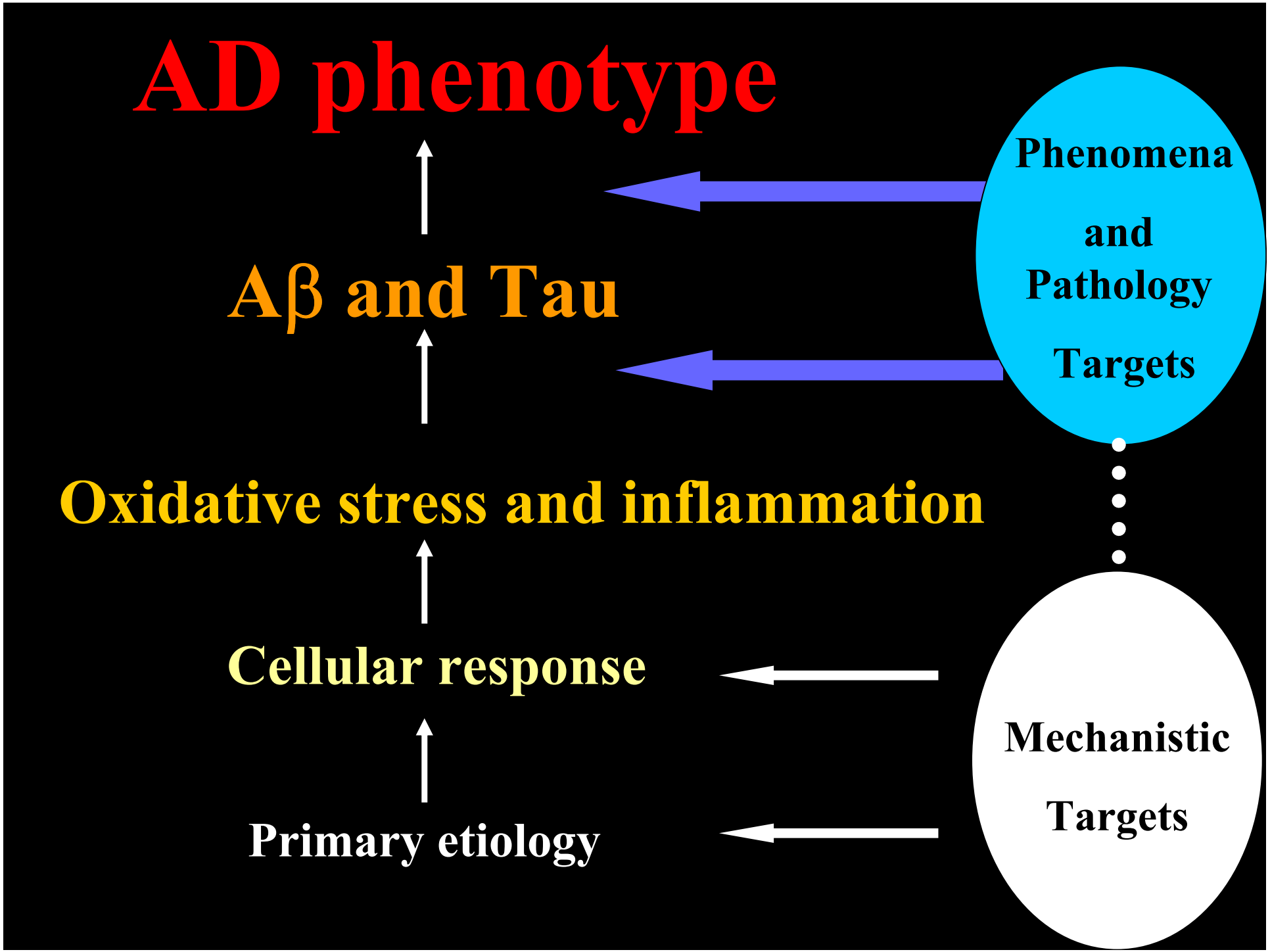
Presymptomatic Tests for AD: the Search for Mechanism

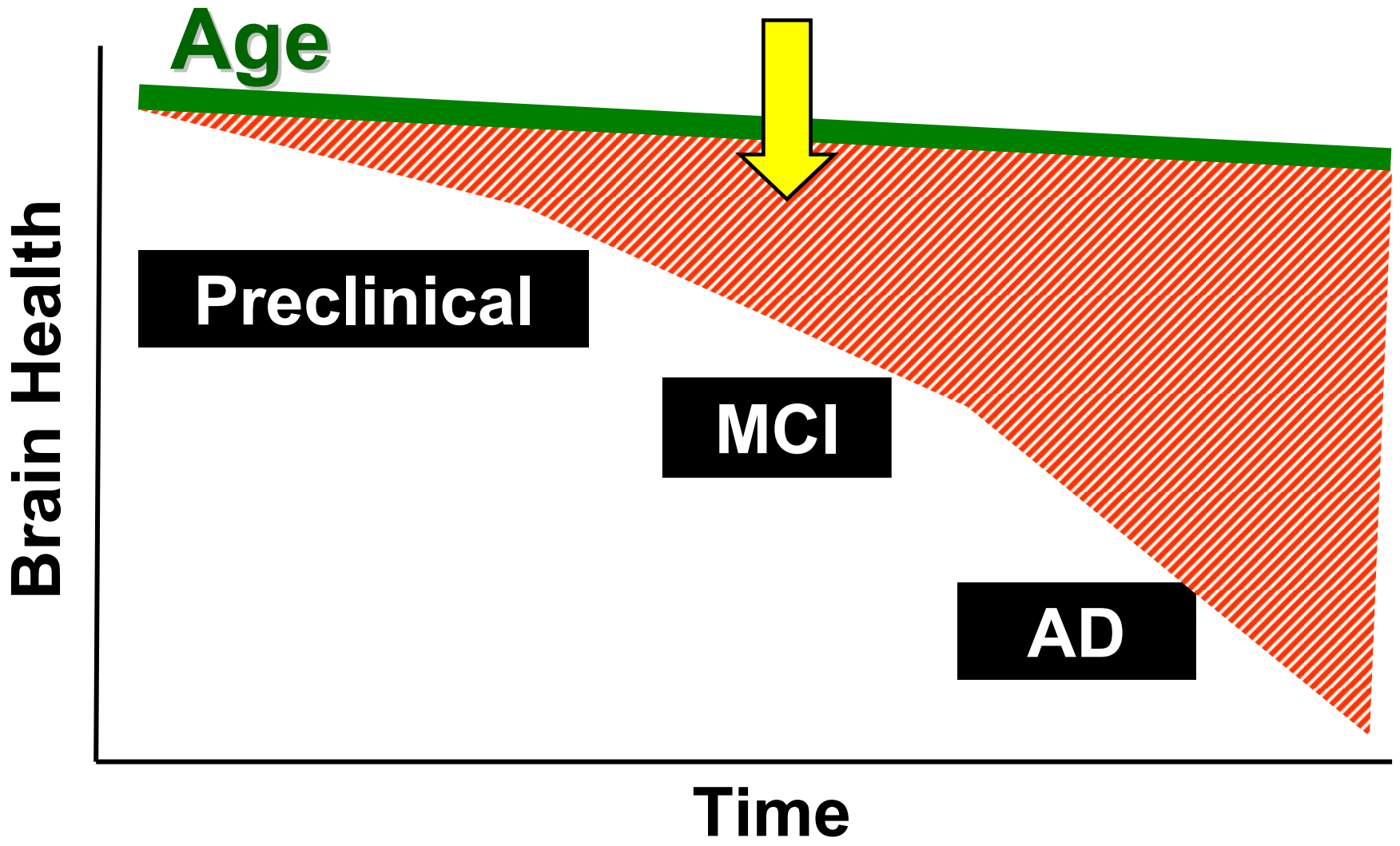
March 9, 2011
Barcelona, Spain

Mony de Leon

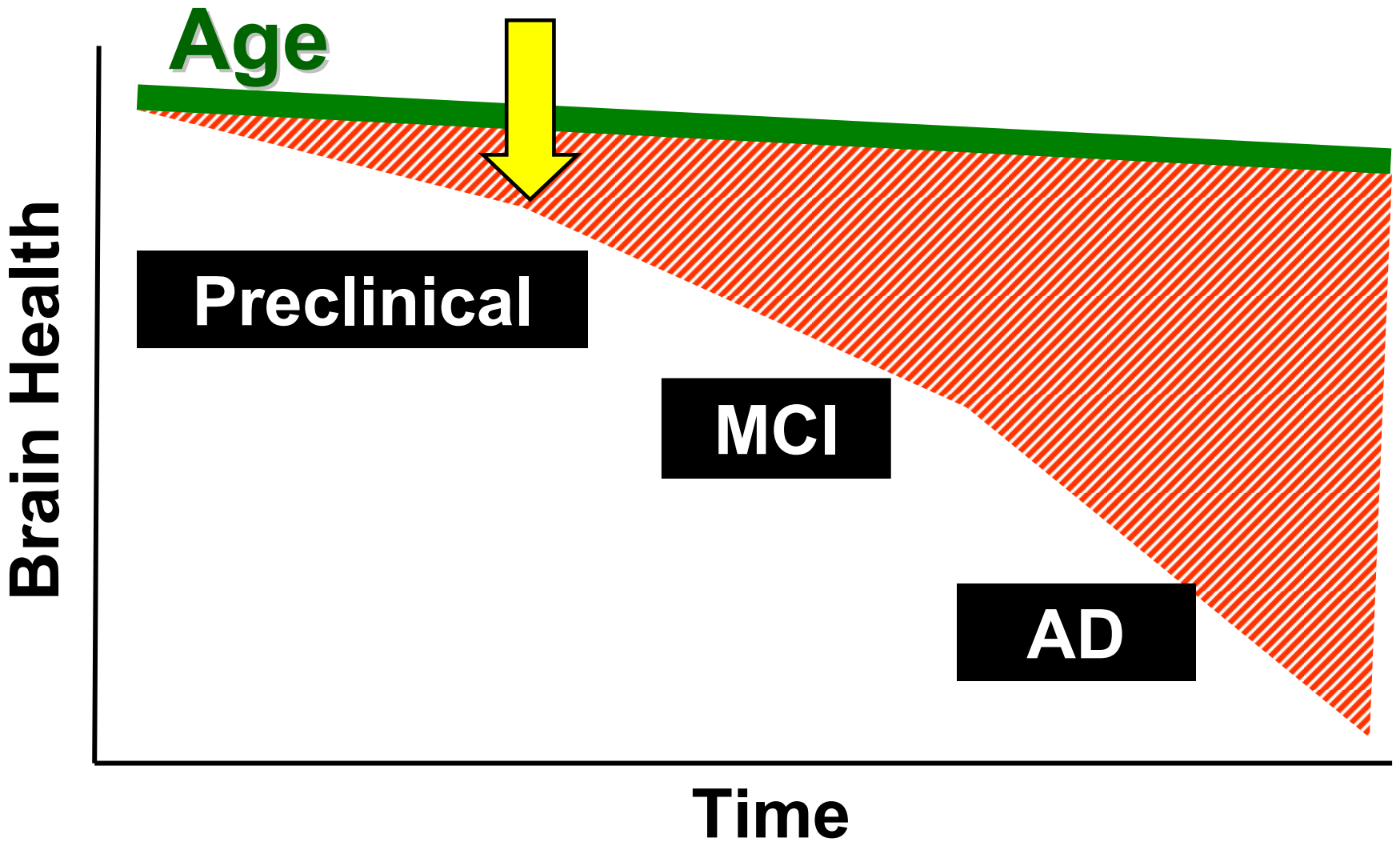
Professor of Psychiatry
NYU School of Medicine

