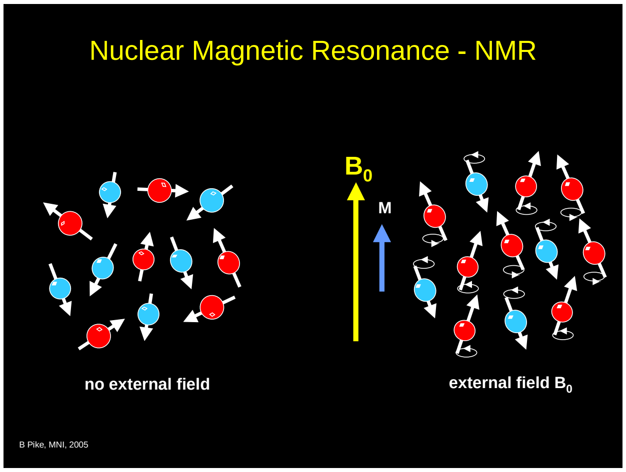
Using Brain Structure to Understand Brain Function

Quantitative methods in structural MRI

- **Measurement techniques**
- **Imaging techniques - quantitative imaging**

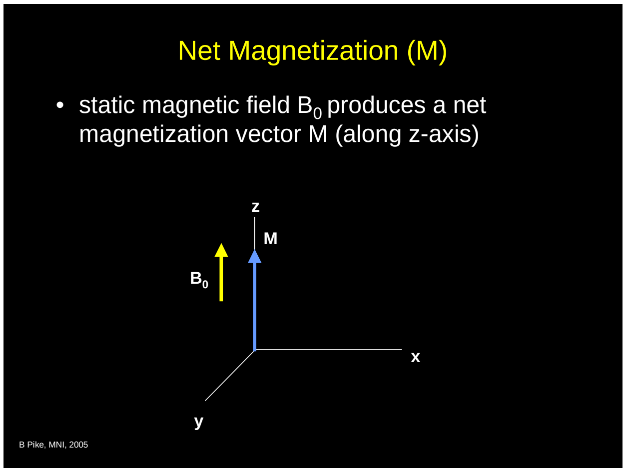
Using Brain Structure to Understand Brain Function

- **Review: MR parameters**
  - **Image contrast**
- **Measurement Techniques**
  - **Planimetry**
  - **Parcellation**: Regions of Interest >> Volumetry
  - **Segmentation** - Tissue classification, Voxel-based analysis, Nonlinear registration
- **Quantitative Imaging Techniques**
  Physiology/Tissue Integrity
  - Magnetization Transfer
  - T2 relaxometry
  - Diffusion Tensor Imaging
  - Magnetic Resonance Spectroscopy



Nuclear Magnetic Resonance - NMR

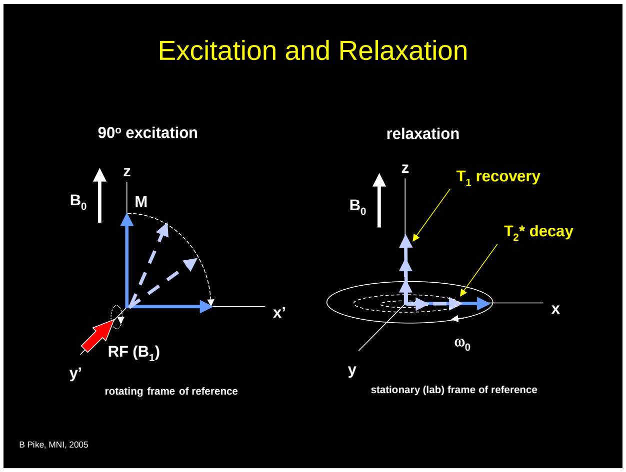
B Pike, MNI, 2005



Net Magnetization (M)

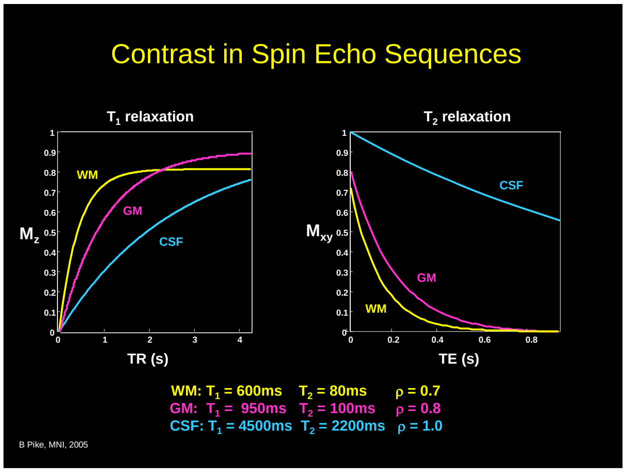
- static magnetic field B_0 produces a net magnetization vector M (along z-axis)

