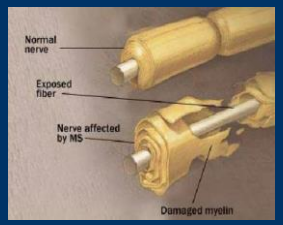
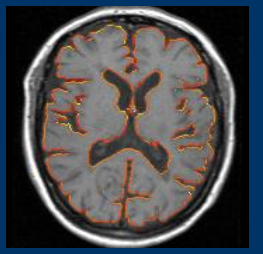
Clinical Relevance of Brain Atrophy in Multiple Sclerosis



Frederik Barkhof

VU University Medical Center

Amsterdam - NL



VU medisch centrum

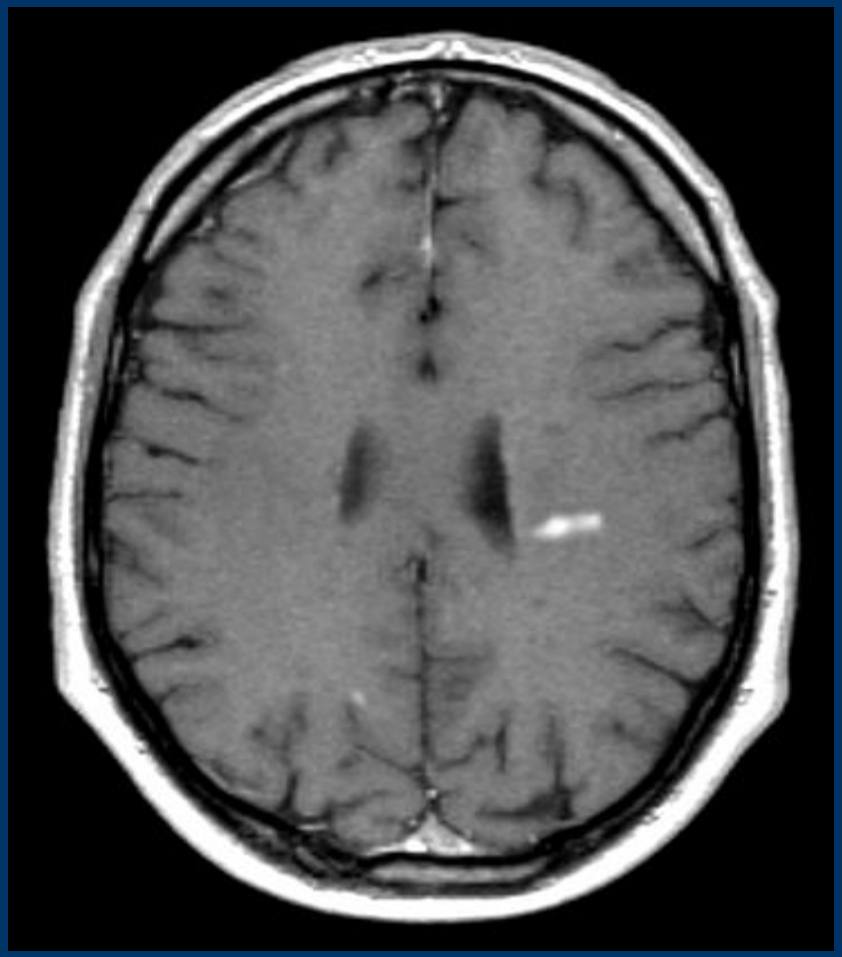
Disclosure

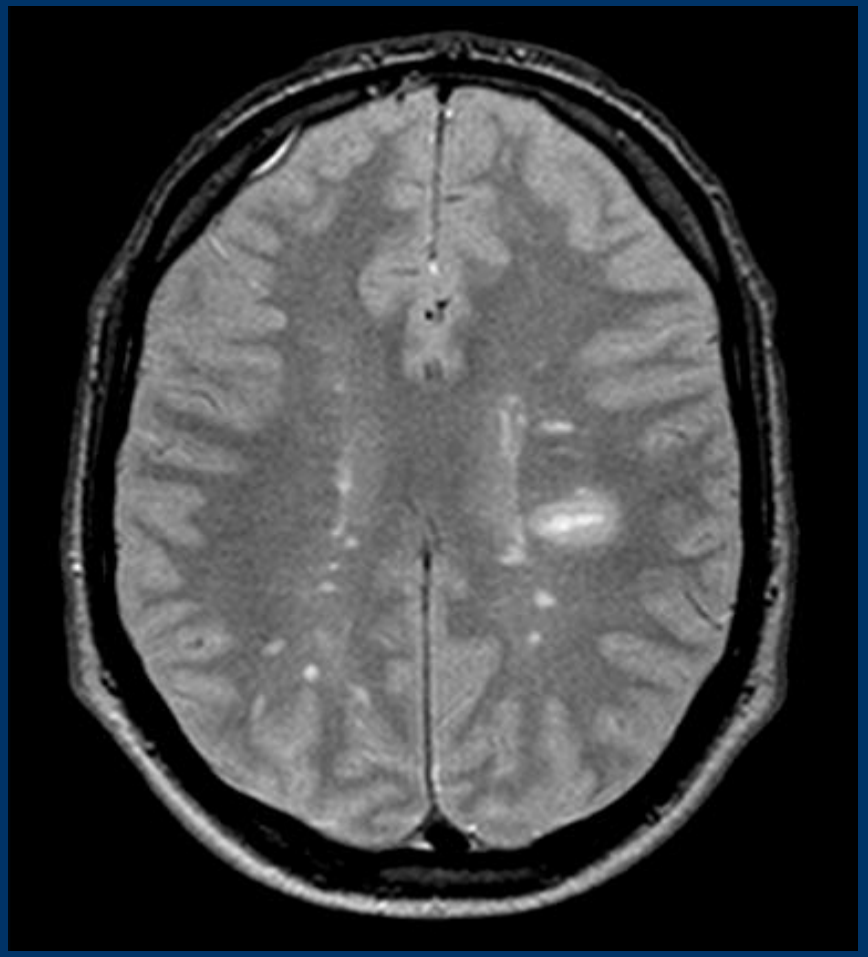
- Scientific director, Image analysis center (IAC)
- Consultant – Sanofi-Aventis, Roche, GE healthcare, Biogen-IDEC, Novartis, Roche, Synthon, Merck-Serono, Bayer-Schering Pharma, TEVA
- Research agreements – Toshiba, Philips, GE
- Sponsor – Dutch Foundation MS Research

Agenda

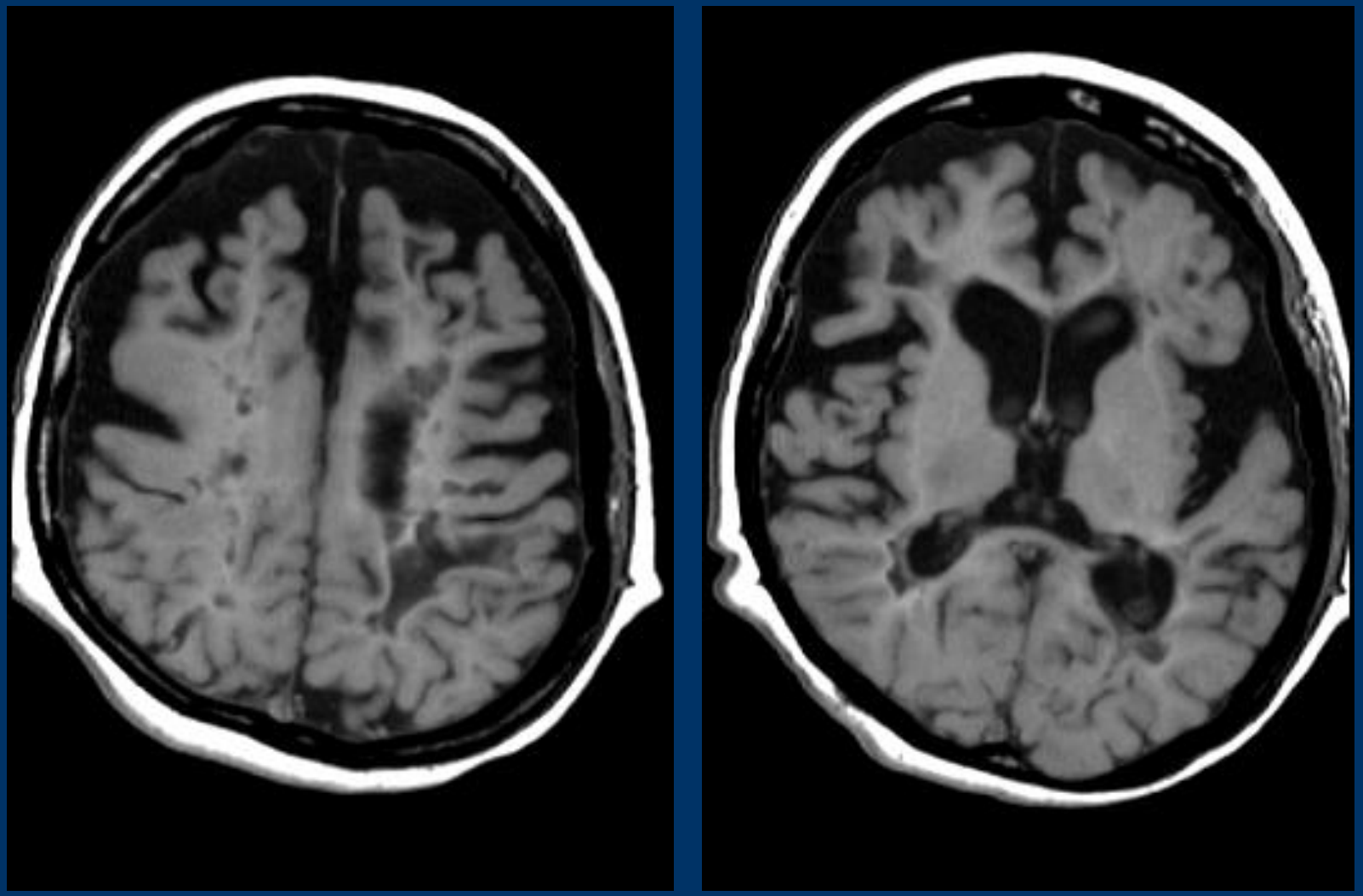
- Evidence for brain atrophy in MS
  - best measurement technique?
- Clinical relevance of brain atrophy
  - group-level predictive value
- Effect of treatment on brain atrophy
  - surrugate marker of neurodegeneration
- Single-subject predictive value
  - thresholds and caveats

