Using Imaging Markers
to Study Drug Effects in AD

MRI, hippocampal atrophy, and cognition: markers for enrichment in clinical trials of MCI

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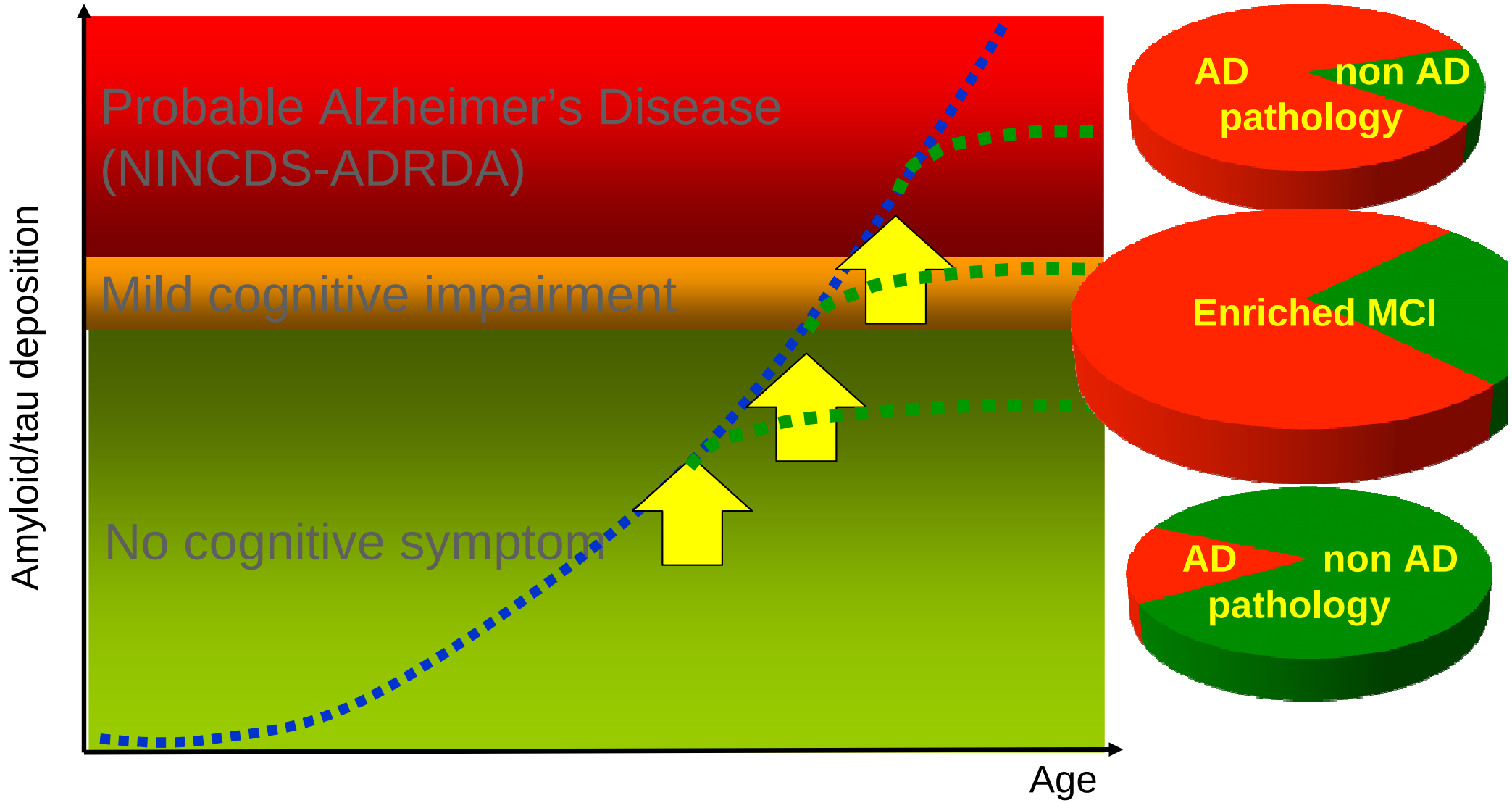
Why enriching study groups in clinical trials of disease modifiers in MCI?

How to and consequences: there's no free lunch

Hippocampal volumetry as enrichment marker

Disease modification in AD



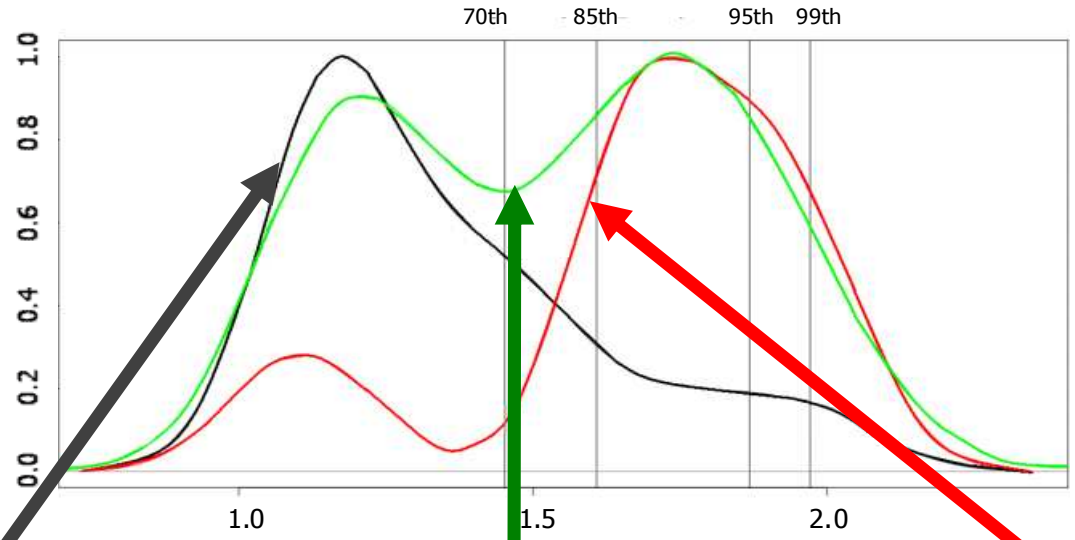
Biomarkers in the IWG and NIA-AA diagnostic criteria

Table. Biomarkers of Alzheimer's disease pathophysiology in the revised NINDS-AA diagnostic criteria for Alzheimer's disease [3-5]. Asterisks denote markers included in an early proposal for revised criteria by Dubois and colleagues [2].

Biomarkers of brain β-amyloidosis	• Increased uptake on amyloid imaging with PET (*) • Decreased CSF Ab42 (*)
Biomarkers of neuronal injury (synaptic dysfunction and neuronal loss)	• Temporoparietal hypometabolism on 18F-FDG PET (*) • Medial temporal (hippocampal) atrophy (*) • Increased CSF tau/phospho-tau (*) • Temporoparietal hypoperfusion on SPECT
Other less validated biomarkers, biomarkers of collateral damage, or serial biomarkers	• fMRI activation studies, resting BOLD functional connectivity, MRI perfusion, MR spectroscopy, diffusion tensor imaging • Inflammatory (cytokines) and oxidative stress biomarkers (isoprostanes) • Rates of brain atrophy

