Computerised MRI project –A new algorithm to assess brain atrophy in MS patients.

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Definition of MS

An immune-mediated inflammatory disease that attacks myelinated axons in the central nervous system (CNS), destroying the myelin and the axon in variable degrees. In most cases, the disease follows a relapsing-remitting pattern, with short-term episodes of neurologic deficits that resolve completely or almost completely. A minority of patients experience steadily progressive neurologic deterioration.

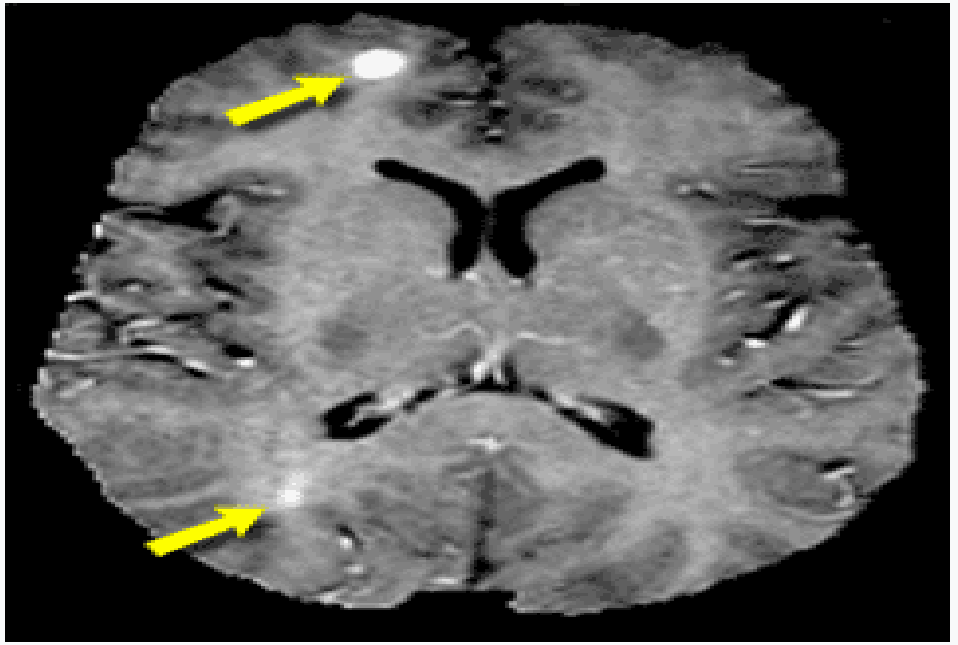
MRI IS THE ONLY WINDOW WE CAN USE TO LOOK DIRECTLY AT PATOLOGICAL PROCESSESS OF THE BRAIN.

Diagnostic criteria for MS

Mc Donald criteria for MS		
ATTACKS	**LESIONS**	**ADDITIONAL CRITERIA FOR DIAGNOSIS MS**
2 or more	**2 or more**	**None.** Clinical evidence alone will suffice
2 or more	**1 lesion**	**Dissemination in space on MR** (or await further clinical attack implicating a different CNS site)
1 attack	**2 lesions**	**Dissemination in time on MR** (or await further clinical attack implicating a different CNS site)
1 attack	**1 lesion**	**Dissemination in space *and* time** (or await further clinical attack implicating a different CNS site)
0 attack progression from onset		One year of disease progression (retrospective or prospective) **AND** at least 2 out of 3 criteria: • Dissemination in space in the brain • Dissemination in space in the spinal cord based on 2 or more T2 lesions • Positive CSF