Early MS: inflammation

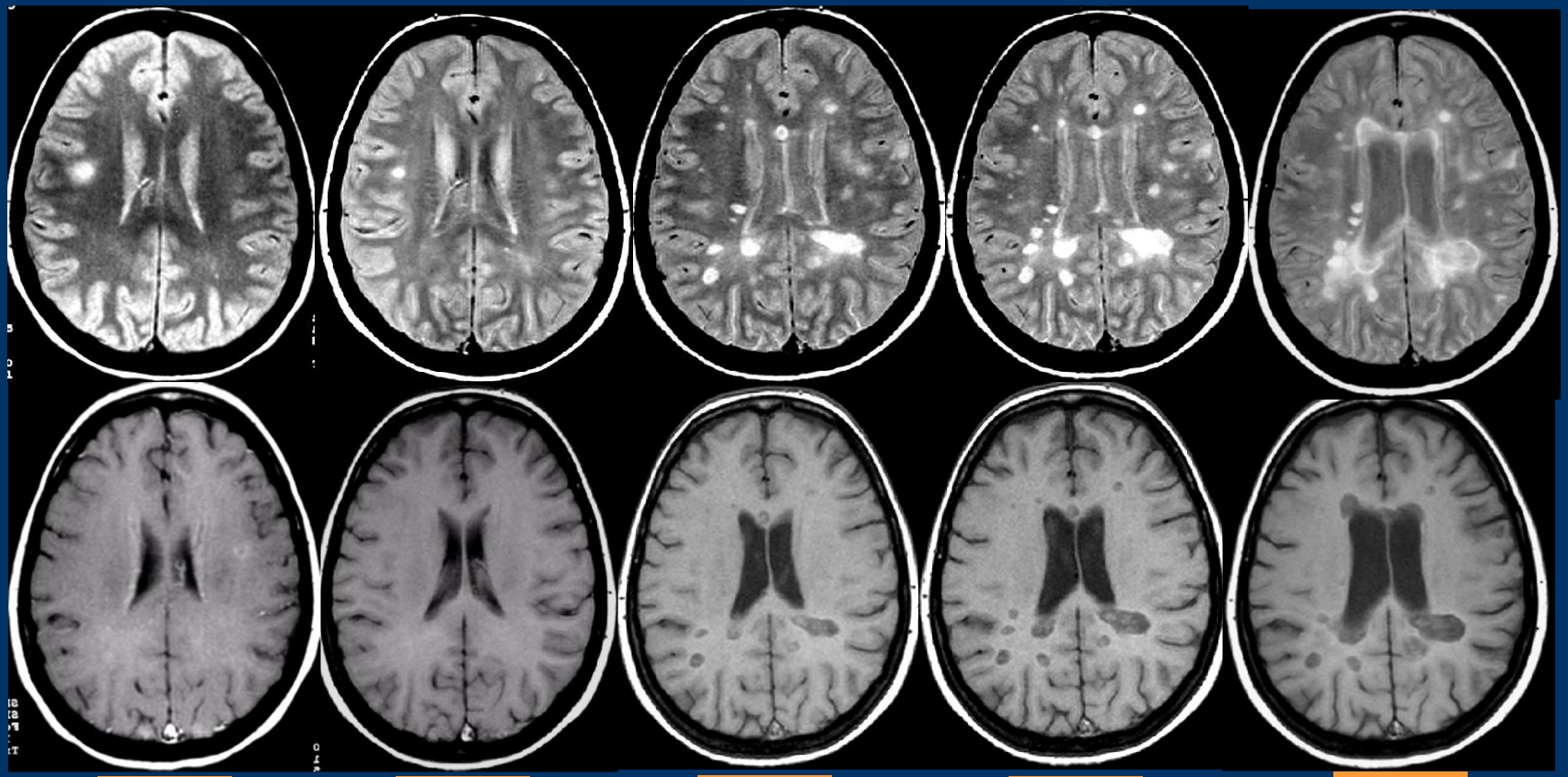




Postmortem MRI – axonal loss



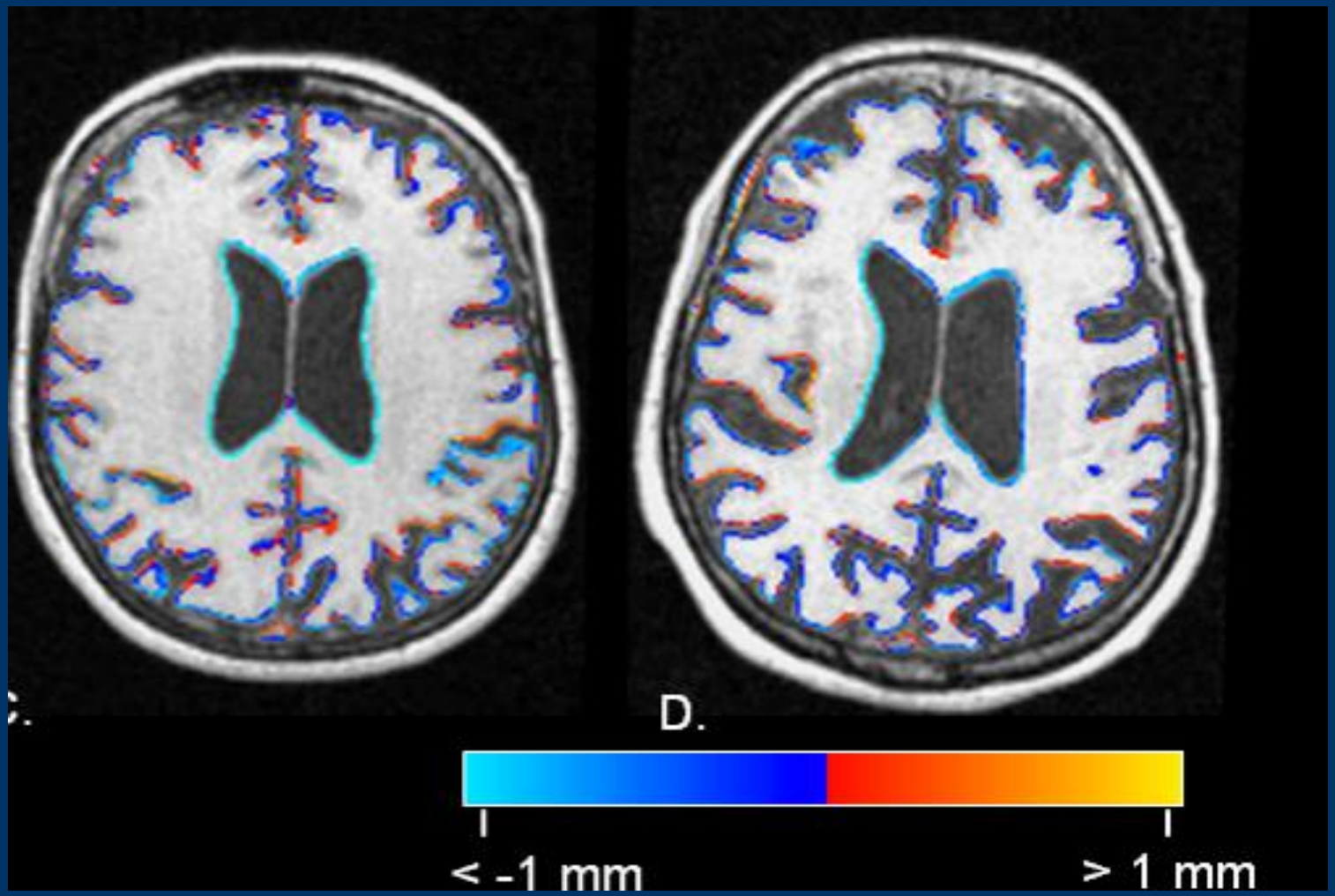
Imaging irreversible tissue damage



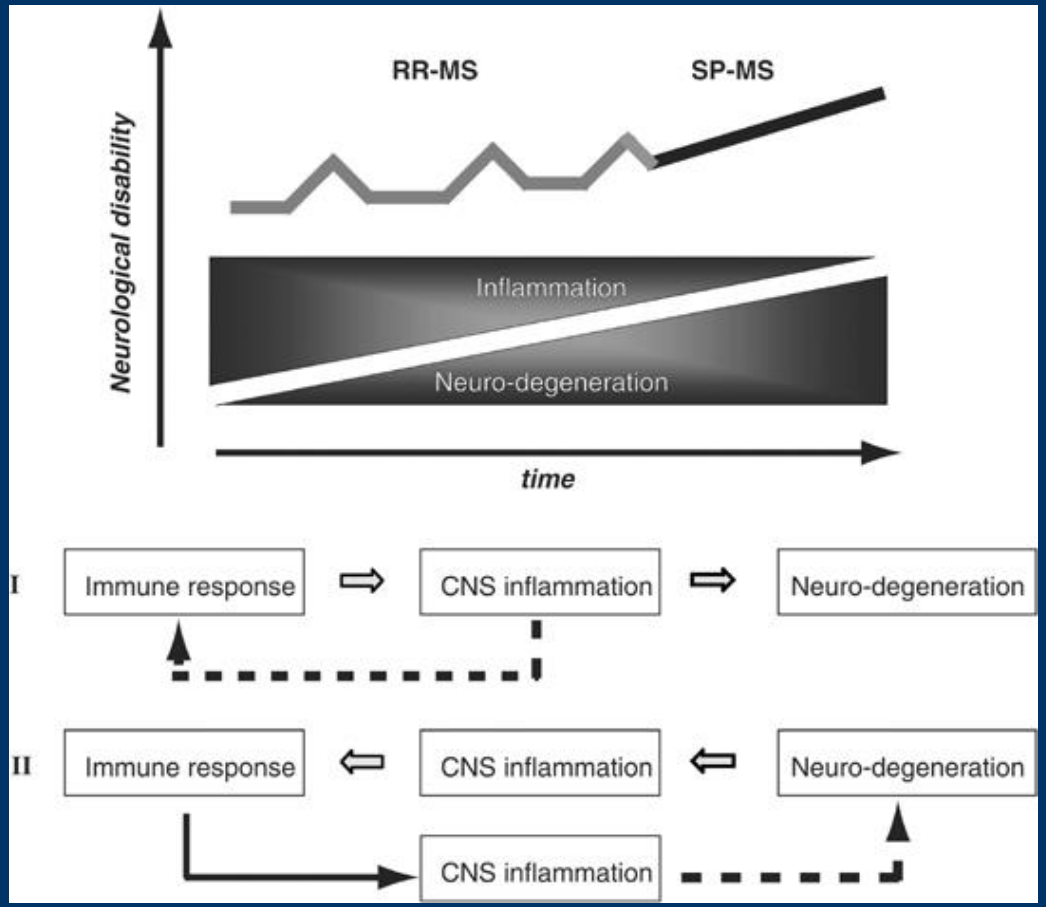
1995 1997 2002 2003 2005

courtesy of Alex Rovira, Barcelona

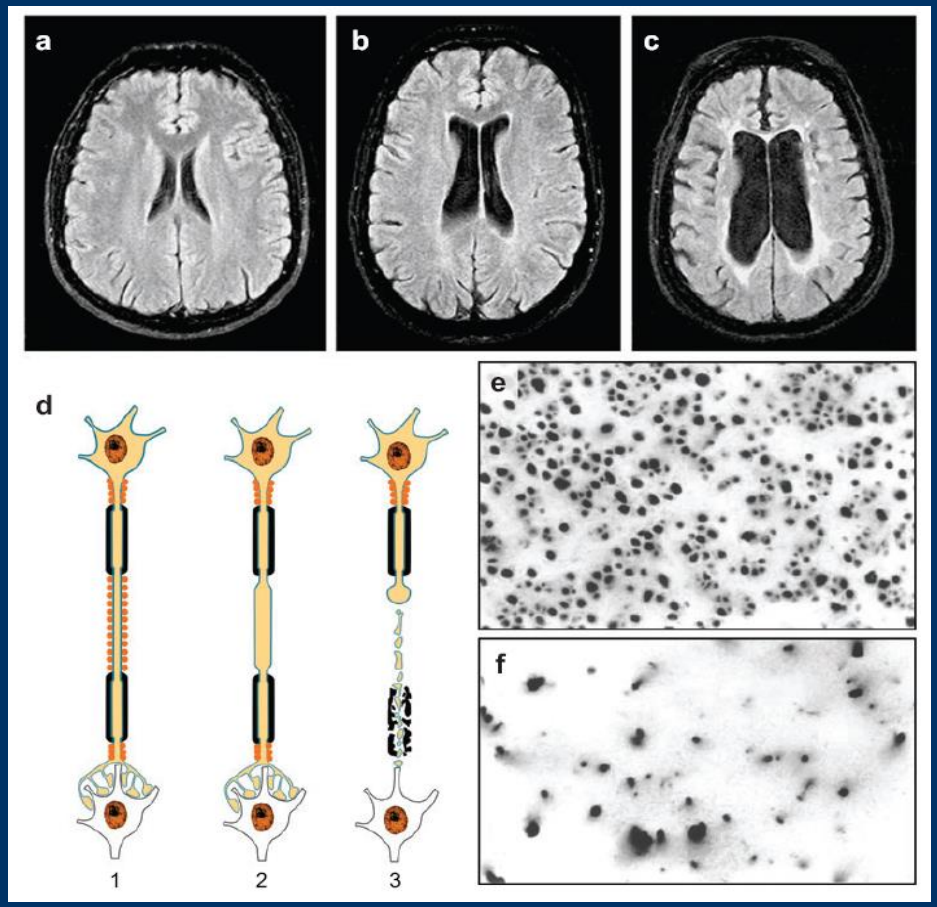
Atrophy measurement - SIENA



Neurodegeneration – when and why?

