Natural history & clinical relevance of brain volume changes in MS

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Magnims

Magnetic Resonance Imaging in Multiple Sclerosis

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Disclosures

- Steering committee and iDMC – Biogen, Roche
- Consultant – Sanofi-Aventis, Roche, Apitope, GeNeuro, Novartis, Roche, Merck, Bayer, IXICO, TEVA, Sanofi-Genzyme
- Research agreements – Toshiba, Philips, GE
- Sponsor – NIHR-UCLH-BRC, Dutch Foundation MS Research, TEVA, Novartis, EC-H2020, EC-JU (IMI)
- Editorial board member – Brain, Neuroradiology, MSJ, Neurology, Radiology

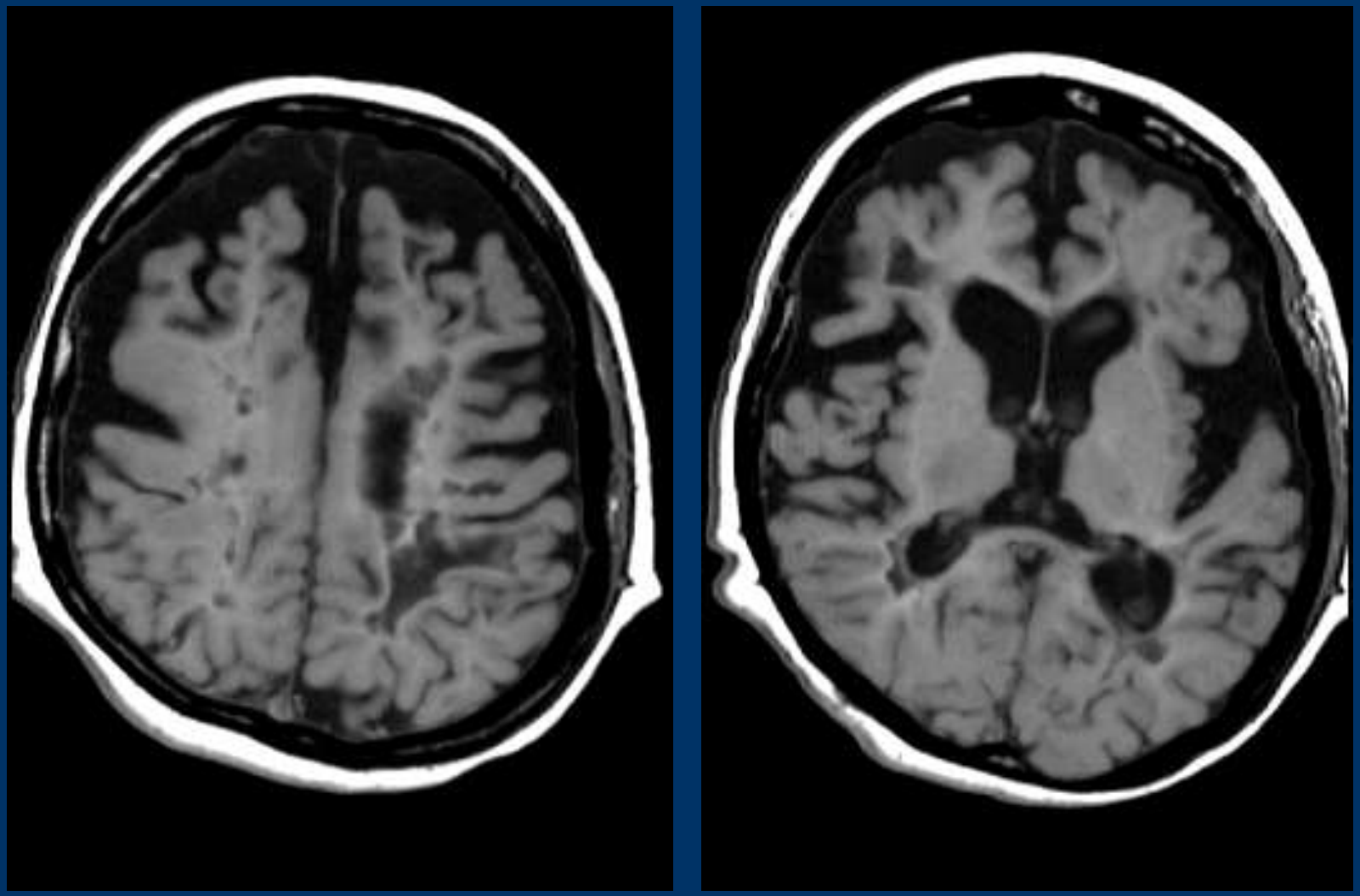
Literature reviews

- Measurement of atrophy in multiple sclerosis: pathological basis, methodological aspects and clinical relevance. Miller DH, Barkhof F, Frank JA, Parker GJ, Thompson AJ. Brain. 2002 Aug;125(Pt 8):1676-9
- Clinical relevance of brain volume measures in multiple sclerosis. De Stefano N, Airas L, Grigoriadis N, Mattle HP, O'Riordan J, Oreja-Guevara C, Sellebjerg F, Stankoff B, Walczak A, Wiendl H, Kieseier BC. CNS Drugs. 2014 Feb;28(2):147-56
- Brain Atrophy in Multiple Sclerosis: Clinical Relevance and Technical Aspects. Sastre-Garriga J, Pareto D, Rovira À. Neuroimaging Clin N Am. 2017 May;27(2):289-300
- Brain MRI atrophy quantification in MS: From methods to clinical application. Rocca MA, Battaglini M, Benedict RH, De Stefano N, Geurts JJ, Henry RG, Horsfield MA, Jenkinson M, Pagani E, Filippi M. Neurology. 2017 Jan 24;88(4):403-413

