Quantitative MRI (qMRI)

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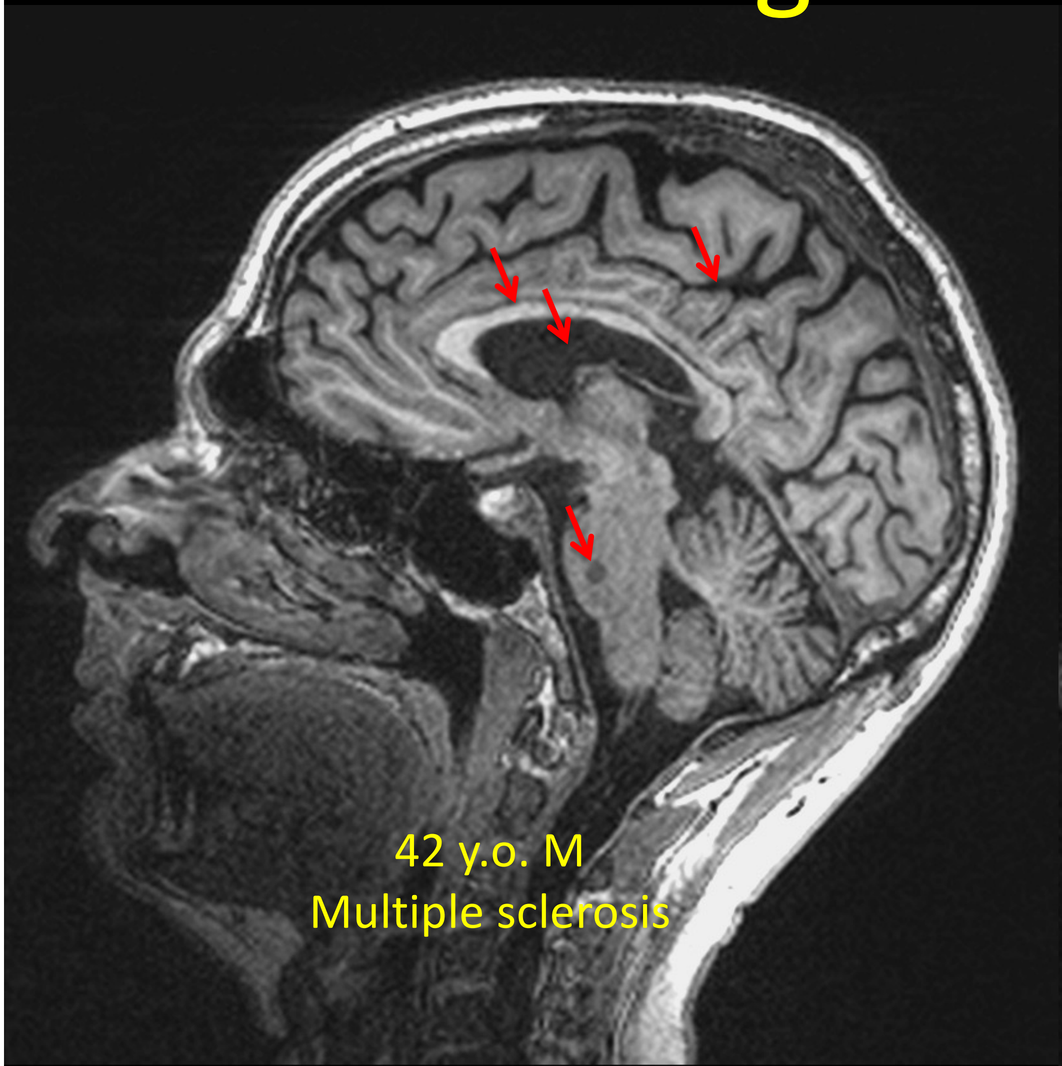
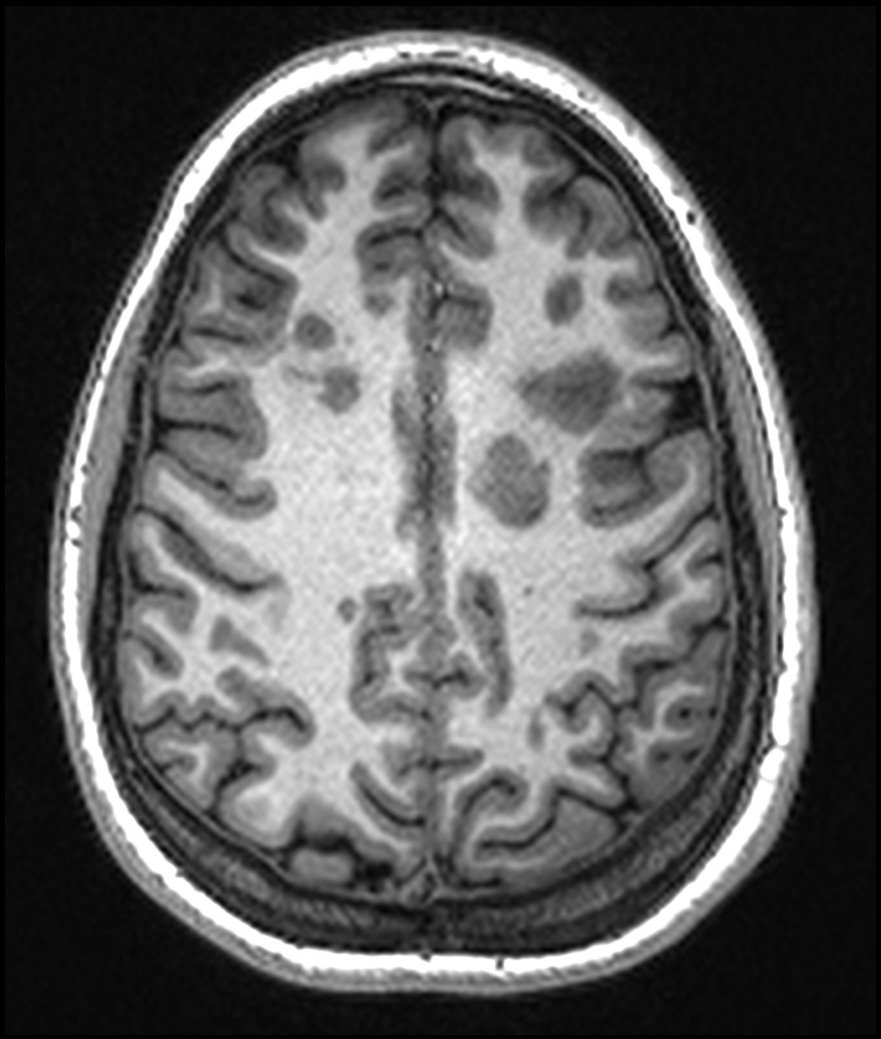
Neurodegenerative Changes

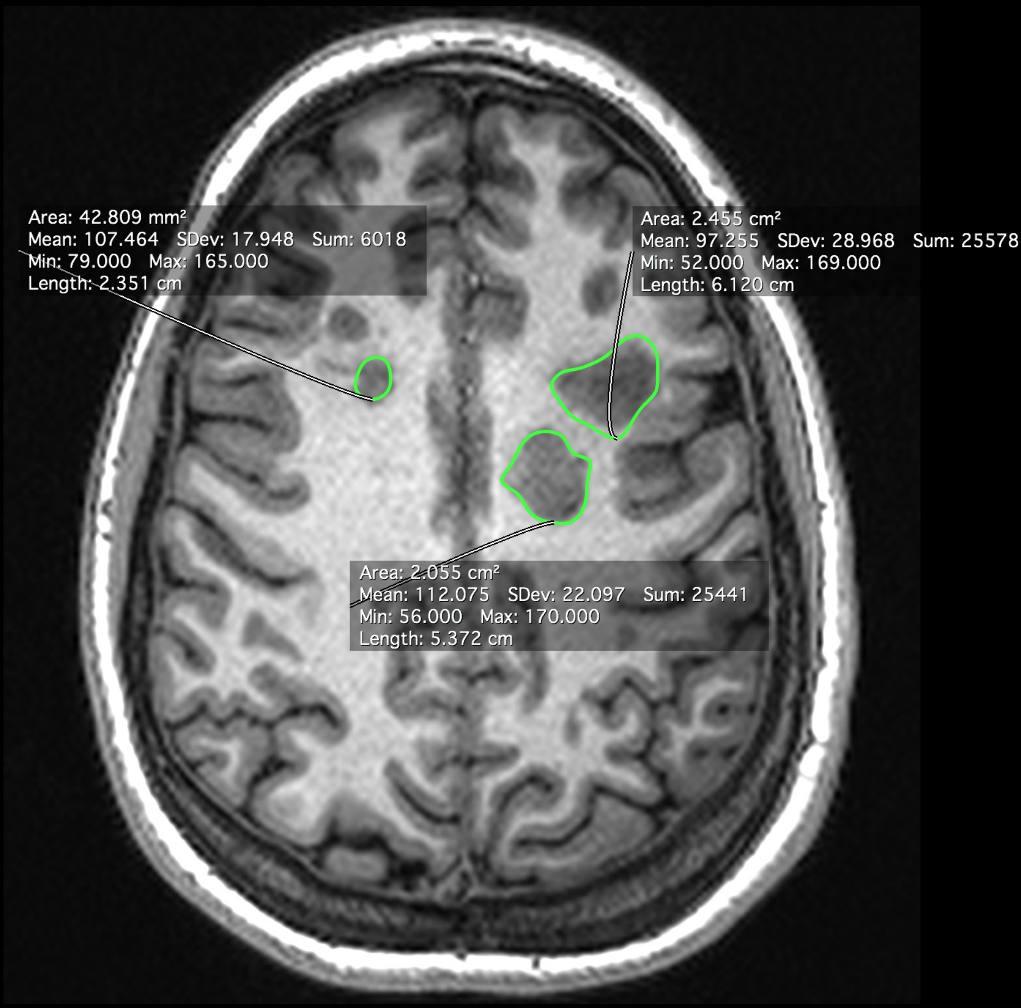


Multiple sclerosis is an immune mediated neurodegenerative disease affecting the myelin, axons, and neurons.

Qualitative vs. Quantitative

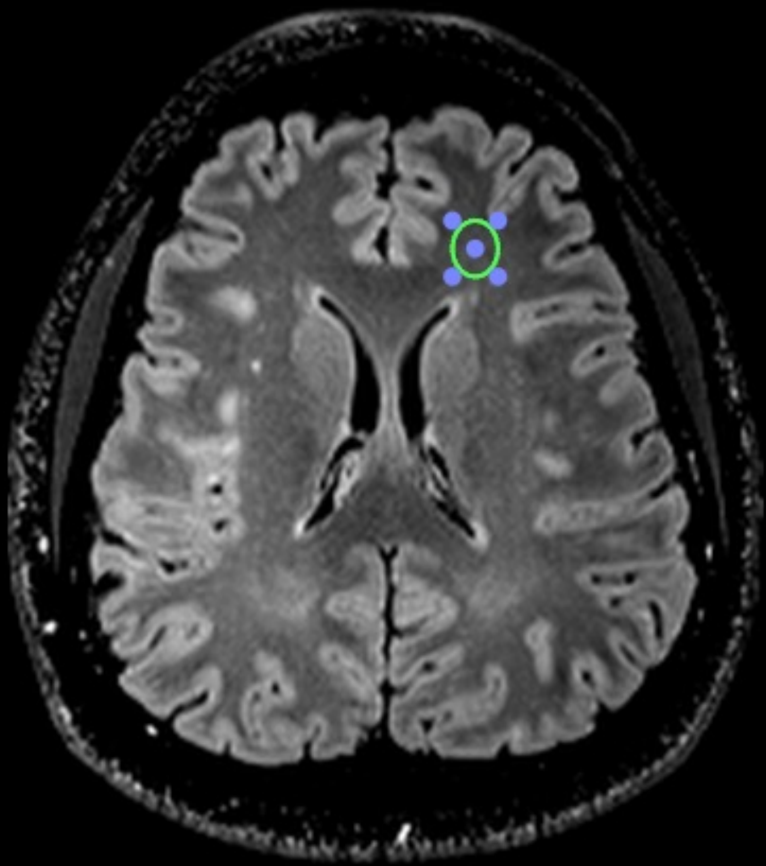


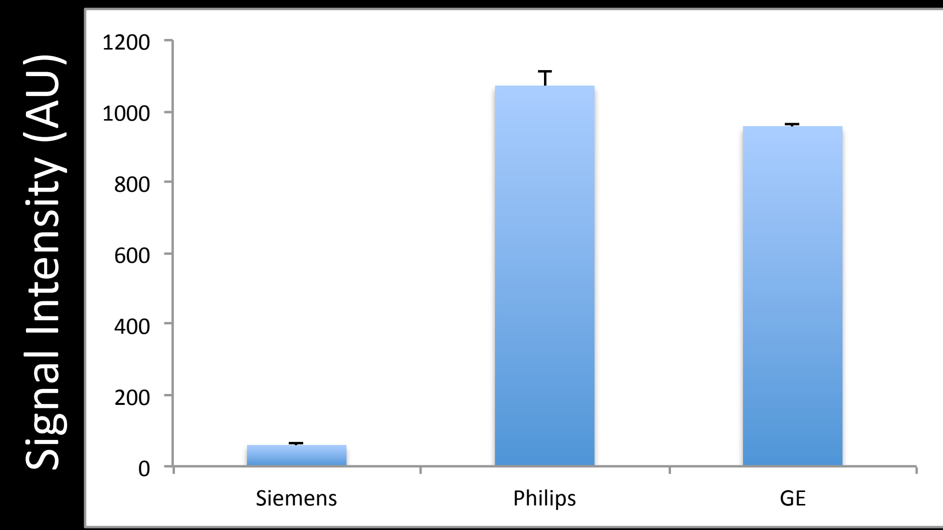
Periventricular hypointensity on T1 MPRAGE.



23 y.o. F, MS

The Trouble with Quantitation

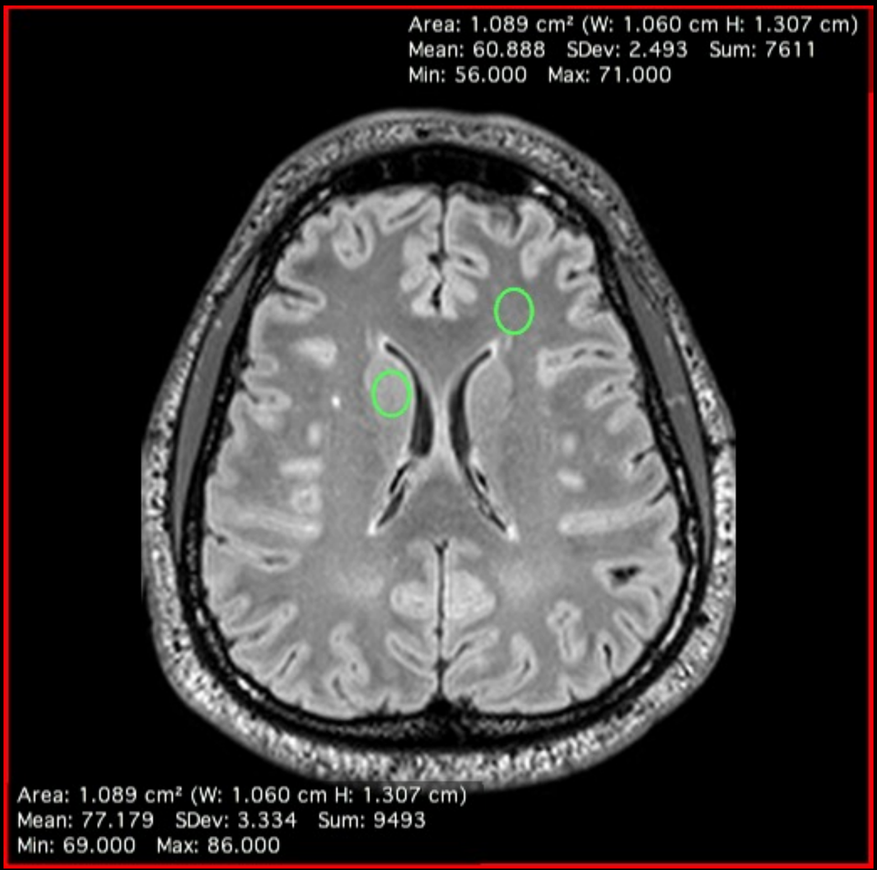


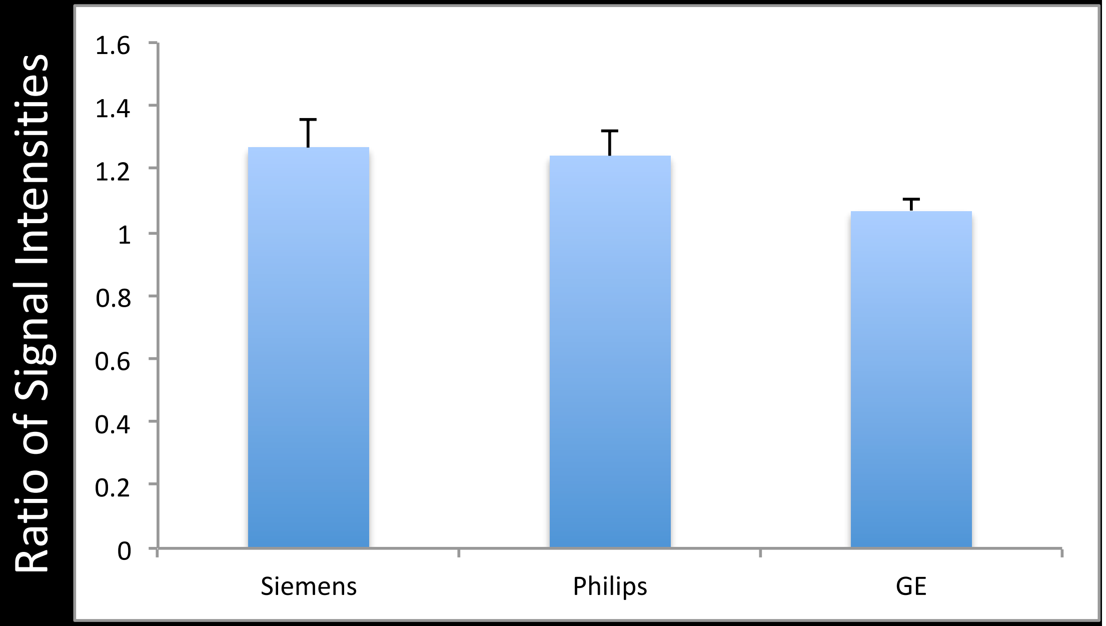


N=3

Different scanners, very similar protocols
FLAIR

The Trouble with Quantitation





N=3

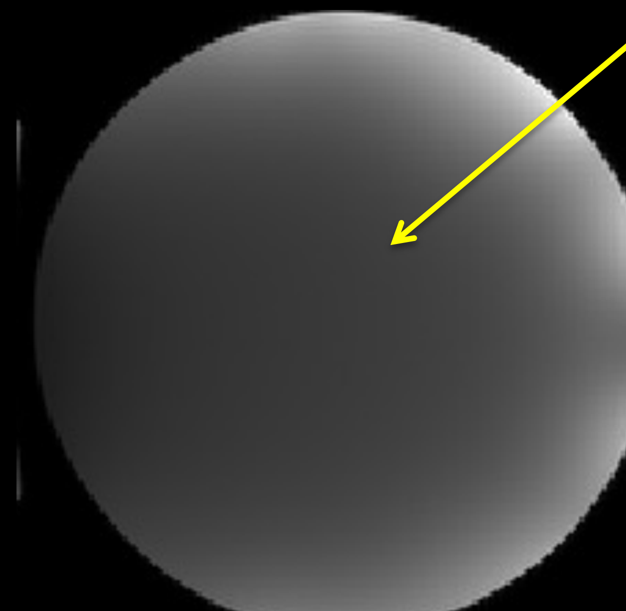
Different scanners, very similar protocols
FLAIR


MR
Positioning Kit

Coil Sensitivities Effect Normalization

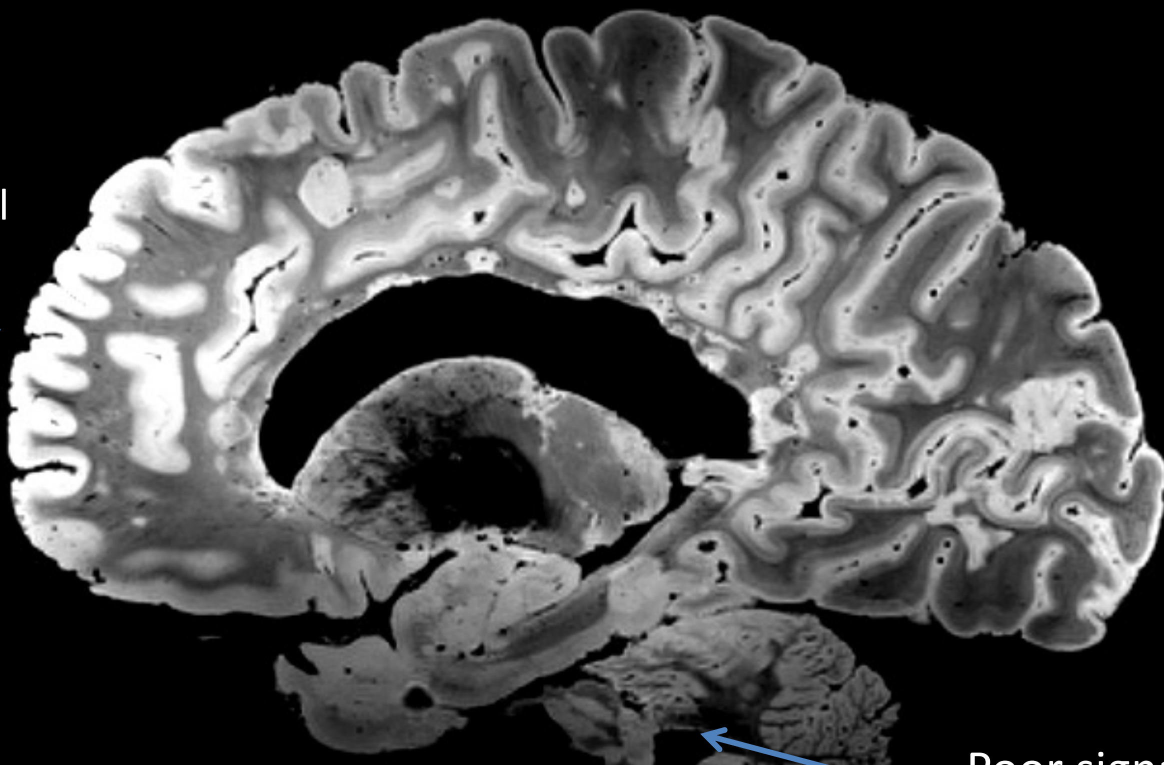
Receiver effects

Transmit effects



(Images of a ball of water should be uniform)

Coil Sensitivities Effect Normalization



Why Bother with Quantitation: Philosophical

"I often say that when you can measure what you are speaking about, and express it in numbers, you know something about it; but when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meager and unsatisfactory kind; it may be the beginning of knowledge, but you have scarcely in your thoughts advanced to the state of Science, whatever the matter may be."