B Pike, MNI, 2005



Excitation and Relaxation

B Pike, MNI, 2005



Contrast in Spin Echo Sequences

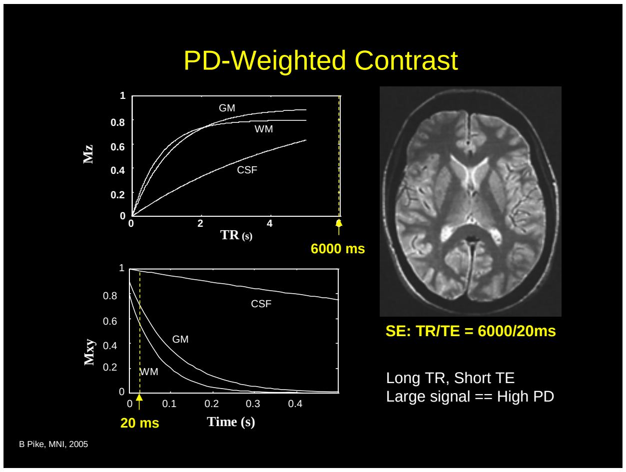
WM: T_1 = 600ms T_2 = 80ms ρ = 0.7
GM: T_1 = 950ms T_2 = 100ms ρ = 0.8
CSF: T_1 = 4500ms T_2 = 2200ms ρ = 1.0

B Pike, MNI, 2005

Contrast in Spin Echo Sequences

- PD, T_1, T_2
  - PD always present
  - T_1 recovery: minimized T_1 contrast with long TR
  - T_2 decay: minimized T_2 contrast with short TE
- PD-weighted: long TR, short TE
  - hyper-intense = high PD
- T_2-weighted: long TR, long TE
  - hyper-intense = long T_2
- T_1-weighted: short TR, short TE
  - hyper-intense = short T_1

