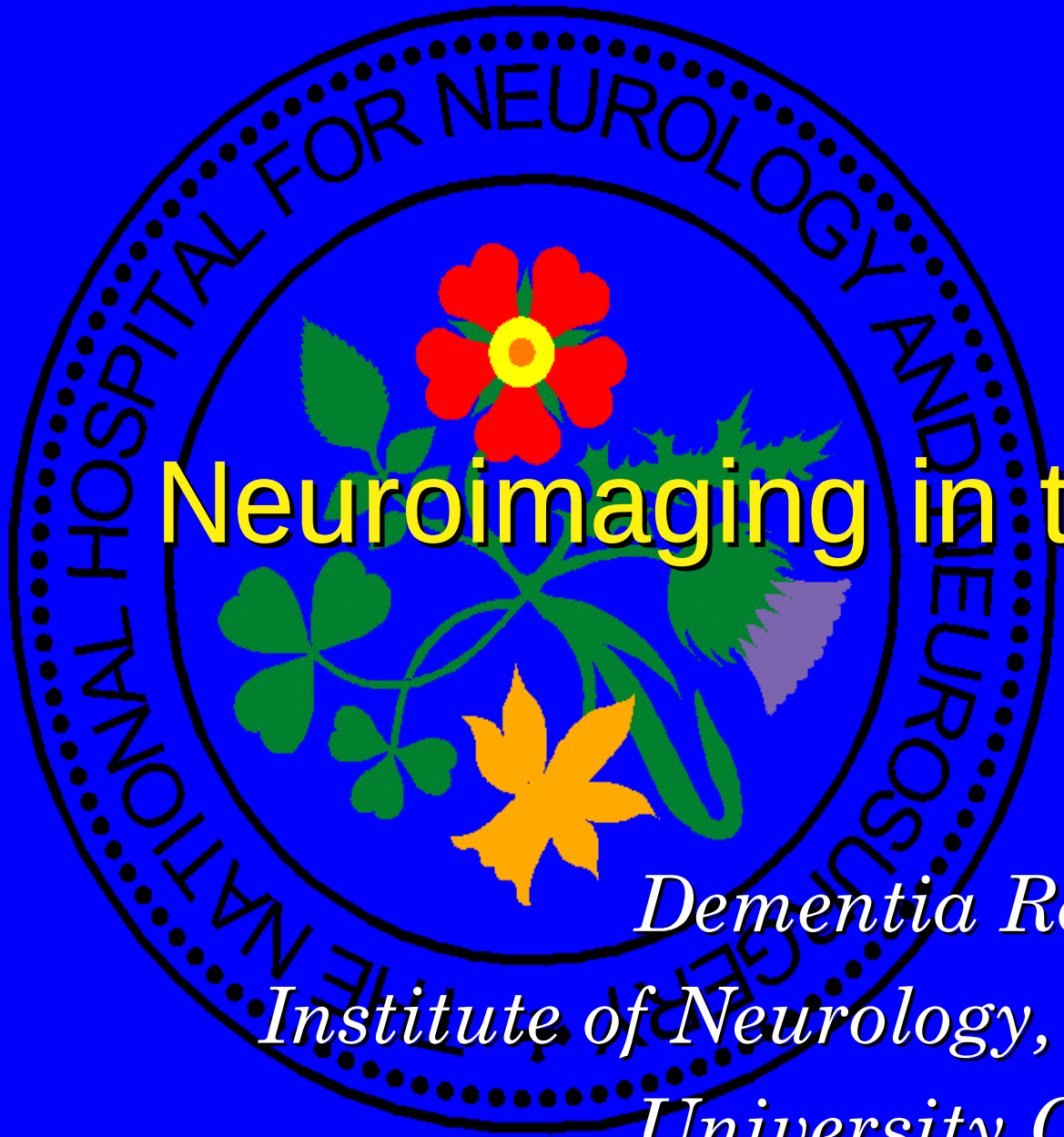

Neuroimaging in trials in AD

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Disclosures & Acknowledgements

- *Work of the members of the Dementia Research Centre (DRC)*
- *The DRC has conducted image analysis for a number of companies and has been a clinical site for sponsored trials*
- *I have advised these and other companies and also the NIH and FDA*
- *I am a member of the MRI-core of ADNI (Alzheimer's disease neuroimaging initiative) – ADNI members have generously shared slides and data for this meeting: including*
  - *Jagust, Weiner, Jack, Foster, Reiman, Klunk*

Overview

- *Why neuroimaging?*
- *Focus on ph2/3 issues*
- *Roles of imaging in AD trials*
  - *Defining target/study populations*
  - *Safety*
  - *Measuring progression*
- *Assessing disease-modification*
  - *Problems and potential*

Why neuroimaging?

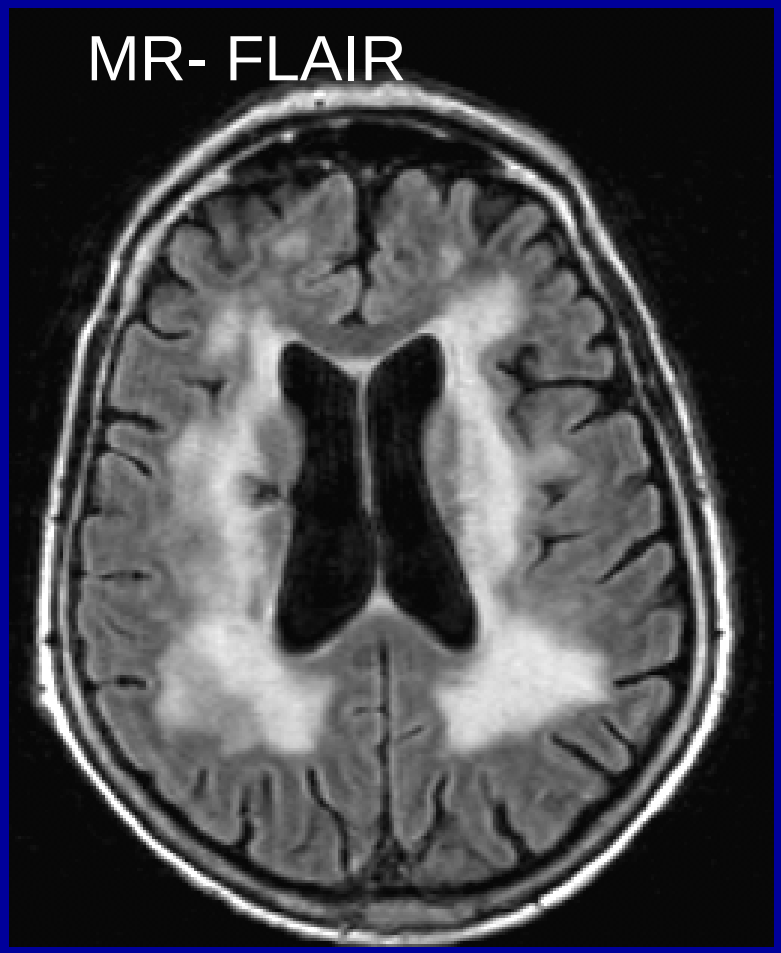
- *Inaccessibility of brain*
  - *To assess pathology*
  - *Drug delivery*
- *Complexity of brain response*
  - *Systems biology*
- *Limitation of clinical measures*
- *Lack simple biomarkers*
- *Imaging allows objective repeated assessment – no practice effects!*