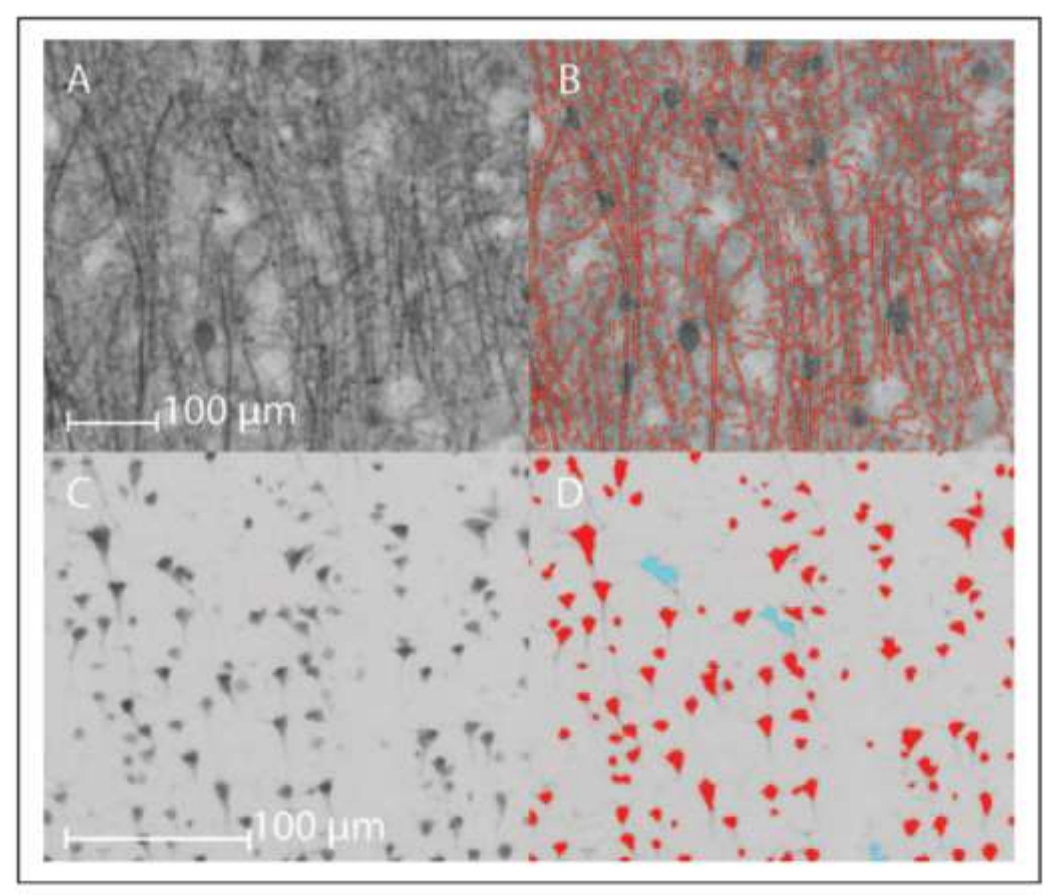
Agenda

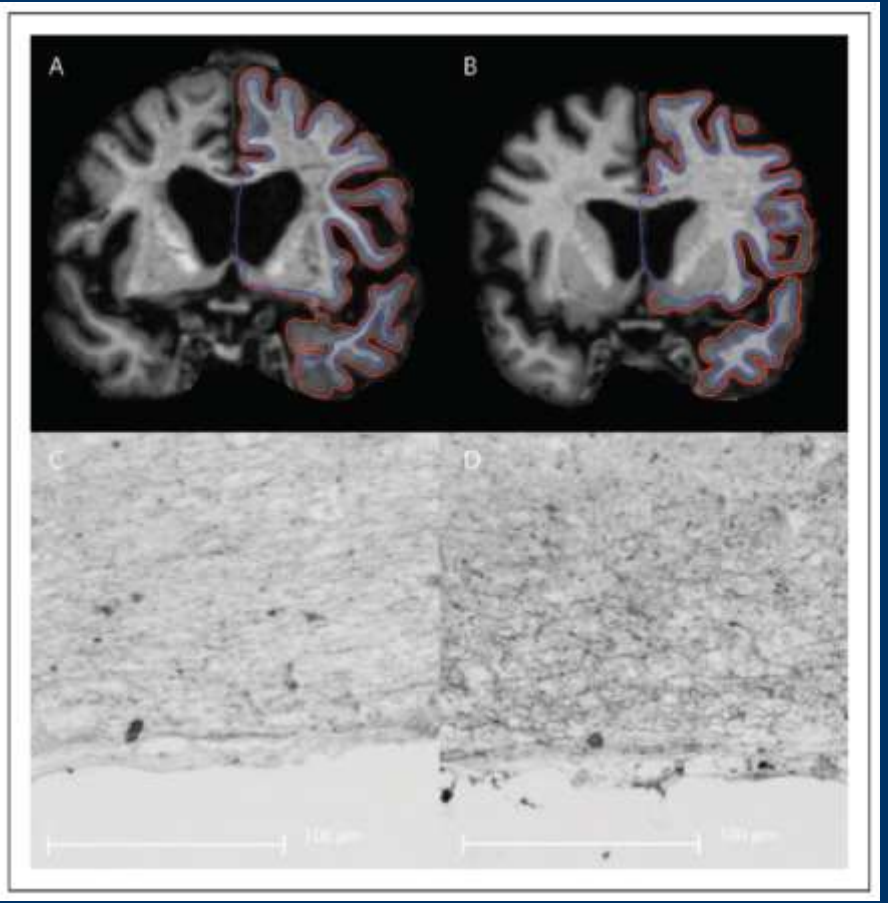
- Global brain volume in MS – marker of atrophy?
  - pathological substrate
  - measurement technique
- Natural history of disease
  - onset of atrophy
  - anatomical pattern
- Clinical significance / predictive value
  - cross-sectional and longitudinal
  - physical disability and cognition

Postmortem MRI – axonal loss



Cortical atrophy – pathology substrate





Neuronal density, neuronal size & axonal density were significant predictors of GM volume

Popescu & Klaver, MSJ 2015
Klaver, MSJ 2016

Imaging irreversible tissue damage

1995 1997 2002 2003 2005

courtesy of Alex Rovira, Barcelona

MCQ-1. Onset of BV loss

When does cerebral atrophy start in MS?

1) in the progressive phase
2) 3-5 years before onset of progression
3) from the onset of disease
4) only in older patients

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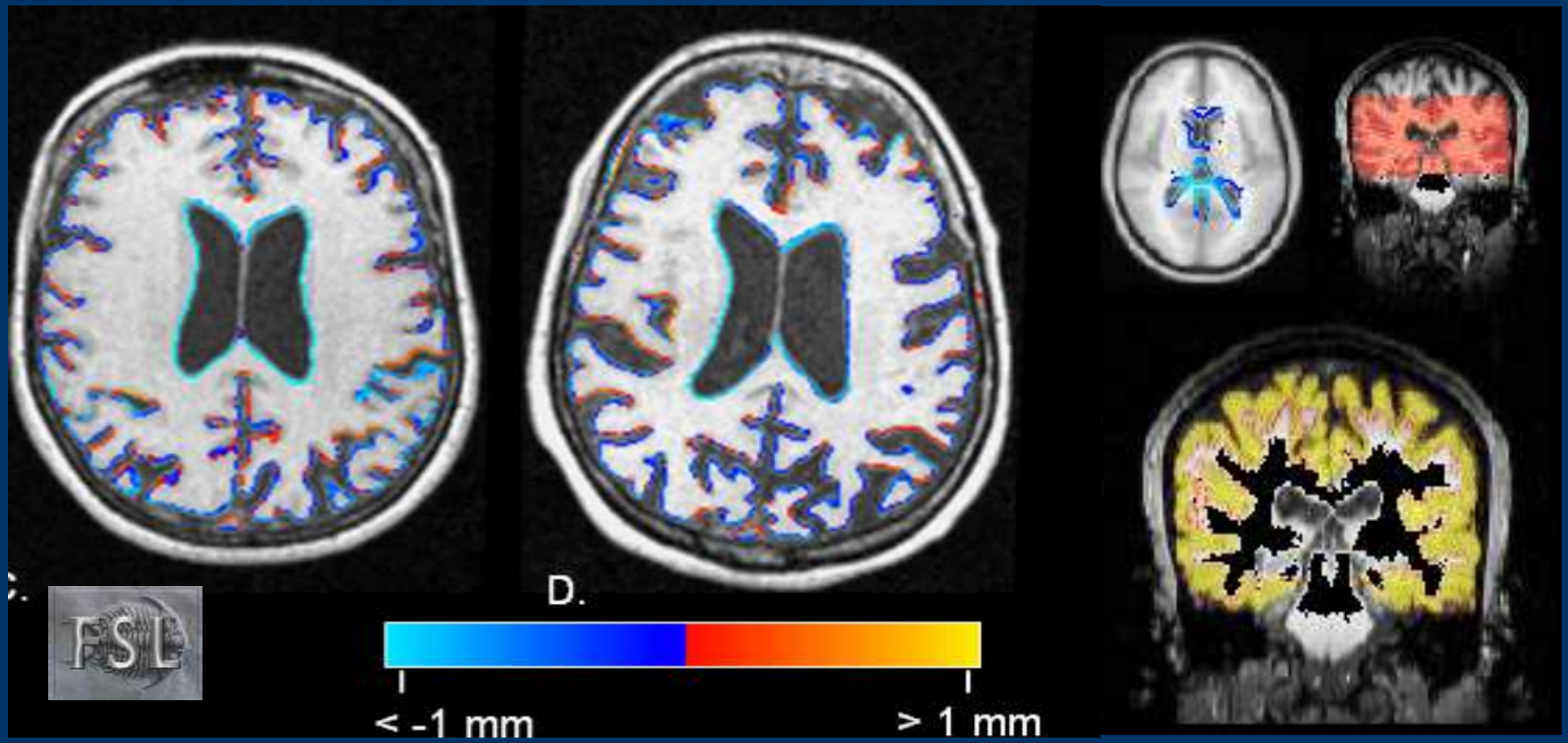
Atrophy measurement technique

Brain atrophy - techniques

- Cross-sectional - segmentation
  - Public domain: SIENAX, BPF, Freesurfer
  - Proprietary: Neuroquant, MSMetrics, NeuroSTREAM
  - VBM (groups)
- Longitudinal – registration / deformation
  - Public domain: SIENA, BSI, TBM / Jacobian
  - Propietary: ?
  - VBM (groups)

Atrophy measurement - SIENA



http://fmrib.ox.ac.uk/

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Brain Health – effect of age & MS