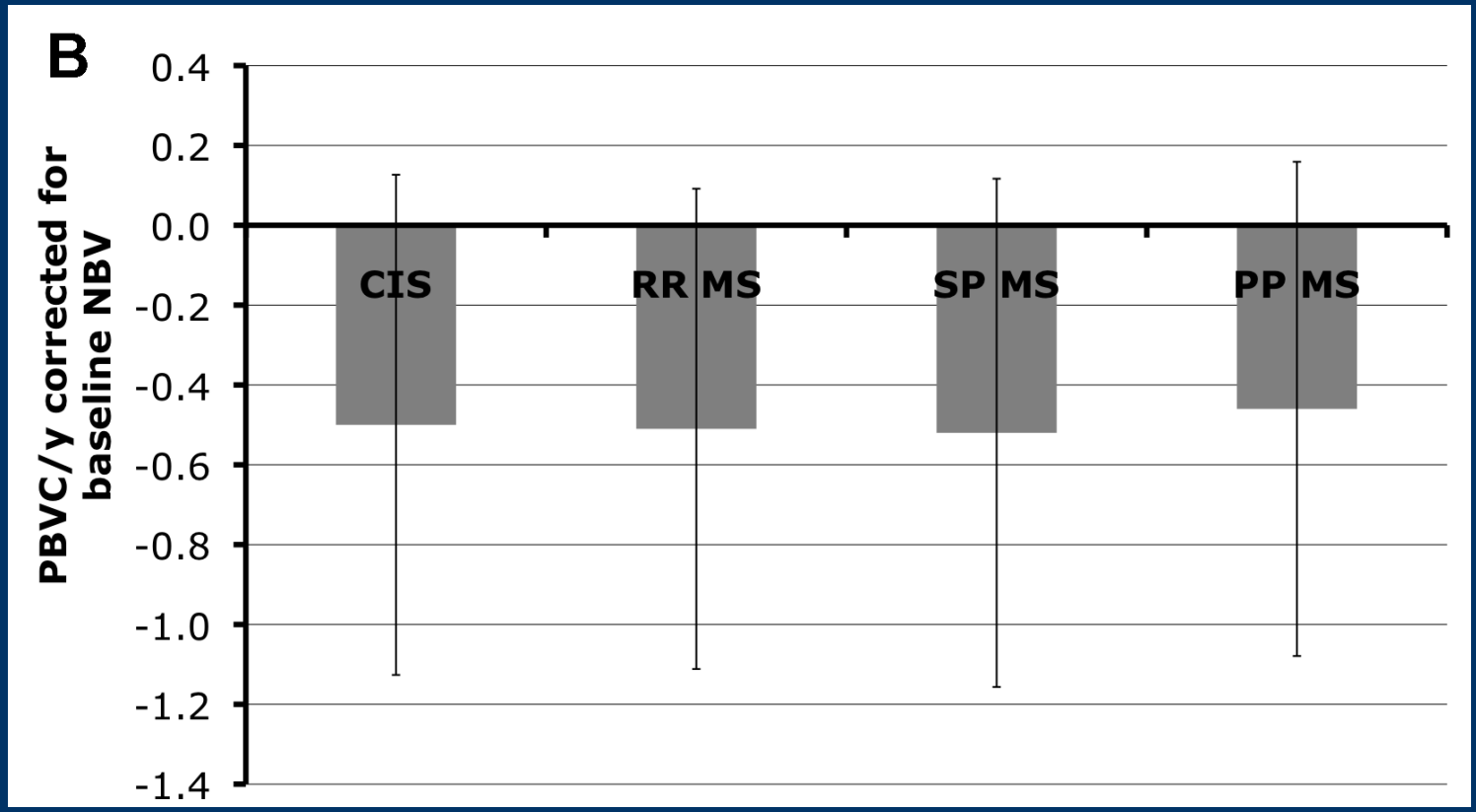


Oksenberg & Barcellos
Genes Immun. 2005



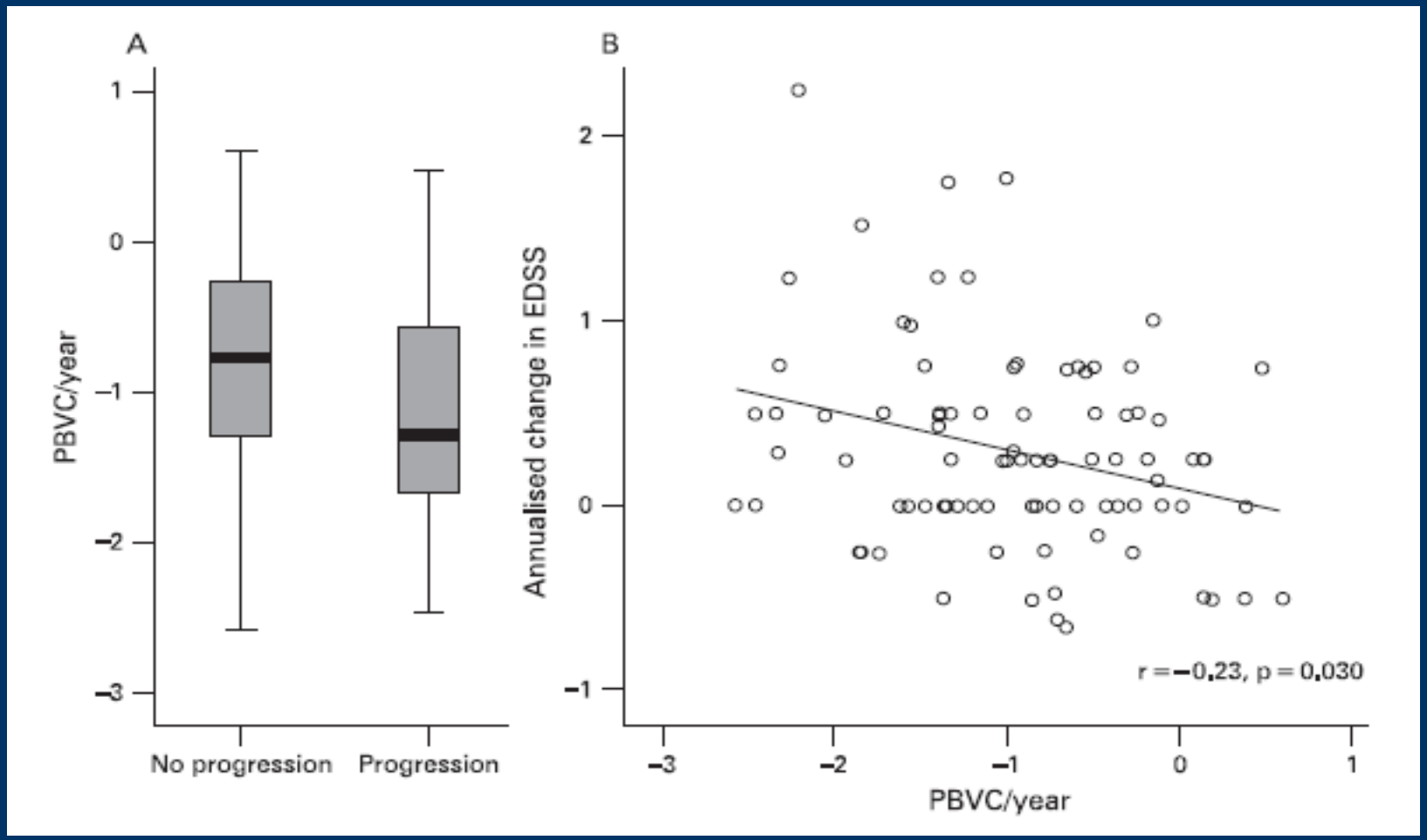
Trapp & Nave
Ann Rev Neurosci 2008

Neurodegeneration – early & profound



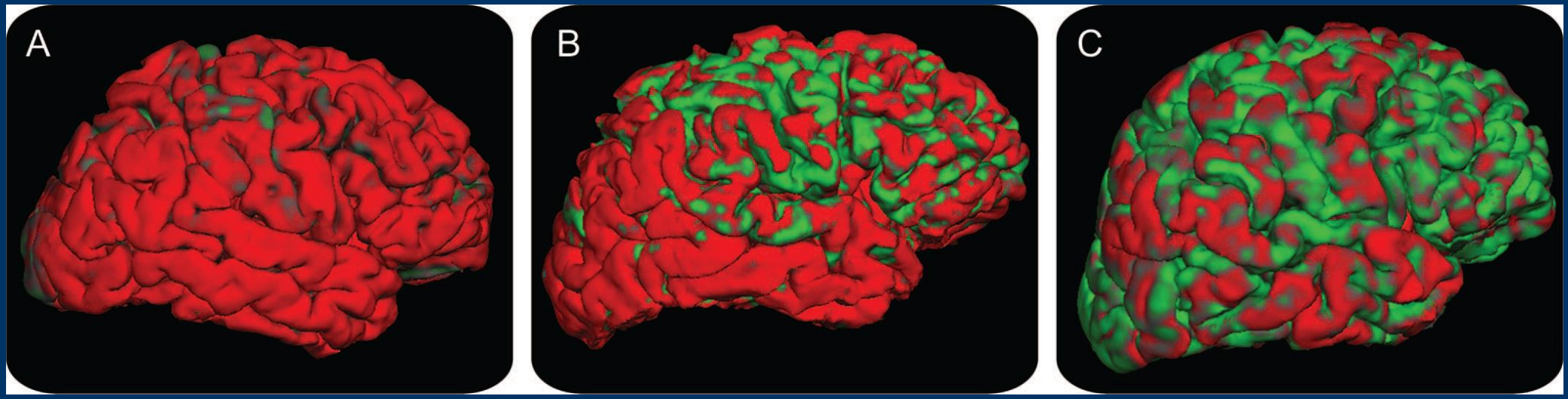
De Stefano, MAGNIMS study group, Neurology 2010