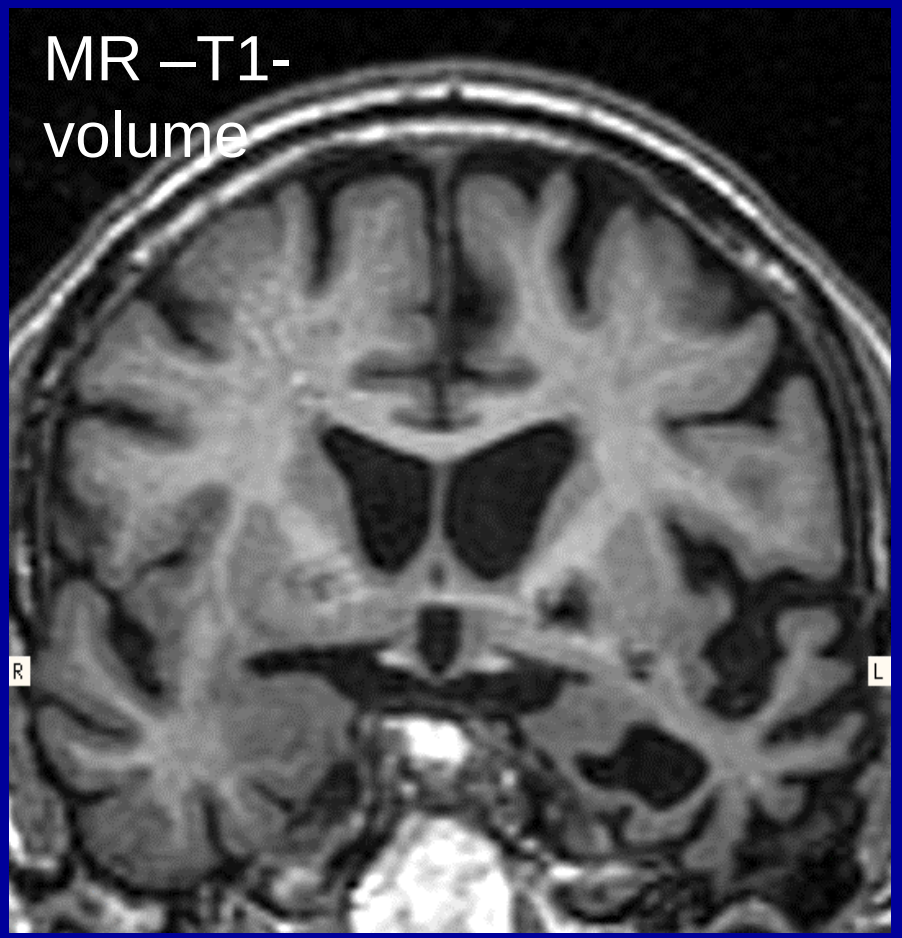
Roles: define study population – exclusion/inclusion and stratification

- *Is this the correct pathology?*
  - *AD vs non AD e.g vascular or FTD pathology*
- *Know what we are treating – adjust if need*
  - *Stage/severity: more homogenous populations?*
  - *Subtypes of AD – e.g biparietal (PCA) variant*
- *Open an early therapeutic window – "enriched MCI" - early or preclinical*

  or presymptomatic AD

Imaging established role in excluding other pathology





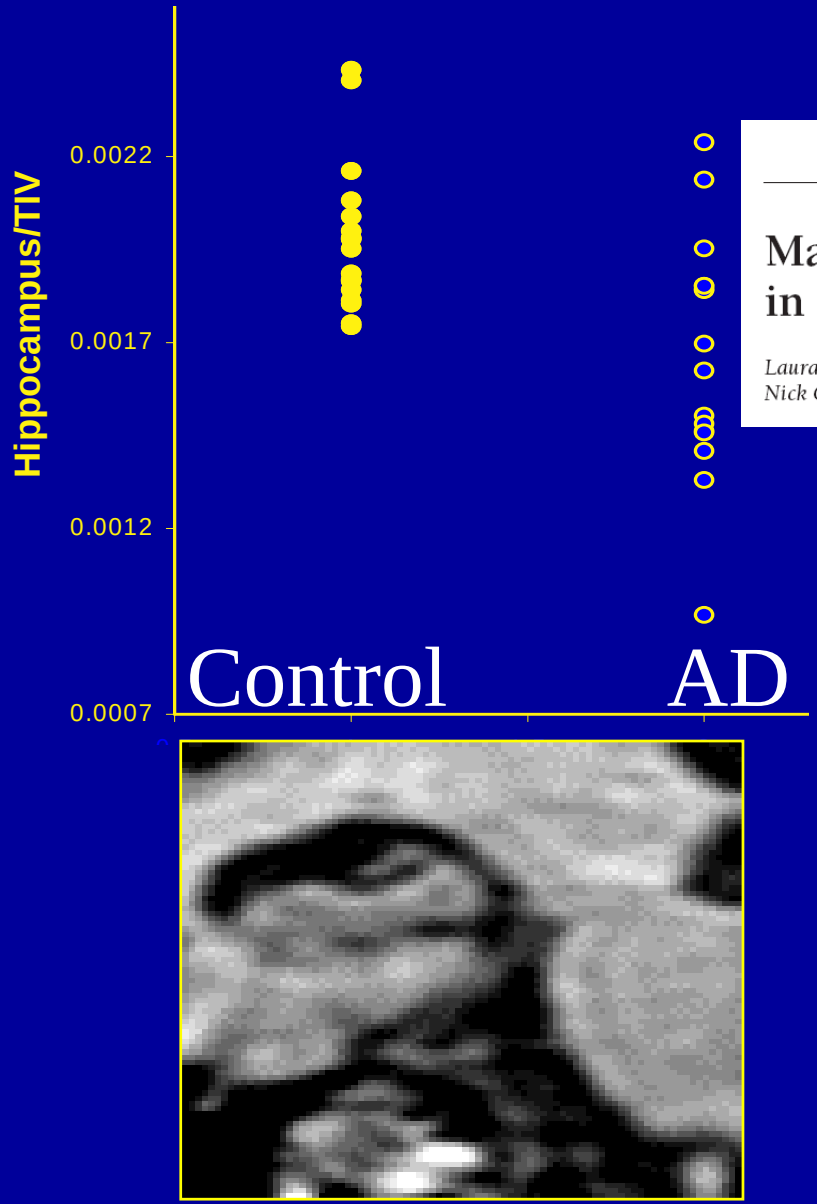
More rigour assessing vascular path, focal atrophy FTD not just tumours etc

Inclusion criteria for AD and opening an earlier therapeutic window: predicting AD

A number of imaging features are predictive of AD pathology

- *Medial temporal lobe atrophy on MRI*
- *Increased rates of atrophy on serial MRI (>90% sens/specificity: AD vs C)*
- *Hypometabolism on PET/SPECT*
- *Amyloid imaging*

