Magnims

Magnetic Resonance Imaging in Multiple Sclerosis

VUmc

VU University
MS Center
Amsterdam

Focal lesion load quantitative MR measures

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ECTRIMS-MAGNIMS Teaching Course 11
"Quantitative MR imaging in the management of multiple sclerosis"
Barcelona, October 7th, 2015

Disclosures for Hugo Vrenken:
Research grants from Novartis, MerckSerono, Pfizer, Teva.
Speaker honoraria from Novartis.
All funds paid directly to his institution.

Outline

- Lesions in MS
- Current use of lesions in MS management
  - in diagnosis, prognosis, treatment response monitoring
- Quantitative lesion load measures in MS management
  - Will they be useful?
  - Can they be measured?
  - How will they be used?

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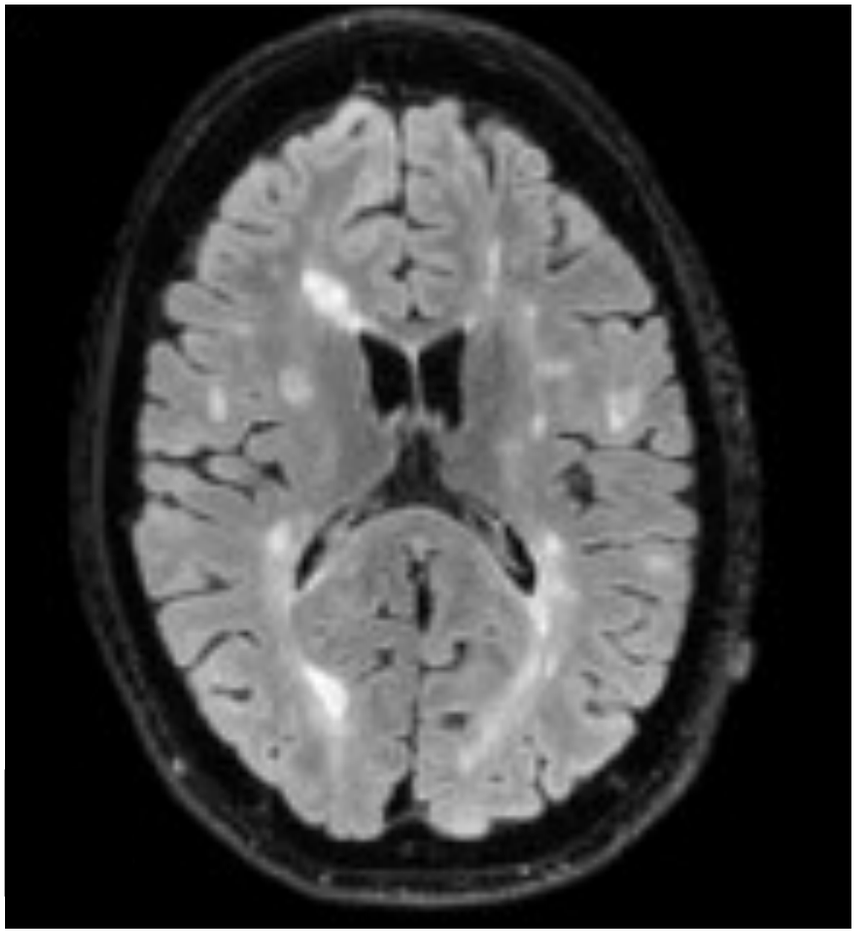
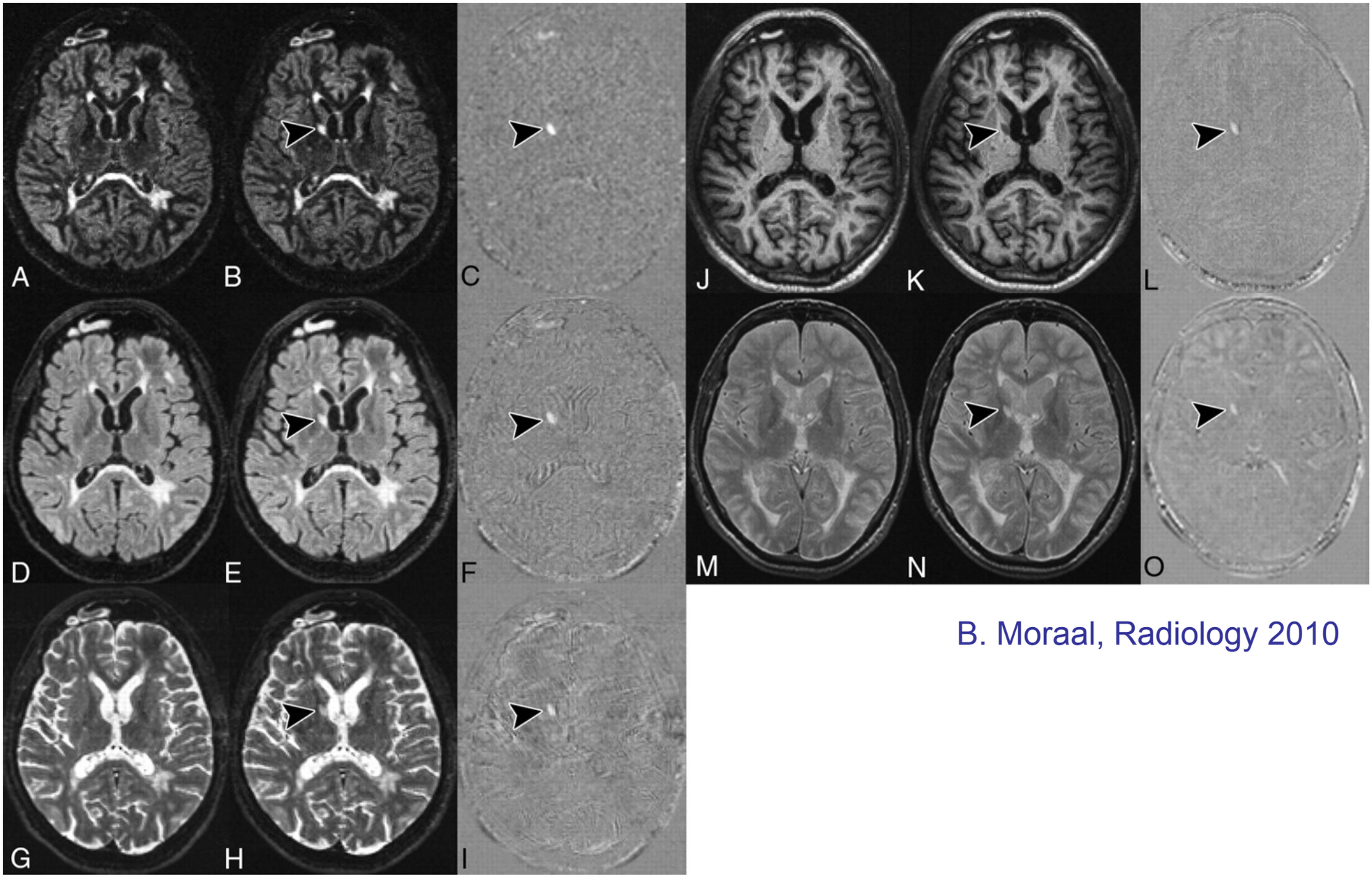
LESIONS IN MS

Lesions in brain WM and GM



MS lesions on various image types



B. Moraal, Radiology 2010

GM lesions

ARTICLES

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

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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

GM lesions scoring & diagnosis?

