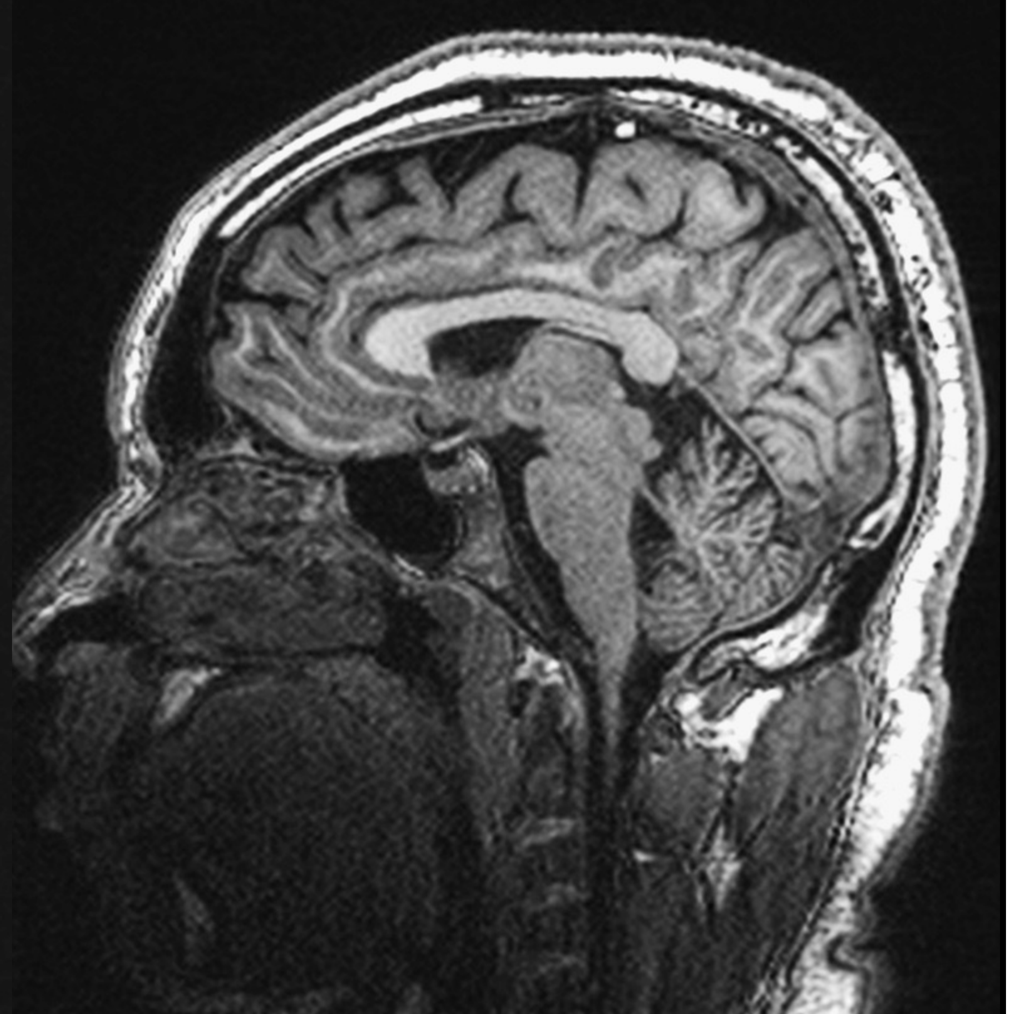
Quantitative MRI

Govind Nair
Staff Scientist, NINDS

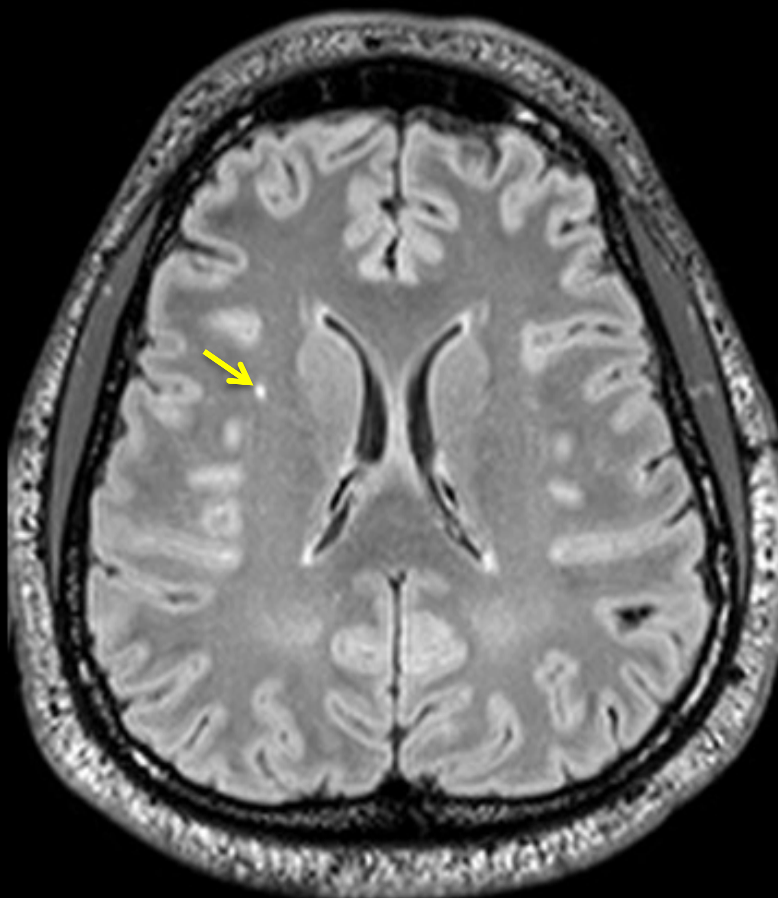
42 y.o. M
Multiple sclerosis

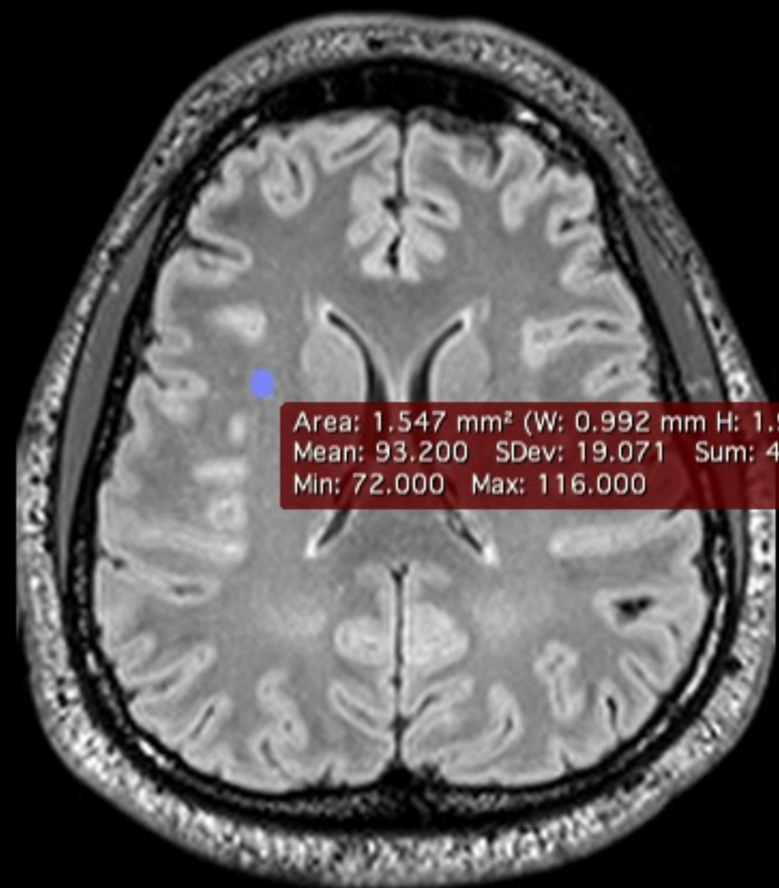
40 y.o. M
Healthy Volunteer



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

Qualitative vs. Quantitative



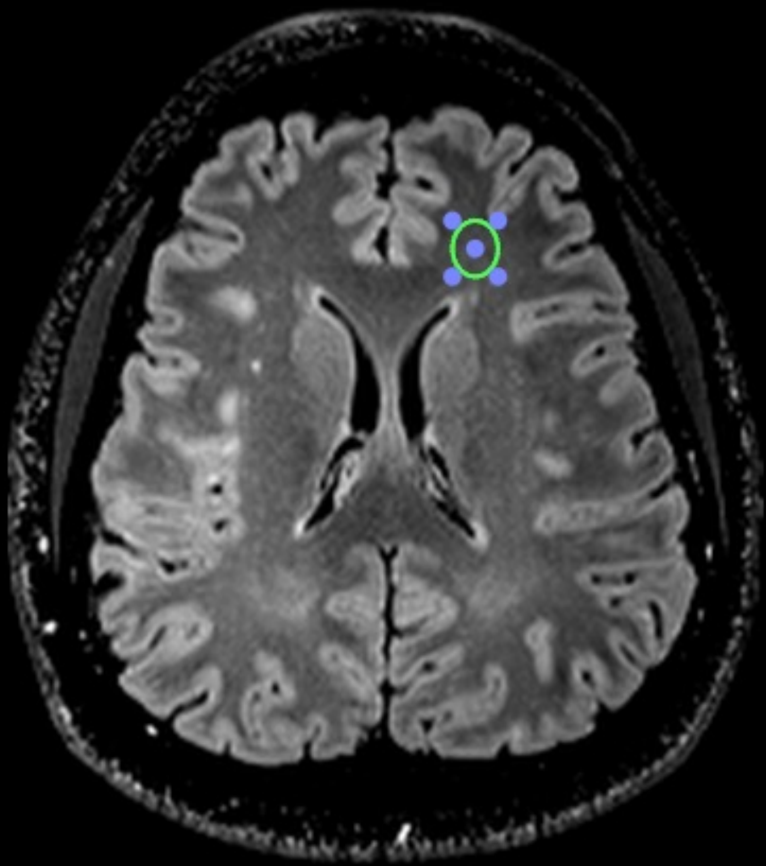


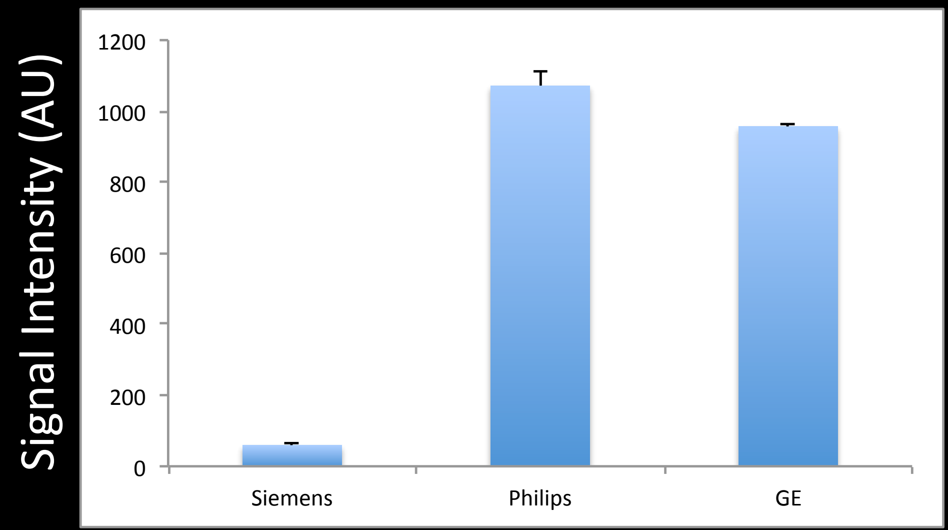
Qualitative: “Hyper-intense lesion seen in the deep white matter”

Fluid-Attenuated Inversion Recovery (FLAIR)

40 y.o. M, HV

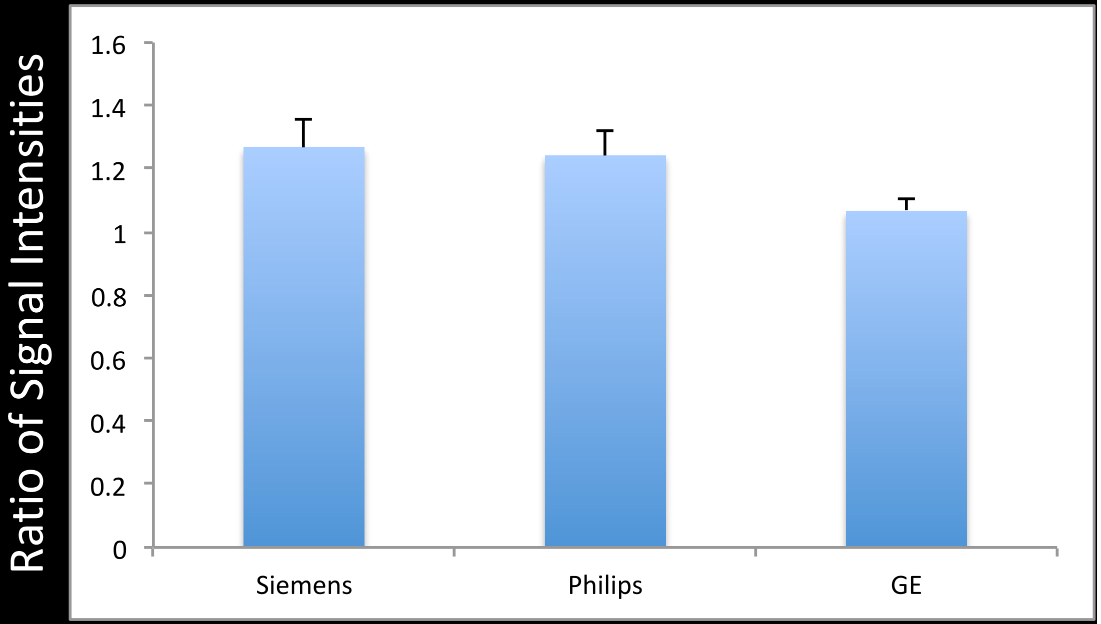
The Trouble with Quantitation





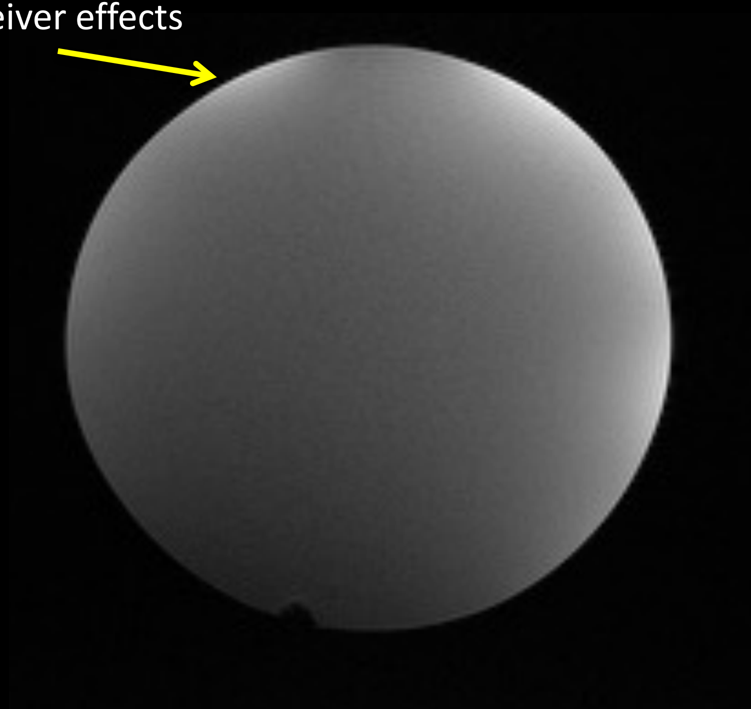
Different scanners, very similar protocols
FLAIR

