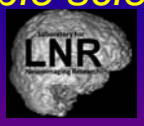
MRI in multiple sclerosis



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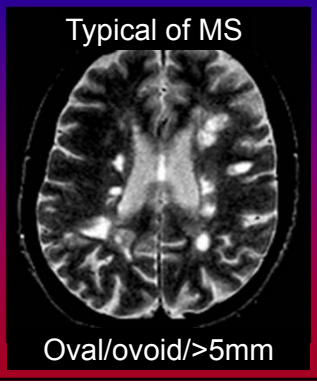
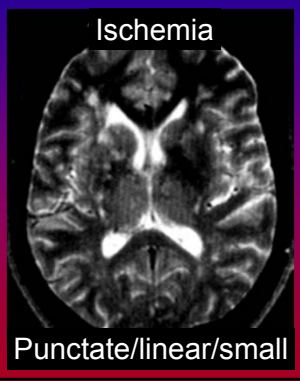
MRI in MS

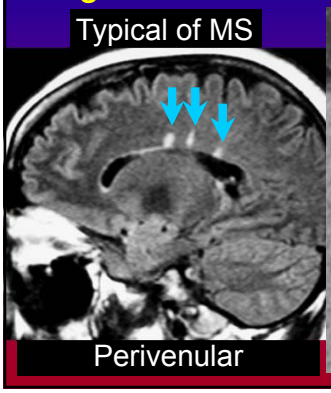
- Conventional MRI lesions
  - –T2, T1, gad
- Atrophy of the CNS in MS
  - –MRI assessment
- Recent MRI advances in MS

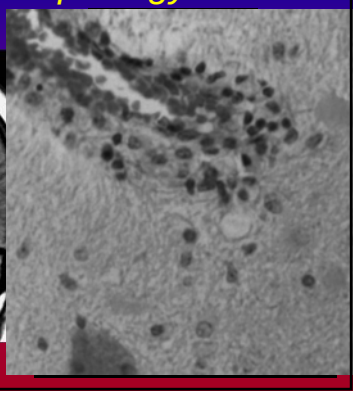
Brain lesions – *Morphology Matters*



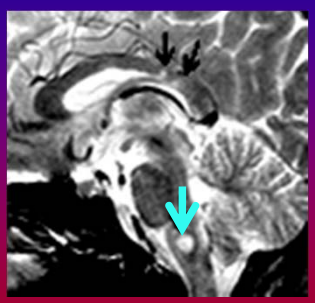


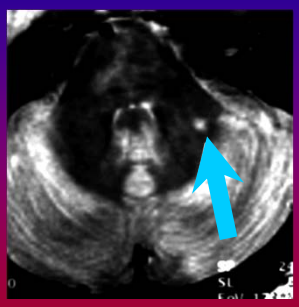
Sagittal FLAIR – *Morphology Matters*





Brain Lesions – *Location Matters*

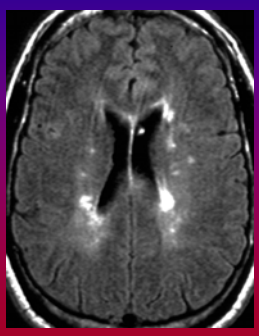




Typical of MS

MS T2 Lesions: Pathology

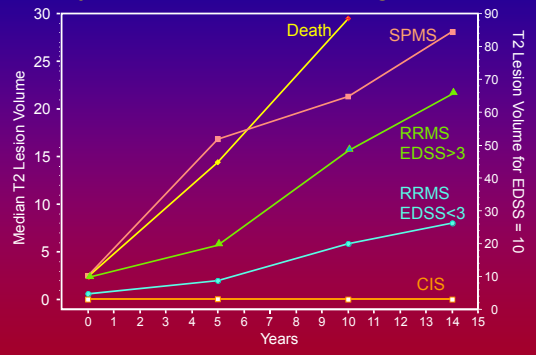
- Non-specific
  - –Demyelination
  - –Remyelination
  - –Inflammation
  - –Edema
  - –Axonal loss
  - –Tract degeneration
- Limited sensitivity



Clinical Correlations of T2 Lesions

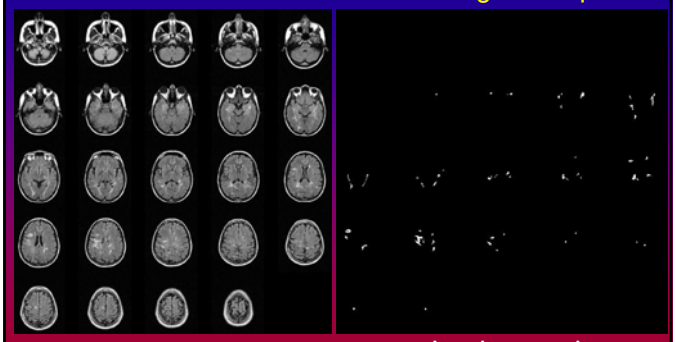
- In cross-sectional studies:
  - mild correlation with clinical status
- Better longitudinal predictive value for:
  - disease progression in established MS
  - development of brain atrophy
  - conversion from CIS to RRMS
- Probably a brain reserve/threshold effect

MRI may predict clinical progression in MS



Brex et al. N Engl J Med. 2002;346:158-164

T2 lesion volume: MRI thresholding technique

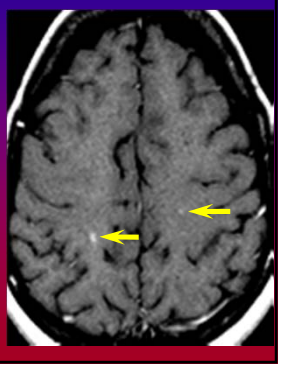


Raw FLAIR Lesions only

Bakshi et al., NeuroRx 2005;2:277-303

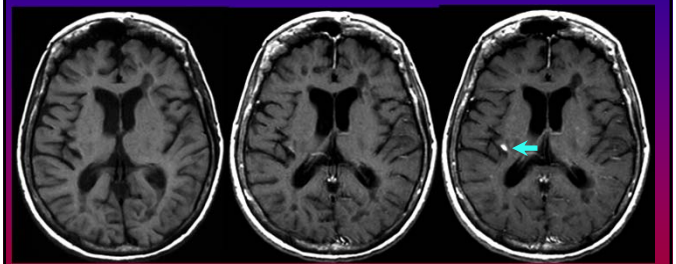
MRI gadolinium enhancement in MS

- Active BBB disruption
- Passage of T cells in to the CNS
- 5–10x more frequent than relapses
- Predictive of relapses, but lessens in SPMS
- Window 2-8 wk; mean 3 wk



