CCSVI and MRI Outcomes in MS

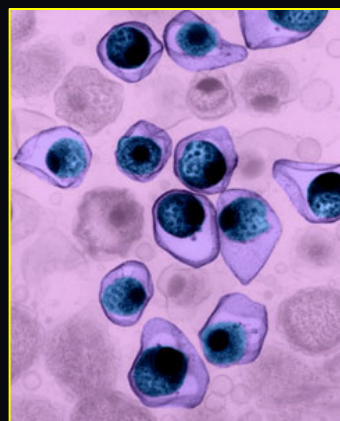
Robert Zivadinov, MD, PhD
The Jacobs Neurological Institute & Baird MS Center
Director, Buffalo Neuroimaging Analysis Center
Associate Professor of Neurology
University at Buffalo, State University of New York

BNAC Buffalo Neuroimaging Analysis Center

JACOBS NEUROLOGICAL INSTITUTE

University at Buffalo The State University of New York

Potential Triggers for Multiple Sclerosis



Genetic predisposition

Infectious agent → Genetic predisposition ← Environmental factors

↓

Abnormal immunologic response → **MS**

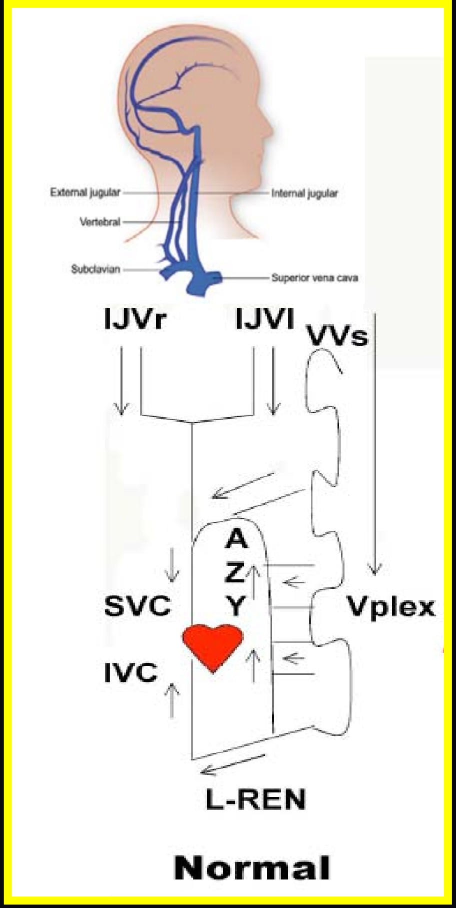
MS = multiple sclerosis

Gilden DH *Lancet Neurol* 2005;4:195-202, Noseworthy et al. *N Engl J Med* 2000;343:938

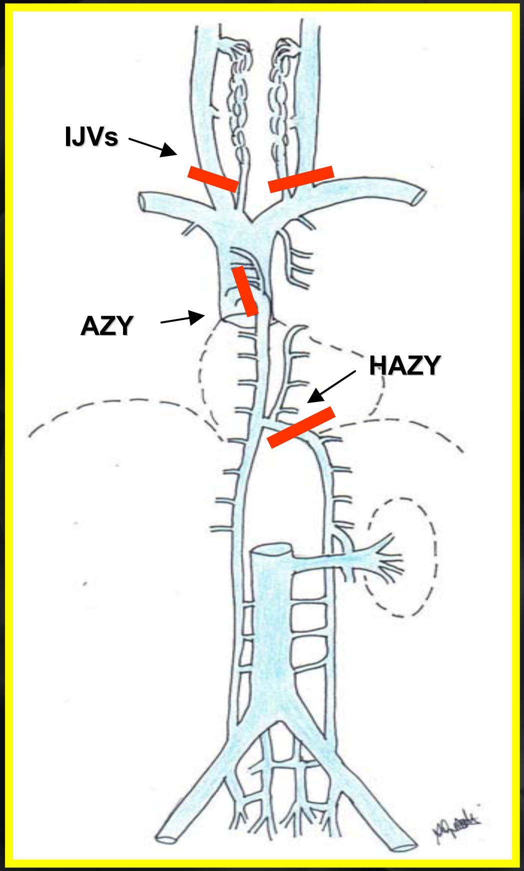
MS a Vascular Disease?

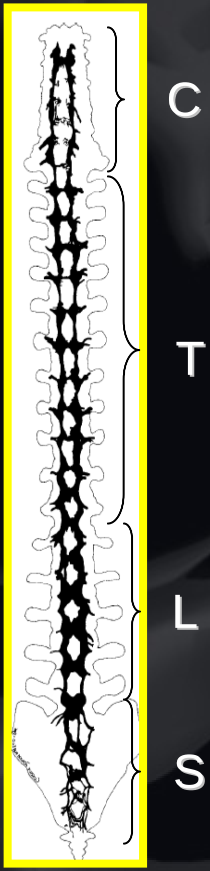
- A vascular pathogenesis for MS was suggested long ago
- The extent of microvascular abnormalities and their relationship to lesions has been difficult to assess until the recent advancements in MRI
- Ultra-high field MRI has become a tool for assessing vascular involvement in MS lesions
- Recent studies show perivenous association of MS lesions on high-contrast 7T susceptibility-sensitive MRI in MS patients

Chronic Cerebrospinal Venous Insufficiency (CCSVI) and Multiple Sclerosis



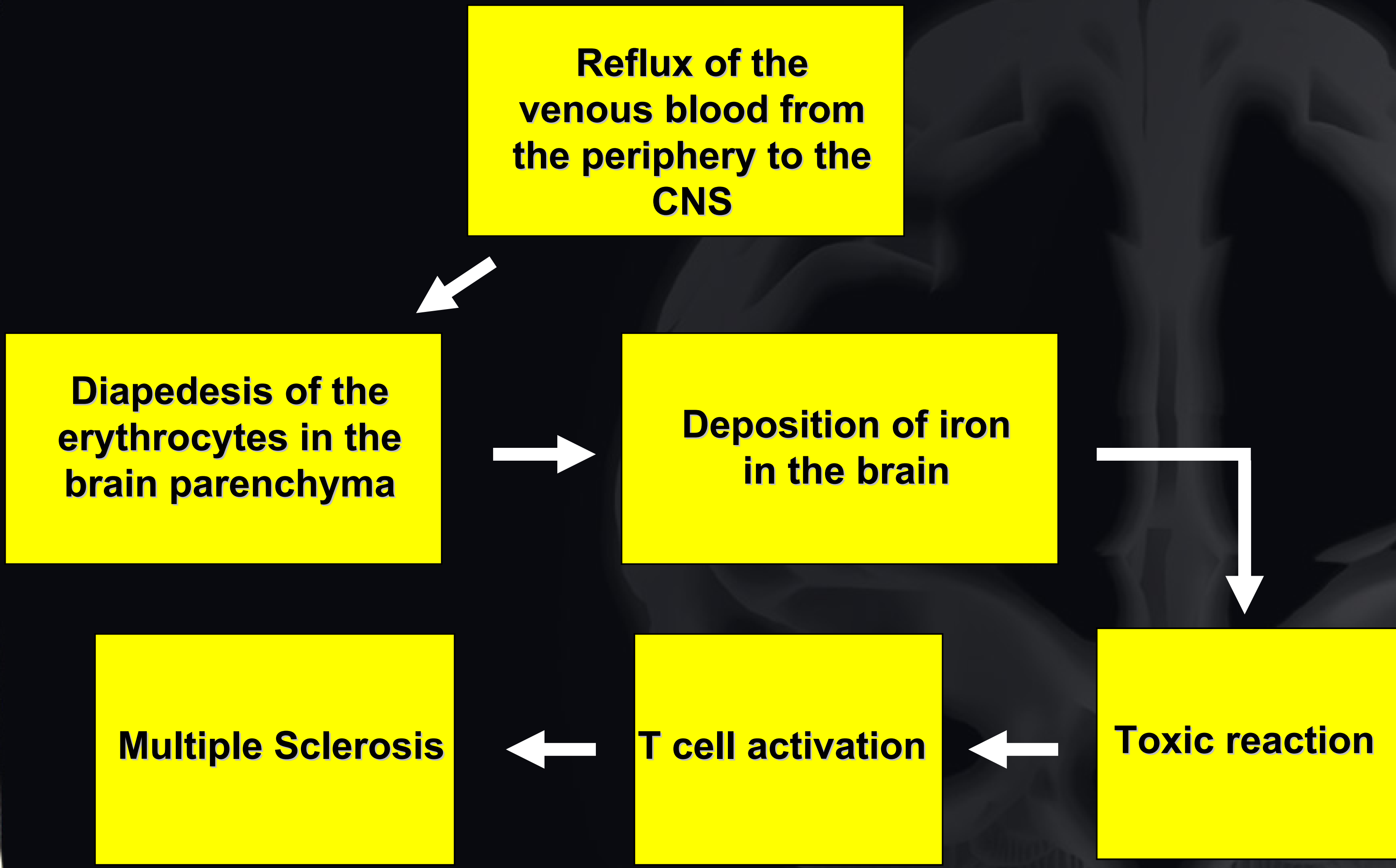
CCSVI →





Zamboni et al. JNNP, 2009 **Zamboni et al. JNS, 2009** **Zamboni et al. J Vasc Surg, 2009**

