Measuring the invisible using Quantitative Magnetic Resonance Imaging

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What is qMRI?

Quantification = measure

Quantity

e.g. body mass

reliable, accurate, reproducible, easy

Quantification

- Quantify – to measure a quantity (size, weight, blood sugar, cholesterol …)
- Medical images have been *qualitative*
  - **Look**; human assessment; experience needed
- Imaging is becoming *quantitative*
  - **Measure** e.g. tumour size, water content, tissue destruction, volume of MS lesions…

Is accuracy important?

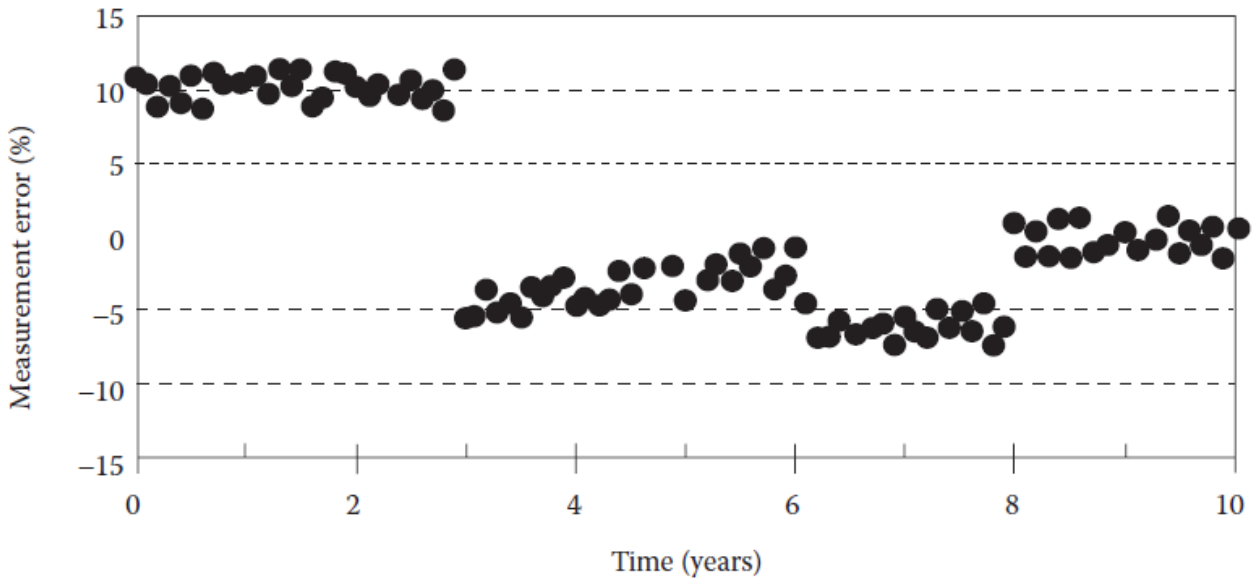


FIGURE 3.3 Long-term precision is dominated by instability in the systematic error. Simulation of fictional change in measurement error over time, during a longitudinal study. Short-term precision is good, and a study completed in the first 3 years is unaffected by the large systematic error (i.e. poor accuracy). A major upgrade at Year 3 dramatically changes the systematic error. A subtle drift in values takes place, followed by two more step changes, at the times of operator change and a minor upgrade. At Year 8 the sources of systematic error are finally identified and removed, giving a system that should provide good accuracy and hence long-term precision for many years.

Is accuracy important?

In a single centre short study – probably not

In longer studies – yes (withstand upgrades)

In multi-centre studies – yes
(unless you can replicate the sources of inaccuracy at each site – 'protocol matching')

Multi-centre studies:
MAGNIMS – MS 20 years
qMRI book pp35,36 and p132 (diffusion)

Why does random error matter?

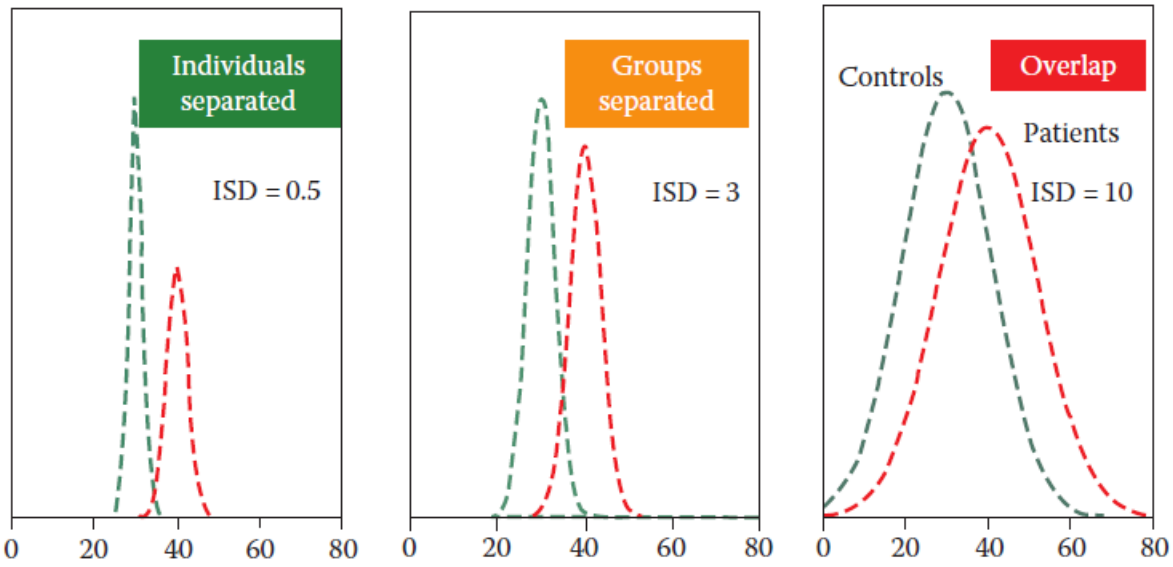


FIGURE 3.5A Simulation showing how magnitude of ISD affects ability to use an MR parameter to separate groups and individuals. Group separation is 10 units. With ISD = 10 (right-hand image), the groups overlap, and considerable statistical power would be needed to separate them (see Chapter 1, Figure 1.3). A reduced ISD = 3 (centre) gives a good group separation c) a further reduction to ISD = 0.5 (left-hand image) enables individuals to be accurately classified into their group.

Why is repeatability important?

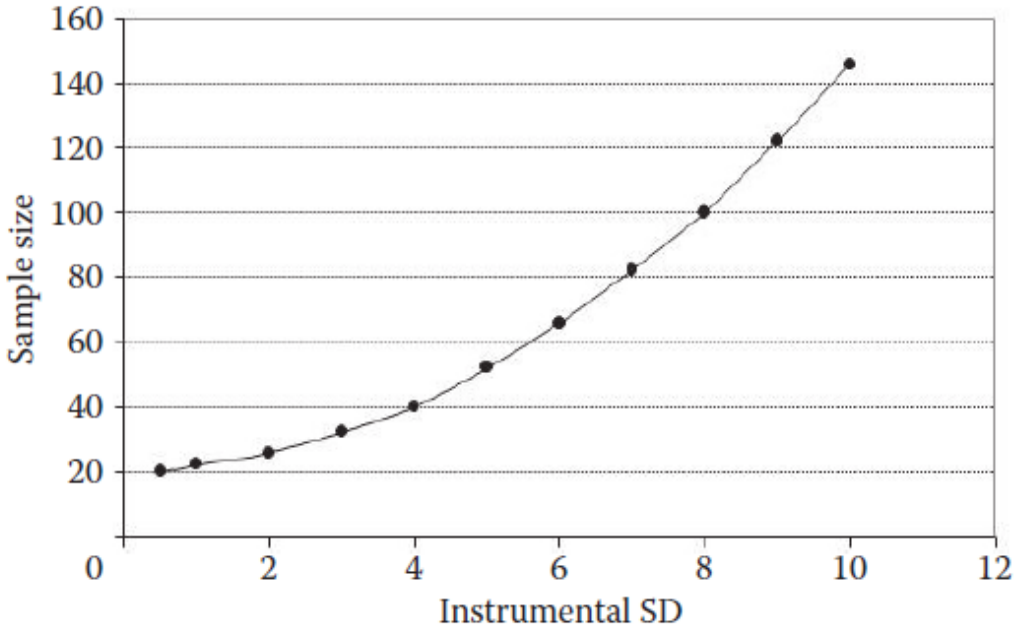


FIGURE 1.3 The effect of instrumental precision (ISD) on the power of a study and the required sample size. By reducing the ISD, the sample size required is dramatically reduced, with a consequent saving in the cost and duration of the study. This is a simulation based on group comparison between controls (parameter value mean = 100, SD = 3) and the same number of patients (effect size = 5, SD = 4.25). Power P = 80%, significance level $\alpha = 0.05$, using G*power3 which is an established software that can be downloaded free of charge.

The Measurement Process: MR Data Collection and Image Analysis

Contents

What causes random variation?

TABLE 3.3 Potential Sources of Error in the MRI Measurement Process[a]

	Random Error	Systematic Error
Biology	Normal variation in physiology	
Data collection	Position of subject in head coil	B_1 error
	Coil loading (corrected by prescan?)	Slice profile
	Prescan procedure setting B_1	K-space sampling (in FSE, EPI)
	Position of slices in head	Partial volume
		Operator training
	Gd injection procedure	Software upgrade
	Patient movement (cardiac pulsation)	Hardware upgrade
	Patient movement (macroscopic)	
	Image noise	
	Temperature (phantoms only)	
Image analysis	ROI creation and placement	Operator training
		Software upgrade

Note: In their simplest forms, random error is associated with short-term unpredictable variation, whilst systematic error is fixed. However some random processes (e.g. positioning) might only show up over a longer time scale (caused e.g. by change of radiographer [technician]), whilst some sources of systematic error might vary with time (e.g. operator training). ROI = region of interest.

B_1 errors

Quality of parameter estimates depends on quality of acquisition

B_1 and image noise often dominate parameter uncertainty

[poor acquisition cannot be fixed by post-processing!]

1% error in flip angle FA gives 2% error in T_1 (in Variable Flip Angle method)

Optimisation of acquisition procedure

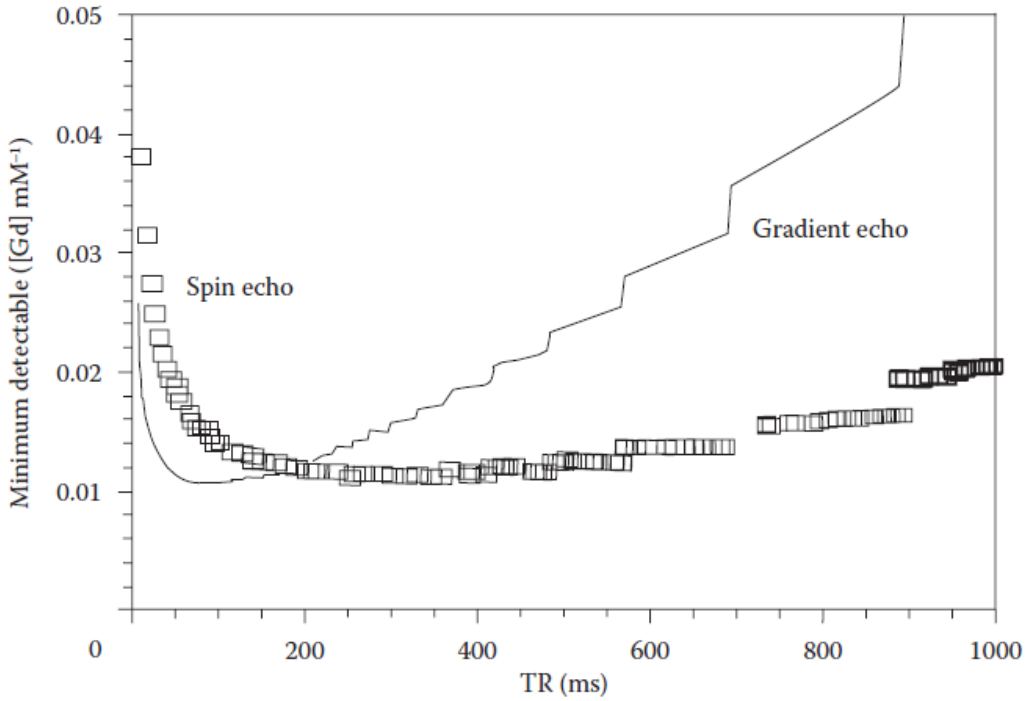


FIGURE 2.5 Sequence optimisation by noise modelling. Mathematical modelling of image noise propagation predicts the minimum amount of Gd contrast agent that can be detected using a T_1-weighted sequence. By optimizing the repetition time, *TR*, in a spin echo or gradient echo sequence, its performance in white matter can be optimised. Theory indicates that, for a spin echo, the optimum $TR = T_1/2$ (here it was assumed $T_1 = 600$ ms). The gradient echo (flip angle, FA = 50°) can achieve the same sensitivity, provided the correct *TR* is used. The examination time was fixed at 10 min. (From Tofts, P.S., *Magn. Reson. Imaging*, 14(4), 373–380, 1996.)