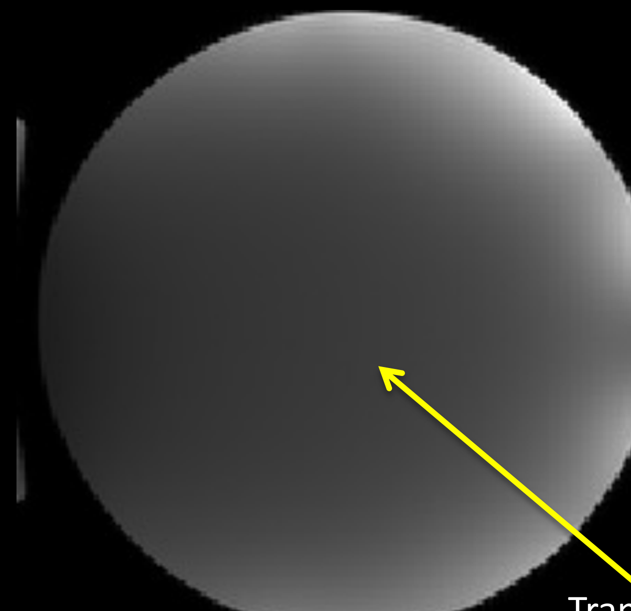
The Trouble with Quantitation

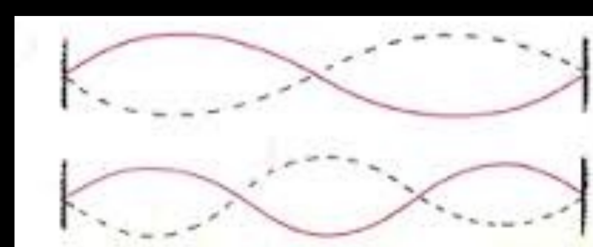


Different scanners, very similar protocols
FLAIR

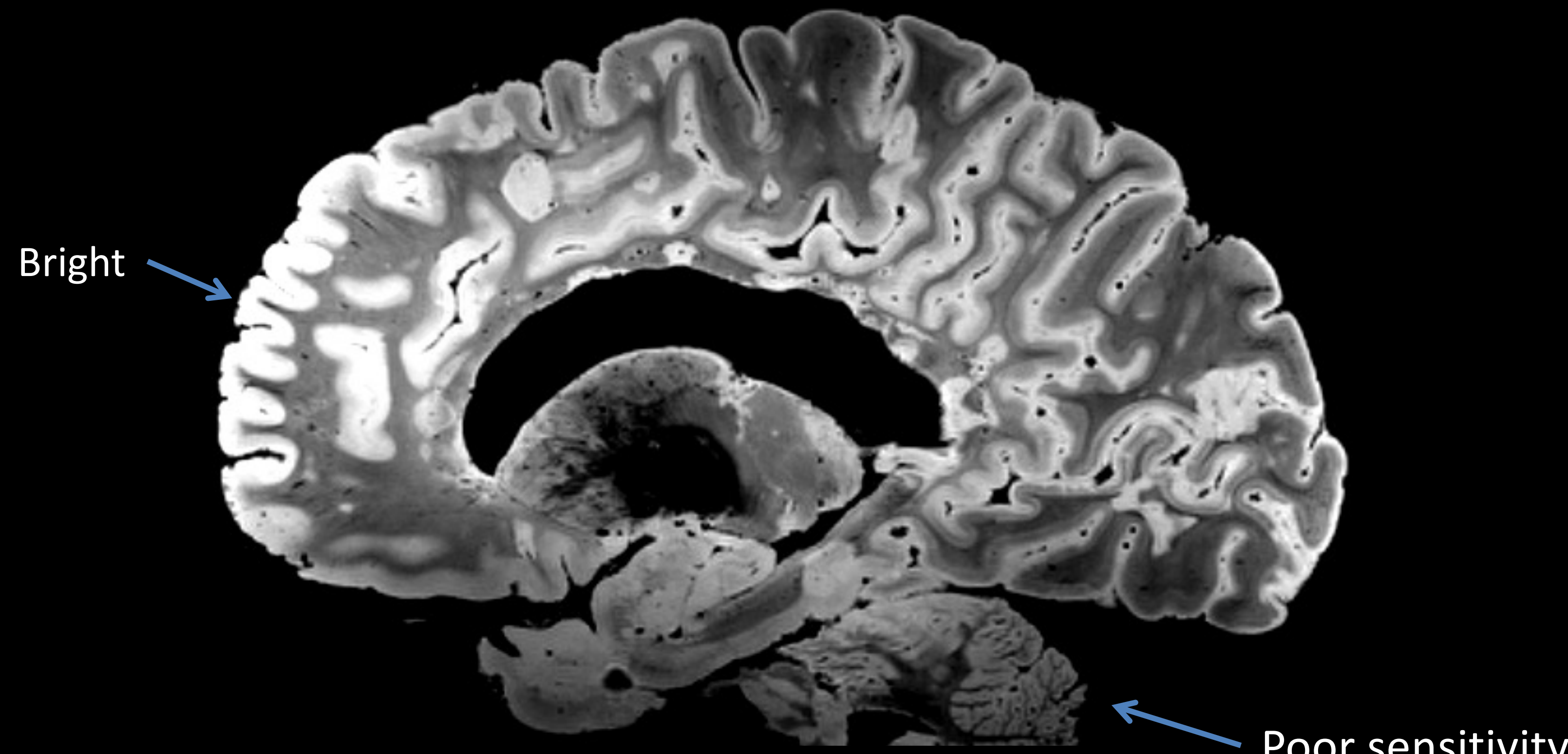
Coil Sensitivities Effect Normalization







Coil Sensitivities Effect Normalization



Why Bother with Quantitation: Philosophical

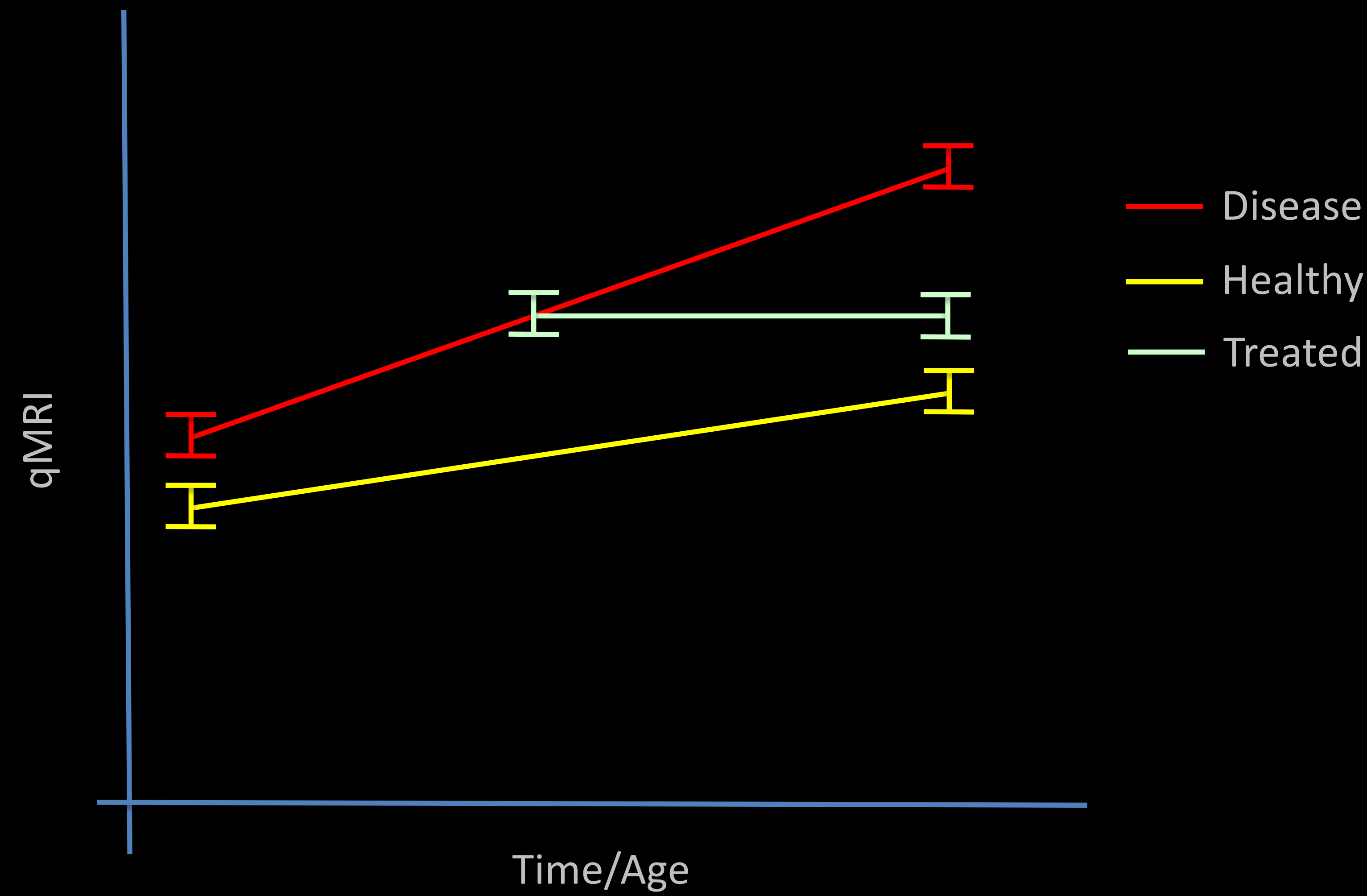
"I often say that when you can measure what you are speaking about, and express it in numbers, you know something about it; but when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meager and unsatisfactory kind; it may be the beginning of knowledge, but you have 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 Glen

qMRI parameters may reflect specific biological processes

Why Bother with Quantitation: Clinical



Commonly used qMRI measures

- Basic MR parameters
  - T_1, T_2, T_2* Relaxometry
  - Diffusion of water in tissue
  - Metabolite concentrations using MR Spectroscopy
  - Volumetrics
  - …
- Derived parameters
  - Blood flowing through tissue (perfusion)
  - Permeability of blood brain barrier
  - …

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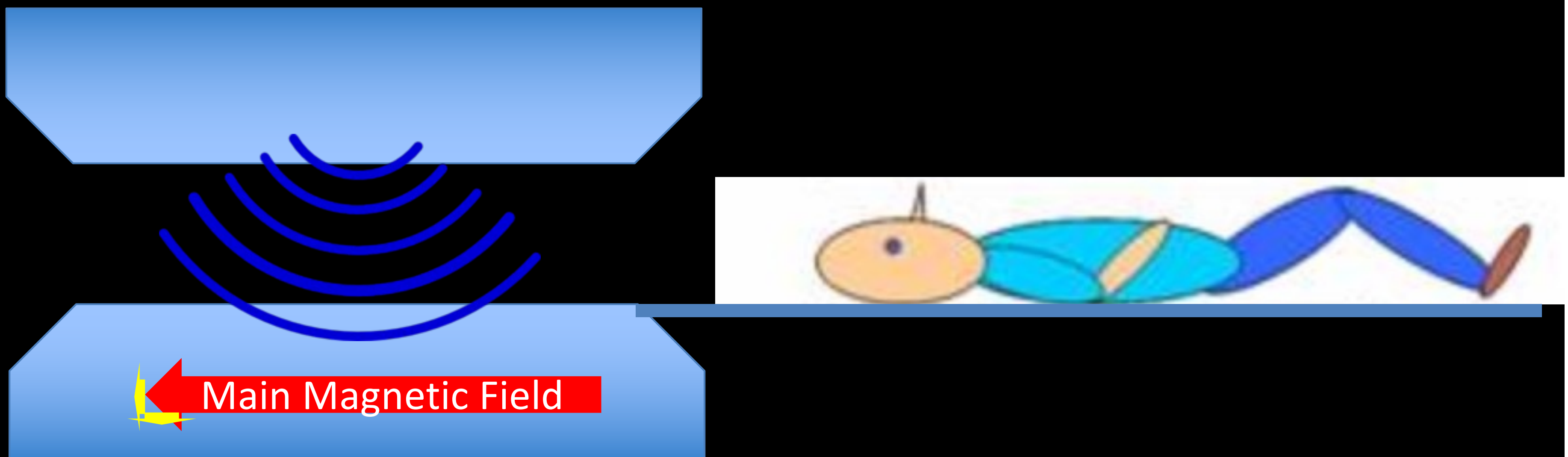
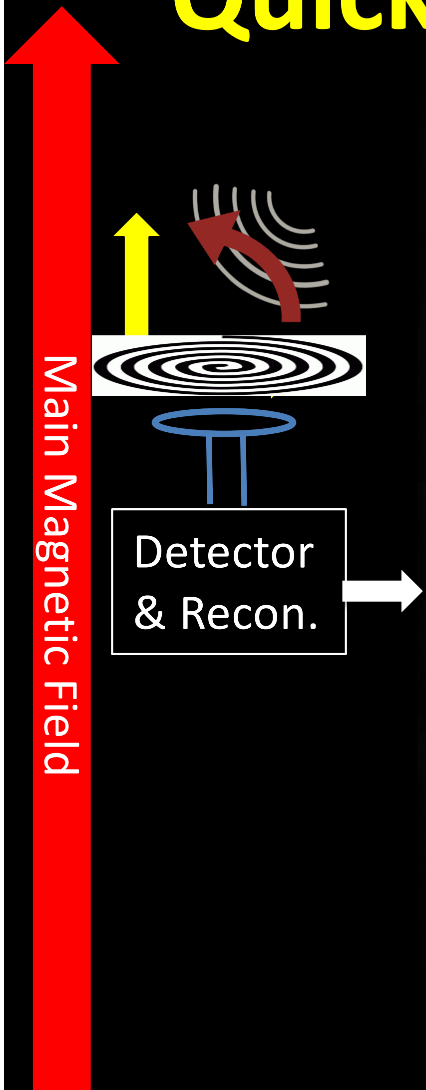
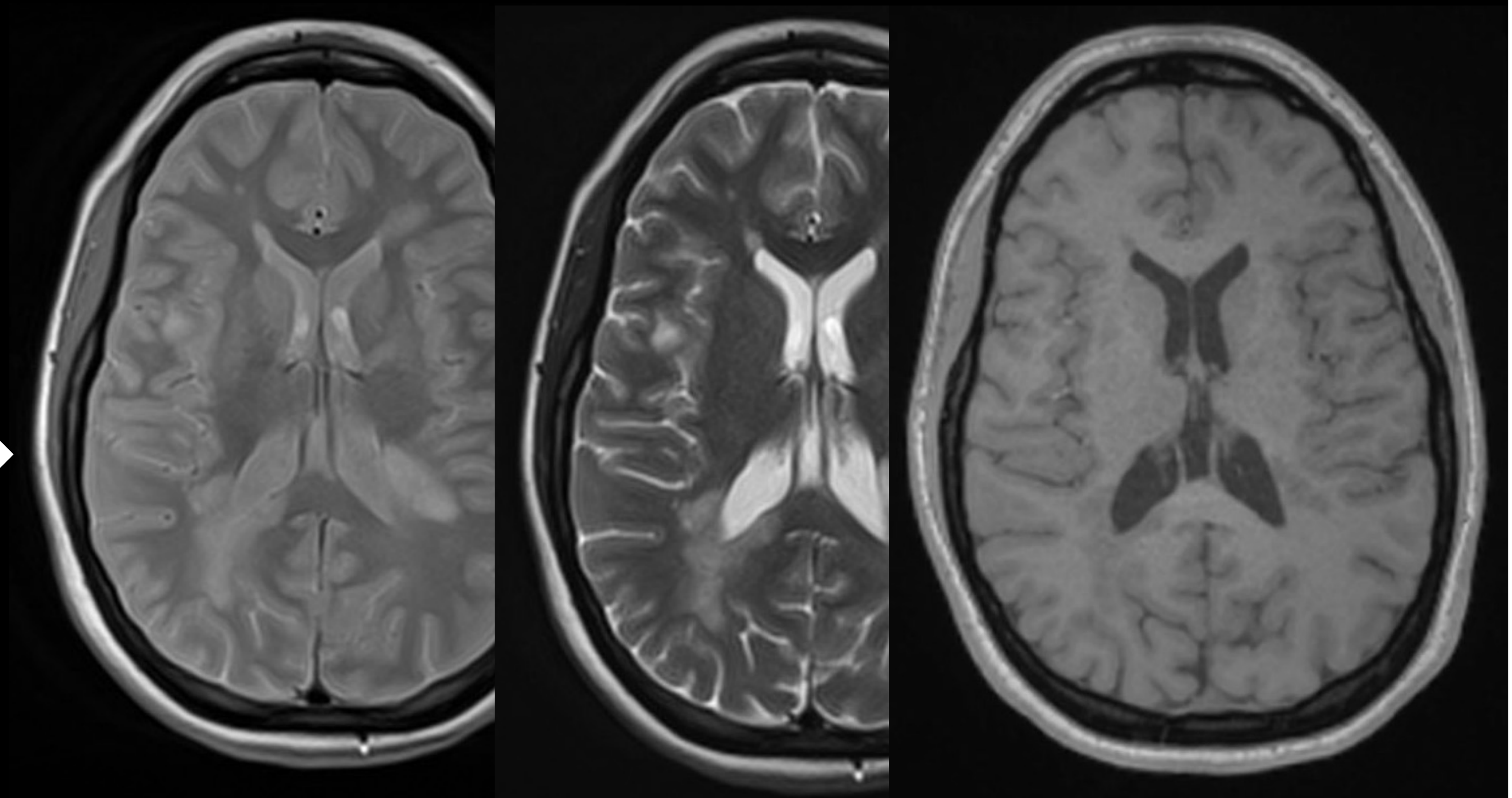
Back to Fundamentals



Quick Review of Basic MRI Contrasts

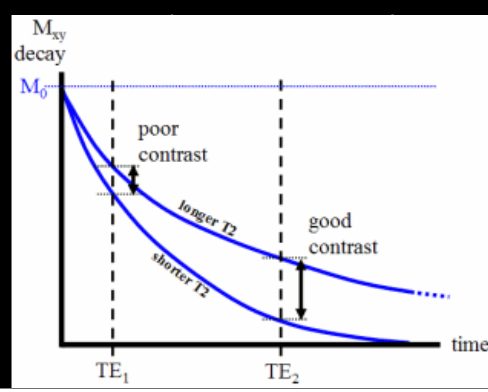


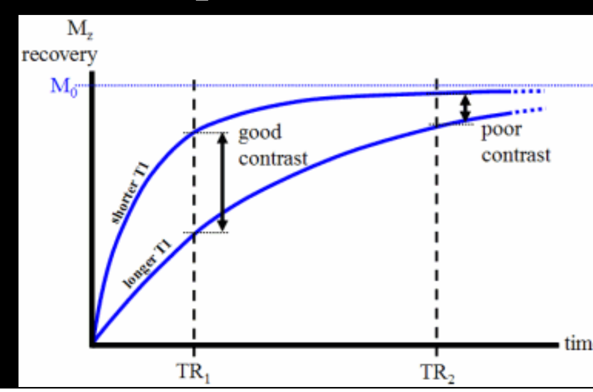


Proton density weighted
(grey image)

