

MRI as a Surrogate Marker for Disease Activity

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Disclosures

- ◇ Research support from:
 - ◇ Biogen Idec
 - ◇ Novartis Pharmaceuticals
 - ◇ MSDx

Educational Objectives

- ◇ Overview of the roles MRI plays in MS
- ◇ Understand the role of MRI as a marker for CNS Inflammatory Activity
- ◇ Understand the role of MRI as a marker for CNS Neurodegeneration
- ◇ Future Directions

The Role of MRI in MS

- ◆ Diagnosis

- ◆ McDonald Criteria 2001, 2005, 2010

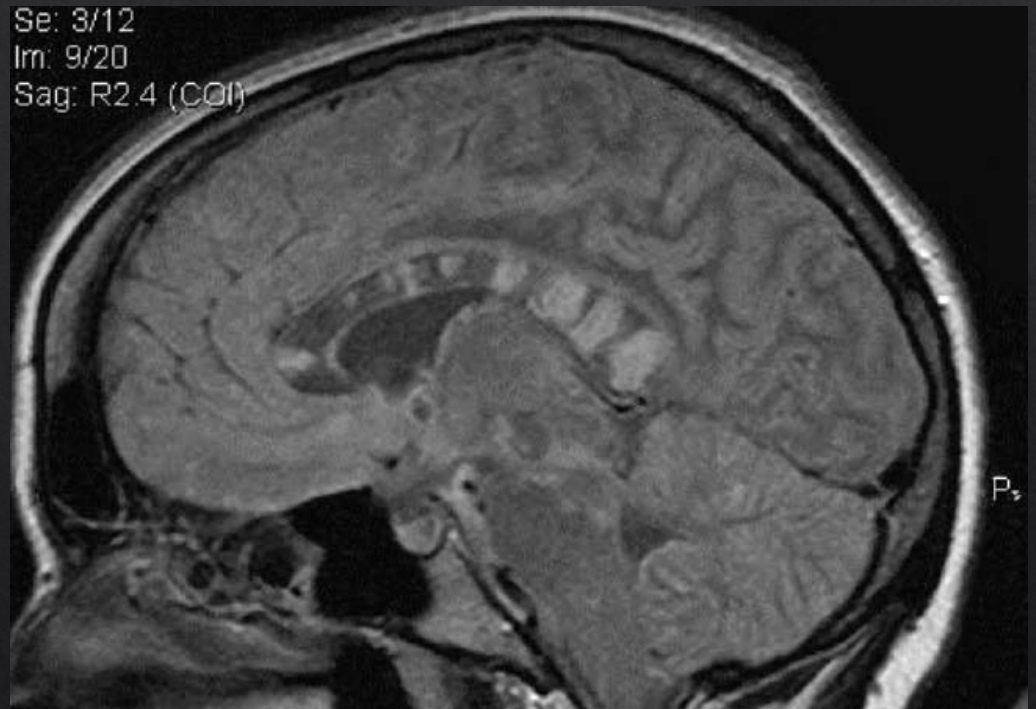


The Role of MRI in MS

◇ Diagnosis

- ◇ McDonald Criteria 2001, 2005, 2010

◇ Differential Diagnosis



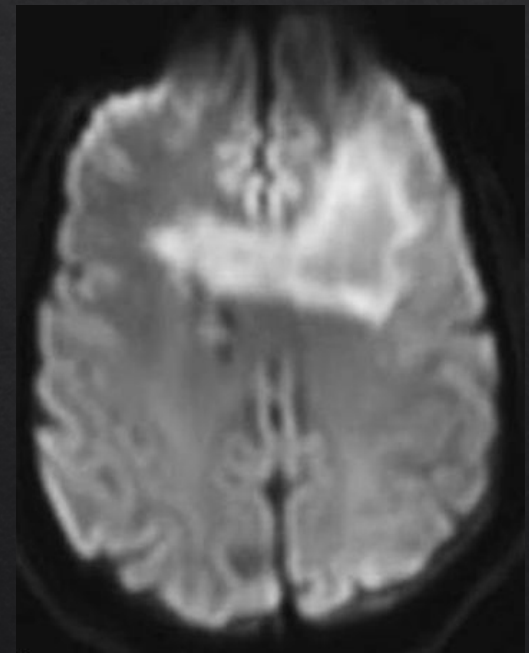
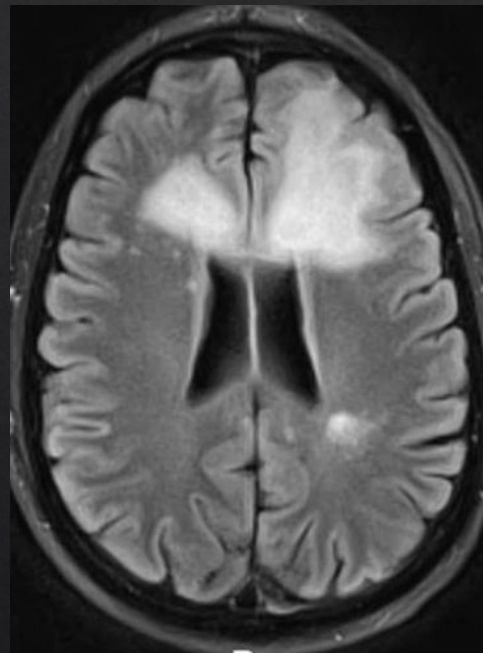
The Role of MRI in MS

- ◆ Diagnosis

- ◆ McDonald Criteria 2001, 2005, 2010

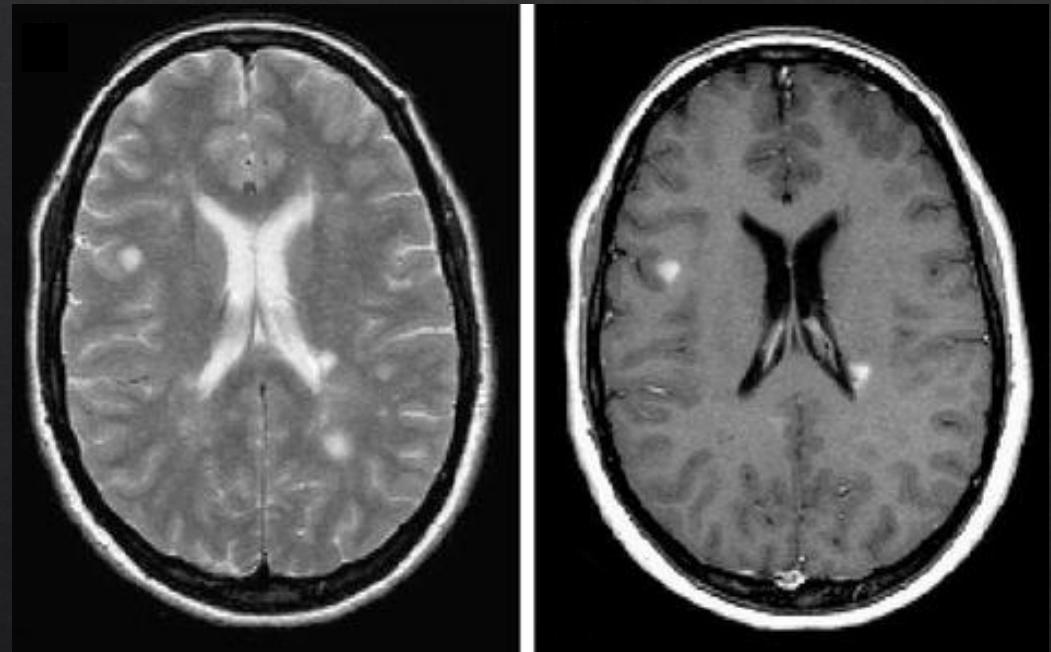
- ◆ Differential Diagnosis

- ◆ Pharmacovigilance

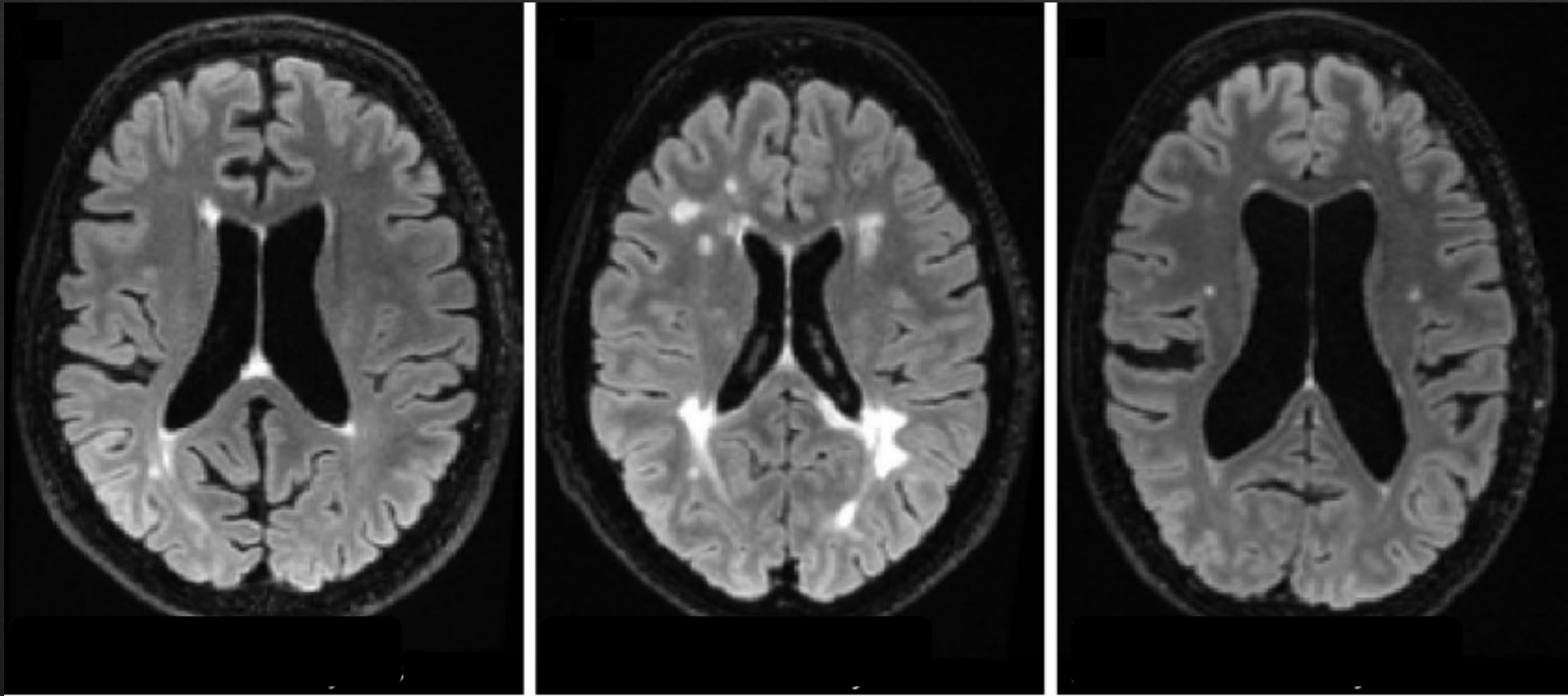


The Role of MRI in MS

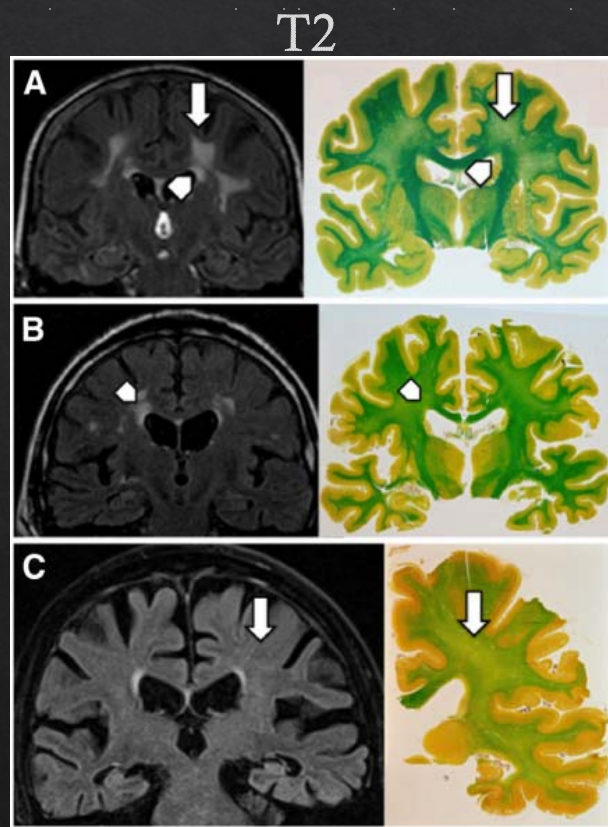
- ◇ Diagnosis
 - ◇ McDonald Criteria 2001, 2005, 2010
- ◇ Differential Diagnosis
- ◇ Pharmacovigilance
- ◇ Monitoring Disease Activity / Treatment Monitoring