Image data analysis

- Region of interest
  - Test a specific location (prior information and hypothesis)
- Histogram
  - Whole brain; unbiased; for diffuse disease
- Voxel-Based Morphometry VBM
  - Unbiased testing of many locations
  - Each location can be correlated with external score (clinical, genetic, proteomic, cognitive)
- Texture
  - 'dirty white matter'
  - tissue often becomes more heterogeneous in disease

Phantoms and healthy Controls for QA

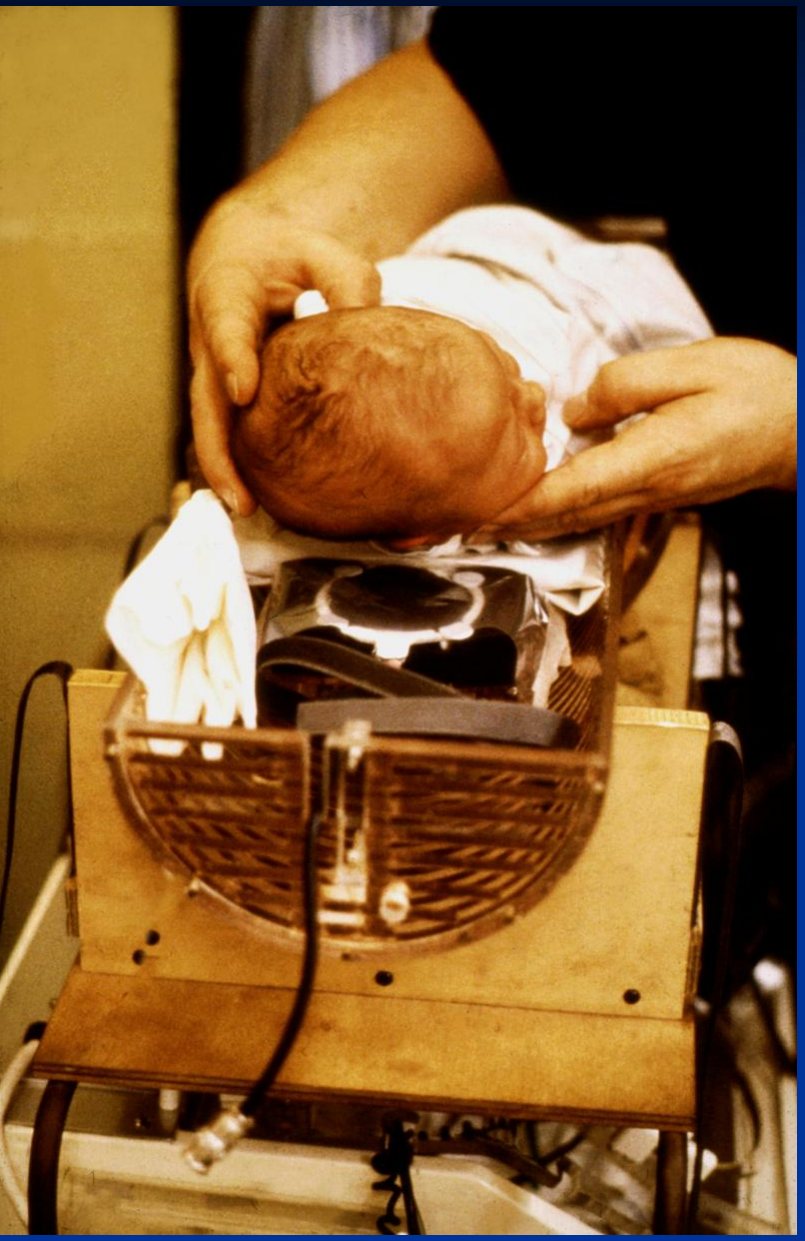
TABLE 3.1 Relative Advantages of Phantoms and Healthy Controls for Quantitative Quality Assurance

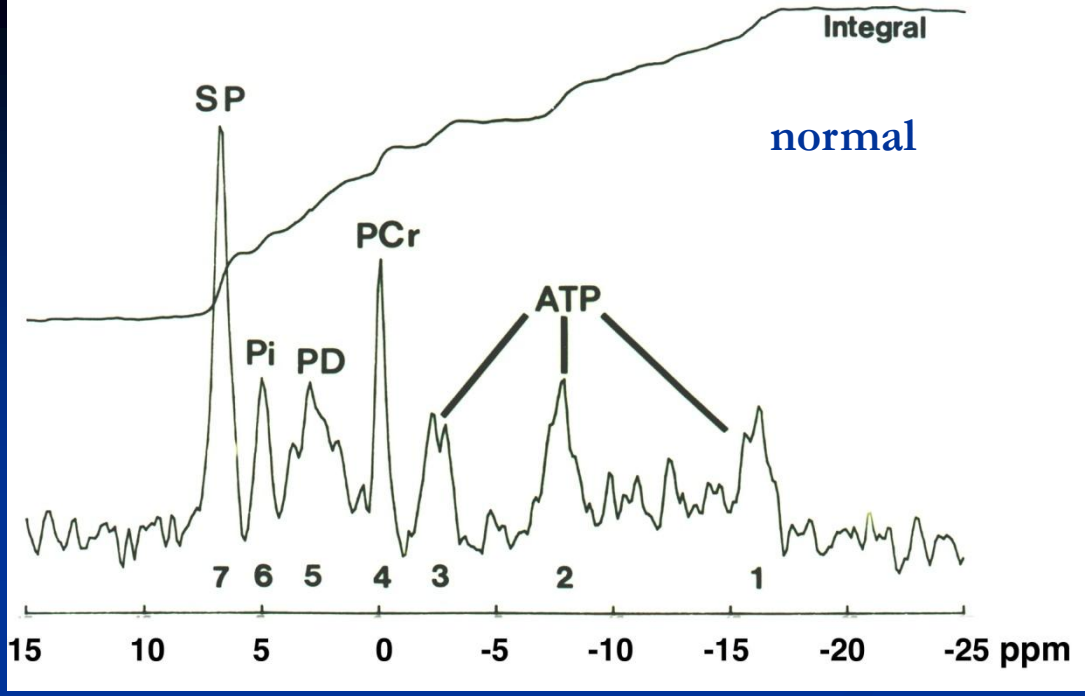
	Simple Phantom (Test Object)	Healthy Control Subjects
Availability[b]	Good	Reasonable
Accuracy	Potentially good (e.g. volume)	True value unknown[a]
Uniformity	Poor in gels, good in liquids	Good in white matter
Temperature dependence	D,T_1,T_2 change 2%–3%/^{O}C	Homeostatic temperature control
Stability	Potentially good (e.g. volume) but can be unstable (e.g. gels)	Usually stable
Realism	Generally poor; *in vivo* changes cannot be realistically modelled; B_1 distribution different	Good but no pathology
Standard design for multicentre studies?	Can be made	Use normal range, or travelling subject(s)

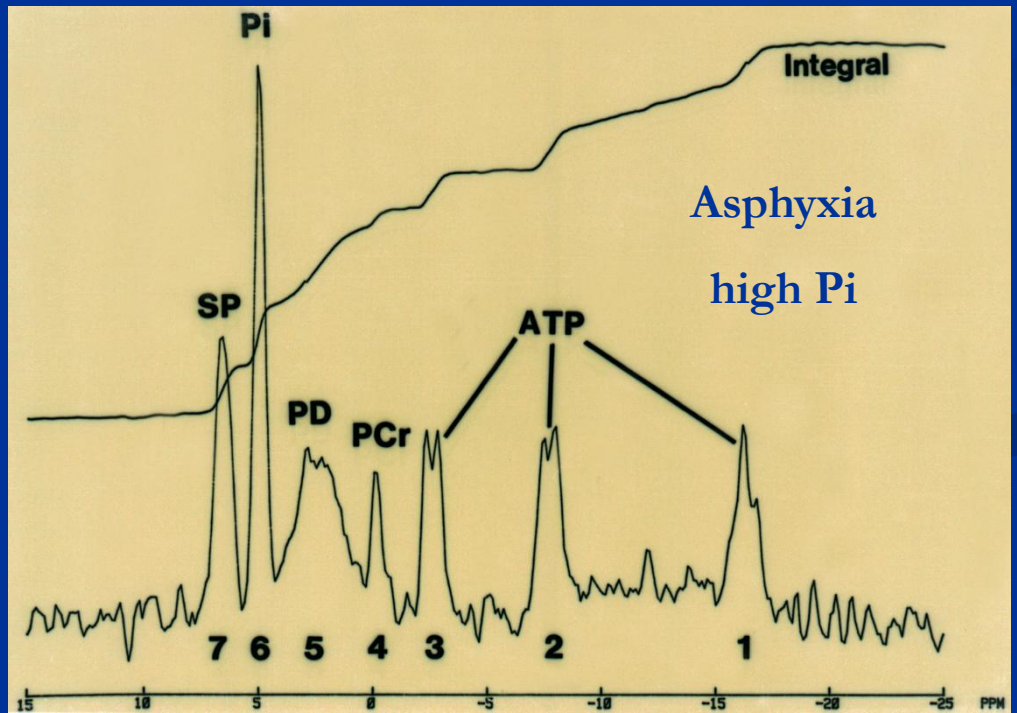
[a] Although normal values have a narrow range – see Table 3.5.
[b] Though see institutional constraints (Section 3.5.1).

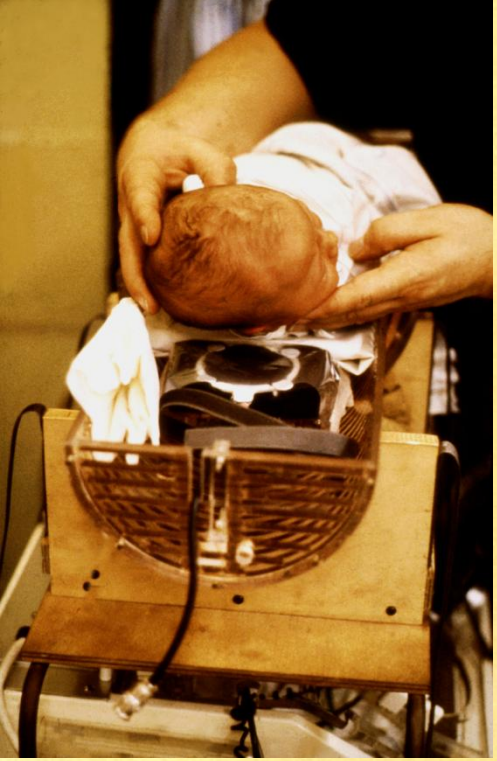
Why are physicist so interested in scanning normals?

- Repeatedly!
  - Understand and minimise all the sources of variation
- Serial study
- Cross-sectional study
- Influence of instrumental variation on sample size in power calculation




Integral
SP
normal
PCr
ATP
Pi
PD
7 6 5 4 3 2 1
15 10 5 0 -5 -10 -15 -20 -25 ppm


Pi
Integral
Asphyxia
high Pi
SP
ATP
PD
PCr
7 6 5 4 3 2 1
PPM



48 hrs
32 hrs
24hrs
9 hrs
15
10
5
0
-5
-10
-15
-20
-25
PPM

6 MR windows into brain biology

volume	atrophy
diffusion	cellular breakdown
magnetisation transfer	macromolecules
T_1,T_2	water content
spectroscopy	metabolites
Gd leakage	blood-brain barrier

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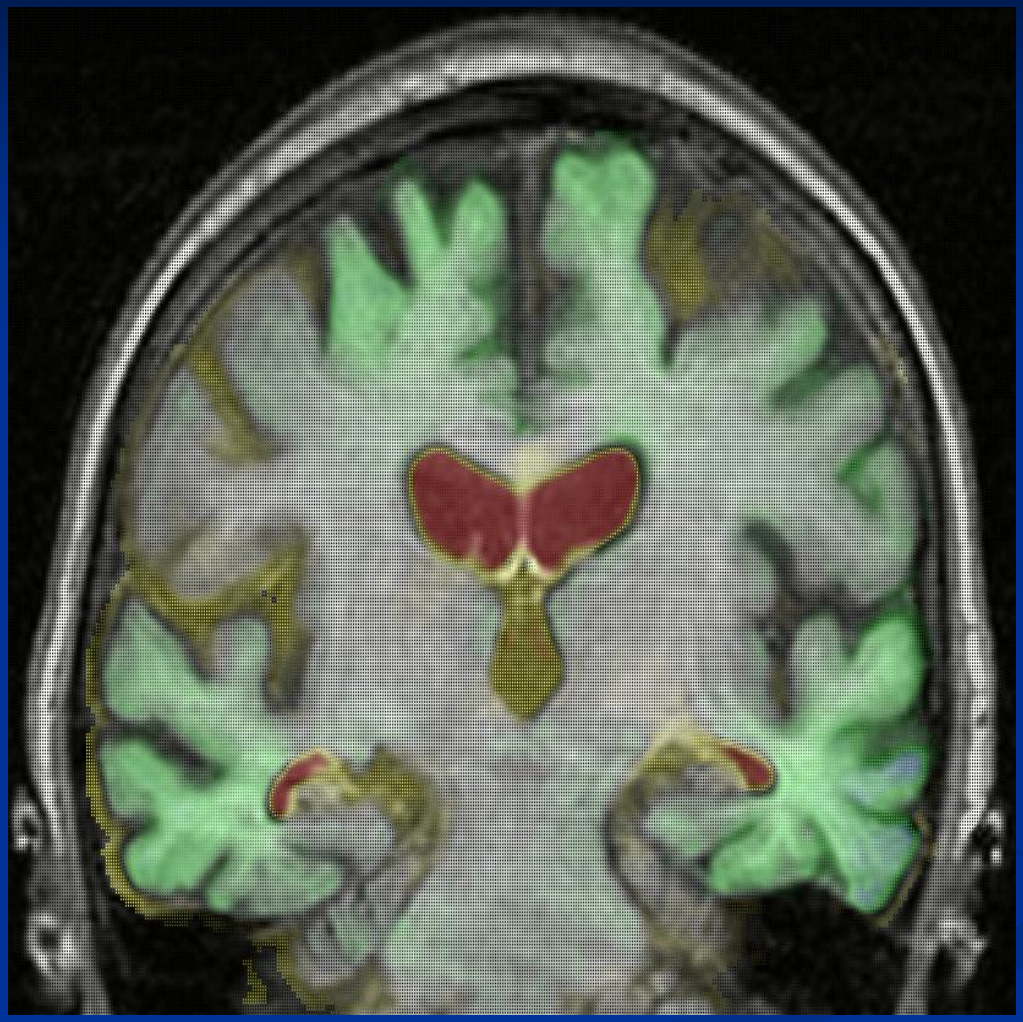
Volume and atrophy

