Magnims
Magnetic Resonance Imaging in Multiple Sclerosis

ESMRMB 2015
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Centre d'Esclerosi Múltiple de Catalunya

Clinical correlates of GM damage in Multiple Sclerosis

Jaume Sastre-Garriga - @J_SastreGarriga

Servei de Neurologia / Neuroimmunologia
Centre d'Esclerosi Múltiple de Catalunya – Cemcat
Hospital Universitari Vall d'Hebron, Barcelona

Vall d'Hebron
Institut de Recerca

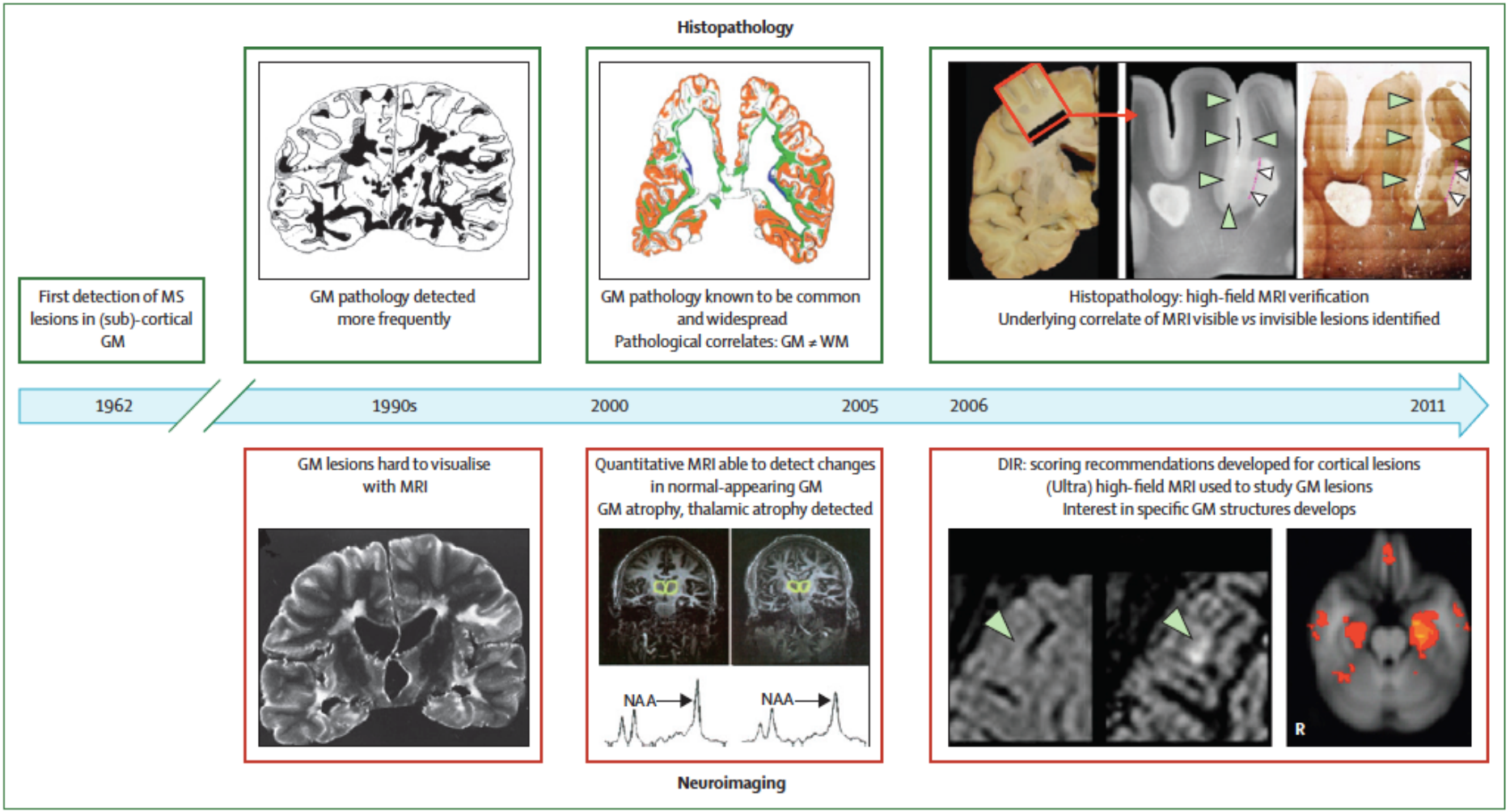
Vall d'Hebron
Hospital
Unitat de Neuroimmunologia Clínica

FEM
Fundació Esclerosi Múltiple

Outline of the talk

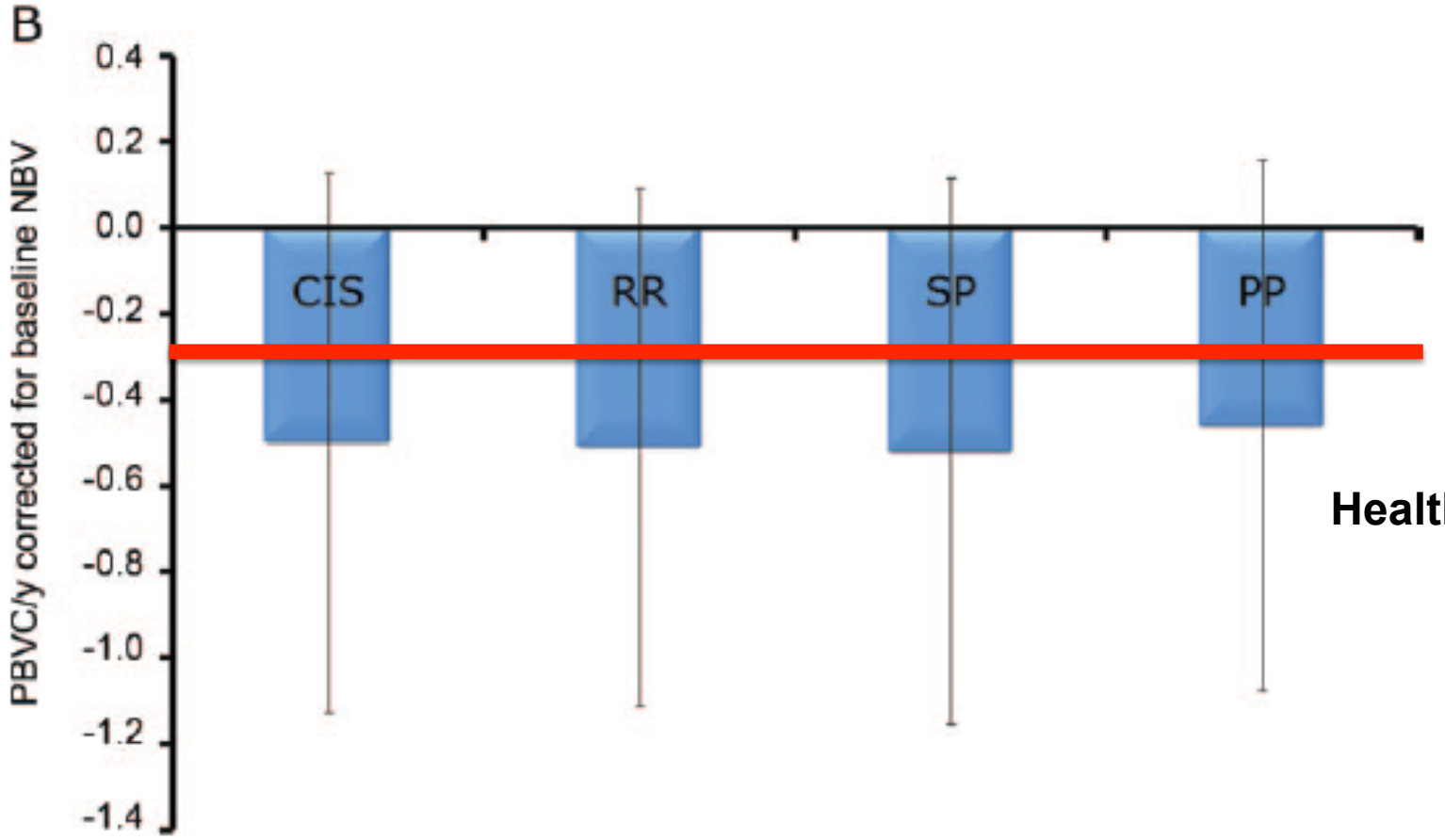
1. GM atrophy in MS:
    - Natural history
    - Clinical correlations
2. Cortical lesions in MS
3. Treatment effects on:
    - GM atrophy
    - Cortical lesions

Grey matter damage in Multiple Sclerosis



Geurts et al., Lancet Neurology 2012

Atrophy – natural history in MS



Healthy subjects

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Giorgio et al., Neurology 2010

GM Atrophy – natural history in MS

Clinical impact of early brain atrophy in clinically isolated syndromes

F Pérez-Miralles[1,2], J Sastre-Garriga[1], M Tintoré[1], G Arrambide[1], C Nos[1], H Perkal[1], J Río[1], MC Edo[1], A Horga[1], J Castilló[1], C Auger[3], E Huerga[3], A Rovira[3] and X Montalban[1]

Table 2. Comparison of brain and tissue-specific volume changes across patients subgroups. Significant *p* values appear in bold.

	2nd attack (*n* = 76)		MRI-only MS (*n* = 32)		Pure CIS (*n* = 68)		*Between groups*
	Mean (SD)	*p*	Mean (SD)	*p*	Mean (SD)	*p*	*p*
PBVC	**– 0.651** (1.345)	**< 0.0001**	– 0.215 (0.899)	0.186	+ 0.059 (1.282)	0.707	**0.0034**
BPF change, %	**– 0.461** (1.791)	**0.028**	– 0.040 (1.256)	0.852	+ 0.023 (1.446)	0.895	0.154
GMF change, %	**– 0.676** (2.315)	**0.013**	**– 0.697** (1.74)	**0.031**	– 0.340 (2.212)	0.209	0.600
WMF change, %	– 0.072 (4.193)	0.881	+ 0.938 (2.806)	0.068	+ 0.695 (3.835)	0.139	0.338

BPF: brain parenchymal fraction; CIS: clinically isolated syndrome; GMF: grey matter fraction; MRI: magnetic resonance imaging; MS: multiple sclerosis; PBVC: percentage brain volume change; SD: standard deviation; WMF: white matter fraction.

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Pérez-Miralles et al, Mult Scler 2013

GM Atrophy – natural history in MS

Gray and white matter volume changes in early RRMS

A 2-year longitudinal study

M. Tiberio, MD; D.T. Chard, MRCP; D.R. Altmann, DPhil; G. Davies, MRCP; C.M. Griffin, MD; W. Rashid, MRCP; J. Sastre-Garriga, MD; A.J. Thompson, FRCP; and D.H. Miller, FRCP

Table 2 *Mean (SD) fractional tissue volume at each timepoint in normal control subjects and patients with multiple sclerosis (MS)*

	Subject type					
	Normal control			MS		
Timepoint	BPF	GMF	WMF	BPF	GMF	WMF
Baseline	0.836 (0.0273)	0.552 (0.0198)	0.284 (0.0119)	0.813 (0.0285)	0.542 (0.0247)	0.270 (0.0161)
Year 1	0.832 (0.0314)	0.548 (0.0223)	0.284 (0.0132)	0.803 (0.0290)	0.534 (0.0263)	0.269 (0.0155)
Year 2	0.831 (0.0288)	0.547 (0.0212)	0.284 (0.0115)	0.801 (0.0293)	0.531 (0.0244)	0.270 (0.0155)

BPF = brain parenchymal fraction; GMF = gray matter fraction; WMF = white matter fraction.

