



What MRI has taught us about Neurodegeneration and MS

Matilde Inglese M.D., Ph.D.
Dept. of Neurology and Radiology
Mount Sinai School of Medicine



Disclosures

Matilde Inglese, MD, PHD

Grants/research support: NIHR01 NS051623

Consultant/advisory board member:

Vaccinex, Inc.

Celgene Cellular Therapeutics



Learning Objectives

At the conclusion of this activity, the participant will be able to:

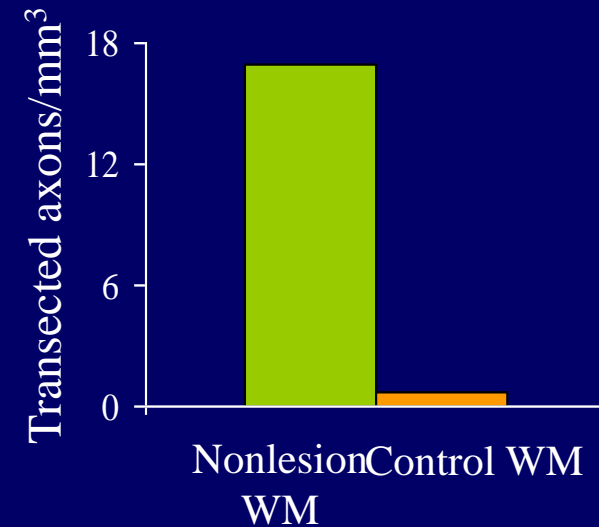
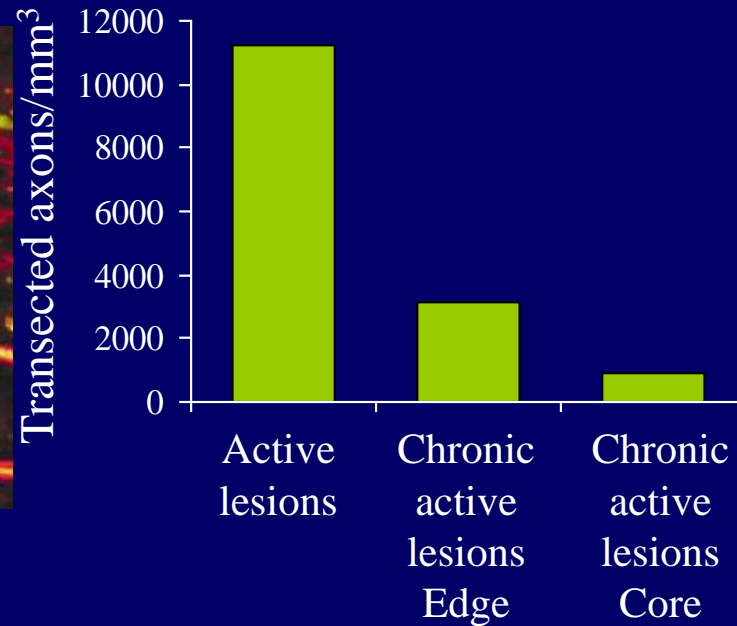
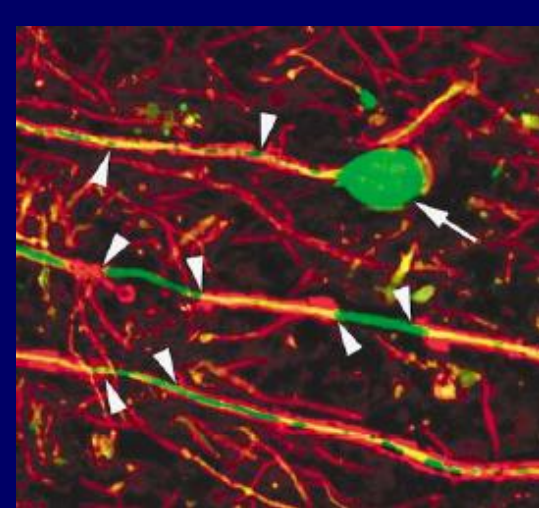
- A. Describe MRI methods for quantitative assessment of neurodegeneration
- B. Discuss new imaging methods for detection of gray matter lesions
- C. Explain the clinical implications of more pathologically specific MRI metrics



OUTLINE

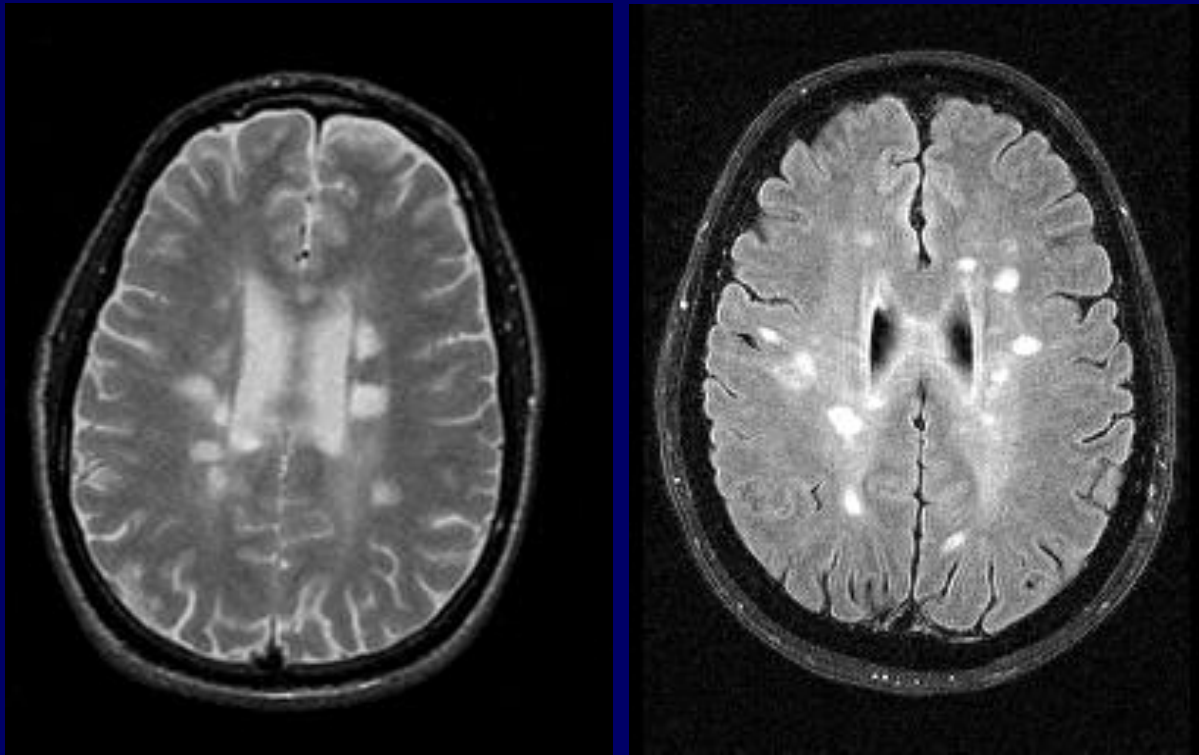
- Evidence of neuro-axonal damage
- MR Spectroscopy and N-acetyl-aspartate
- Brain atrophy
- MRI measures of gray matter damage
 - GM atrophy
 - Cortical GM lesions