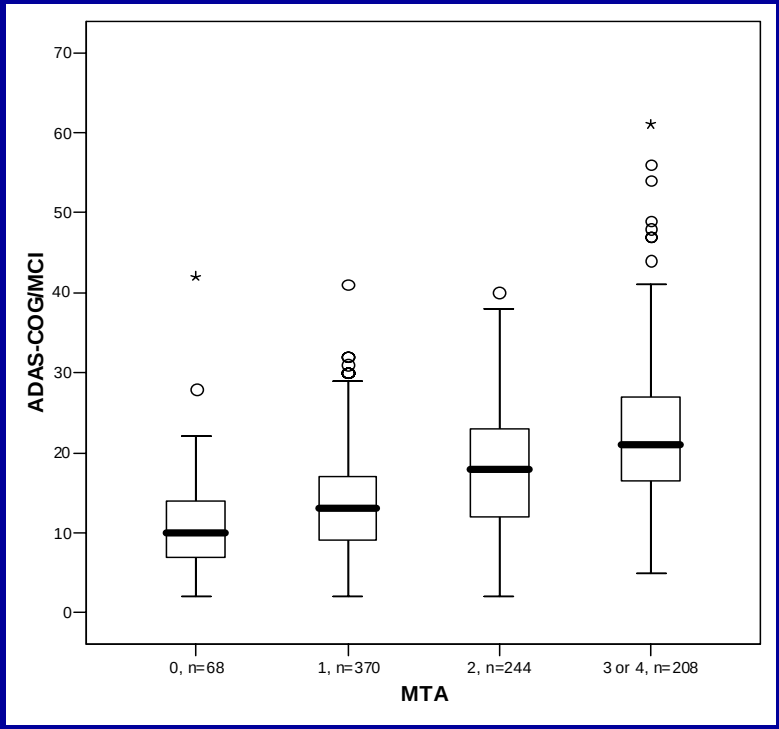
Hippocampus reduced by 20% in early AD



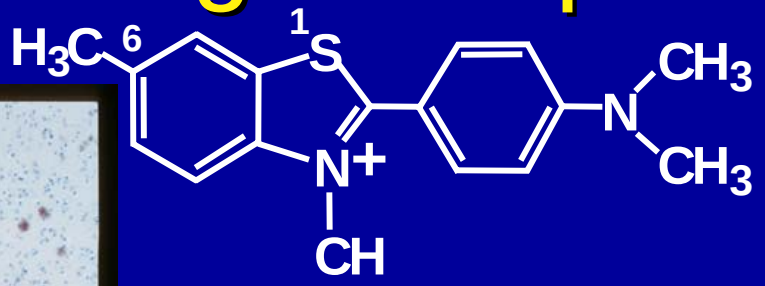
ORIGINAL CONTRIBUTION

Magnetic Resonance Imaging Predictors of Cognition in Mild Cognitive Impairment

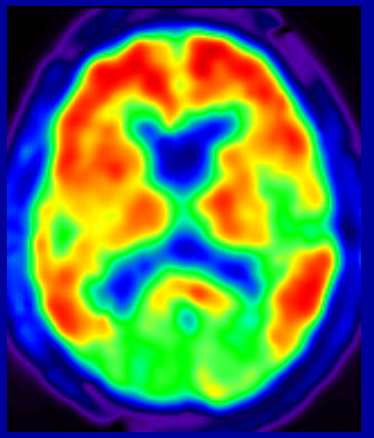
Laura A. van de Pol, MD; Esther S. C. Korf, MD; Wiesje M. van der Flier, PhD; H. Robert Brashear, MD; Nick C. Fox, MD, FRCP; Frederik Barkhof, MD, PhD; Philip Scheltens, MD, PhD

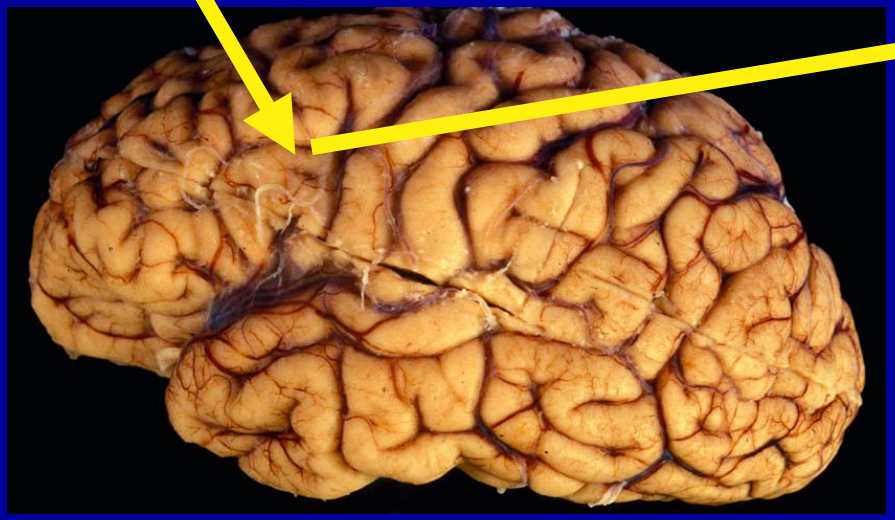


In vivo Amyloid Imaging with Pittsburgh Compound B (PIB)