Tiberio, M et al. Neurology 2005

GM Atrophy – natural history in MS

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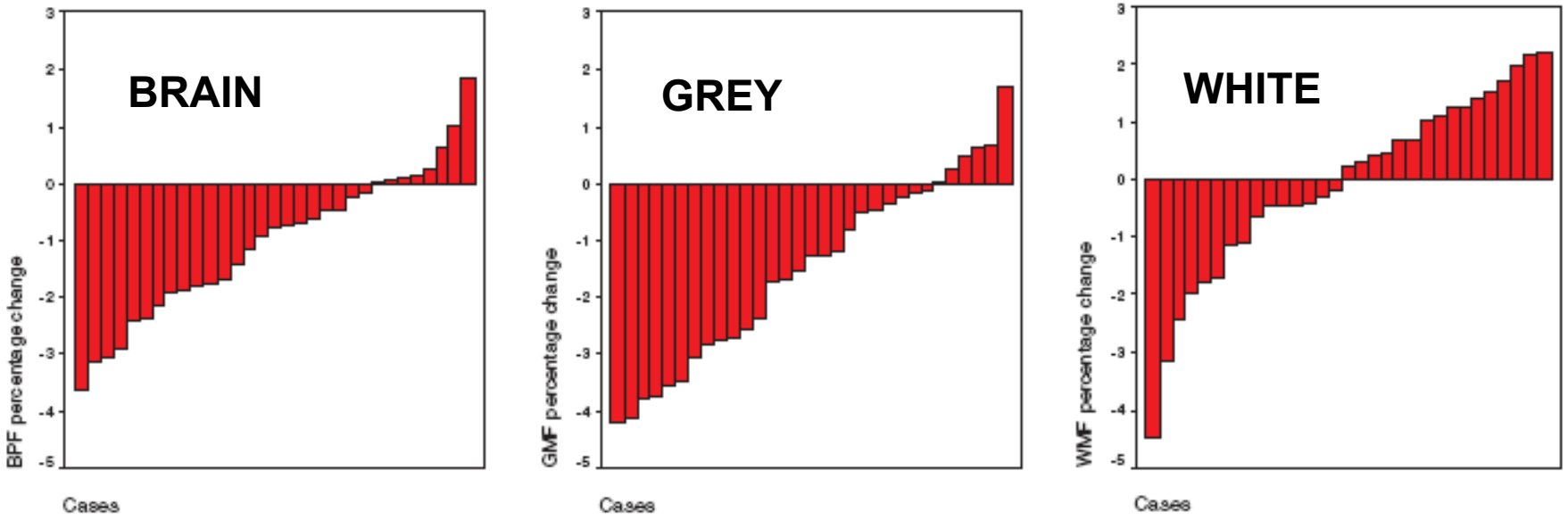
Tiberio, M et al. Neurology 2005

GM Atrophy – natural history in MS

doi:10.1093/brain/awh498 *Brain* (2005), **128,** 1454–1460

Grey and white matter volume changes in early primary progressive multiple sclerosis: a longitudinal study

Jaume Sastre-Garriga, Gordon T. Ingle, Declan T. Chard, Mara Cercignani, Lluís Ramió-Torrentà, David H. Miller and Alan J. Thompson



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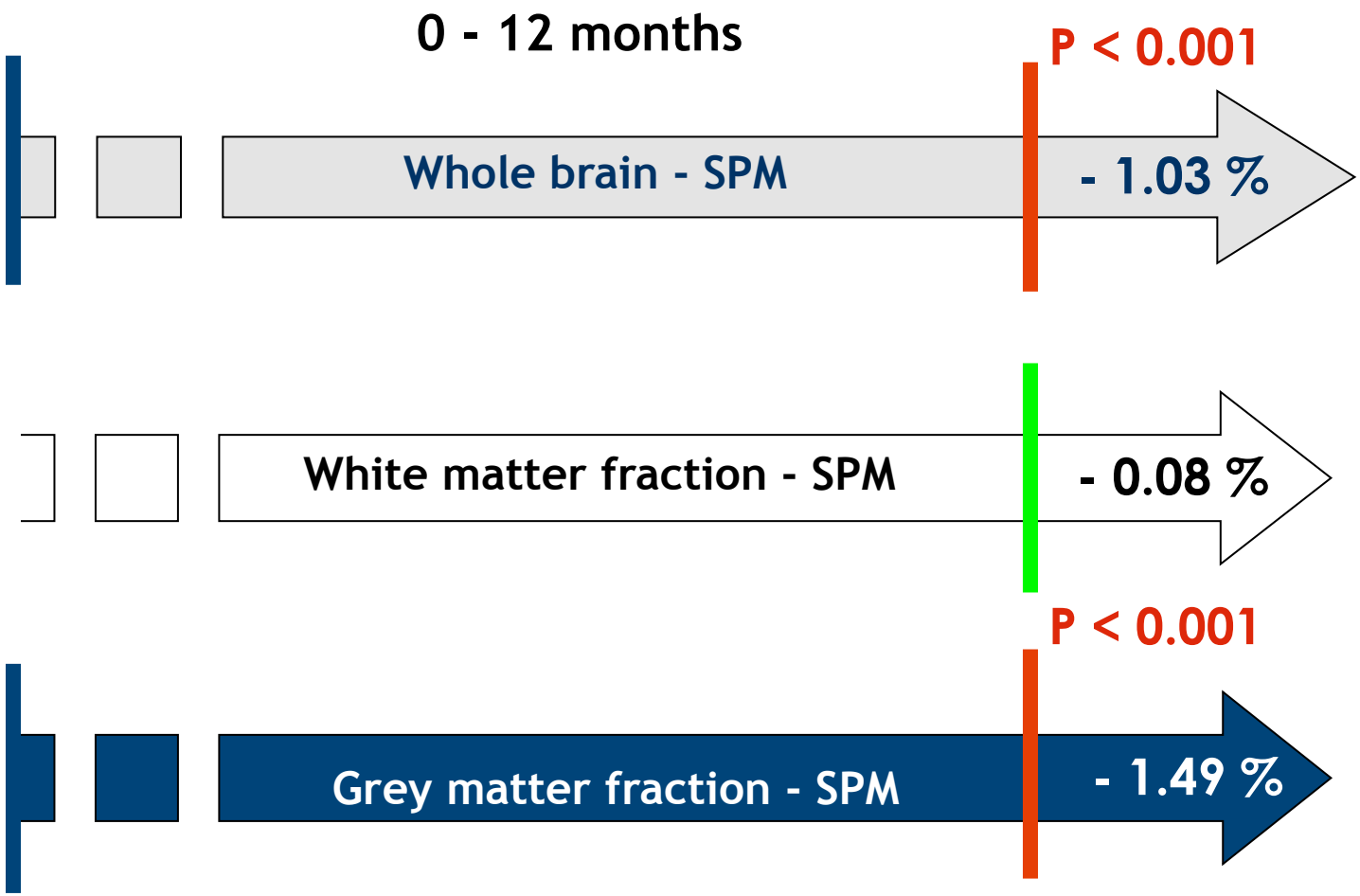
Sastre-Garriga, J et al. Brain 2005

GM Atrophy – natural history in MS



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Sastre-Garriga, J et al. Brain 2005

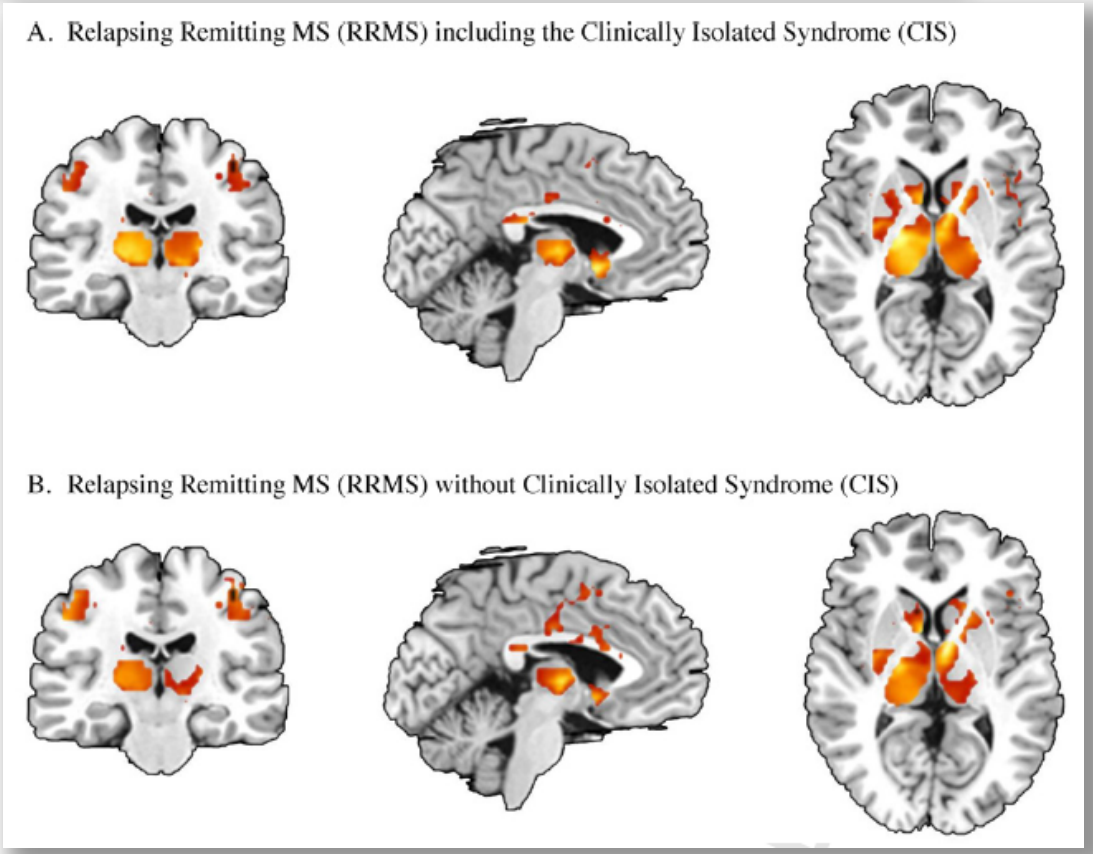
GM Atrophy – natural history in MS

Localized grey matter atrophy in multiple sclerosis: A meta-analysis of voxel-based morphometry studies and associations with functional disability

