Introduction: what do we mean by Quantitative MRI?

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Overview

1. Quantification: the word
2. Paradigm shift
3. Measurement
4. Sensitivity & reproducibility
5. Sensitivity & biology
6. Specificity & biology
7. Tissue parameters
8. Accuracy
9. Ideal biomarker
10. More..

This talk is on: http://qmri.org

1. Quantification: the words

Quantify means 'to measure'

Quantitative Analysis was first used in a chemical context, meaning 'analysis designed to determine the amounts or proportions of the components of a substance'

Quantity: the thing we are measuring e.g. volume, T_1, permeability

Quantification – the operation of quantifying

(also Quantitation – means the same)

Quantitate – is not a word! (Oxford English Dictionary)

- is a 'back formation' (Webster)

2. Paradigm shift

Paradigm = a way of viewing the world, a mindset

Paradigm shift: e.g. Newtonian physics to Quantum Physics

MR imager: '*happy snappy camera*', images reported by radiologists

To: *scientific instrument*, set up by physicists, images analysed by neuroscientists, psychologists

Traditions to guide us: astronomy, measurement science, school science

New concepts: accuracy = systematic error

Precision = random error (reproducibility)

Within-individual variation: instrumental, biological

(all a long way from traditional radiology) accessing the invisible

everyday examples of quantification

Body mass

Blood test

We expect: reliable, accurate, reproducible, easy

We hope that instrumental variation « biological variation

3. three components of good quantification
could a quantity be useful?

Sensitivity: how small a biological change can be measured?

random error; precision

Specificity: what kind of biological change took place?

patients or histology

Accuracy: how close is the measurement to the true value?

systematic error

Need to: Understand the Process of Measurement

The Measurement Process

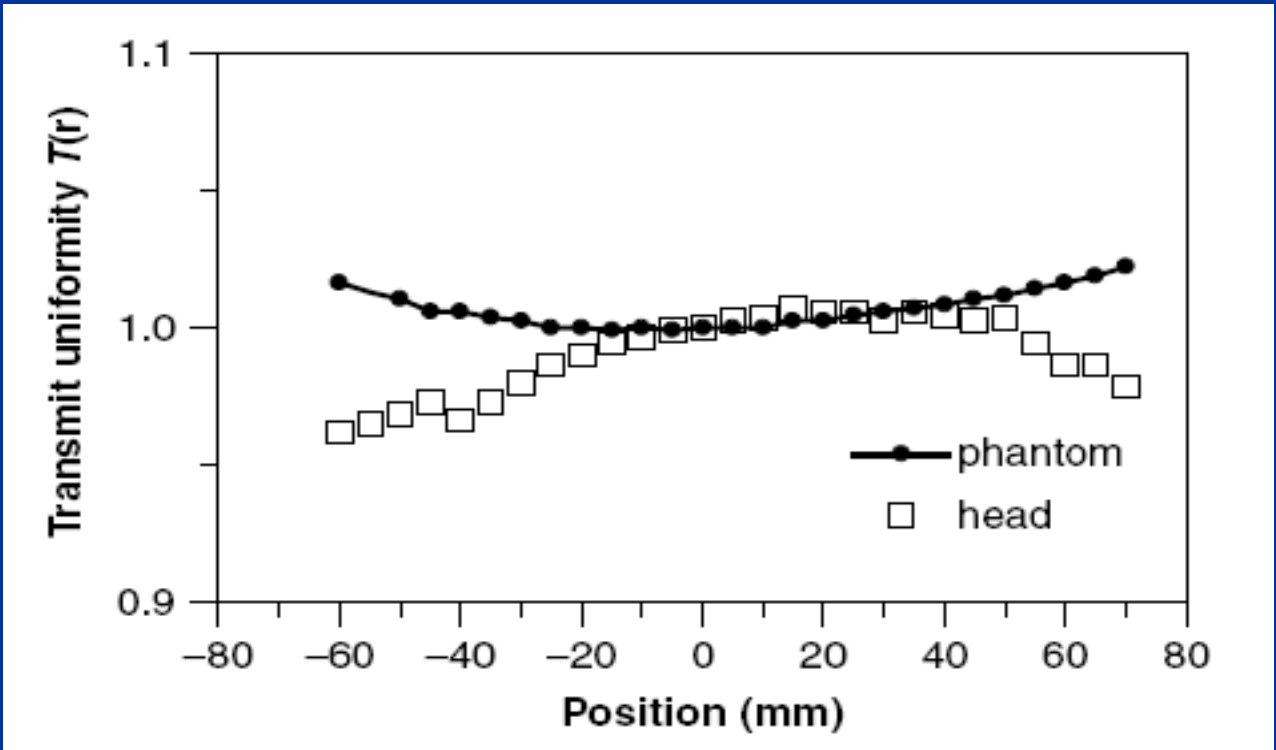
Data collection – the Scan

Hardware (coils), Pulse sequence, Subject positioning, Subject variation, any subjective elements of scanning, FA variation, receive variation, image noise