Intracortical lesions

Relevance for new MRI diagnostic criteria for multiple sclerosis

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ABSTRACT

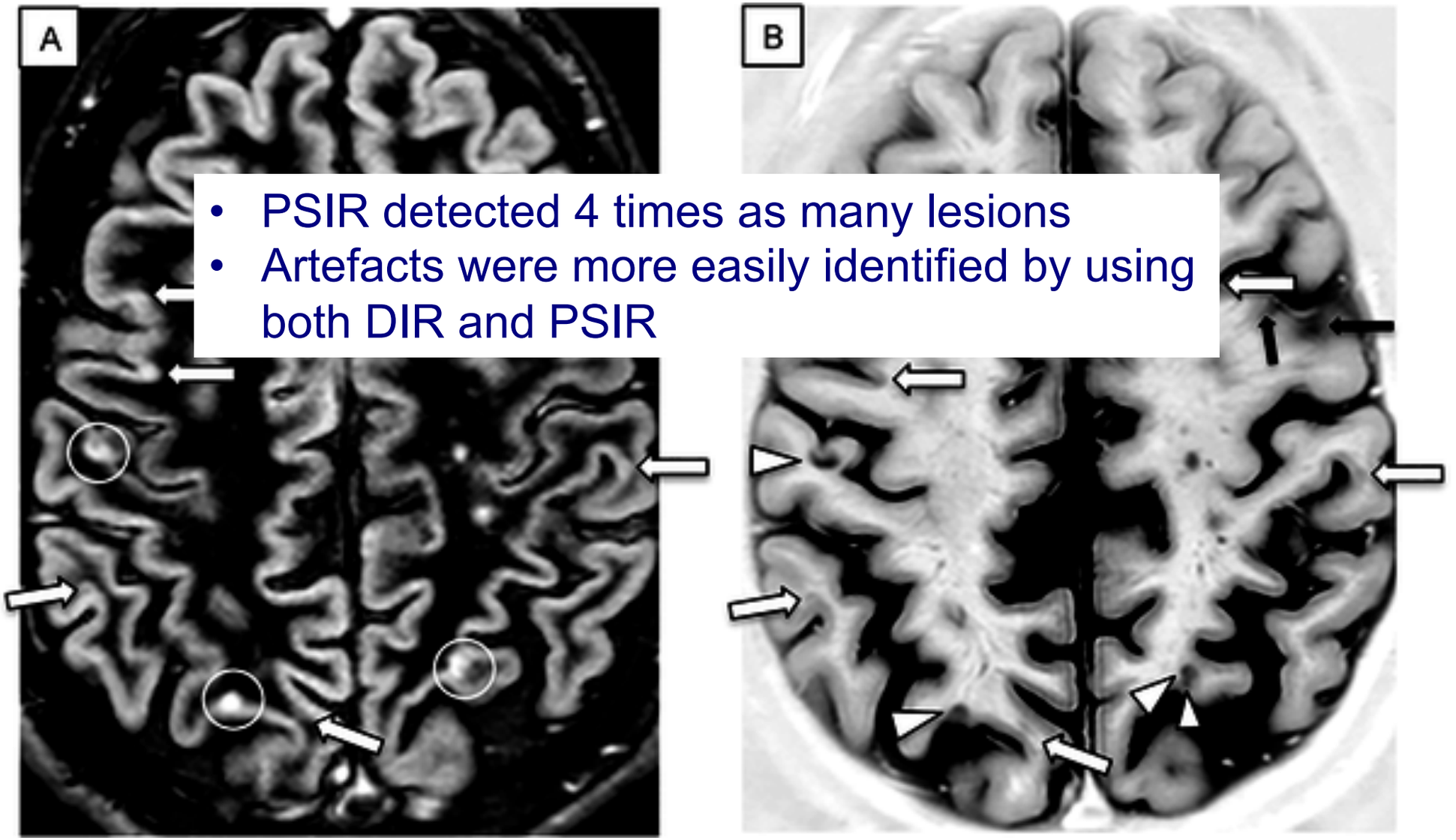
Objective: To generate and validate new MRI diagnostic criteria for multiple sclerosis (MS) taking into account not only white matter lesions but also intracortical lesions (ICLs).

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 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

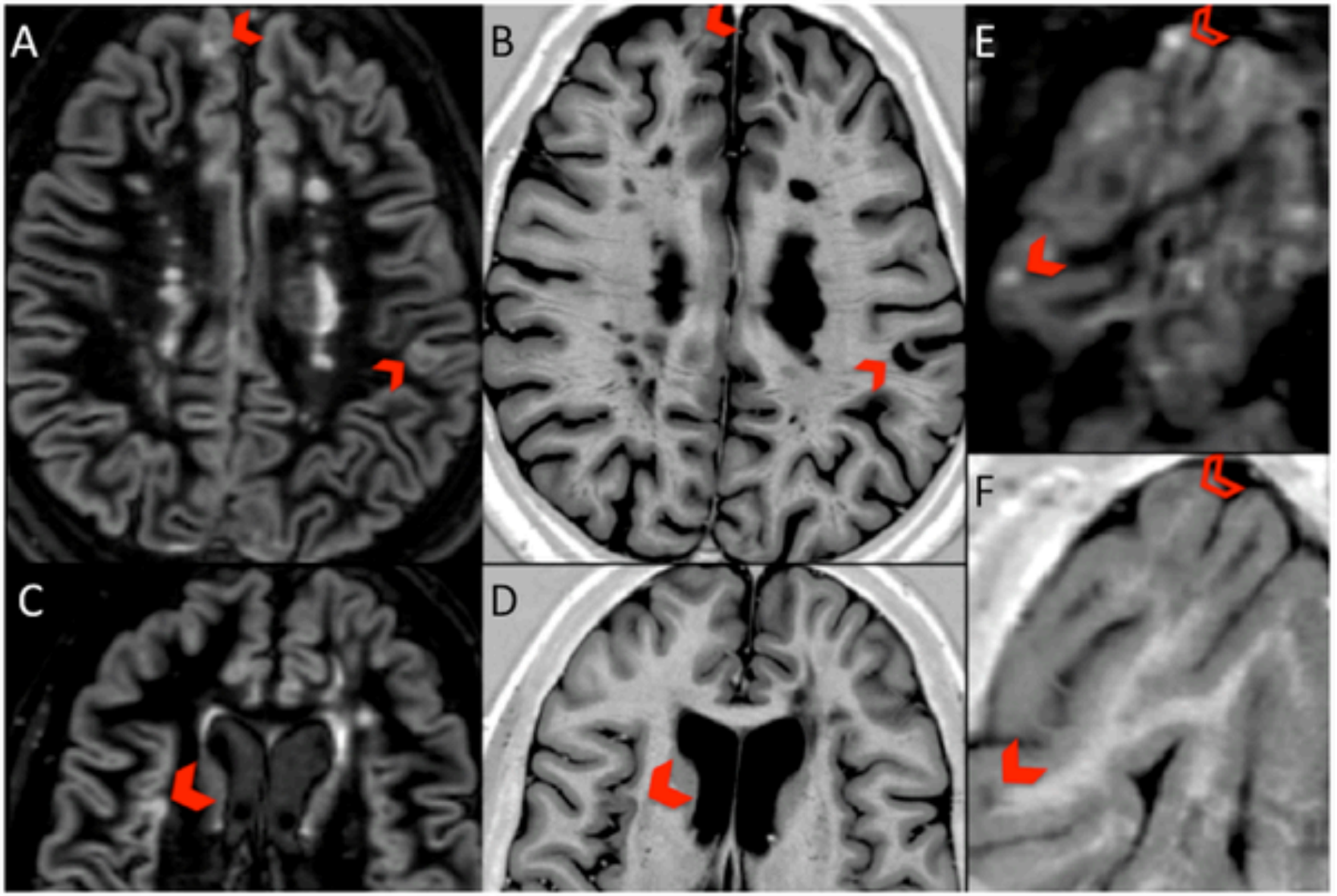
GM lesions: DIR and PSIR



- PSIR detected 4 times as many lesions
- Artefacts were more easily identified by using both DIR and PSIR

Favaretto et al. Plos One 2015

Is PSIR better than DIR for determining GM lesion locations?



