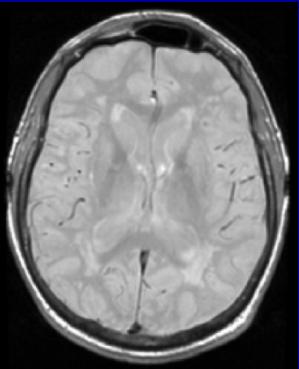


Example of Fazekas 3 Scores

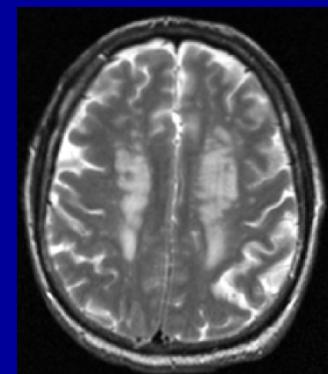
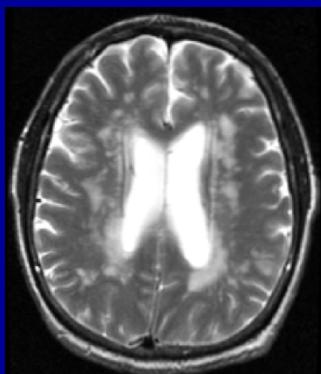
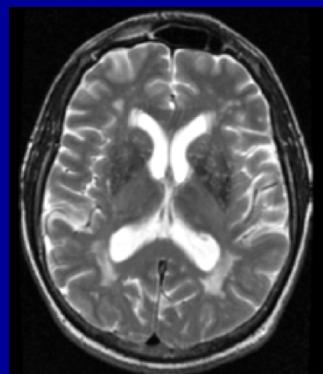
FLAIR