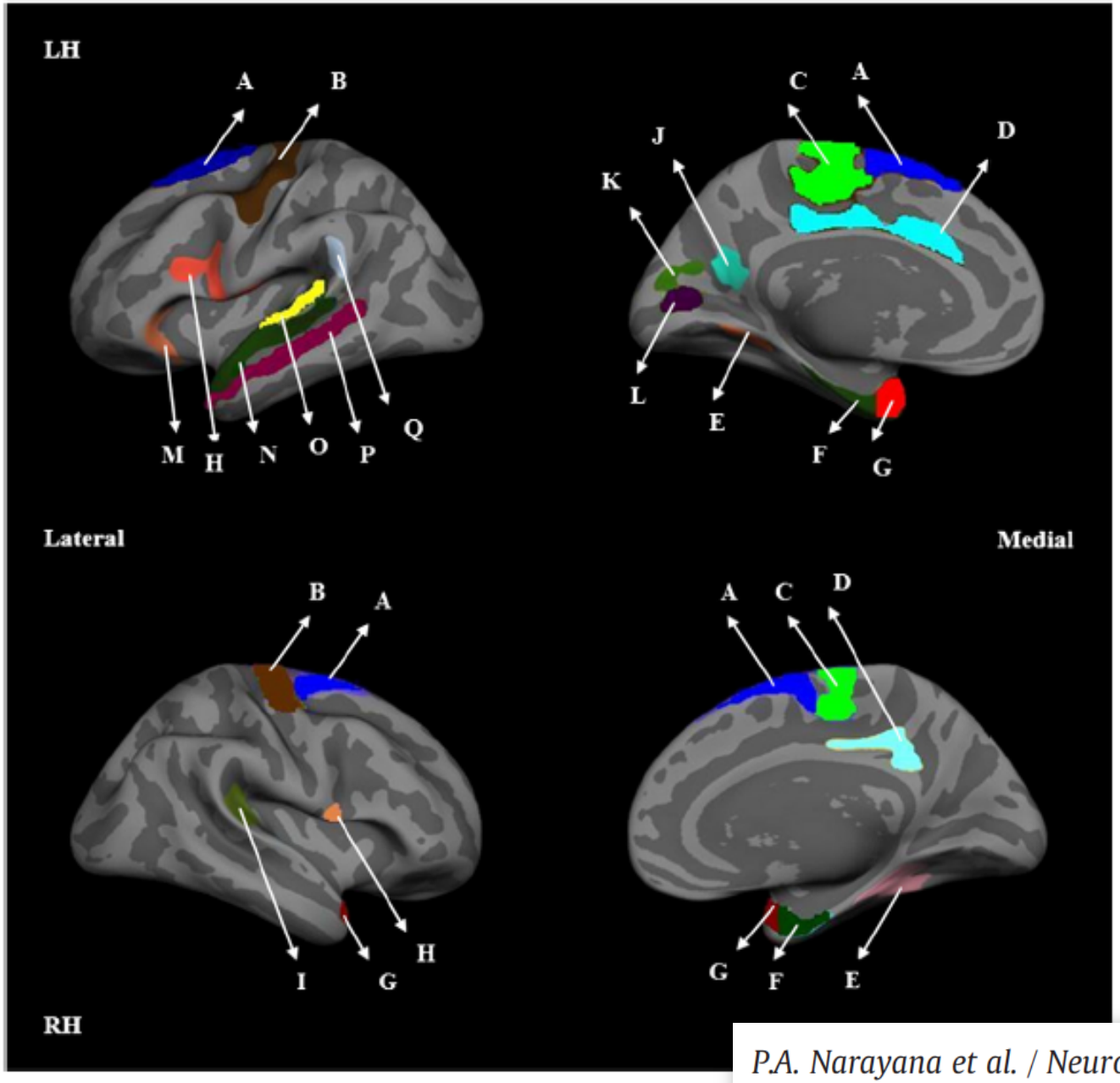
J. Lansley[a,*], D. Mataix-Cols[b], M. Grau[b], J. Radua[b,c], J. Sastre-Garriga[d]

Regions of gray matter loss (a) participants with RRMS + CIS (top row) and (b) RRMS only subgroup (bottom row)

Basal ganglia bilaterally / pre and post central bilaterally / cingulate bilaterally



Lansley et al, Neurosci Biobehav Rev 2013



Comparison of healthy individuals with MS patients

P.A. Narayana et al. / NeuroImage: Clinical 2 (2013) 120–131

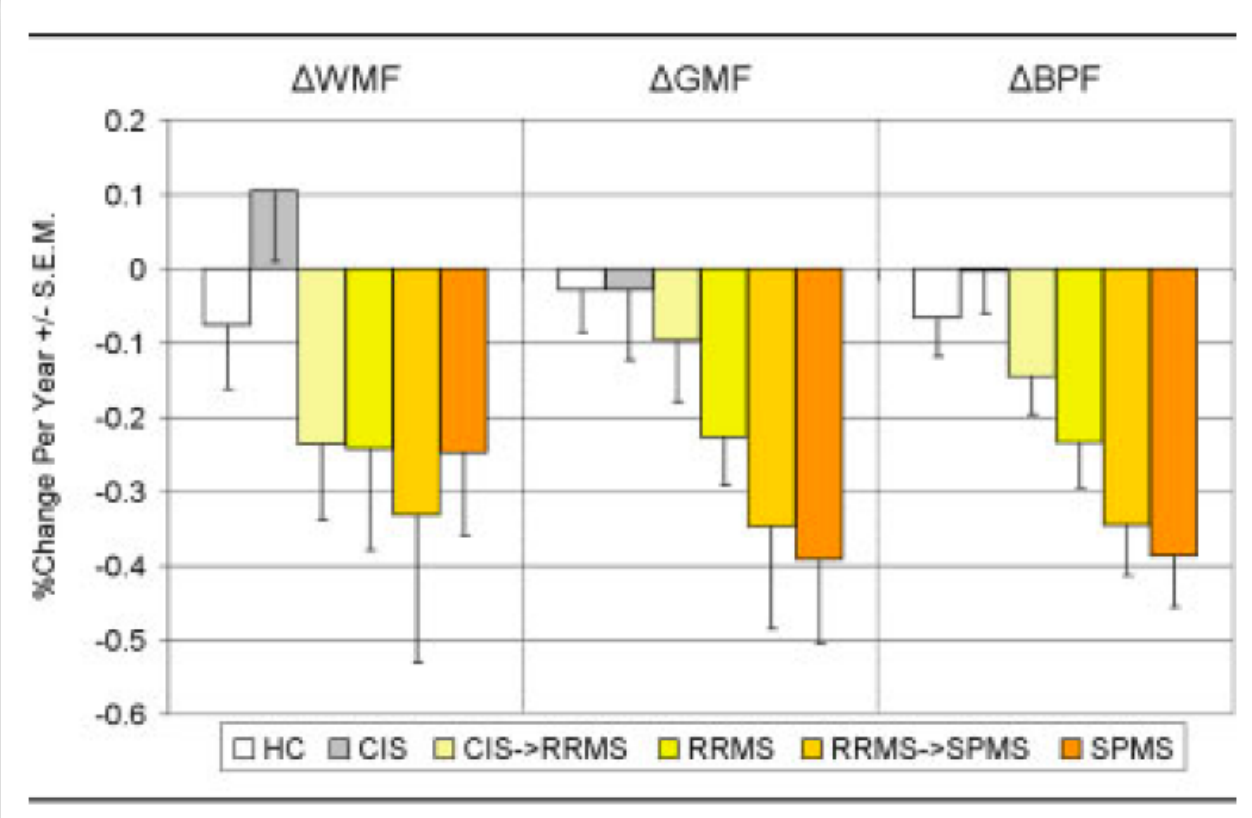
Fig. 3. Lateral (left column) and medial (right column) views of inflated left (LH; top row) and right (RH; bottom row) hemispheres. Images depict the group difference maps highlighting significantly thinner regions in 250 MS patients compared to 125 normal controls. The highlighted regions are: (A) superior frontal, (B) precentral, (C) paracentral, (D) cingulate, (E) fusiform, (F) entorhinal, (G) temporal pole, (H) pars opercularis, (I) transverse temporal, (J) precuneus, (K) cuneus, (L) pericalcerine, (M) pars orbitalis, (N) superior temporal, (O) transverse and parts of the superior temporal gyrus, (P) middle temporal and (Q) supramarginal.

Clinical correlations of GM atrophy

ORIGINAL ARTICLE

Gray Matter Atrophy in Multiple Sclerosis: A Longitudinal Study

Elizabeth Fisher, Ph.D.,[1] Jar-Chi Lee, M.S.,[2] Kunio Nakamura, B.S.,[1] and Richard A. Rudick, M.D.[3]



Fisher et al, Ann Neurol 2008

Clinical correlations of GM atrophy: CIS

DOI: 10.1093/brain/awh126 *Brain* (2004), **127,** 1101–1107

Early development of multiple sclerosis is associated with progressive grey matter atrophy in patients presenting with clinically isolated syndromes

Catherine M. Dalton,[1] Declan T. Chard,[1] Gerard R. Davies,[1] Katherine A. Miszkiel,[2] Dan R. Altmann,[1,4] Kryshani Fernando,[1] Gordon T. Plant,[3] Alan J. Thompson[1] and David H. Miller[1]

Table 2 *Year 3 minus baseline changes in BPF, GMF, WMF and VV in the MS and CIS groups*

Atrophy	Multiple sclerosis		CIS (combined)		Baseline adjusted between-group difference	
	Mean change (CI)	*P* value	Mean change (CI)	*P* value	Mean multiple sclerosis – CIS difference (CI)	*P* value
BPF	–0.012 (–0.016 to –0.008)	0.001	–0.005 (–0.010 to –0.0003)	0.038	–0.008 (–0.014 to –0.001)	0.022
GMF	–0.017 (–0.022 to –0.011)	0.001	–0.005 (–0.011 to 0.004)	0.03*	–0.014 (–0.021 to –0.006)	0.001
WMF	0.005 (0.0007 to 0.009)	0.023	0.0005 (–0.004 to 0.005)	0.820	0.006 (0.0003 to 0.0123)	0.040
VV (ml)	2.410 (1.301 to 3.518)	0.001	0.170 (–1.018 to 1.358)	0.775	2.305 (0.651 to 3.958)	0.007

No statistical differences were noted in mean differences in BPF, GMF, WMF and VV changes from baseline to year 3 between the CIS groups with and without lesions so these groups were combined for statistical purposes.
CI = 95% confidence interval.
*Bootstrap-derived *P* value.

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Dalton et al, Brain 2004

Clinical correlations of GM atrophy: RRMS

Gray Matter Atrophy Is Related to Long-Term Disability in Multiple Sclerosis

Leonora K. Fisniku, MRCP,[1,2] Declan T. Chard, PhD,[1,2] Jonathan S. Jackson, MSci,[1,2] Valerie M. Anderson, BSci,[1,2] Daniel R. Altmann, PhD,[1,3] Katherine A. Miszkiel, MRCP,[4] Alan J. Thompson, PhD,[1,5] and David H. Miller, MD[1,2]

Table 2. Age- and Sex-Adjusted Mean Difference between Patient Subgroups and Control Subjects

Group Comparisons	GMF	WMF
MS-c		
MS-C		
SPM		
RRM		
SPM		
RRM		
SPM		
Benig		
CIS-c		
Benign		
GMF		
CIS =		

Table 3. Correlations of Brain Volume Measurements with Clinical Features

	rs (p)				
	EDSS (n = 73)[a] (44[b])	MSFC (n = 67)[a] (41[b])	Z-PEG (n = 70)[a] (42[b])	Z-WALK (n = 68)[a] (40[b])	Z-PASAT (n = 68)[a] (42[b])
GMF[a]	−0.48 (<0.001)	0.56 (<0.001)	0.59 (<0.001)	−0.40 (0.001)	0.27 (0.026)
GMF[b]	−0.41 (0.005)	0.55 (<0.001)	0.44 (0.003)	−0.49 (0.001)	0.32 (0.038)
WMF[a]	−0.20 (0.086)	0.03 (0.784)	0.16 (0.176)	−0.11 (0.337)	−0.07 (0.537)
WMF[b]	−0.11 (0.443)	0.10 (0.526)	0.28 (0.071)	−0.09 (0.560)	−0.04 (0.761)

[a]All patients.
[b]Multiple sclerosis (MS) subgroup only.
rs = Spearman's rank correlation coefficient; EDSS = expanded disability status scale; MSFC = multiple sclerosis functional composite score; GMF = gray matter fraction; WMF = white matter fraction.