- *Lord Kelvin [PLA, vol. 1, "Electrical Units of Measurement", 1883-05-03]*

Courtesy of Daniel Glenn

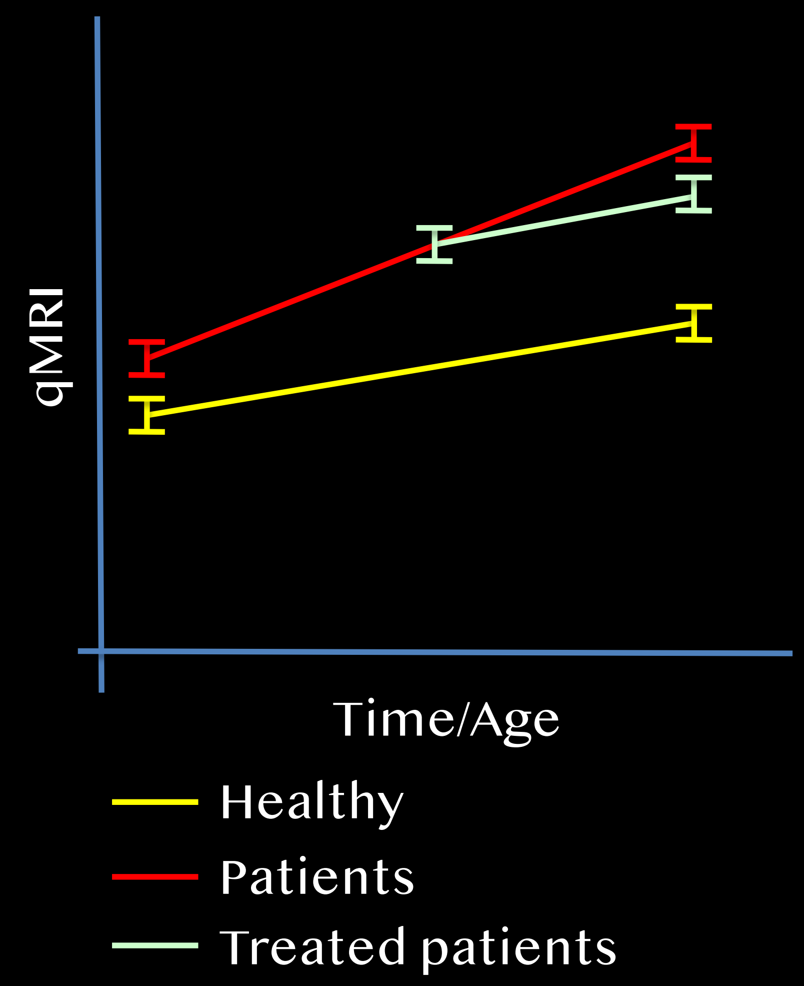
(Pre)clinically Available qMRI

qMRI technique	Biological processes affecting them
Diffusion Tensor Imaging (DTI)	Demyelination, axonal loss, vasogenic edema, ischemia, inflammation…
Magnetization Transfer Ratio (MTR/MTC)	Macromolecular composition, cellularity, edema, iron accumulation…
MRI relaxometry (qT_1, qT_2, qT_2*)	Demyelination, gliosis, tissue loss, iron accumulation, edema, macromolecular composition
Quantitative susceptibility mapping (QSM)	Demyelination, iron accumulation…
Dynamic contrast-enhanced MRI (DCE)	Blood Brain Barrier permeability…
MR Spectroscopy (qMRS)	Neuronal loss (NAA), glial cell activation (mI), lactate accumulation (Lac), cellular debris, infections…
Labeling with MRI contrast agents (Iron oxide, Mn)	Cellular migration or tracking, cellular activation (when conjugated with Ab)…
Volumetrics	Atrophy, segmentation errors, edema, pressure…

Remember: robust, repeatable, and biologically relevant

Quantitative MRI

- Robust, repeatable, and biologically relevant.
- Independent of scanner, software, hardware.



Laboratory results

WBC		4.57	[4.23-9.07 K/uL]
RBC		4.36 ↓	[4.63-6.08 M/uL]
HGB		13.2 ↓	[13.7-17.5 g/dL]
HCT		37.8 ↓	[40.1-51.0 %]
MCV		86.7	[79.0-92.2 fL]
MCH		30.3	[25.7-32.2 pg]
MCHC		34.9	[32.3-36.5 g/dL]
RDW		11.8	[11.6-14.4 %]
Platelet Count		256	[161-347 K/uL]
MPV		10.3	[9.4-12.4 fL]
Nucleated RBC		0.0	[0.0-0.2 /100 WBC]
Nucleated RBC Absolute		0.00	[0.00-0.01 K/uL]
Neutrophils		45.4	[34.0-67.9 %]
Bands	with Neutrophil		
Immature Granulocytes		0.2	[0.0-0.4 %]
Lymphocytes		43.5	[21.8-53.1 %]
Monocytes.		8.3	[5.3-12.2 %]
Eosinophils		2.2	[0.8-7.0 %]
Basophils		0.4	[0.2-1.2 %]
Neutrophil Absolute		2.07	[1.78-5.38 K/uL]
Immature Granulocytes Absolute		0.01	[0.00-0.03 K/uL]
Lymphocyte Absolute		1.99	[1.32-3.57 K/uL]
Monocyte Absolute		0.38	[0.30-0.82 K/uL]
Eosinophil Absolute		0.10	[0.04-0.54 K/uL]
Basophil Absolute		0.02	[0.01-0.08 K/uL]

qMRI results

qMRI parameter	Subject	Normative range
Grey matter volume	750 cc	[600-800 cc]*
FA White matter	0.65	[0.5-0.8]*
T1 GM	1523 ms	[1200-1600 ms]*
…		

*made up values

qMRI in Neuroinflammation

Morphometry

- Atrophy of the brain.
- Atrophy of the spinal cord.
- Lesion volume.

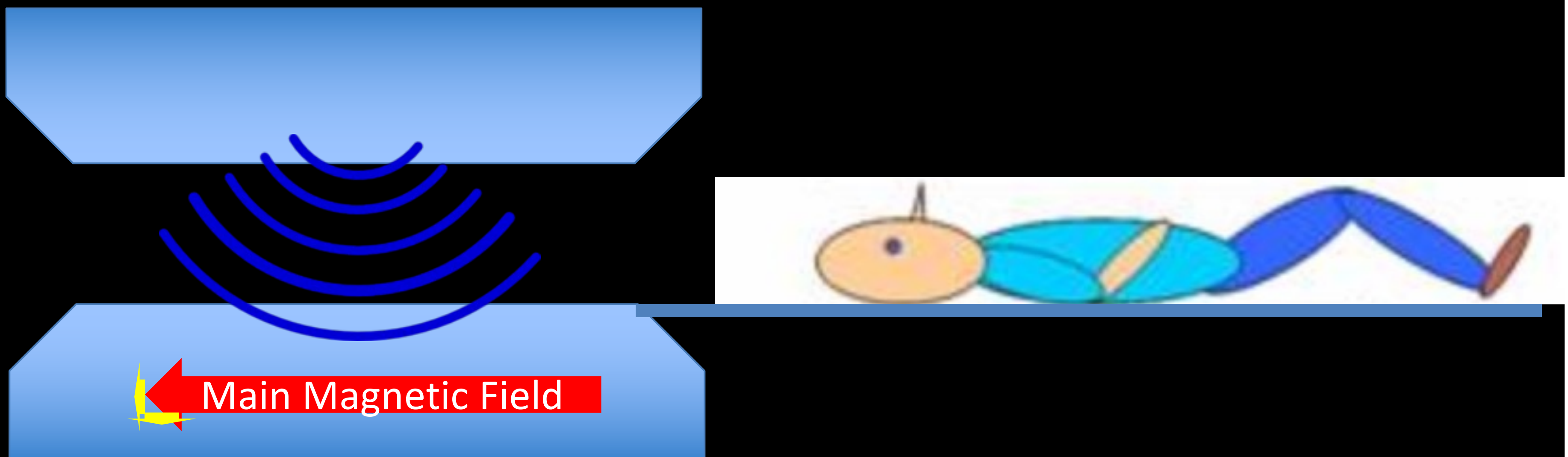
Microstructural changes

- Relaxometry (T_1, T_2, T_2*)
- Diffusion Tensor Imaging
- Magnetization Transfer Ratio
- Spectroscopy
- Functional connectivity
- …

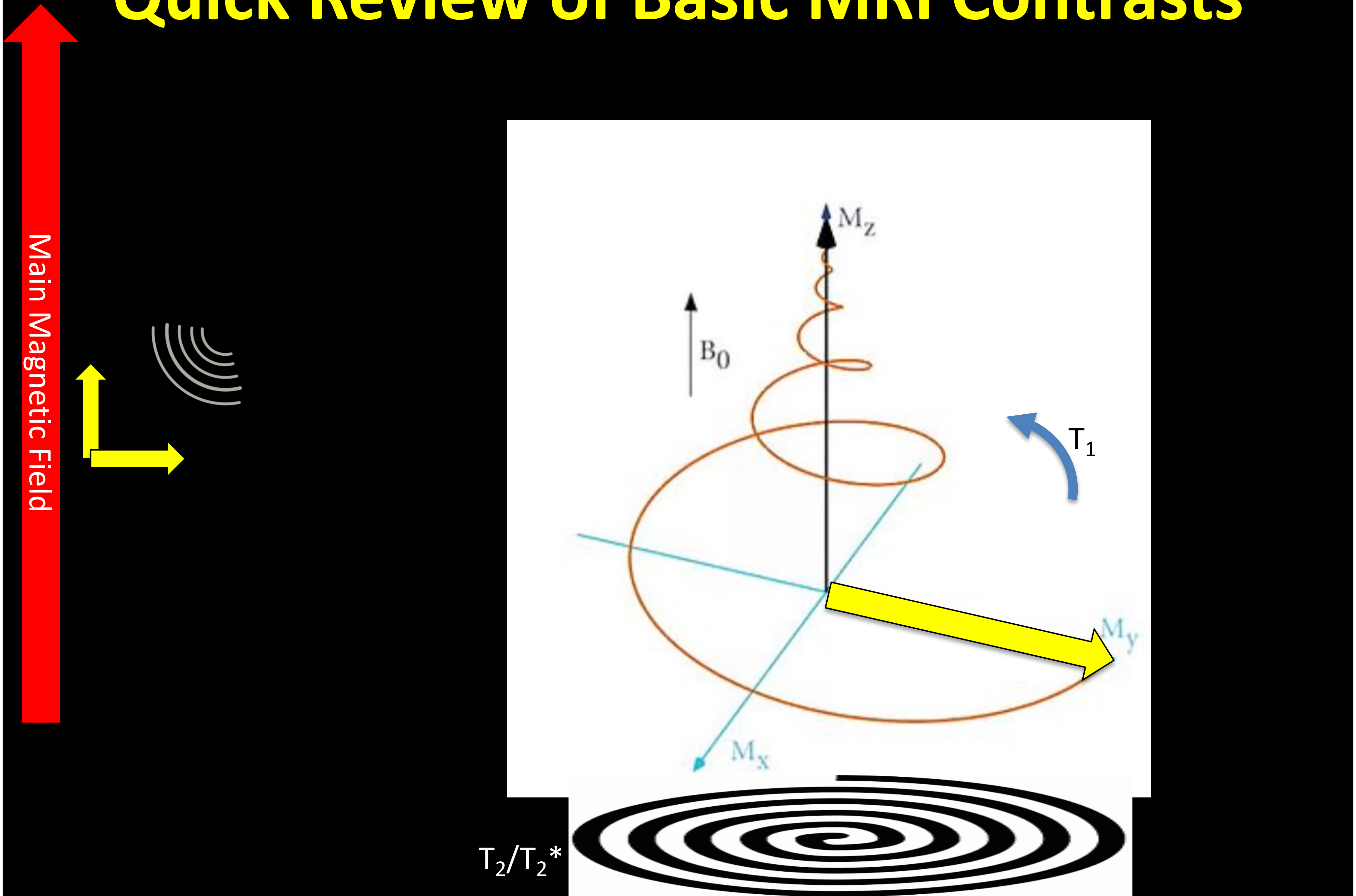
Inflammatory markers

- Blood perfusion imaging
- BBB permeability

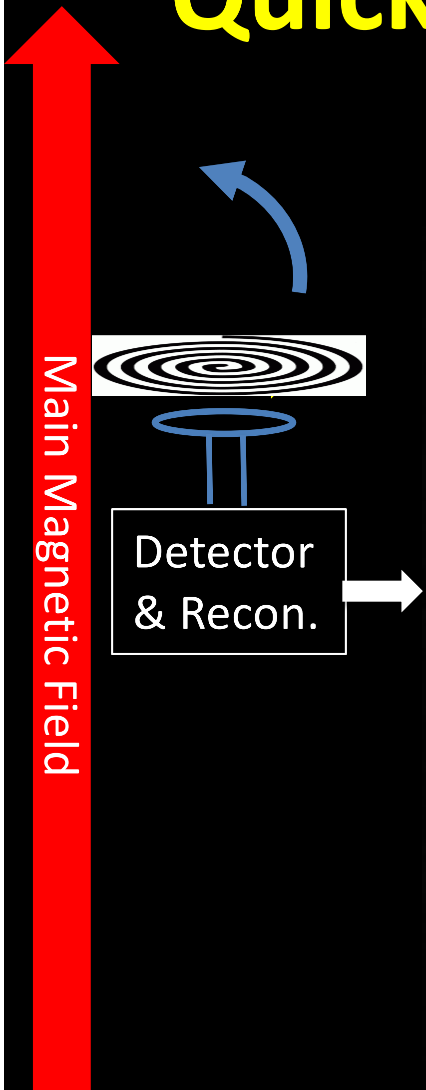
MRI Basics



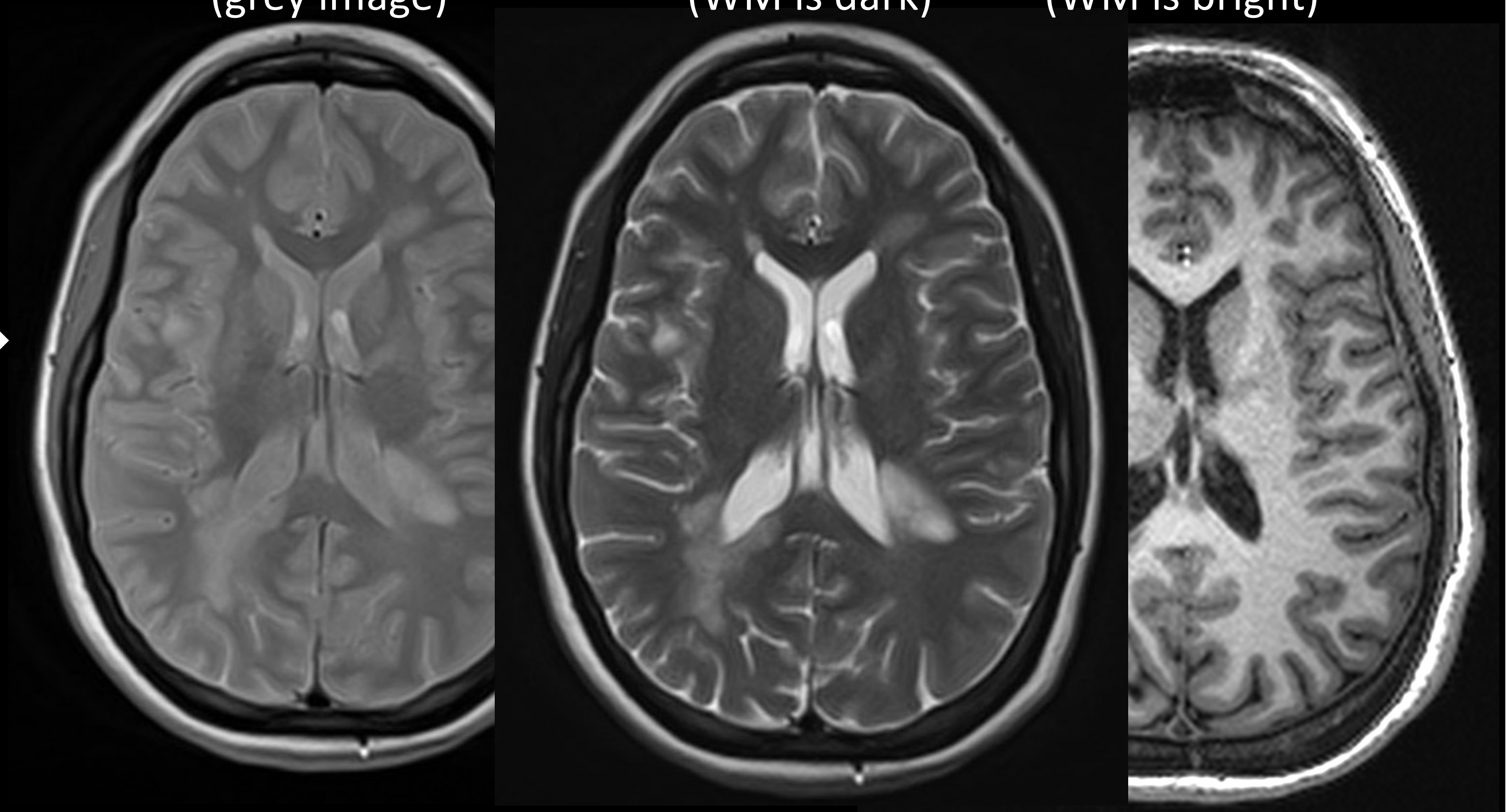
Quick Review of Basic MRI Contrasts



Quick Review of Basic MRI Contrasts



Proton density weighted (grey image) | T_2-weighted (WM is dark) | T_1-weighted (WM is bright)

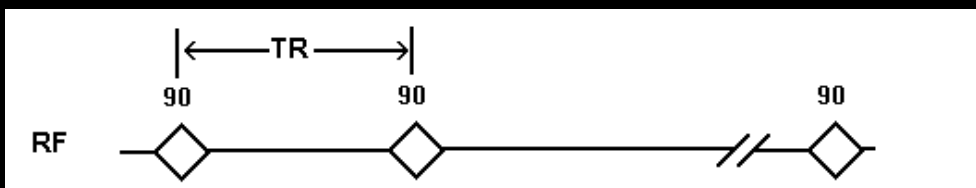


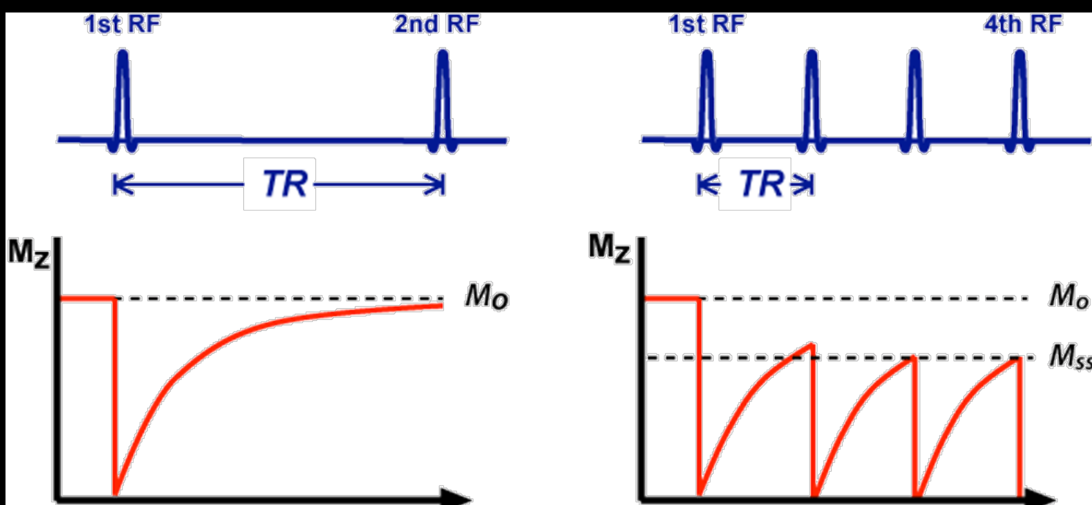
Biological changes are likely to change relaxation properties.