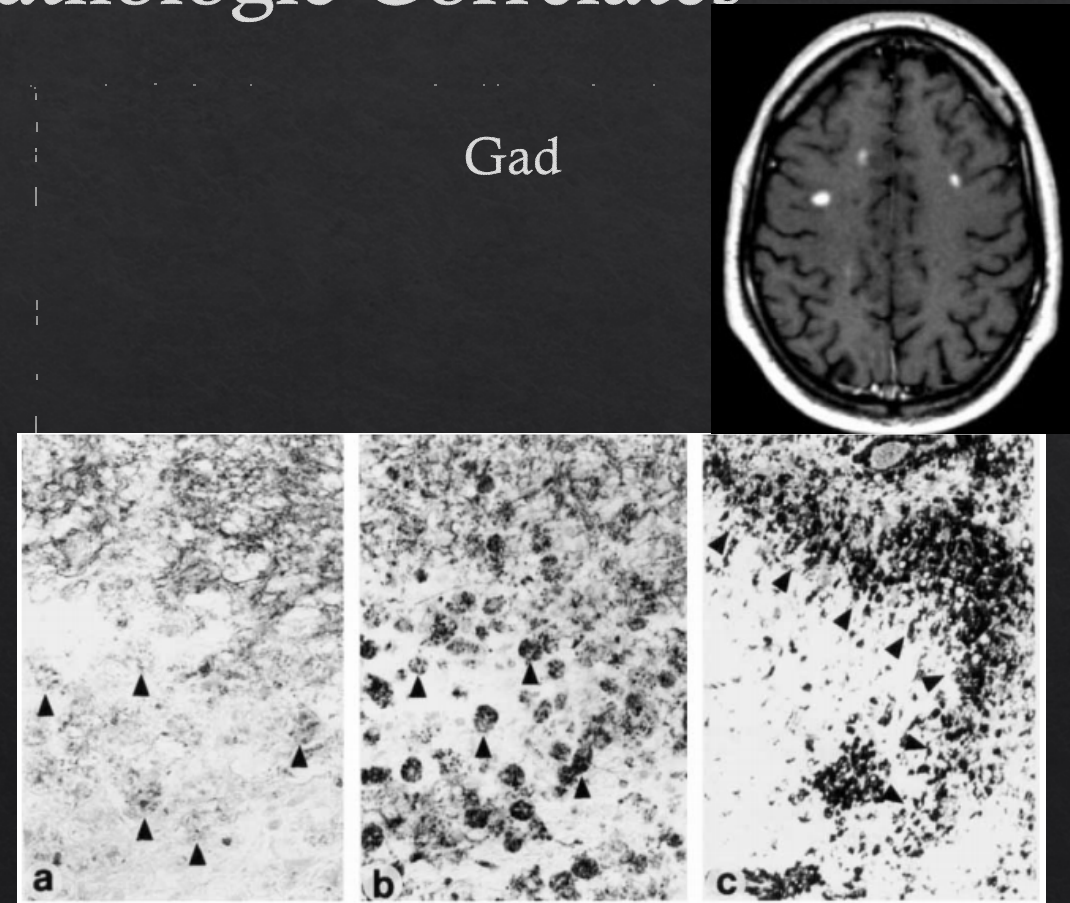
Radiologic Clinical Dissociation / Paradox



MRI Lesions – Pathologic Correlates

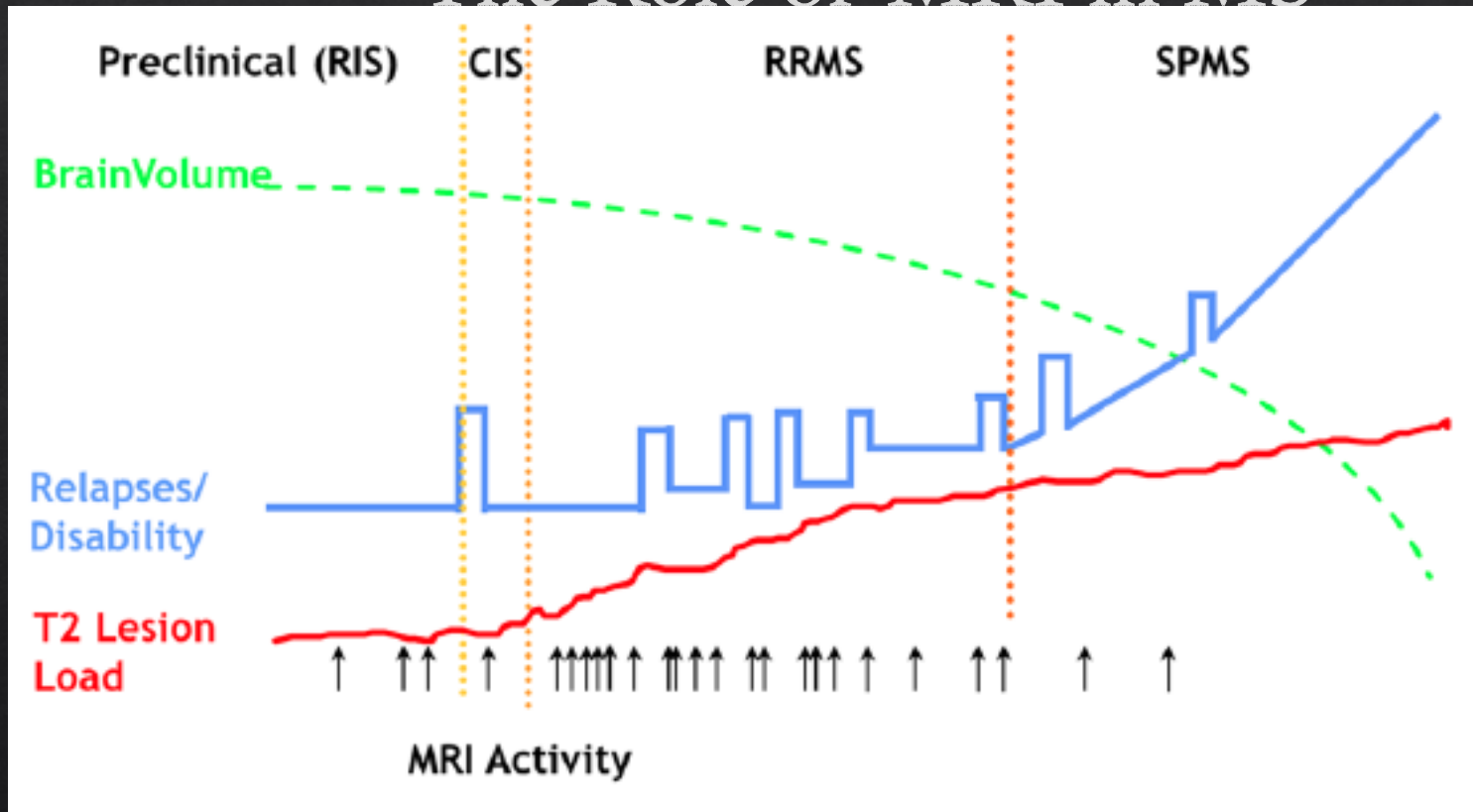


Haller et al. Acta Neuropathologica. 2013.

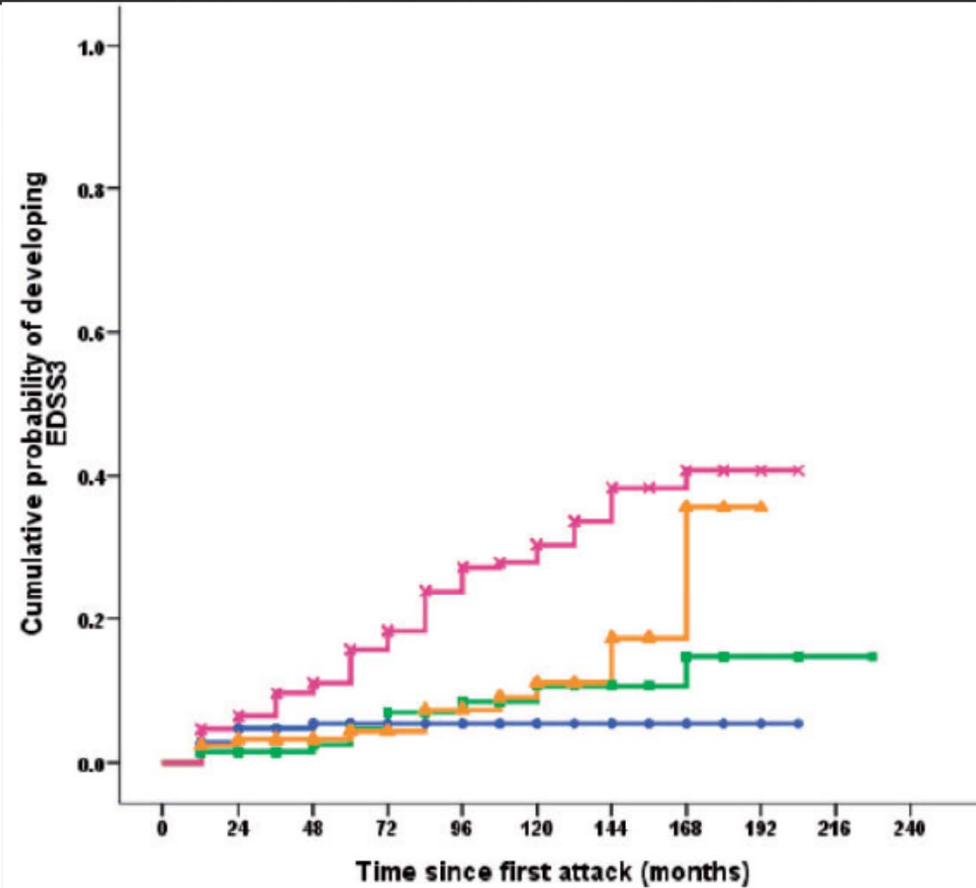
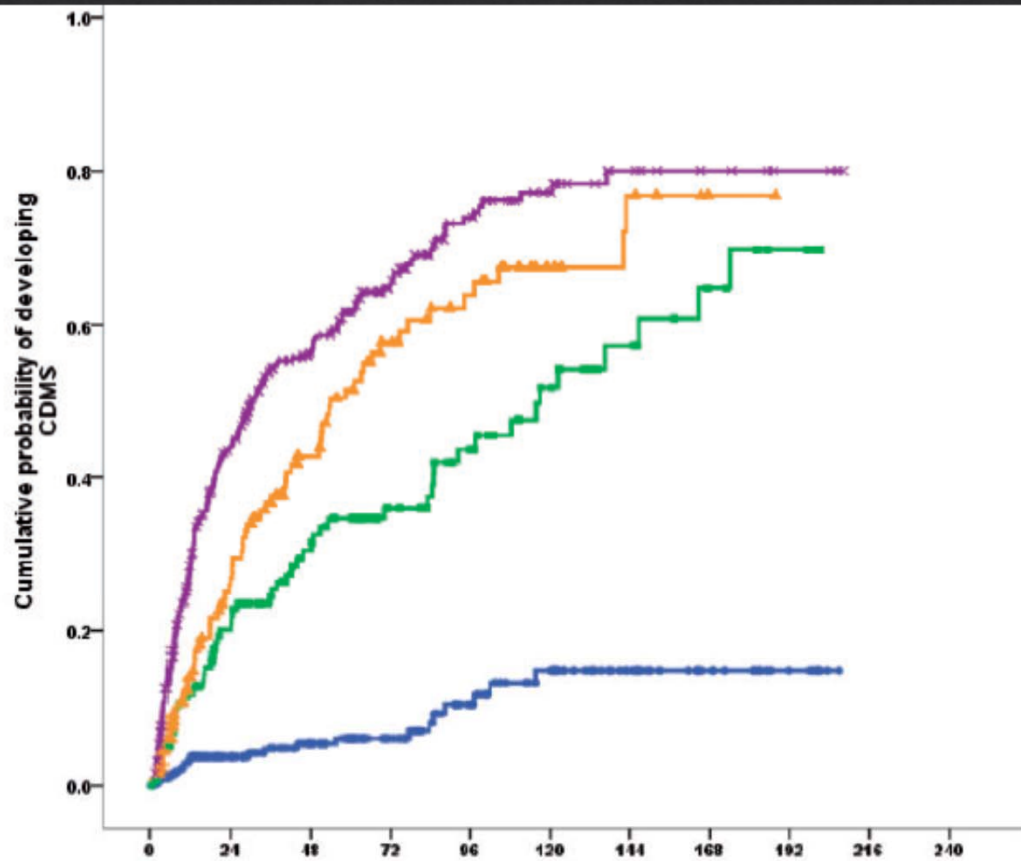