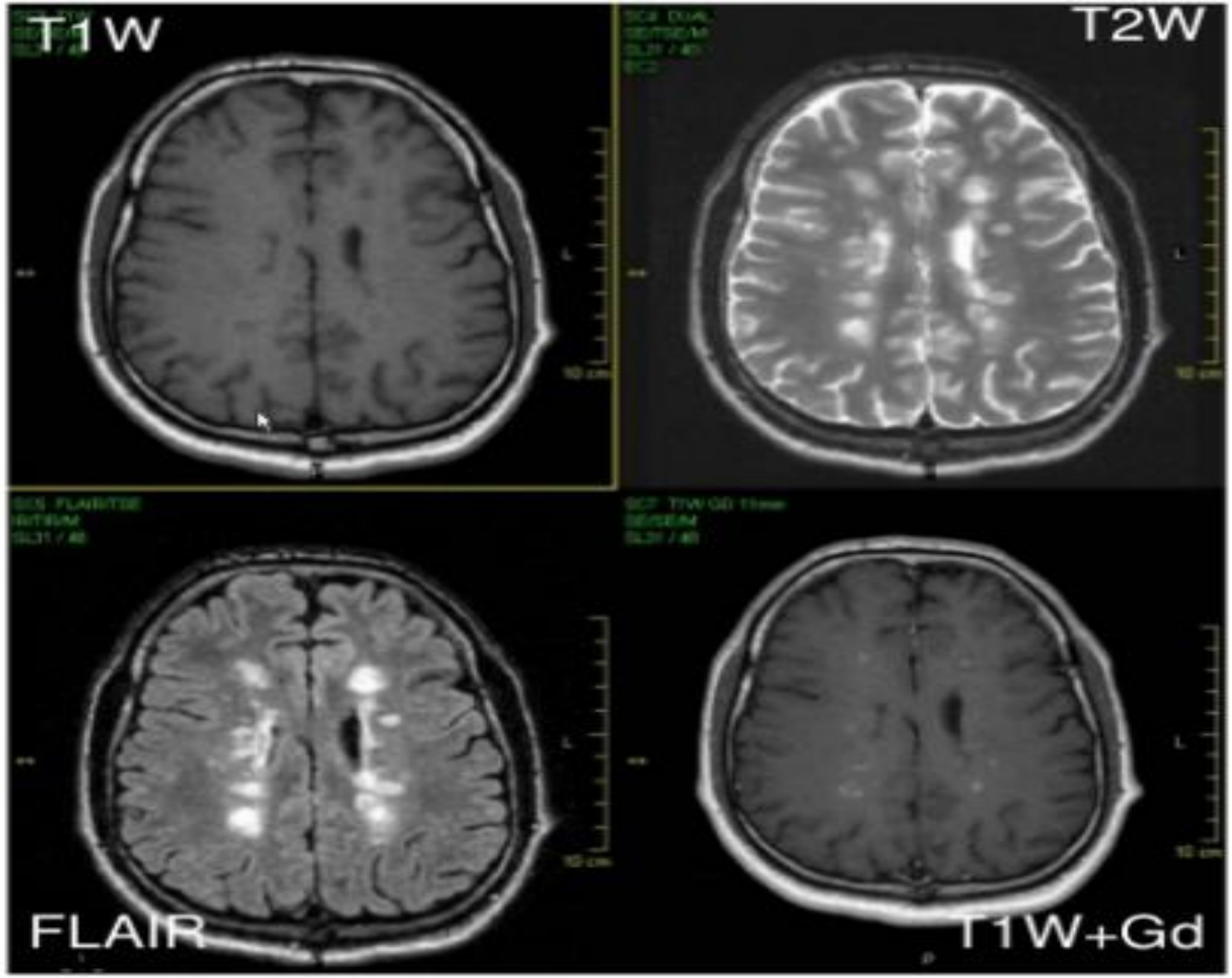
McDonald criteria

Medical diagnostics



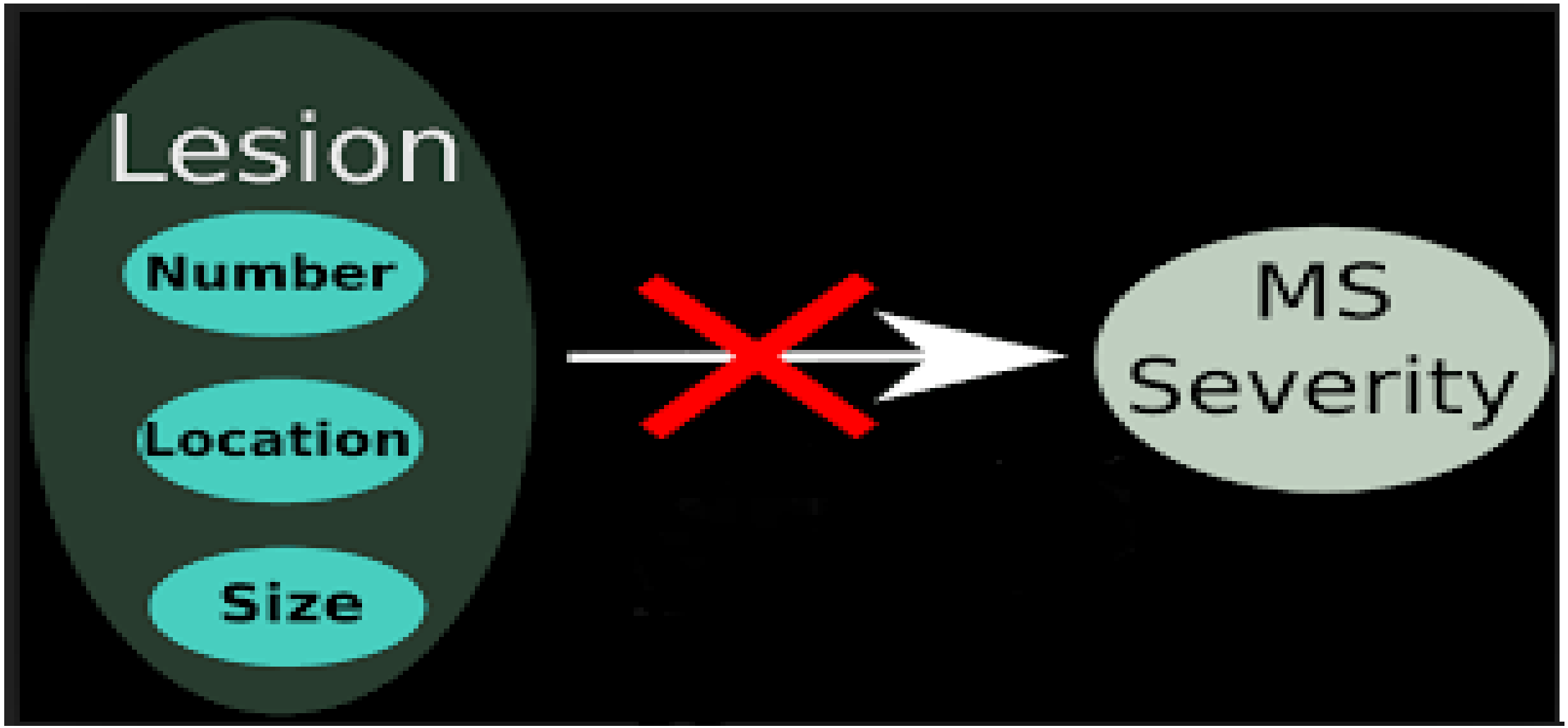
Animation showing dissemination of multiple sclerosis lesions in time and space as demonstrated by monthly MRI studies along a year