Sethi et al. Plos One 2013

GM lesions: DIR and PSIR and MPRAGE

Multiple Sclerosis and Related Disorders (2014) 3, 253-257

Available online at www.sciencedirect.com

ScienceDirect

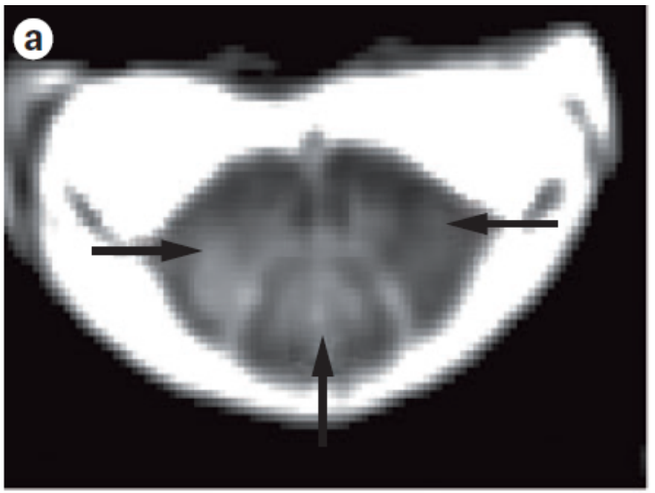
journal homepage: www.elsevier.com/locate/msard

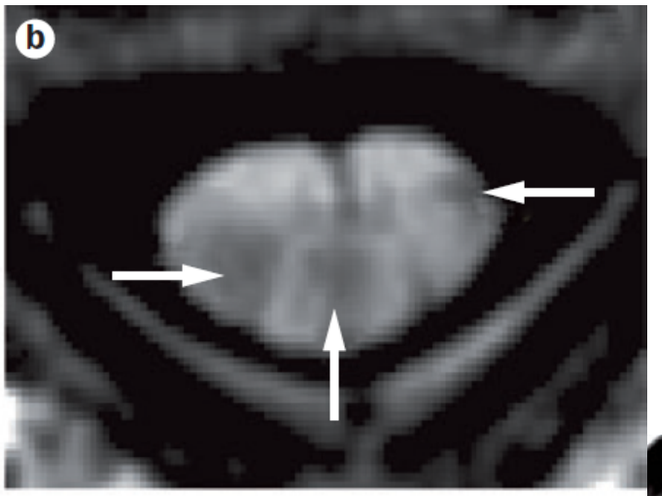
Is 3D MPRAGE better than the combination DIR/PSIR for cortical lesion detection at 3 T MRI?

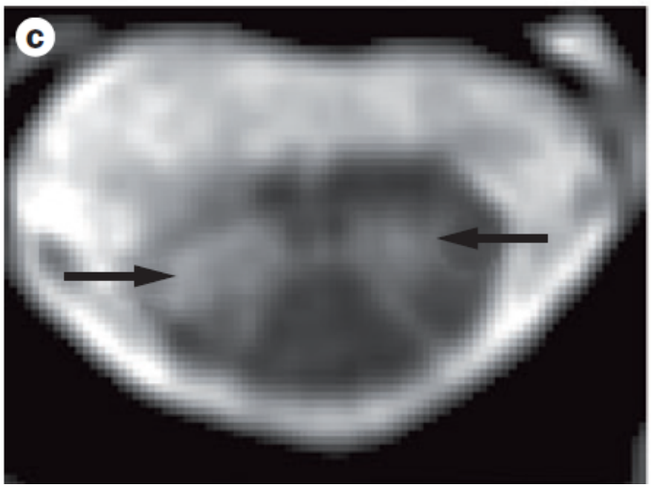
Flavia Nelson[a,*], Aziz Poonawalla[b], Sushmita Datta[b], Jerry Wolinsky[a], Ponnada Narayana[b]

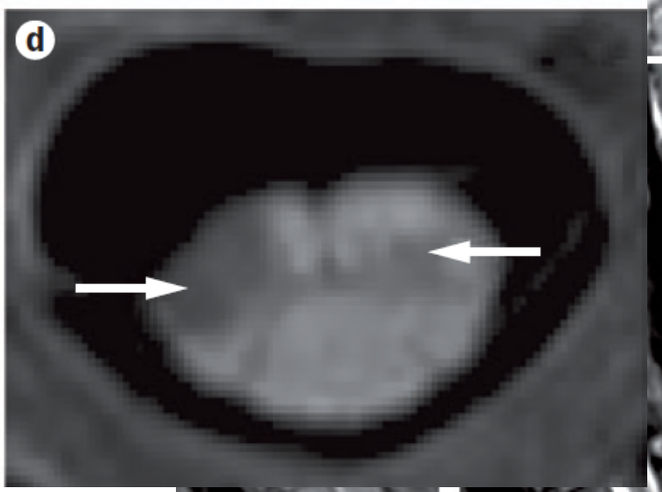
Conclusions: Combination DIR/PSIR at 3 T is superior to 3D MPRAGE for detection of cortical gray matter lesions in MS. The contrast-to-noise ratio of CL appears to be inferior on the MPRAGE images relative to DIR/PSIR

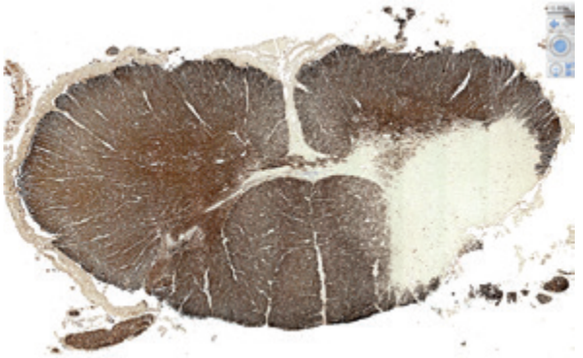
Lesions in the spinal cord



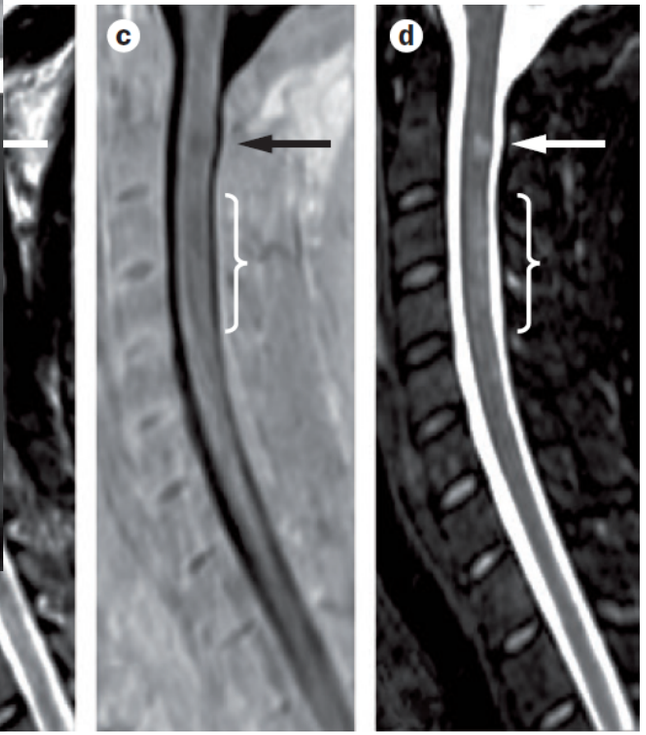








Kearney *et al.*,
Nat Rev Neurol 2015



Axial imaging is time-consuming!

Quantification of lesion loads: brain WM lesions

- Most work on segmentation → brain WM lesions on T2 & FLAIR
- Therefore focus here on T2/FLAIR brain WM lesions

J Neurol (2013) 260:2458–2471
DOI 10.1007/s00415-012-6762-5

REVIEW

Recommendations to improve imaging and analysis of brain lesion load and atrophy in longitudinal studies of multiple sclerosis

H. Vrenken · M. Jenkinson · M. A. Horsfield · M. Battaglini · R. A. van Schijndel · E. Rostrup · J. J. G. Geurts · E. Fisher · A. Zijdenbos · J. Ashburner · D. H. Miller · M. Filippi · F. Fazekas · M. Rovaris · A. Rovira · F. Barkhof · N. de Stefano · MAGNIMS Study Group

Vrenken *et al.*, J Neurol 2013

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- Lesions in MS
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CURRENT USE OF LESIONS IN MS MANAGEMENT

Handbook of Clinical Neurology, Vol. 122 (3rd series)
Multiple Sclerosis and Related Disorders
D.S. Goodin, Editor

Chapter 18

MRI outcomes in the diagnosis and disease course of multiple sclerosis

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- Clear overview
- Helpful background considerations

Lesions in diagnosis

VUmc VU University MS Center Amsterdam

Polman et al: 2010 Revisions to MS Diagnosis

TABLE 1: 2010 McDonald MRI Criteria for Demonstration of DIS

DIS Can Be Demonstrated by ≥1 T2 Lesion[a] in at Least 2 of 4 Areas of the CNS:
Periventricular
Juxtacortical
Infratentor[illegible]
Spinal cord

Based on Sw
[a]Gadolinium
DIS.
[b]If a subject
symptomatic
not contribu
MRI = magn
nation in spa

- Visual evaluation by neuroradiologist
- Lesion counts, not volumes

TABLE 2: 2010 McDonald MRI Criteria for Demonstration of DIT

DIT Can Be Demonstrated by:
1. A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI
2. Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time

Based on Montalban et al 2010.[24]
MRI = magnetic resonance imaging; DIT = lesion dissemination in time.