Prognostic value of MRI – atrophy



Minneboo JNNP 2008

Cortical thickness in MS



35-y male control
mean CTh 2.53

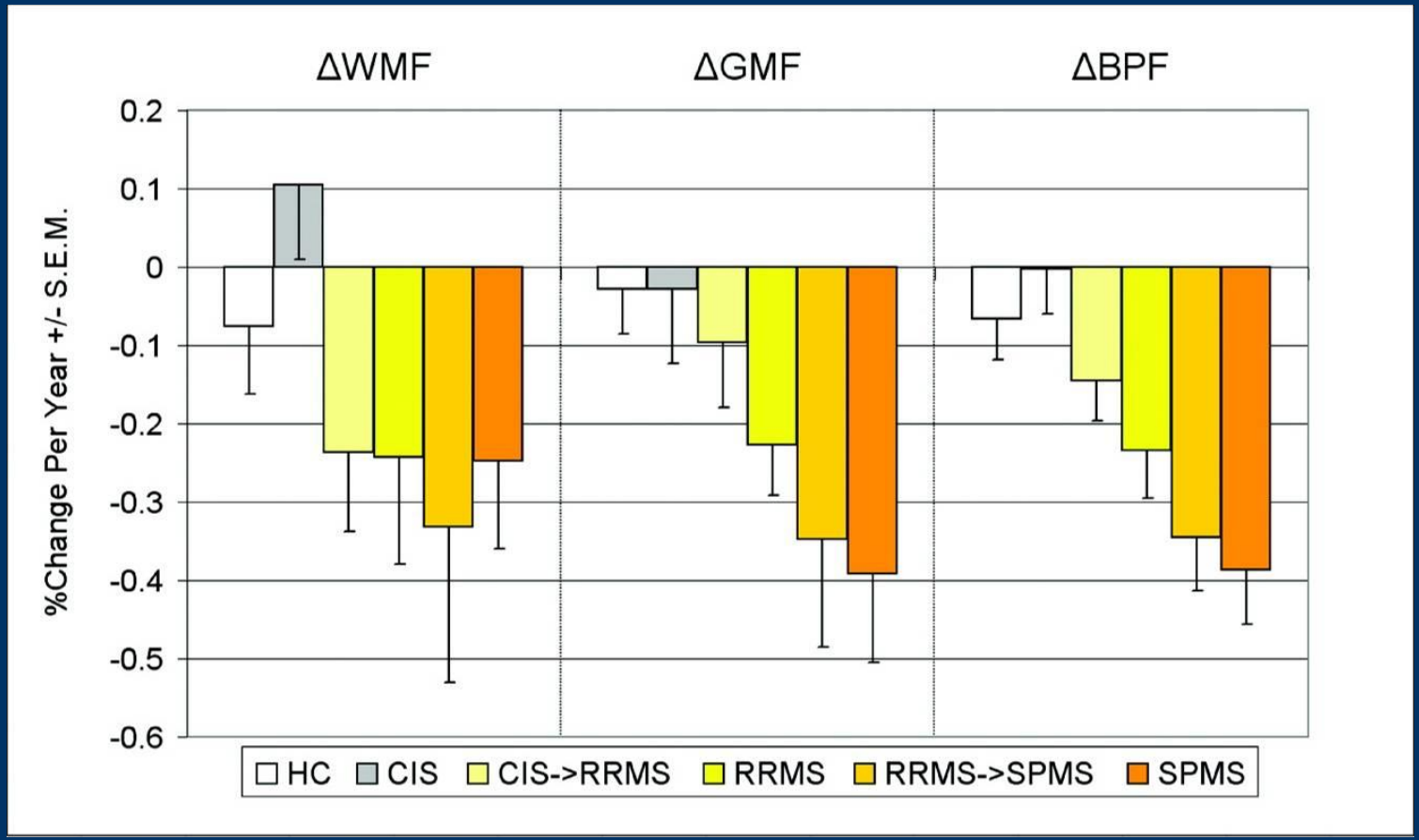
36-y CN-RRMS
mean CTh 2.32

34-y MCI-RRMS
mean CTh 2.05

http://surfer.nmr.mgh.harvard.edu/

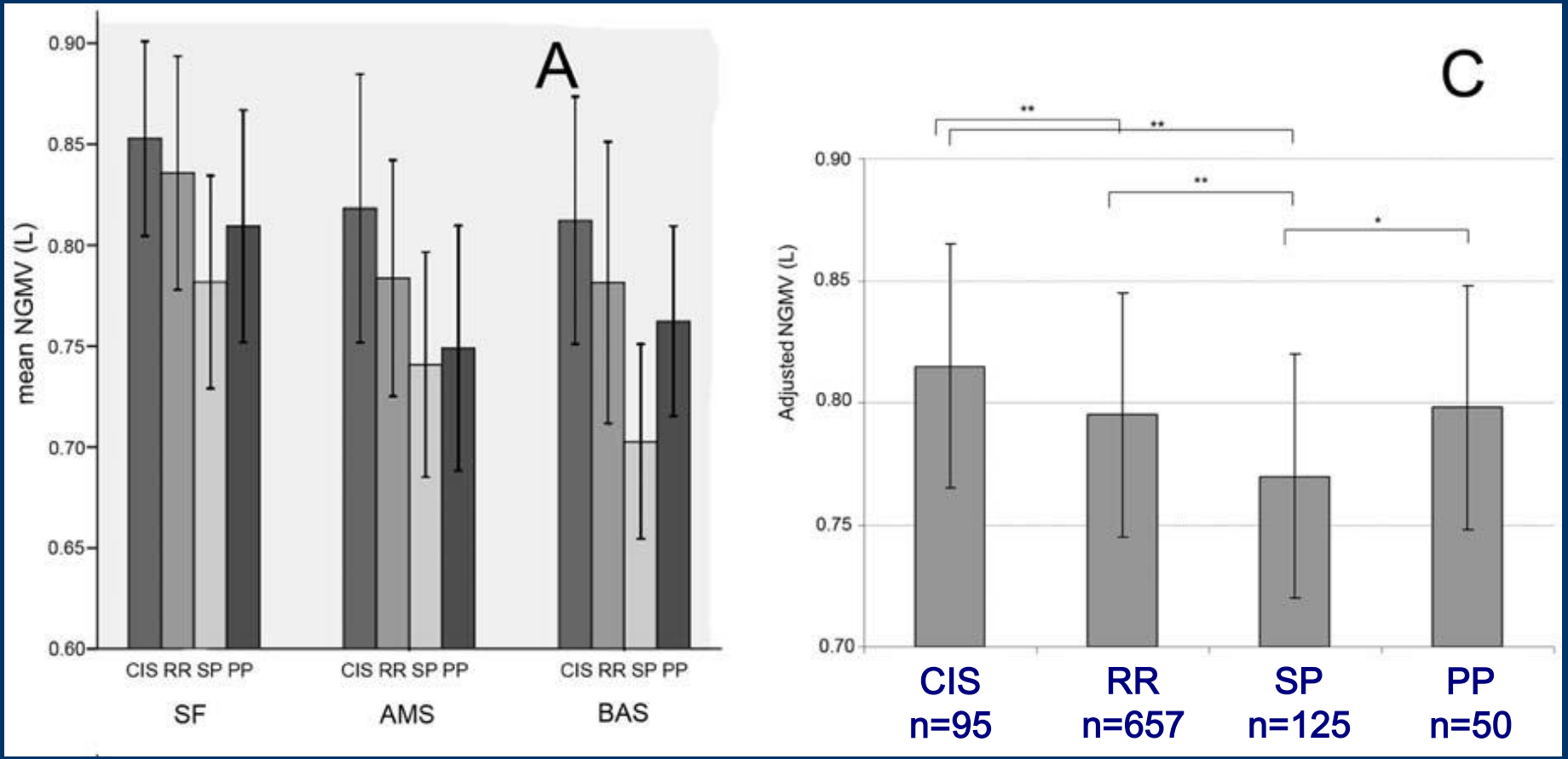
Calabrese M, Neurology 2010

GM atrophy – acceleration in SPMS



Fisher E. Ann Neurol 2008

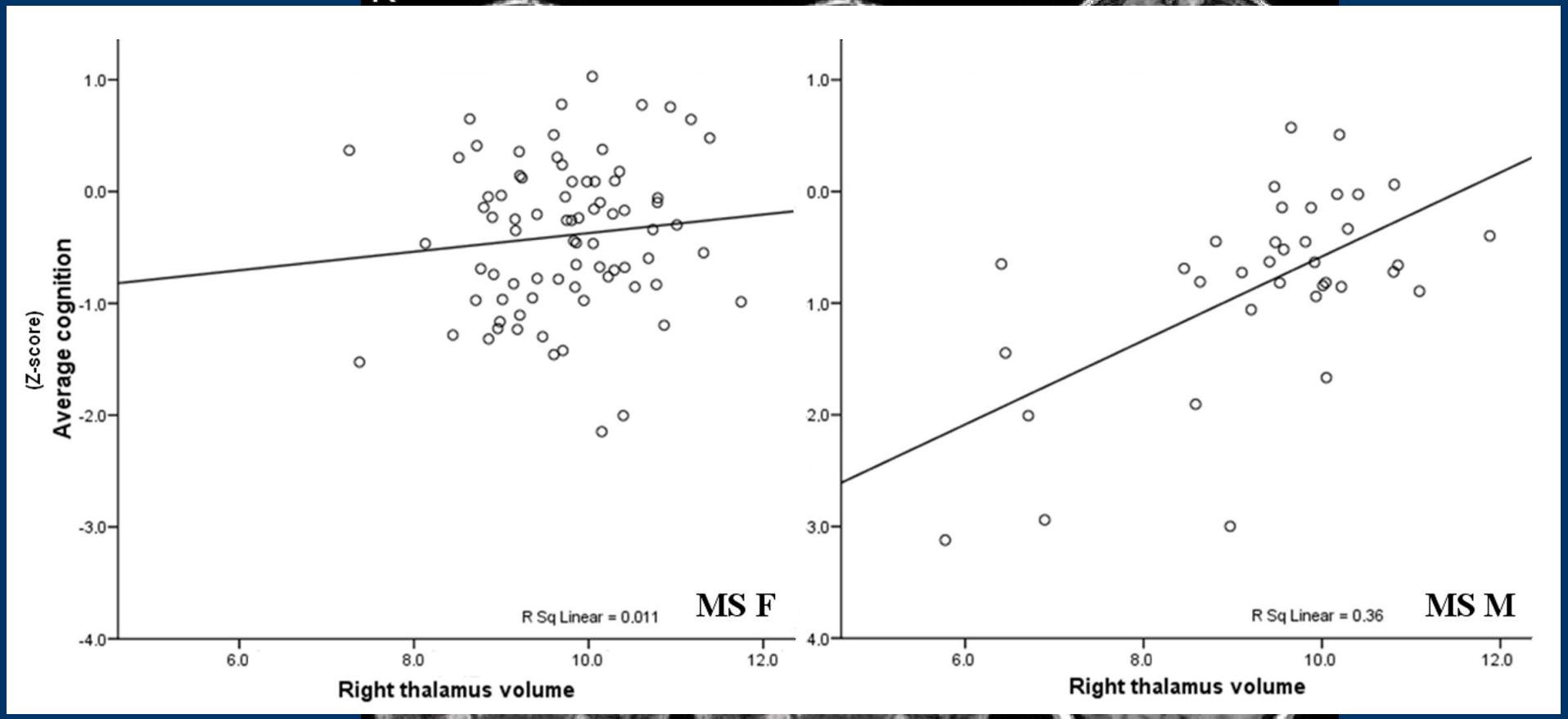
GM atrophy – more marked in SPMS



GM atrophy best MRI predictor of both EDSS and PASAT

Roosendaal SD, MSJ 2012

Thalamic atrophy in male MS

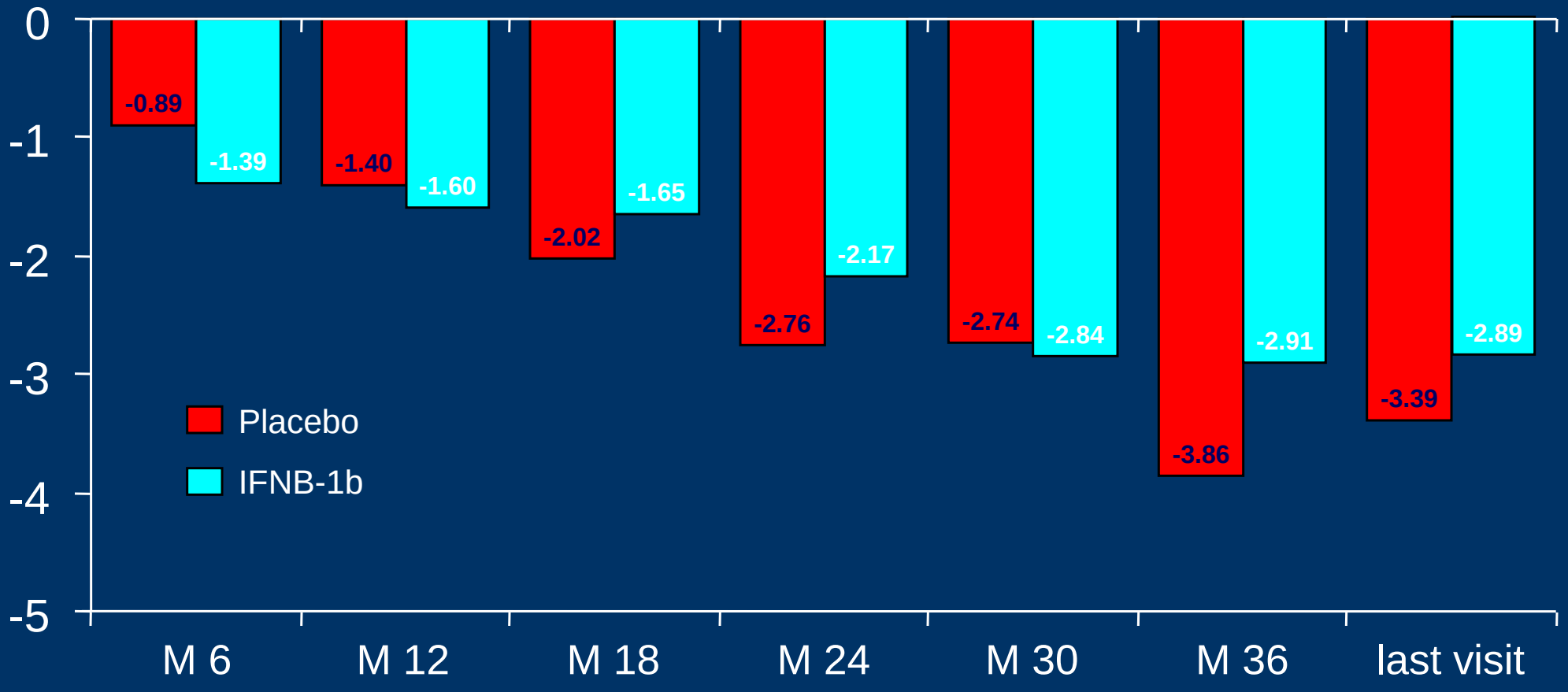


Schoonheim M. Neurology 2012

Treatment - neuroprotection & repair

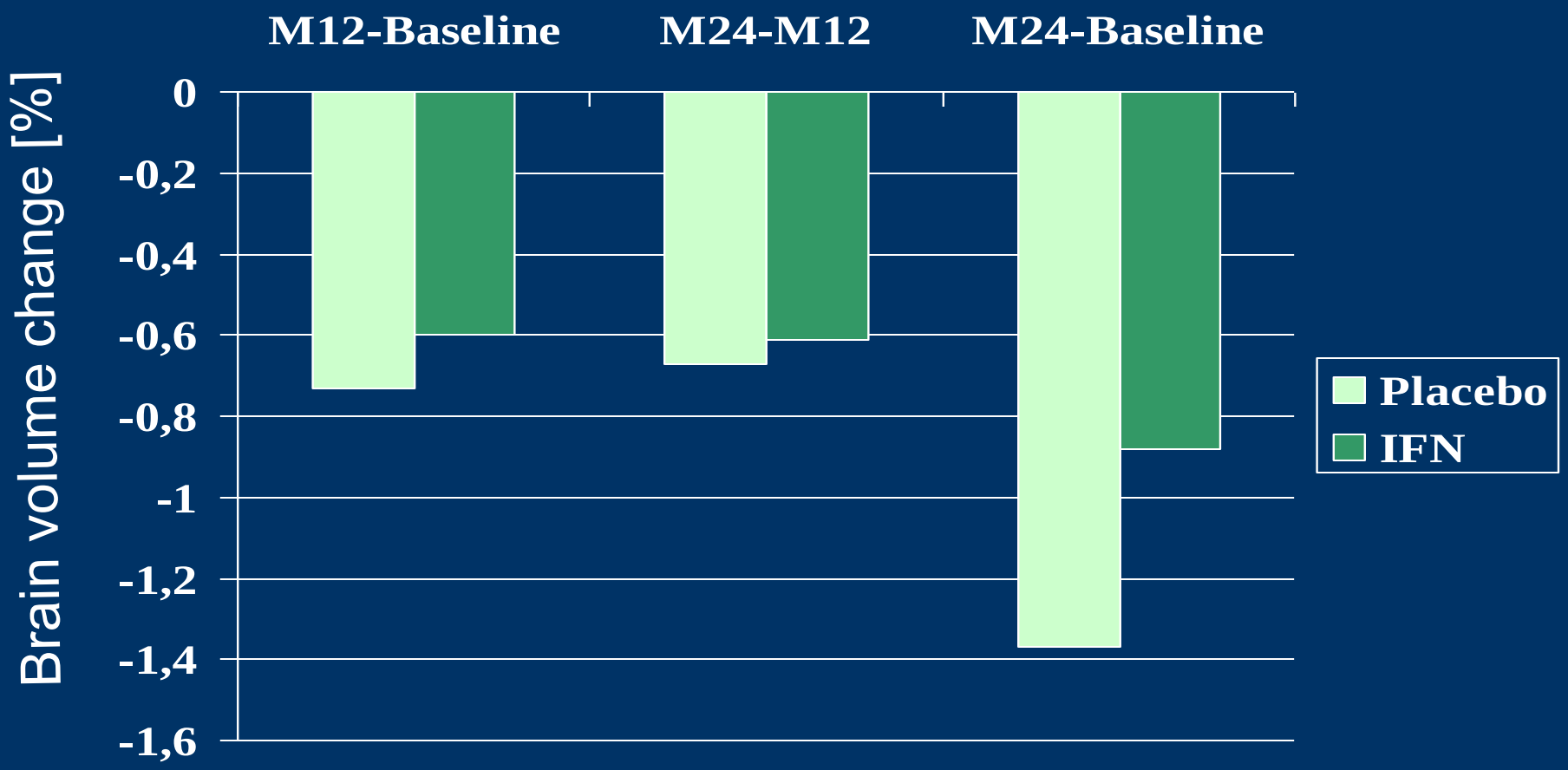
- GA, IFN, FTY, laquinimod – dual mode of action?
- Glutamate antagonists (e.g. riluzole)
- Na-channel blockade (e.g. phenytoin, lamotrigine)
  - K/Ca channel blockage (e.g. 4-AP)
- Cannaboid-receptor agonists
- Statins (e.g. lovastatine)
- PDE-4 inhibitors (e.g. rolipram, ibidulast)
- Neurotrophic & gliotrophic factors (e.g. BNDF)
- Stem-cell transplantation

