Breakthroughs in Imaging Neurovascular Diseases such as Multiple Sclerosis: Technical Aspects, Clinical Ramifications and Understanding the Etiology of the Disease

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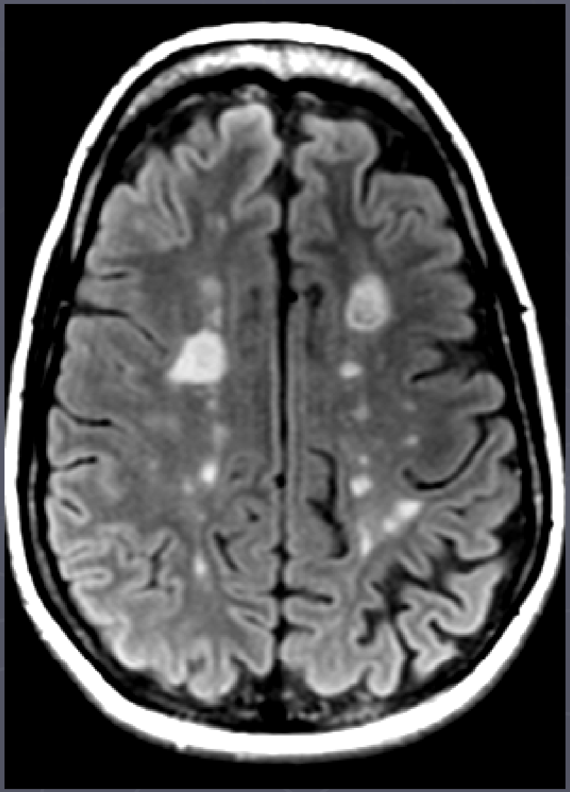
MULTIPLE SCLEROSIS

Facts about MS:

- Cause unknown…there is no cure
- 2 to 3 times more women than men
- The symptoms - mild to debilitating :
  - vision problems;
  - loss of balance and/or coordination,
  - extreme fatigue,
  - speech or memory failure;
  - muscle stiffness and paralysis.



MULTIPLE SCLEROSIS

In Canada: 

- 55,000-75,000 MS patients
- most common neurological disease affecting young adults
- **~1,000** new cases of MS diagnosed each year
- Economic impact > **$1 billion** annually
- **In the USA multiply by roughly 8!**

MULTIPLE SCLEROSIS

- Multiple Sclerosis (MS) was first recognized by J.M. Charcot in 1868

  - MS - scarring & hardening of the sheath around the nerves in the brain, spinal cord, and optic nerve

MULTIPLE SCLEROSIS

- 1903 – Borst et al recognize perivascular hemorrhages in lesions of MS patients
- 1916 - James Dawson explains further damage in MS
- **1935 - Tracey Putnam's animal studies confirm linkage to venous obstruction**
- 1958 - studies confirm linkage to immune system
- 1972 - MR imaging revolutionizes non-invasive diagnosis of disease
- 1987 – MR angiography becomes a clinical tool
- 1997 – SWI to image iron and the veins is invented
- **2009 – CCSVI is proposed by Dr. Zamboni**

CCSVI

Chronic cerebro-spinal venous insufficiency

Zamboni noted narrowing of the veins at the neck or spine was restricting blood flow and dangerous levels of iron were accumulating in the brain (65 case studies)

Outline

- Introduction to MRI
- Phase imaging and iron content
- Susceptibility weighted imaging applications
- Anatomy and flow of abnormal veins in MRI
- The CCSVI protocol and the NICE database

Magnetic Resonance Imaging: Listening to the music your body plays

- Proton MRI is very good at imaging the soft tissues in our body because of its high water content or spin density.
- We use a large magnet which in a sense acts like a giant speaker system where we can not only use the main field but play with the local fields that help create this music alluded to above.

Magnetic Resonance Imaging

Paul Lauterbur and Peter Mansfield won the 2003 Nobel Prize in Medicine for their pioneering work in MRI

Dr. Lauterbur Sir Mansfield

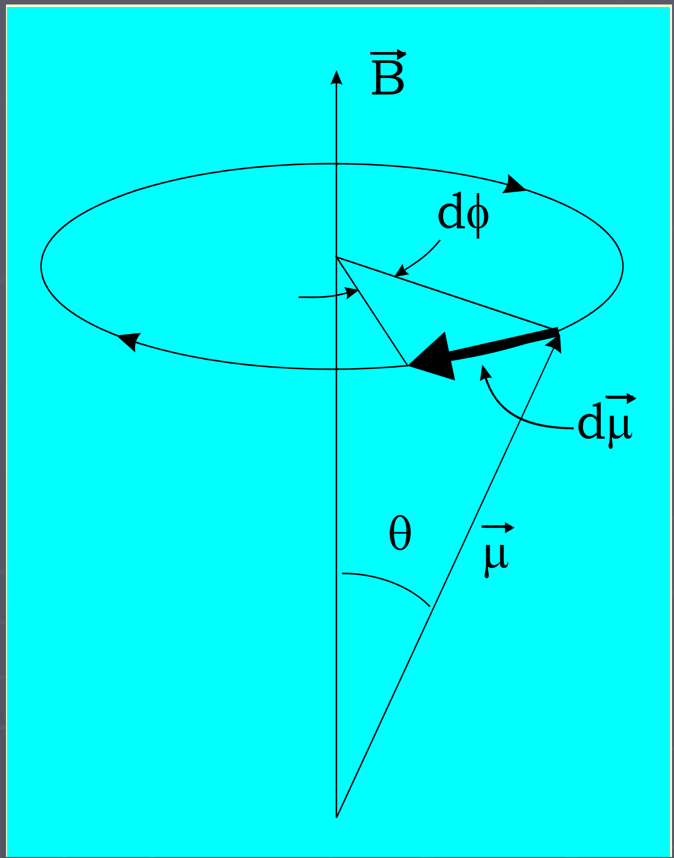
Basic MRI concepts

$\omega = \gamma * B$

B is the applied magnetic field

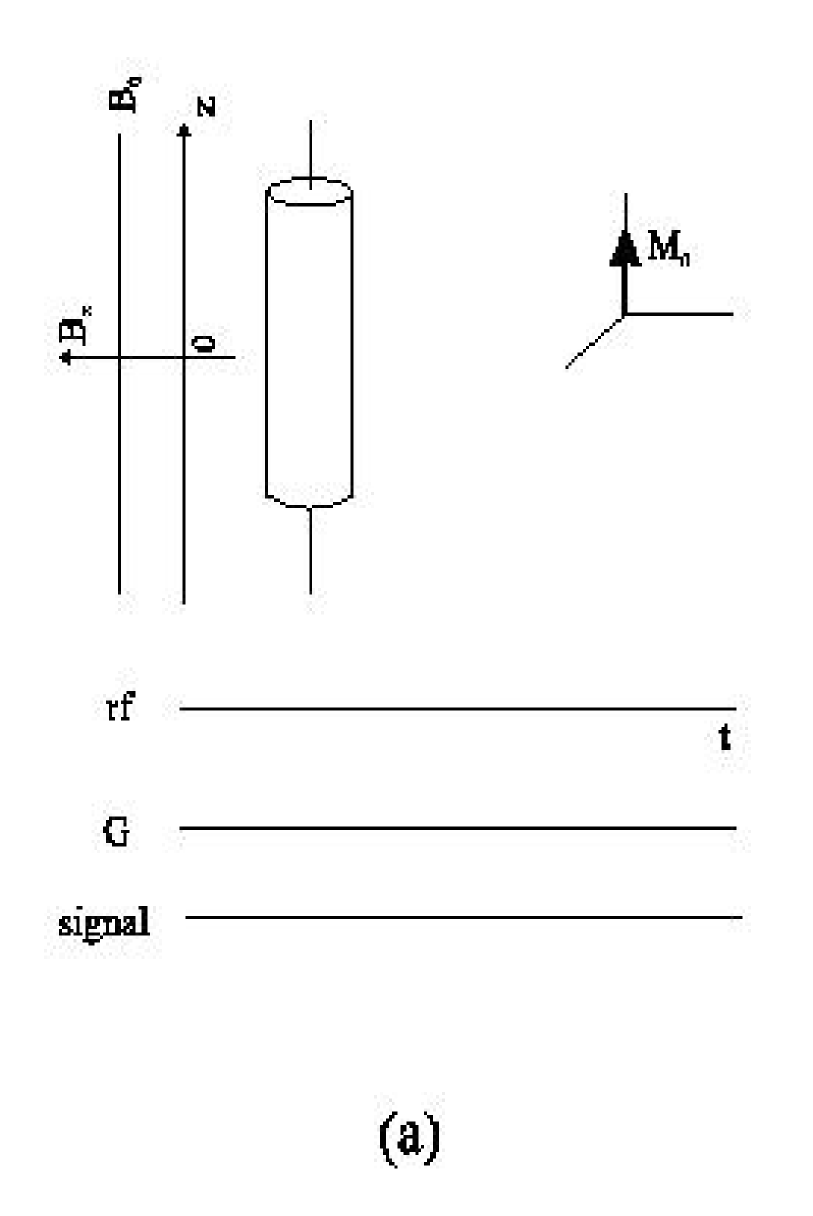
γ is the gyromagnetic ratio for the proton which is 2π*42.6 MHz/T

ω is the frequency



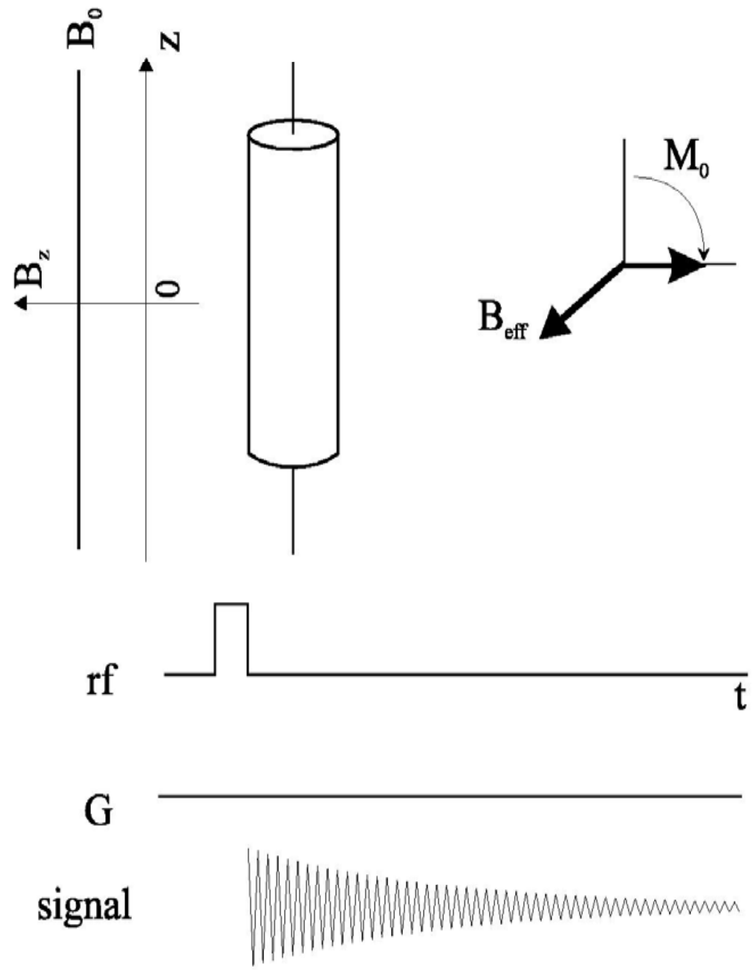
A cylindrical object in a constant magnetic field.

Its bulk magnetization lies parallel to the main field.



Applying an oscillating rf field along the x-axis rotates M_o from the z-axis into the transverse plane so that it lies along the y-axis.

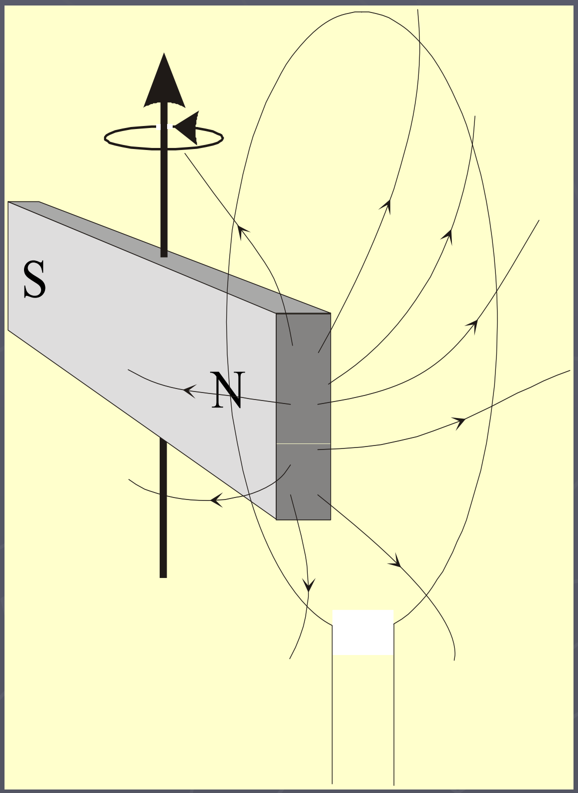
At this time, the rf field is turned off and the transverse magnetization precesses about the main field B_o.



(b)

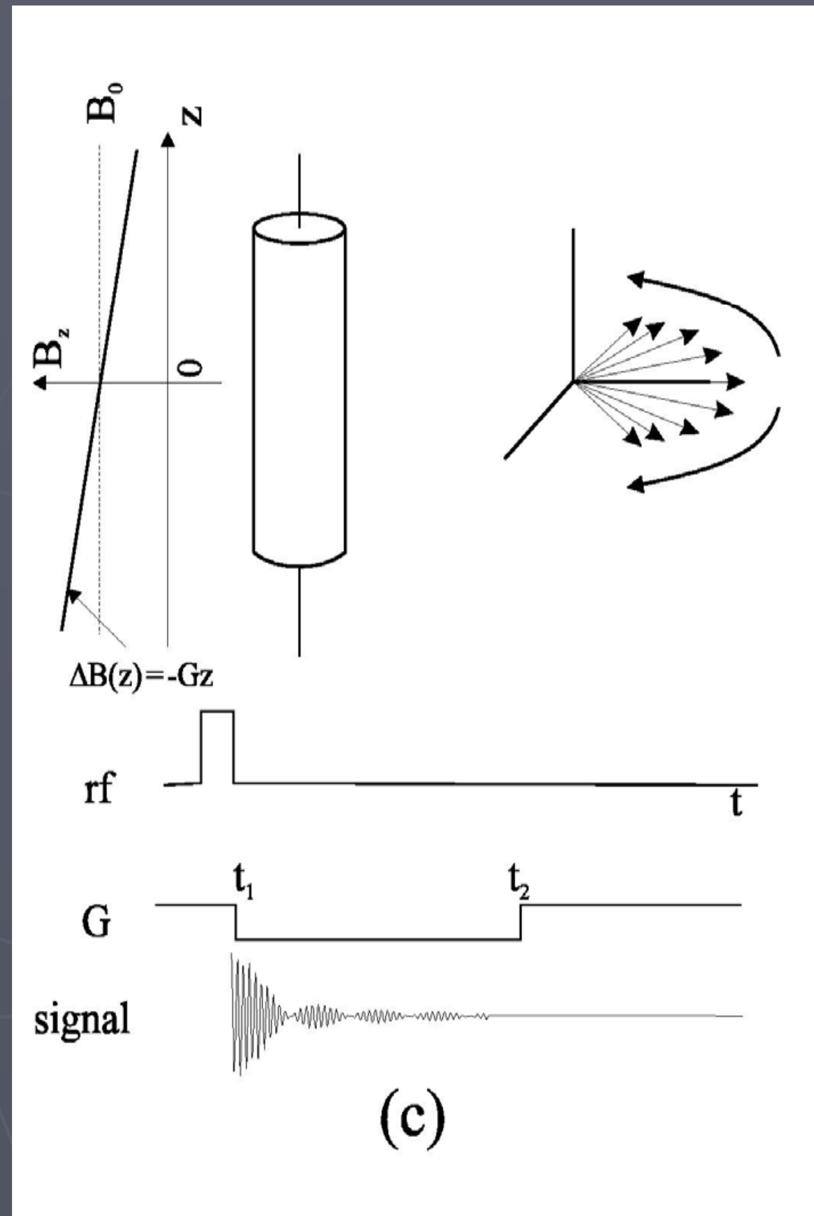
MR Signal Readout

The precessing transverse component induces a voltage in a coil which is placed so that it sees a changing magnetic flux as the spin magnetization sweeps across its surface.