Cotton et al., Neurology 2003;60:640-646

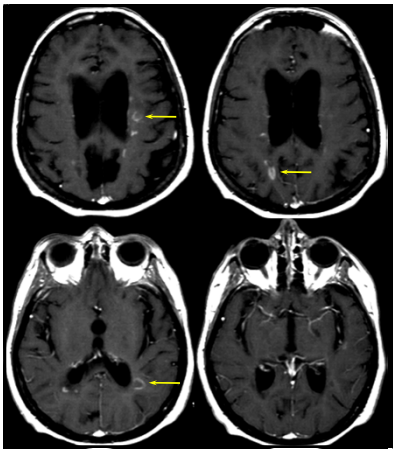
MS & Gadolinium: Optimization



T1-non T1-gad *immediate* T1-gad *5-min delay*

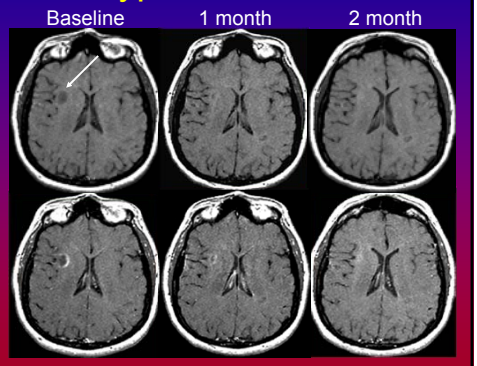
Gadolinium MRI in MS

The Open Ring Sign



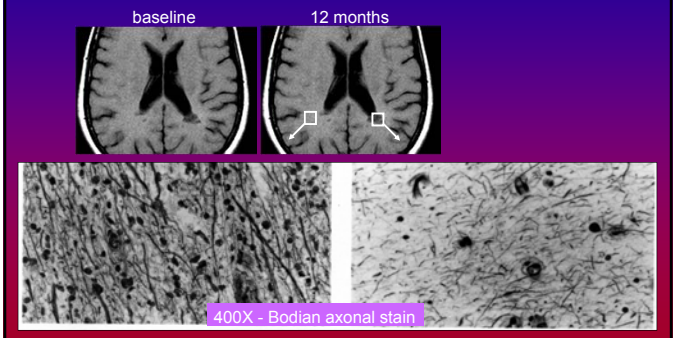
-52 y.o. MS patient in relapse

Evolution of T1-hypointense Lesions



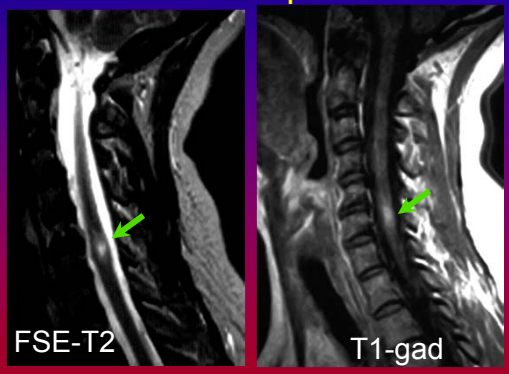
Bakshi et al., NeuroRx 2005;2:277-303

Persistent T1 black holes in MS



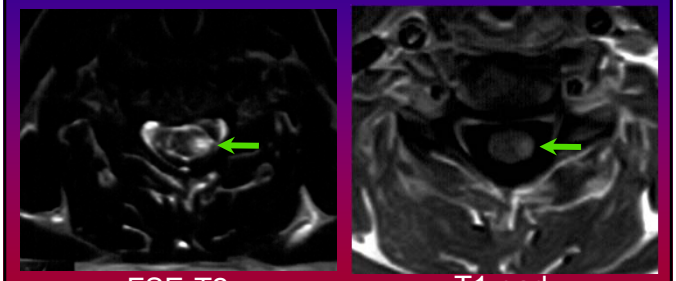
Van Walderveen et al. Neurology 1998;50:1282

MRI of acute spinal MS



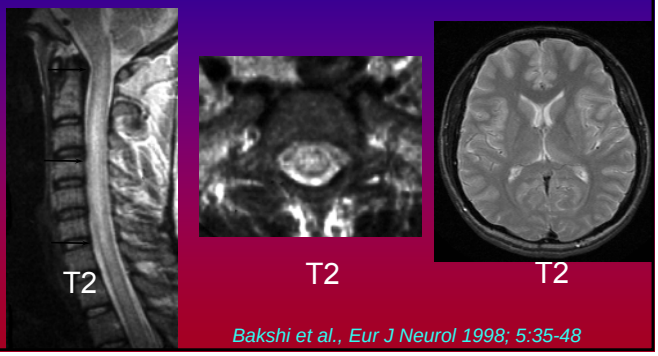
Bakshi et al., Neurology 2004;63(Suppl 5):S3-S11