Image data analysis – the retrospective measurement

Software, subjective components, can be automated

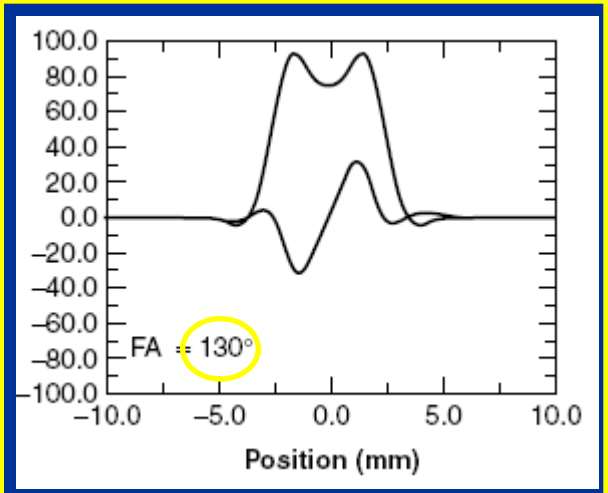
- 1.5T birdcage coil – transmit field
  - Transverse sensitivity
  - oil phantom – increase in sensitivity near bars of birdcage
  - Head – dielectric resonance gives ‘doming’



Barker 1998

It gets worse…….

- *Slice selection*
  - In 2D sequences
    - FA varies across slice profile
    - slice profile varies with position (if B_1 is nonuniform).
    - Poor slice profile can degrade quantification.
    - correction using knowledge of selective pulse and $B_1(r)$
  - $B_1(r)$ mapping is a growing subject
  - 3D sequences preferred
    - harder, broadly-selective RF pulse.



Selective pulse designed to give 5mm slice with 90^0

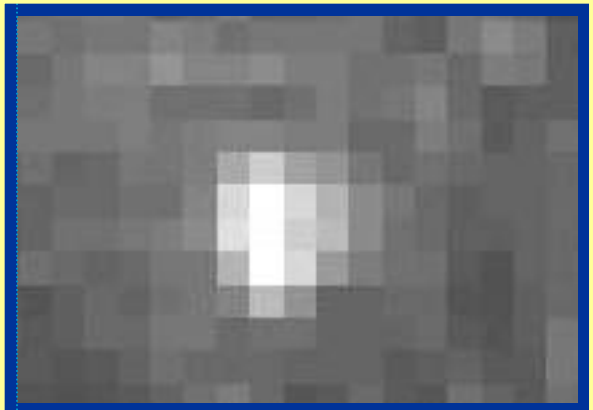
Parker 2001

image analysis includes….

- *ROI analysis*
- *Histogram analysis*
- *Voxel-based group mapping*
- *Statistical analysis*
  - *Negative results (FN → TP?)*
  - *False positive results*
  - *Correlation*
  - *Classification*

ROI analysis

- Partial volume effects (voxel too large or elongated) often prevent us measuring a pure tissue (e.g. grey matter).
  - Use small isotropic voxels where possible (compromise with SNR).



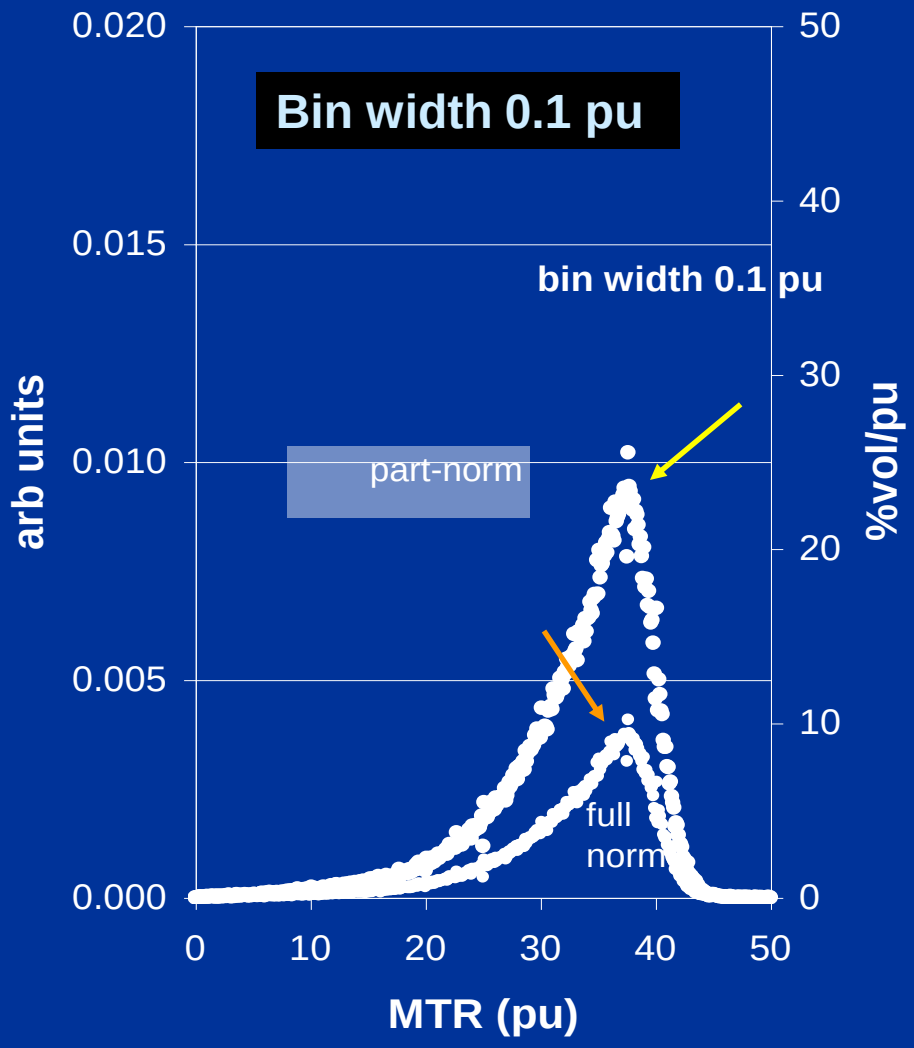
Small MS lesion.