SP-MS: Cerebral volume (n=95)



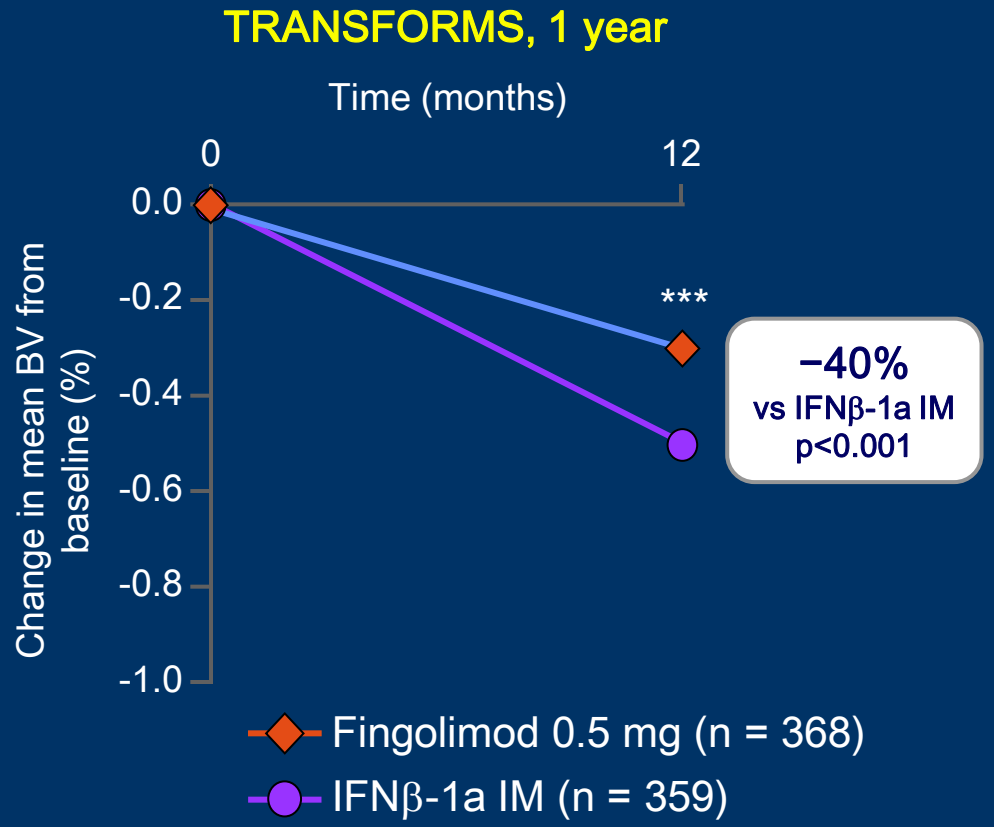
ETOMS/BRAIN ATROPHY

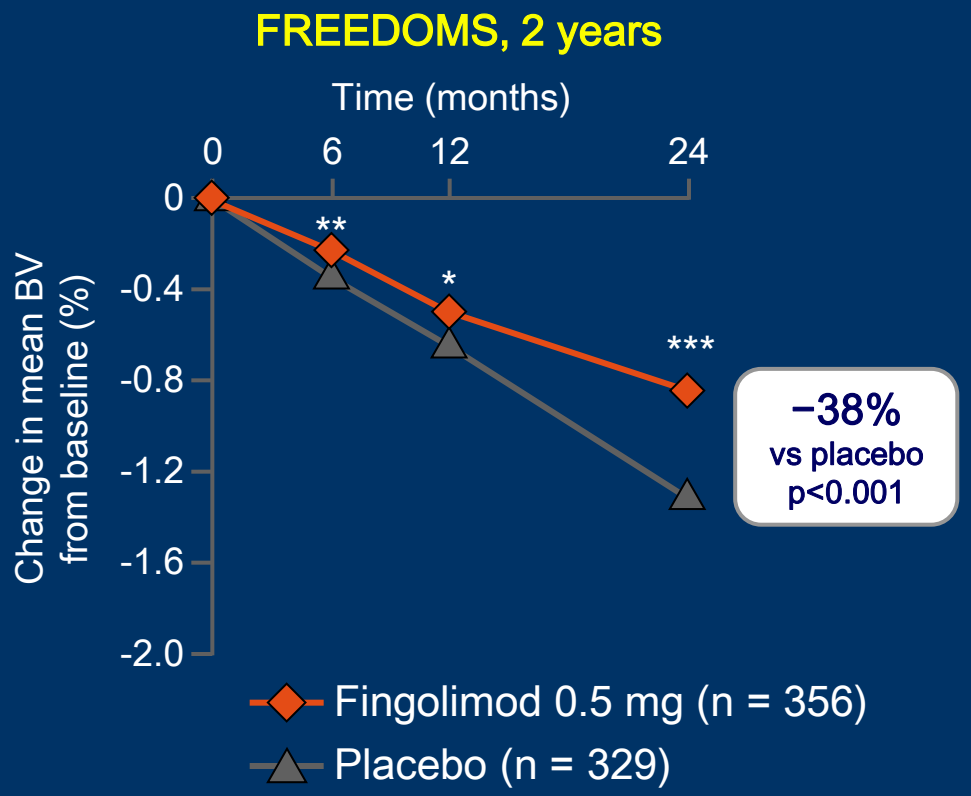
Treatment effect



Filippi M, *Lancet* 2004;364:1489

Brain Volume – fingolimod phase 3

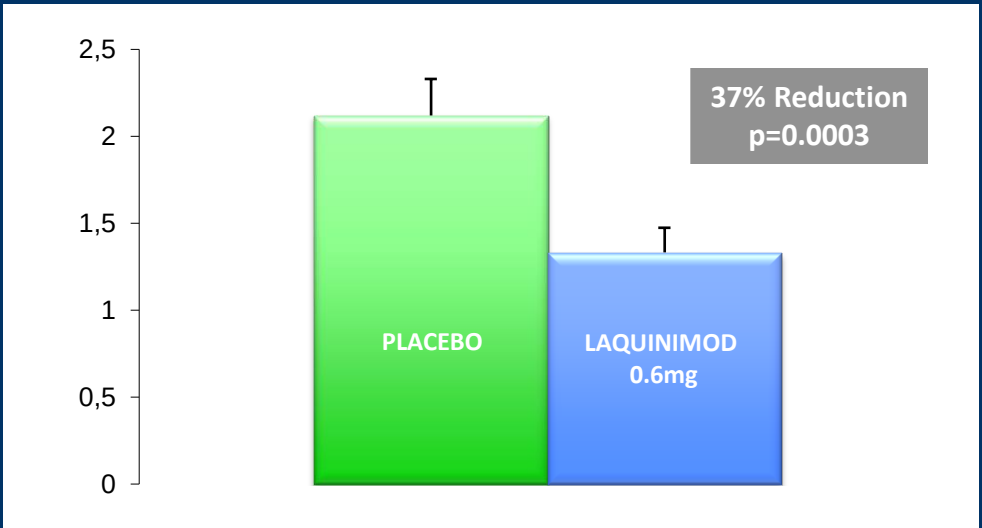




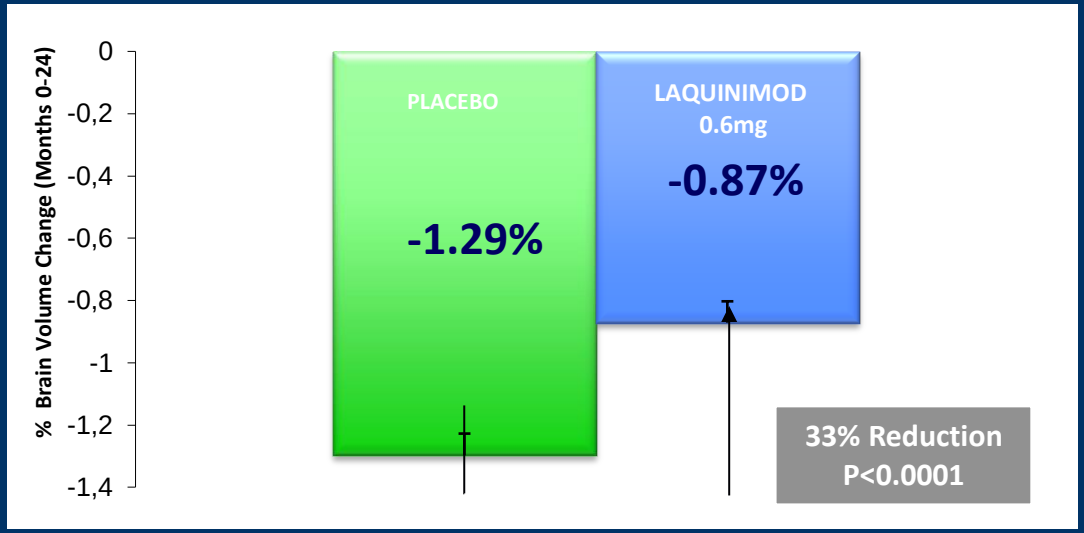
ITT population with evaluable MRI images. Note: n numbers for FREEDOMS data reflect the number of patients with available data at 24 months. *p<0.05; **p<0.01; ***p<0.001 vs comparator; p-values are for comparisons over Months 0-6, Months 0-12, Months 0-24 BV, brain volume; ITT, intent-to-treat. Gilenya™ Prescribing Information 19 April 2012. Reproduced with permission. Kappos L *et al. N Engl J Med* 2010; 362: 387-401, and Cohen JA *et al. N Engl J Med* 2010; 362: 402-415. Copyright © 2011 Massachusetts Medical Society. All rights reserved

Phase III ALLEGRO – Laquinimod 0.6mg

Cumulative Gd-T1 lesions
(months 12 & 24)