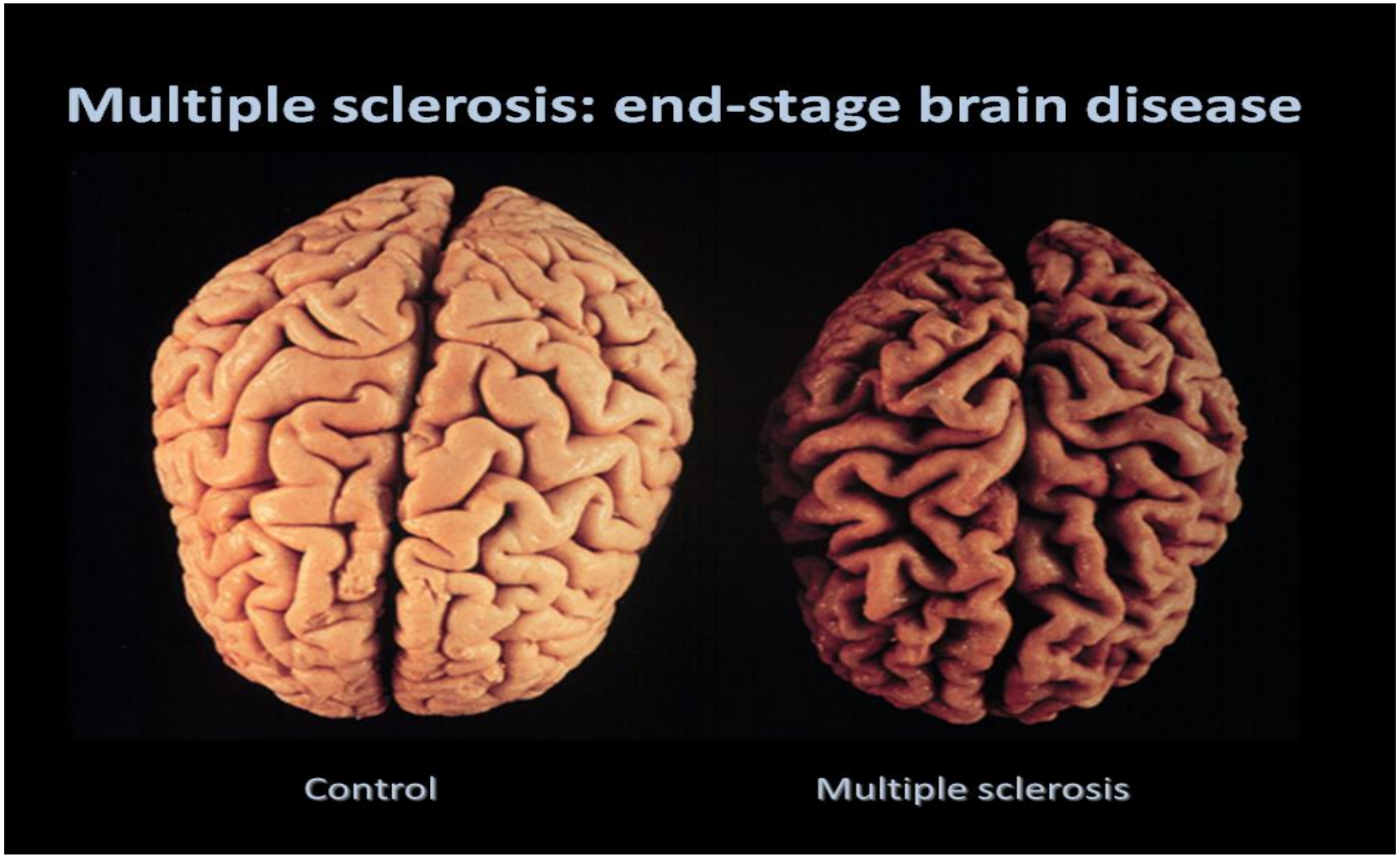
CONVENTIONAL



MRI TECHNIQUES

Clinico-radiological Paradox

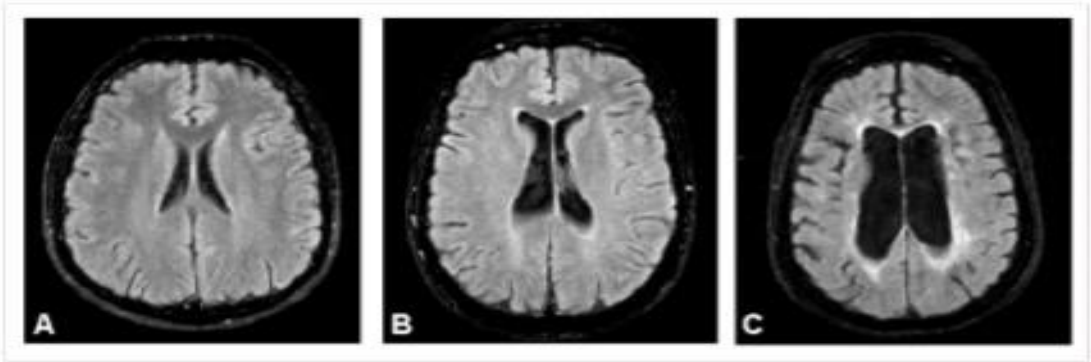



Multiple sclerosis: end-stage brain disease
Control
Multiple sclerosis

Why should we measure brain atrophy?

- Brain atrophy in multiple sclerosis (MS) was classically thought of as a late-stage phenomenon.

- Over the past two decades, understanding of brain atrophy in MS has been substantially revised**. It is now clear that atrophy begins very early in the disease can progress relatively independently of overt lesions** (Fisniku et al., 2008), affects both gray matter (GM) and WM, **and proceeds at up to 5 times the rate associated with normal aging** (Miller et al., 2002).



Healthy controls 0.1-0.3 % per yr
MS 0.5-1.35 % per yr

Nicola De Stefano, CNS Drugs, 2014

- Quantitative measurements of **atrophy have been shown to be the best correlates and long-term predictors of both cognitive and clinical disability** (Benedict et al., 2006; De Stefano et al., 2014; Summers et al., 2008; Zivadinov et al., 2016b).

- This revised understanding of the importance and clinical relevance of brain atrophy in MS encouraged the emergence of quantitative image-based computational techniques for measuring brain atrophy more precisely and accurately than is possible by eye.

- There is a need for a brain volume measure applicable to the clinical routine scans. Nearly every multiple sclerosis (MS) protocol includes low-resolution 2D T2-FLAIR imaging

The results are good at a group level but difficult to apply at an individual level

Need to gather patients and divide them to groups by different parameters such as disease course, treatment and etc….

Collect data all over the world and create an universal Atlas

NeuroSTREAM project

Background: There is a need for a brain volume measure applicable to the clinical routine scans. Nearly everymultiple sclerosis (MS) protocol includes low-resolution 2D T2-FLAIR imaging.