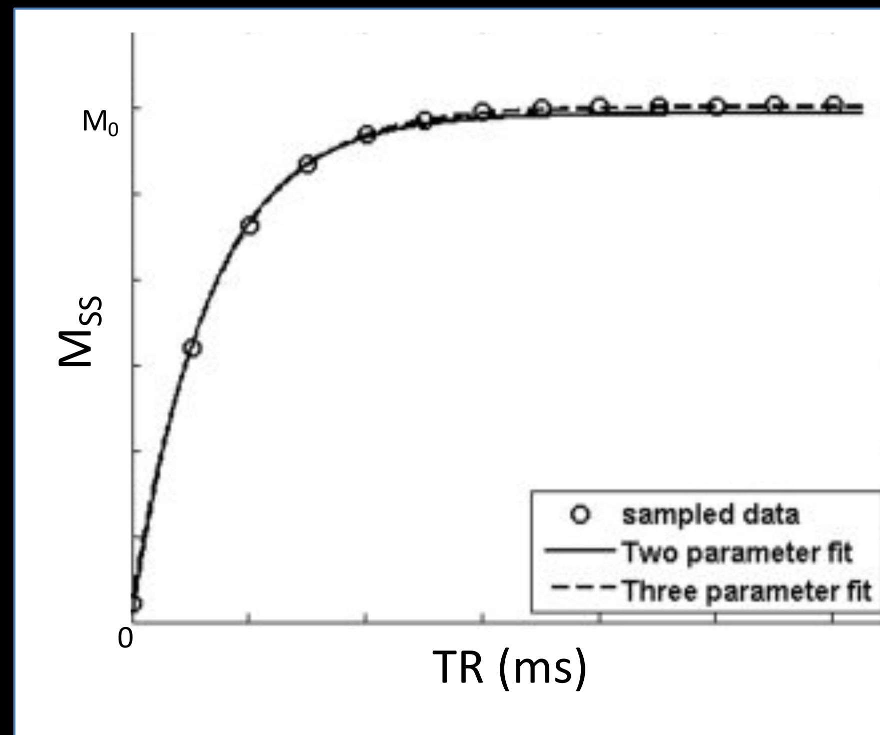
Patient with multiple sclerosis

Measuring Rate of T_1 Relaxation

Saturation recovery (SR)



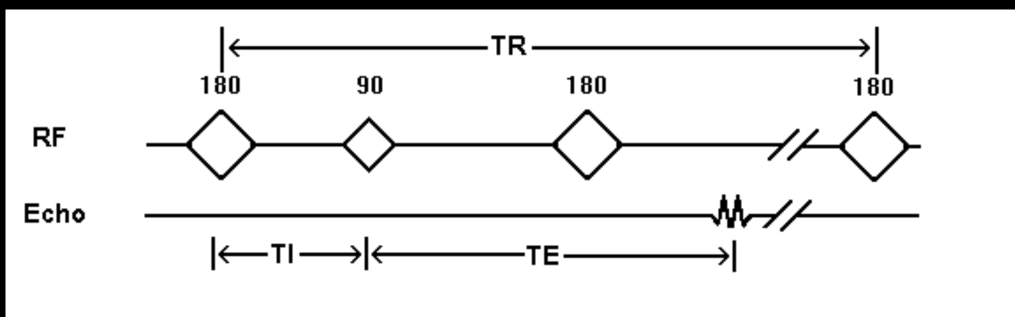


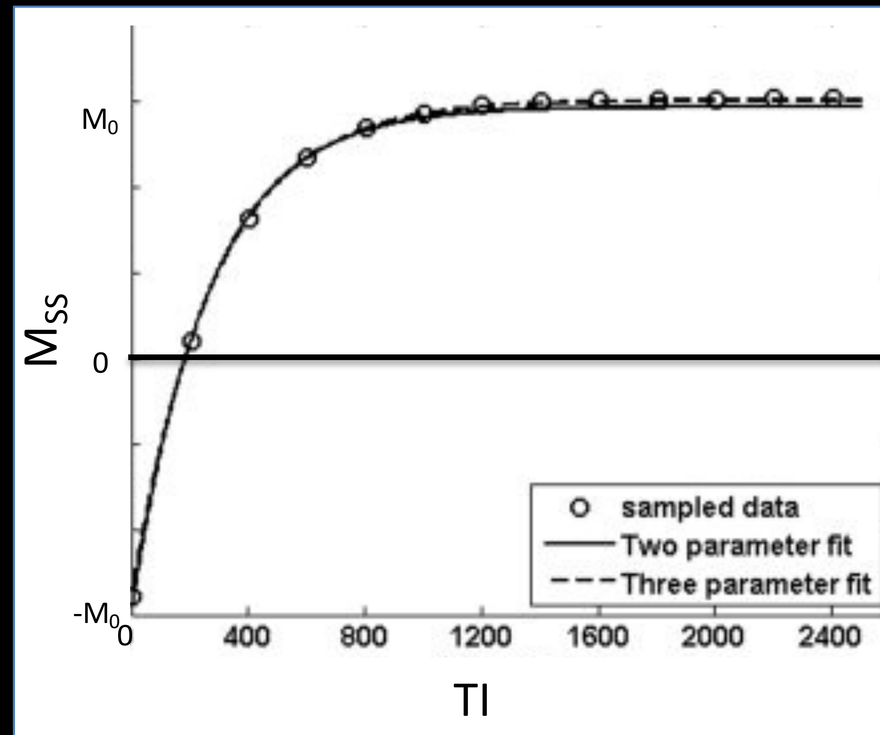


$$M_{ss} = M_0 * (1 - \alpha * e^{-TR/T1})$$

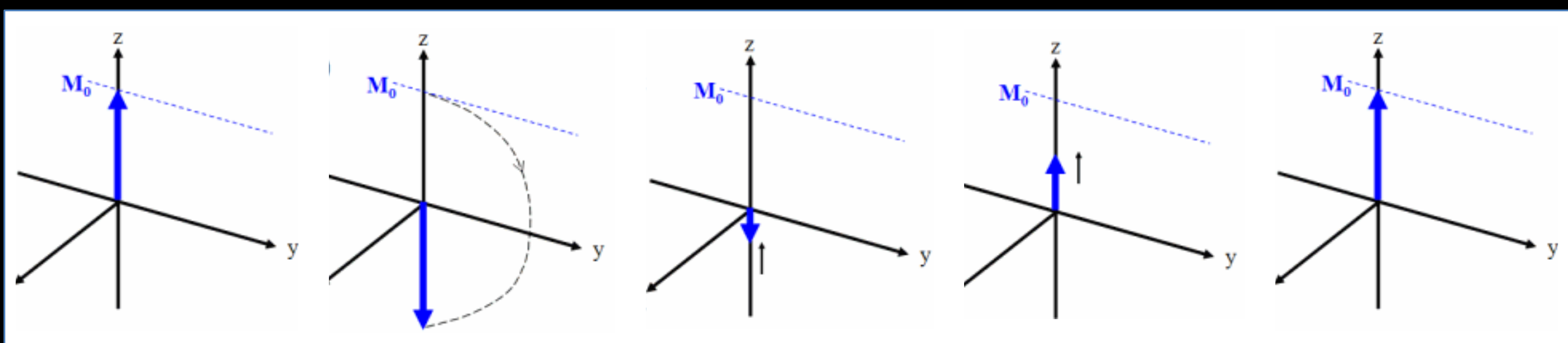
Measuring Rate of T_1 Relaxation

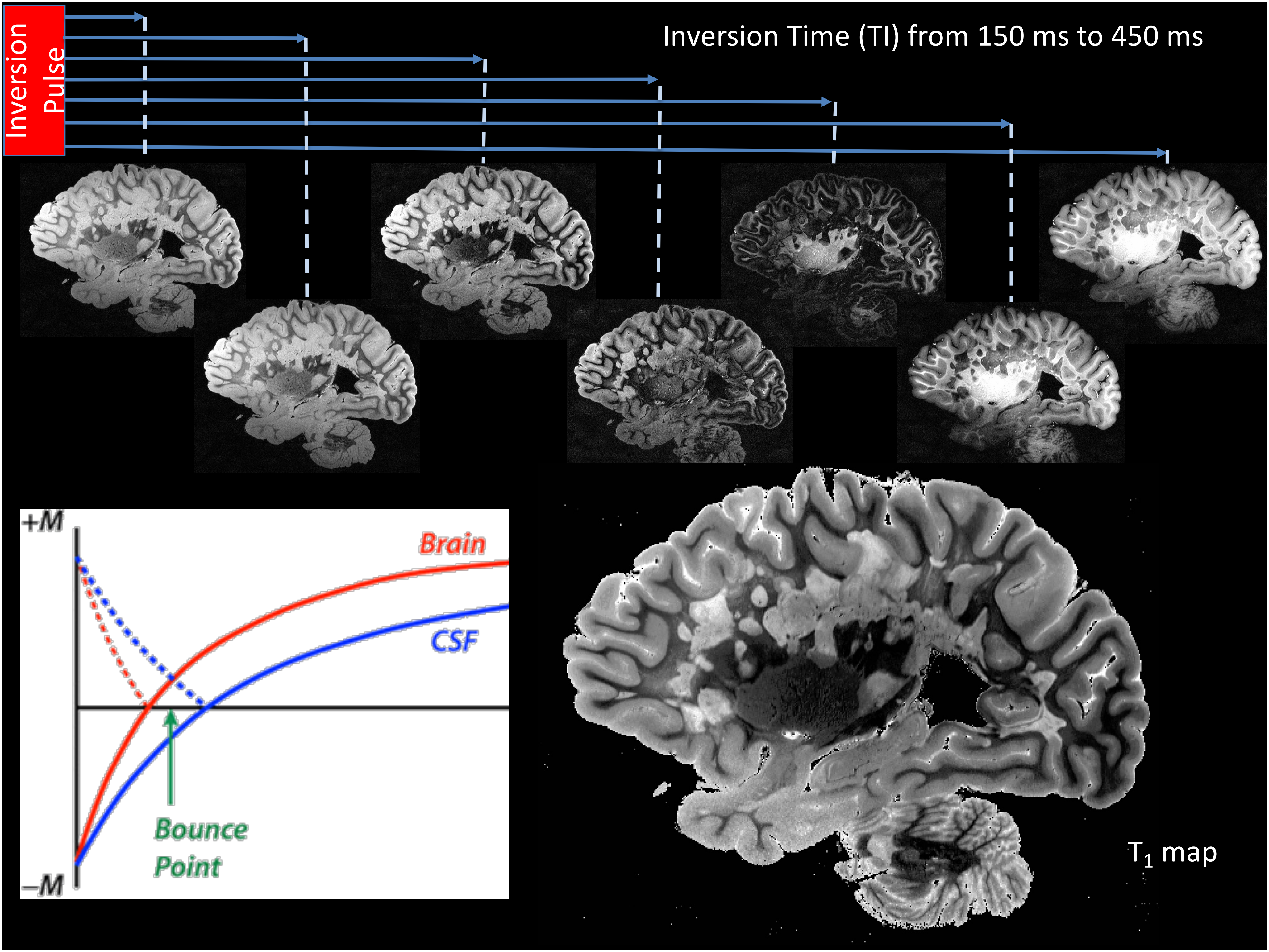
Inversion recovery (IR)



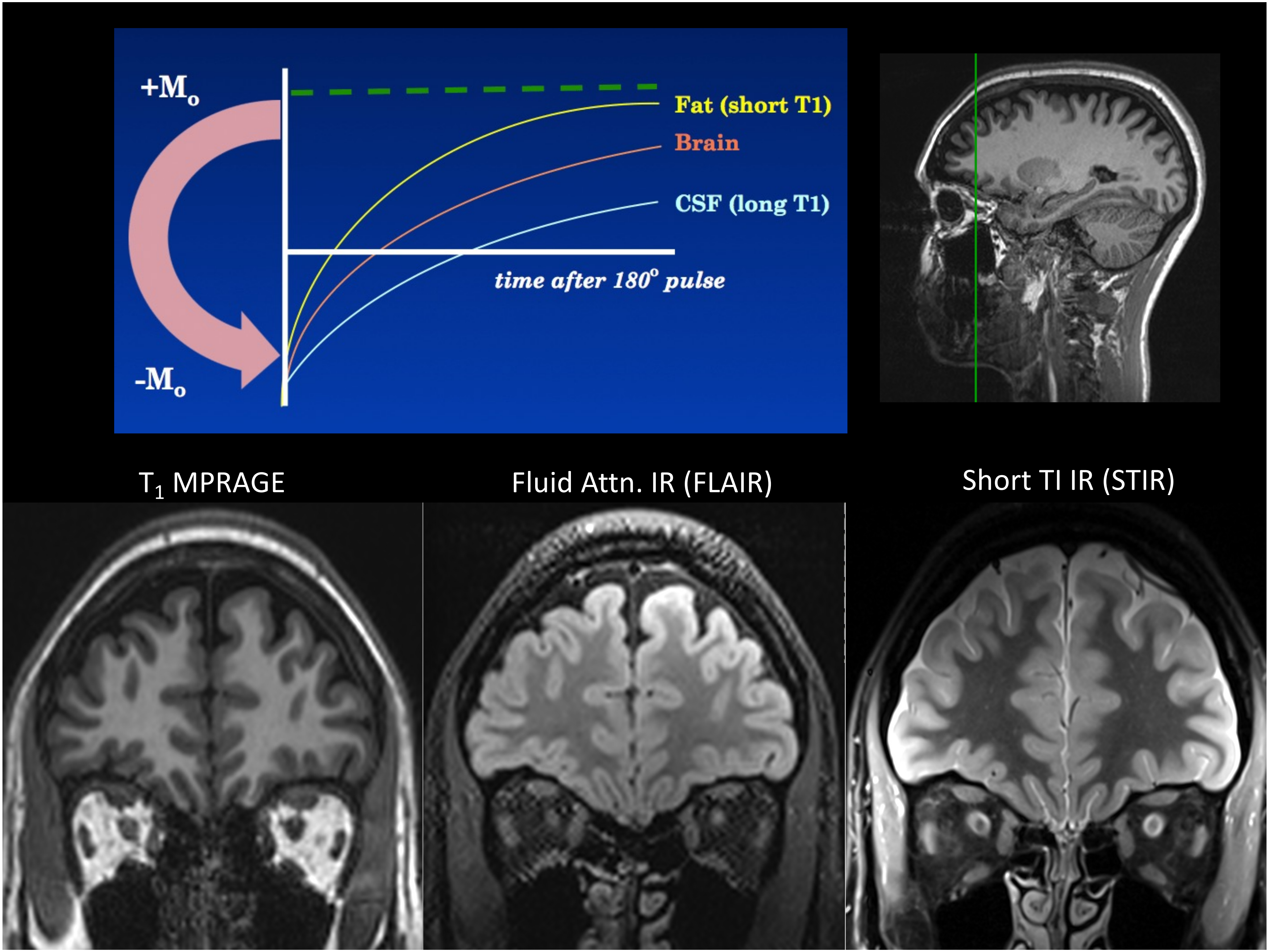


$$M = M_0 *(1 - 2\, \alpha * e^{-TI/T1})$$

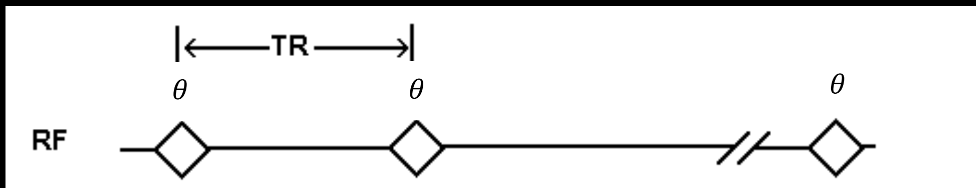




Inversion Pulse
Inversion Time (TI) from 150 ms to 450 ms
+M
Brain
CSF
Bounce Point
−M
T_1 map


+M_o
-M_o
Fat (short T1)
Brain
CSF (long T1)
time after 180° pulse
T_1 MPRAGE
Fluid Attn. IR (FLAIR)
Short TI IR (STIR)

Measuring Rate of T_1 Relaxation



$$S = M_0 \frac{(1 - e^{-TR/T1})\sin\theta}{1 - e^{-TR/T1}\cos\theta}.$$

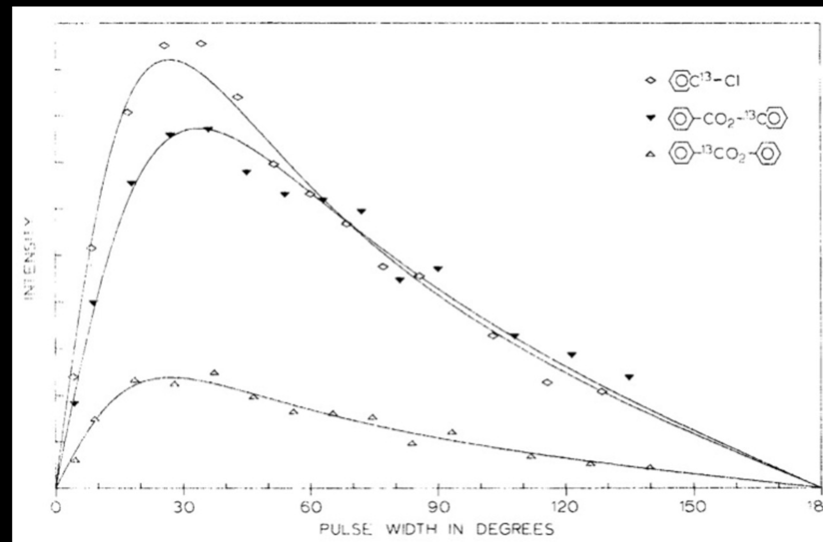
θ is the flip angle and S the signal at that flip

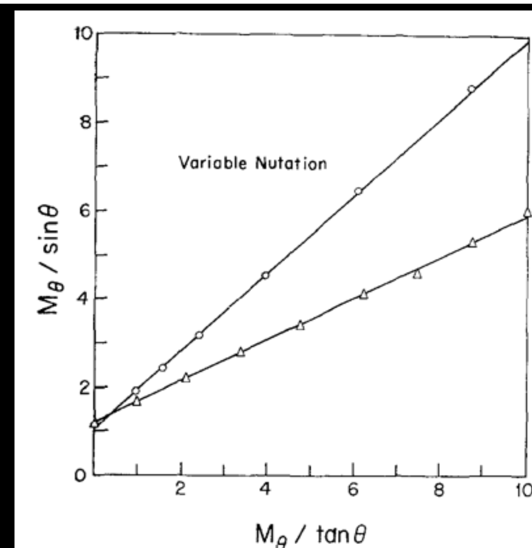
$$\frac{M_\theta}{\sin\theta} = e^{-T/T_1}\frac{M_\theta}{\tan\theta} + M_0(1 - e^{-T/T_1})$$

Of the form: $Y = bX + a$

$$T1 = -\frac{TR}{\ln b}.$$

However, transmit coil profiles are not corrected automatically since FA needs to be specified.