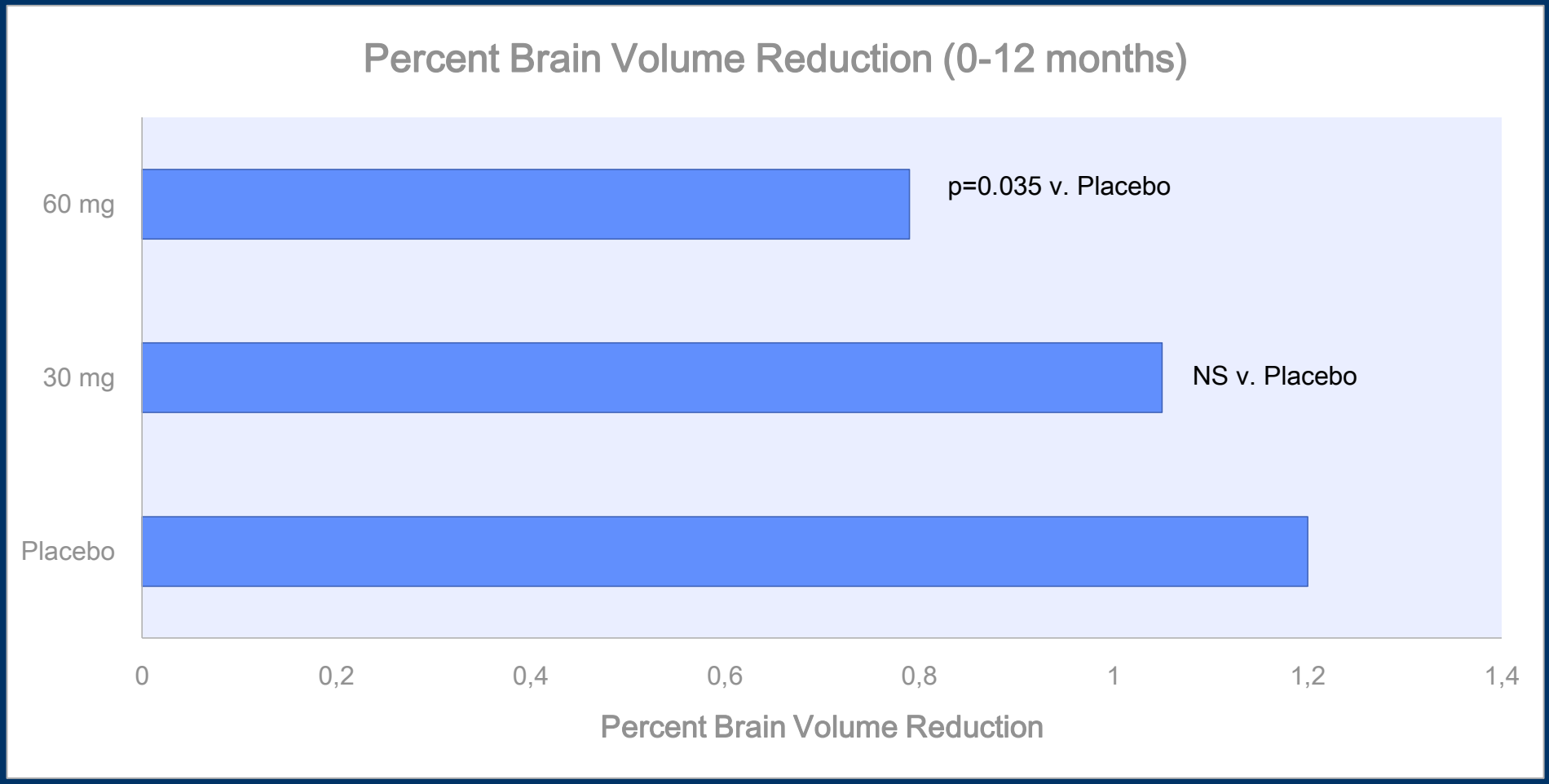


% Brain Volume Change
(baseline to month 24)



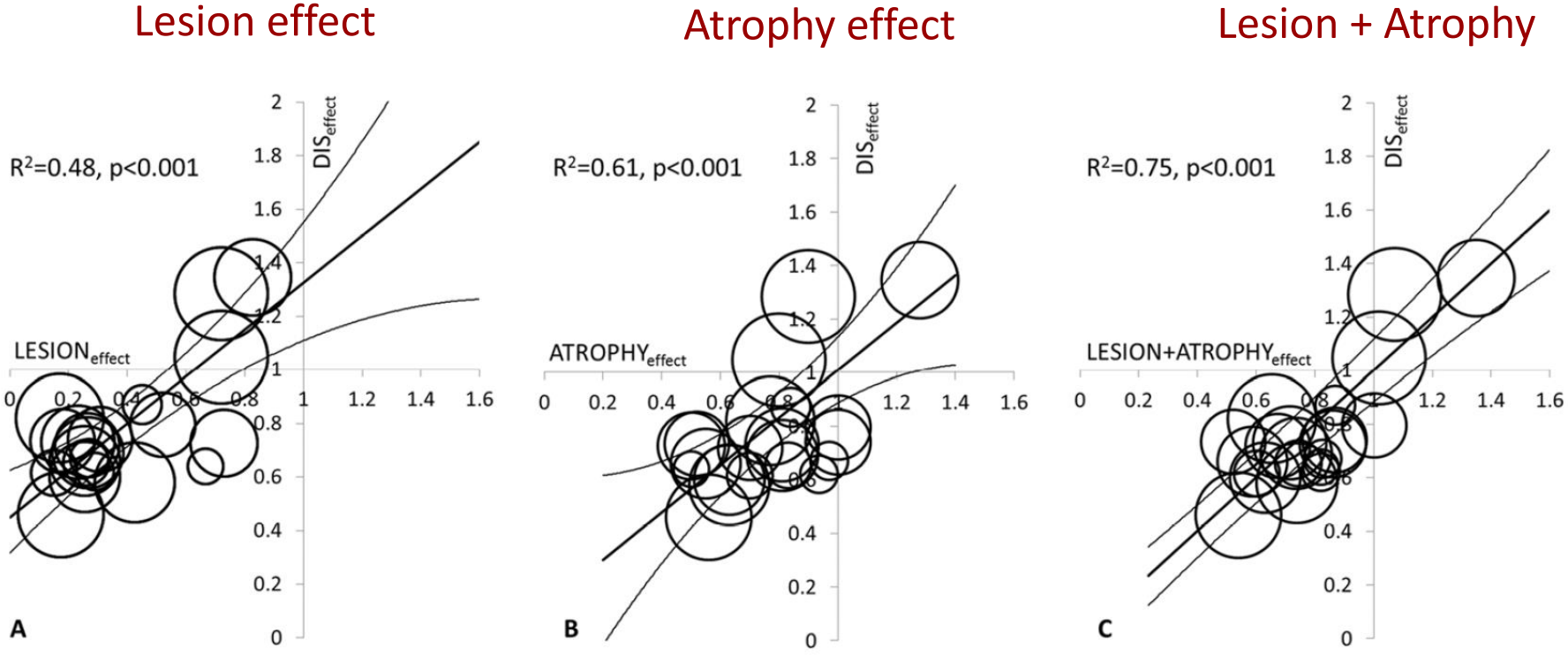
Comi G. et al. Oral laquinimod reduced relapse rate and delayed progression of disability in Allegro, a placebo-controlled phase III trial for RRMS. Presented at the Late-Breaking Science Session of the 63rd Annual Meeting of the American Academy of Neurology; April 9-16, 2011; Honolulu, HI

Ibudilast – neuroprotective?



Barkhof F, Neurology 2010

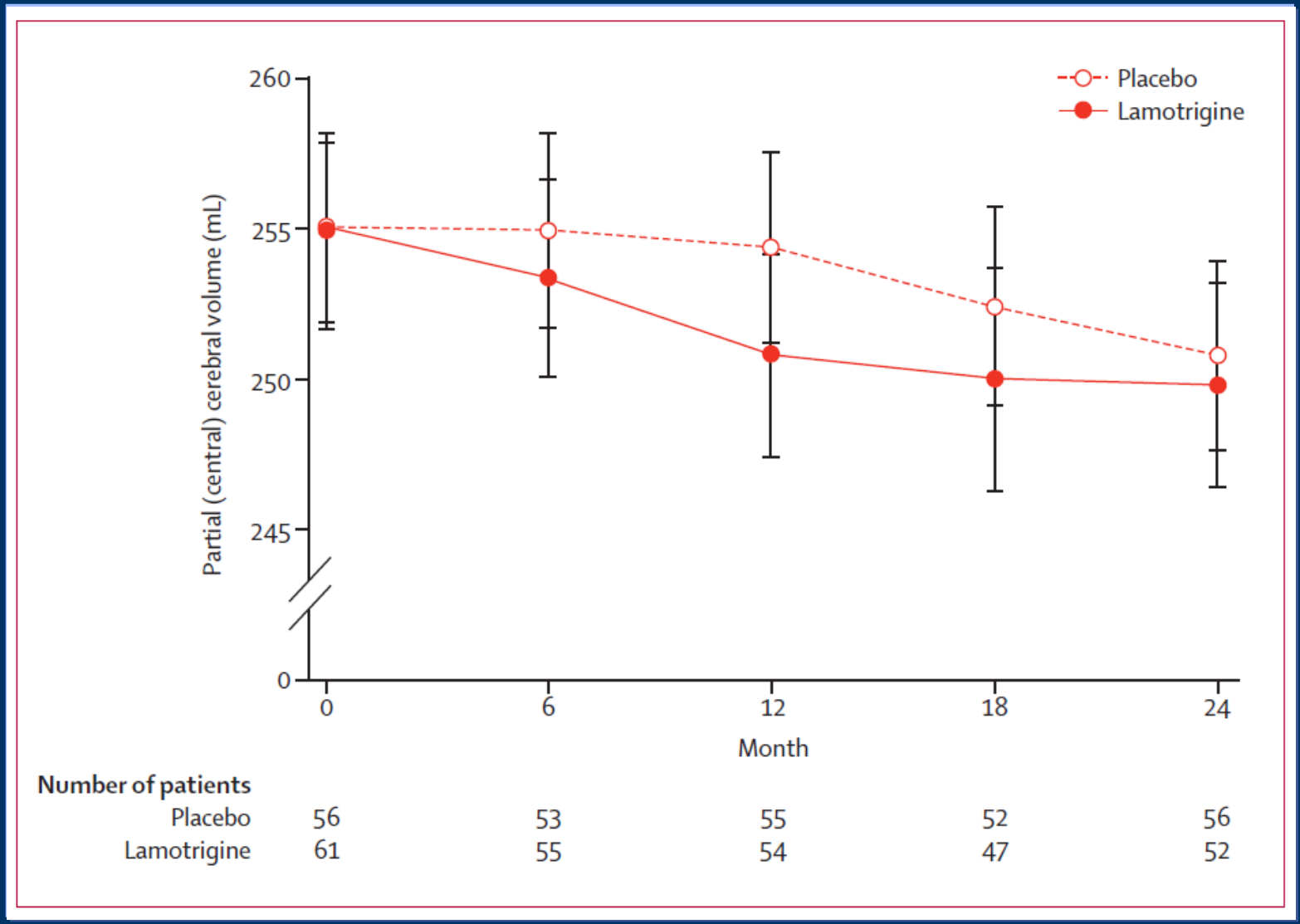
Rx effect on atrophy predicts disability



