Quantitative Neuroimaging-
Gray and white matter Alteration in Multiple Sclerosis

Lior Or-Bach

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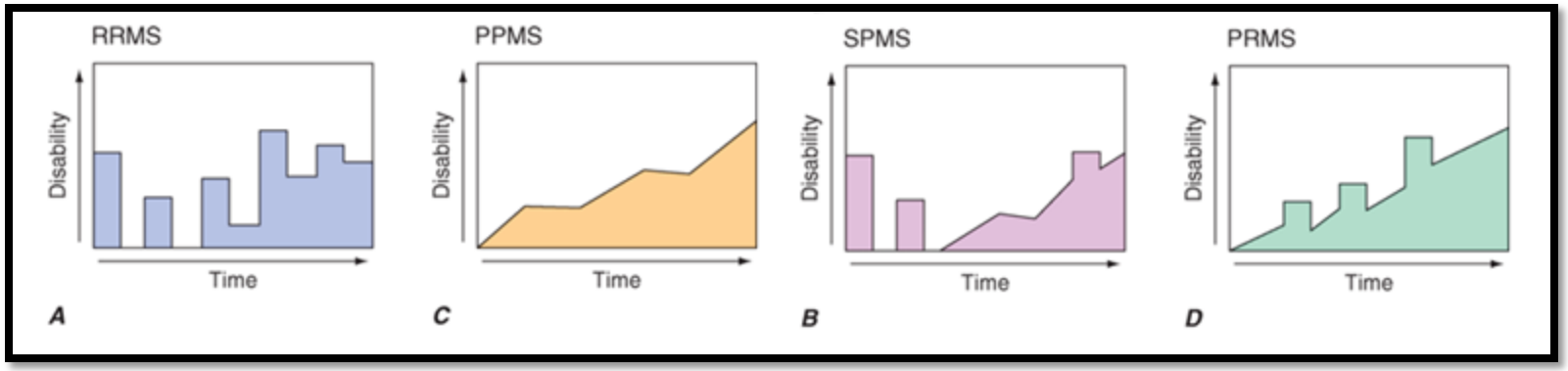
INTRODUCTION

- Multiple Sclerosis – general background
- Gray Matter pathology
- Treatment - Tysabri and B-ferron

Multiple Sclerosis

- Multiple sclerosis (MS) is a chronic disease characterized by inflammation, **demyelination**, gliosis (scarring), and neuronal loss.
- Axonal damage occurs in every newly formed MS lesion, and cumulative axonal loss causes **irreversible neurologic disability** in MS
- Involves both white and **gray matter**.



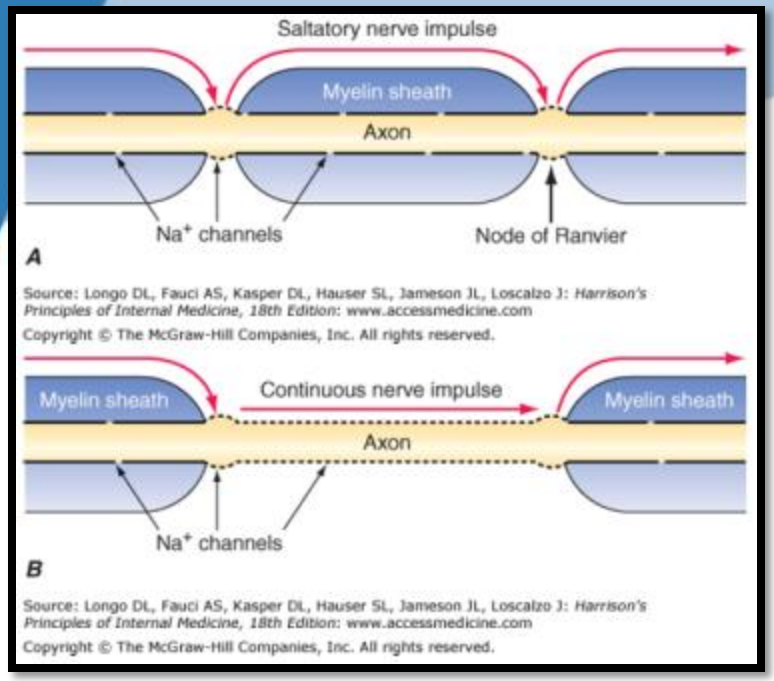
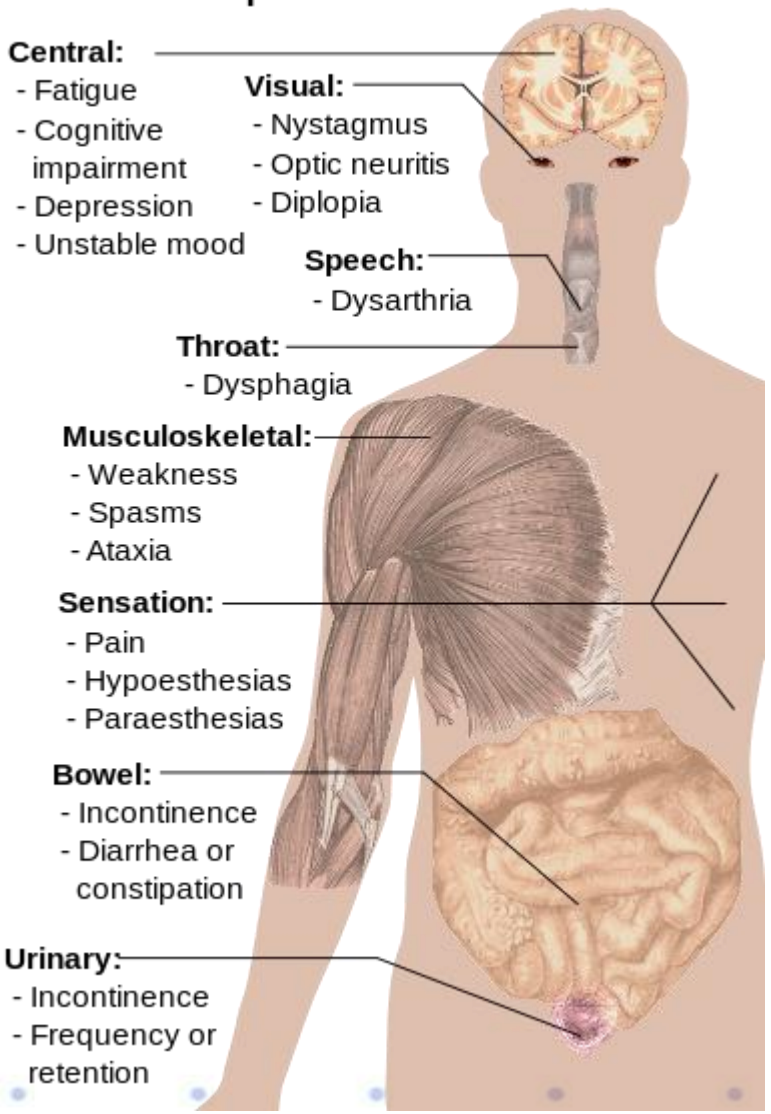


Table 380-2 Initial Symptoms of MS

Symptom	Percent of Cases	Symptom	Percent of Cases
Sensory loss	37	Lhermitte's	3
Optic neuritis	36	Pain	3
Weakness	35	Dementia	2
Paresthesias	24	Visual loss	2
Diplopia	15	Facial palsy	1
Ataxia	11	Impotence	1
Vertigo	6	Myokymia	1
Paroxysmal attacks	4	Epilepsy	1
Bladder	4	Falling	1

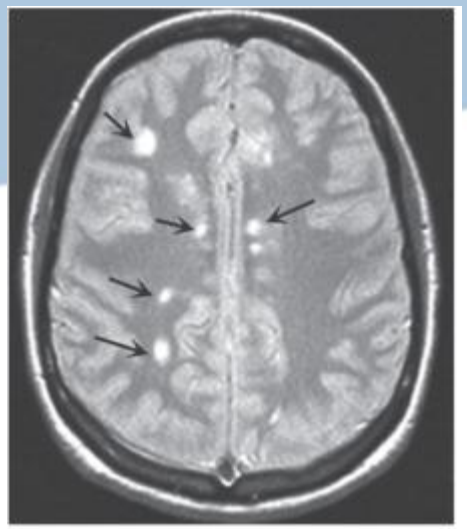
Source: After WB Matthews et al, McAlpine's Multiple Sclerosis, New York, Churchill Livingstone, 1991.