By purposely adding a gradient field G, we can spatially distinguish the spins by their frequency content since now

$\omega(x) = 2\pi\gamma\,(B_o + Gx)$

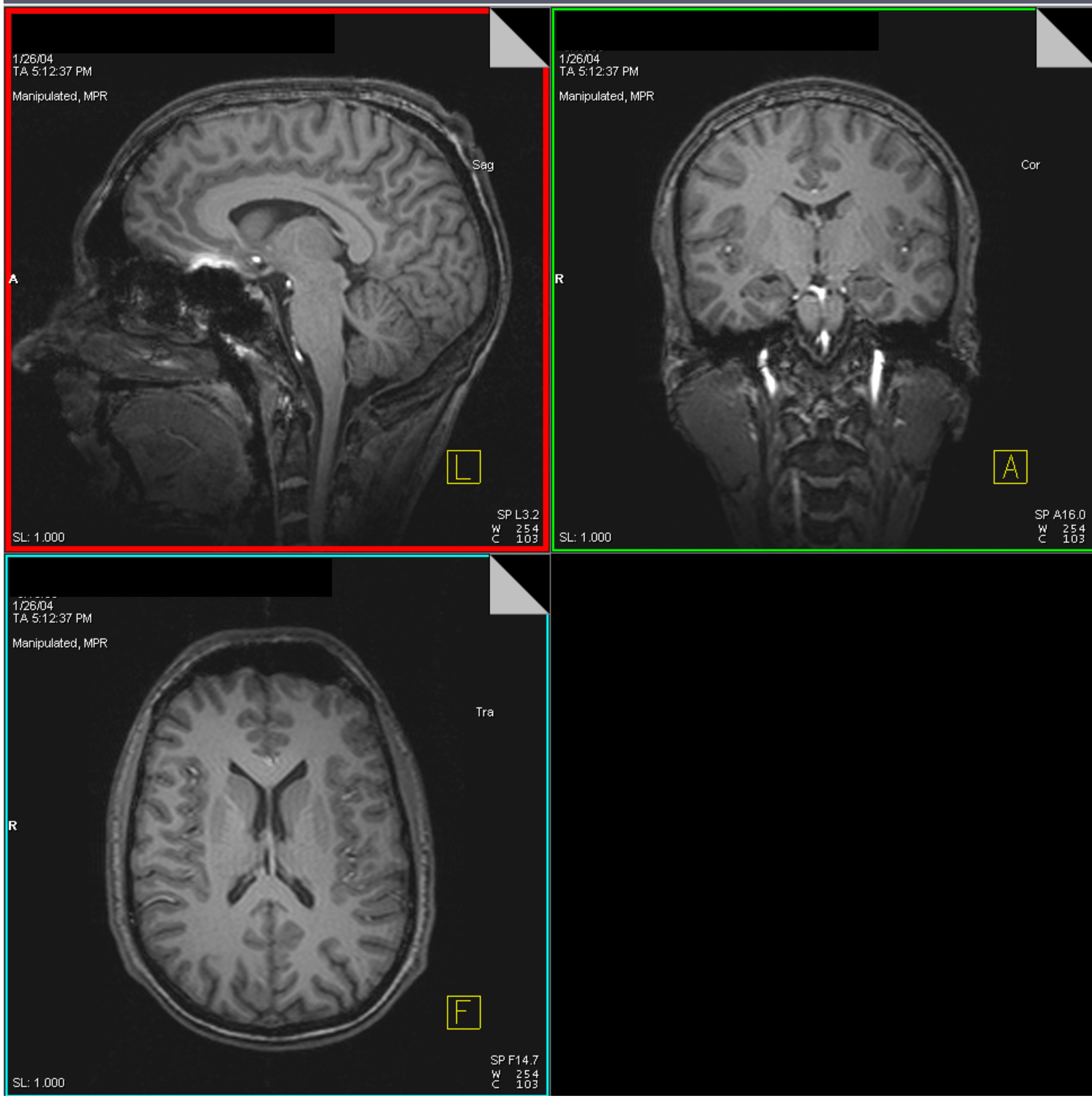


Rembrandt's 1632 "The Anatomy Lesson of Dr. Tulp"

"Our research efforts today create our own works of art."

The Cardiovascular MR Lesson

3D MP-RAGE



Structural Imaging:

- T1 3D MPRAGE
- 1.0 x 1.0 mm² in plane resolution
- 1 mm slice thickness
- 176 slices
- TE 5 ms
- TR(total) 2500 ms
- Flip angle: 12 °
- Bandwidth 200 Hz/Px
- Scan time: 10:32 min

MRA at 4T

resolution:
0.5mm x
0.5mm x
1.0mm

Phase dependence of B_o and TE

When B_o is not uniform, the spin density becomes a complex quantity:

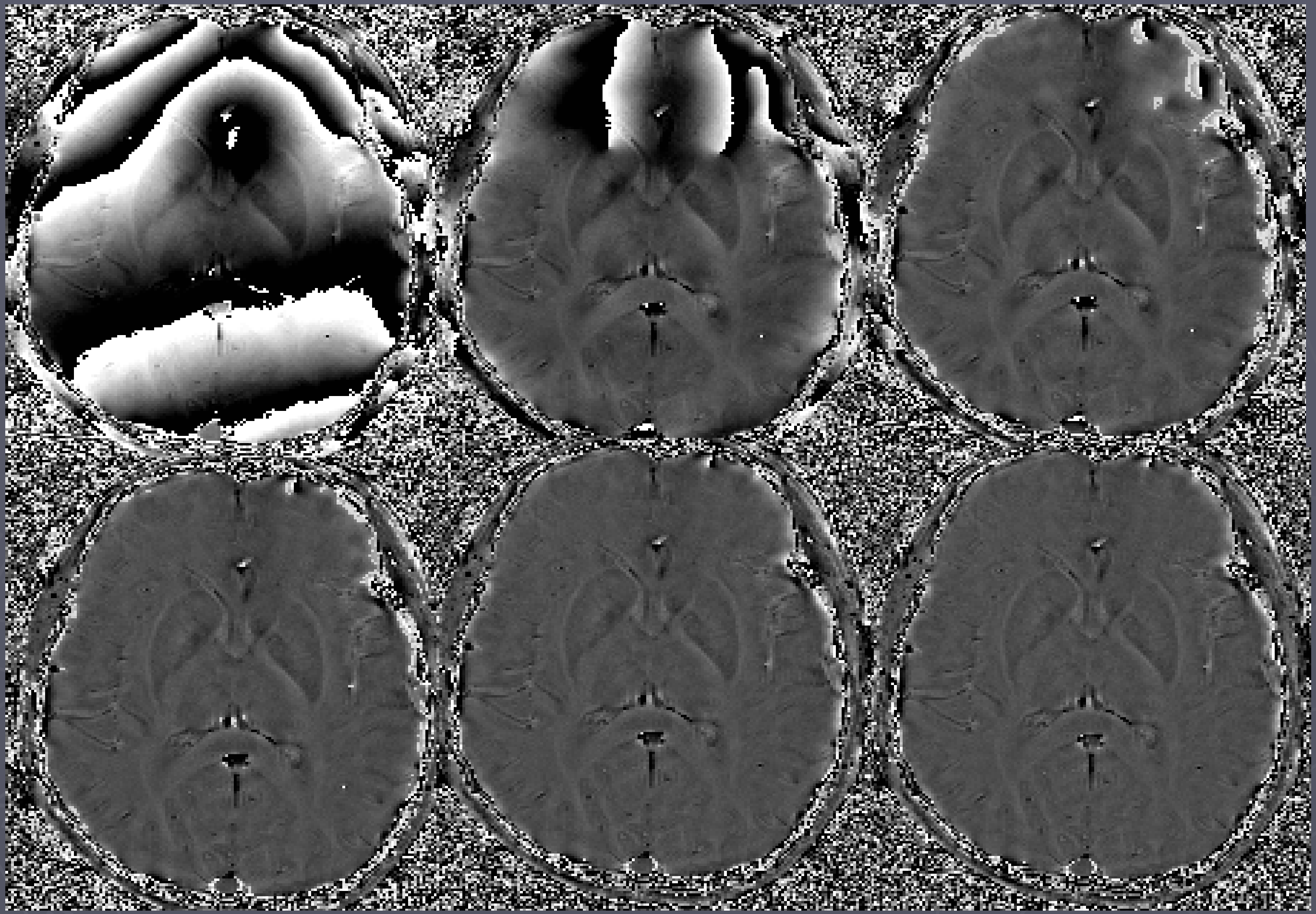
$$\rho_c(x) = \rho_m(x) \exp(-i\gamma\Delta BTE)$$

where DB is the change in the local field. Local magnetic field changes will lead to a phase change of:

$$\varphi = \gamma\Delta Bt$$

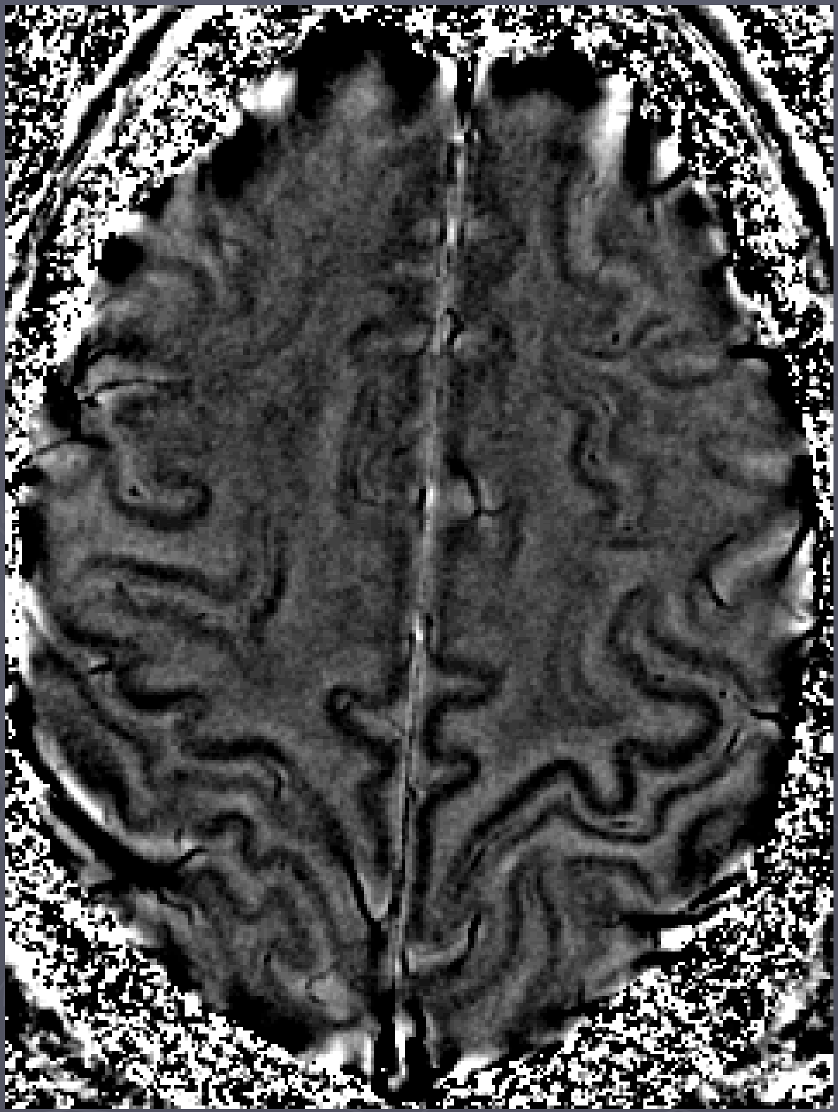
The critical point is to be able to separate the local effects of interest from those caused by a poor magnet design or air/tissue interfaces in the body.

High pass filter to reduce low spatial frequency background



(a) no filter, (b) 16x16,(c) 32x32, (d) 48x48, (e) 56x56, and (f) 64x64.

Filtered Phase Image at 3.0T



Motor cortex has higher iron which is likely in the form of ferritin

At 3T with parallel imaging we can reduce the time for whole brain coverage from 16 min to 4 min.

Normal thalamostriate veins

Caudate veins and the thalamostriate venous drainage system as seen with SWI at 7T.

Iron in Multiple Sclerosis

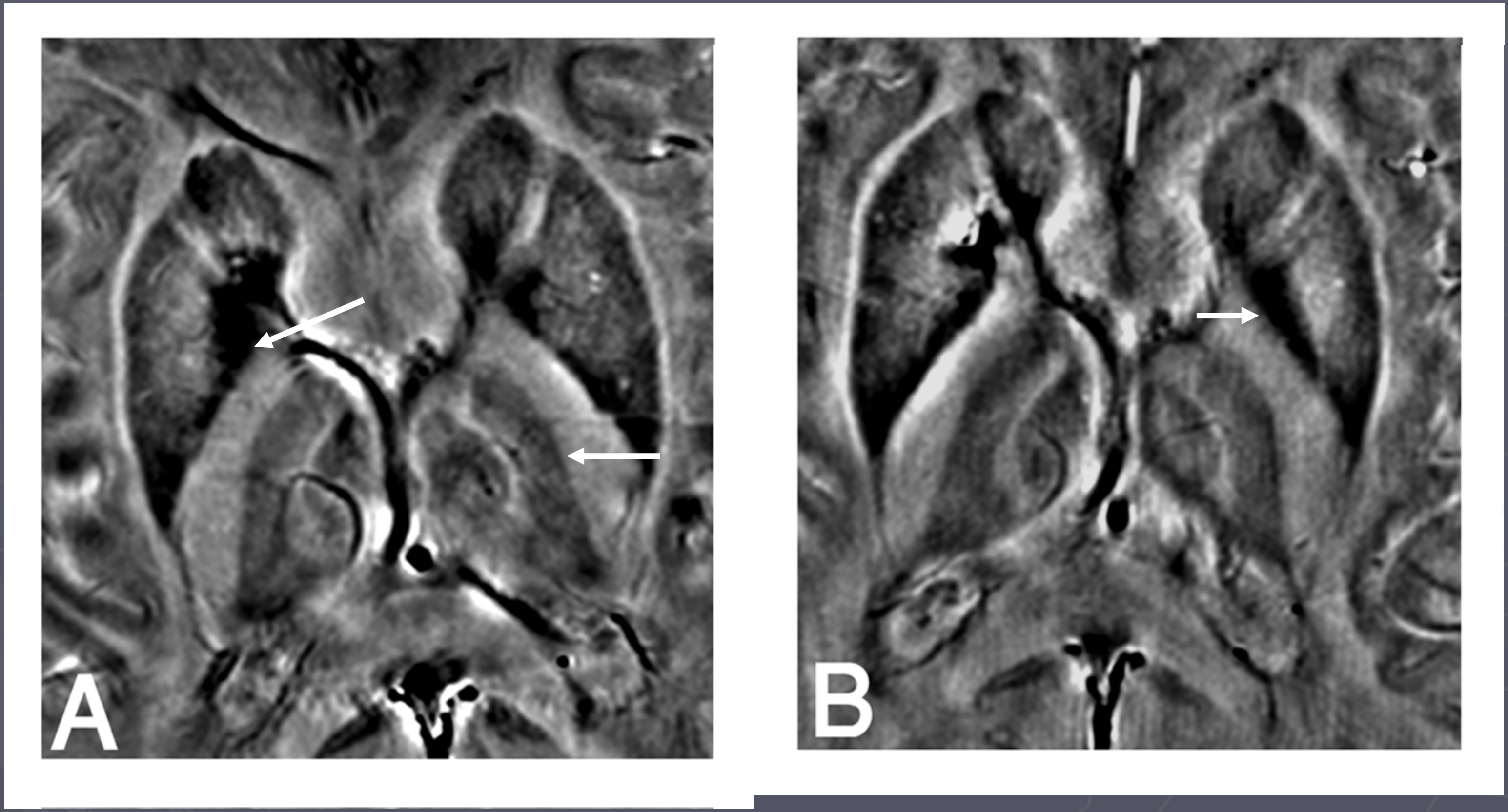
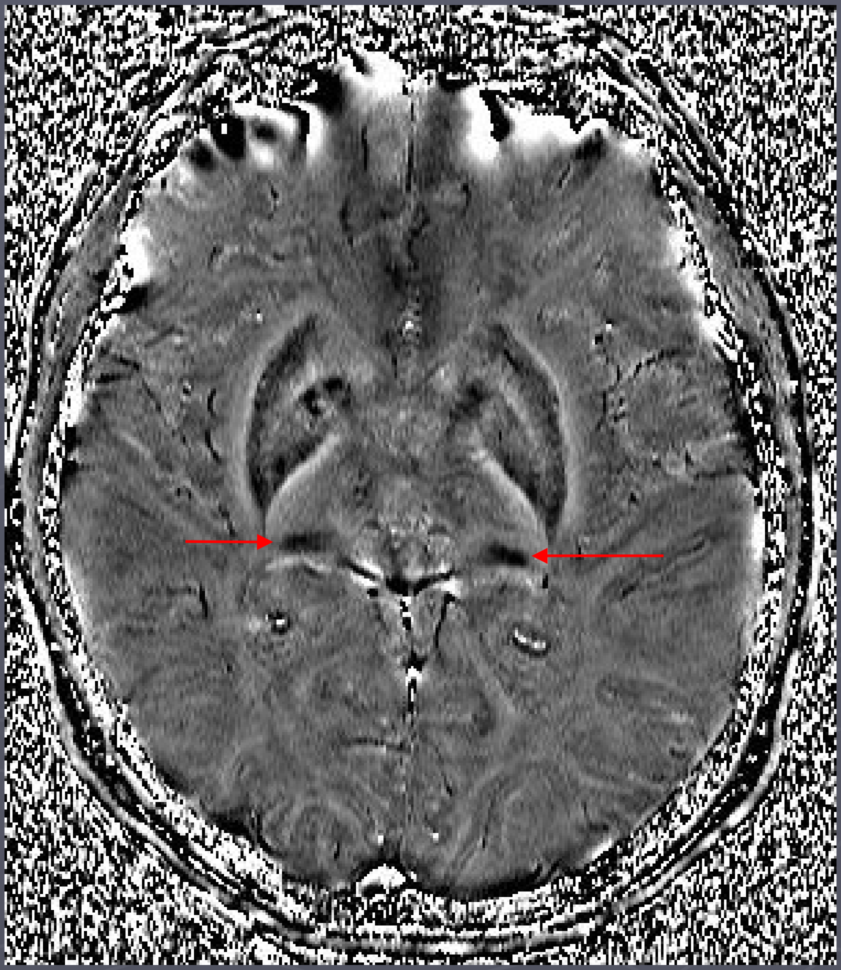