Fisniku et al, Ann Neurol 2008

Clinical correlations of GM atrophy: RRMS

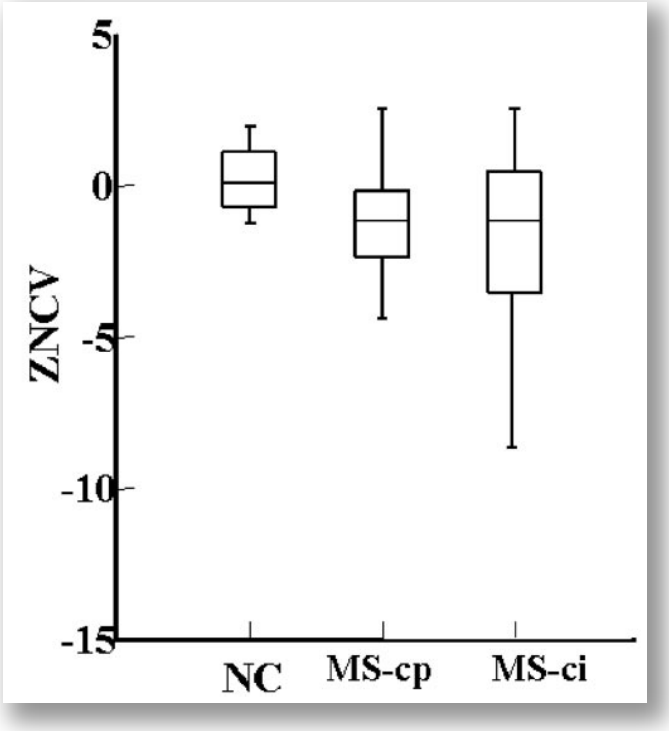
CME

Neocortical volume decrease in relapsing–remitting MS patients with mild cognitive impairment

M.P. Amato, MD; M.L. Bartolozzi, MD; V. Zipoli, MD; E. Portaccio, MD; M. Mortilla, MD; L. Guidi, MD; G. Siracusa, MD; S. Sorbi, MD; A. Federico, MD; and N. De Stefano, MD

Table 3 Correlations between normalized cortical volumes and neuropsychological test scores

Test	All MS patients	MS-cp	MS-ci
SRT-LTS	0.44*	0.34	0.51†
SRT-CLTR	0.42*	0.41	0.39
SRT Delayed	0.32†	0.15	0.37
SPART	0.1	−0.02	0.01
SPART Delayed	0.22	0.32	0.1
SDMT	0.47*	0.19	0.65*
PASAT 3	0.24	0.05	0.32
PASAT 2	0.14	−0.13	0.30
WLG	0.39†	0.17	0.51†
MADRS	−0.30	−0.39	−0.23

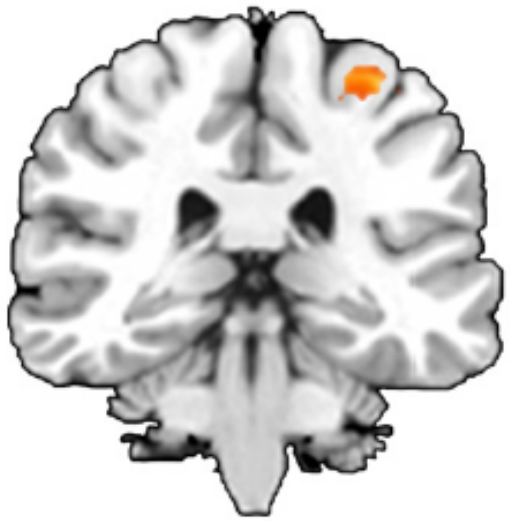


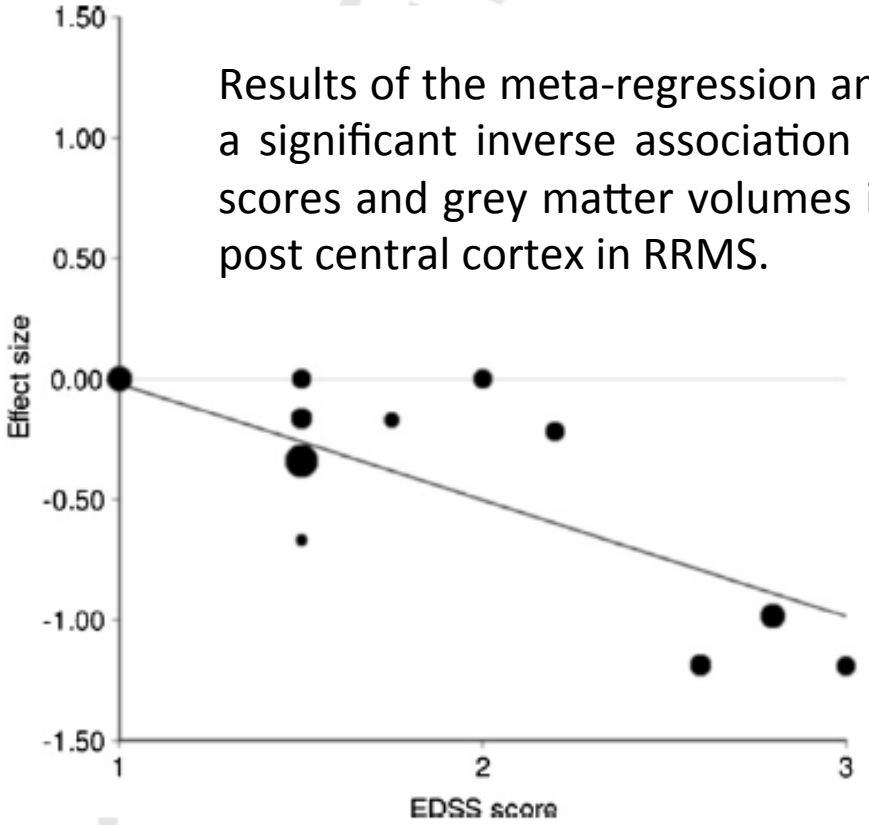
Amato et al, Neurology 2004

Clinical correlations of GM atrophy: RRMS

Localized grey matter atrophy in multiple sclerosis: A meta-analysis of voxel-based morphometry studies and associations with functional disability

J. Lansley[a,*], D. Mataix-Cols[b], M. Grau[b], J. Radua[b,c], J. Sastre-Garriga[d]





Results of the meta-regression analysis showing a significant inverse association between EDSS scores and grey matter volumes in the left pre/ post central cortex in RRMS.

Lansley et al, Neurosci Biobehav Rev 2013

Clinical correlations of GM atrophy: CIS

Table 2 Mean thickness (mm) of the main cortical areas and volume (cm^3) of thalamus and putamen in normal controls and patients with CIS[a]

	Precentral gyrus	Superior frontal gyrus	Thalamus	Putamen	Global CTh
NC (n = 42)	2.38 ± 0.21 (1.84-2.70)	2.75 ± 0.14 (2.15-3.11)	7.9 ± 0.6 (6.4-8.8)	5.5 ± 0.6 (4.6-6.0)	2.48 ± 0.08 (1.84-2.70)
DIS−/CONV− (n = 27)	2.40 ± 0.28 (1.81-2.65)	2.69 ± 0.18 (2.05-3.08)	7.7 ± 0.9 (5.9-8.9)	5.6 ± 0.8 (4.2-6.0)	2.44 ± 0.15 (1.82-2.57)
DIS+/CONV− (n = 19)	2.27 ± 0.21 (1.64-2.59)	2.54 ± 0.21 (1.99-3.01)	7.0 ± 0.8 (5.5-8.5)	5.0 ± 0.6 (4.6-5.4)	2.41 ± 0.12 (1.80-2.74)
All CONV− (n = 46)	2.34 ± 0.28 (1.64-2.65)	2.64 ± 0.21 (1.99-3.08)	7.4 ± 0.9 (5.5-8.9)	5.3 ± 0.8 (4.2-6.0)	2.42 ± 0.15 (1.80-2.74)
DIS−/CONV+ (n = 13)	2.29 ± 0.23 (1.62-2.65)	2.61 ± 0.18 (2.23-3.03)	7.0 ± 0.9 (5.4-8.2)	4.9 ± 0.6 (4.2-5.3)	2.42 ± 0.15 (1.82-2.57)
DIS+/CONV+ (n = 46)	2.18 ± 0.19 (1.58-2.61)[a,b]	2.45 ± 0.20 (1.98-3.01)[c,d]	6.1 ± 0.7 (5.0-7.1)[c,d]	4.5 ± 0.7 (4.0-5.2)[c,d]	2.37 ± 0.10 (1.84-2.70)
All CONV+ (n = 59)	2.21 ± 0.23 (1.58-2.61)[a,b]	2.50 ± 0.21 (1.98-3.03)[a,d]	6.3 ± 0.8 (5.0-8.2)[a,d]	4.6 ± 0.6 (4.0-5.3)[c,d]	2.38 ± 0.15 (1.82-2.70)

Table 4 Univariate correlation between clinical and MRI measurements

	Precentral gyrus, *r*	Superior frontal gyrus, *r*	Thalamus, *r*	Putamen, *r*	Cerebellum, *r*
EDSS	−0.49[a]	−0.52[a]	−0.51[a]	−0.54[a]	−0.55[a]
EDSS change	−0.56[a]	−0.45[a]	−0.58[a]	−0.48[a]	−0.51[a]
T2-WM-LV	0.34[b]	0.39[a]	0.45[a]	0.29[b]	0.32[b]

Abbreviations: EDSS = Expanded Disability Status Scale; T2-WM-LV = T2 white matter lesion volume.
[a] $p < 0.001$.
[b] $p < 0.05$.

Calabrese et al, Neurology 2011

Clinical correlations of GM atrophy: CIS

Table 3 Patients with CIS divided according to the presence of DIS of the lesions, gray matter atrophy, and conversion to definite MS[a]

	CONV+ (n = 59)	CONV− (n = 46)	χ^2, *p* value
DIS+			
A+	44	2	
A−	2	17	
DIS−			
A+	9	20	
A−	4	7	
DIS+ total	46	19	14.7, $p < 0.001$
DIS− total	13	27	
A+ total	53	22	22.3, $p < 0.001$
A− total	6	24	

The patients were clustered (A+/A-) according to the presence of significant atrophy (i.e., 2 SD below the NC mean) in:

- superior frontal gyrus
- thalamus
- cerebellum

The risk of developing MS in the subsequent 4 years was:

OR 9.6 in A+ CIS

OR 5.0 in DIS+ CIS

	Sensitivity	Specificity	Accuracy
DIS	78%	59%	69%
Focal GM	90%	52%	73%

Calabrese et al, Neurology 2011

Cortical lesions

	Method	N	Main findings
Calabrese et al, 2007[50]	1·5 T; DIR	380 MS, 40 controls	The number of cortical lesions correlated with the EDSS score (r=0·48, p=0·001)
Calabrese et al, 2009[51]	1·5 T; DIR	48 benign, 96 relapsing–remitting MS	Low number of cortical lesions and low cortical lesion volume associated with benign course of the disease (low disability 15 years after disease onset)
Roosendaal et al, 2009[52]	1·5 T; DIR	13 MS	Cortical lesions increase substantially over 3 years, are most frequent in patients with secondary progressive MS, and are associated with cognitive impairment
Calabrese et al, 2009[53]	1·5 T; DIR	70 MS	Cortical lesion volume correlated with cognitive impairment index and with almost all cognitive tests of Rao's brief repeatable battery
Calabrese et al, 2009[54]	1·5 T; DIR	48 primary progressive MS	Cortical lesion volume at baseline was the best predictor of percentage change in grey matter volume and disability accumulation during the subsequent 2 years
Calabrese et al, 2010[55]	1·5 T; DIR	107 MS	Cortical lesion volume correlated with baseline EDSS and is the best predictor of EDSS accumulation over 3 years in relapsing–remitting and secondary progressive MS
Bagnato et al, 2010[56]	3 T; IRSPGR	21 MS, 21 controls	Cortical lesions affect cognitive impairment, not independently from white matter disease
Mike et al, 2011[57]	3D IRSPGR	26 MS	Cortical lesion number and volume correlated with SDMT and EDSS; number correlated with CVLT-II scores
Nelson et al, 2011[58]	3 T; DIR/PSIR	39 MS	Cortical lesions have an important role in cognitive impairment. The size of the cortical lesion, and not the tissue-specific location, may best explain their correlation with cognitive impairment
Nielsen et al, 2011[59]	7 T; T2*-2D FLASH	17 MS	Subpial cortical lesions better detected with FLASH-T2* at 7 T than with DIR at 3 T

DIR=double inversion recovery. MS=multiple sclerosis. EDSS=expanded disability status scale. SDMT=symbol digit modality test. CVLT-II=California verbal learning test, second edition. IRSPGR=inversion-recovery spoiled gradient- recalled echo. PSIR=phase-sensitive inversion recovery. FLASH=fast low angle shot.