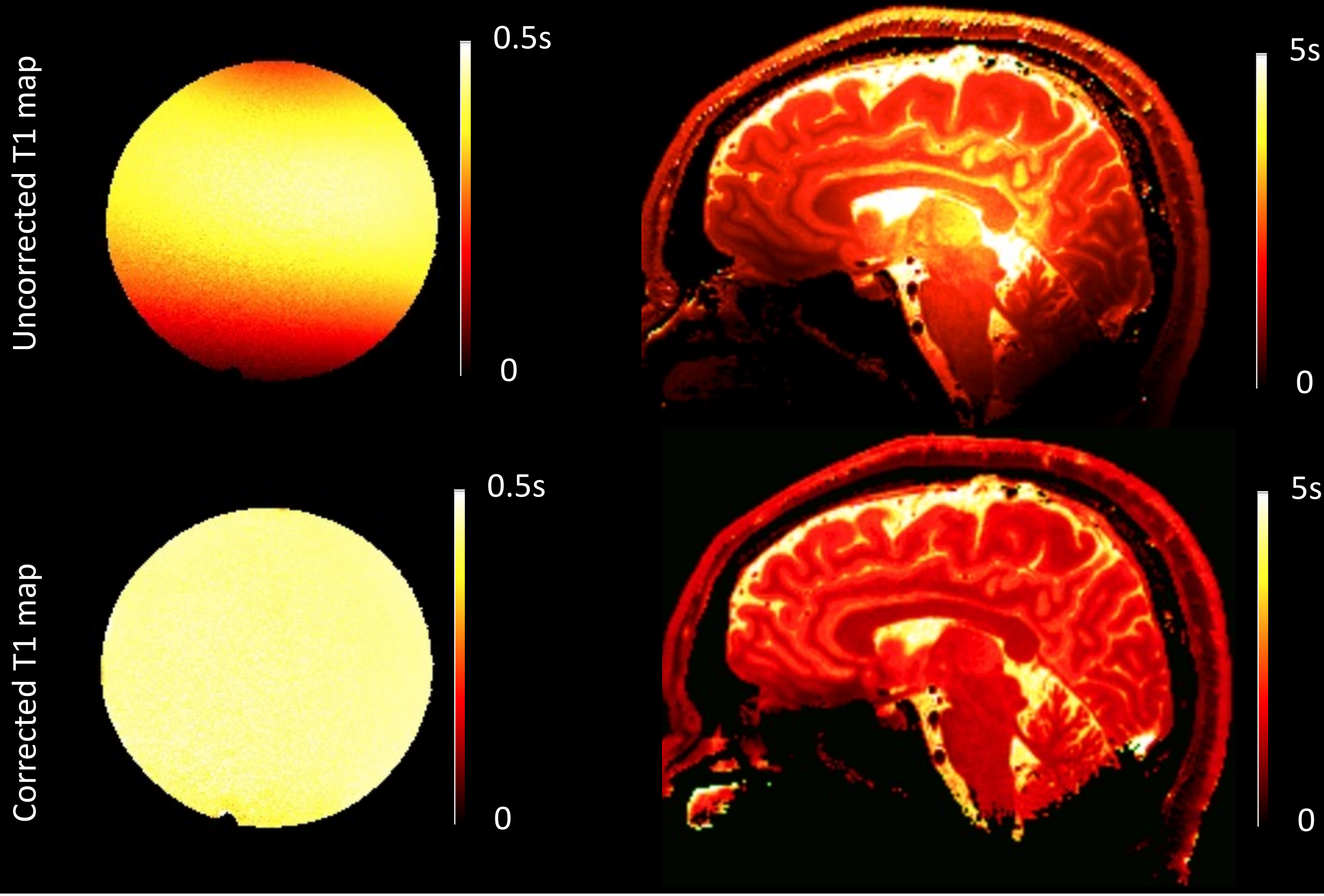




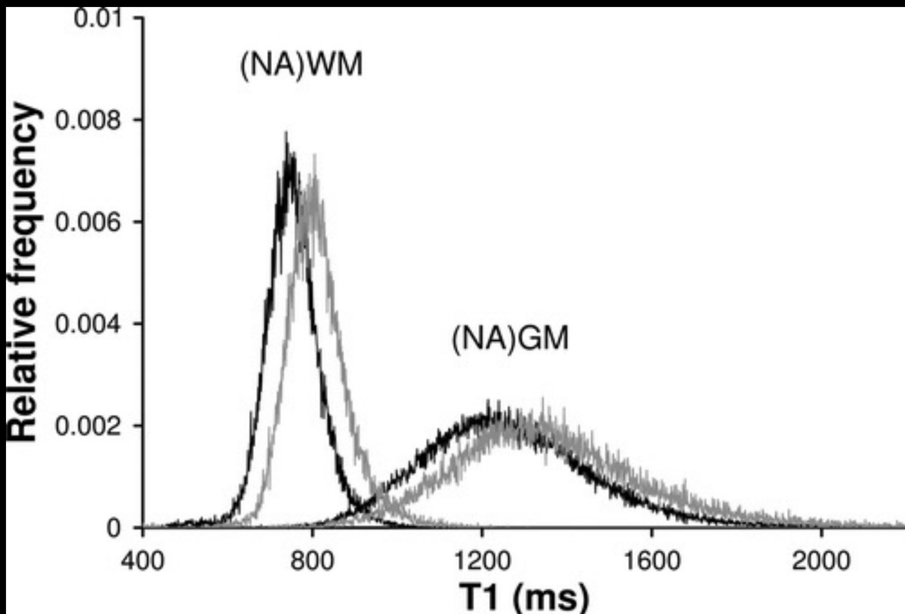
Line fitting

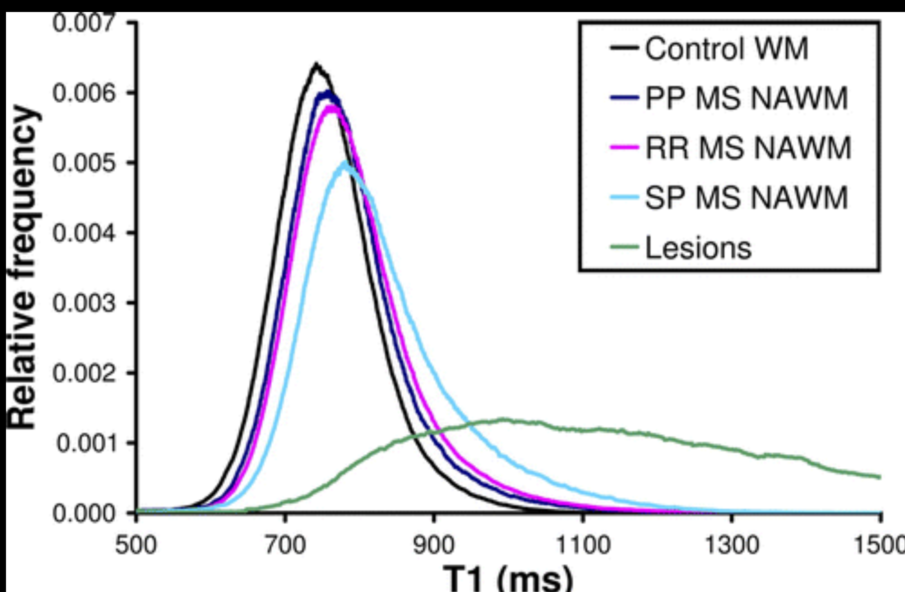
Christensen et. al. J Phys Chem 78(19):1971 (1974); Gupta J Mag Res 25:231 (1977)

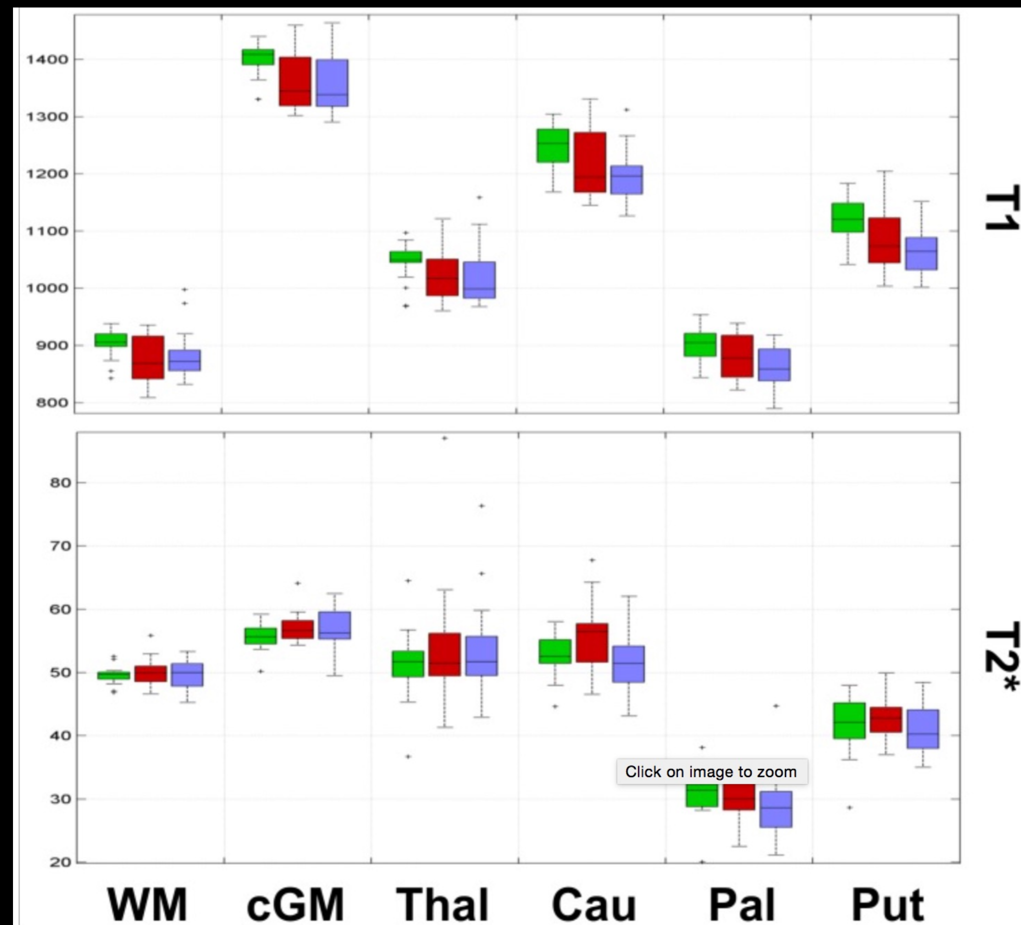
Correcting for B1



Can qMRI Improve Sensitivity?

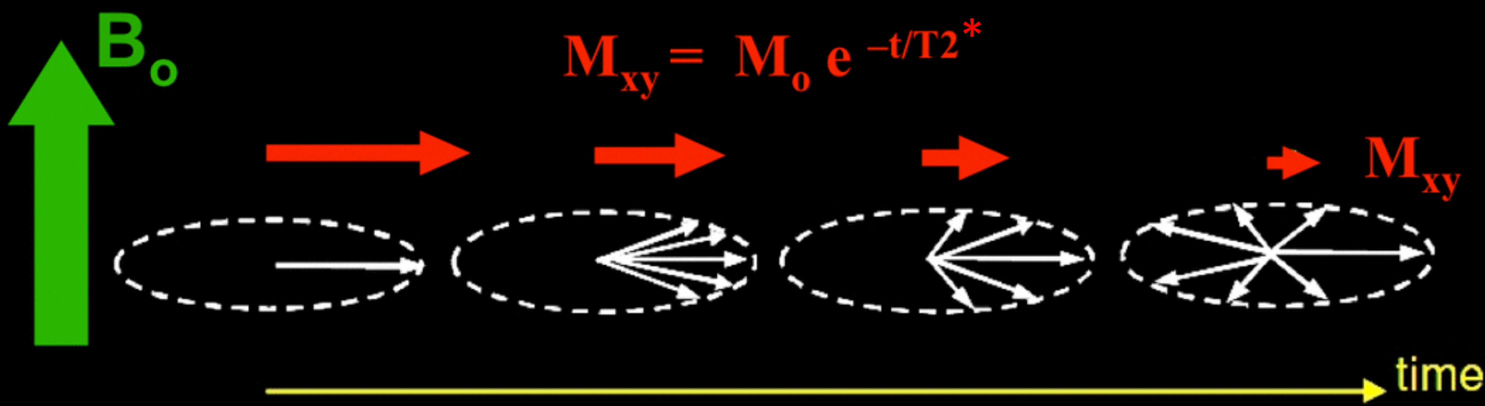


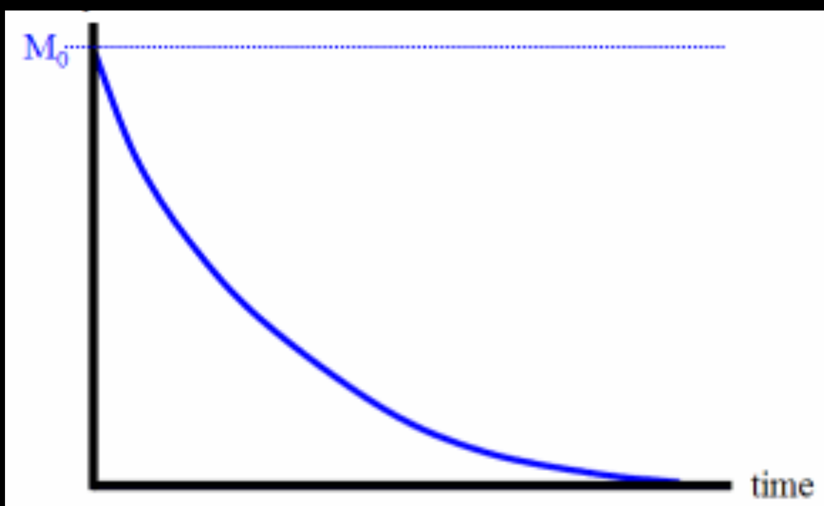


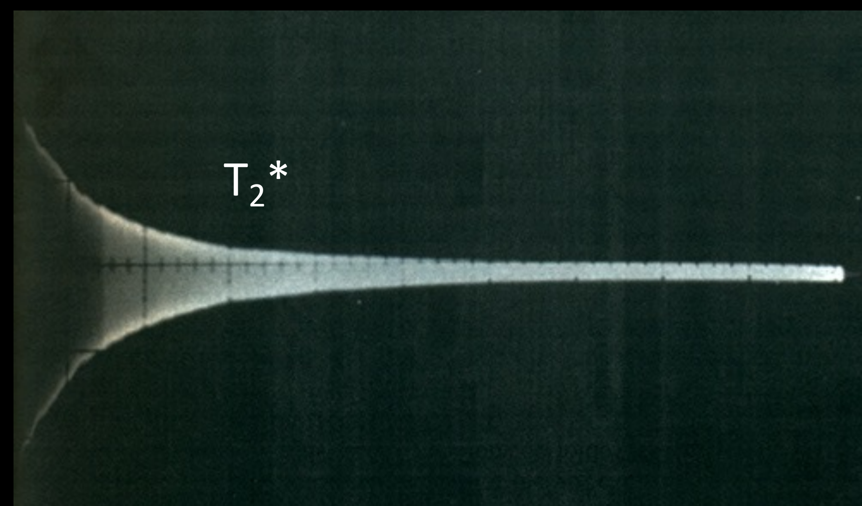


Vrenken et al. 2006 Radiology 240(3) 811;
Granziera et al. PLoS One. 2013; 8(9): e72547.