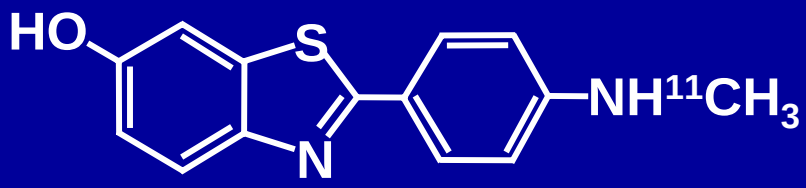


Histology - Thioflavin T



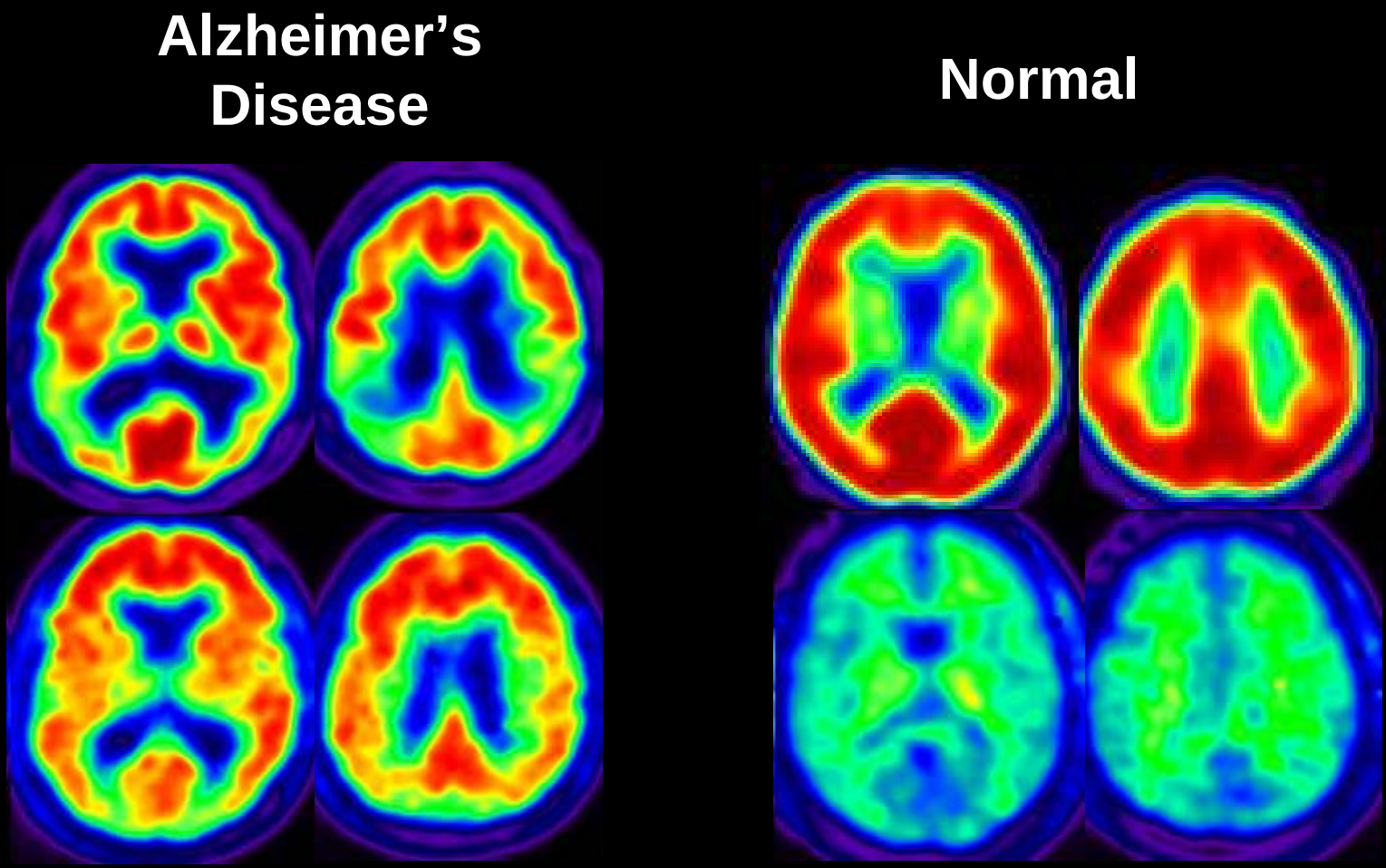


PET Imaging - [^{11}C]6-OH-BTA-1 (PIB)