Table 1: **Cross-sectional and longitudinal studies of relation between cortical lesions and disability**

A number of studies have made clear the presence of MRI-visible cortical lesions and their clinical relevance

Open issues:

1. Relevance for diagnosis
2. Technical issues
   - Sequences
   - Scoring

Geurts et al., Lancet Neurology 2012

Cortical lesions: clinical correlations

Intracortical lesions

Relevance for new MRI diagnostic criteria for multiple sclerosis

M. Filippi, MD
M.A. Rocca, MD
M. Calabrese, MD
M.P. Sormani, PhD
F. Rinaldi, MD
P. Perini, MD
G. Comi, MD
P. Gallo, MD, PhD

Address correspondence and reprint requests to Dr. Massimo Filippi, Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience, Scientific Institute and University Hospital San Raffaele, via Olgettina, 60, 20132 Milan, Italy
filippi.massimo@hsr.it

ABSTRACT

Objective: To generate and validate new MRI diagnostic criteria for multiple sclerosis (MS) taking into account not only white matter lesions but also intracortical lesions (ICLs).

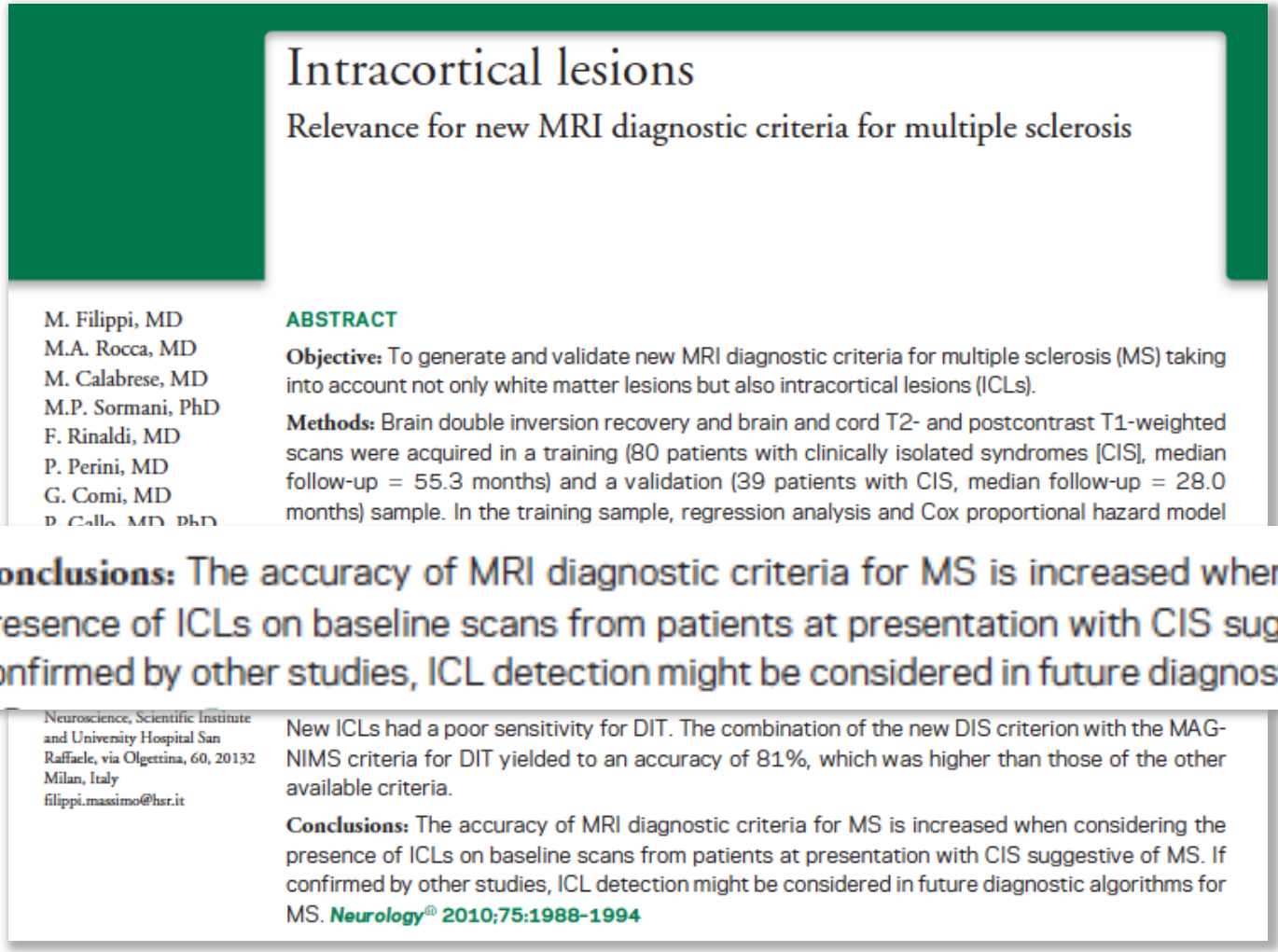
Methods: Brain double inversion recovery and brain and cord T2- and postcontrast T1-weighted scans were acquired in a training (80 patients with clinically isolated syndromes [CIS], median follow-up = 55.3 months) and a validation (39 patients with CIS, median follow-up = 28.0 months) sample. In the training sample, regression analysis and Cox proportional hazard model were used to identify MRI variables independently predicting the evolution to clinically definite (CD) MS. The best criterion selected was then validated. The performance of the new and previously available MRI criteria for disease dissemination in space (DIS) and time (DIT) were tested.

Results: The final multivariate model showed that ≥1 ICL ($p < 0.001$), ≥1 infratentorial ($p = 0.03$), and ≥ 1 gadolinium-enhancing or ≥1 spinal cord lesion ($p = 0.004$) were independent predictors of CDMS. The presence of at least 2 of these variables was the best DIS criterion in both samples. New ICLs had a poor sensitivity for DIT. The combination of the new DIS criterion with the MAGNIMS criteria for DIT yielded to an accuracy of 81%, which was higher than those of the other available criteria.

Conclusions: The accuracy of MRI diagnostic criteria for MS is increased when considering the presence of ICLs on baseline scans from patients at presentation with CIS suggestive of MS. If confirmed by other studies, ICL detection might be considered in future diagnostic algorithms for MS. *Neurology*® 2010;75:1988-1994

Filippi et al., Neurology 2010

Cortical lesions: clinical correlations



Intracortical lesions

Relevance for new MRI diagnostic criteria for multiple sclerosis

M. Filippi, MD
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ABSTRACT

Objective: To generate and validate new MRI diagnostic criteria for multiple sclerosis (MS) taking into account not only white matter lesions but also intracortical lesions (ICLs).

Methods: Brain double inversion recovery and brain and cord T2- and postcontrast T1-weighted scans were acquired in a training (80 patients with clinically isolated syndromes [CIS], median follow-up = 55.3 months) and a validation (39 patients with CIS, median follow-up = 28.0 months) sample. In the training sample, regression analysis and Cox proportional hazard model

Conclusions: The accuracy of MRI diagnostic criteria for MS is increased when considering the presence of ICLs on baseline scans from patients at presentation with CIS suggestive of MS. If confirmed by other studies, ICL detection might be considered in future diagnostic algorithms for

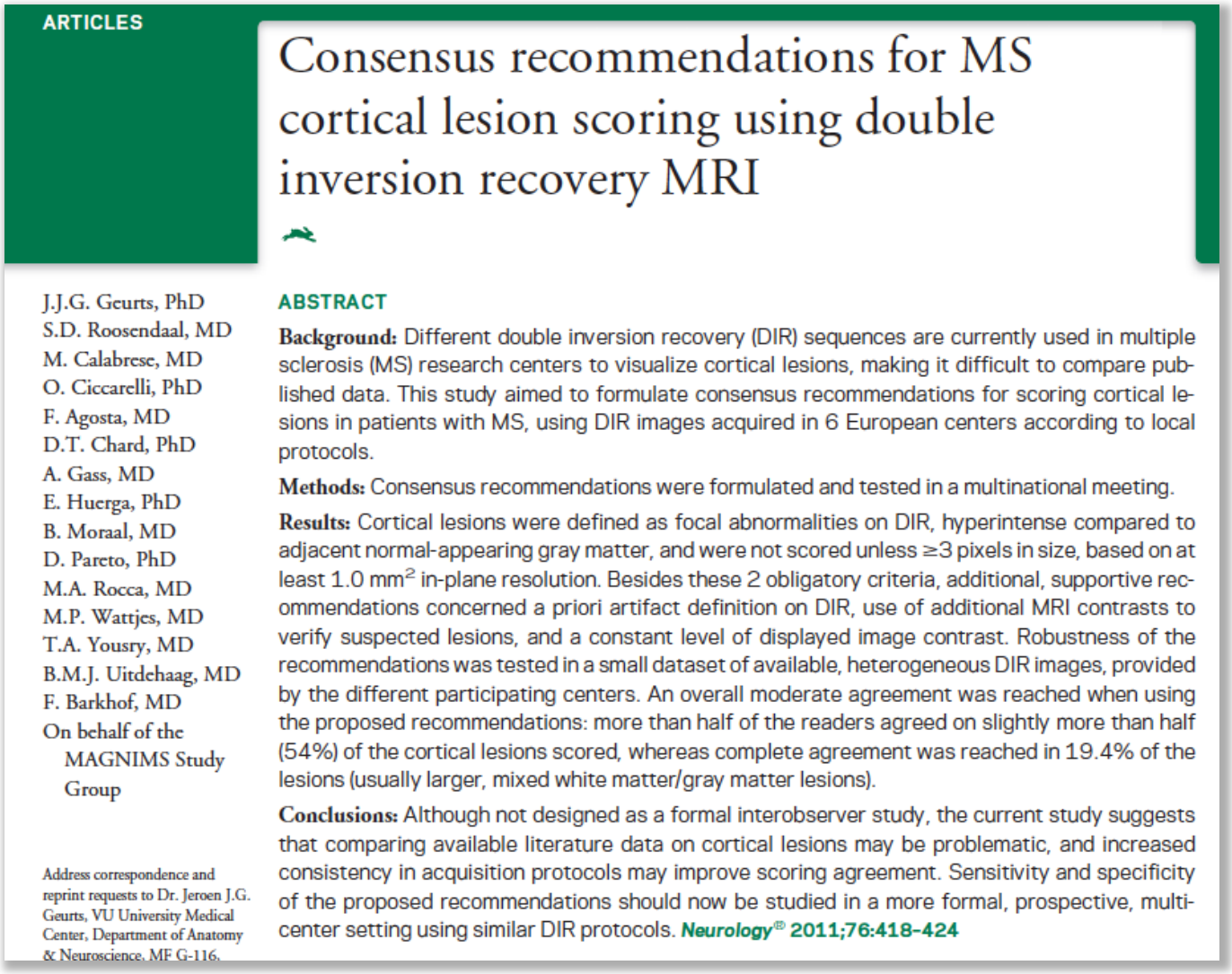
Neuroscience, Scientific Institute and University Hospital San Raffaele, via Olgettina, 60, 20132 Milan, Italy
filippi.massimo@hsr.it

New ICLs had a poor sensitivity for DIT. The combination of the new DIS criterion with the MAGNIMS criteria for DIT yielded to an accuracy of 81%, which was higher than those of the other available criteria.