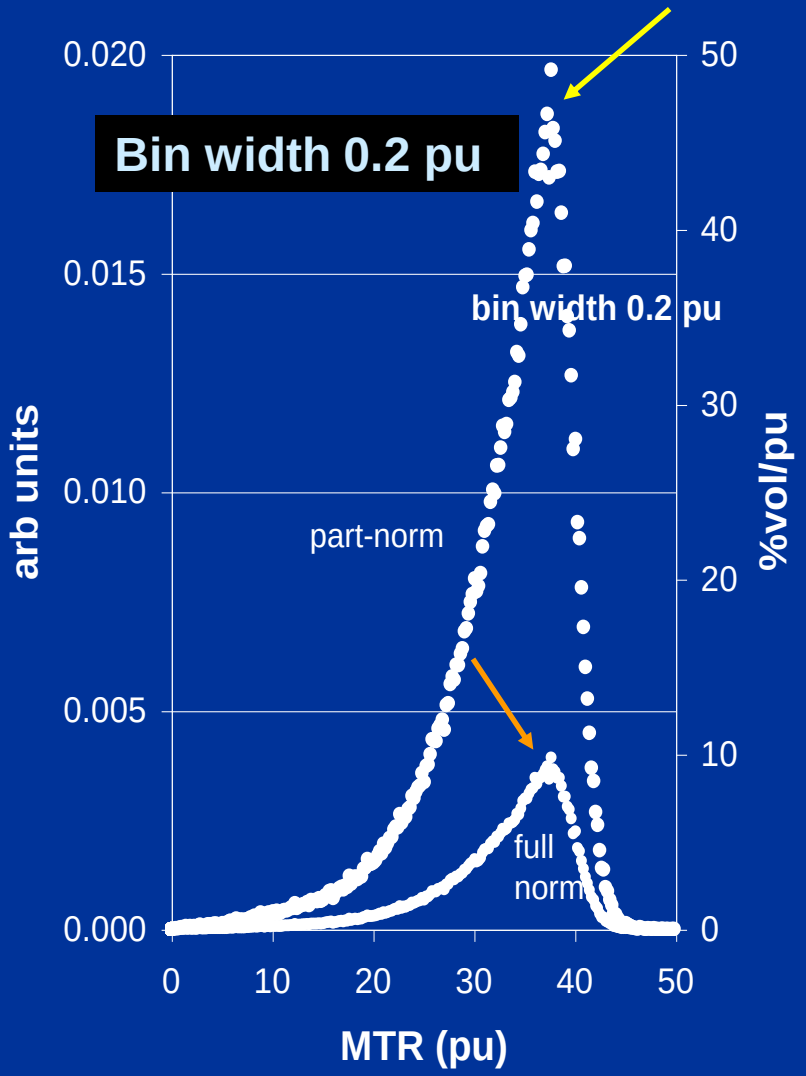
mean intensity?

size?