MRI of acute spinal MS



Bakshi et al., Neurology 2004;63(Suppl 5):S3-S11

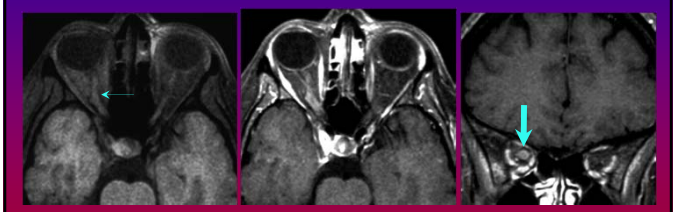
Non MS Acute Myelitis



Bakshi et al., Eur J Neurol 1998; 5:35-48

Acute Optic Neuritis

Enhanced fatsuppressed MRI

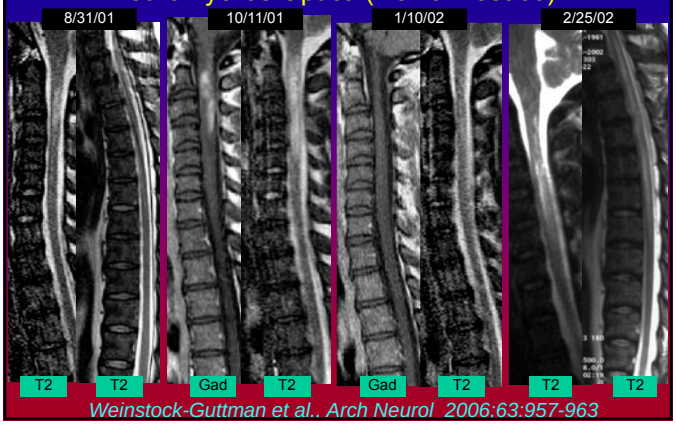


Bakshi & Ketonen, Baker/Joynt's Clinical Neurology, 2004

MRI findings in MS
Differential diagnosis

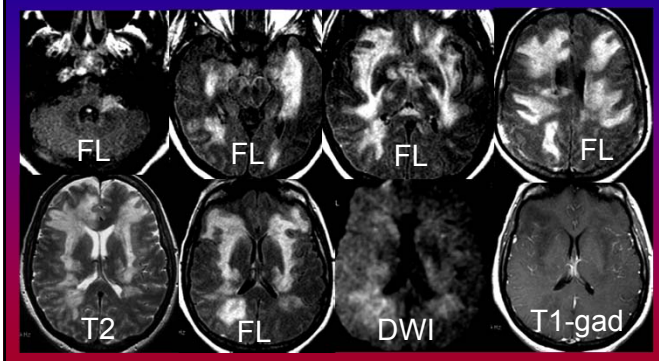
- Related inflammatory/demyelination
  - –Devic, Balo
  - –Acute disseminated encephalomyelitis
- Vascular ischemic disease, vasculitis
- Autoimmune/collagen vascular disease
- Aging, perivascular spaces
- Infection, sarcoid
- Trauma, toxin, metabolic

Neuromyelitis Optica (Devic Disease)



Weinstock-Guttman et al., Arch Neurol 2006;63:957-963

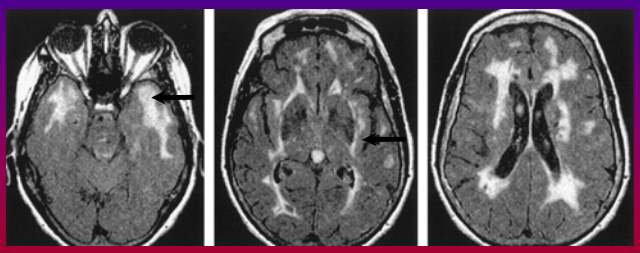
Fatal ADEM: 51 yo W post-URI



Bakshi & Ketonen, Baker/Joynt's Clinical Neurology, 2004

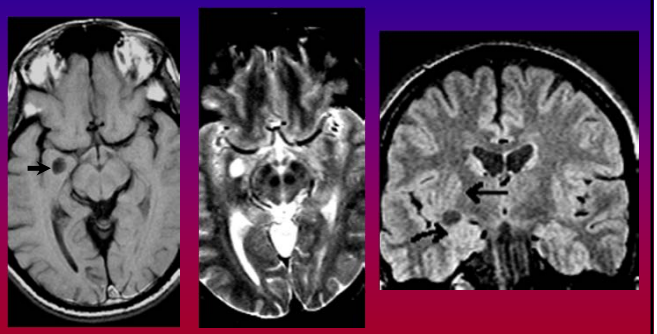
CADASIL

Cerebral autosomal dominant arteriopathy with subcortical infarcts & leukoencephalopathy



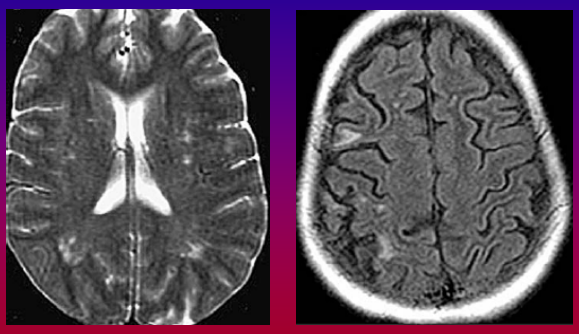
Markus HS et al., Neurology 2002;59:1134

Benign or MS?



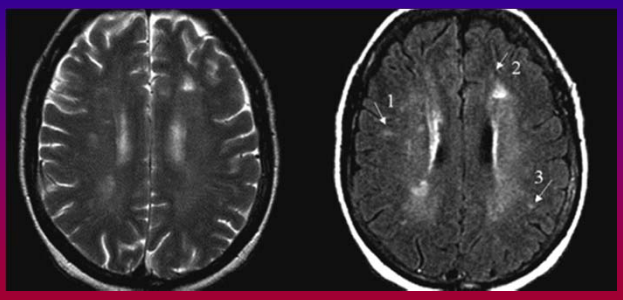
Bakshi & Ketonen, Baker/Joynt's Clinical Neurology, 2004