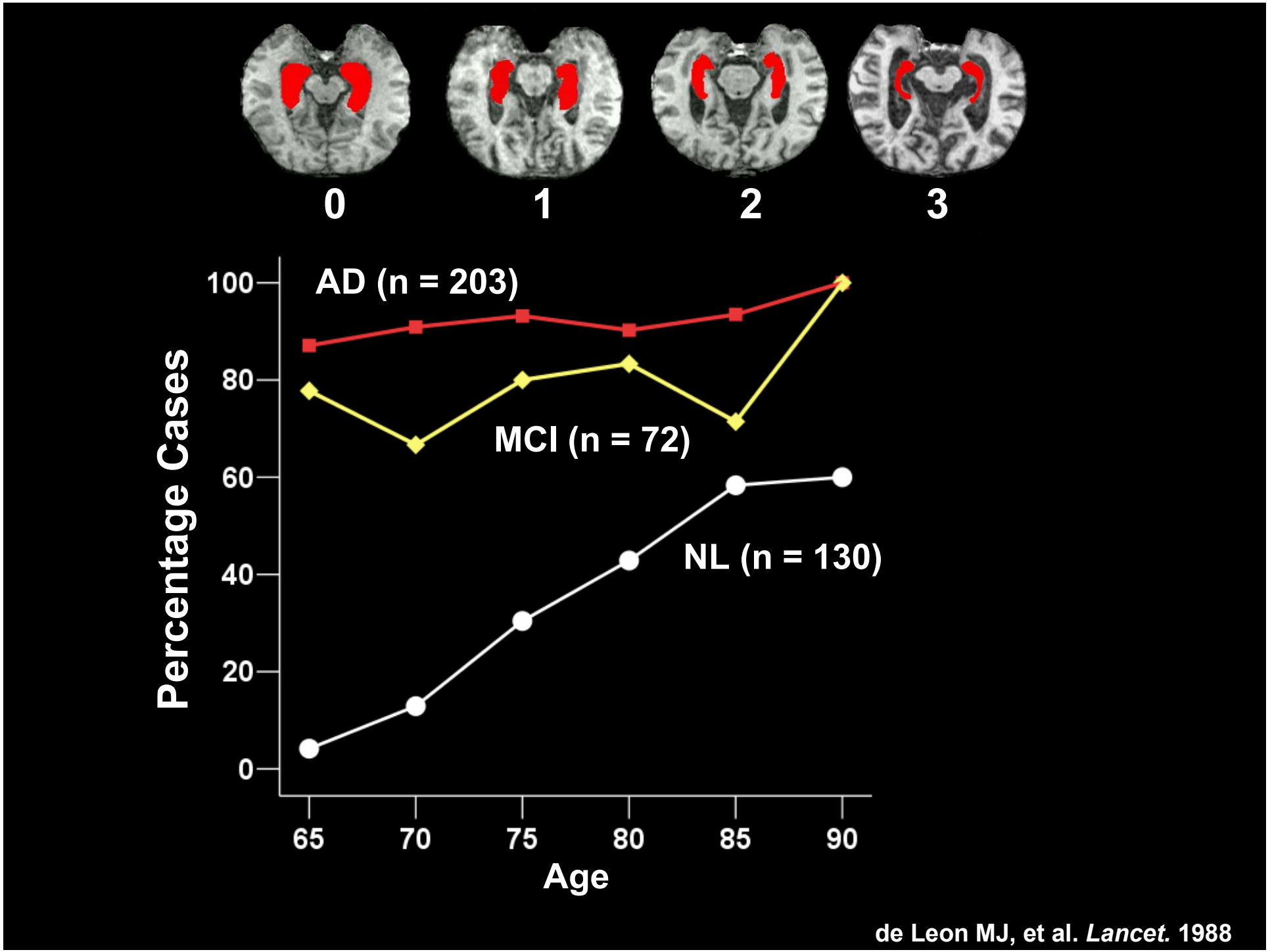

AD phenotype
Aβ and Tau
Oxidative stress and inflammation
Cellular response
Primary etiology
Phenomena and Pathology Targets
Mechanistic Targets

Objective of Early Diagnosis



Objective of Early Diagnosis





de Leon MJ, et al. *Lancet.* 1988

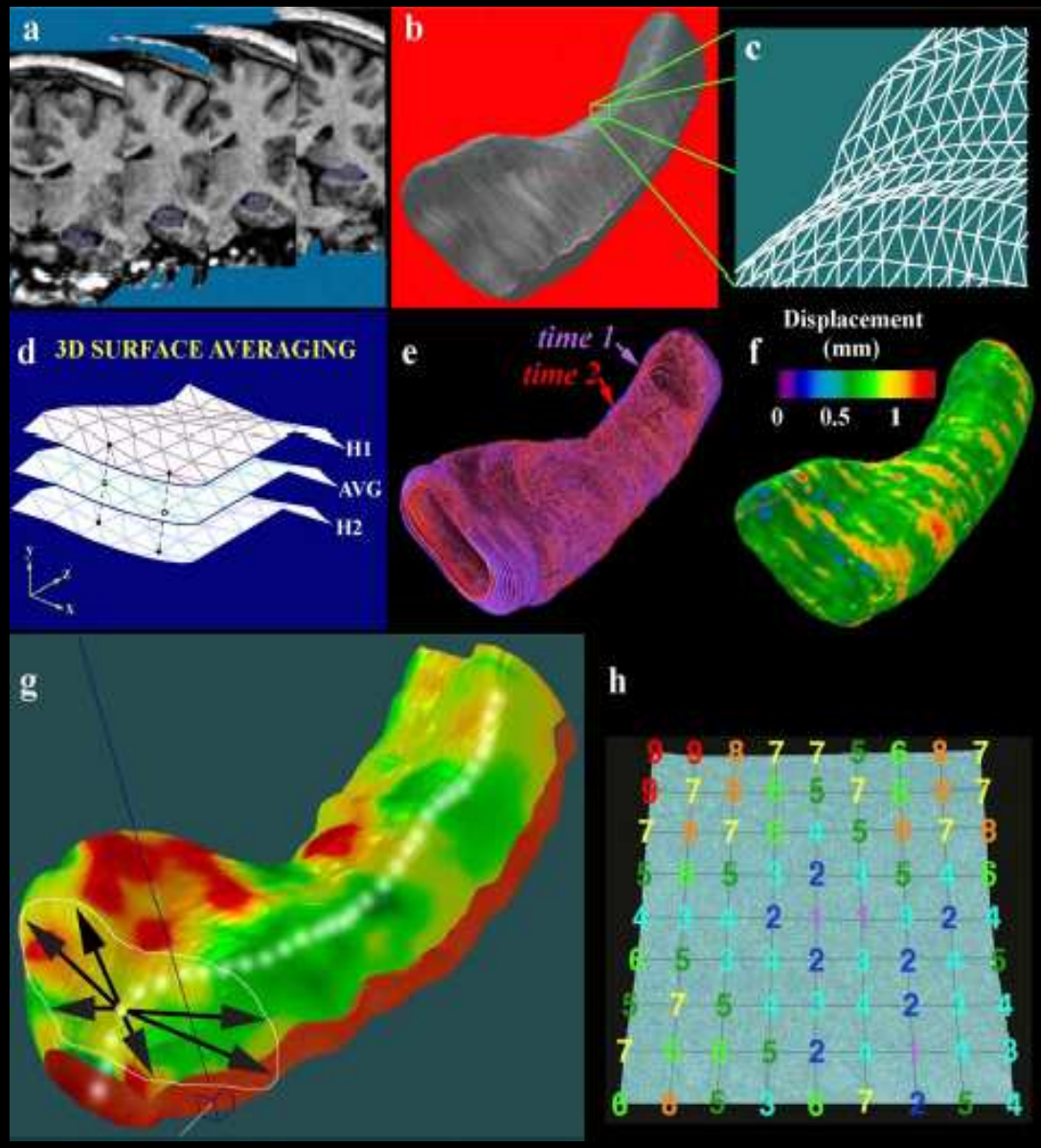
Automated MRI Regional Boundary Shift

6-year prediction of Normal to MCI

	Prediction of MCI
Accuracy	89%
SS/SP (n=13,32)	91/85%

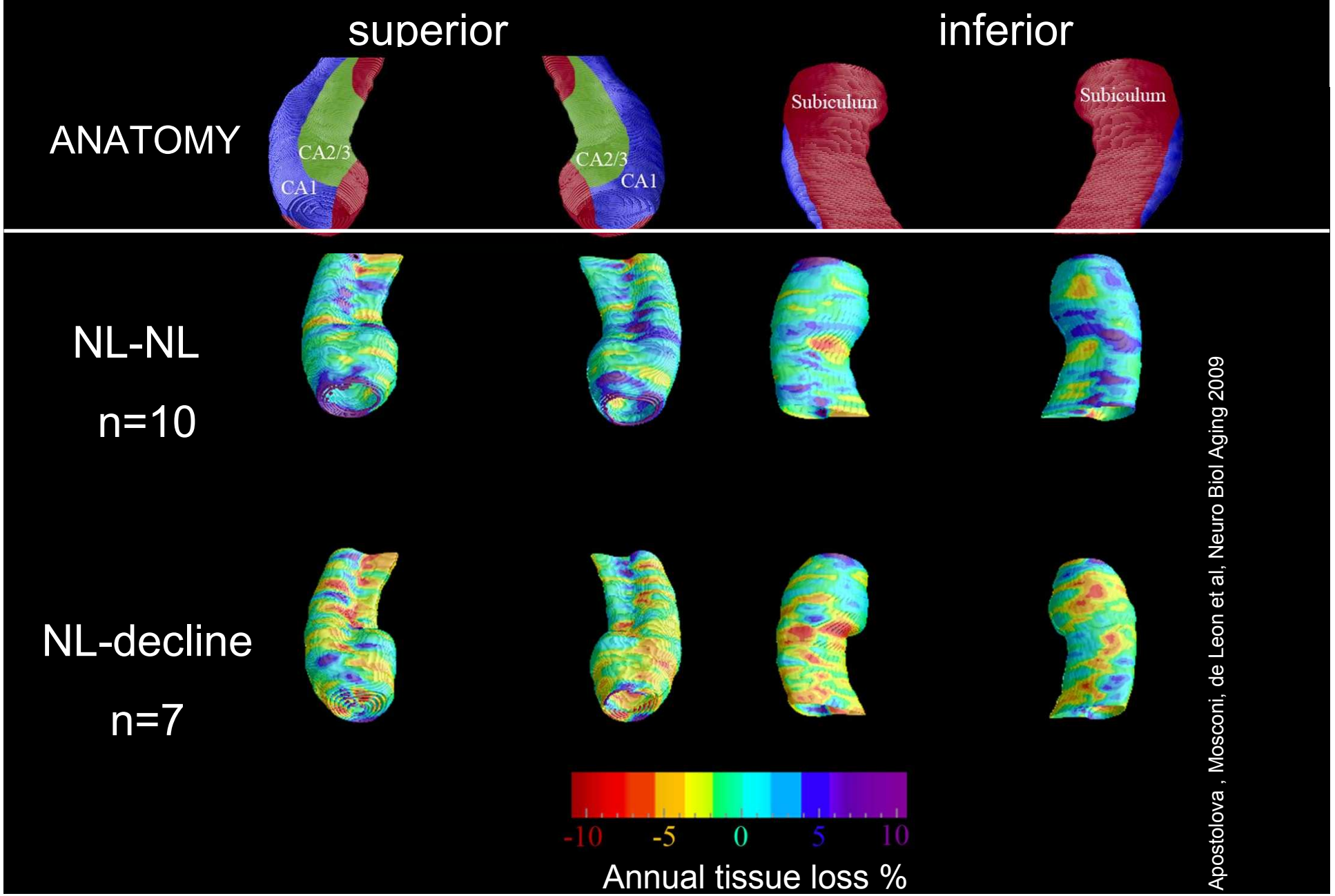
Rusinek H, de Leon, MJ et al. *Radiology.* 2003;229:691-696.