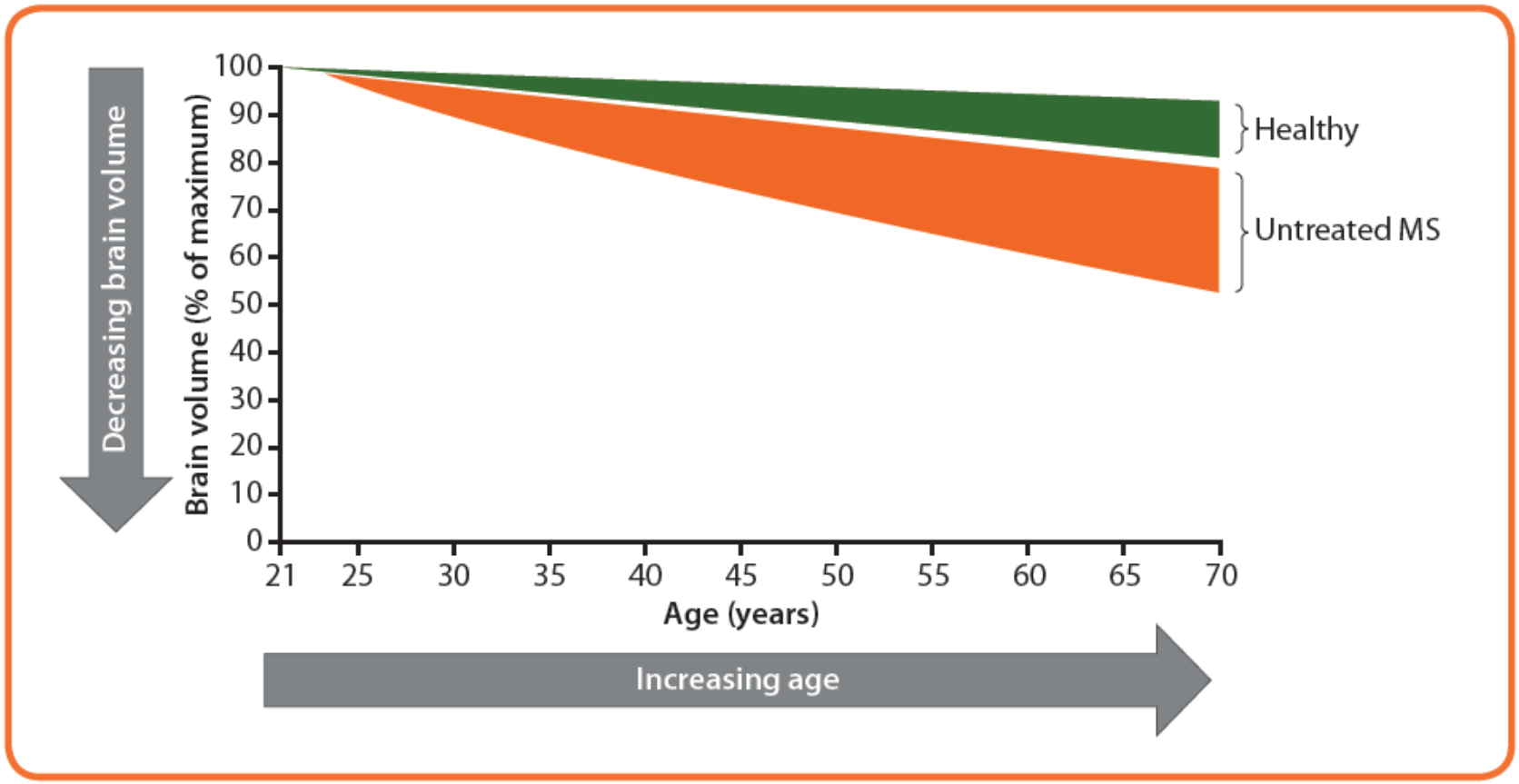
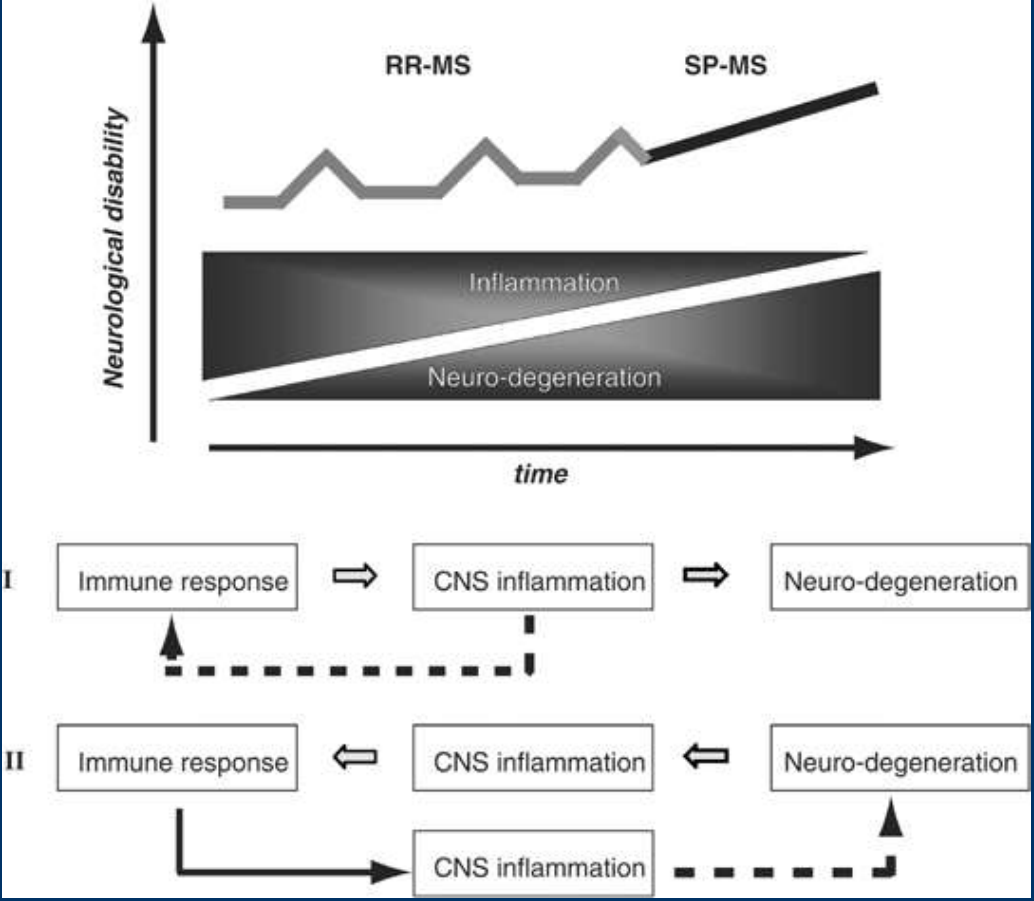


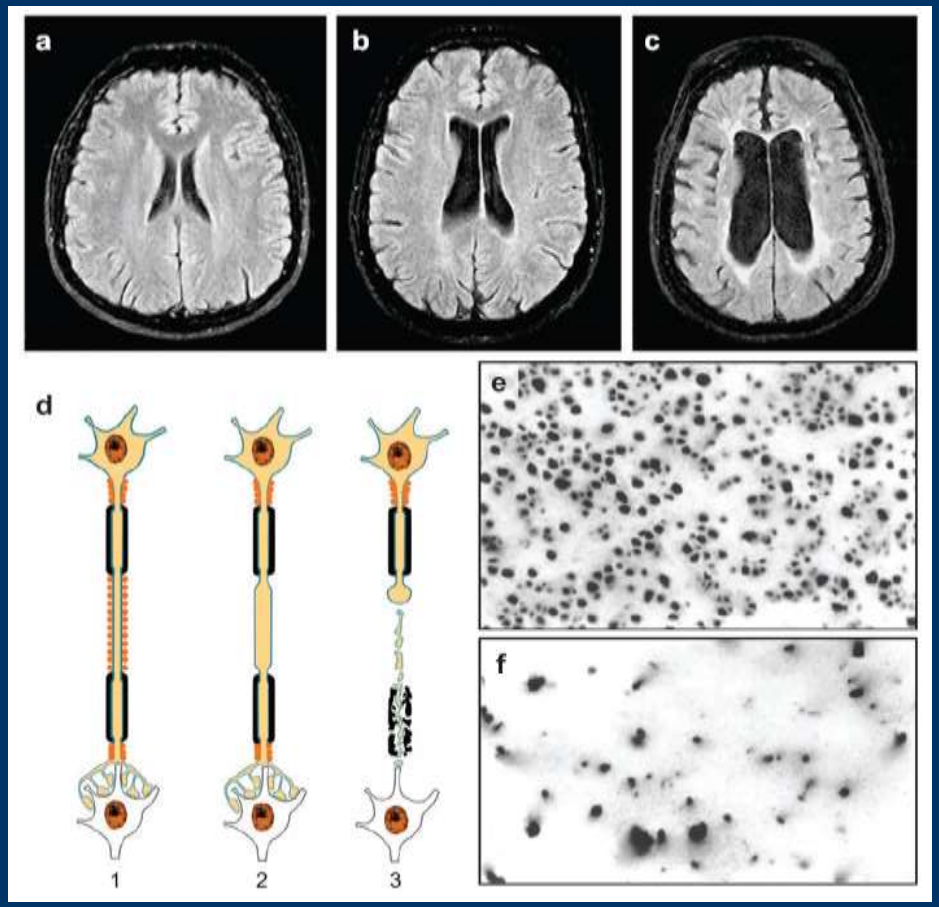
Figure 1. Brain atrophy in many people with MS is faster than usual and proceeds throughout the disease course.[36,37] This examples illustrates how brain atrophy is accelerated in untreated MS, beginning at 25 years of age.

http://www.msbrainhealth.org/

Neurodegeneration – when and why?