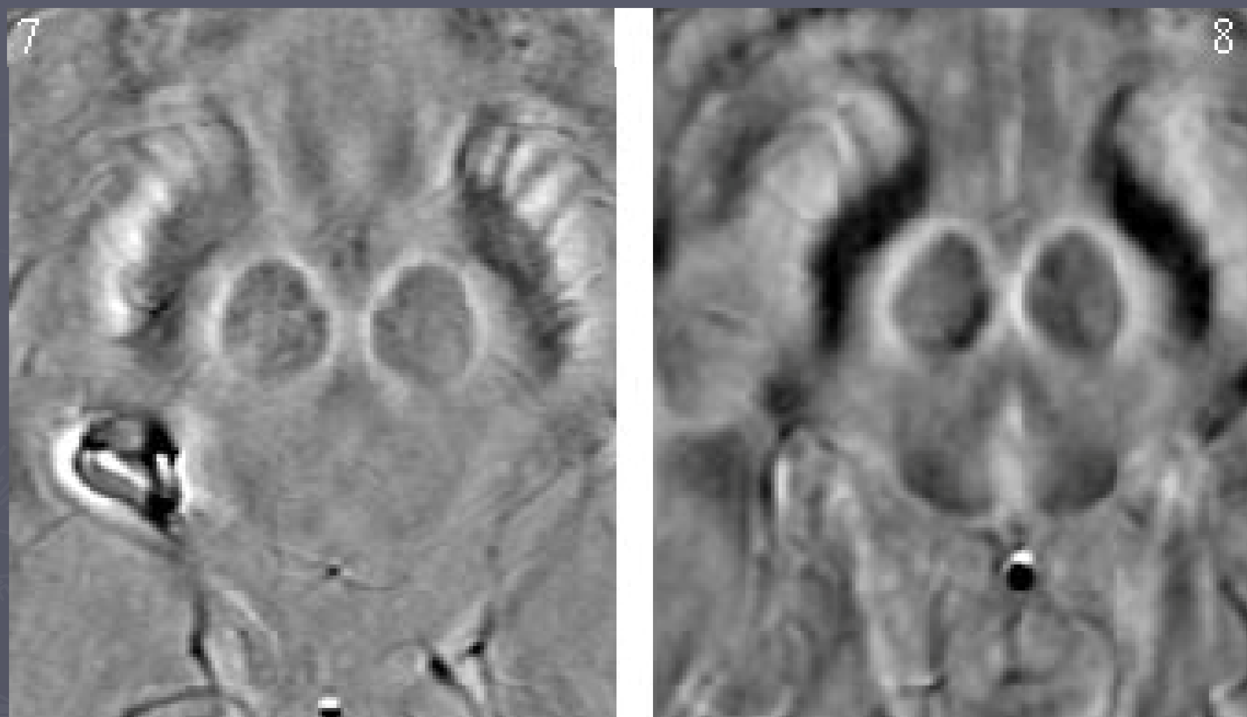
Figure A is from 10-10-2006

Figure B is from 3-25-2008

Iron in pulvinar thalamus

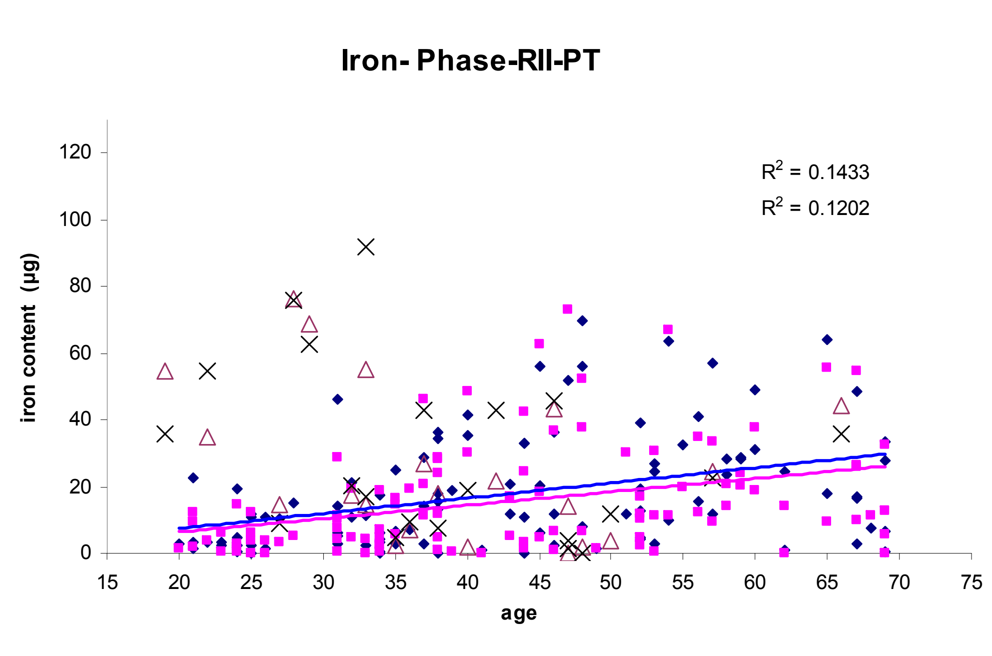


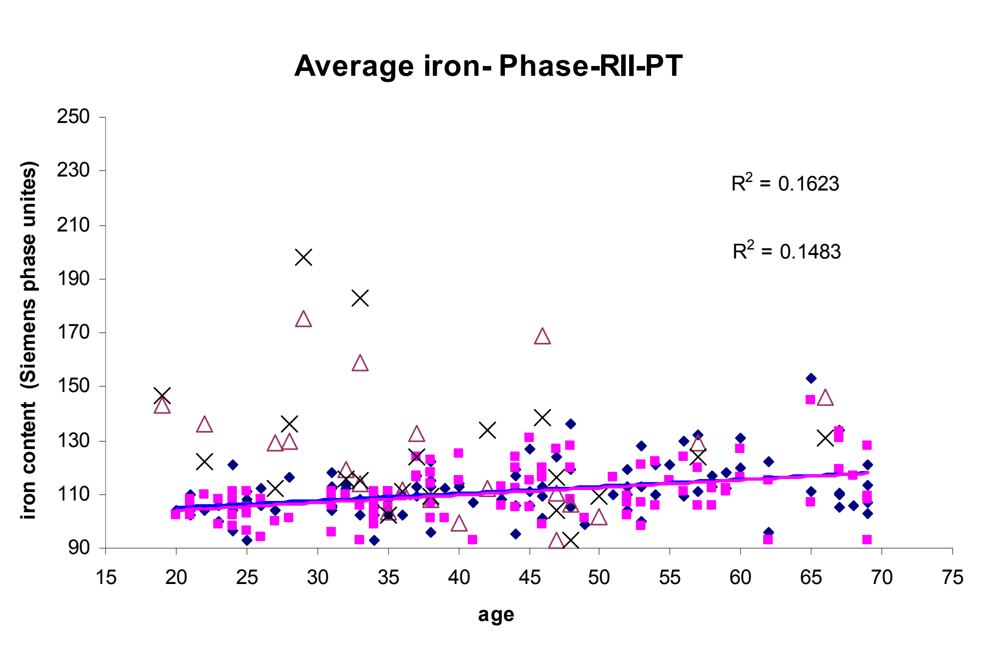
Can MS iron in SN mimic Parkinson's disease?



Iron in the midbrain - Normal

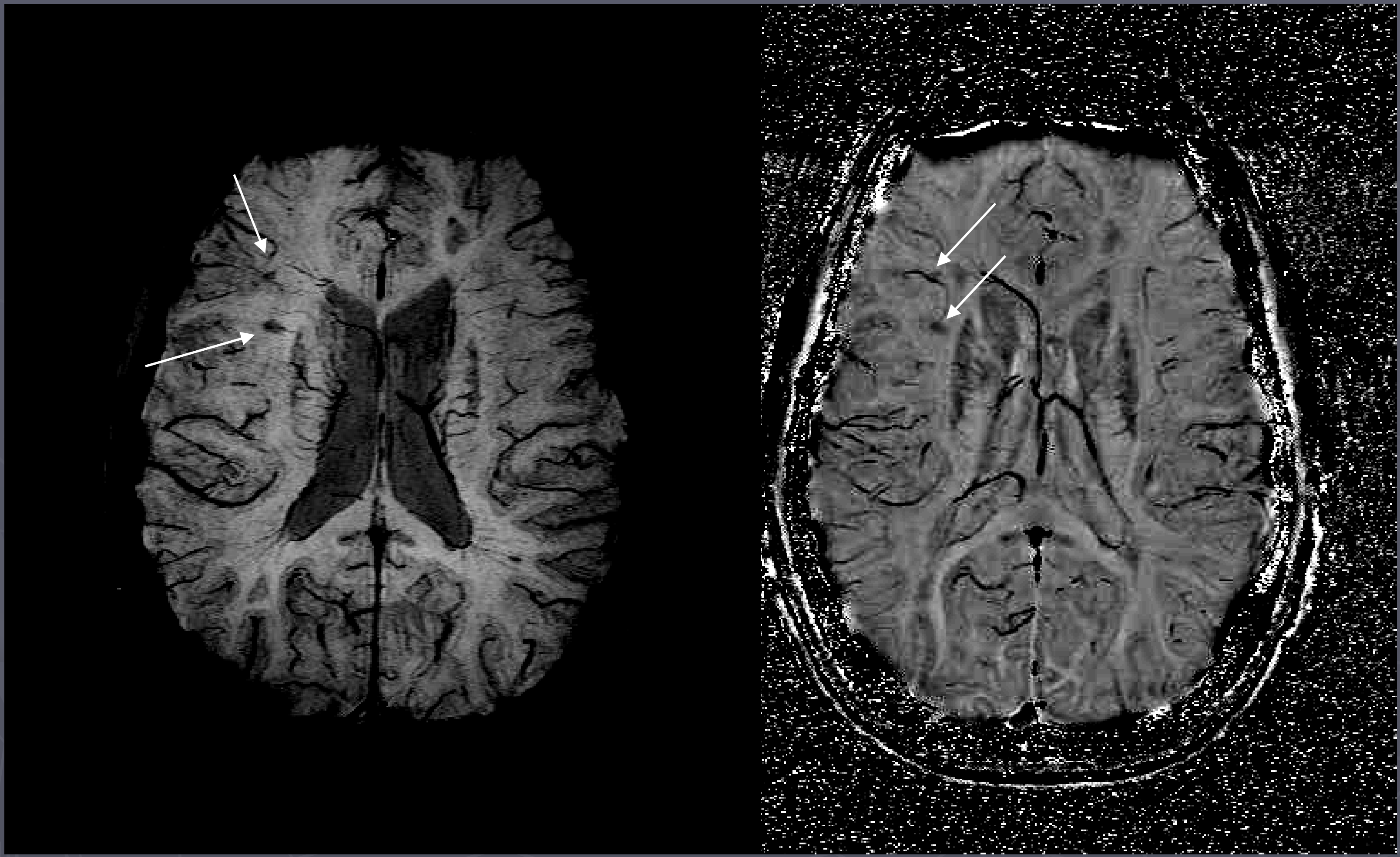
Iron in the midbrain - MS



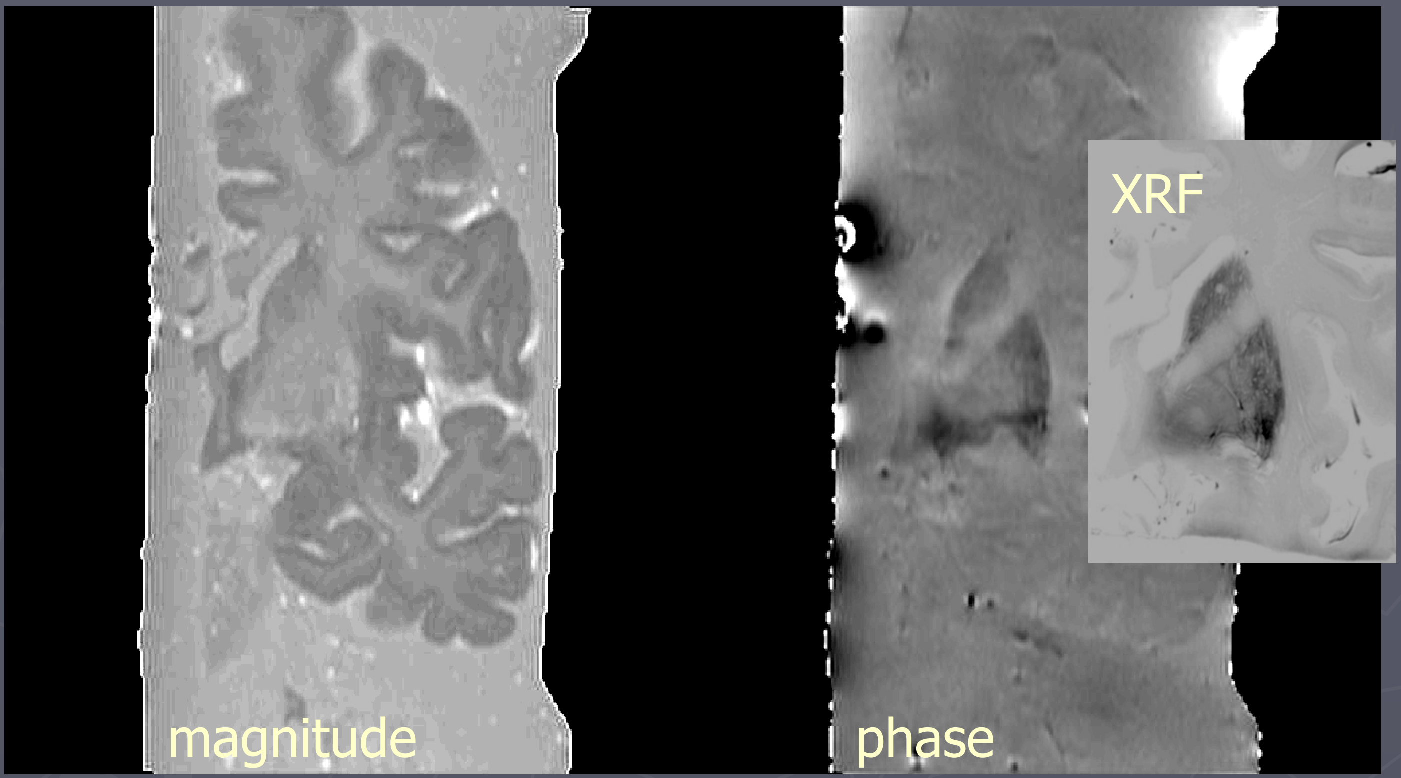


SWI putative iron content as measured with high pass filtered phase data shows a clear iron increase in younger subjects compared to age matched normals.

This is a classic example of a Dawson finger with this ovoid lesion containing rather unifrom iron content.



SWI and XRF scanning



susceptibility weighted imaging: 500µ resolution

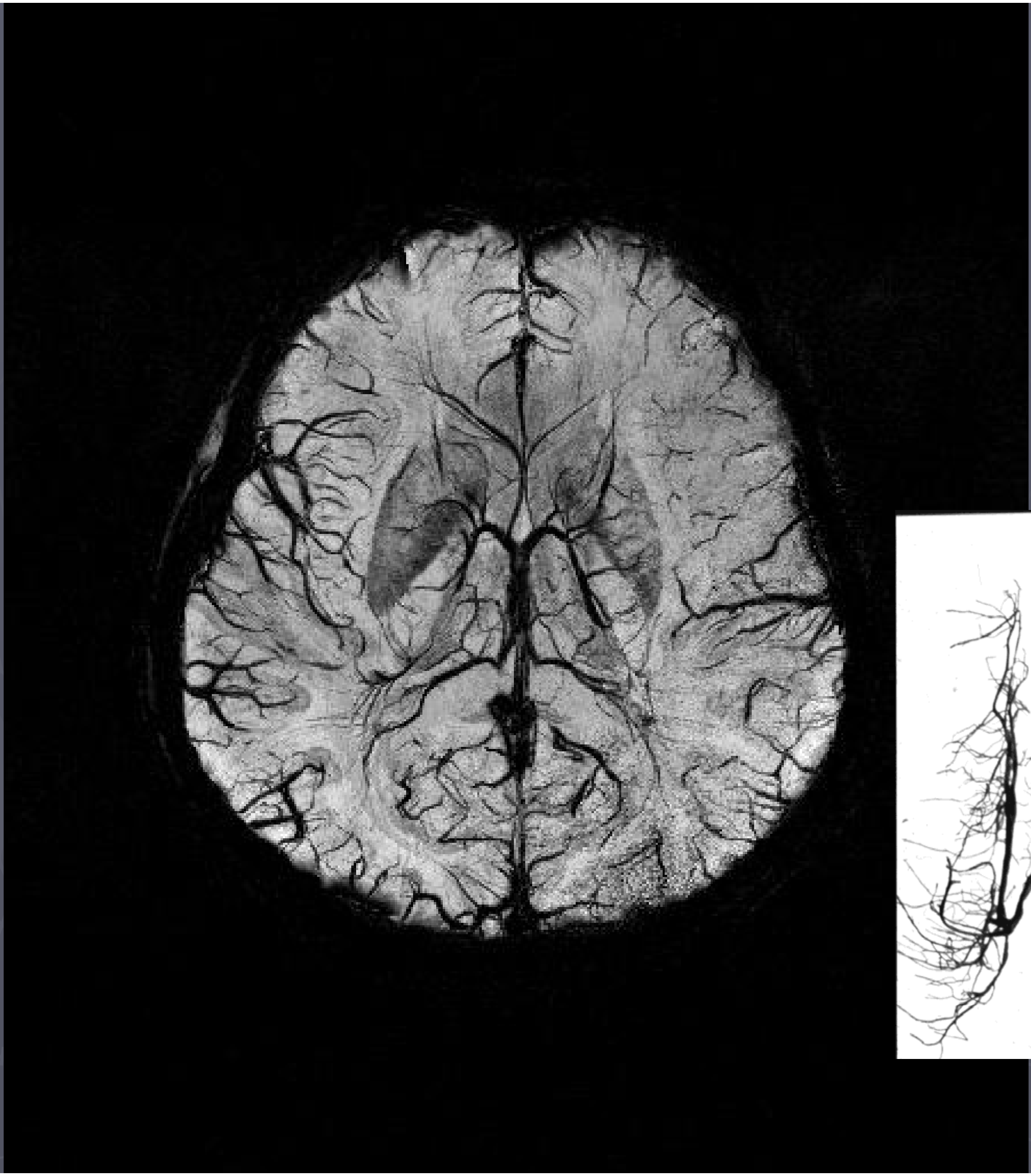
x-ray fluorescence imaging: 50µ resolution

images courtesy of: Helen Nichol and Richard McCrea

Dept of Anatomy and Cell Biology, University of Saskatchewan.