Transverse Relaxation

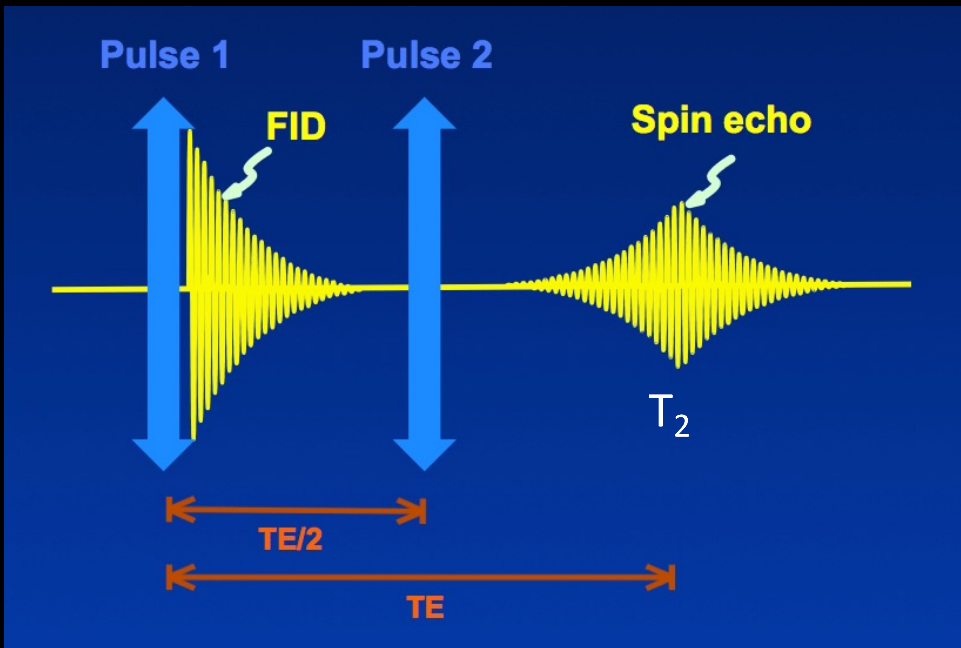


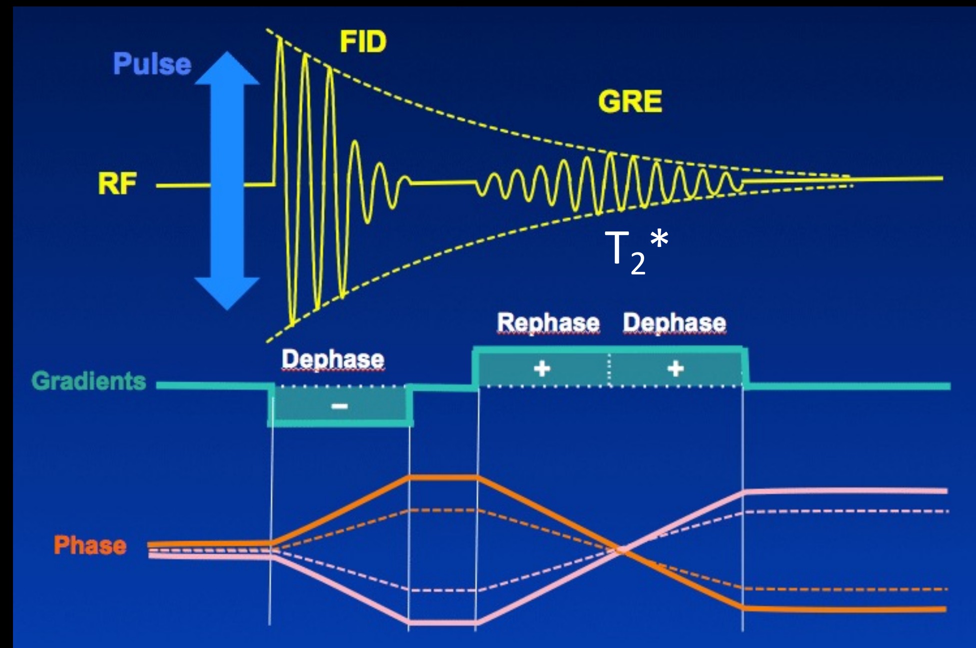


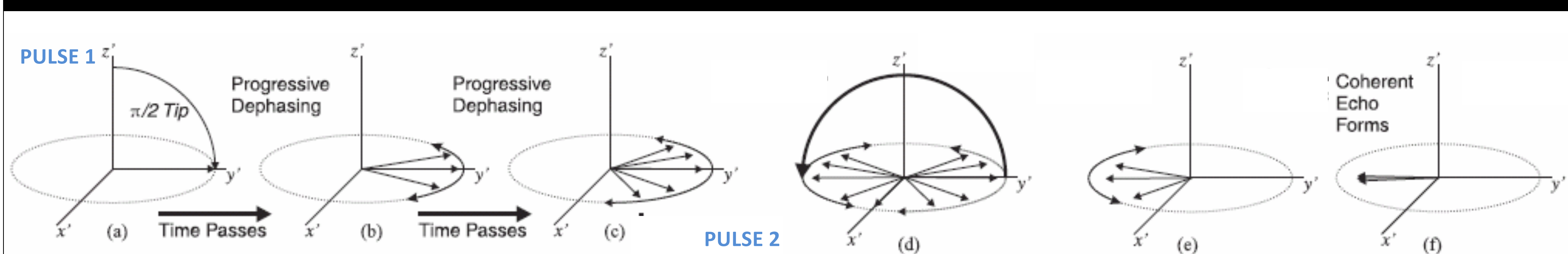


Free Induction Decay

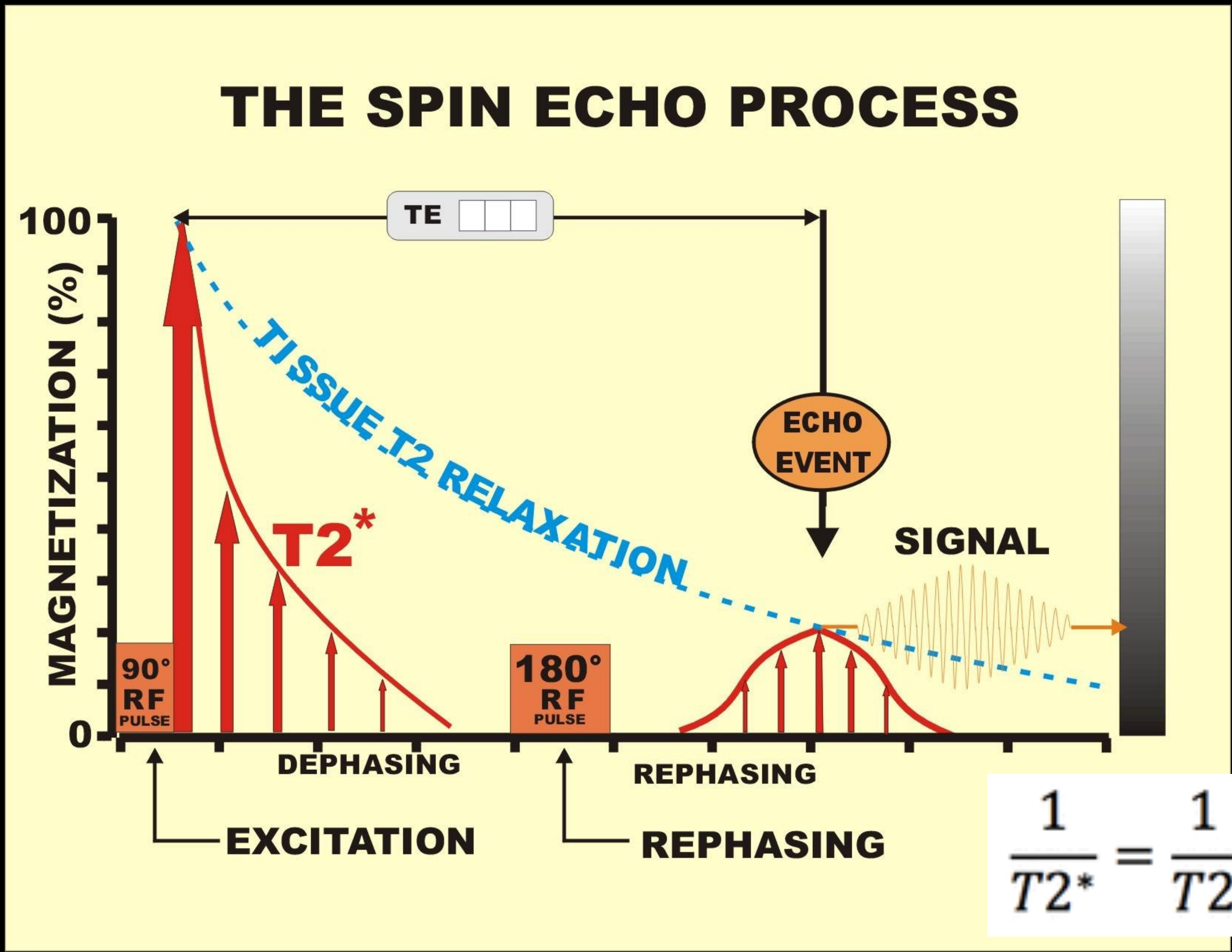
Spin Echo vs. Gradient Echo







T2 vs. T2*



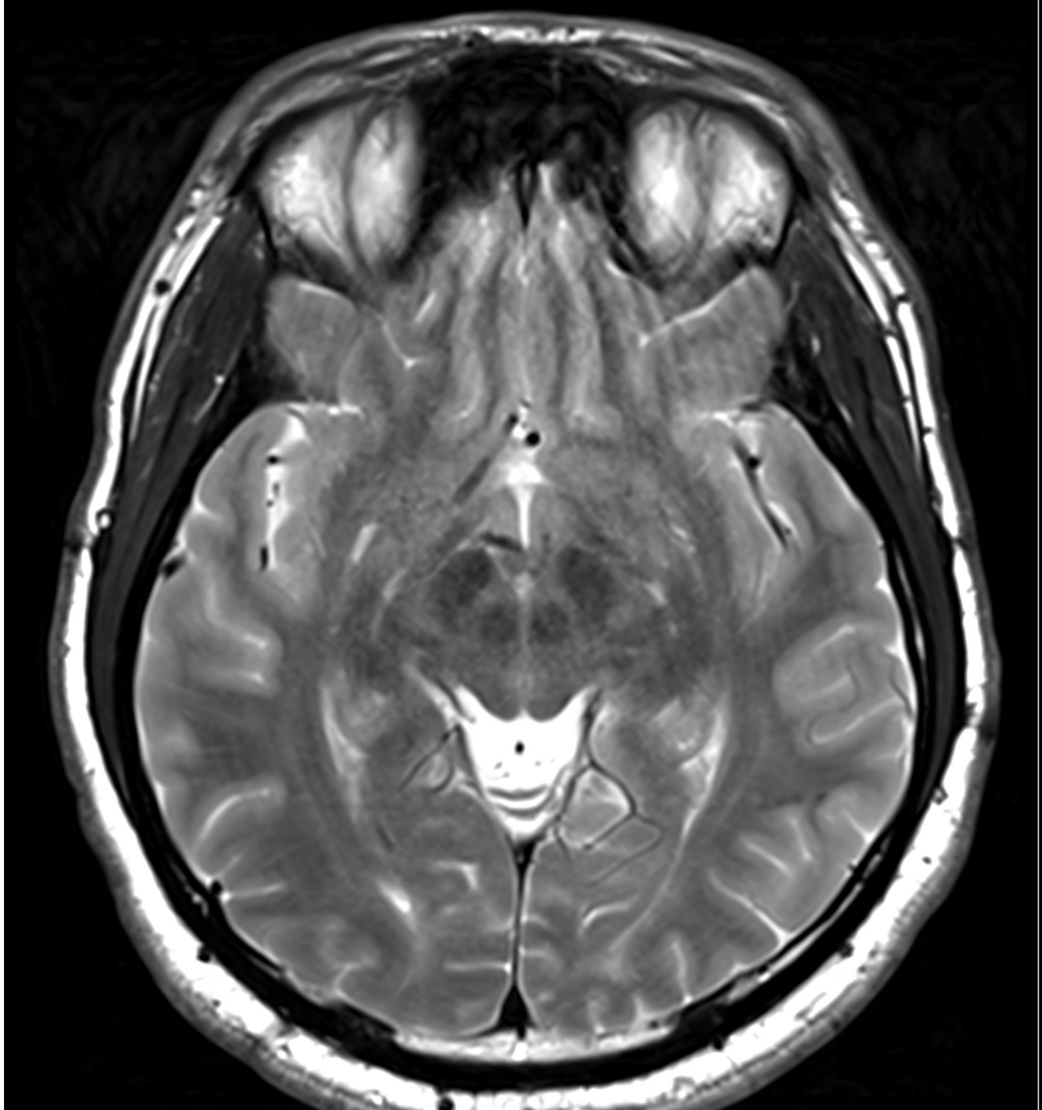
$$\frac{1}{T2^*} = \frac{1}{T2} + \frac{1}{T2_i}$$

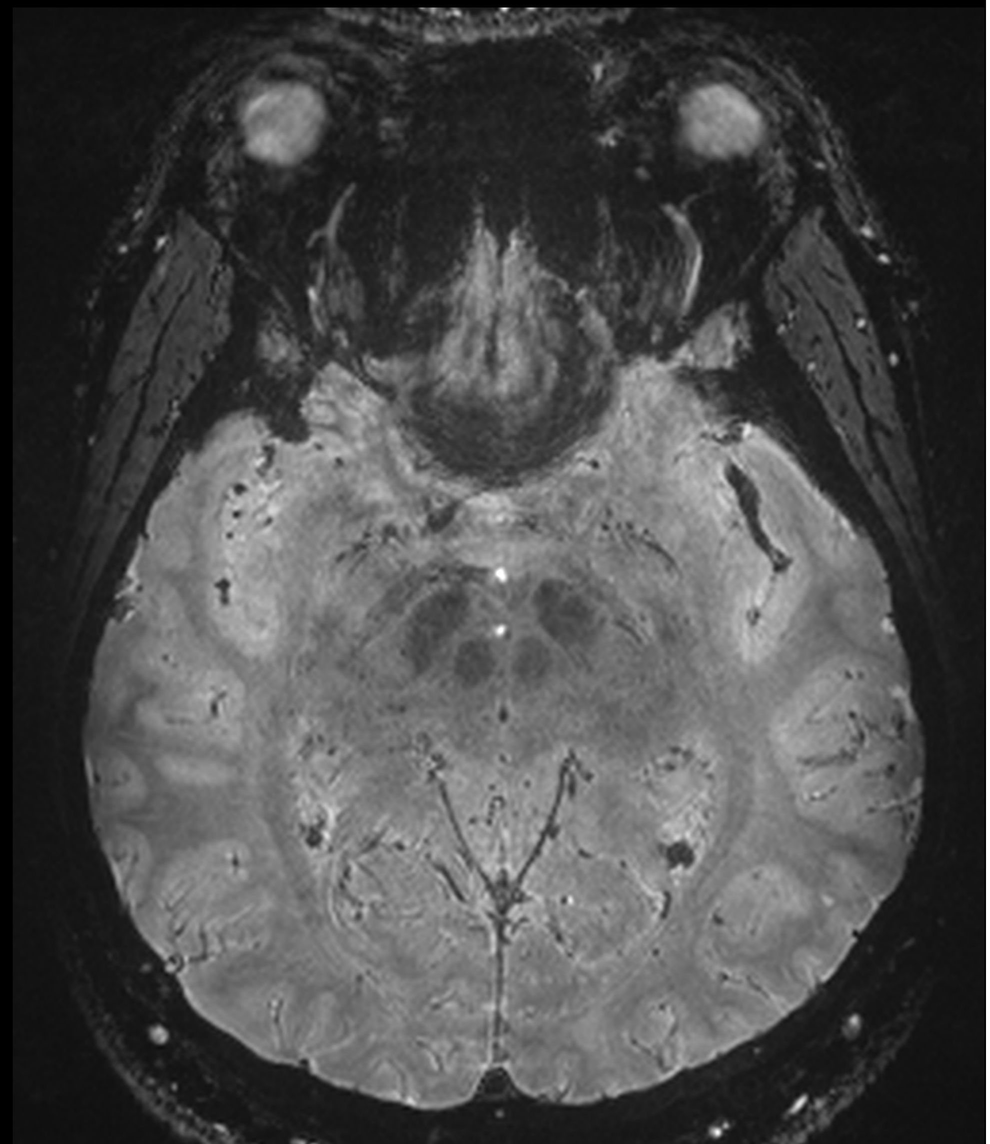
Signal loss due to:

- (Macroscopic) magnetic field inhomogeneities (refocused by the 180° pulse)
- Local environment (presence of paramagnetic molecules, viscosity…) – T_2

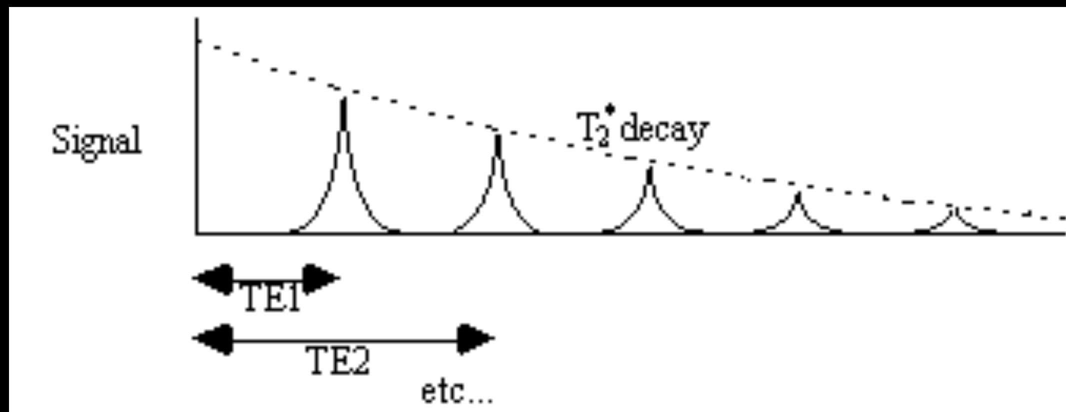
http://www.sprawls.org/mripmt/MRI06/index.html