T_2-weighted

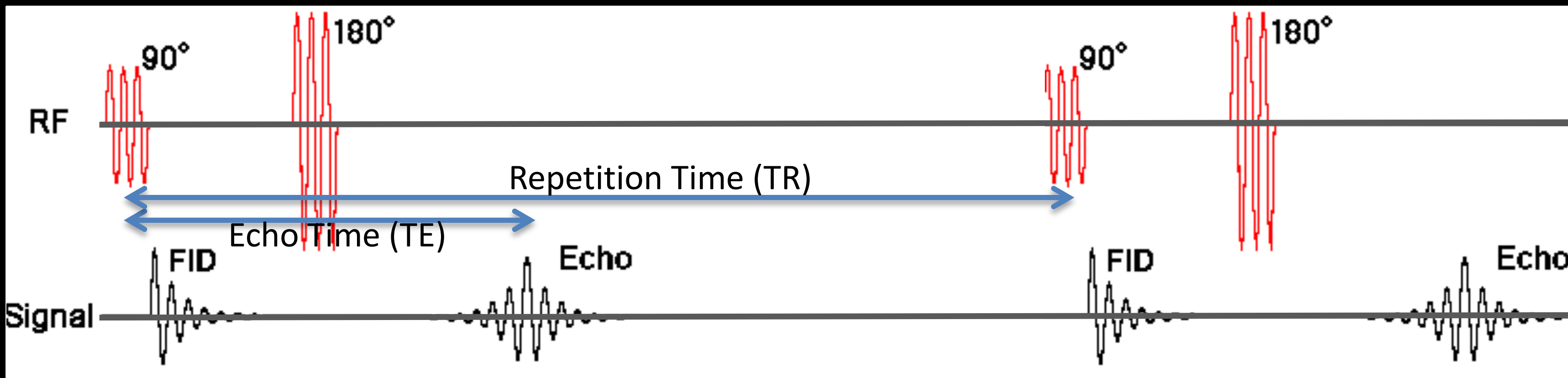
T_1-weighted





Patient with multiple sclerosis

Engineering the Contrast



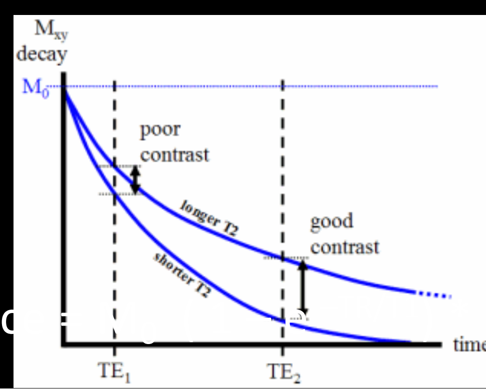
T$_2$ Relaxation:

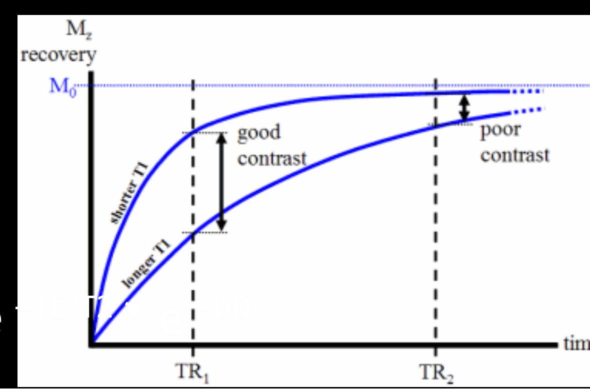
$$M = M_0 \ e^{-TE/T2}$$

T$_1$ Relaxation:

$$M = M_0 \ (1 - e^{-TR/T1})$$

Signal from Spin Echo sequenc





Signal from Gradient Echo Sequence

$$S = k\,[H]\,\frac{\sin\alpha\,(1-e^{-TR/T1})}{(1-(\cos\alpha)\,e^{-TR/T1})}\,e^{-TE/T2^{*}}$$

Signal from MPRAGE

$$\frac{1-\varphi+\frac{\varphi\cdot\cos(\theta)\cdot(1-\delta)\cdot\left(1-\mu^{N-1}\right)}{1-\mu}+\varphi\cdot\cos(\theta)\cdot\mu^{N-1}+\rho\cdot\cos(\alpha)\cdot\cos^{N}(\theta)}{1-\rho\cdot\cos(\alpha)\cdot\cos^{N}(\theta)}$$

$\delta=\exp\left(-{}^{\tau}/_{T_1}\right)$, $\varphi=\exp\left(-{}^{TD}/_{T_1}\right)$, and $\mu=\delta\cdot\cos(\theta)$

Signal from Steady State Sequences

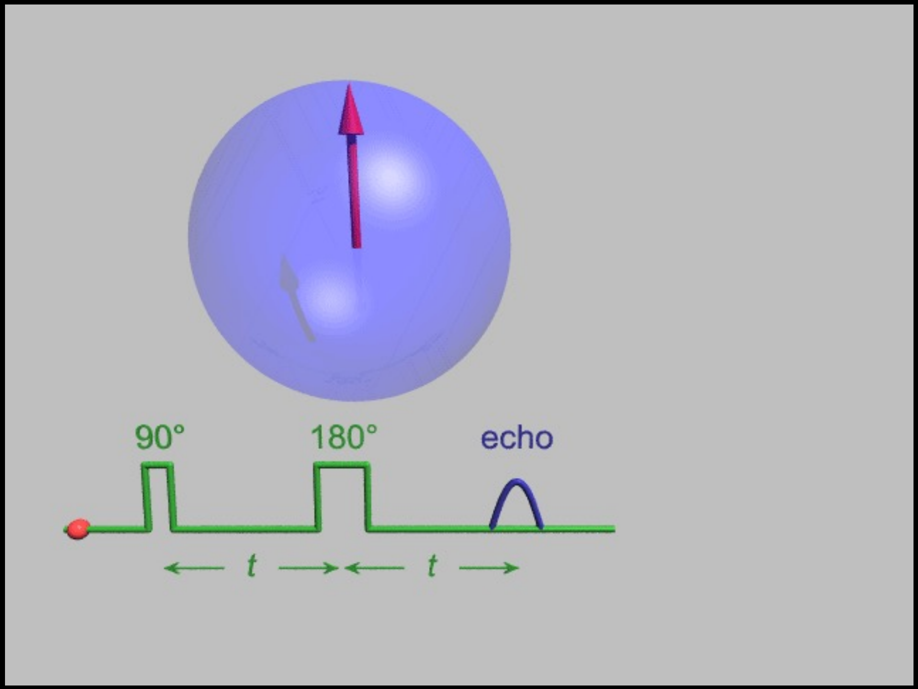
M_0(sqrt(sin(FA) * E_2(1-E_1))]/1-(E_1-E_2)*cos(FA) – E_1*E_2]
Where E_1 = exp(-T_R/T_1) and E_2 = exp (-T_R/T_2)

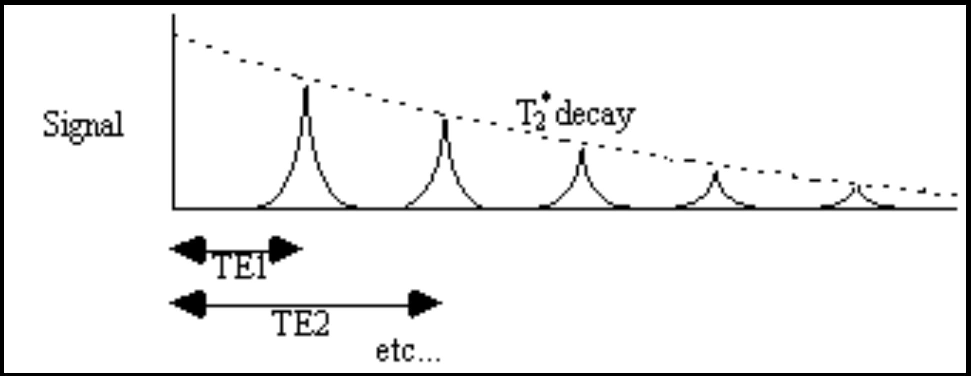
$$S_{FISP} = k\,\tan(\alpha/2)\left[1-(e^{TR/T1}-\cos\alpha)\sqrt{\frac{1-e^{-2TR/T2}}{(1-e^{-TR/T1})^{2}-e^{-2TR/T2}(e^{-TR/T1}-\cos\alpha)^{2}}}\right]e^{-TE/T2^{*}}$$

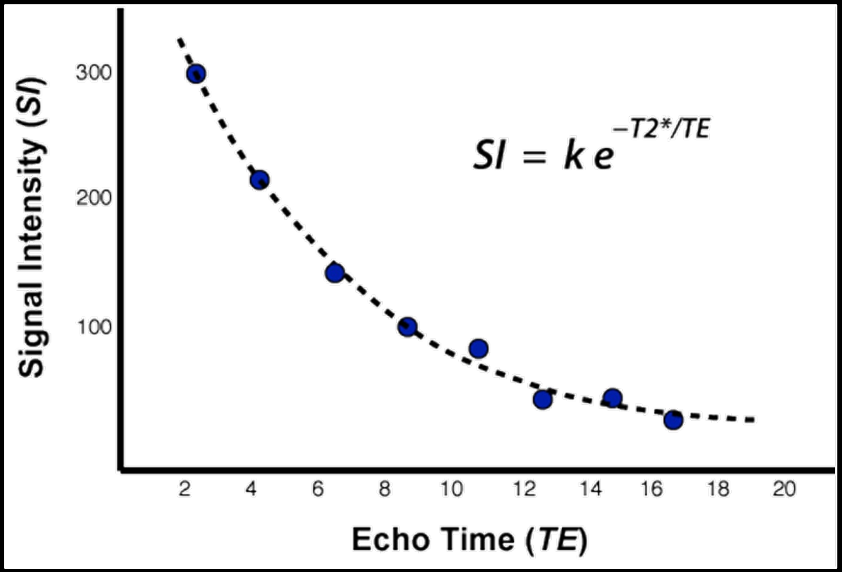
$$S_{PSIF} = k\,\tan(\alpha/2)\left[1-(1-e^{TR/T1}\cos\alpha)\sqrt{\frac{1-e^{-2TR/T2}}{(1-e^{-TR/T1})^{2}-e^{-2TR/T2}(e^{-TR/T1}-\cos\alpha)^{2}}}\right]e^{-TE/T2}$$

Wang J et. Al. PLoS ONE 2014: 9(5) e96899; Gyngell JMR 81 (1989) 474; Hänicke W et. Al. (2003) MRM 49: 771

T_2 Relaxation







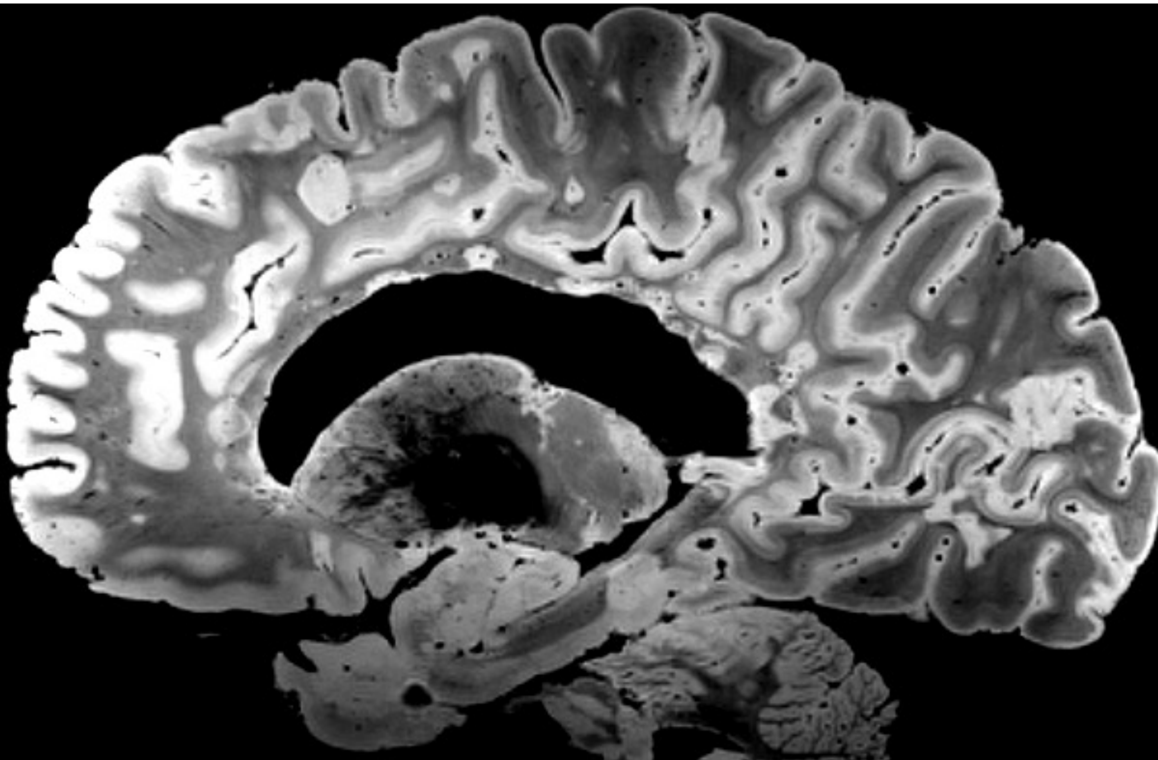
Signal loss due to:

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

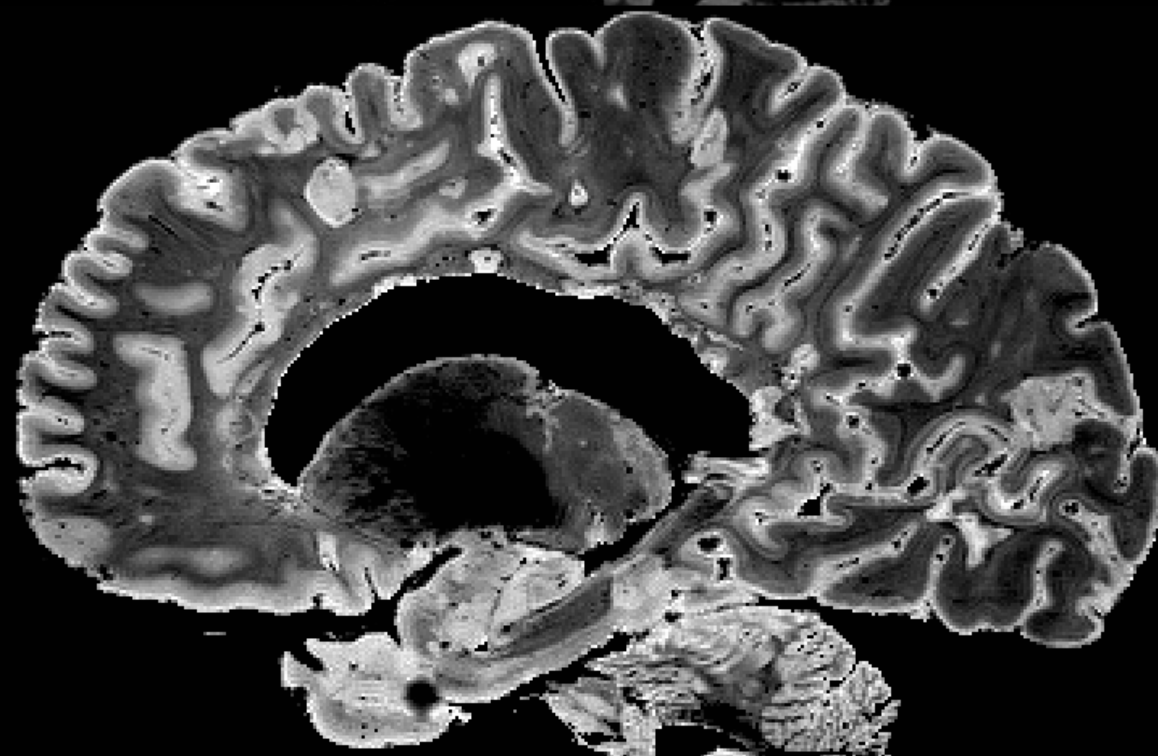
T2 map now reflects a property of the tissue

