Iron in the Normal and Pathologic Human Brain

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Acknowledgements:

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Outline

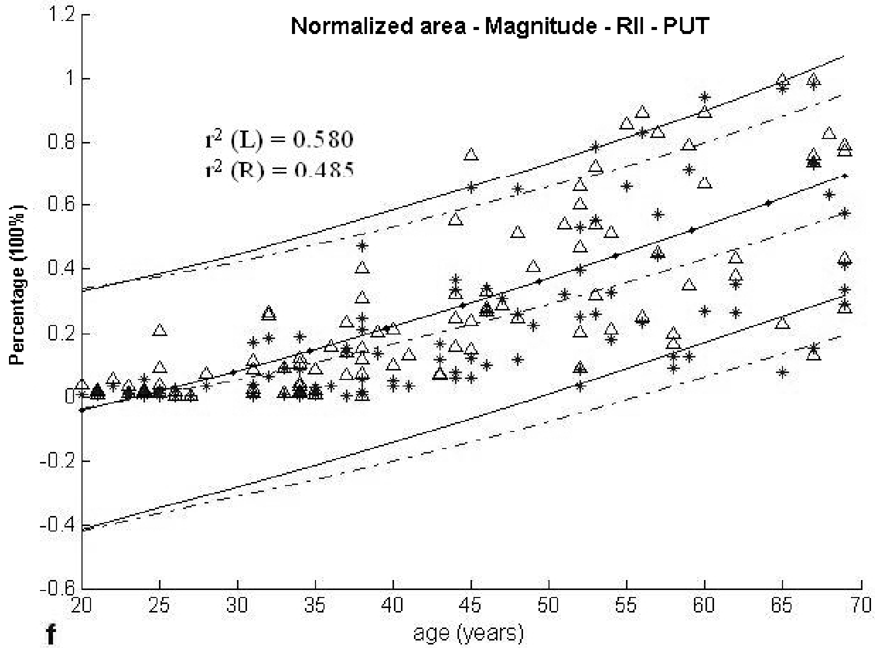
- Preamble: some facts about iron in the body.
- Diseases related to iron.
- Measuring iron with MRI and other techniques.
- Future applications.

Preamble

- Iron has long been considered as a key nutrient for the body and many physiologic reactions.
- The idea of iron leading to detrimental effects was foreign to most people in medicine up until a few short decades ago.
- For example, the thought that high iron levels could predispose someone for higher risks for cancer, infection and its role as a key catalyst for oxidative reactions was not considered at all until the late 20th century.

Iron

- We absorb 0.5mg to 4mg per day with an average of about 1mg per day.
- Iron appears in hemoglobin, myoglobin and ferritin or hemosiderin, with small amounts in transferrin and lactoferrin.
- There is no mechanism for the excretion of iron.
- Iron can be removed by phlebotomy (blood letting).
- To quote Burton Drayer, "We all rust as we get older."



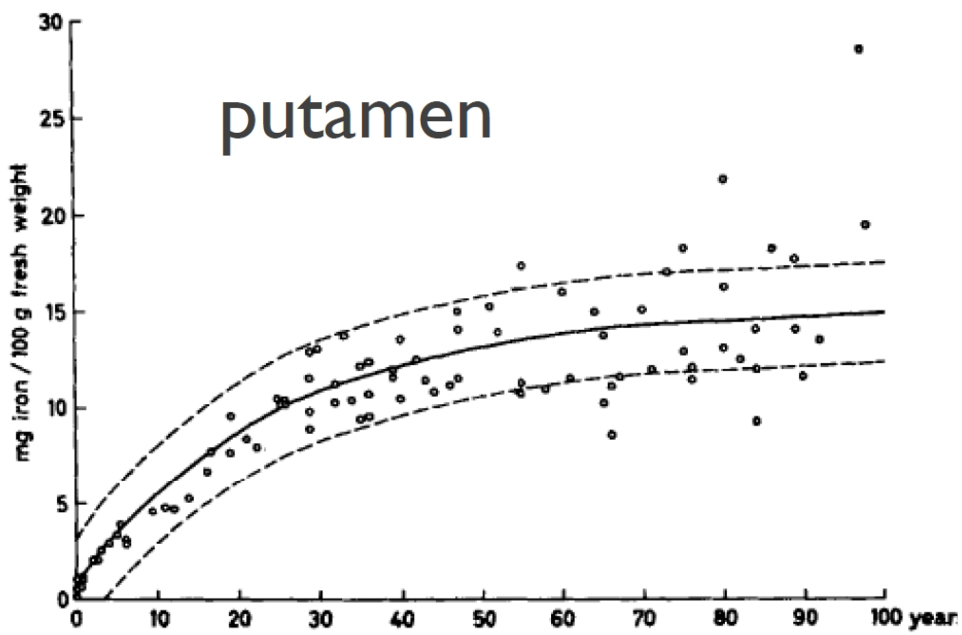


FIG. 3. Non-haemin iron in the putamen. S.E. of estimate = ±2·60.

Rusting as a Function of Age:

The most rapid rise occurs in the first 20 years, after this the rate of iron uptake seems to diminish.

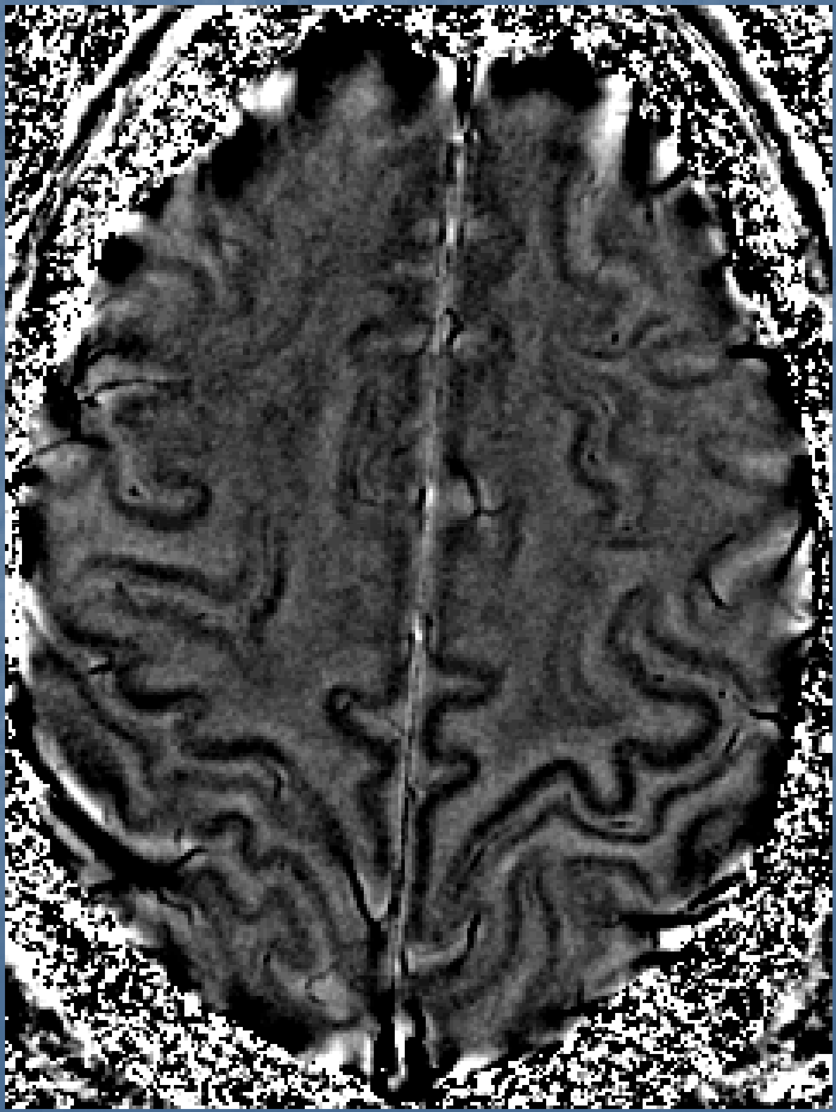
The Storage Protein Ferritin

- Nature has developed a number of iron binding proteins for transportation and storage.
- Ferritin is similar to ferrihydrite $5Fe_2O_39H_2O$.
- Ferritin is a soluble storage protein able to hold up to 4500 iron atoms.
- Ferritin has 24 H (heavy) and L (light) subunits.

Heavy and Light Ferritin

- H-ferritin is associated with high iron utilization and low iron storage and has a ferrioxidase activity that is responsible for converting harmful Fe^{+2} to Fe^{+3}.
- L-rich ferritins are more thermostable than H-rich and promote iron mineralization at the ferritin core.
- Microglia contain only L-ferritin (to scavange iron).
- Neurons contain only H-ferritin.
- Oligodendrocytes contain both.

Filtered Phase Image at 3.0T

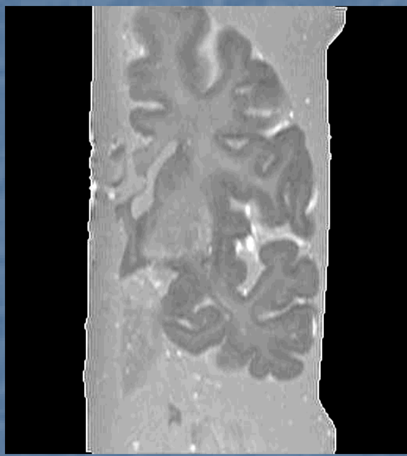


- Motor cortex has higher iron which is likely in the form of ferritin
- At 3T with parallel imaging we can reduce the time for whole brain coverage from 16 min to 4 min with a resolution of

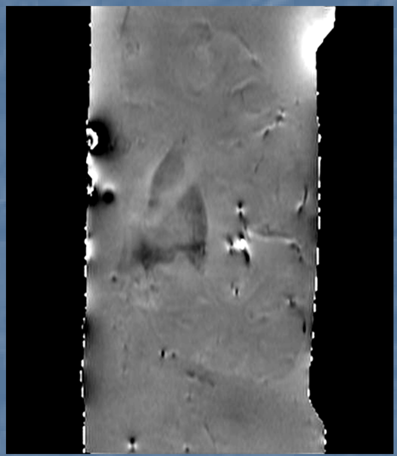
  0.5mm x 1.0mm x 2mm.

SWI / XRF in MS

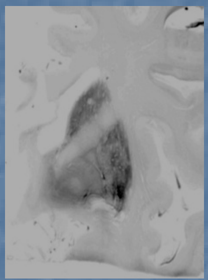
- Previous work in SWI/XRF correlation based on phase images



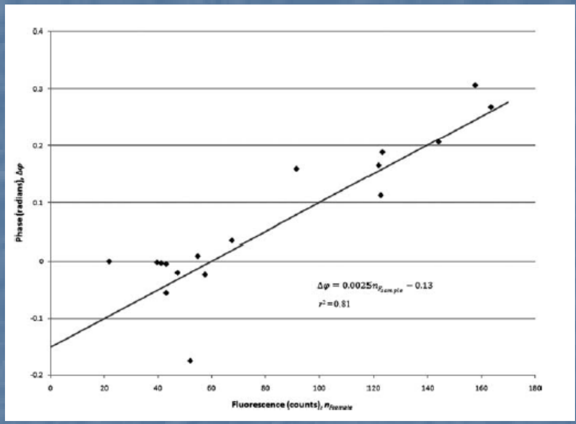
Magnitude



Phase



XRF -iron



Hopp et al, 2010, JMRI

Images courtesy of: Helen Nichol and Richard McCrea

Dept of Anatomy and Cell Biology, University of Saskatchewan

Iron Mobilization from Ferritin

- Iron can be mobilized from ferritin in vitro in several ways.
- Direct chelation can occur via a number of natural chelators in the cells such as:
  - Various sugars
  - Thiols (dihydrolipoate and dihydrolipoamide
  - Suntheic chelators
  - Microbial siderophores
  - Superoxides
  - Flavoprotein oxidases
  - Dehydrogenases (xanthine oxidase)

Iron excess

- A breakdown in the regulation of iron can occur when there is an excessive uptake of iron. Causes can be:
  - Defects in iron uptake in intestinal mucosa
  - Hemochromatosis
  - Excessive breakdown of erthrocytes due to abnormal globin synthesis enhanced by blood transfusion (beta-thalassemia)
- A defect in the heme synthesis pathway (porphyria cutanea tarda).
- Excessive iron intake from diet/chronic alcohol intake.