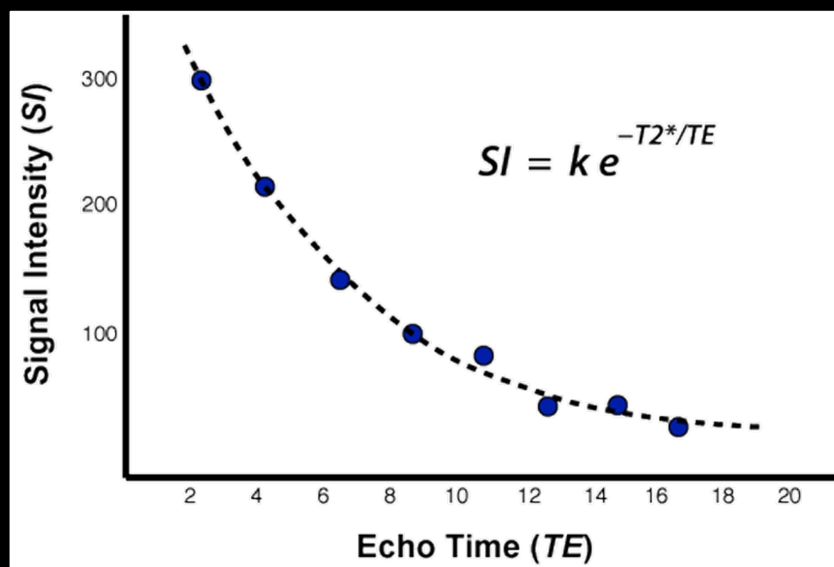
T2 vs. T2*





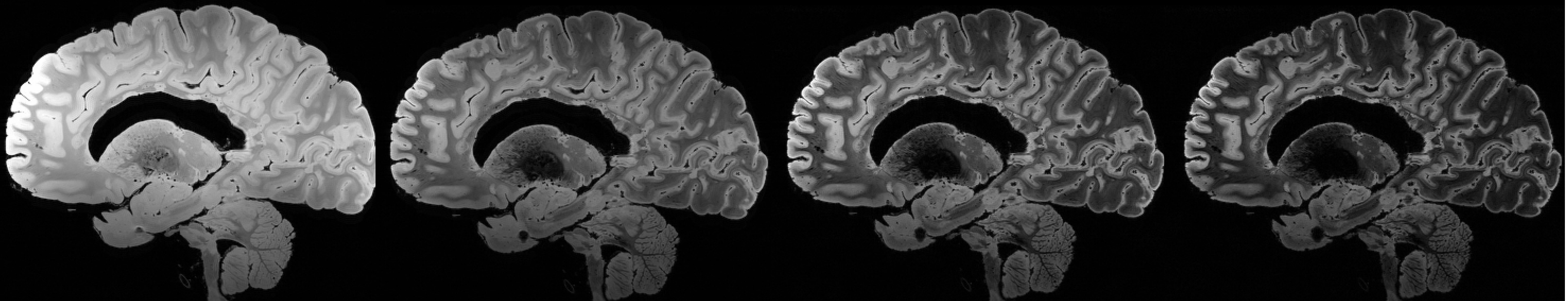
Measuring Rate of T_2 Relaxation



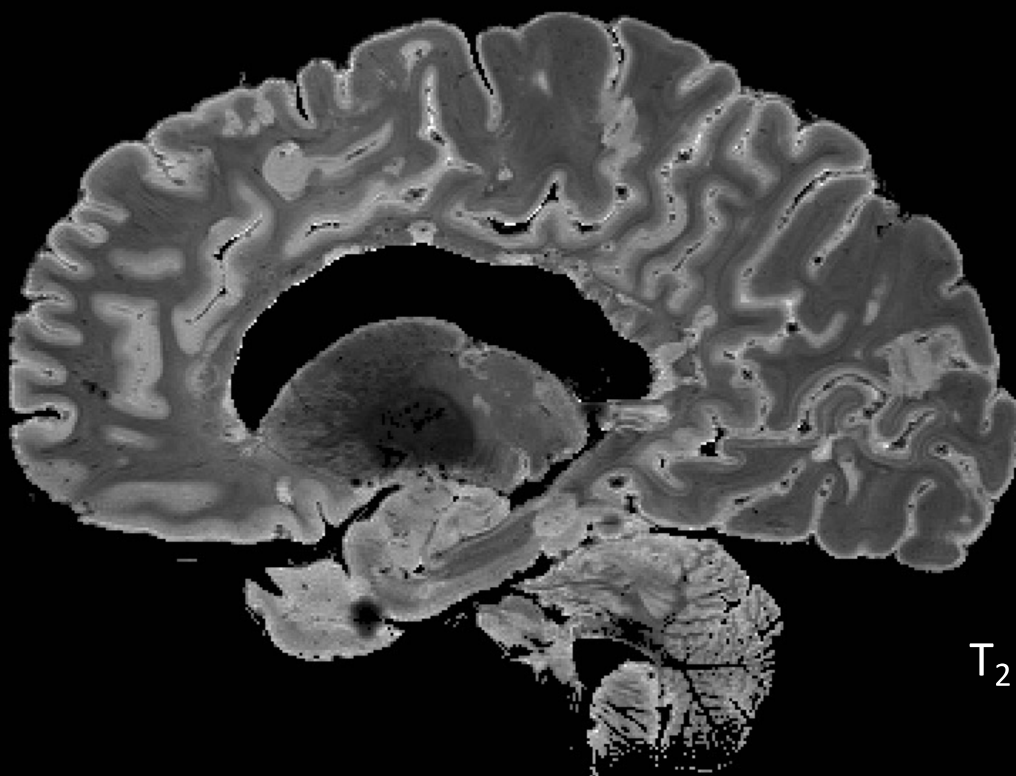


Wikipedia

Measuring Rate of T_2* Relaxation

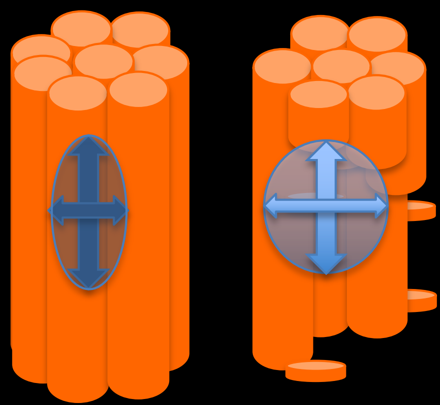


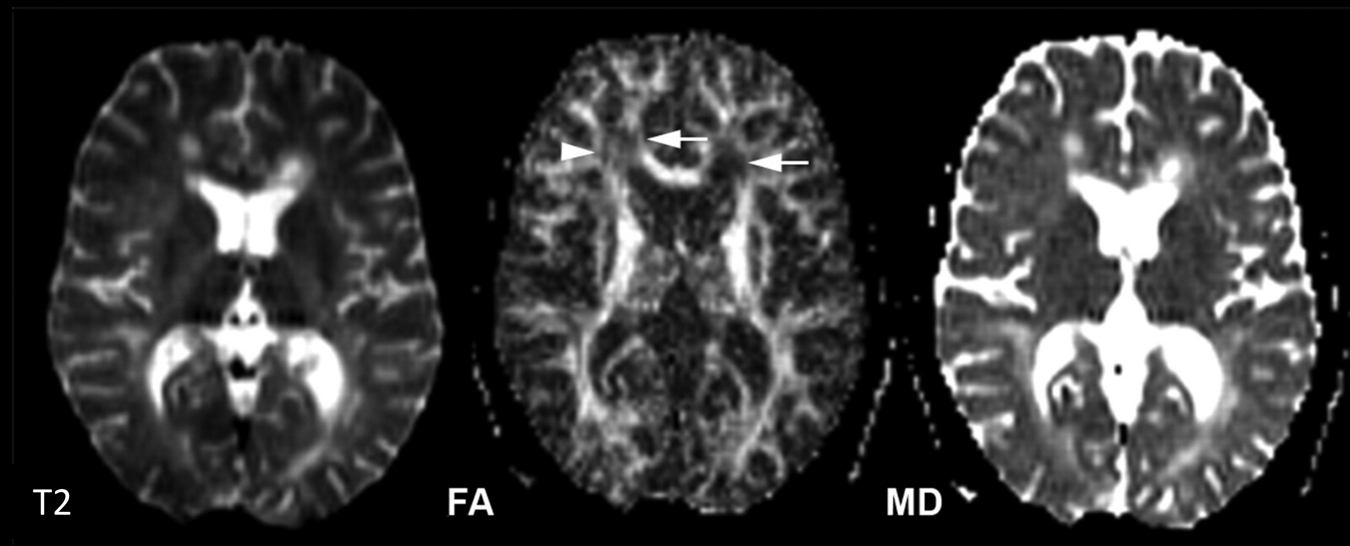
TE= 6 ms 16 ms 26 ms 36 ms

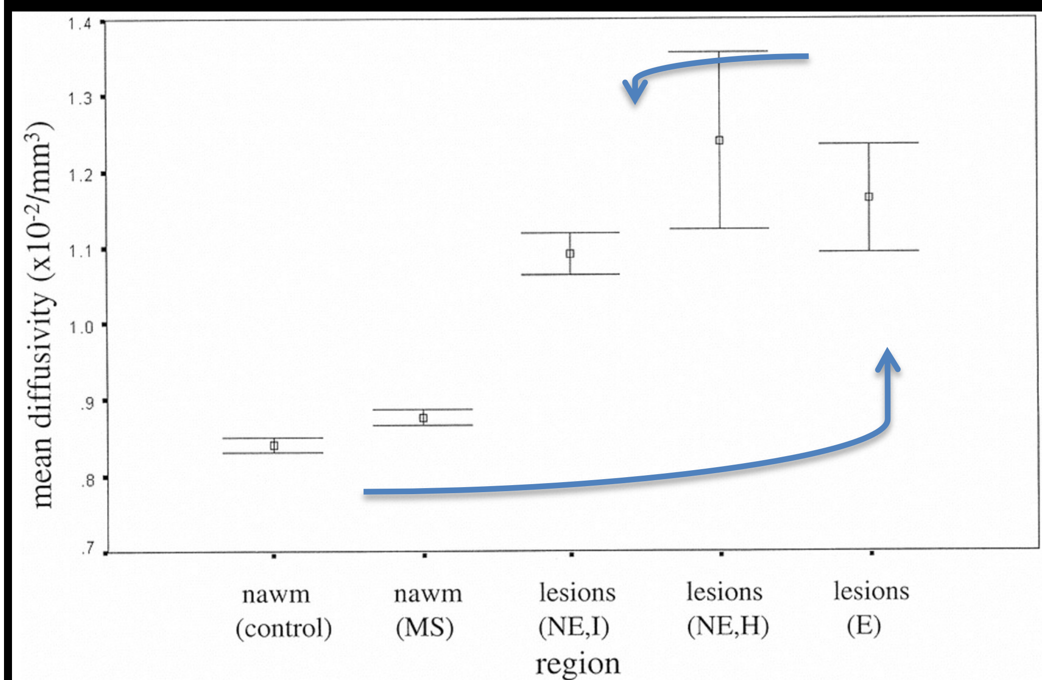


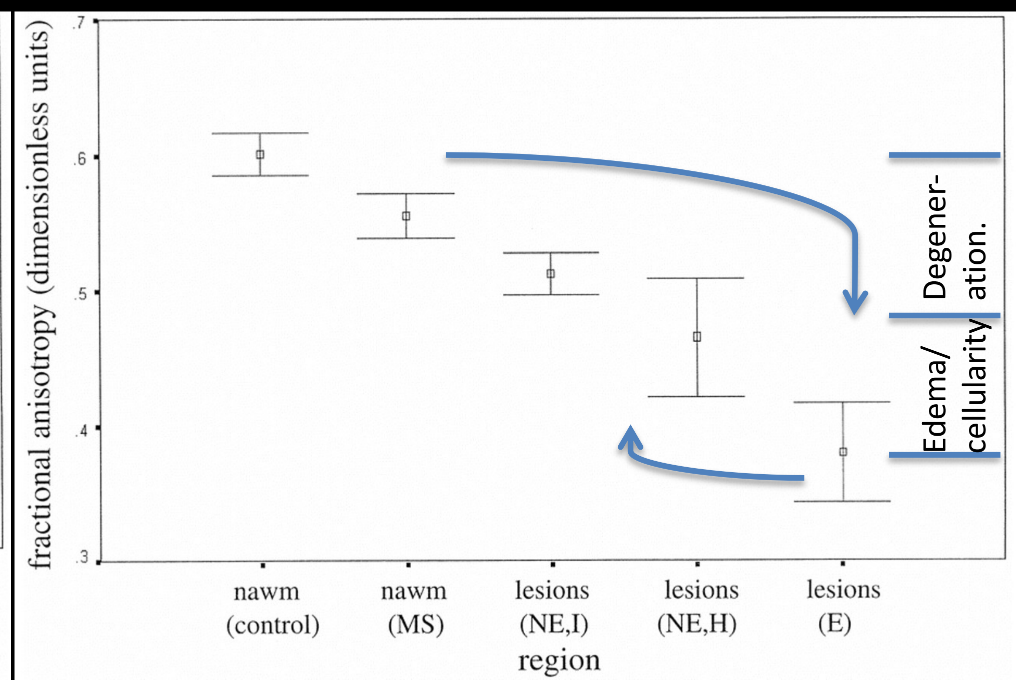
T_2 map

Diffusion Tensor Imaging



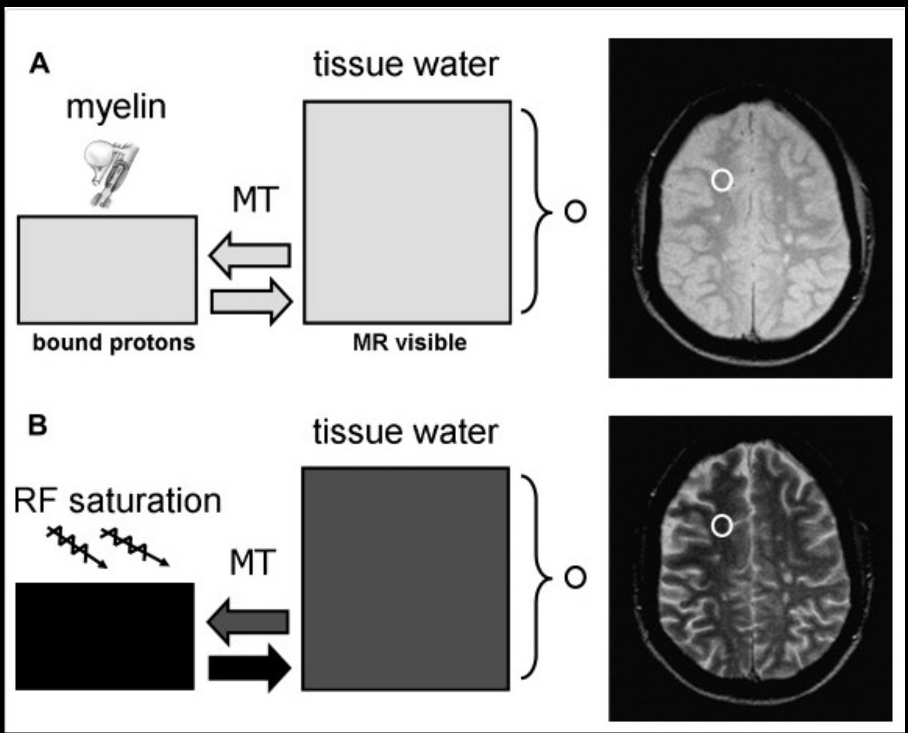


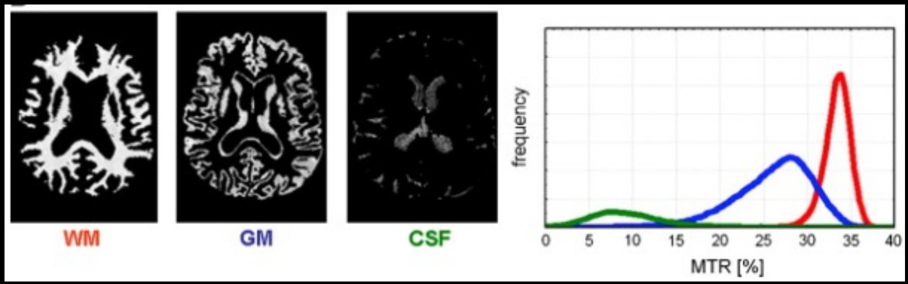


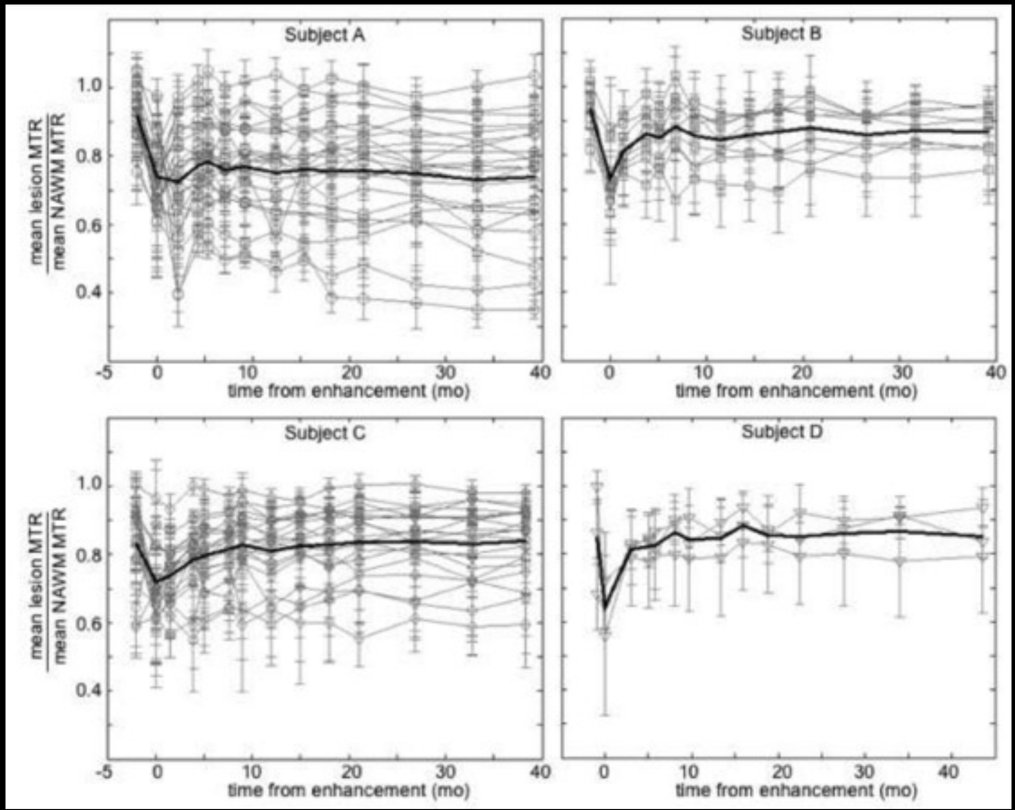


Y. Ge AJNR Am J Neuroradiol 2006;27:1165. Werring et al. Neurology 1999;52(8):1626

Magnetization Transfer Ratio



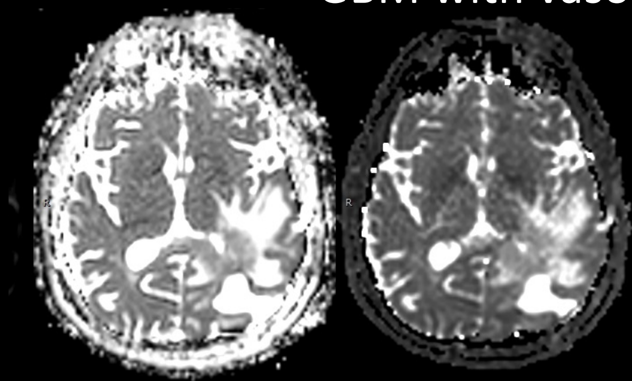




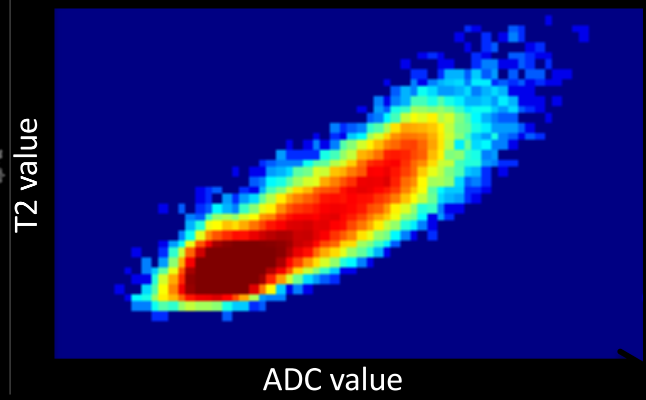
Chen et al. Ann Neurol 2008;63:254. Ropele and Fazekas Neuroimaging clinics 19(1):27

Multiparametric Approach to Improve Specificity

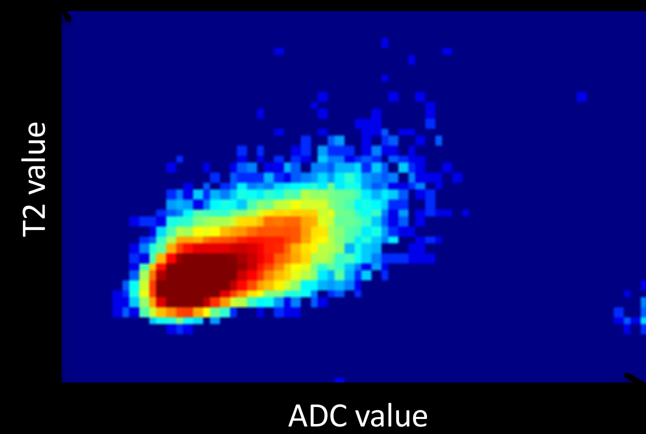
GBM with vasogenic edema



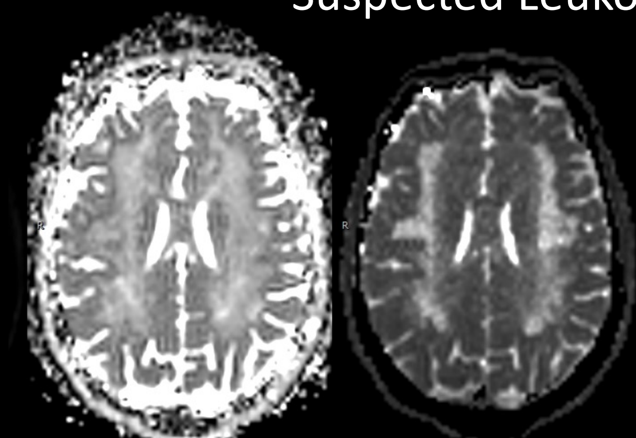
ADC map T2 map



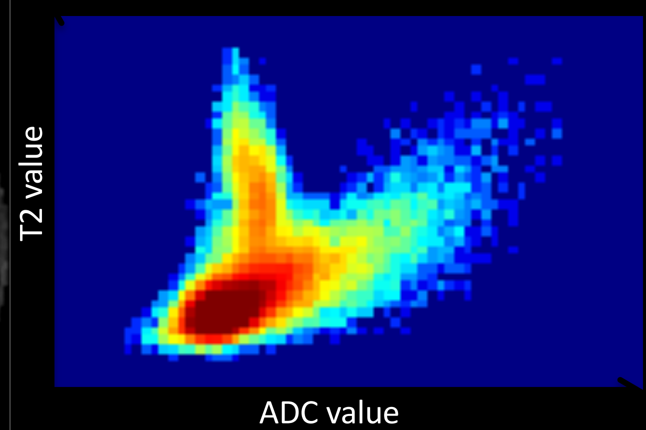
Typical distribution



Suspected Leukoencephalopathy

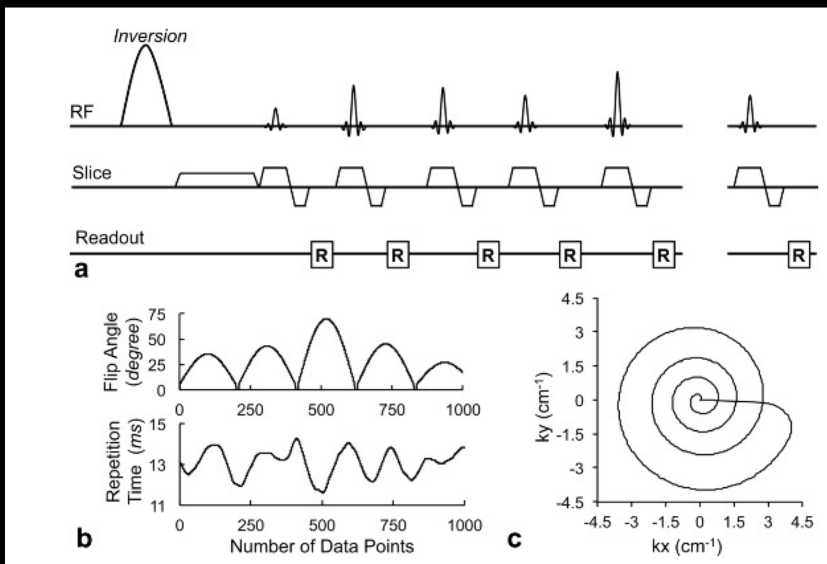


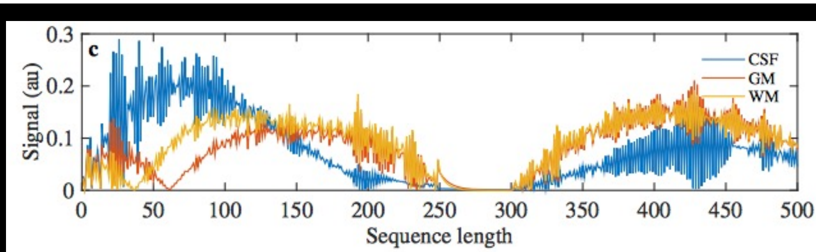
ADC map T2 map

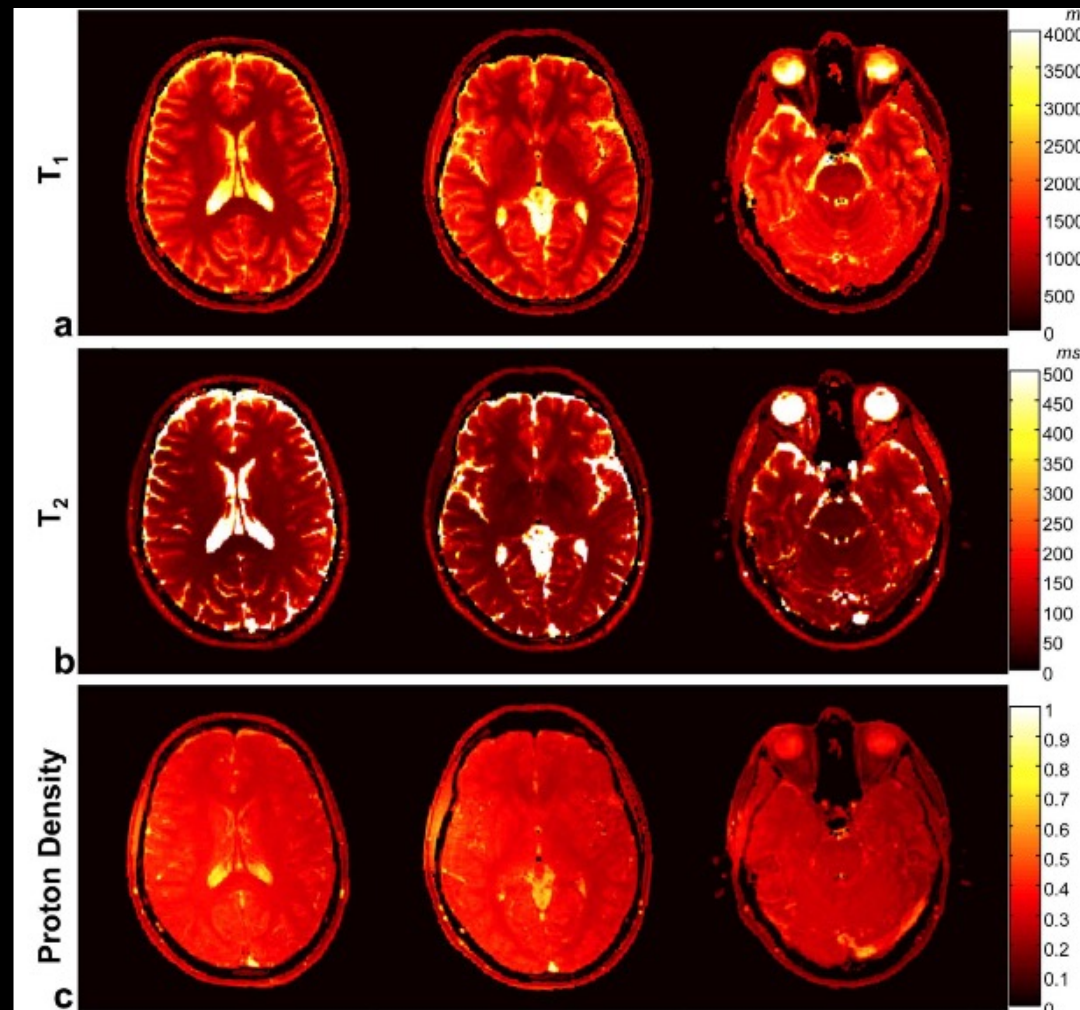


John Butman, NIH, Education Exhibit (EdE) – Adult Brain; EdE-38, ASNR 2016

MR Fingerprinting (Also MAGiC*)







qMRI in Neuroinflammation

Morphometry

- Atrophy of the brain.
- Atrophy of the spinal cord.
- Lesion volume.

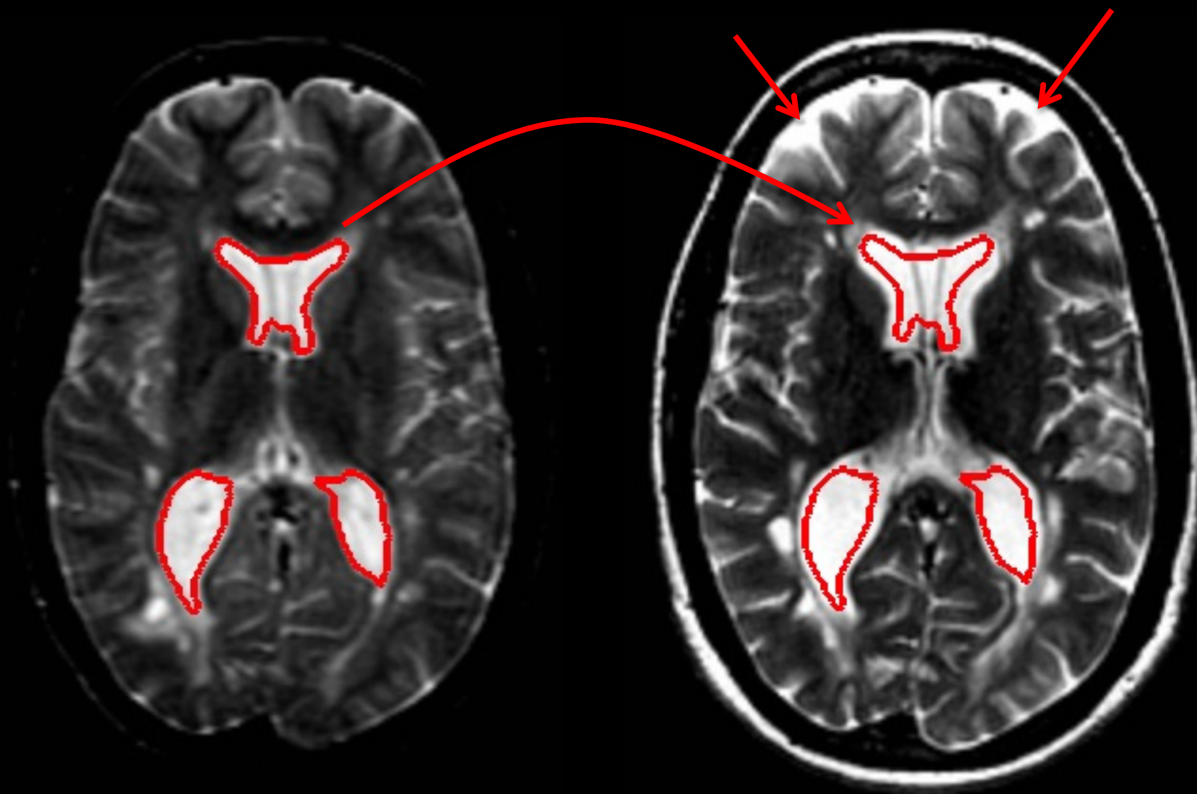
Microstructural changes

- Relaxometry (T_1, T_2, T_2*)
- Diffusion Tensor Imaging
- Magnetization Transfer Ratio
- Spectroscopy
- Functional connectivity
- …

Inflammatory markers

- Blood perfusion imaging
- BBB permeability

Cerebral Atrophy in Multiple Sclerosis



1995 2014

Female
Clinically diagnosed with multiple sclerosis
YOB: 1963

MS patient – T2-weighted images, 19 years apart

"[Atrophy] is the ultimate consequence of destructive pathological changes… within lesions or in normal appearing tissue": Miller et al Brain (2002) 125: 1677