Main symptoms of
Multiple sclerosis

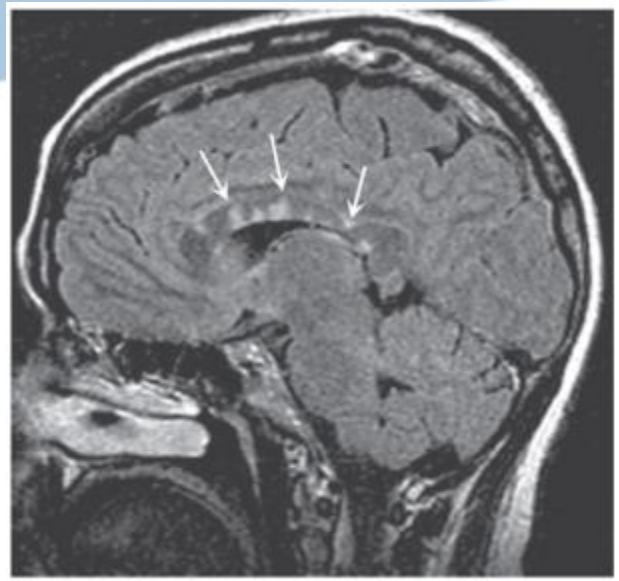


Magnetic Resonance Imaging

- MRI has revolutionized the diagnosis and management of MS
  - characteristic **abnormalities are found in >95%** of patients.
  - more than 90% of the lesions visualized by MRI are asymptomatic.
  - No specific “fingerprint”



A



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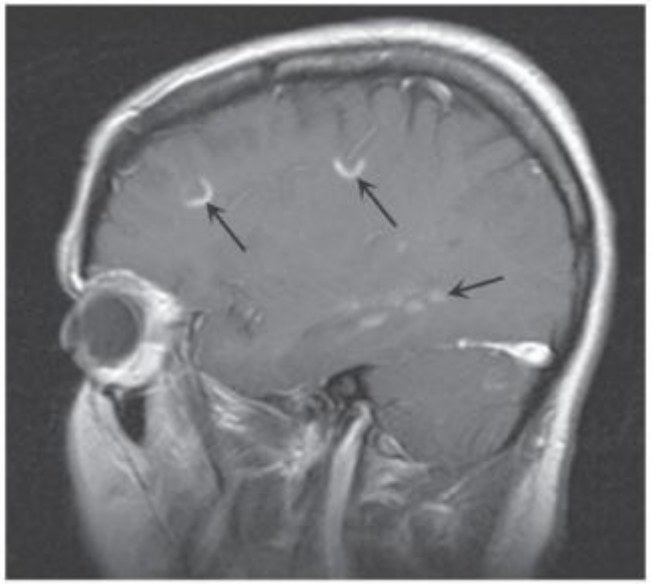

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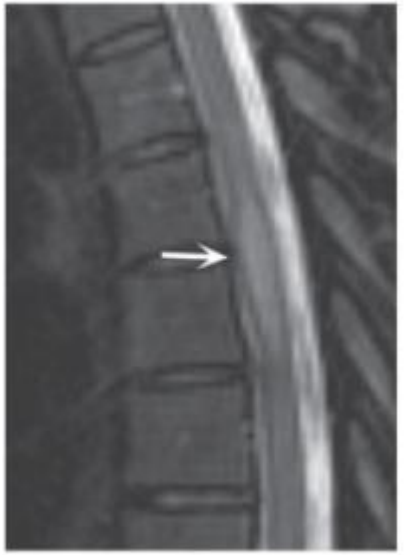
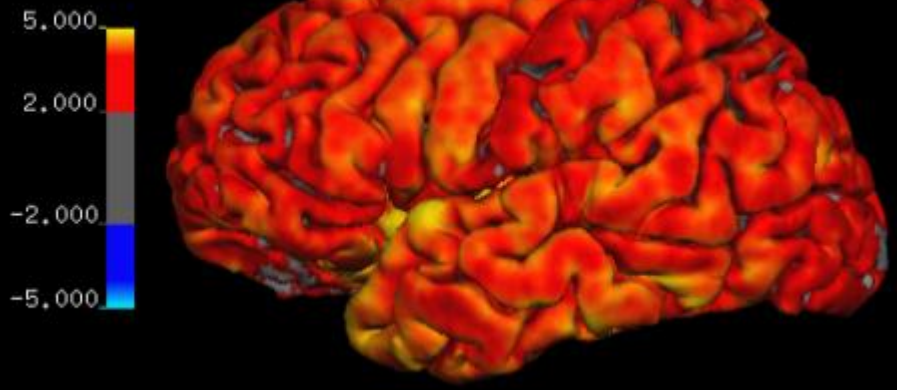


C

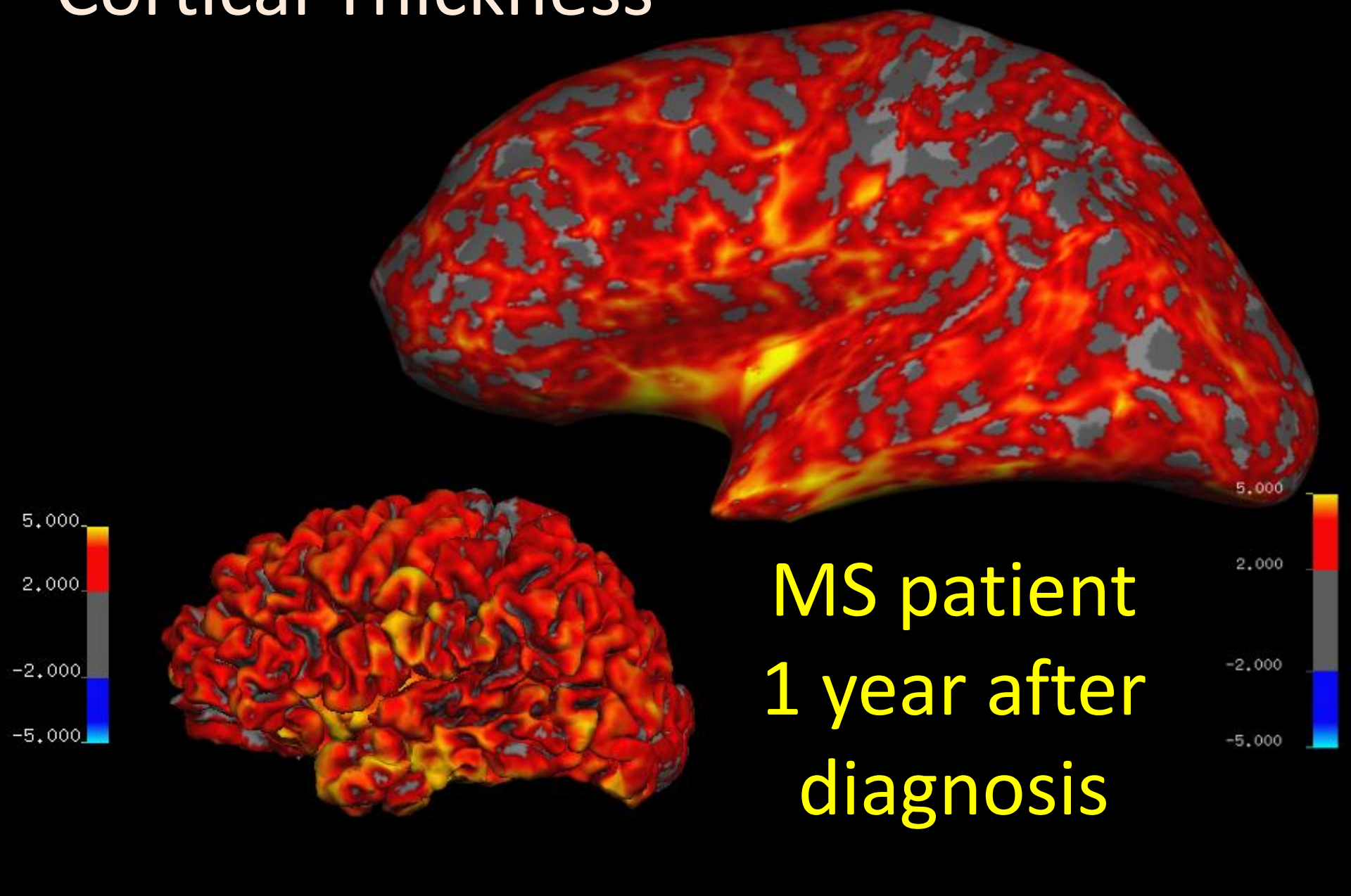
Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com