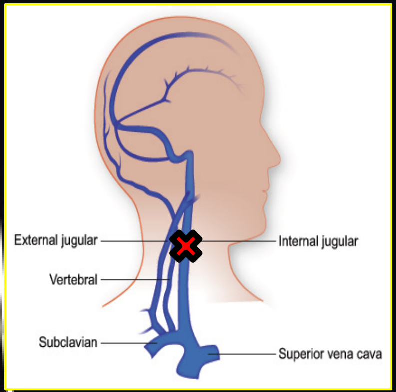
Hypothesis of Pathogenesis of CCSVI and MS



Potential Triggers for Multiple Sclerosis

Infectious agent

Genetic predisposition



CCSVI

Iron deposition

Environmental factors

Abnormal immunologic response and neurodegeneration

MS

MS = multiple sclerosis

Adapted from Gilden DH *Lancet Neurol* 2005;4:195-202, Noseworthy et al. *N Engl J Med* 2000;343:938

Susceptibility Weighted Imaging *

- 3D gradient echo with magnitude and phase image
- High resolution to reduce conventional spin dephasing
- Fully flow compensated in 3 dimension
- Modifying the contrast in the magnitude image using phase mask
- mIPping the images to create an angiographic effect (venography)

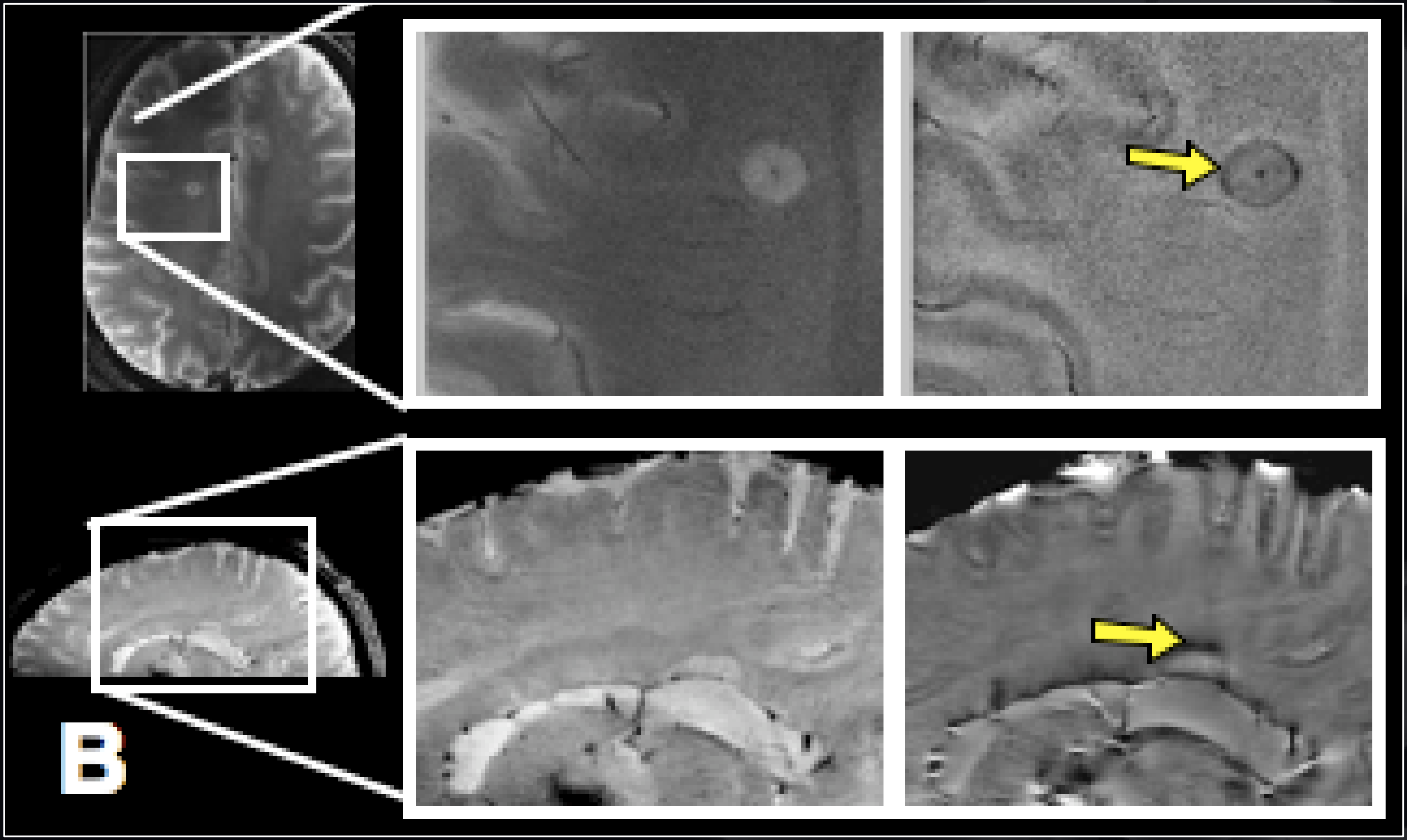
Magnitude

Phase

mIP

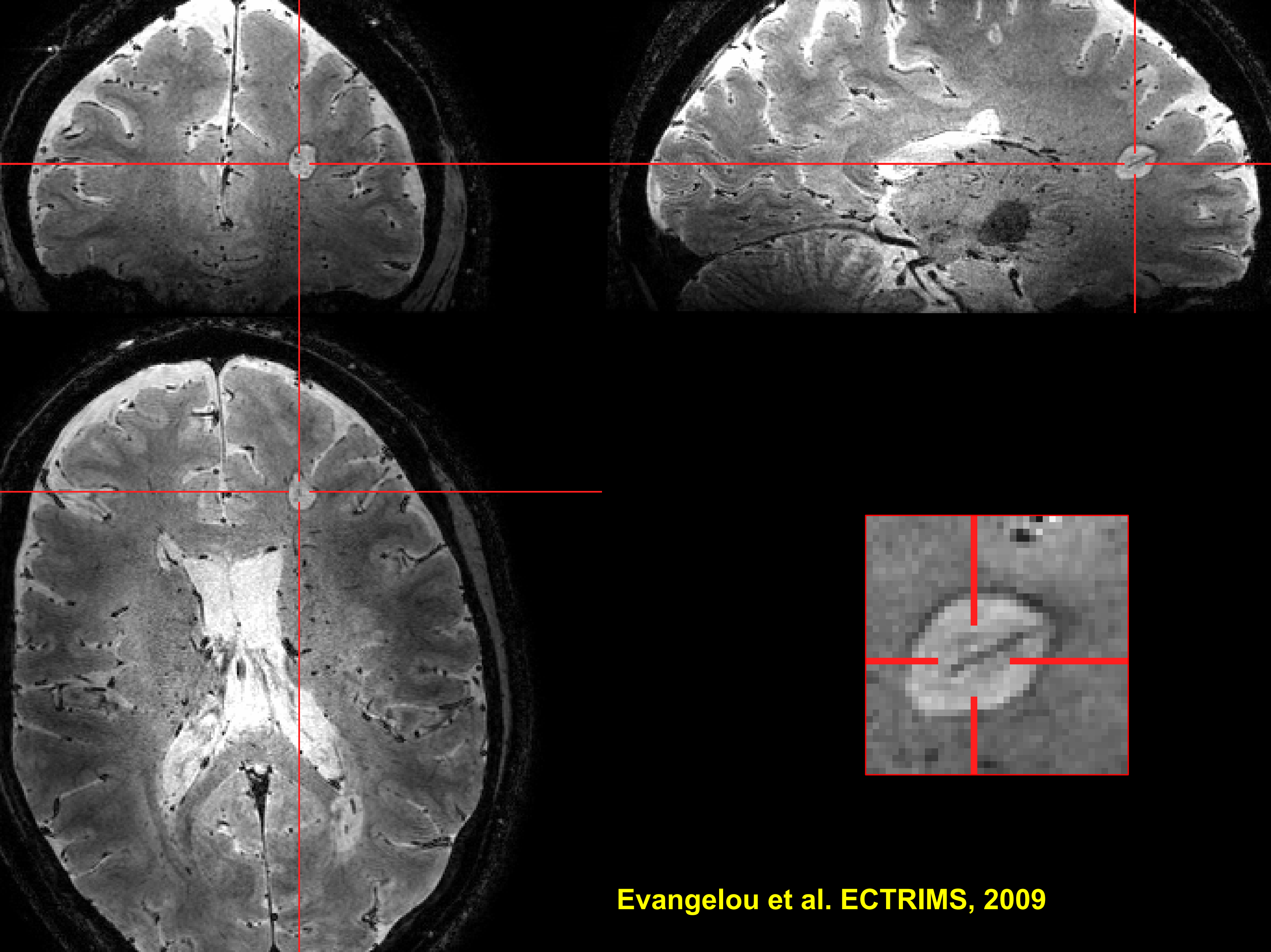
* Haacke EM 2004, MRM

Phase Imaging of MS at 7T

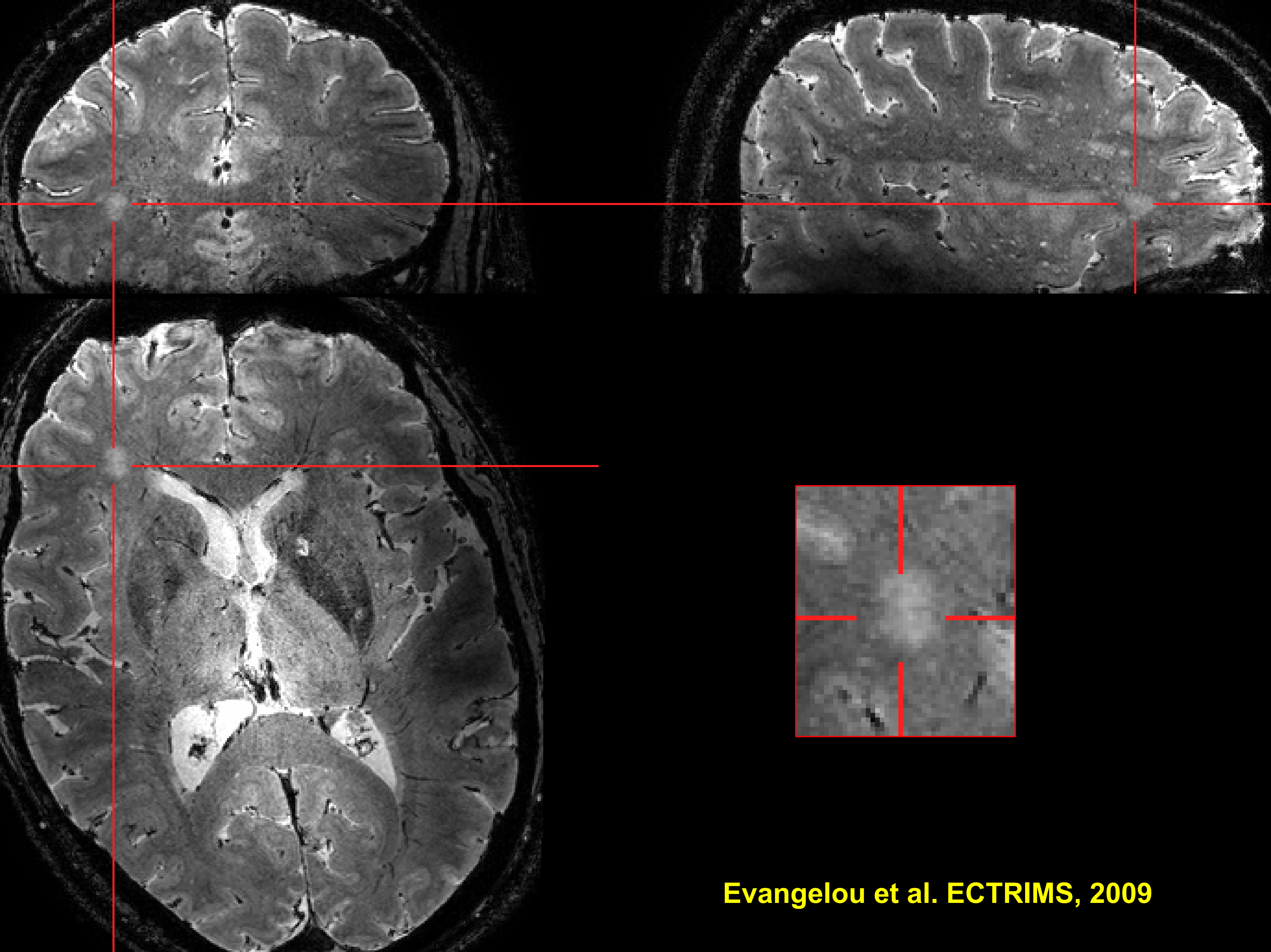


Magnitude images   Phase images

Hammond et al. Ann Neurol, 2008



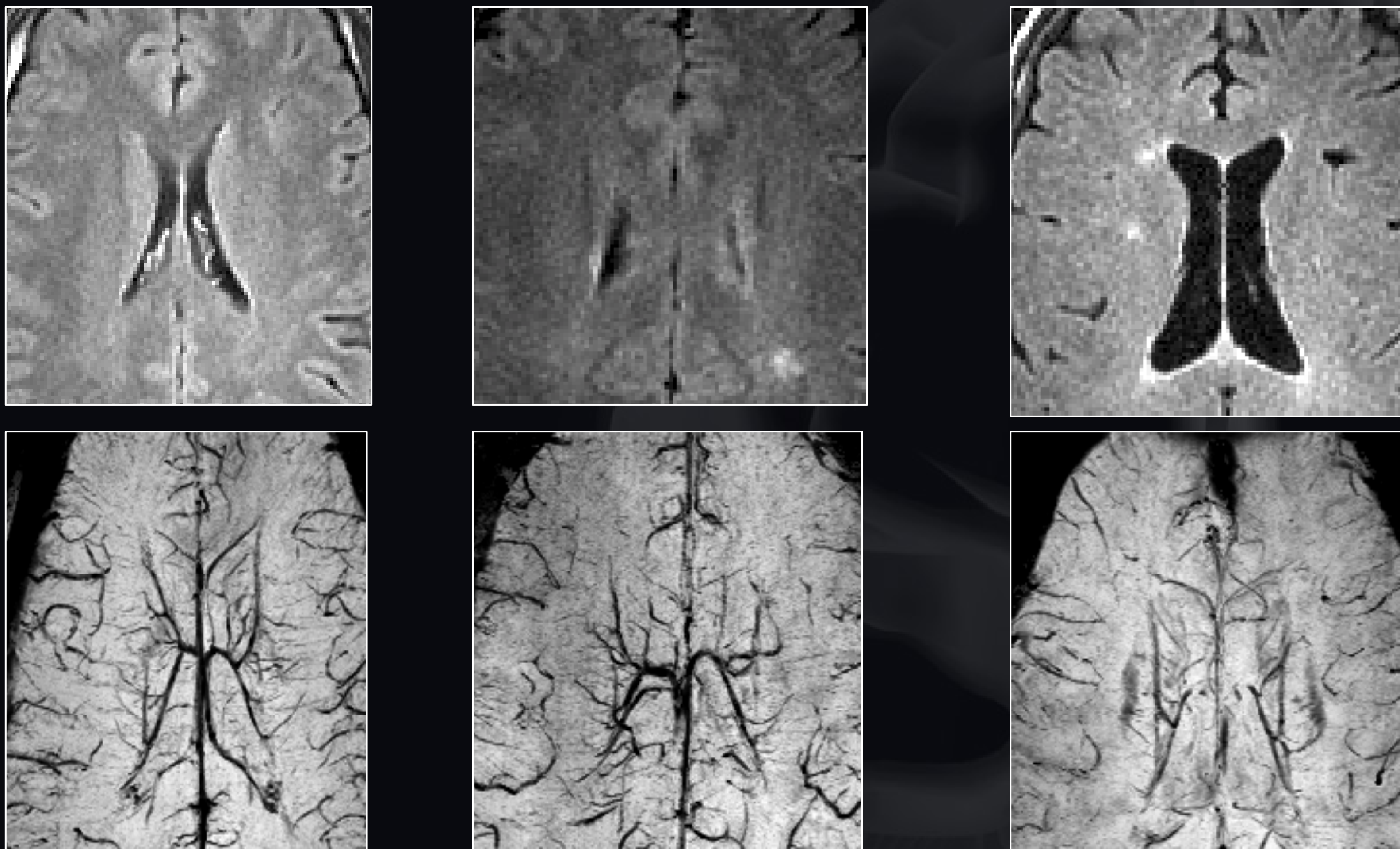
Evangelou et al. ECTRIMS, 2009



Evangelou et al. ECTRIMS, 2009

SWI in Multiple Sclerosis and Healthy Controls

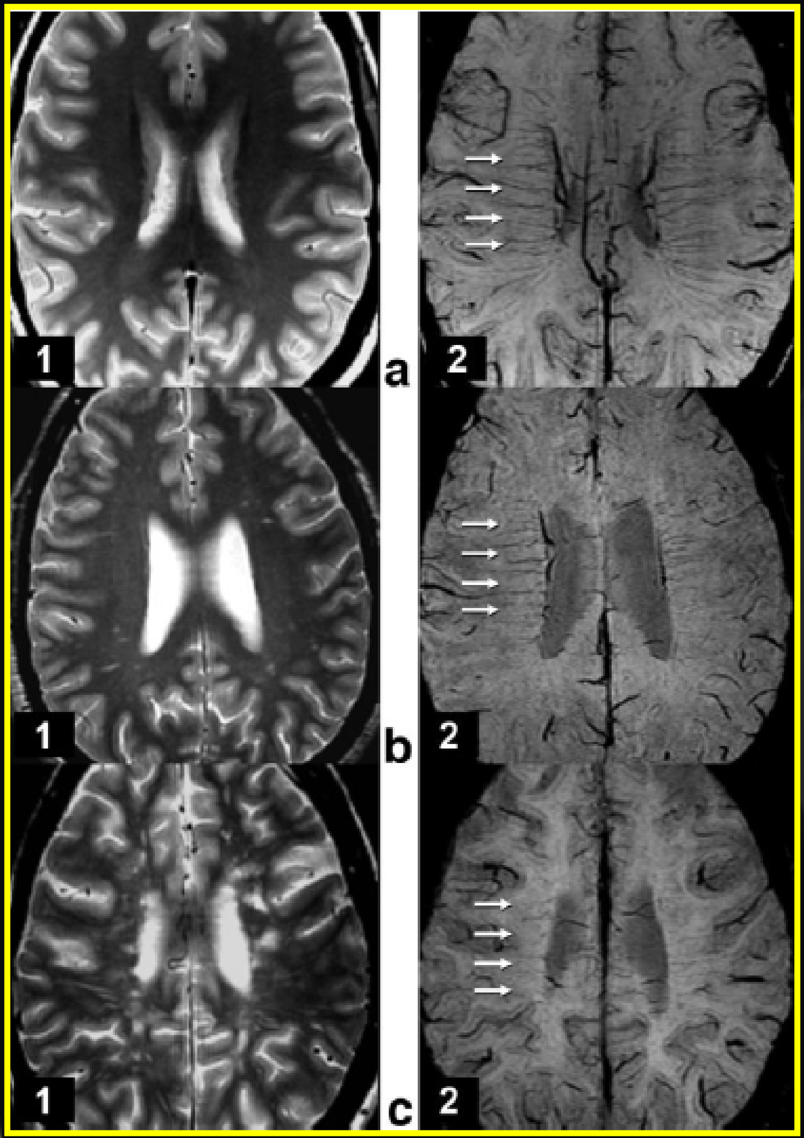
- ↓ oxygen utilization due to tissue destruction → less deoxyhemoglobin in the venous blood ?
- Occlusion of vessels ?