Axonal transection in the lesions of multiple sclerosis





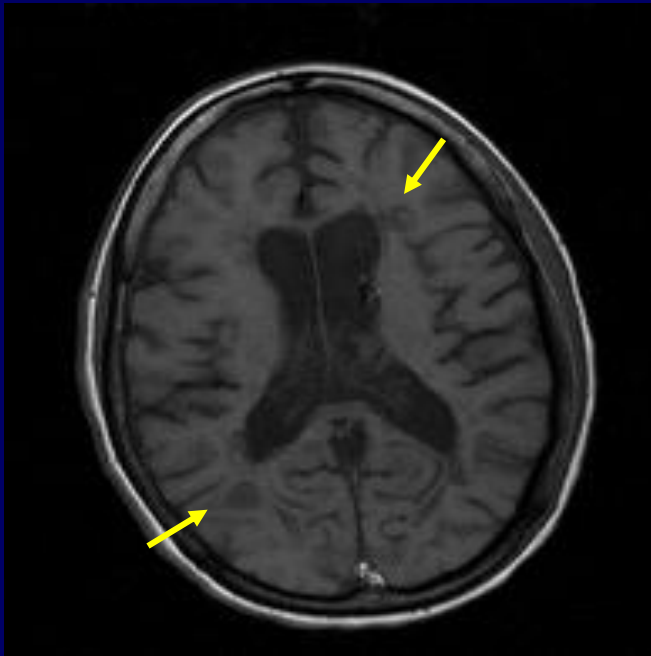
Clinical MRI



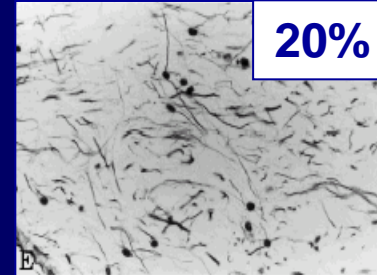


HISTOPATHOLOGIC CORRELATES OF BLACK HOLES

T1 Hypointensity Directly Correlates to Degree of Axonal Loss

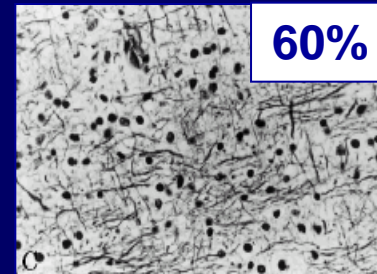


Bodian: axonal density



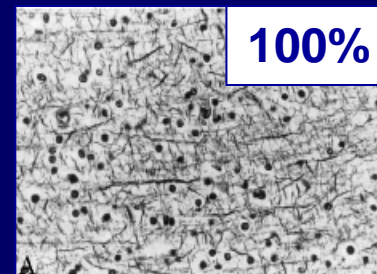
20%

1: strongly hypointense



60%

2: mildly hypointense



100%

3: NAWM



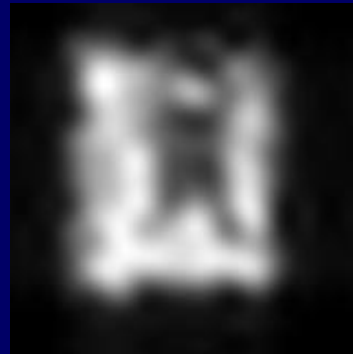
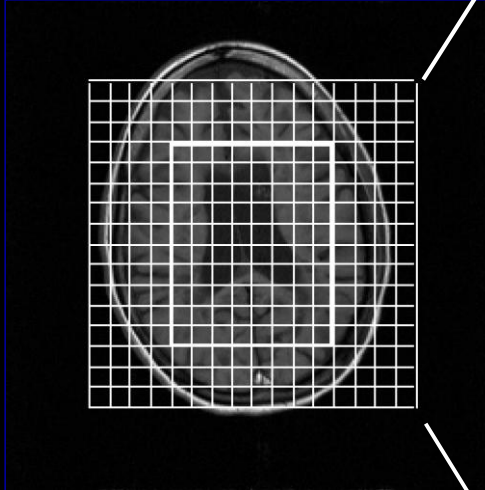
OUTLINE

- Evidence of neuro-axonal damage
- **MR Spectroscopy and N-acetyl-aspartate**
- Brain atrophy
- MRI measures of gray matter damage
 - GM atrophy
 - Cortical GM lesions

^1H -MRS



Single-voxel ^1H -MRS

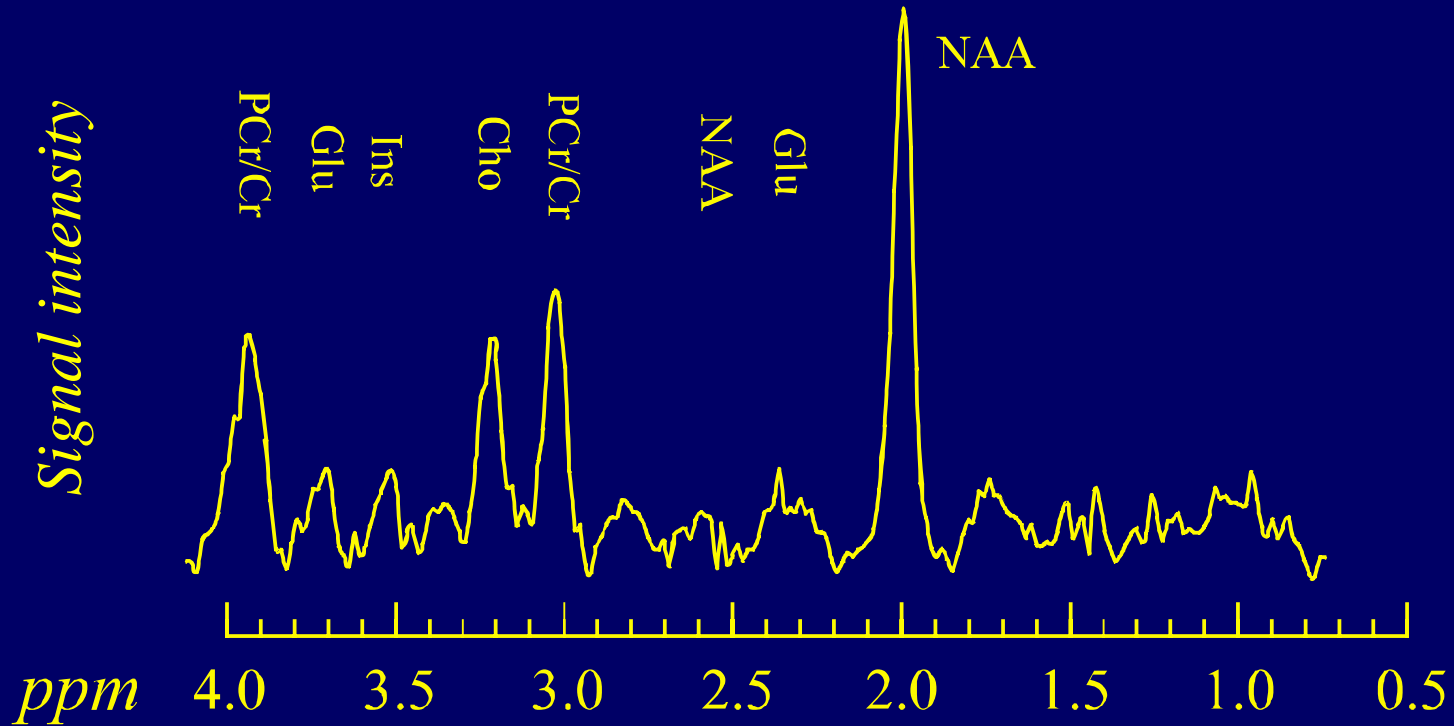


Multi-voxel ^1H -MRS
Chemical shift Imaging
MRSI

Arbitrary chemical shift frequency spectrum acquired from a single voxel. The spectrum shows peaks corresponding to different metabolites. The x-axis represents chemical shift in ppm, and the y-axis represents signal intensity. The spectrum is typically acquired from a single voxel, and the resulting signal is a sum of all metabolites present in that voxel. The spectrum is then processed to identify individual metabolites, which is a challenging task due to the overlapping peaks and the presence of noise. The spectrum is typically acquired from a single voxel, and the resulting signal is a sum of all metabolites present in that voxel. The spectrum is then processed to identify individual metabolites, which is a challenging task due to the overlapping peaks and the presence of noise.