Bruck et al. Annals of Neurology. 2004.

The Role of MRI in MS



Prognostic Value of Baseline MRI

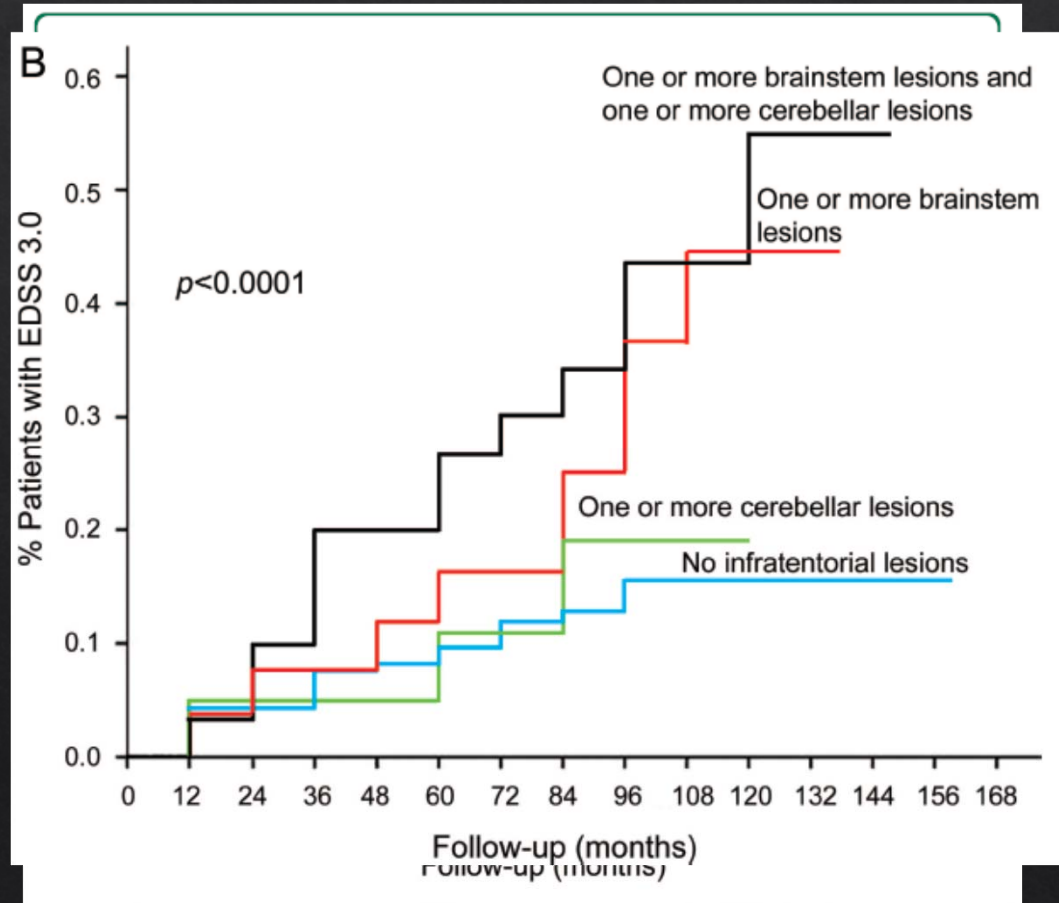


Tintore, M et al. Brain. 2015.

Prognostic Value of Baseline MRI

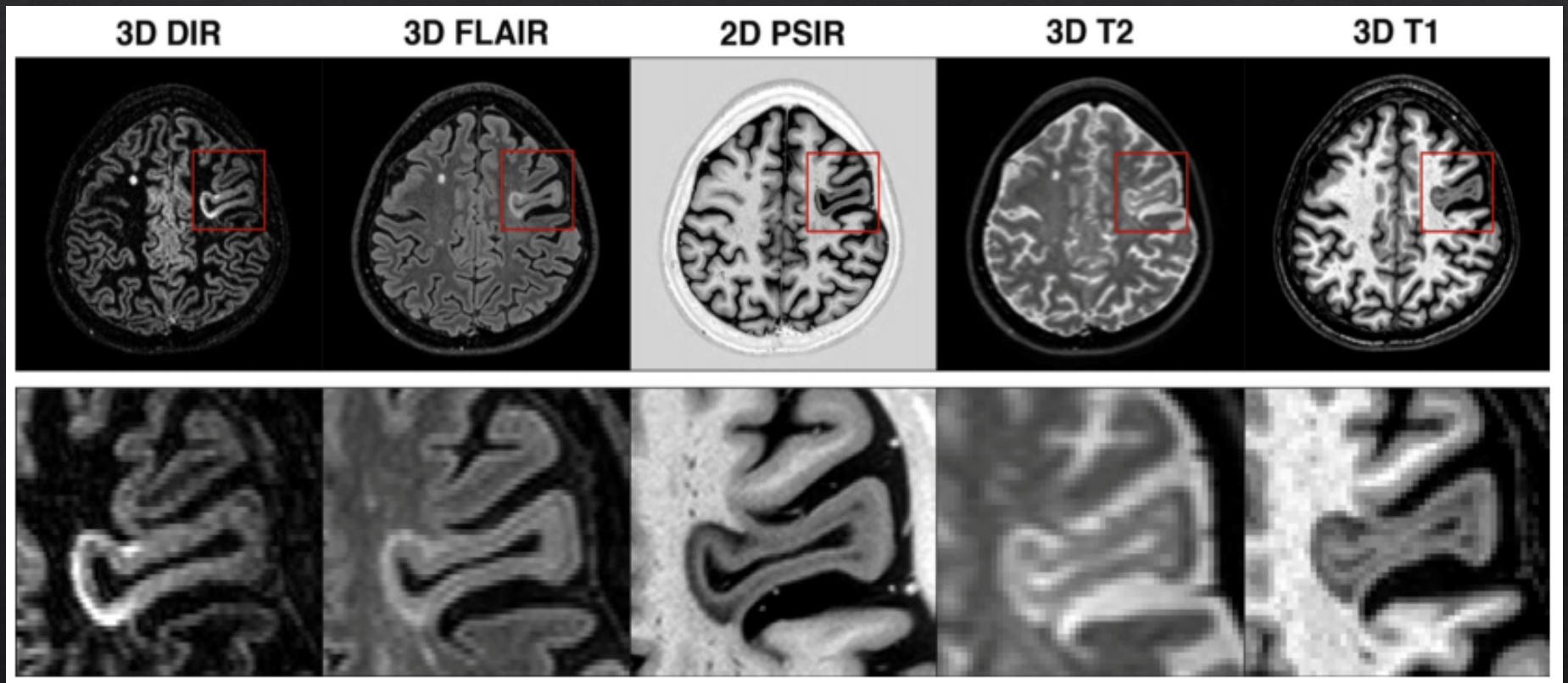
Table 1 HR and 95% CI for conversion to CDMS and disability progression according to baseline MRI parameters

	No.	HR ^a	95% CI
Infratentorial			
0	169	1.0 ^b	
≥1	77	2.4	1.3-4.3
Infratentorial			
0	169	1.0 ^b	
≥1 Cerebellar	20	1.3	0.3-4.2
≥1 Brainstem	26	2.5	1.1-5.4
≥1 Brainstem and ≥1 cerebellar	31	3.1	1.5-6.4



Tintore, M et al. Neurology. 2010.

Cortical Lesions



Correlation between Cortical Lesions and Disability

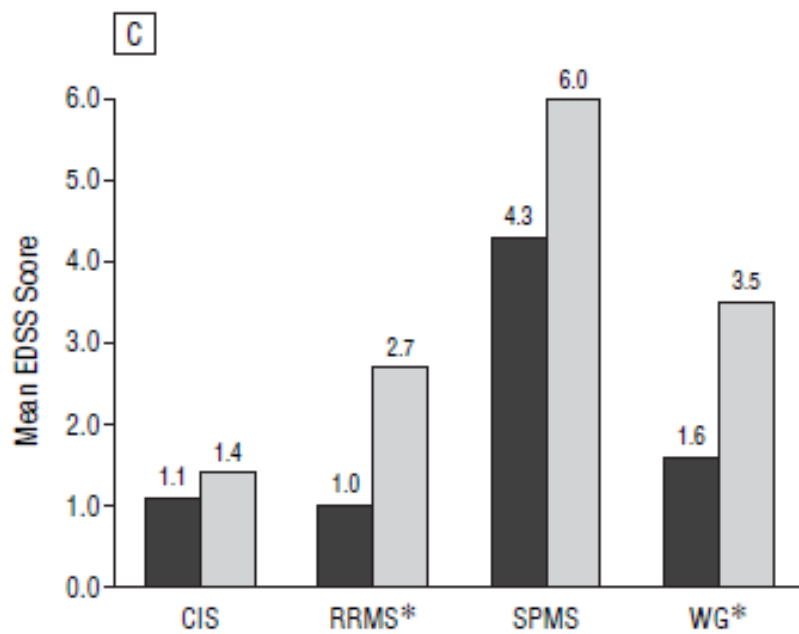


TABLE 3: Correlations of Baseline Cortical Lesion Number and Volume with Clinical and MRI Measures at Baseline and at 3-Year Follow-up

Property	RRMS Patients		SPMS Patients		Entire Group	
	CL Number	CL Volume	CL Number	CL Volume	CL Number	CL Volume
Disease duration	$r = 0.45$	$r = 0.51$	$r = 0.38$	$r = 0.42$	$r = 0.40$	$r = 0.47$
EDSS baseline	$r = 0.38$	$r = 0.42$	NS	NS	$r = 0.37$	$r = 0.36$
Gmf baseline ^a	NS	$r = -0.42$	NS	$r = -0.40$	$r = -0.34$	$r = -0.47$
T2-WM-LV baseline	NS	NS	NS	NS	NS	NS
EDSS change	NS	$r = 0.55$	NS	$r = 0.43$	$r = 0.34$	$r = 0.51$
PGVC ^b	$r = 0.30$	$r = 0.47$	NS	$r = 0.37$	$r = 0.30$	$r = 0.45$
T2-WM-LV change	NS	NS	NS	NS	NS	NS

All reported r values correspond to $p \leq 0.001$.