Aim: To develop and validate cross-sectional and longitudinal brain atrophy measures on clinical-quality T2-FLAIR images in MS patients

Methods: A real-world dataset from 109 MS patients from 62 MRI scanners was used to develop a lateral ventricular volume (LVV) algorithm with a longitudinal Jacobian-based extension, called NeuroSTREAM. Measurement at different field strengths was tested in 76 healthy controls and 125 MS patients who obtained both 1.5T and 3T scans in 72 hours. Clinical validation of algorithm was performed in 176 MS patients who obtained serial yearly MRI 1.5T scans for 10 years.

Results: NeuroSTREAM showed comparable effect size(d =0.39–0.71) in separating MS patients with and without confirmed disability progression, compared toSIENA and VIENA.

Conclusions: Brain atrophy measurement on clinical quality T2-FLAIR scans is feasible, accurate, reliable, and relates to clinical outcomes.

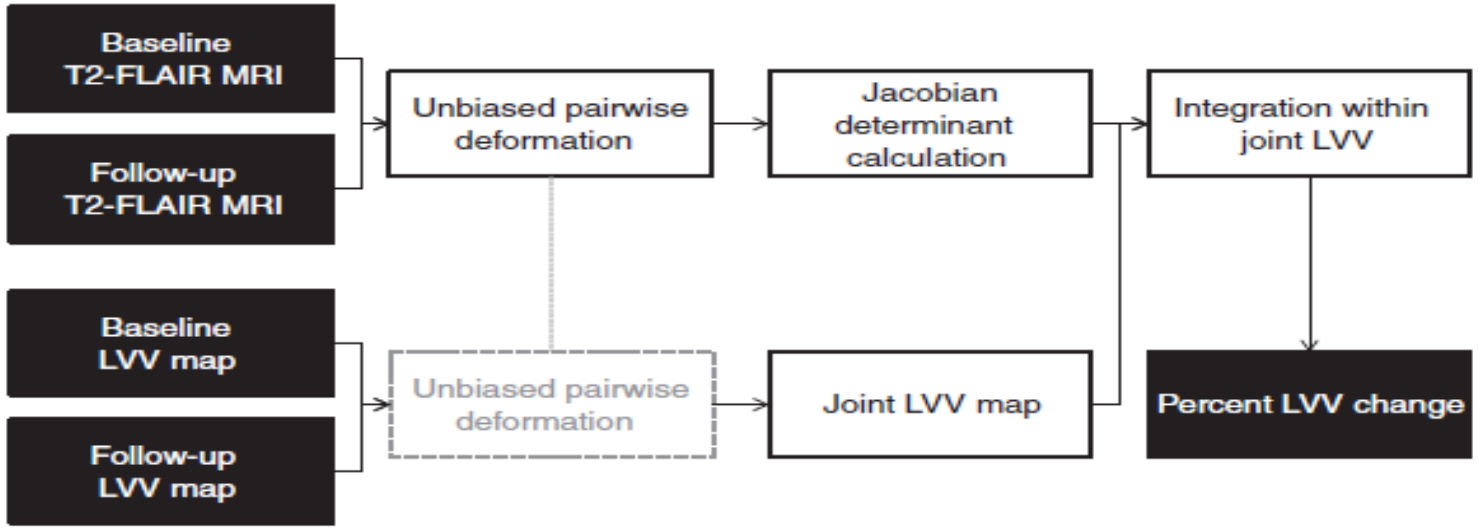


Fig. 4. Schematic overview of the longitudinal Jacobian-based extension to NeuroSTREAM. Shaded area indicates that pairwise deformation results are also used to bring a joint LVV map into a halfway space. LVV = lateral ventricular volume.