Frisoni Hampel O'Brien Ritchie Winblad, Lancet Neurol 2011

Distribution of AD markers in MCIs

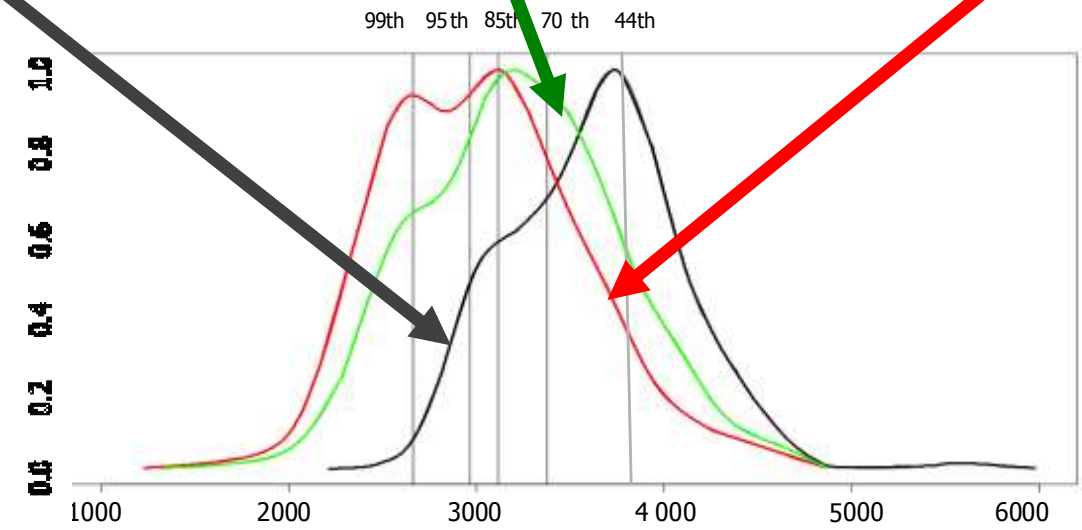


PIB uptake

MCI non converters

All MCIs

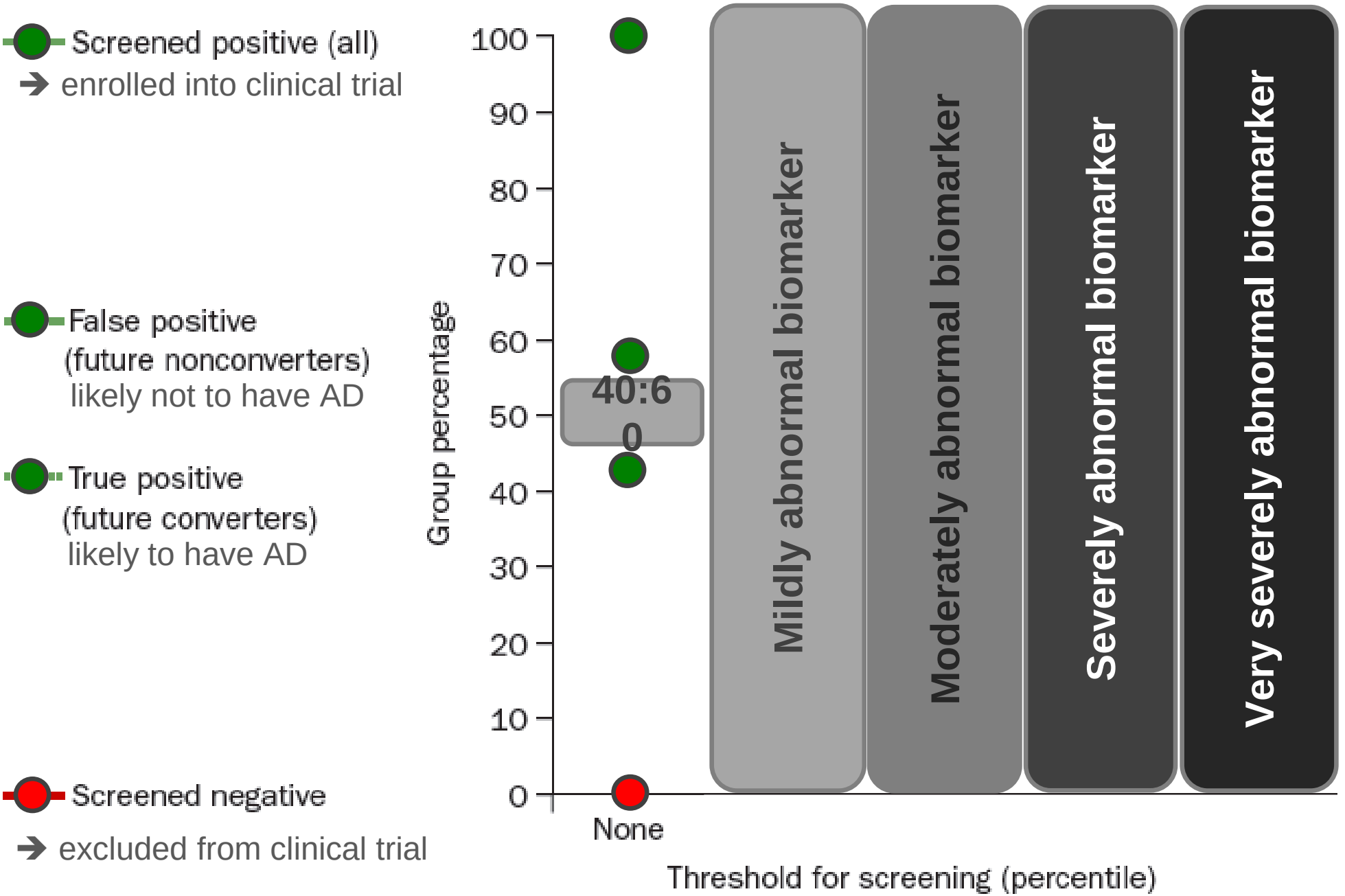
MCI converters to dementia



Hippocampal volume

Lorenzi et al., Neurobiol Aging 2010

THE PAYOFF OF ENRICHMENT IN MCI CLINICAL TRIALS (Nat Reviews Neurol 2010)



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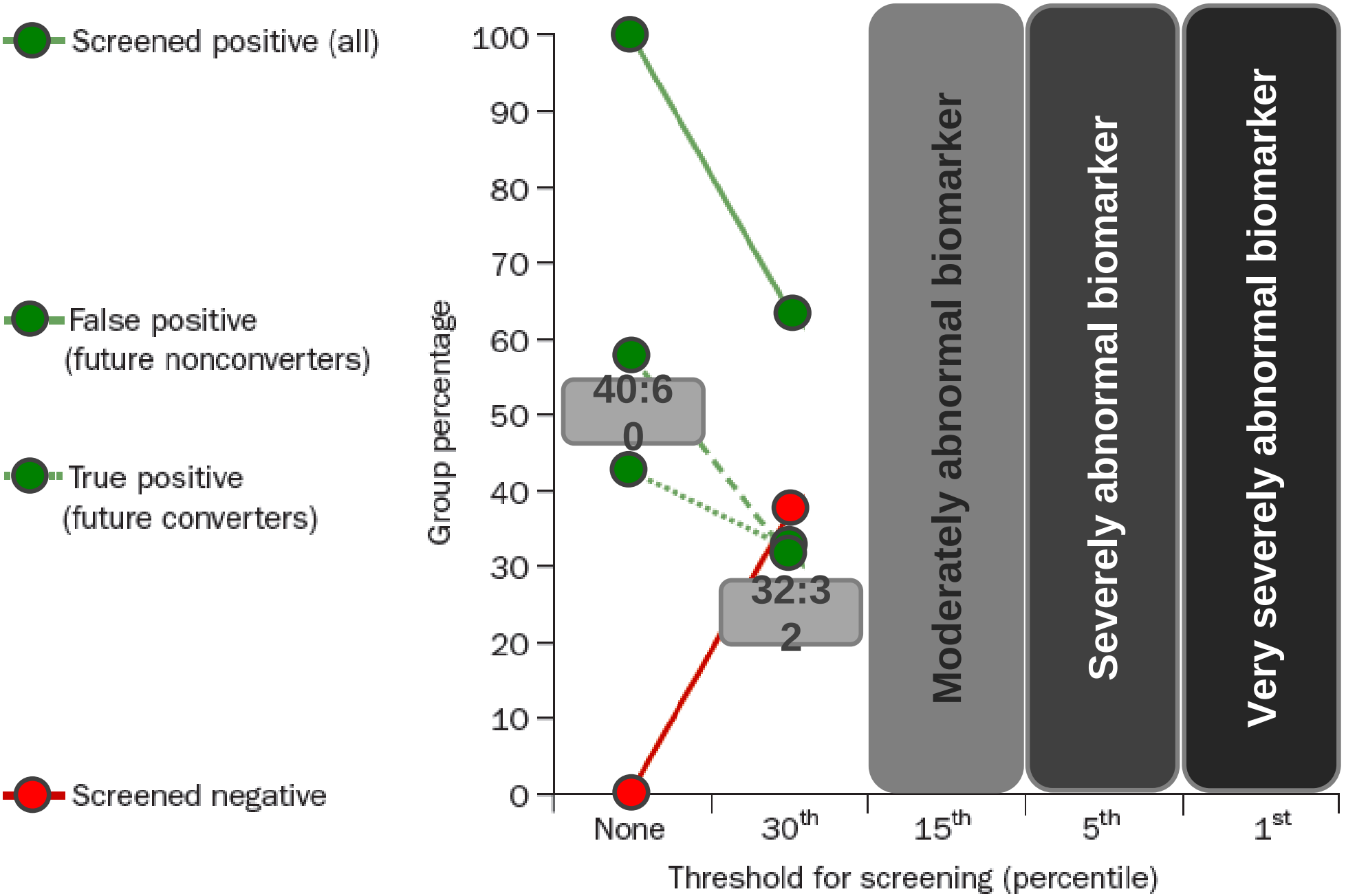

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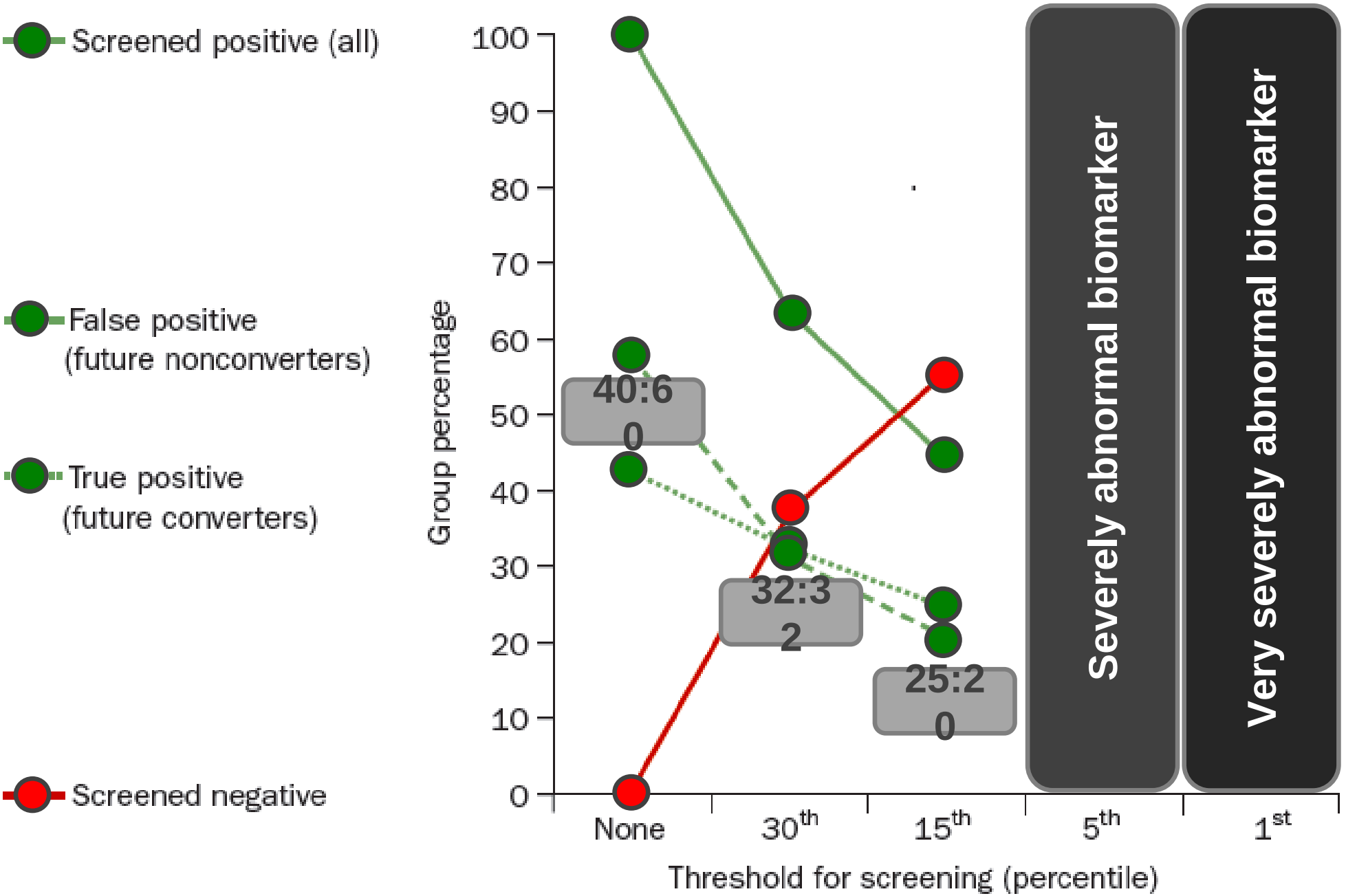