Conclusions: The accuracy of MRI diagnostic criteria for MS is increased when considering the presence of ICLs on baseline scans from patients at presentation with CIS suggestive of MS. If confirmed by other studies, ICL detection might be considered in future diagnostic algorithms for MS. *Neurology*® 2010;75:1988-1994

Filippi et al., Neurology 2010

Cortical lesions: scoring difficulties



ARTICLES

Consensus recommendations for MS cortical lesion scoring using double inversion recovery MRI

J.J.G. Geurts, PhD
S.D. Roosendaal, MD
M. Calabrese, MD
O. Ciccarelli, PhD
F. Agosta, MD
D.T. Chard, PhD
A. Gass, MD
E. Huerga, PhD
B. Moraal, MD
D. Pareto, PhD
M.A. Rocca, MD
M.P. Wattjes, MD
T.A. Yousry, MD
B.M.J. Uitdehaag, MD
F. Barkhof, MD
On behalf of the MAGNIMS Study Group

Address correspondence and reprint requests to Dr. Jeroen J.G. Geurts, VU University Medical Center, Department of Anatomy & Neuroscience, MF G-116,

ABSTRACT

Background: Different double inversion recovery (DIR) sequences are currently used in multiple sclerosis (MS) research centers to visualize cortical lesions, making it difficult to compare published data. This study aimed to formulate consensus recommendations for scoring cortical lesions in patients with MS, using DIR images acquired in 6 European centers according to local protocols.

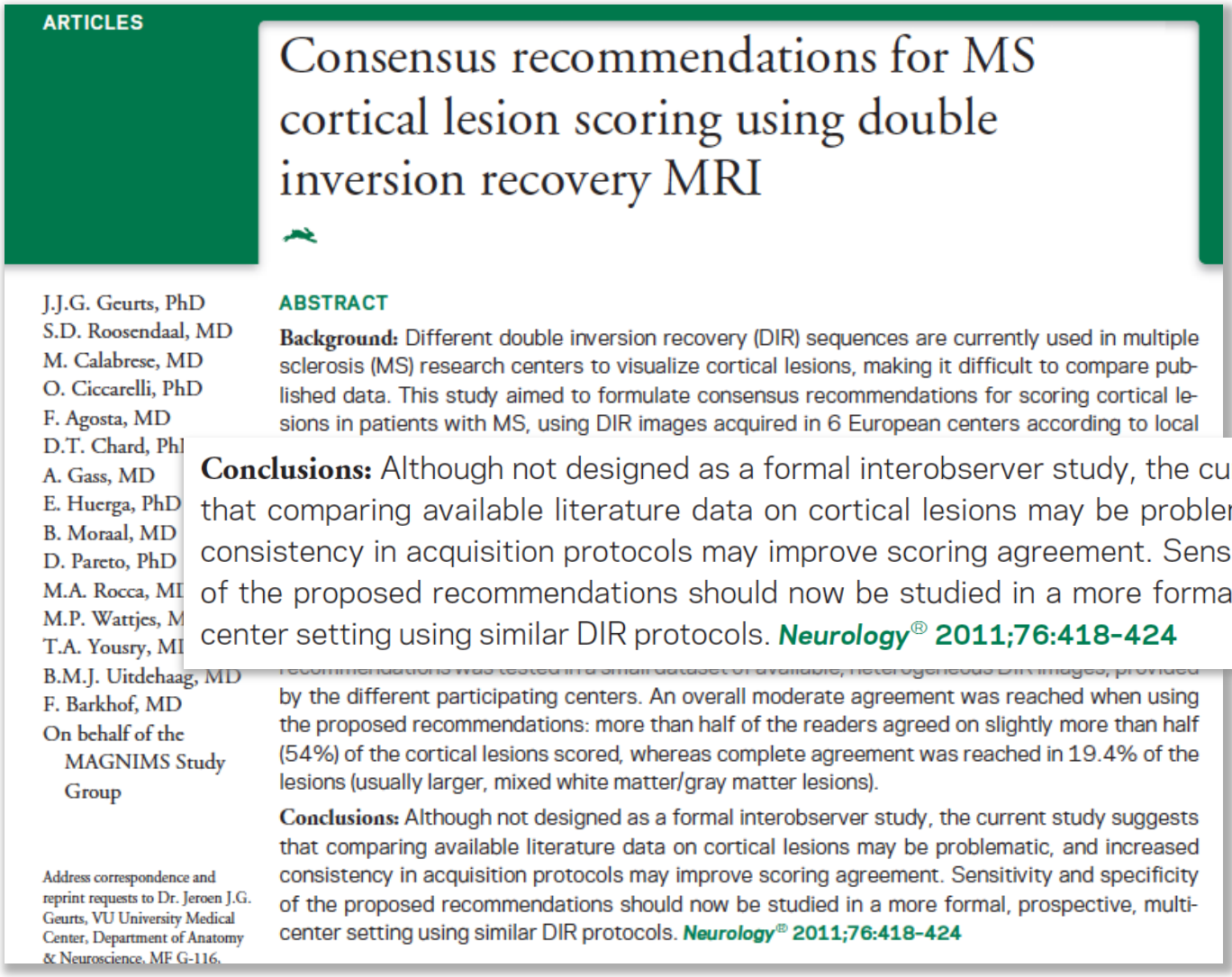
Methods: Consensus recommendations were formulated and tested in a multinational meeting.

Results: Cortical lesions were defined as focal abnormalities on DIR, hyperintense compared to adjacent normal-appearing gray matter, and were not scored unless ≥3 pixels in size, based on at least 1.0 mm^2 in-plane resolution. Besides these 2 obligatory criteria, additional, supportive recommendations concerned a priori artifact definition on DIR, use of additional MRI contrasts to verify suspected lesions, and a constant level of displayed image contrast. Robustness of the recommendations was tested in a small dataset of available, heterogeneous DIR images, provided by the different participating centers. An overall moderate agreement was reached when using the proposed recommendations: more than half of the readers agreed on slightly more than half (54%) of the cortical lesions scored, whereas complete agreement was reached in 19.4% of the lesions (usually larger, mixed white matter/gray matter lesions).

Conclusions: Although not designed as a formal interobserver study, the current study suggests that comparing available literature data on cortical lesions may be problematic, and increased consistency in acquisition protocols may improve scoring agreement. Sensitivity and specificity of the proposed recommendations should now be studied in a more formal, prospective, multicenter setting using similar DIR protocols. *Neurology*® 2011;76:418–424

Geurts et al., Neurology 2011

Cortical lesions: scoring difficulties



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Geurts et al., Neurology 2011

Atrophy – treatment effects

Handy Manny

Clinical trials - atrophy results licensed drugs (<2013)

TRIAL	Form	Drug	Reported results
ETOMS	CIS	IFN	**Positive**
BENEFIT	CIS	IFN	Negative
CHAMPS	CIS	IFN	Not reported
PRECISE	CIS	GA	Negative
Pivotal Betaferon®	RRMS	IFN	Not reported
PRISMS	RRMS	IFN	Not reported
Pivotal Avonex®	RRMS	IFN	Negative
Eu-Can Copaxone®	RRMS	GA	Negative
AFFIRM	RRMS	NTZ	Negative
FREEDOMS I & II	RRMS	FTY	**Positive**
EUSPMS	SPMS	IFN	Negative
IMPACT	SPMS	IFN	Not reported
SPECTRIMS	SPMS	IFN	Not reported
PROMISE	PPMS	GA	Negative
Barcelona DBPC	PPMS	IFN	Negative
London DBPC	PPMS	IFN	Negative

Atrophy – treatment effects

Treating relapsing–remitting multiple sclerosis: therapy effects on brain atrophy

Angela Vidal-Jordana[1] · Jaume Sastre-Garriga[1] · Alex Rovira[2] · Xavier Montalban[1]

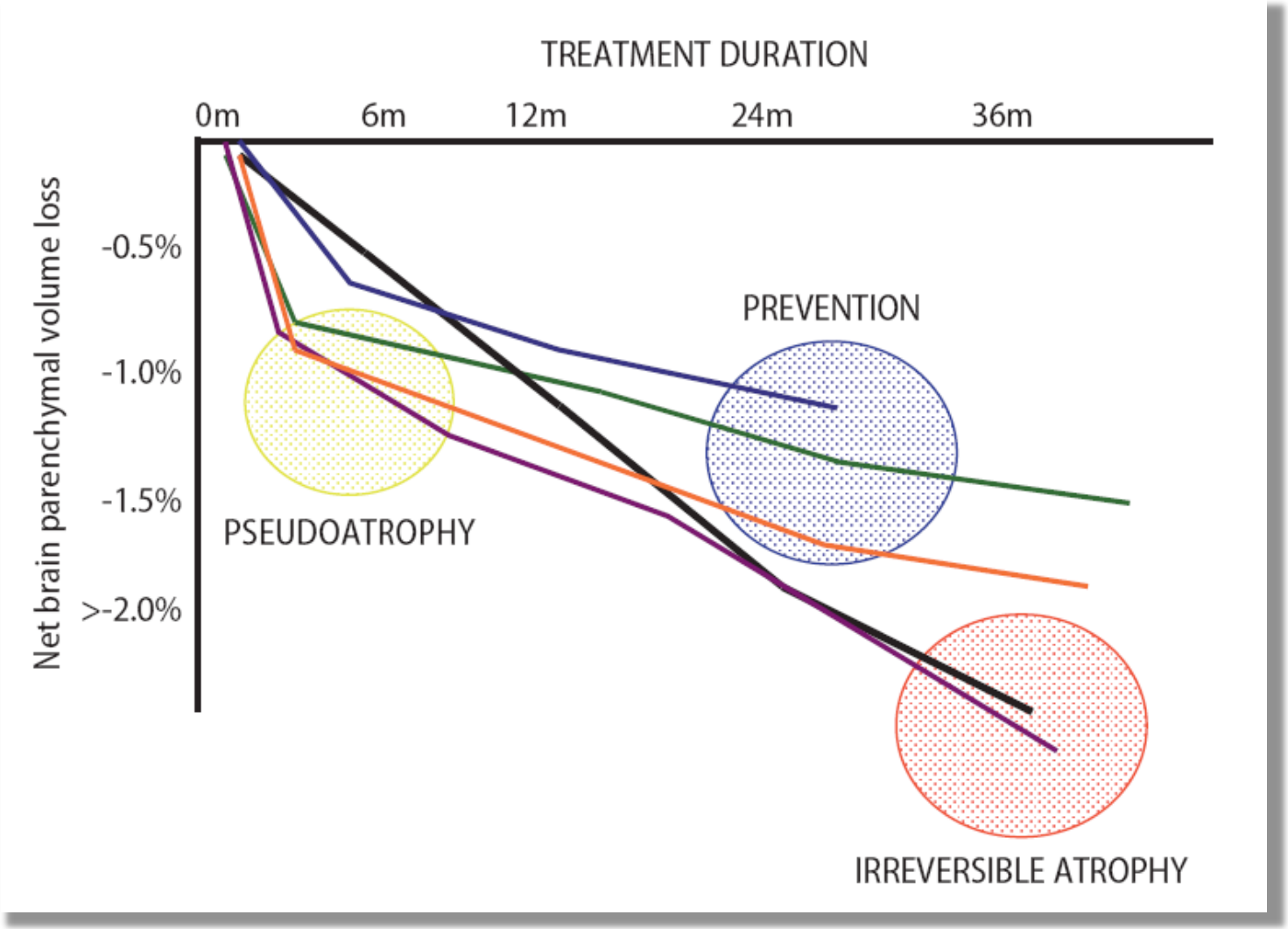
Table 2 Immediate and delayed therapy effects on brain volume changes in the double-blind phase of relapsing remitting multiple sclerosis trials

Drug	Global effect on brain volume[a]	Immediate effect on brain volume[b]	Delayed effect on brain volume[c]	Able to cross blood–brain barrier
Placebo-controlled studies				
Interferon beta 1a	No	No	Yes	No
Glatiramer acetate	No	No[e]	NA[f]	No
Fingolimod	Yes	Yes	Yes	Yes
Dimethyl-fumarate	Yes[g]	No[h]	Yes[h]	No
Teriflunomide	No	No	No	No
Laquinimod	Yes	NA	NA	Yes
Natalizumab	No	No	Yes	No
Active comparator[d]				
Interferon vs glatiramer acetate	Yes (GA)[i]	Yes (GA)[i]	Yes (GA)[i]	No
Fingolimod vs im IFN-β-1a	Yes (FTY)	Yes (FTY)	NA[j]	Yes (FTY)
Alemtuzumab vs sc IFN-β-1a 44 µg	Yes (AL)	NA[k]	NA[k]	No