Lupus Cerebritis



Sundgren et al., Neuroradiology 2005;47:576–585

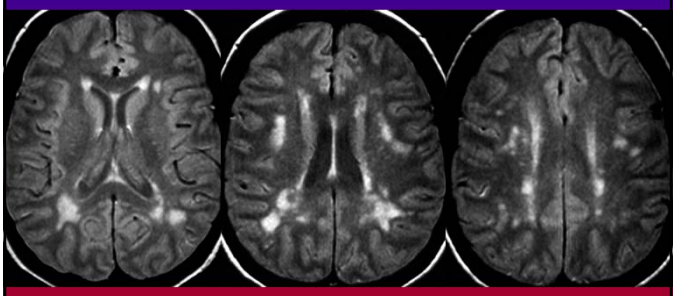
Sjögren's syndrome



Morgen et al., Semin Arthritis Rheum 2004;34:623-30

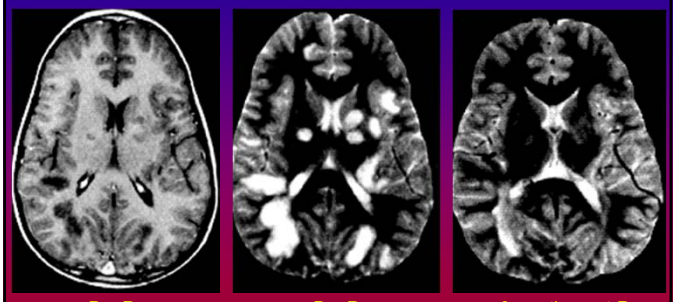
LYME OF THE BRAIN

- Lesions difficult to distinguish from MS



Bakshi & Ketonen, Baker/Joynt's Clinical Neurology, 2004

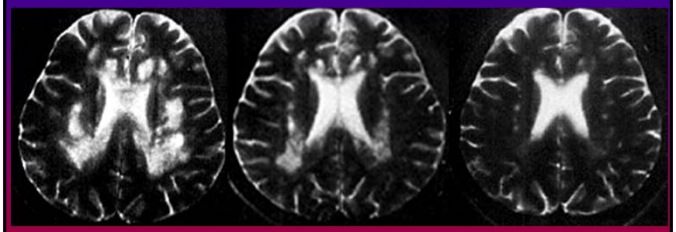
Whipple's Disease



Pre-Rx Pre-Rx 6 months post-Rx

Duprez et al., AJNR 17:1589, 1996

Vitamin B_{12} deficiency



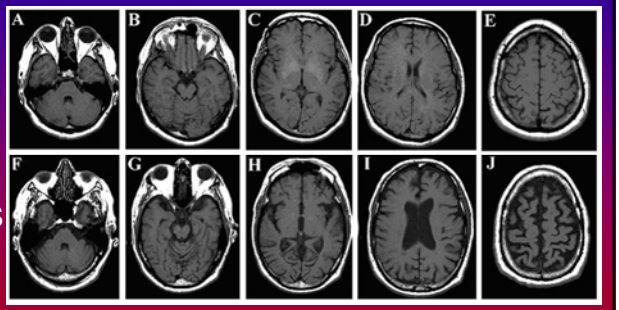
Pre-Rx 8 wk 4 yr

Stojsavljevic et al., Neurology 1997

Brain atrophy in MS

NL

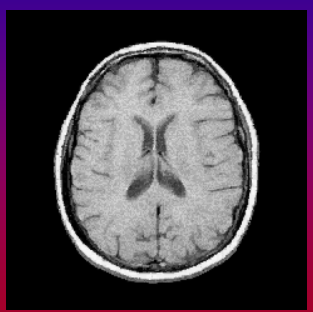
MS



Neema et al., Neurotherapeutics 2007;4:602-617

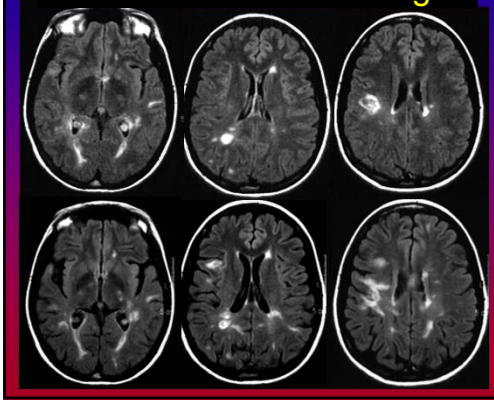
Brain Atrophy in MS

MRI over 7 years in an untreated patient



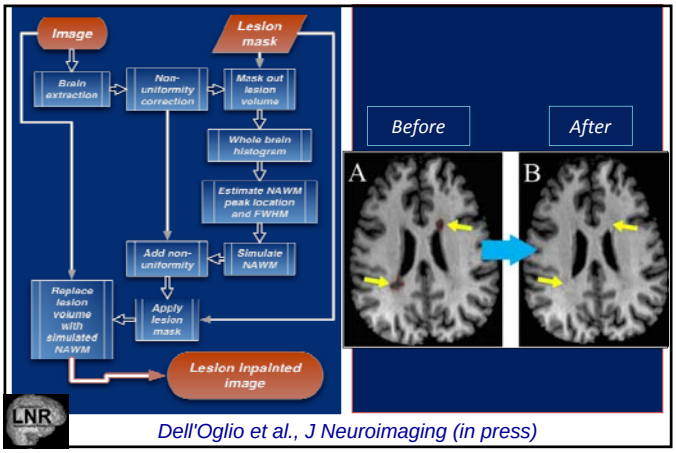
The MS Collaborative Research Group

Serial FLAIR-MRI: findings?



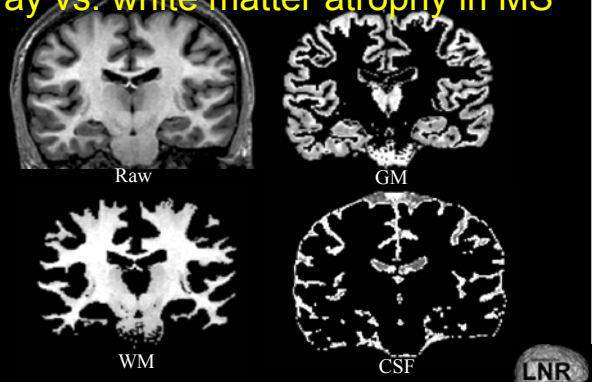
3/00
EDSS 1.0
BPF 0.88

9/01
EDSS 4.0
BPF 0.84



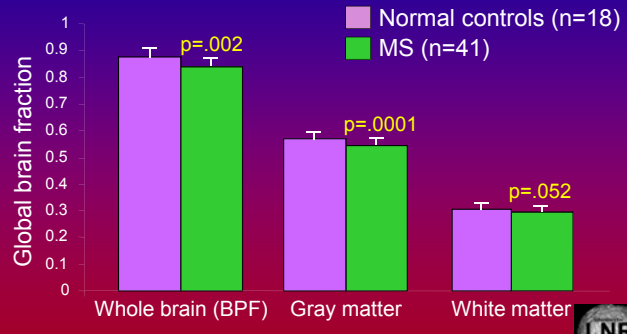
Dell'Oglio et al., J Neuroimaging (in press)