Histogram normalisation – multicentre comparisons

Full-norm PH=10%vol/pu; fwhm≈10pu; area under histogram =100%vol





4. Sensitivity needs reproducibility

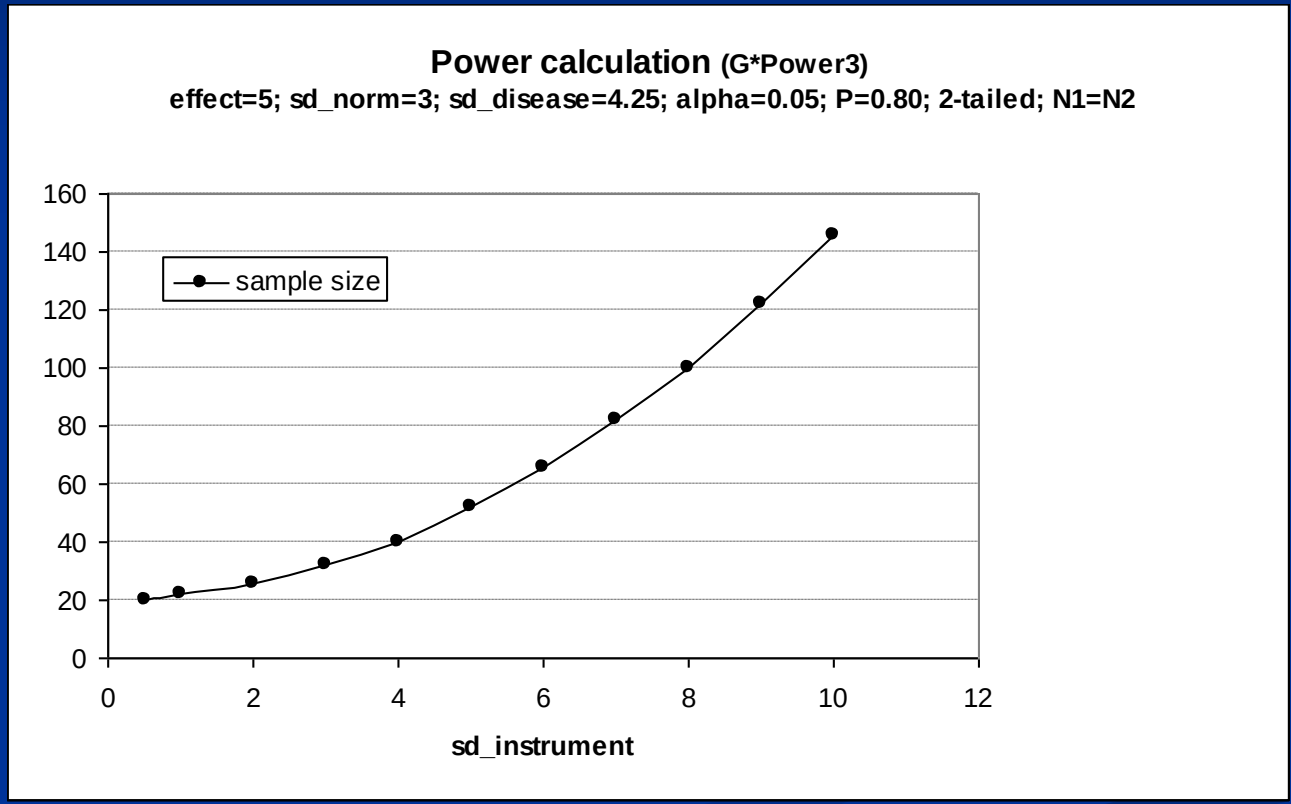
- We want instrumental sd ISD << biological variation
  - cross-sectional study :ISD << (normal) group variation
  - serial study: ISD << within-subject variation - harder
- Measure ISD by repeated imaging of normals (healthy volunteers)
  - Bland-Altman analysis: look at SD of difference of repeats
- Many clinical studies are limited in power by the ISD
  - See poster #2999 by Rebecca Haynes

Cross-sectional study

effect of ISD on sample size; the perfect instrument

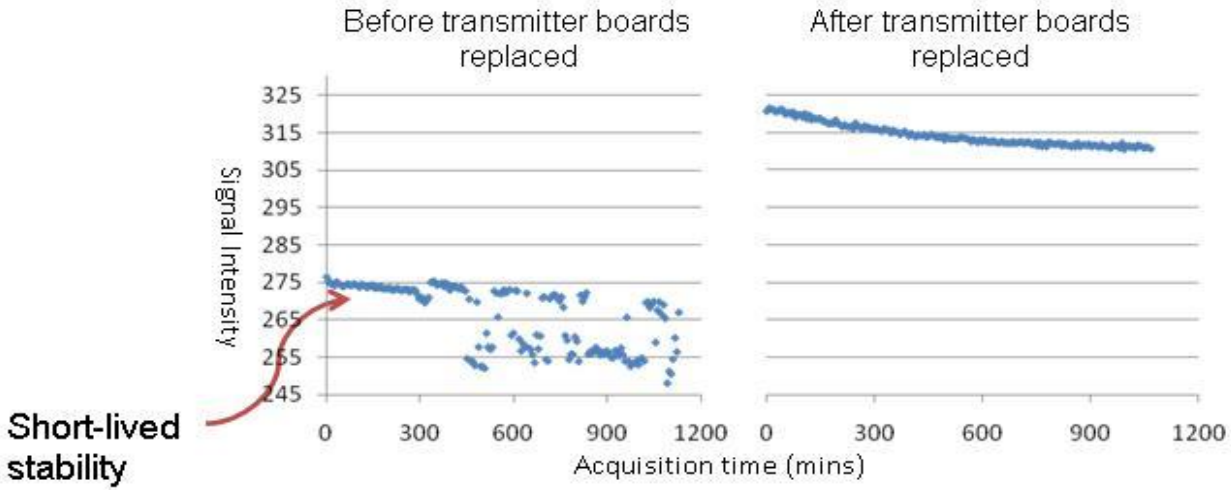
- Normal tissue value = 100
- sd_normal = 3
- disease effect = 5
- *perfect instrument**:
  sd << sd_normal
  sd << 3