Susceptibility Weighted Imaging (SWI): Imaging veins and blood products

- marry the magnitude and phase information to enhance areas with susceptibility differences
- performing a minimum intensity projection over a number of slices (usually 4 but up to 20) for good visualization of the veins
- enhanced contrast for visualizing blood with increased deoxyhemoglobin levels
- enhanced visibility of microbleeds

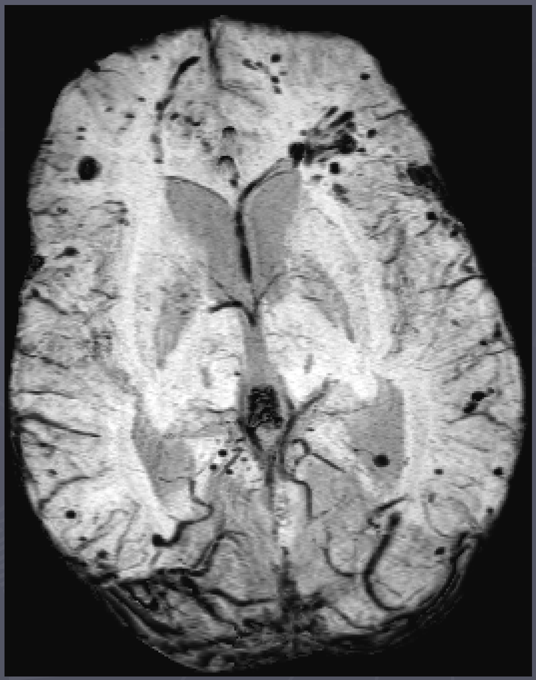


4T SWI

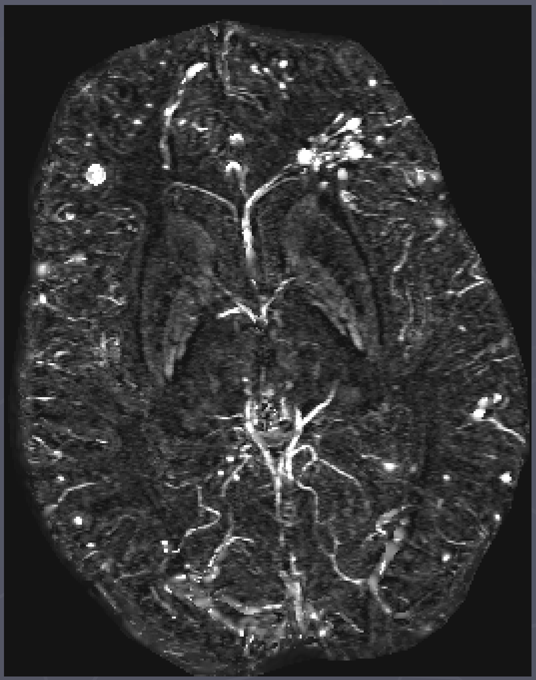
0.5 x 0.5 x 1.0 mm^3
image from WSU

Image courtesy of
Georges Saloman

Susceptibility Mapping in Traumatic Brain Injury (TBI)

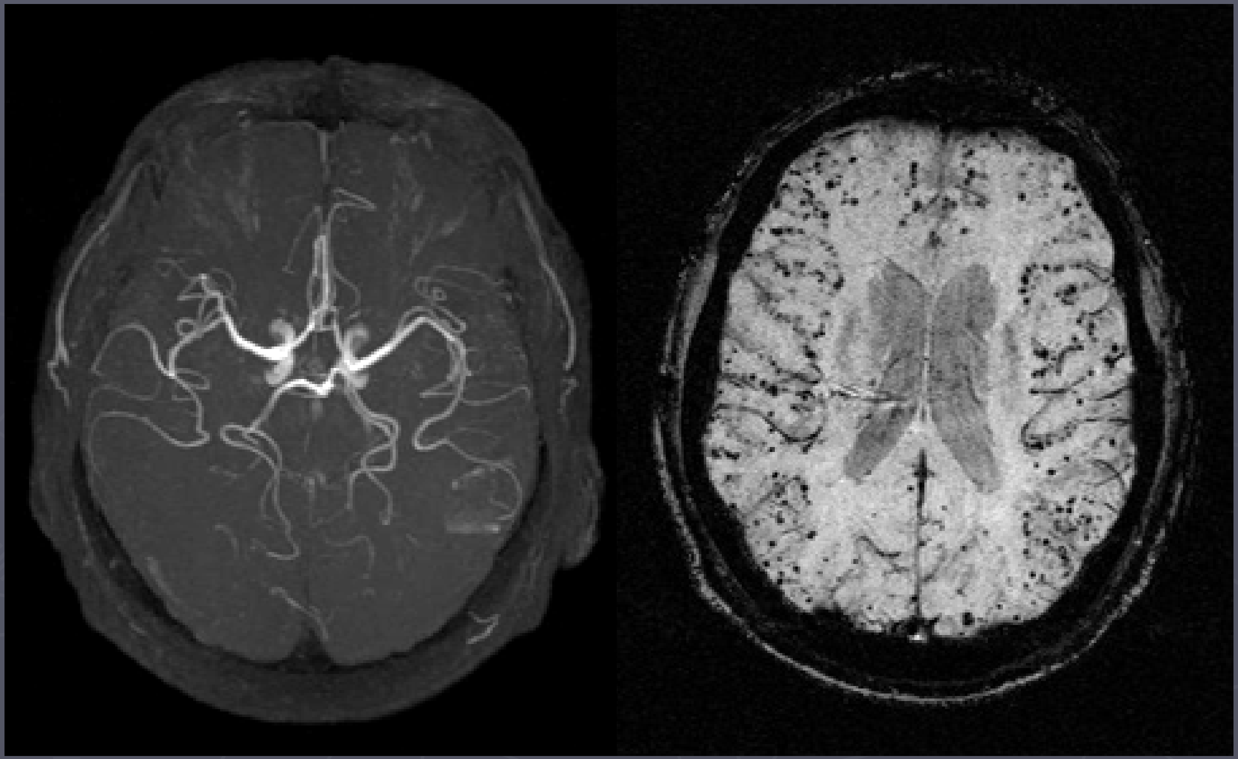


SWI minIP image projected over 16mm



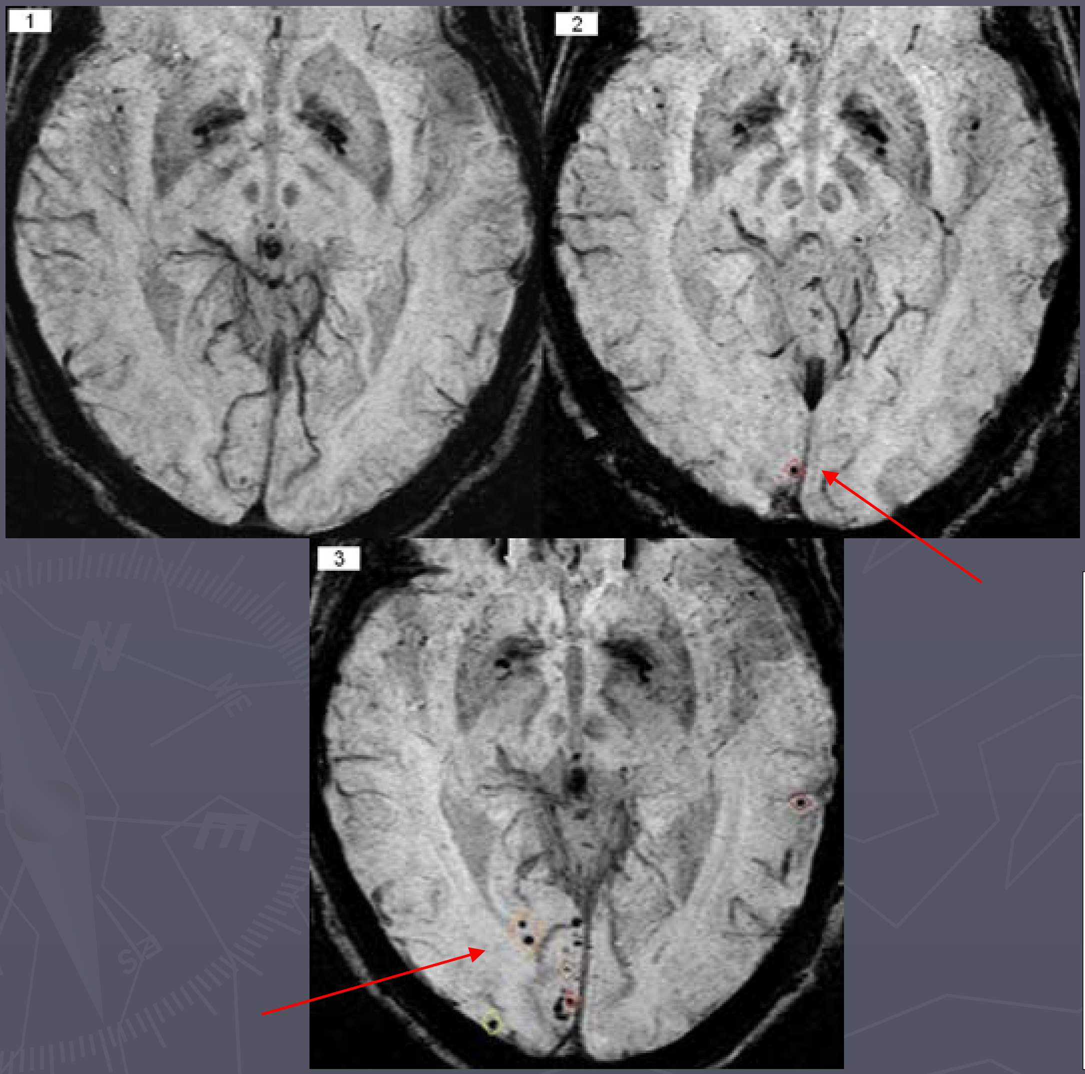
Corresponding MaxIP susceptibility map image projected over 16mm

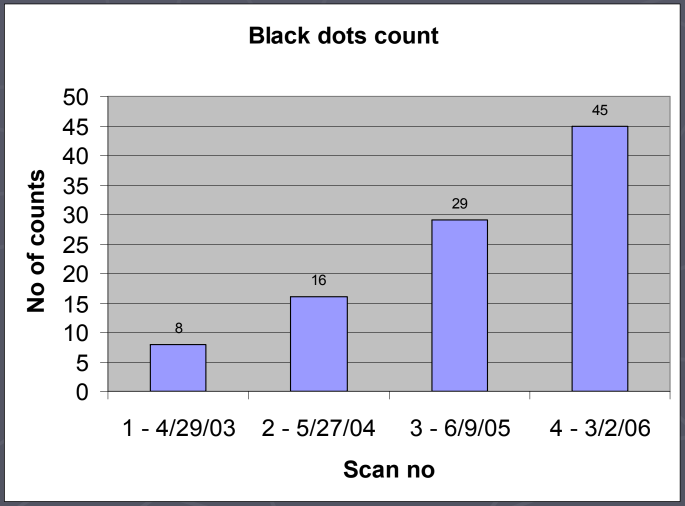
Dementia and cerebral amyloid angiopathy



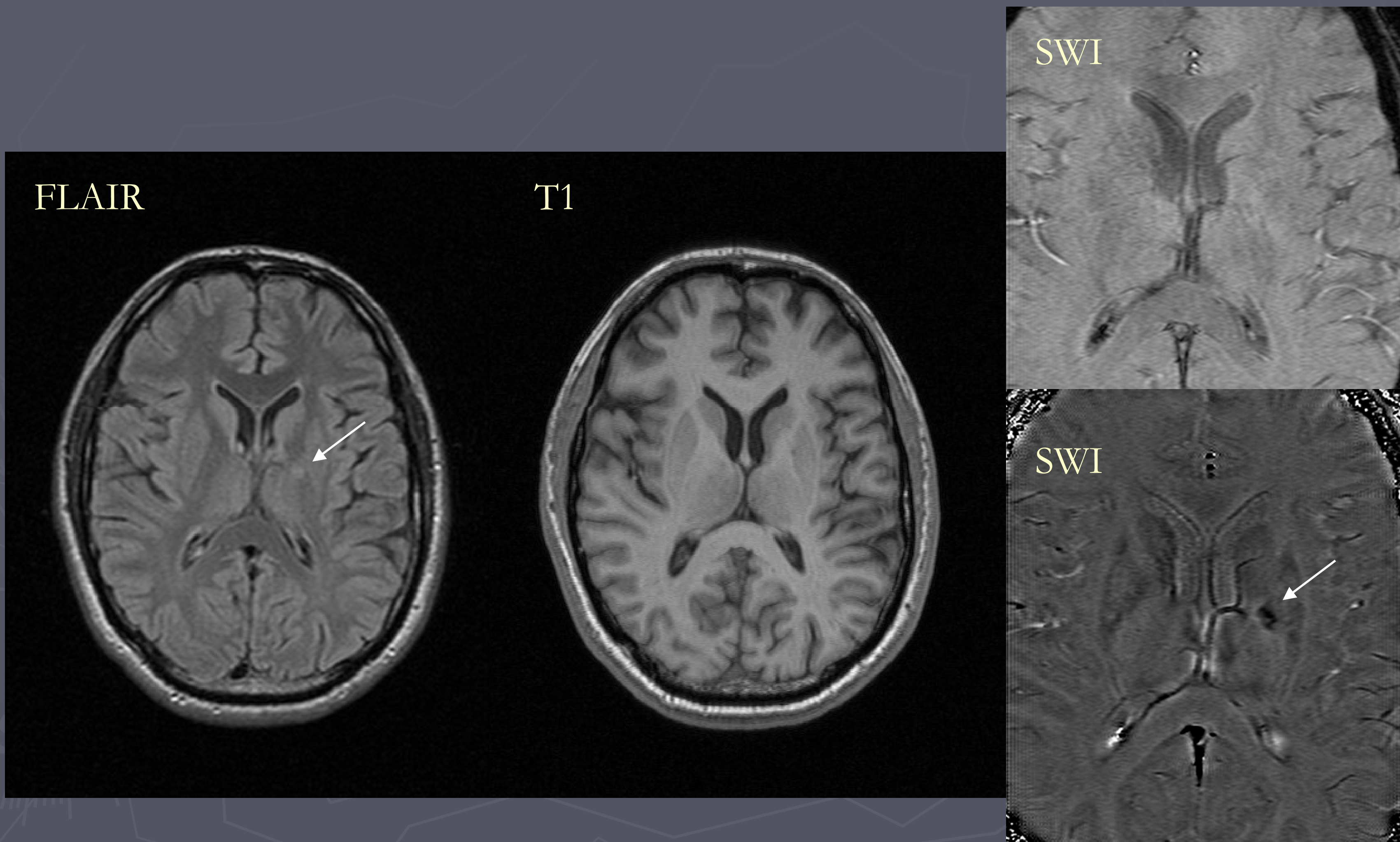
50µ objects can manifest as 1mm^3 objects

time to go sailing

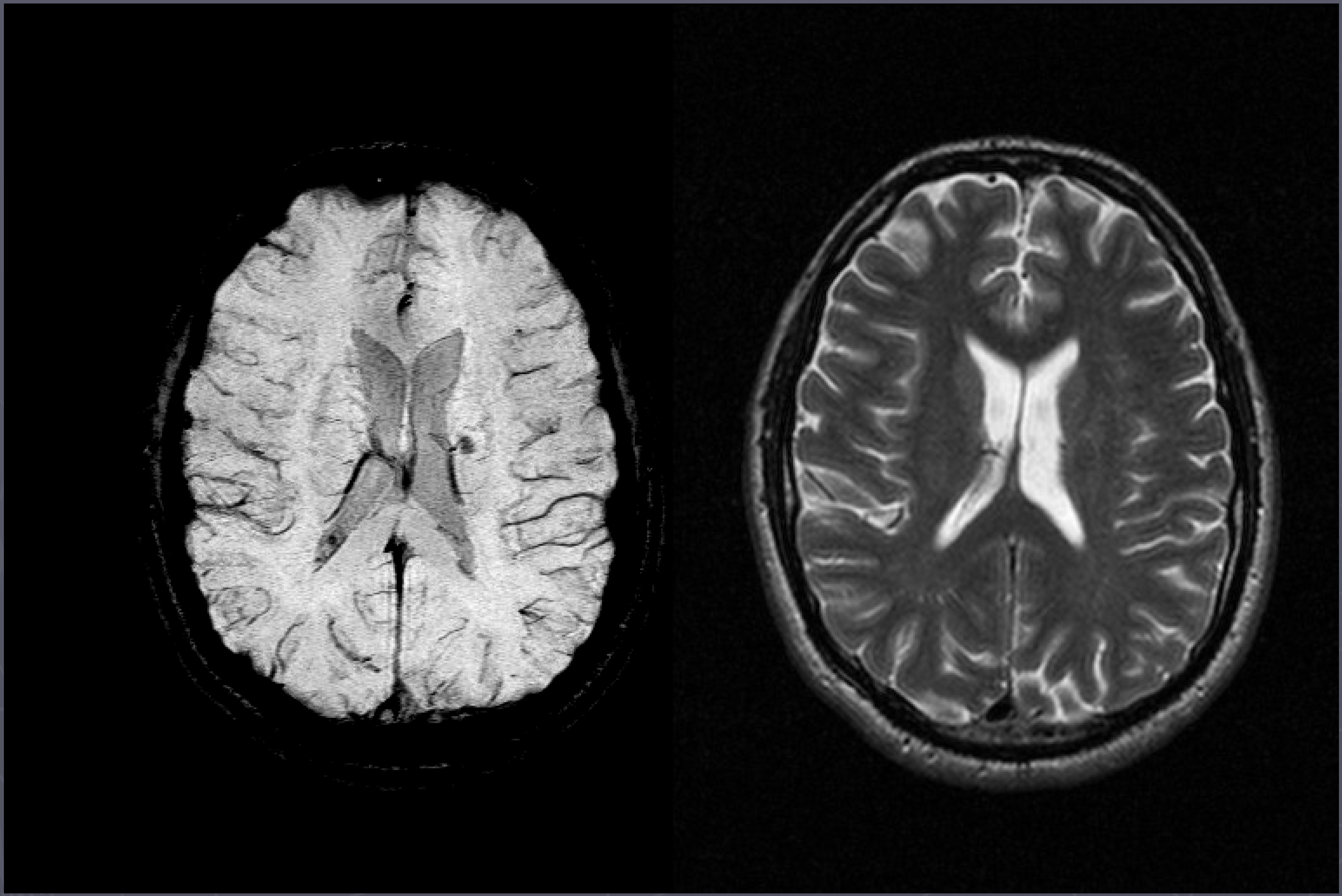




Low concentration iron is still seen on 7 slices with SWI and barely discernable on FLAIR!