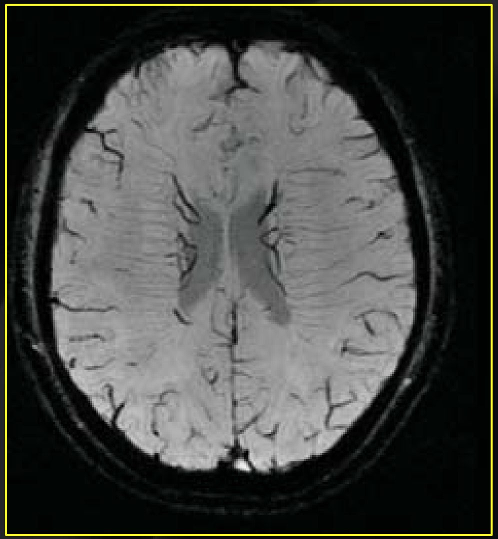


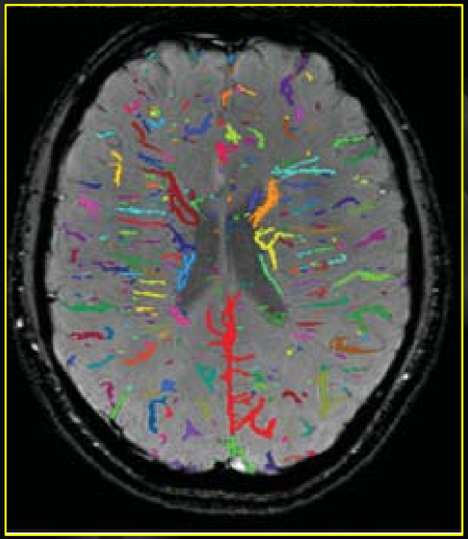
HC | RRMS (EDSS 2.0) | RRMS (EDSS 4.0)

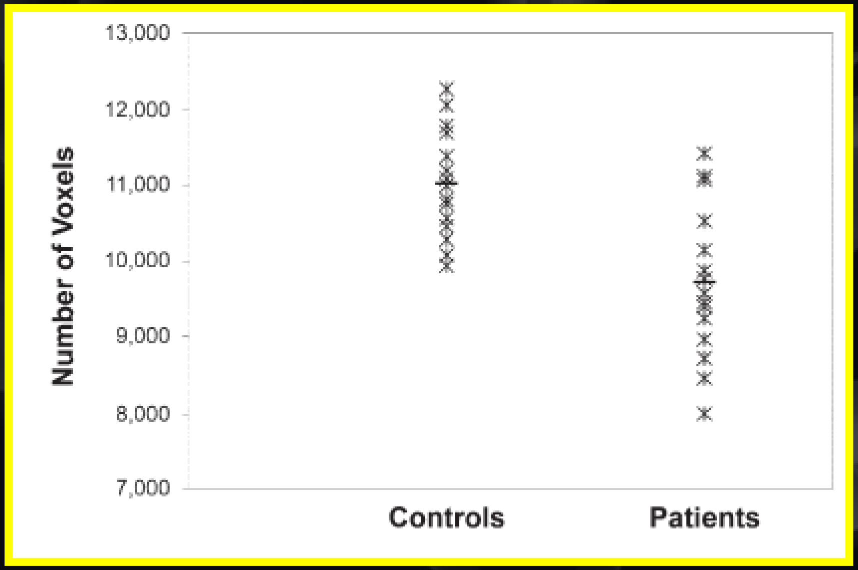
Schirda et al. AAN, 2009

Diminished Visibility of Cerebral Venous Vasculature in MS by SWI at 3.0 Tesla



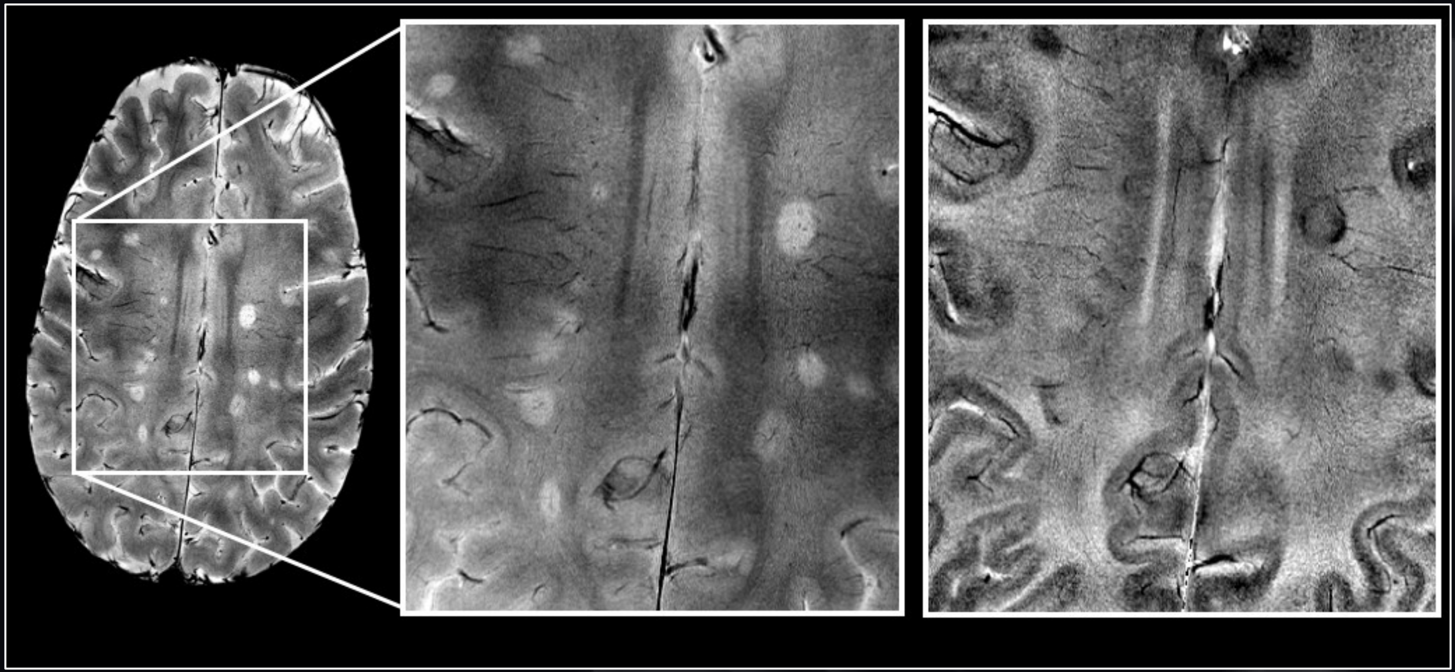






Ge et al. JMRI, 2009

Phase Imaging of MS at 7T

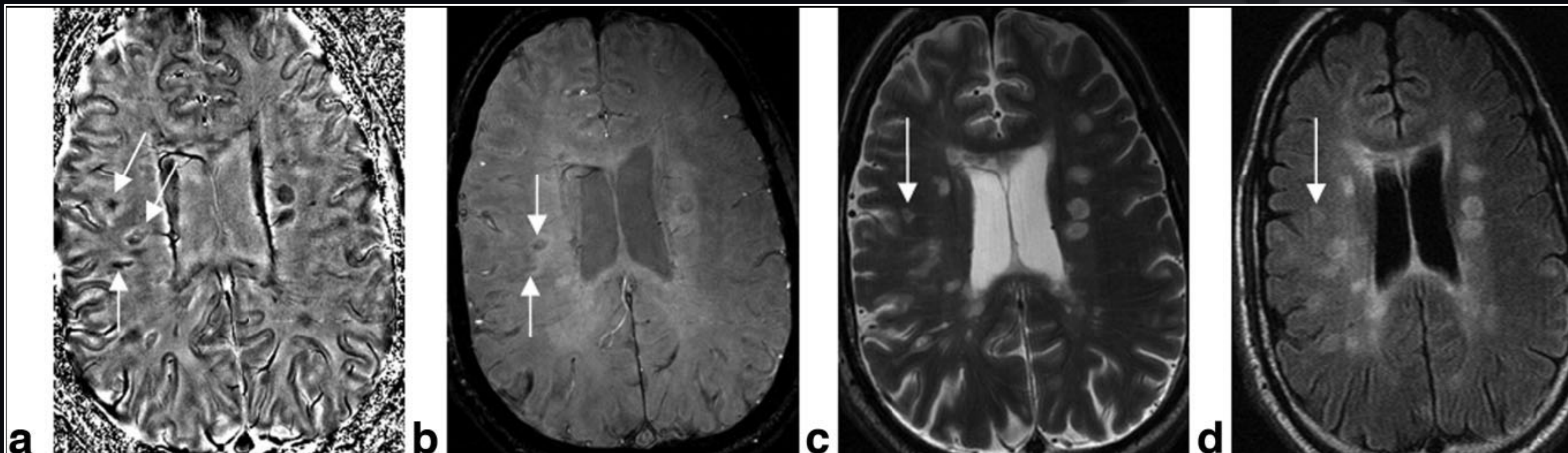


- Phase images of demyelinating lesions highlighted:
- periphery of lesions, the site of iron-rich macrophages*
- penetrating vessels in 70% of lesions
- 30% more lesions than seen in magnitude