AL alemtuzumab, *BID* two times a day, *FTY* fingolimod, *GA* glatiramer acetate, *IFN-β* interferon beta, *im* intramuscular, *NA* not applicable, *sc* subcutaneous, *vs* versus

Vidal-Jordana et al, J Neurol 2015

Atrophy – treatment effects



Zivadinov et al., J Neurol 2008

Atrophy – treatment effects

MRI outcomes in a placebo-controlled trial of natalizumab in relapsing MS

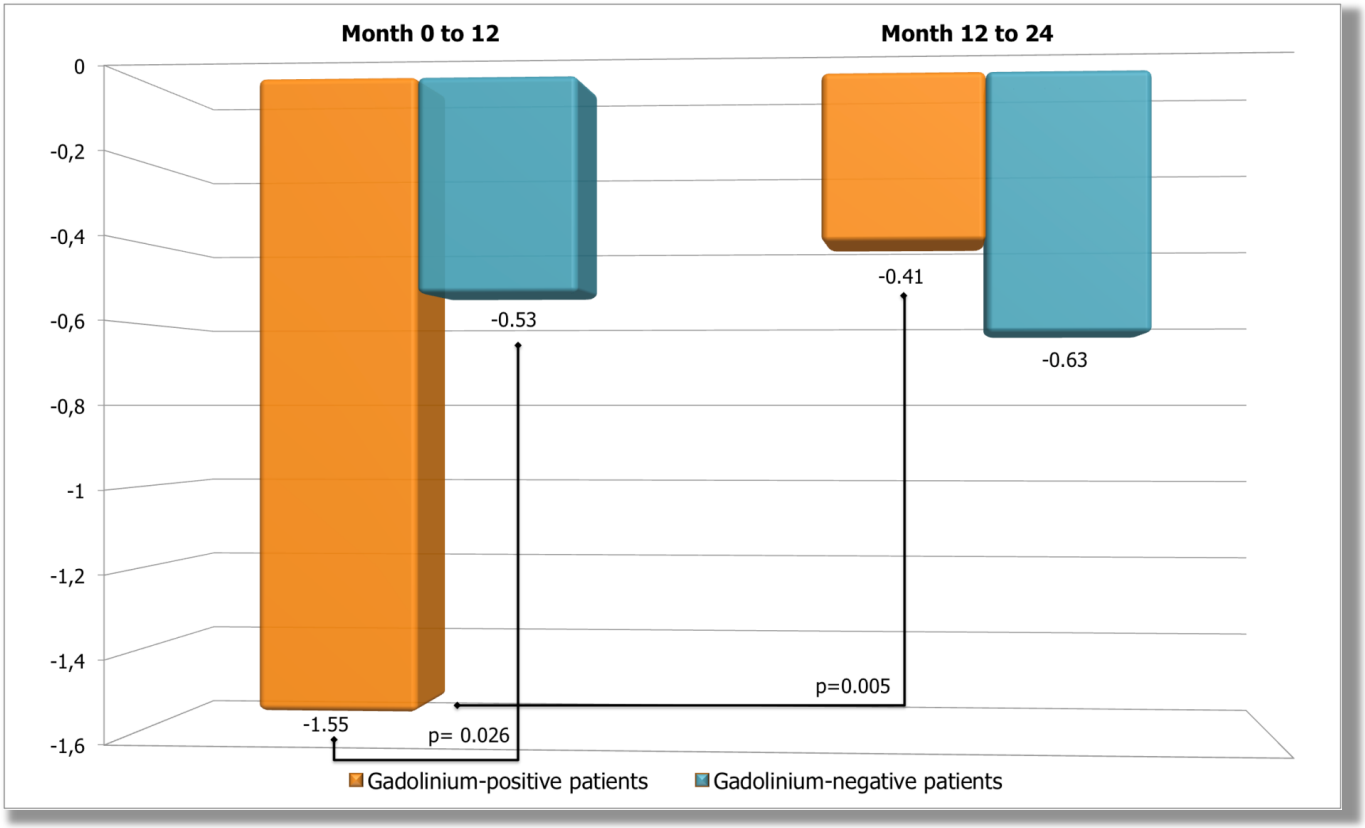
	NTZ	PLC	*p*
Baseline – 12 months	**-0.56%**	-0.40%	**0.002**
12 months – 24 months	**-0.24%**	-0.43%	**0.004**
Baseline – 24 months	-0.80%	-0.82%	0.822

Miller et al., Neurology 2007

Atrophy – treatment effects

Early brain pseudoatrophy while on natalizumab therapy is due to white matter volume changes

Angela Vidal-Jordana, Jaume Sastre-Garriga, Francisco Pérez-Miralles, Carmen Tur, Mar Tintoré, Alejandro Horga, Cristina Auger, Jordi Río, Carlos Nos, Mari C Edo, María J Arévalo, Joaquín Castilló, Alex Rovira and Xavier Montalban



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Vidal-Jordana et al., Mult Scler 2013

Atrophy – treatment effects

	N	Duration (years)	Trial design	Results
Zivadinov et al, 2007[110]	54	3	Non-randomised; intramuscular interferon beta-1a *vs* untreated	Decreased grey matter atrophy with interferon beta
Nakamura et al, 2010[111]	131	2	Randomised; intramuscular interferon beta-1a *vs* placebo	Decreased grey matter atrophy with interferon beta; pseudoatrophy mainly in white matter
Bendfeldt et al, 2010[112]	86	2	Non-randomised; interferon beta-1a subcutaneous *vs* intramuscular *vs* glatiramer acetate *vs* untreated	Differences in regional grey matter atrophy in (differentially) treated *vs* non-treated patients with relapsing–remitting multiple sclerosis
Kapoor et al, 2010[113]	120	2	Randomised; lamotrigine *vs* placebo	Suggestion of white matter pseudoatrophy; no effect on grey matter atrophy
Calabrese et al, 2012[114]	165	2	Randomised; interferon beta-1a subcutaneous *vs* interferon beta-1a intramuscular *vs* glatiramer acetate	Cortical thinning comparable between treatment groups

Table 4: **Effects of therapeutic intervention on grey matter atrophy**

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Geurts et al., Lancet Neurology 2012

Atrophy – treatment effects

Predictive value of early brain atrophy on response in patients treated with interferon β

OPEN

Francisco Carlos Pérez-Miralles, MD
Jaume Sastre-Garriga, MD
Angela Vidal-Jordana, MD
Jordi Río, MD, PhD
Cristina Auger, MD
Deborah Pareto, RT
Mar Tintoré, MD, PhD
Alex Rovira, MD
Xavier Montalban, MD, PhD

Correspondence to Dr. Sastre-Garriga: jsastre-garriga@cem-cat.org

ABSTRACT

Objective: To investigate the association between brain volume loss during the first year of interferon treatment and clinical outcome at 4 years.

Methods: Patients with multiple sclerosis initiating interferon β were clinically evaluated every 6 months for the presence of relapses and assessment of global disability using the Expanded Disability Status Scale (EDSS). MRI scans were performed at baseline and after 12 months, and the percentage of brain volume change (PBVC), brain parenchymal volume change (BPVc%), gray matter volume change (GMVc%), and white matter volume change (WMVc%) were estimated. Patients were divided based on the cutoff values for predicting confirmed EDSS worsening obtained by receiver operating characteristic analysis for all atrophy measurements. Survival curves and Cox proportional hazards regression to predict disability worsening at last observation were applied, adjusting for demographic, clinical, and radiologic variables.

Results: Larger PBVC and WMVc% decreases were observed in patients with disability worsening at 4 years of follow-up, whereas no differences were found in BPVc% or GMVc%. Cutoff points were obtained for PBVC (−0.86%; sensitivity 65.5%, specificity 71.4%) and WMVc% (−2.49%; sensitivity 85.3%, specificity 43.8%). Patients with decreases of PBVC and WMVc % below cutoff values were more prone to develop disability worsening (unadjusted hazard ratio [HR] 3.875, $p = 0.005$; HR 4.246, $p = 0.004$, respectively). PBVC (HR 4.751, $p = 0.008$) and the interaction of new T2 lesions with WMVc% (HR 1.086, $p = 0.005$) were found to be independent predictors of disability worsening in the multivariate analysis.

Conclusions: At the patient level, whole-brain and white matter volume changes in the first year of interferon β therapy are predictive of subsequent clinical evolution under treatment. ***Neurol Neuroimmunol Neuroinflamm* 2015;2:e132; doi: 10.1212/NXI.0000000000000132**

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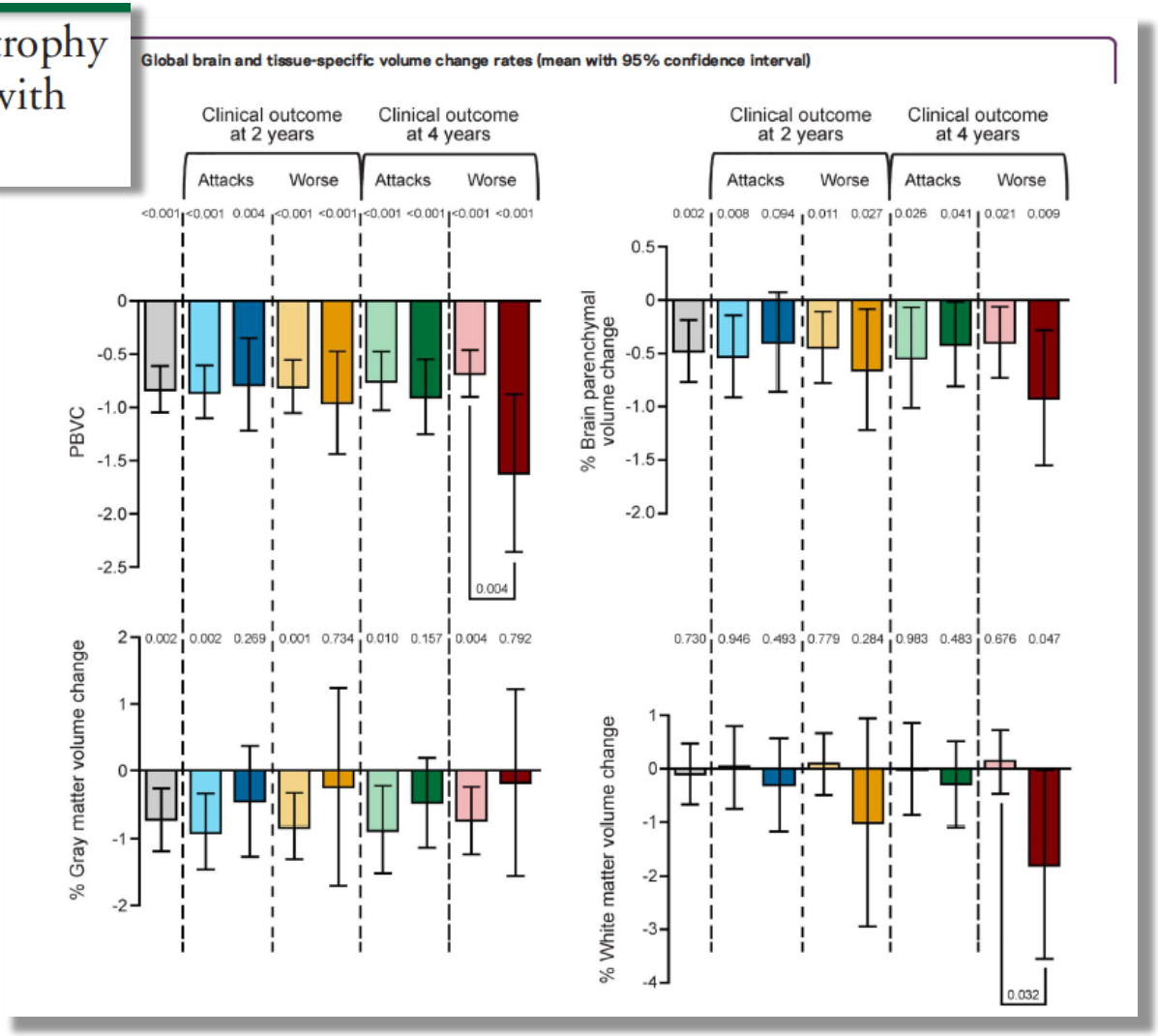
Pérez-Miralles et al, Neurol Neuroimmunol Neuroinflamm 2015