Serum Ferritin

- Serum ferritin correlates with total iron load which is for males roughly 750 mg versus females 250 mg

(1 µg/l corresponds to 7.5mg iron stores)

- But there is a huge variance:
  - 58 to 127 µg/l SFC for men
  - 6 to 618 µg/l SFC for women
- Another study gives:
  - Mean 94 range 27 to 329 µg/l SFC for men
  - Mean 34 range 9 to 125 µg/l SFC for women

Non-heme and heme iron

- Iron is key to survival of eukaryotic/prokaryotic cells.
- The active site of many cytoplasmic enzymes requires iron – for example ribonuclease reducase uses it to reduce ribonucletides to deoxynucleotides (a step which regulates DNA synthesis during cell proliferation and development).
- Heme is formed by chelating iron into protoporphyrin IX by ferrochelatase.
- Erythrocytes make large amounts of heme iron.
- Transferrin carries iron to be stored in ferritin.

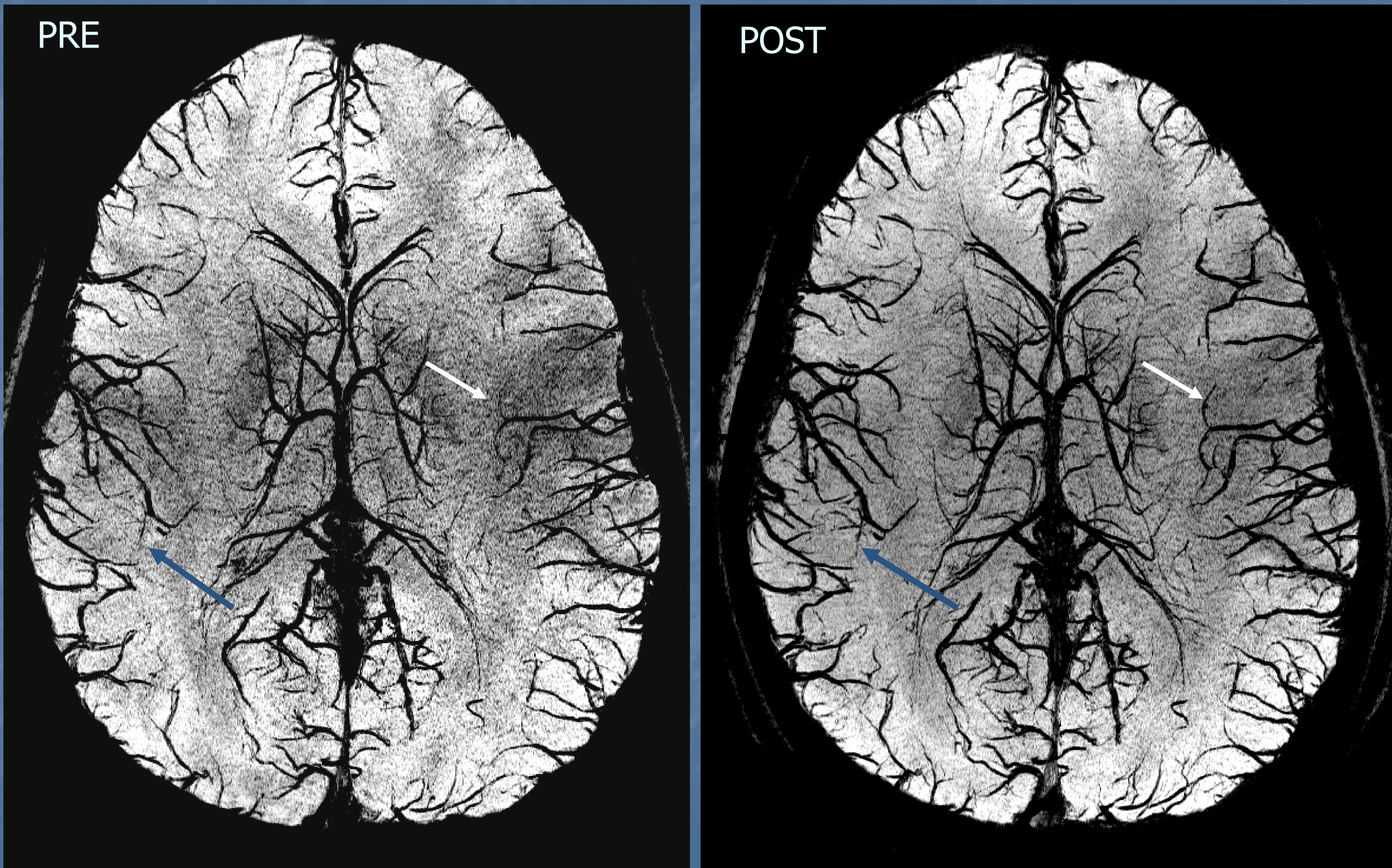
Caffeine decreases blood flow to the brain

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 and post two cups of coffee