- Serial study:
- ***perfect instrument ****
  sd << sd_within subject
  sd << 1

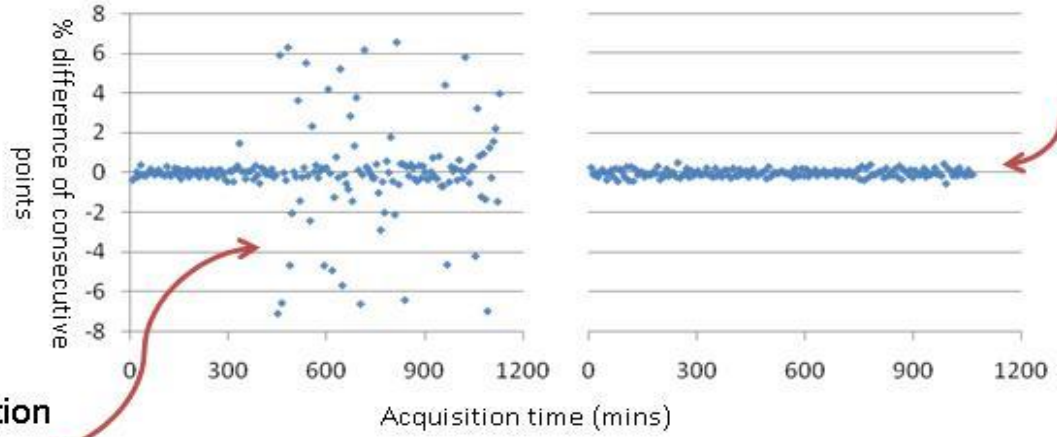


** An instrument which is so precise that it does not introduce any significant variation to the existing biological variation*