- High-resolution structural scan
- Volumes of WM and GM
  - Normalise with skull size
  - (x-sectional)
- Serial scans and spatial registration
  - Progressive atrophy
  - Normal: 0.5% pa; AD: 3% pa
  - MS shows progression in WM and GM

Progressive atrophy in a patient with Alzheimer's Disease



contracting

expanding

Nick Fox

Queen Square

UCL

Total lesion volume in Multiple Sclerosis trials

- Clinical trials are expensive and long
  - Clinically variable disease; needs lots of subjects (100+) and time (1-3y)
- Increasingly MRI is used as a 'surrogate marker'
  - observe biological effects of disease and treatment more directly and quickly
  - more specific MRI measures to indicate biology

6 MR windows into brain biology

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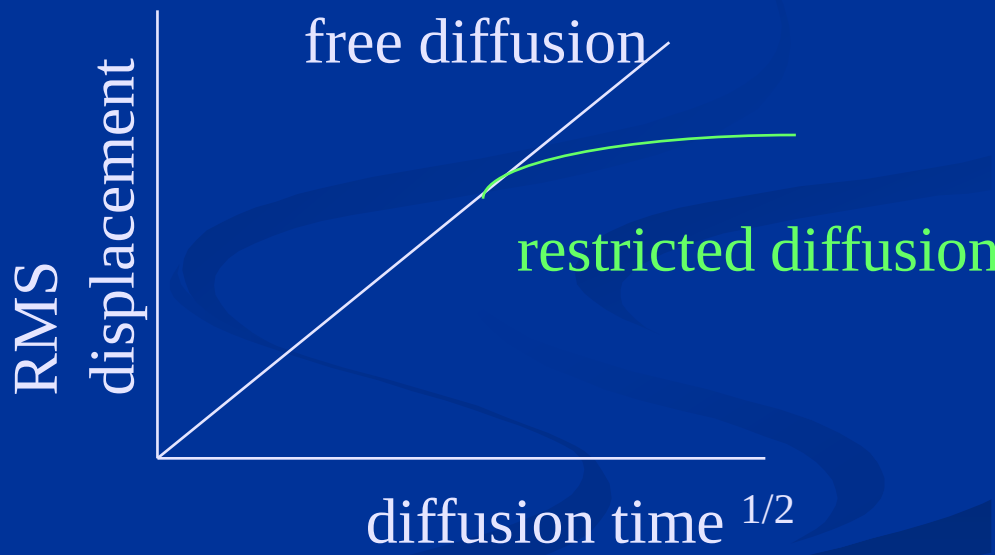
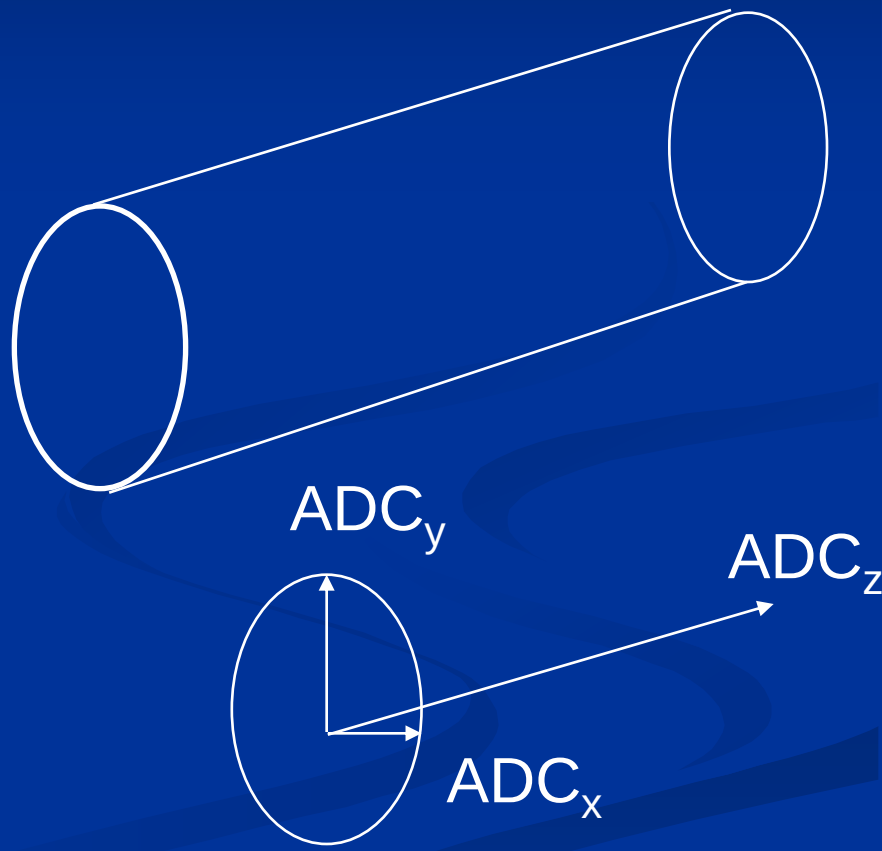
Diffusion Basics

- In a test tube, diffusion of water is largely unhindered (*free*)
  - characterised by the diffusion constant
- In the brain diffusion is *restricted* or *hindered*
  - characterised by the apparent diffusion coefficient (ADC)
  - Water diffuses 60μ in 100ms; far enough to meet restrictions



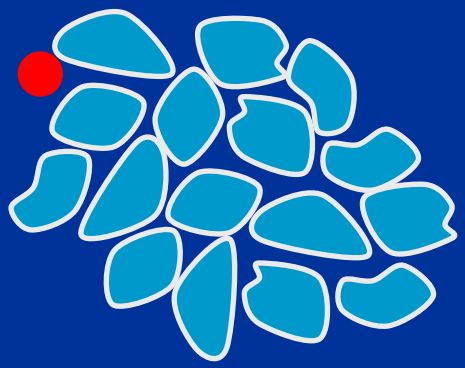
Diffusion Basics - 2

- In a test tube, diffusion is largely isotropic (same in all directions)
  - characterised by a single diffusion constant
- In the brain, diffusion may be anisotropic
  - barriers to diffusion (e.g. axon walls, cellular microstructures) are oriented
  - characterised by different ADCs in different directions
  - Think CELERY!

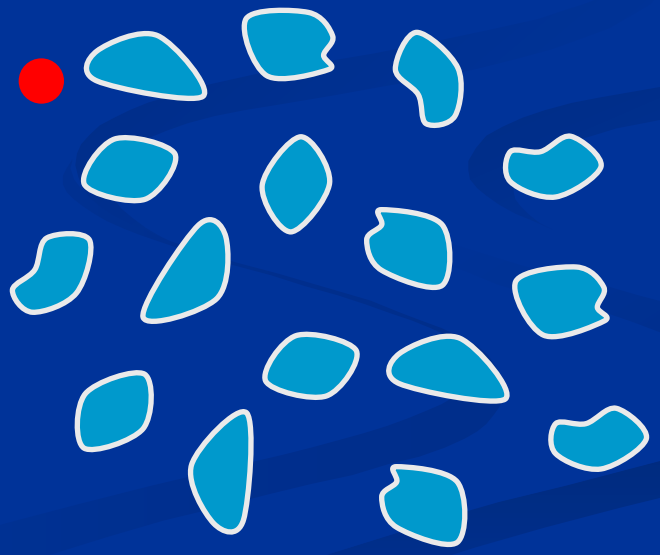


Apparent Diffusion Coefficient (ADC)

- The extent of diffusion can be characterised by an Apparent Diffusion Coefficient (ADC)
- Fewer barriers to diffusion results in greater diffusion coefficient



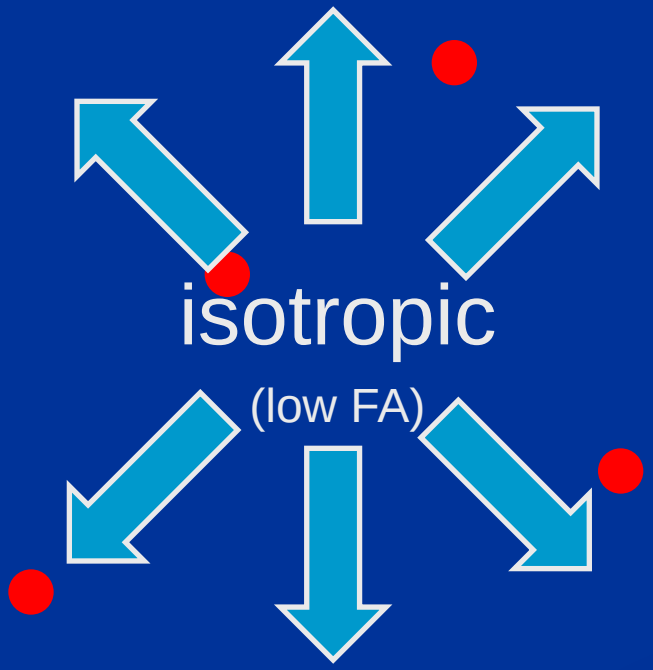
Low ADC

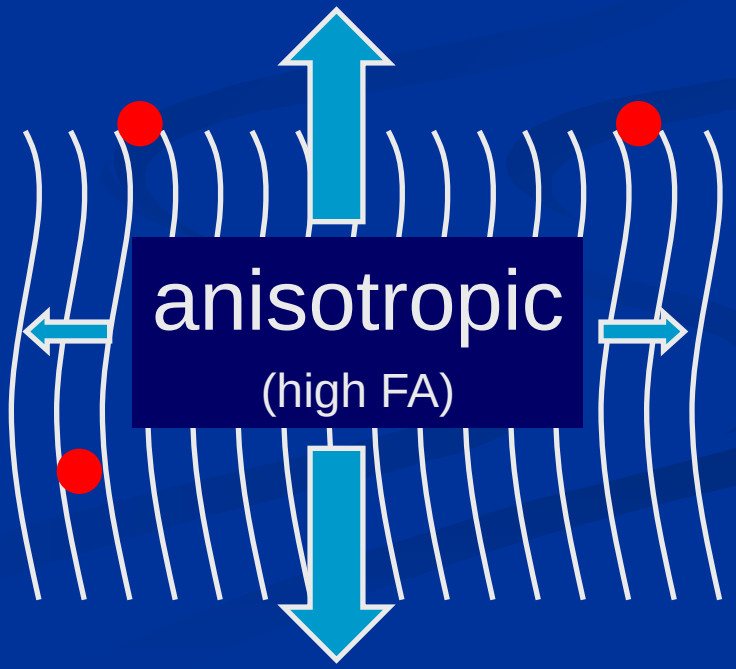


High ADC

Fractional Anisotropy (FA)

- The direction of water diffusion is influenced by directional order in tissue e.g. white matter tracts
- FA can range from 0 (isotropy) to 1 (anisotropy)