- *Phase provides a novel MR contrast for studying neurodegeneration, one sensitive to the presence of iron.*

Hammond et al. Ann Neurol, 2008

Focal Iron Deposition in MS and SWI



Lesion Counts for 14 Patients at 1.5 T

	T2	T2-FLAIR	FLAIR	SWI Only	Total
Seen on SWI	30	30	3	78	141
Not seen on SWI	18	27	3		48
Total	48	57	6	78	189

Table 6
Lesion Counts for Seven Patients at 3 T

	T2	SWI Only	Total
Seen on SWI	38 p + 32 m	20	90
Not seen on SWI	21		21
Total	91	20	111

m = magnitude, p = phase.

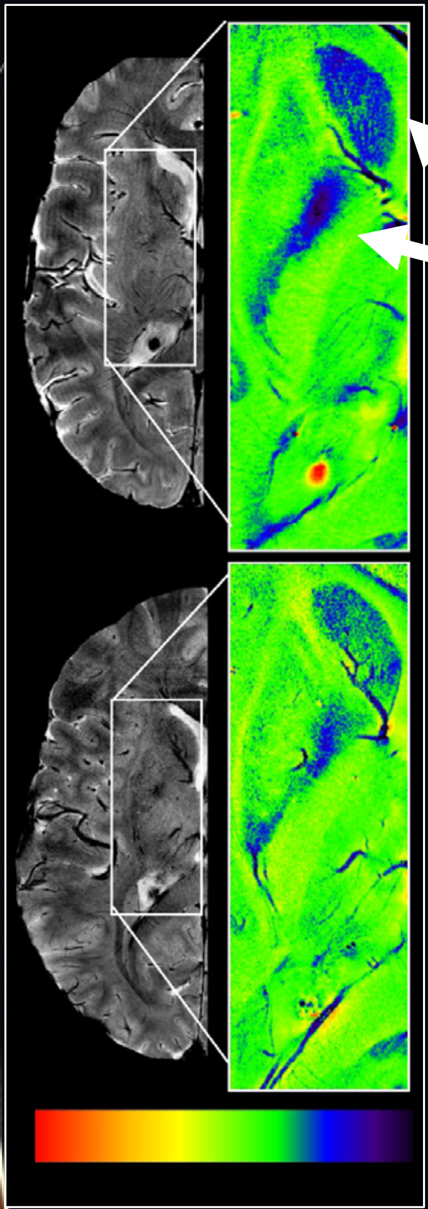
Table 7
Lesion Counts for Six Patients at 4 T

	T2	FLAIR	SWI Only	Total
Seen on SWI	33 p + 18 m	20	45	116
Not seen on SWI		6		6
Total	51	26	45	122

m = magnitude, p = phase.

Haacke et al. JMRI, 2009

Phase Imaging of MS at 7T



The basal ganglia in MS patients was more paramagnetic (P<0.05) than in controls, suggesting increased iron deposition:

Region	Patients Mean ± SD	Controls Mean ± SD	P
Putamen	4.29 ± 1.13 *(N = 14)*	2.82 ± 0.52 *(N = 14)*	<0.01
Globus pallidus	6.35 ± 1.67 *(N = 12)*	4.71 ± 1.24 *(N = 14)*	<0.01
Thalamus	3.03 ± 0.98 *(N = 13)*	2.49 ± 0.64 *(N = 14)*	<0.05
Head of caudate	5.85 ± 1.40 *(N = 14)*	4.84 ± 1.09 *(N = 15)*	<0.05
Splenium of corpus callosum	0.66 ± 0.15 *(N = 14)*	1.02 ± 0.43 *(N = 15)*	0.77

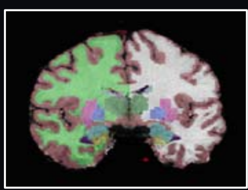
Hammond et al. Ann Neurol, 2008

[Left] Quantitative color-coded B0 field (phase) maps

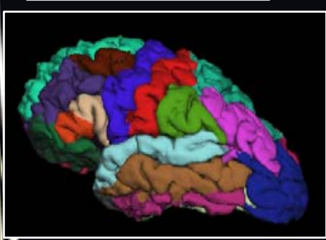
Regional Brain Atrophy Measures in MS

Normal control, 26 year old female

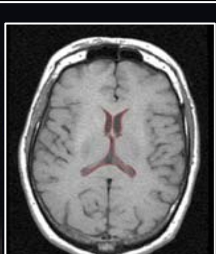
NBV diff -2.9%
NGMV diff -6.3%
NWMV diff -1.3%



Thalamus diff -20.1%
Caudate diff -3.1%
Putamen diff -18.3%
Hippocampus diff -8.8%

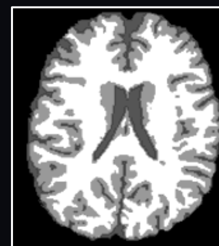


Postc diff -7.1%
Prec diff -8.7.%
CC diff -15%
EN diff -2.1%

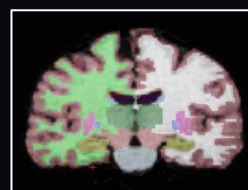


LVV diff +57%

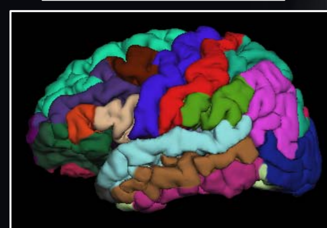
Clinically-isolated syndrome, 27 year old female; DD=1 year; EDSS=1.0



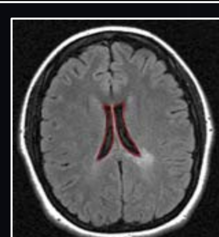
NBV diff -8.9%
NGMV diff -13.9%
NWMV diff -3.6%



Thalamus diff -32.9%
Caudate diff -20.8%
Putamen diff -31.2%
Hippocampus diff -20.4%

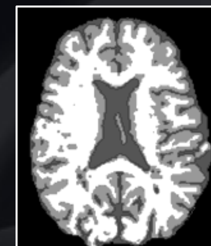


Postc diff -12.2%
Prec diff -11%
CC diff -25
EN diff -5.9

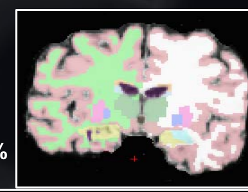


LVV diff +208.5%

Relapsing-remitting MS, 27 year old female; DD=7 years; EDSS=3.0

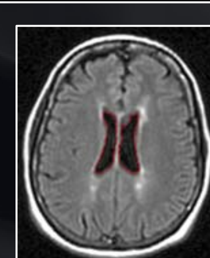


NBV diff -14.7%
NGMV diff -18.9%
NWMV diff -7.4%



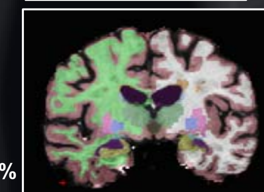
Thalamus diff -43.4%
Caudate diff -29.2%
Putamen diff -43.3%
Hippocampus diff -29.7%

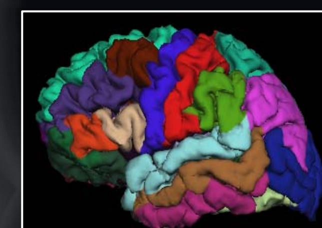
Postc diff -13.8%
Prec diff -14.8%
CC diff -27%
EN diff -13.7%