Cortical Thickness



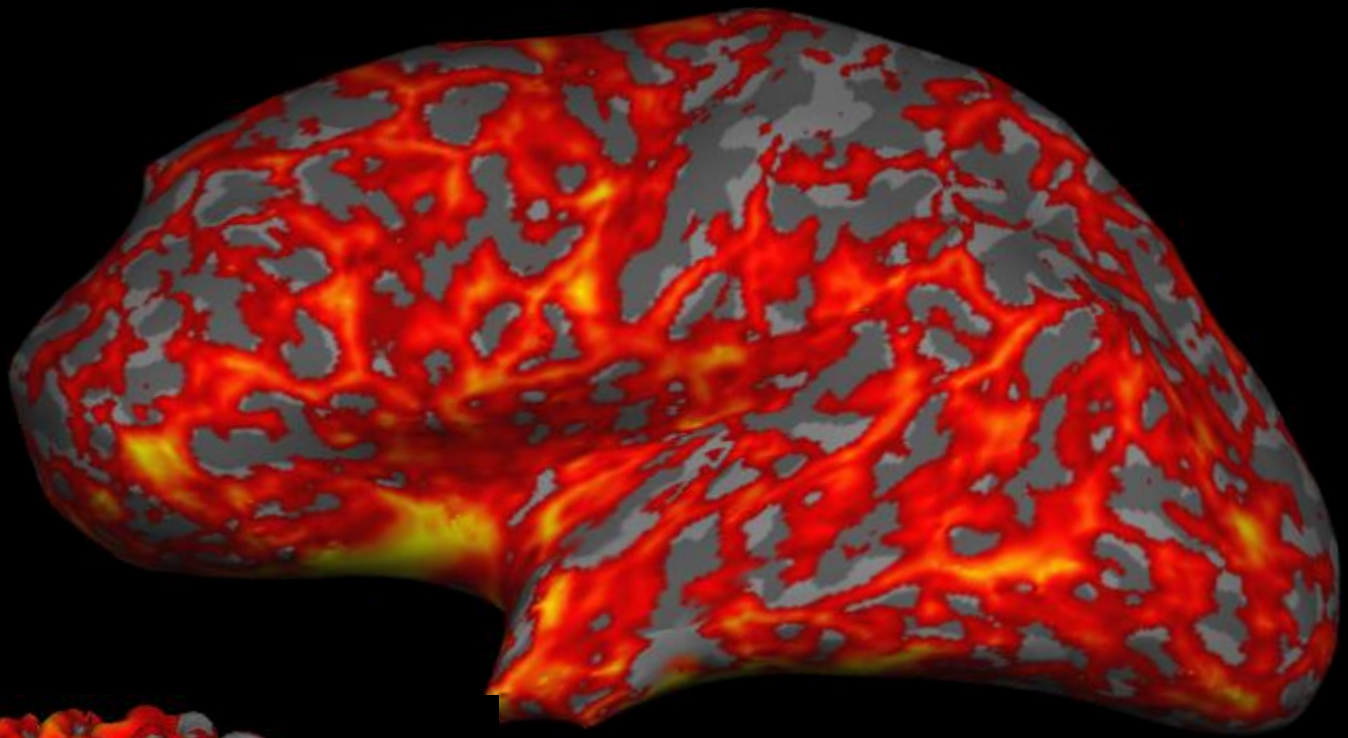
Normal Brain

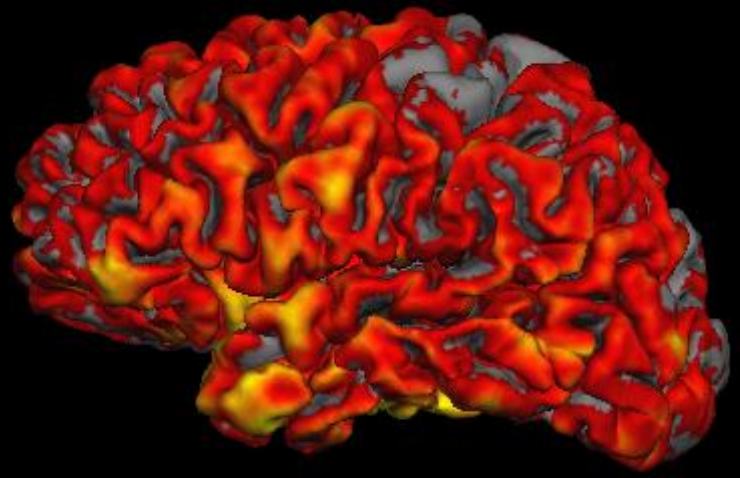
Cortical Thickness



MS patient
1 year after
diagnosis

Cortical Thickness

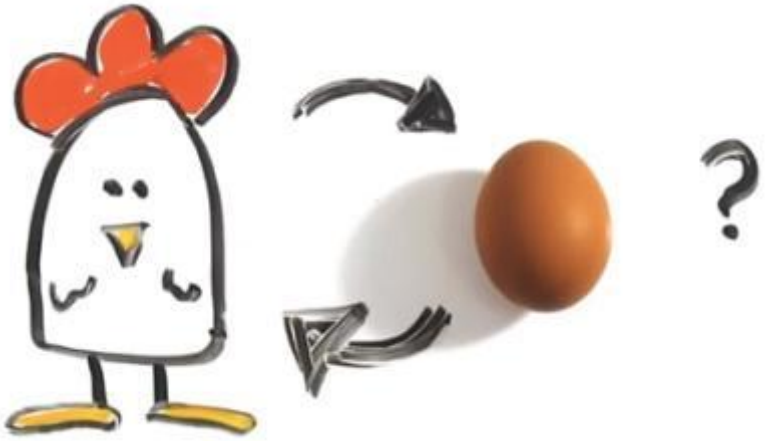




MS patient
4 year after
diagnosis

Neuro-inflammation (WM)

Neuro-degeneration (GM)



which came first, the chicken or the egg ?

Measurement and clinical effect of grey matter pathology in multiple sclerosis

Jeroen J G Geurts, Massimiliano Calabrese, Elizabeth Fisher, Richard A Rudick

Lancet Neurol 2012; 11: 1082–92

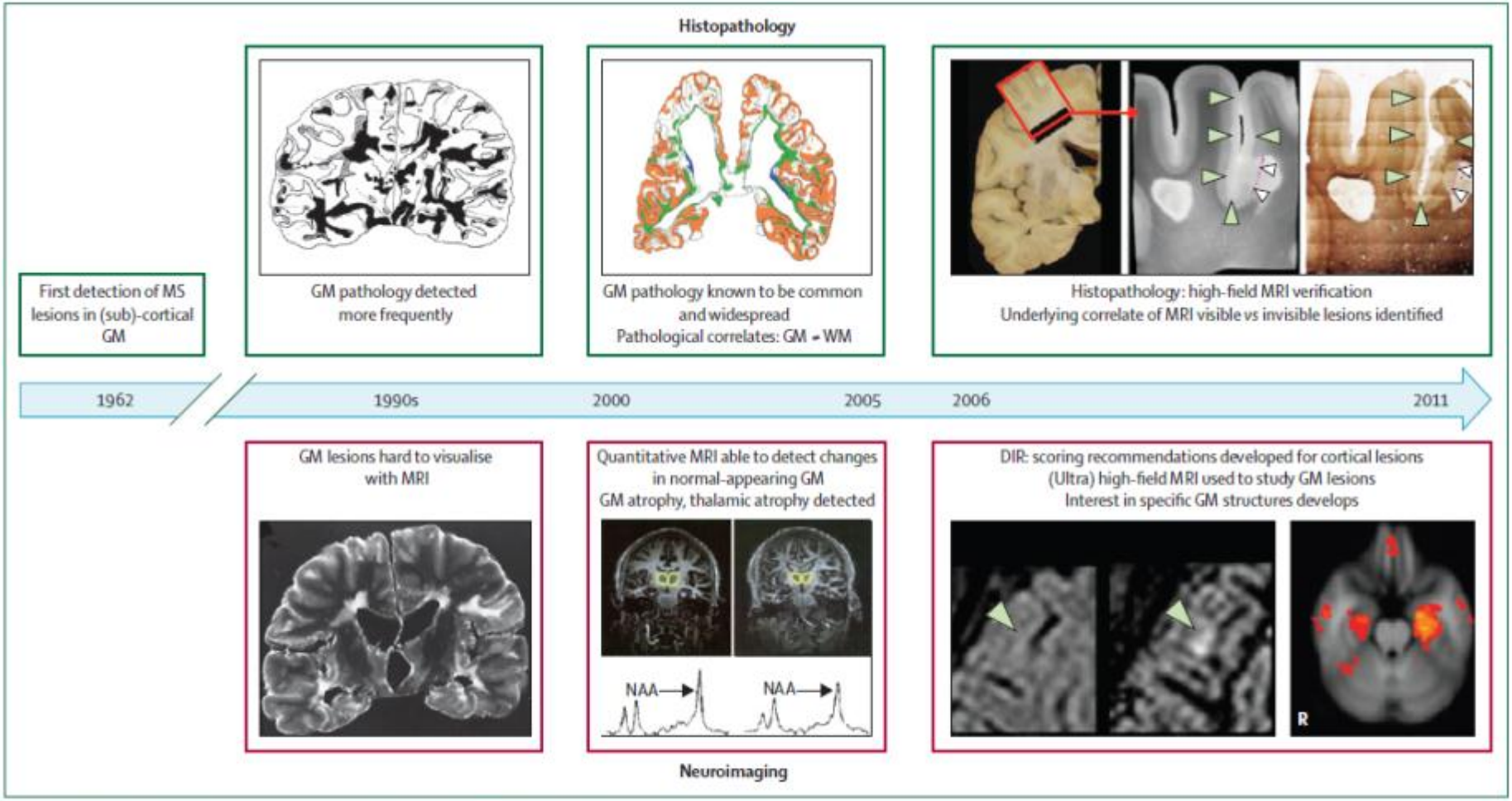
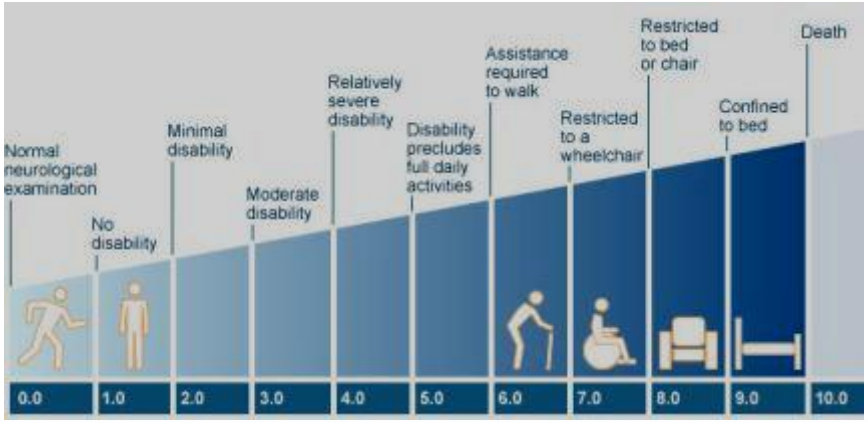


Figure 2: **Timeline of developments in grey matter imaging and pathology in multiple sclerosis**
MS=multiple sclerosis. GM=grey matter. WM=white matter. NAA=N-acetyl aspartate. DIR=double inversion recovery. Adapted with permission from Hulst and Geurts.[8]