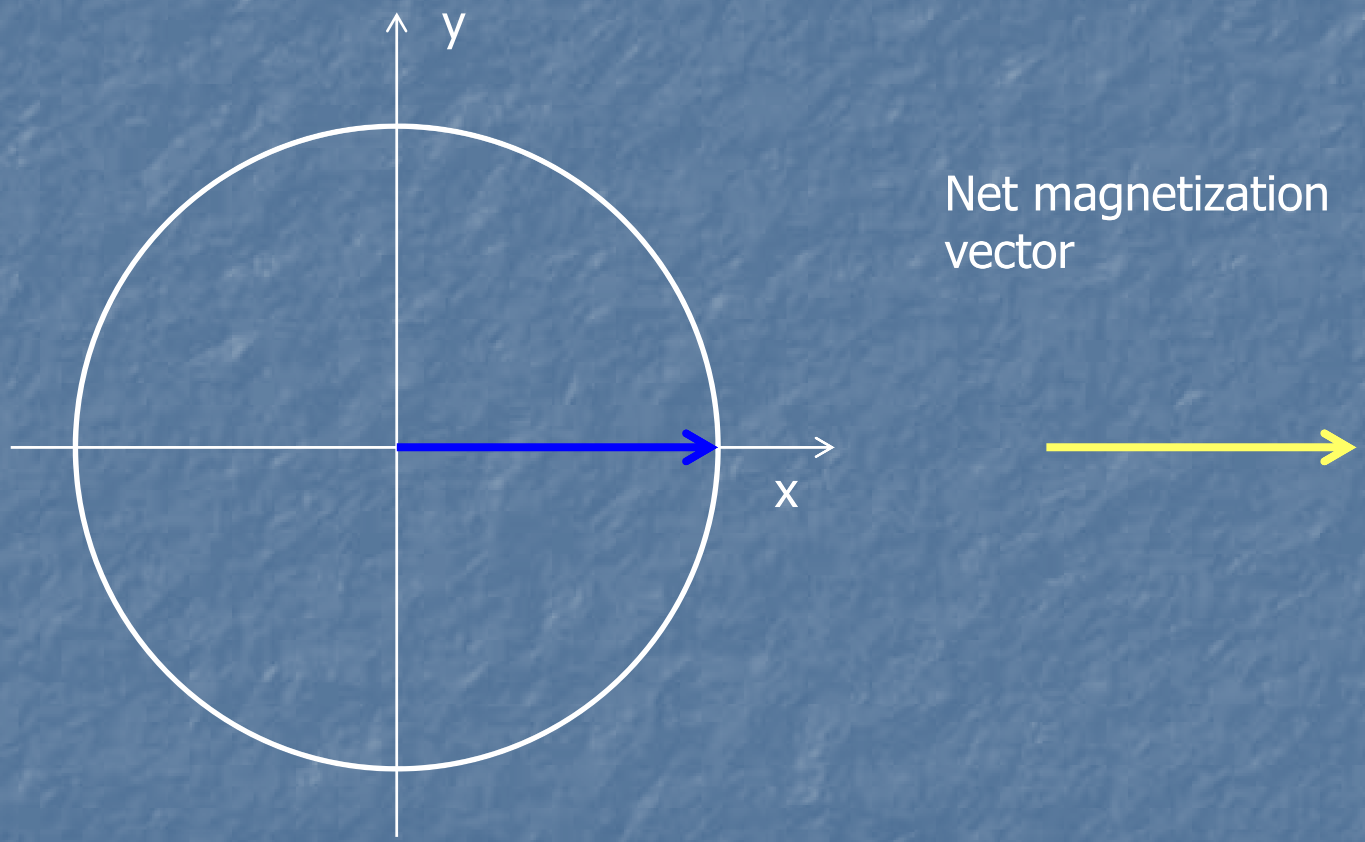


MinIP of caffeine/Gd over 28 slices with 4 phase multiplications

Clinical Applications

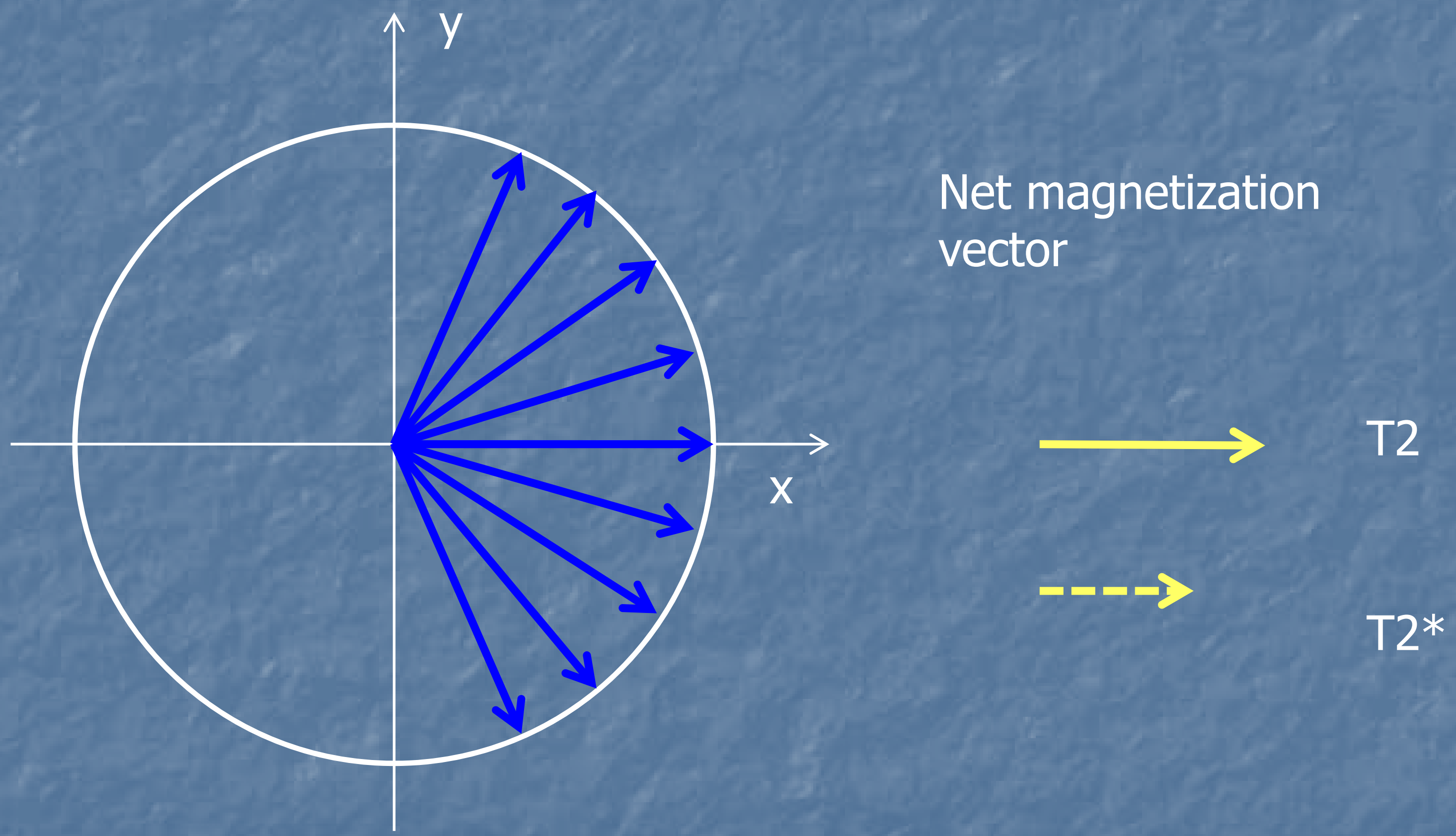
- Cardiovascular disease and atherosclerosis
- Ischemia and hypoxic reperfusion injury and stroke
- Infection and Cancer
- Radiation damage
- Rheumatoid arthritis
- Liver and Thalassemia
- Hereditary ferritonapathies and acerulaoplasminemia
- Huntington disease and Friedrich ataxia
- Blood transfusions and sickle cell disease
- Malaria and hemozoin
- Aging
- Parkinson’s
- Multiple sclerosis