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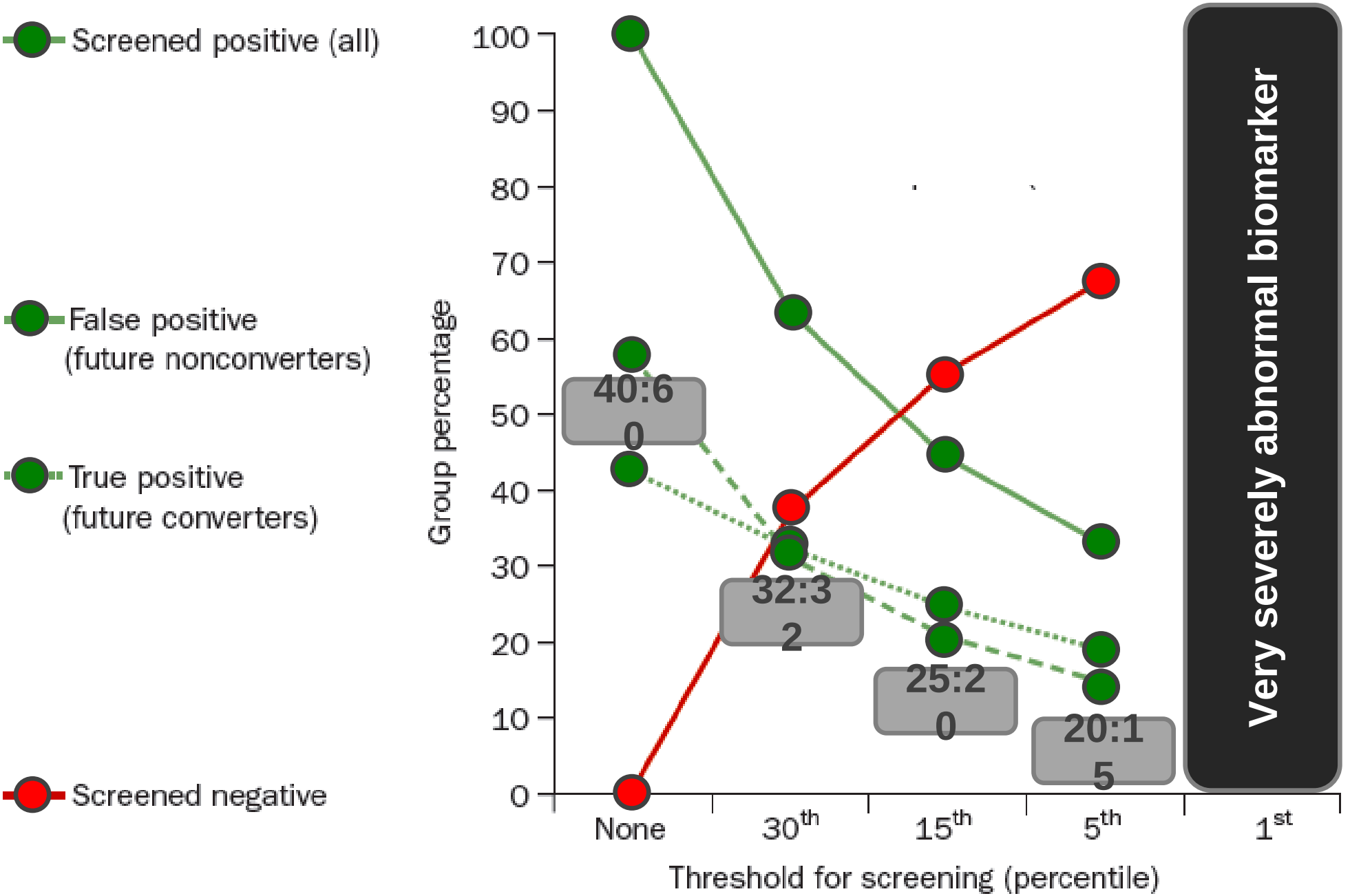

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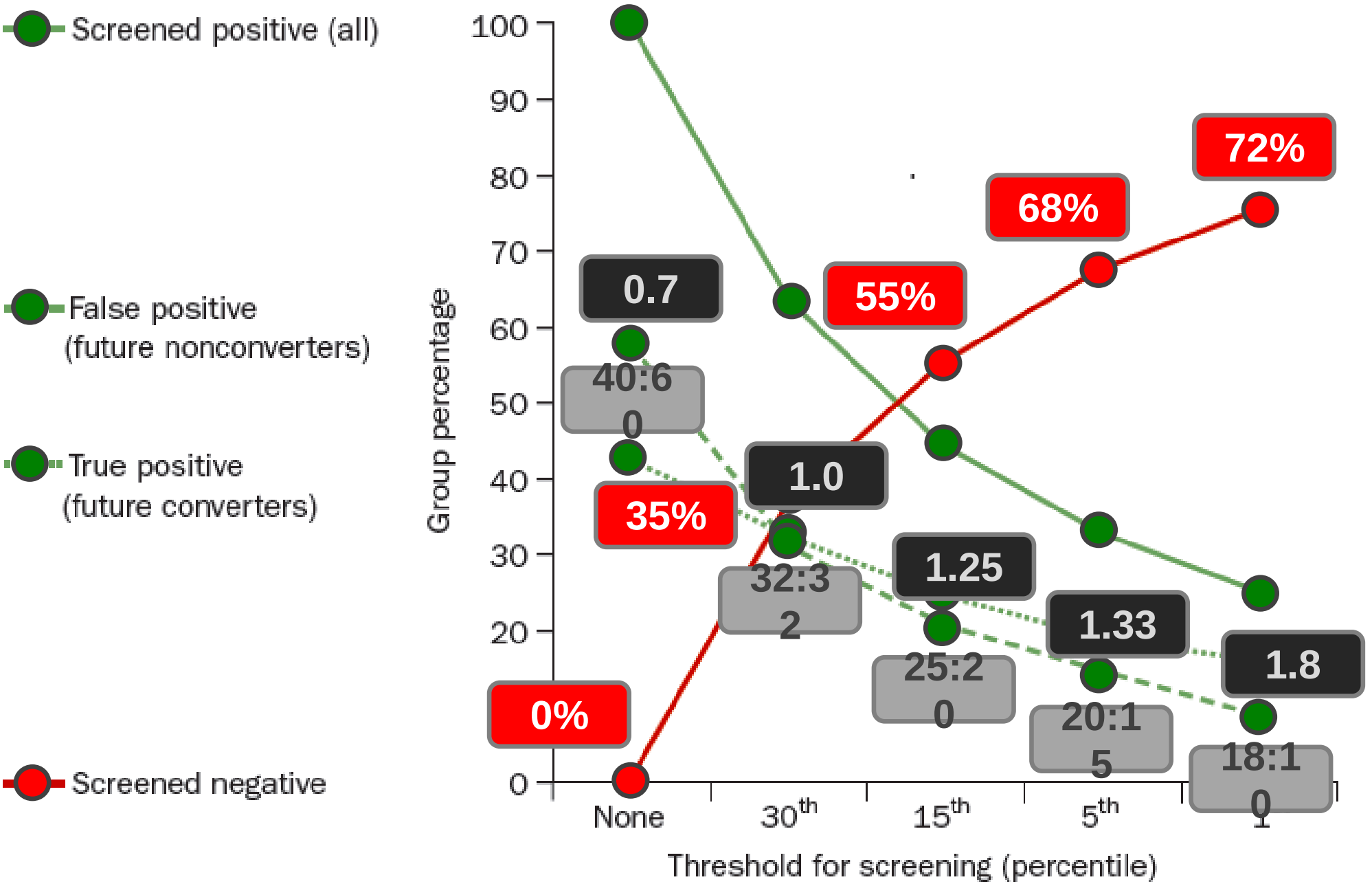


10 February 2011
EMA/CHMP/SAWP/102001/2011
Procedure No.: EMEA/H/SAB/005/1/QA/2010
Committee for Medicinal Products for Human Use (CHMP)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Qualification Opinion of Alzheimer's Disease Novel Methodologies/biomarkers for BMS-708163

17 November 2011
EMA/CHMP/SAWP/809208/2011
Committee for Medicinal Products for Human Use (CHMP)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