TABLE 4: The 2010 McDonald Criteria for Diagnosis of MS

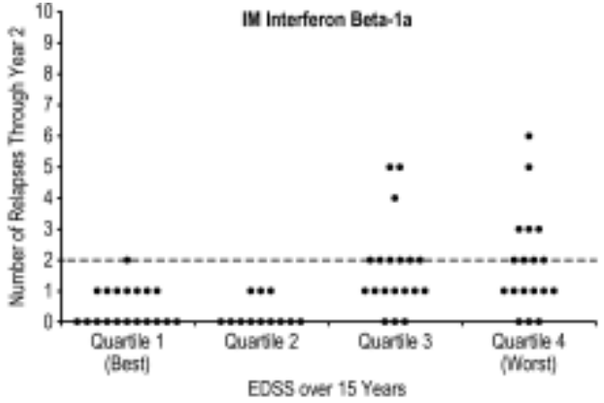
Clinical Presentation	Additional Data Needed for MS Diagnosis
≥2 attacks[a]; objective clinical evidence of ≥2 lesions or objective clinical evidence of 1 lesion with [illegible]	None[c]
	on in space, demonstrated by: n in at least 2 of 4 MS-typical regions of the CNS lar, juxtacortical, infratentorial, or spinal cord)[d]; or her clinical attack[a] implicating a different CNS site
	on in time, demonstrated by: s presence of asymptomatic gadolinium-enhancing ancing lesions at any time; or nd/or gadolinium-enhancing lesion(s) on follow-up ective of its timing with reference to a baseline scan; or nd clinical attack[a]
	on in space and time, demonstrated by:
evidence of 1 lesion (clinically isolated syndrome)	For DIS: ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)[d]; or Await a second clinical attack[a] implicating a different CNS site; and For DIT: Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or Await a second clinical attack[a]
Insidious neurological progression suggestive of MS (PPMS)	1 year of disease progression (retrospectively or prospectively determined) plus 2 of 3 of the following criteria[d]: 1. Evidence for DIS in the brain based on ≥1 T2 lesions in the MS-characteristic (periventricular, juxtacortical, or infratentorial) regions 2. Evidence for DIS in the spinal cord based on ≥2 T2 lesions in the cord 3. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

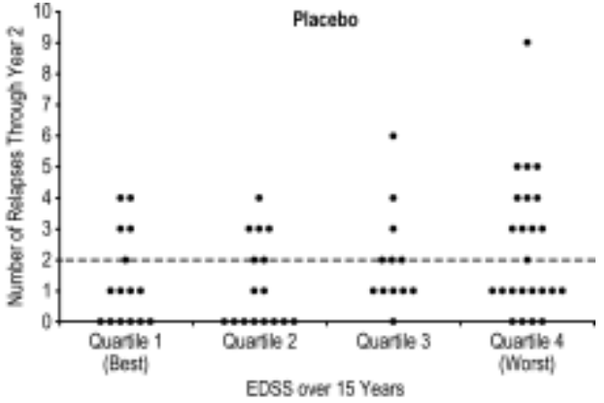
Lesions in prognosis

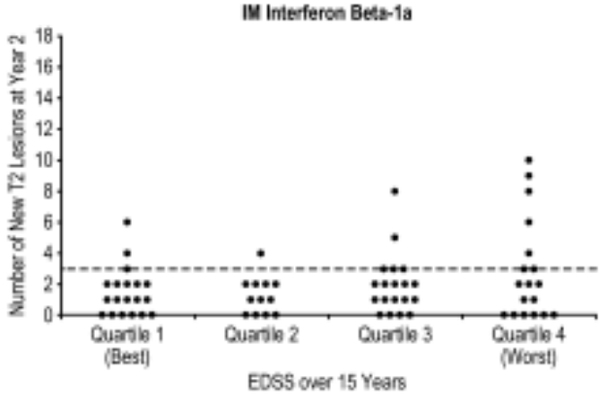
- Lesion counts

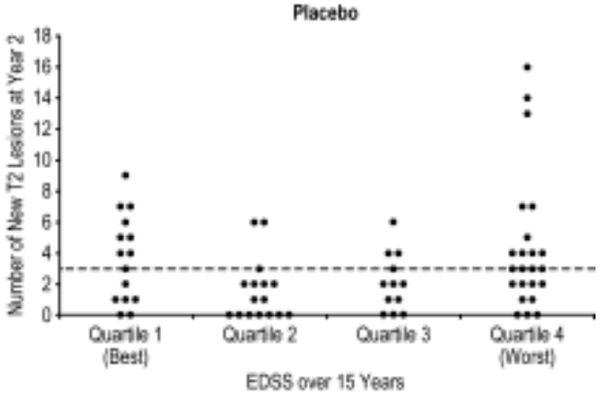
New lesions under IFNβ-1a treatment: poorer outcome?

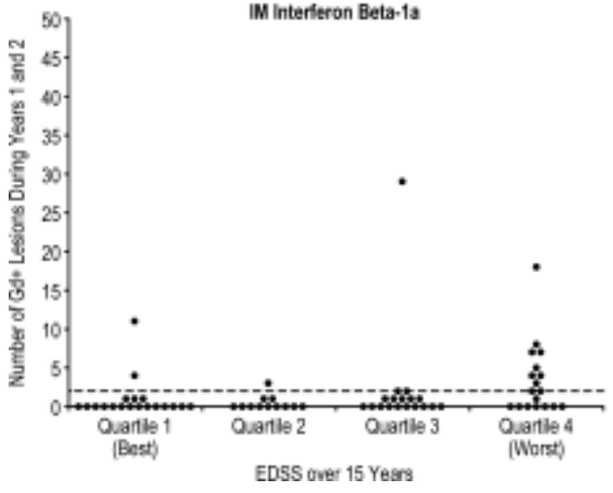
VU University MS Center Amsterdam

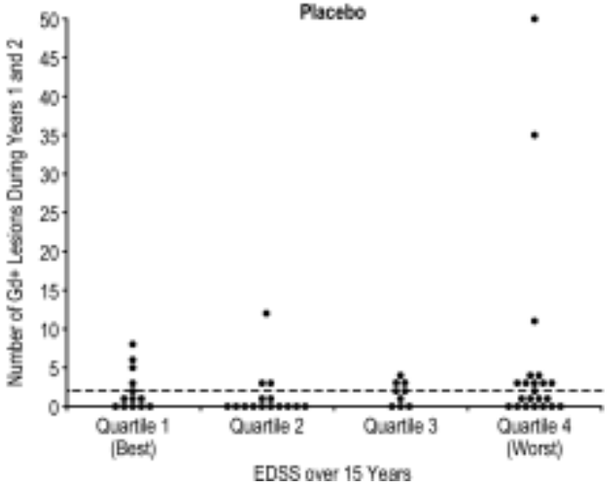


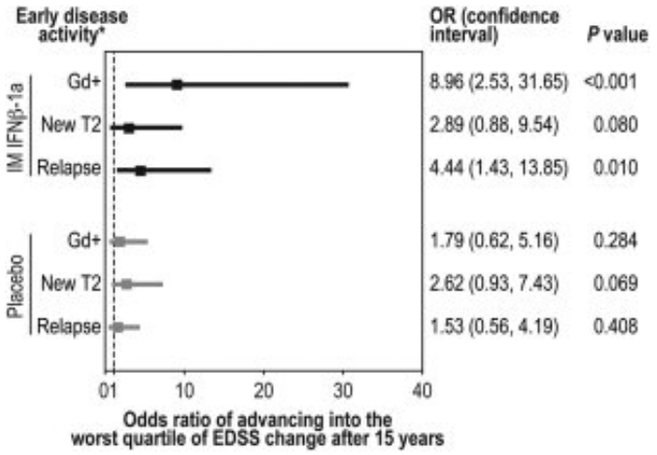












- 136 patients
- IFNβ-1a
- 2-year trial
- 15-year EDSS

Bermel *et al.*, Ann Neurol 2013

Lesions in prognosis: volumes

Multiple sclerosis

RESEARCH PAPER

Brain atrophy and lesion load predict long term disability in multiple sclerosis

Veronica Popescu,[1] Federica Agosta,[2] Hanneke E Hulst,[1,3] Ingrid C Sluimer,[1] Dirk L Knol,[4] Maria Pia Sormani,[5] Christian Enzinger,[6] Stefan Ropele,[6] Julio Alonso,[7] Jaume Sastre-Garriga,[8] Alex Rovira,[8] Xavier Montalban,[7] Benedetta Bodini,[9] Olga Ciccarelli,[9,10] Zhaleh Khaleeli,[9] Declan T Chard,[9,10] Lucy Matthews,[11] Jaqueline Palace,[12] Antonio Giorgio,[13] Nicola De Stefano,[13] Philipp Eisele,[14] Achim Gass,[14,15] Chris H Polman,[16] Bernard M J Uitdehaag,[4] Maria Jose Messina,[17] Giancarlo Comi,[17] Massimo Filippi,[2,17] Frederik Barkhof,[1] Hugo Vrenken,[1,18] on behalf of the MAGNIMS Study Group[19]