Gray vs. white matter atrophy in MS



Dell'Oglio et al., J Neuroimaging (in press)

GM vs. WM Brain Atrophy



Sanfilipo et al., Neuroimage 2005;26:1068–77

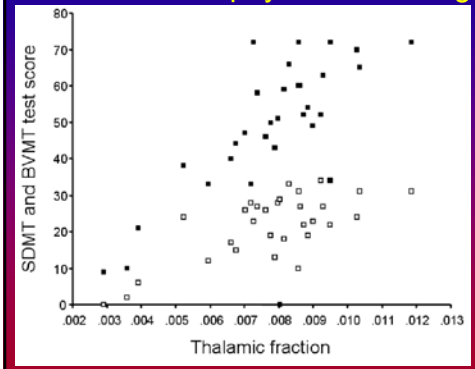
Regional brain atrophy in MS: 3T MRI

Early RRMS vs. normal controls

- Voxel-based morphometry study from 3T MRI scans
- Caudate and thalamus were the only GM structures showing atrophy in MS

Ceccarelli et al., AJNR 2012;33:1596-601

Thalamic atrophy related to cognition in MS

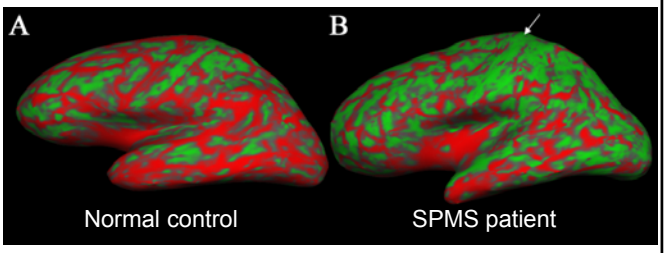


$r = 0.658$, $p < 0.0001$ (SDMT)

$r = 0.724$, $p < 0.0001$ (BVMT)

Houtchens et al., Neurology 2007;69:1213-23

3T MRI: cortical thickness w/Freesurfer



Comparison of the reconstructed brain cortical surface. Significant thinning (< 2 mm) is shown in green, while red represents cortical areas > 2 mm. Marked cortical thinning is seen in various areas including the sensorimotor cortex (arrow) in MS.

AS method to measure C2-C5 spinal cord volume

Horsfield et al., Neuroimage 2010;69:1213-23

The AS method is highly reproducible

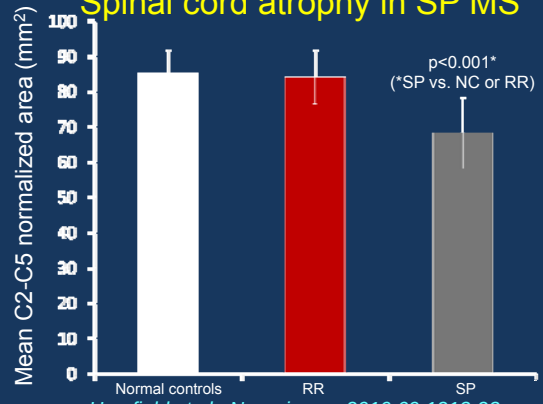
(n=60)

COV = (SD/mean) × 100%

Method	Intra-Observer	Inter-Observer
Losseff method C2-3	2.15 %	7.95 %
AS method C2-3	0.59 %	1.36 %
AS method C2-C5	0.44 %	1.07 %

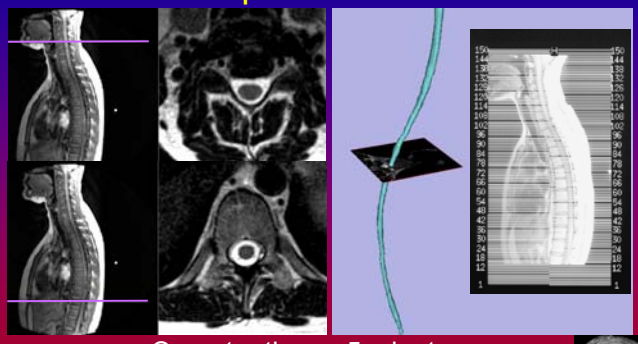
Horsfield et al., Neuroimage 2010;69:1213-23

Spinal cord atrophy in SP MS



Horsfield et al., Neuroimage 2010;69:1213-23

Whole spinal cord volume



Operator time = 5 minutes

Kim et al. Eur J Radiol (in revision)

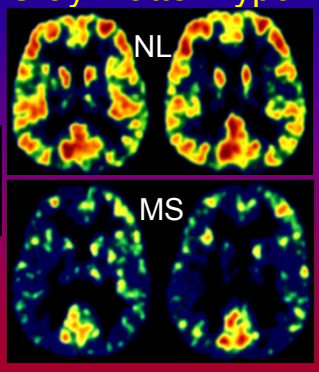
Uncoupling of brain & cord MS damage

	Spinal cord MRI Measures:												
	Volume measures*								Lesion measures				
	C2-C3		Cervical		Thoracic		Whole cord		Cervical		Thoracic		Whole cord	
Brain MRI measures:	r	P	r	P	r	P	r	P	r	P	r	P	r	P
GMF^	.307	.189	.302	.196	.234	.320	.229	.331	−.119	.618	.009	.971	−.104	.661
WMF^	.323	.164	.359	.120	.229	.331	.272	.245	.226	.339	.097	.683	.258	.273
BPF^	.365	.113	.375	.103	.272	.245	.285	.224	−.008	.972	.044	.854	.015	.950
FLLV	.092	.699	.062	.794	.035	.883	.098	.682	.085	.720	.443	.050	.307	.188

GMF = brain gray matter fraction; WMF = brain white matter fraction; BPF = global brain parenchymal fraction; FLLV = Brain fluid-attenuated inversion recovery hyperintense lesion volume; *spinal cord volumes are normalized by number of slices and intracranial volume (see Methods section). ^brain volumes are normalized by intracranial volume (see Methods section).