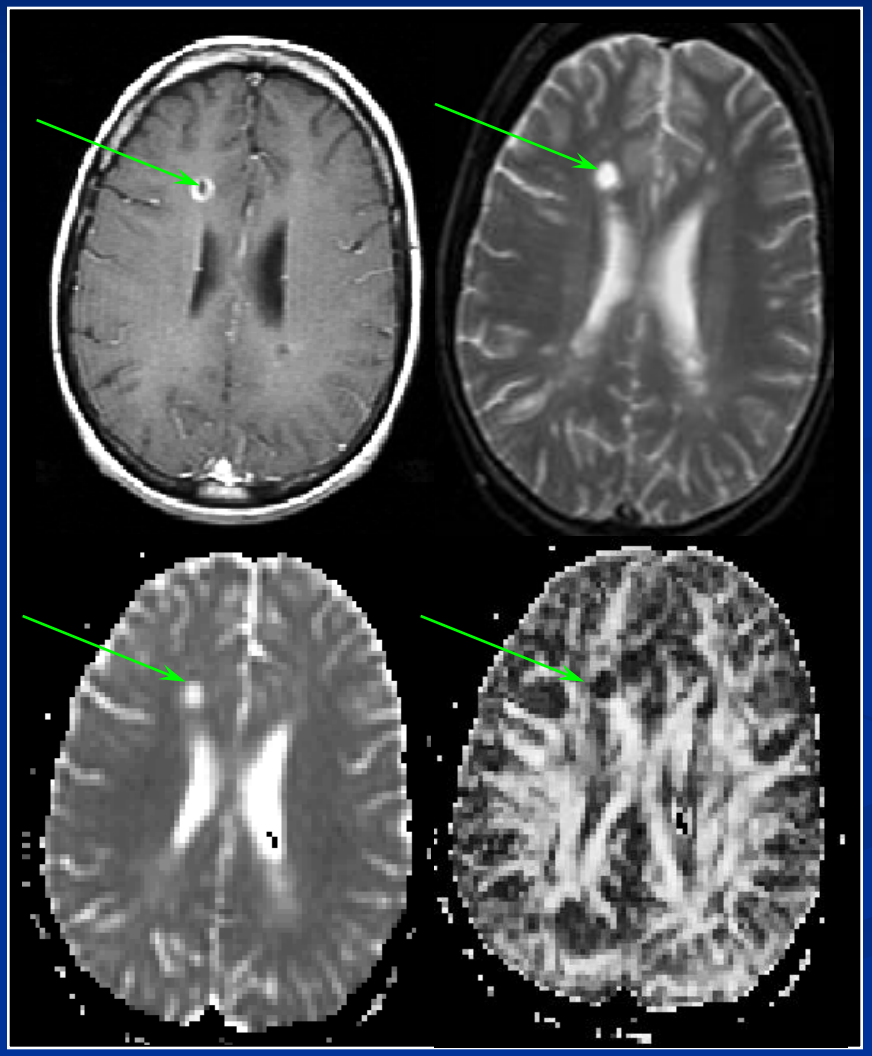




Diffusion tensor MRI

Acute enhancing MS lesion

T_1 Gd

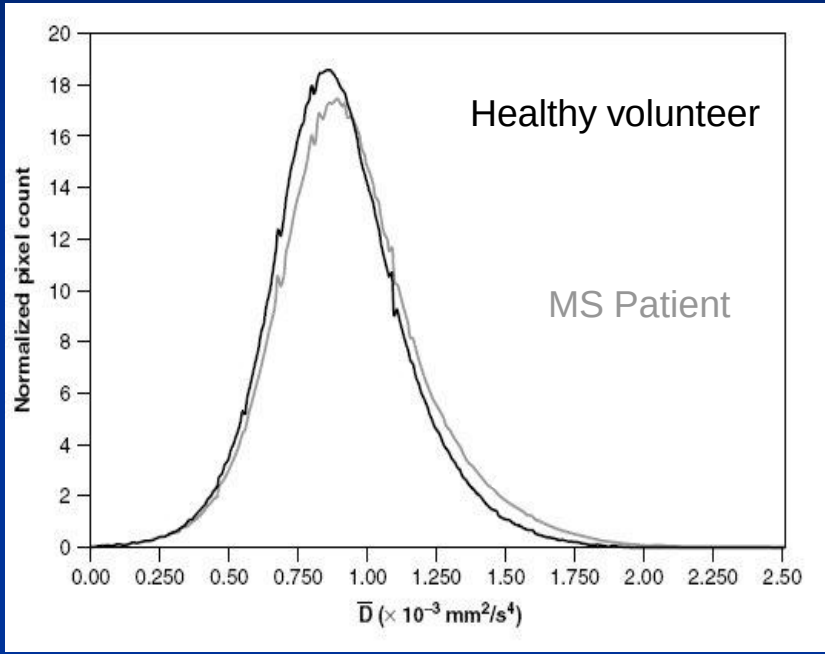


T_2

mean diffusivity

fractional anisotropy

ADC histograms in MS



Cercignani, *Neurology*, 54,1139 (2000)

- In normal appearing brain matter there is a slight increase in diffusion compared to controls
- Whole brain analysis histograms shifted to higher ADC values with a reduction in peak height

6 MR windows into brain biology

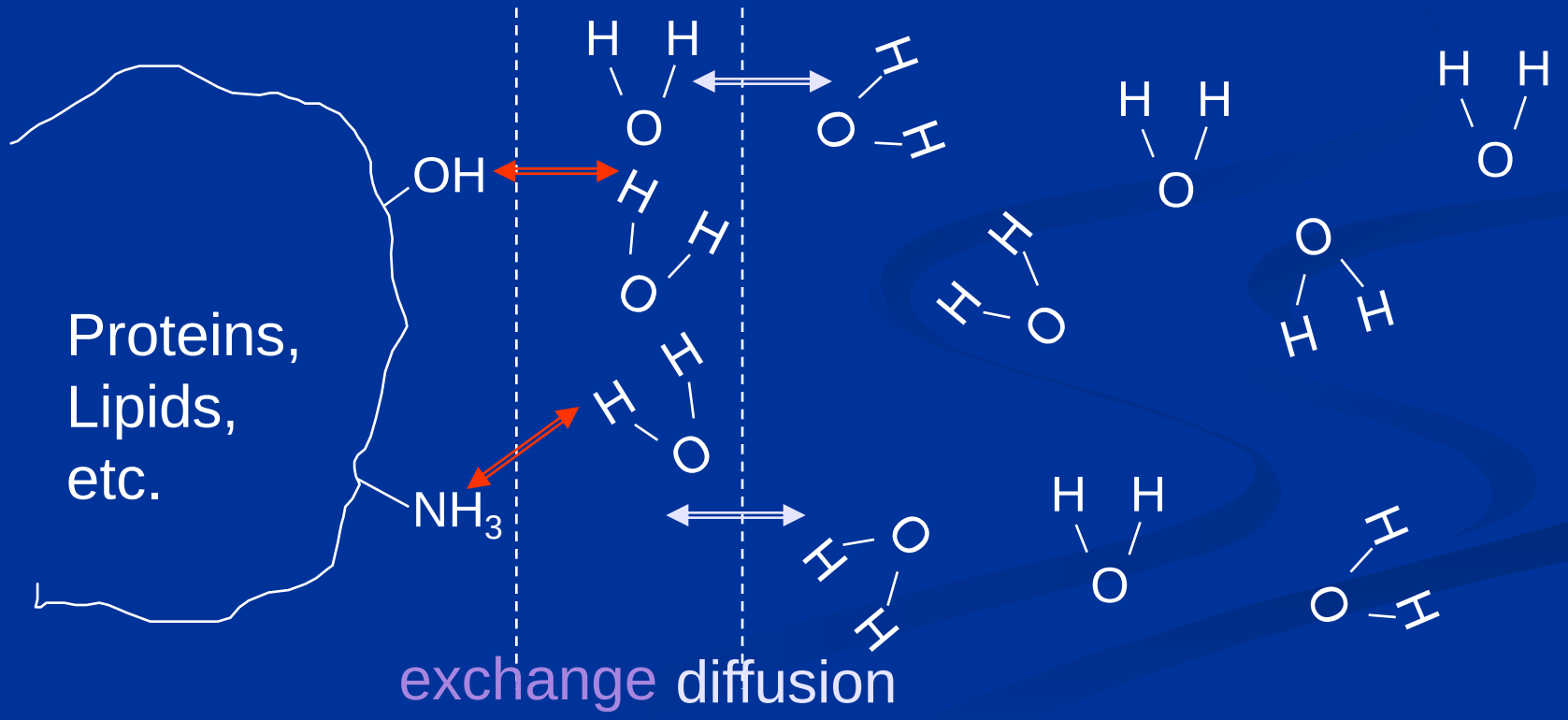
volume	atrophy
diffusion	cellular breakdown
magnetisation transfer	macromolecules
T_1,T_2	water content
spectroscopy	metabolites
Gd leakage	blood-brain barrier

Magnetisation Transfer

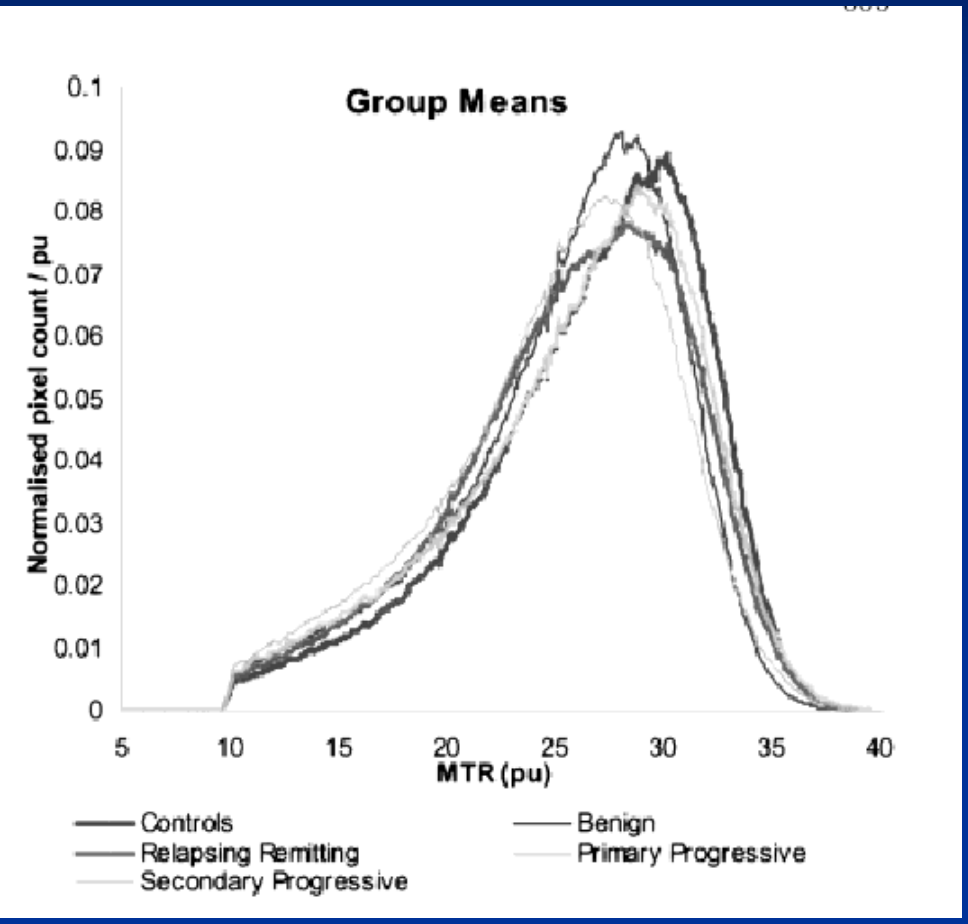
Macro molecules (invisible)
(bound protons - short T_2)

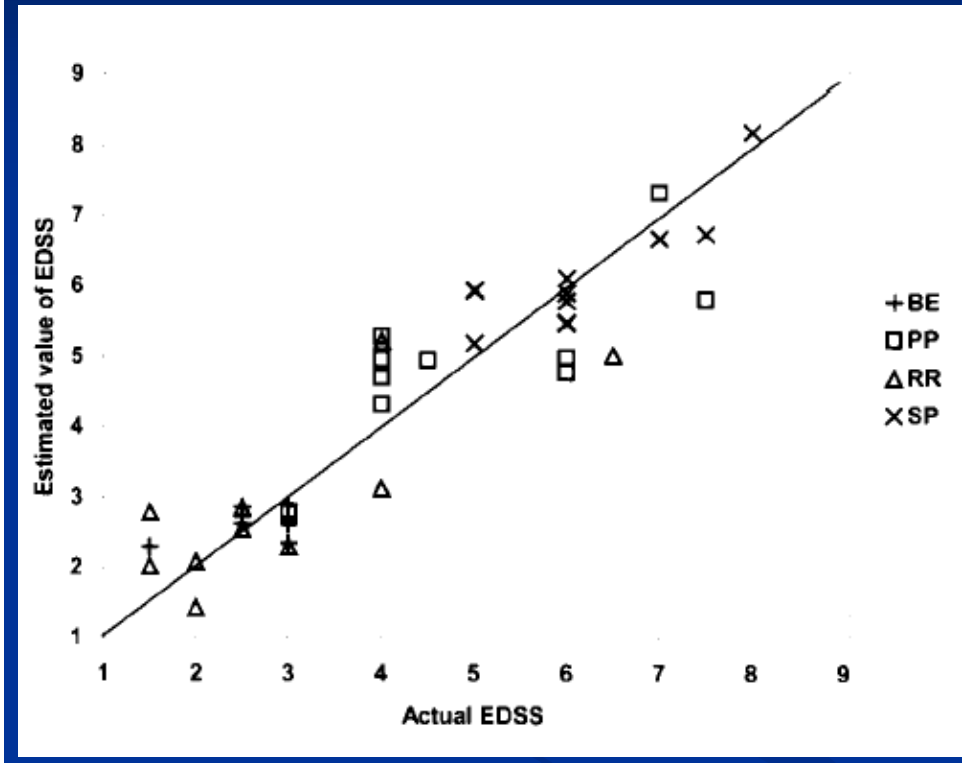
Surface

Bulk water (visible)
(free protons- long T_2)