Measuring iron with T2*



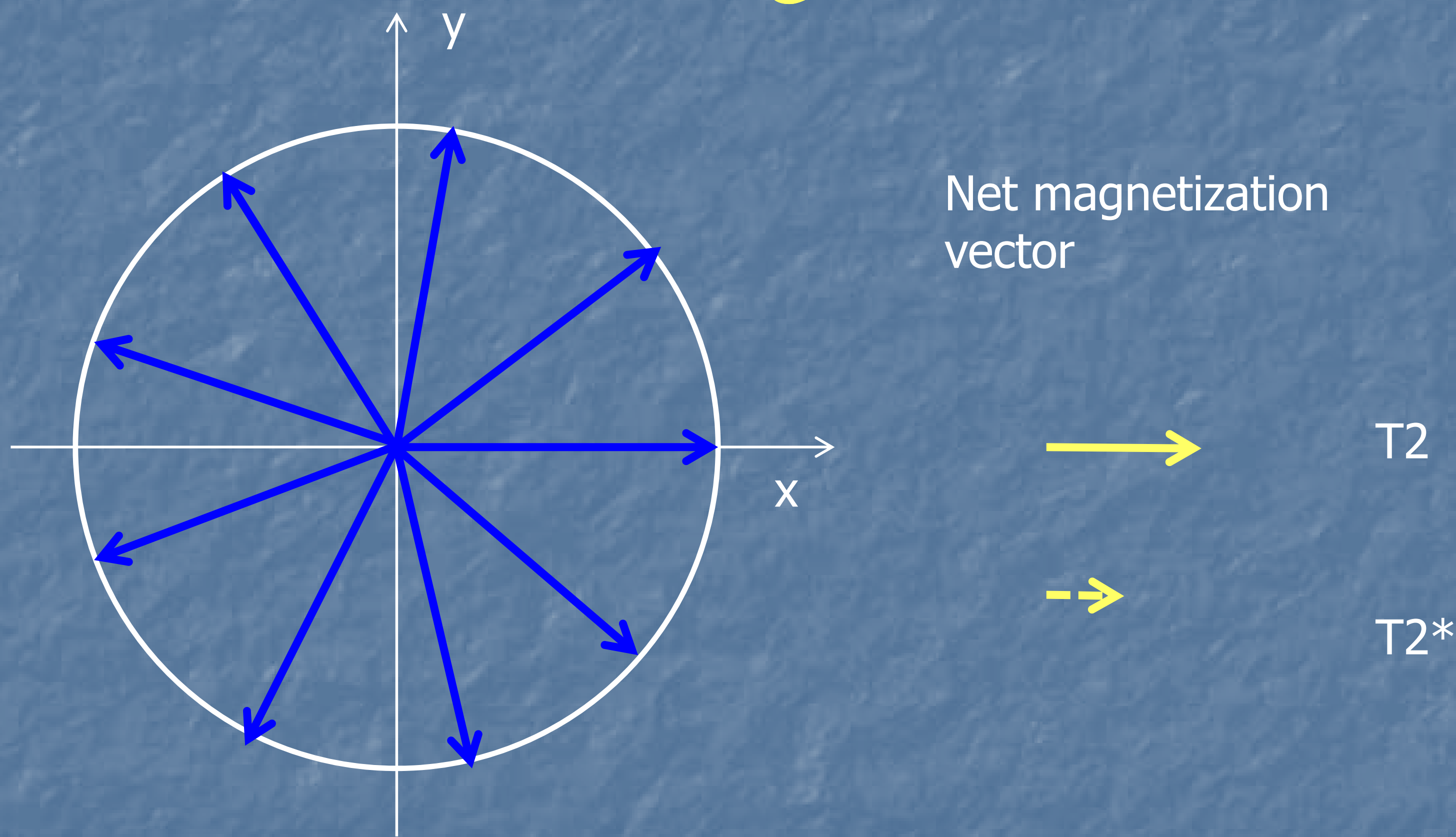
Spin Dephasing

Spin Dephasing



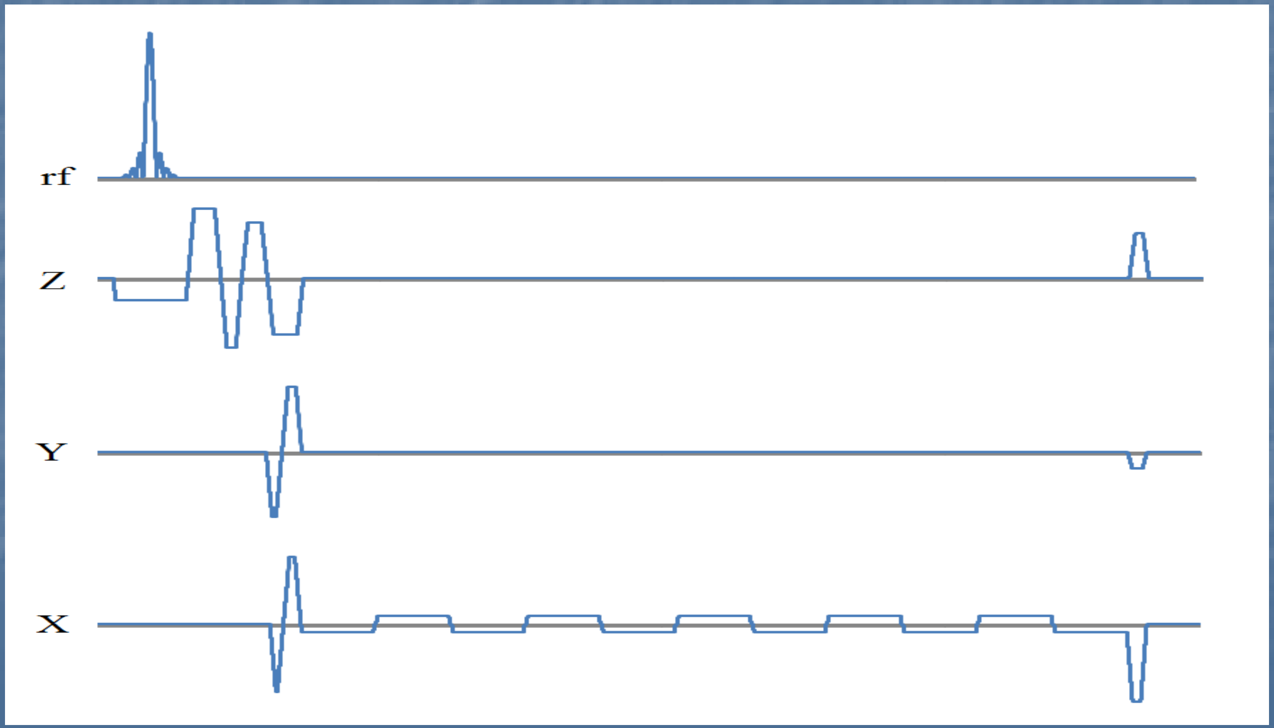
Spin Dephasing

$e^{-t/T2^*}$

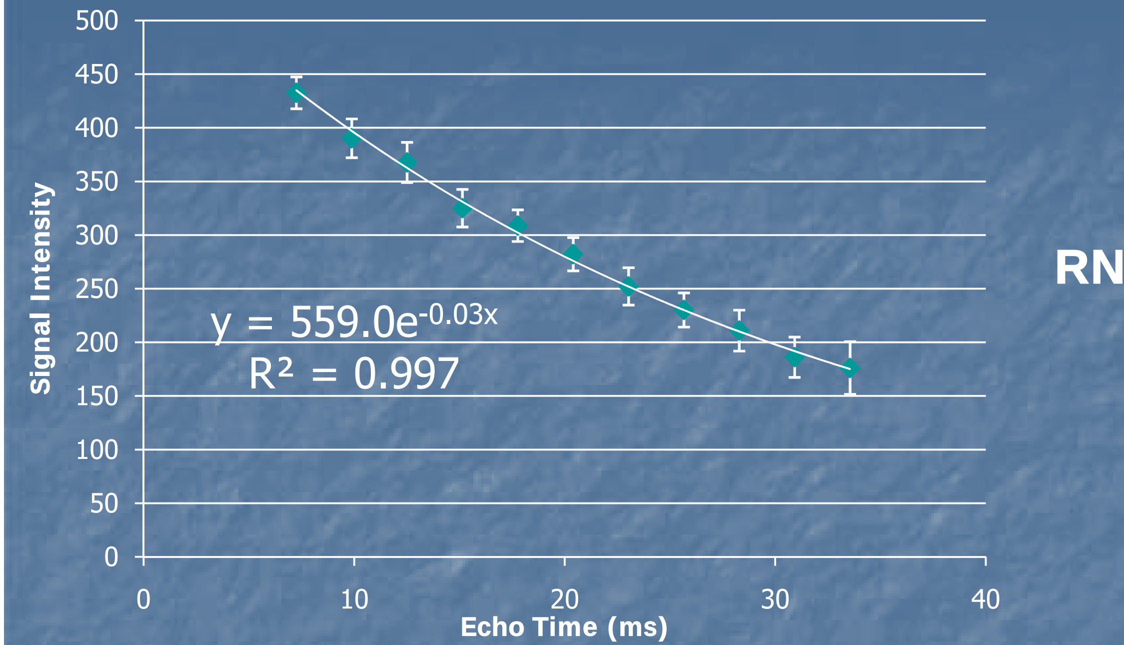


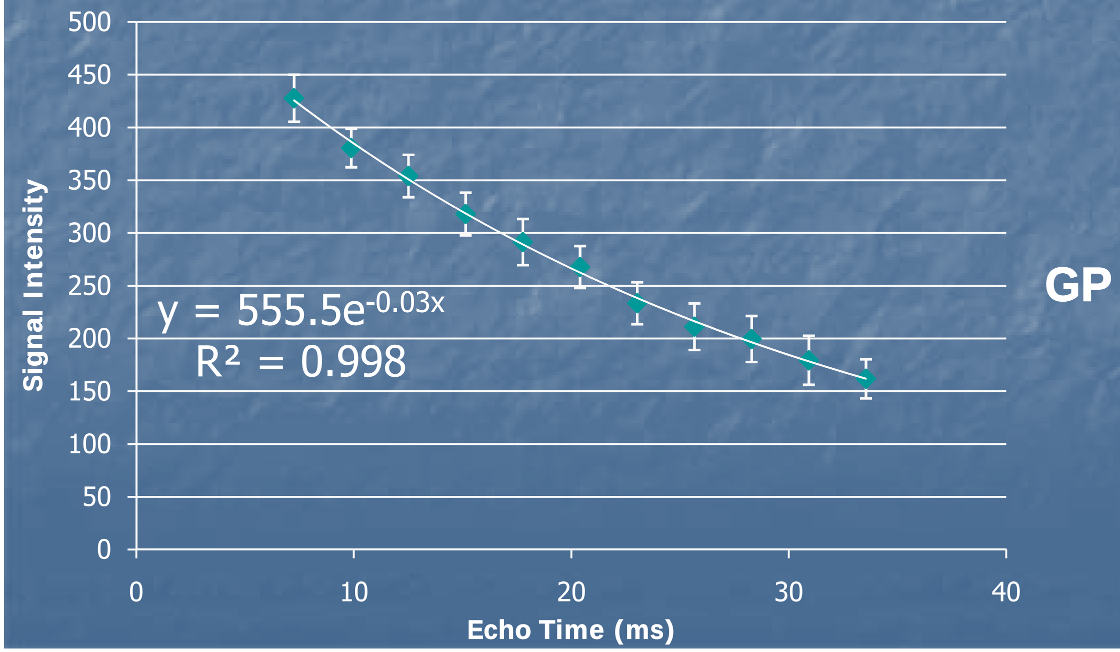
Generating T2* maps from a multi-echo gradient echo sequence

- 11-echo SWI Sequence diagram
- The first echo is flow compensated in three dimensions, others are flow compensated in the readout direction.



Exponential decay seen in human data



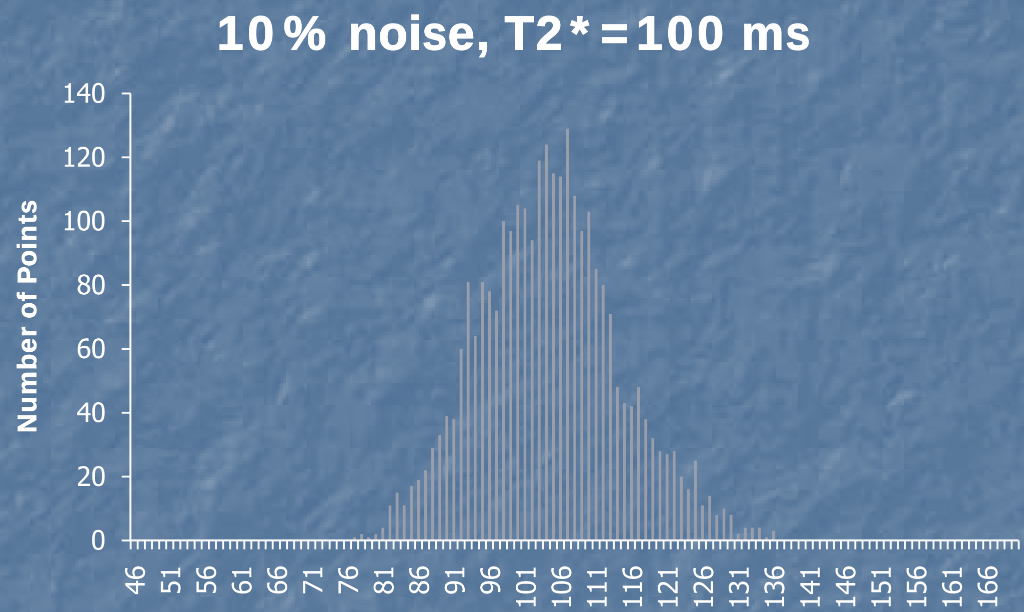


The nice thing about having many echoes is that you can validate whether or not the signal does indeed decay exponentially or at least is consistent with an exponential decay.

The disadvantage is collecting and storing all that data.

Understanding noise in a T2* map

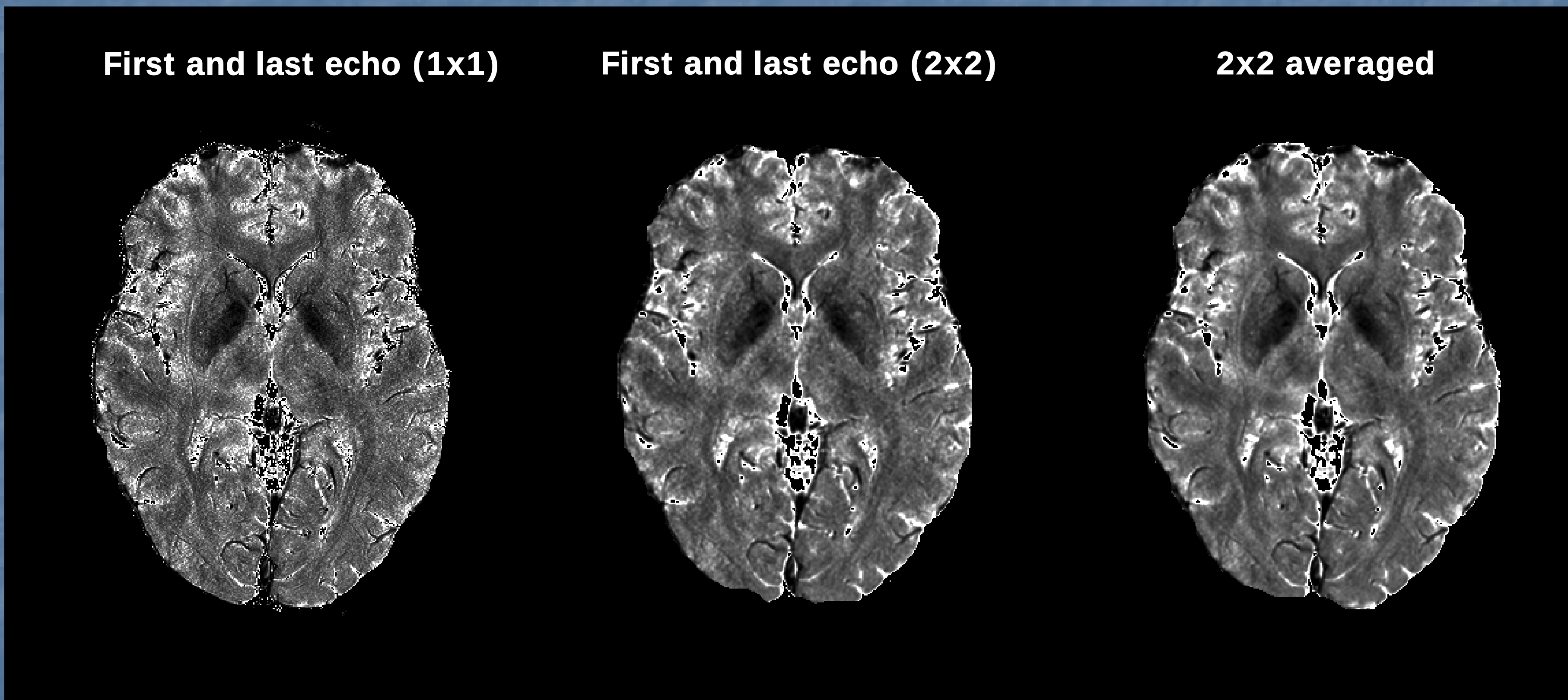
Mean: 103
SD: 10



Things to note:

- The noise is low enough that the T2* map is essentially still Gaussian.
- A 10% noise in the image represents roughly a 10% noise in T2*.
- A change across echo times of 25ms is enough to reasonably accurately and reasonably precisely estimate T2* for tissues with T2* = 100ms.

T2* maps comparison with either two or eleven echoes

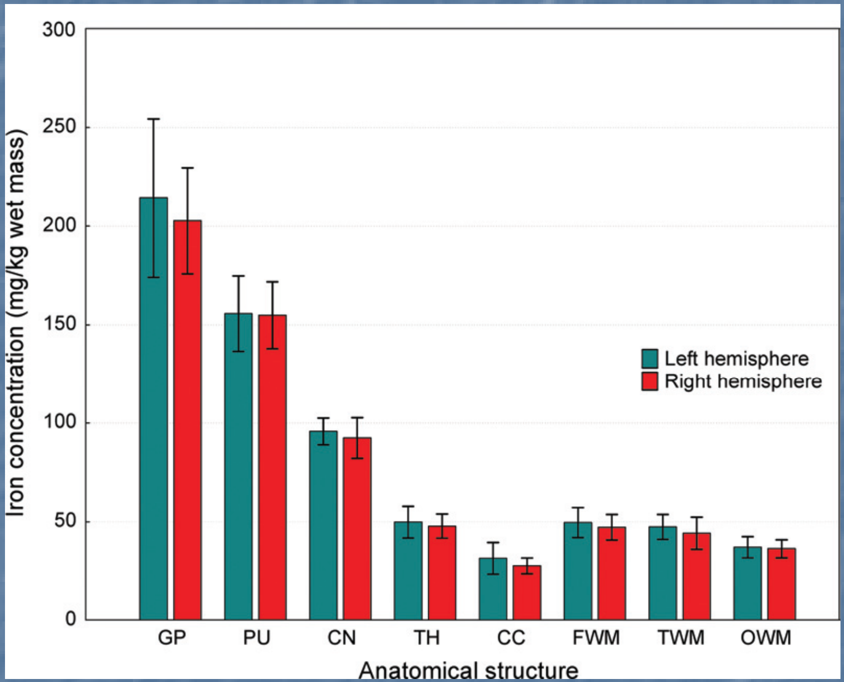


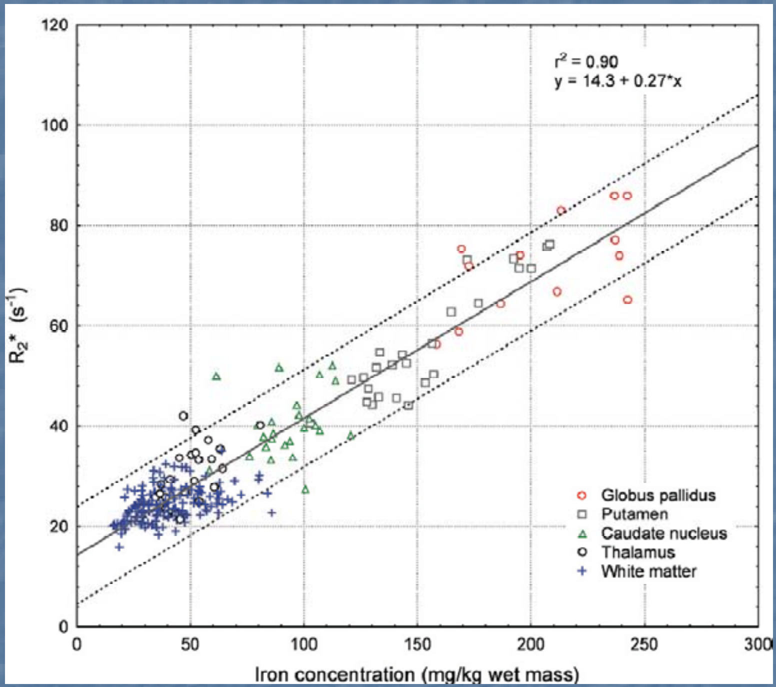
The effect of the number of echoes on the SNR for T2* measurements (in msec) at 3T.