MCCT – Mindstream Computerized Cognitive TEST

EDSS Score



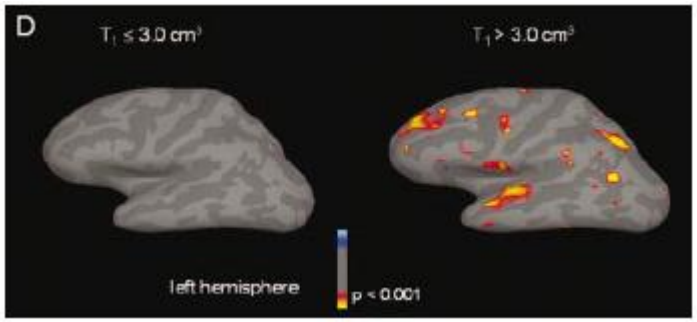
NeuroTrax®

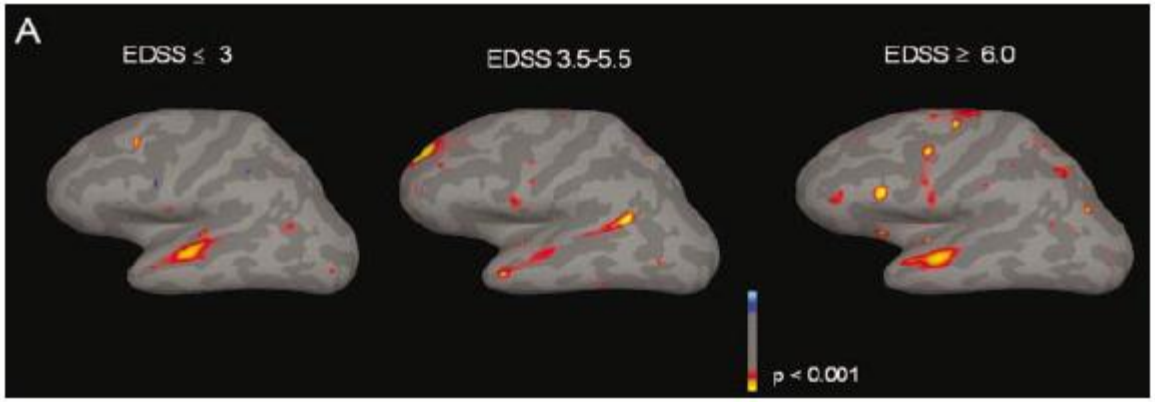
DOI: 10.1093/brain/awg175 *Brain* (2003), **126,** Page 1 of 11

Focal thinning of the cerebral cortex in multiple sclerosis

Michael Sailer,[1] Bruce Fischl,[2,3] David Salat,[1] Claus Tempelmann,[1] Mircea Ariel Schönfeld,[1] Evelina Busa,[2] Nils Bodammer,[1] Hans-Jochen Heinze[1] and Anders Dale[2,3]

The mean overall thickness of the cortical ribbon was reduced in multiple sclerosis patients compared with controls [2.30 mm (SD 0.14) versus 2.48 mm (SD 0.11)], showing a significant main effect of group (controls versus patients). In patients, we found significant main effects for disability, disease duration, T2 and T1 lesion volumes.





Treatment

Interferon β–

- IFN-β is a class I interferon.
- immunomodulatory properties
- IFN- β reduces the attack rate and improves disease severity measures.
- IFN-β-1b (Betaseron), 250 mg, is administered by subcutaneous injection every other day

Natalizumab (Tysabri)-

- humanized monoclonal antibody directed against the α4 subunit of α4β1 integrin.
- prevents lymphocytes from binding to endothelial cells.
- IV – once a month.
- Risk of PML (JCV).

OBJECTIVE

- Assessing longitudinal structural alterations in MS patients.
- Assessing Therapeutic effect of IFN-b and Tysabri on GM pathology.
  - Research groups:

Interferon β–

- 28 Patients
- 16 Females, 12 Males
- 27 Right handed, 1 Left handed

IFN-b, N=28	age	age of onset	Diseas duration	followup duration
Mean	42.8	36.9	5.9	1.2
Median	41.8	36.7	3.8	1.2
Std. Deviation	10.5	11.6	5.9	0.3

Natalizumab (Tysabri)-

- 30 Patients
- 25 Females, 5 Males
- 25 Right handed, 5 Left handed.

Tysabri, N=33	age	age of onset	Diseas duration	followup duration
Mean	39.9	33.1	6.8	1.2
Median	39.5	32.0	6.0	1.1
Std. Deviation	12.9	13.9	5.3	0.3

ARTICLE Multiple Sclerosis 2007; 13: 490–501

Interferon beta-1a slows progression of brain atrophy in relapsing-remitting multiple sclerosis predominantly by reducing gray matter atrophy

R Zivadinov[1], L Locatelli[2], D Cookfair[1], B Srinivasaraghavan[1], A Bertolotto[3], M Ukmar[4], A Bratina[2], C Maggiore[2], A Bosco[2], A Grop[1], M Catalan[2] and M Zorzon[2]

R Zivadinov et al.

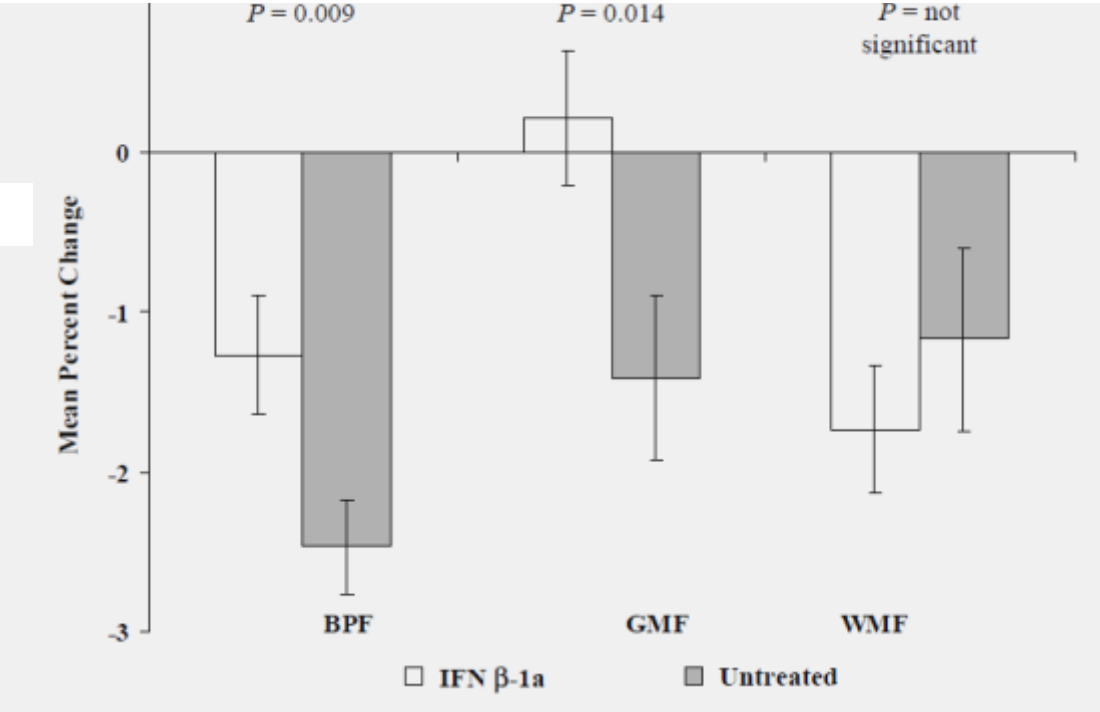
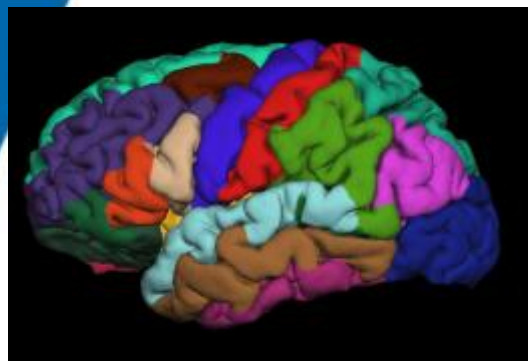


Figure 3 Effect of interferon beta-1a (IFN β-1a) on brain atrophy. Mean percent change (± standard error of the mean) in brain parenchymal fraction (BPF), gray matter fraction (GMF), and white matter fraction (WMF) in IFN β-1a-treated and untreated patients over three years.

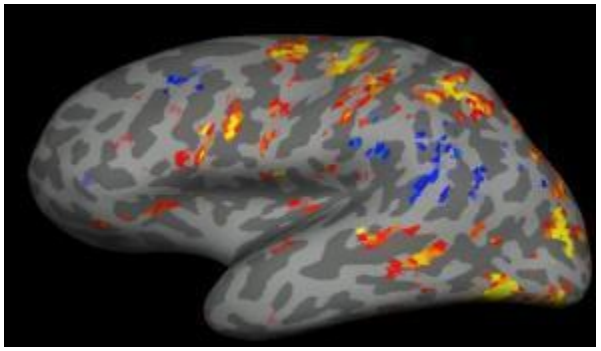
METHODS

- High resolution MRI – 1 mm^3 voxel, sagital 3D FSPGR.
- Freesurfer Analysis - software by **Martinos Center for Biomedical Imaging - MGH.**
  - Fully automatic structural imaging stream for processing cross sectional and longitudinal data.
  - Registration into “common space”.
  - Cortical and sub-cortical segmentation of grey and white matter.
  - Statistical analysis – ROI and Group analysis.