MTR histograms in Multiple Sclerosis





Current clinical score can be predicted from histogram

(using principle components analysis - PCA)

Whole-brain histogram depends on MS subtype; sensitive to demyelination

Dehmeshki et al MRM 2001

qMT in MS

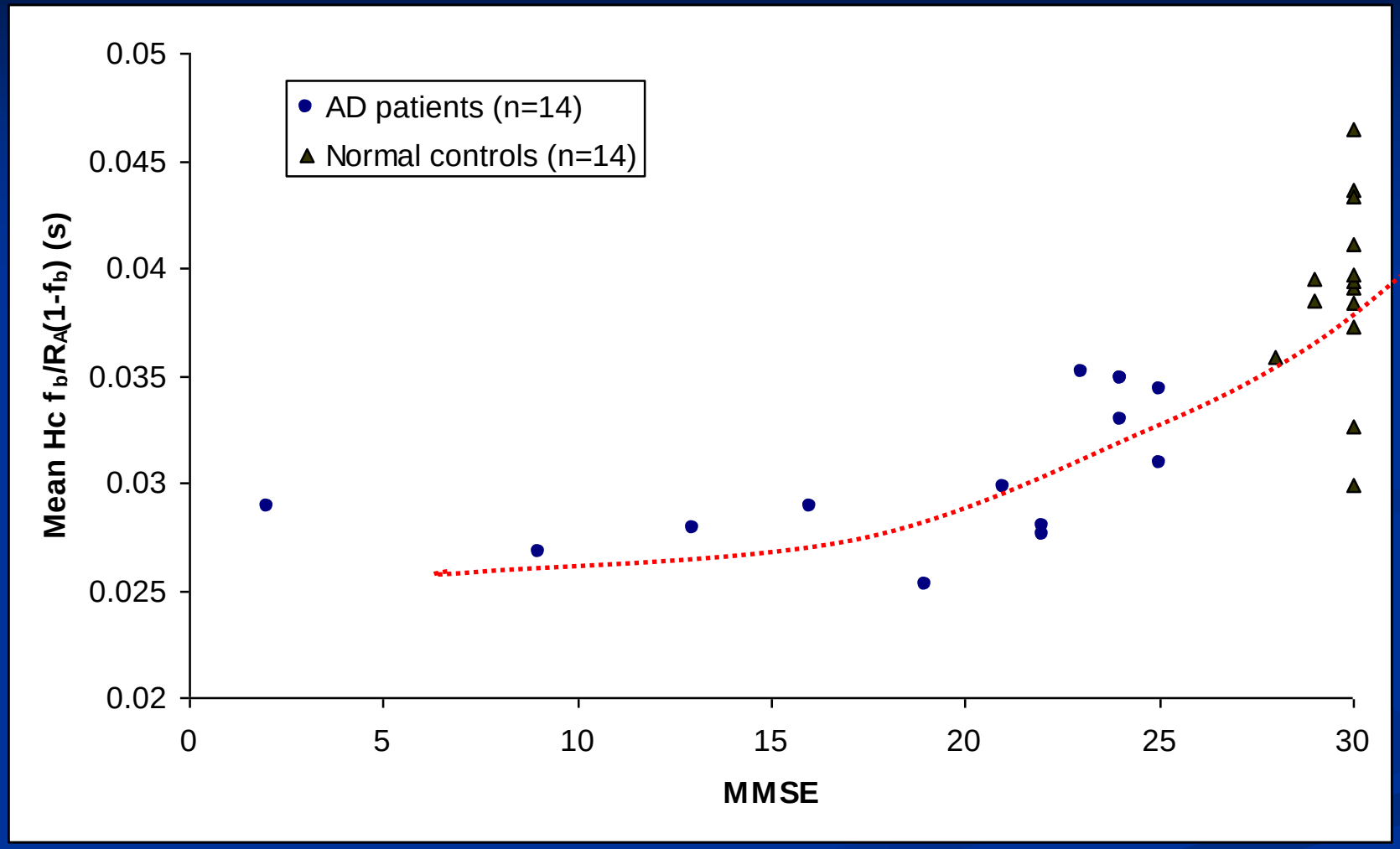
Frontal WM	f_b (%)	p
Control	9.8	
NAWM	8.6	<0.01
Lesion	4.6	<0.01

f_b = fraction of protons that are bound

≈ myelin concentration

Davies et al Mult Scler 2004; 10:607

Alzheimer's disease



Hippocampal qMT parameter (~ f_b) vs clinical score

Ridha, Fox, Tofts. Quantitative magnetization transfer imaging in Alzheimer disease Radiology 2007; 244:832

Principle Component Analysis of MTR histograms

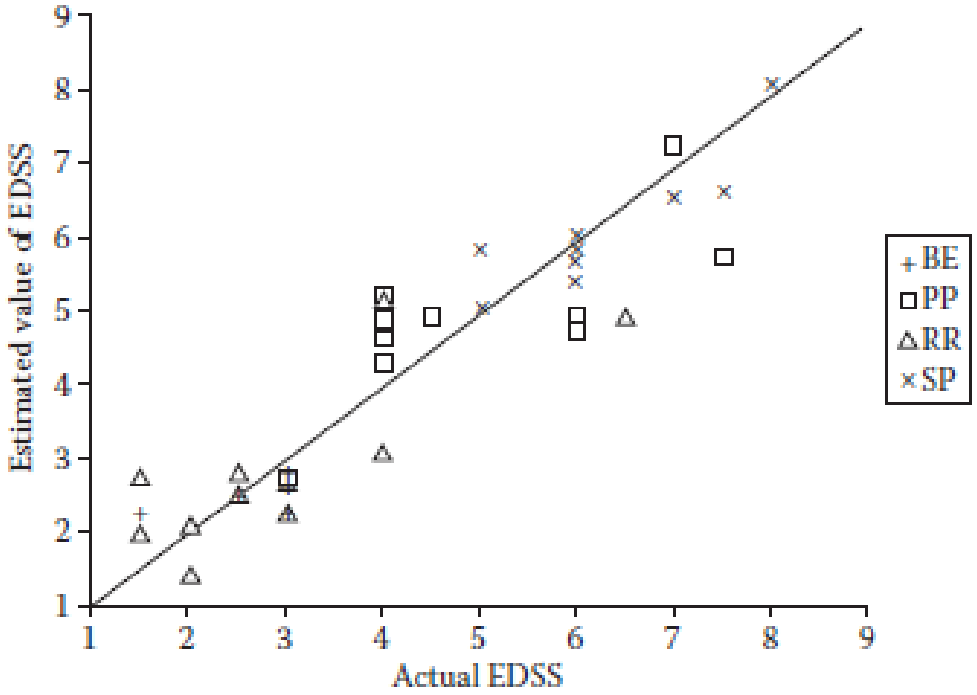


FIGURE 2.10 Correlation of Expanded Disability Status Scale (EDSS, a clinical score used in multiple sclerosis, MS) with principle components enables a 'predicted EDSS' to be calculated for each subgroup of people with MS, solely from the MTR histogram and knowledge of the subgroup. These are usually within one point of the actual clinically measured EDSS value. Compared with conventional features, PCA gives better correlation coefficients. (From Dehmeshki, J., *et al.*, *Magn. Reson. Med.*, 46(3), 600–609, 2001.)

6 MR windows into brain biology

volume	atrophy
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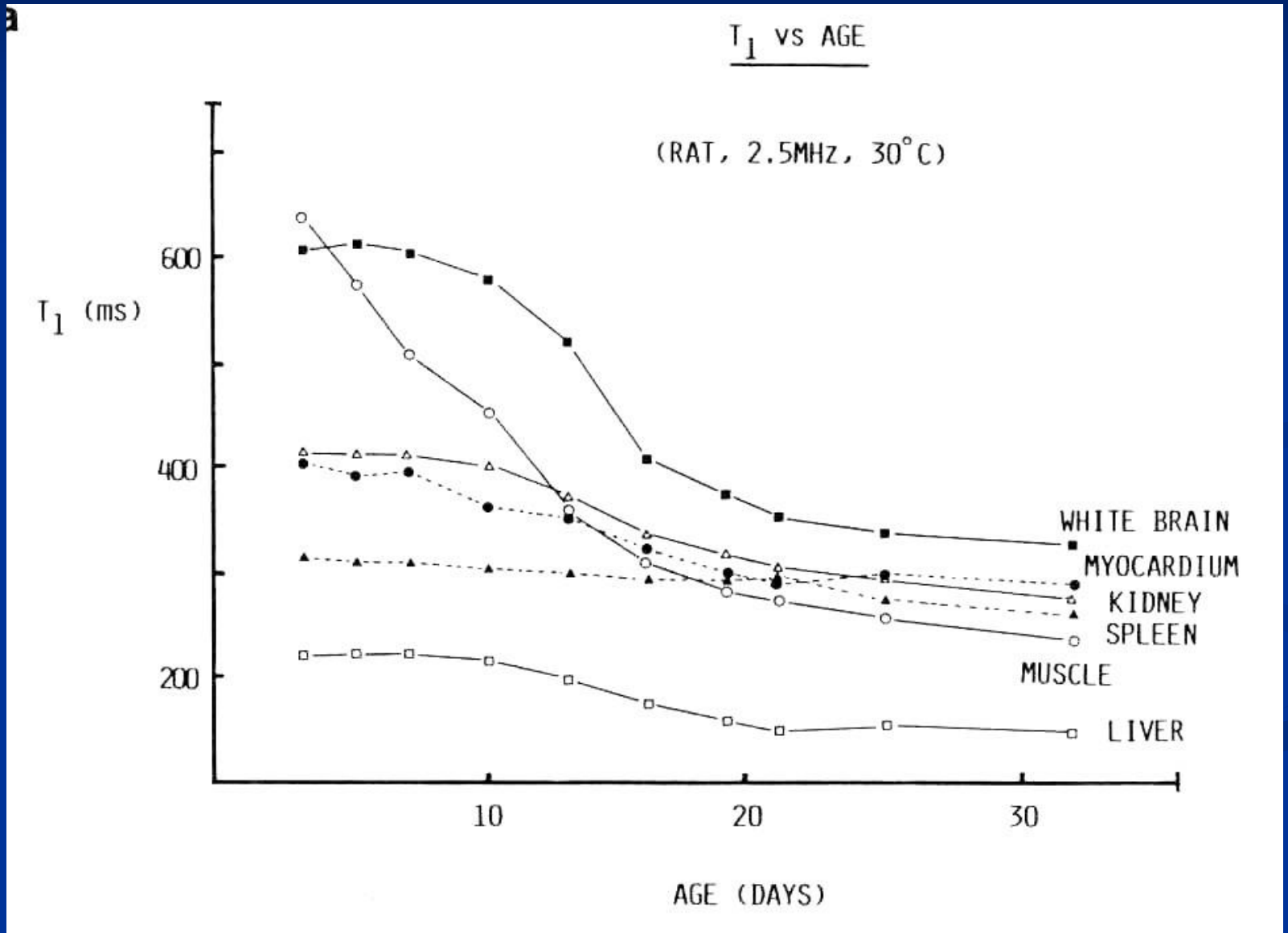
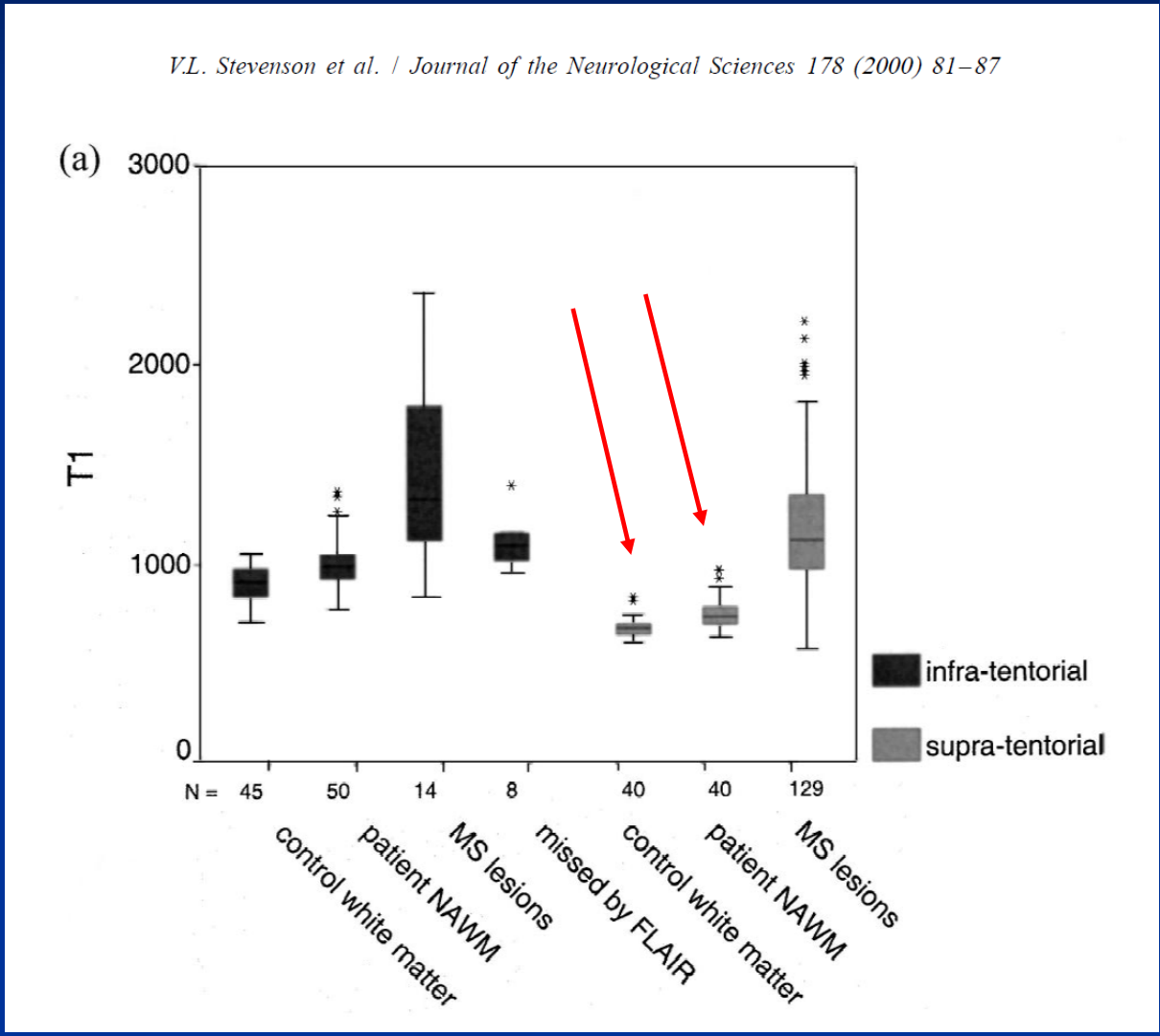
magnetisation transfer	macromolecules
T_1,T_2	water content
spectroscopy	metabolites
Gd leakage	blood-brain barrier