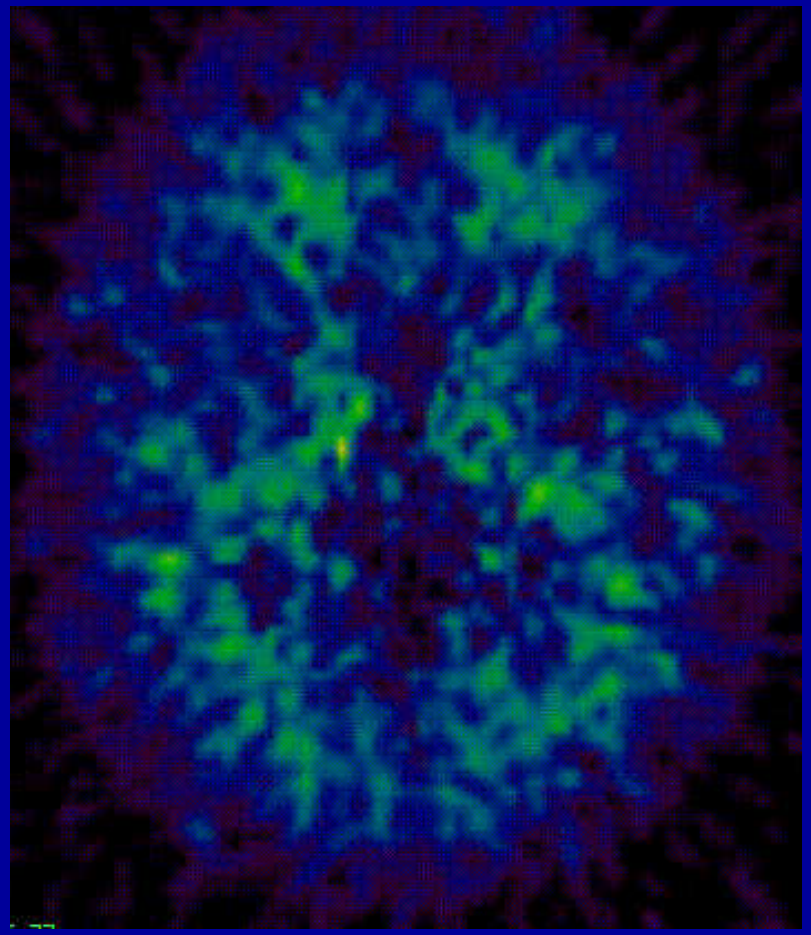
Courtesy of Bill Jagust

Structure/Function: Topography
Molecules: Proteomic Specificity

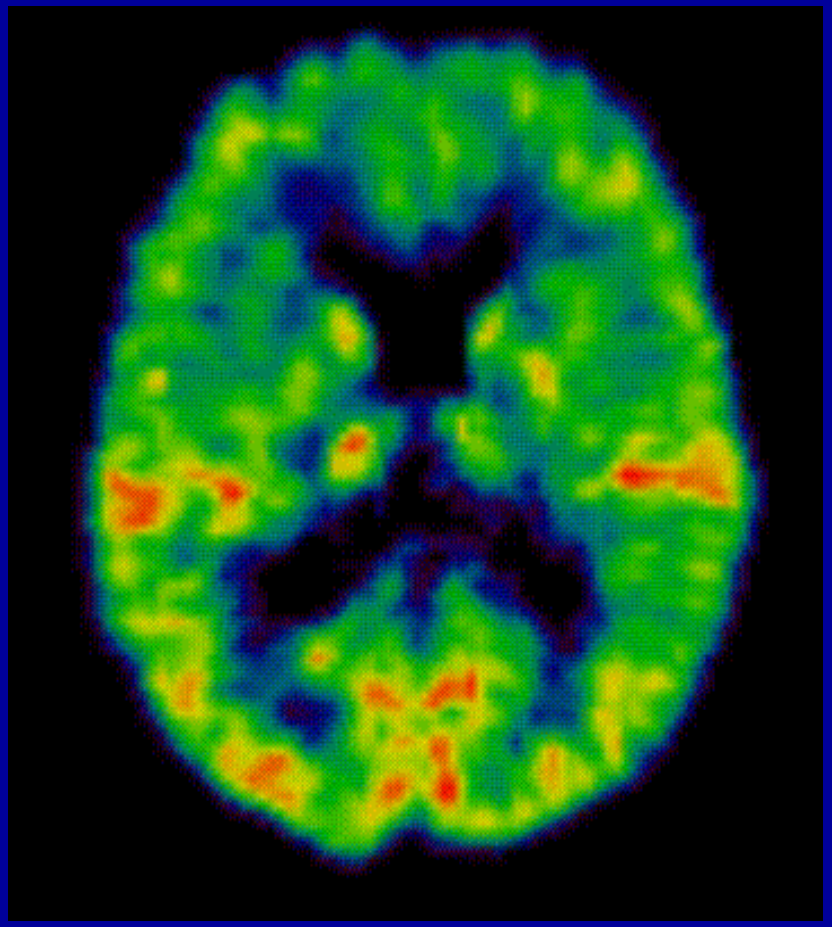


Courtesy of Bill Jagust

MCI non-converter PIB



MCI converter PIB

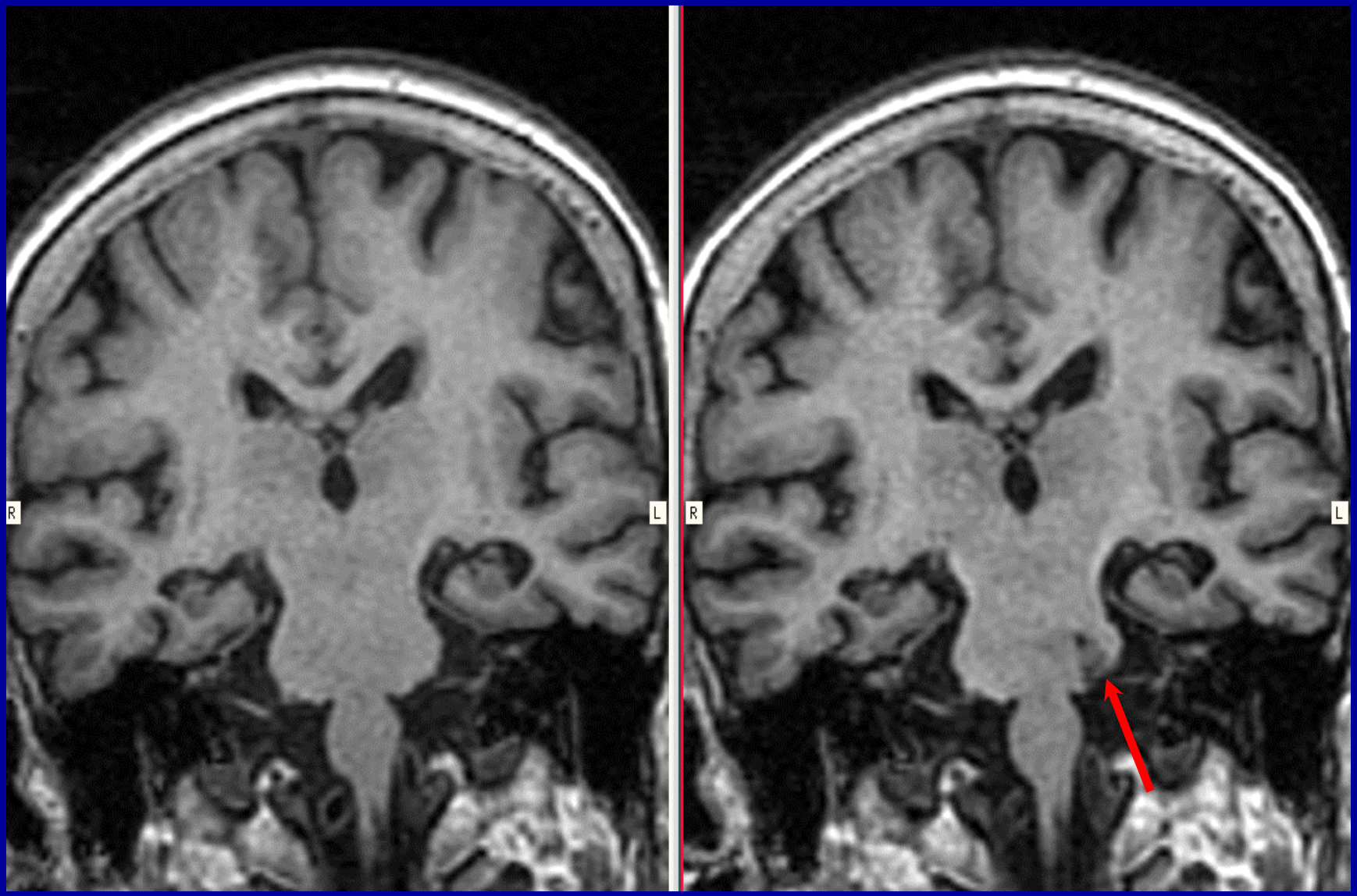


Archer, Okello, Brooks, Rossor

Imaging measures of drug effect

- *Safety*
  - *Haemorrhage*
  - *Inflammation*
- *Unrelated adverse events*
- *Efficacy*

Registration of serial MRI allows clear recognition of new lesions



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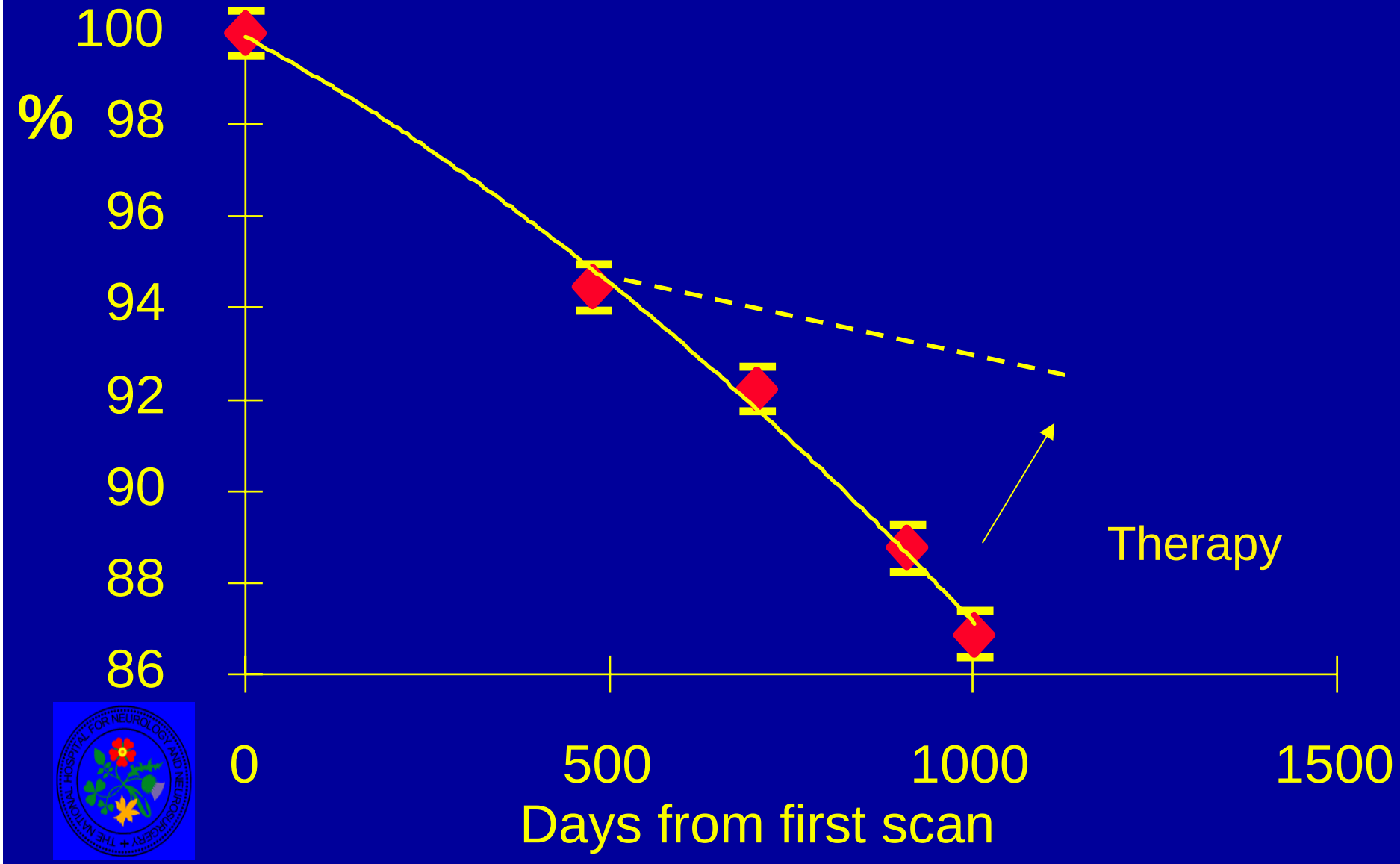
Imaging markers of disease-modification