meta-analysis of 13 trials with >13500 RRMS patients

Sormani et al. Ann Neurol 2013

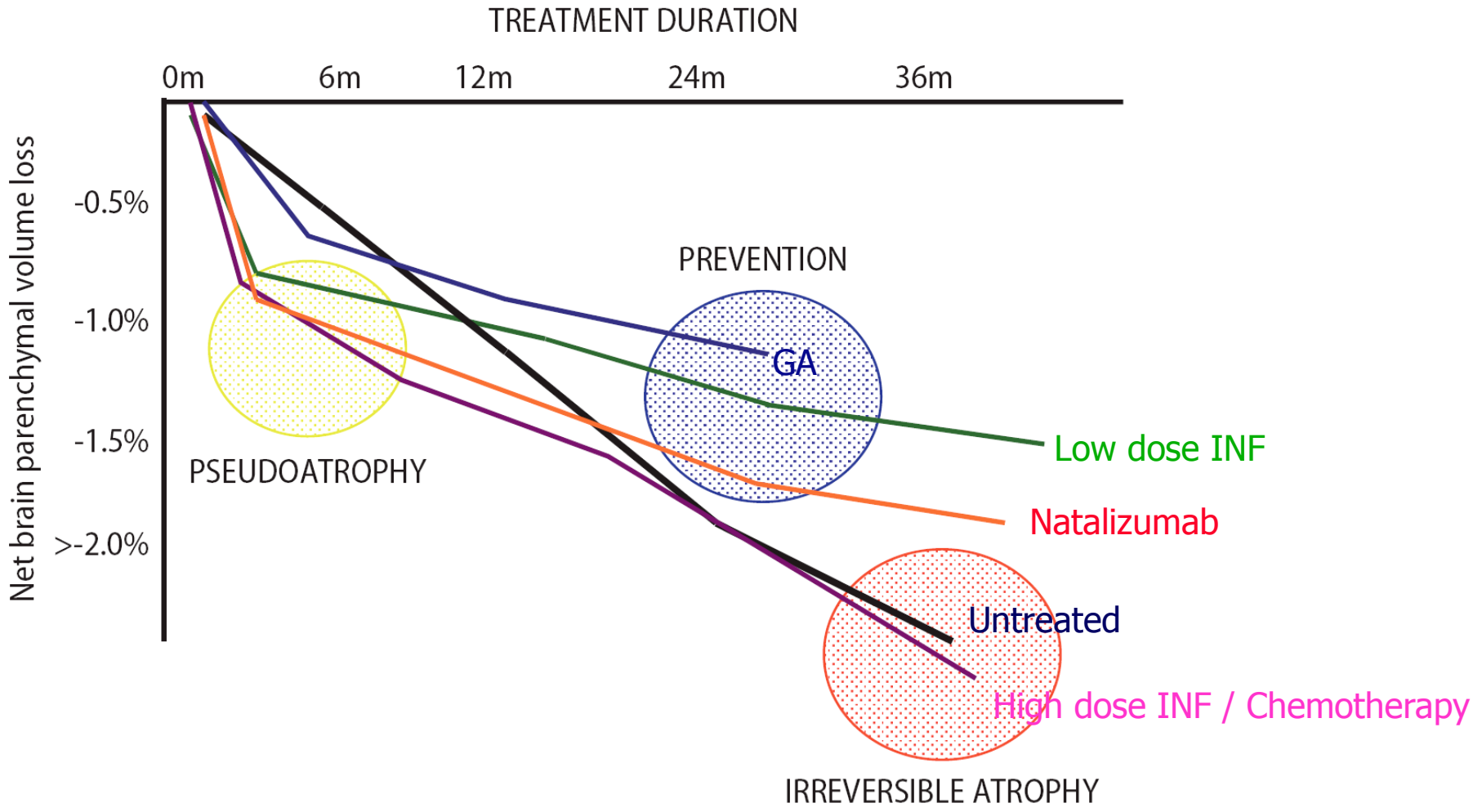
Pseudoatrophy - lamotrigine



Number of patients					
Placebo	56	53	55	52	56
Lamotrigine	61	55	54	47	52

Kapoor R. Lancet Neurol 2010

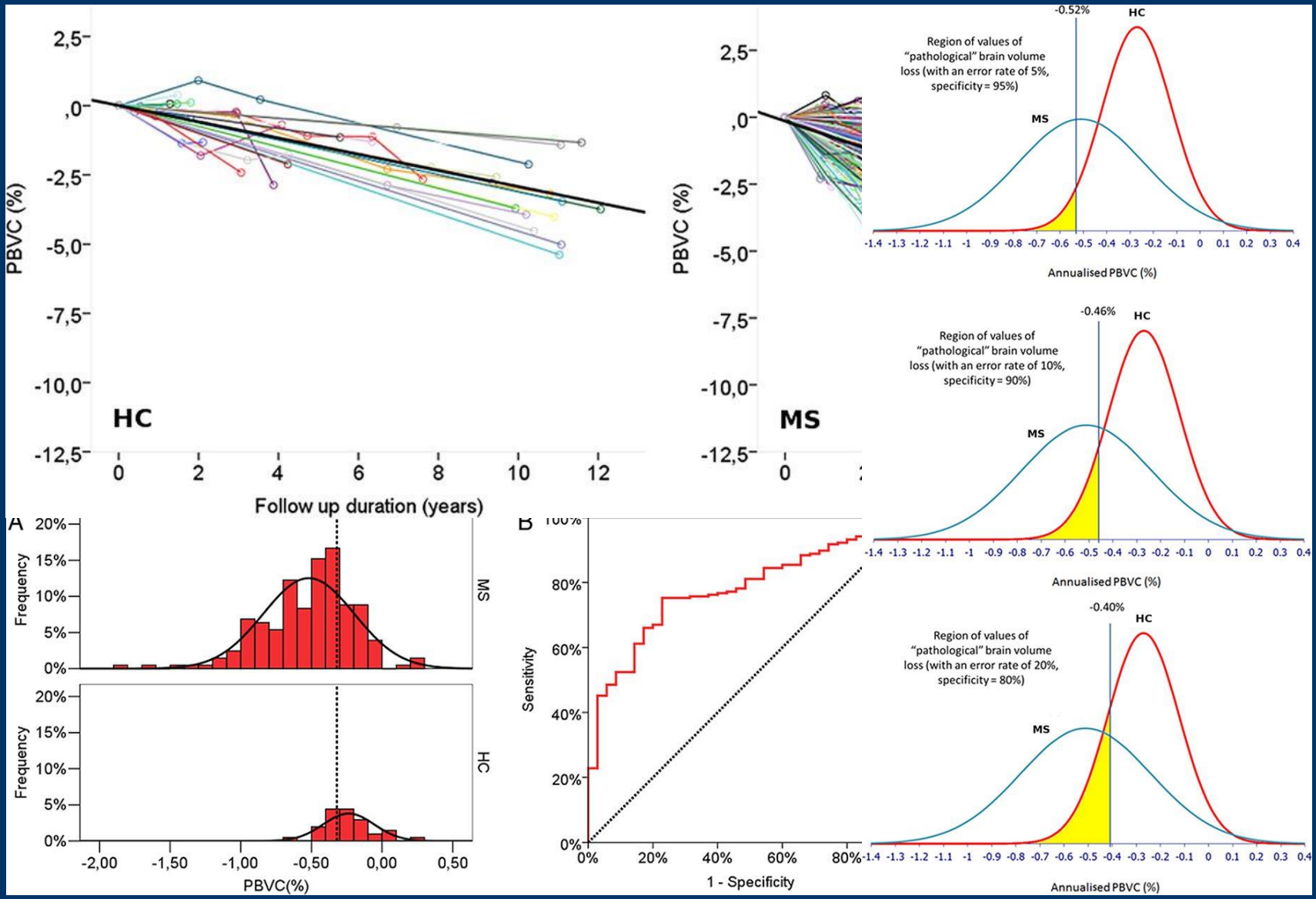
Effect of Treatment on brain atrophy in MS



Zivadinov et al. *J Neurol 2008*

BV: single-subject application?

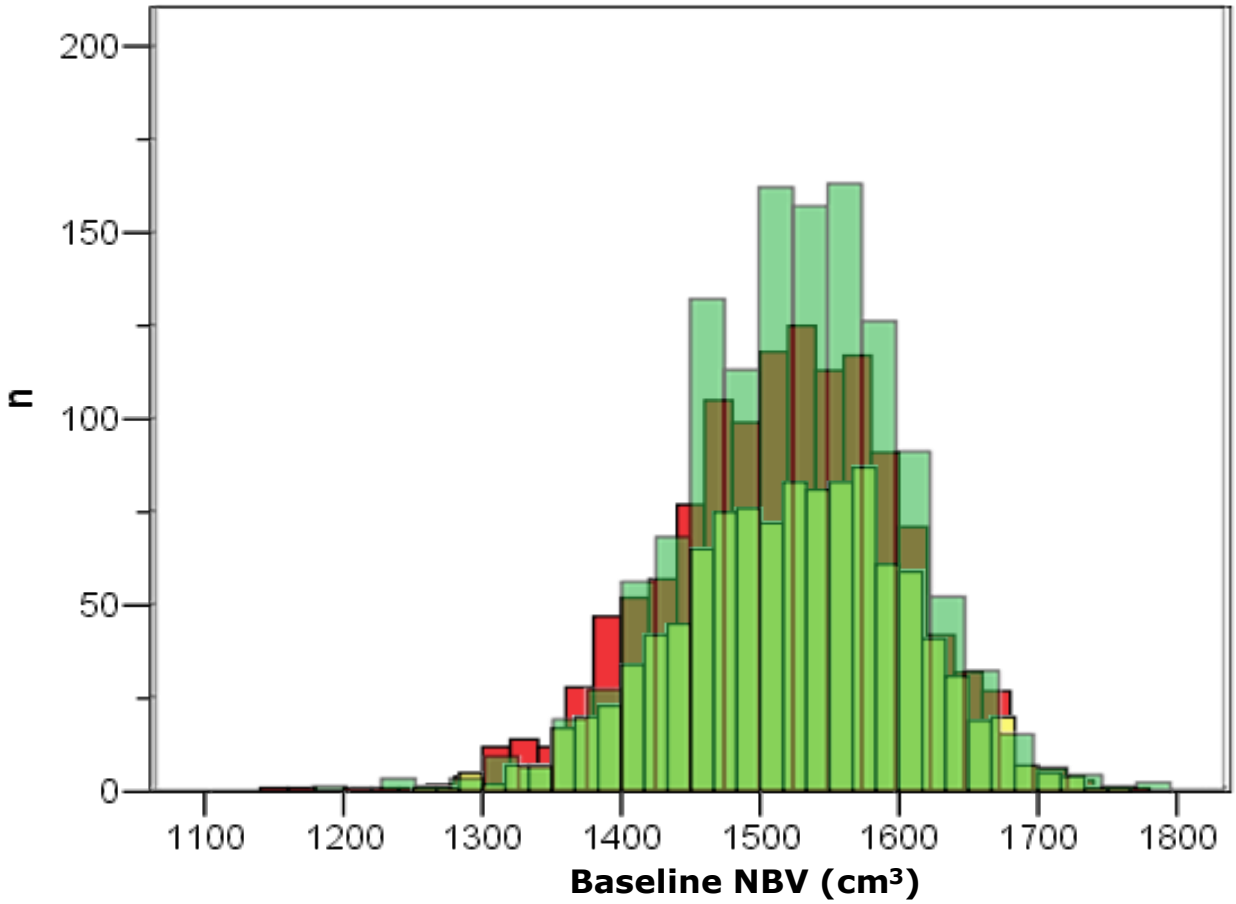
- Whole brain atrophy best studied
  - SIENA(X), FreeSurfer, MSmetrics, etc.
  - requires off-line processing
- Neuroprotection difficult to measure
  - technical variability (scanner, algorithm)
  - single-subject variablity (diurnal, drugs)
  - thresholds needed: work Sormani



de Stefano, JNNP 2015

Fingolimod Phase 3 studies – NBV data distribution

3592 patients with complete baseline data (NBV)



FREEDOMS:
mean NBV=1514 cm^3 (SD=85 cm^3)

FREEDOMS II:
mean NBV=1521 cm^3 (SD=83 cm^3)

TRANSFORMS:
mean NBV=1525 cm^3 (SD=79 cm^3)

NBV=Normalized Brain Volume

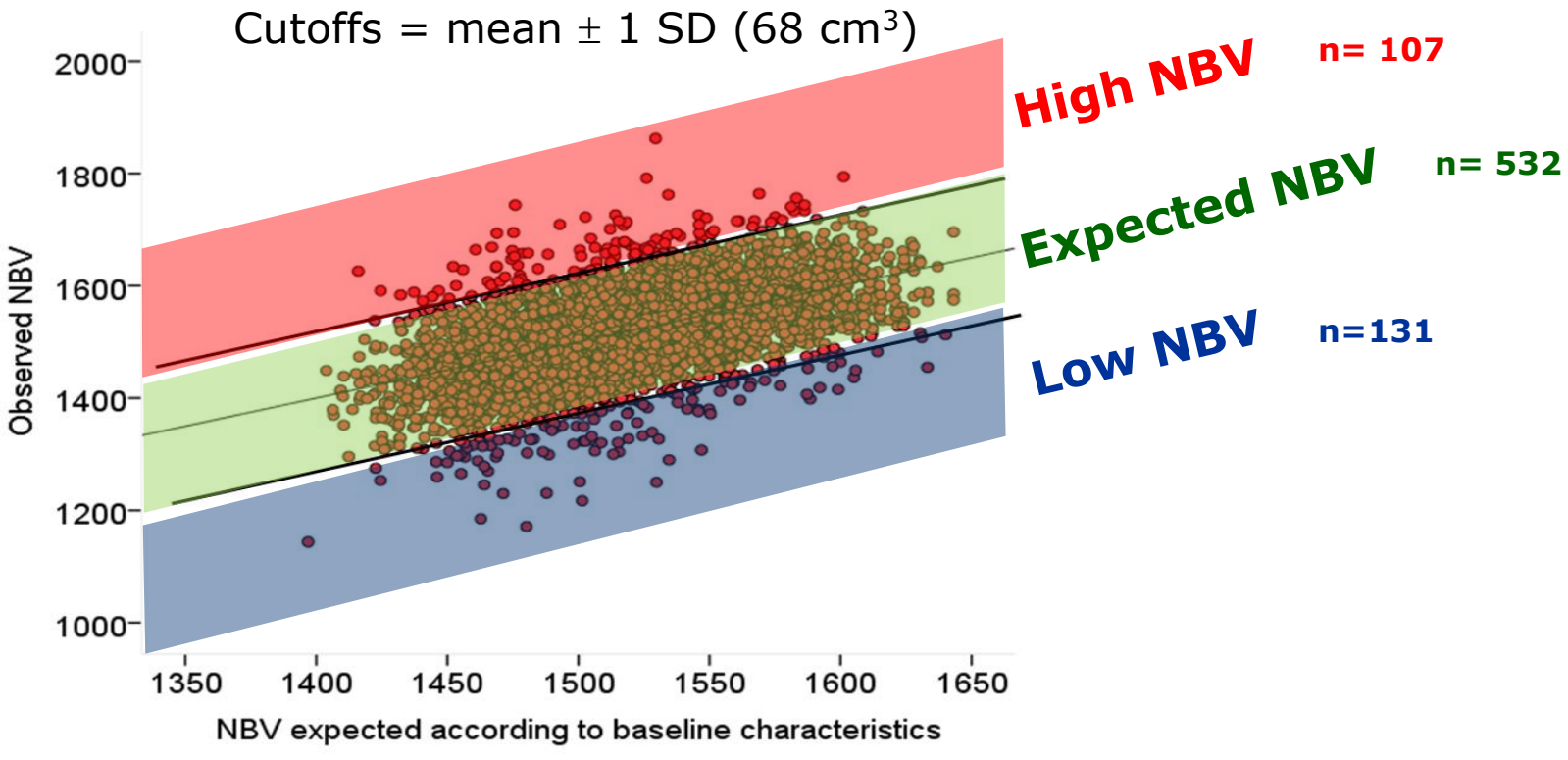
Predictors of NBV - multiple regression model

Baseline characteristics	Unit	Coefficient (cm^3)	P-value
T2LV	Tertiles steps	-31	<0.001
Age	1 year	-3	<0.001
EDSS	1 point	-6.5	<0.001
MS duration	Tertiles steps	-10	<0.001
Sex	M vs F	-15	<0.001
Trials	FREEDOMS	ref	<0.001
	FREEDOMS II	+14	
	TRANSFORMS	+3	

A multiple regression model adjusted for relevant covariates was used to calculate the expected NBV according to baseline characteristics of the **pooled intent-to-treat** population from FREEDOMS, FREEDOMS II and TRANSFORMS.