MESH MODELING



Thompson et al, Neuroimage 2004

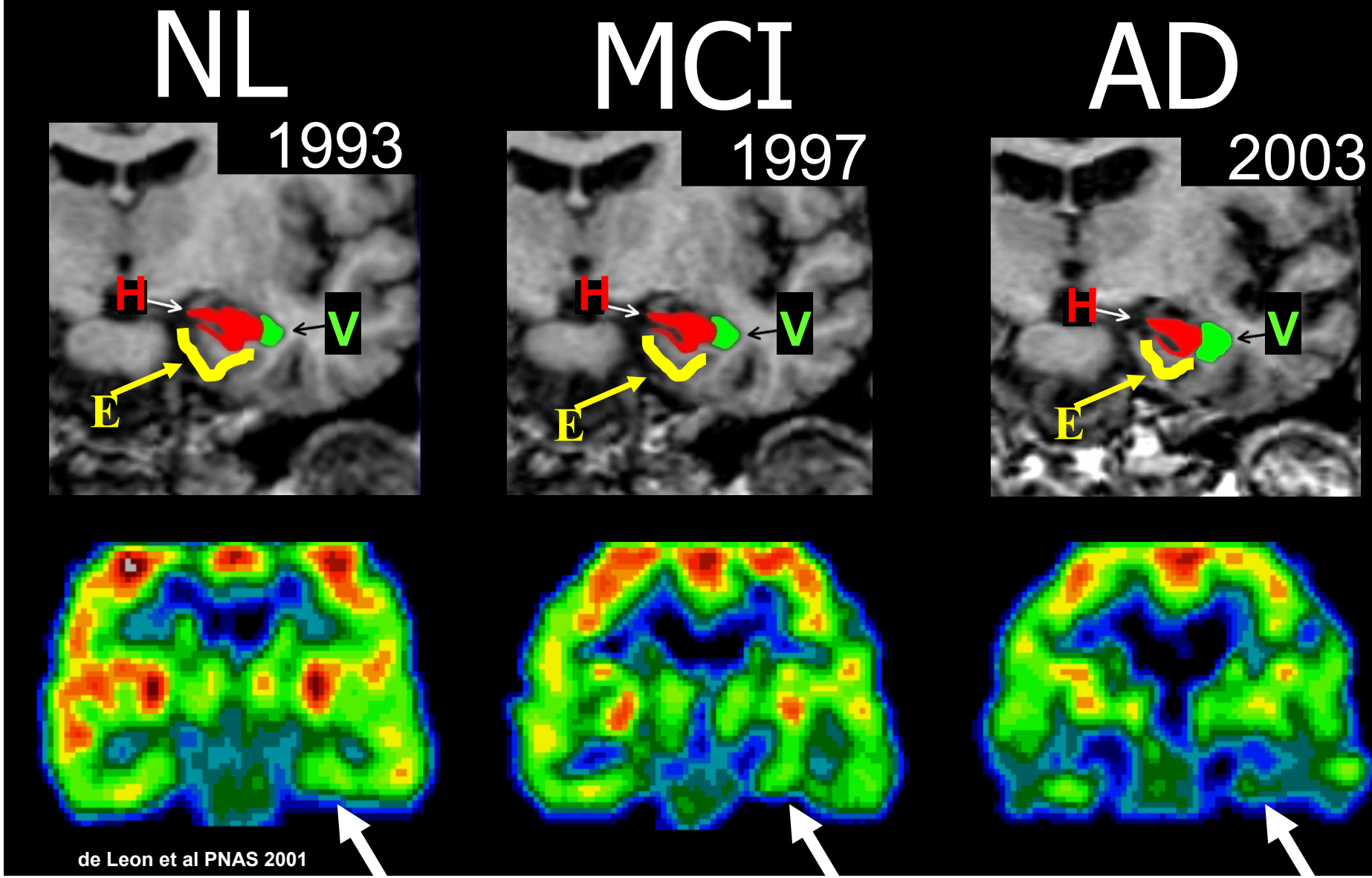
3-year MRI hippocampal atrophy rate



Apostolova , Mosconi, de Leon et al, Neuro Biol Aging 2009

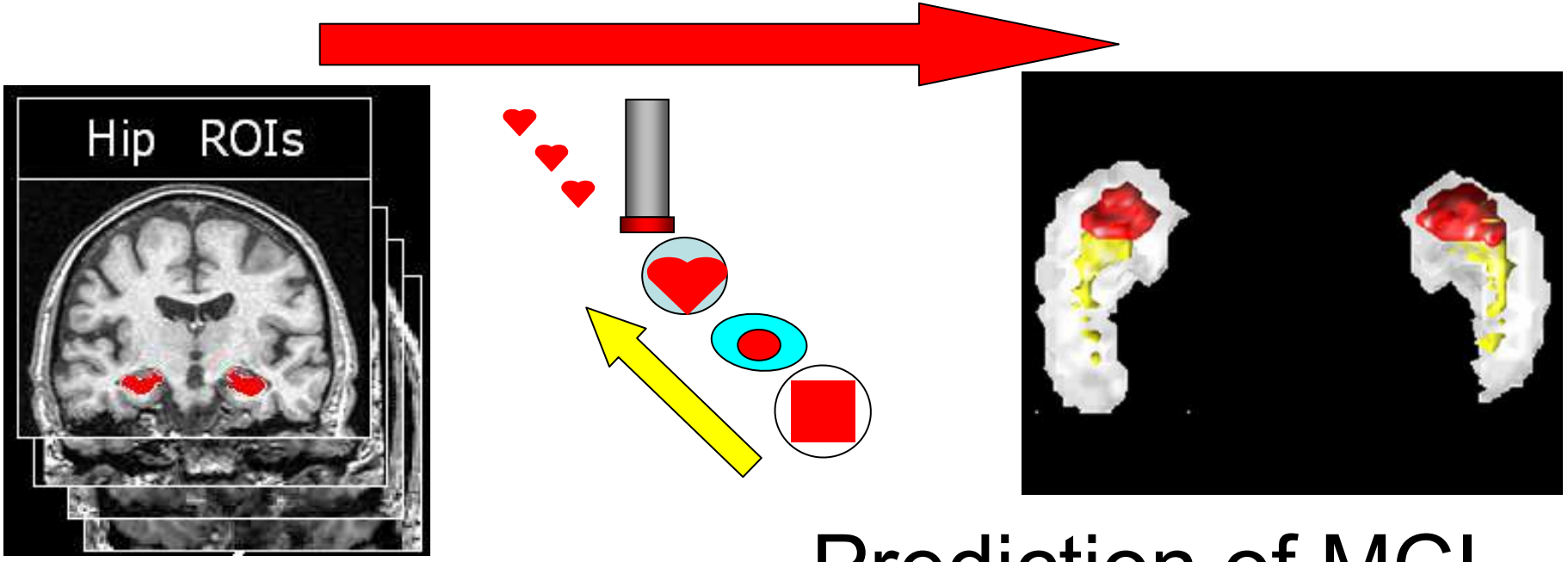
Atrophy and Metabolism

10-Year decline from NL to AD



Automated Hippocampus Sampling

7-year advanced prediction of Normal to MCI and AD

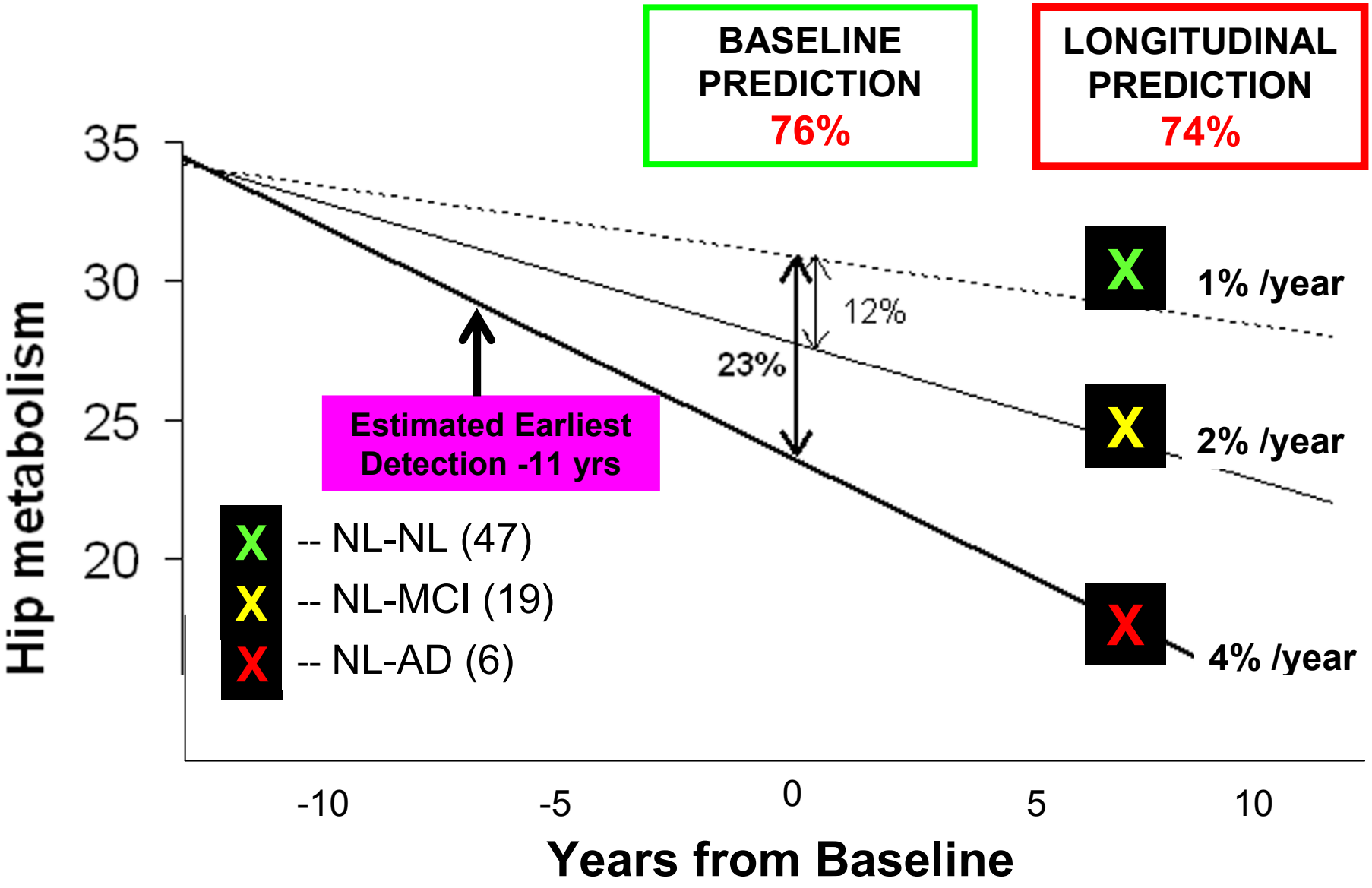


Prediction of MCI

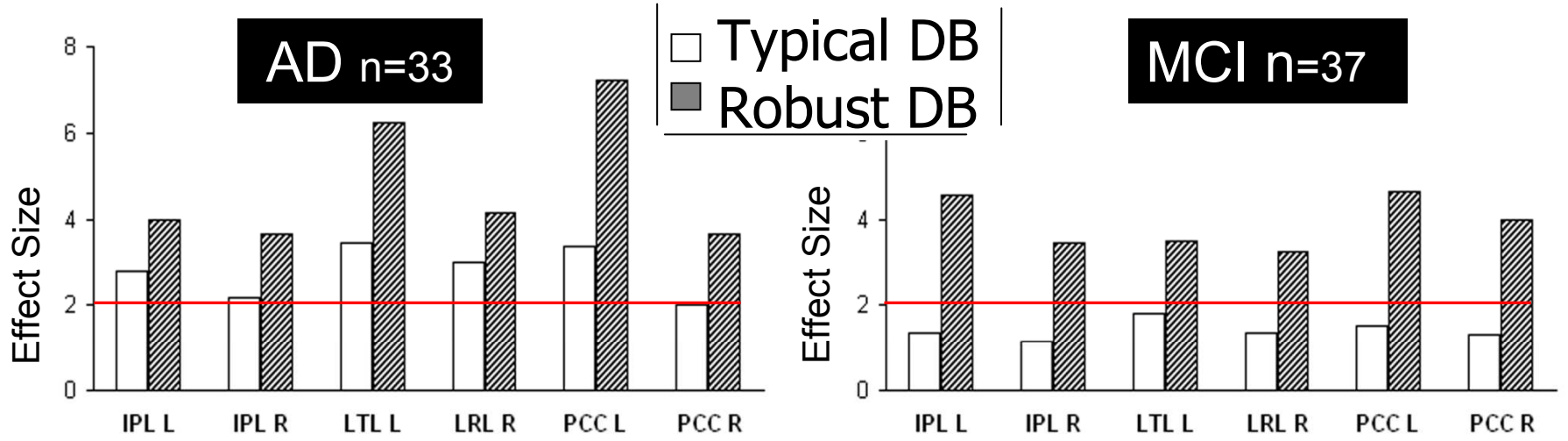
Accuracy	76%
SS/SP (n=25,47)	82/79%

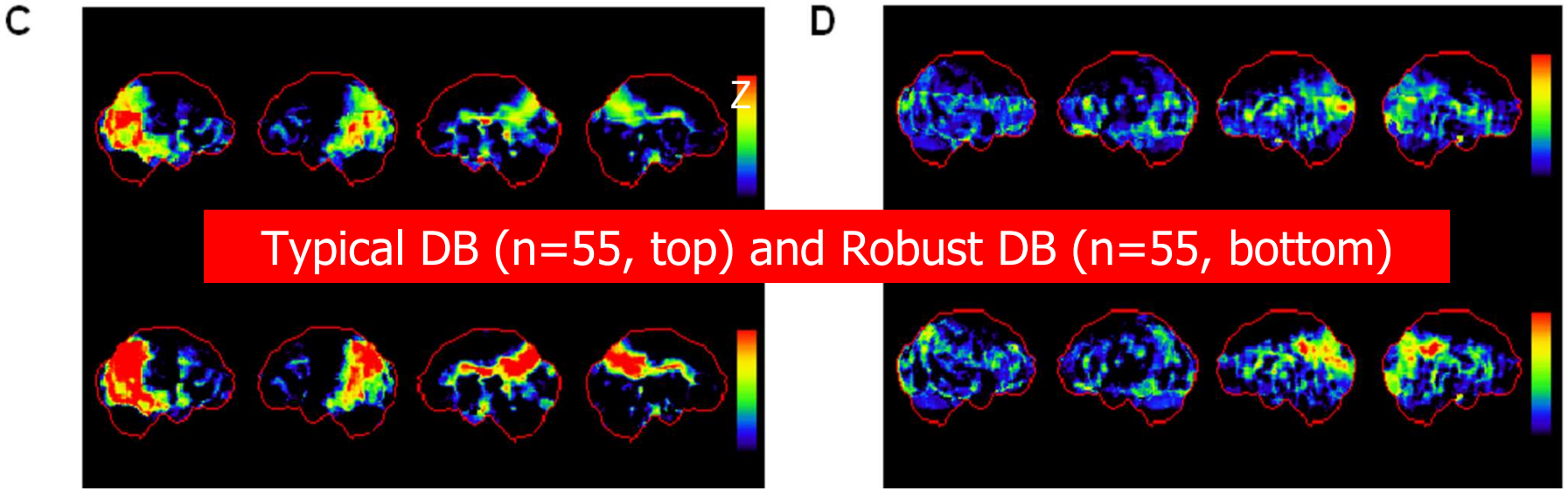
Mosconi L, de Leon MJ et al. *Neurobiol Aging.* 2008;29:676-692.