- *Measure a feature of disease that should predict clinical response (imaging change being necessary and sufficient to predict that response)*
  - *Associated with disease pathology*
  - *Progresses with clinical progression*
  - *On the pathogenic pathway*
- *Clinically meaningful*

AD: brain volume vs time



Need to maximise efficiency and interpretability of trials in AD

- *Clinical scales - high variance drives sample sizes*

$$\text{Size of trial} \propto \frac{\text{Variance of atrophy rate in each group}}{(\text{Anticipated treatment effect})^2}$$

$$\text{Note}: \text{Variance} = \text{SD}^2$$

Milameline trial in AD

Estimated sample size (per arm) needed to show a 50% effect on progression over 1 year

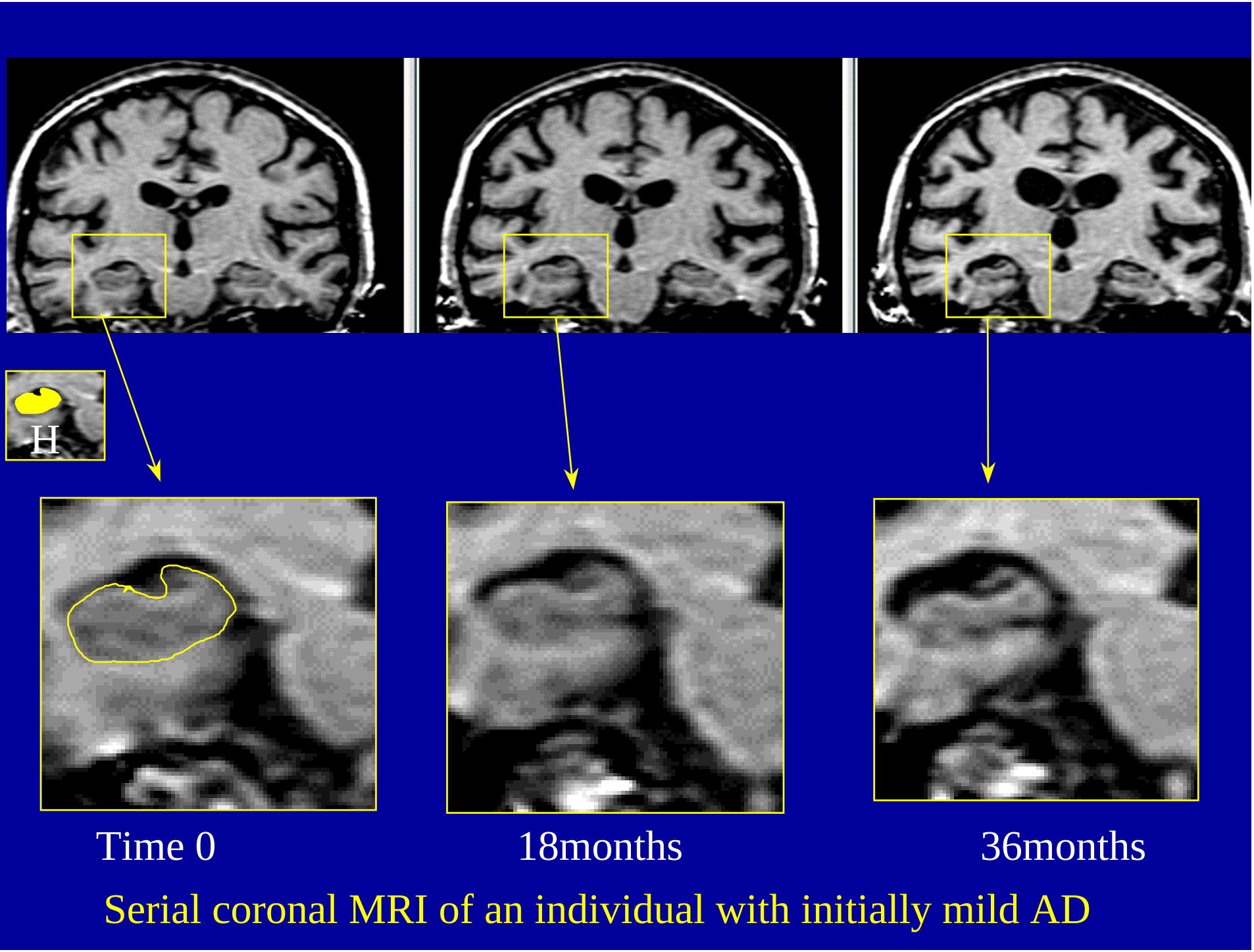
- *ADAS-Cog score* — *320*
- *MMSE score* — *241*
- *Hippocampal volume* — *21*