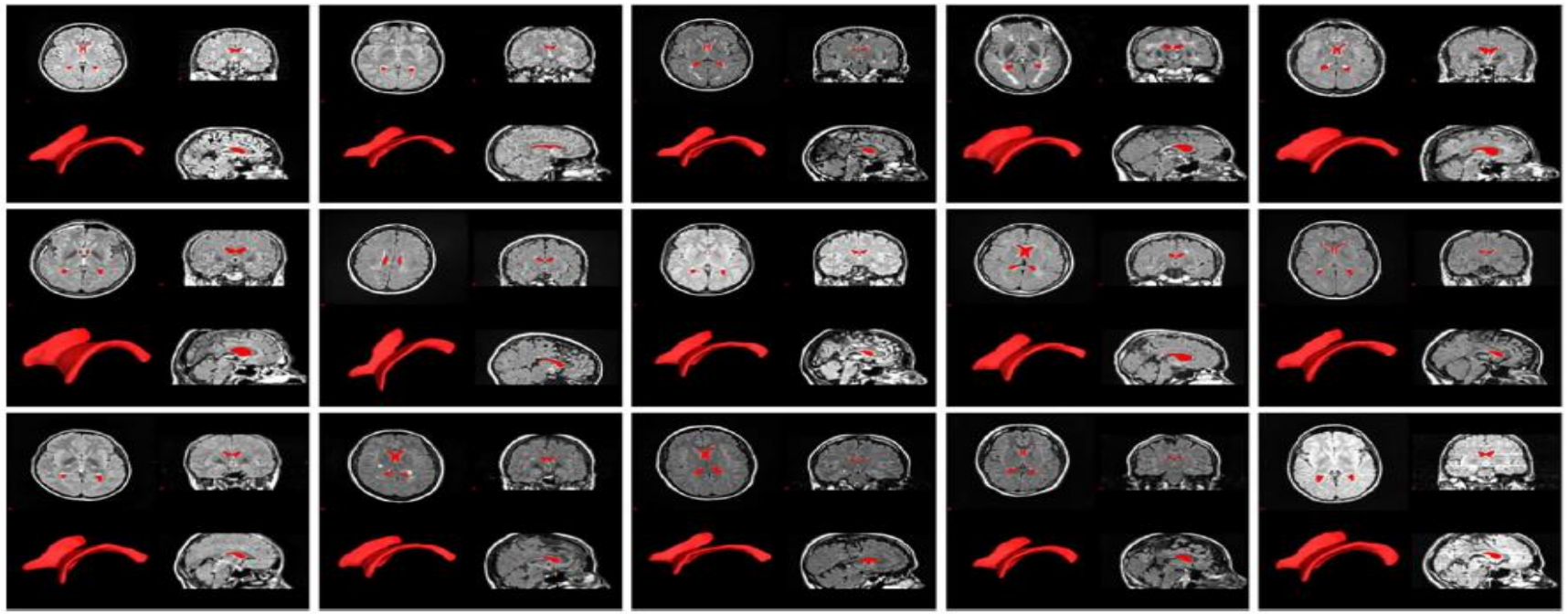


Fig. 5. Sample NeuroSTREAM LVV segmentations demonstrating the range of scan types, intensity profiles, resolutions, ventricular anatomy, and atrophy levels capable of being successfully segmented and quantified. Each sub-image shows an axial (upper left), coronal (upper right), and sagittal (lower-right) view, along with a 3D render of the extracted LVV (lower-left). LVV = lateral ventricular volume.