Proton Spectroscopy (^1H -MRS)

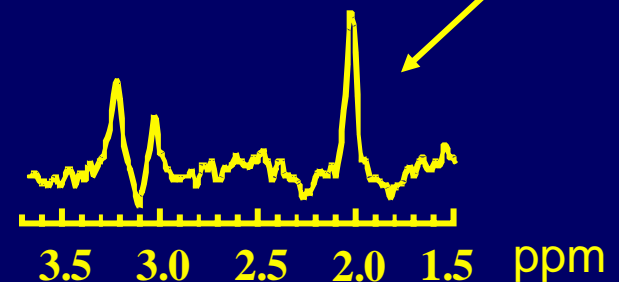
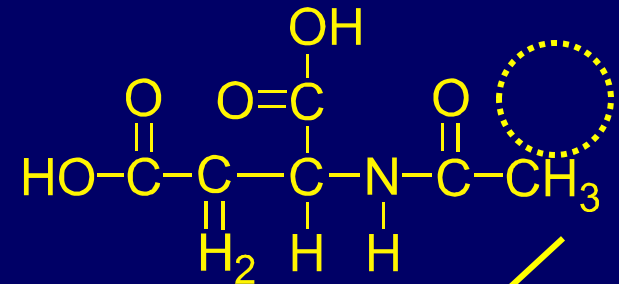
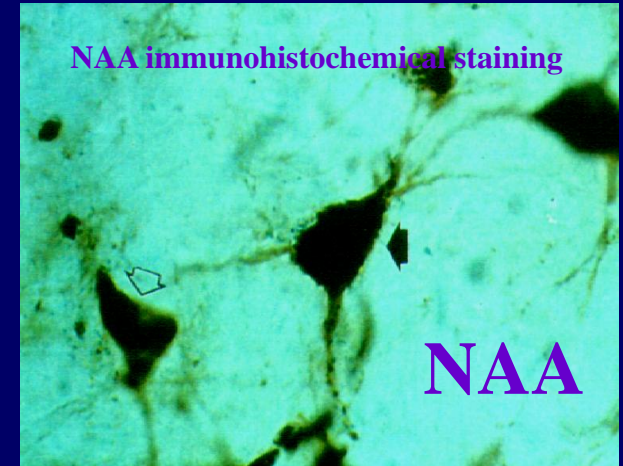




^1H -MRS

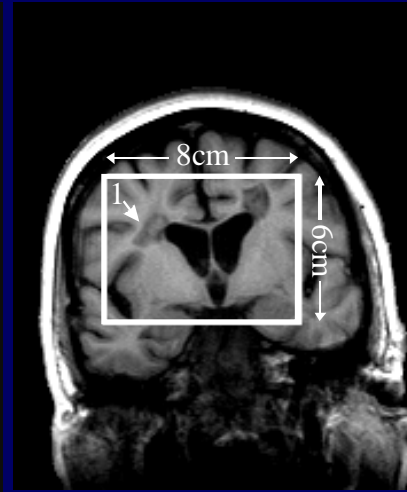
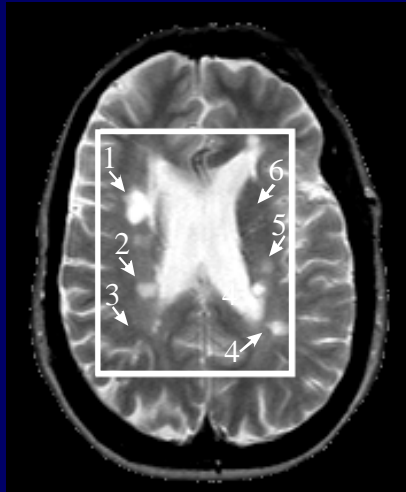
and N-acetyl-aspartate (NAA)

- Second most abundant amino-acid in the brain
- Localized in neurons and their processes
- Synthesized in mitochondria
- Function not known



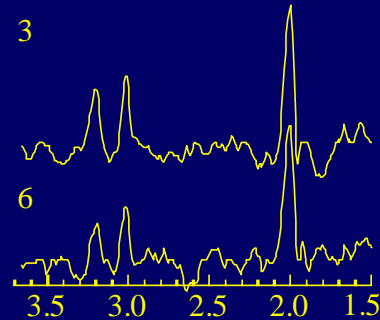
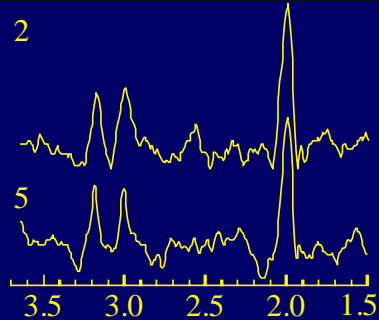
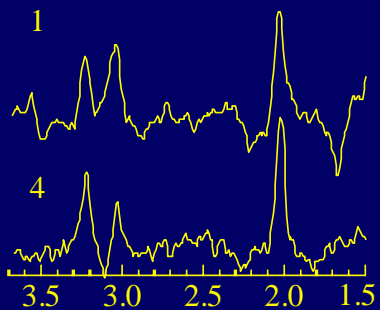


N-acetyl-aspartate (NAA)



NAA decreases in:

- Acute lesions
- Chronic lesions
- NAWM
- Cortical GM
- Sub-cortical GM

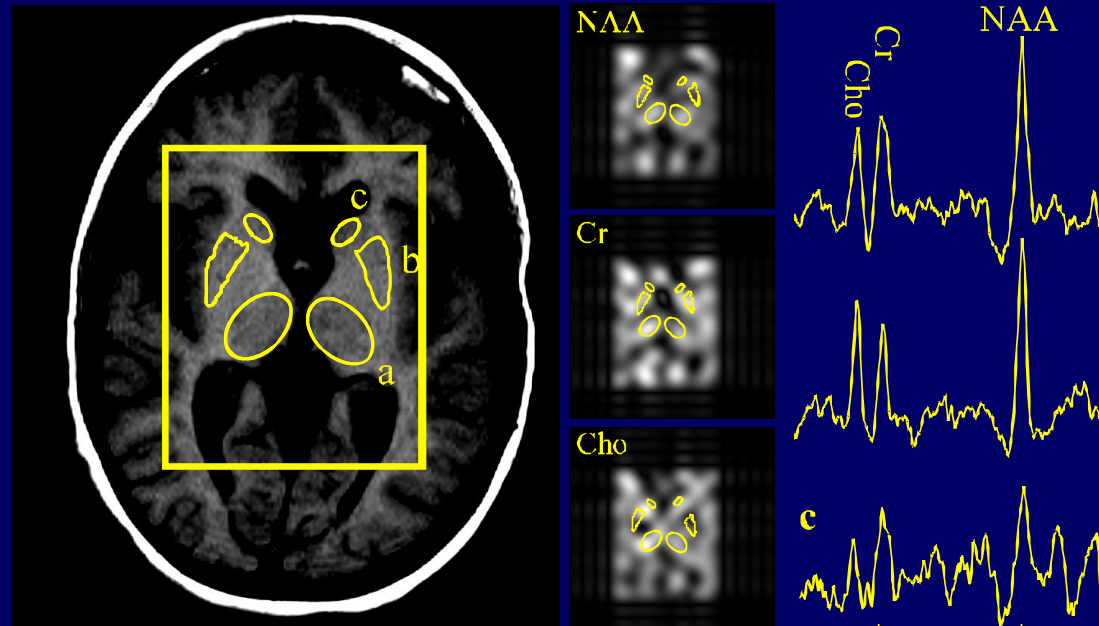


Adapted from He J et al. Radiology 2004

Arnold D et al. Magn Reson Med 1990
De Stefano et al. Magn Reson Med 1994
Davie C et al. JNNP 1997
Sharma R et al. Mult Scler 2001
Inglese M et al. Neurology 2004