Wikipedia

T_2*-weighted
TE=16 ms



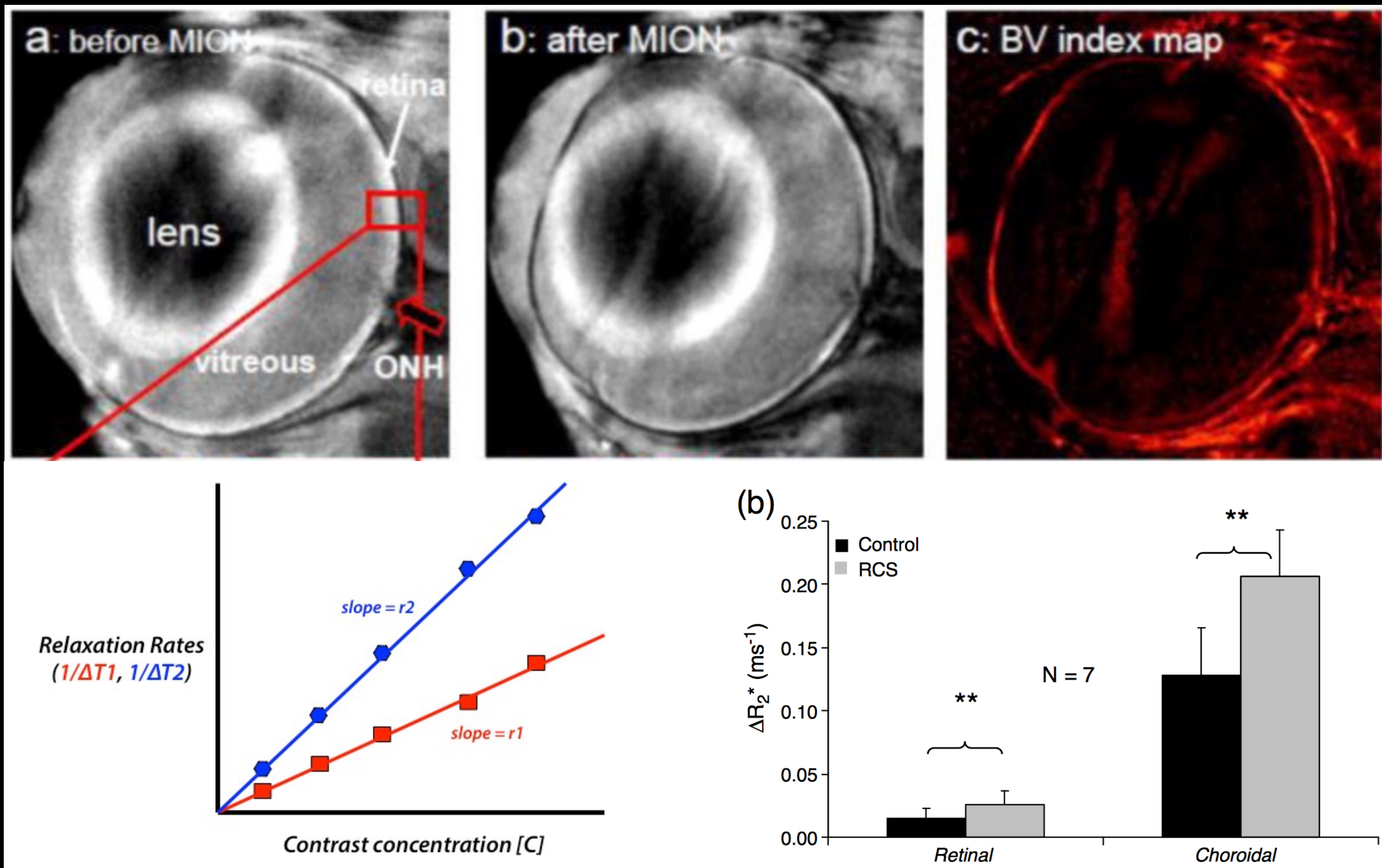
T_2*-map



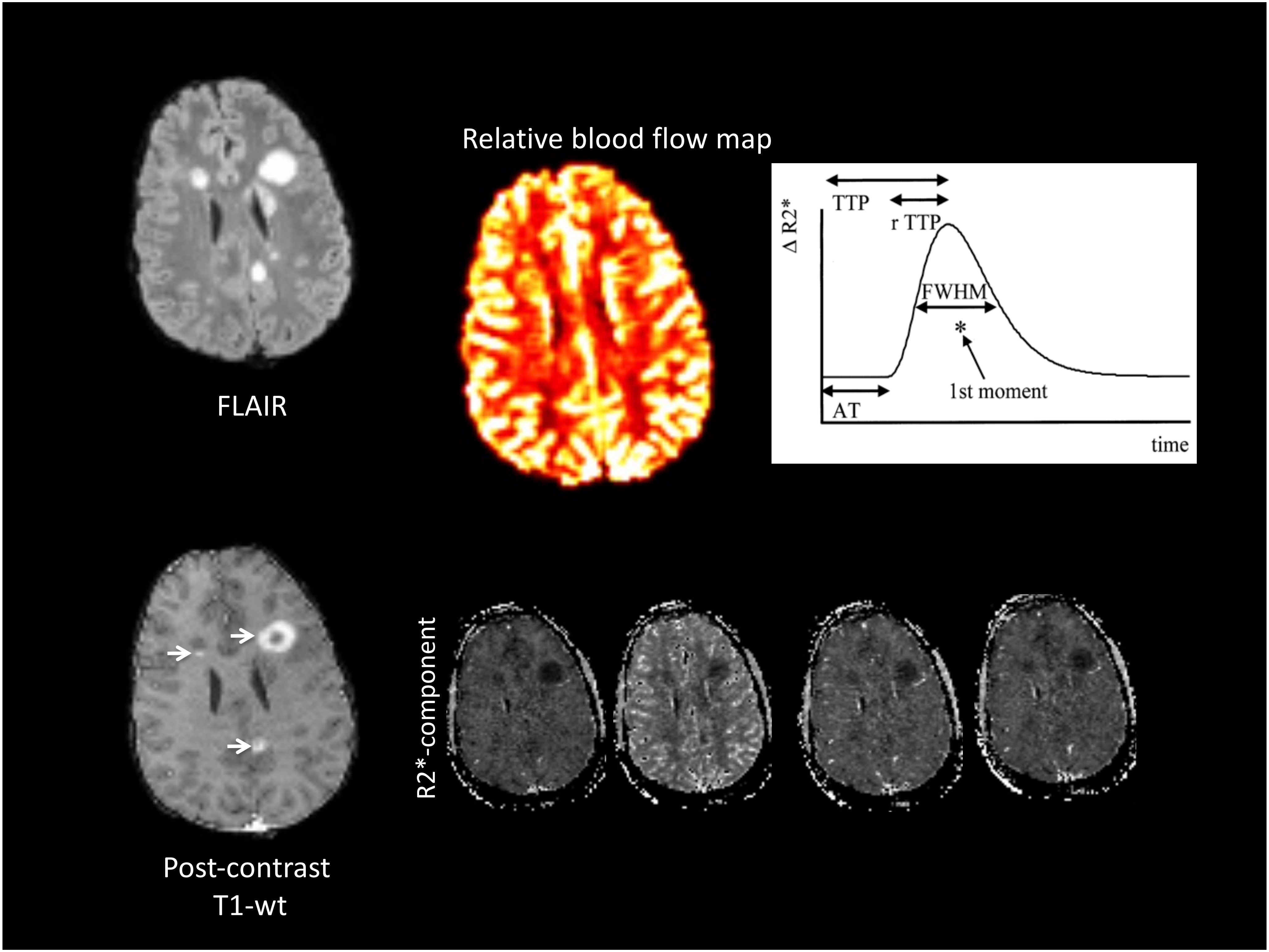
Pros
- Intensity may actually mean something

Cons
- Fitting errors and related artifacts

Applications: Exogenous Contrast Agents



Nair et. al. Neuroimage. (2011) 54(2): 1063


Relative blood flow map
FLAIR
TTP
r TTP
Δ R2*
FWHM
*
1st moment
AT
time
R2*-component
Post-contrast
T1-wt

Application: T_2 of CSF

Elements	Relaxivity r_2	Concentration in control CSF	Extrapolated R_2 (s^{-1})	% of R_2 change in control CSF
Zn	$-8x10^{-3}$ $mM^{-1}.s^{-1}$	$3x10^{-4}$ mM	$-2.4x10^{-6}$	0%
Cu	0.6 $mM^{-1}.s^{-1}$	$1.4x10^{-4}$ mM	$7.8x10^{-5}$	0.02%
Fe	3x2 $mM^{-1}.s^{-1}$	< $5.4x10^{-4}$ mM	< $1.7x10^{-3}$	< 0.4%
Mn	124 $mM^{-1}.s^{-1}$	< $2x10^{-5}$ mM	< $2.5x10^{-3}$	< 0.5%
Proteins (BSA)	$1.3x10^{-3}$ $mg/dL^{-1}.s^{-1}$	47 mg/dL	$6.1x10^{-2}$	13%
Glucose	$4x10^{-3}$ $mg/dL^{-1}.s^{-1}$	45-80 mg/dL [a]	0.2 – 0.3	39 – 69%

a. Tichy et al., 1970

Brain is fully immersed in CSF and changes in brain are often reflected in CSF (But can they be measured using MRI?):

- The low metal concentration doesn't impact CSF T_2 value
- Total protein is responsable for 13% of T_2 value
- Glucose is responsable for ~54% of T_2 value

Alexia Daoust, Unpublished

Tumor Detection by Nuclear Magnetic Resonance

Abstract. *Spin echo nuclear magnetic resonance measurements may be used as a method for discriminating between malignant tumors and normal tissue. Mea-*

Table 1. Spin-lattice (T_1) and spin-spin (T_2) relaxation times (in seconds) of normal tissues.

Rat No.	Weight (g)	Rectus muscle T_1	Rectus muscle T_2	Liver T_1	Liver T_2	Stomach T_1	Small intestine T_1	Kidney T_1	Brain T_1
1	156	0.493	0.050	0.286	0.050	0.272	0.280	0.444	0.573
2	150	.548	.050	.322	.060	.214	.225	.503	.573
3	495	.541	.050	.241	.050	.260	.316	.423	.596
4	233	.576 (0.600)*	.070	.306 (0.287)*	.048	.247 (0.159)*	.316 (0.280)*	.541 (0.530)*	.620 (0.614)*
5	255	.531		.300		.360	.150	.489	.612
Mean and standard error									
		0.538 ± 0.015	0.055 ± 0.005	0.293 ± 0.010	0.052 ± 0.003	0.270 ± 0.016	0.257 ± 0.030	0.480 ± 0.026	0.595 ± 0.007

* Spin-lattice relaxation time after the specimen stood overnight at room temperature.

Table 2. Spin-lattice (T_1) and spin-spin (T_2) relaxation times (in seconds) in tumors.

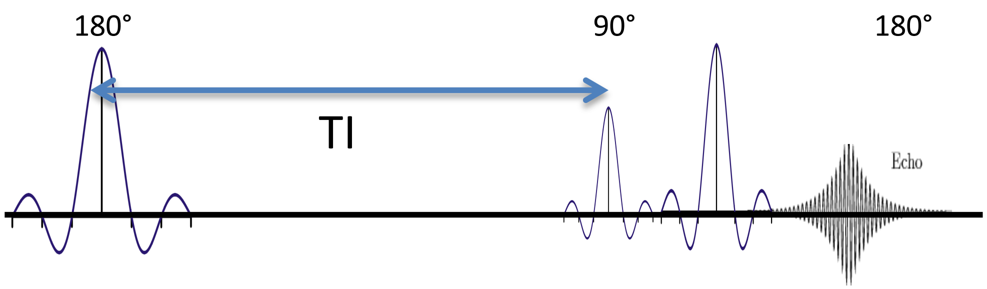
Rat No.	Weight (g)	T_1	T_2
Walker sarcoma			
6	156	0.700	0.100
7	150	.750	.100
8	495	.794 (0.794)*	.100
9	233	.688	
10	255	.750	
Mean and S.E.		0.736 ± 0.022	.100
P		< .01†	
Novikoff hepatoma			
11	155	0.798	0.120
12	160	.852	.120
13	231	.827	.115
Mean and S.E.		0.826 ± 0.013	0.118 ± 0.002
P		< .01†	

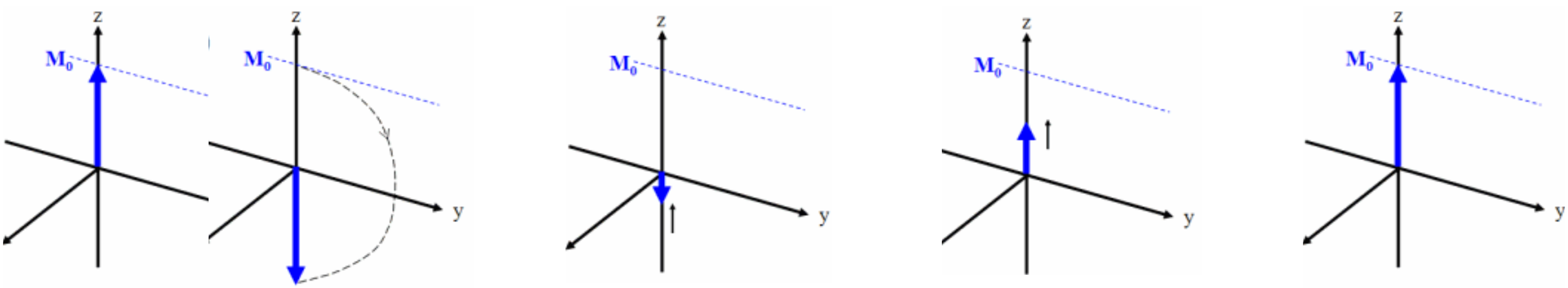
tion. The considerable increase in relaxation times for the hepatoma (T_1, 0.826 second; T_2, 0.118 second) relative to normal liver (T_1, 0.293 second; T_2, 0.050 second) suggests a significant decrease in the degree of ordering of intracellular water (*2*) in malignant tissue. In addition, it is apparent from the prolonged relaxation times of the two malignant tumors reported in Table 2 that NMR techniques would make it possible for one to detect the presence of metastatic infiltrates of the liver from either Walker sarcoma or Novikoff hepatoma.