PD



T2



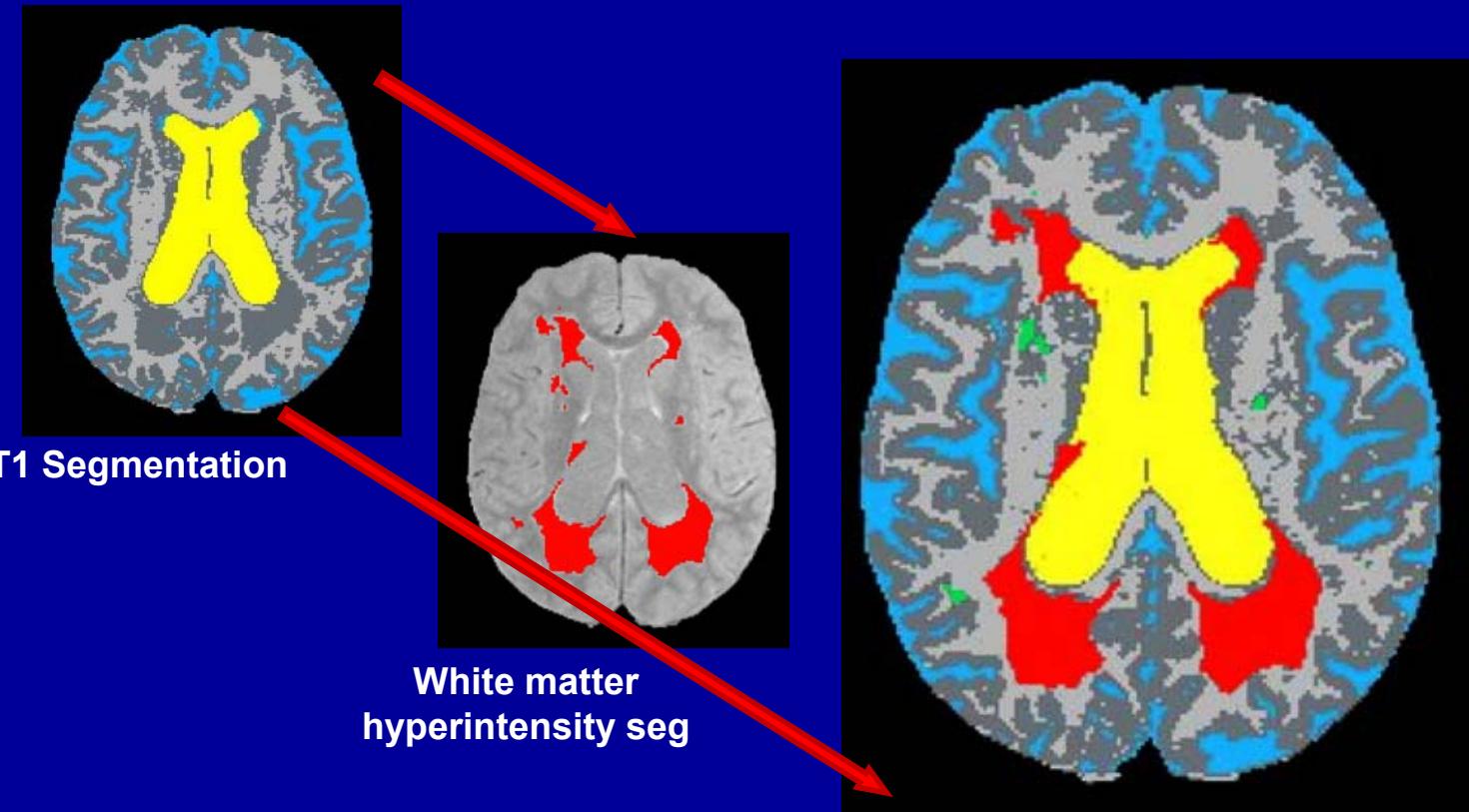
Subjects and procedures

Study protocol

- 3T-MRI (structural, DTI, TF-MRI), FDG-PET, 18 florbetapir PET, Neuropsychological Testing, Blood Sampling (Apoe E e4) at baseline and at 12 months
- Analysis pipelines designed to derive total supratentorial