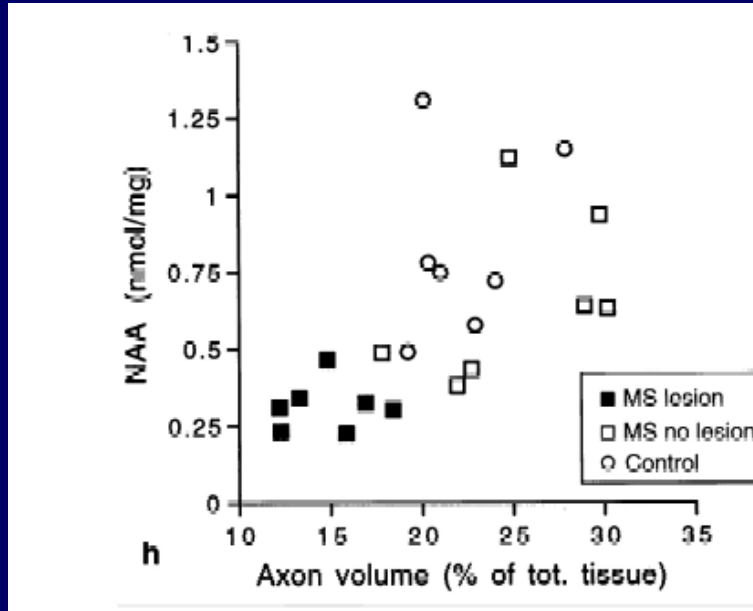
3D-¹H-MRS of Deep Gray Nuclei in RRMS

MS Patient

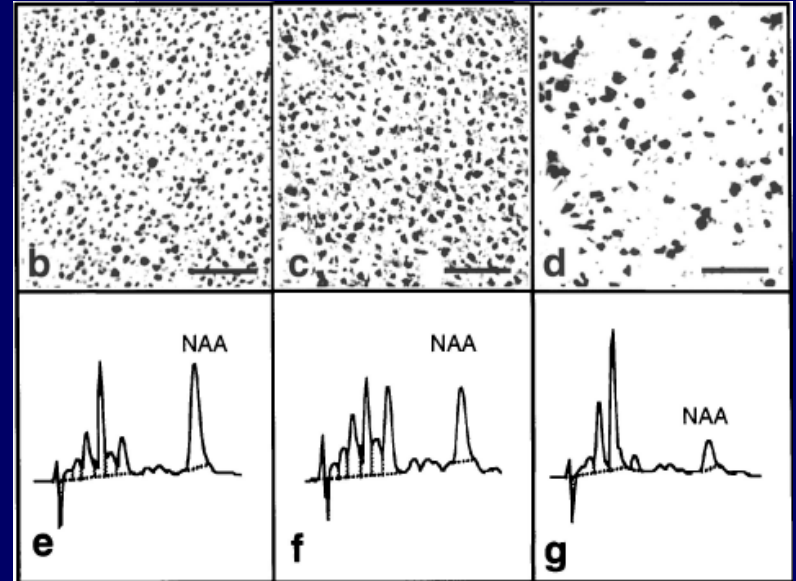


	RR MS	Controls	<i>p</i>	
[NAA]	8.85 2.18	9.50 1.97	<0.02	(-7%)
[Cr]	6.43 1.53	6.51 1.62	n.s.	
[Cho]	2.16 0.55	1.86 0.47	<0.02	(+14%)

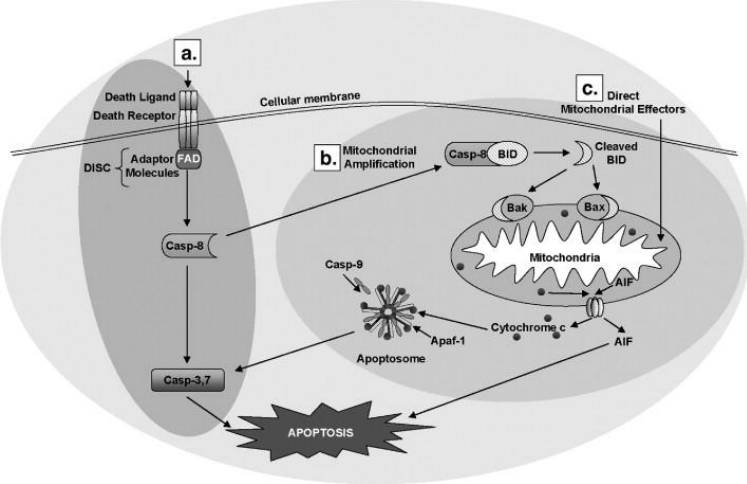
Neurological Disability correlates with axonal loss



CTRL WM MS NAWM MS lesion



- Axonal loss in lesions ranged from 45 to 84% and averaged 68%.
- NAA levels were significantly reduced (>50%)
- ↓ NAA correlated with axonal numbers within lesions
- NAA levels were significantly reduced in NAWM (30-40%)



A significant component of NAA decrease represents potentially reversible metabolic dysfunction

Mitochondrial Dysfunction as a Cause of Axonal Degeneration in Multiple Sclerosis Patients

Ranjan Dutta, PhD,¹ Jennifer McDonough, PhD,¹ Xinghua Yin, MD,¹ John Peterson, PhD,¹
 Ansi Chang, MD,¹ Thalia Torres, BS,¹ Tatyana Gudz, PhD,¹ Wendy B. Macklin, PhD,¹ David A. Lewis, MD,³
 Robert J. Fox, MD,² Richard Rudick, MD,² Karoly Mirnics, MD,³ and Bruce D. Trapp, PhD¹



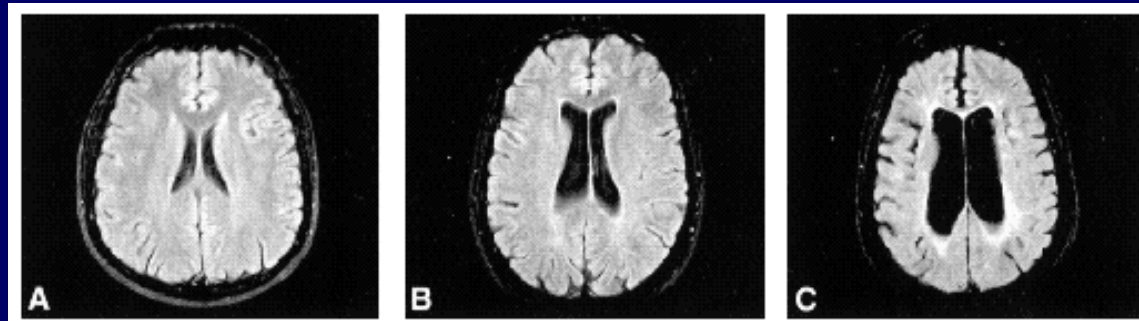
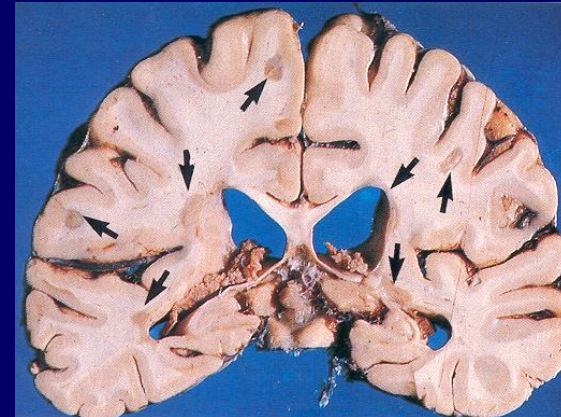
OUTLINE

- Evidence of neuro-axonal damage
- MR Spectroscopy and N-acetyl-aspartate
- **Brain atrophy**
- MRI measures of gray matter damage
 - GM atrophy
 - Cortical GM lesions