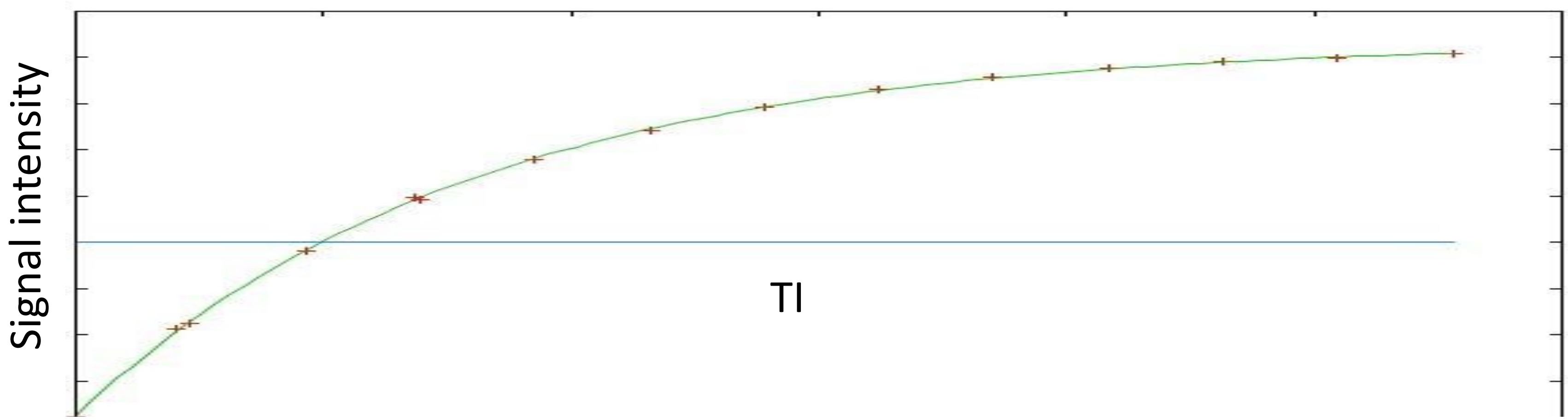
Ex-vivo specimen @ 0.56 T

Raymond Damadian, Science 171 (1971):1151

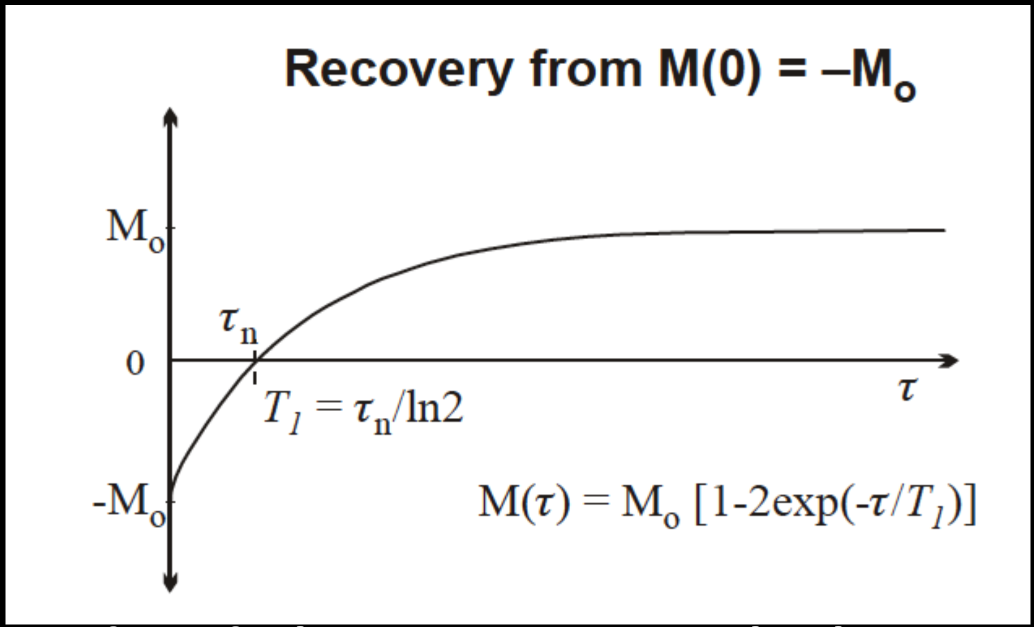
T_1 mapping Using Inversion Preparation







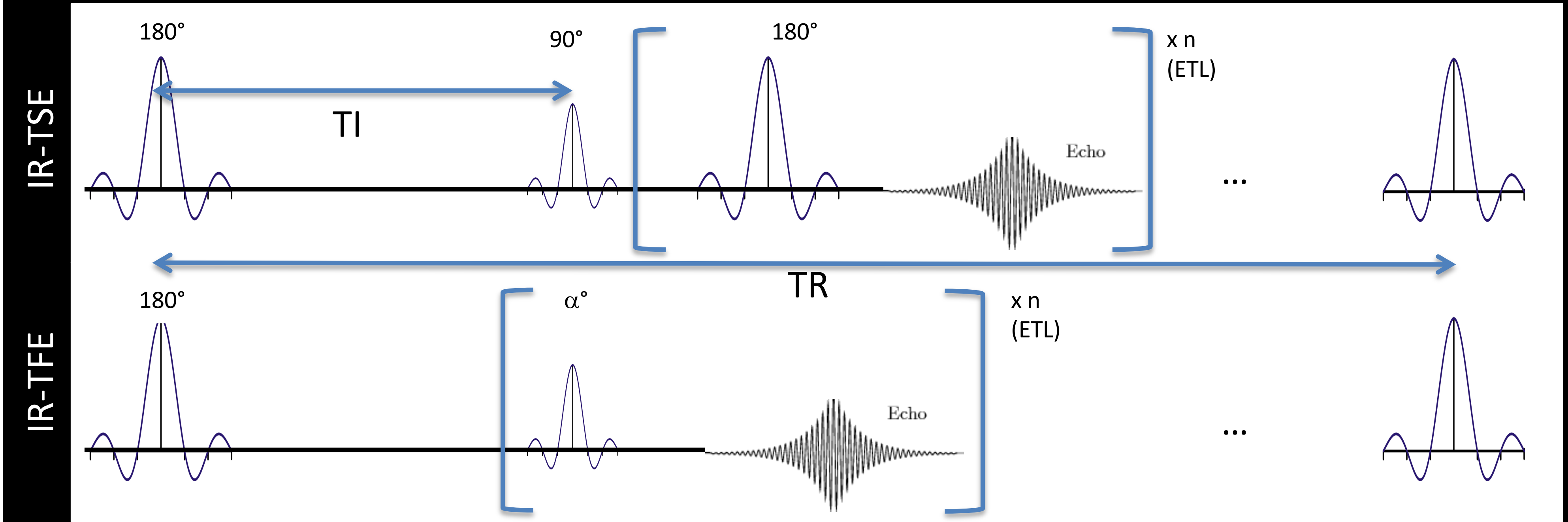
Inversion Preparation

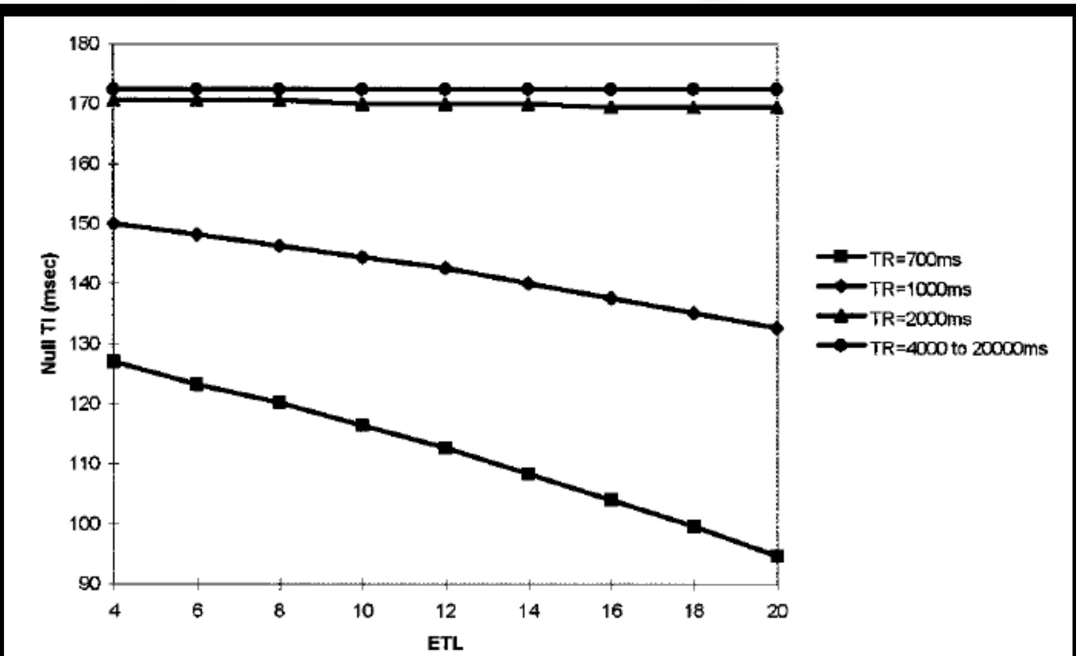


- Gold standard, but extremely long experiment
  - TR ~ 5 x T_1.
  - 5 to 6 TIs for reliable data fitting.
  - Not practical on awake human subjects.

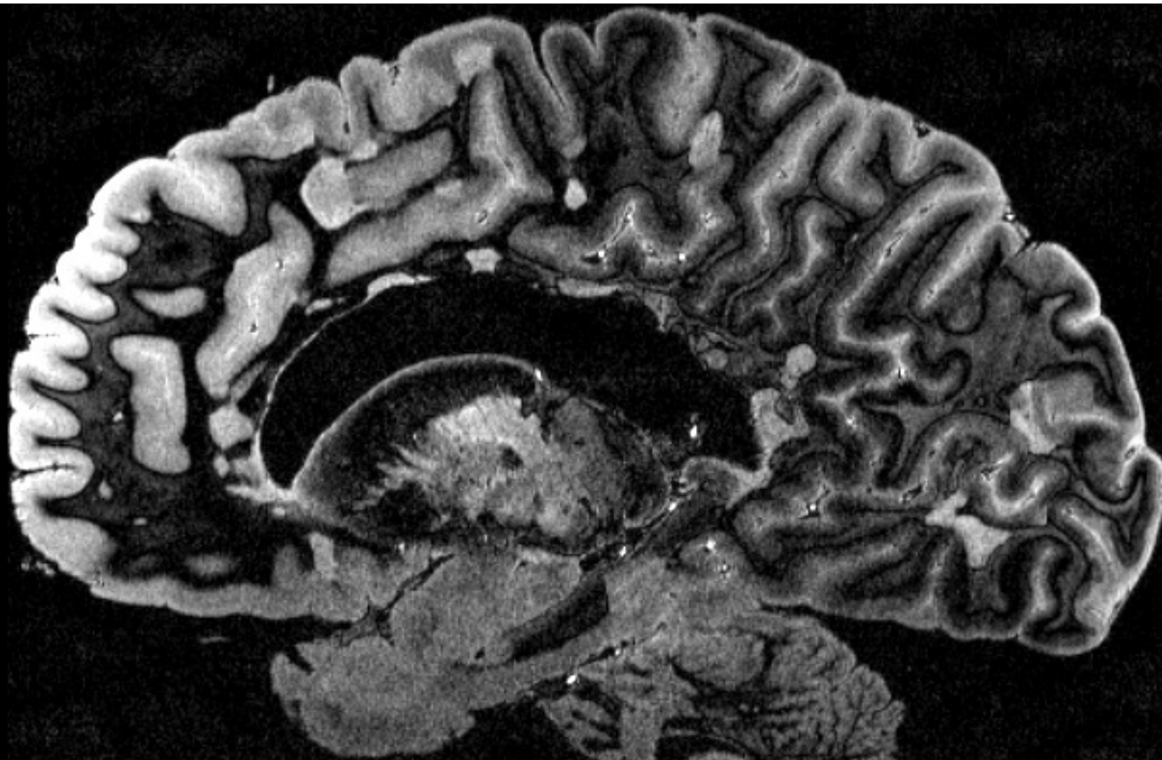
www.chem.wisc.edu/~cic/nmr/Guides/VUG/VUG-T1.pdf

Speeding it up

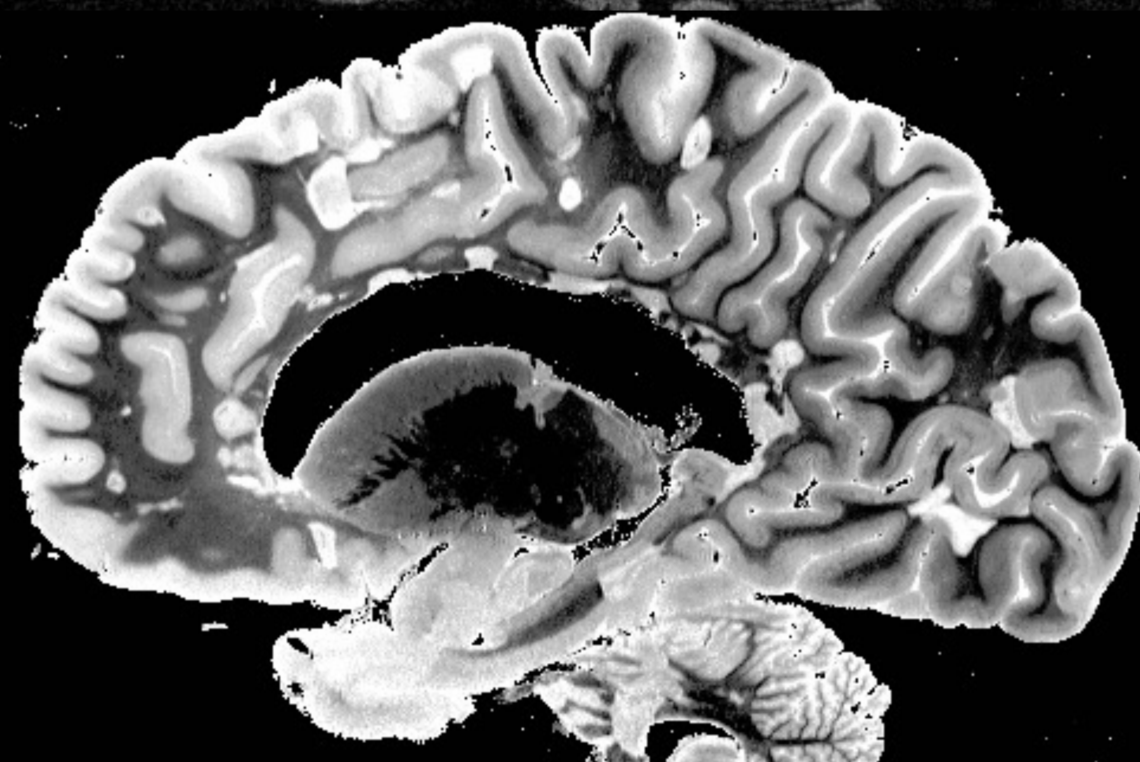




T_1-weighted
TI=250 ms



T_1-map

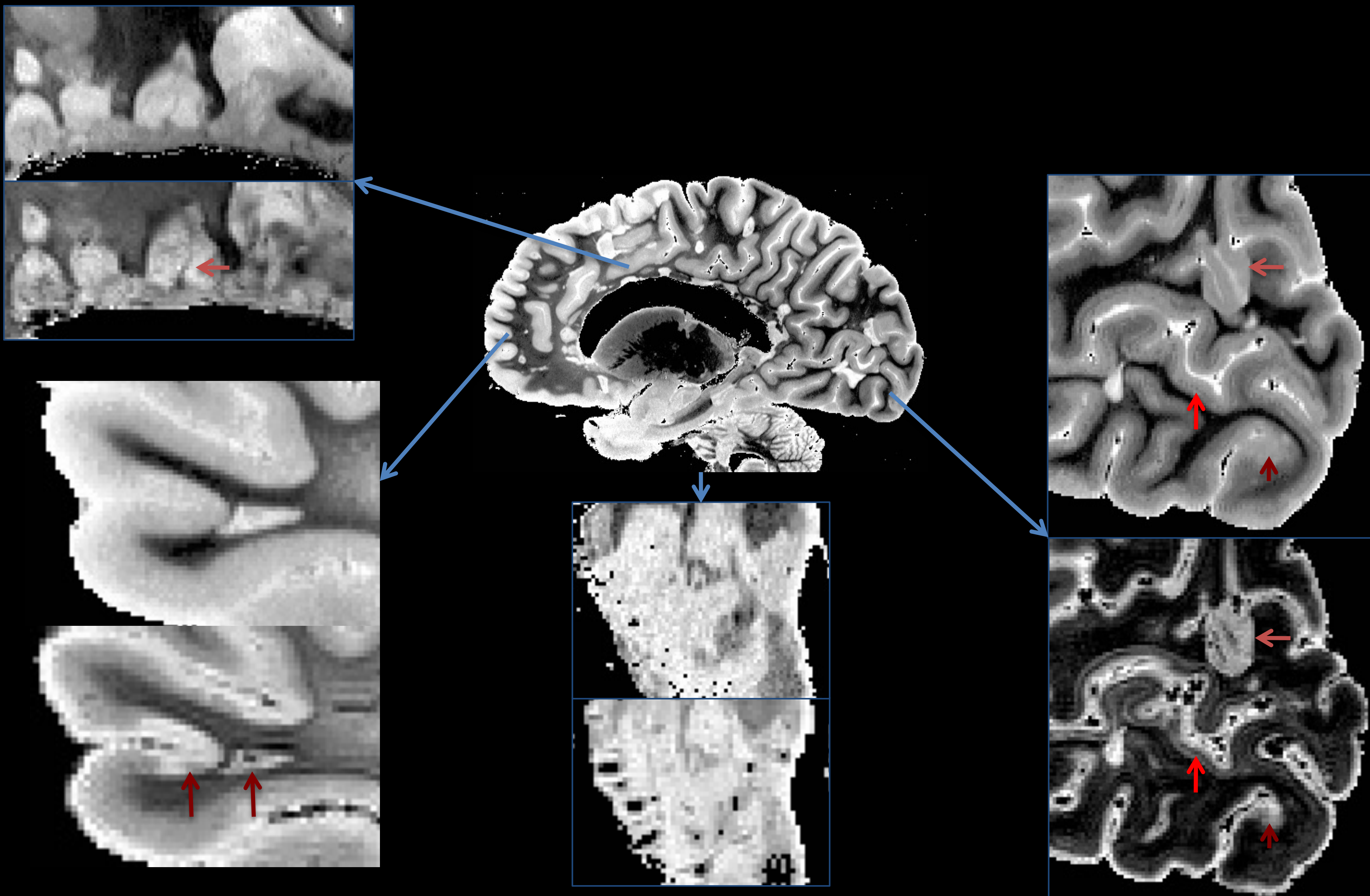


Pros
- Signal may actually mean something

Cons
- Fitting errors and related artifacts
- Slow

Ex-vivo brain at 7T

Do we need both qT_1 and qT_2



Rapid T_1 calculation

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

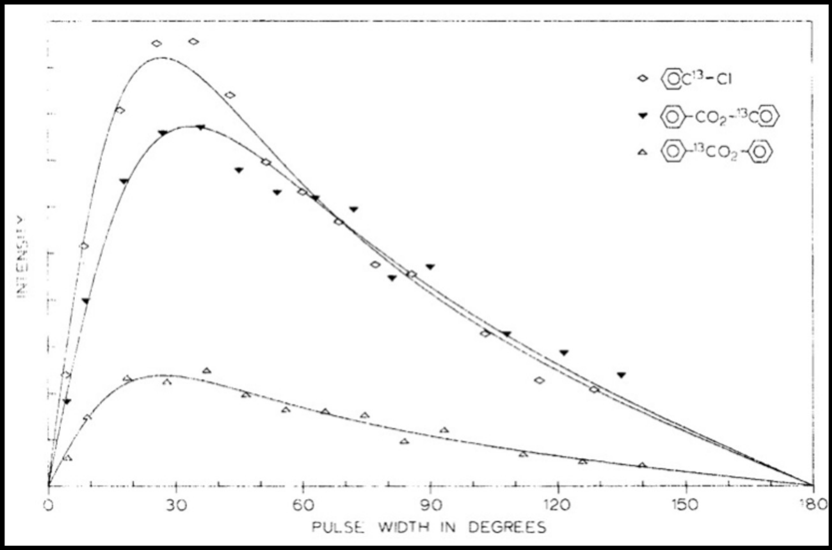
θ is the flip angle and S the signal at that flip

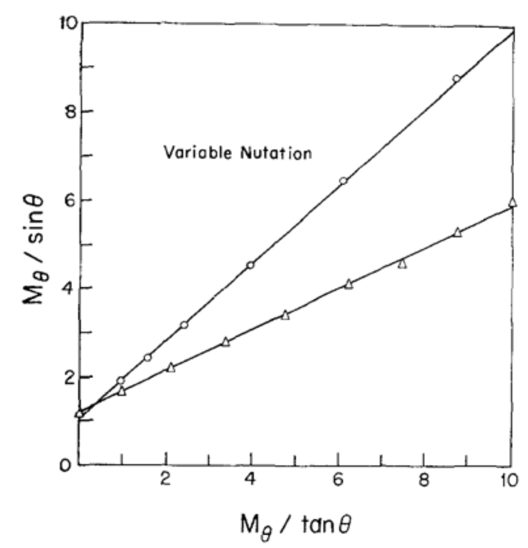
$$\frac{M_\theta}{\sin\theta} = e^{-T/T_1}\frac{M_\theta}{\tan\theta} + M_0(1 - e^{-T/T_1})$$

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.