FDG-PET for Prediction and Progression: NL Aging



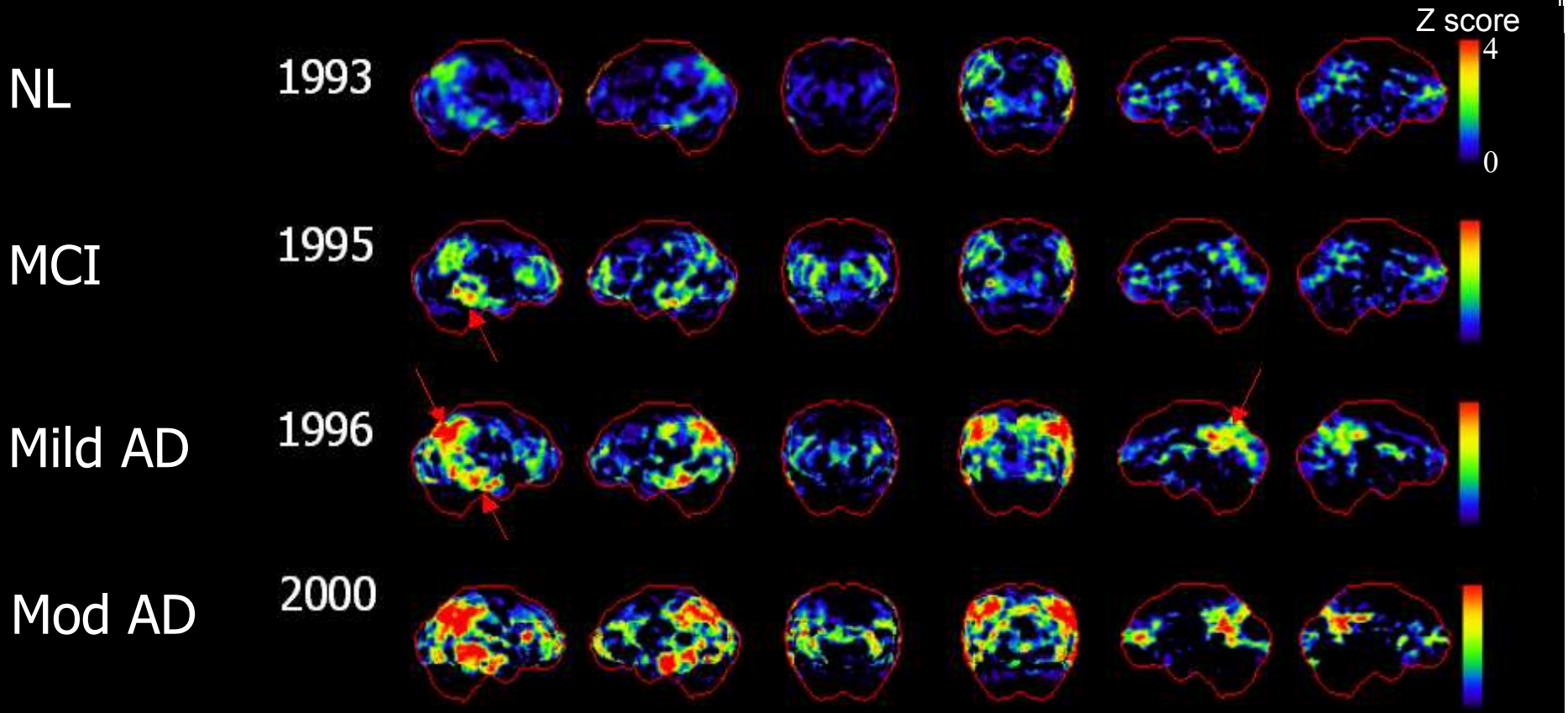
Typical vs. Robust Normal Reference Databases