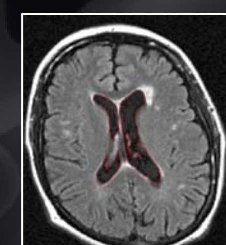


LVV diff +533%

Secondary-progressive MS, 34 year old female; DD=15 years; EDSS=5.5





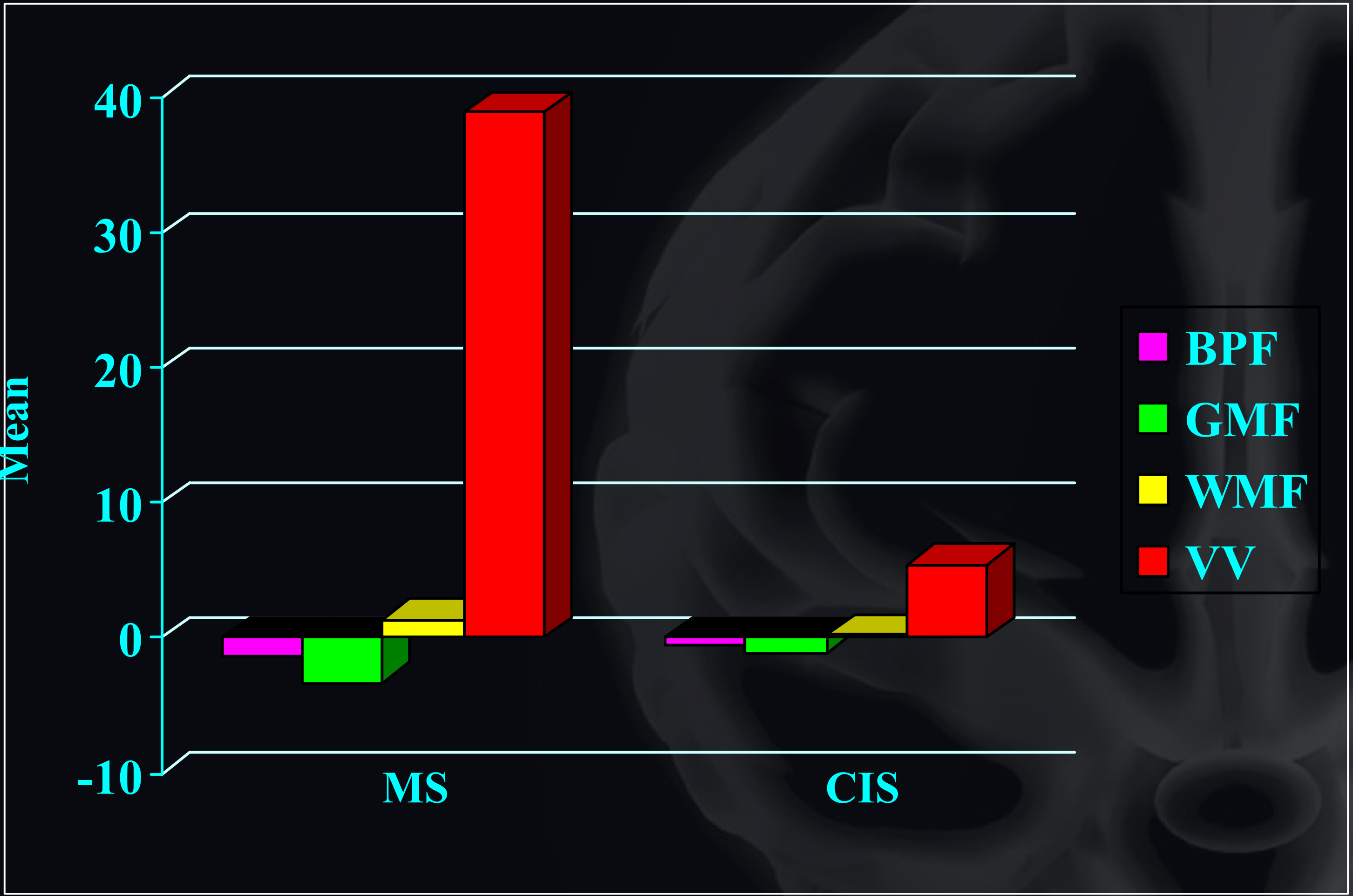


Benedict et al. JNNP, 2009

Ramasamy et al. J Neurol Sci 2009

-SIENAX, -LVV, 3VW, Feesurfer subcortical segmentation, Freesurfer ortical segmentation; Postc- Postcentral; Prec- Precentral; CC- Corpuscallosum; EN- Entorhinal: Colors: Light torquiose-Superior frontal, Violet-Rostral middle frontal, Dark brown-Caudal middle frontal, Dark green-Lateral orbitofrontal, Orange-Parstriangularis, Skin tone-Parsopercularis, Blue-Precentral, Crimson Red-Postcentral, Parrot green-suupramarginal,Dark torquoise-SuperiorParietal, Light blue-SuperiorTemporal, Light Pink-InferiorParietal, Light brown-Middle temporal, Dark Blue-Lateral Occipital, Dark pink-Inferior Temporal