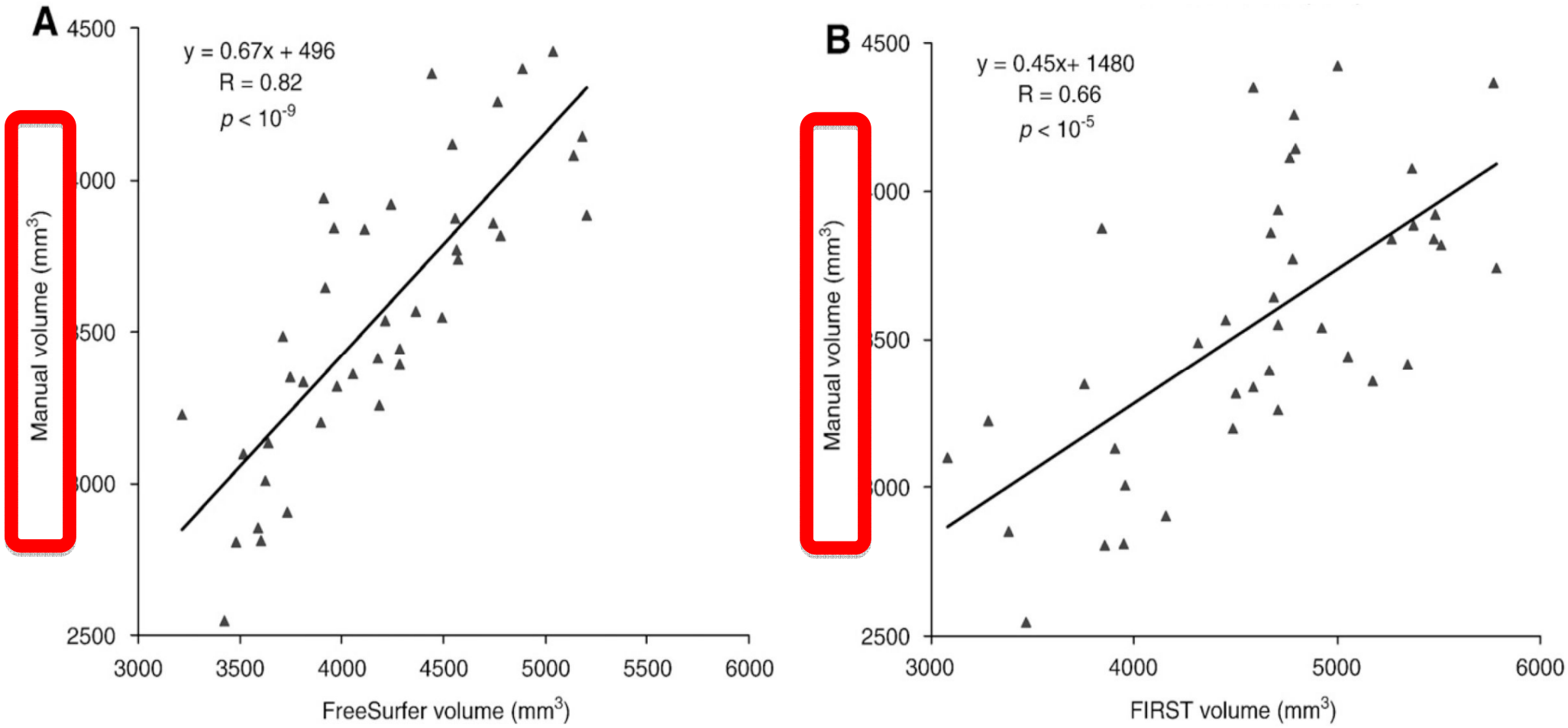
Qualification opinion of low hippocampal volume (atrophy) by MRI for use in clinical trials for regulatory purpose - in pre-dementia stage of Alzheimer's disease

EMA conclusions

“Low hippocampal volume … dichotomized … appears to help enriching recruitment into clinical trials aimed at studying drugs potentially slowing the progress/conversion to AD dementia [and] … might be considered a marker of progression to dementia in subjects with … predementia stage of AD (Dubois 2007), **for the purposes of enriching a clinical trial population**.”

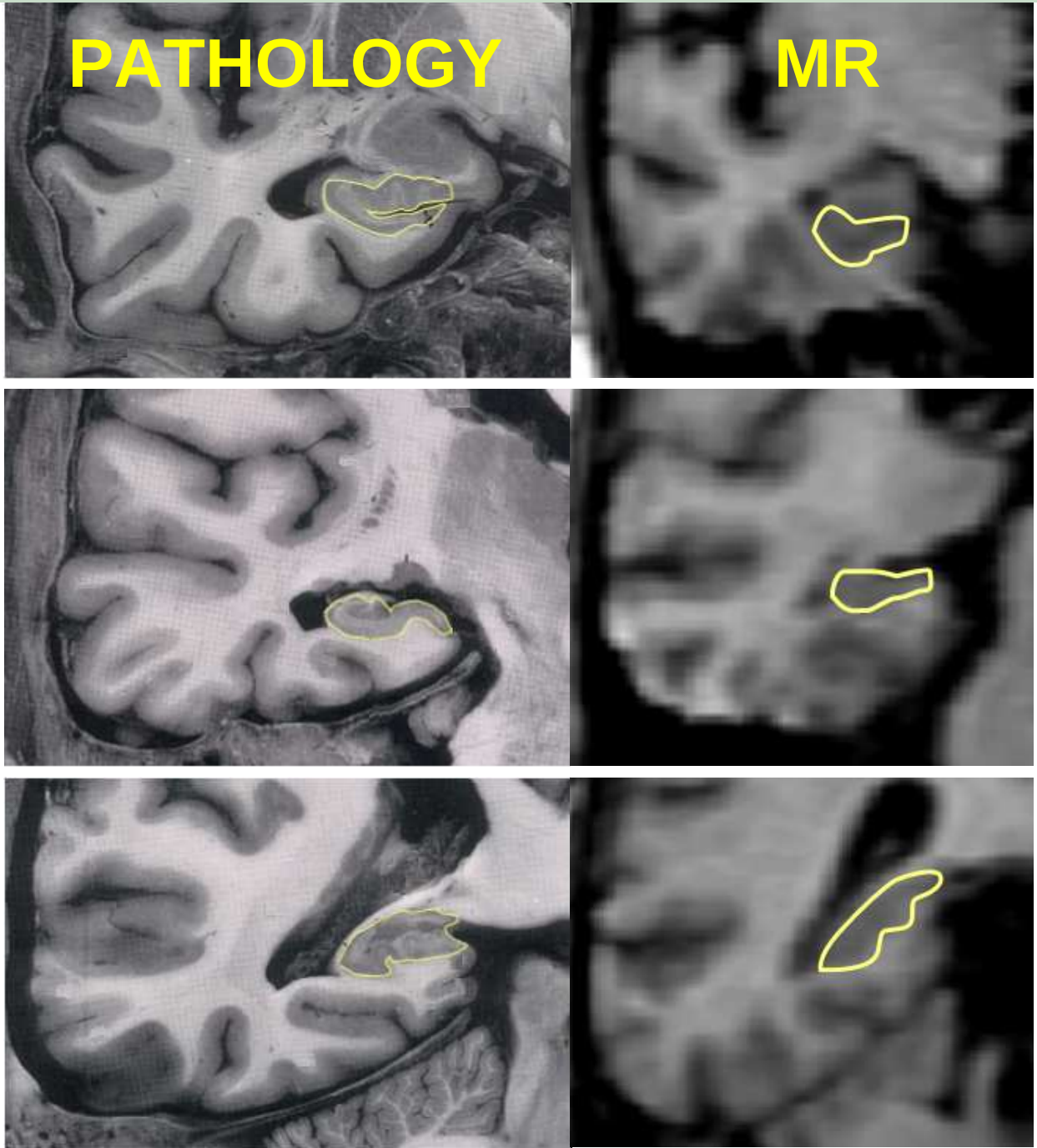
“Collection, handling and measurements of Low hippocampal volume, as measured by MRI should be performed **according to Good Clinical Practice and to the specific highest international standards**.”

AUTOMATED SEGMENTATION:
Valid versus what?



Morey et al., NeuroImage 2009

MANUAL SEGMENTATION OF THE HIPPOCAMPUS



There's more than 40 (very!) different ways to manually segment the hippocampus, resulting in wildly different volume estimates

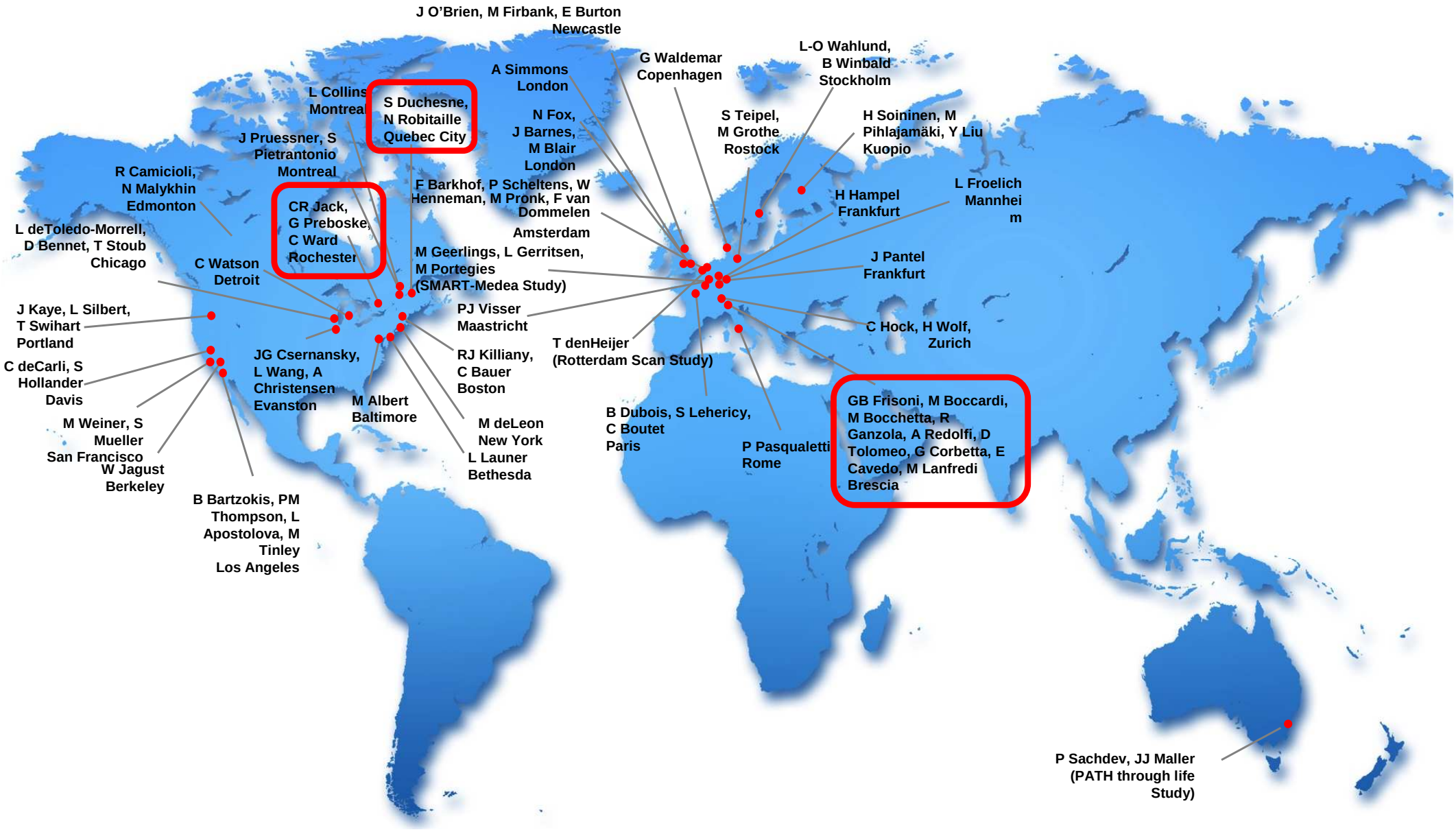
Ref.	Med border	Lat border	Inf border	Norm. hippo vol (cm^3)	
				Left	Right
Watson et al.	Mesial edge of temporal lobe	Temp horn of lat ventr	Incl subicular complex & uncal cleft w/ border separating subicular complex	**4.903**	**5.264**
Zipursky et al.	Regional outline at choroidal fissure	Not mentioned	hippocampal tissue and parahippocampal gyrus white matter	**1.990**	**2.070**