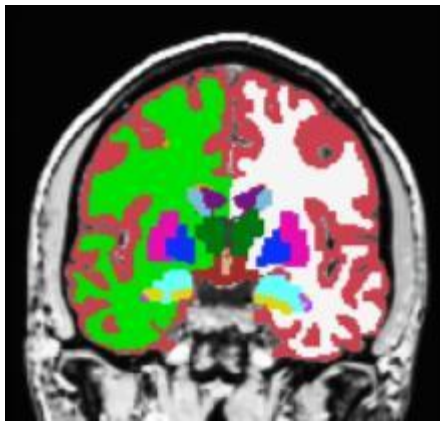
Surface and Volume Analysis



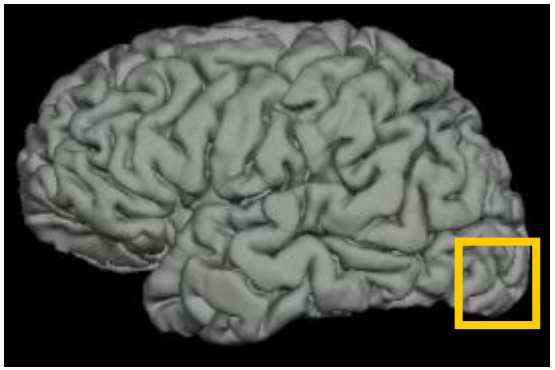
Cortical Reconstruction and Automatic Labeling

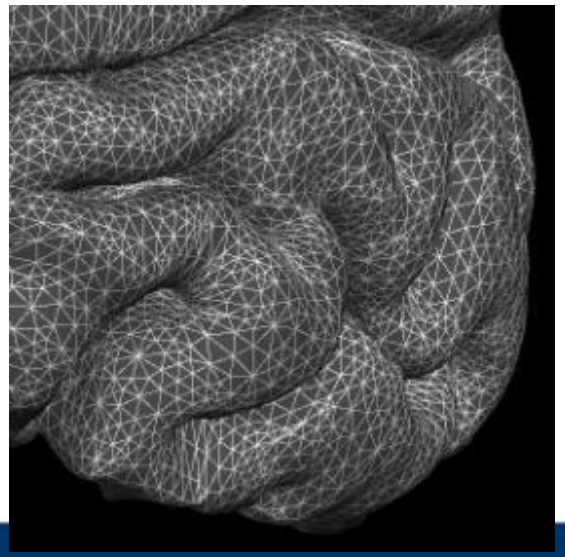


Inflation and Functional Mapping



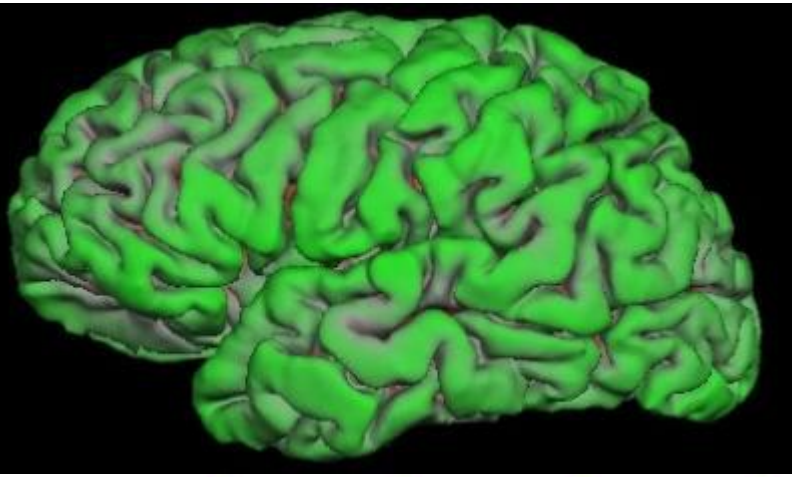
Automatic Subcortical Gray Matter Labeling



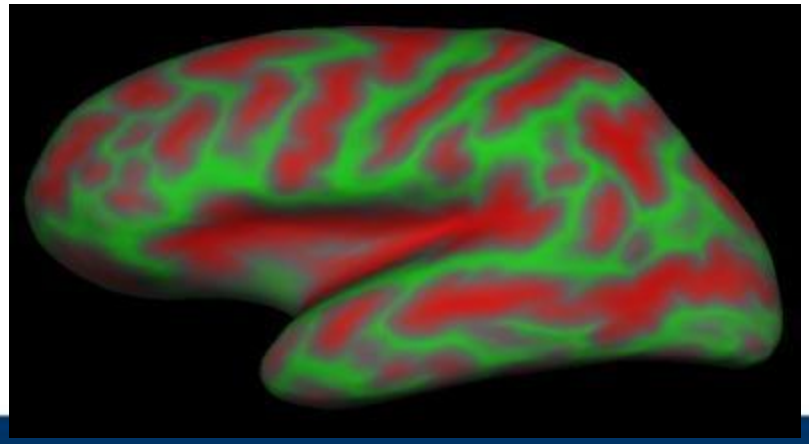


Cortical Surface-Based Analysis

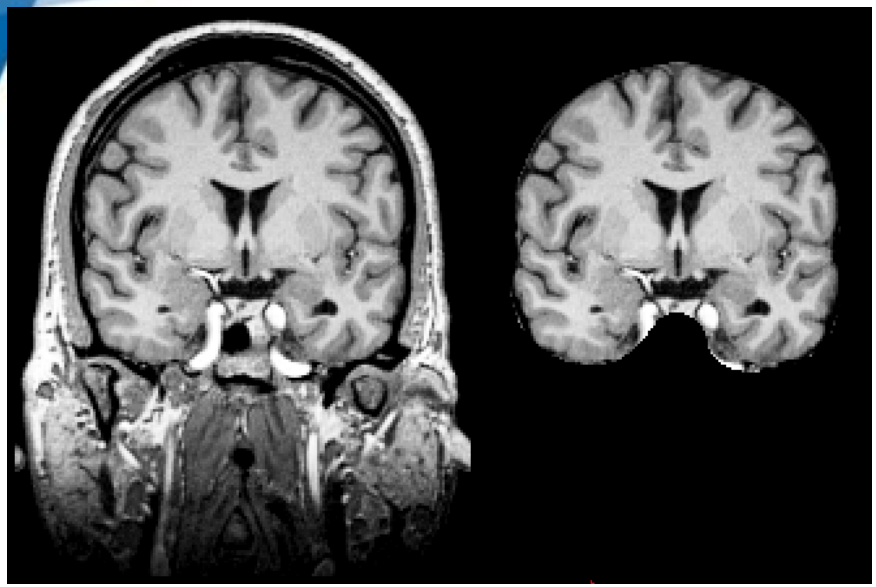
"The surface of the human cerebral cortex is a highly folded sheet with the majority of its surface area buried within folds".

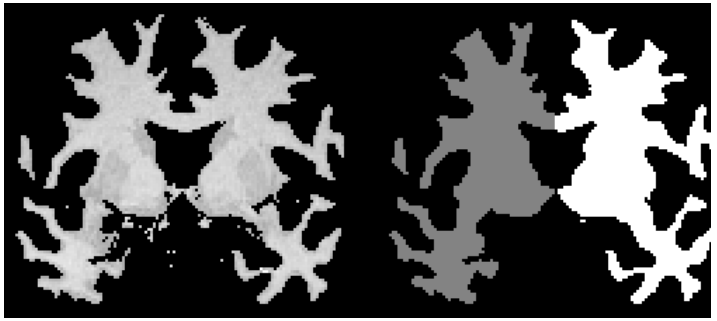


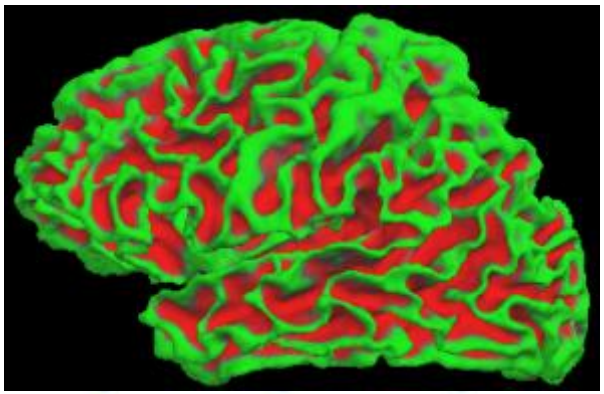
Fischl et al. 1998

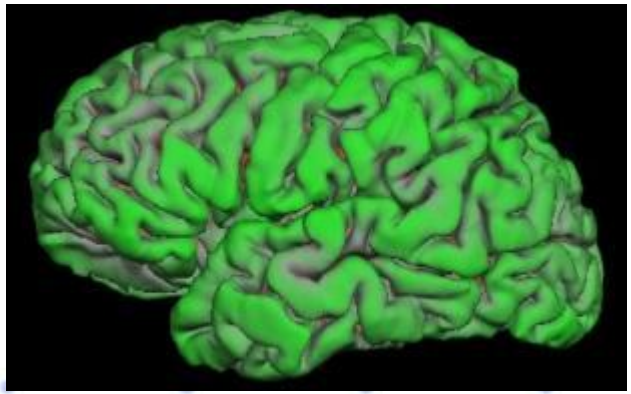


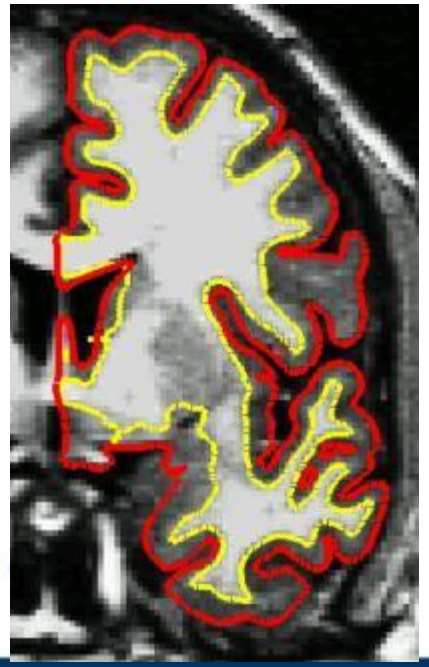
MRI Segmentation and Surface Reconstruction











Why Is a Model of the Cortical Surface Useful?