^aControlling for baseline T2-WM-LV.

^bControlling for T2-WM-LV change.

MRI = magnetic resonance imaging; RR = relapsing remitting; MS = multiple sclerosis; SP = secondary progressive; CL = cortical lesions; EDSS = Expanded Disability Status Scale; NS = not significant; Gmf = grey matter fraction; T2-WM-LV = T2 white matter lesion volume; PGVC = percentage grey matter volume change.

Prognostic Value of New Lesions

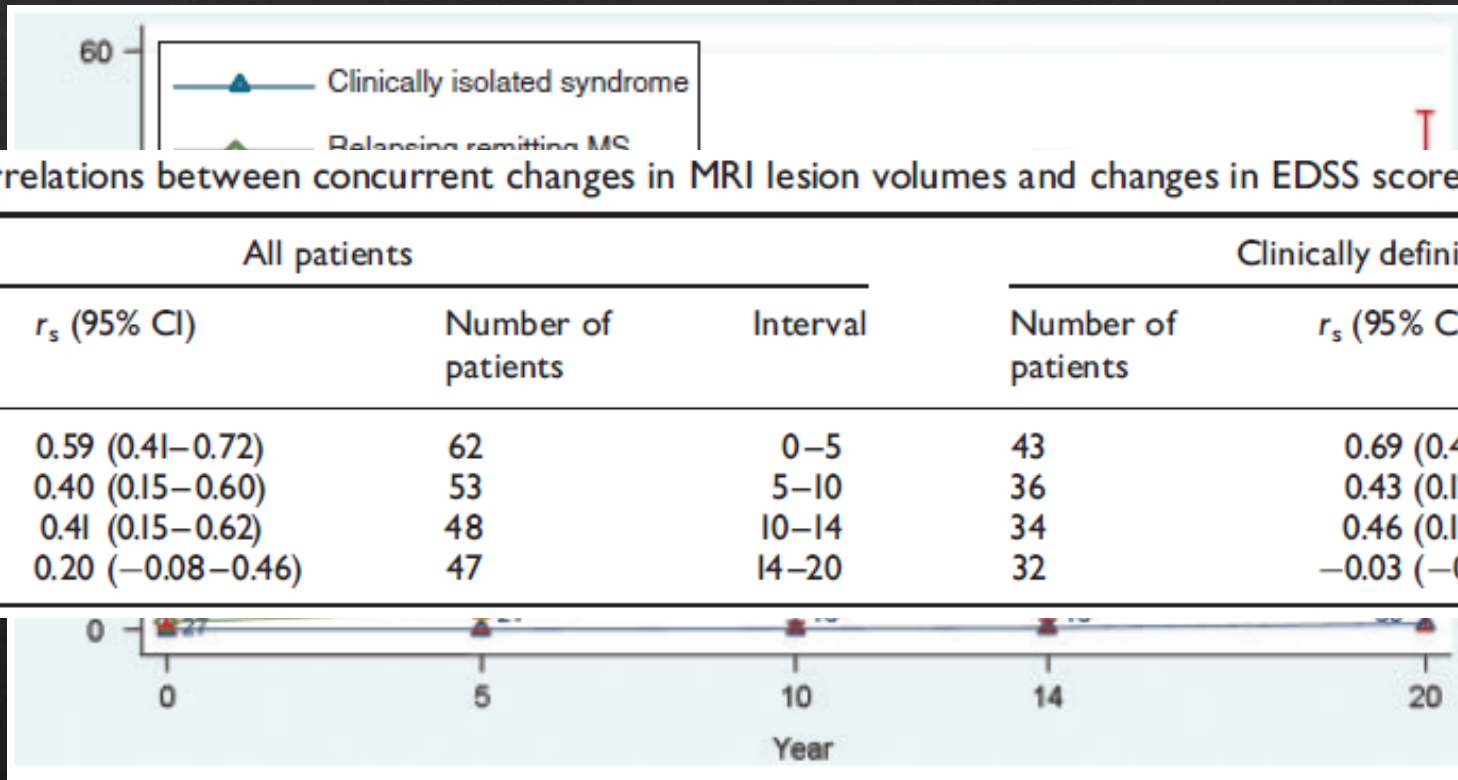
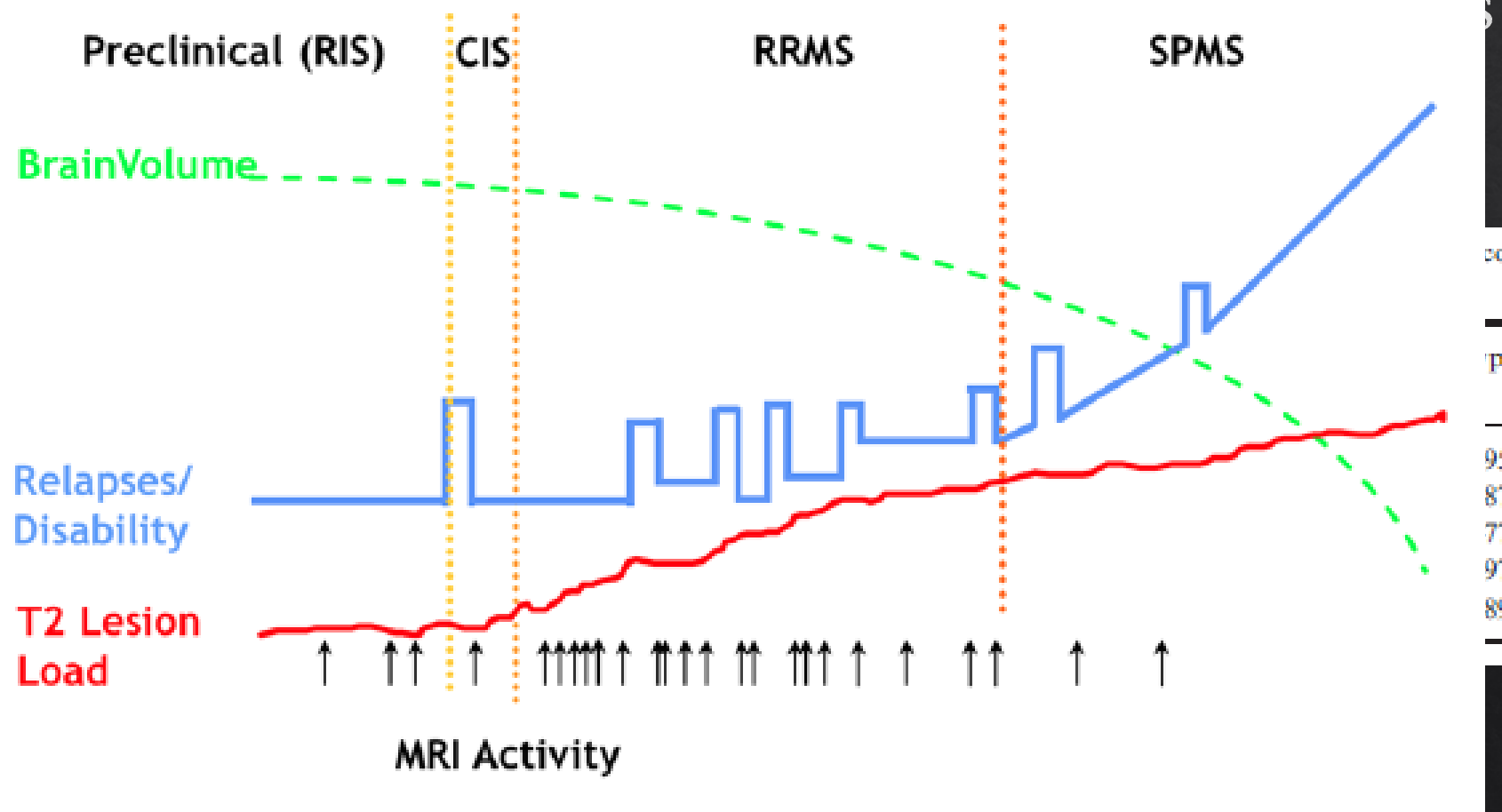


Table 6 Correlations between concurrent changes in MRI lesion volumes and changes in EDSS score