2.5-fold difference

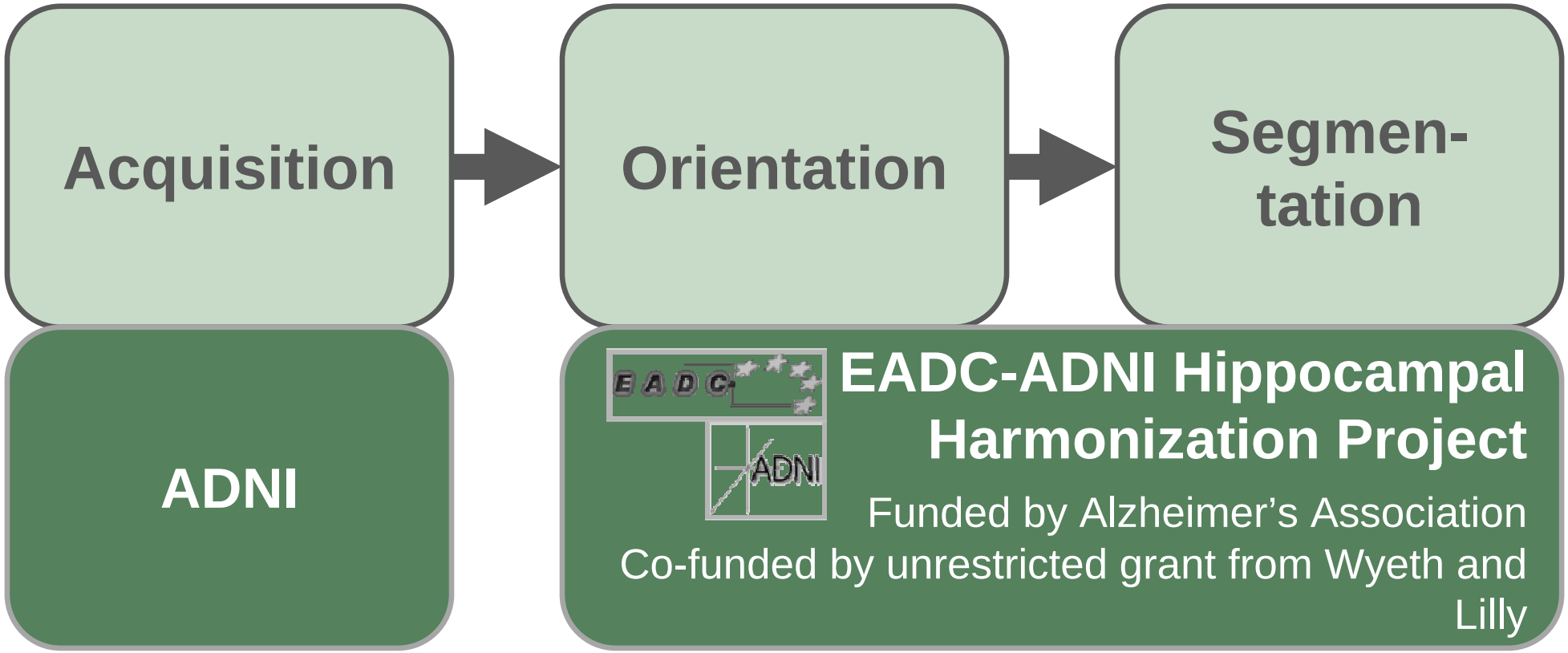
Geuze et al., Mol Psychiatry 2005;10:147-59

The EADC-ADNI Working Group on the Harmonized Protocol for Hippocampal Volumetry

Frisoni & Jack, Alzh Dement 2011; Boccardi et al., JAD 2011; Boccardi et al., Alzh Dement submitted

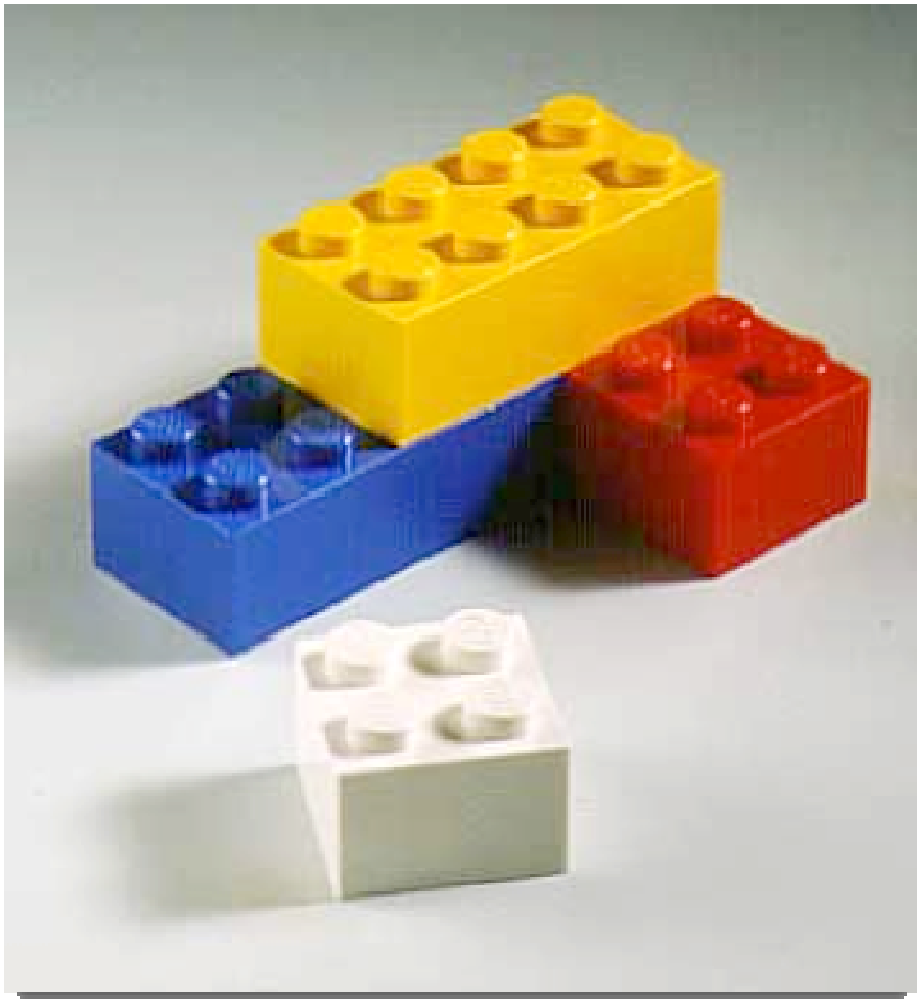


Standardization of manual hippocampal volumetry



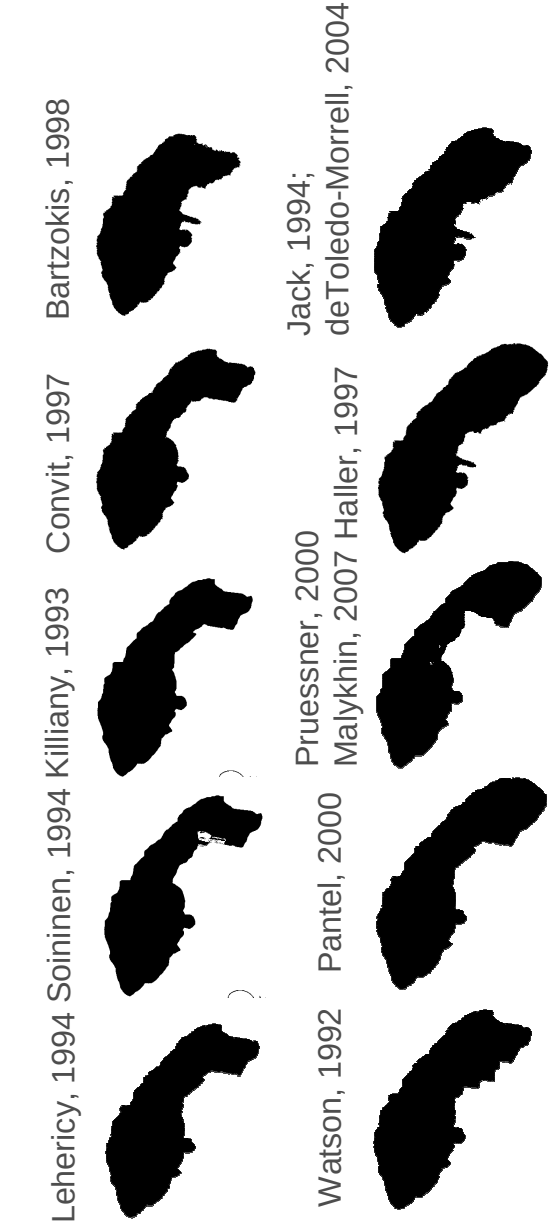
Extraction of largest possible common units (“LEGO blocks” or Segmentation Units)