Use FreeSurfer

Be Happy

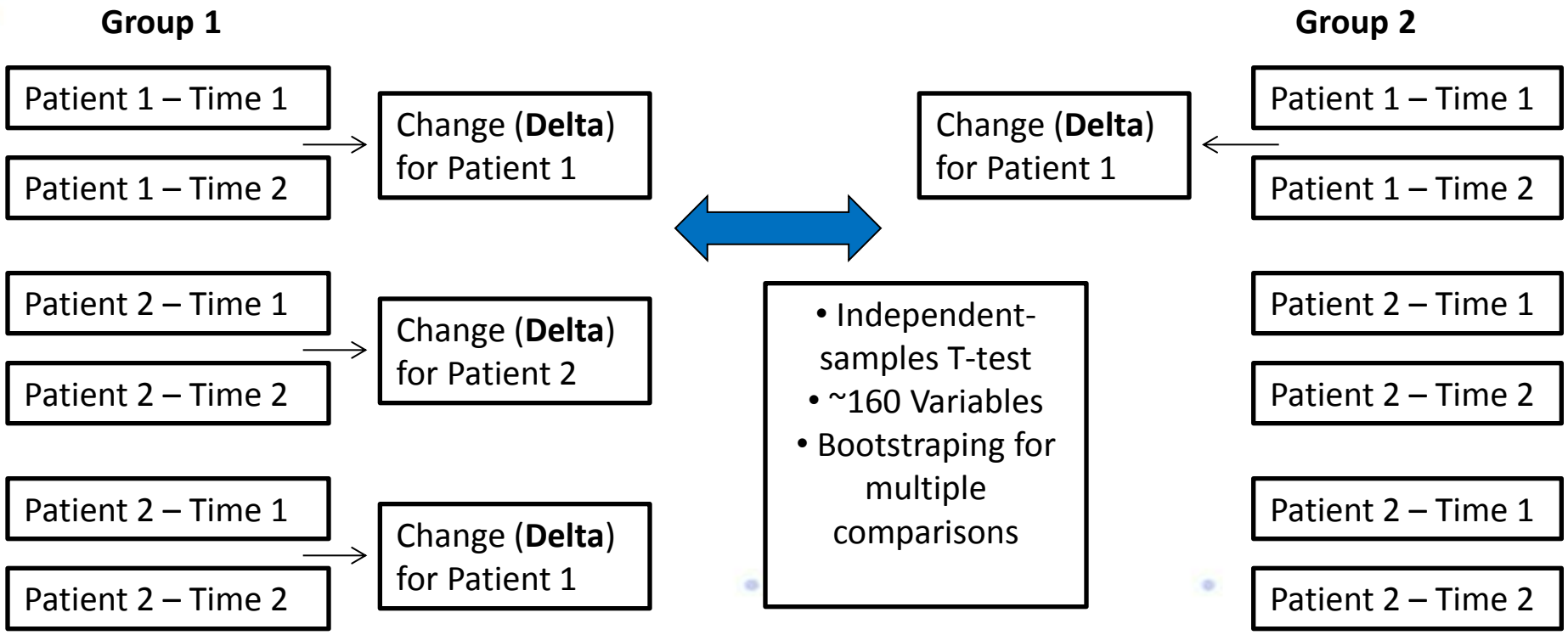
LONGITUDINAL ANALYSIS RESULTS

Statistics tables

- 116 MRI scans
- 2 groups, 2 time points for each subject.
- ~120 Variables:
  - Cortical segmentation
  - Sub-cortical GM

age_onset	DD_symp	DD_diag	Hand	Diag	EDSS	MCCT_GCS	MCCT_MEMO	MCCT_ExFun	MCCT_VisSpa	MCCT_VerbFu	MCCT_atten	MCCT_IPS	MCCT_MotSk	rh_bankssts_thicknessh_caudalant
22.7	9.4	8.9	R	RRMS	5.0	102.5	108.5	104.6	94.4	106.9	101.5	102.8	99	2.442
22.7	10.4	9.9	R	RRMS	4.5	99.7	102.5	105.5	94.4	106.9	105.8	89.8	92.9	2.403
13.9	0.4	0.4	R	RRMS	2.0	98.1	97.3	107.4	92.9	103.9	87.8	93.3	104.2	3.09
13.9	1.4	1.4	R	RRMS	1.0	102.2	103	107.7	92.9	89.4	106.1	100.7	115.6	2.891
38.9														
38.9														
40.2														
40.2														
37.5														
37.5	12.5	3.1	R	RRMS	3.0	NA	NA	NA	NA	NA	NA	NA	NA	2.072
17.1	9.5	8.8	R	RRMS	1.0	102.8	86.2	112.8	86.7	87.1	114.7	122.9	108.8	2.914
17.1	10.1	9.4	R	RRMS	2.0	104.6	106.6	104.5	113.5	87.1	113.4	103.3	103.7	2.714
44.9	6.2	5.8	R	SPMS	4.5	72.4	100.7	76.6	NA	81.8	62.4	53.2	59.9	2.493
44.9	7.8	7.4	R	SPMS	4.5	81	108.2	69.3	118.4	92.4	58.1	60.7	60.1	2.419
43.0	31.0	10.1	R	RRMS	1.0	107.4	108.7	108.6	108.6	104.2	109.3	107.3	105.3	2.273
43.0	32.5	11.6	R	RRMS	2.0	NA	NA	NA	NA	NA	NA	NA	NA	2.278
14.9	4.3		R	RRMS	1.5	99.3	102.1							
14.9	5.2		R	RRMS		NA	NA							
17.8	10.4	10.3	L	RRMS	1.5	92.4	91.8							
17.8	12.2	12.1	L	RRMS	1.5	94.4	105							
32.6	4.3		R	RRMS		103	108.5							
32.6	3.9		R	RRMS			102.8	101.8						
37.7	20.8	1.9	R	RRMS	5.5	74.3	77.6							
37.7	22.2		L	RRMS	5.0	68.4	67.1							
32.0	9.9		L	RRMS	4.0	91.5	88.9							
32.0	11.3	11.2	L	RRMS	4.0	96.7	99.2							
17.1	3.5		R	RRMS	3.5	79.4	45.8							
17.1	5.4	5.3	R	RRMS	0.0	79.9	42							
30.9	8.5	8.5	R	RRMS	4.5	79.9	45.8							
30.9	9.6		L	RRMS	4.0	92.6	93.1							
23.5	12.6		L	RRMS	4.0	92.1	80.8							
23.5	13.5	13.3	R	RRMS	4.0	92.6	81.6							
39.2	11.4	3.6	R	PPMS	6.0	67	79.8							
39.2	12.4	4.5	R	PPMS	6.0	68.5	71.5							
19.8	7.4	5.1	L	RRMS	1.5	103.2	106.3							
19.8	8.7	6.3	L	RRMS	1.0	104.4	106.2							
39.0	24.5	2.1	R	RRMS	6.0	88.8	104.8							
39.0	26.0	3.6	R	RRMS	6.0	86.6	98.5							
28.5	2.2	2.1	R	RRMS	4.0	93.6	98.5							
28.5	3.7	3.7	R	RRMS			NA							
52.8	22.5	22.5	R	RRMS			82.4							
52.8	24.1	24.1	R	RRMS	6.0	83.1	78.5	88.2	84.9	69.3	96.1	NA	81.9	2.702
50.9	3.5	2.2	R	RRMS	3.0	91.9	101.6	90.1	98.6	104.2	83.9	59.5	105.6	2.287
50.9	4.7	3.4	R	RRMS	4.0	86.8	77.8	80.4	93.8	87.7	88.1	NA	92.8	2.229
25.8	16.9	11.3	L	RRMS	1.5	100.6	94	105.6	88.1	106.9	102.8	99.3	107.7	2.698
25.8	17.9	12.2	L	RRMS	1.5	103.6	101.7	102.2	94.4	109.3	105.8	105.1	107	2.781
41.7	3.6	2.4	R	RRMS	2.0	101.2	107.8	94.6	110.2	76.8	107.8	NA	109	2.717
41.7	4.6	3.5	R	RRMS	1.5	NA	NA	NA	NA	NA	NA	NA	NA	2.622
25.1	14.6	10.6	R	RRMS	4.0	94.9	86.4	94.6	89.5	107.3	102.6	94	90	2.169
25.1	15.8	11.8	R	RRMS	3.0	98	103.1	86.3	89.5	109.8	99.9	99.5	97.7	2.316
23.4	14.5	14.5	R	RRMS	3.5	79.6	100.6	72.2	88.1	103.3	62.3	79.1	51.6	2.422
23.4	15.6	15.6	R	RRMS	3.0	90.3	105.3	81.5	88.1	103.3	94.3	108	51.8	2.287
41.0	30.6	16.0	R	RRMS	4.0	94.1	94.9	95	78.8	98.3	93.7	NA	104.2	2.132

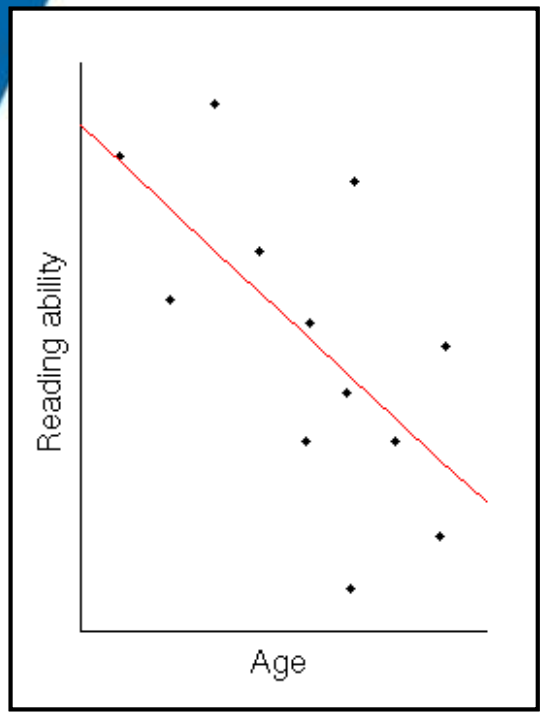
Study Design – Differences between groups