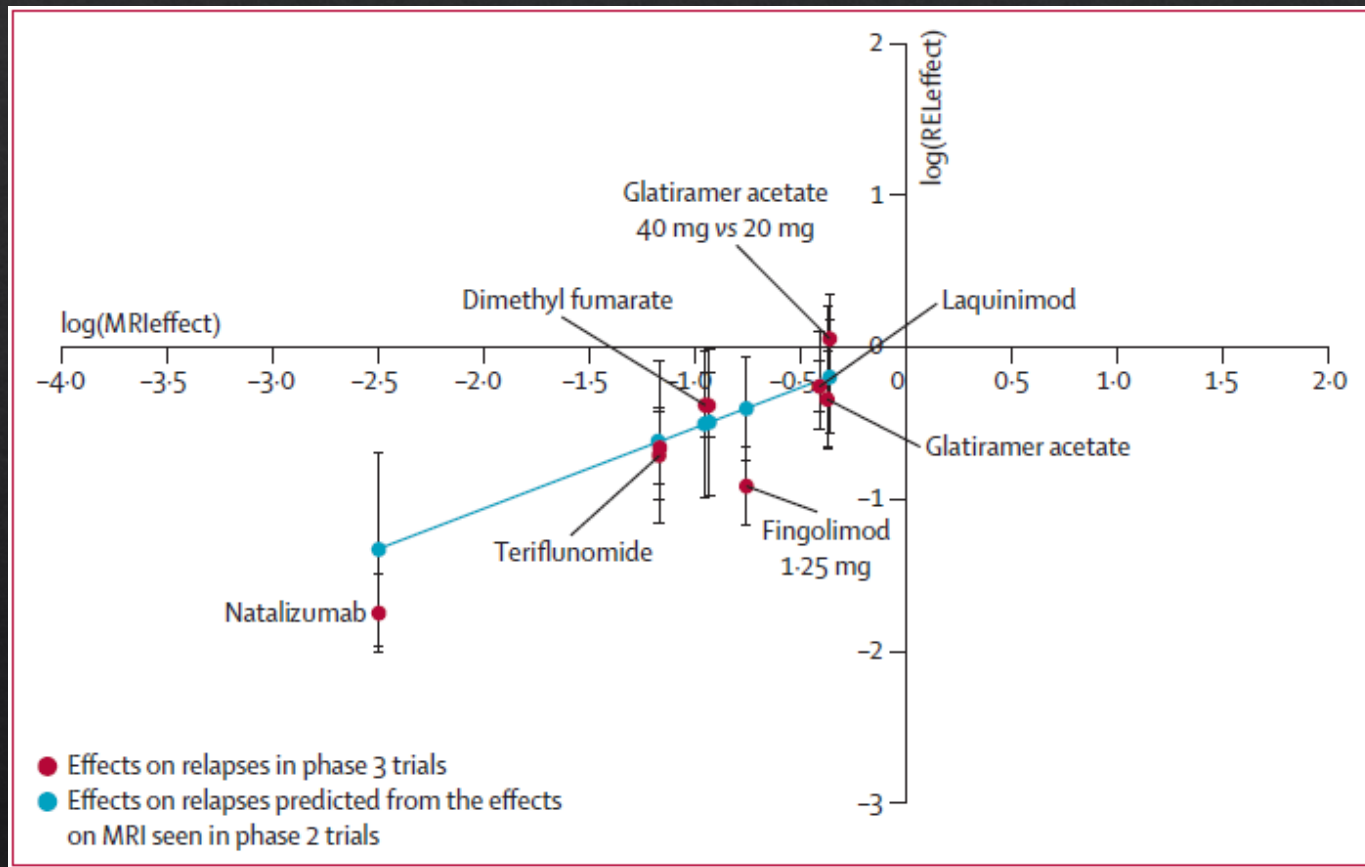
All patients				Clinically definite MS only		
P-value	r_s (95% CI)	Number of patients	Interval	Number of patients	r_s (95% CI)	P-value
<0.001	0.59 (0.41–0.72)	62	0–5	43	0.69 (0.49–0.82)	<0.001
0.002	0.40 (0.15–0.60)	53	5–10	36	0.43 (0.12–0.66)	0.008
0.002	0.41 (0.15–0.62)	48	10–14	34	0.46 (0.14–0.69)	0.006
0.165	0.20 (–0.08–0.46)	47	14–20	32	–0.03 (–0.37–0.31)	0.853

Brain Volume, Relapses/Disability, and T2 Lesion Load in Multiple Sclerosis



Properini et al. European Journal of Neurology. 2009

Effect of Treatment of MRI & Relapses



Sormani et al. Lancet. 2013.

MR Scoring Systems

Table 2
MR imaging criteria to predict treatment response

Criterion	Outcome Measure	Result
Three or more active lesions in 1 y ⁴²	Disability progression over 3 y	OR 8.3 71% sensitivity 71% specificity
3 or more active and ≥1 relapse of ≥1 point confirmed EDSS score increase in 1 y (Rio score ≥2) ²⁶	Relapse rates and/or disability progression over 3 y	OR 3.3–9.8 for relapses OR 6.5–7.1 for progression
Modified Rio score ≥2 y, >5 new T2 lesions plus 1 relapse; or >1 relapse ³¹	Relapse rates and/or disability progression over 4 y	24% sensitivity 97% specificity
≥1 relapse and ≥9 T2 lesions or ≥1 enhancing lesion ³²	Relapse rates and/or disability progression over 4 y	34% sensitivity 90% specificity
≥1 relapse or ≥1 enhancing lesion ³²	Relapse rates and/or disability progression over 4 y	68% sensitivity 80% specificity
≥1 enhancing lesion or ≥2 new T2 lesions ³²	Relapse rates and/or disability progression over 4 y	61% sensitivity 83% specificity

All included patients were treated with IFN-β.

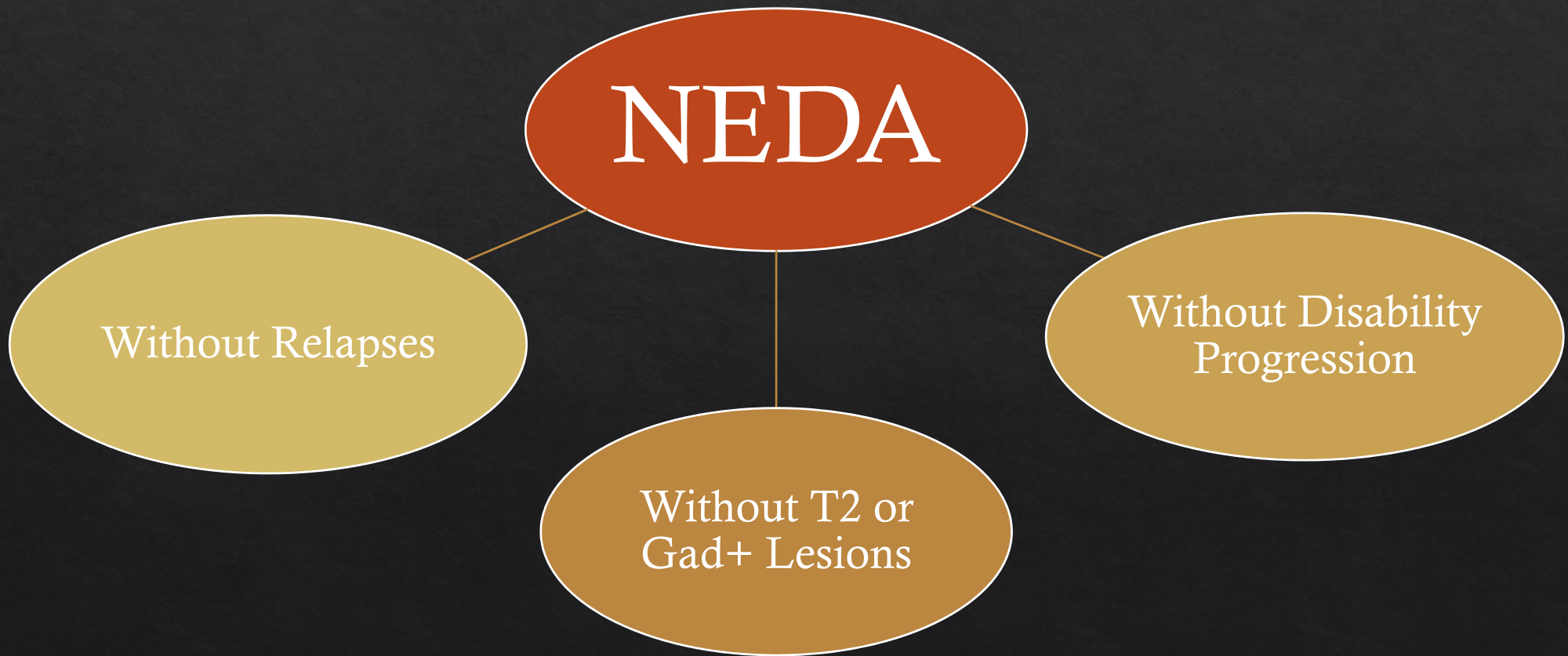
Abbreviations: EDSS, Expanded Disability Status Scale; OR, odds ratio.

Table 3
Rio score and Modified Rio score

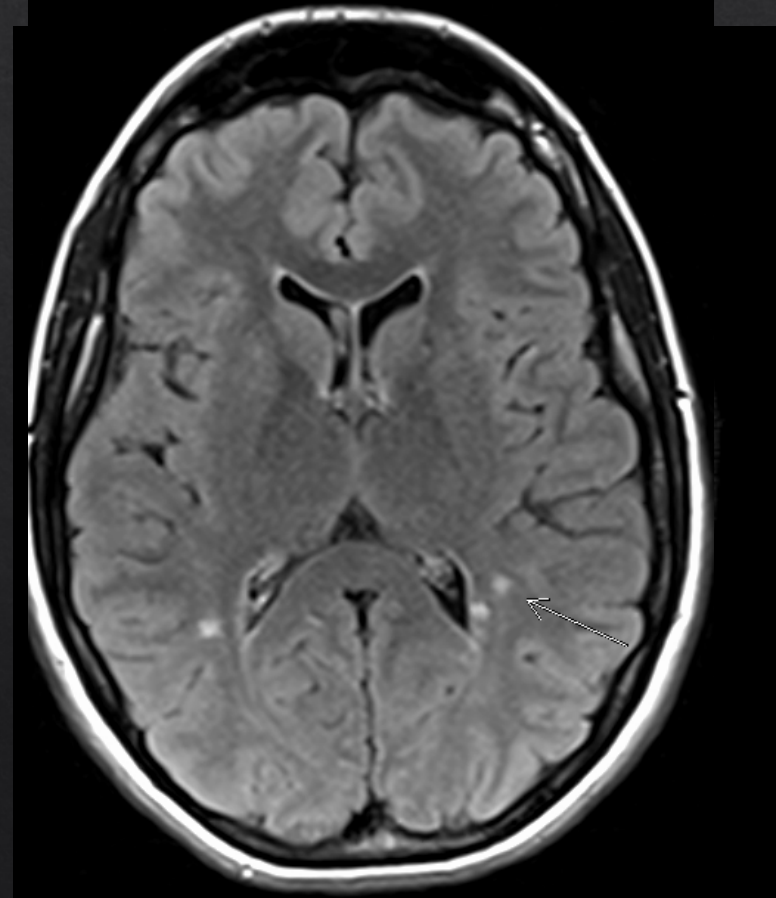
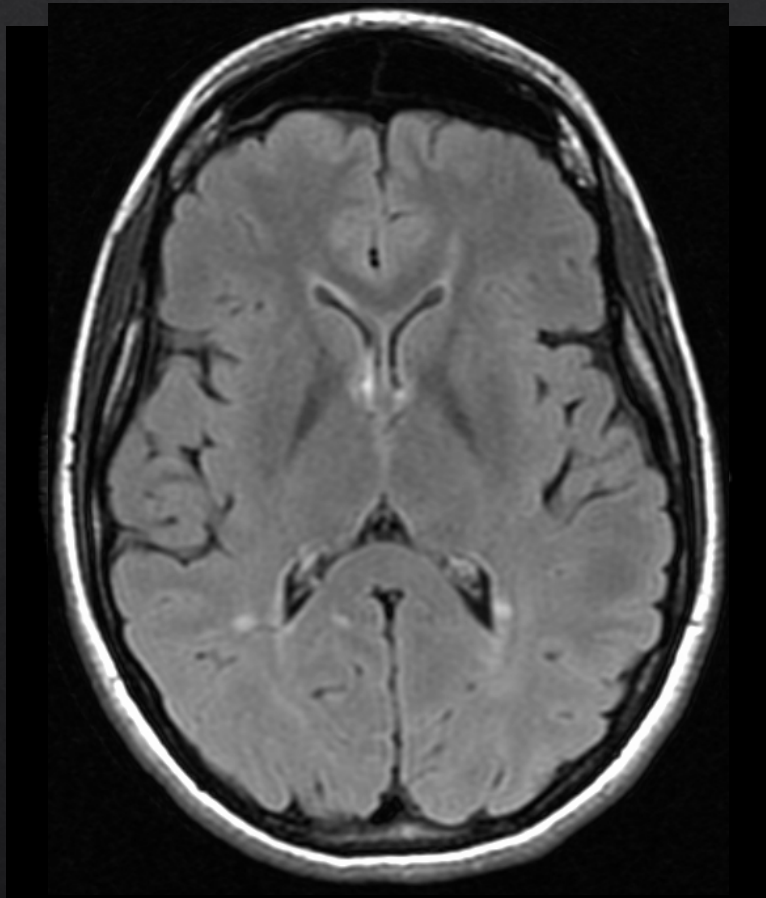
Rio Score ²⁶		Modified Rio Score ³¹	
Criterion	Change in First Year	Criterion	Change in First Year
Criterion MR imaging = 0	<2 active lesions	Criterion MR imaging = 0	<5 new T2 lesions
Criterion MR imaging = 1	>2 active lesions	Criterion MR imaging = 1	>4 new T2 lesions
Criterion relapse = 0	No relapses	Criterion relapse = 0	No relapses
Criterion relapse = 1	≥1 relapse	Criterion relapse = 1	1 relapse
		Criterion relapse = 2	≥2 relapses
Criterion EDSS = 0	<1 EDSS point	Criterion EDSS = 0	Not included
Criterion EDSS = 1	≥1 EDSS point	Criterion EDSS = 1	

Active lesions = new T2 lesions and/or enhancing lesions.