T2LV= T2 Lesion Volume; EDSS: Expanded Disability Status Scale; NBV=Normalized Brain Volume

Definition of cutoffs for NBV



- For each patient the expected brain volume is calculated, according to his/her baseline characteristics (x-axis)

NBV distance from expected= NBV observed – NBV expected

NBV=Normalized Brain Volume SD= Standard Deviation

NBV cutoffs - Example

Patient 1

Age=20, EDSS=1, male, disease duration<5y, Low T2 lesion volume

Low NBV < 1548 cm^3
Medium NBV 1548 - 1684 cm^3
High NBV > 1684 cm^3

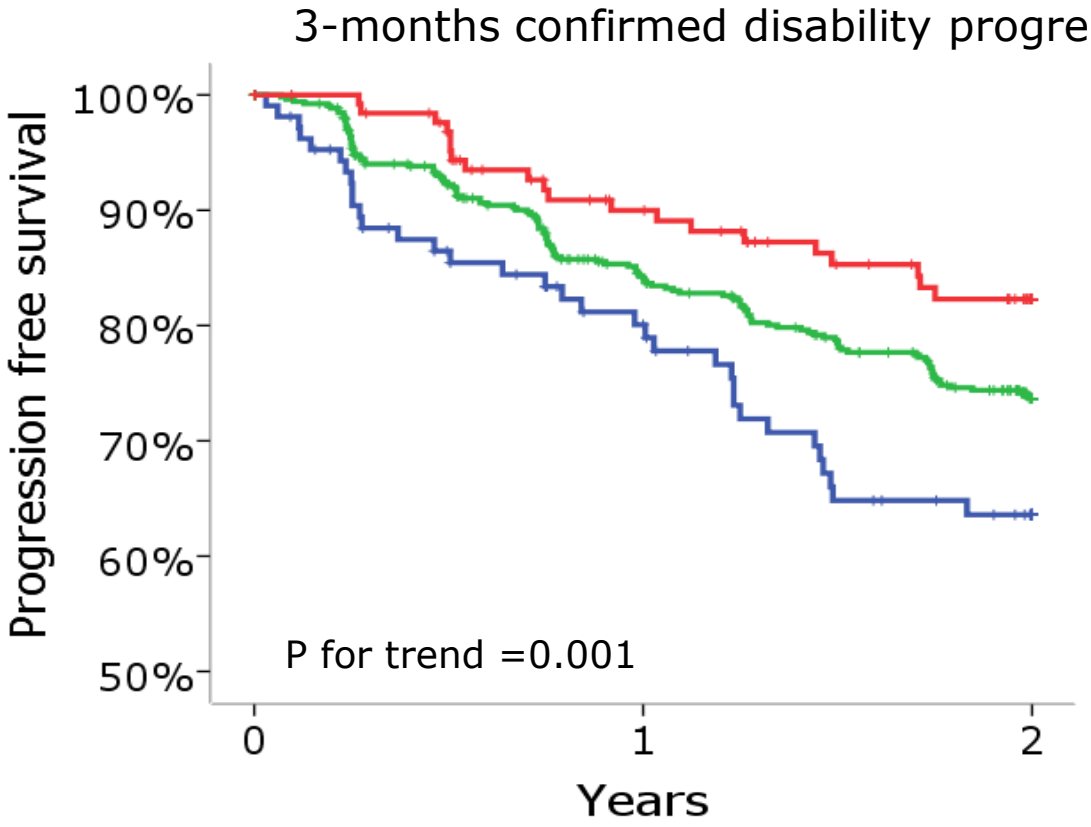
Patient 2

Age=60, EDSS=5, male, disease duration>20y, High T2 lesion volume

Low NBV < 1347 cm^3
Medium NBV 1347 - 1482 cm^3
High NBV > 1482 cm^3

Prognostic value of the NBV cutoffs

Pooled FREEDOMS and FREEDOMS II
placebo patients over 2 years (n=770)



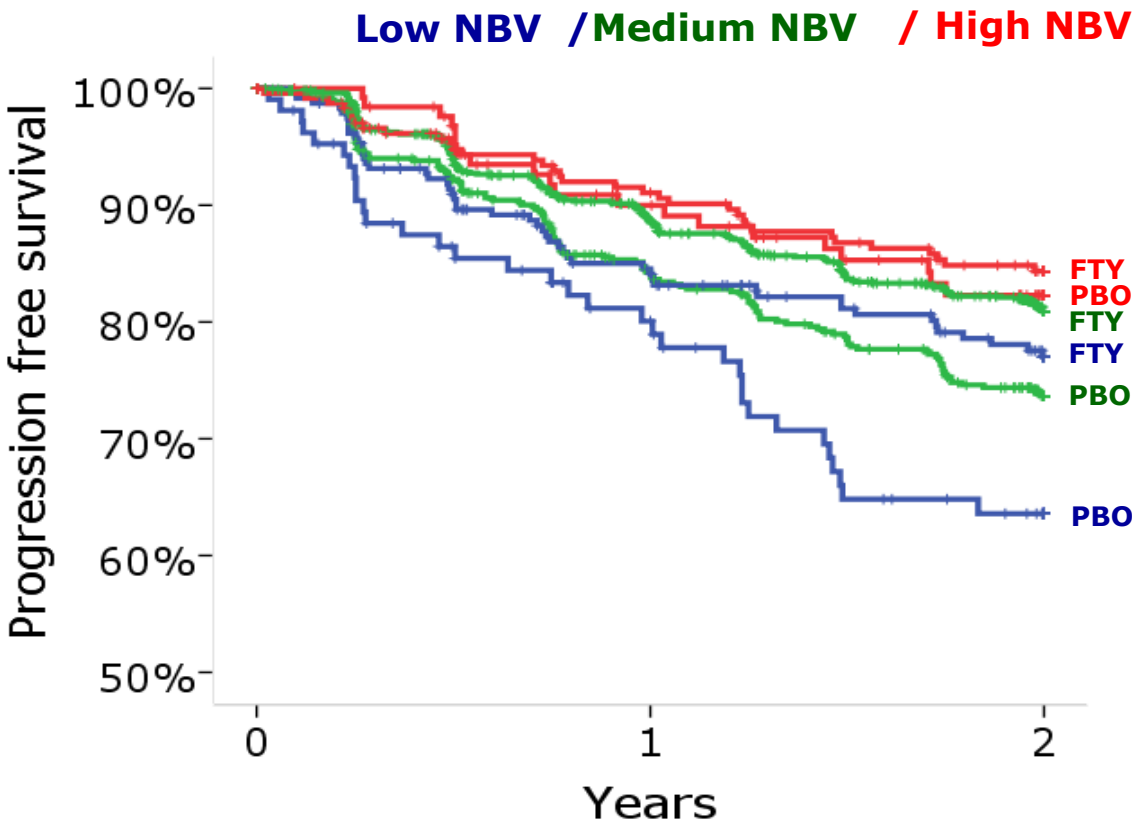
Cut-off	n	% Progression	HR
High NBV	131	18%	
Medium NBV	532	26%	1.6
Low NBV	107	36%	2.4

The same analysis on 6-months confirmed disability progression showed a similar pattern (p<0.001)

NBV=Normalized Brain Volume

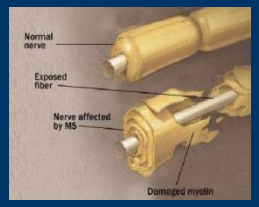
Fingolimod treatment effect

Pooled FREEDOMS and FREEDOMS II (n=2342), 3-month confirmed disability progression

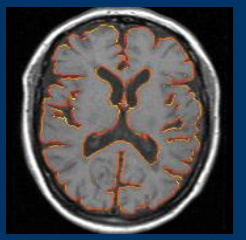


Cut-off	HR	95% CI	Tx effect
High NBV	0.89	0.51; 1.55	-11%
Medium NBV	0.69	0.55; 0.87	-31%
Low NBV	0.59	0.38; 0.91	-41%

p for global treatment effect <0.001
p for interaction =0.24



Neuroprotection - summary

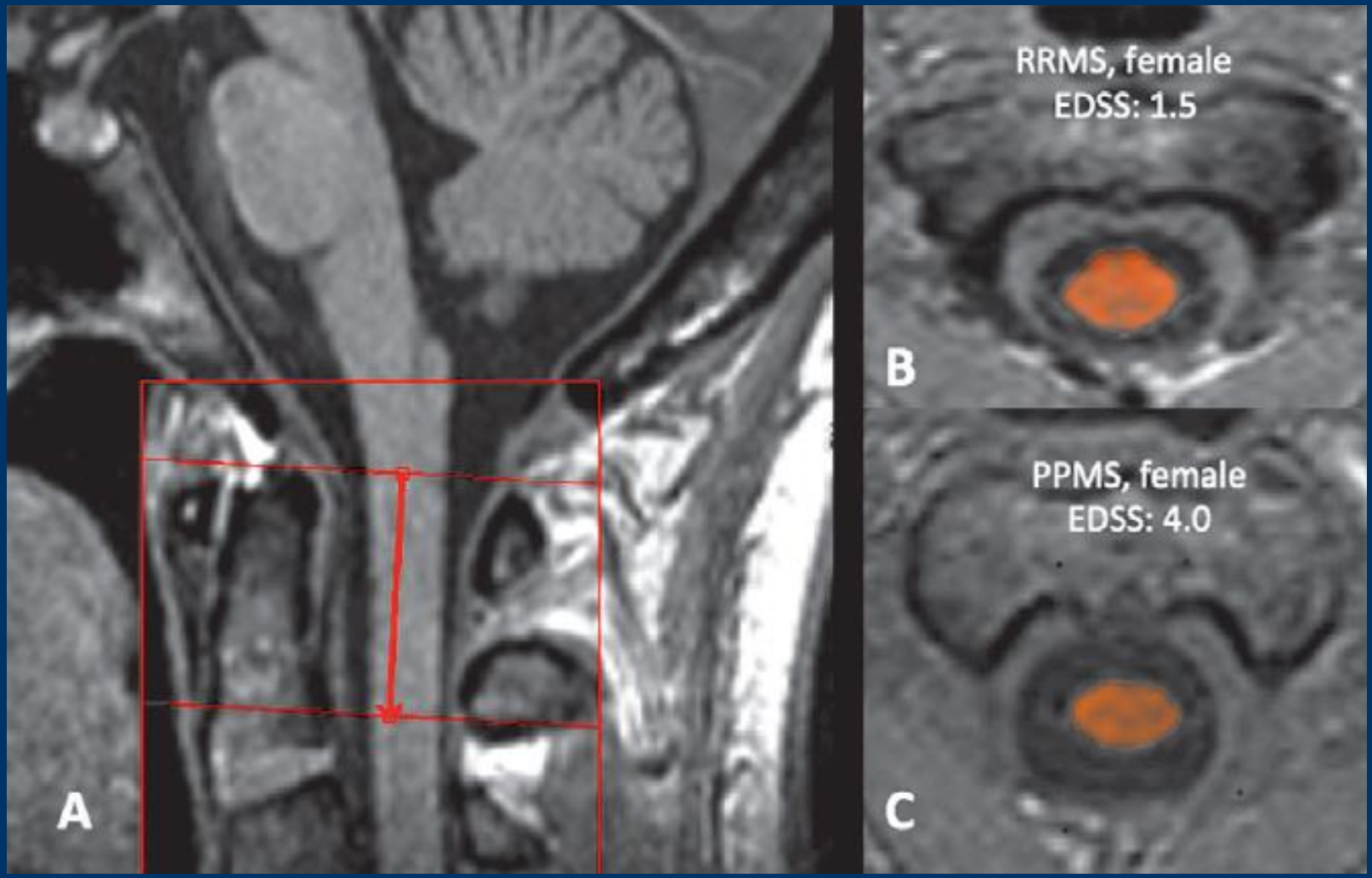


- Whole brain atrophy best studied
  - neurodegeneration starts early
- Clinical relevance established
  - BV modulates outcome of treatment effect
- Application to individual patients?
  - software not available on scanner / PACS
  - single-subject variability (diurnal, scanner)
  - thresholds for patient monitoring needed

MAGNIMS study group - 2009

MAGNIMS study group - 2012

Cervical cord atrophy most relevant?



Lukas C, Radiology 2013