Structure/ (mean/SD)	1x1	2x2	3x3	first & last echo	2x2 first & last echo	Other people's results
RN	28.2/3.8	28.4/1.9	28.4/1.7	28.5/6.1	28.6/3.0	
SN	25.3/3.6	24/1.8	24.1/1.7	24.3/4.4	24.7/2.7	
DN	38.7/6.3	38.1/3.7	38.1/3.3	39.3/7.0	38.0/3.0	
CN	**53.5/4.5**	52.7/2.7	52.8/2.4	52.6/11.4	**50.4/4.8**	40ms
PUT	42.7/5.4	41.9/3.6	42.2/3.4	43.6/6.7	41.9/3.7	30-40ms
GP	28.8/4.8	28.7/2.4	28.7/2.2	30.1/6.3	28.4/4.3	15-30ms
PT	44.4/3.8	44.3/2.5	44.4/2.4	44.4/8.2	43.5/1.7	
WM	55.7/9.3	54.9/4.4	54.9/4.0	57.6/15.2	55/4.7	40-50ms

We can bring the SNR for T2* in line with the 11 echo using just two echoes if we filter the images. This requires much less data storage and allows for the use of a double echo SWI sequence for collecting both phase and magnitude data.

Comparison of iron measurements using mass spectrometry, R2 and R2*



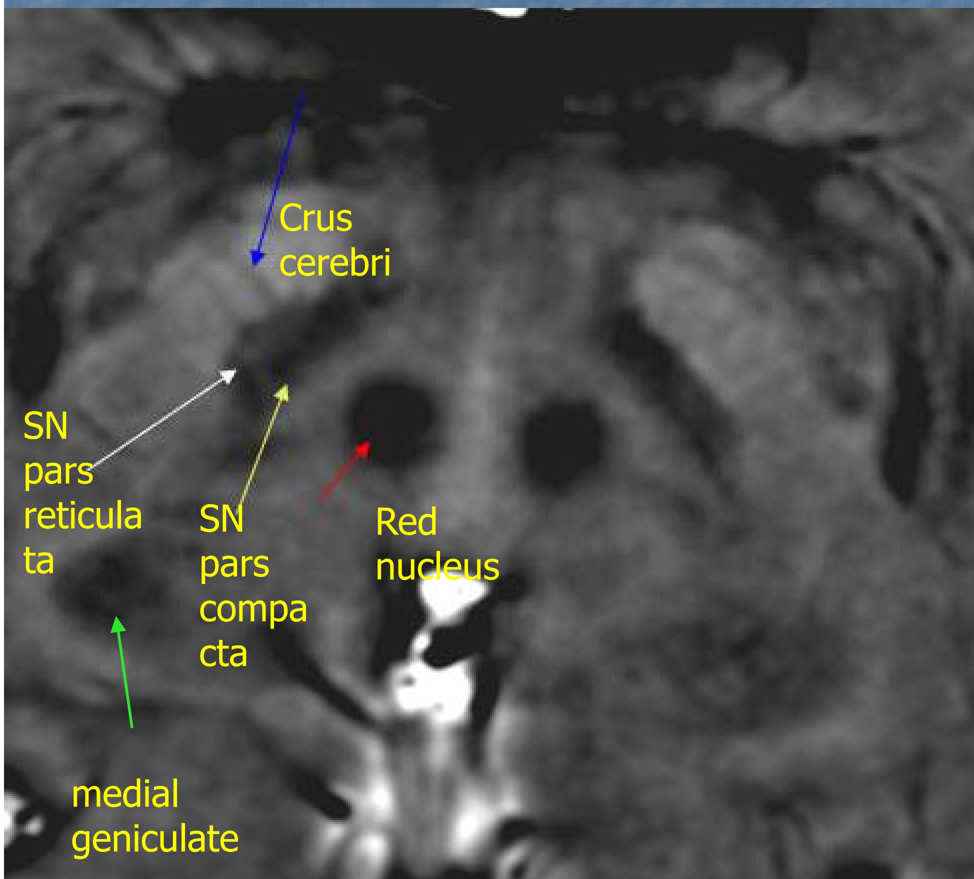


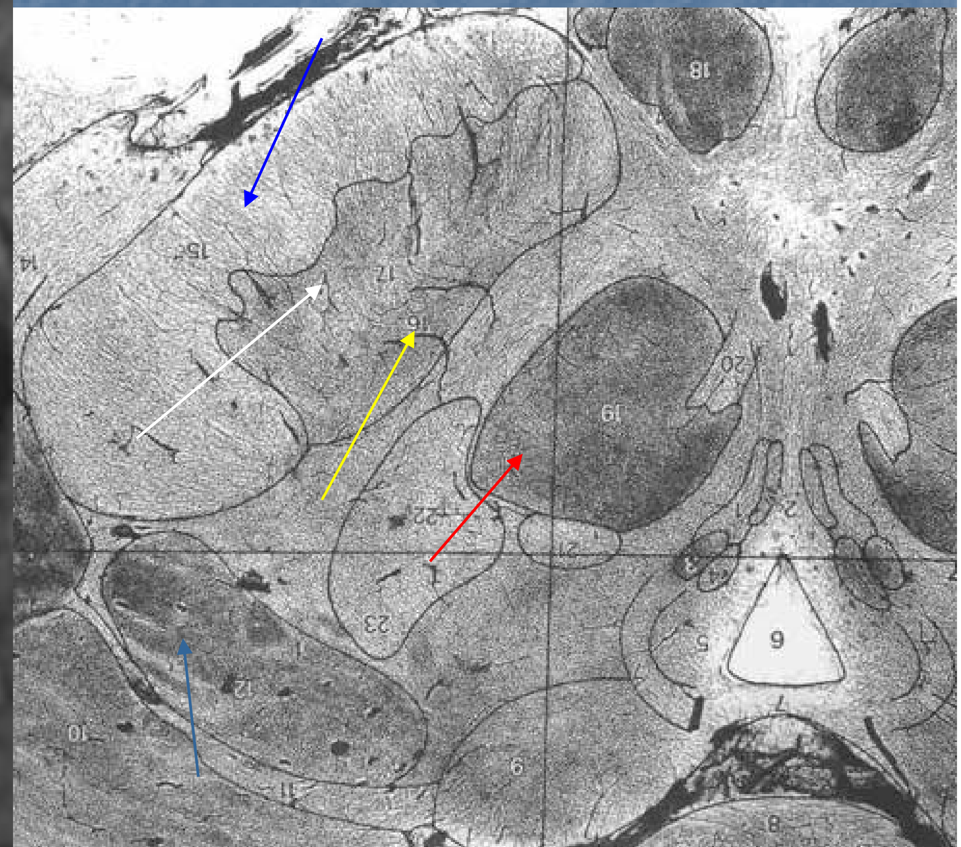
C. Langkammer et al. Quantitative imaging of brain iron: a postmortem validation study. Radiology 257;455:2010.

Iron associated with blood vessels

- H-ferritin is found near blood vessels (BV) and in clusters throughout WM typically with BV at their core.
- L-ferritin is mostly in endothelial cells.
- Morris notes that iron-positive granules appear to be free in the neuropil and around blood vessels.
- Glial cells can become filled with granules and can become replete with iron.

SWI Phase Image in Midbrain

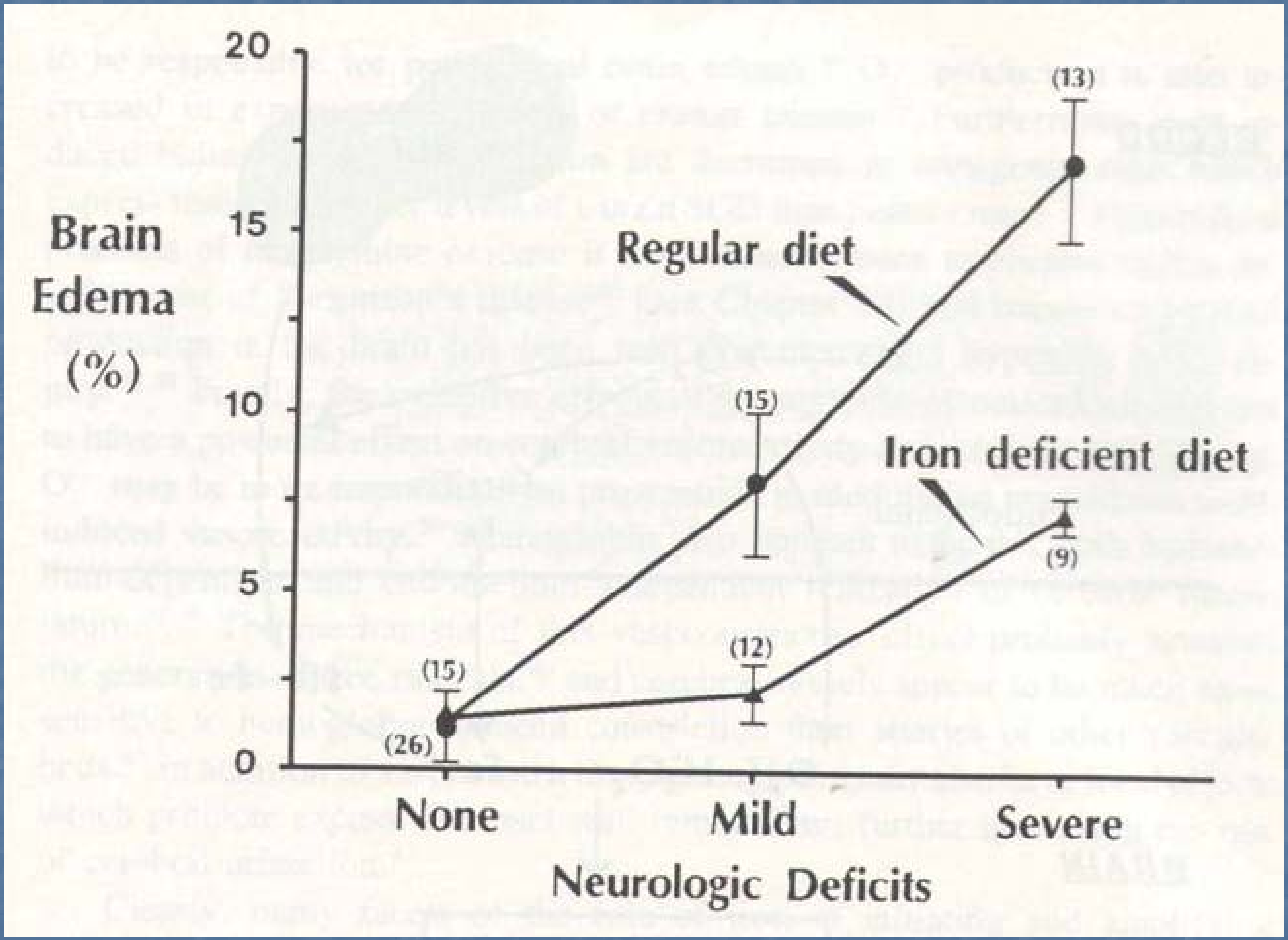




SWI filtered phase image

India ink stained brain

Gerbils with mild or severe neurological deficits had graded increases in brain edema