Boccardi et al., JAD 2011

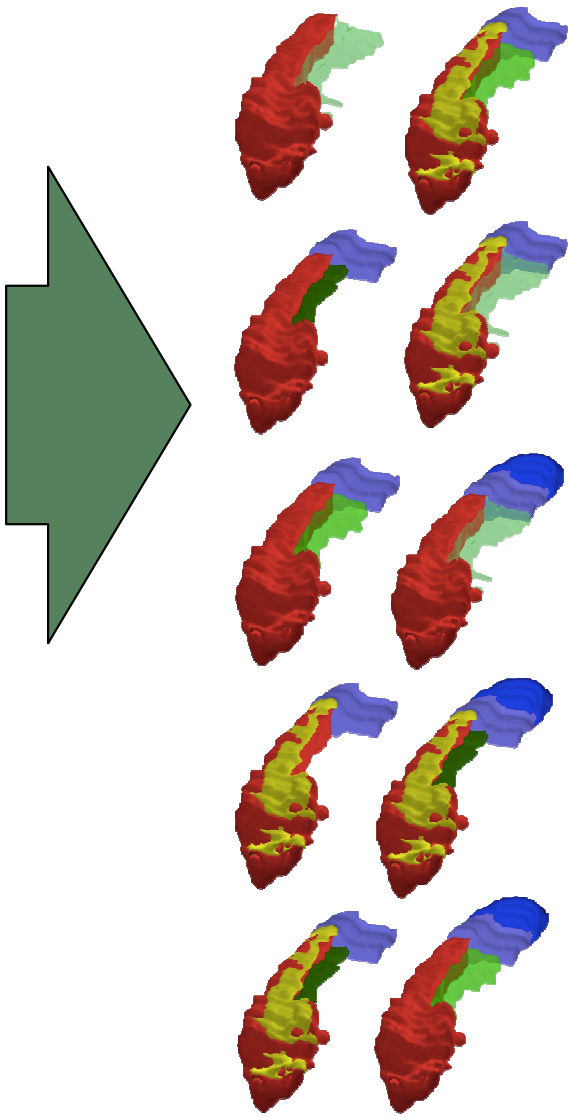


METHODS

Survey and operationalization



Break down into segmentation units



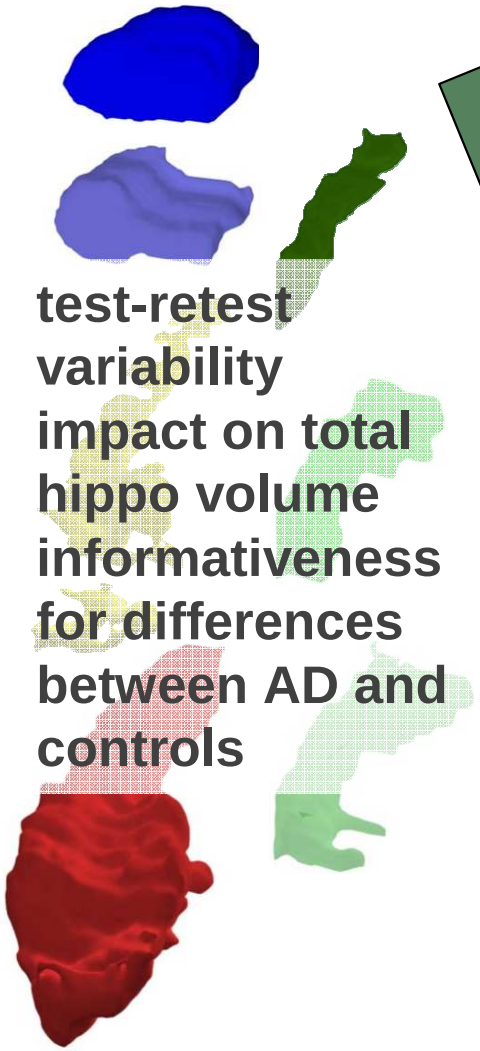
Assessment of measurement properties of SUs

Boccardi et al., JAD 2011; Boccardi et al., Alzh Dement submitted

METHODS

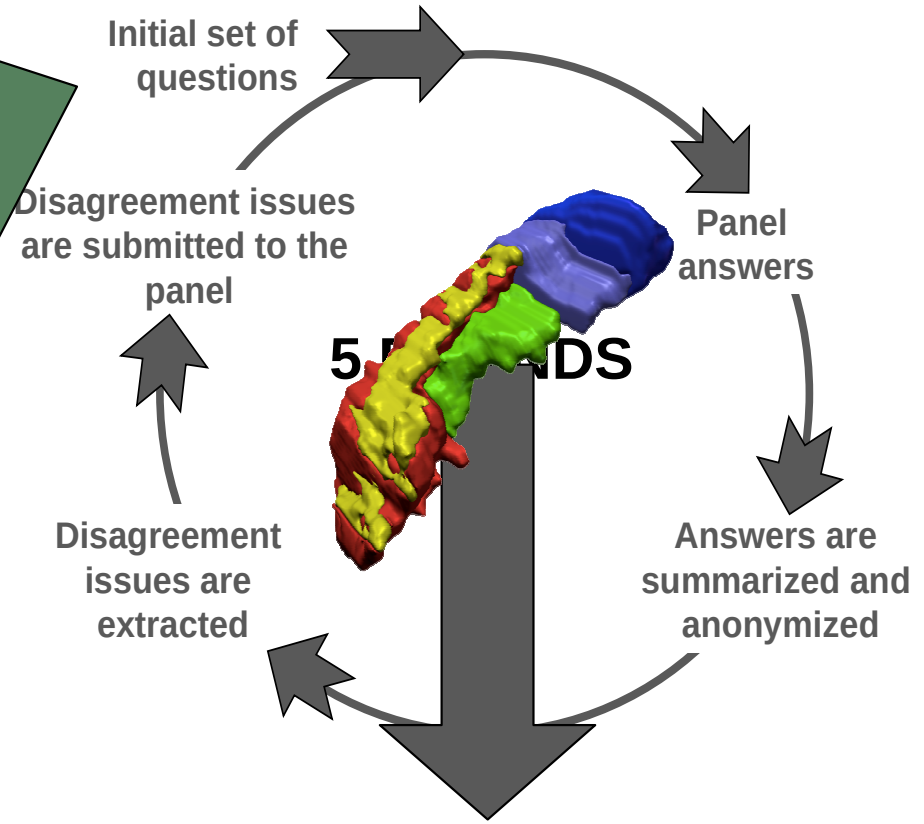
Boccardi et al., JAD 2011; Boccardi et al., in preparation

Assessment of measurement properties of SUs



1) test-retest variability
2) impact on total hippo volume
3) informativeness for differences between AD and controls

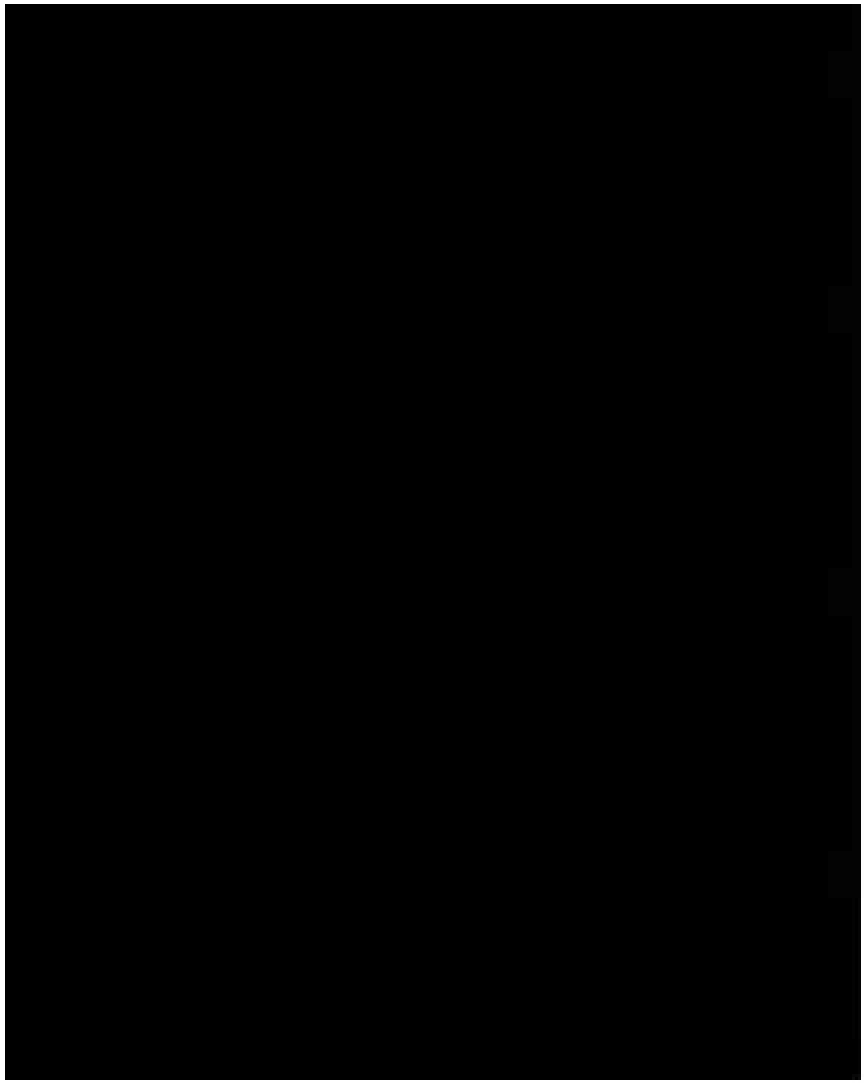
Delphi panel



Covers **100%** of hippo proper
Captures **100%** of AD atrophy
Very high IRR & TRTR: **<.96**

How is the Harmonized Protocol Working?