V. Popescu *et al.*, JNNP 2013

Lesions in prognosis: volumes

- 1-year T2 lesion volume change predicted 10-year EDSS score
  - in the whole group
  - in relapse-onset MS
  - …but explained only few % of variance

Table 2 MRI characteristics of the patients

	Whole group	Relapse onset MS	Minimally impaired relapse onset MS, EDSS baseline=0–3.5	Moderately impaired relapse onset MS, EDSS baseline=4–6	CIS	RRMS	SPMS	PPMS
No of patients	261	184	111	55	18	97	69	77
NBV baseline (l)*	1.37 (1.3–1.43)	1.37 (1.3–1.43)	1.38 (1.35–1.45)	1.31 (1.27–1.41)	1.43 (1.39–1.46)	1.38 (1.33–1.43)	1.33 (1.29–1.41)	1.36 (1.3–1.42)
WBA rate*	−0.69 (−1.17 to −0.19)	−0.69 (−1.17 to −0.19)	−0.61 (−1.15 to −0.11)	−0.74 (−1.22 to −0.25)	−0.31 (−0.49 to 0.15)	−0.69 (−1.2 to −0.19)	−0.81 (−1.2 to −0.23)	−0.64 (−1.2 to −0.19)
CBA rate*	2.58 (0.42–5.1)	2.59 (0.39–4.78)	2.6 (0.38–4.41)	2.05 (0.13–5.14)	0.76 (−0.84–3.02)	2.87 (0.81–5.24)	1.92 (0.12–4.86)	2.47 (0.58–5.69)
T2LV baseline (ml)*	5.91 (2.07–13.82)	5.89 (1.96–13.68)	3.56 (1.45–7.77)	10.44 (4.54–19.66)	2.28 (1.43–3.92)	3.75 (1.44–7.39)	12.55 (5.68–23.75)	6.25 (2.42–15.7)
1 year T2LV (ml)*	9.03 (4.29–19.59)	9.23 (4.36–19.71)	6.51 (3.9–13.12)	14.72 (7.72–26.28)	4.56 (3.92–8.36)	6.73 (3.63–13.6)	14.88 (9.3–27.11)	8.62 (3.83–18.78)
T2LV difference per year	1.94 (0.59–3.99)	1.92 (0.62–3.96)	1.76 (0.6–3.6)	2.51 (0.85–5.61)	2.36 (1.72–3.52)	1.88 (0.63–3.97)	1.91 (0.2–3.98)	1.98 (0.54–4.34)

The columns represent the results for the: whole group, relapse onset MS, minimally impaired group (relapse onset patients with baseline EDSS=0–3.5), moderately impaired group (relapse onset patients with baseline EDSS=4–6), CIS, RRMS, SPMS and PPMS patients at baseline. The CIS, RRMS, SPMS and PPMS groups include all patients regardless of their baseline EDSS value.
*Data reported as median (IQR).
CBA rate, central brain atrophy rate (percentage ventricular volume change/year); CIS, clinically isolated syndrome; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; NBV, normalised brain volume; PPMS, primary progressive MS; RRMS, relapsing–remitting MS; SPMS, secondary progressive MS; T2LV, T2 lesion volumes; WBA rate, whole brain atrophy rate (percentage brain volume change/year).

V. Popescu *et al.*, JNNP 2013

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V. Popescu *et al.*, JNNP 2013

Lesions in prognosis

- Still largely unused in clinical practice

Lesions in treatment response monitoring

- With more treatments available, response monitoring needed

Lesions in treatment response *prediction*

Table 1 | MRI criteria for predicting treatment response

Criteria	Outcome measure	Results
Three or more active lesions in 1 year[134]	Disability progression over 3 years	OR 8.3 71% sensitivity 71% specificity
Three or more active lesions plus one or more relapse or ≥1 point confirmed EDS in 1 year[67]	Relapse rates and/or disability progression over 3 years	OR 3.3–9.8 for relapses OR 6.5–7.1 for progression
Modified Rio S than five new relapse; or mo		24% sensitivity 97% specificity
One or more relapse and nine or more T2 lesions or a minimum of one CEL[80]	Relapse rates and/or disability progression over 4 years	34% sensitivity 90% specificity
One or more relapse, or at least one CEL[80]	Relapse rates and/or disability progression over 4 years	68% sensitivity 80% specificity
One or more CELs, or at least two new T2 lesions[80]	Relapse rates and/or disability progression over 4 years	61% sensitivity 83% specificity

All patients in these observational studies had relapsing–remitting multiple sclerosis treated with a formulation of IFN-β. Odds ratios refer to the probability that patients meeting the criteria will demonstrate the outcome measure, relative to patients who do not meet the criteria. Abbreviations: CEL, contrast-enhancing lesion; EDSS, Expanded Disability Status Scale.

Recommendations focus on visual assessment of new / enlarging lesions

Wattjes *et al.*, Nat Rev Neurol 2015

Lesions in treatment response monitoring

- With more treatments available, response monitoring needed
- Quantitative MRI outcomes may be useful
- What is needed to allow those to be used?

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QUANTITATIVE LESION LOAD MEASURES IN MS MANAGEMENT

Will quantitative lesion load be useful in the MS clinic?

- New / enlarged lesions indicate disease activity
- As more treatments become available, accurate lesion load change measurement can be one of a set of measures to assess efficacy of current treatment

Can quantitative lesion load be measured in the MS clinic?

- A large number of automated WM lesion segmentation methods exist
- Based on different approaches

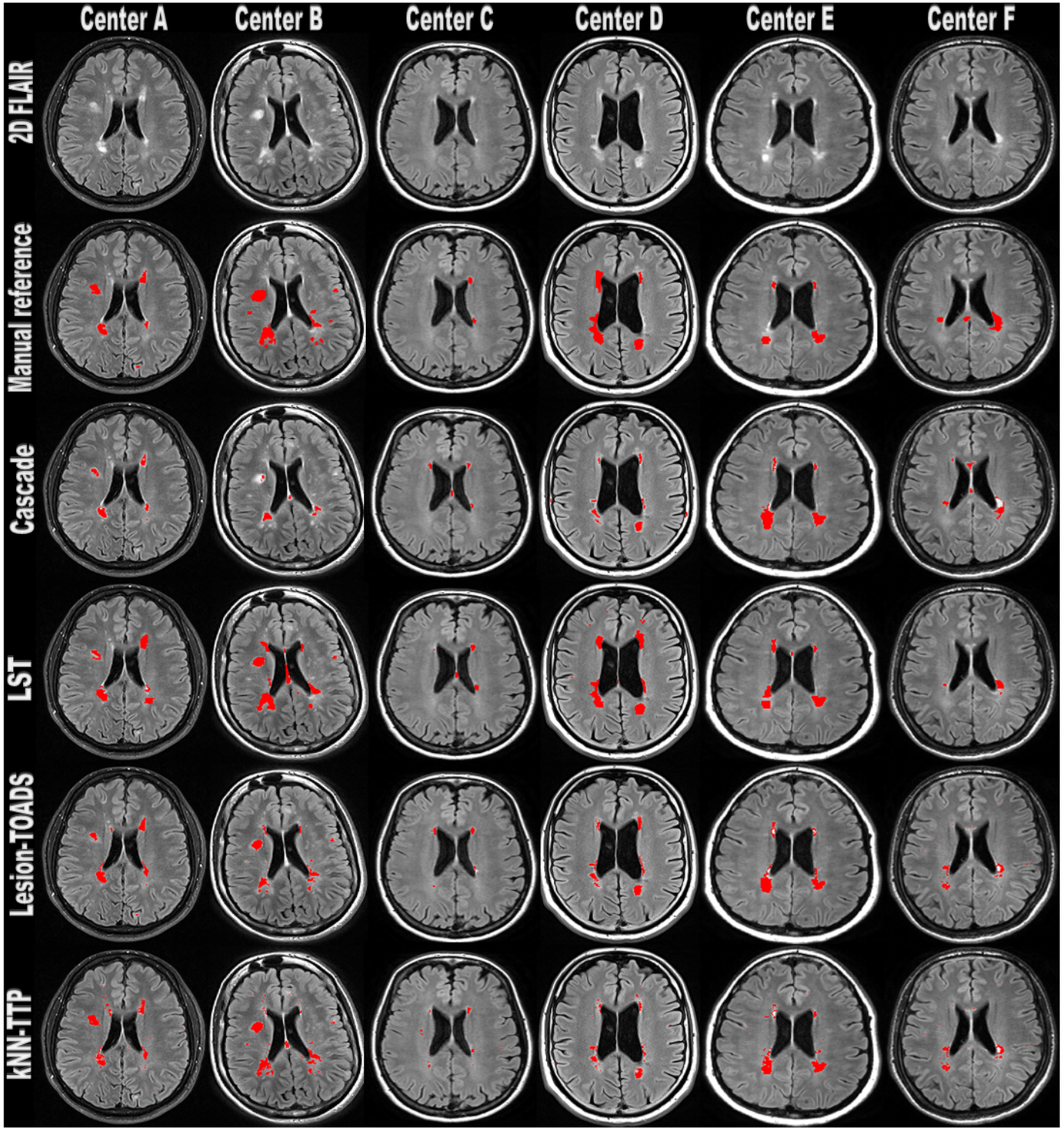
Table 4 Comparison of individual methods