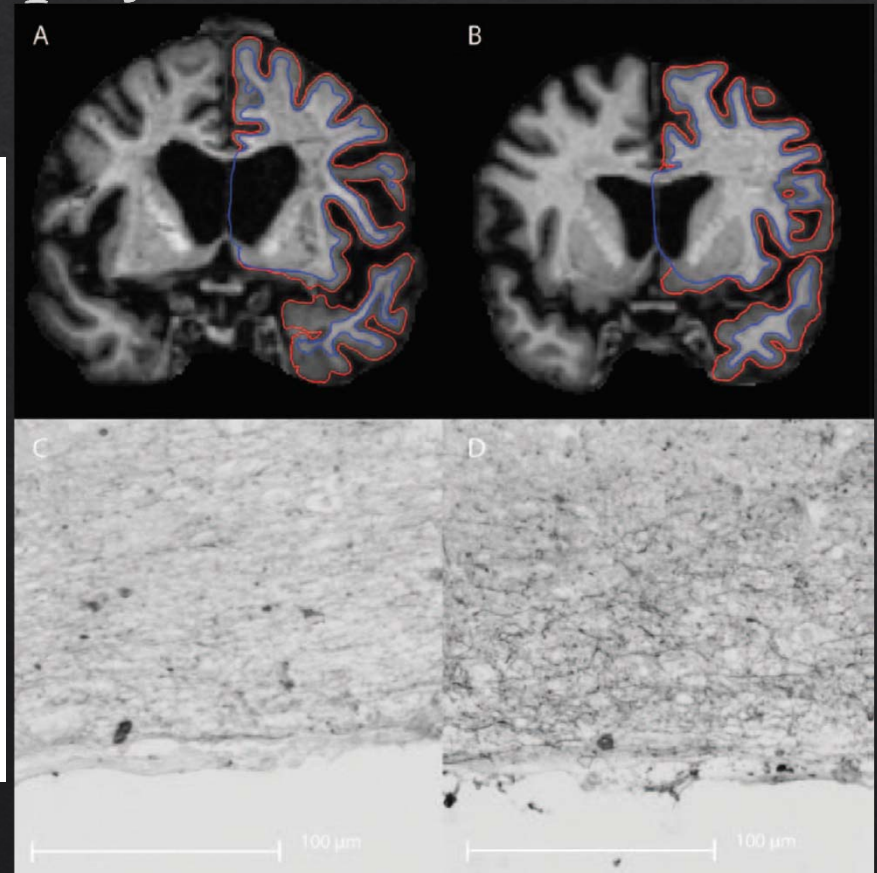
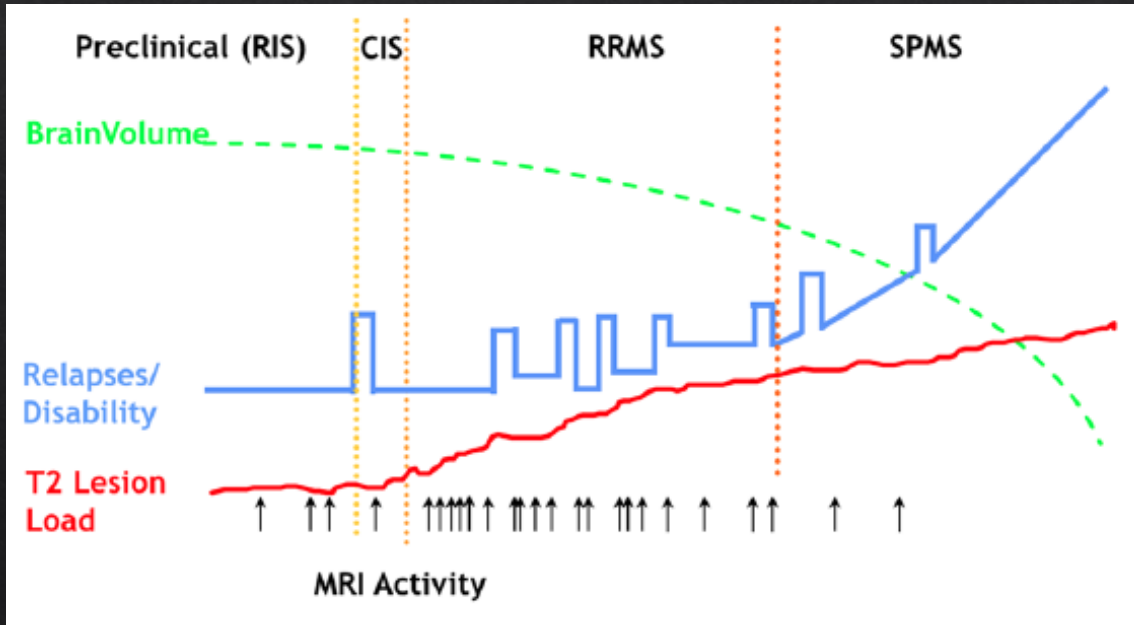
NEDA as a Treatment Goal



Monitoring MS in the Modern Era



Brain Atrophy



Prognostic Value of Brain Volume Loss

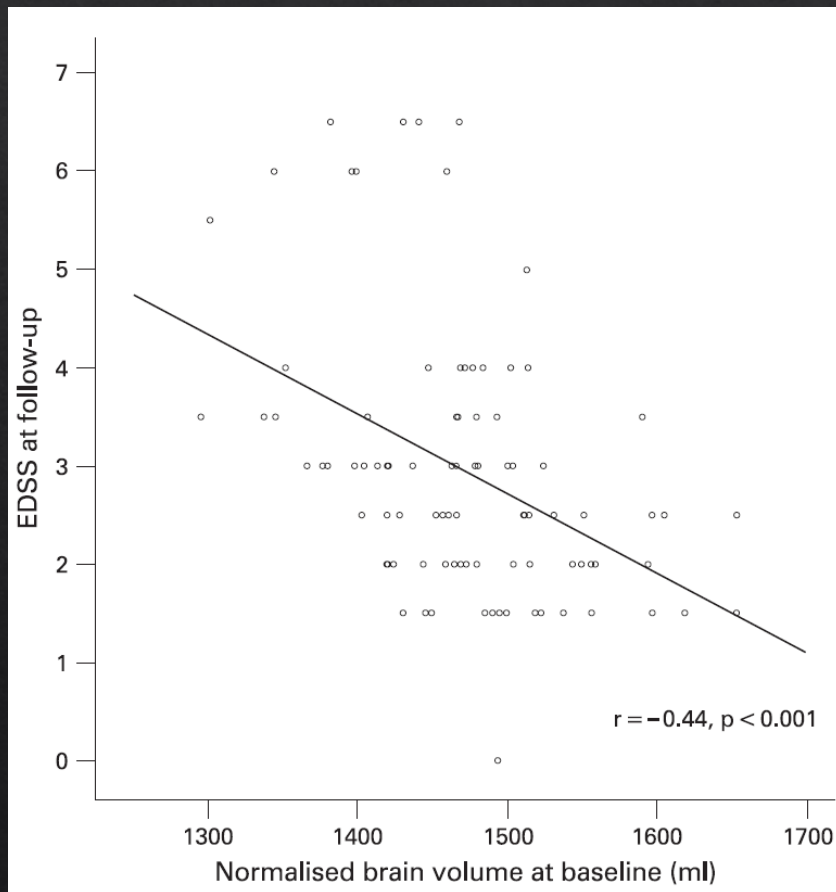
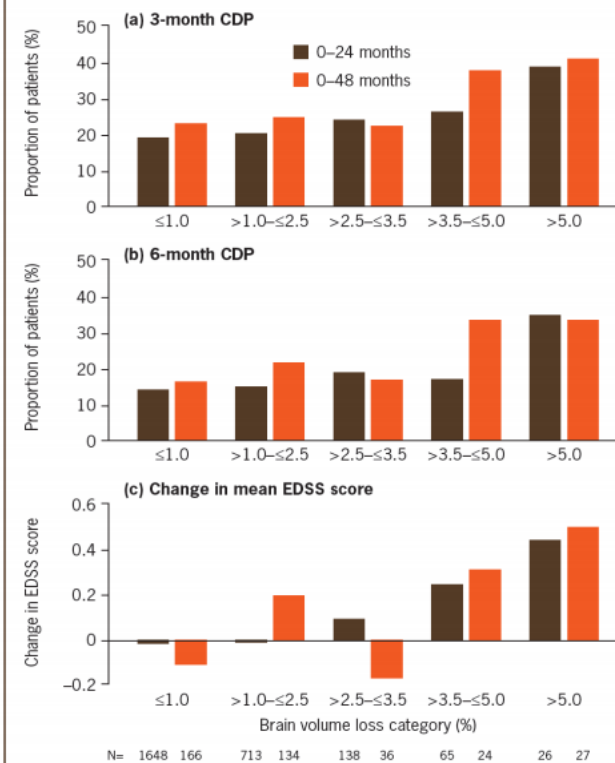
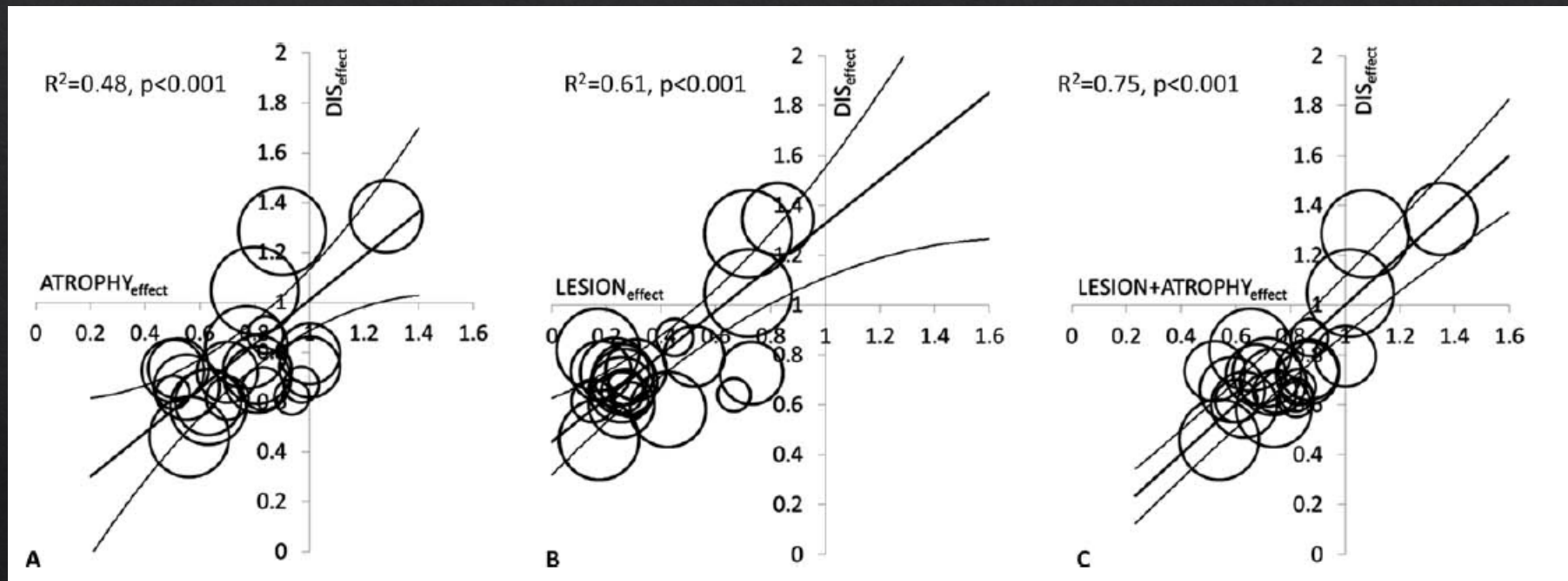