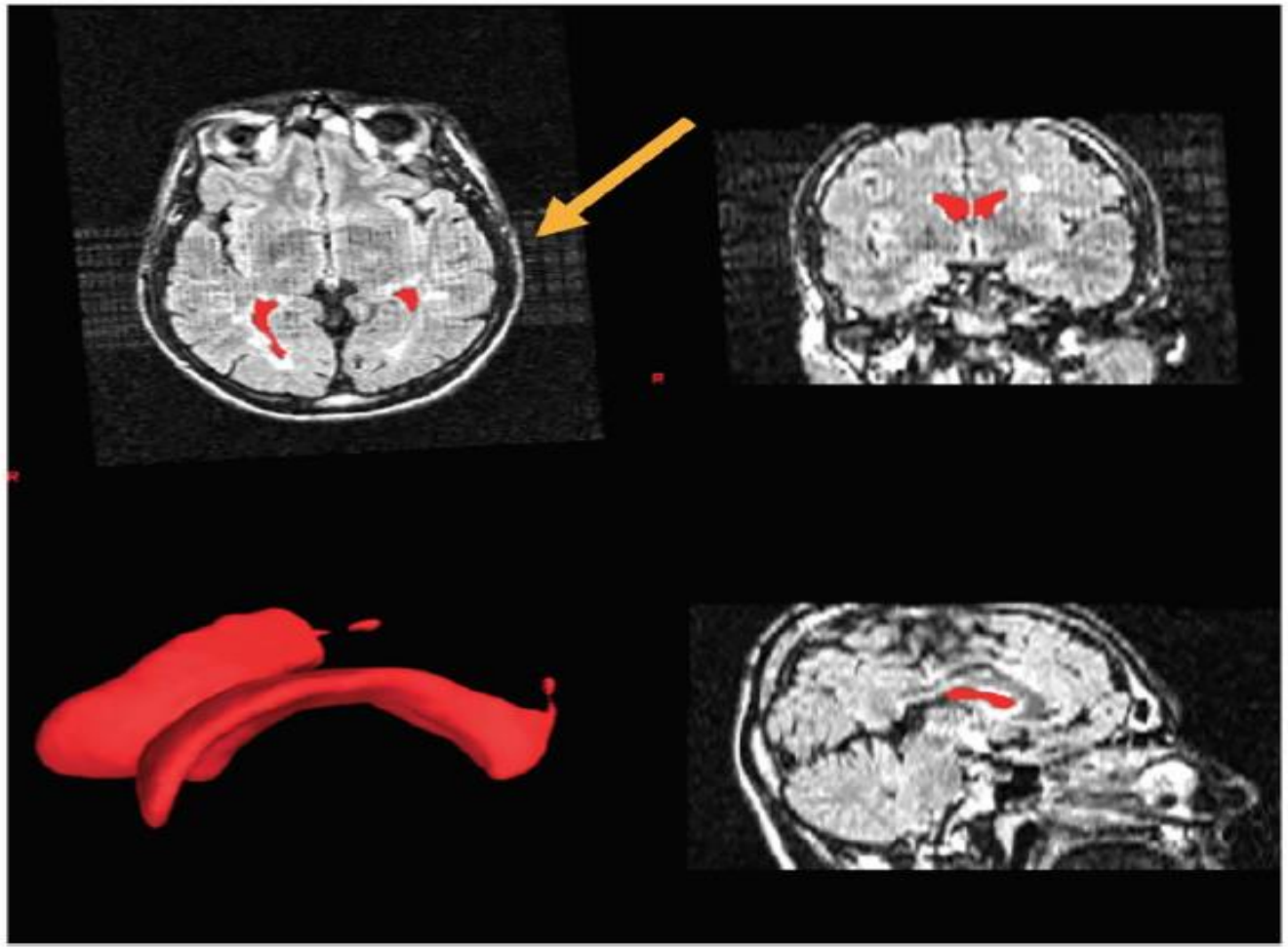


Fig. 6. Representative image of NeuroSTREAM algorithm performance on a scan with substantial RF artifact. The high-contrast of the ventricles, the multi-atlas approach, and the spatial regularization of the level-set refinement allow the algorithm to be very robust to artifacts like this that are common in clinical routine imaging.

code	METL68-1	METL68-2	BNML65-1	BNML65-2	SHZV67-1
Inc_Criteria	yes	yes	yes	yes	yes
Exc_Criteria	no	no	no	no	no
Age_MRI	45.46	46.99	50.38	51.59	47.38
date of MRI before treatment	11/04/2014	11/04/2014	16/01/2016	16/01/2016	09/04/2015
EDSS at first MRI	6.5	6.5	6	6	6
Steroids_30days before first MRI	no	no	no	no	no
date of MRI after treatment	24/10/2015	24/10/2015	27/03/2017	27/03/2017	02/09/2016
EDSS at second MRI	7	7	5.5	5.5	6
Steroids_30days at second MRI	no	no	no	no	no
Age_Onset	36.18	36.18	37.29	37.29	27.97
Ddy	9.273	10.809	13.098	14.292	19.398
Sex	female	female	male	male	female
Education	16	16	15	15	14
Race.1	white	white	white	white	white
Race.2					
Race.3					
Race.4					
Dx_Course	SPMS	SPMS	RRMS	RRMS	RRMS
EDSS_Type	estimate	estimate	estimate	estimate	estimate
RelapseDate_24mo.1	07/11/2012	07/11/2012	02/11/2015	02/11/2015	12/01/2014
RelapseDate_24mo.2	18/06/2013	18/06/2013			28/10/2014
RelapseDate_24mo.3					23/11/2014
RelapseDate_24mo.4					
RelapseDate_24mo.5					
DMT	Lemtrada	Lemtrada	Lemtrada	Lemtrada	Lemtrada
Pyramidal_Score	4	5	4	4	3
Cerebellar_Score	2	2	2	2	2
Brainstem_Score	1	1	1	1	1
BowBlad_Score	2	3	3	2	0
Visual_Score	0	0	0	0	0
Cerebral_Mental_Score	0	0	0	0	0
Ambulation_Score	6.5	7	6	5	6

Efficacy of Alemtuzumab treatment in active RRMS – A real-life study

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Background

- Alemtuzumad (Alem) is a monoclonal anti-CD52 antibody which depletes circulating lymphocytes followed by their reconstitution in a distinctive pattern which includes changes in the number, proportions and properties of lymphocytes subsets, hence changing the balance of the immune system.
- Alem was proved as effective treatment for active relapsing remitting multiple sclerosis (RRMS), reducing the number annualized relapse rate and retention of sustained disability.

Objective

To evaluate the efficacy of Alem treatment in active RRMS in real-life settings assessing treatment effects on relapse rate and disability progression.