Method	Accuracy	Calculation Time	Storage Memory	Complexity	Popularity (%)
Thresholding	Low	High	Low	Low	6
Region growing	Low	Low	Low	Low	2
Hierarchical	Medium	Medium	Medium	Medium	2
ICM	Medium	Medium	Low	Medium	2
kNN	Medium	High	High	Medium	18
EM	Medium	Medium	Low	Medium	20
kNN+EM+HMRF	High	High	High	High	4
AMM	Medium	Medium	Low	Medium	2
SVM	High	High	High	Medium	2
ANN	Medium	Very high	High	High	12
FCM	Medium	Medium	Low	Medium	18
Fuzzy connectedness	Medium	High	Low	Medium	6
FIS	High	Low	Low	Very high	2
Deformable contours	Medium	High	Low	Medium	4

Mortazavi *et al.*, Neuroradiology 2012

Example lesion segmentations for four methods

VUmc VU University MS Center Amsterdam



In preparation;
A. de Sitter,
A. Ruet, M.D.
Steenwijk *et al.*
MAGNIMS
Study Group

Can quantitative lesion load be measured in the MS clinic?

- Performance of all methods leaves something to be desired!
- Dice's Similarity Index typically 0.4-0.7, where 1 is perfect
- Volumes of misclassified voxels ~20-30% of lesion volume!!
- More work needed
- Challenge from 2008: http://www.ia.unc.edu/MSseg/

Can quantitative lesion load be measured in the MS clinic?

- Technical limitations

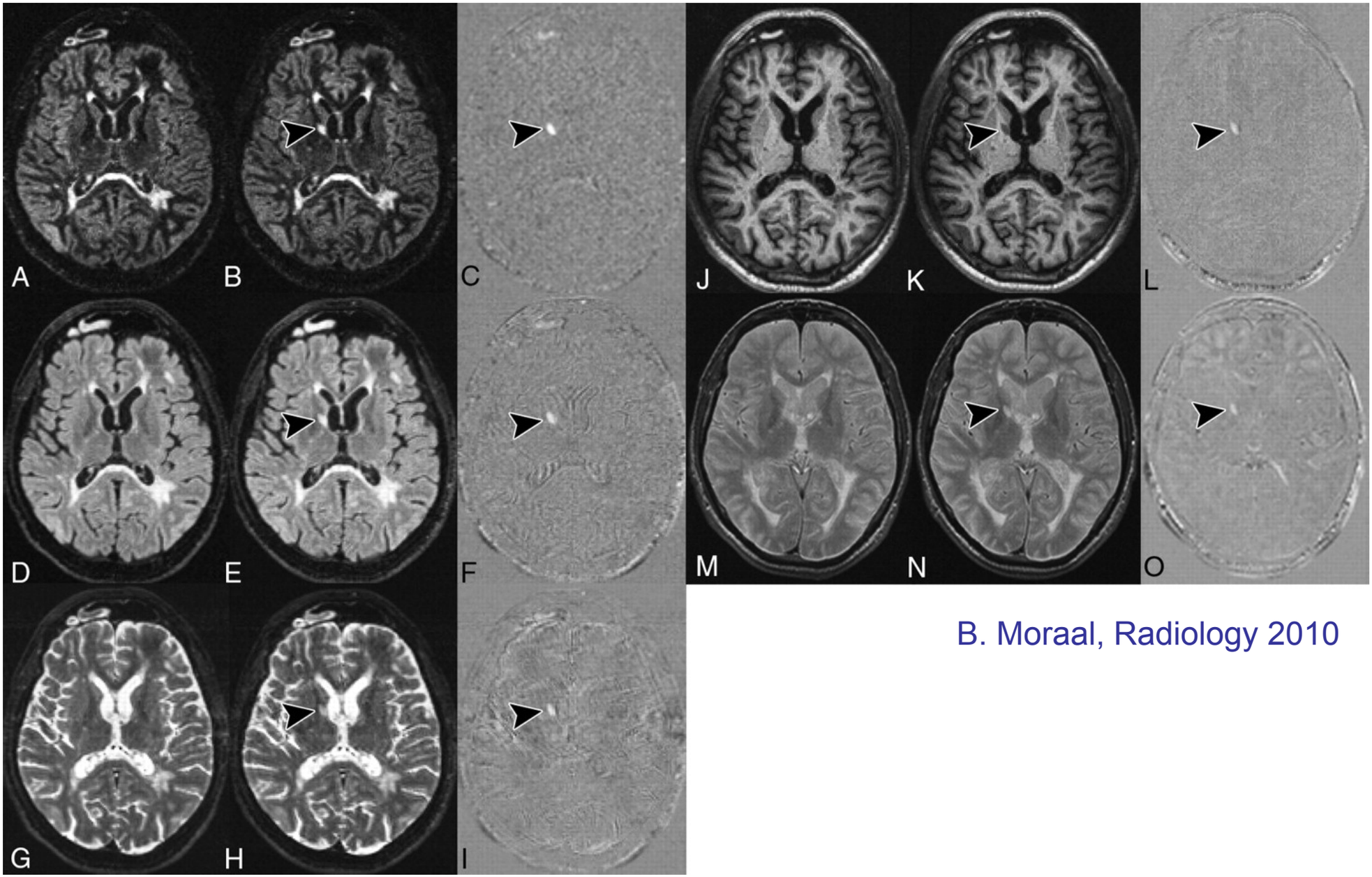
- Heterogeneity across MR protocols
  - Spatial resolution
  - 2D vs 3D acquisition
  - field strength
  - pulse sequence
  - acquisition parameters
  - geometrical distortion due to gradient non-uniformity

- Suggested standardized protocol: http://www.mscare.org/?page=MRI_protocol

Can quantitative lesion load **change** be measured in the MS clinic?