Mosconi, DeSanti, de Leon et al, J Nucl Med 2007

NL-AD (1993-2003) **Post-mortem validated AD**

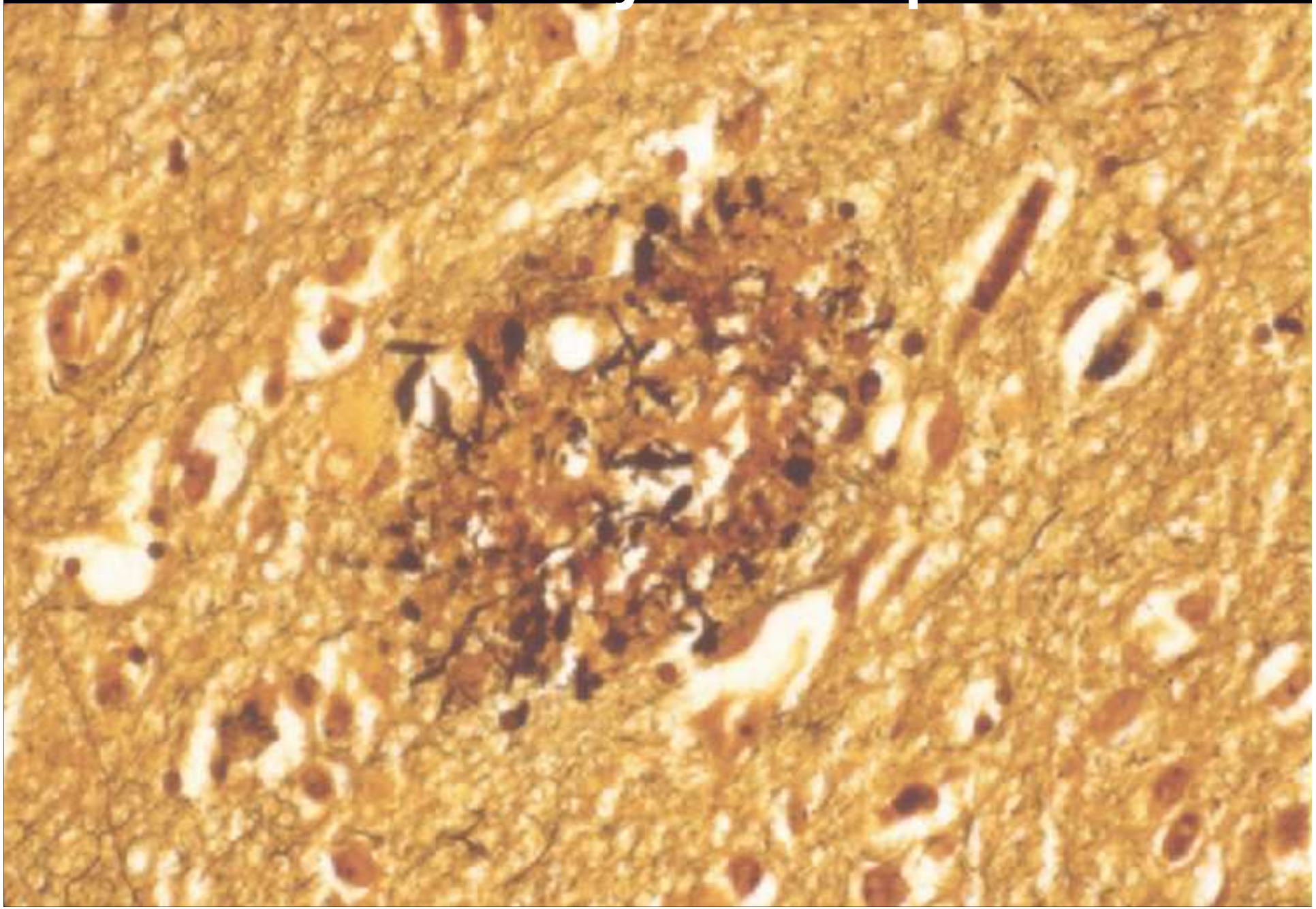


Path: AD 2003 CERAD definite, Braak stage C-VI

Mosconi, de Leon, et al Eur J Nuc Med 2009

Best Paper of the Year European Journal of Nuclear Medicine 2009

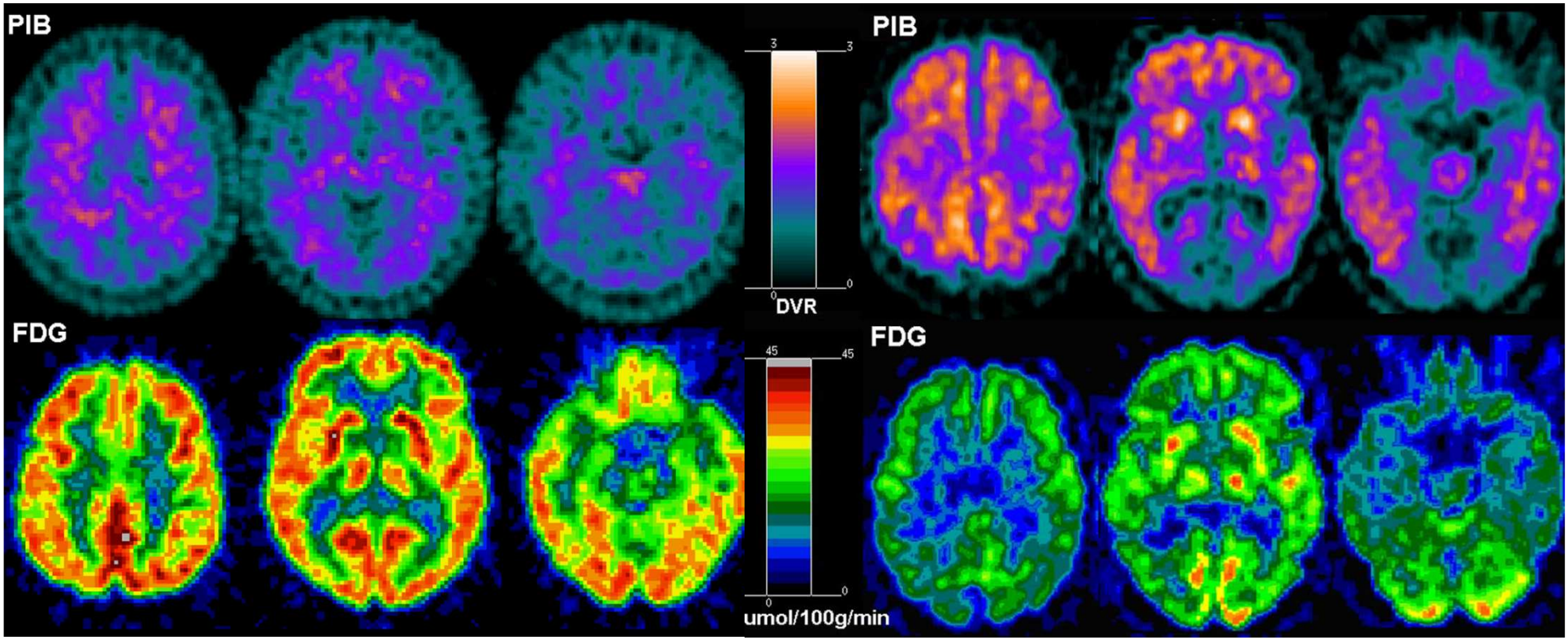
Senile or Amyloid Plaque



PIB and FDG

NL

AD



65 year old male

71 years old male

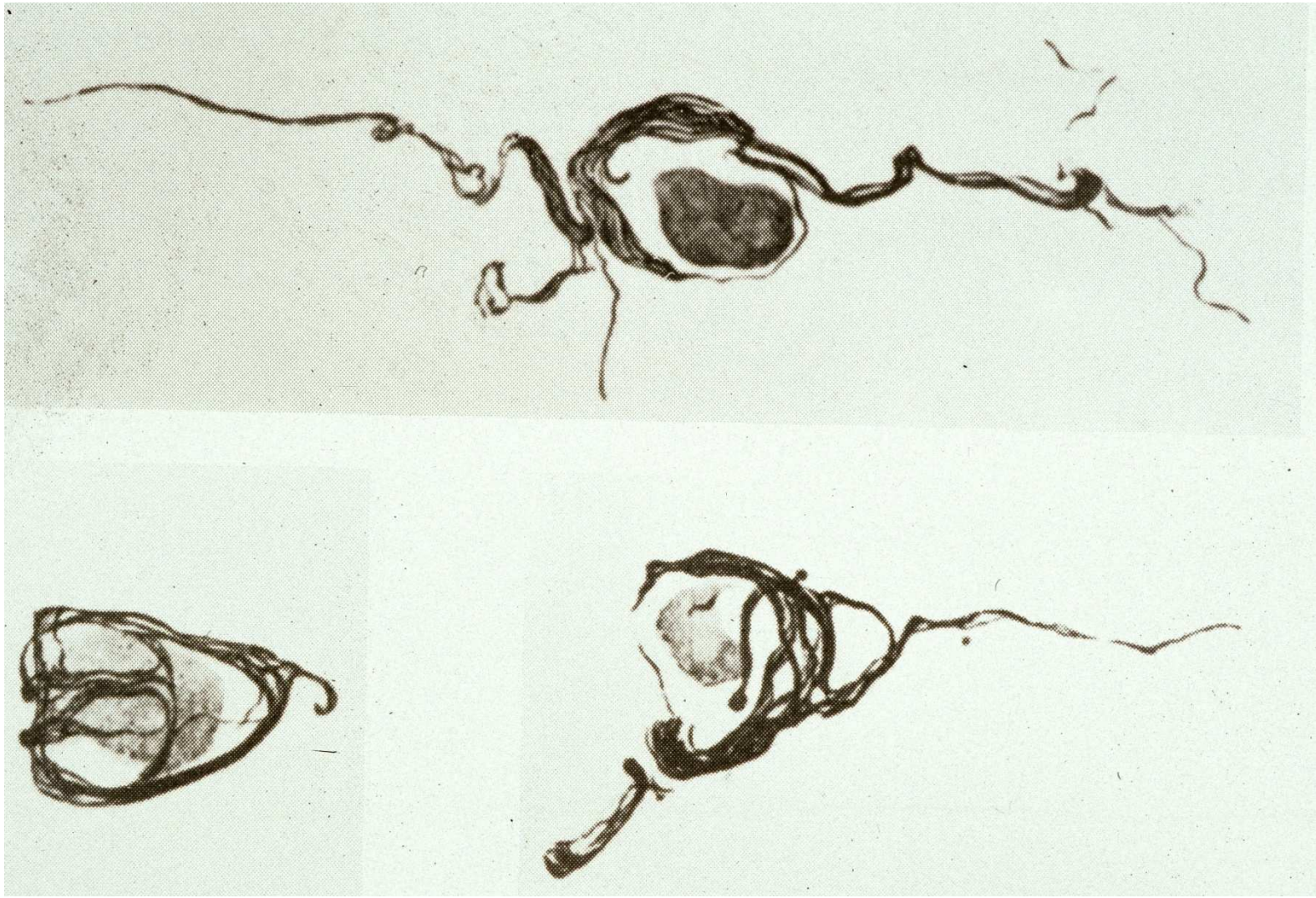
Best Paper of the Year European Journal of Nuclear Medicine 2008

Li , Rinne, de Leon Eur.J.Nuc.Med. 2009

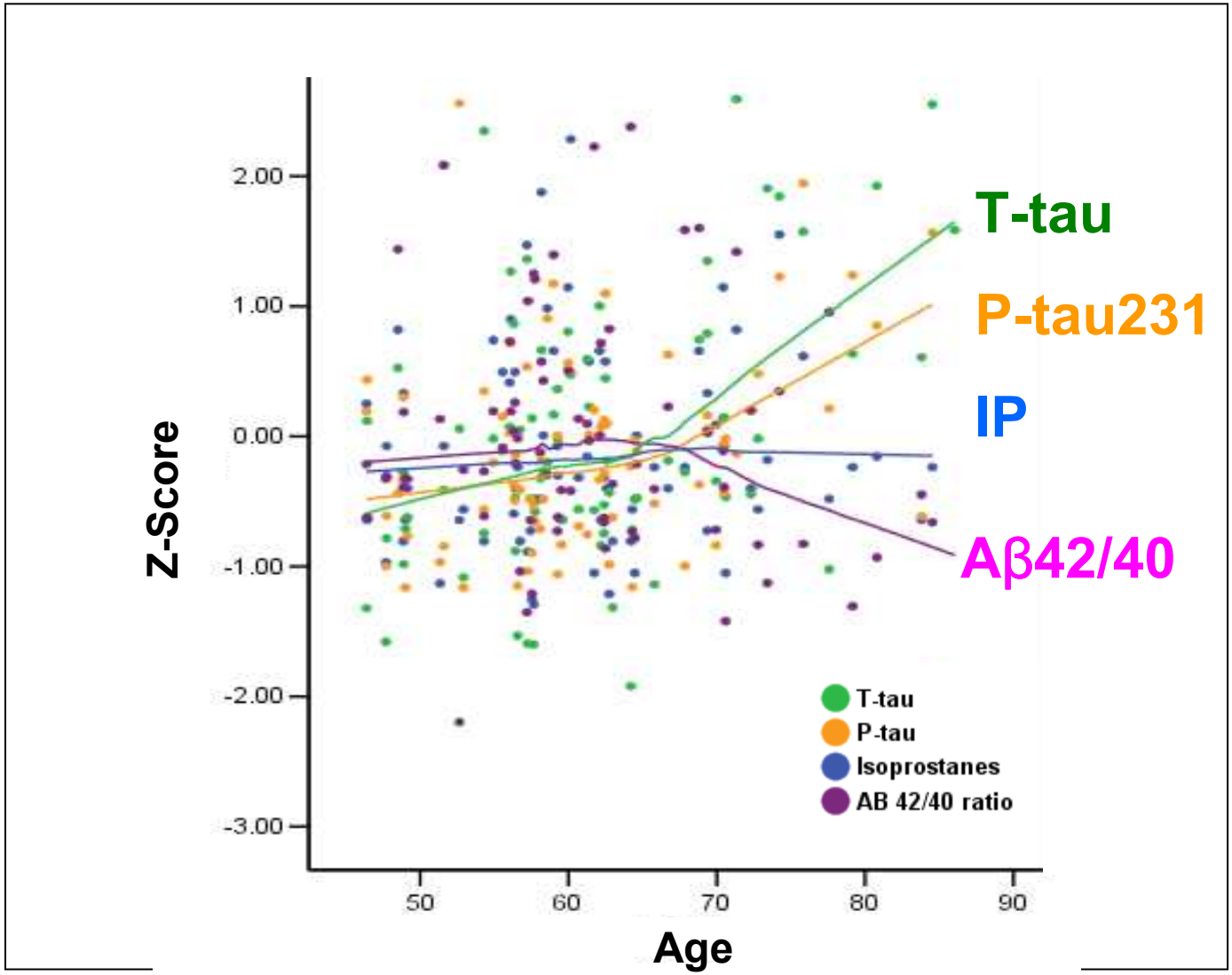
Dx Accuracy for FDG and PIB

	AD vs NL	**MCI vs NL**
FDG Accuracy (%)	92	85
PIB Accuracy (%)	96	75
% Agreement	94	54 ?

Li , Rinne, de Leon Eur.J.Nuc.Med. 2008

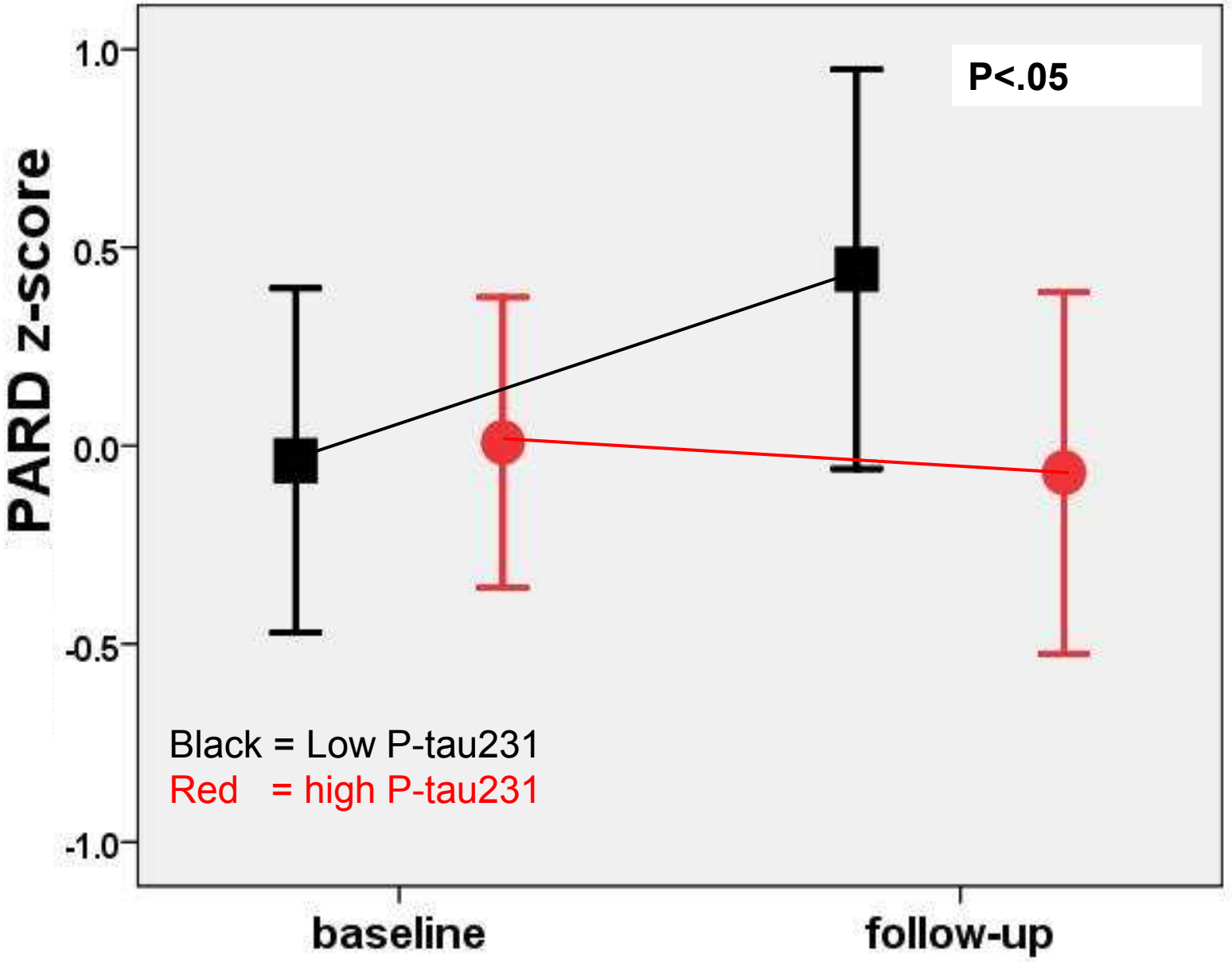


CSF Analytes in Normal Aging n=78



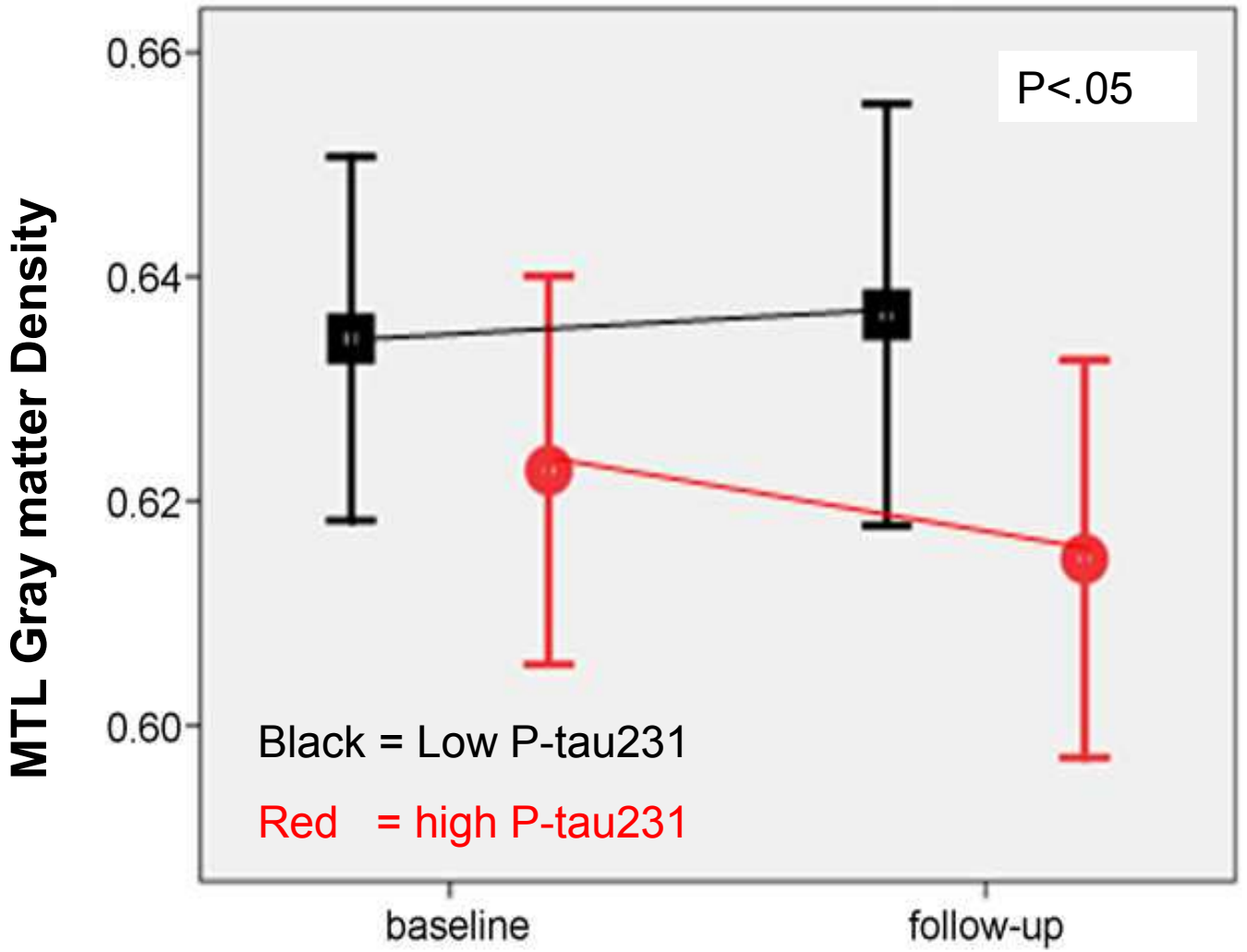
Glodzik-Sobanska L, de Leon, MJ. et al. *Neurobiol Aging.* 2007