Stroke with almost imperceptible bleeding



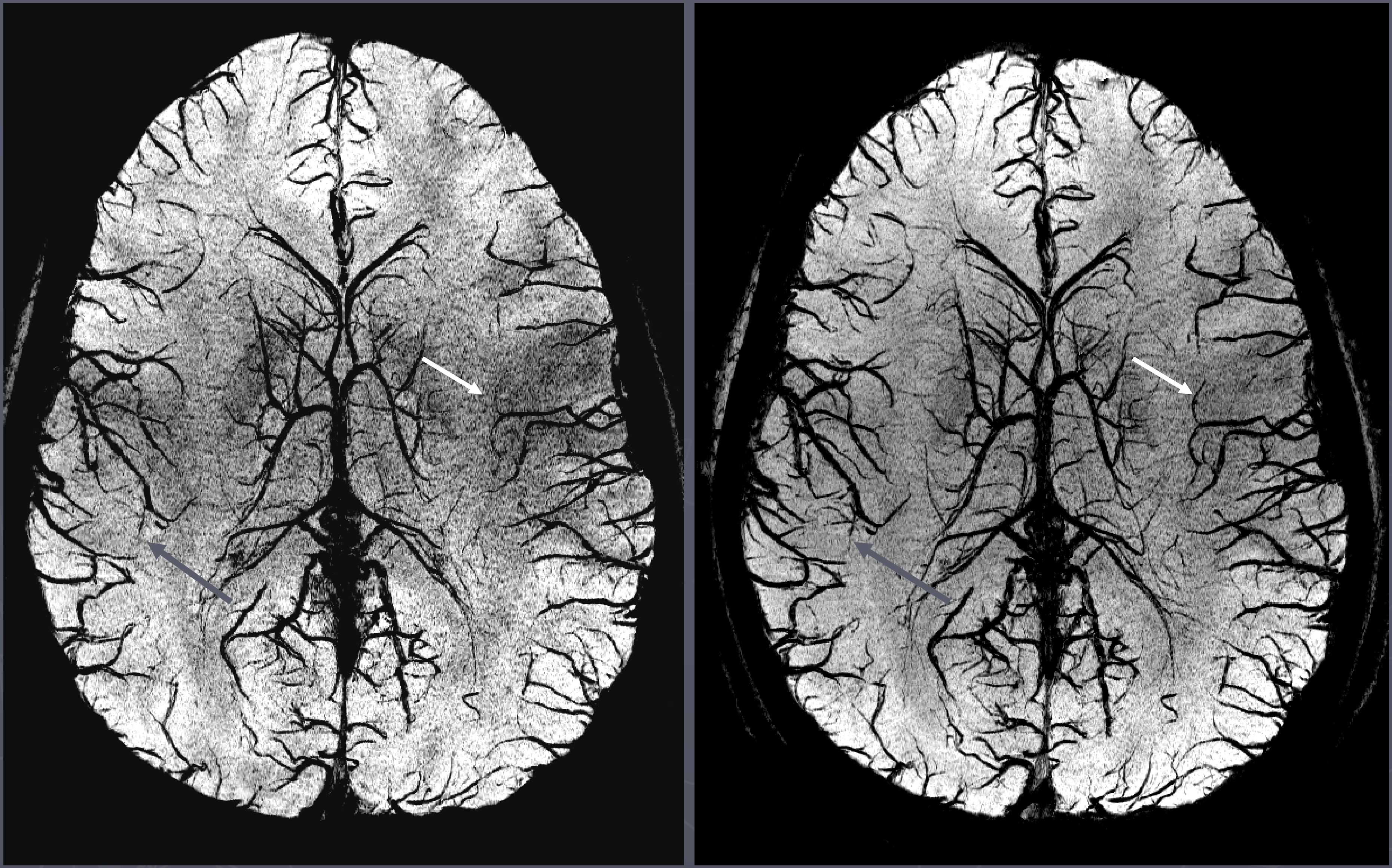
SWI shows even more of the bleed Conventional short TE GRE T1

Using caffeine decreases blood flow to the brain

two cups of coffee and you will have a major change of blood flow to the brain

maybe we should approach Starbucks for funding

at least it is a relatively harmless contrast agent to use to study the brain and a heck of a lot cheaper



PRE

POST

MinIP of caffeine/Gd over 28 slices with 4 phase multiplications

Mapping Susceptibility

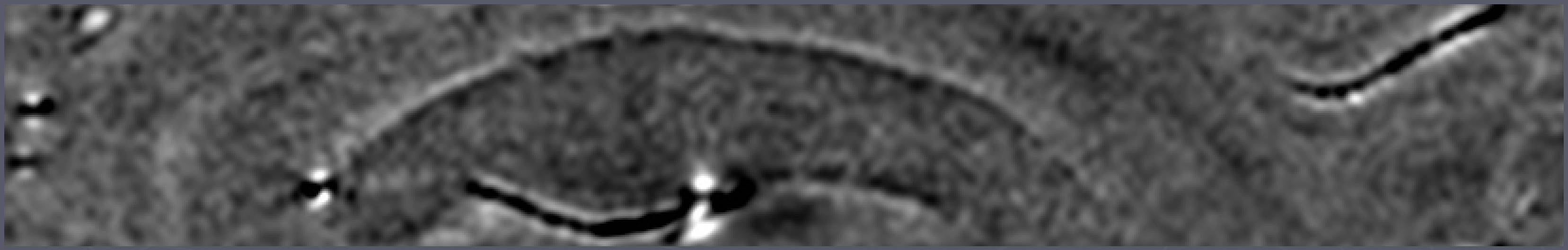
We can obtain $\Delta\chi(r)$, i.e., the susceptibility map, provided we have $\Delta B_{local\ tissue}(r)$ from:

$$\Delta\chi(r) = FT^{-1}\left[\, FT[\Delta B_{local\ tissue}(r)] \cdot G^{-1} \,\right]$$

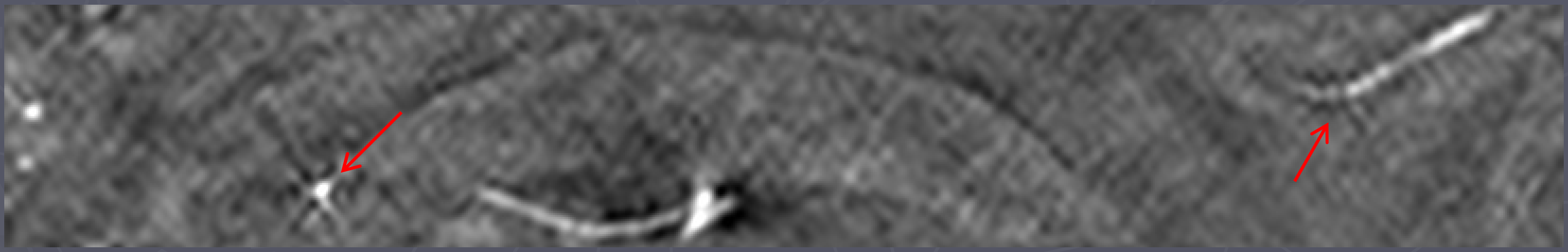
where

G^{-1} denotes the inverse of the Green's function / filter function. Practically G^{-1} has to be regularized to obtain a solution.

Susceptibility Mapping for Visualizing Veins



Phase Image

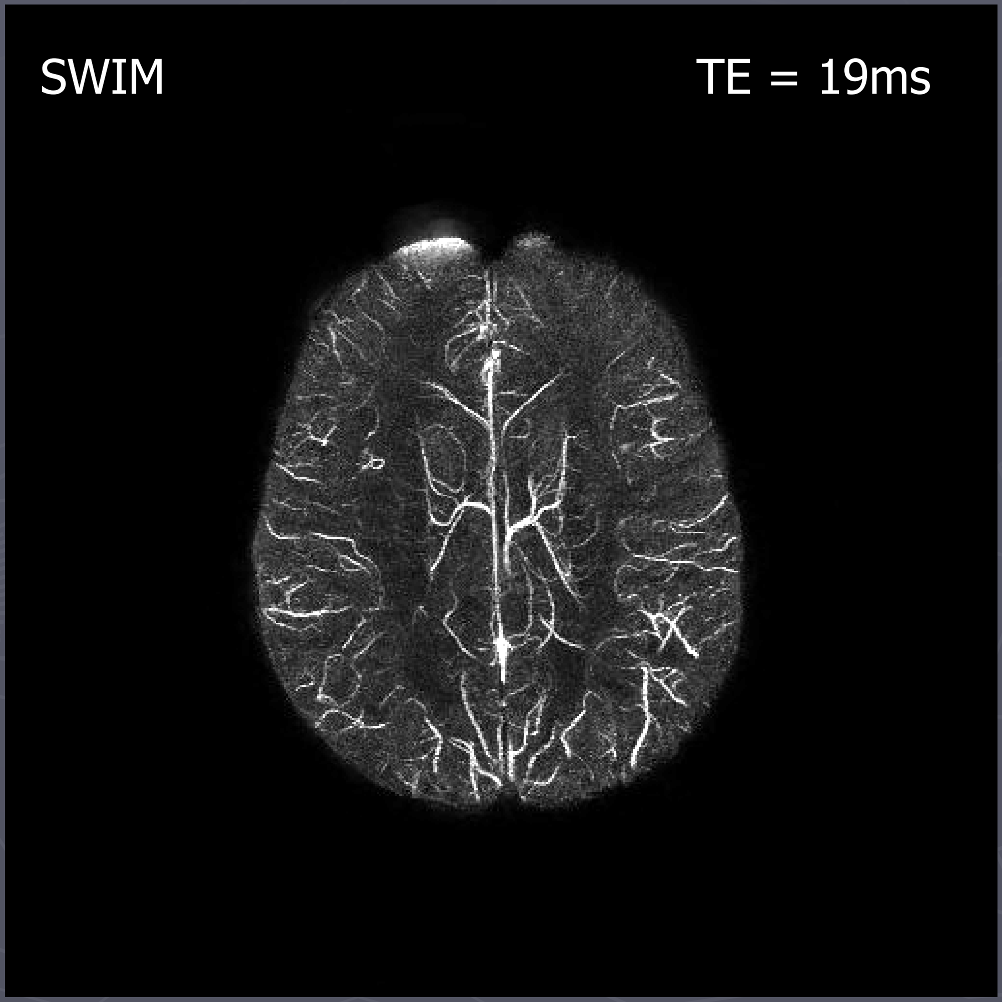


Susceptibility Map

Another set of phase images and the corresponding Susceptibility map (SM) showing the venous vessels. Note the streak artifacts around the vessel due to the inverse processing.

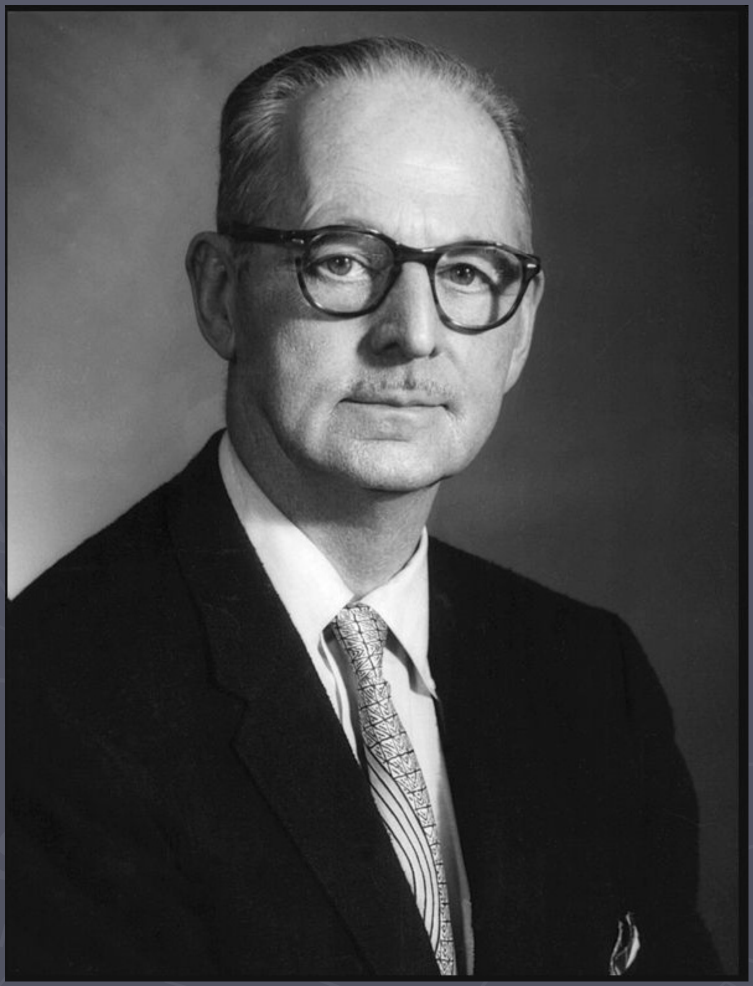
More work is warranted for removing artifacts like these by improving the inverse processing and better regularization process.

SWIM full brain analysis:
a first attempt to quantify oxygen saturation of the veins in the brain



Paolo Zamboni and his team's proof

Recall 1935 work on venous obstruction



Tracey Putnam, Boston City Hospital, developed an experimental dog model of venous obstruction to study MS. His work supports the recent rediscovery of this concept by Dr. Paolo Zamboni of Italy.

He stated:

"The similarity between such lesions and many of those seen in cases of multiple sclerosis in man is so striking that the conclusion appears almost inevitable that venular obstruction is the essential immediate antecedent to the formation of typical sclerotic plaques."

Putnam (1935). Studies in multiple sclerosis: encephalitis and sclerotic plaques produced by venular obstruction. Archives of Neurology and Psychiatry. 33: 929-940.

Imaging MS patients with ultrasound

Zamboni's ultrasound conditions

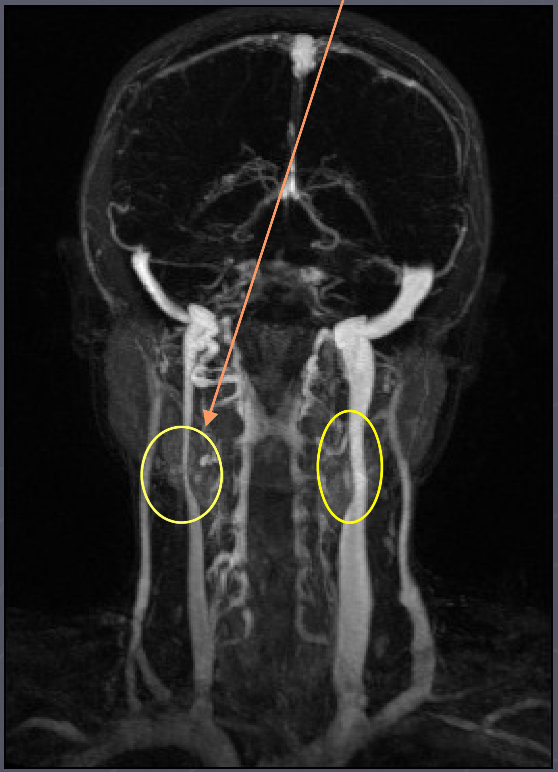
- Reflux constantly present in the IJV
- Reflux in the deep cerebral veins
- High resolution evidence of stenoses
- Flow not detectable in IJV or VV
- Decreases in IJV cross section when changing from sitting to supine