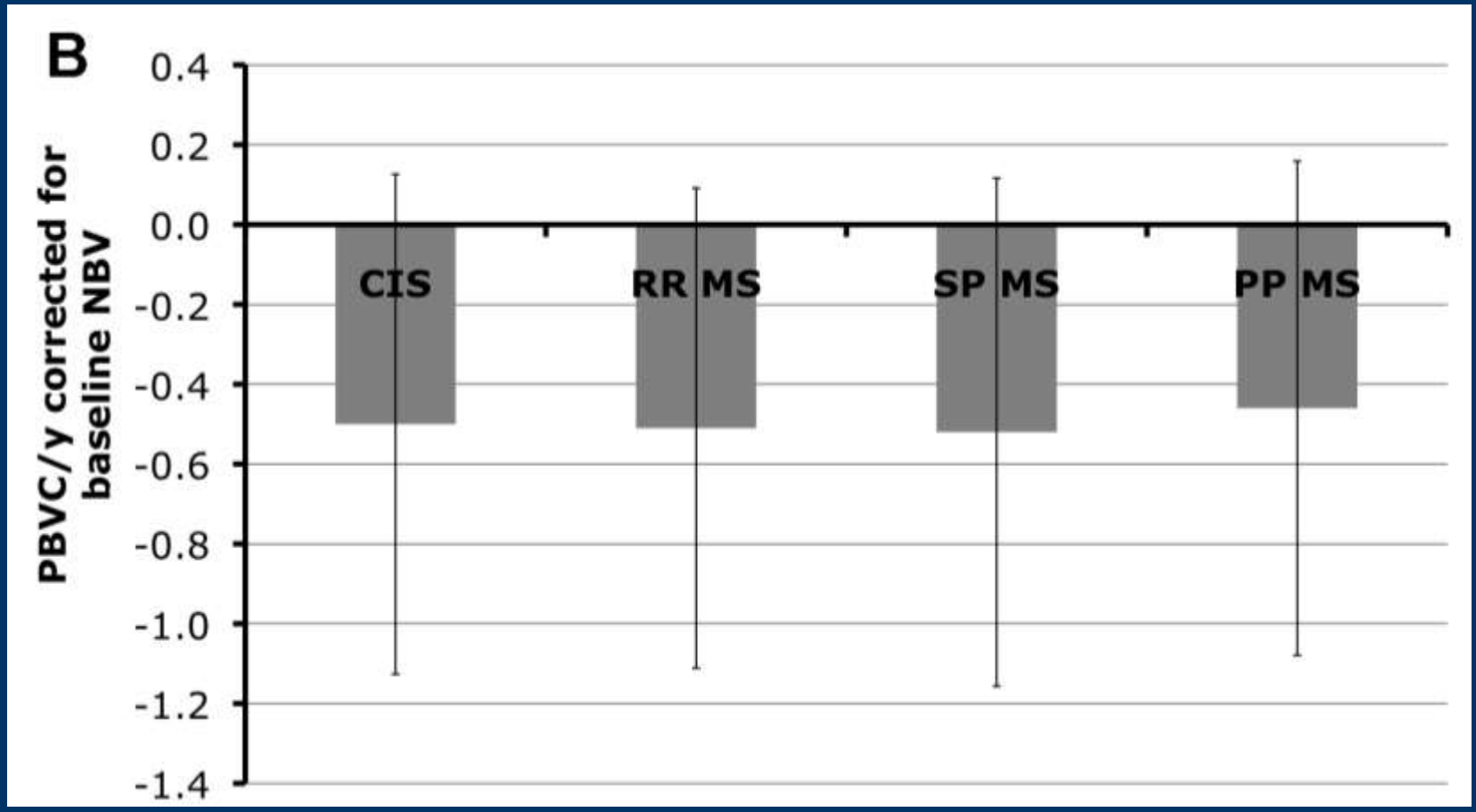


Oksenberg & Barcellos
Genes Immun. 2005



Trapp & Nave
Ann Rev Neurosci 2008

Neurodegeneration – early & profound



De Stefano, MAGNIMS study group, Neurology 2010

MCQ-2. Compartments affected

Where does brain atrophy occur first?

1) cortex
2) thalamus
3) white matter
4) brainstem

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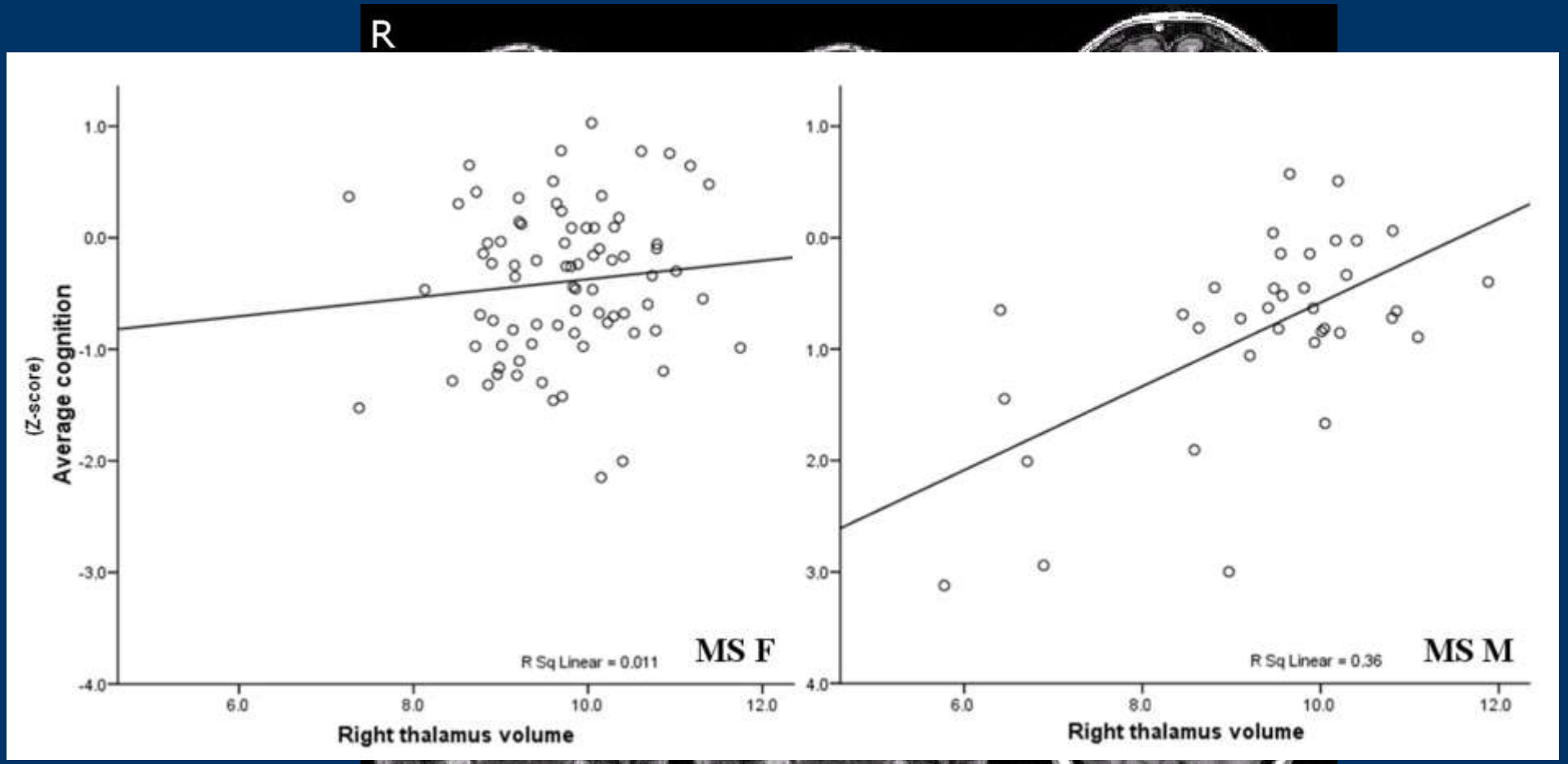
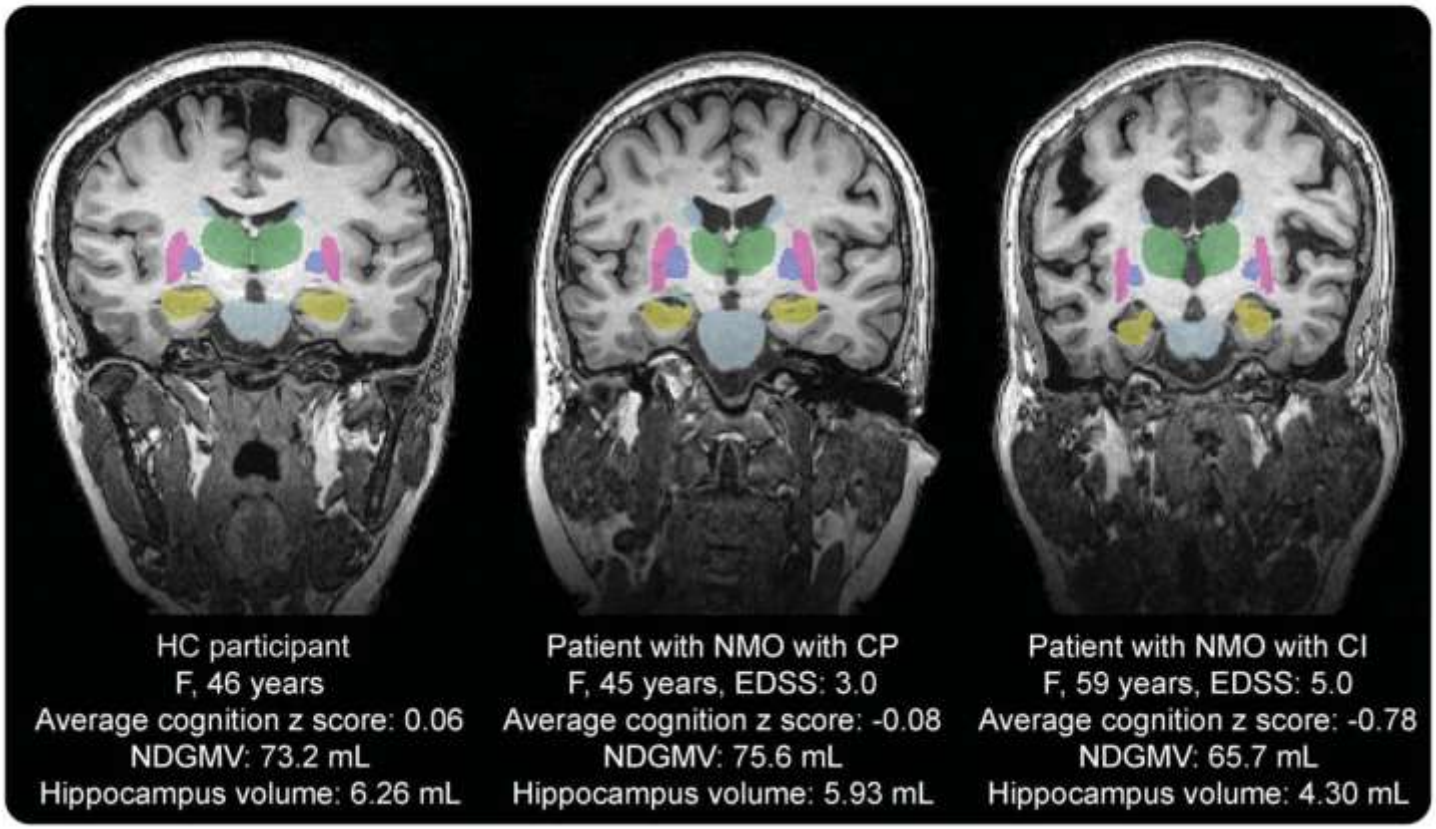
Early thalamic atrophy in MS