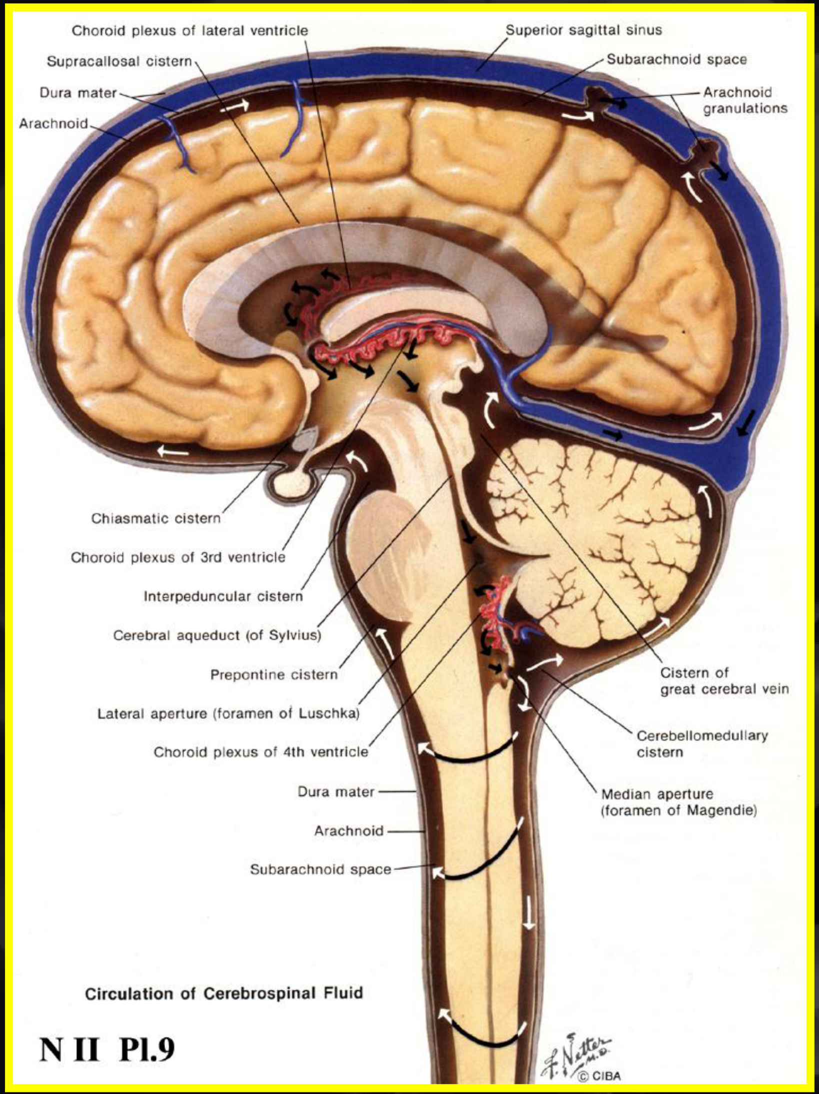
Brain Atrophy Changes over 3 Years



Dalton et al. Brain, 2004

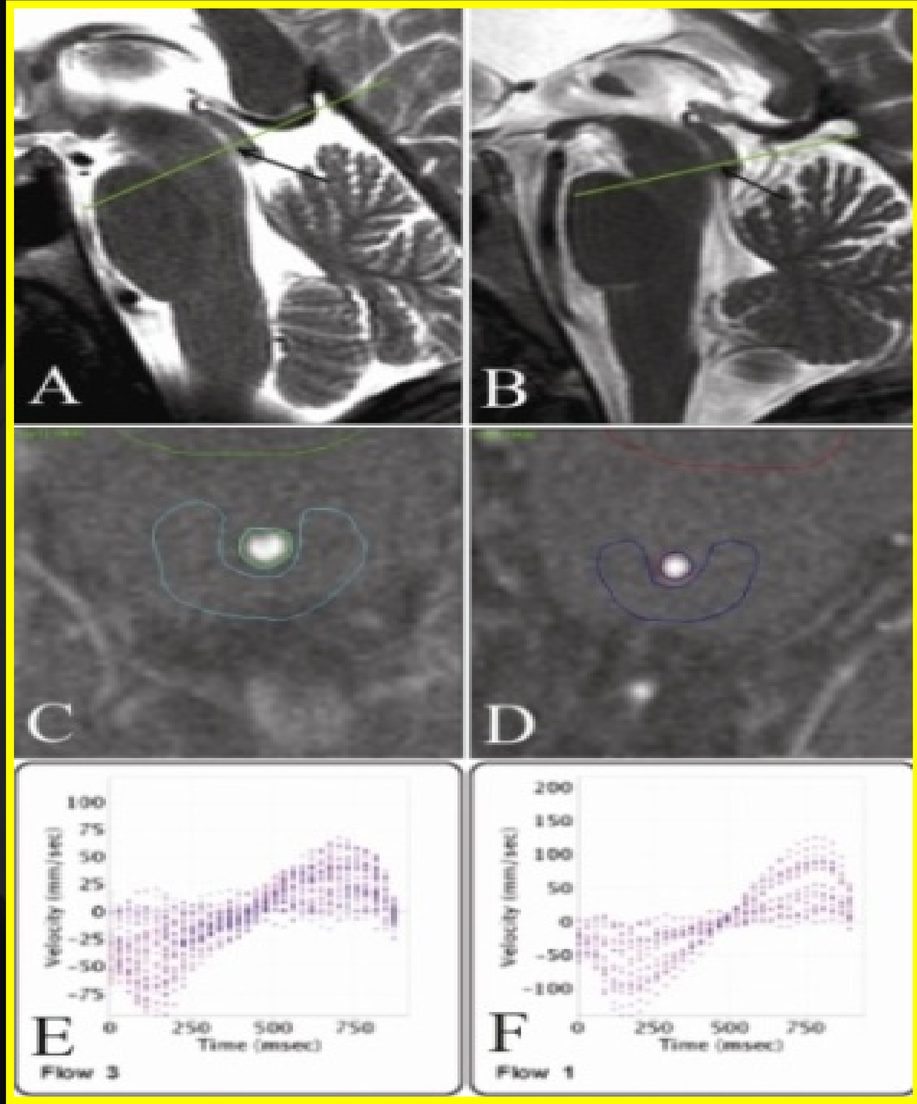
Venous Drainage & CSF Dynamics

- CSF dynamics is dependent on the venous drainage
- It is a balance:
  - between CSF ultra-filtration from veins of the lateral ventricles and
  - the CSF re-absorption into the venous system at the level of dural sinuses



Cine CSF Flow Imaging

- CSF flow measurement in the aqueduct of Sylvius for HC (left) and MS patient (right).
- A-B. Saggital T2 scans showing positioning for the MRI Cine acquisition. Slice orientation is perpendicular on the aqueduct.
- C-D. Aqueduct and background ROIs drawn on the magnitude image.
- E-F. CSF velocity distribution within the aqueduct of Sylvius ROIs, for the 32 phases, calculated using the GE ReportCard software



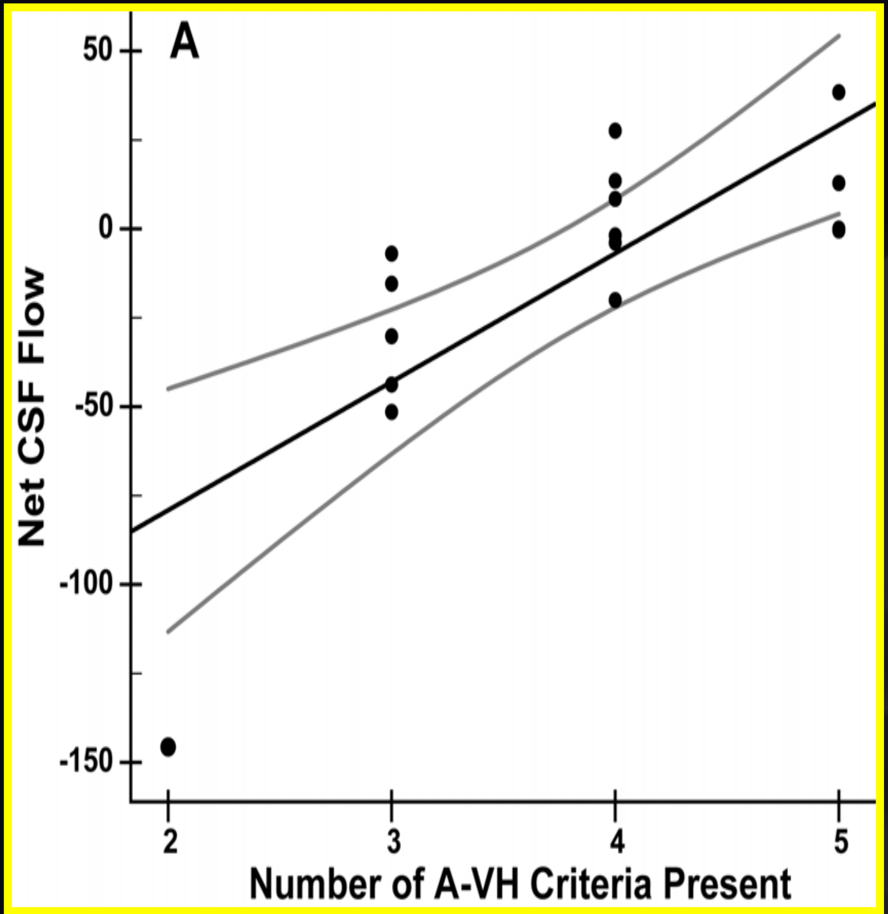
Zamboni et al. Funct Neurol, 2009; Schirda et al. AAN 2010; ISMRM 2010

Chronic Venous Insufficiency in MS (CVIMS Study)

- Cross-sectional study
- 16 consecutive RRMS patients and 8 age- and sex-matched HC
- Equal numbers from Bellaria Hospital, Bologna, Italy and from the Jacobs Neurological Institute, University at Buffalo, NY, USA
- Mean age 36.1±7.3 yrs, mean disease duration 7.5 ±1.9 yrs and median EDSS 2.5
- All 16 MS patients fulfilled the diagnosis of CCSVI (median VH=4, median VHISS=9) and none of the HC

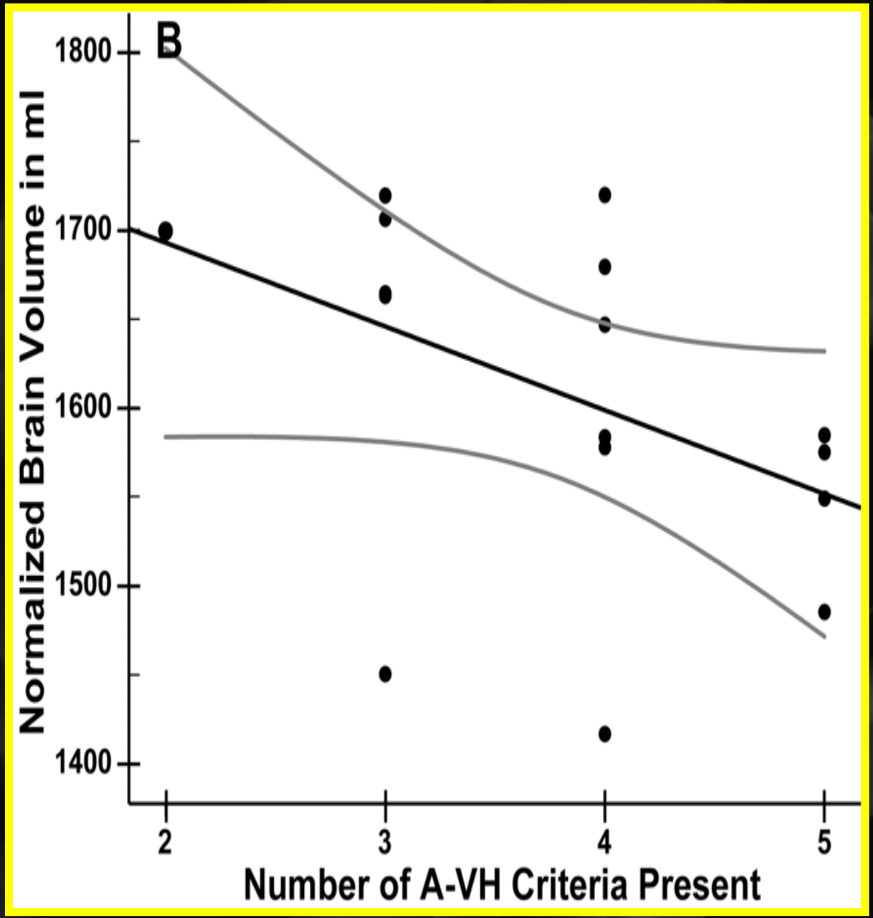
Zamboni et al. Funct Neurol, 2009; Zamboni et al. Int Angiolog (in press)