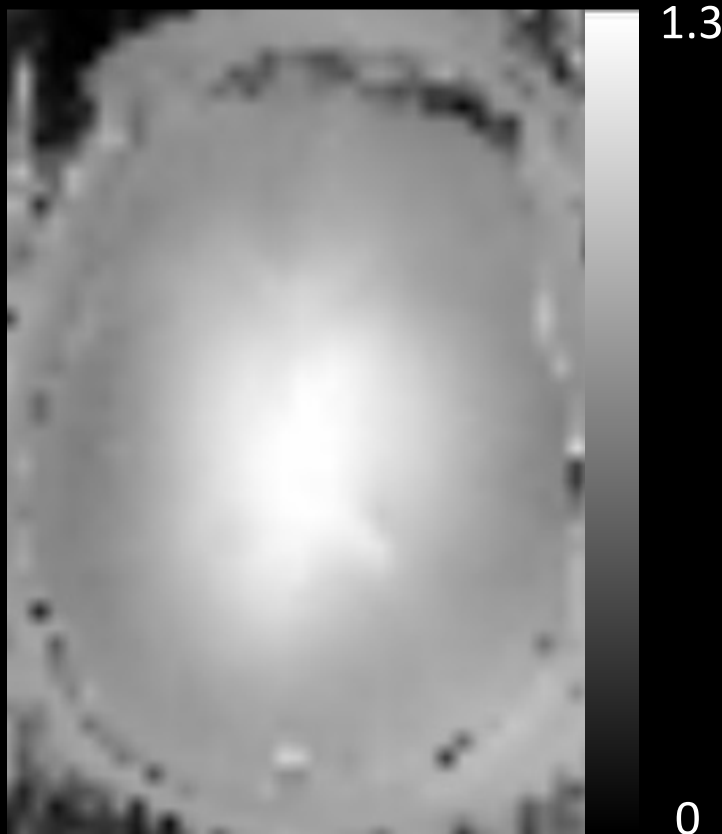


Line fitting

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

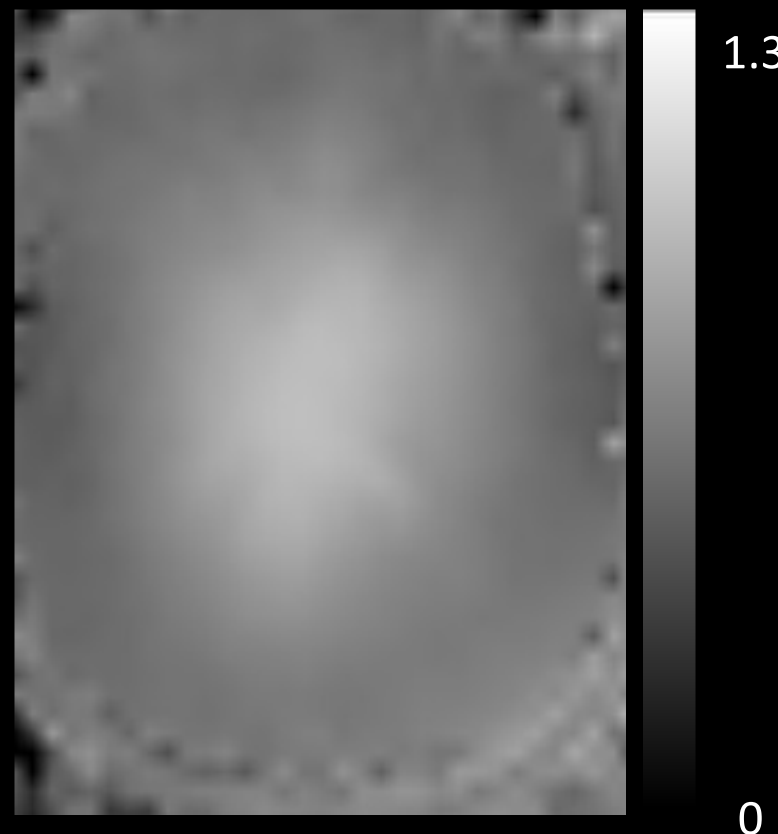
Volumetric B1-map

Double-angle method



2D acquisition, α-2α method,
Tissue T1 dependent,
Relative to applied voltage

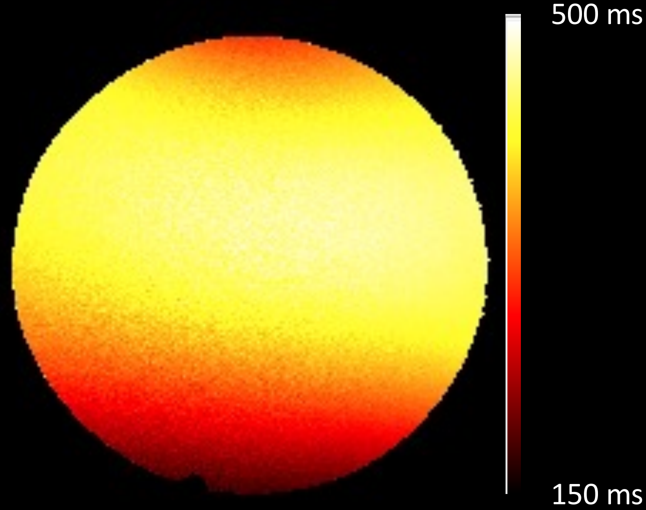
Bloch-Siegert method



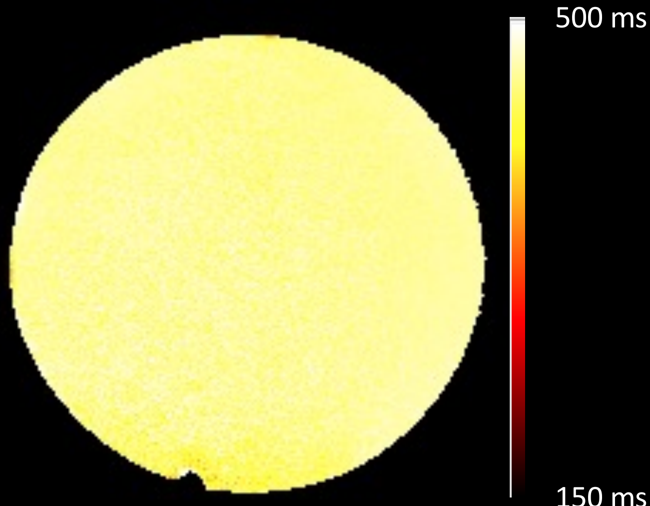
Volumetric acquisition,
Tissue T1 independent,
As a fraction of RF pulse angle

Bloch et. al. Phys. Rev.57(6):522 (1940); Sacolick et. al. MRM 63(5): 1315 (2010); Sacolick et. al. MRM 63(5): 1315 (2010); **Duan et. al.** NMR Biomed. 26:1070 **(2013).**

Uncorrected T_1 map



+ B1 map

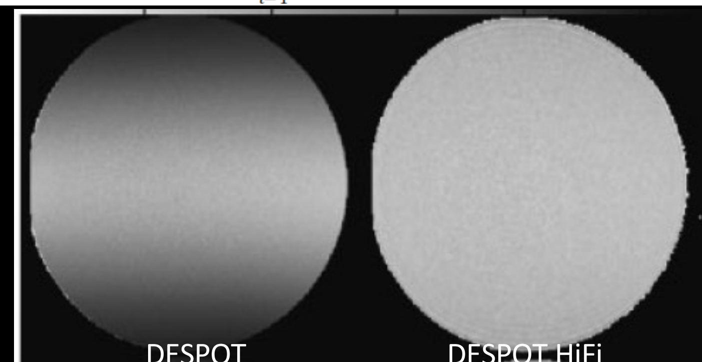


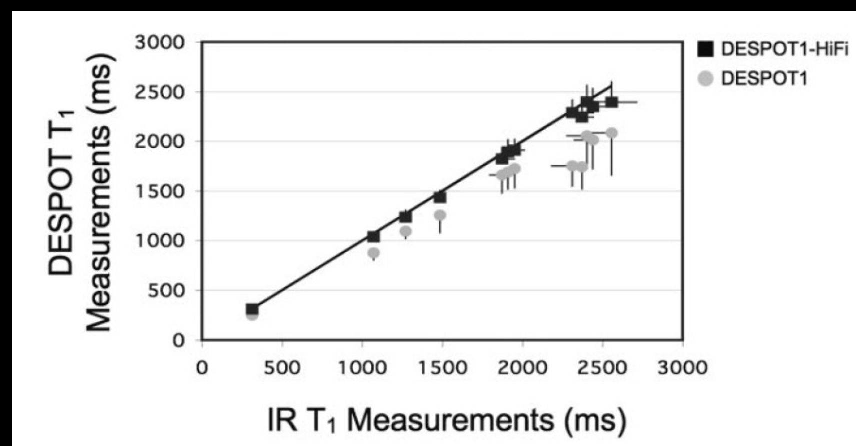
Corrected T_1 map

DESPOT1-HiFi Correction

From the combined multiangle DESPOT1 and IR-SPGR data, a unique solution for κ, T1, and ρ can be found through the least squares minimization of the combined DESPOT1 and IR-SPGR data to Eqs. [1] and [6] for the three parameters, i.e., minimization of the function:

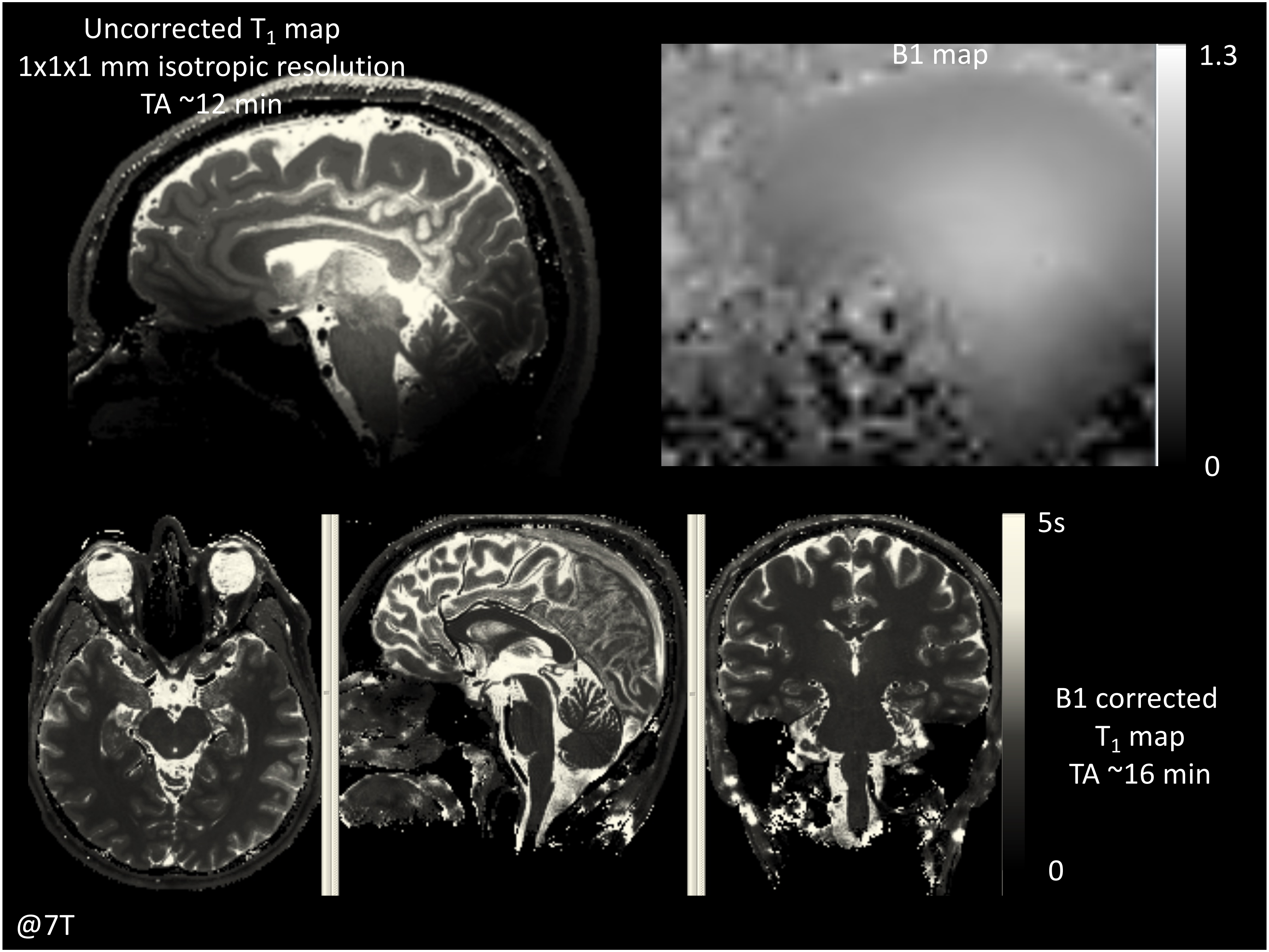
$$f(\rho, T_1, \kappa) = \sum_{i=1}^{i=NTI} [\rho \sin\kappa\alpha_P (1 - 2e^{-TI_i/T_1 + e^{-T_R/T_1}}) - S_{IR\text{-}SPGR}(i)]^2 + \sum_{i=1}^{i=N\alpha} \left[\frac{\rho(1-E_1)\sin\kappa\alpha_{P,i}}{1-E_1\cos\kappa\alpha_{P,i}} - S_{SPGR}(i) \right]^2 \quad (7)$$





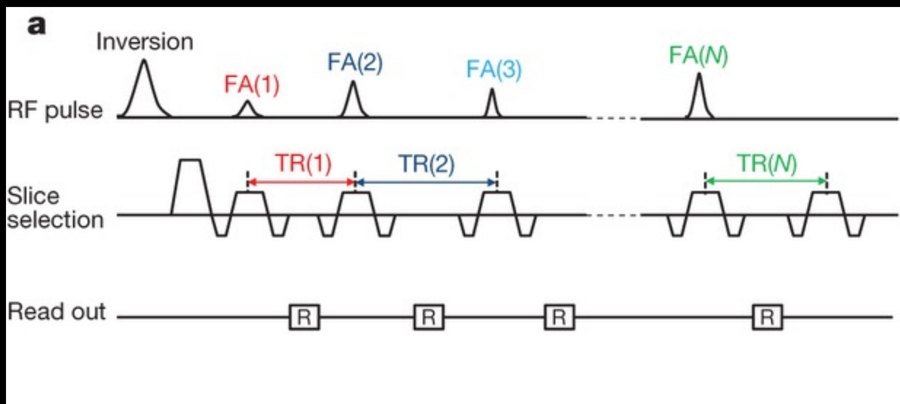
Duan et. al. NMR Biomed. 2013; 26: 1070–1078

Deoni, JMRI, 26:1106–1111

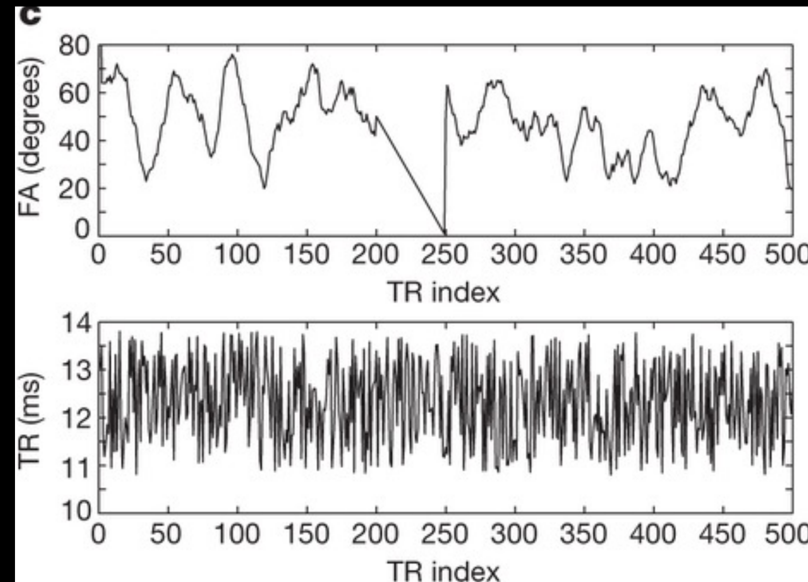


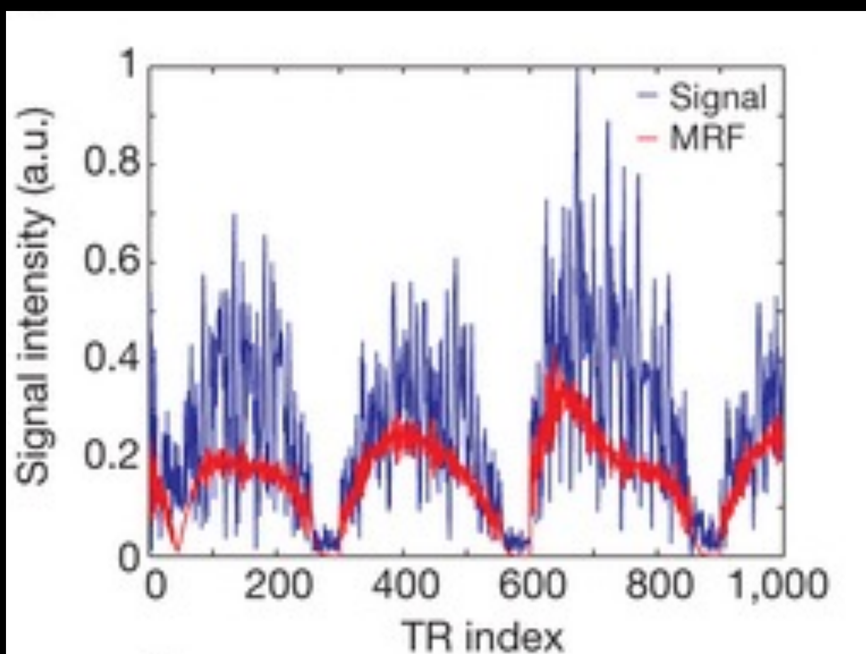
Uncorrected T_1 map
1x1x1 mm isotropic resolution
TA ~12 min
B1 map
1.3
0
5s
B1 corrected
T_1 map
TA ~16 min
0
@7T