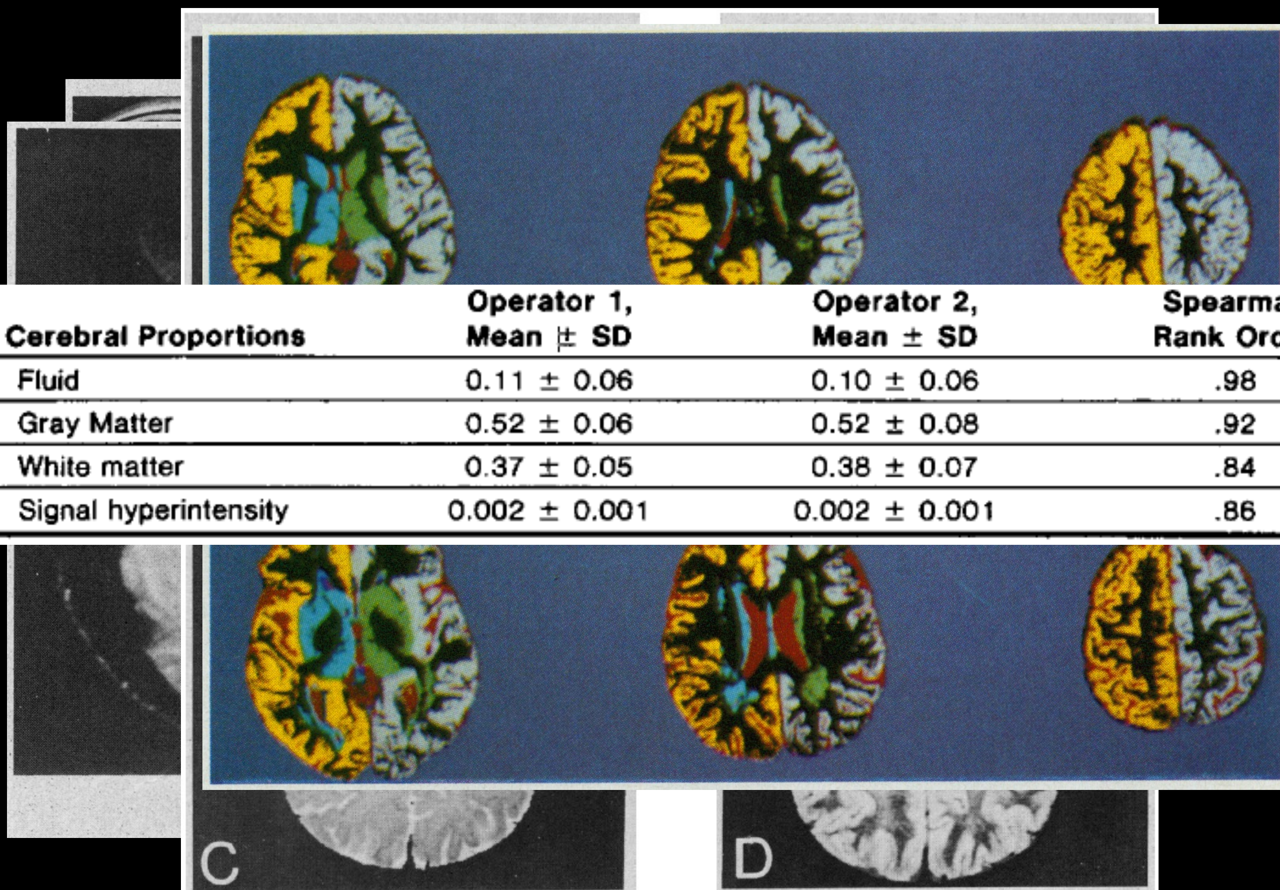
Methods for Measuring Brain Morphologic Features on Magnetic Resonance Images

Validation and Normal Aging

Terry L. Jernigan, PhD; Gary A. Press, MD; John R. Hesselink, MD

(*Arch Neurol.* 1990;47:27-32)

Establishing a standard imaging protocol → Exclusion of non-brain areas → Pixel classification → Calculate volume, reliability analysis



Cerebral Proportions	Operator 1, Mean ± SD	Operator 2, Mean ± SD	Spearman Rank Order
Fluid	0.11 ± 0.06	0.10 ± 0.06	.98
Gray Matter	0.52 ± 0.06	0.52 ± 0.08	.92
White matter	0.37 ± 0.05	0.38 ± 0.07	.84
Signal hyperintensity	0.002 ± 0.001	0.002 ± 0.001	.86

Imaging protocol → Exclusion of non-brain areas → Pixel classification → Calculate volume, reliability analysis

Table 1. Methods Used for Whole-Brain Atrophy Measurement in Multiple Sclerosis

Method	Segmentation	Registration	Normalization	Automation	Comments
Brain parenchymal fraction	Brain parenchyma, ventricular CSF	No	Brain + ventricular CSF	Full	Used on commonly acquired MR images Includes only ventricular CSF
Index of brain atrophy	Brain parenchyma, ventricular CSF	No	Brain + ventricular and sulcal CSF	Semi	Only measures above midbrain High-resolution images
Whole-brain ratio	Intradural volume, CSF volume	No	Intradural volume	Semi	Manual editing of lesions
Brain to intracranial capacity ratio	Gray matter, white matter, lesions, CSF; Bayesian tissue classification	Yes	Intracranial volume	Full	Limited coverage in reported cases Intensity correction
3DVIEWNIX	Gray matter, white matter, lesions, CSF; fuzzy connectedness–based thresholding	Yes	Intracranial volume	Semi	Time-consuming operator input Intensity correction
Statistical parametric mapping	Gray matter, white matter, CSF; stereotactic space	Yes	Intracranial volume	Semi for MS lesions	Manual editing of misclassified voxels
Template-driven segmentation	Template-driven, brain parenchyma, CSF	Yes	Intracranial volume	Full	Limited application in MS
Alfano	Gray matter, white matter, lesions, CSF; relaxometric characterization	No	Intracranial volume	Full	Intensity correction
Structural image evaluation using normalization of atrophy X/SIENA	Brain and skull	Yes	Head size	Full	No CSF segmentation needed
Brain boundary shift integral	No	Yes	Brain size	Semi and full versions	Strongly depends on accuracy of registration No segmentation needed
Voxel-based morphometry	Gray matter, white matter, CSF	Yes	Intracranial volume (possible)	Full	Lesion mask needed for white matter analysis Complex statistical analysis

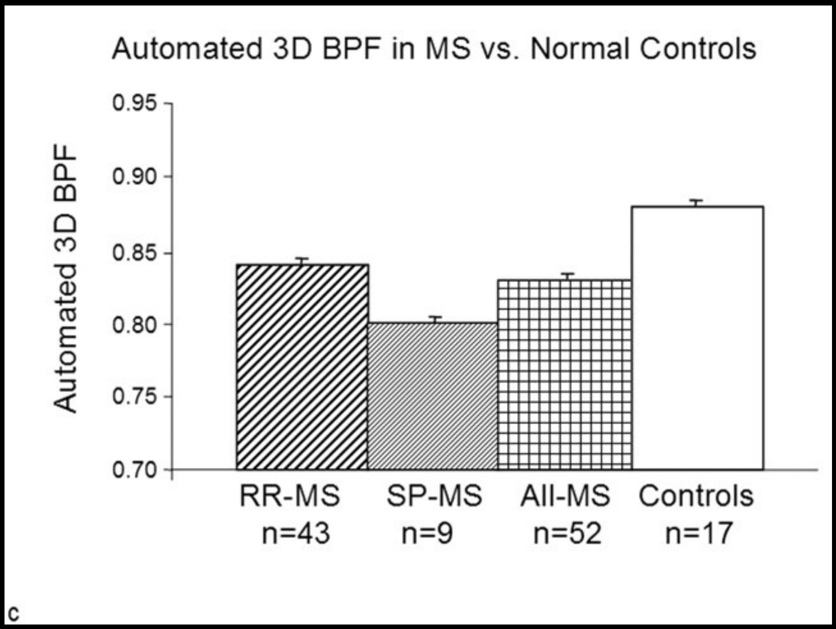
CSF = cerebrospinal fluid, MR = magnetic resonance, MS = multiple sclerosis.

Need for automation, especially in large cohort studies

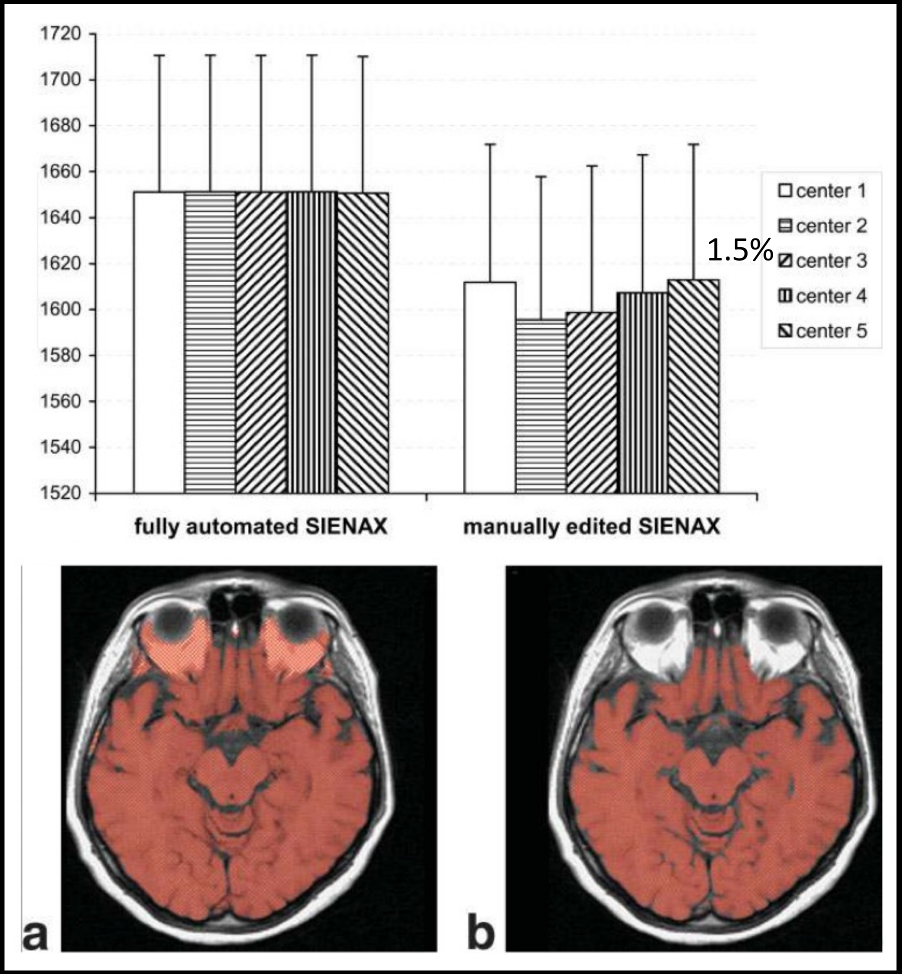
Pelletier et al. Journal of Neuroimaging Vol 14 No 3 (Supplement)

Couple of Examples

BPF

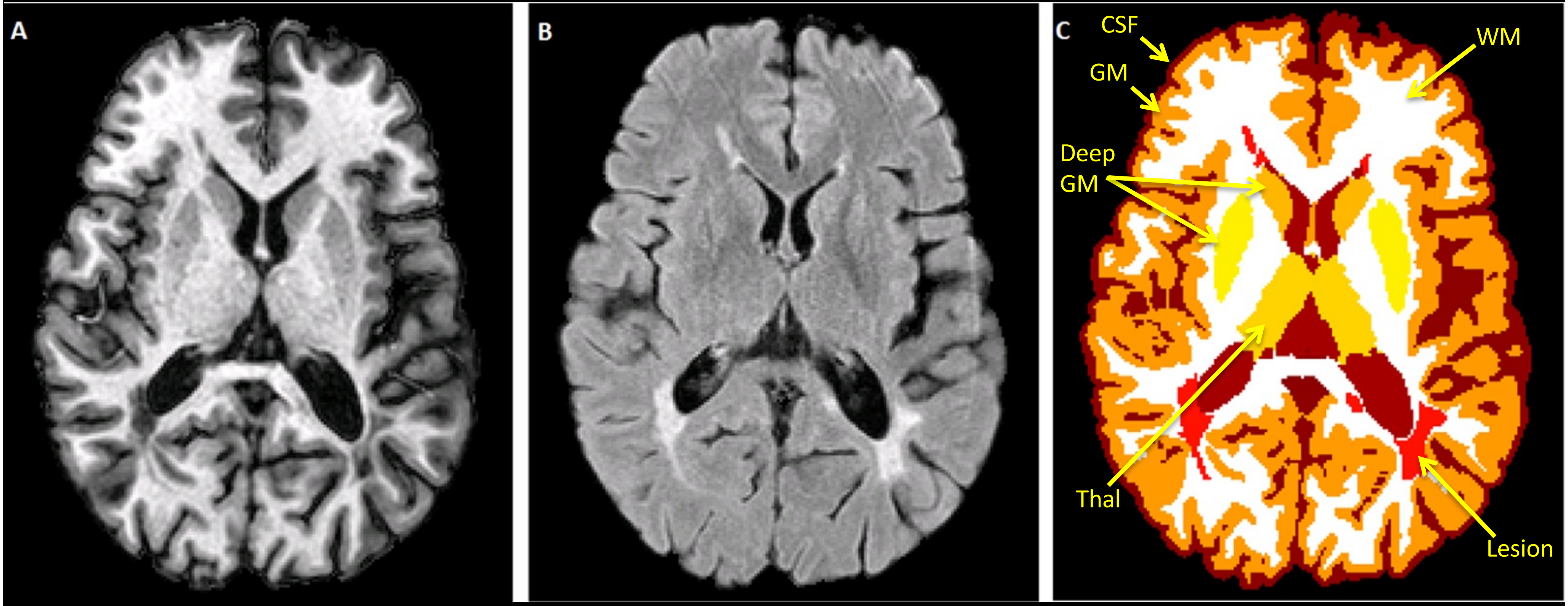


SIENAX



Jitendra Sharma et al. Am J Neuroradiol ;25:985. Jasperse et al. J Magn Reson Imaging. Oct;26(4):881-5

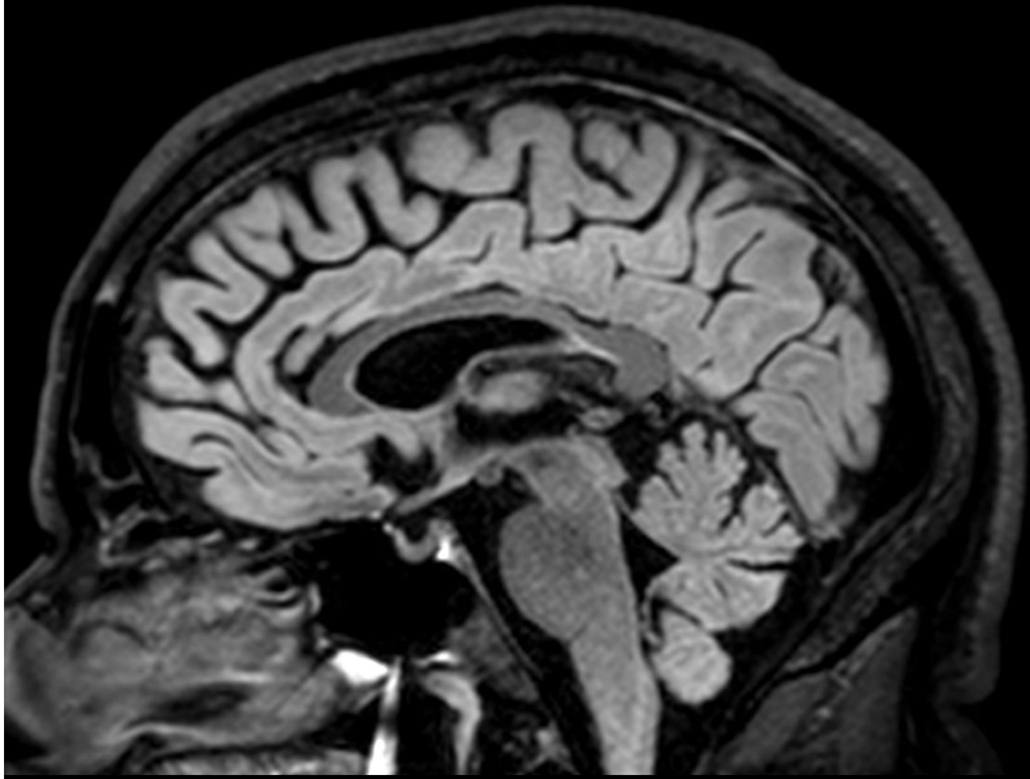
Volumetrics - LesionTOADS



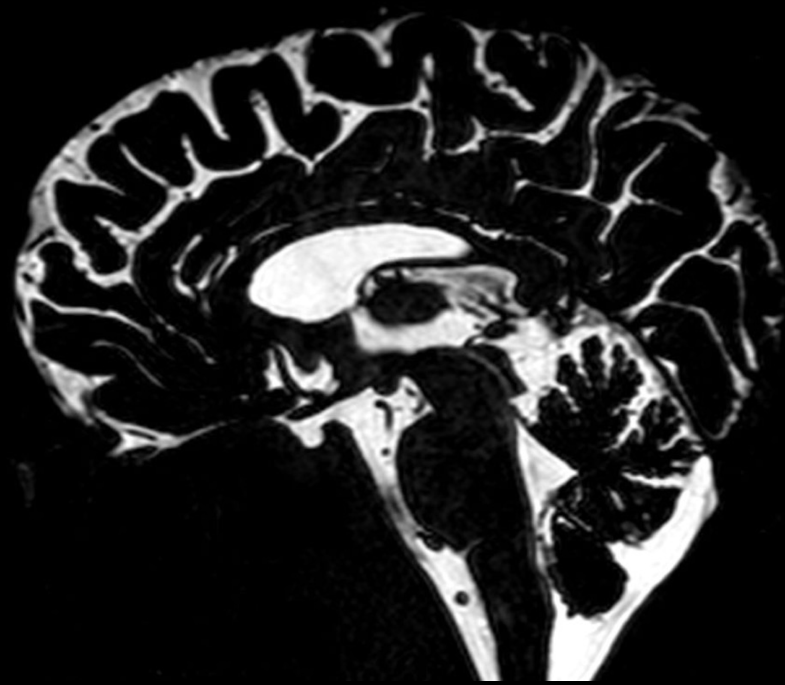
MPRAGE | 2D FLAIR | Tissue classification

Shee et. al. PLoS ONE 7(5): e37049

Global Cerebral Atrophy – Brain Free Water Imaging



FLAIR – unprocessed
Generally, 1 mm isotropic

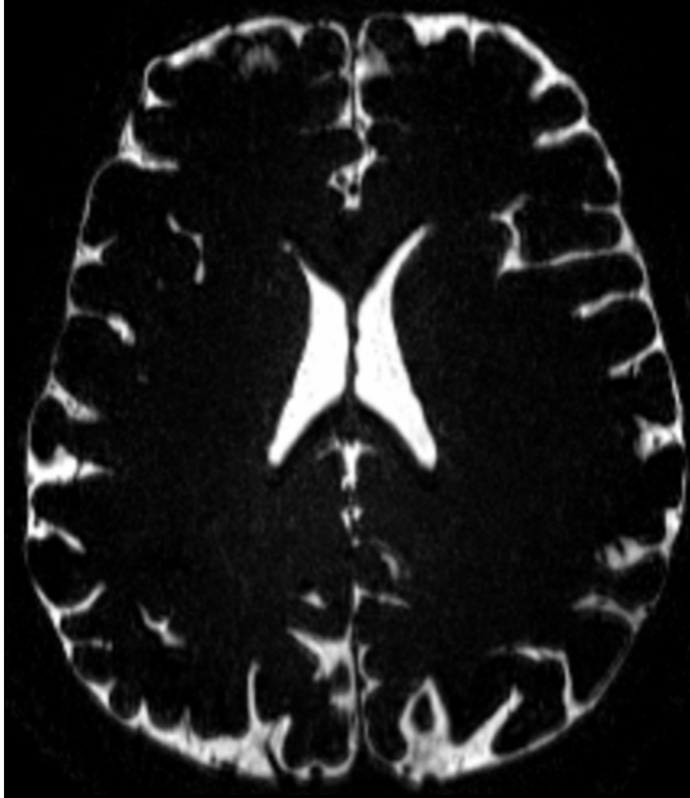


BFWI - unprocessed
The only thing that is bright is fluids
Done at 0.65 mm isotropic