Atrophy – treatment effects

Predictive value of early brain atrophy on response in patients treated with interferon β



Pérez-Miralles et al, Neurol Neuroimmunol Neuroinflamm 2015

Atrophy – treatment effects

Research Paper

MULTIPLE SCLEROSIS JOURNAL | MSJ

Multiple Sclerosis Journal
0(0) 1–10

DOI: 10.1177/1352458513475723
msj.sagepub.com
SAGE

Magnetic resonance imaging outcomes from a phase III trial of teriflunomide

Jerry S Wolinsky[1], Ponnada A Narayana[2], Flavia Nelson[1], Sushmita Datta[2], Paul O'Connor[3], Christian Confavreux[4], Giancarlo Comi[5], Ludwig Kappos[6], Tomas P Olsson[7], Philippe Truffinet[8], Lin Wang[9], Aaron Miller[10] and Mark S Freedman[11] for the Teriflunomide Multiple Sclerosis Oral (TEMSO) Trial Group

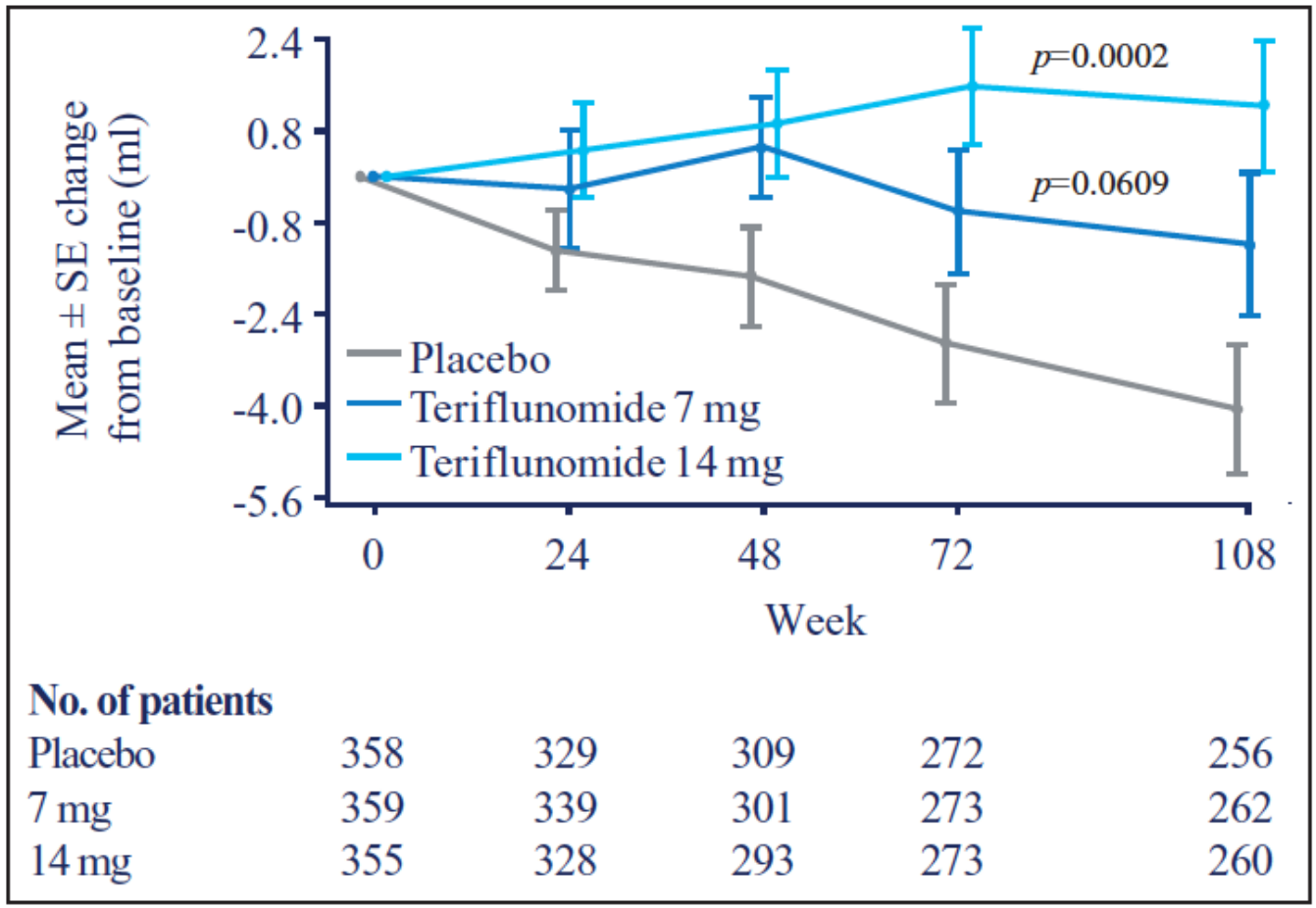
RESEARCH PAPER

Placebo-controlled trial of oral laquinimod in multiple sclerosis: MRI evidence of an effect on brain tissue damage

Massimo Filippi,[1,2] Maria A Rocca,[1,2] Elisabetta Pagani,[1] Nicola De Stefano,[3] Douglas Jeffery,[4] Ludwig Kappos,[5] Xavier Montalban,[6] Alexei N Boyko,[7] Giancarlo Comi,[2] on behalf of the ALLEGRO Study Group

Wolinsky et al, Mult Scler 2013 & Filippi et al, JNNP 2013

Atrophy – treatment effects



No. of patients					
Placebo	358	329	309	272	256
7 mg	359	339	301	273	262
14 mg	355	328	293	273	260

Figure 6. Change from baseline in volume of white matter.

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Wolinsky et al, Mult Scler 2013 & Filippi et al, JNNP 2013

Atrophy – treatment effects

Table 1 Per cent changes (calculated from absolute values) from baseline of white matter, grey matter and thalamic volumes*

	White matter values median (range)	Grey matter values median (range)	Thalamic values LS mean (SE)
% Change from baseline to month 12			
Placebo (n=457)	−0.4 (−22.2 to 40.8)	−0.8 (−25.3 to 21.1)	−1.0 (0.12)†
Laquinimod (n=472)	0.0 (−24.7 to 11.9)	−0.3 (−19.4 to 22.4)	−0.6 (0.12)
p Value	p=0.004	p=0.004	p=0.005
Treatment effect	0.394*	0.502*	0.408‡
% Change from month 12 to month 24			
Placebo (n=409)	−0.2 (−21.1 to 10.6)	−0.6 (−14.3 to 32.5)	−0.9 (0.13)†
Laquinimod (n=419)	−0.2 (−15.3 to 15.0)	−0.7 (−11.5 to 16.6)	−0.7 (0.13)
p Value	p=0.857	p=0.664	p=0.13
Treatment effect	−0.013*	−0.078*	0.233‡
% Change from baseline to month 24			
Placebo (n=409)	−0.5 (−25.7 to 39.8)	−1.2 (−16.9 to 24.3)	−1.8 (0.15)†
Laquinimod (n=418)	−0.3 (−27.3 to 19.2)	−0.9 (−17.4 to 21.2)	−1.3 (0.15)
p Value	p=0.035	p=0.078	p=0.003
Treatment effect	0.327*	0.372*	0.600‡

*Hodges-Lehmann median estimate for treatment difference.
†Patients evaluable for thalamic volume at month 12 were n=468 laquinimod, n=454 placebo; for thalamic volume at month 12 and month 24 were n=402 laquinimod, n=400 placebo; and for thalamic volume at month 24 were n=408 laquinimod, n=404 placebo.
‡Least square mean difference. Data generated using mixed model repeated measures for % change between baseline to month 12 and month 24 and with analysis of covariance for % change between month 12 to month 24 as described in statistical methods.

Wolinsky et al, Mult Scler 2013 & Filippi et al, JNNP 2013

Cortical lesions – treatment effects

Research Paper

MULTIPLE SCLEROSIS JOURNAL | MSJ

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18(12) 1760–1767

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Natalizumab strongly suppresses cortical pathology in relapsing–remitting multiple sclerosis

F Rinaldi[1,*], M Calabrese[1,*], D Seppi[1], M Puthenparampil[1], P Perini[1] and P Gallo[1]

Cortical lesions – treatment effects

Natalizumab strongly suppresses cortical pathology in relapsing–remitting multiple sclerosis

Table 2. Clinical and MRI changes over 2 years.

	Natalizumab-treated	IMA-treated	Untreated
ARR	0.1 (0.4; 0–1)[a,b]	0.5 (0.6; 0–3)	1.2 (0.8; 0–4)
EDSS change	–0.3 (0.5; -1.5–+1.0)	0.6 (0.5; 0–2.0)	0.7 (0.6; 0–2.0)
New T2 WM lesions	0.3 (0.5; 0–2)[a,b]	1.2 (0.8; 0–4)	2.0 (1.6; 0–5)
New Gd+ lesions	0.03 (0.2; 0–1)[b]	0.2 (0.4; 0–3)	1.1 (1.1; 0–4)
New CLs	0.2 (0.6; 0–3)[a,b]	1.3 (1.1; 1–6)	2.9 (1.5; 1–8)
CTh change (%)	1.7[a,b]	3.7	4.6

[a]$p<0.05$ vs IMA.
[b]$p<0.001$ vs untreated.
Data are reported as mean (SD; range).
ARR: annualized relapse rate; CLs: cortical lesions; EDSS: Expanded Disability Status Scale; Gd+: gadolinium enhancing; GMF: grey matter fraction; IMA: immunomodulatory agents; WM: white matter; CTh: cortical thickness.

Rinaldi et al, Mult Scler 2012

Conclusions

Grey matter atrophy takes place early in Multiple Sclerosis and is observed in patients in their first months or years after Multiple Sclerosis initial clinical manifestations and seems to show regional differences, whereas not much change has been observed in white matter volume.

Grey matter atrophy is clinically relevant, whereas clinical correlations with white matter atrophy are scarce or non-existent

Cortical lesions have been also demonstrated in a number of studies in Multiple Sclerosis and maybe clinically relevant, but their reliable depiction using MRI at conventional field is still challenging

There is evidence of a positive effect of present Multiple Sclerosis therapies on grey matter atrophy and cortical lesions, but their use as a treatment monitoring tool is still far from demonstrated and it may be that white matter measurements are more useful for this purpose

BIG THANKS!

UAB Universitat Autònoma de Barcelona

Vall d'Hebron Institut de Recerca

Vall d'Hebron Hospital

FEM Fundació Esclerosi Múltiple

IDI INSTITUT DE DIAGNÒSTIC PER LA IMATGE

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Magnetic Resonance Imaging in Multiple Sclerosis

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.

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ESMRMB 2015
European Society for Magnetic Resonance in Medicine and Biology
32nd Annual Scientific Meeting October 1-3, Edinburgh/UK

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Centre d'Esclerosi Múltiple de Catalunya

Clinical correlates of GM damage in Multiple Sclerosis

Jaume Sastre-Garriga - @J_SastreGarriga

Servei de Neurologia / Neuroimmunologia
Centre d'Esclerosi Múltiple de Catalunya – Cemcat
Hospital Universitari Vall d'Hebron, Barcelona

Vall d'Hebron
Institut de Recerca

Vall d'Hebron
Hospital
Unitat de Neuroimmunologia Clínica

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