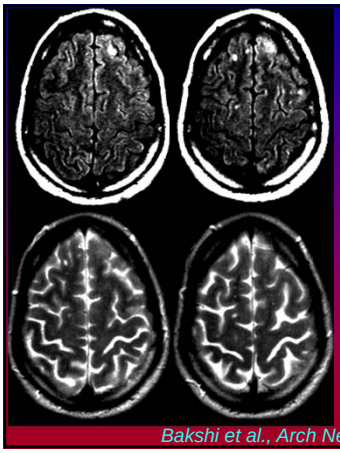
Cohen et al. J Neuroimaging 2012;22:122-128

Gray matter hypometabolism in MS



- MS (n=25) vs. NL
- 9% whole brain hypometabolism
- Across all 20 ROIs
  - Cerebral cortex
  - Basal ganglia
  - Thalamus
- Range 3%-18%

Bakshi et al., J Neuroimaging 1998;8:228-234



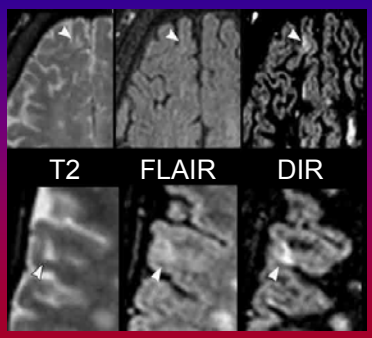
FLAIR

Cortical Lesions in MS

T2WI

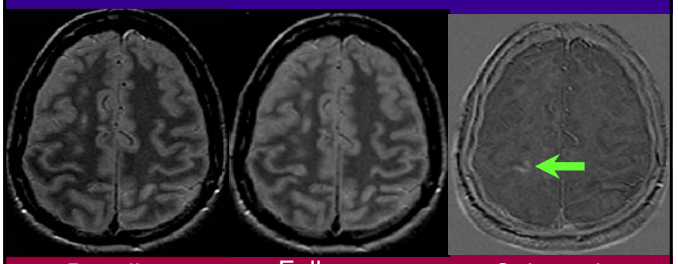
Bakshi et al., Arch Neurol, 2001;58:742

Double Inversion Recovery MRI
Cortical lesions in MS



Guerts et al., Radiology 2005;236:254–260

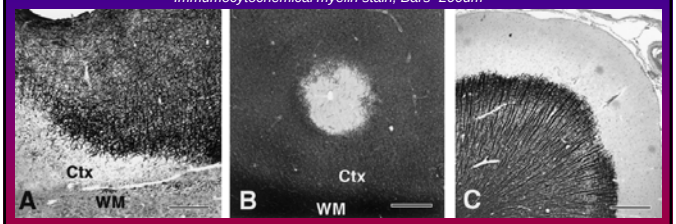
Subtraction Imaging



Duan et al., AJNR 2008;29:340-6

MS Cortical lesions: *Neuropathology*

Immumocytochemical myelin stain, Bars=200um



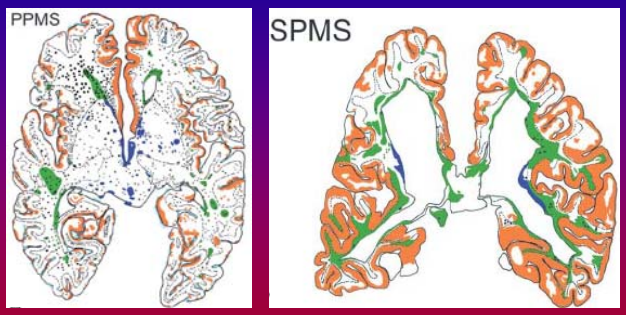
Type I
WM + Cortex

Type II
Cortex, perivascular

Type III/IV
Pial/subpial

Peterson et al., Ann Neurol 2001;50:389–400

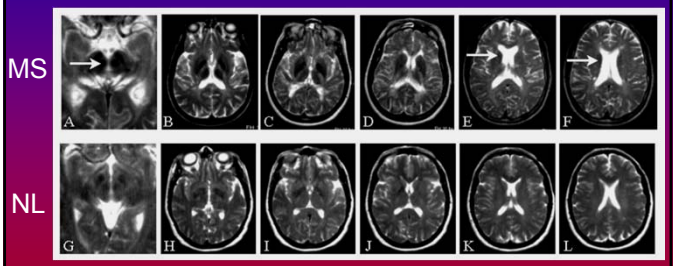
MS Cortical lesions: *Neuropathology*



Orange=cortical plaque; Green=WM plaque; Blue=deep GM plaque

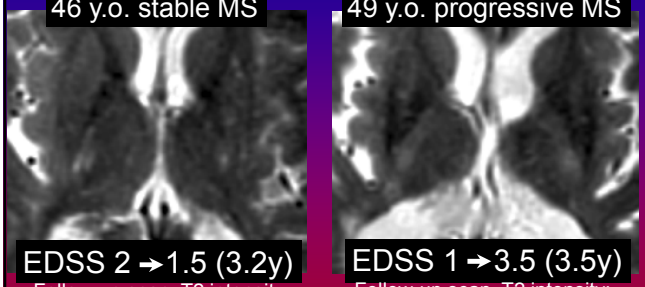
Kutzelnigg et al., Brain 2005;128:2705–2712

T2 hypointensity in gray matter



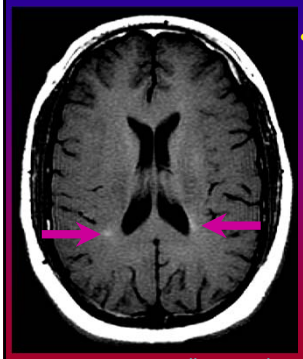
Bakshi et al., Arch Neurol 2002;59:62-68