HIV patient – ALL HANDS

Gao et. al. NeuroImage 100 (2014):370-378

Comparison: BFWI vs. LesionTOADS



Original

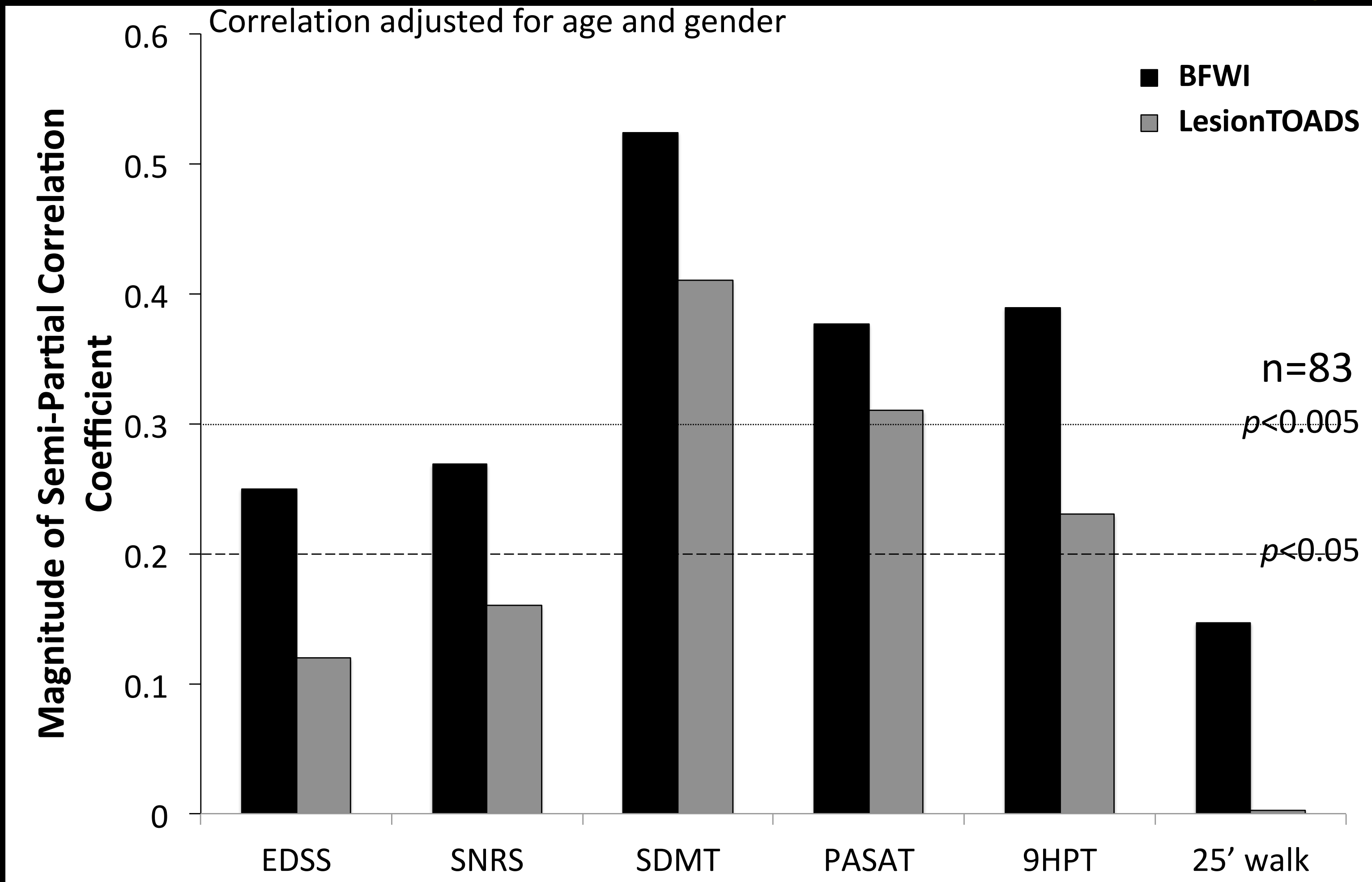
LesionTOADS - processed

BFWI - processed

MS patient – TNU

Gao et. al. NeuroImage 100 (2014):370-378

What does it mean clinically?

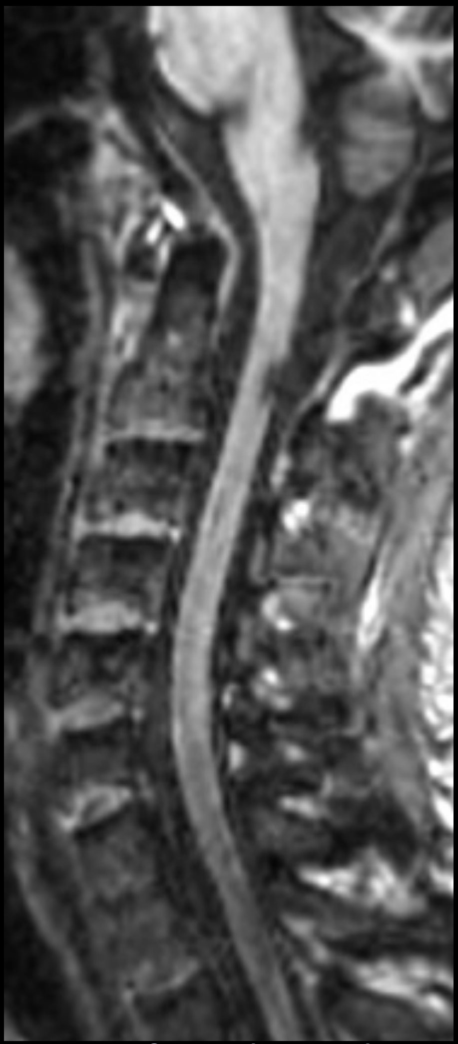


EDSS: Kurtzke Expanded Disability Status Scale
SNRS: Scripps Neurologic Rating Scale
SDMT: Symbol Digit Modalities Test
PASAT: Paced Auditory Serial Addition Test
9HPT: 9-Hole Peg Test
25' walk: 25-foot Walk Test

Gao et. al. NeuroImage 100 (2014):370-378

Atrophy of the Spinal Cord

38 y.o. male, healthy volunteer

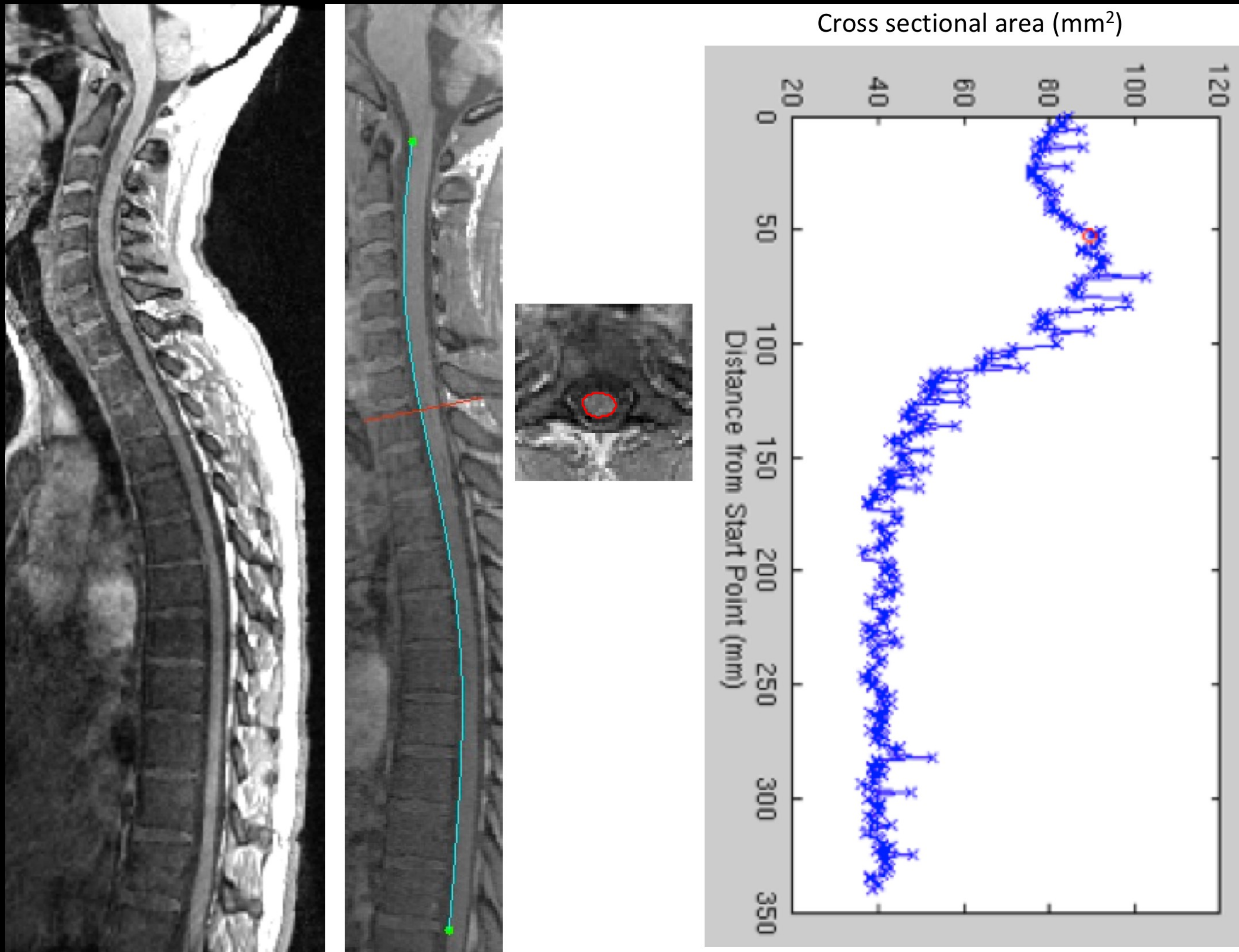


31 y.o. female with MS

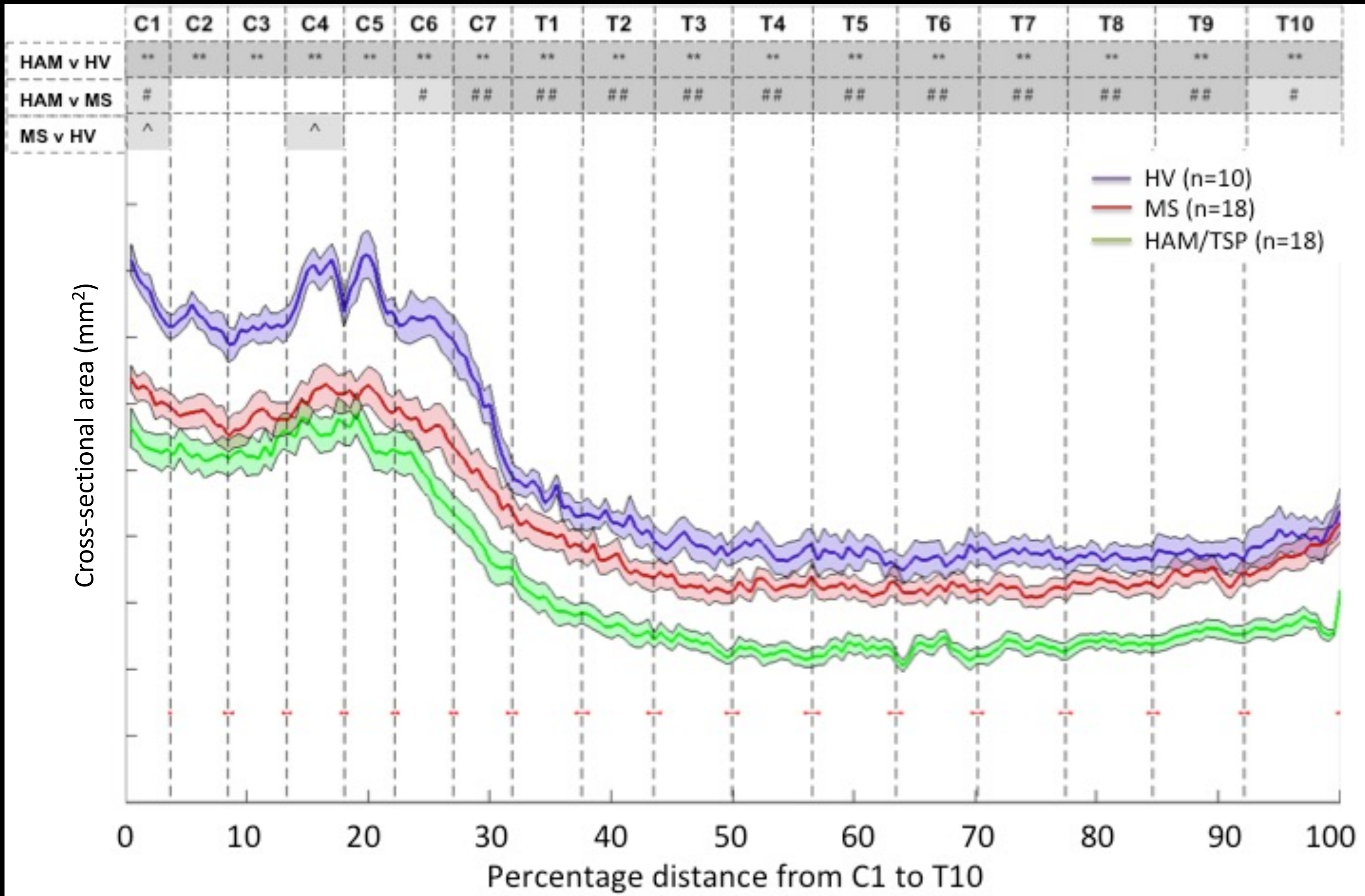
Atrophy in MS

In comparison - 38% smaller cross-sectional area

NIC, NINDS; http://rad.desk.nl/en/4f789faf60fa4



Liu et al. Ann Neurol. 2014 Sep; 76(3): 370. Horsfield et al., NeuroImage (2010)50:446



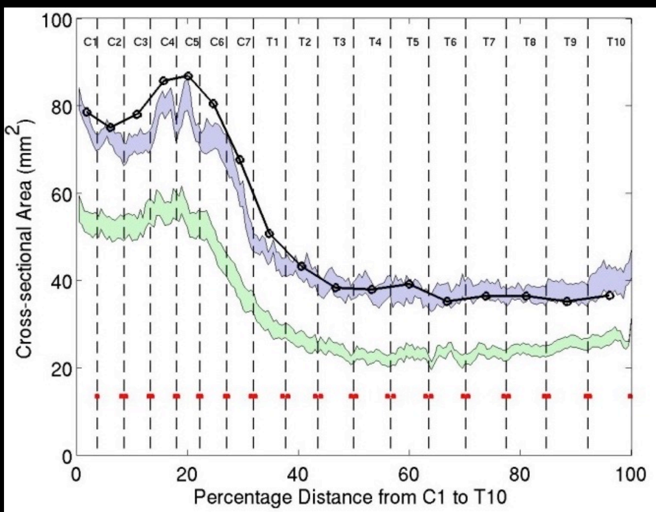
HAM/TSP (*n*=18)	C1	C2	C3	C4	C5	C6	C7	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	C	T
SNRS	0.14	0.14	0.22	0.24	0.09	0.22	0.16	0.29	0.20	0.14	0.22	0.18	0.25	0.29	0.19	-0.03	0.01	0.20	0.19
EDSS	-0.33	-0.36	-0.39	-0.46	-0.44	-0.44	-0.46	-0.56	-0.57	-0.55	-0.51	-0.50	-0.59	-0.50	-0.36	-0.22	-0.15	-0.45	-0.48
IPEC	0.07	0.06	-0.05	-0.09	-0.01	-0.01	0.07	0.02	-0.07	0.02	-0.04	-0.02	-0.02	0.02	0.03	0.05	0.06	0.00	0.00
Ambulation Index	-0.46	-0.53	-0.54	-0.58	-0.58	-0.46	-0.46	-0.57	-0.65	-0.57	-0.59	-0.61	-0.72	-0.63	-0.49	-0.44	-0.34	-0.54	-0.57
Disease Duration	-0.66	-0.62	-0.63	-0.64	-0.61	-0.65	-0.61	-0.62	-0.58	-0.52	-0.51	-0.48	-0.47	-0.46	-0.32	-0.30	-0.32	-0.68	-0.49
Proviral load	-0.02	-0.14	-0.13	-0.14	-0.09	-0.24	-0.27	-0.30	-0.23	0.01	-0.19	-0.18	-0.04	-0.06	0.07	-0.01	-0.18	-0.17	-0.13
MS (*n*=18)																			
SNRS	0.62	0.65	0.61	0.58	0.52	0.56	0.49	0.66	0.61	0.61	0.71	0.70	0.63	0.65	0.53	0.49	0.23	0.63	0.64
EDSS	-0.75	-0.67	-0.63	-0.57	-0.51	-0.51	-0.44	-0.53	-0.54	-0.54	-0.52	-0.58	-0.58	-0.51	-0.45	-0.43	-0.28	-0.61	-0.55

HAM/TSP: Human T-cell lymphotropic virus type 1 Associated Myelopathy/Tropical Spastic Paraperesis

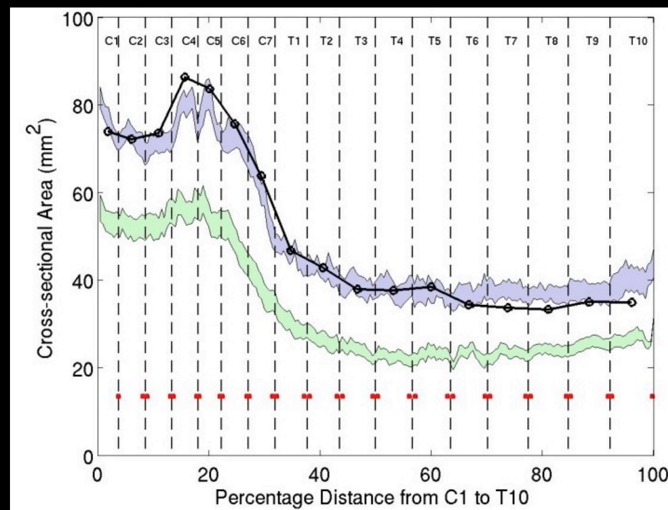
Liu et al. Ann Neurol. 2014 Sep; 76(3): 370

Longitudinal Monitoring of Cord Atrophy

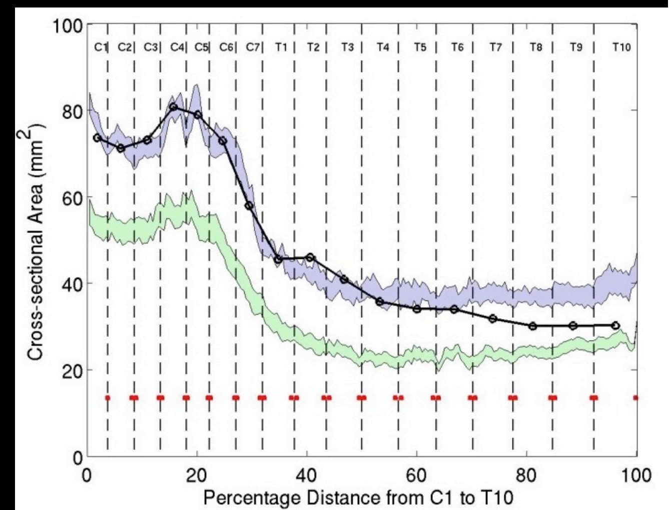
2/27/13



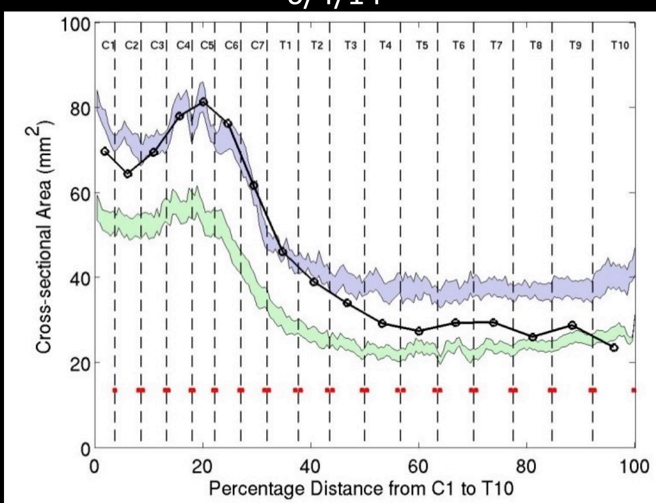
4/24/13, AI=4



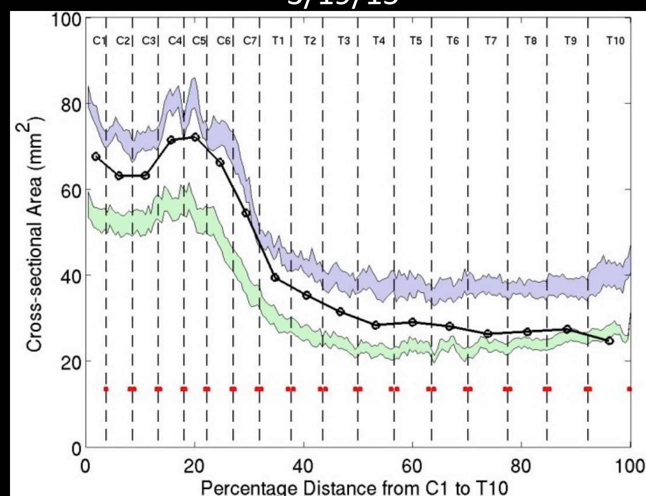
3/6/14, AI=5



6/4/14



3/19/15



37 y.o. Jamaican female with clinical diagnosis of HAM/TSP.

Symptom start 8/2012, progressive weakening.

Cervical: 7.8% reduction/year.
Thoracic: 11% reduction/year.

Shiela Azodi, Emily Charlip, NINDS (unpublished)

Summary

- Several biologically relevant qMRI measurements are readily available on most modern scanners.
  - Important to understand the imaging protocol and analysis methods for reliable measurement.
- Some qMRI measures are more specific to biological processes than others.
  - Multiparametric techniques may offer more specificity and a better understanding of the biological processes.
- Longitudinal measurements may be more fruitful.

Thank you.