Longitudinal memory by high and low P-tau231 in 57 NL



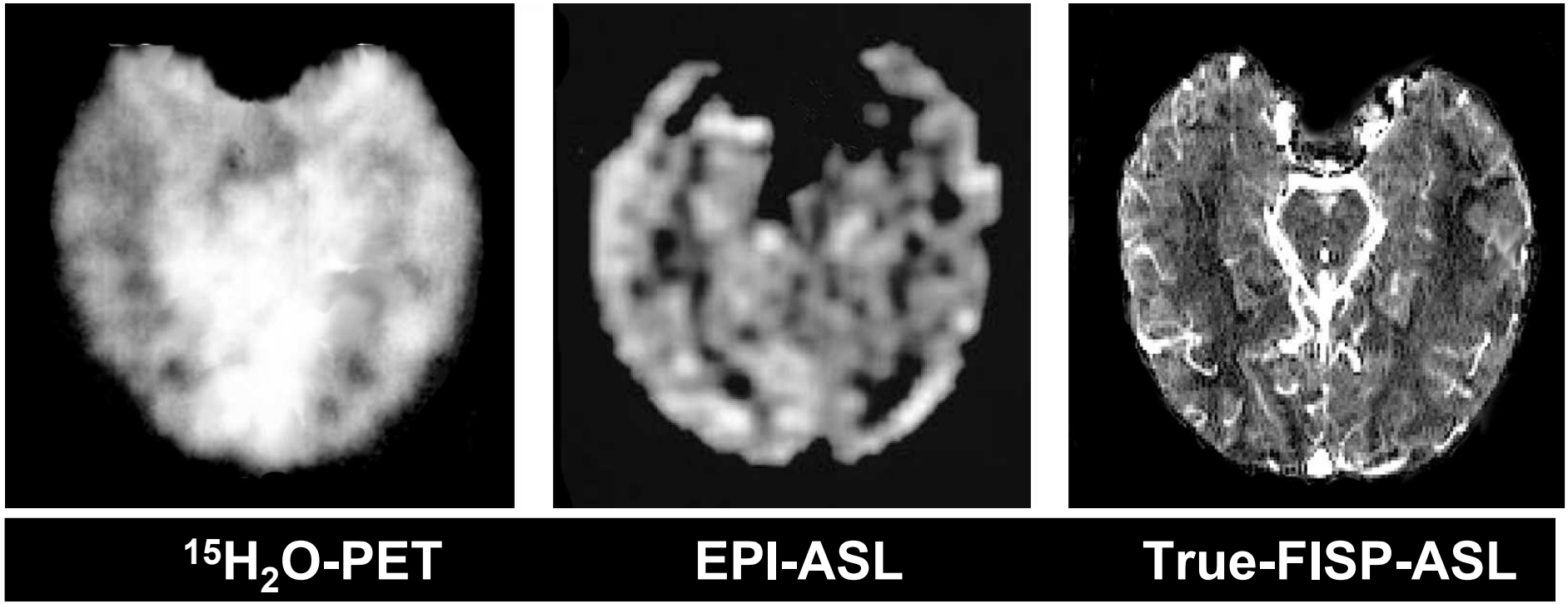
Glodzik, de Leon et al Neurobiol. Aging 2010

Longitudinal MTL-GM by high and low P-tau231 in 57 NL

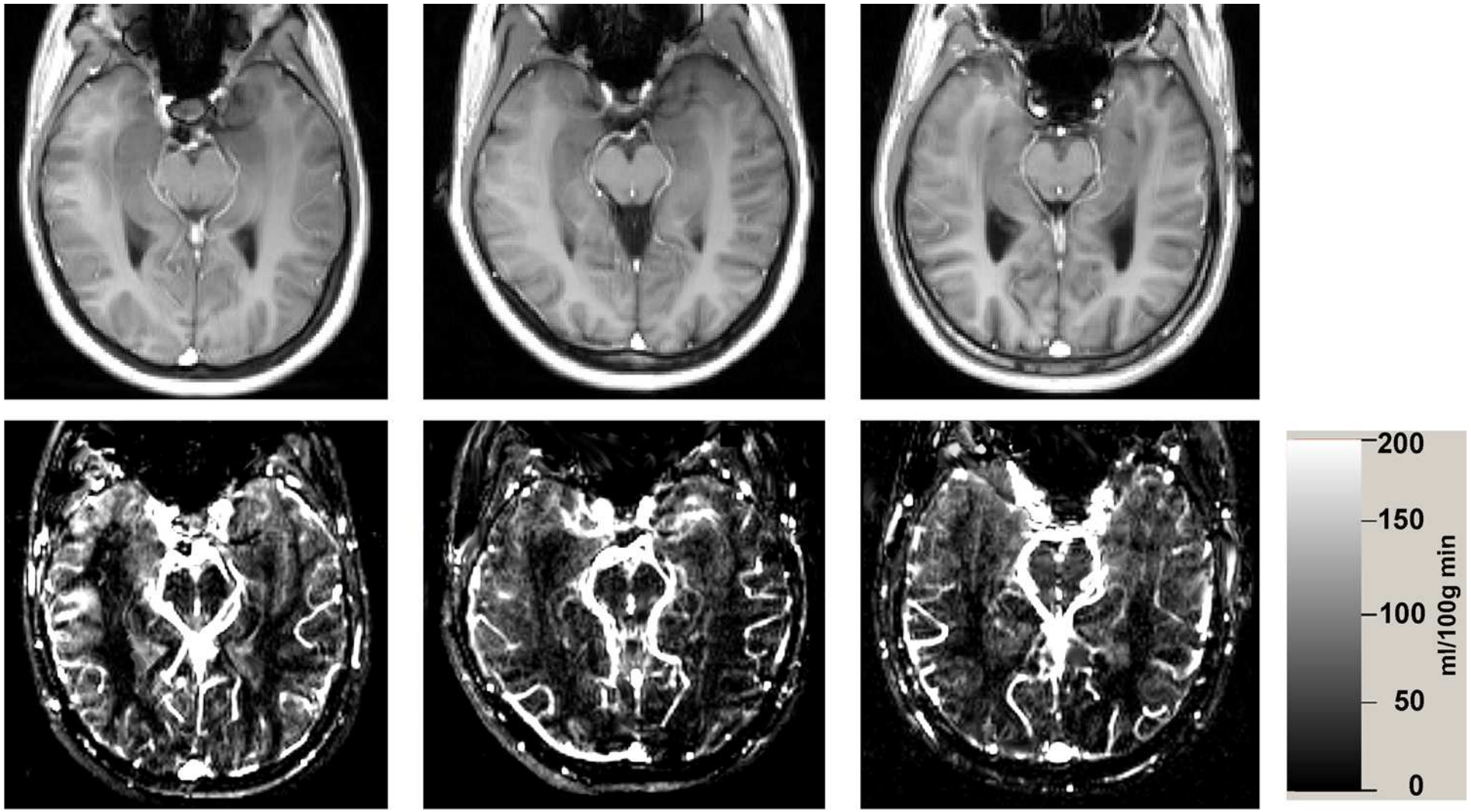


Glodzik, de Leon et al Neurobiol. Aging 2010

The Search for Mechanism


$^{15}H_2O$-PET
EPI-ASL
True-FISP-ASL

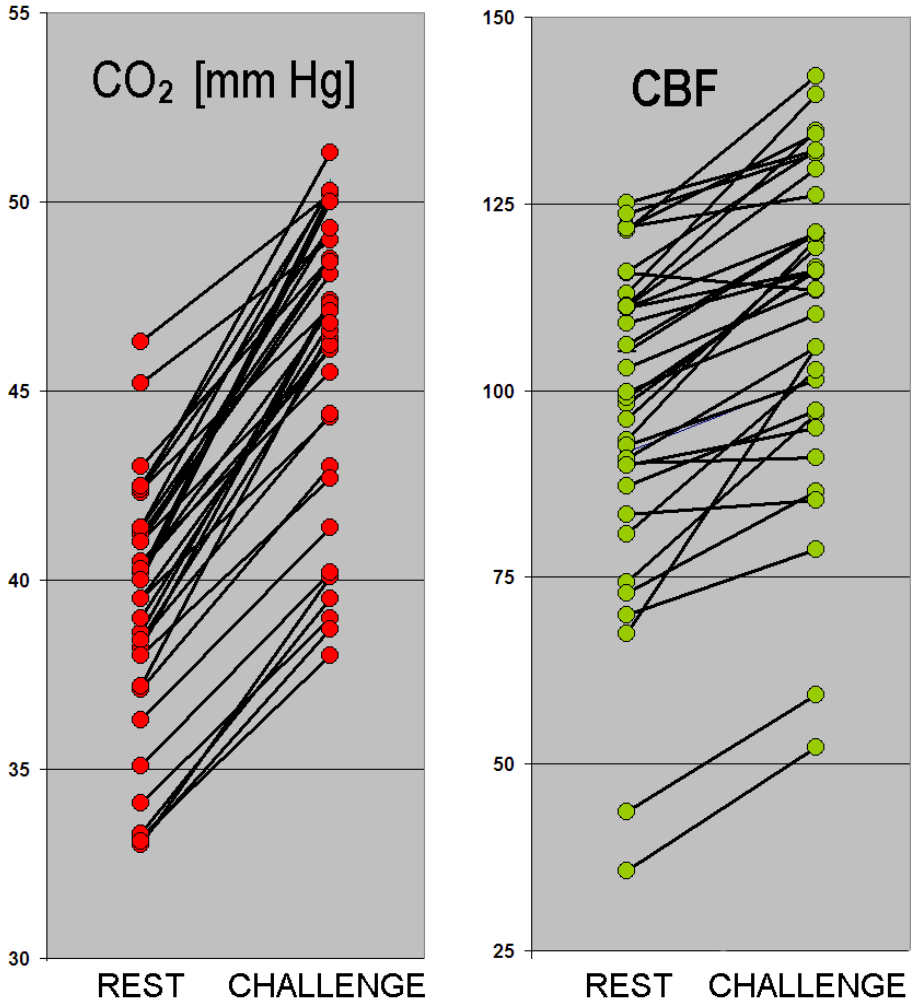
MRI True-FISP Hippocampal Perfusion Imaging