T2 hypointensity and disability



Neema et al., J Neuroimaging 2009;19:3-8

MRI T1 shortening in MS lesions

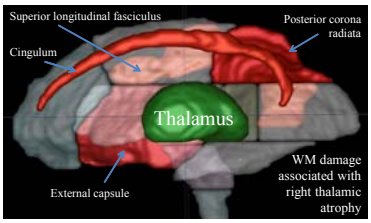


- Cause?
- Iron or other metal
- Calcium
- Melanin
- Free radicals
- Lipid-laden macrophages
- Proteinaceous substance

Janardhan et al., Radiology 2007;244:823-31

Thalamic atrophy is related to WM damage in MS

DGM area	WM region	P-value
Left thalamus	Cerebral peduncle	0.01
Right caudate	External capsule	0.01
Right thalamus	Posterior corona radiata	0.02
Right thalamus	External capsule	0.04
Right thalamus	Cingulum	0.01
Right thalamus	Superior longitudinal fasciculus	0.01

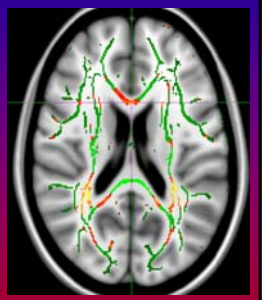


- GREEN: right thalamus
- RED/PINK: WM areas whose damage correlates with thalamic volume in patients
- GRAY: areas showing non-significant correlation

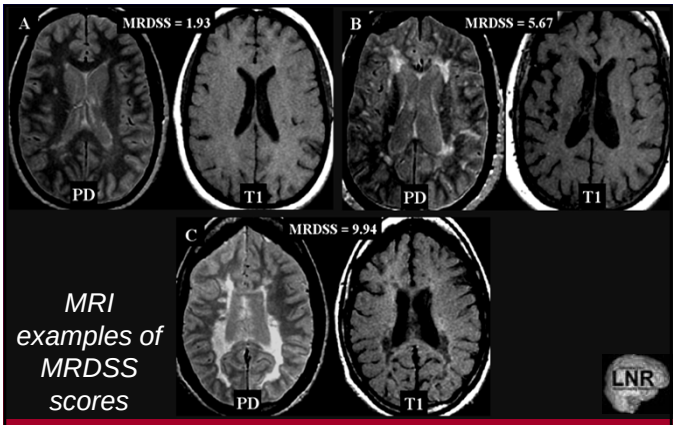
AAN 2013

Evolving WM tract damage over 1y

- 25 mildly-disabled MS pts; 9 normal controls; 3T DTI
- Over 1y: Decreasing FA (yellow-red) in WM tracts (overlaid on the green FA skeleton) in MS vs. NC
- Thalamic volume at baseline linked to on-study decreasing FA in the corpus callosum ($p<0.05$)



AAN 2013



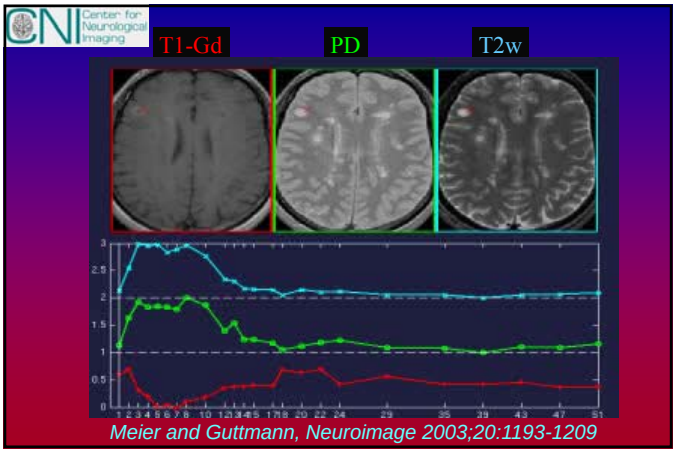
Bakshi et al., Archives of Neurology 2008;65:1449-53

Longitudinal change in MRDSS (n=84)

MRI:	Baseline	3 years	Change	p-value
MRDSS	4.8 ± 2.5	5.5 ± 2.3	0.64 ± 0.8	1.5×10^{-10}
BPF	0.83 ± 0.05	0.82 ± 0.05	-0.01 ± 0.02	8.8×10^{-5}
T2	6.9 ± 5.5	7.2 ± 6.2	0.3 ± 2.6	0.31
T1/T2	0.15 ± 0.2	0.2 ± 0.2	0.06 ± 0.1	1.6×10^{-6}

Key: MRDSS=Magnetic Resonance Disease Severity Scale; BPF=brain parenchymal fraction; T2=T2 hyperintense lesion volume; T1=T1 hypointense lesion volume; values are mean±SD

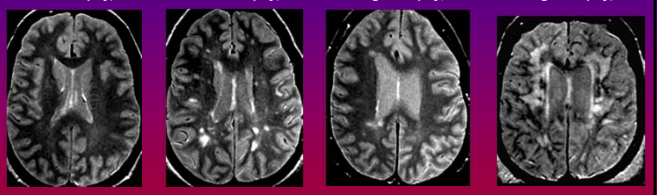
Moodie et al., J Neurol Sci 2012;315:49–54



Meier and Guttmann, Neuroimage 2003;20:1193-1209

MRI-defined phenotypes in MS

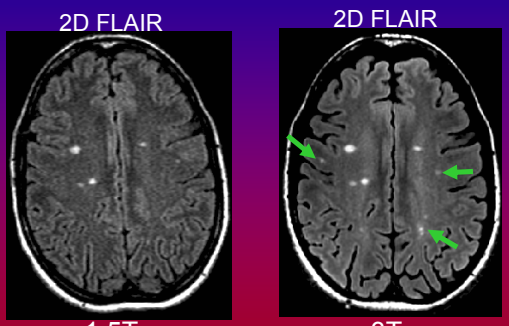
Type I (low lesions/ mild atrophy) | **Type II** (high lesions/ mild atrophy) | **Type III** (low lesions/ high atrophy) | **Type IV** (high lesions/ high atrophy)