Schoonheim M. Neurology 2012

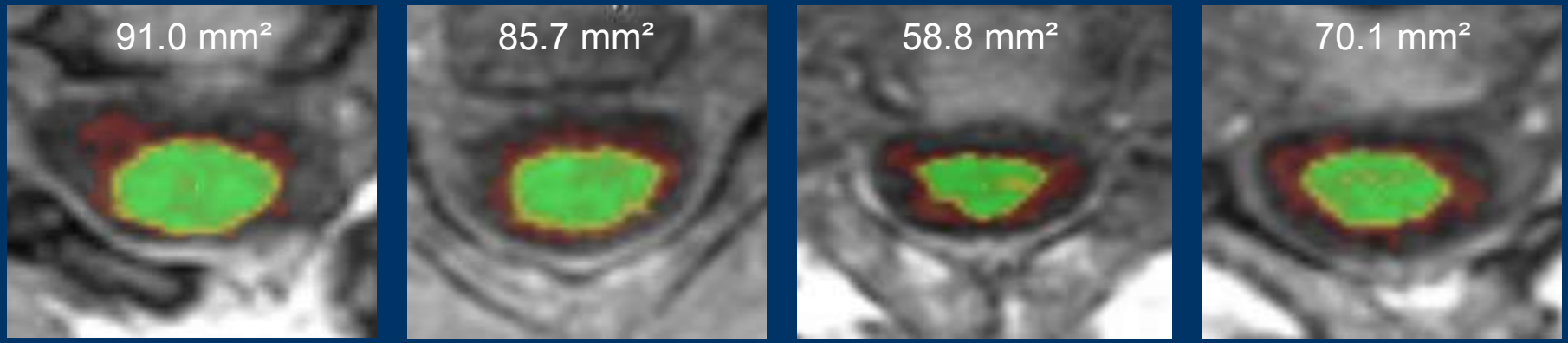
GM predictors of cognition in NMO

Figure 1 Representative deep gray matter segmentations of participants



Liu Y, Neurology 2015

Cord atrophy by MS phenotype



Control	RRMS	PPMS	SPMS
(male, 53 y)	(male, 43 y) EDSS=3	(male, 57 y) EDSS=3.5	(male, 49 y) EDSS=7.5

MUCCA – Mean Upper Cervical Cord Area

Daams M, et al. MSJ 2014

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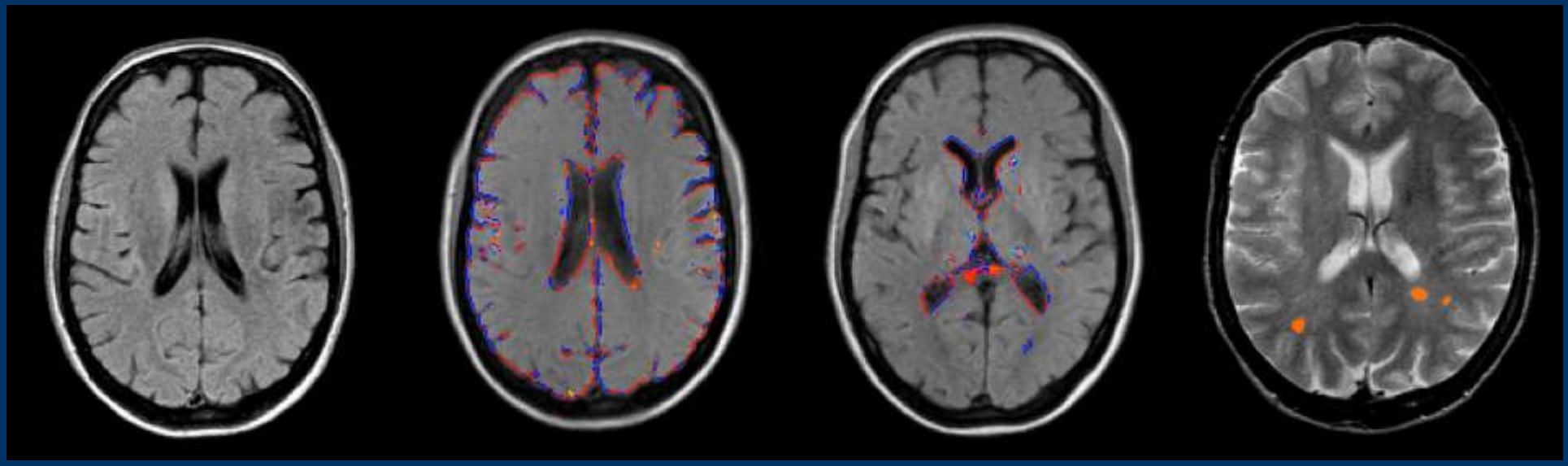
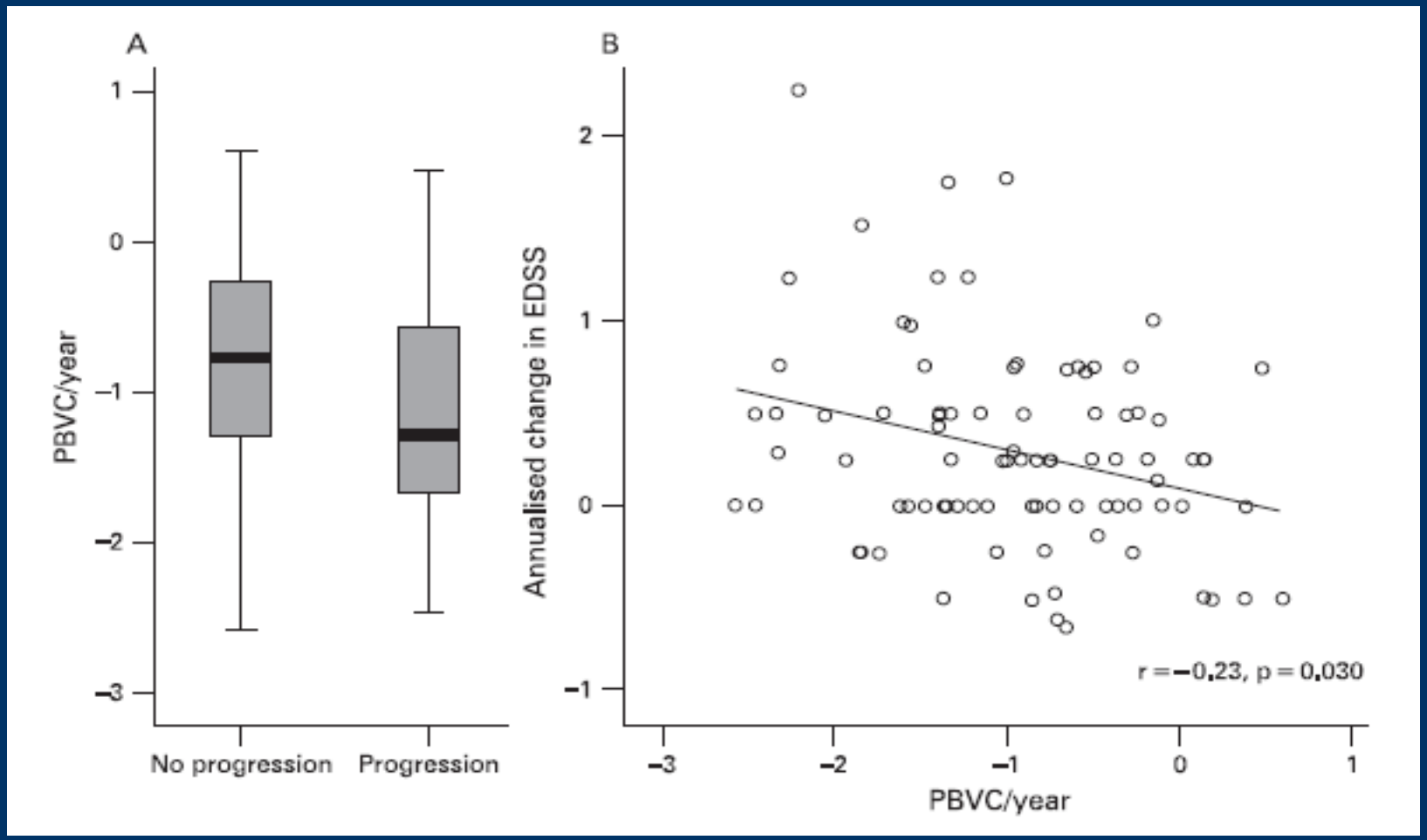
Long-term predictive value of PBVC



- N=261 from 8 MAGNIMS centers with short interval (0-2 yr) MRI
  - pseudo-T1-weighted images and SIENA
- Central atrophy & ΔT2LV helped predicting 10-yr EDSS (R^2=0.74)
  - stronger effects of Baseline EDSS, Center, DMT usage

Popescu V, JNNP 2013

PBVC in RRMS predicts progression



Minneboo JNNP 2008

MCQ-3. Clinical prediction

What are the consequences of brain atrophy?