Variation in Phantom Signal Intensity



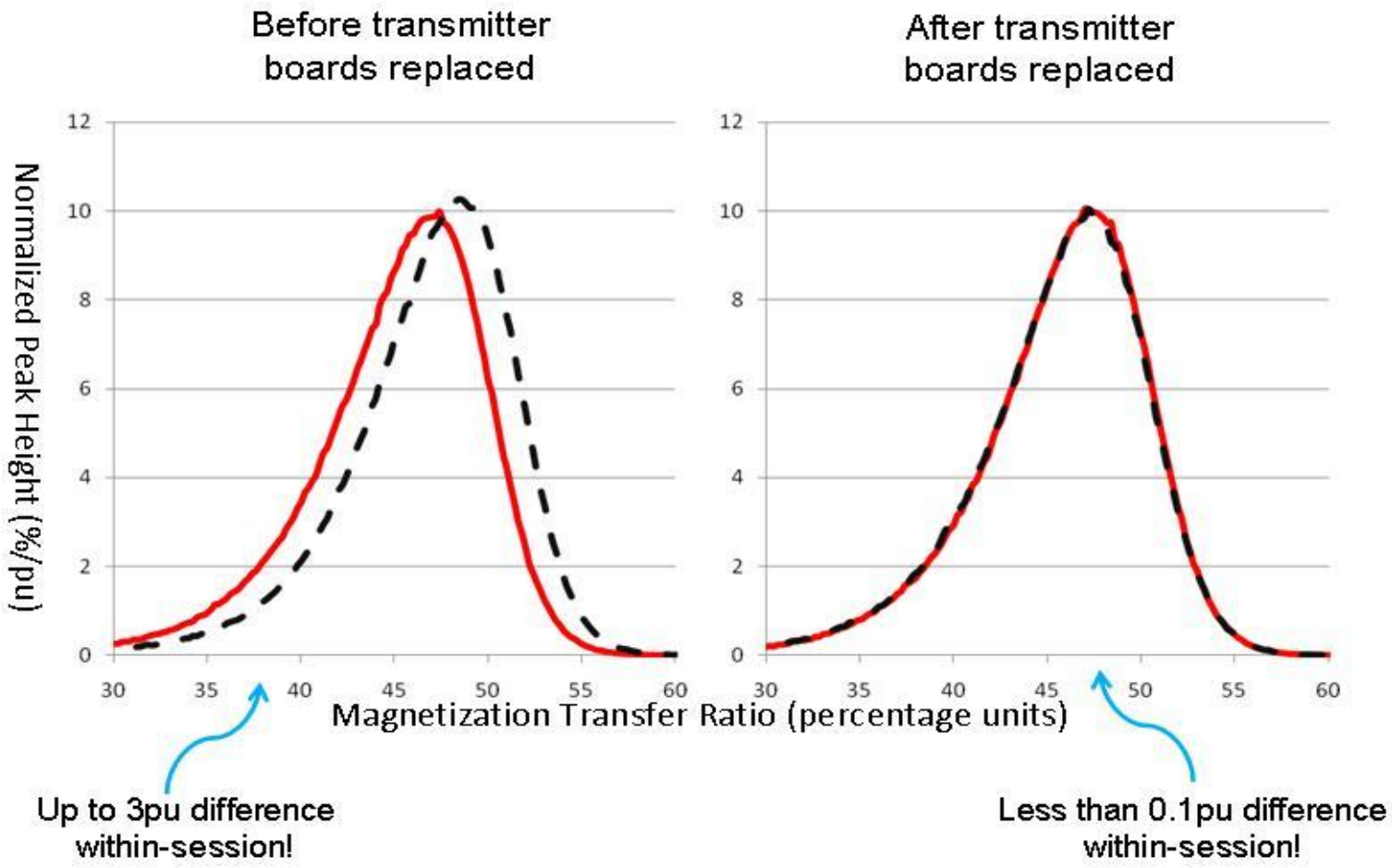
Short-lived stability



Less than 0.5% variation (SD <0.2%)

Up to 8% variation (SD >2.1%)

Whole-Brain MTR Histograms



5. Sensitivity to biology

- A technique could be perfectly reproducible, yet completely insensitive to biological change (caused by for example disease).
- Thus after good reproducibility has been shown (often in healthy volunteers), sensitivity to biological change should be demonstrated. E.g. by:
- measuring *patients* in which a particular change is already known (e.g. reduction in renal function) or
- *Histo-pathological* studies (e.g. reduction in myelin in PM MS brain tissue samples seen with MTR) or
- in *healthy volunteers* where a particular change can ethically be brought about (e.g. increase in lactic acid concentration in muscle after application of a tourniquet).

Quantitative MT in Multiple Sclerosis

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

Quantitative Magnetisation Transfer (qMT) measures bound proton fraction f_b
In brain. most bound protons are in myelin
In MS, loss of myelin (demyelination)
Reduction seen in lesions (as expected) and
Also *sensitive* enough to see in Normal Appearing White Matter

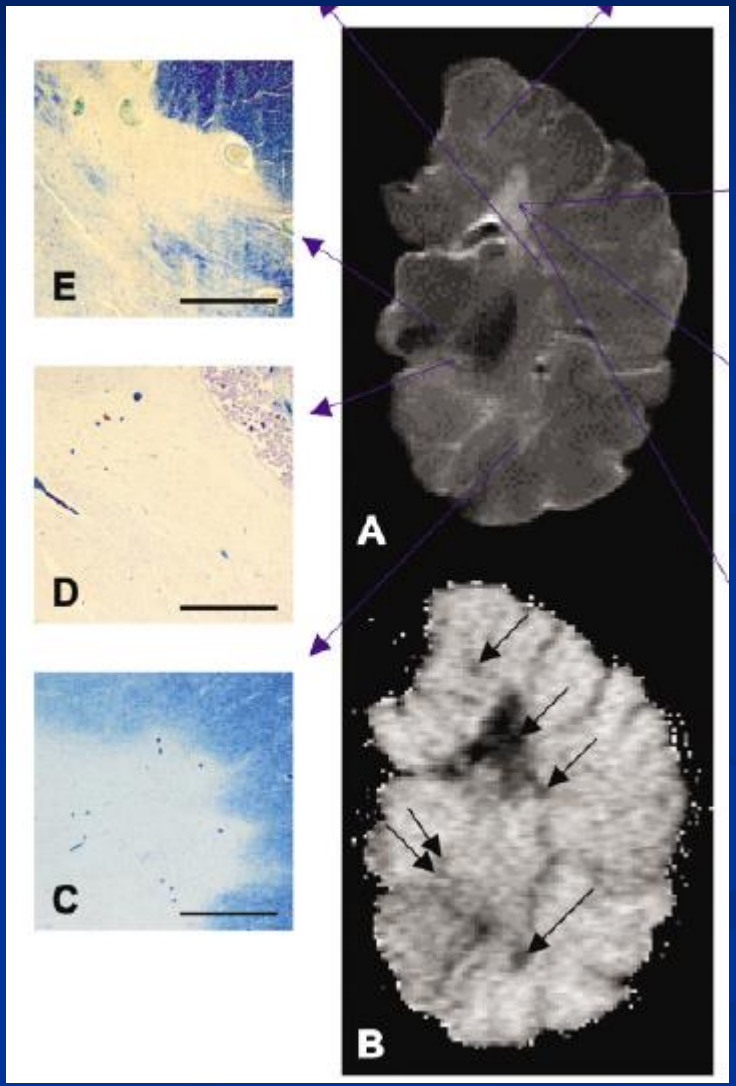
Davies et al Mult Scler 2004; 10:607

histopathology

Luxol Fast Blue stain shows myelin

areas with low MTR show less blue = low myelin concentration

Myelin concentration correlates with MTR
(r=-0.84 from myelin transmission value)