Jack et al, Neurology

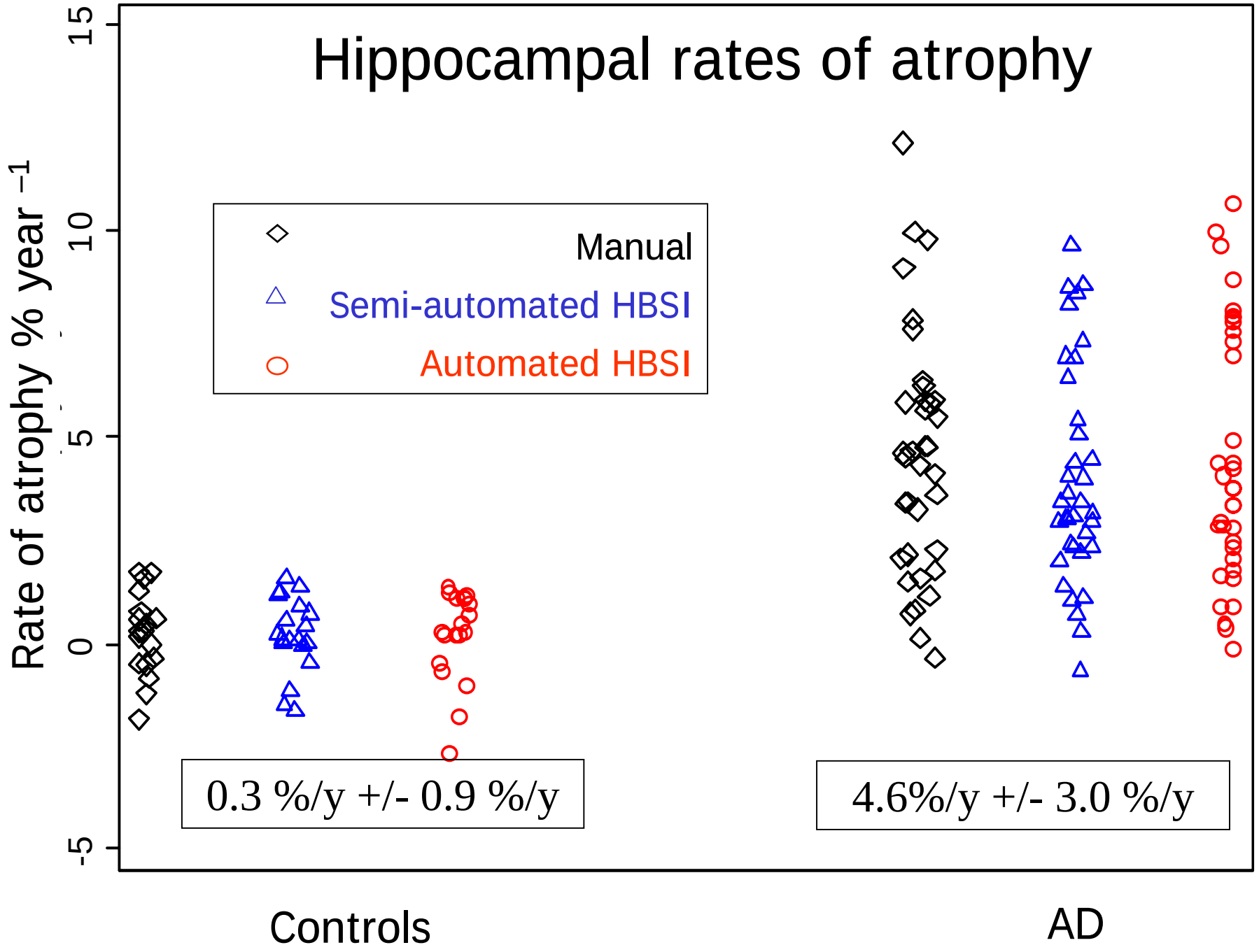
Imaging – disease modification markers

- *Structural MRI*
  - *Hippocampi, entorhinal cortex*
  - *Whole brain, ventricles*
  - *Cortical thickness*
- *Functional - PET/SPECT*
- *Molecular - Amyloid imaging – PIB*

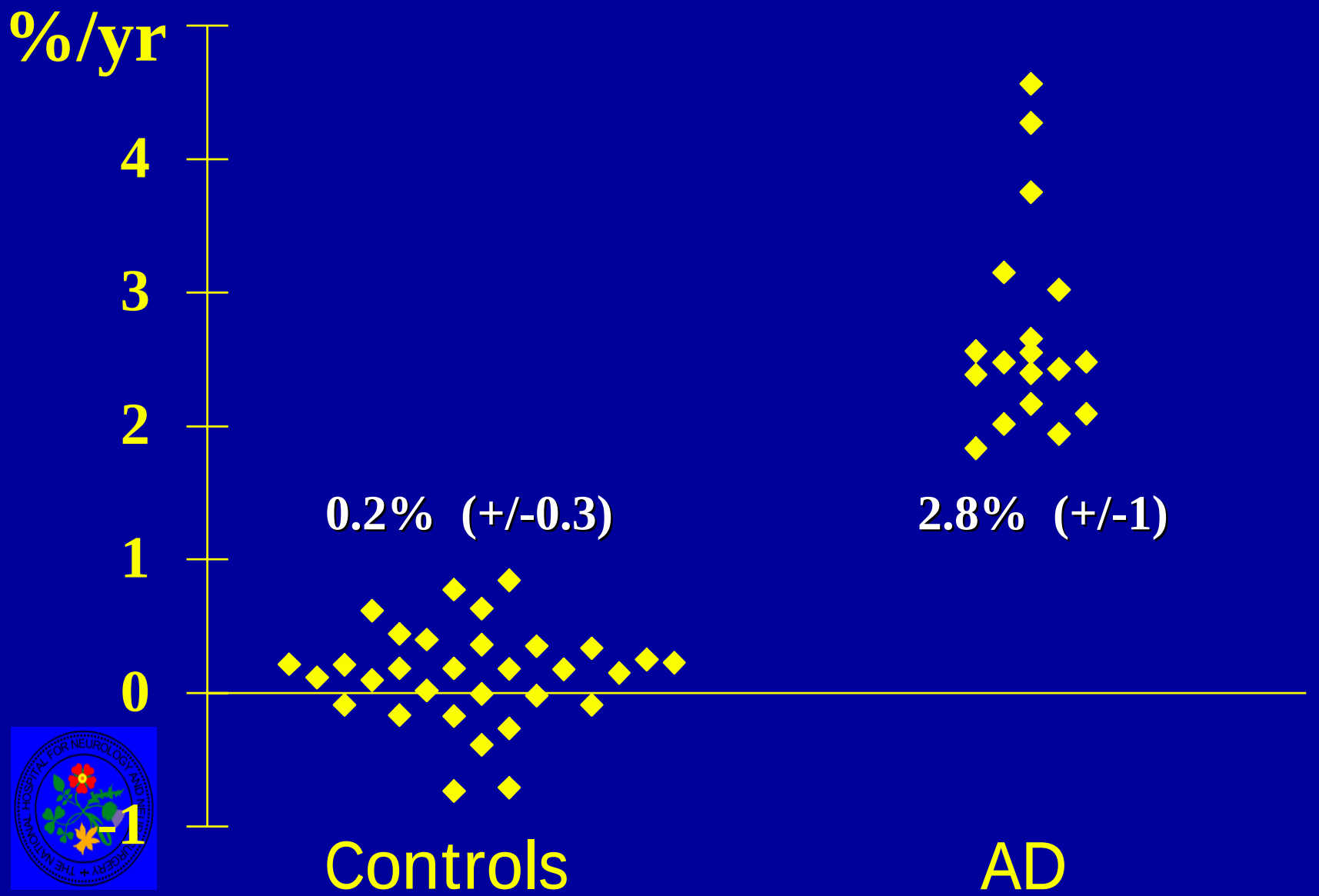
- *Spectroscopy, diffusion, MTR, fMRI …*