Agreement among L Apostolova (UCLA), M Bocchetta (IRCCS FBF), and G Preboske (Mayo)



FUTURE STEPS

1. **Develop reference probabilistic masks (ongoing)**

- 5 “master tracers”

2. Develop a qualification procedure, environment, and thresholds for

- naïve tracers
- automated algorithms

3. Validate on:

- 1800 ADNI hippocampi segmented by 20 human tracers
- MR-pathological datasets (volume on pathology, neuronal density, volume on *ex vivo* MR)

4. Segmentation protocol and benchmark masks:

- available to beta-testers based on *ad hoc* agreements until the end of validation process (summer 2013),
- no restrictions afterwards

CONCLUSIONS

Enrichment of clinical trials of disease modifiers in MCI is critical to detect signal of efficacy

There is no magic enrichment recipe: a matter of earn/pay balance

Hippocampal volumetry is conceptually mature for enrichment purposes

Operational procedures might be refined with the harmonized manual segmentation protocol as benchmark

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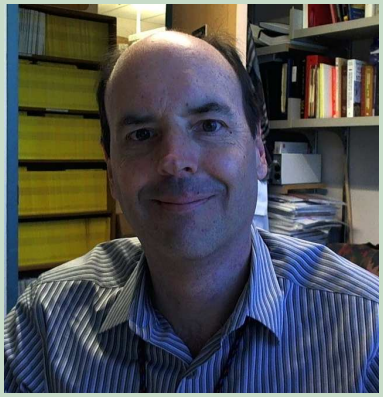

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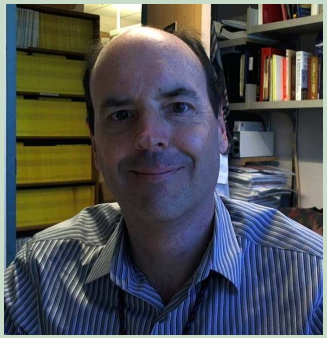

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MASTER TRACERS

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The National Centre for Alzheimer's Disease, Brescia

Hippo Harmo Team
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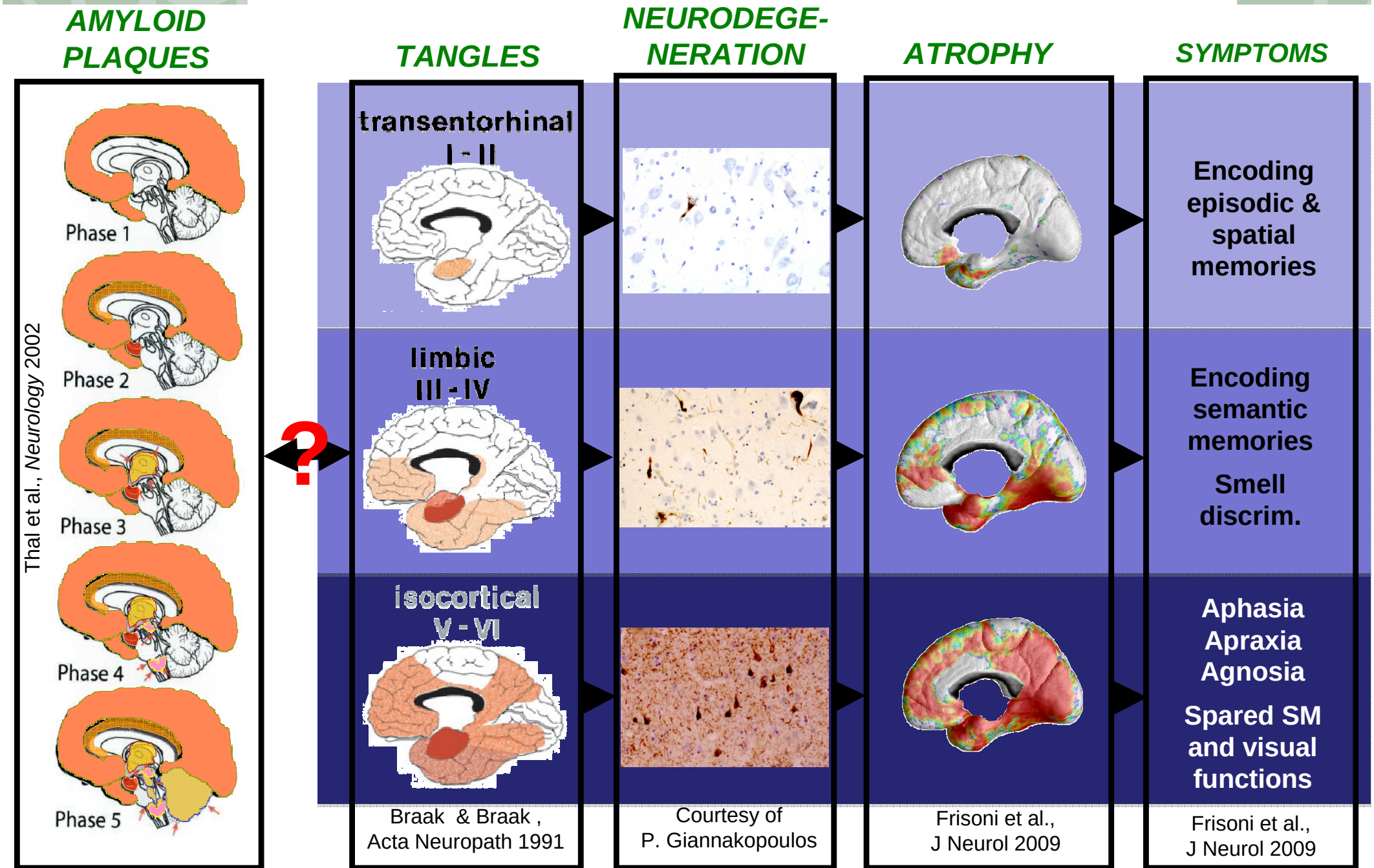
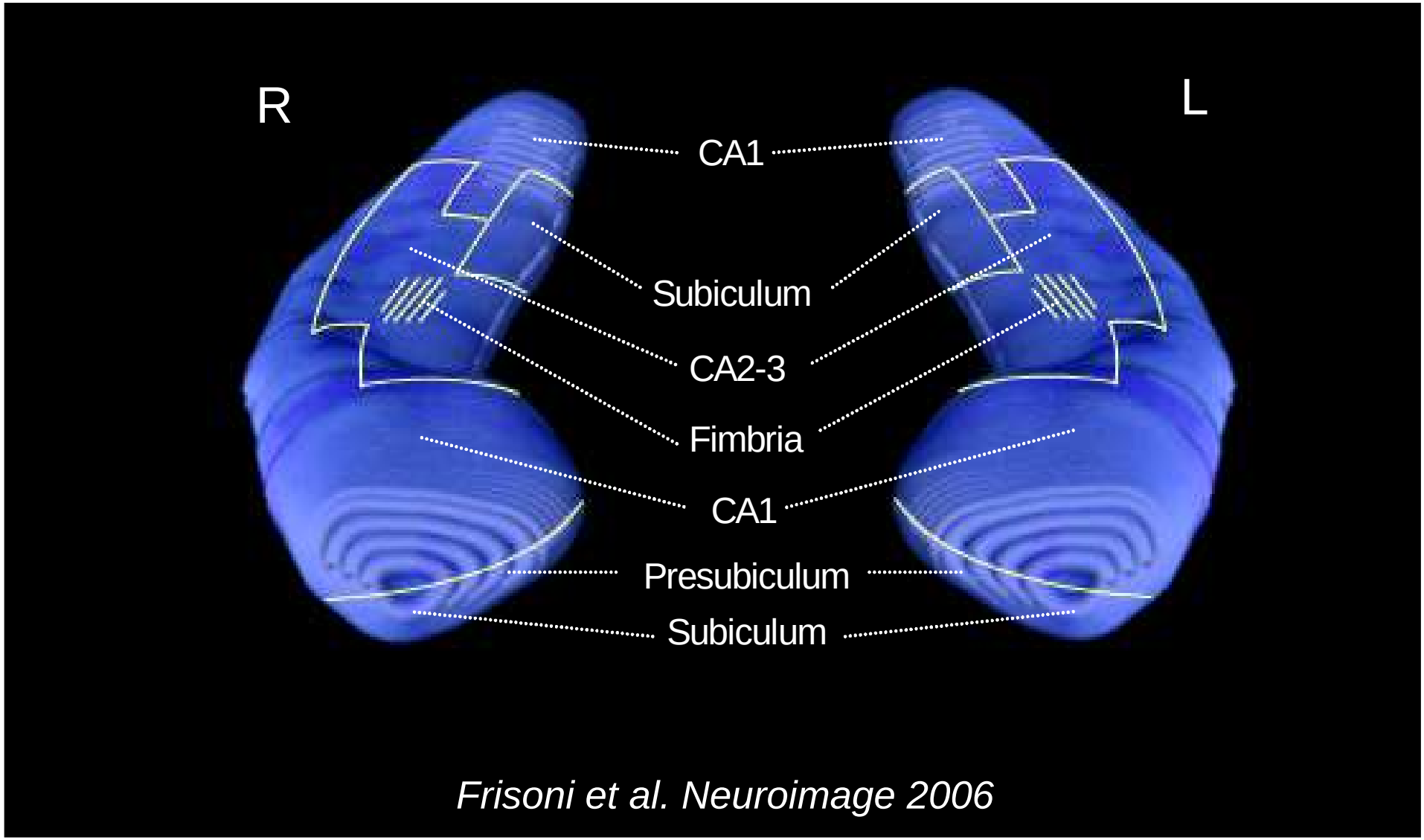
A Redolfi, G Corbetta, D Tolomeo