T_1 decreases during development



T_1 and T_2 in MS

T1 and T2 raised in Normal Appearing White Matter



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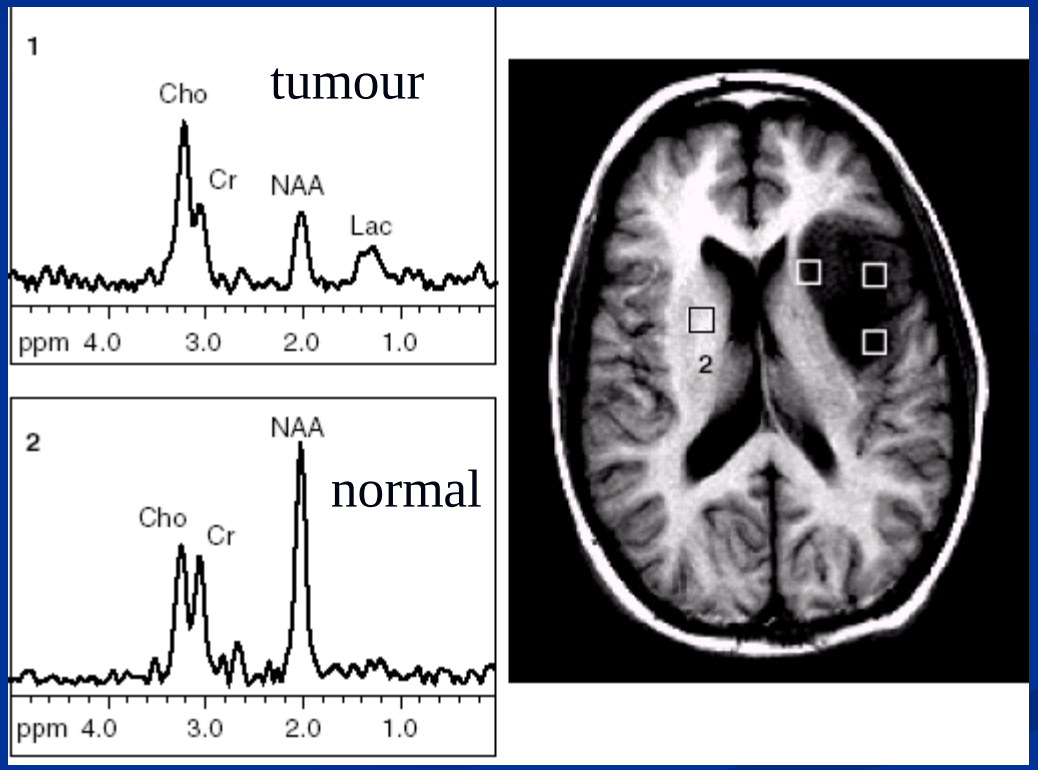
spectroscopy

- NAA - neuronal marker
  - reduced in NAWM in MS
- Choline - membrane turnover
- Lactate – anaerobic metabolism
- Myo-inositol – raised in AD

- Poor reproducibility – about 15%

Magnetic Resonance Spectroscopy

- Measurement of concentrations of biochemicals in living subjects
- Each peak corresponds to a distinct chemical
- Tumour increased Cho, Lac, decreased NAA, compared to normal tissue



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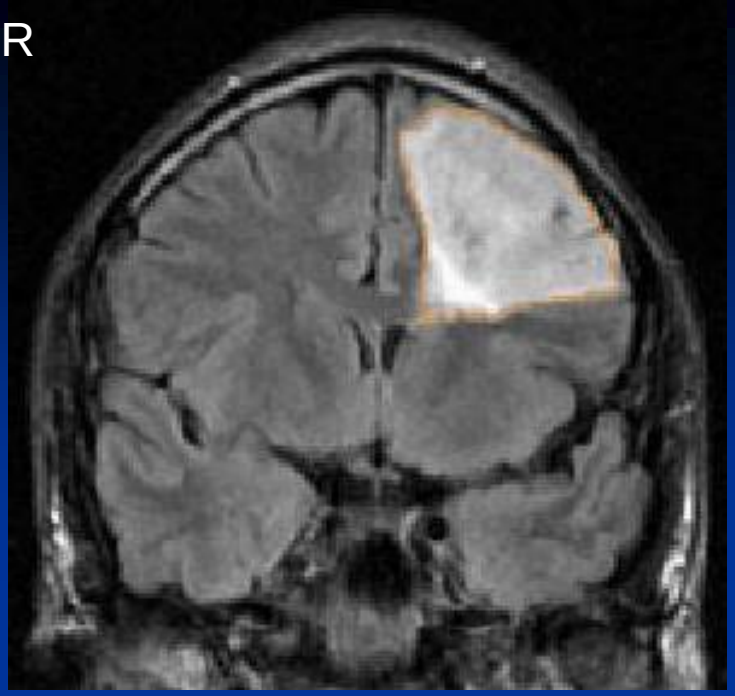
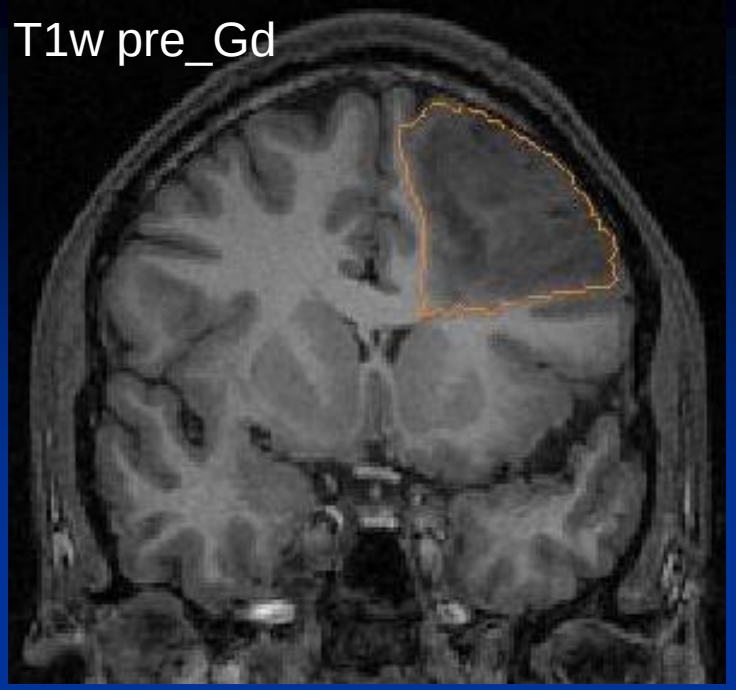
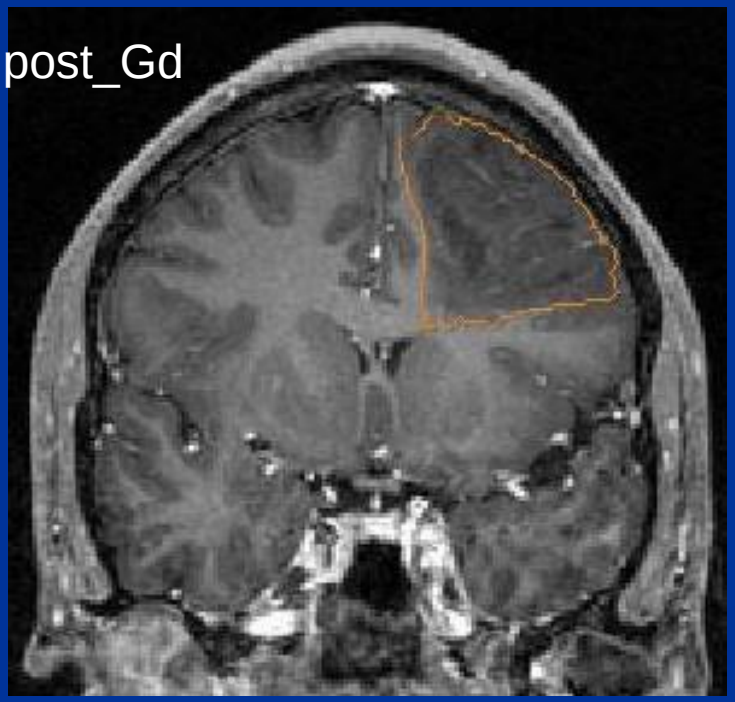




Low Grade Glioma

'not visibly enhancing'



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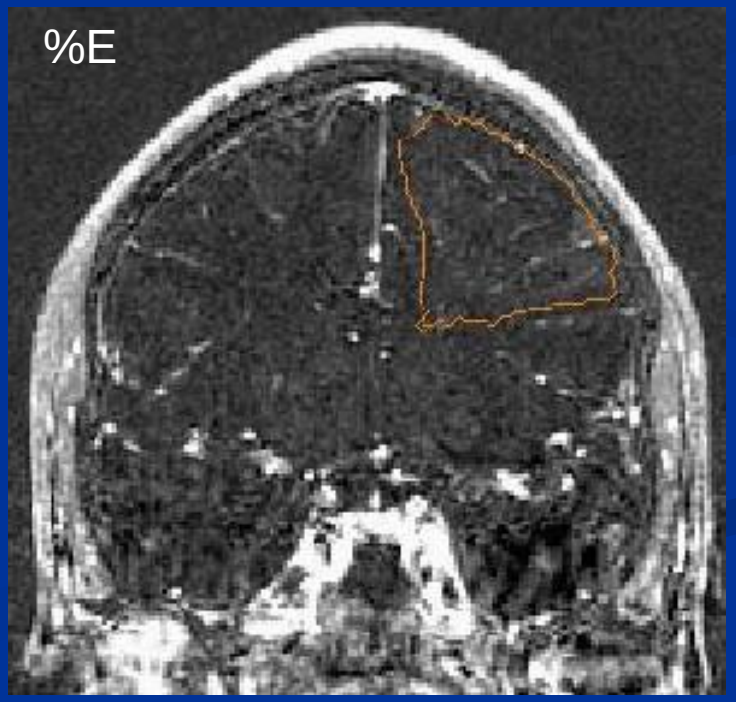