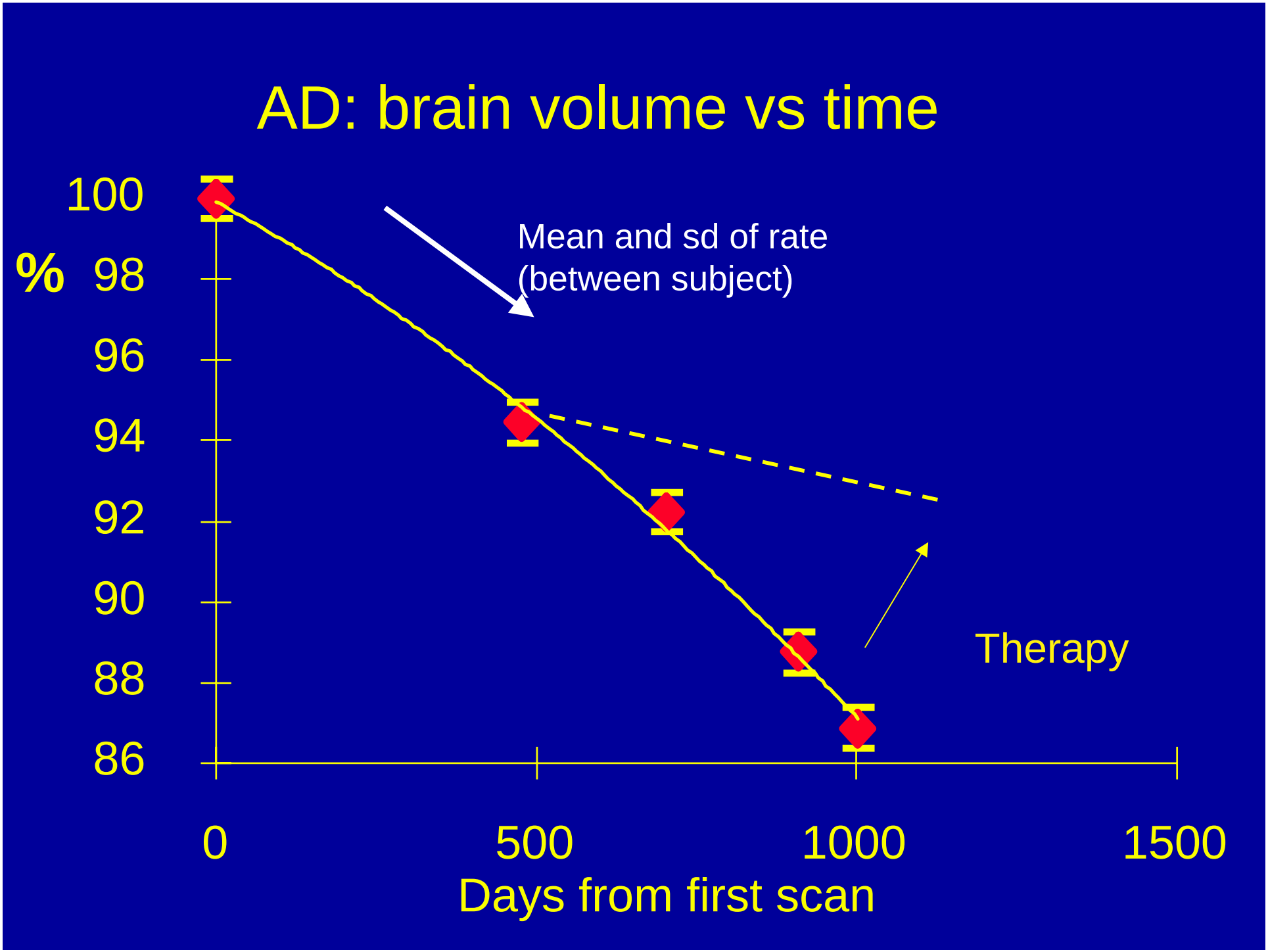


Serial coronal MRI of an individual with initially mild AD


Hippocampal rates of atrophy
Rate of atrophy % year −1
15
10
5
0
-5
Manual
Semi-automated HBSI
Automated HBSI
0.3 %/y +/- 0.9 %/y
4.6%/y +/- 3.0 %/y
Controls
AD

Rate of brain atrophy in early-onset AD




AD: brain volume vs time
100
%
98
96
94
92
90
88
86
Mean and sd of rate
(between subject)
Therapy
0
500
1000
1500
Days from first scan

Previously Estimated Number of AD Patients per Treatment Group Needed to Detect an Effect with 80% Power in One Year

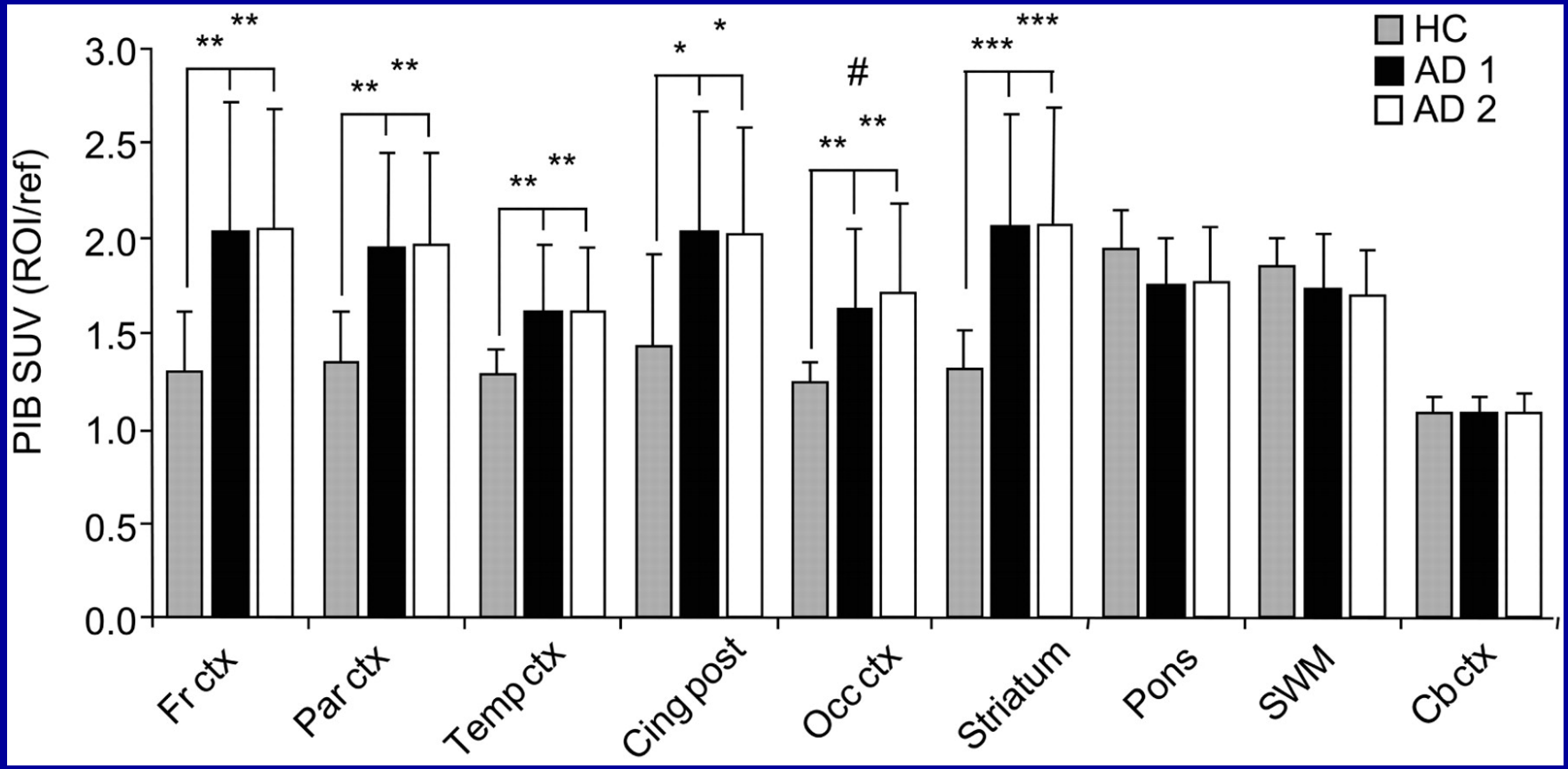
	Treatment Effect			
	20%	30%	40%	50%
Frontal	85	38	22	14
Parietal	217	97	55	36
Temporal	266	119	68	44
Cingulate	343	153	87	57

P=0.01 (two-tailed, uncorrected for multiple comparisons)

Alexander et al, *Am J Psychiatry* 2002

PIB retention stable over 2 years

healthy controls (HC) and Alzheimer patients at baseline (AD 1) and follow-up (AD 2)



Engler, H. et al. Brain 2006 129:2856-66

Disease modification: differing views and difficult issues

"an effect on the underlying disease pathophysiological progression"

"a long-lasting(> 18 months) effect on disability"

Surrogates need to capture "full effects of an intervention"

Conclusions

- *Imaging has an under used role in inclusion as well as exclusion for trial*
- *Safety imaging markers increasingly important*
- *Imaging may provide evidence to show effect on brain structure, metabolism or amyloid load – to understand effect of intervention*
- *Evidence for modification is more difficult:*
  - *Robust, multiple markers & multiple time points*
  - *To support clinical endpoint effects*

Trials will increasingly need to incorporate these markers in a considered evidence-based manner