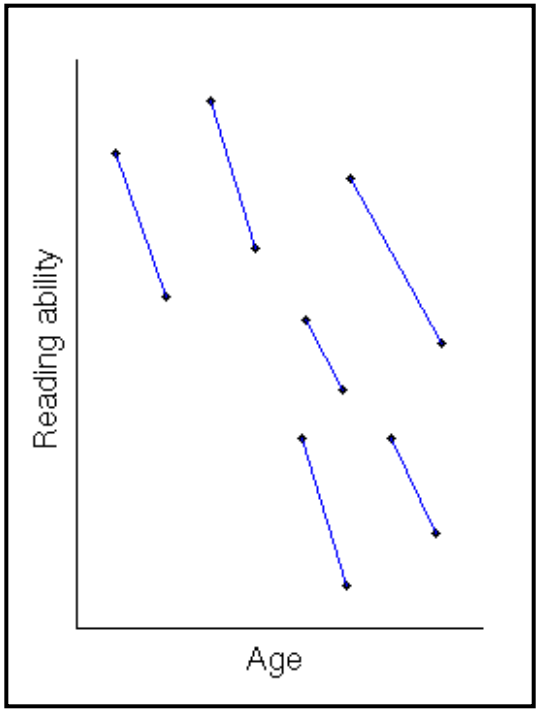


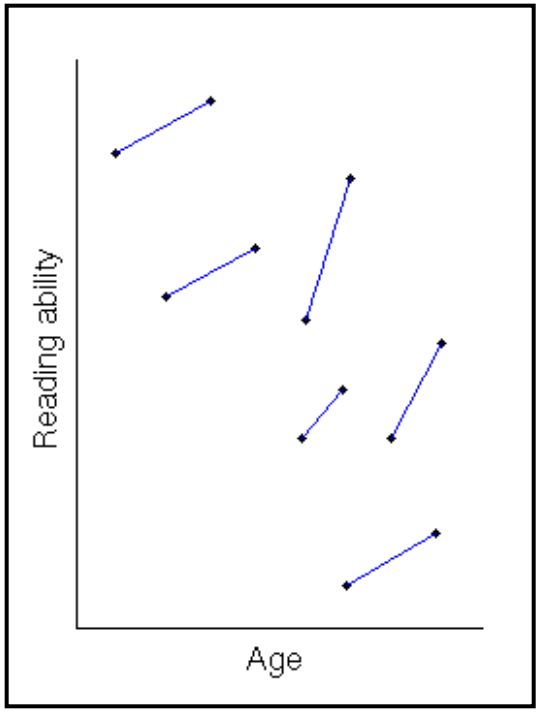
Limitations

- Follow up duration - neuronal atrophy is a slow chronic process
- Demographic and clinical differences between groups – adjustment and corrections might be needed
- Statistical validation

Paired / Longitudinal analysis







Paired / Longitudinal analysis

- **Reduce inter-individual variability effect –**
  - Age
  - Sex
  - Disease duration
  - Education

Sig. differences between Treatments

Cortical gray matter

Bootstrap for Independent Samples Test

	Mean Difference	Bootstrap[a]			
		Std. Error	Sig. (2-tailed)	95% Confidence Interval	
				Lower	Upper
lh_superiorfrontal_thickness	-.059	.0235	.018	-.106	-.015
lh_transversetemporal_thickness	.141	.0497	.007	.040	.238

- **Only 2 areas with sig. change out of 68 cortical GM segmantations**

Sig. differences between Treatments

Sub-cortical gray matter

Bootstrap for Independent Samples Test

	Mean Difference	Bootstrap[a]			
		Std. Error	Sig. (2-tailed)	95% Confidence Interval	
				Lower	Upper
Left-Caudate	125.645	41.914	0.003	47.456	204.430
Right-Caudate	100.693	34.009	0.006	33.105	171.593
Right-Amygdala	55.698	26.006	0.040	4.222	106.147

- **Only 3 areas with sig. change out of 55 subcortical segmantations**
- Mean difference - change in mm^3 (volume)
- Mean difference = Tysabri (change) - Interferron-B (change).

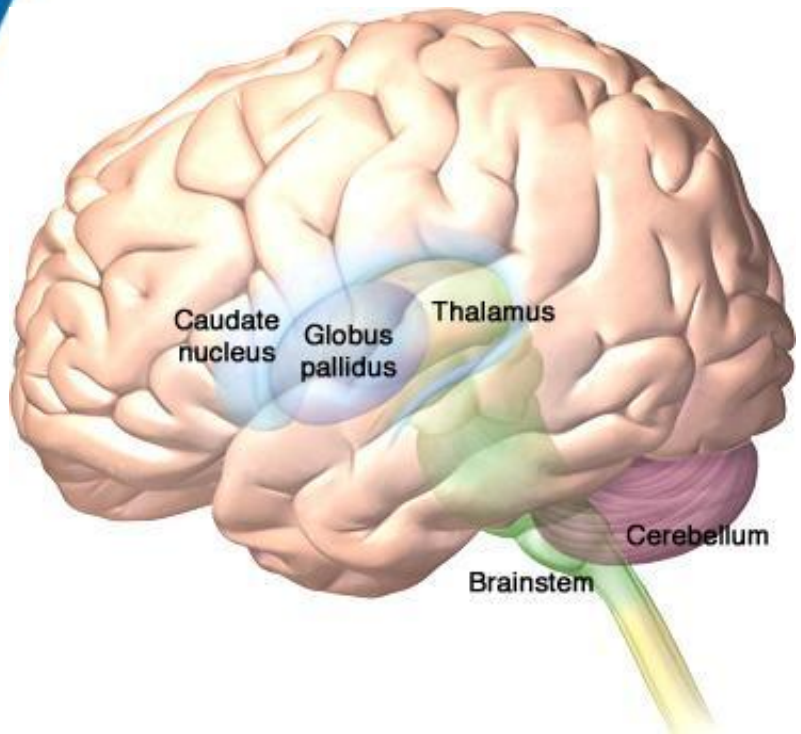
e.g. – positive value – relatively less atrophy for Tysabri treatment.

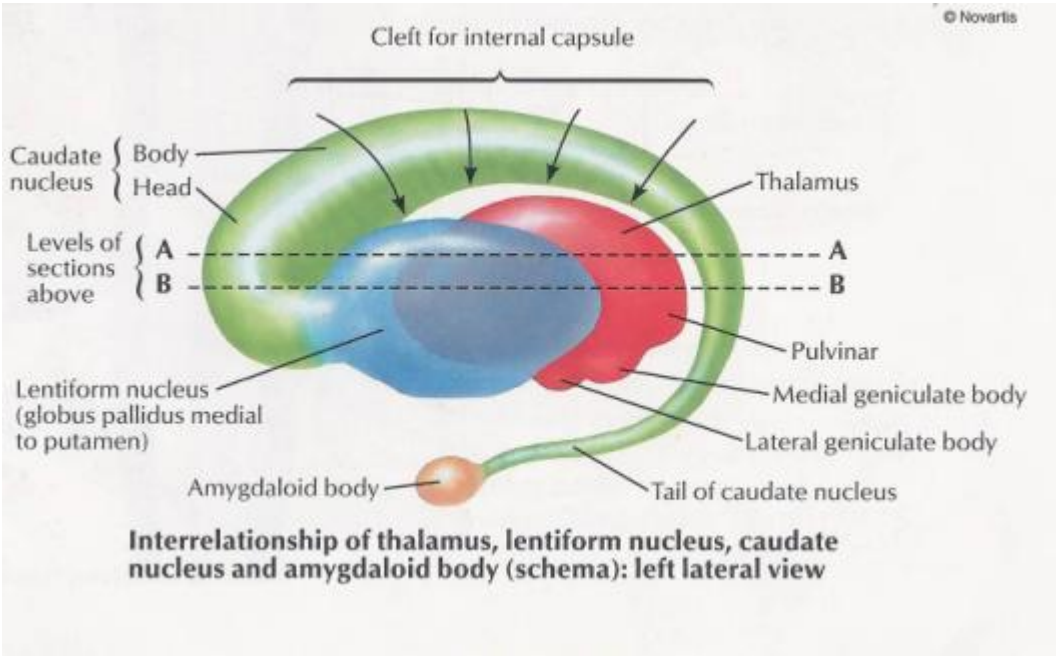
Interferon beta Vs Tysabri

- The Vast majority of GM and WM segmentations did not exhibit significant change in thickness / volume.
- GM alterations – specific regions exhibit better outcome for Tysabri treatment = **less atrophy with Tysabri**
- **This is a preliminary conclusion !!!!**

Caudate Nucleus

- **Cognitive functions: Goal-Directed Action - executive functioning. Memory, Learning, Sleep, Emotion, Language, Threshold control.**
- Motor function: Spatial Mnemonic Processing, Directed Movements.





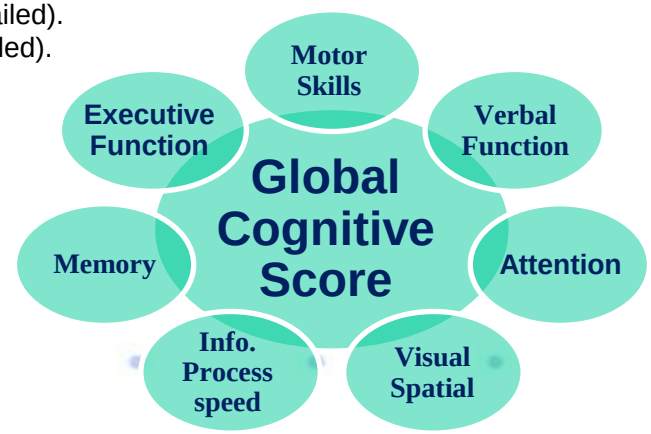
Correlation with change in cognitive tests

Correlations

		EDSS	GCS	Memory	Executive function	MCCT_VisSpa	Verbal function	Attention	MCCT_IPS	Motor skill
Left-Caudate	Pearson Correlation	.114	.085	-.197	-.012	-.252	-.202	.340*	.436*	.227
	Sig. (2-tailed)	.396	.634	.263	.946	.157	.268	.049	.016	.204
	N	57	34	34	34	33	32	34	30	33
Right-Caudate	Pearson Correlation	.214	.207	-.054	.217	-.136	-.045	.518**	.108	.164
	Sig. (2-tailed)	.110	.239	.763	.217	.450	.808	.002	.569	.362
	N	57	34	34	34	33	32	34	30	33

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).