1) disability progression
2) conversion from CIS to CDMS
3) cognitive impairment
4) all of the above

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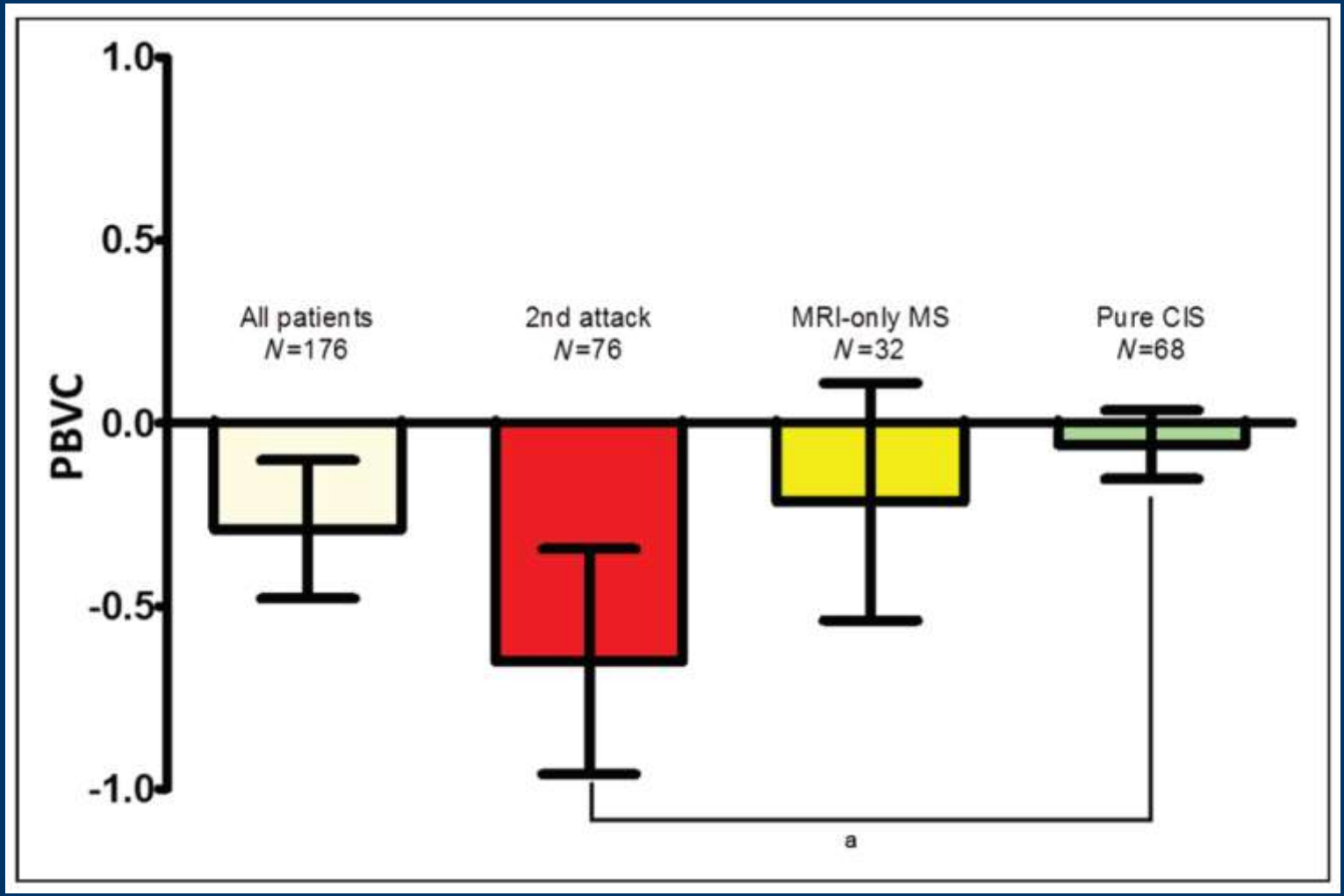
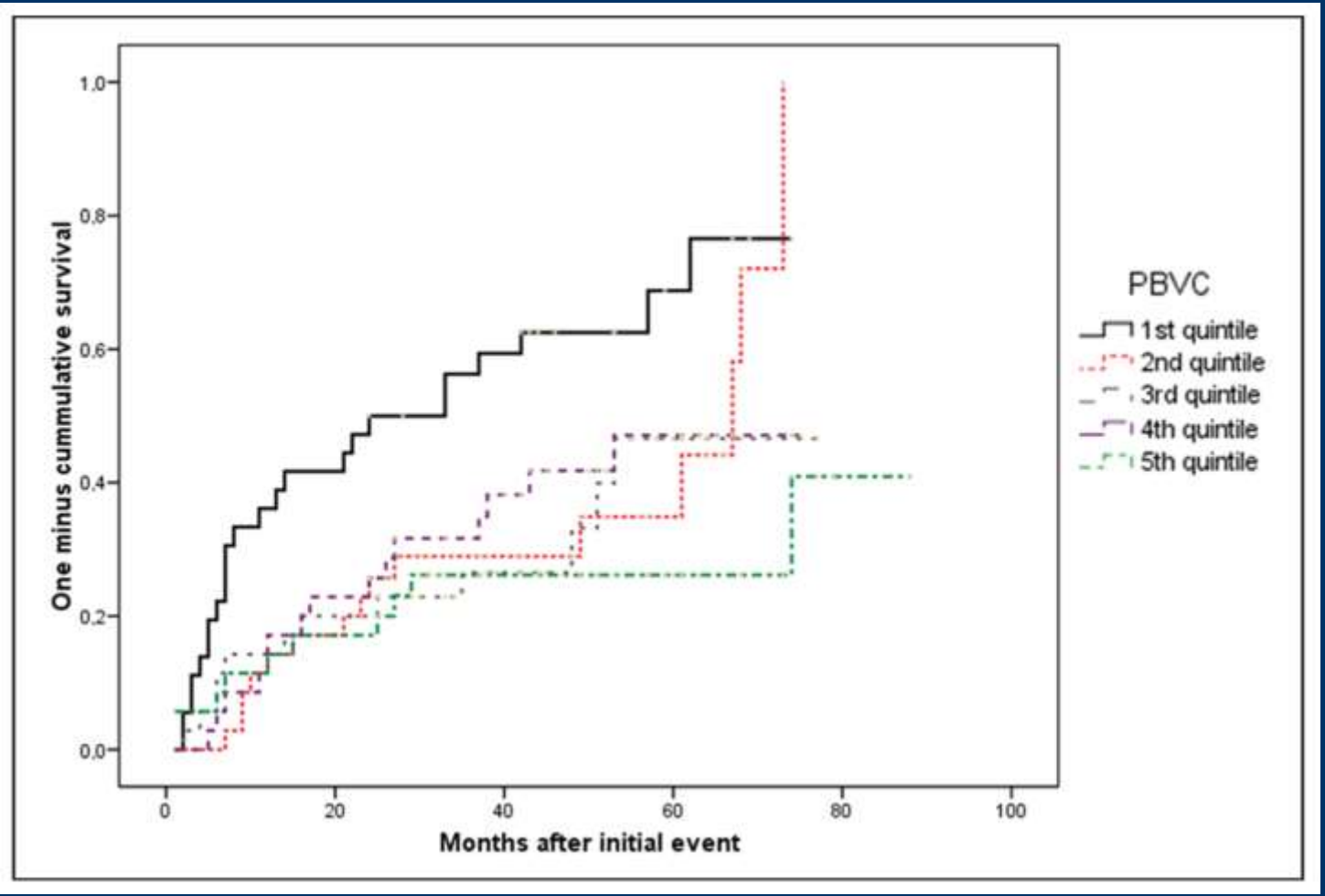
Brain atrophy rate in CIS