Normal control

Time resolved MRA-MRV

MaxIP of Carotid Artery

Narrow jugular vein



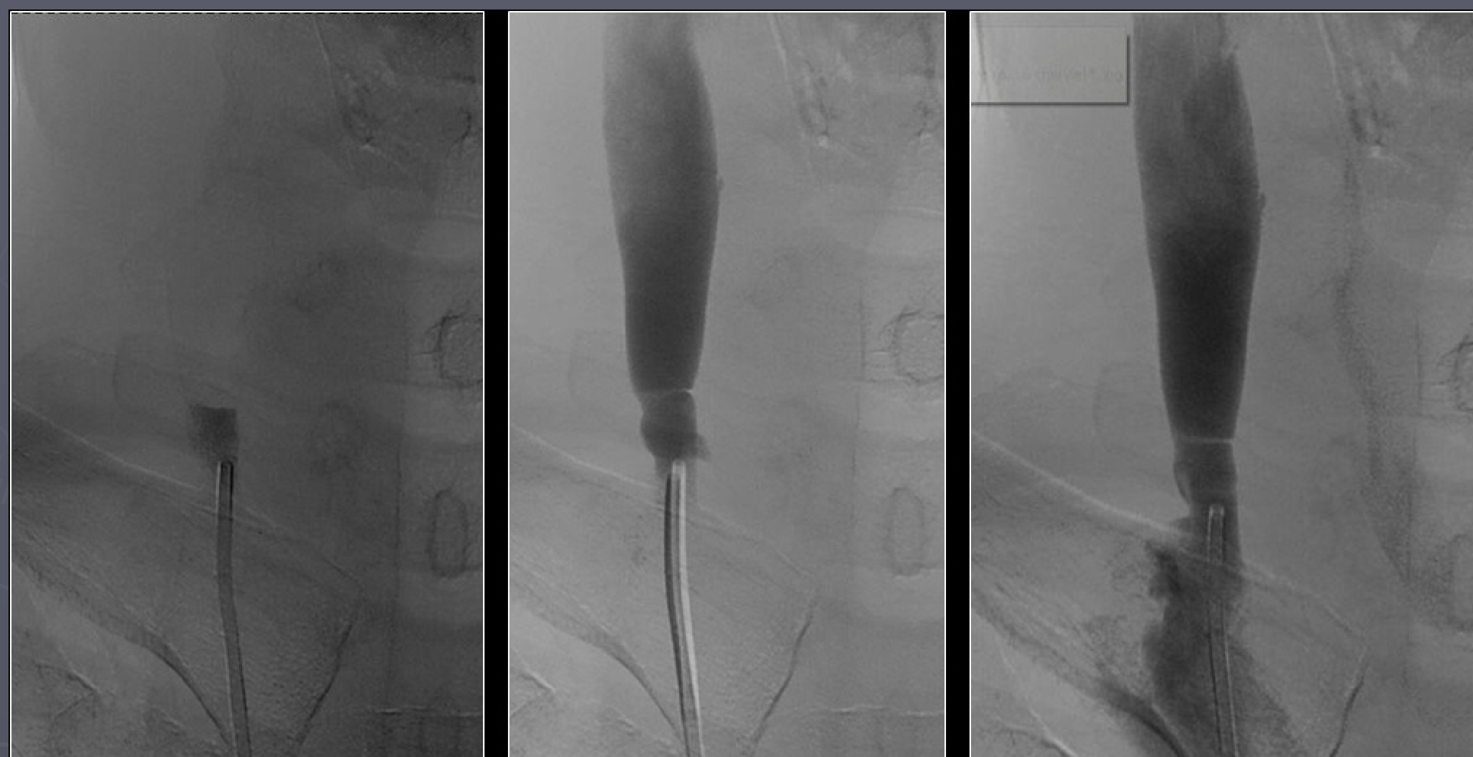
MaxIP of Jugular Vein

Recent MR examples of CCSVI in MS patients

Stenosed RIJV

Multiple stenoses in RIJV

Tough to find septum



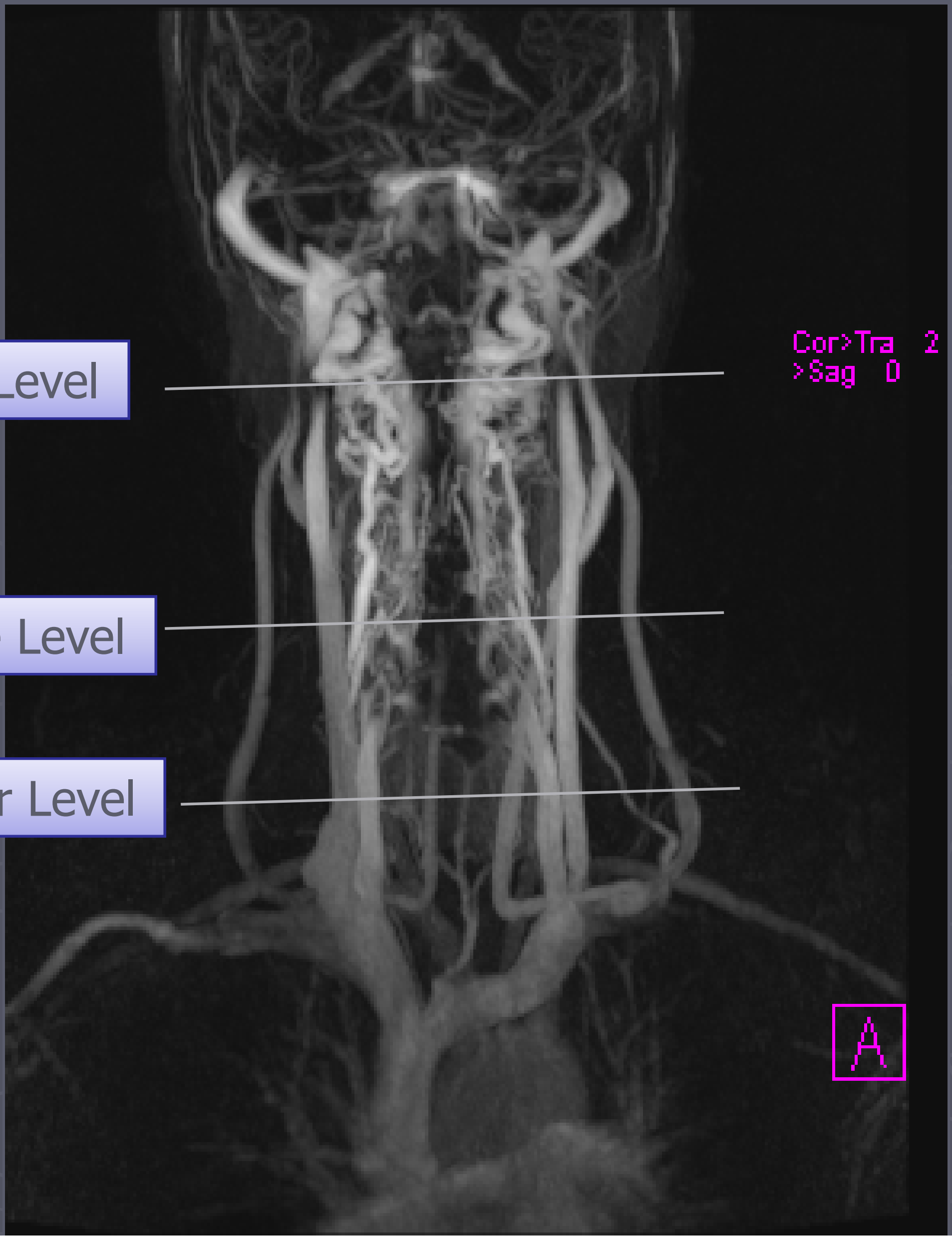
Images courtesy of Salvatore Sclafani, SUNY Downstate College of Medicine, Brooklyn, New York

Slice positions

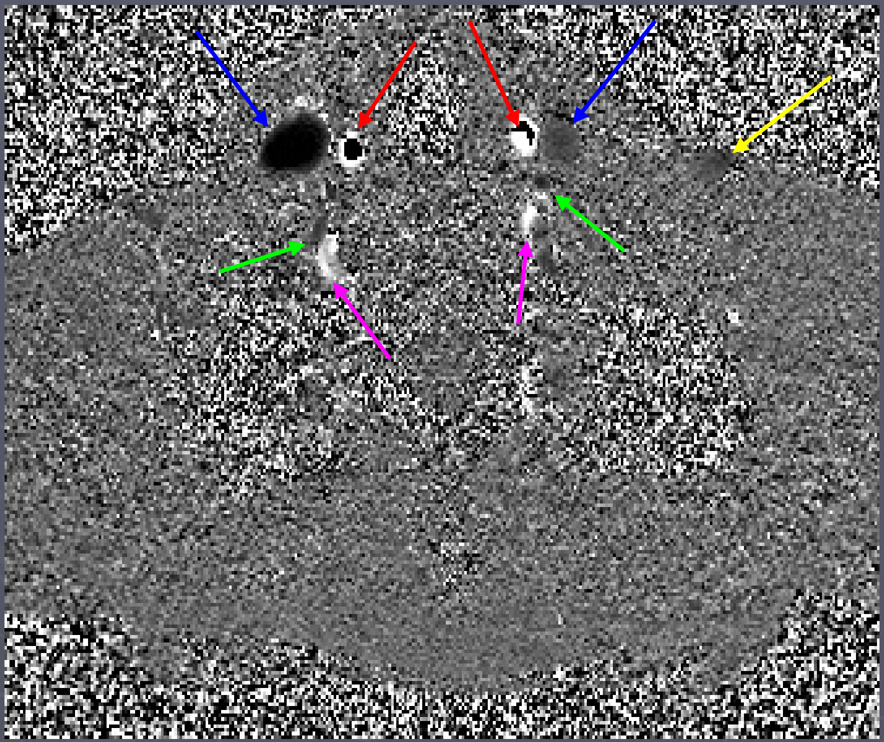
Upper Level

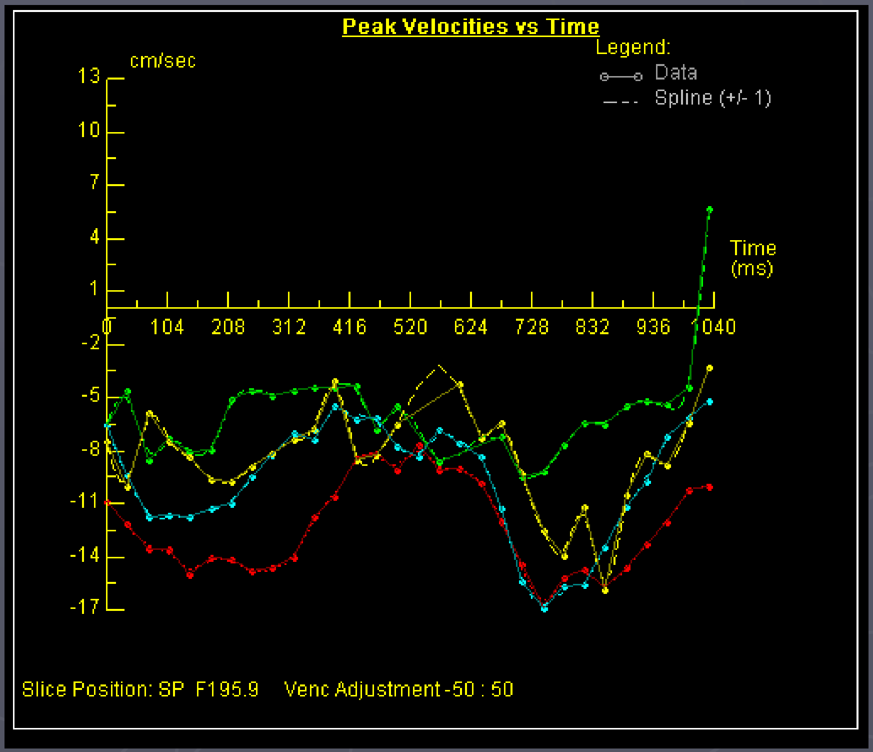
Middle Level

Lower Level



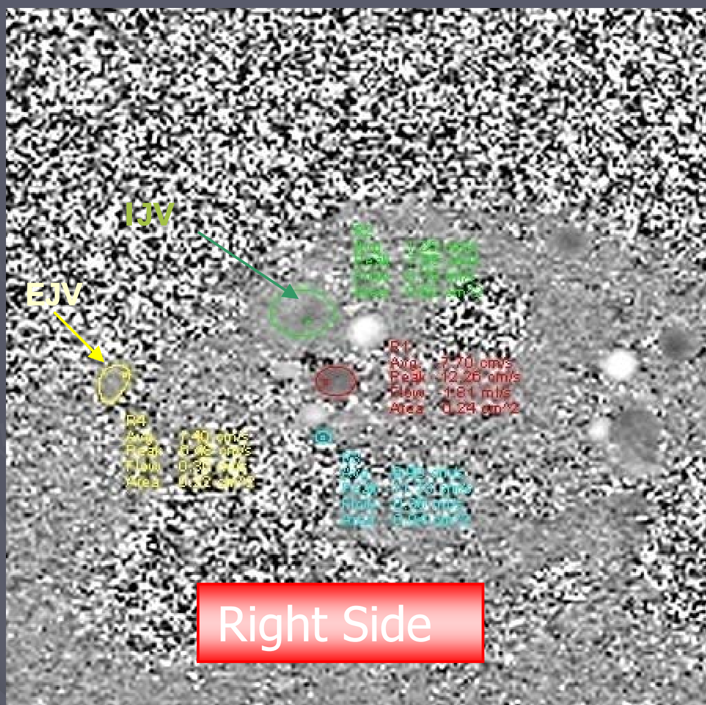
Flow Quantification

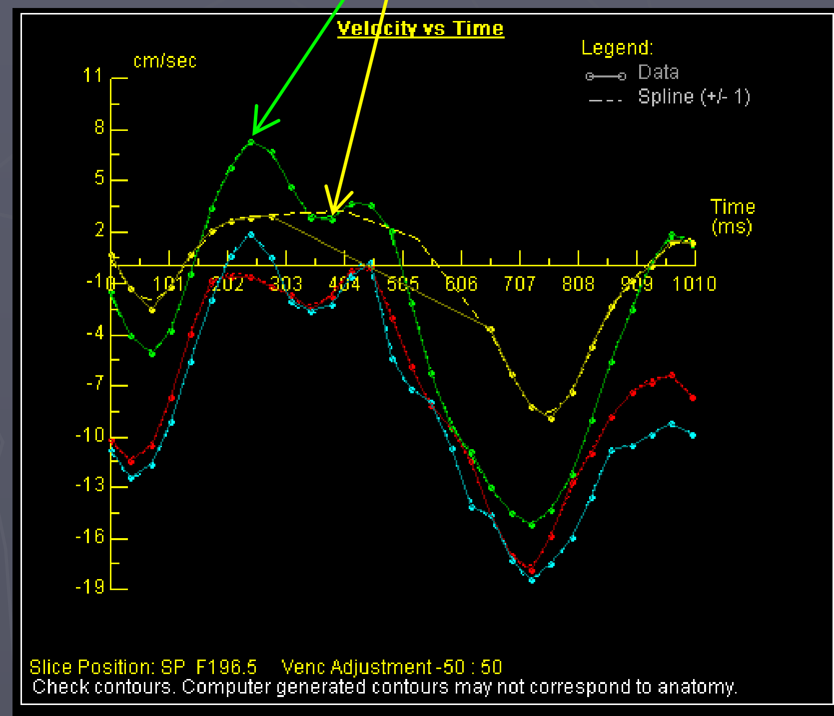




Negative velocity values indicate flow towards the heart. Positive values indicate flow towards the brain.