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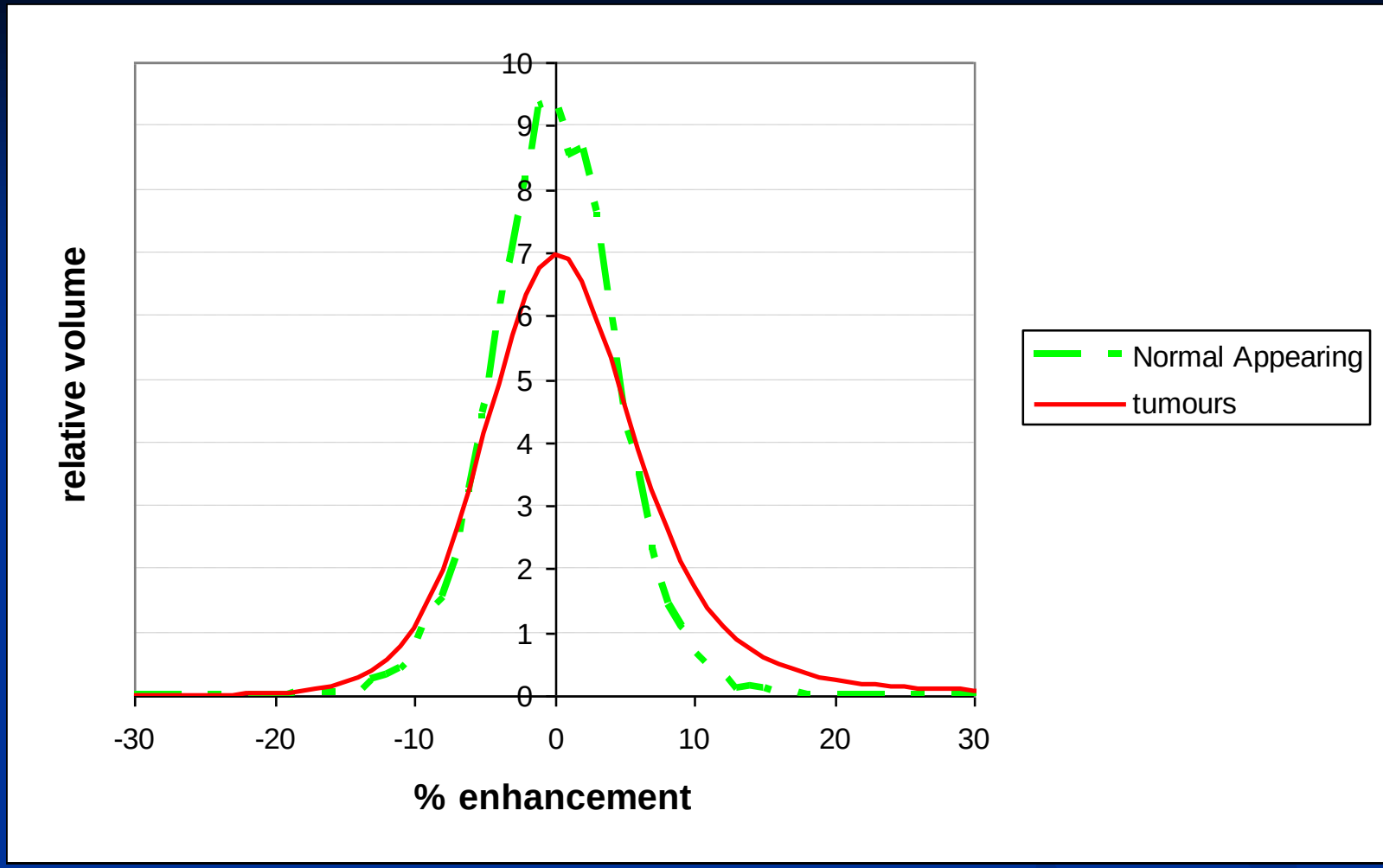
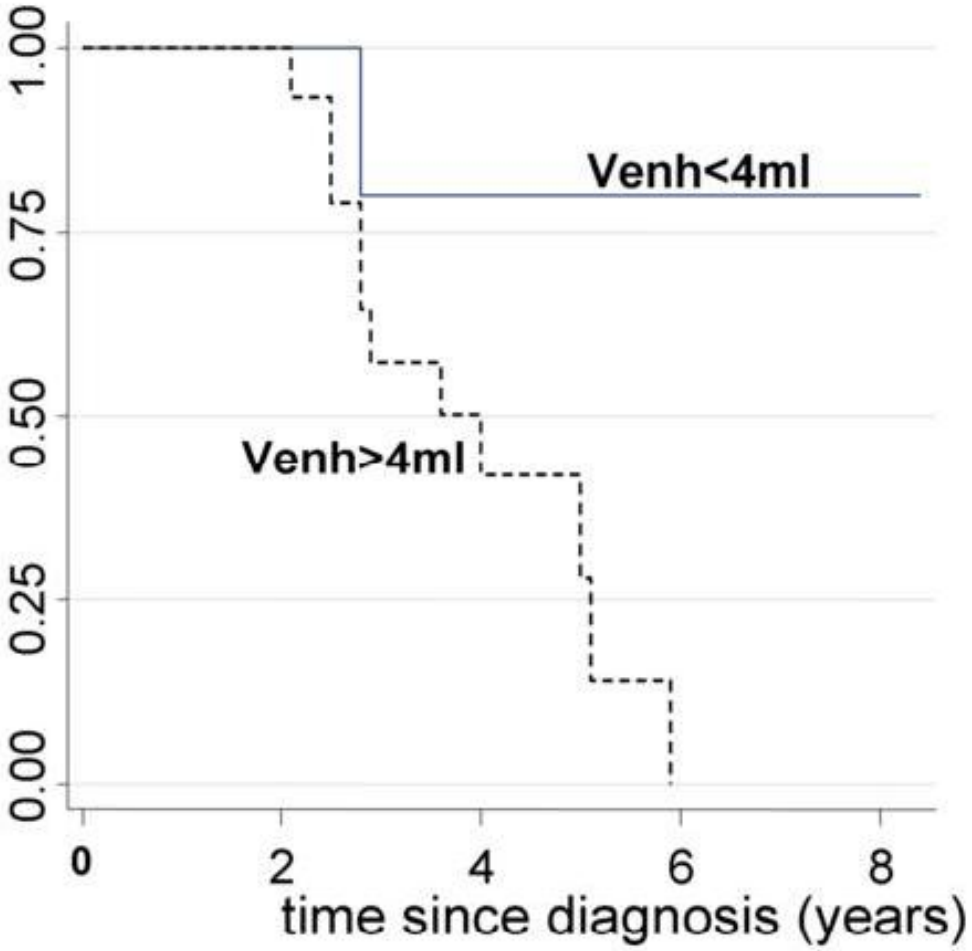


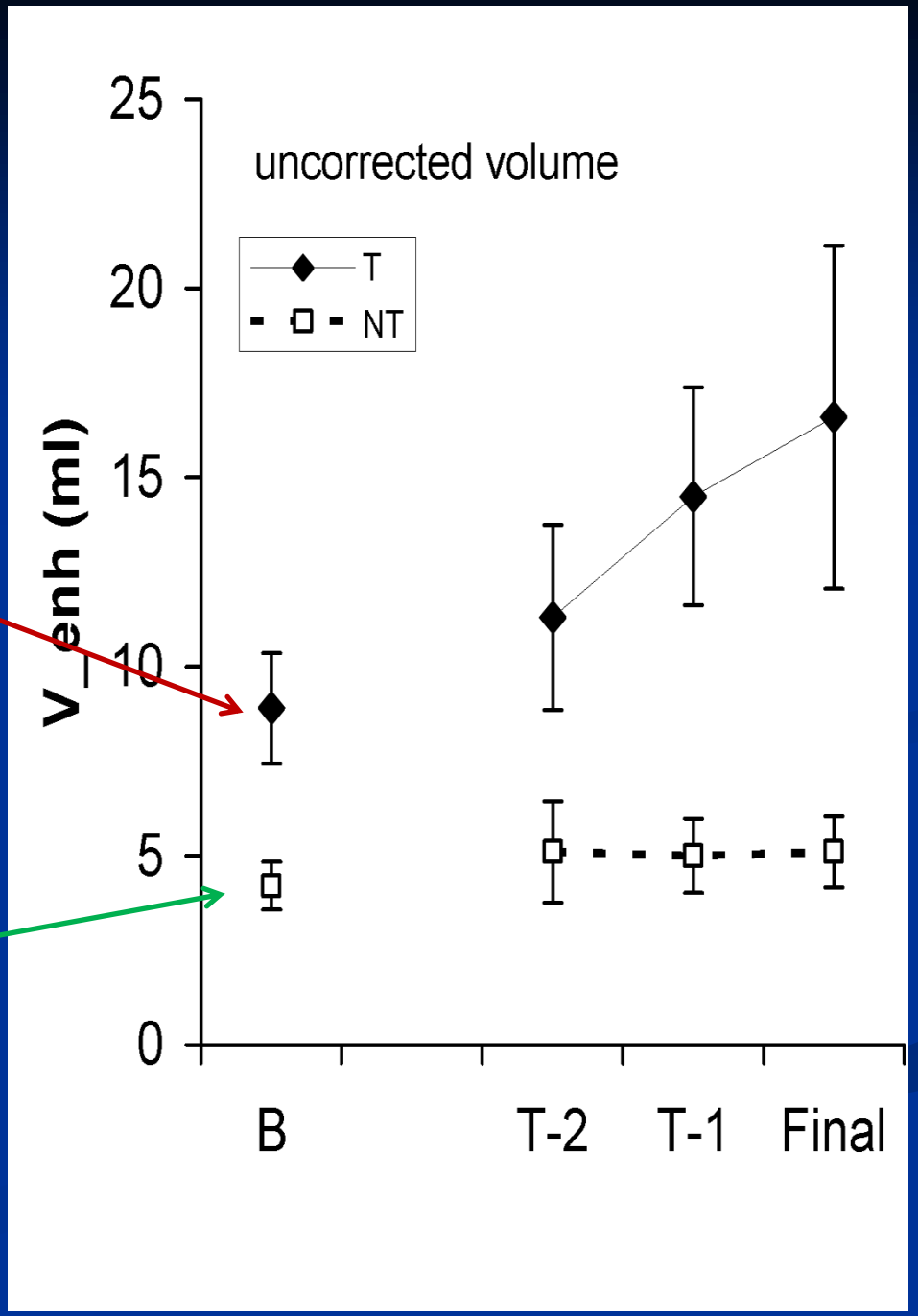
Measure size of RHS tail = volume of abnormal tissue



Kaplan-Meier survival plot, using uncorrected volume from baseline scan

p<0.039 at 5 years

- Transformers show progressive increase in enhancing volume
  - different from NT even at baseline
- Non transformers are stable
  - small SD; homogeneous group



Perfection is possible

A Perfect Quantitative MRI machine is one that, in making a measurement, contributes no significant extra variation to that which already exists from biological variation.

TABLE 1.3 qMRI Medals for Perfect Machines: A Proposal

Medal	Target Study	Criterion	Motivation
Bronze	Group comparison	ISD < 0.3 GSD	(a)
Silver	Multicentre study	BCSD < GSD	(b)
Gold	Serial study	ISD < 0.3 WSSD	(c)

Note: SD: standard deviation; BSD: biological SD; GSD: group SD; ISD: instrumental SD; ICSD: inter-centre SD; BCSD: between-centre SD; WSSD: within-subject SD.

[a] In a group comparison, within-group variation GSD^2 should dominate (i.e. machine variation ISD makes an insignificant contribution to total within-group variation).

[b] The effect of between-centre variation (BCSD) should be less than within-group variation.

[c] In a serial study, total within-subject variation $WSSD^2$ should dominate (i.e. machine variation ISD makes an insignificant contribution to total within-subject variation).

Normal range depends on repeatability

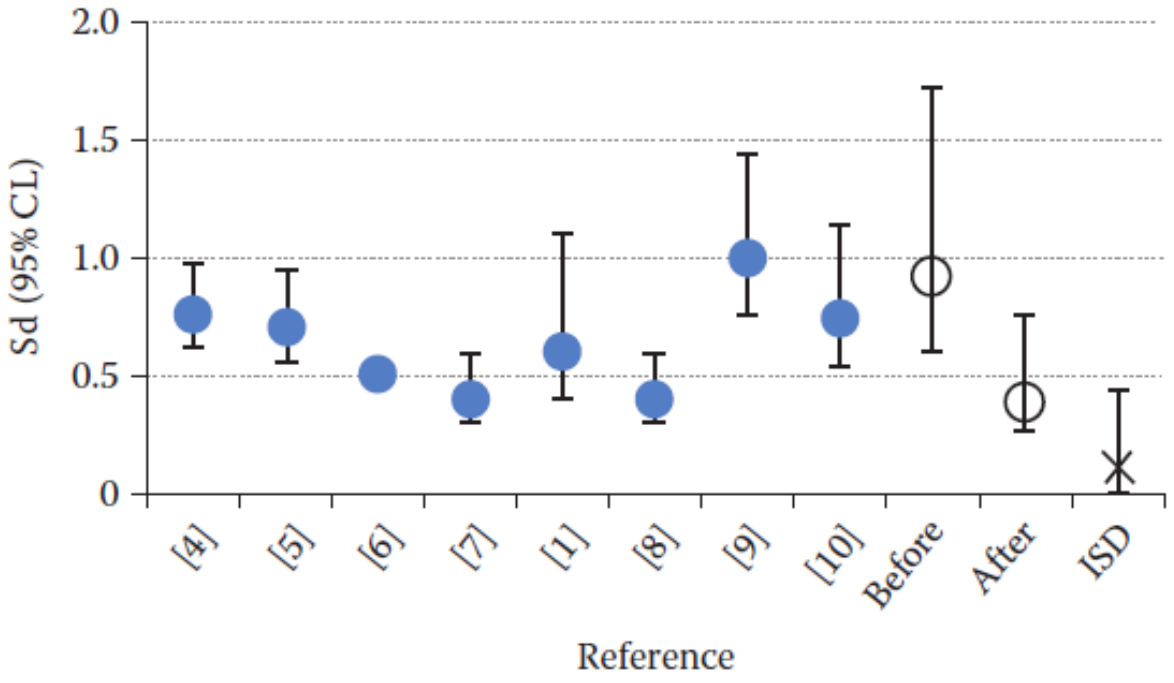


FIGURE 3.8 Normal variation for white matter MTR, and influence of ISD. Blue circles are published values of SD (units for MTR are pu; mean was 38–40 pu) from eight centres; error bars show uncertainty in sd estimate (Equation 3.2). *Before* is authors' first value, almost the highest value of nine centres. After solving a scanner instability problem (Figure [stability] in Chapter 2), ISD was low (≃0.2 pu) and the re-measured normal range (*after)* dropped to the lowest value of nine centres. (Adapted from