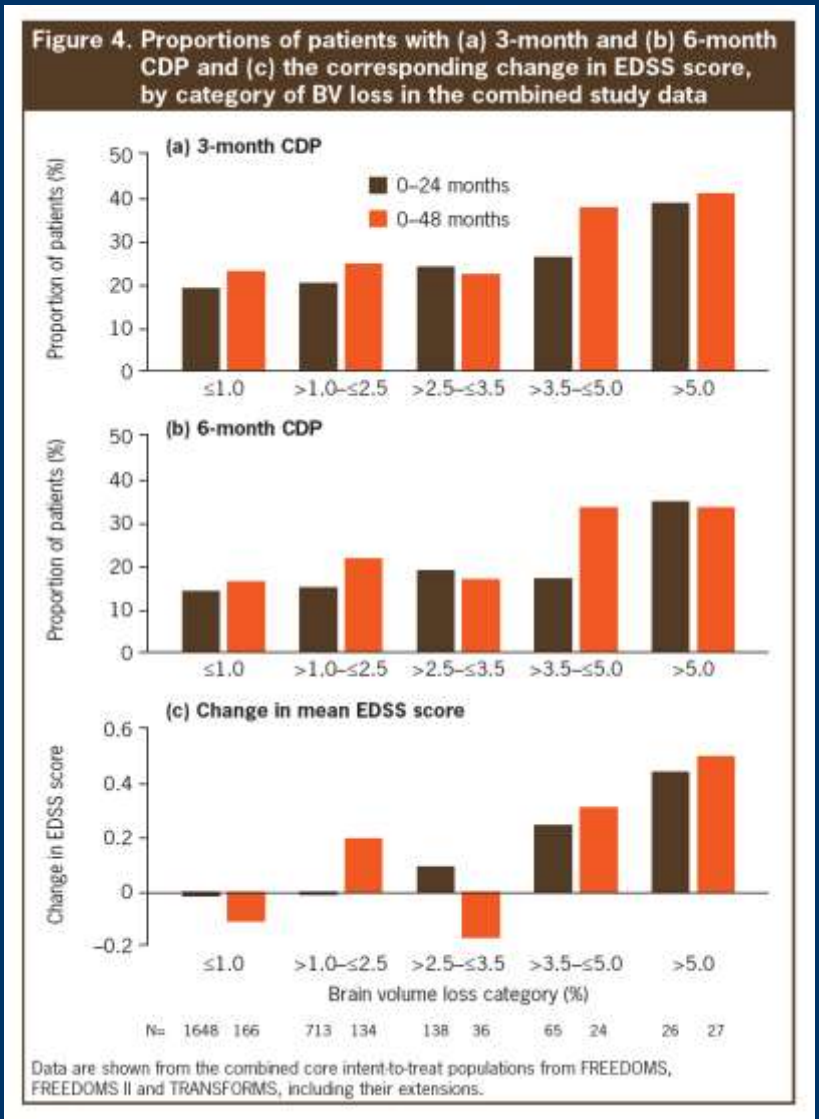
Pérez-Miralles F, et al. MSJ 2013

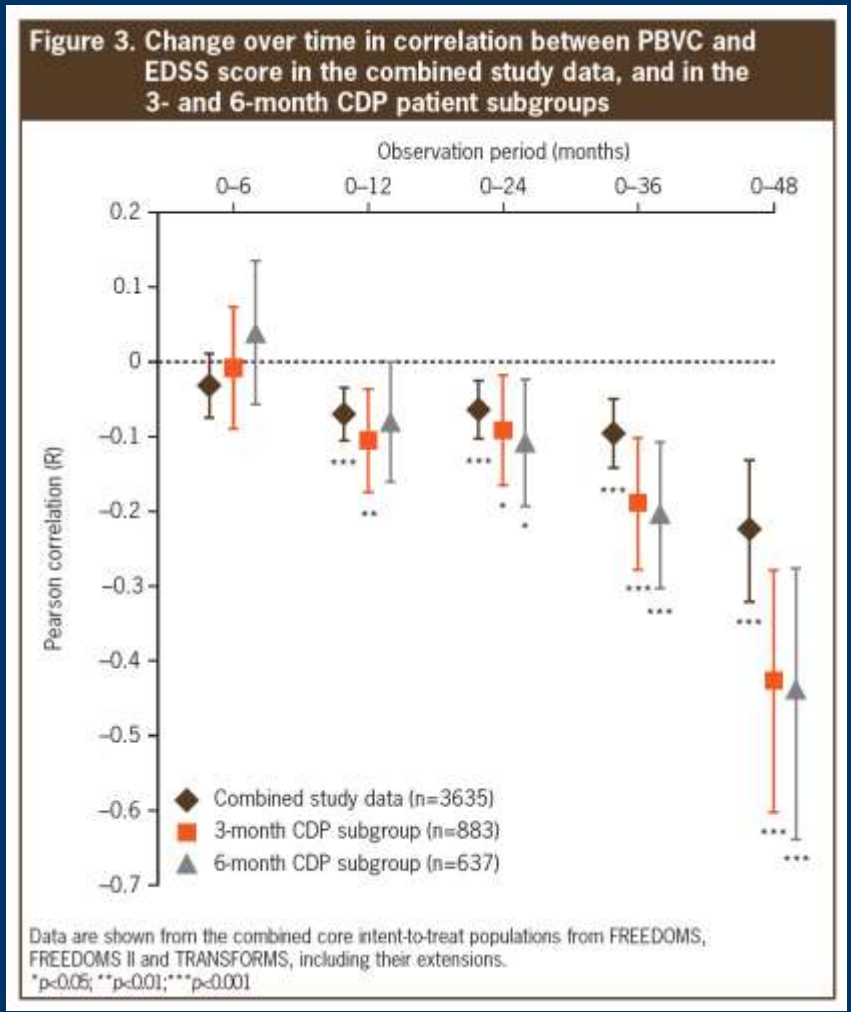
PBVC in CIS predicts 2nd attack



Pérez-Miralles F, et al. MSJ 2013

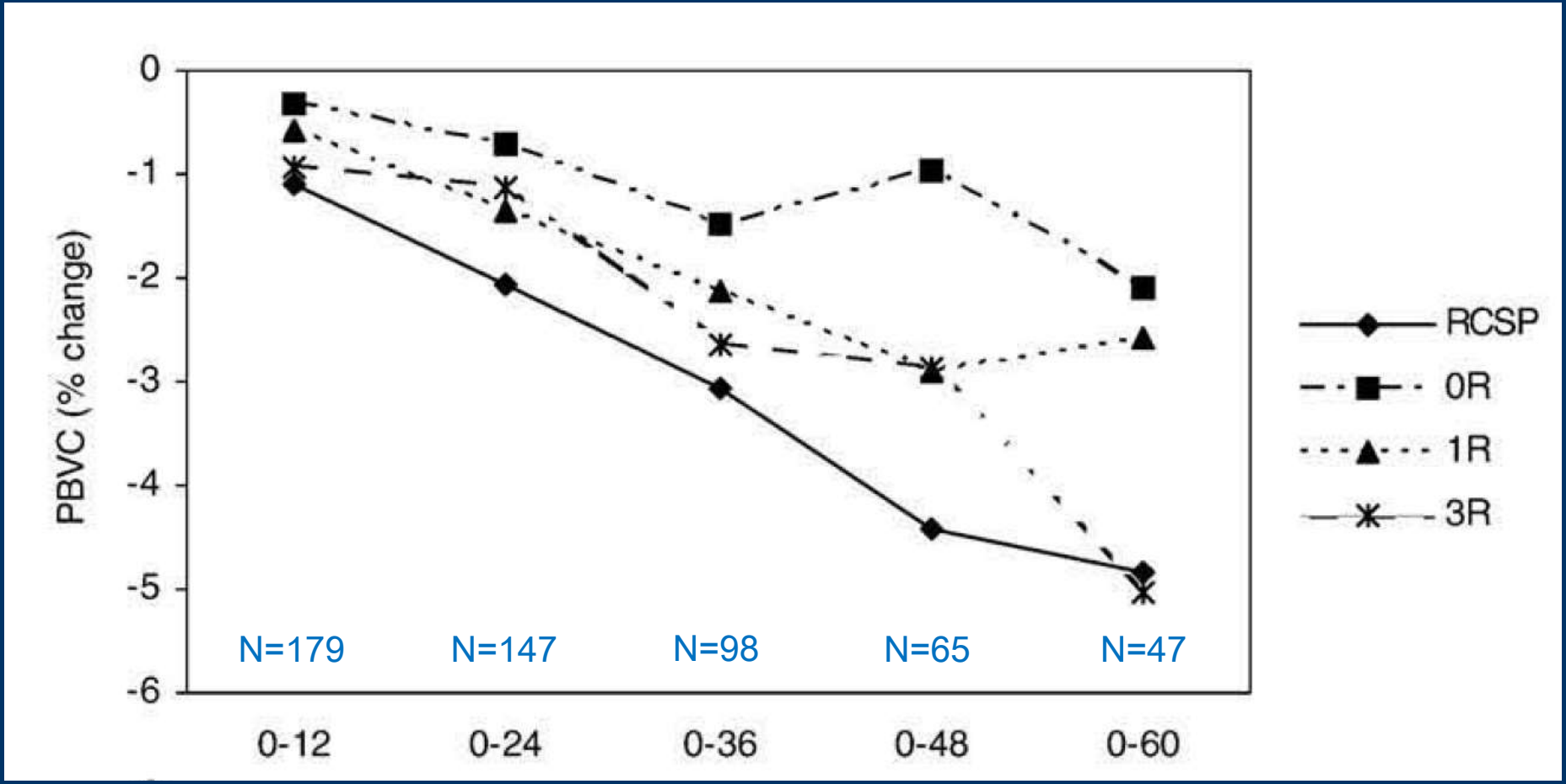
PBVC under FTY treatment predicts EDSS





Barkhof, ECTRIMS 2013
Radue, Neurology 2015

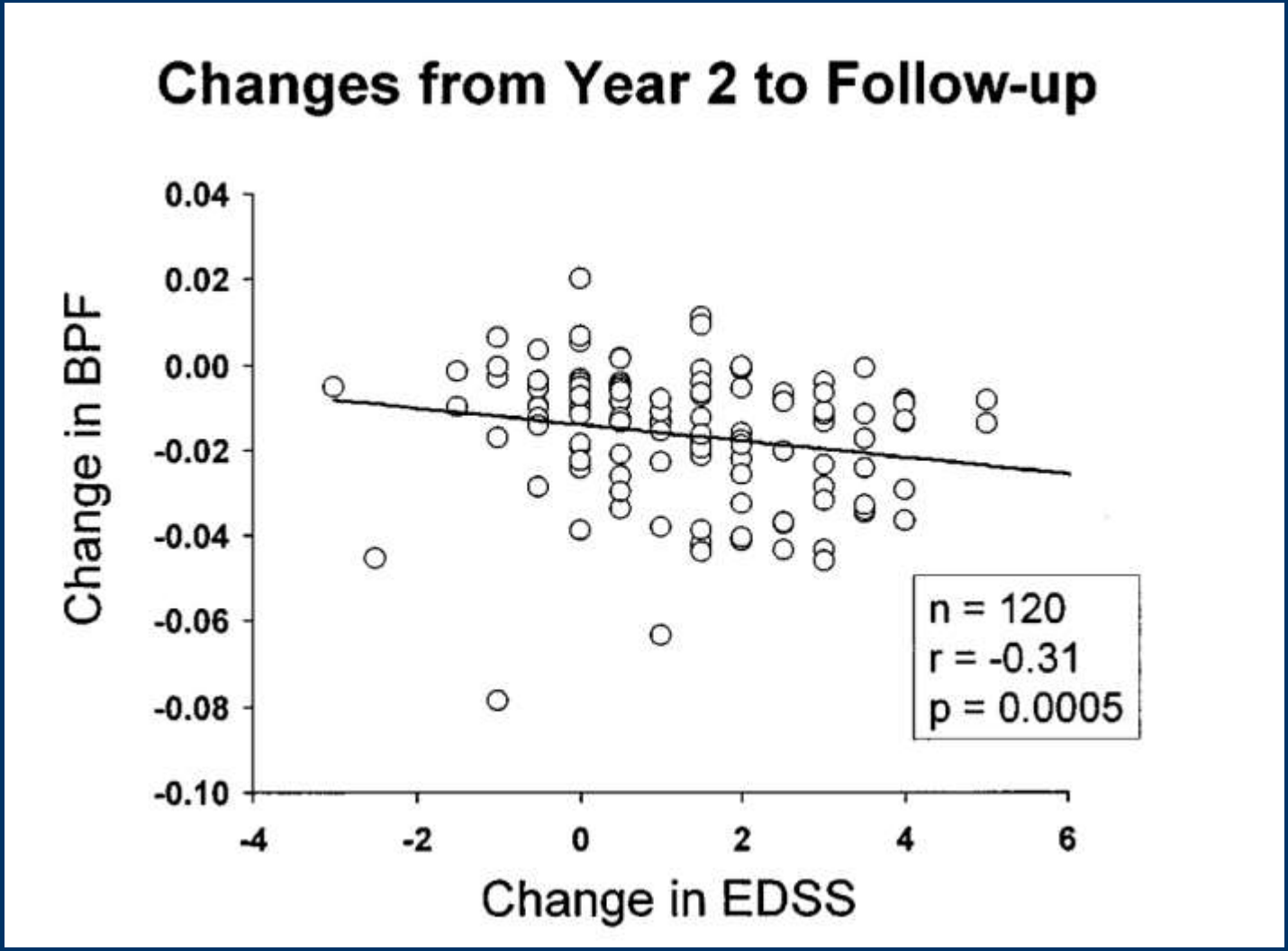
PBVC in ASA - sustained progression



RCSP = reach confirmed sustained progression; R=relapse

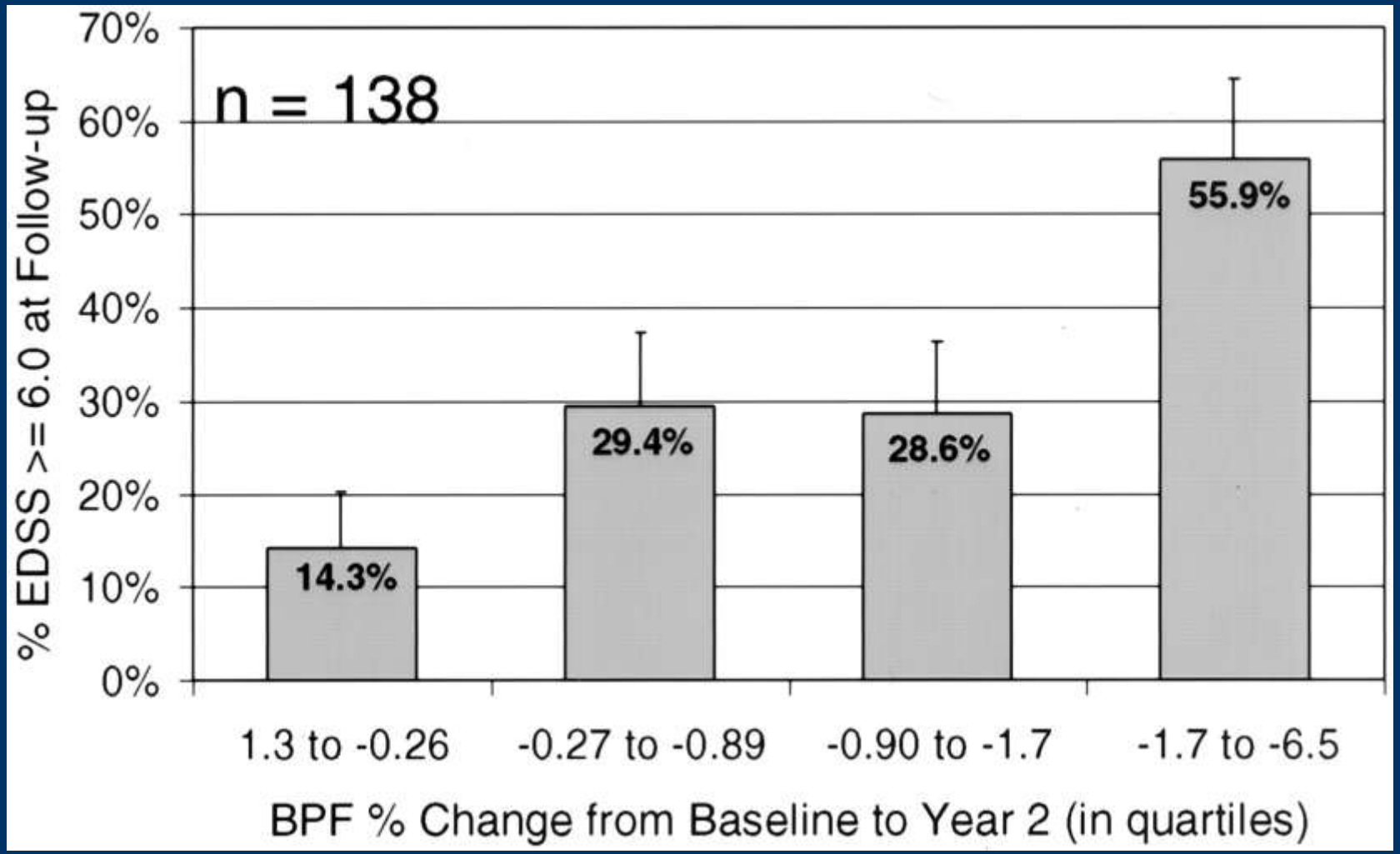
Horakova D, JNS 2009

Avonex pivotal study – BPF vs EDSS



Fisher E, MSJ 2000

Avonex 8-yr FU - predicting EDSS 6



Fisher E, Neurology 2002

Brain volume and cognition

- BRB correlates better with NBV that T2LL
  - Cognitive index (r=0.427) and SDMT (0.537)
- Computerized testing strongly related with NBV
  - Strong relationship (r=0.68) with speed of attention
- Comprehensive cognitive testing in long-DD
  - Correlates better with NBV (r=0.548) than T2LL
  - Final model selected NDGMV and FA of WM (R^2 0.49)

Lazeron RCH, MSJ 2005 & 2006

Daams M, MSJ 2015

Take home messages

- Whole brain atrophy well studied
  - Reflects neuronal loss and demyelination
  - Neurodegeneration starts early
  - Effect of acquisition/analysis technique
- Clinical relevance established (group-level)
  - Strongest relationship with cognition
  - Long-term predictive value moderate
  - More clear in early (CIS) patients?
- Modification by brain reserve (active/passive)

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2018 ECTRIMS-MAGNIMS Research Fellowship

Applications are now open

The deadline for application will close on 01 / February / 2018

MAGNIMS (Magnetic Resonance Imaging in MS) is a European network of academics that share a common interest in the study of multiple sclerosis using magnetic resonance imaging techniques.