T_2w image of brain slice

MTR map of brain slice; dark areas indicate demyelination

6. Specificity and biology

- *Specificity* is the ability to distinguish between several kinds of biological abnormality that may be present (e.g. In brain, oedema vs. demyelination)
- Sometimes this is an important reason for using a particular quantity
- E.g. When monitoring response of tumour to treatment,
  - Size is traditional measure (but cannot tell if tumour is alive or not)
  - Signal enhancement after Gd injection gives more idea (but qualitative; also depends on T_1 of tumour)
  - K^{trans} has a known dependence on blood perfusion and capillary wall permeability, and better indicates the tumour biology
  - Spectroscopy often very specific (but not reproducible or precise)
- Often hard to establish specificity for in-vivo studies:
  - Specificity is desirable but not always achievable

7. Tissue parameters

Principle quantities that are candidates for quantitative biomarkers are:

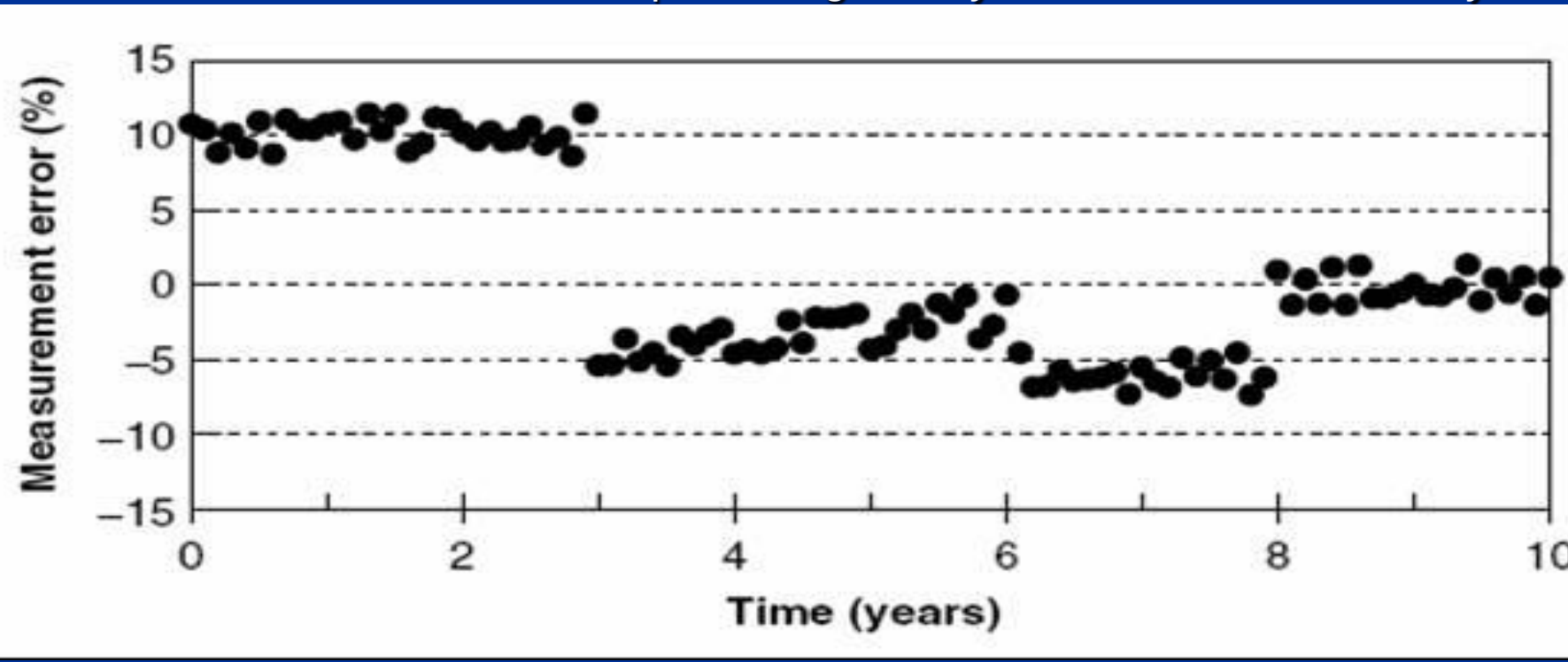
- Proton Density (PD) (gives water content)
- longitudinal relaxation time T_1
- transverse relaxation time T_2
- diffusion and its tensor
- magnetisation transfer: ratio (MTR) and 'quantitative MT'
- spectroscopy (gives metabolite concentrations)
- dynamic T_1-weighted MRI (measure transfer constant K^{trans} from uptake of contrast agent, particularly in tumours)
- dynamic $T_2^{(*)}$-weighted MRI (for blood flow and volume),
- blood perfusion (flow) using Arterial Spin Labelling (ASL).