Materials & Methods

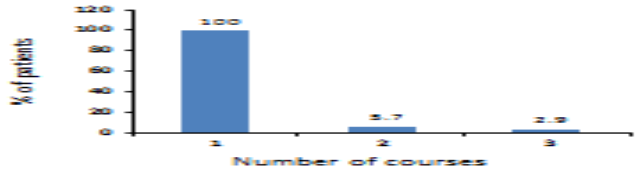
- Study design: Retrospective analysis of RRMS patients treated with Alem and followed at Sheba MS Center for at least 2 years.
- All patients were treated previously with various immunomodulatry drug treatments (IMDs) and were switched to ALEM treatment due to (1) increased relapse rate or (2) increased disability by the EDSS score and (3) MRI Gd activity.
- Relapse rate, EDSS change and adverse events were analysed.

Results

- 35 active RRMS patients, 19:16 F:M, figure 1A, mean age 38 years, mean disease duration 14.2 years, median EDSS score 4.5, Std 1.7.

Figure 1A. Gender proportion

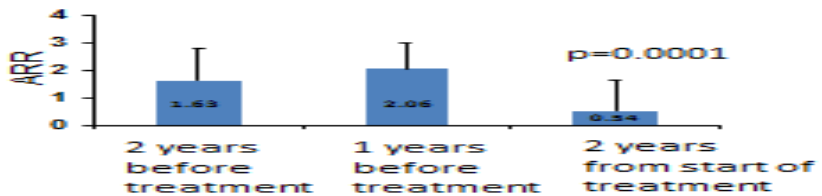
Figure 1B. Number of Alem courses



A. Demographic Analysis. 35 RRMS patients (19:16 F:M).
B. Number of Alem treatment Courses. 1 treatment course - 100% of patients, 2 treatment courses - 5.7 % of patients, 3 treatment courses - 2.9% of patients.

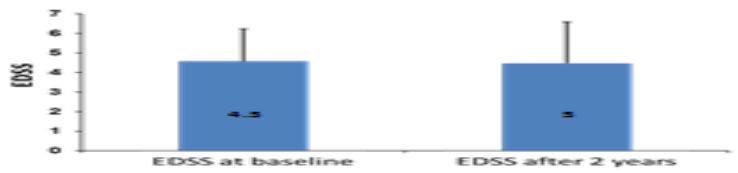
- Number of Alem courses- most of the patients in the study received the standard treatment of baseline Alem course and one-year course. The number of Alem additional treatments that the patients received after completing the standard treatment, shown in figure 1B. The very active patients received additional 2 Alem treatments (2 patients) and 1 patient received 3 additional treatments.
- Treatment related adverse events: Immediate side effects, all patients developed urticaria between day 3 to 5 of treatment. Long term side effects, 13 patients (13/35) had adverse events as follows: during the first year- 7 patients had urinary tract infection, 4 patients had cutaneous Herpes-Zoster and 1 patient was diagnosed with gastric carcinoma. Two patients developed hypothyroidism after the second Alem treatment, figure 3.

Figure 2A. ARR under Alem treatment



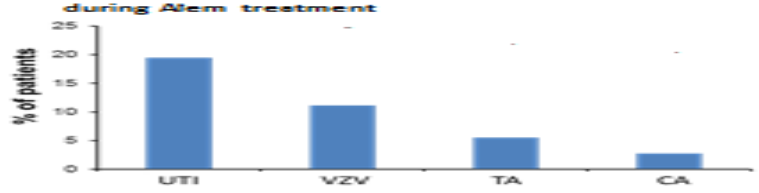
(A) ARR change during Alem treatment mean annualized relapse rate at 1 year prior Alem treatment was 2.06 and 1.63 at 2 years prior the treatment. At 2 years of post-infusion follow-up, the mean annualized relapse rate was 0.54. The mean change in number of relapses within 2 years from start treatment from 2 year prior treatment -1.09, (P value <.0001).

2B. Stable neurological disability by the EDSS score 2 years after initiation of Alem treatment



(B) EDSS change 2 years after initiation of Alem treatment
The median EDSS at the baseline was 4.5, EDSS after 2 years 5.0.
There was no significant EDSS change from baseline (P value = 0.6177).

Figure 3. Proportion of long term side effect during Alem treatment



Treatment related adverse events. Urinary tract infection (UTI) 20% of patients. Cutaneous Herpes-Zoster (VZV) 11% of patients. Thyroid abnormality hypothyroidism (TA) 5% of patients. Gastric Carcinoma (CA) 2% of patients.

Conclusions

Alem treatment reduced significantly the annualized relapse rate and prevented disability progression during two years of follow-up. Treatment-related adverse events were minor and tolerability of treatment was high.


Thank
you!!