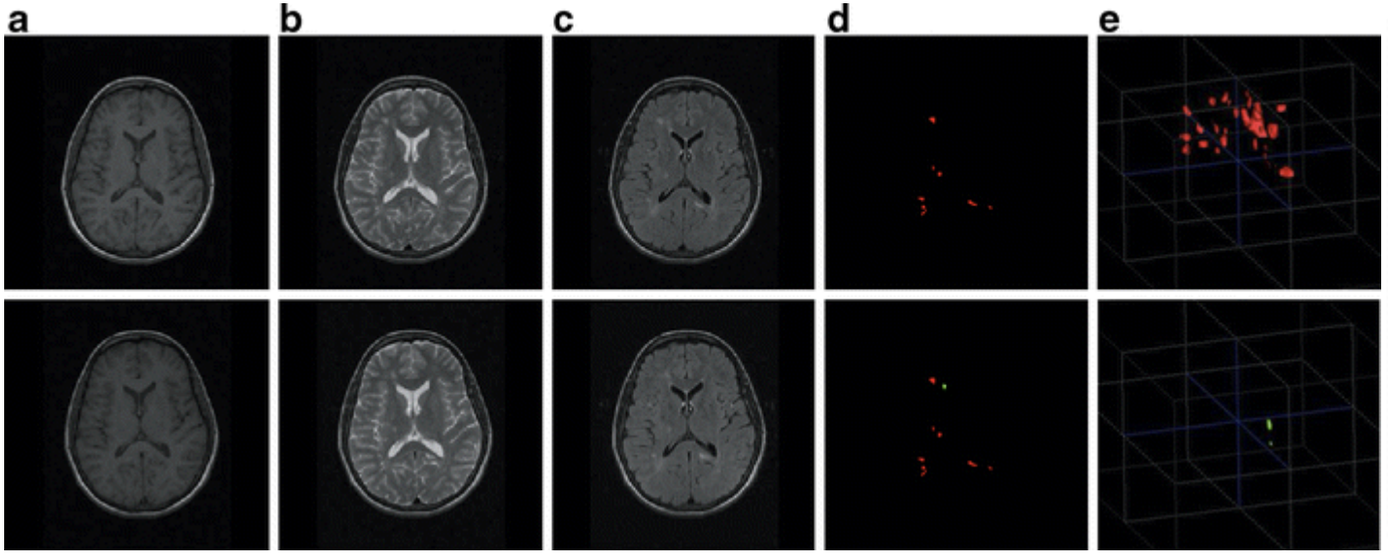
- Lesion segmentation from one scan is challenging
- …but what we're really interested in is **CHANGE OVER TIME**
- How reliably can **lesion change** be measured?

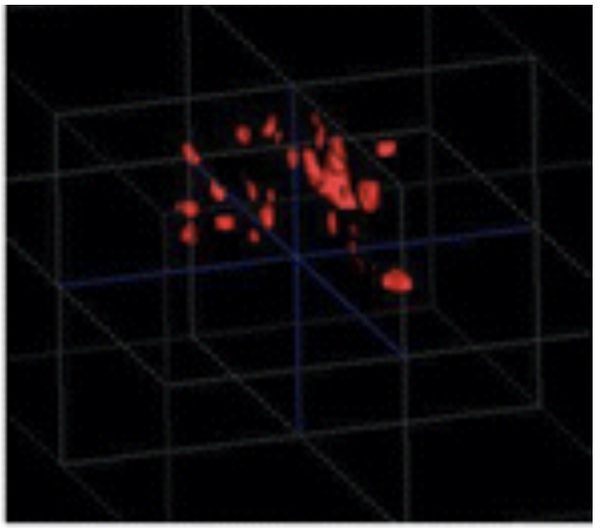
Lesion load change assessment

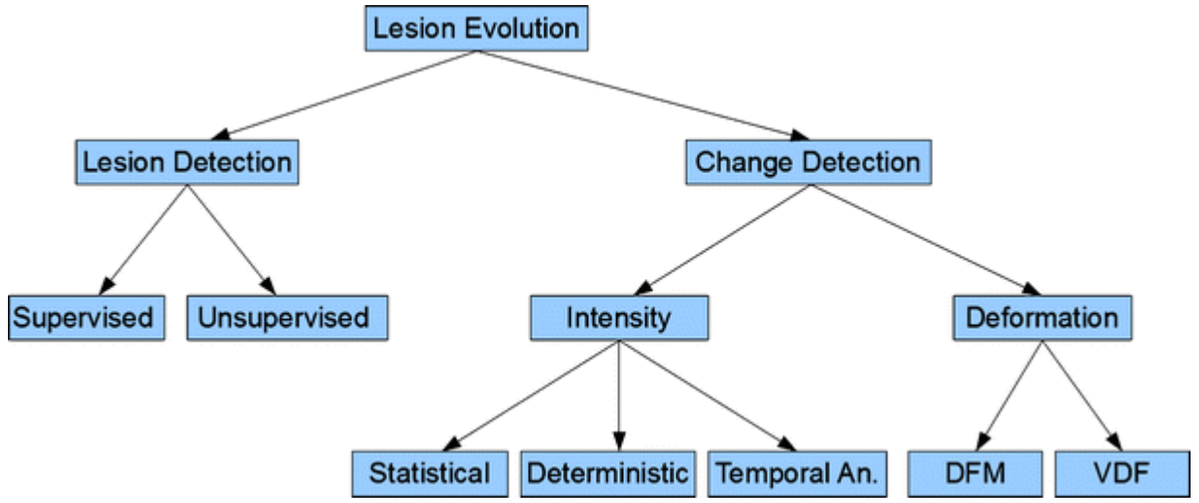


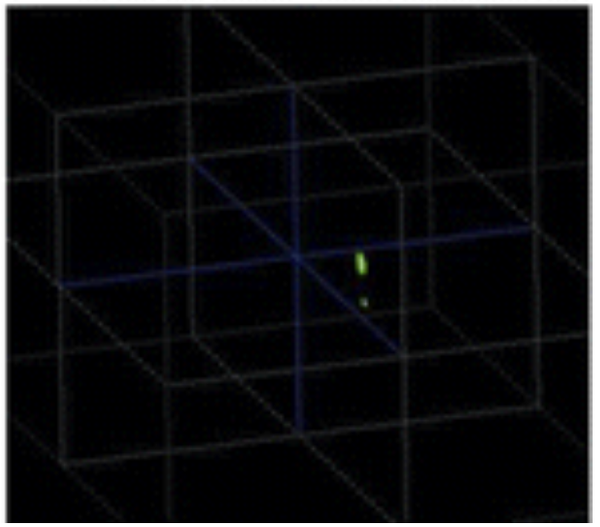
B. Moraal, Radiology 2010

Can quantitative lesion load **change** be measured in the MS clinic?