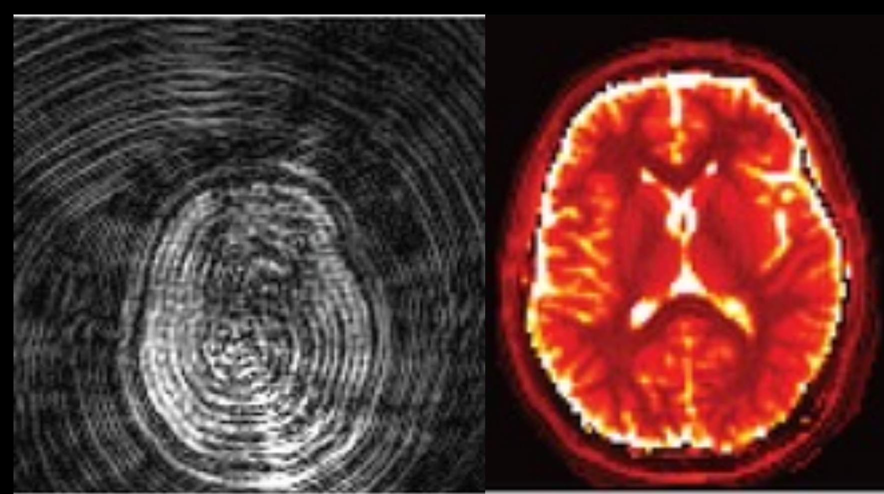
MR Fingerprinting



$M_0(\text{sqrt}(\sin(FA) * E_2(1-E_1))]/1-(E_1-E_2)*\cos(FA) - E_1*E_2]$
Where $E_1 = \exp(-T_R/T_1)$ and $E_2 = \exp(-T_R/T_2)$