intracranial volume, tissue segmentation including grey, white, lesion subtypes (lacunar, deep and periventricular hyperintensities), with adapted free surfer application

Lesion Explorer Segmentation

Summary of Outputs



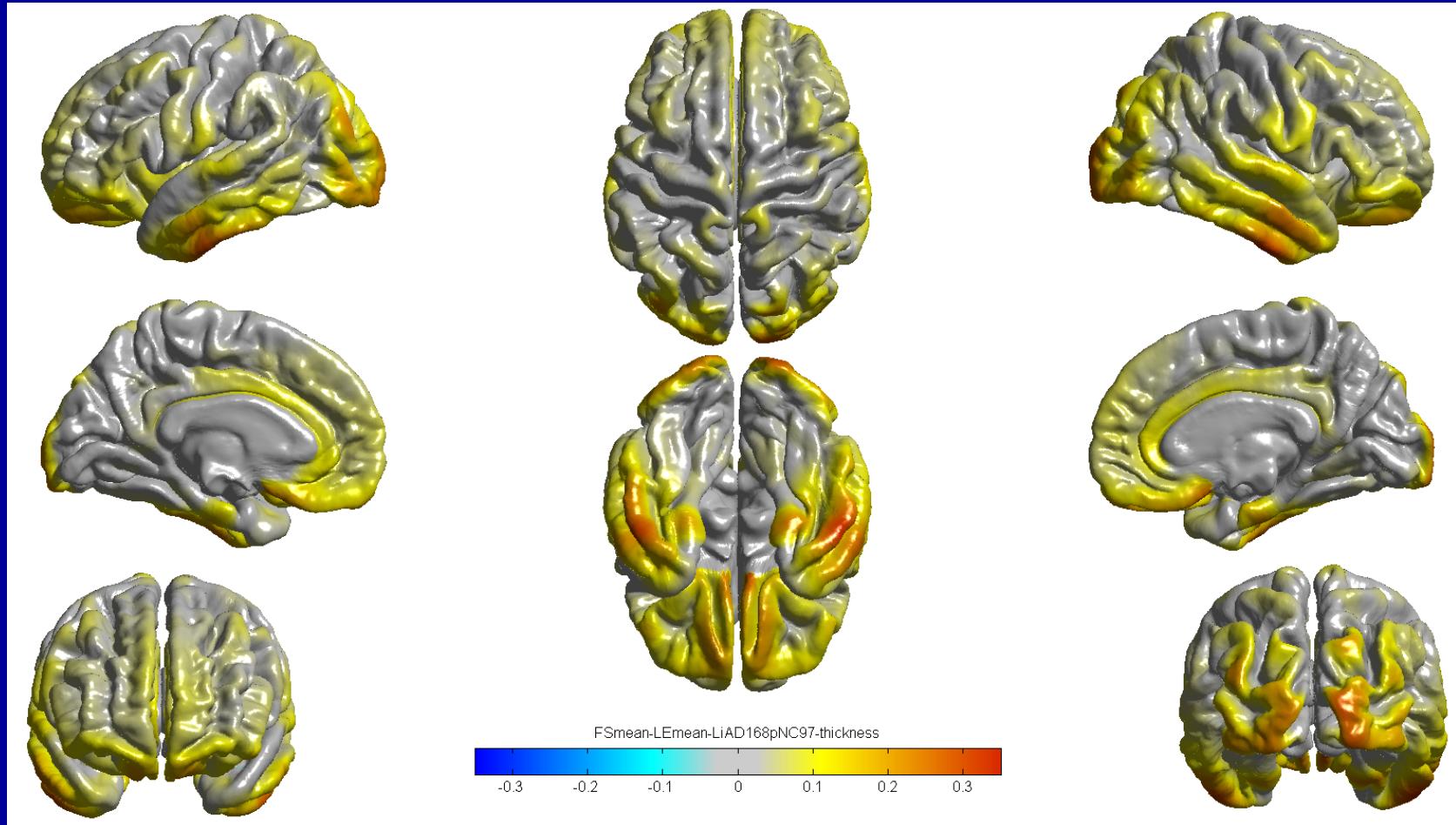
Final Segmentation Tissue Classes:

1. GM
2. WM
3. sCSF
4. vCSF
5. pvSH
6. dwSH
7. lacunes

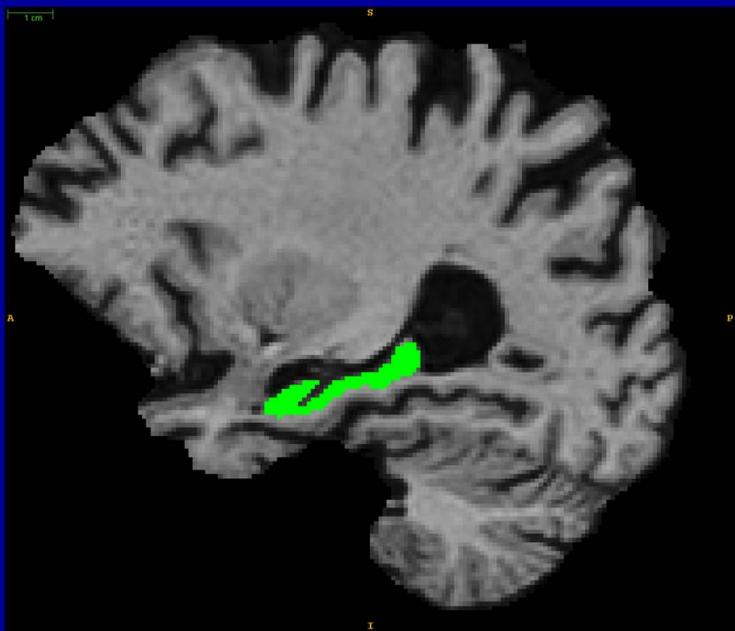
SEBlack SHSC UofT

Ramirez Neuroimage 2011

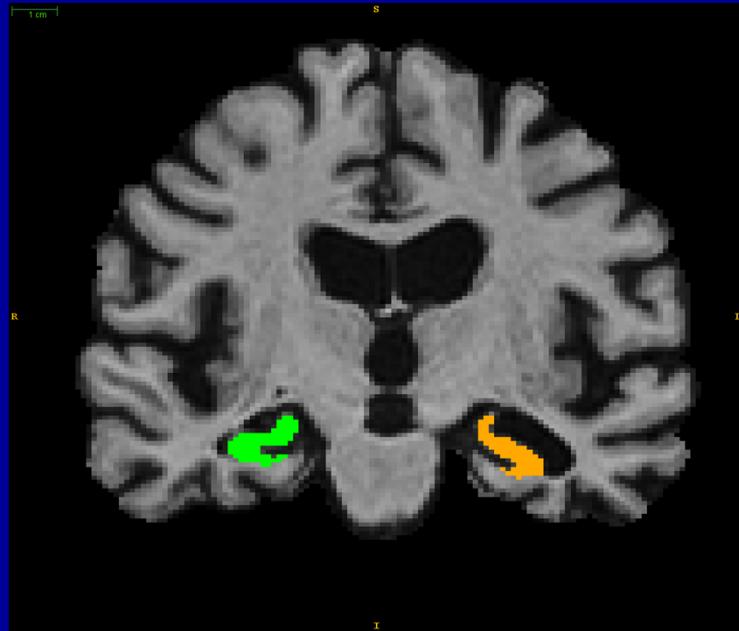
Differences in mean cortical thickness (FreeSurfer alone vs FS+Lesion Explorer) for AD =168 vs NC =97



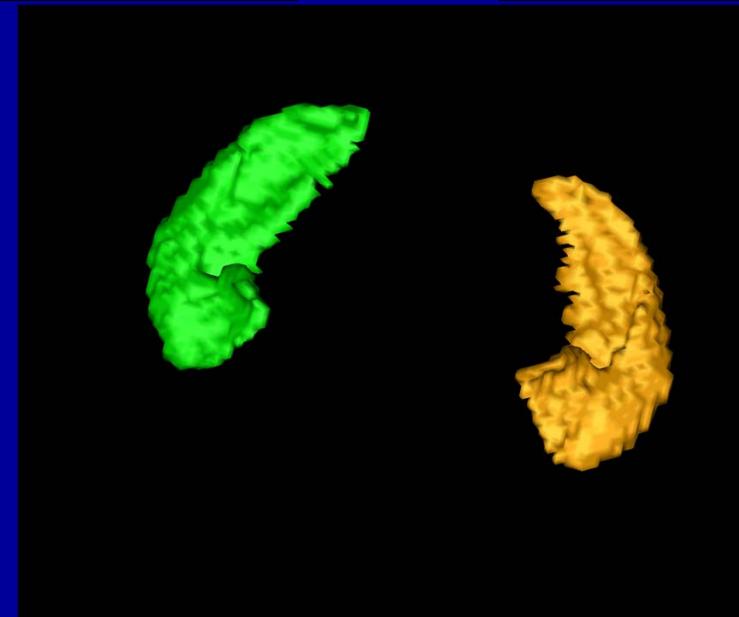
A



B



C



Conclusions

1. The pathophysiology of AD is complex and still not fully understood though our ignorance is increasingly informed— oxidative stress, innate immunity, and poor clearance of amyloid all play a role in sporadic disease
2. Heterogeneity of AD is important to recognize including co-morbidities, especially vascular
3. Small Vessel Disease includes both disease arteriolar, capillary and venous mechanisms relevant to the pathophysiology of AD

Research Team

Executive Committee

- Jean-Claude Tardiff
- Richard Frayne
- Frank Prato
- Eric Smith
- Stephen Strother
- John Valliant

Recruitment sites starting up in Toronto, Vancouver, London, Hamilton with 7 more planned

Acknowledgement of Financial Support

Personal support

- Brill Chair in Neurology; Brain Research , SRI, Dept of Med, SHSC, U of Toronto

Peer-reviewed Funding

- Canadian Institute of Health Research
- National Institutes of Health-ADNI
- Ontario Brain Institute

Contract Research

Lilly-Avid: florbetapir

Philanthropy: L. C. Campbell, Slaight, Odette. Levy Foundations

HSF Centre for Stroke recovery & LC Campbell Cognitive Neurology Research Unit

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