Lower Net CSF Flow and Lower Brain Volume in MS Patients is Related to CCSVI



Net CSF flow vs. total number of pathologic VHISS

Zamboni et al. Funct Neurol, 2009



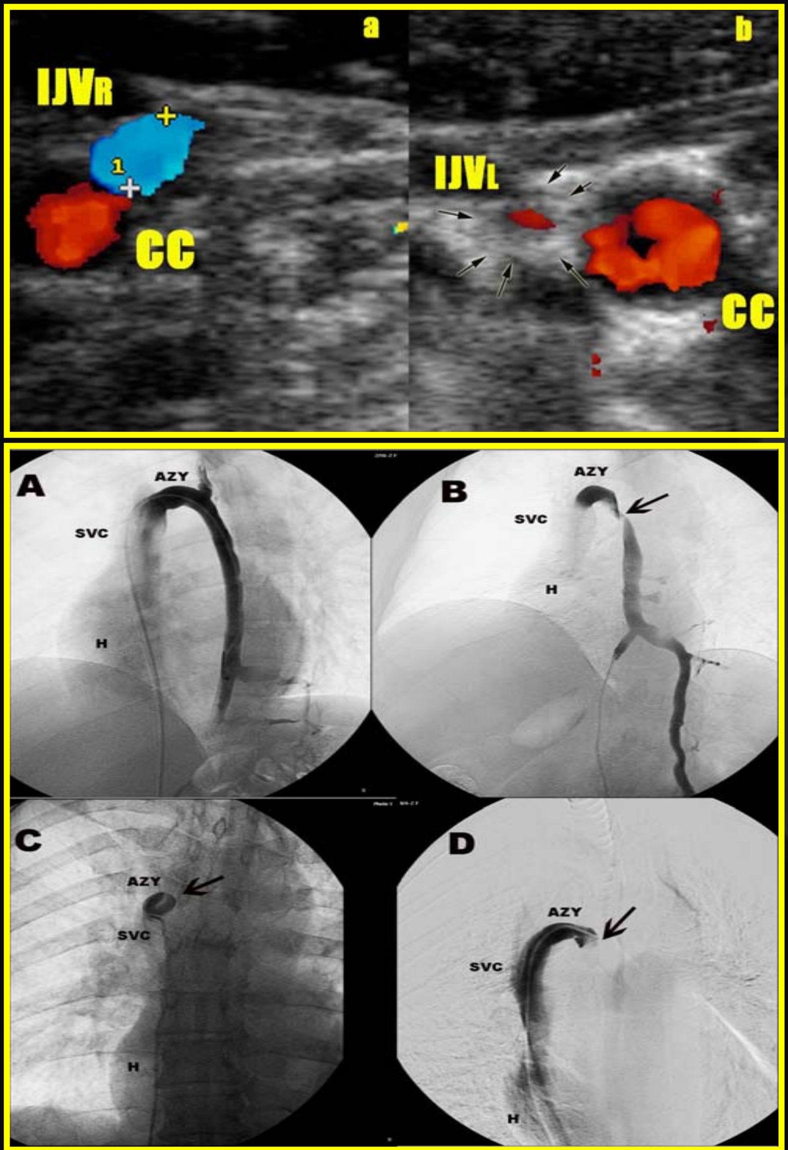
Brain Atrophy vs. total number of pathologic Venous Hemodynamic Criteria

Zamboni et al. Int Angiolog (in press)

Diagnosis of CCSVI

"Vascular picture characterized by combined stenosies of the principal pathways of extracranial and extravertebral venous drainage"

Venous Hemodynamic (VH) Criteria for CCSVI in MS



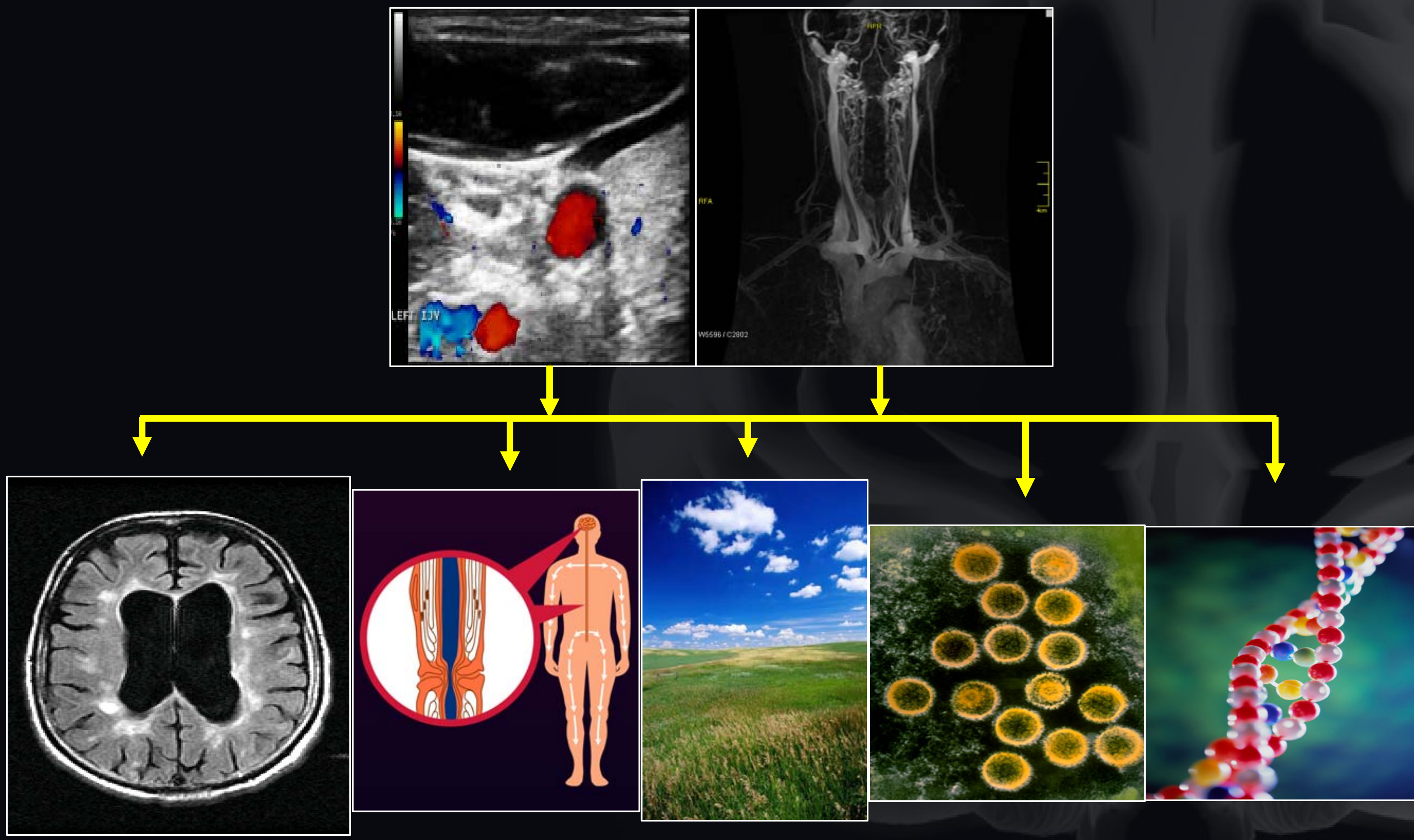
- **Criterion 1**: Reflux in the IJVs and/or in the vertebral veins (VVs) assessed in both sitting and supine posture
- **Criterion 2**: Reflux in the deep cerebral veins (DCVs)
- **Criterion 3**: B-mode detection of stenosis in the IJVs in the form of annulus, webs, septum, or malformed valves
- **Criterion 4**: Absence of Doppler signal in the IJV and/or in the VVs
- **Criterion 5**: The presence of a negative difference in the cross sectional area (CSA) of the IJV
  - **VH (0-5; ≥2 is considered pathologic)**

- VHISS (Venous Hemodynamic Insufficiency Severity Score 0-16)

Zamboni et al. JNNP, 2009

Zamboni et al. Funct Neurol, 2009

Combined Transcranial and Extracranial Venous Doppler Evaluation in Multiple Sclerosis and Related Diseases (CTEVD study)



Zivadinov et al. AAN 2010

Study Population (1700 subjects)

50 Pediatric MS

300 Adult Healthy and Familial Controls

50 Pediatric Healthy and Familial Controls

900 Adult CDMS

500 RRMS

300 SPMS

50 PPMS

50 NMO

50 CIS

150 CNS Autoimmune-Vascular Disorders

SLE
PALP
Vascular

50 RIS

150 CNS Neurodegenerative Disorders

AD
PD
Epilepsy

Zivadinov et al. AAN 2010

Combined Transcranial and Extracranial Venous Doppler Evaluation in Multiple Sclerosis and Related Diseases (CTEVD study)

- Unblinding is planned in 3 different time frames:
  - 500 subjects - Jan 2010
  - 1000 subjects – Fall 2010
  - 1700 subjects – Spring 2011
- Current status as of Feb 1, 2010:
  - 500 subjects underwent examinations
  - Recruitment extended nation-wide (>13,000 MS pts on the waiting list)

Zivadinov et al. AAN 2010

Collaborators

- University of Buffalo
  - Bianca Weinstock-Guttman
  - David Hojnacki
  - Murali Ramanathan
  - Ralph Benedict
  - Frederick Munschauer
  - Colleen Miller
  - Kim Dressler
  - Dawn Lefevre
  - Karen Marr
  - Makki Elfadil
  - Claudiu Schirda
  - Cristopher Magnano
  - Cheryl Kennedy
  - Michelle Andrews
  - Justine Reuther
  - Christina Brooks
  - Kristin Hunt
  - Ellen Carl
  - Jennifer L. Cox
  - Michael G. Dwyer
  - Niels Bergsland
  - David Wack
  - Sara Hussein
  - Mari Heininen-Brown
  - Deepa. P. Ramasamy
  - Jackie Durfee
  - Laura Willis
  - Mariya Cherneva
  - Eve Salczynski

- University of Ferrara
  - Paolo Zamboni
  - Roberto Galleoti
  - Erica Menegatti
  - Anna M Malagoni
- Univeristy of Bologna
  - Fabrizio Salvi
  - Ilaria Bratolomei
- University of Pavia
  - Stefano Bastianello
  - Guy Poloni
- University of Alabama
  - Garry Cutter
- Wayne State University
  - Marck Haacke
- University of Barcelona
  - Alexandra Lopez

Thank You for Your Attention

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