Enrichment
M Lorenzi

Atrophy is an intermediate phenotype between neurodegeneration and clinical symptoms



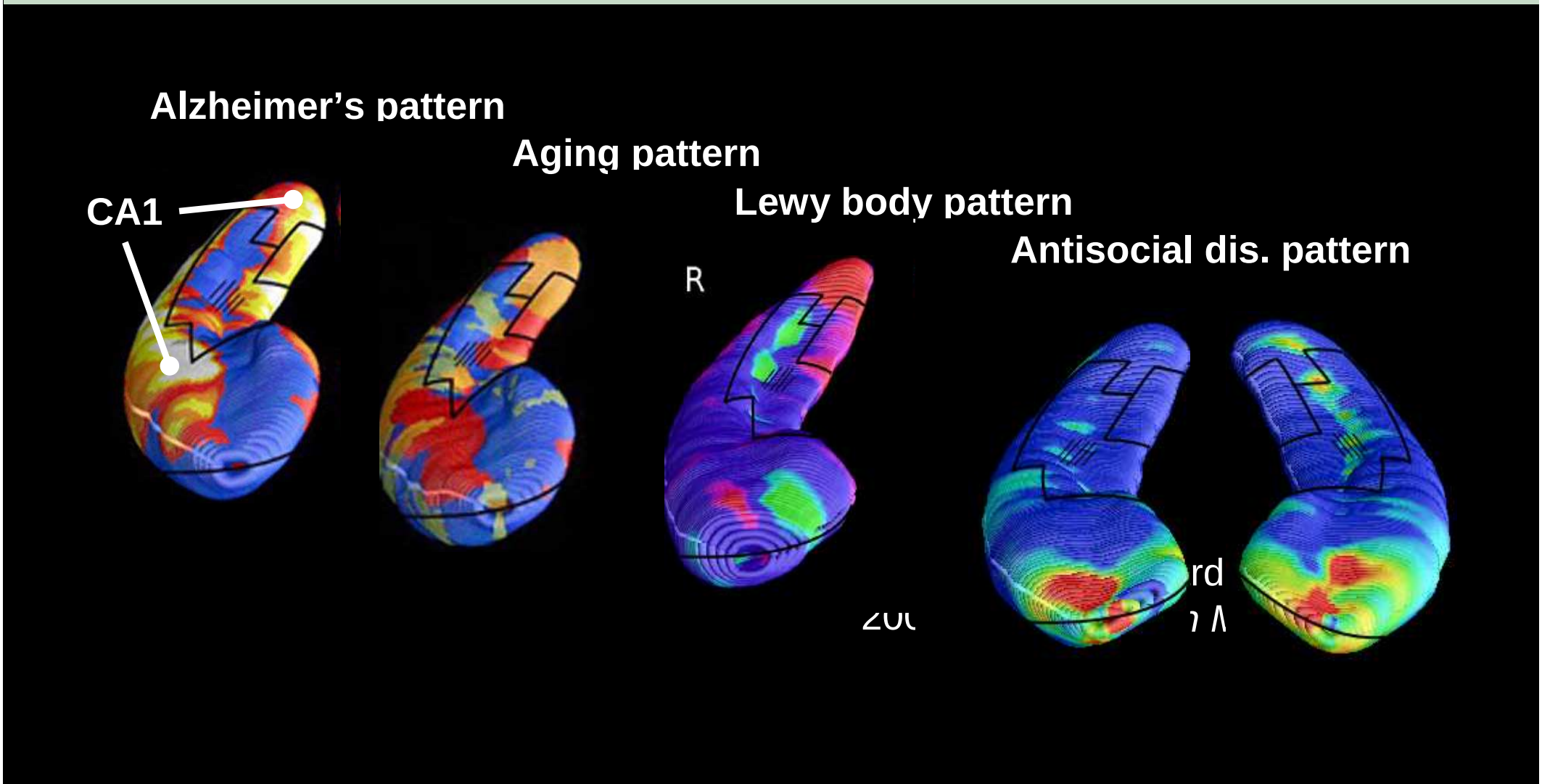
HIPPOCAMPAL MAPPING
The method 2



Frisoni et al. Neuroimage 2006

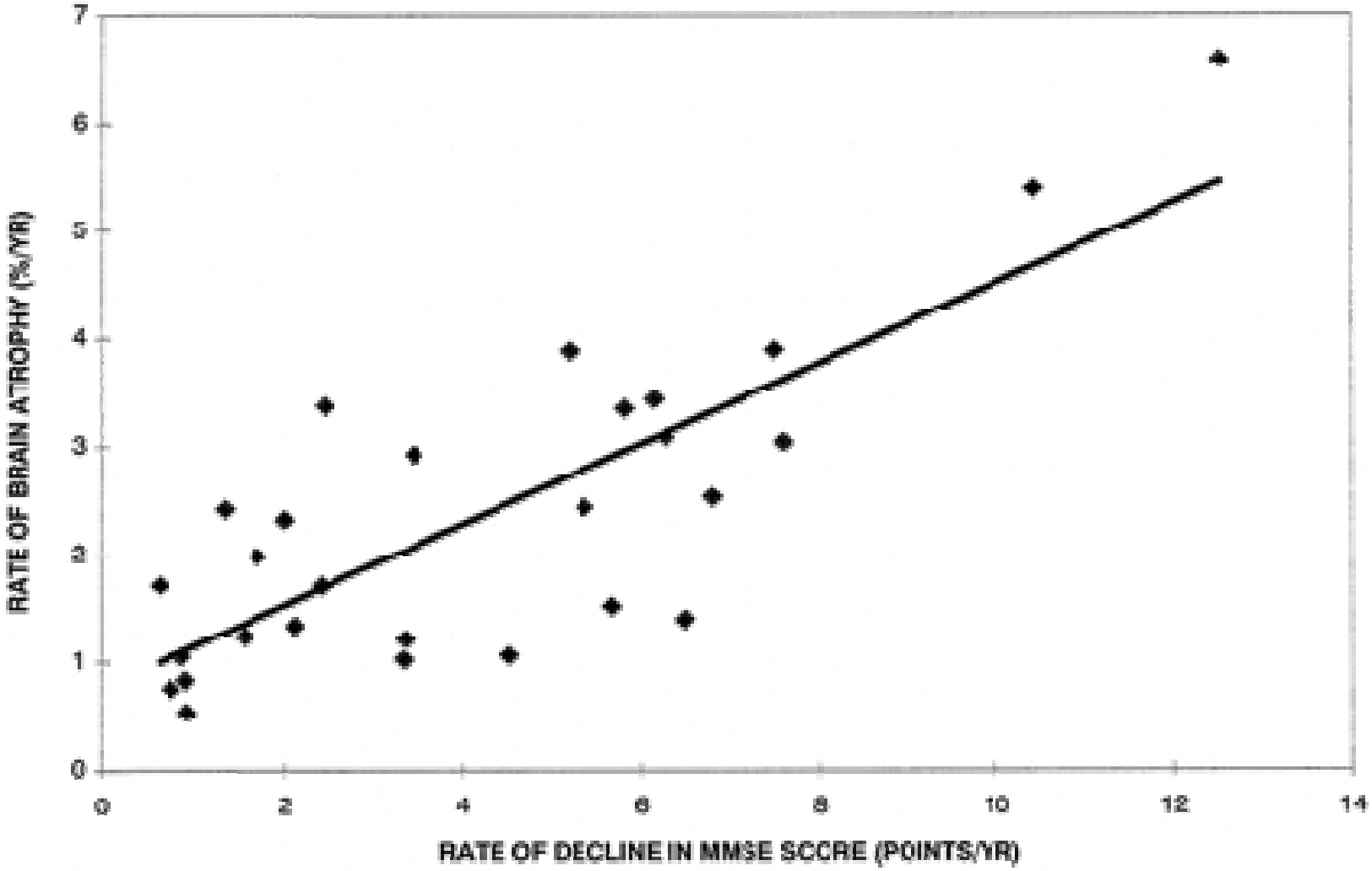
Atrophy in AD maps onto areas known to be affected by tau pathology and is specific to AD

L’atrophie dans la MA mappe sur les régions atteintes par le dépot de tau et elle est spécifique à la MA



Correlation of brain atrophy with rate of MMSE decline in 29 AD patients ($r = 0.80$, $p < 0.001$).

Fox et al., Neurology 1999;52:1687



THE TRADEOFF OF ENRICHMENT IN MCI CLINICAL TRIALS

RATIO CONV./NON CONV.

% SCREENED OUT

			Sample size		Screened out
A. Threshold maximizing % of MCI converters AMONG screened-in					
No enrichment	None	0.56	834 (631–1,154)	0%	0
ADAS-Cog	99th	0.98	617 (430–959)	56%	785 (547–1,220)
CSF tau	70th	0.89	531 (361–860)	38%	325 (221–527)
CSF Abeta42	70th	0.87	500 (347–780)	35%	269 (187–420)
CSF tau/abeta42	85th	0.89	453 (310–723)	46%	386 (264–616)
Hippocampal volume	99th	1.46	434 (293–711)	77%	1,452 (981–2,380)
CSF p-tau	85th	0.87	396 (269–643)	55%	484 (329–786)
[18F]-FDG PET	99th	1.14	260 (151–553)	86%	1,597 (927–3,397)

Lorenzi et al., Neurobiol Aging 2010