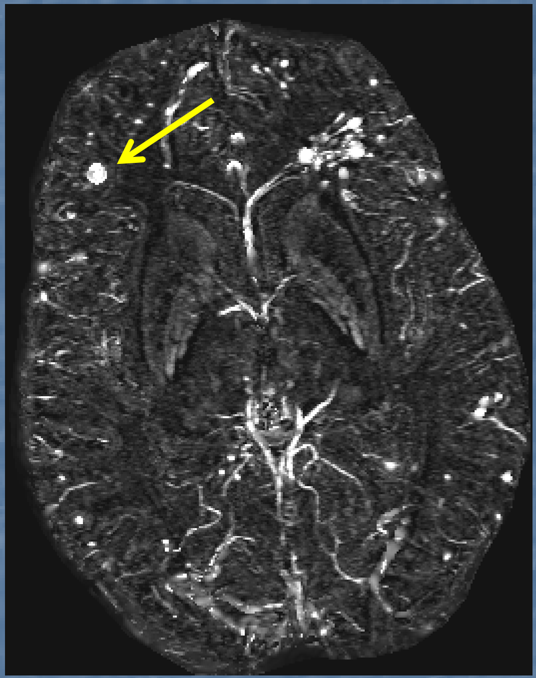
Brain edema was decreased ($p < 0.05$) in symptomatic gerbils fed an iron-deficient diet compared with gerbils fed a control diet, following unilateral carotid artery occlusion-release.

The role of hypoxic reperfusion

- If the tissue is under stress and either in a hypoxic or ischemic state then during this period the endothelium may be most vulnerable.
- If the tissue is re-perfused bringing with it lots of oxygen and the vessel wall has not yet returned to normal there may be a resulting hypoxic reperfusion injury.
- One of the breakdown products during ischemia is xanthine oxidase which can mobilize iron from ferritin producing an environment now rich in iron and hydrogen peroxide (H_2O_2) and lead to the production of free radicals.

The First Clinical Applications of SWIM in Traumatic Brain Injury (TBI)

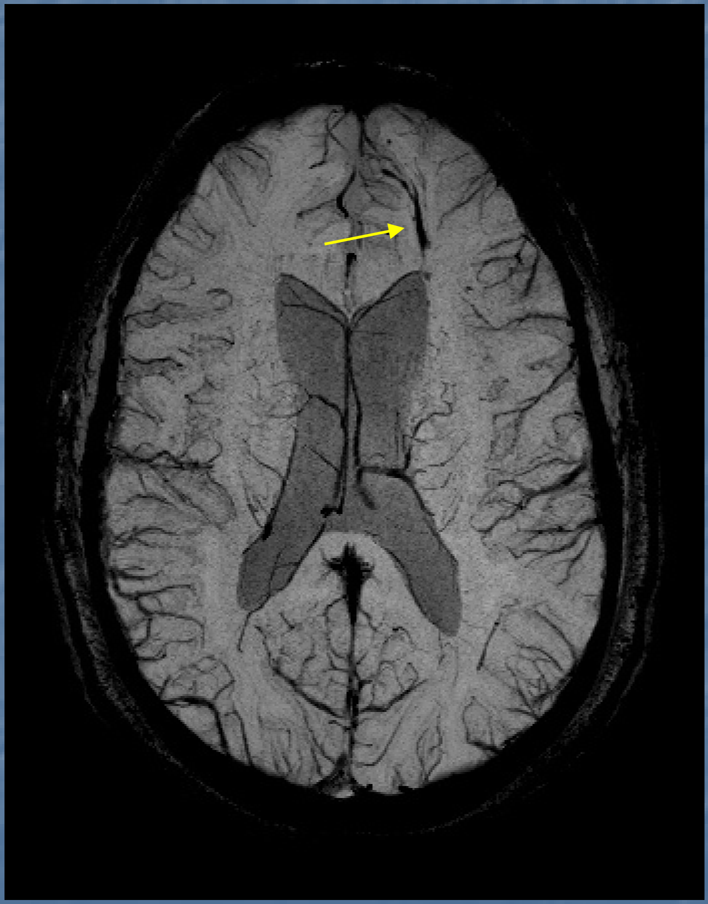
SWI minIP image
projected over 16mm



Corresponding MaxIP
susceptibility map image
projected over 16mm

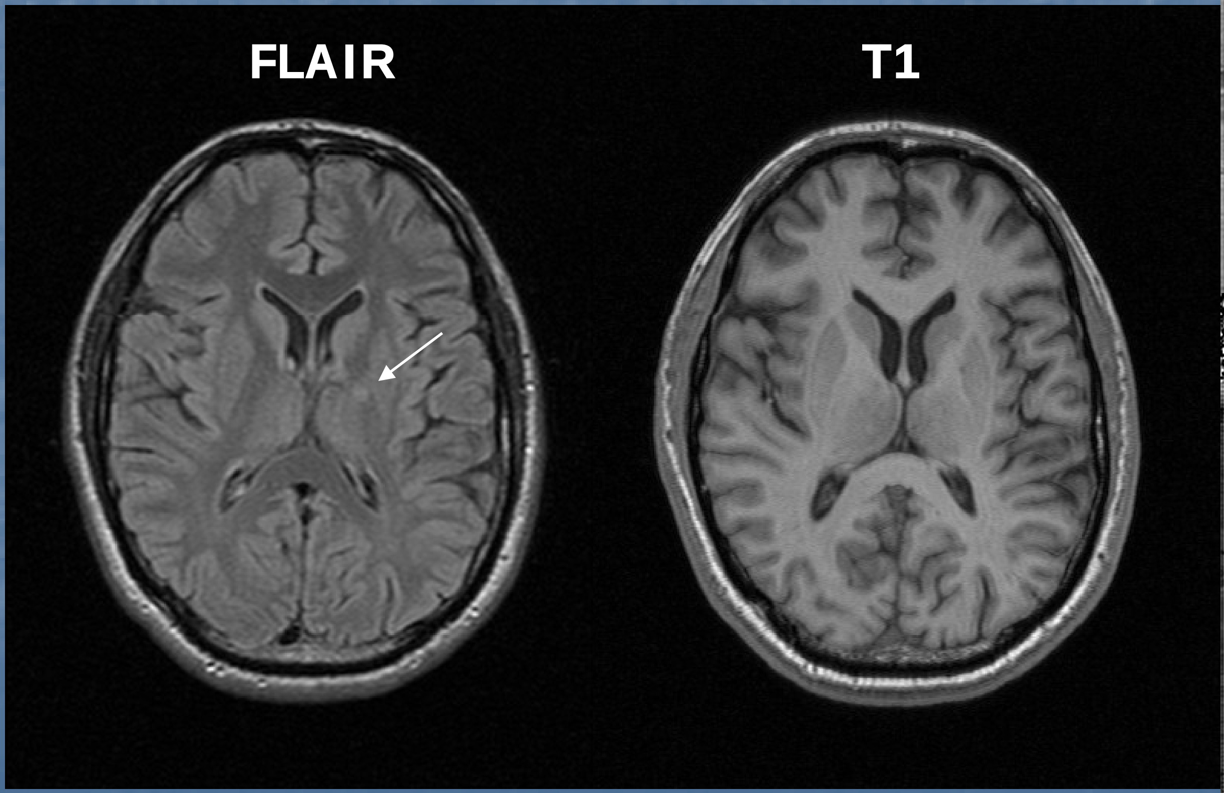
Consider a microbleed with a radius of 1mm and it grows to 1.2mm, then its volume change is 73% but you won't see this by the naked eye. However, *the susceptibility map will show it clearly as a 73% increase in iron content.*

Medullary vein damage in TBI

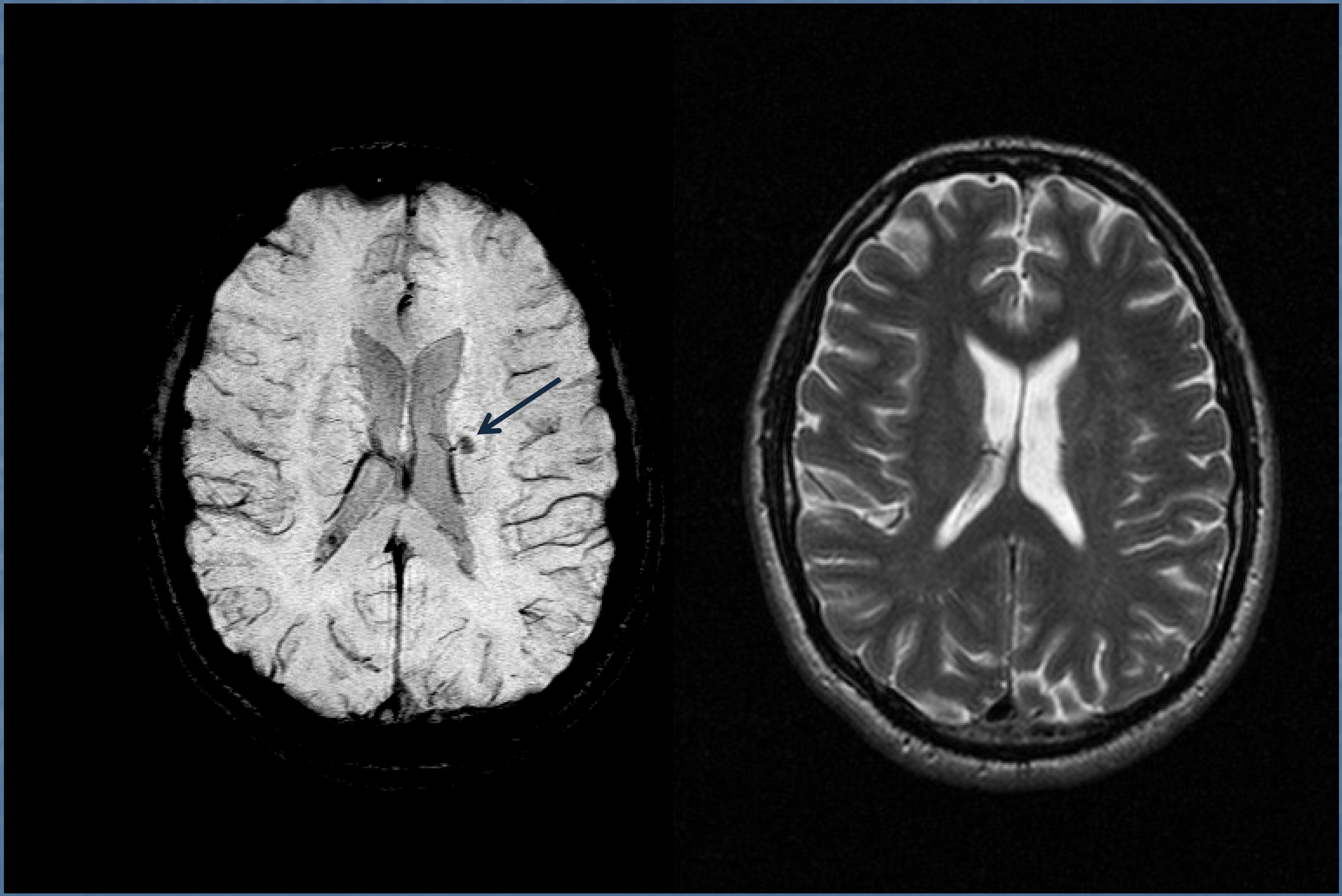


We have seen this type of venous vascular damage in 35 out of 100 cases of mild, moderate and severe TBI.