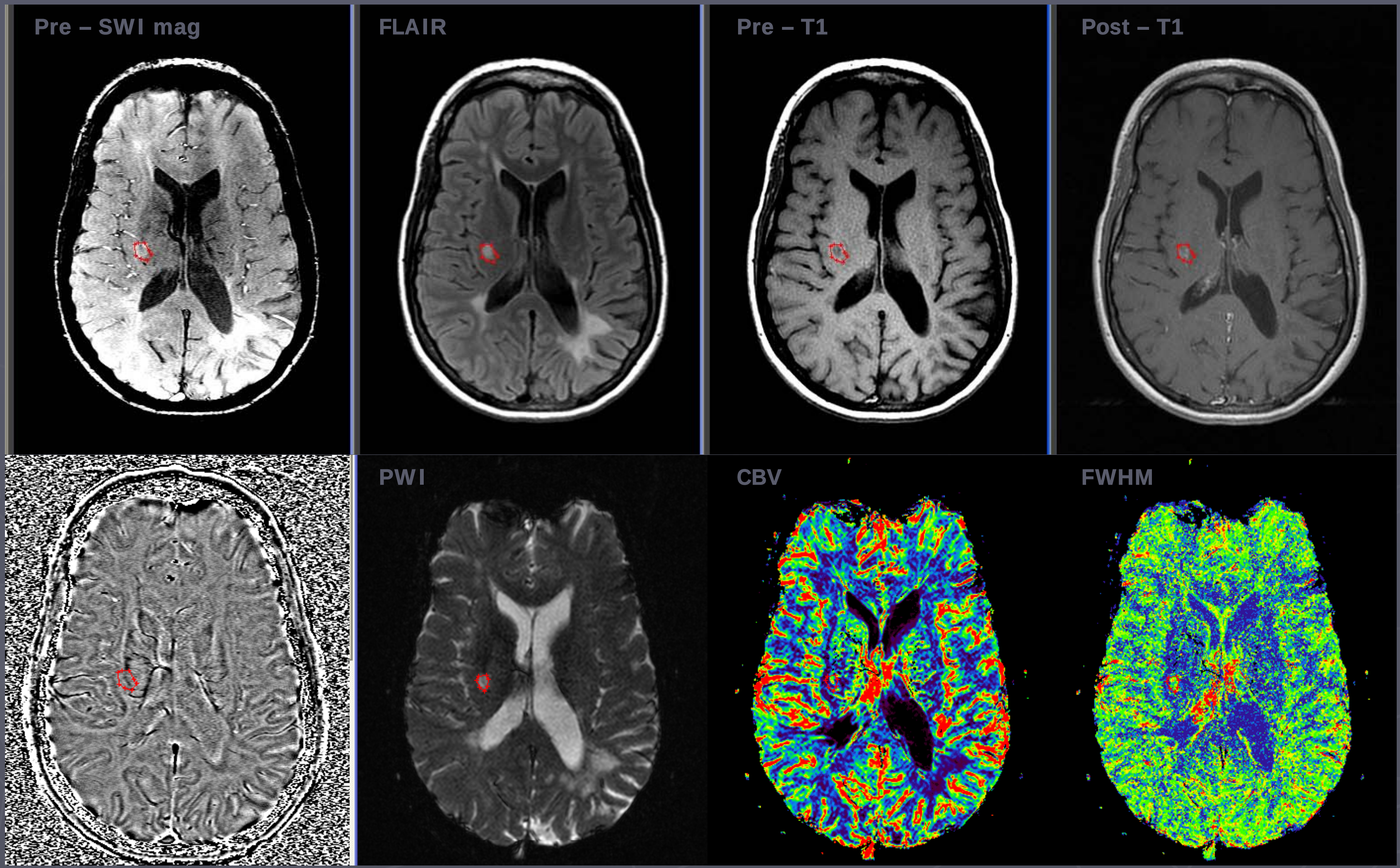
Reverse flow



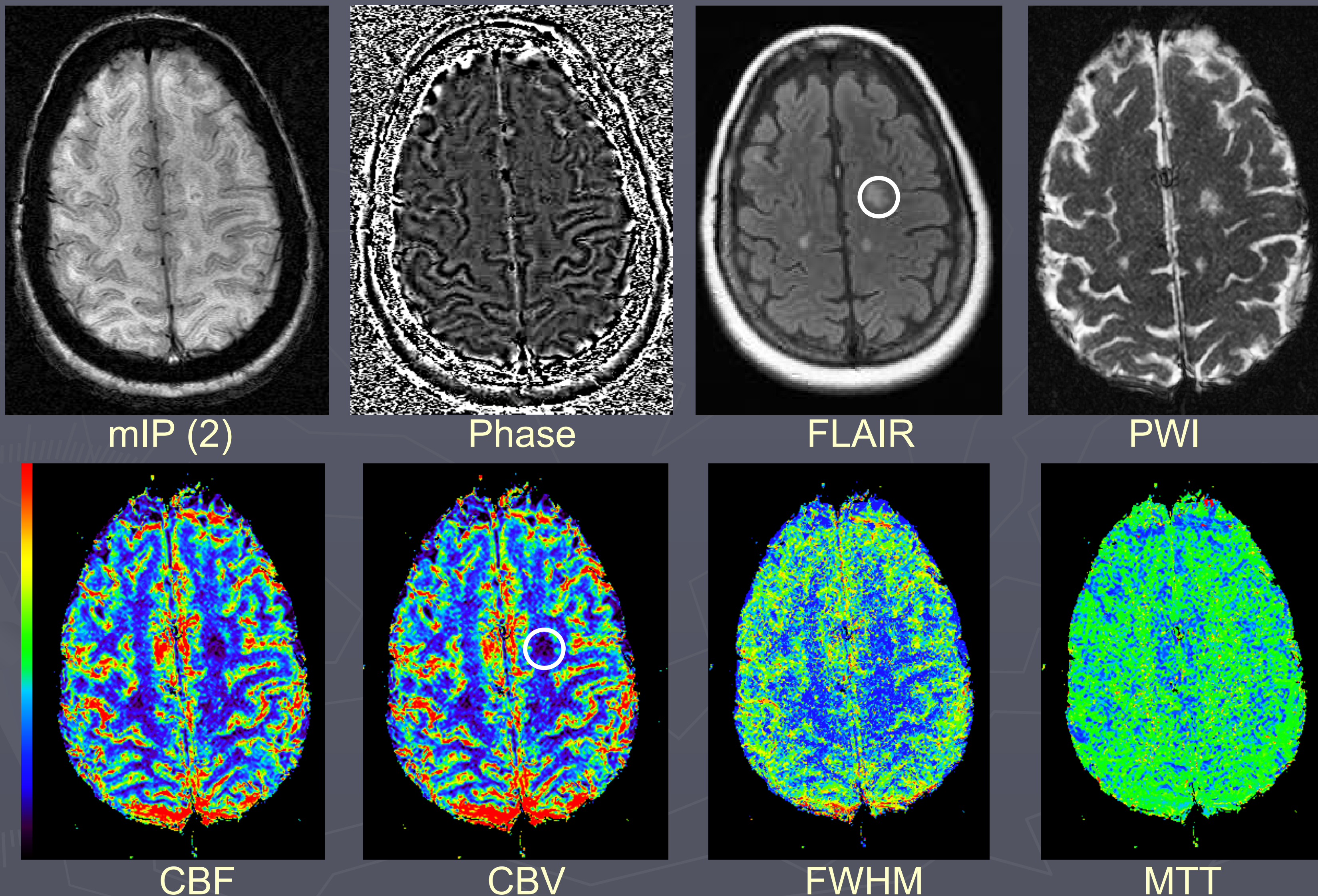


Reflux in the veins in the lower neck

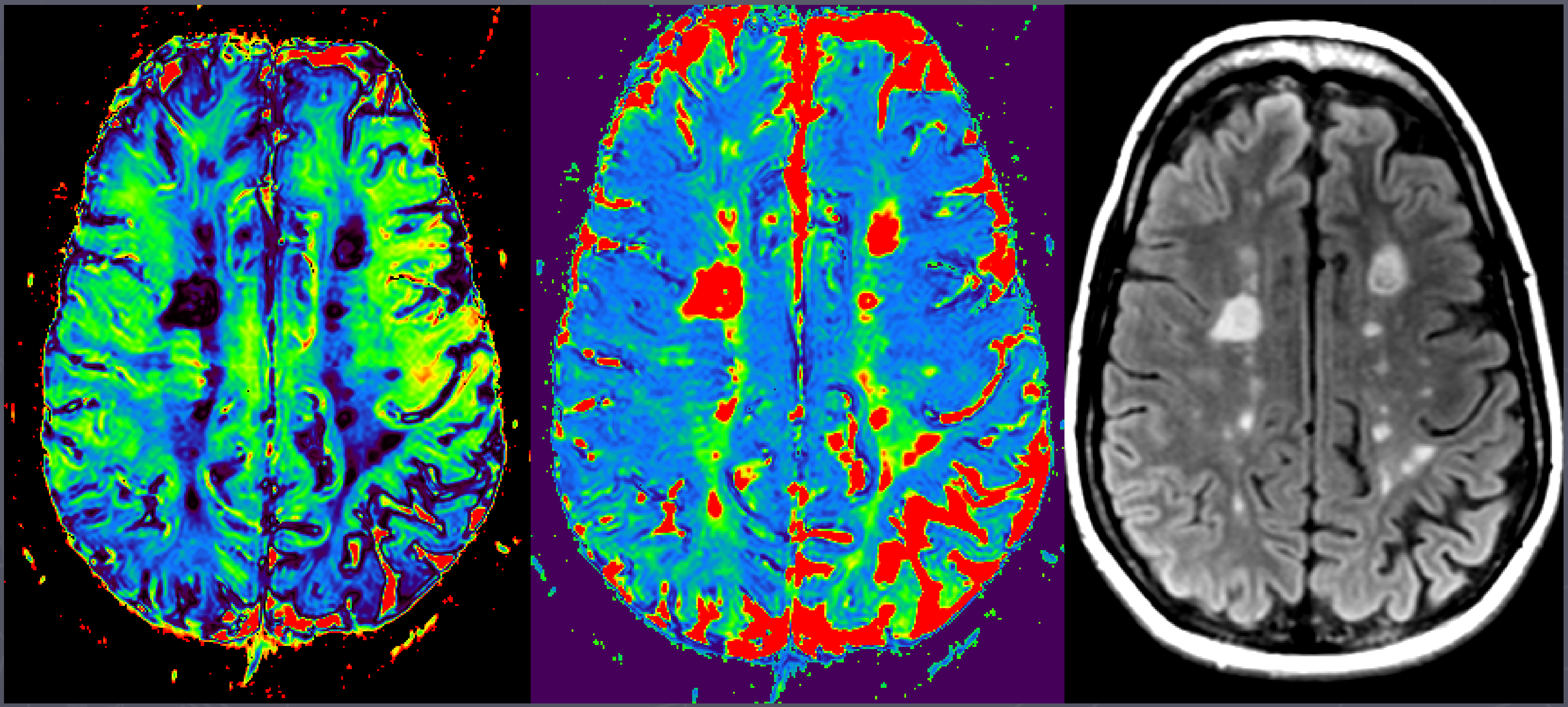
MS acute lesion: Increased CBV



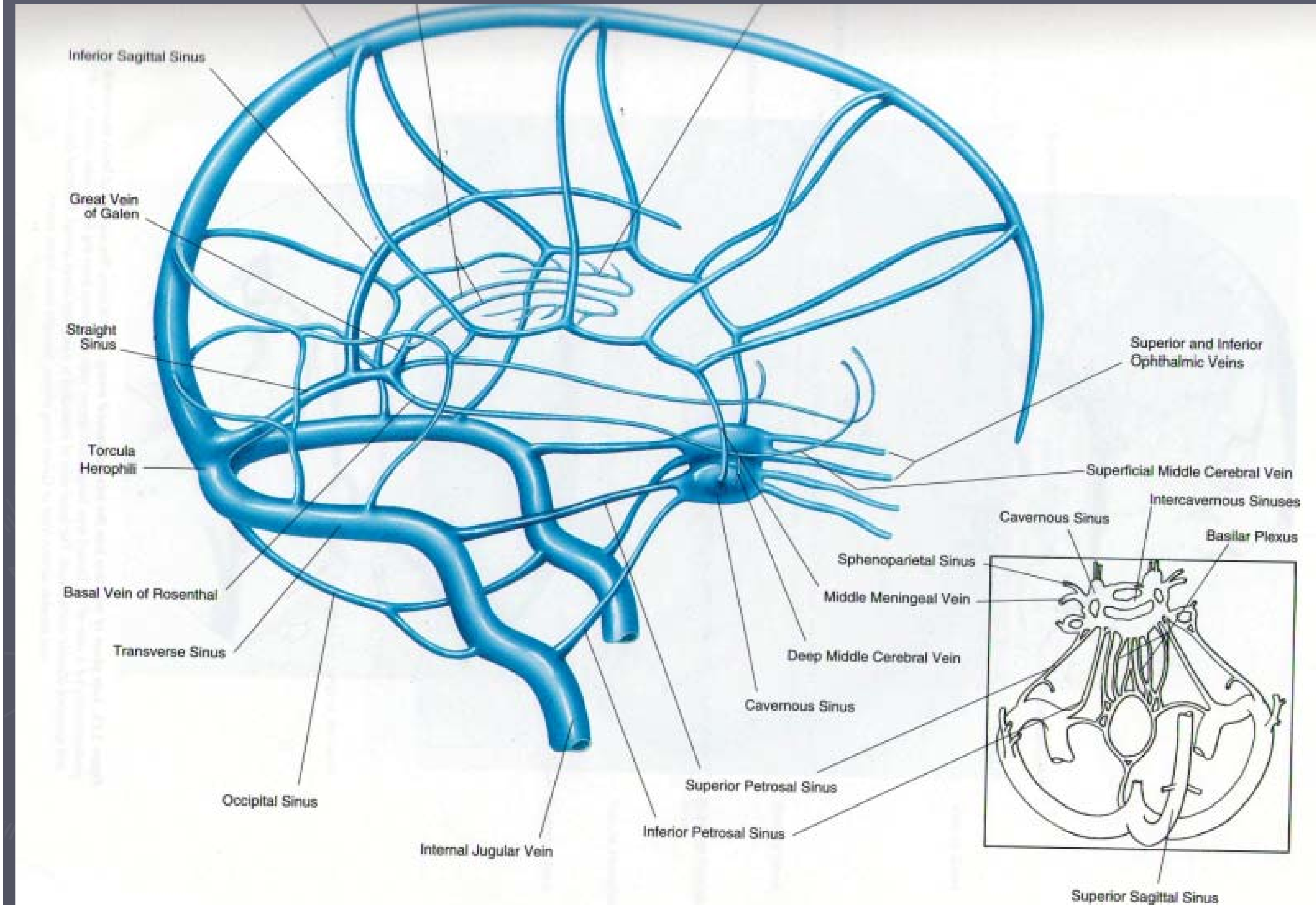
PWI shows loss of CBV in chronic lesion



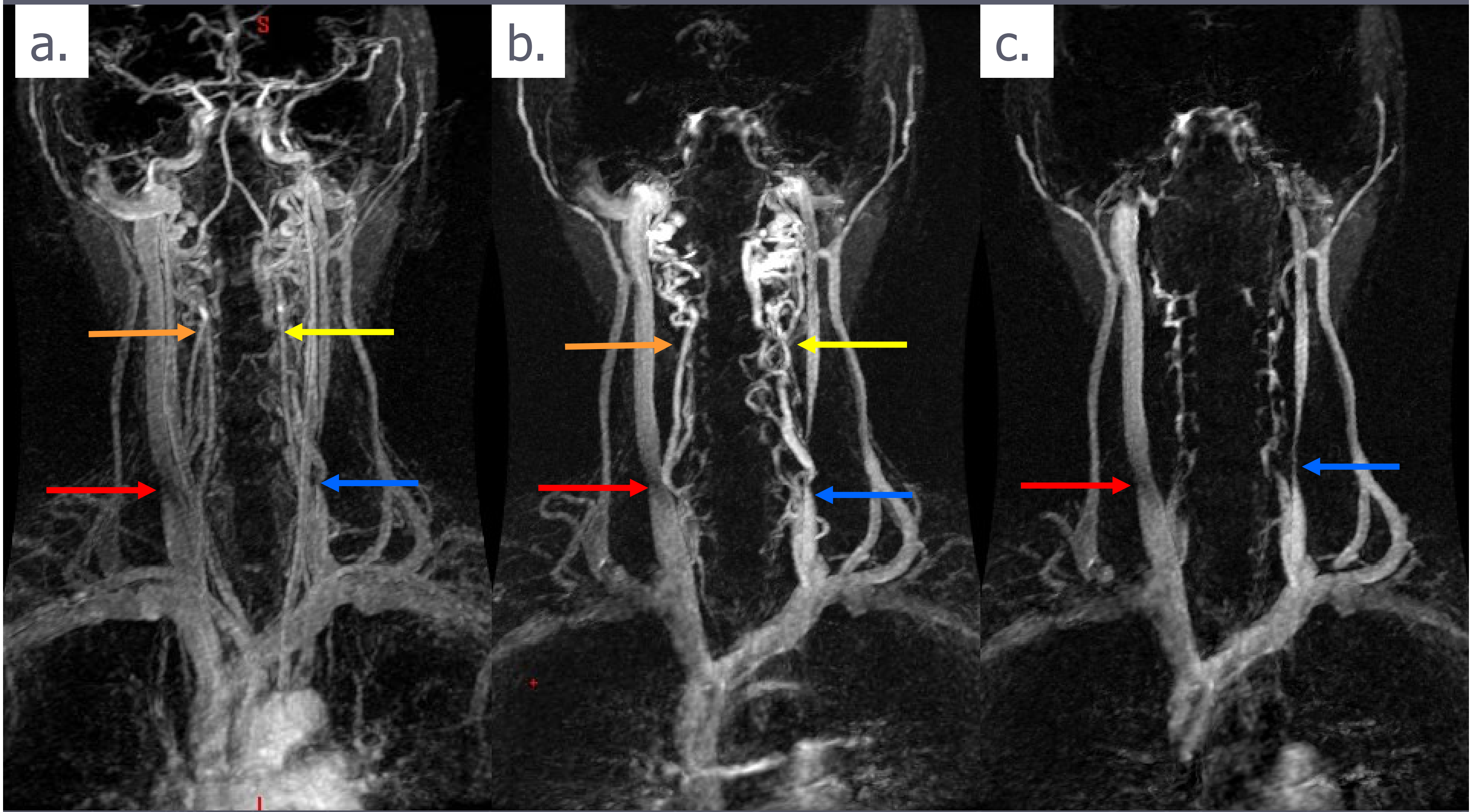
Application of PWI and TSM in MS



nulling lesions | nulling veins | FLAIR

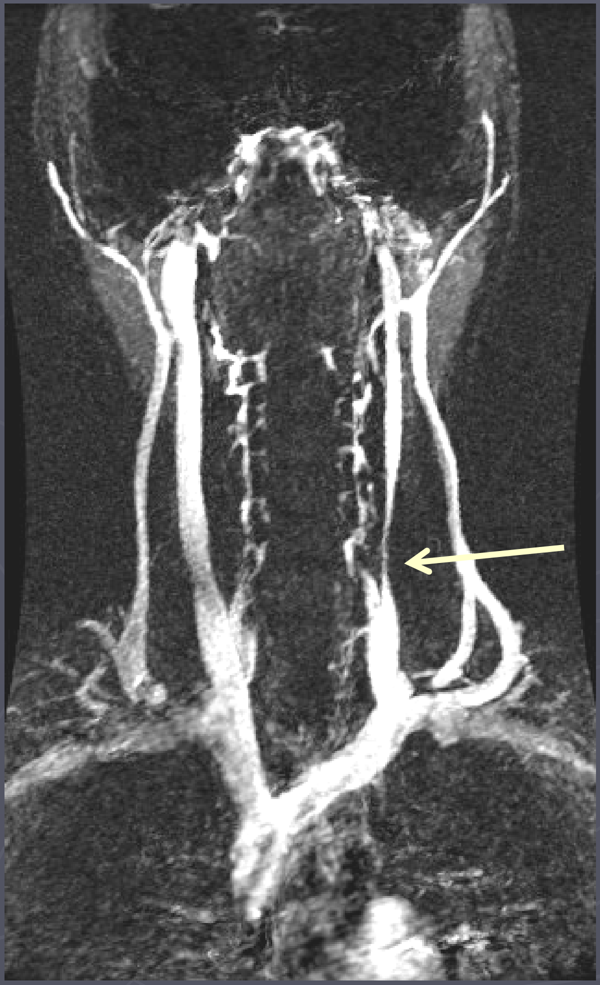

Inferior Sagittal Sinus
Great Vein of Galen
Straight Sinus
Torcula Herophili
Basal Vein of Rosenthal
Transverse Sinus
Occipital Sinus
Internal Jugular Vein
Inferior Petrosal Sinus
Superior Petrosal Sinus
Cavernous Sinus
Deep Middle Cerebral Vein
Middle Meningeal Vein
Sphenoparietal Sinus
Superior and Inferior Ophthalmic Veins
Superficial Middle Cerebral Vein
Intercavernous Sinuses
Cavernous Sinus
Basilar Plexus
Superior Sagittal Sinus