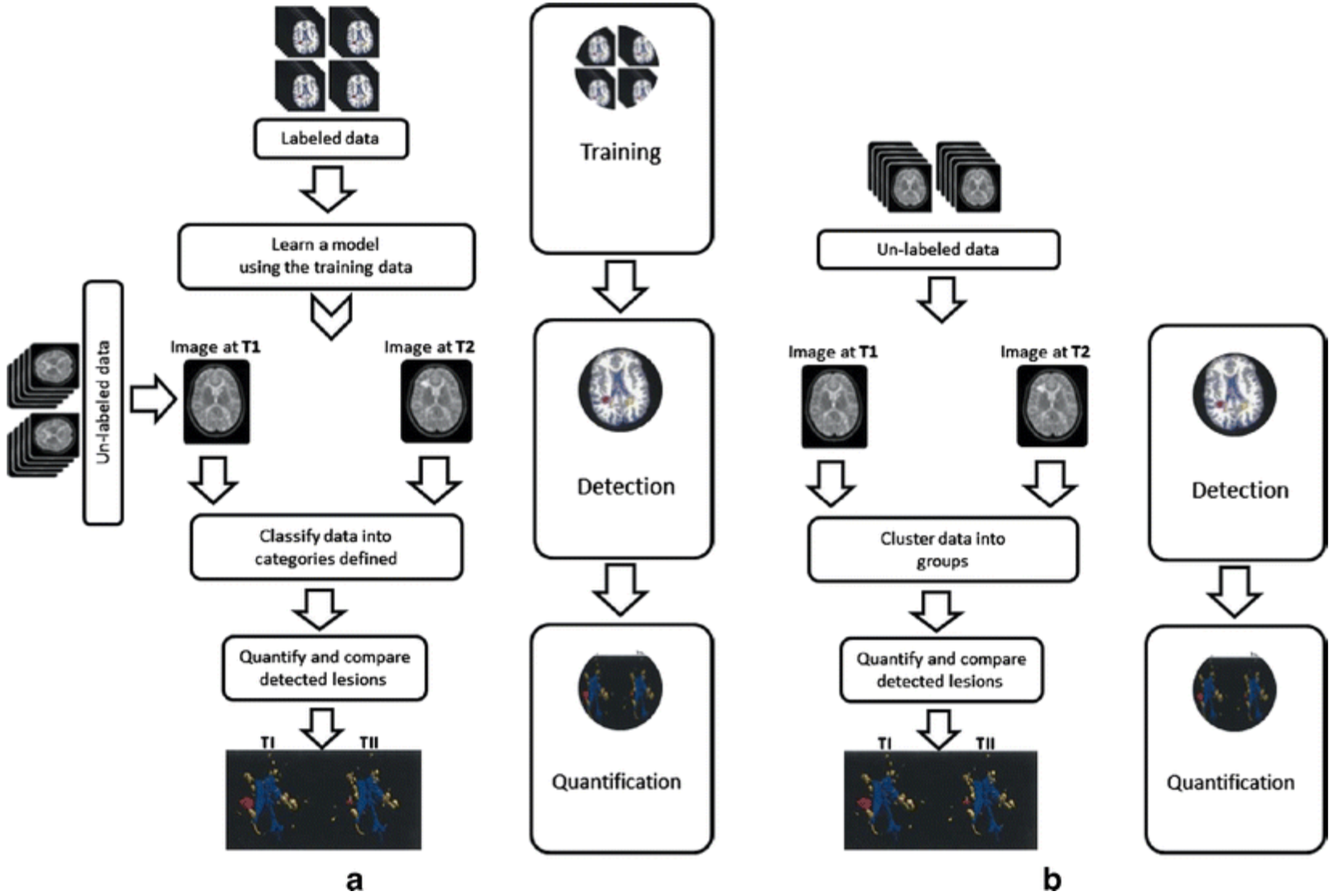






Lladó *et al.*, Neuroradiology 2012

Can quantitative lesion load **change** be measured in the MS clinic?



Lladó *et al.*, Neuroradiology 2012

Can quantitative lesion load **change** be measured in the MS clinic?

- The same technical limitations as for cross-sectional imaging
- + longitudinal stability issues
- + scanner changes etc.
- + atrophy and other disease-inflicted changes

- Measurement uncertainty has to be weighed in!

J Neurol (2013) 260:2458–2471
DOI 10.1007/s00415-012-6762-5

REVIEW

Recommendations to improve imaging and analysis of brain lesion load and atrophy in longitudinal studies of multiple sclerosis

H. Vrenken · M. Jenkinson · M. A. Horsfield · M. Battaglini · R. A. van Schijndel · E. Rostrup · J. J. G. Geurts · E. Fisher · A. Zijdenbos · J. Ashburner · D. H. Miller · M. Filippi · F. Fazekas · M. Rovaris · A. Rovira · F. Barkhof · N. de Stefano · MAGNIMS Study Group

Vrenken *et al.*, J Neurol 2013

Can quantitative lesion load **change** be measured in the MS clinic?

- Average lesion load changes in treatment trials:
  - Up to 2 mL (2-y, 1-34% of baseline volumes of 6-7 mL)[1]
  - But getting lower with more successful suppression of new lesion formation…

- Volumetric error of automated methods (cross-sectional):
  - E.g. False negatives ~ 20-30% typically[2]
    (mean lesion volume 16.3 mL → 3-5 mL false negatives!)

- More work needed to achieve reliable measurement of lesion volume change[3]
- Recent challenge: http://iacl.ece.jhu.edu/MSChallenge

[1]Kappos NEJM 2010; [2]Steenwijk Neuroimage: Clinical 2013 [3]Lladó Neuroradiology 2012

Outline

- Lesions in MS
- Current use of lesions in MS management
  - in diagnosis, prognosis, treatment response monitoring
- Quantitative lesion load measures in MS management
  - Will they be useful?
  - Can they be measured?
  - How will they be used?

How can clinicians use focal lesion load measures?

- Supposing that technical “error” is lowered to acceptable levels
- Guidelines will be needed
- Guidelines should incorporate
  - measurement uncertainty
    - due to imaging, image analysis
  - prognostic value
  - evolution under treatment
  - indications for treatment change

Conclusion

- Despite much work, automated quantification of WM MS lesion (change) remains far from perfect
- Application in individual patient care and treatment requires
  - overcoming remaining technical challenges
  - evidence-based guidelines on how to use these outcomes

Acknowledgements

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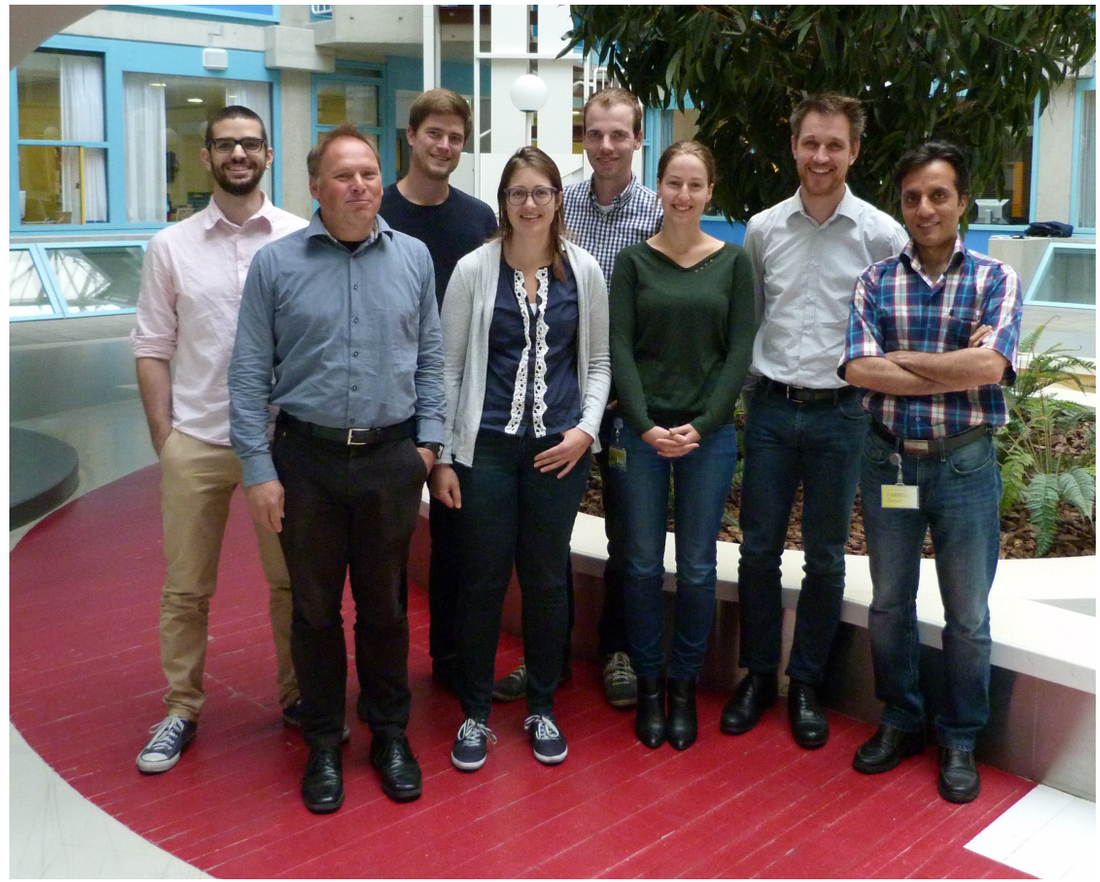

- Structural Brain Imaging Group
  - Houshang Amiri
  - Fabian Bartel
  - Mara ten Kate
  - *Yaou Liu*
  - *Christiane Möller*
  - *Veronica Popescu*
  - Carolina Rimkus
  - *Aurélie Ruet*
  - Ronald van Schijndel
  - Jorge Simoes
  - Alexandra de Sitter
  - Martijn Steenwijk
  - Adriaan Versteeg
  - *Hyon-Ah Yi*
- Collaborators VUMC
  - Frederik Barkhof
  - Wiesje van der Flier
  - Jeroen Geurts
  - Joep Killestein
  - Joost Kuijer
  - Jan de Munck
  - Petra Pouwels
  - Bernard Uitdehaag
- External collaborators
  - Carsten Lukas (Bochum)
  - Marco Battaglini, Nicola de Stefano (Siena)
  - Federica Agosta, Massimo Filippi, Mara Rocca (Milano)
  - Mark Jenkinson (Oxford)
  - Charles Guttmann (Boston)
  - MAGNIMS Study Group

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Magnetic Resonance Imaging in Multiple Sclerosis