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BRAIN

Diffusion Tensor–MRI Evidence for Extra-Axonal Neuronal Degeneration in Caudate and Thalamic Nuclei of Patients with Multiple Sclerosis

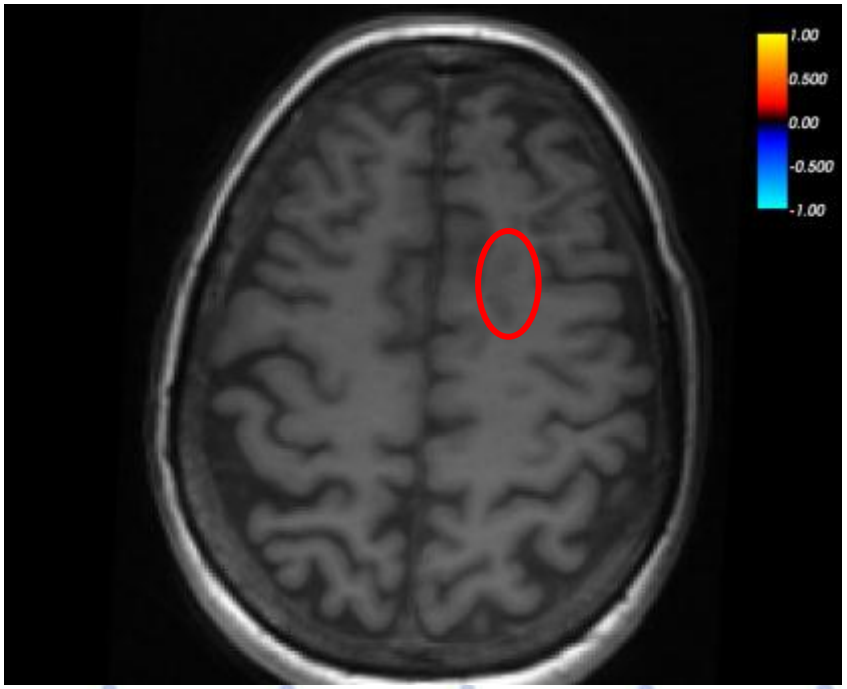
S. Hannoun[a], F. Durand-Dubief[a,b], C. Confavreux[b], D. Ibarrola[e], N. Streichenberger[c], F. Cotton[a,d], C.R.G. Guttmann[f] and D. Sappey-Marinier[a,e]

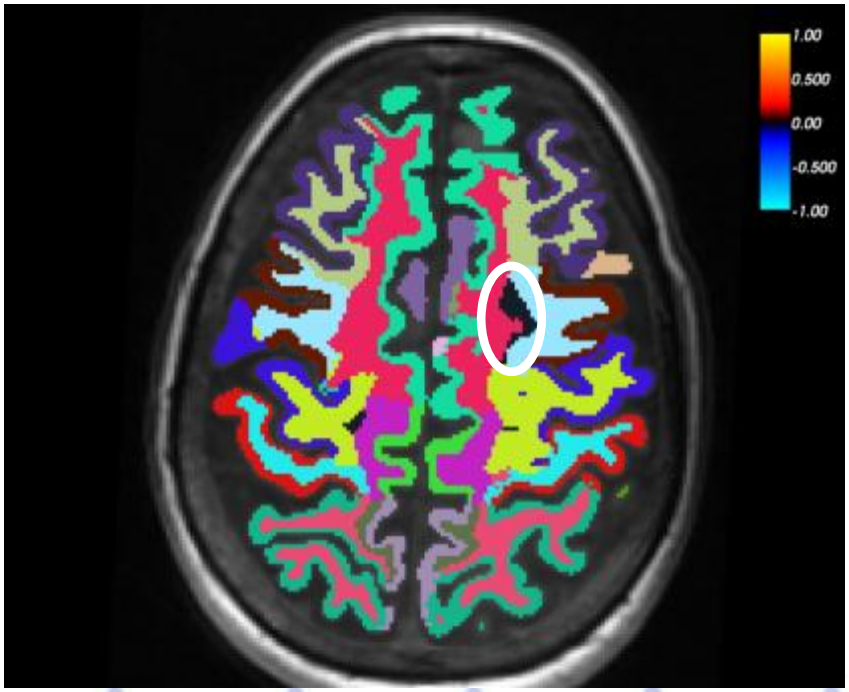
RESULTS:
FA was significantly (P .001) increased in the caudate and the thalamus of patients with MS compared with controls, and was higher in SP compared with RR patients. Increased FA was **associated with volume decreases of caudate** (r 0.712; P .001) and thalamus (r 0.407; P .01) in patients with MS. WM T2 lesion load was significantly associated with caudate (r 0.611; P .001) and thalamic (r 0.354; P .05) FA. Caudate FA, and, to a lesser extent, thalamic FA, were associated with functional deficits, as measured by EDSS and MSFC.

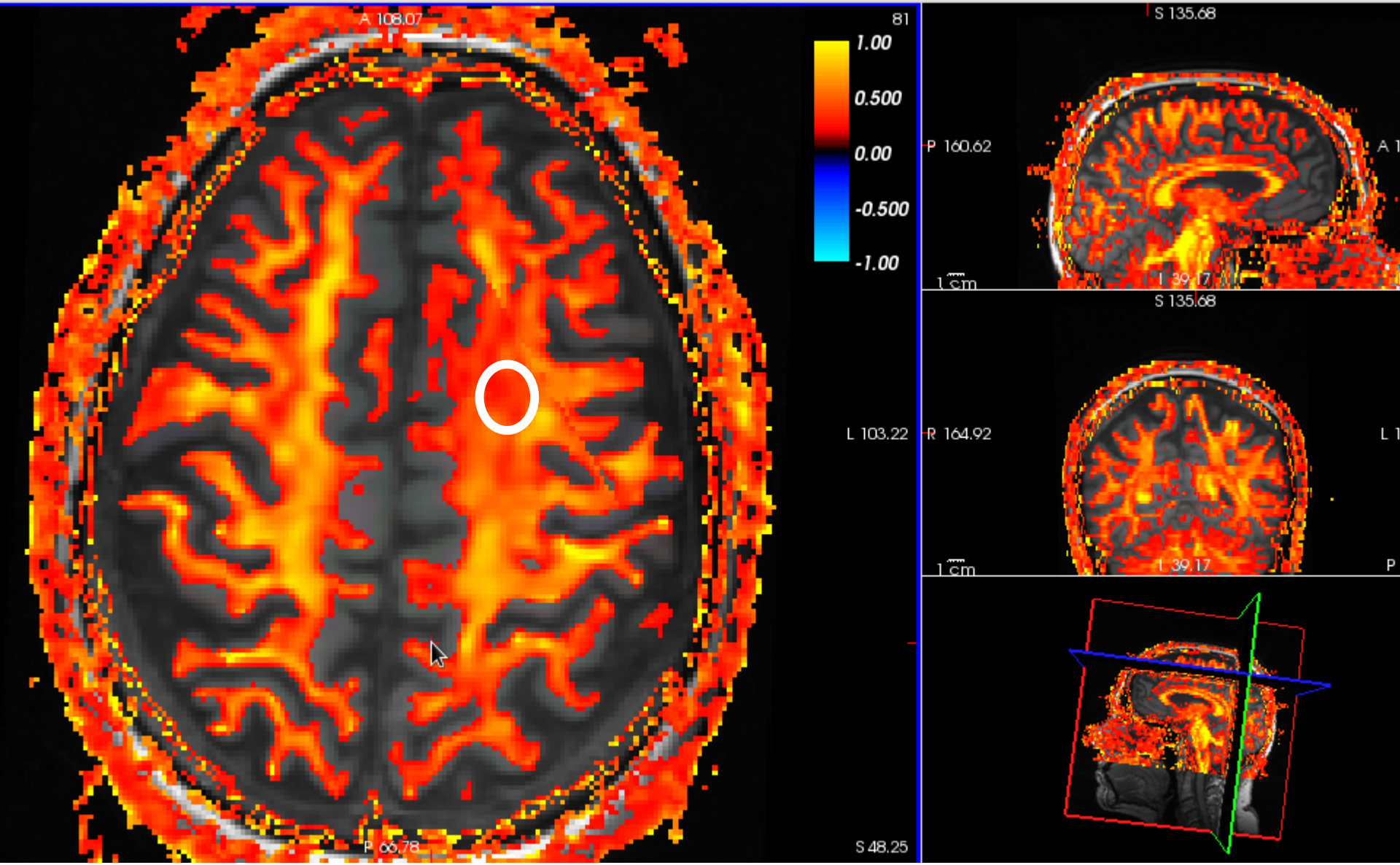
CONCLUSIONS: Increased FA in the **caudate** and the thalamus may constitute **a sensitive marker of MS pathologic processes**, such as loss of dendrites and/or swelling of neuronal cell bodies.

Multi Modality Integration

- Integrating anatomical segmantations with functional acquisitions (DTI).



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1.00
0.500
0.00
-0.500
-1.00
L 103.22
P 66.78
S 48.25
S 135.68
P 160.62
1 cm
I 39.17
S 135.68
R 164.92
1 cm
I 39.17

DISCUSSION

- Better understanding of Treatment effects and management.
- Understanding GM Pathology Vs. WM Pathology

FUTURE RESEARCH PLAN

- Statistical validation.
- Writing a paper.
- Extend data to 2 years.
- Compare data to gilenya treatment.
- **Multi-modality – combine DTI with anatomical data.**

QUESTIONS