Image analysis techniques include volume, histograms and texture (applied to any of the above).

8. Accuracy

- Accuracy (closeness to the truth) is often helpful:
  - Establishes credibility of the measure
  - Accuracy sometimes not vital
    - small systematic error can often be tolerated (in a single centre – short study), but...
  - Systematic errors are not usually stable
  - Comparison of studies, and multicentre studies are confounded by variable systematic error
- Measurement of accuracy:
  - Quality Assurance using phantoms (truth is known)
  - Humans good to establish accuracy by comparison with other studies
  - (Humans also good for stability)

- does systematic error matter?
  - In short-term single-centre study – NO
  - In multi-centre studies – YES
  - In long studies – PROBABLY
    - systematic error (if present, and not understood) can vary with centre and with time. BEWARE UPGRADES
    - Fictitious example: changes in systematic error wreck study



- Normal Controls vs phantoms (test objects)

	control	phantom
Stability over time	Good	Geometric good; **others poor (decay)**
Stable temperature?	Very good	**Often ±2°C (≈5%)**
realistic?	yes (but no pathology)	**no**
Truth known?	**No**	Yes
convenient?	**No**	Yes

- Use both, according to the MR quantity and purpose

- Phantoms exist for many MR quantities
  - but not all – use normal controls
  - Volume
    - easy – stable, well-defined geometric objects
    - Acrylic (perspex, plexiglass) and water
  - T_1 T_2
    - doped agarose gels - stability?
    - Ni T_1 is temperature independent
  - Diffusion
    - ADC: alkanes (although T_1 T_2 too long); iced water
    - DTI – hard. Need bundles of small fibres.
  - MT (MTR, qMT)
    - BSA (Bovine Serum Albumin) – stability?
  - Temperature
    - control and monitoring possible to 0.1^{o}C (Jackson ismrm 2006)

9. Ideal biomarker

- Imaging biomarker (as defined by FDA) is similar to a quantitative measure
- Interest is increasing rapidly in the use of surrogate markers as primary measures of the effectiveness of investigational drugs in definitive drug trials. Many such surrogate markers have been proposed as potential candidates for use in definitive effectiveness trials of agents to treat neurologic or psychiatric disease, but as of this date, there are no such markers that have been adequately "validated," that is, shown to predict the effect of the treatment on the clinical outcome of interest. Katz 2004 (US Food and Drug Administration FDA)

- For any new proposed quantitative measure (biomarker), ask these questions!
- 1. Is it reproducible in-vivo? (precision)
  - What is the smallest change that can reliably be detected?
- 2. Is it accurate in-vivo?
  - Is it robust in the face of flip angle error and being off-resonance?
- 3. Is it specific to a particular aspect of the biology?

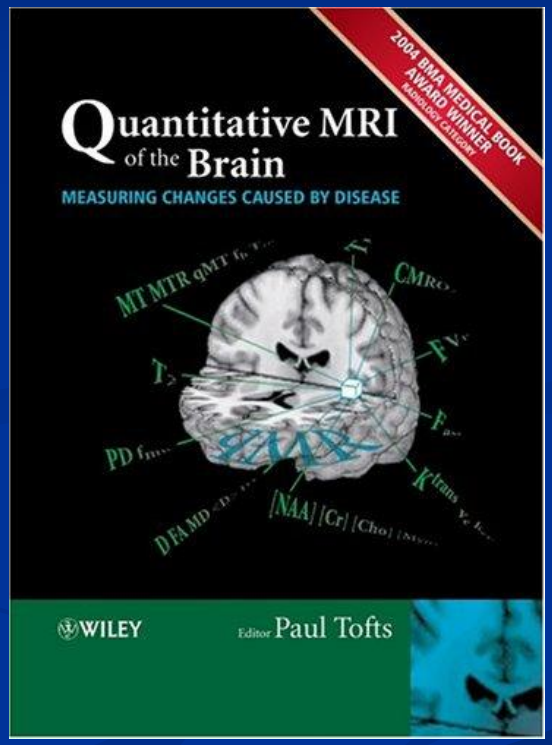
- Practise this today!

10. More....

This oral presentation is on
http://www.paul-tofts-phd.org.uk/talks/

The qMRI site http://qmri.org has a variety of information and is growing.

The book [1] gives a comprehensive tour of the issues, and surveys the principle qMR tissue parameters
(although the clinical applications are now a little dated).



1. Tofts PS. Quantitative MRI of the brain: measuring changes caused by disease. John Wiley, 2003.