Brain Atrophy

- Brain parenchyma loss is a global process (demyelination and axonal loss). It occurs in MS patients up to 1.0%/year
- Brain volume changes can be detected in CIS
- Brain volume changes are clinically relevant
- Atrophy is used as an outcome measure in clinical trials





VIEWS & REVIEWS

Mechanisms of action of disease-modifying agents and brain volume changes in multiple sclerosis

R. Zivadinov, MD,
PhD
A.T. Reder, MD
M. Filippi, MD
A. Minagar, MD
O. Stüve, MD, PhD
H. Lassmann, MD
M.K. Racke, MD
M.G. Dwyer
E.M. Frohman, MD,
PhD
O. Khan, MD

ABSTRACT

Disease-modifying agents (DMAs), including interferon beta (IFN β) and glatiramer acetate (GA), are the mainstays of long-term treatment of multiple sclerosis (MS). Other potent anti-inflammatory agents like natalizumab and different types of chemotherapeutics are increasingly being used for treatment of MS, particularly in patients with breakthrough disease activity. Brain volume (BV) loss occurs early in the disease process, accelerates over time, and may be only partially affected by DMA therapy. Low-dose, low frequency IFN β administered once weekly and GA appear to partially reduce BV decline over the second and third years of treatment. High dose, high frequency IFN β demonstrated no clear effect on BV loss during this time period. Current evidence suggests that changes in BV after immunoablation may not be due entirely to the resolution of edema but may be related to potential chemotoxicity of high dose cyclophosphamide. Natalizumab reduces the development of BV decline in the second and third years of treatment.



OUTLINE

- Evidence of neuro-axonal damage
- MR Spectroscopy and N-acetyl-aspartate
- Brain atrophy
- **MRI measures of gray matter damage**
 - GM atrophy
 - Cortical GM lesions



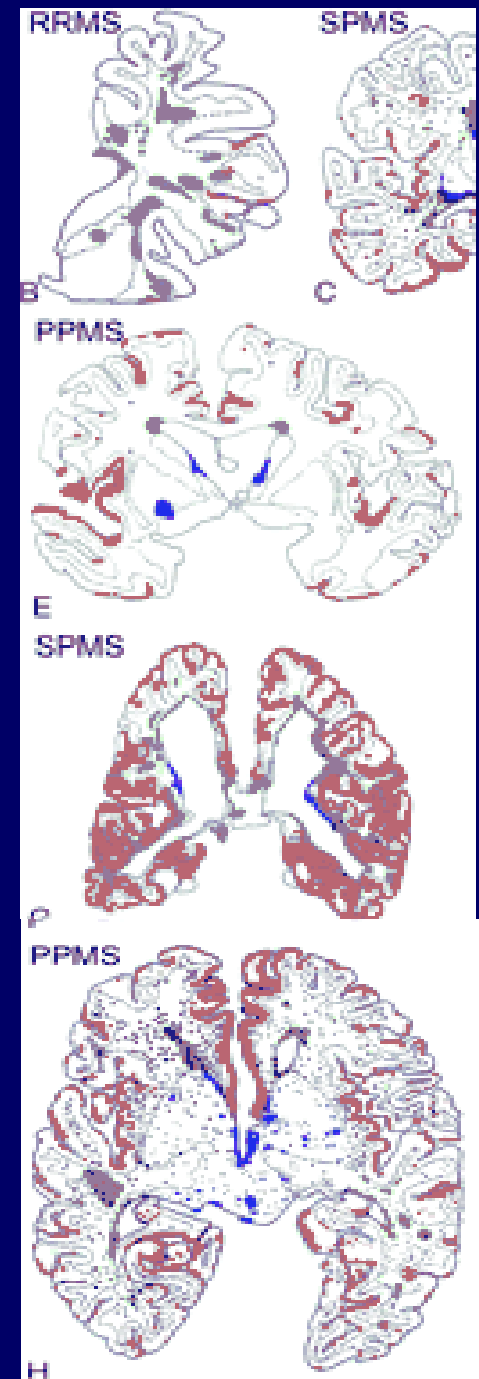
Cortical Demyelination

• Acute MS and Relapsing MS

- Inflammation is focal
- Classical active plaques are predominant

• Progressive MS

- Inflammation is global
- Associated with diffuse injury in NAWM
- Cortical demyelination is a characteristic feature, prominent in both PP and SP
- Focal WM plaques are either inactive or show slow expansion on their edges



Gray Matter Atrophy Is Related to Long-Term Disability in Multiple Sclerosis

Leonora K. Fisniku, MRCP,^{1,2} Declan T. Chard, PhD,^{1,2} Jonathan S. Jackson, MSci,^{1,2}
Valerie M. Anderson, BSci,^{1,2} Daniel R. Altmann, PhD,^{1,3} Katherine A. Miszkiel, MRCP,⁴
Alan J. Thompson, PhD,^{1,5} and David H. Miller, MD^{1,2}

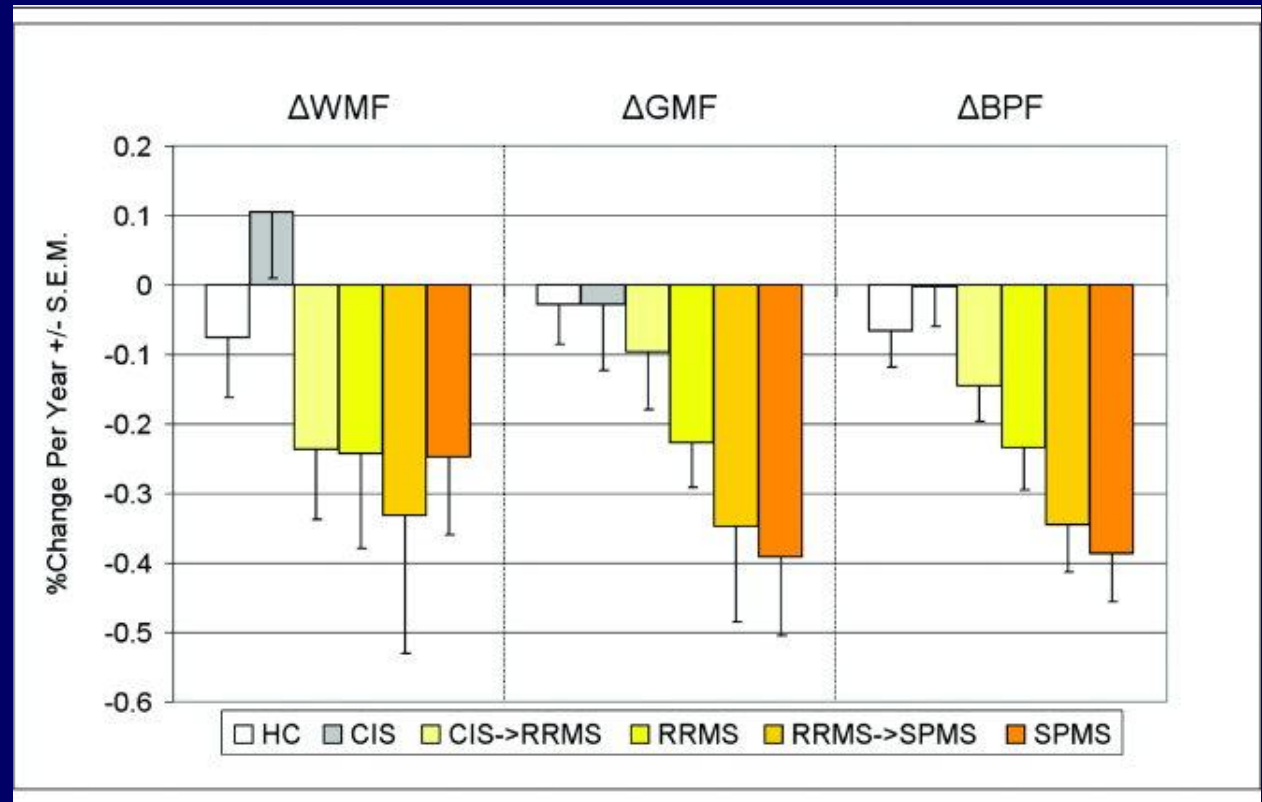


There was significantly more GM, but not WM atrophy
in SP-MS vs RR-M
in RR-MS vs CIS