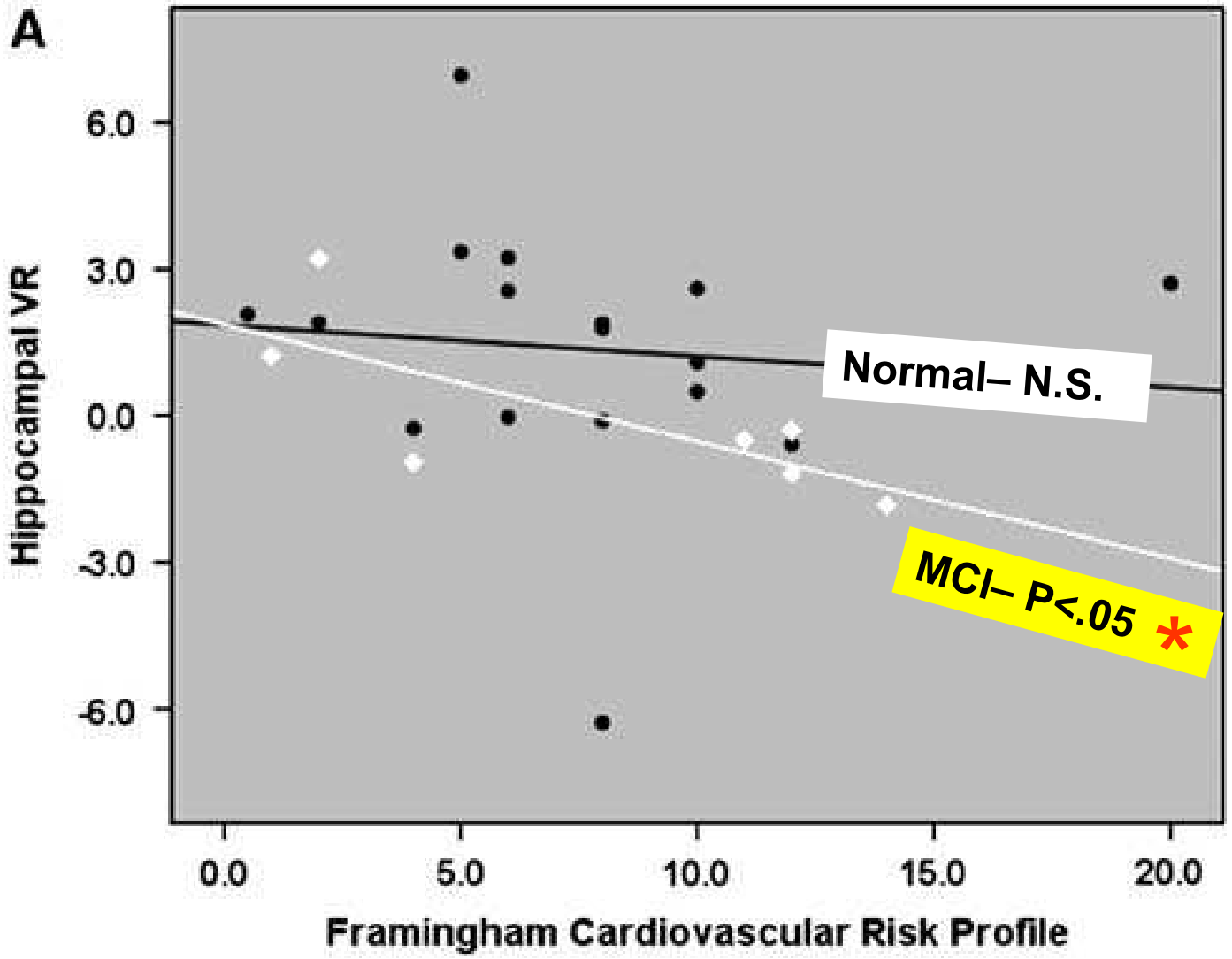
MRI with rebreathing apparatus

Vasoreactivity to CO_2 challenge

~2% CBF change/mmHg change in CO_2

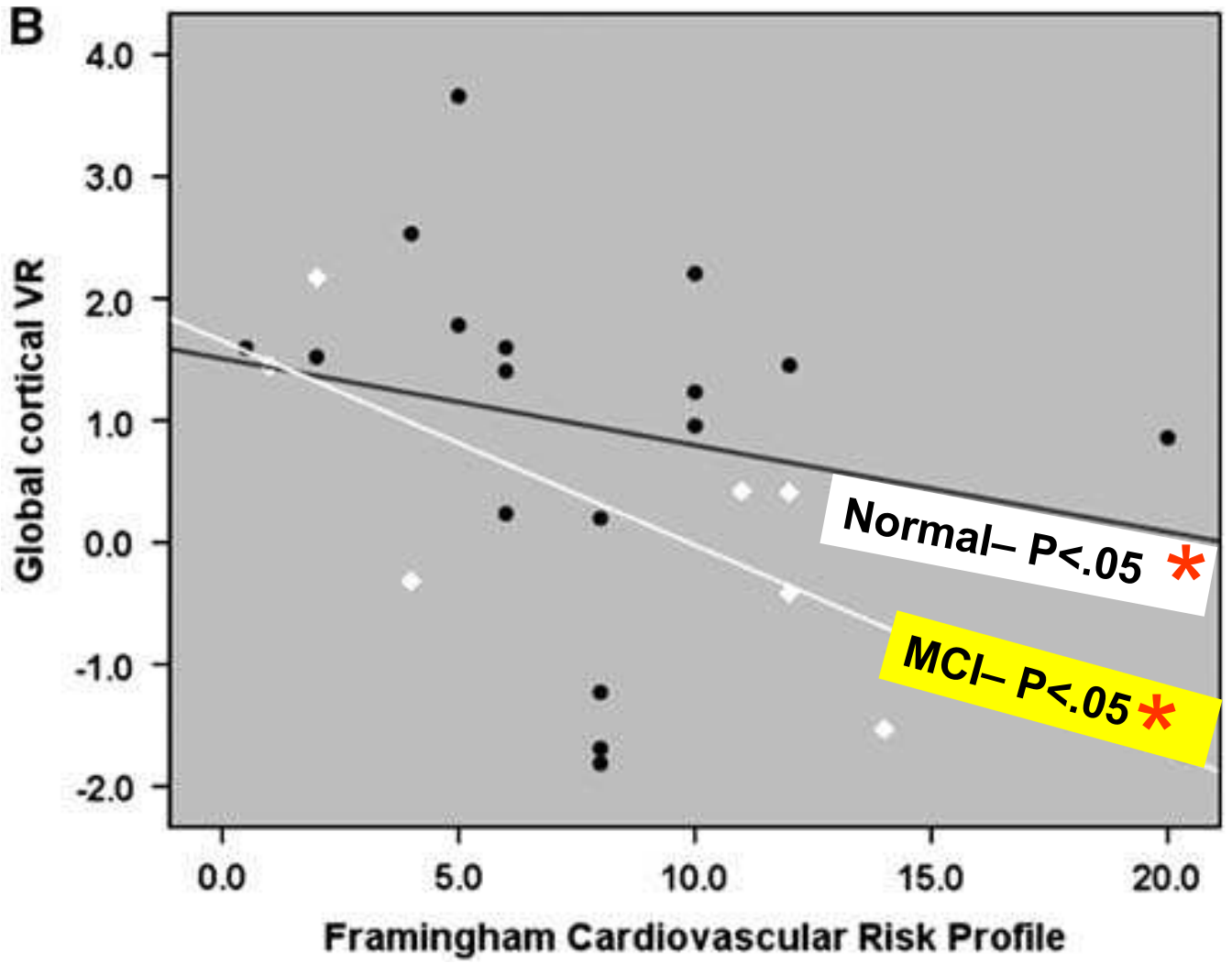


Hippocampal Vasoreactivity and Cardiovascular Risk

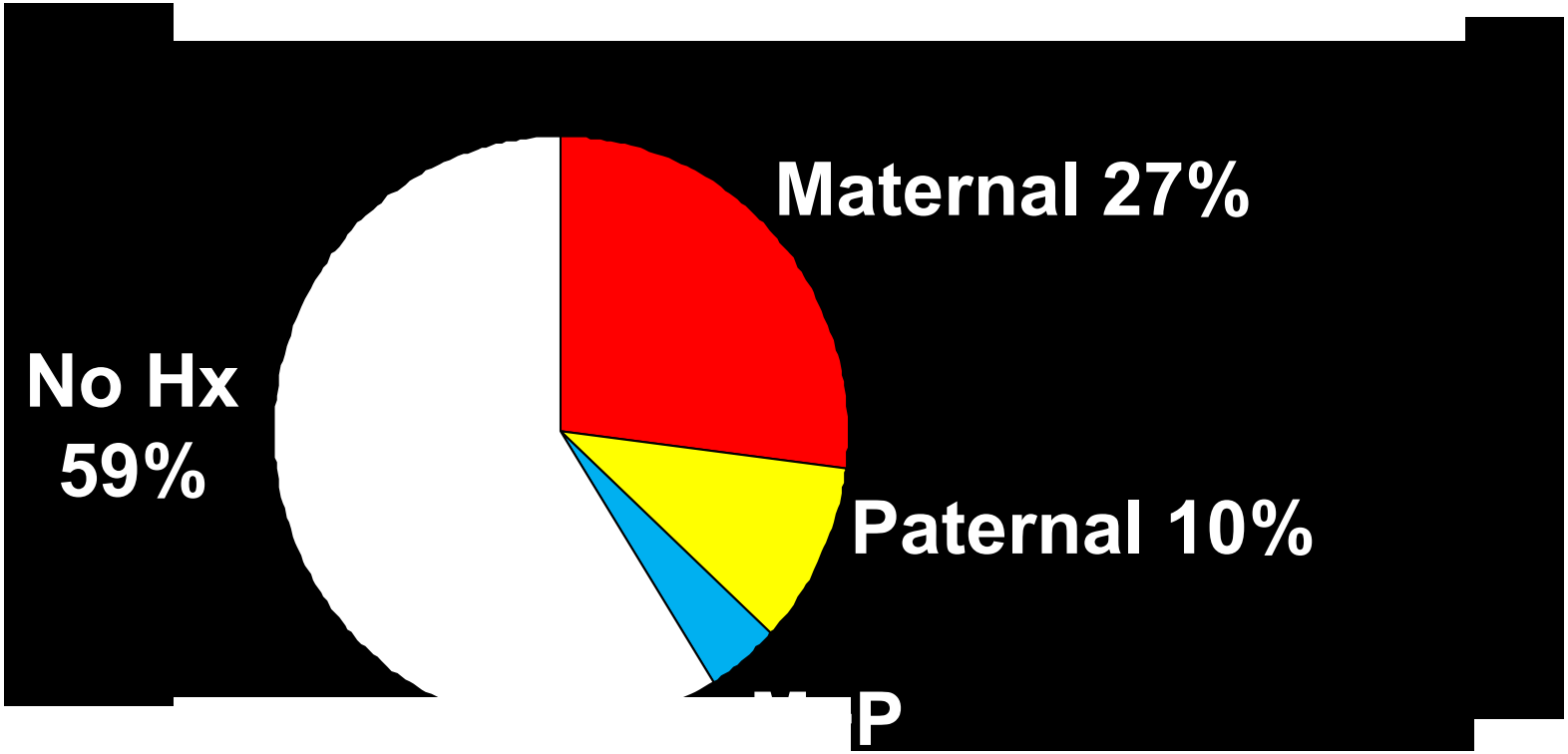


Glodzik, Rusinek… de Leon et al. JCBF 2010

Cortical Vasoreactivity and Cardiovascular Risk

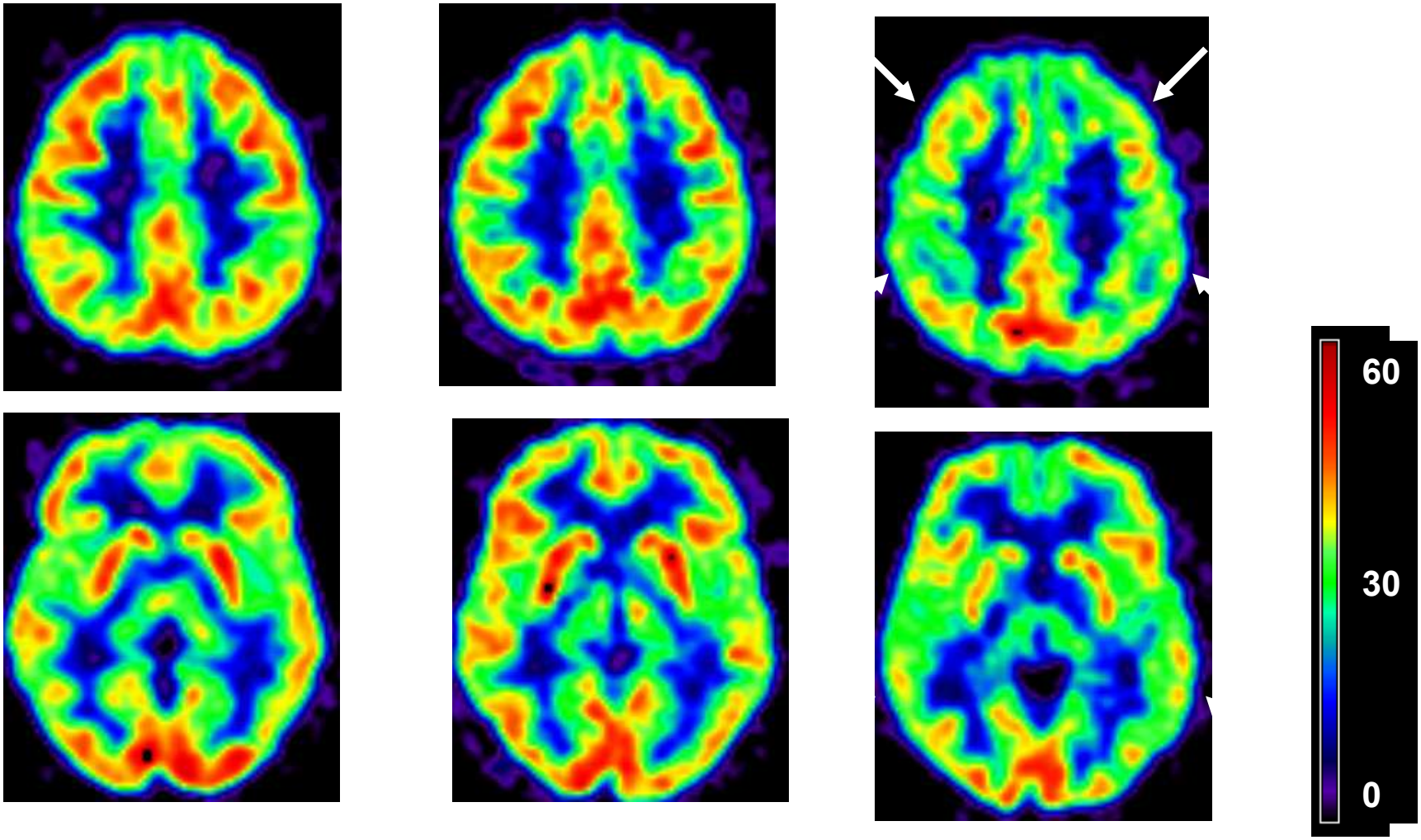


Glodzik, Rusinek … de Leon et al. JCBF 2010

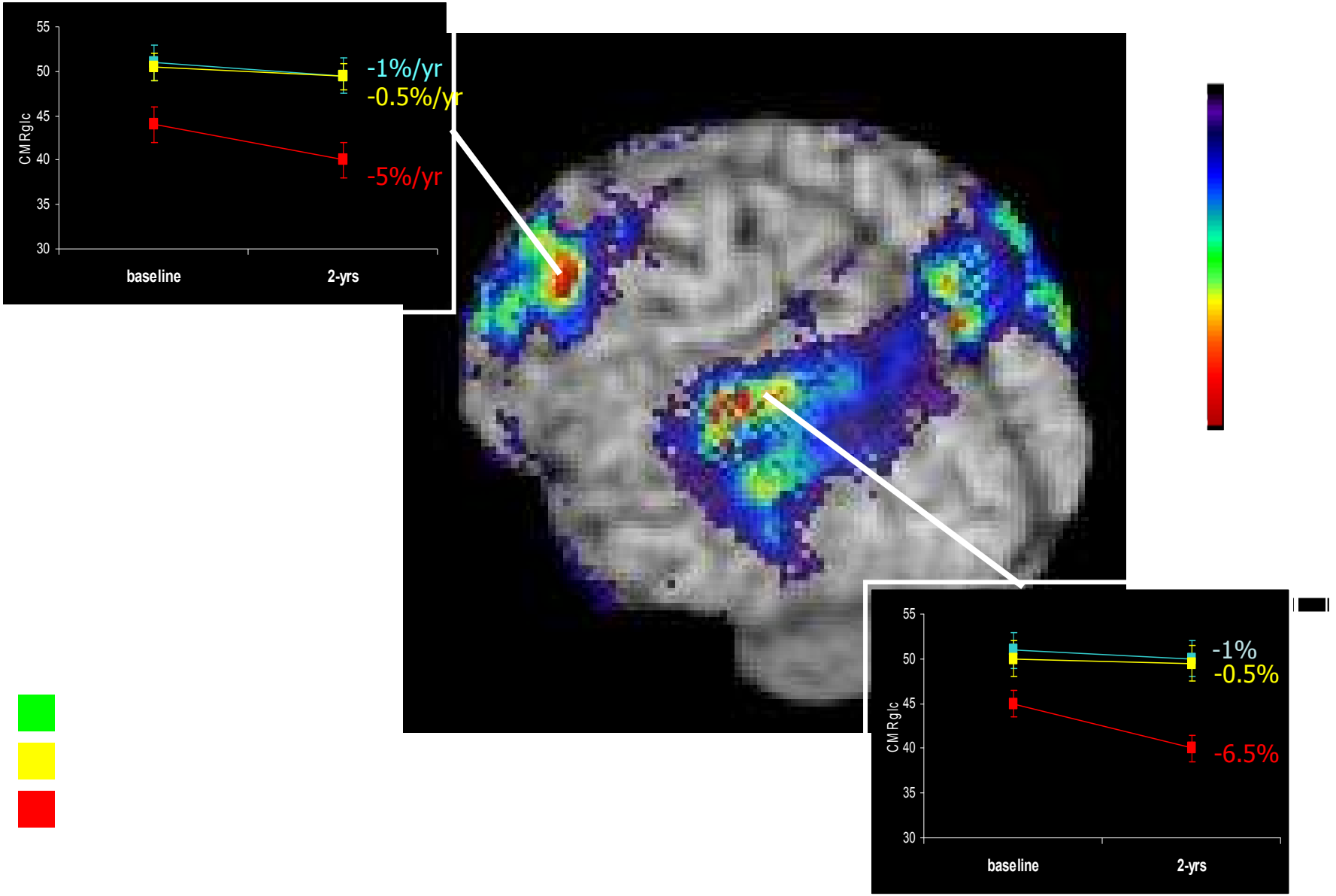


Normal cognition, MMSE 28-30
Age 48-80 yrs
Education>11yrs

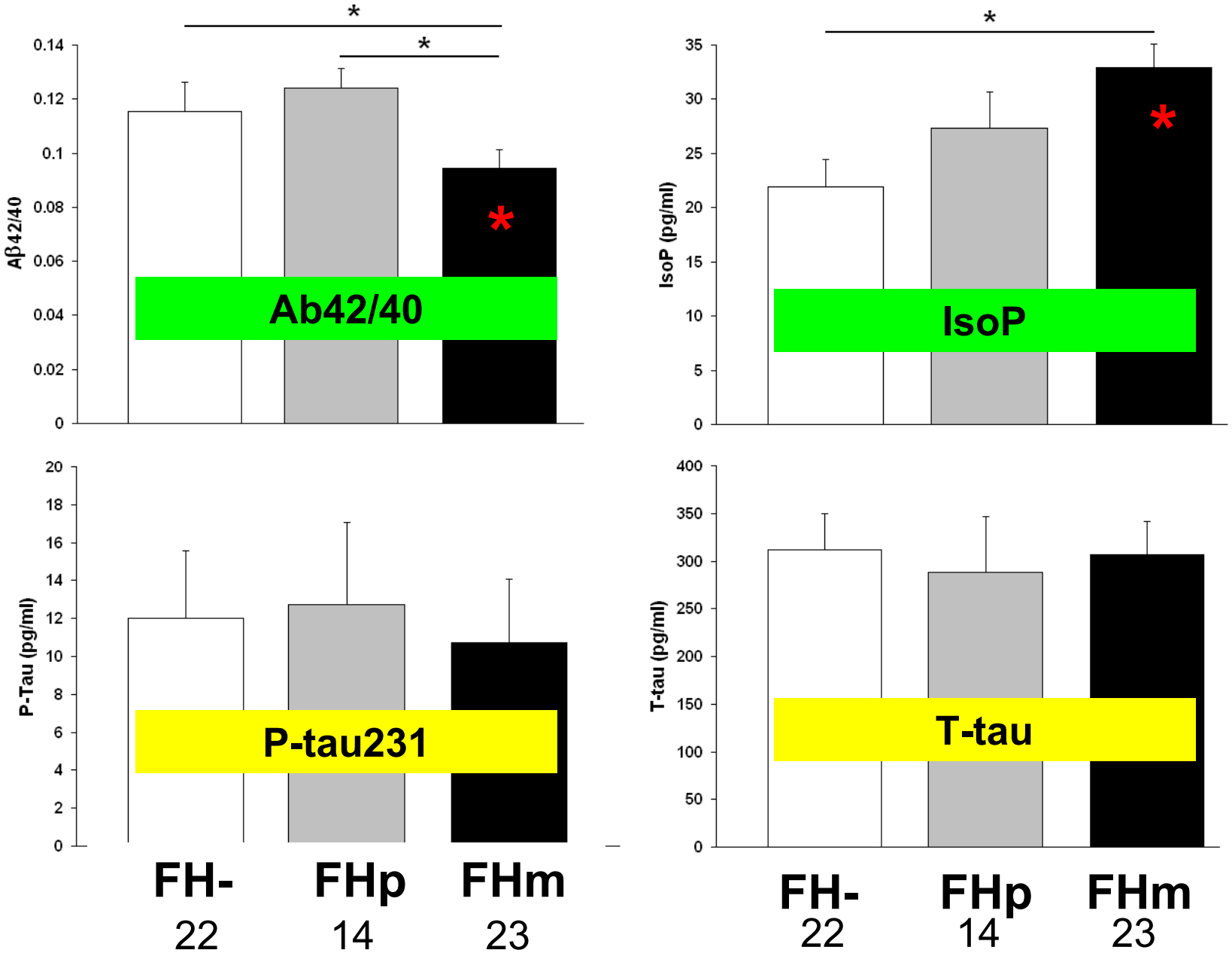
FDG-PET in individual cases



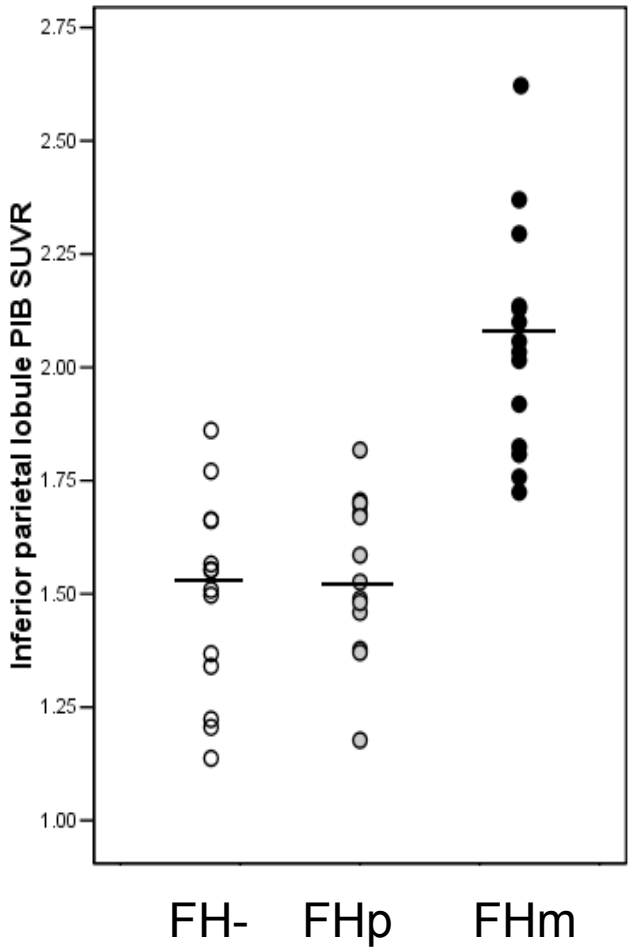
Longitudinal change in NL with AD mothers



CSF Biomarkers and AD Maternal History in NL

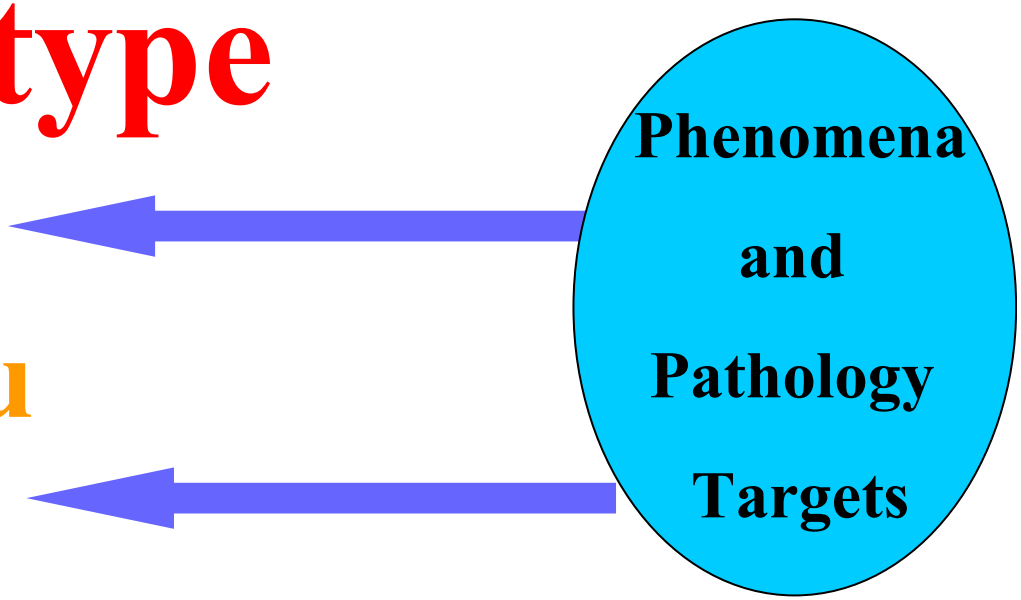


Parietal PIB-PET Uptake in NL with Maternal History of AD



Mosconi, de Leon et al PNAS et al 2010

AD phenotype



Aβ and Tau

Oxidative stress and inflammation

Cellular response

Conclusions

- PET and MR imaged hippocampal pathology appears early and is progression sensitive.
- The pathology specific P-tau231 and Ab also appear early but are not progression sensitive.
- Imaging and biomarkers may have a role in identifying mechanisms of AD-progression by considering energetics and vascular function.

Collaborating Scientists

- **NYU**
  - Lidia Glodzik
  - Lisa Mosconi
  - Henry Rusinek
  - Wai Tsui
  - Elizabeth Pirraglia
  - Yi Li
- Institute Basic Research
  - Pankaj Mehta
- Cornell University
  - Shankar Vallabhajosula
  - Stanley Goldsmith
- Temple University
  - Domenico Pratico
- Einstein College of Medicine
  - Peter Davies
- University of California L.A.
  - Liana Apostolova
  - Paul Thompson
- Applied Neurosolutions
  - Ray Zinkowski
- Turku U. Finland
  - Juha Rinne
- Sahlgrenska U. Goteborg
  - Kaj Blennow
  - Henryk Zetterberg
  - Anders Wallin