Low concentration of iron is only seen on the phase images.



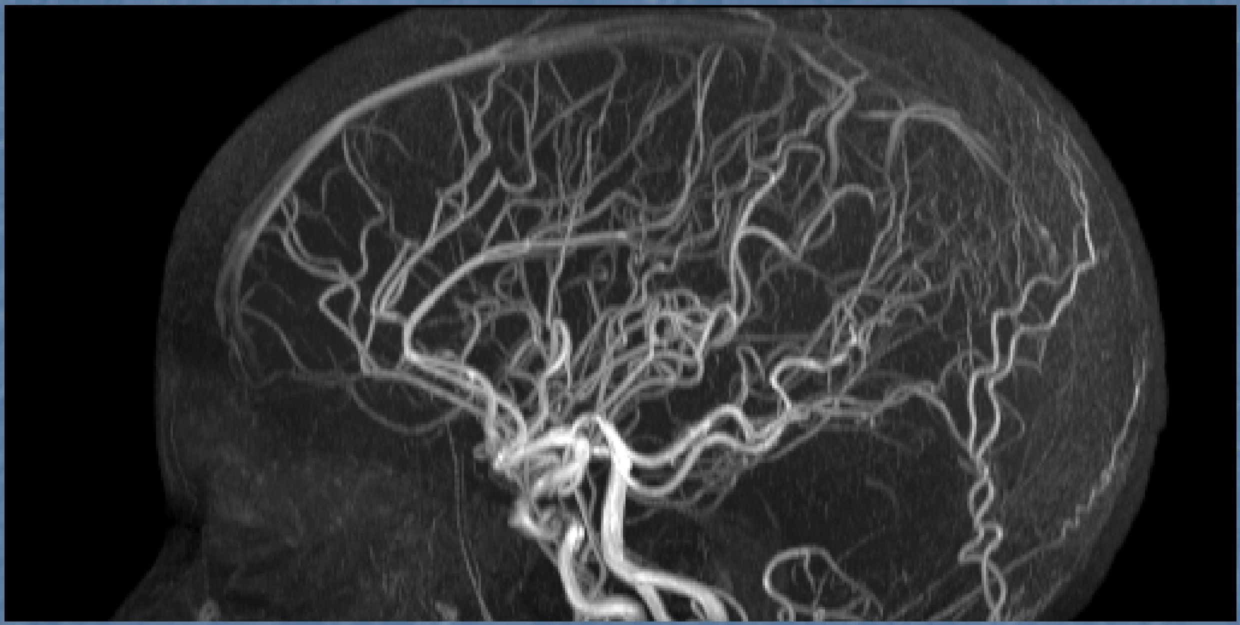
SWI clearly reveals the location of the stroke



SWI shows the bleed

short TE GRE T1

CCSVI, FLOW and SWI in imaging neurodegenerative disease



E. Mark Haacke, PhD
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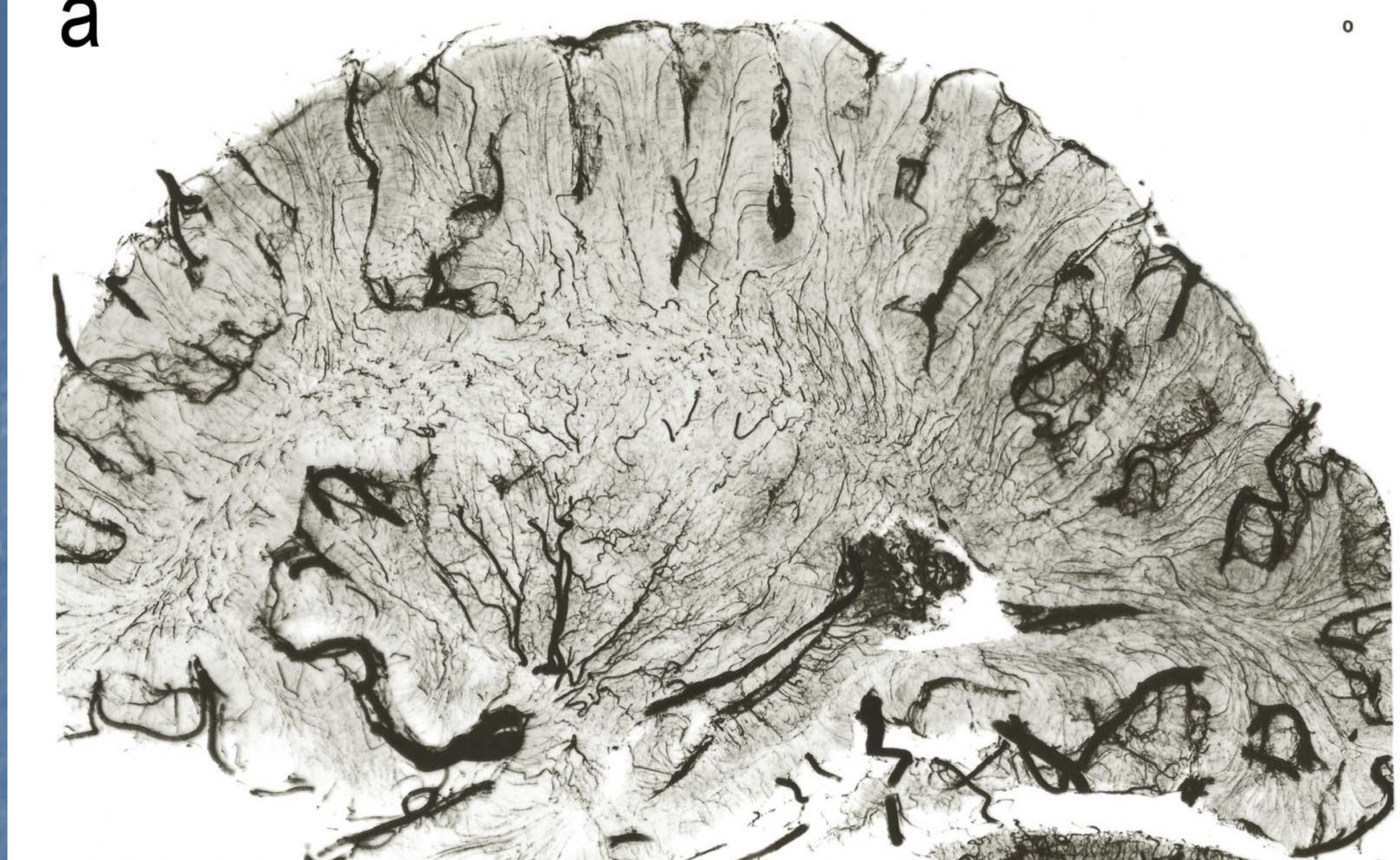
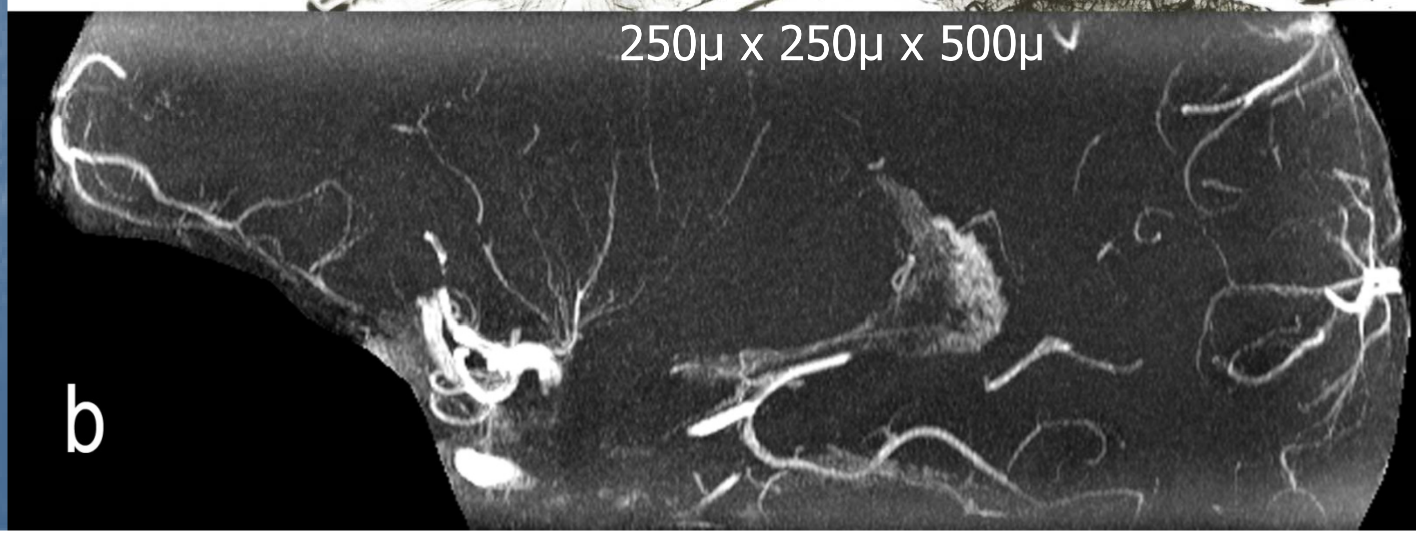
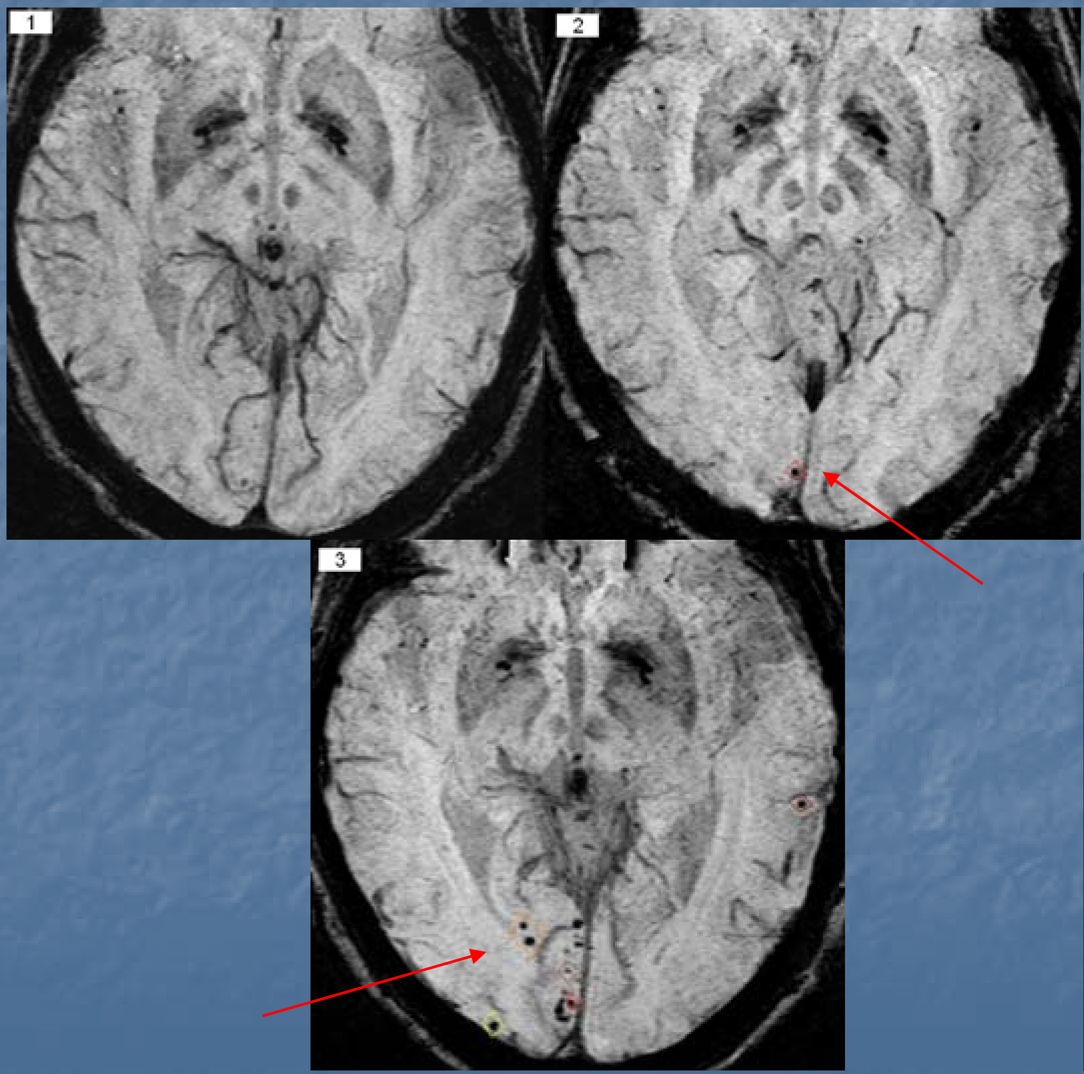
Detroit, Michigan and Adjunct Professor of Electrical and Computer Engineering, McMaster University
Hamilton, Ontario