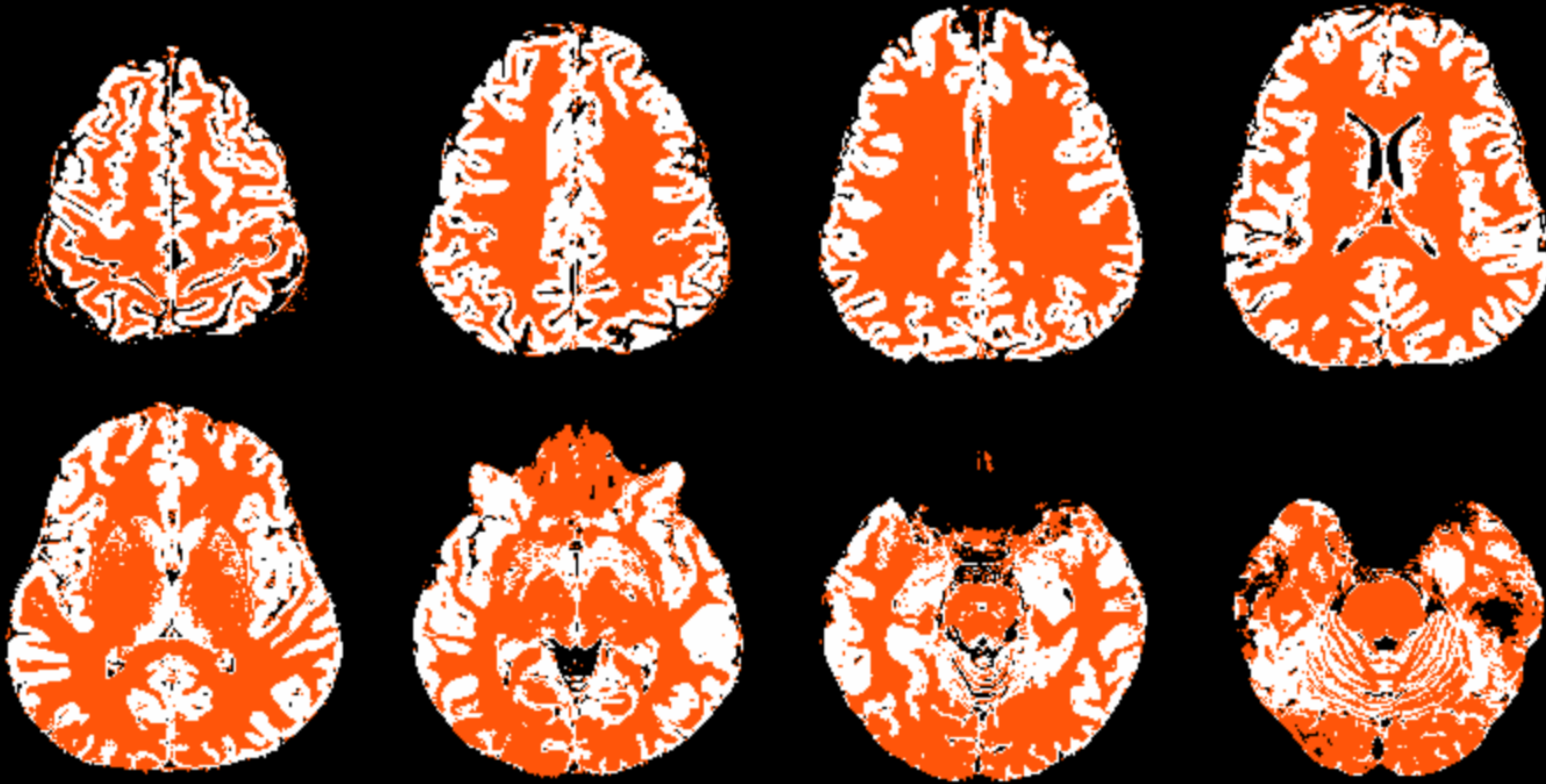






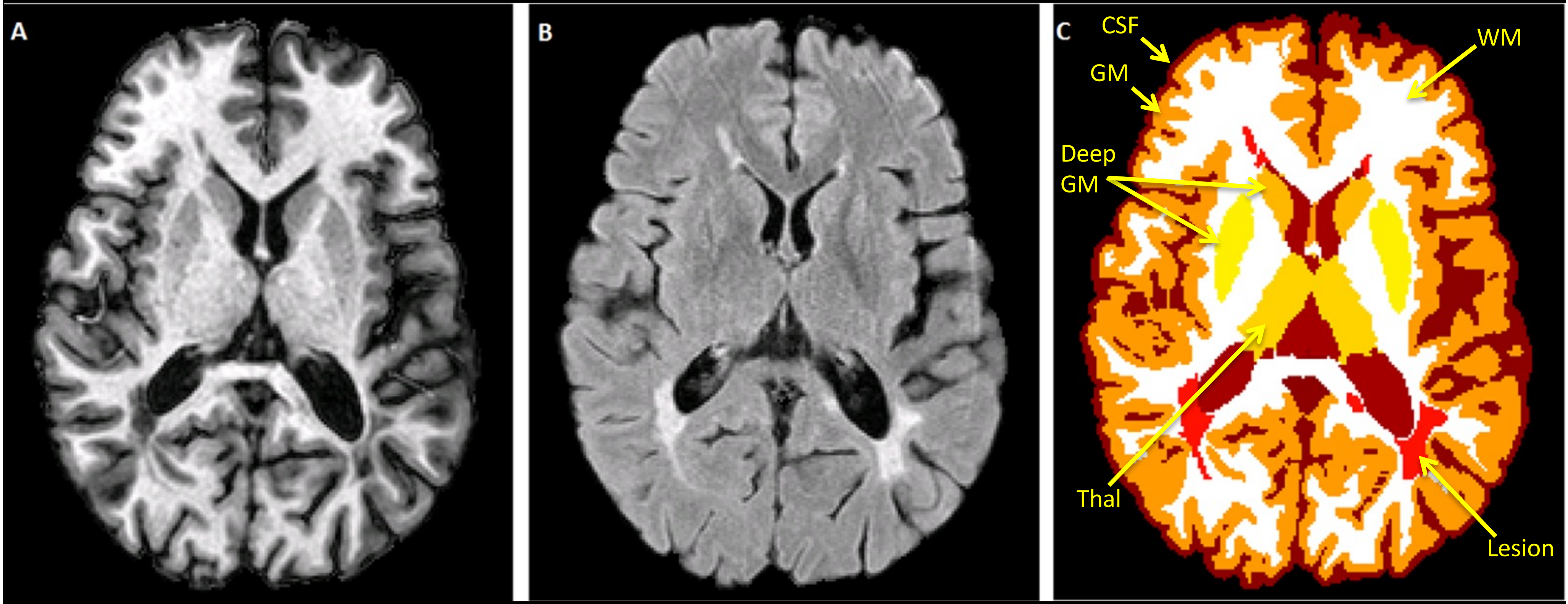
Ma et. Al. *Nature* 495, 187

Applications: image segmentation



40 y.o. M

Volumetrics - LesionTOADS



MPRAGE

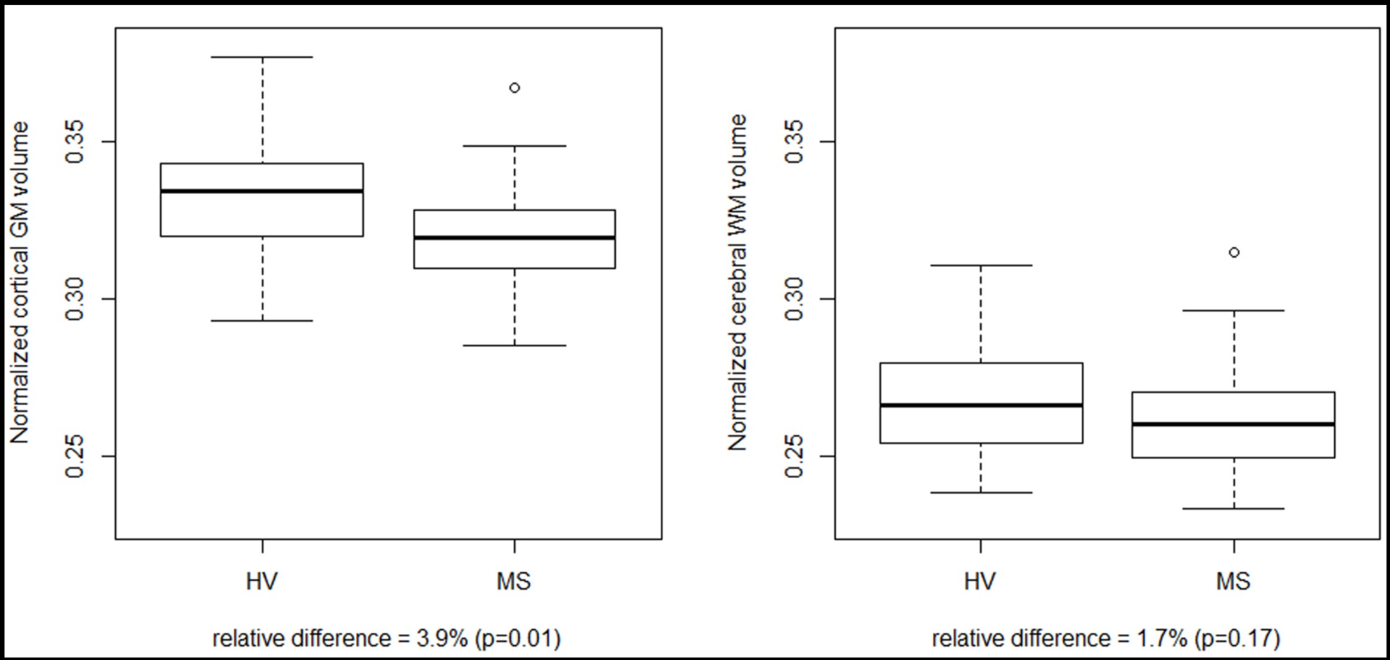
2D FLAIR

Tissue classification

Freesurfer,
AFNI,
FSL,
Slicer…

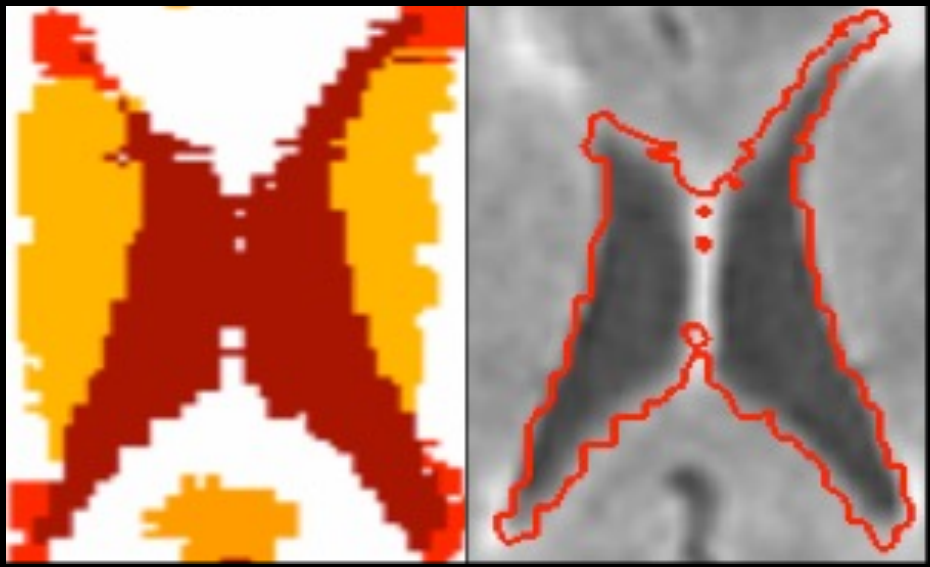
Shee et. al. PLoS ONE 7(5): e37049

Estimating Brain Atrophy - LesionTOADS



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

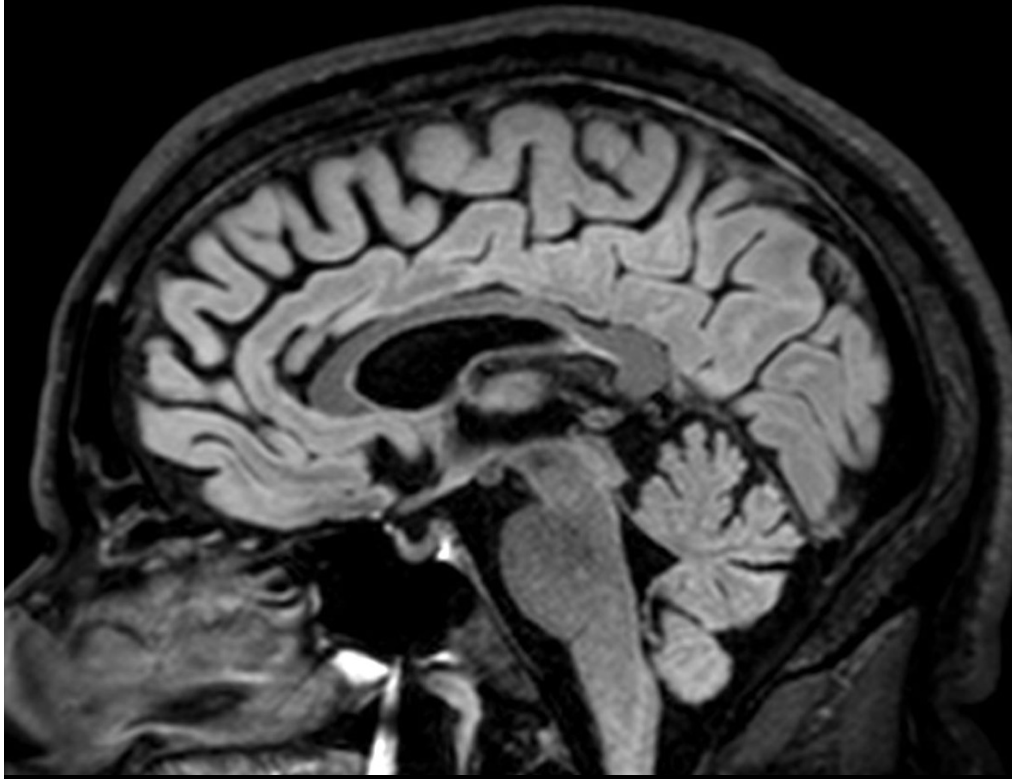
Tissue Segmentation Errors



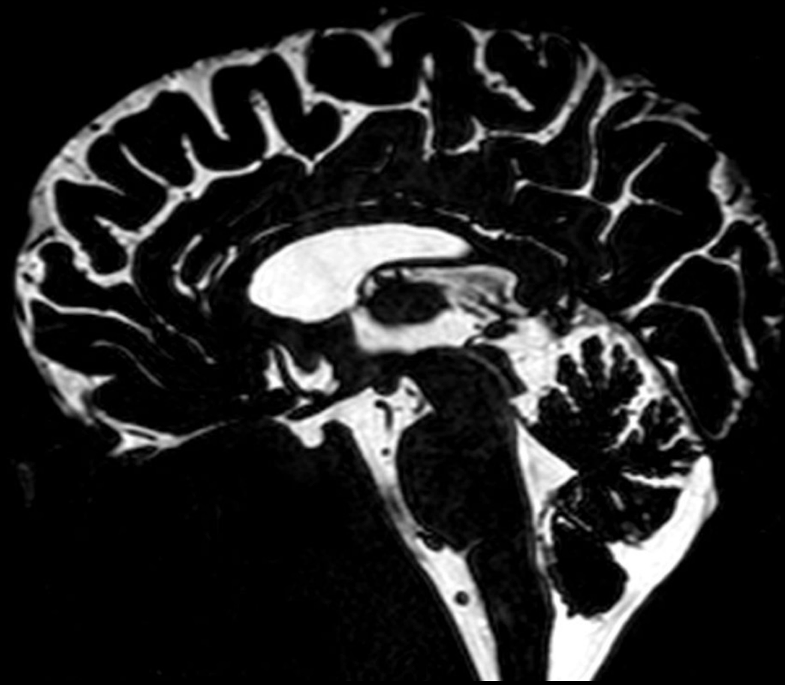
Segmentation FLAIR

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

Global Cerebral Atrophy – Brain Free Water Imaging



FLAIR



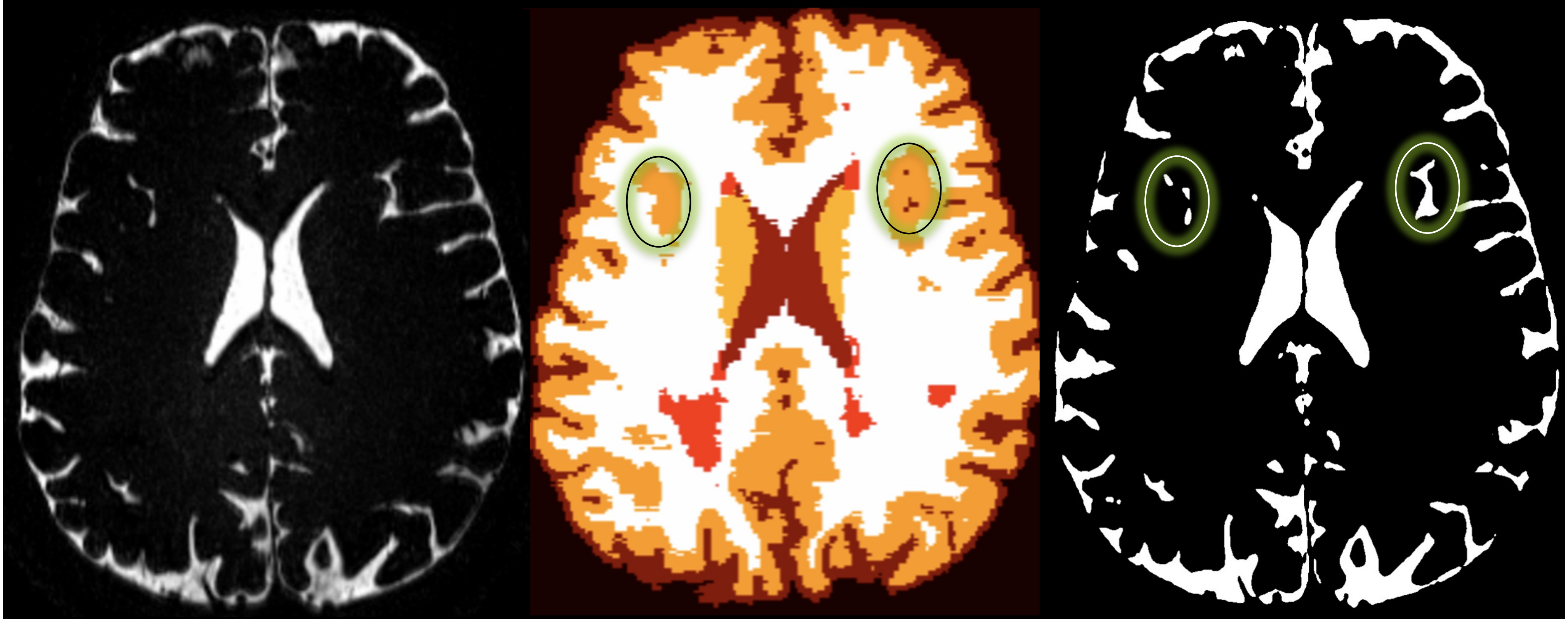
Brain Free-Water Imaging

The only thing that is bright is CSF

HIV patient – ALL HANDS

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

Comparison: BFWI vs. LesionTOADS



Original LesionTOADS - processed BFWI - processed

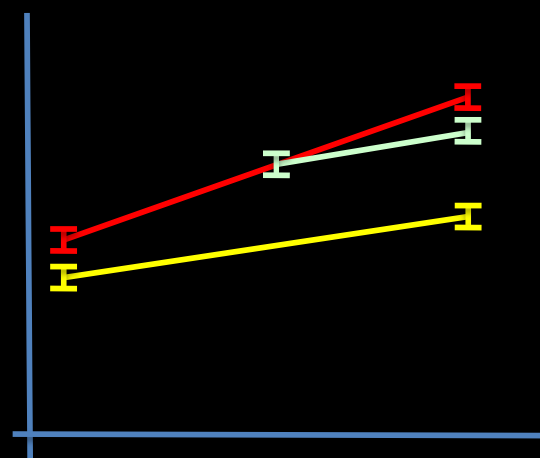
MS patient – TNU

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

Reproducibility

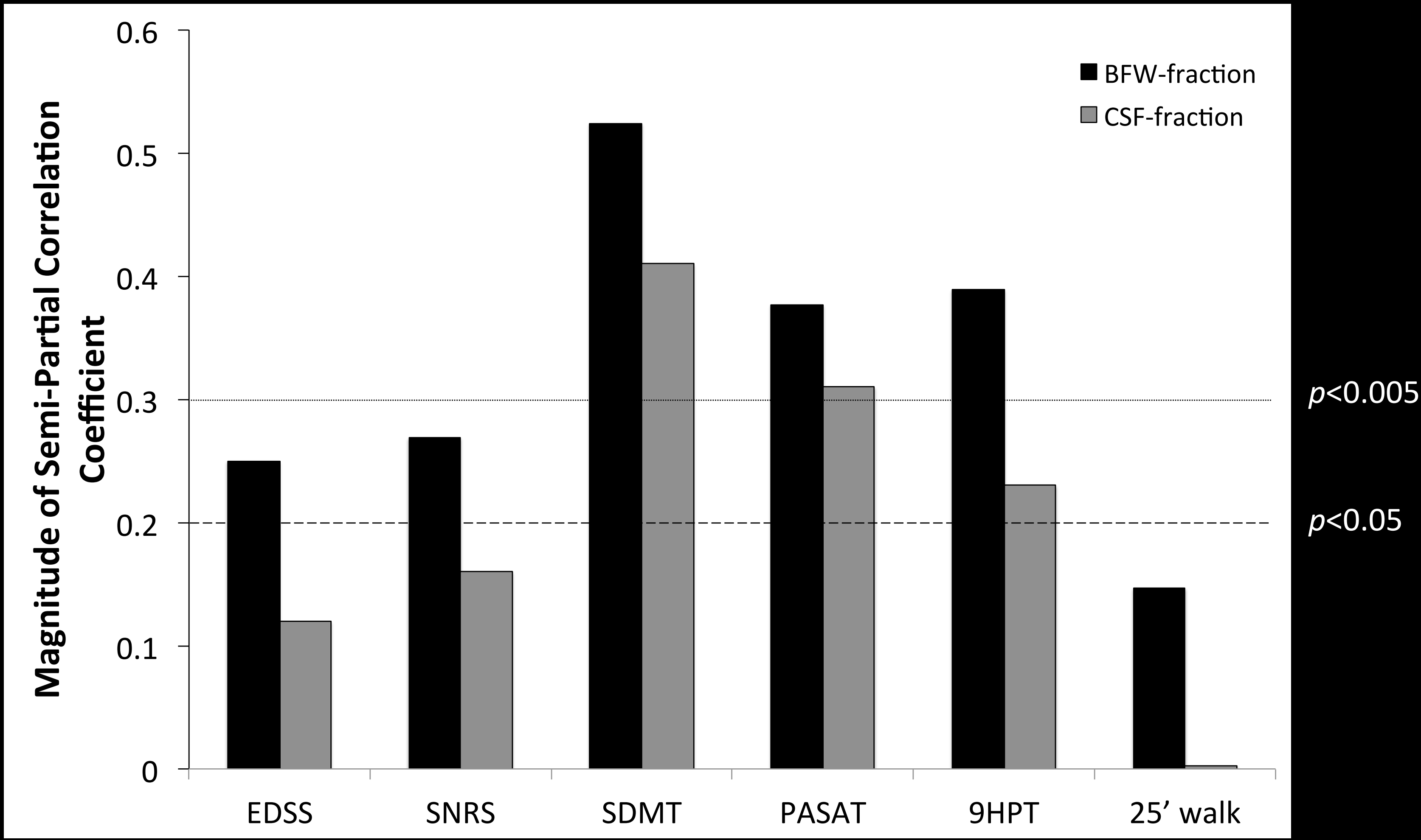
Mean COVs in 12 subjects

	CSF volume	Brain volume
Brain free water	1.5%	~0.3%
LesionTOADS	0.6%	
SIENAX		2.3%



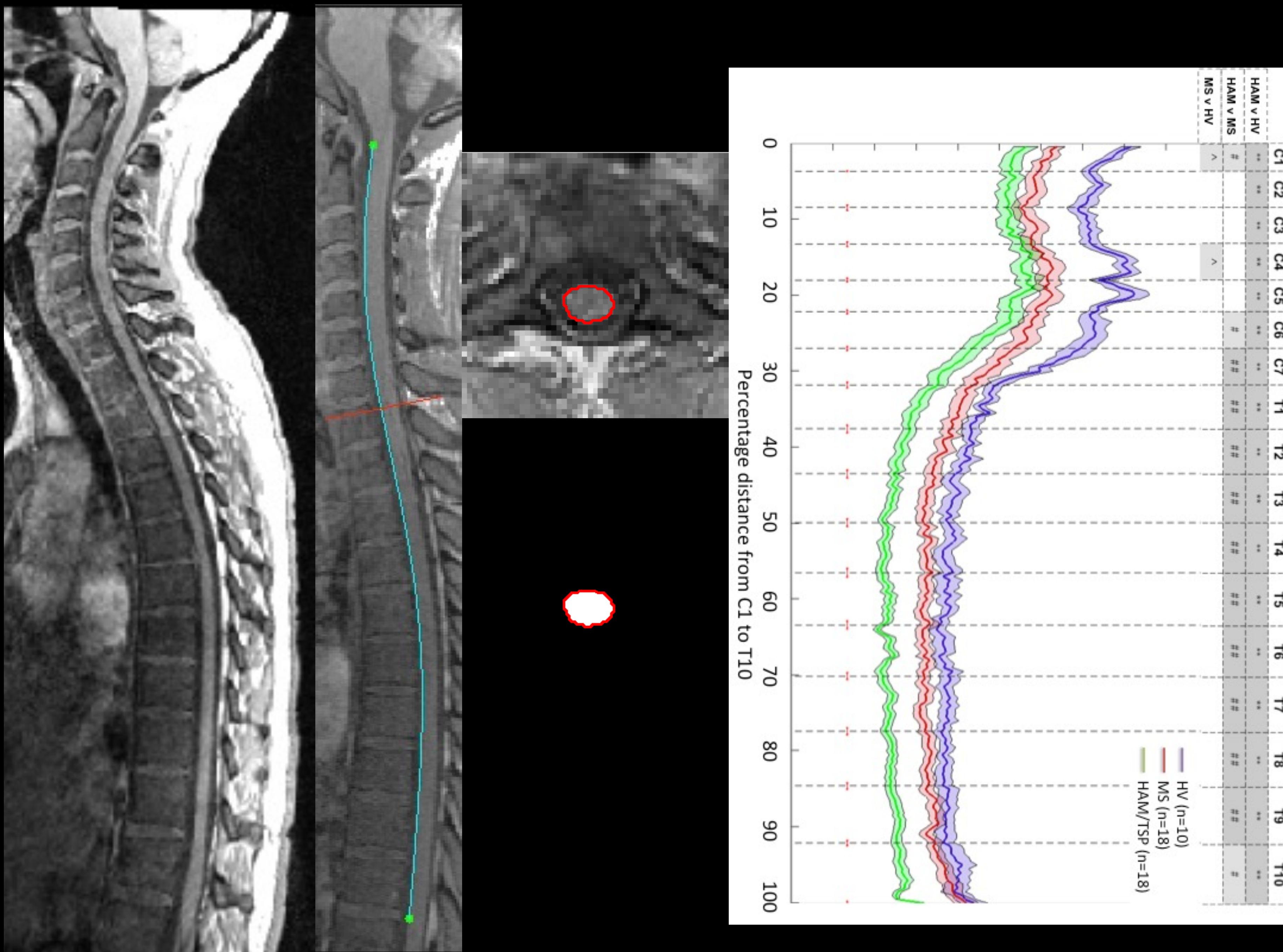
Gao et. al. NeuroImage 100 (2014):370-378

What does it mean clinically?

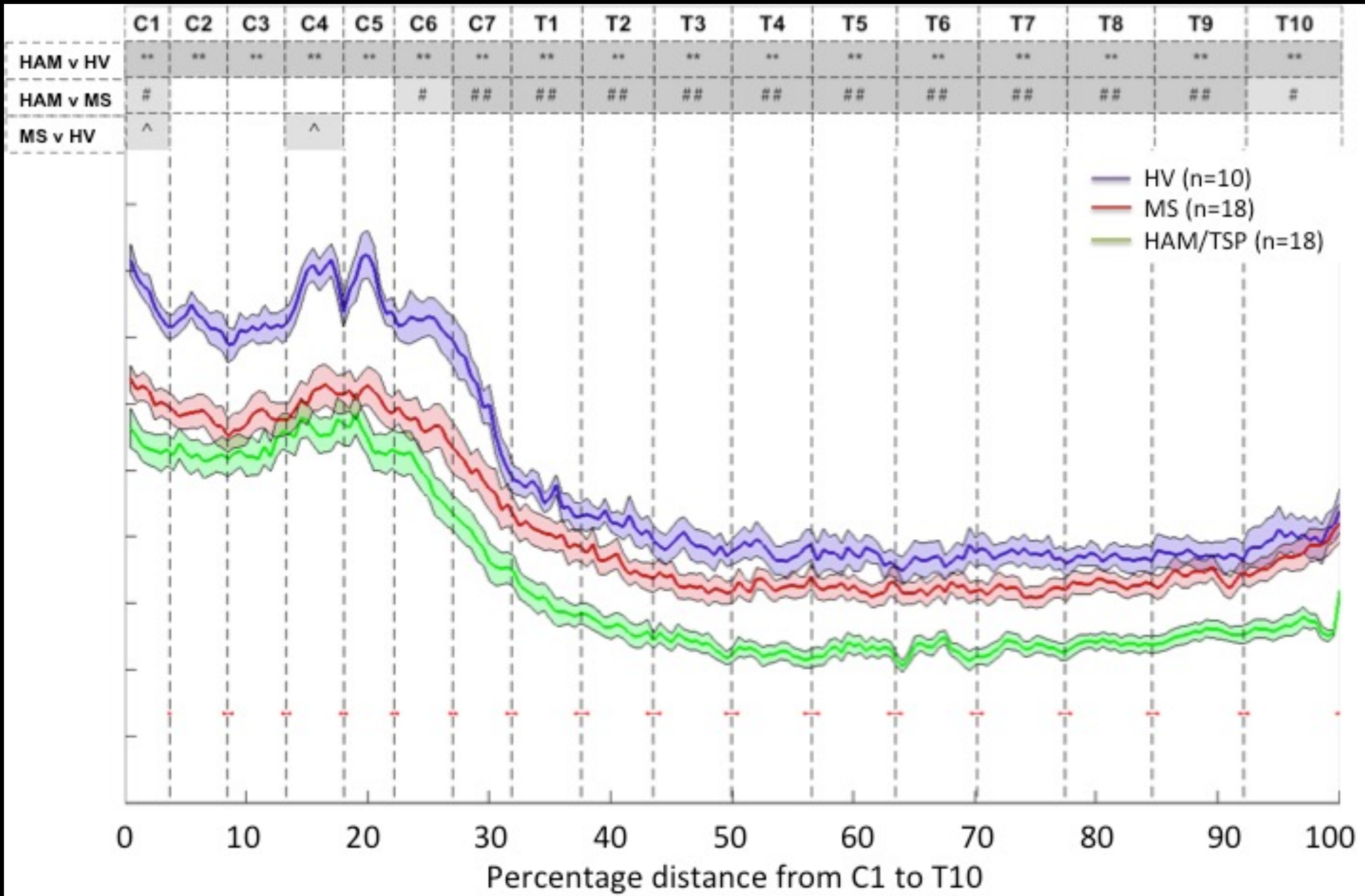


Adjusted for age and gender

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



Liu et. al., Annals of Neurology 76(3):370



Liu et. al., Annals of Neurology 76(3):370

Conclusion

- Several qMRI techniques have shown sensitivity to biological and disease processes
  - Correction for various scanner effects and bias fields are available, and have to be used.
  - Can be acquired in clinically acceptable time at high resolution (~1 mm isotropic).
  - Careful experimental design, avoid over-interpretation.
- However, the specificity remains an issue
  - qMRI value could change from an unrelated process.

Source of Errors and Variability

- User induced
  - Sequence and protocol selection (filters, distortion correction, resolution/ETL…)
  - Analysis methods, assumptions, and models…
- Manufacturer dependent
  - Equivalent sequences may still be slightly different (RF pulse, gradient slopes, coil combination, acceleration)
  - Hardware (e.g. OEM 7T head coil, gradient distortions, eddy current)

Future: Understanding the Origins

Solution in a tube:

$$\frac{1}{T_1}=\frac{6}{20}\frac{\hbar^2\gamma^4}{b^6}\left[\frac{\tau_c}{1+\omega^2\tau_c^2}+\frac{4\tau_c}{1+4\omega^2\tau_c^2}\right],$$

$$\frac{1}{T_2}=\frac{3}{20}\frac{\hbar^2\gamma^4}{b^6}\left[3\tau_c+\frac{5\tau_c}{1+\omega^2\tau_c^2}+\frac{2\tau_c}{1+4\omega^2\tau_c^2}\right].$$

In vivo: "Presence of locally disordered macromolecular environments"
- compartments with solids, couplings, and different exchange regimes…

Extremely Heterogeneous Environment

Solomon I; Physical Review vol 99 (1955) no 2 pp559, Brynt and Korb Magnetic Resonance Imaging 23 (2005) 167–173; Koenig, Acad Radiol 1996;3:597

Thank you.