GM, but not WM fraction correlated
with clinical disability (EDSS)

On the regression models, only NGMV independently
predicted clinical disability

Gray Matter Atrophy



GM 3.4 fold normal in CIS converting to RR-MS
GM 8.0 fold normal in RR-MS
GM 14 fold normal in SP-MS
WM ~3 fold normal; constant across disease stages



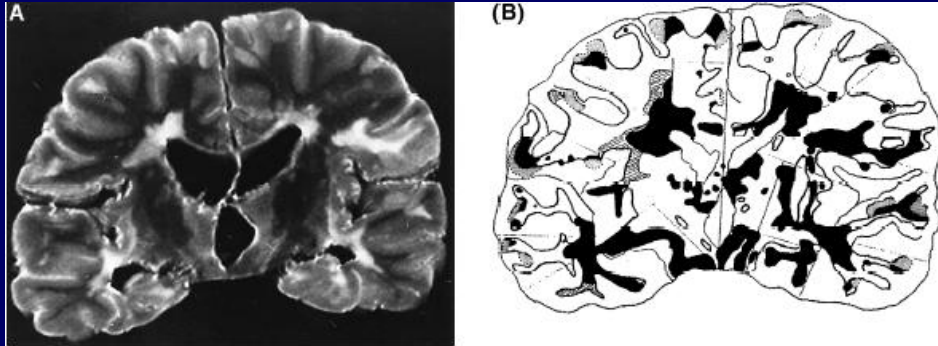
Gray Matter Atrophy



- GM atrophy develops faster than WM atrophy
- GM atrophy occurs in the earliest stages of the disease
- It is related to physical disability, cognitive impairment and quality of life
- In patients with RR-MS and PP-MS there is a positive correlation between progressive WM lesion load and GM volume decrease

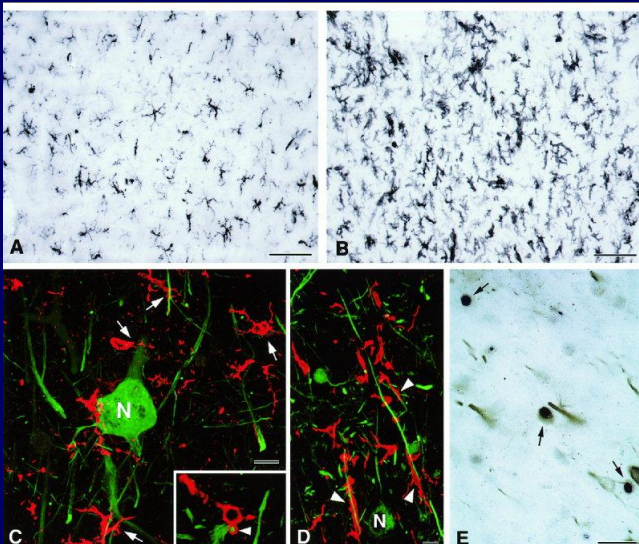


Cortical lesions frequently detected at *post mortem* examination Kidd D. *et al. Brain* 1999



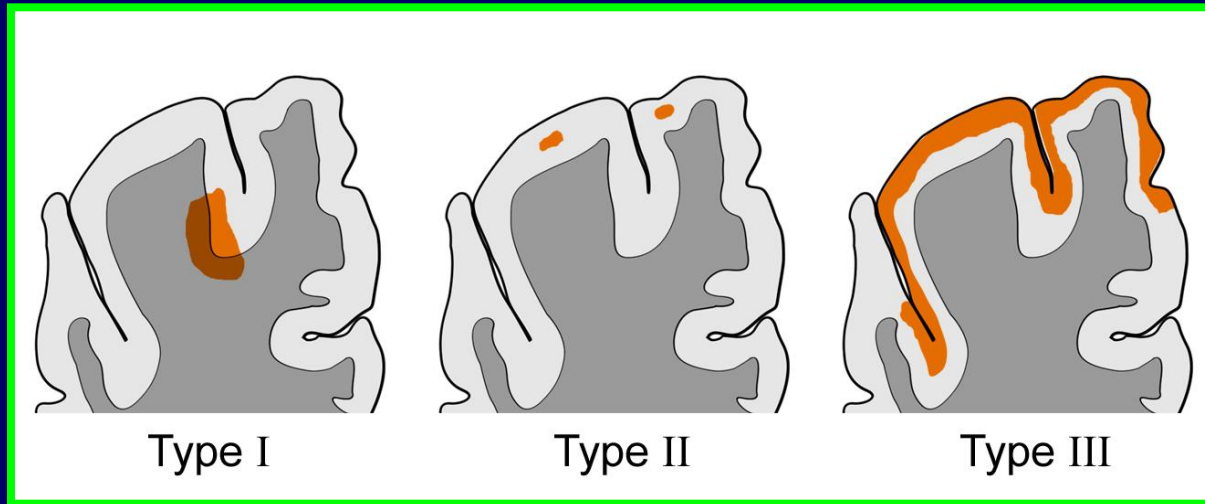
Neuronal Apoptosis in Cortical MS Lesions

- Present and significant in most MS brains (70-90%)
- Low lymphocyte infiltration, Low complement deposition
Less BBB disruption
- Demyelination and microglial activation
- Neuritic transection and neuronal apoptosis



Peterson JW *et al. Ann Neurol* 2001

Cortical MS lesions



Cortical lesion type I

Leucocortical: Mixed WM/GM lesion

Cortical lesion type II

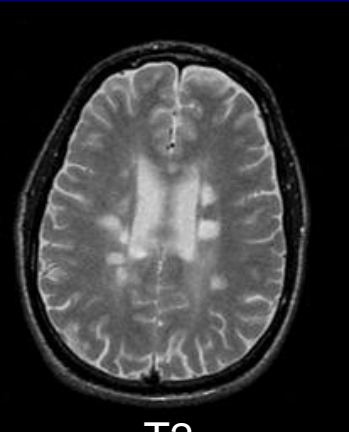
Small, intracortical lesion

Cortical lesion type III-IV

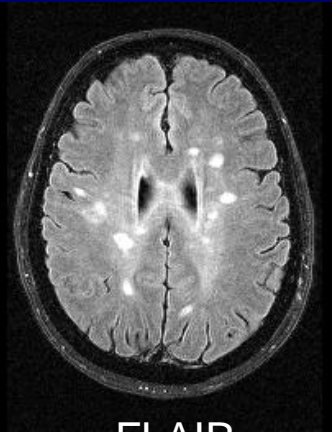
Subpial cortical demyelination, reaching from the pia downwards into the cortex. Does not reach the WM-GM border. Can grow extensively



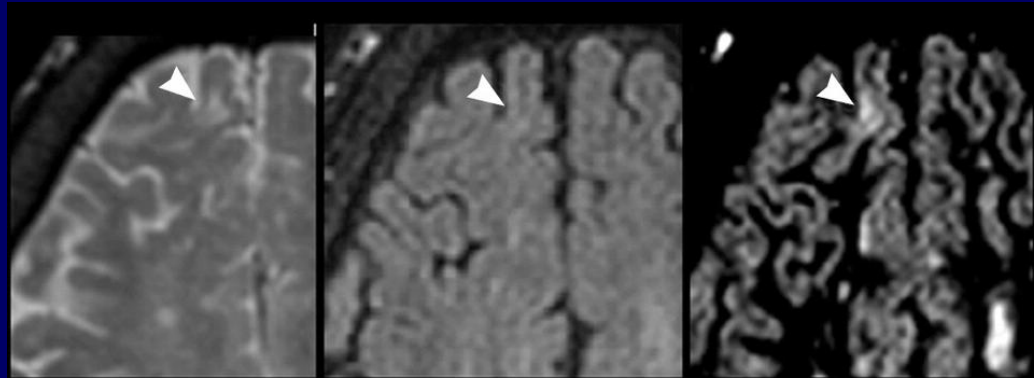
Double Inversion Recovery (DIR)