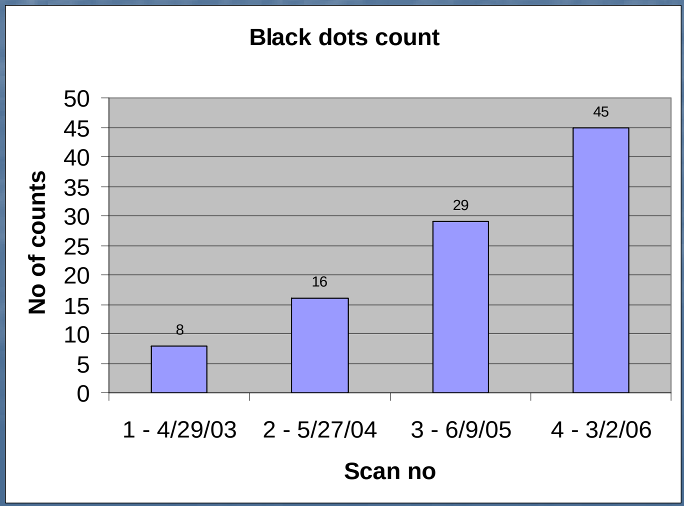
11) Salamon, G., 1971. Atlas of the arteries of the human brain. Sandoz, Paris.



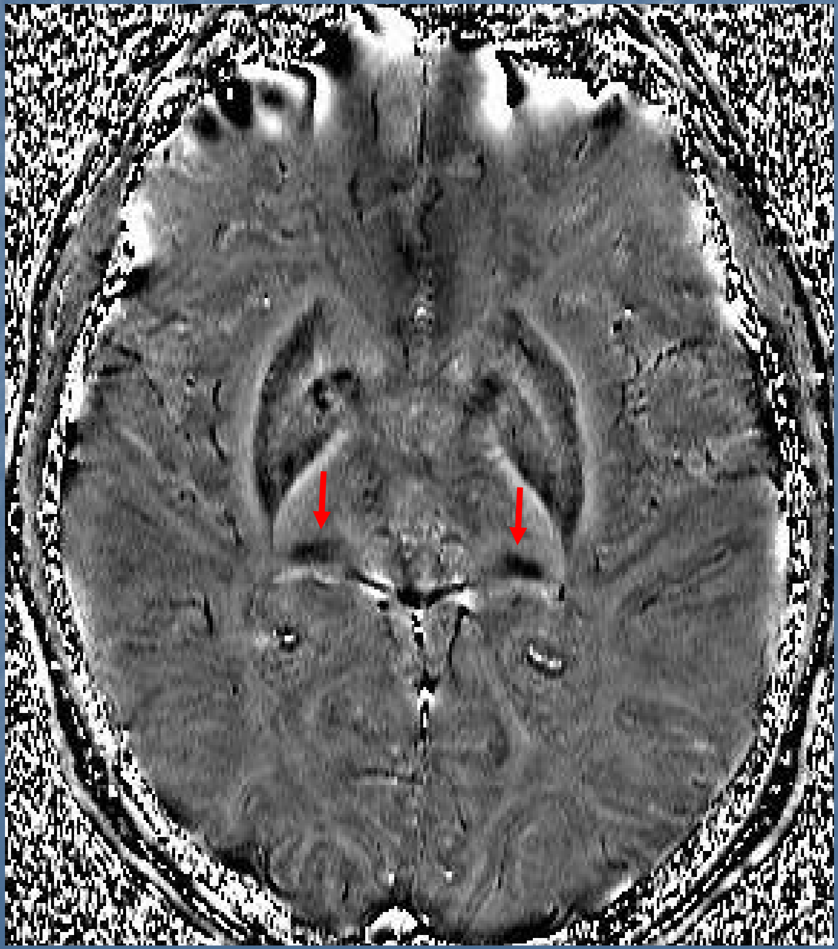


time to go sailing: CMBs as a biomarker for vascular dementia

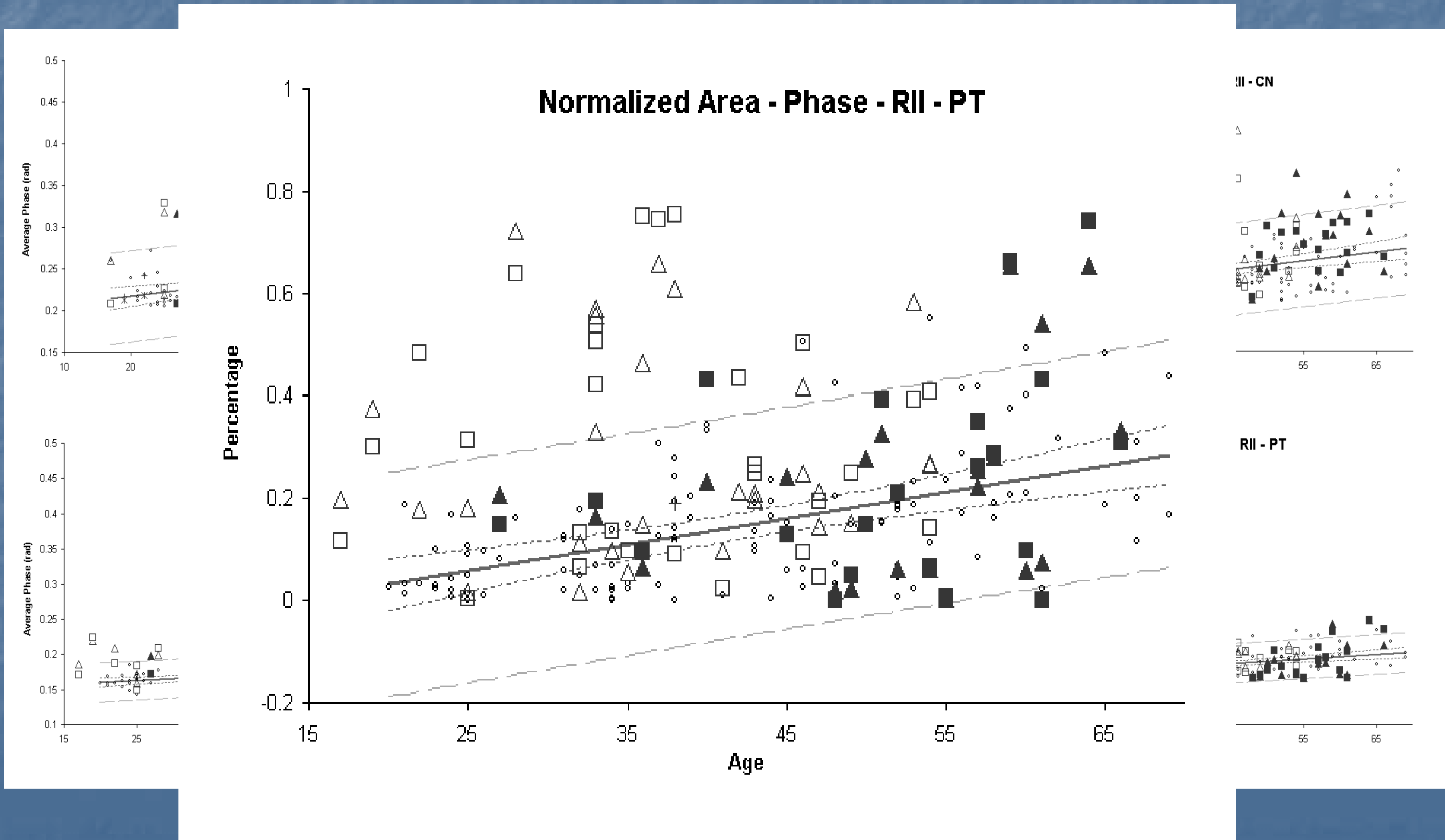




Iron in the pulvinar thalamus as a biomarker for MS



Results


Normalized Area - Phase - RII - PT
Percentage
Age
1
0.8
0.6
0.4
0.2
0
-0.2
15
25
35
45
55
65
Average Phase (rad)
RII - PT

Conclusions

- MR is a means by which we can both visualize and quantify iron and a means by which we can monitor changes in iron longitudinally.
- As such MRI has the potential to evaluate, diagnose and even lead to new understandings of the etiology of some diseases.
- For in vivo data:
  - [Fe] = 8R2* (μg Fe/gm tissue) with R2* in Hz

Despite the uncertainties we are getting very close to an absolute quantification of iron and oxygen saturation in venous blood