From thick slices to thinner slices: the advantages of 3D imaging



Red arrow: right IJV; blue arrow: left IJV; yellow arrows: vertebral veins

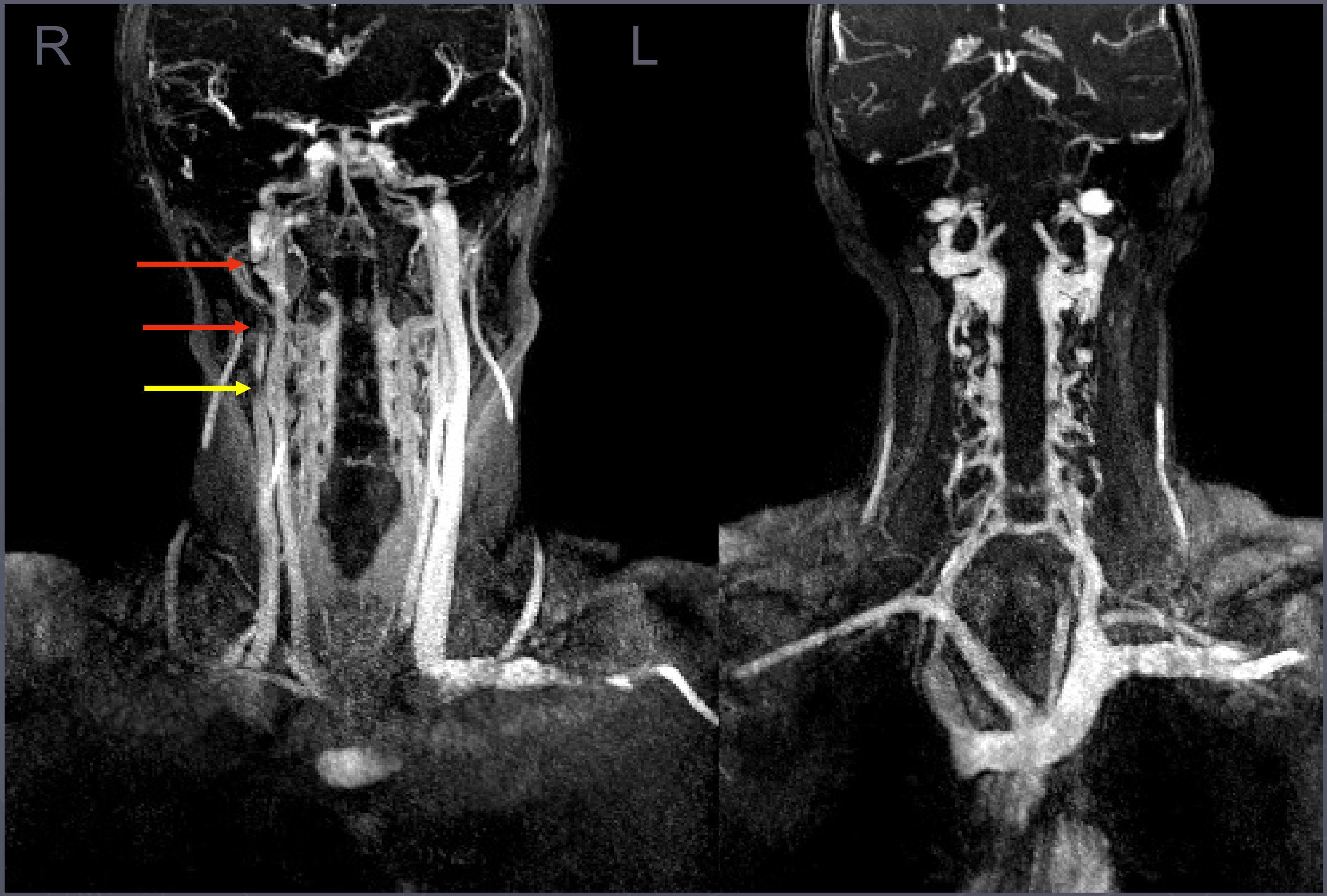
Stenosis at the stump of the LIJV with collateral input



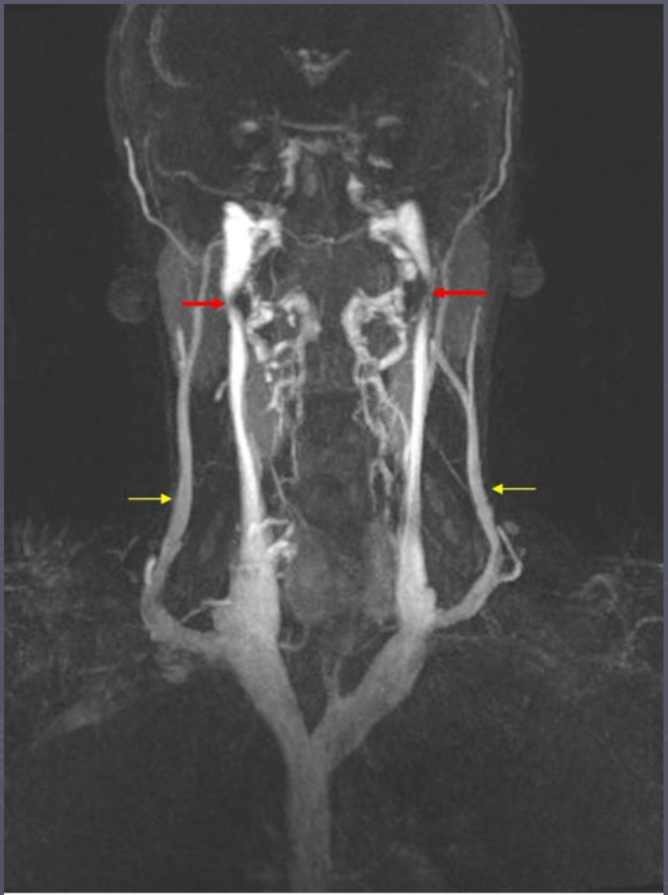
String stenosis

String like RIJV along the entire neck (yellow arrow). Notice the enhanced vertebral system on the same side (short white arrow).

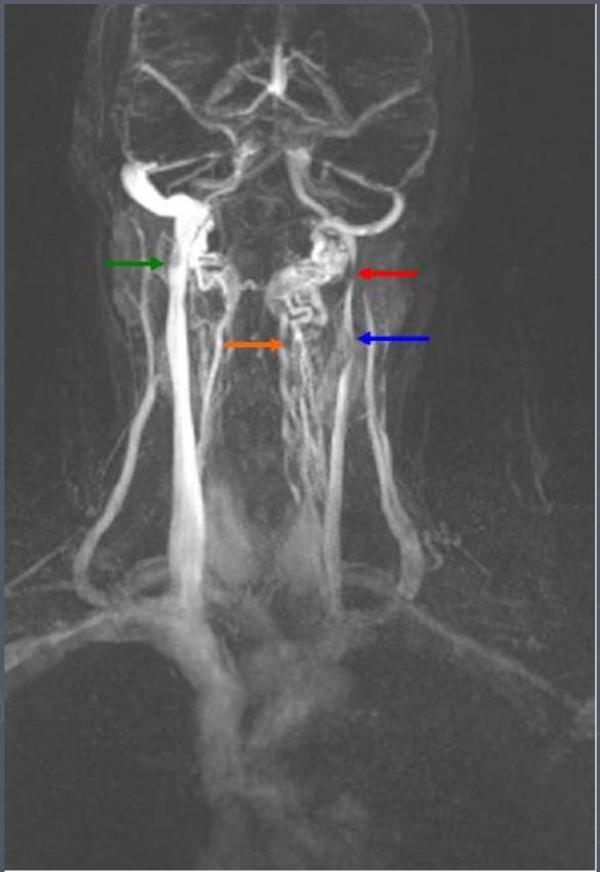
Narrowing and clearly developed vertebral plexus



Upper level stenoses



Bilateral stenosis of the internal jugular veins (upper neck level); yellow arrows=external jugular veins



Stenosis of the left internal jugular vein at upper (red arrow) and middle neck level (blue arrow); green arrow=right internal jugular vein; orange arrow=deep cervical plexuses

What can be done when there is a disconnect?

Stenosis of the right internal jugular vein at upper and lower neck levels (red arrows); blue arrow=left internal jugular vein; green arrow=vertebral plexuses; yellow arrow=external jugular vein

Stenosis of the right internal jugular vein (red arrows); yellow arrow=external jugular vein

Truncular Venous Malformations: Disconnects


Stenosis of the left internal jugular vein at upper neck level; truncular venous malformation of the right internal jugular vein; the right jugular stump is feed by small branches from the vertebral plexuses.


Truncular venous malformation of the RIJV; RIJV narrows and merges with the REJV with a slight widening at the confluence(white arrow). There is a jugular stump at lower neck level.

Middle truncular venous malformation

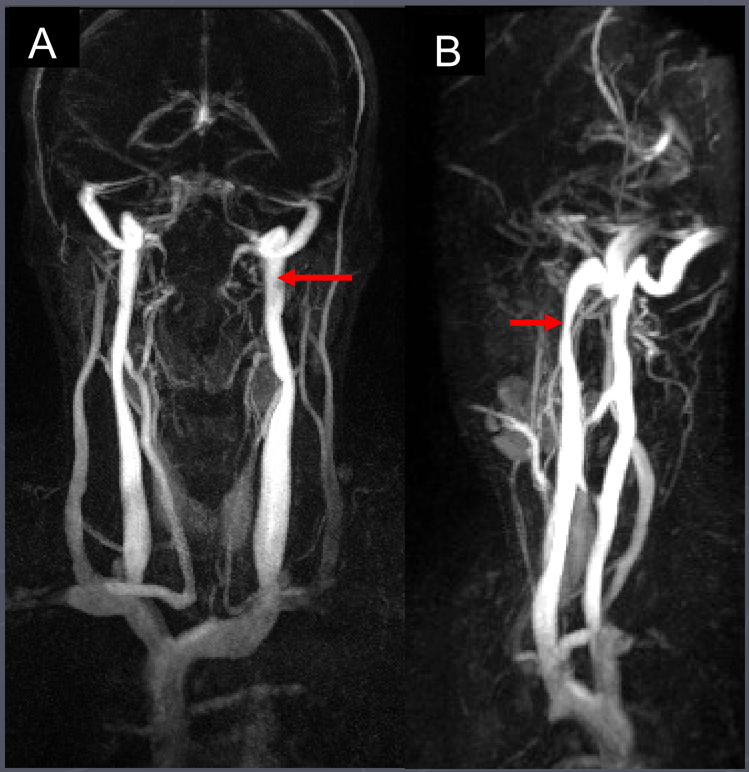
Jugular stenosis

Bilateral stenosis in the internal jugular vein at upper and lower neck level (red arrows)

Normal but narrowed jugular vein

3D rotation shows narrowing with best angle

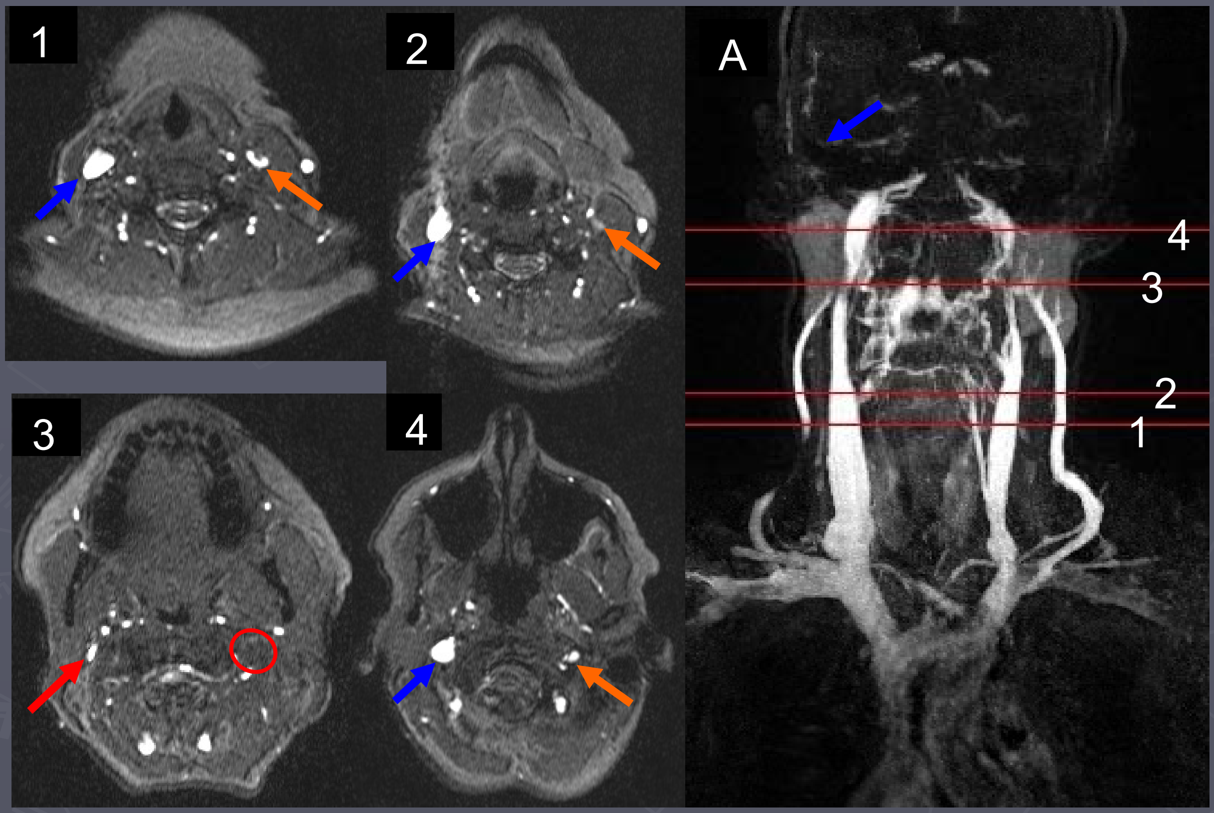
Coronal MIP



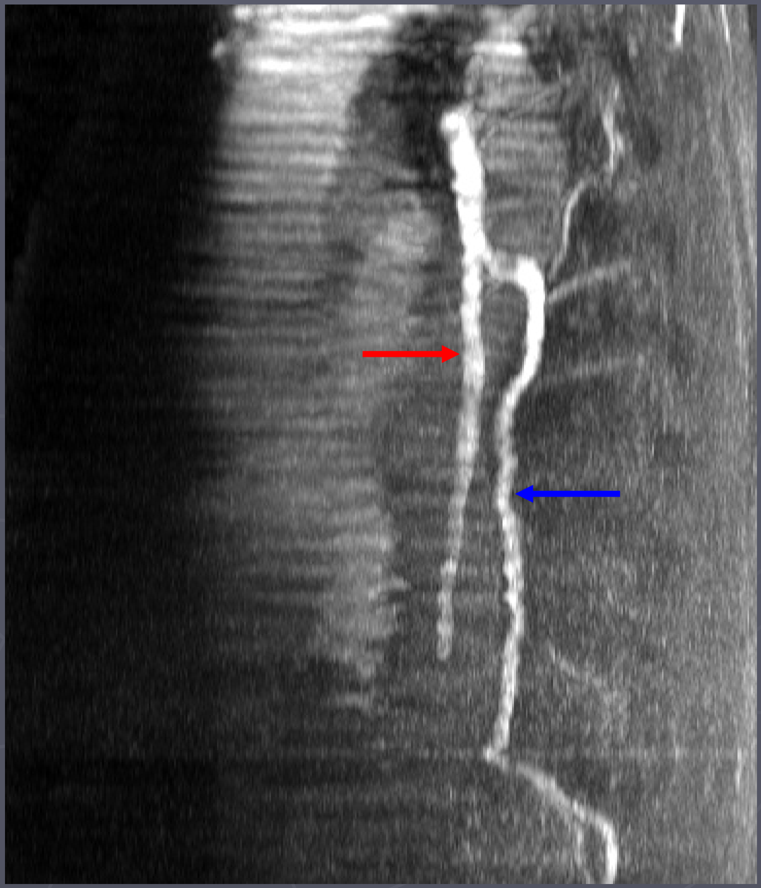
3D MIP Rotation:

Presenting an angle that best shows the normal narrowing

Axial 2D TOF MRV compared to the 3D MIP



Azygous and Hemi-azygous



Imaging MS patients with MRI: Potential CCSVI criteria

- Clear stenoses in one or multiple major veins
- The presence of truncular venous malformations
- Lack of flow in one or more of the major veins
- Dilated IJV near the confluence with the brachiocephalic and subclavian veins
- Stuck or malfunctioning valves (seen as jetting/refilling)
- Circulatory flow
- Reflux present in the IJV or the deep cerebral veins
- Very high flow rates to accommodate slow or reflux flow

Future directions

- combine ultrasound and MR imaging
- continue to characterize the venous problems
- ensure patients get imaged to be able to map out changes over time and to help surgeons plan therapy if this is to be done
- map out the fluid dynamics of the venous system
- study the cardiac input/output to the brain before and after treatment
- create an international imaging protocol
- create an international database

The NICE Protocol: Creating an International Database for CCSVI/SWI Imaging

What can MRI do to assess CCSVI?

- ✓***Post contrast time resolved MRA: to find the stenoses***
- ✓***Flow quantification: to find the abnormal fluid dynamics***
- ✓***SWI: to find the iron and venous damage***
- ✓ ***Quantify these effects before/after balloon angioplasty***

Please visit our site www.ms-mri.com for more information.

NICE = Neurovascular Imaging Center of Excellence

The viral effect in imaging and treating CCSVI

Worldwide there have been roughly 1000 imaging cases and 1000 surgeries.

But as of last week a new IRB allowing a national registry to use the CCSVI or Haacke protocol pre and post treatment appears to have created a tidal wave response by the interventional and soon hopefully the imaging communities.

March to July 2010	100 cases
August to October	200 cases
October to December	400 cases

From only 3 sites so far

Number of sites could now double every three months
At this rate we will have well over 1600 cases by next summer making us by far the largest provider of single protocol processed MS data in the world.

The odds are it will keep doubling, possibly for the next few years.

NOW imagine this for Parkinson's disease, stroke, traumatic brain injury, and perhaps down the line Alzheimer's disease.

The oncoming tidal wave: A viral effect

The following sites are currently collaborating with us:

Mark Godley at the False Creek site in Vancouver, BC

David Hubbard at the Hubbard Foundation in San Diego

Mylène Therrien and Jean-Luc Gariepy at IRM in Quebec City

There are several other sites currently under discussion with us

And in the last week more than 40 sites have expressed interest.

Investigating other neurological diseases

Other diseases that are waiting to be studied in the same NICE fashion:

Aging and Alzheimer’s disease, Parkinson’s disease, stroke and last but not least traumatic brain injury (TBI).

Conclusions and future directions

Can neurodegenerative diseases be vascular in origin?
Or do they contain a major connection to the vascular system?
We can answer these questions quickly and efficiently if there are centers of excellence set up across the country.

The NICE database, the national registry set up by David Hubbard, and coordinated research efforts can lead to a more rapid understanding of certain aspects of disease. This must be approached with a focused national effort, linked not just to academic community but to the practicing clinical community. This type of imaging research can be used to dramatically enhance medical research in some diseases by collecting and evaluating new protocols for 100,000s of cases. We are beginning that process now.