An invisible problem

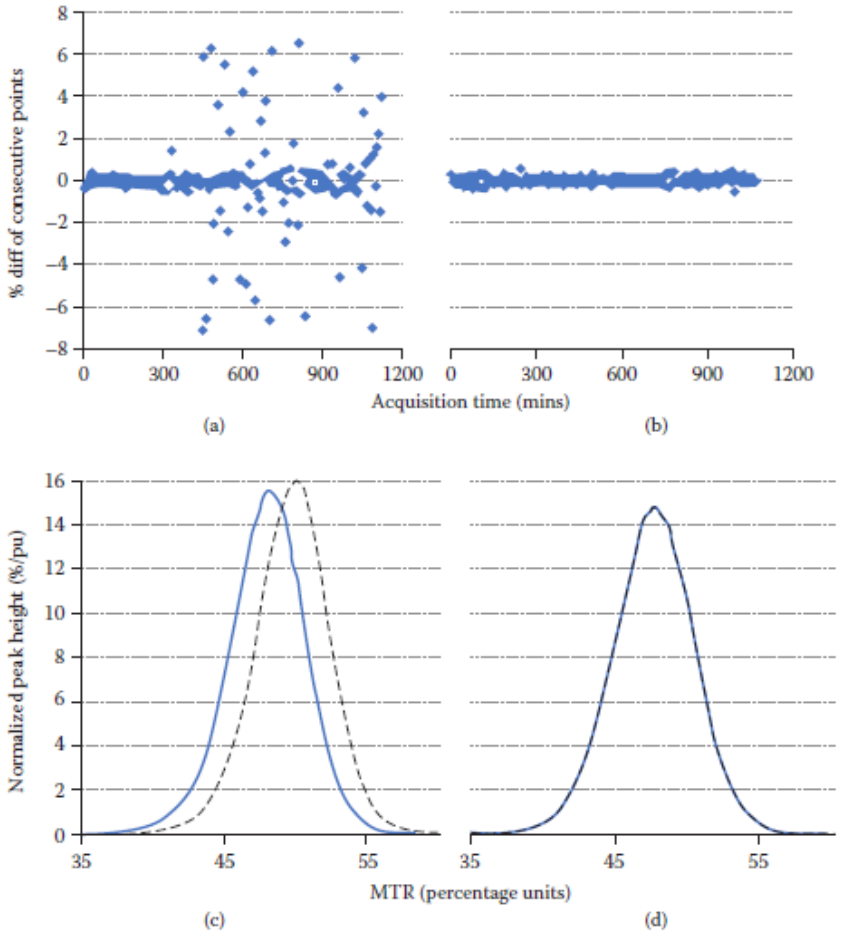


FIGURE 2.8 Unsuspected scanner instability – an invisible problem. MTR histograms showed a large within-subject variation (c). Repeated scanning of a phantom overnight showed large random variation (a). After changing transmitter boards, the scanner was stable (b) and MTR histograms were reproducible (d). (Data from NG Dowell, originally presented in (Haynes *et al.*, 2010) (From Haynes, B.I.,*et al.*, Measuring scan-rescan reliability in quantitative brain imaging reveals instability in an apparently healthy imager and improves statistical power in a clinical study. ISMRM annual scientific meeting, Stockholm, p. 2999, 2010.)

Between-centre difference can be eliminated

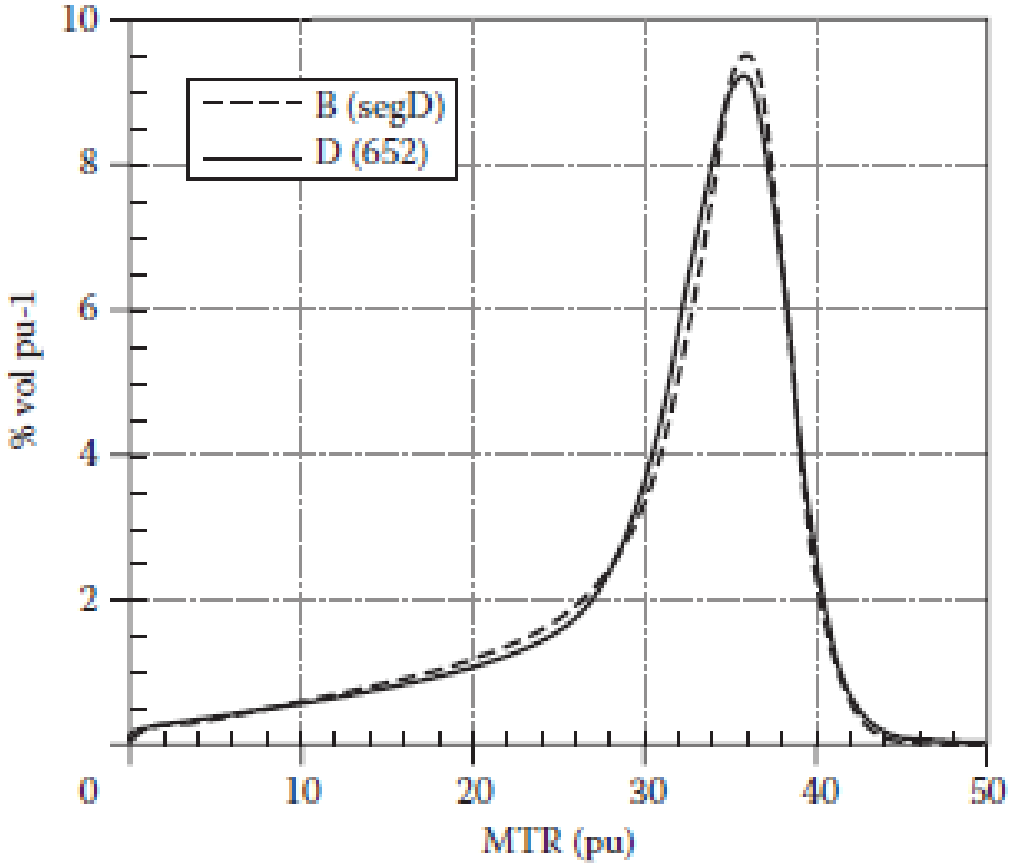


FIGURE 2.9 Matching MTR group histograms from two centres with 1.5T scanners from different manufacturers. By using body coil excitation and standardised histogram generation, inter-centre differences were eliminated. (From Tofts, P.S., *et al.*, *Magma*, 19(4), 209–222, 2006.)

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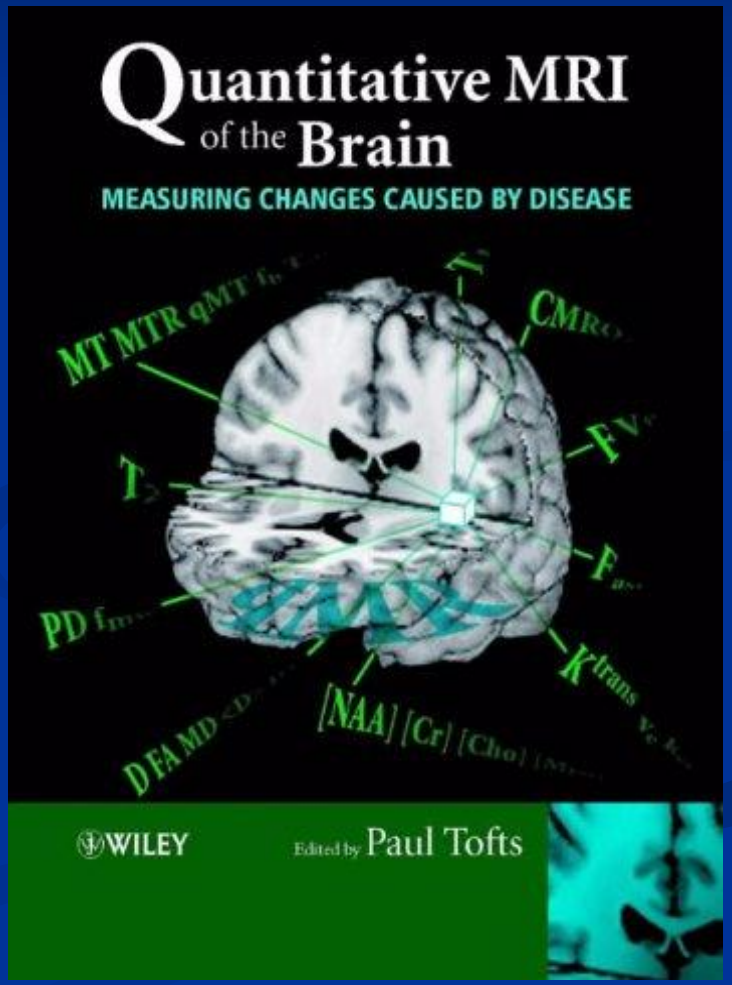

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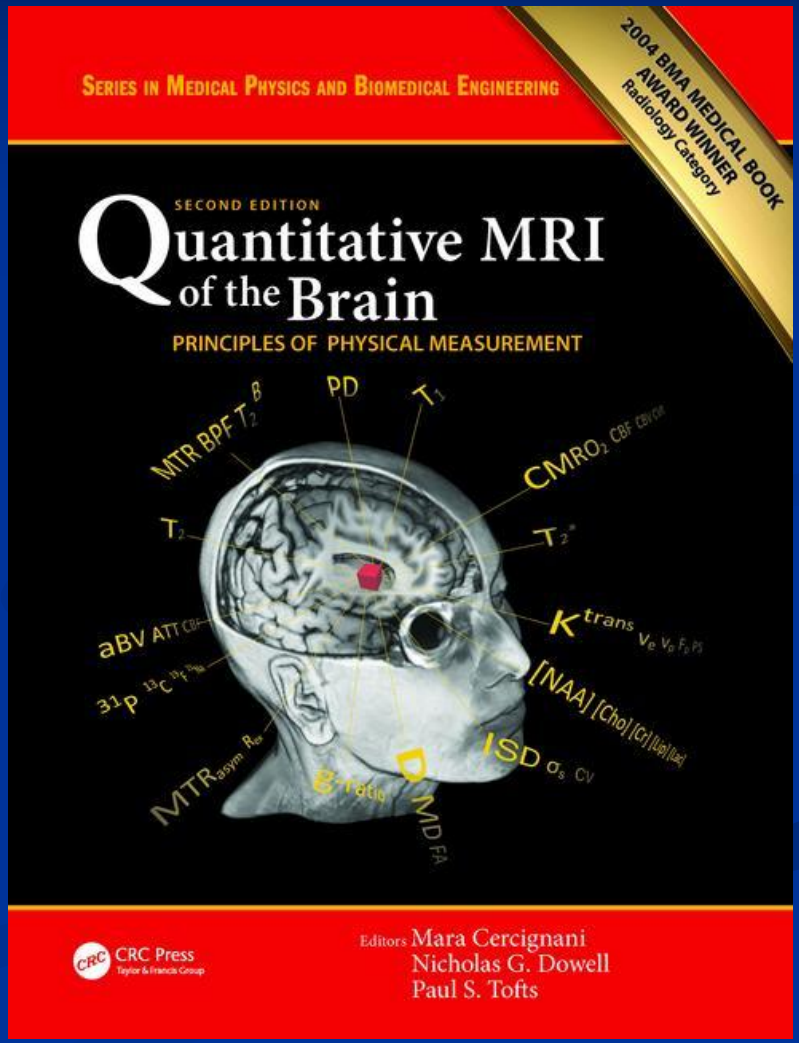

Why is qMR needed?

'Quantitative measurement of disease ... needs to become the future of radiology in particular, and medicine in general'

Robert Grossman MD

1. Measurement concepts - sources of variation

2. Specificity - new quantities

qMRI - 2

qMRI:

Scientific instrument

- following long tradition of measurement
- astronomy, physics, chemistry, electrical engineering…

Measure subtle 'invisible' changes

- diffuse or small
- In 'Normal-Appearing' brain tissue

Measurements by physicists

qMR – the future

qMR is becoming a turn-key application

Happy Snappy MRI Camera
transforming into
Scientific Instrument

We are witnessing
paradigm shift
technological revolution