T2



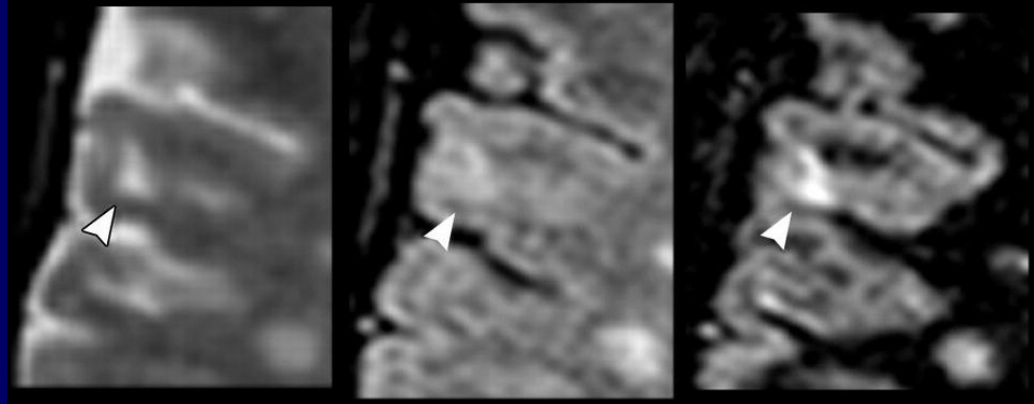
FLAIR



T2

FLAIR

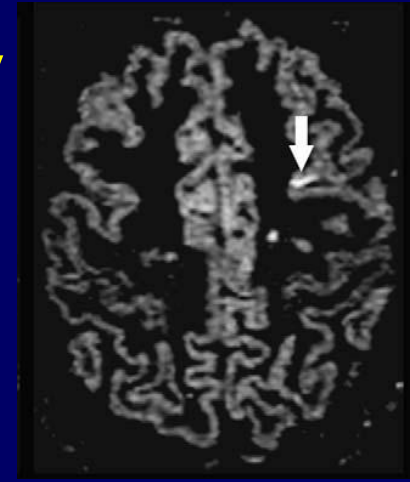
DIR



T2

FLAIR

DIR

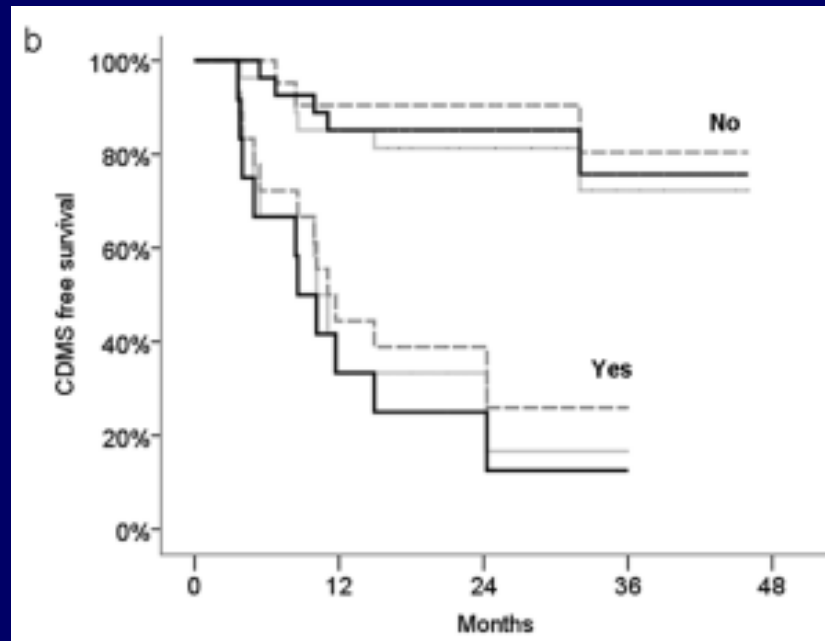


DIR vs FLAIR: average 152%
DIR vs T2-W: average 500%



Intracortical lesions : Relevance for new MRI diagnostic criteria for multiple sclerosis

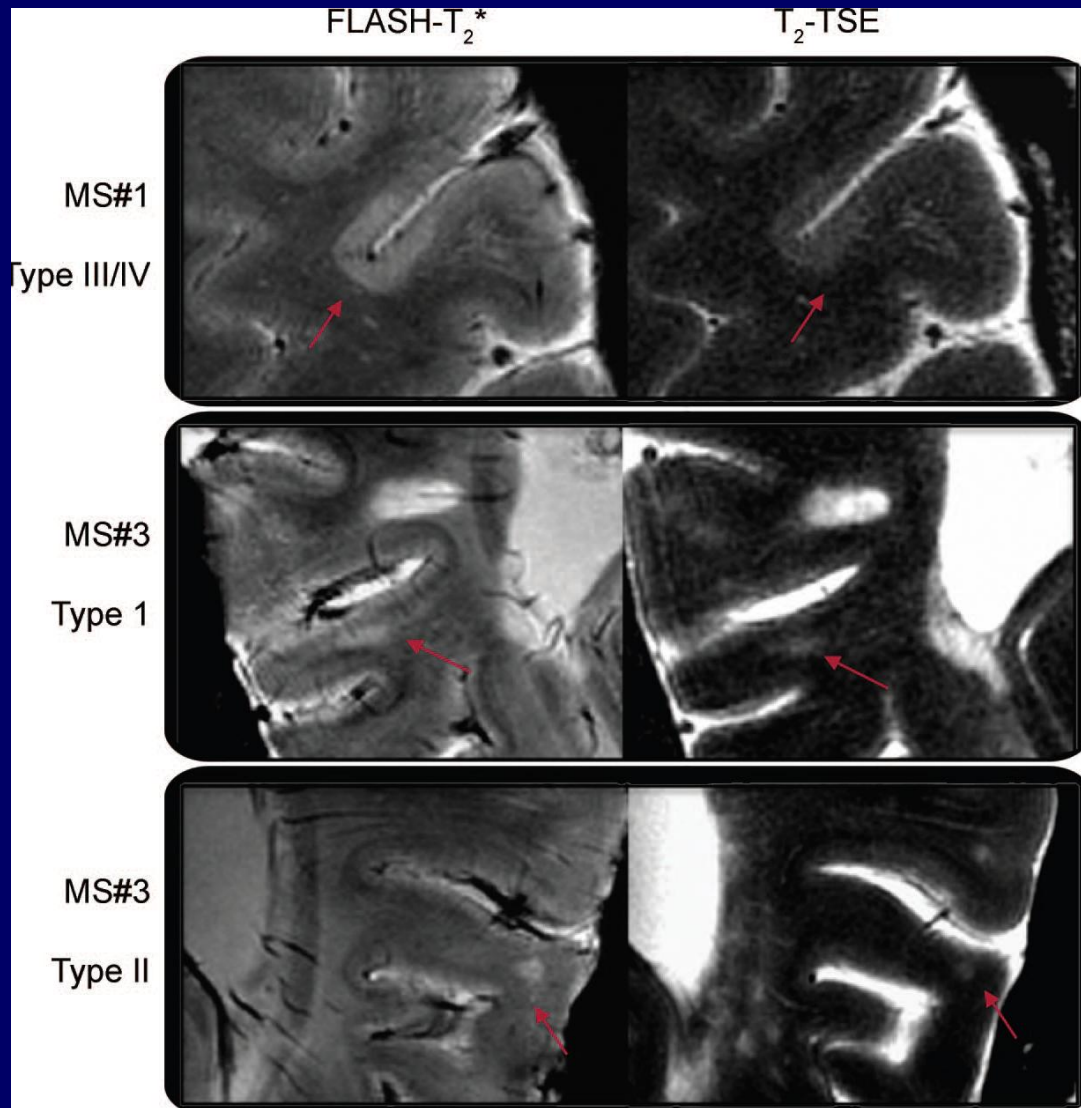
M. Filippi, M.A. Rocca, M. Calabrese, et al.
Neurology 2010;75:1988
DOI 10.1212/WNL.0b013e3181ff96f6