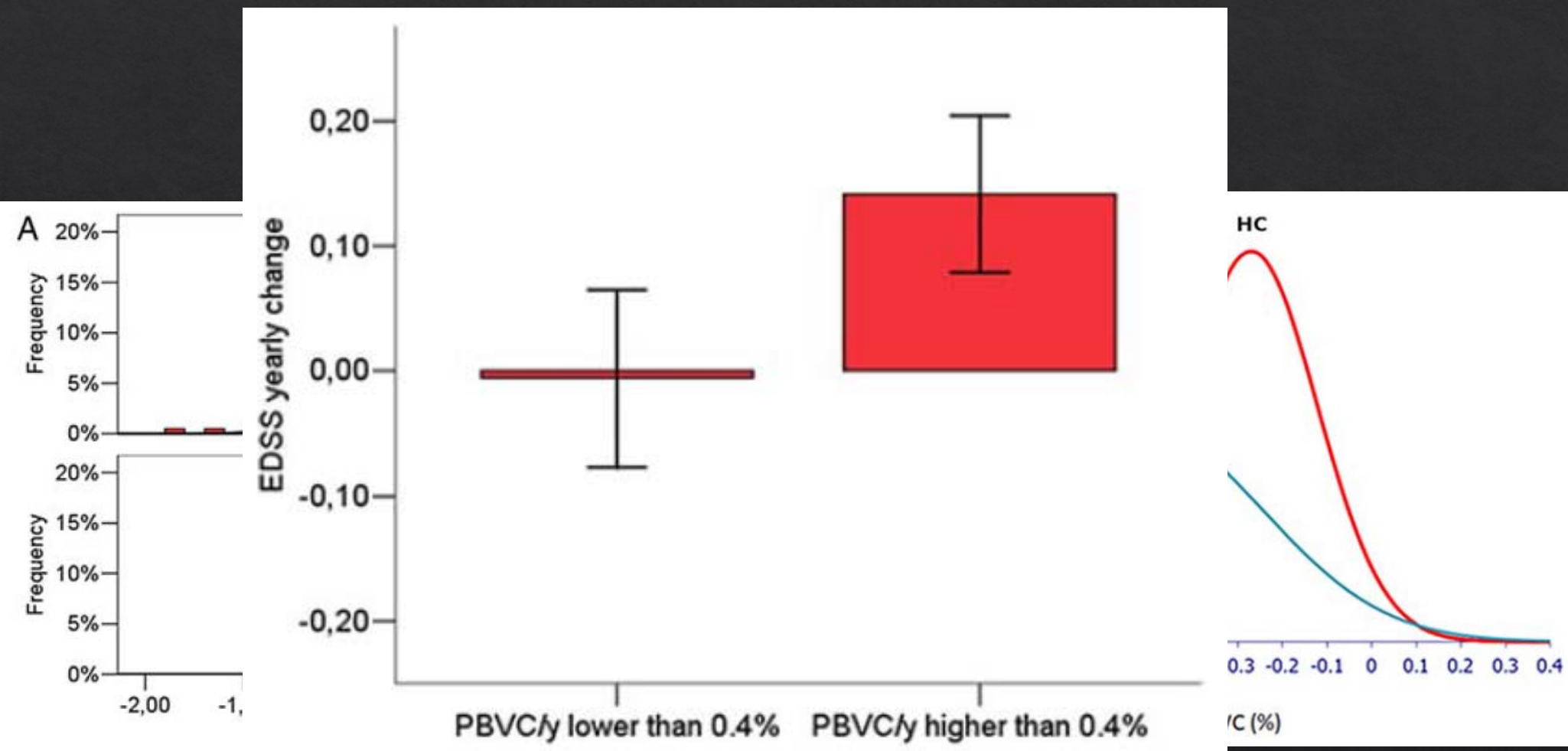
Figure 4. Proportions of patients with (a) 3-month and (b) 6-month CDP and (c) the corresponding change in EDSS score, by category of BV loss in the combined study data



Data are shown from the combined core intent-to-treat populations from FREEDOMS, FREEDOMS II and TRANSFORMS, including their extensions.

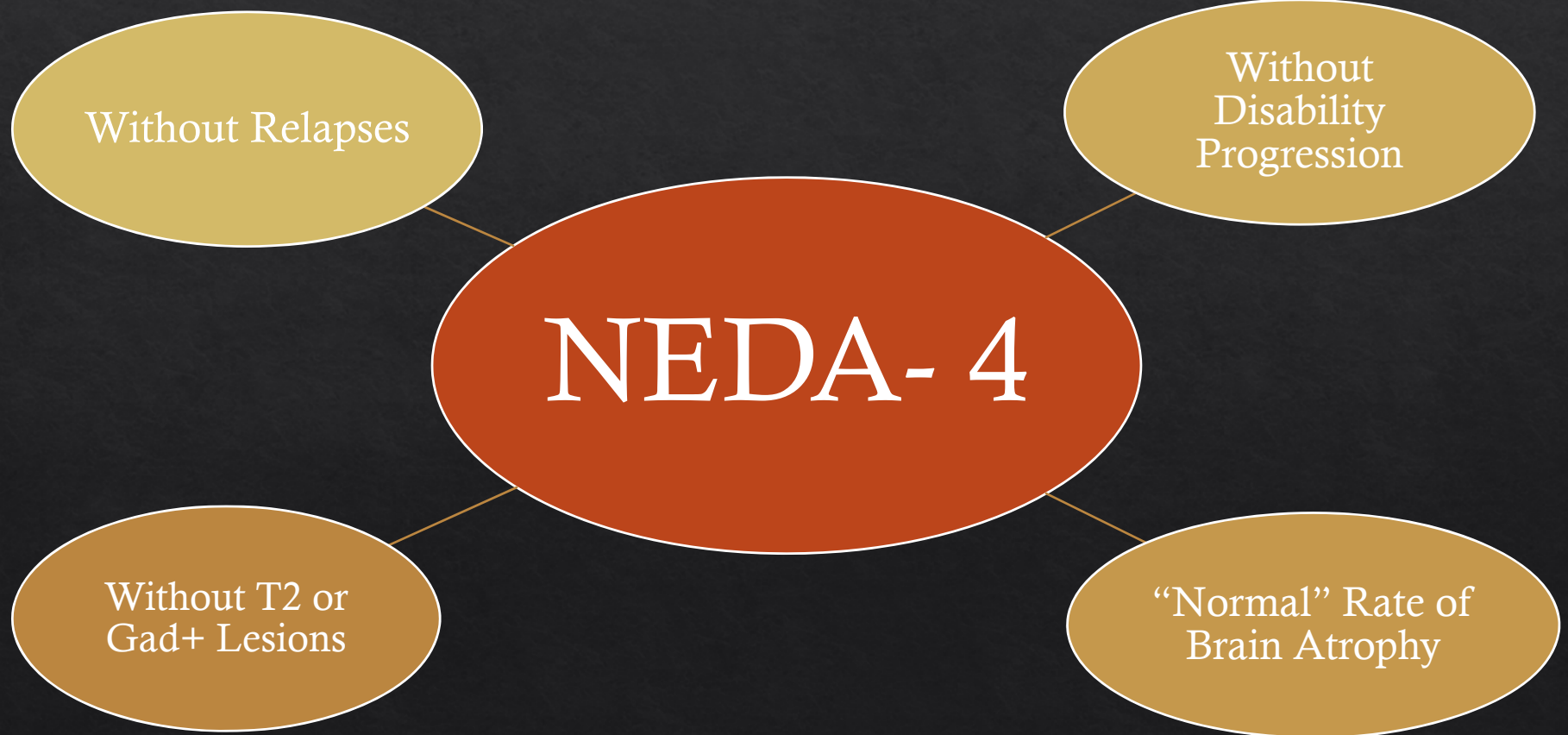
Atrophy Treatment Effect

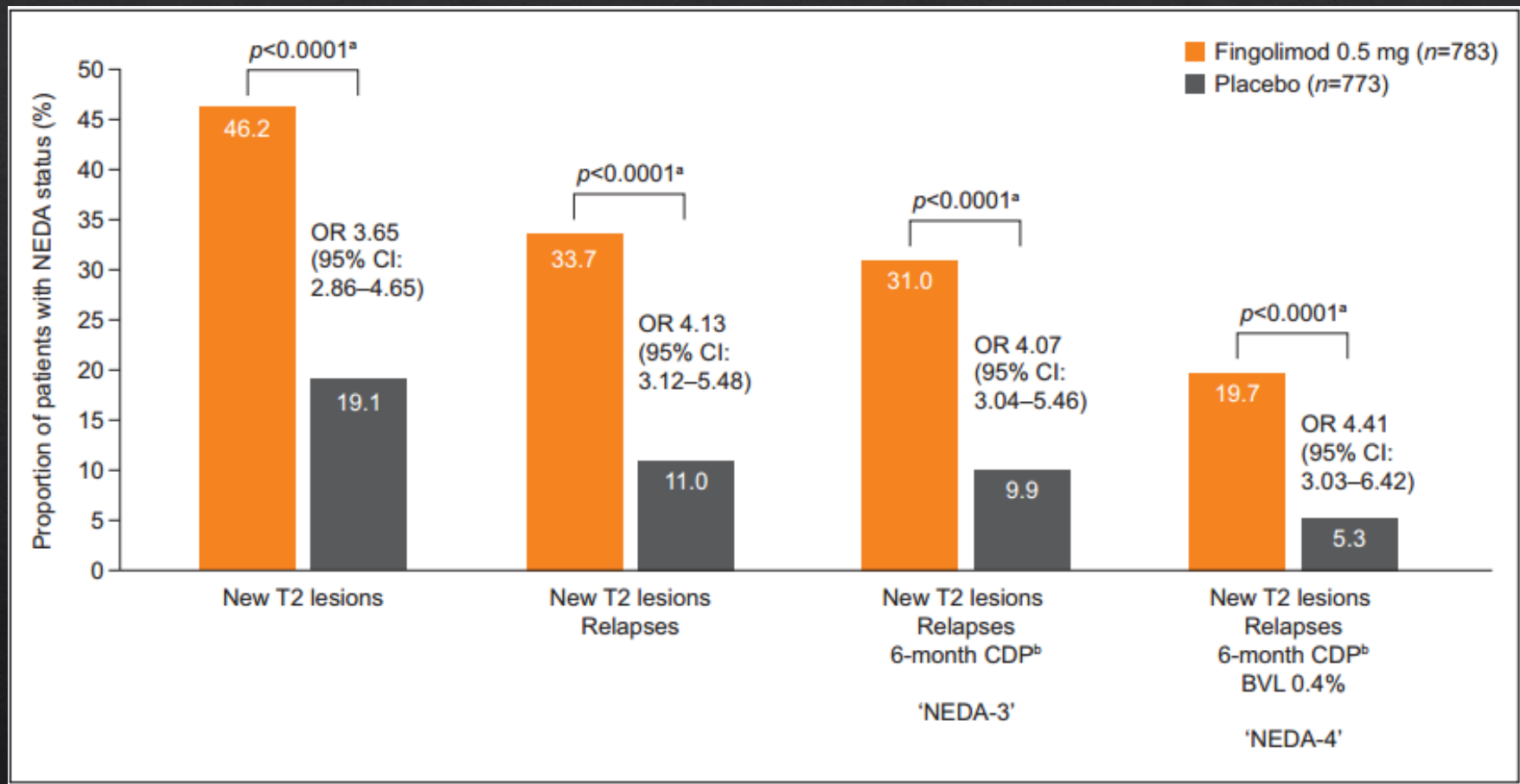




Stefano et al. J Neurol Neurosurg Psychiatry. 2015.