The majority of patients (phenotypes I, II and III) showed clinical-MRI paradox & dissociation between lesions and brain atrophy

Tauhid et al., J Neurol Sci 2014;346:250-254

MS brain hyperintensities: 1.5T vs. 3T



Bakshi et al., Lancet Neurology 2008;7:615-625

MS brain hyperintensities: 1.5T vs. 3T

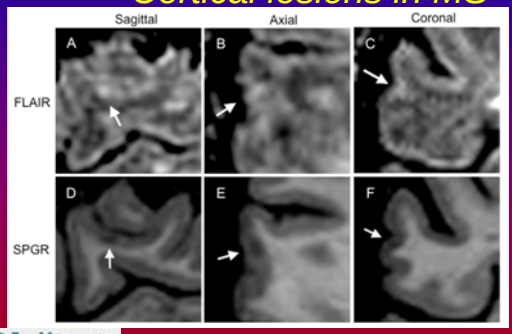
Table 4: Correlation between cognitive measures and brain MRI lesions at 1.5T vs. 3T

Cognitive test	1.5T FLLV		3T FLLV	
	r	p-value	r	p-value
PASAT2	-0.37	0.09	-0.55	0.01*
PASAT3	-0.28	0.21	-0.30	0.16
COWAT	-0.19	0.40	-0.27	0.22
BVMT DR	-0.40	0.06	-0.56	0.007*
BVMT TL	-0.41	0.06	-0.37	0.09
JLO	-0.44	0.04*	-0.66	0.0008*
SDMT	-0.49	0.02*	-0.73	0.0001*
CVLT TL	-0.23	0.30	-0.42	0.05*
CVLT DR	-0.44	0.04*	-0.61	0.003*
DKEFS CS	-0.26	0.24	-0.36	0.10
DKEFS DS	-0.22	0.33	-0.33	0.13

Key: r is Spearman partial correlation coefficient controlling for age and depression. FLLV= Fluid-attenuated inversion-recovery hyperintense lesion volume; PASAT=Paced Auditory Serial Addition Test, 2 and 3 second delay; COWAT=Controlled Oral Word Association Test; BVMT=Brief Visuo-spatial Memory Test (DR=delayed free recall, version TL=total recall), JLO=Judgment of Line Orientation; SDMT=Symbol Digit Modalities Test; CVLT=California Verbal Learning Test (TL=five trial recall, DR=Delayed Recall), DKEFS=Delis-Kaplan Sorting test (CS=total confirmed correct sorts, DS=total description score.) *indicates p<0.05 statistical significance.

Stankiewicz et al., J Neuroimaging 2011;21:e50-e56

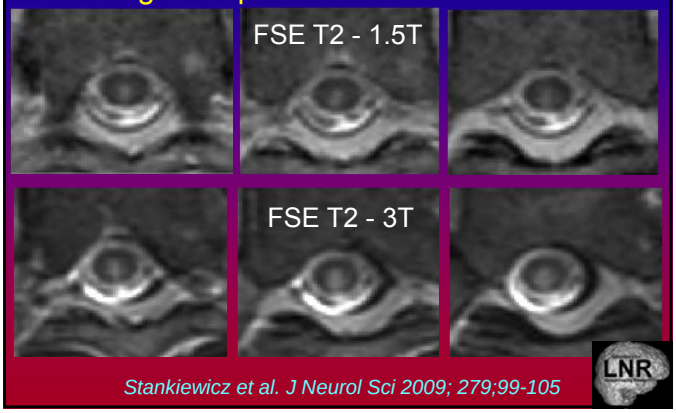
3T FLAIR & SPGR MRI *Cortical lesions in MS*



Type II cortical lesion

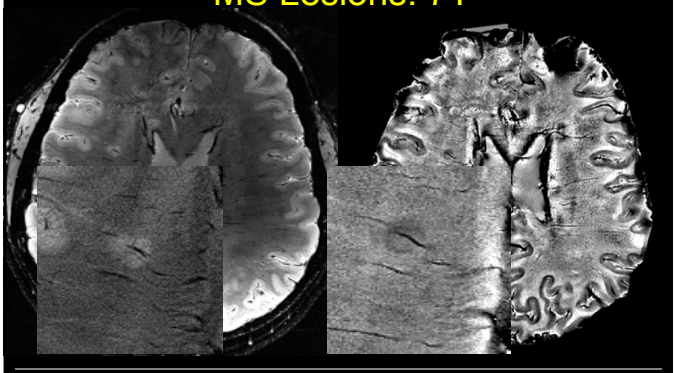
Mike et al., AJNR 2011;32:515-521

Detecting MS Spinal Cord Lesions: 1.5T vs. 3T



Stankiewicz et al. J Neurol Sci 2009; 279;99-105

MS Lesions: 7T



*200 μm * 200 μm* 38 y/o with 1 year of MS; EDSS score 1.0 *Dr. F. Bagnato*

MS Lesions: 8T
Cortical pathology

Kottil Rommohan et al.

Use of MRI for routine MS care

- Brain MRI
  - T1/T2/FL ax, FL sag, T1-Gd sag/ax
- Spinal cord MRI
  - T1/T2-SE sag, T2-SE ax, T1-Gd sag
- For diagnosis and annually in active patients
- More often in CIS
- Less often in stable patients
- MRS, MTI, DWI not for routine care

Bakshi et al. Neurology 2004;63(Suppl 5):S3-11; Simon et al. AJNR 2006;27:455-61; Filippi et al. Eur J Neurol 2006,13:313-25

Conclusions

- MRI is a powerful tool for diagnosing MS
- MRI is a valuable marker of biologic disease activity and disease severity
- Worsening of MRI findings even if clinically silent probably impacts on long term clinical outcomes
- MRI technology continues to unfold and requires validation

MRI in multiple sclerosis

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