Kaplan Meier survival curves showing the probability to convert to CDMS for patients classified based on the fulfillment of disease dissemination in space (DIS) (yes/no) according to the new criterion taking into account intracortical lesions (black lines), the revised international panel (IP) criteria (dotted gray lines), and the Swanton/MAGNIMS criteria (gray lines)



Gray Matter lesions at 7.0 Tesla



50.2%

36.2%

13.6%



DIR and MS

- Cortical lesions (CLs) are detected since the earliest stages of the disease - CIS (37%).
- The number of CLs correlates with EDSS score, WM T2-LV and brain volume.
- CLs increases at a greater rate in MS patients with clinical progression.
- Baseline CLs volume predicts disability progression and GM atrophy.
- MS patients with cognitive deficits have greater CLs and GM atrophy than patients without cognitive deficits.
- MS patients with seizure have five times more CLs than seizure-free patients



What causes GM pathology?

Why GM damage accelerates in progressive MS?

Grey matter volume in a large cohort of MS patients: relation to MRI parameters and disability

Multiple Sclerosis Journal
0(00) 1–9
© The Author(s) 2011
Reprints and permissions:
sagepub.co.uk/journalsPermissions.nav
DOI: 10.1177/1352458511404916
msj.sagepub.com



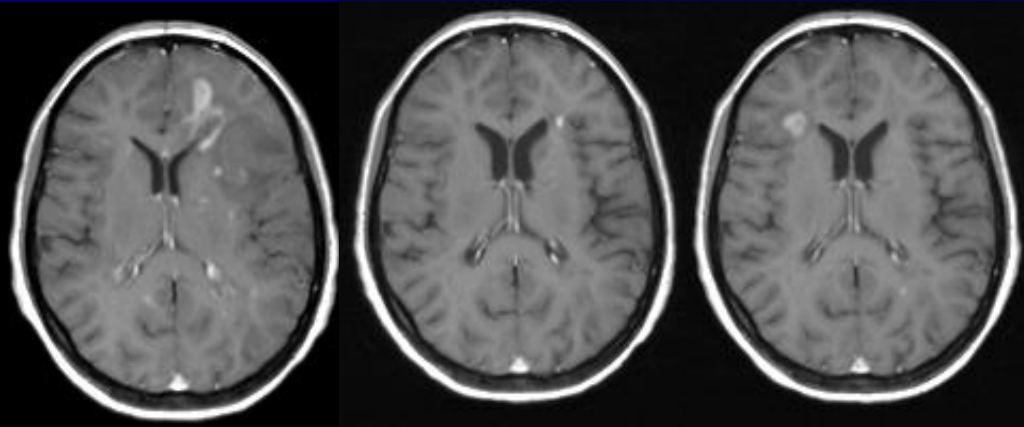
Stefan D Roosendaal¹, Kerstin Bendfeldt², Hugo Vrenken¹,
Chris H Polman¹, Stefan Borgwardt², Ernst W Radue²,
Ludwig Kappos², Daniel Pelletier³, Stephen L Hauser³,
Paul M Matthews^{4,5}, Frederik Barkhof¹ and Jeroen JG Geurts¹

Table 2. (Multiple) linear regression for NGMV, statistically adjusted for centre

	Linear regression			Multiple linear regression ^a		Multiple linear regression ^b	
	Beta	p-value	Adjusted R ²	Beta	p-value	Beta	p-value
Age	-0.52	<0.001	0.47	-0.44	<0.001	-0.43	<0.001
Sex (female: 0; male:1)	-0.17	<0.001	0.23	-0.18	<0.001	-0.16	<0.001
Disease duration	-0.4	<0.001	0.36	-0.1	<0.001	-0.1	<0.001
LogT2LV	-0.38	<0.001	0.34	-0.27	<0.001	-	-
LogT1LV	-0.39	<0.001	0.36	-	-	-0.27	<0.001
NWMV	0.14	0.001	0.21	-	>0.1	-	>0.1



Ongoing axonal loss is not exclusively and directly dependent on inflammation



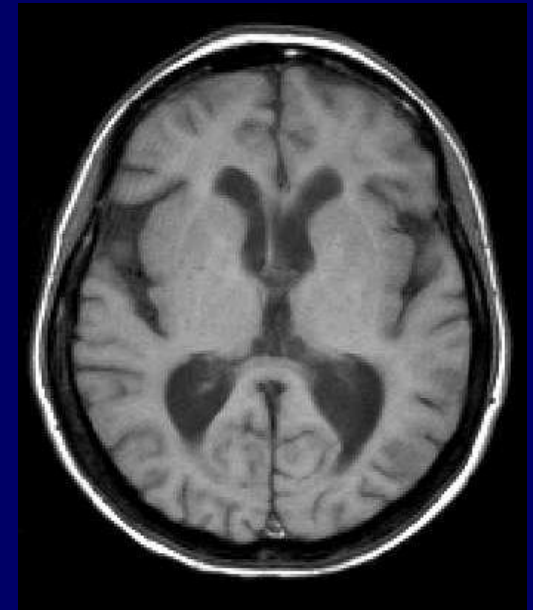
Month 1

Month 2

Month 3



?





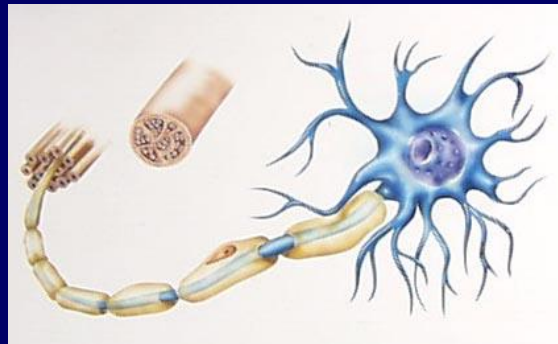
Delayed Neuroaxonal Loss

Demyelination

Altered glial biology

Glutamate Toxicity

Reduction of trophic factors



Ion-channel alterations

Mythochondrial dysfunction



Summary

Conventional MRI lacks pathological specificity for detecting and monitoring neurodegeneration

NAA level is a specific marker of neuro-axonal integrity and viability

Gray matter lesions and atrophy occur since the early stage of the disease, have clinical relevance and prognostic value

GM lesion visualization and measure of GM atrophy provide potential markers for monitoring neuroprotective treatments



Acknowledgments

Center for Biomedical Imaging NYU

Lazar Fleysher

Donatello Arienzo

Guillaume Madelin

Glyn Johnson

Dan Sodickson

Graham Wiggins

Ryan Brown

James Babb

Hina Jaggi

Department of Neurology NYU

Joseph Herbert

CGD Center for MS at MSSM

Fred Lublin

Aaron Miller

Stephen Krieger

Siemens Medical Solutions

Niels Oesingmann

Bernd Stoeckel

NIH grants: RO1 NS051623



Obtaining CME Credit

- If you would like to receive CME credit for this activity, please visit:

<http://www.pesgce.com/PVAsummit2011/>

- This information can also be found in the Summit 2011 Program on page 8.