NEDA - 4







◆ NeuroQuant



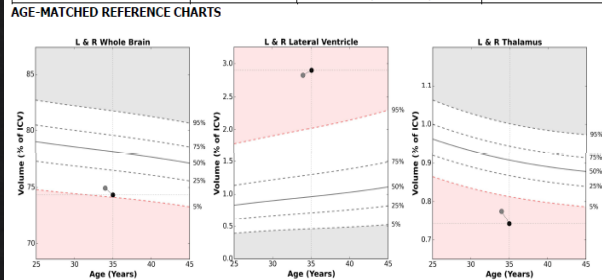
◆ Neuroreader



◆ MSMetrix

PATIENT INFORMATION			
Patient ID:	Patient Name:	Sex:	Age:
Accession Number:	Referring Physician:	Exam Date:	

MORPHOMETRY RESULTS (1 of 2)			
Brain Structure	Volume (cm ³)	% of ICV (5%-95% Normative Percentile*)	Normative Percentile*
Whole Brain	1188.89	74.34 (74.13 - 81.73)	6
Lateral Ventricles	46.35	2.90 (0.46 - 2.02)	> 99
Thalami	11.87	0.74 (0.81 - 1.00)	< 1



Results				
The estimated total intracranial volume (eTIV) = 1617 ml.				
Structures	Vol ml	Vol/eTIV ratio	95% Conf Interval	Z-score
Whole Brain Matter	963.14	59.550193	1004.10 - 1036.72	-7.0
Hippocampus	7.19	0.444369	6.71 - 7.21	1.8
Right Hippocampus	3.64	0.225245	3.37 - 3.63	2.1
Left Hippocampus	3.54	0.219124	3.33 - 3.59	1.2
Amygdala	2.40	0.148082	2.42 - 2.63	-2.4
Right Amygdala	1.35	0.083717	1.21 - 1.33	2.8
Left Amygdala	1.04	0.064365	1.19 - 1.31	-7.2
Putamen	8.77	0.542368	7.79 - 8.48	3.7
Right Putamen	4.10	0.253625	3.82 - 4.16	1.3
Left Putamen	4.67	0.288744	3.96 - 4.33	5.7
Thalamus	14.05	0.868704	12.13 - 12.73	10.8
Right Thalamus	7.30	0.451232	6.02 - 6.30	15.8
Left Thalamus	6.75	0.417473	6.10 - 6.45	5.5
Ventral Diencephalon	7.48	0.462361	7.81 - 8.34	-4.4
Right Ventral Diencephalon	3.70	0.228584	3.89 - 4.15	-5.0
Left Ventral Diencephalon	3.78	0.233777	3.91 - 4.19	-3.9
Frontal Lobe	346.18	21.404136	338.01 - 353.56	0.1
Right Frontal Lobe	174.68	10.800501	167.97 - 175.78	1.4
Left Frontal Lobe	171.50	10.603636	169.91 - 177.91	-1.2

NAME	ID	DATE OF BIRTH	MRI DATE
icomatrix	ICO-ID_01 ICO-ID_02	1966-02-01	2013-11-10 01:01:01 2015-03-30 01:01:01

QC Status: INTERNAL
Remarks: This report is for internal reviewing only.

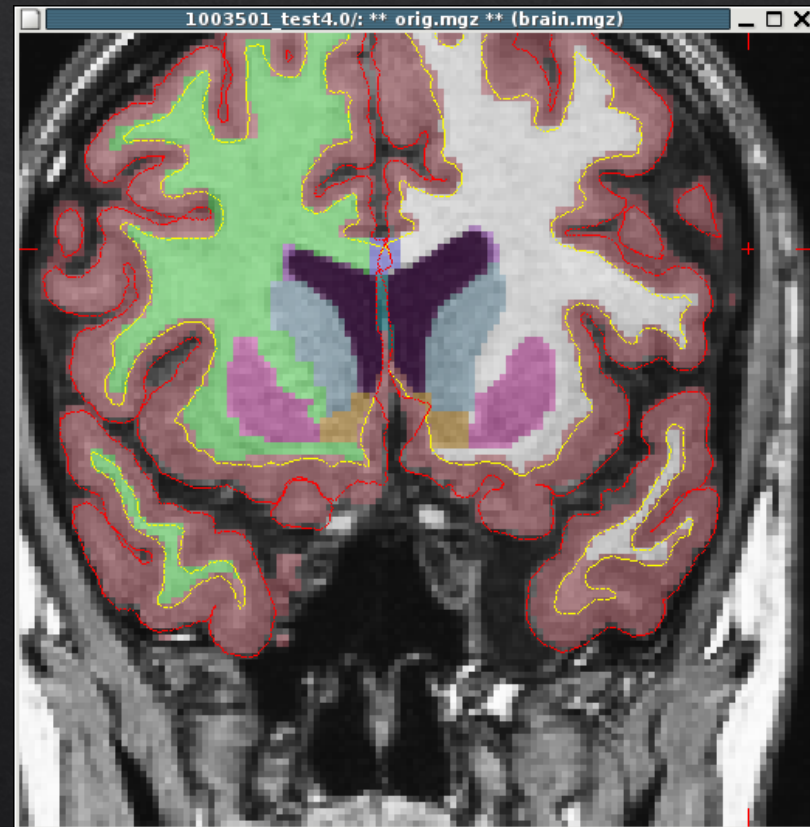
Brain structure	Volume (current MRI)	Normal range (5th and 95th percentiles)	Normative percentile	Annual Atrophy
Whole brain volume	1387.1 ml*	1492-1565 ml*	< 1	0.56 %
Grey matter volume	830.9 ml*	899-985 ml*	< 1	0.58 %

* Displayed brain volumes are normalised for head size. The normalisation factor for this patient equals 0.71.

Type	Lesion volume (current MRI)	Lesion volume change (compared to previous MRI)
FLAIR lesions	5.67 ml	1.02 ml
New FLAIR lesions	-	0.78 ml
Enlarging FLAIR lesions	-	0.36 ml
Gd enhanced lesions	-	-

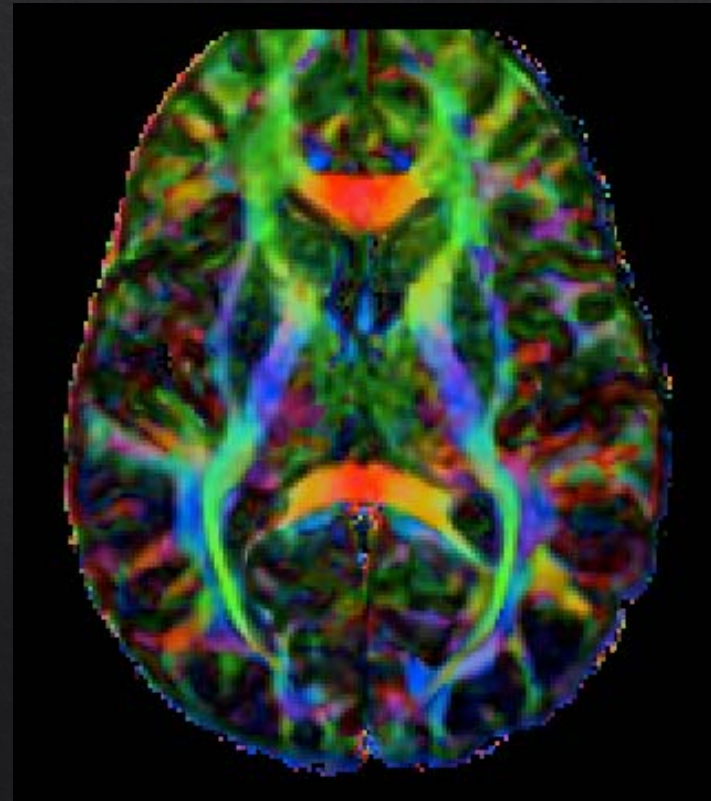
The Future

◆ Gray Matter Atrophy



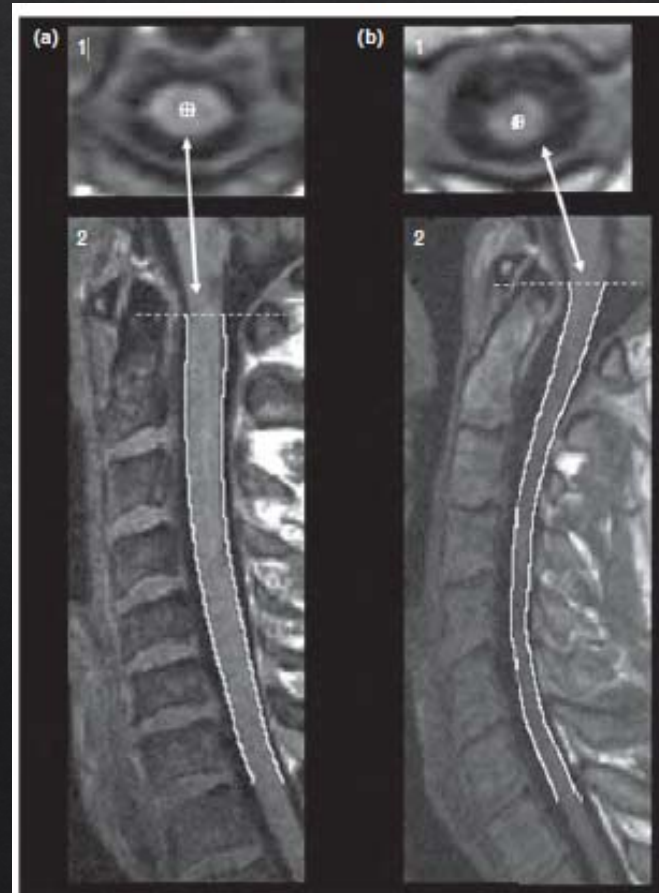
The Future

- ◇ Gray Matter Atrophy
- ◇ Brain tissue microstructure
- ◇ Cord cross sectional area



The Future

- ◇ Gray Matter Atrophy
- ◇ Brain tissue microstructure
- ◇ Cord cross sectional area



Conclusions

- ◇ MRI can be used as a surrogate measure of focal CNS inflammation and neurodegeneration
- ◇ No single MRI measurement in isolation is sufficient to monitor disease.
- ◇ T2 lesions are far more sensitive than Gad+ lesions
- ◇ Atrophy measures may allow us to assess patients for unmet disease burden.