B Pike, MNI, 2005

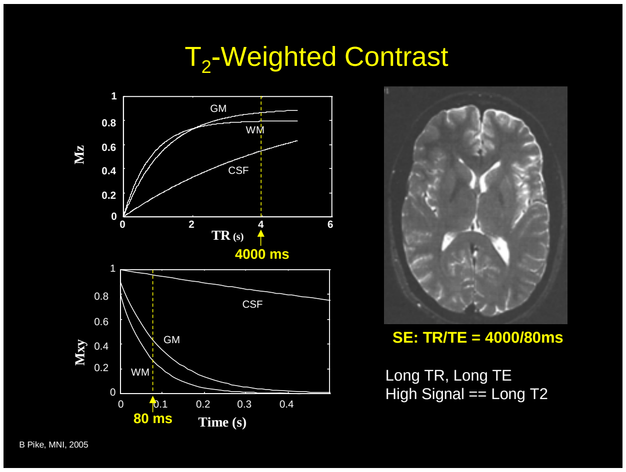


PD-Weighted Contrast

SE: TR/TE = 6000/20ms

Long TR, Short TE
Large signal == High PD

B Pike, MNI, 2005

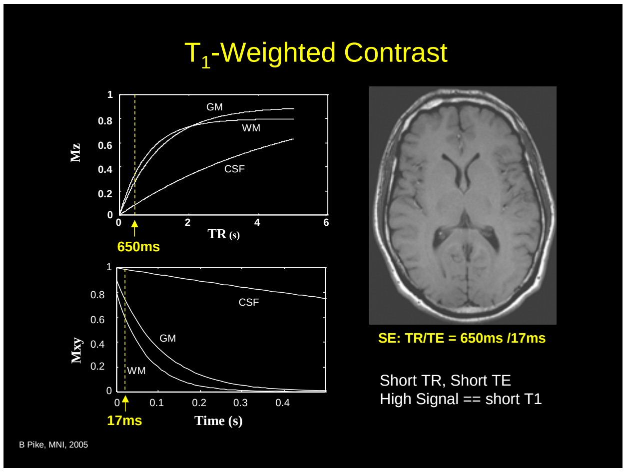


T_2-Weighted Contrast

SE: TR/TE = 4000/80ms

Long TR, Long TE
High Signal == Long T2

B Pike, MNI, 2005



T_1-Weighted Contrast

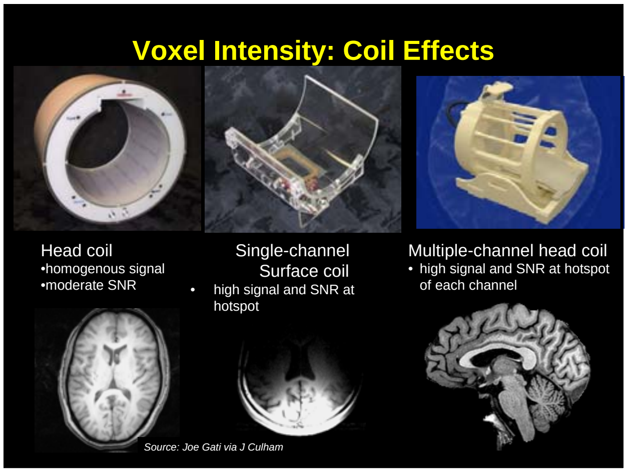
SE: TR/TE = 650ms /17ms

Short TR, Short TE
High Signal == short T1

B Pike, MNI, 2005

Voxel Intensity

1) MR parameters: Spin Density, T1, T2 relaxation
2) Type of imager, coil, presence of inhomogeneities
3) Susceptibility and other Artifacts



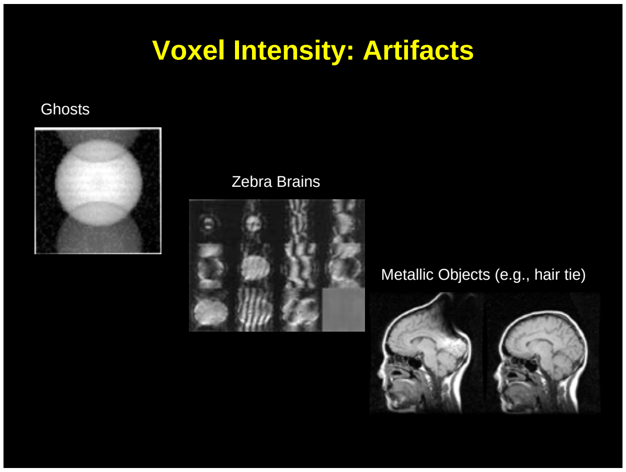
Voxel Intensity: Coil Effects

Head coil
- homogenous signal
- moderate SNR

Single-channel Surface coil
- high signal and SNR at hotspot

Multiple-channel head coil
- high signal and SNR at hotspot of each channel

Source: Joe Gati via J Culham

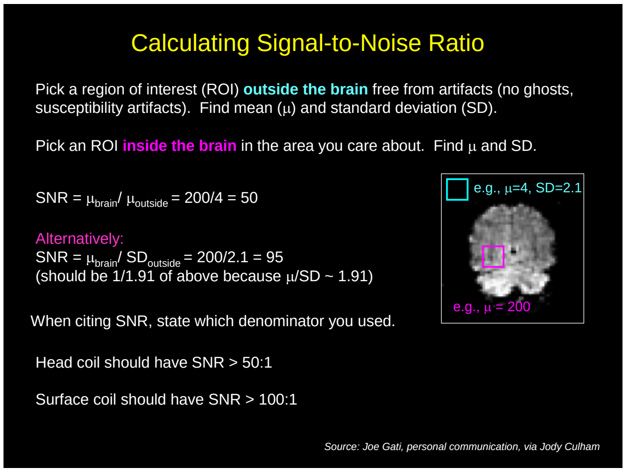


Voxel Intensity: Artifacts

Ghosts

Zebra Brains

Metallic Objects (e.g., hair tie)



Calculating Signal-to-Noise Ratio

Pick a region of interest (ROI) **outside the brain** free from artifacts (no ghosts, susceptibility artifacts). Find mean (μ) and standard deviation (SD).

Pick an ROI **inside the brain** in the area you care about. Find μ and SD.

$SNR = \mu_{brain} / \mu_{outside} = 200/4 = 50$

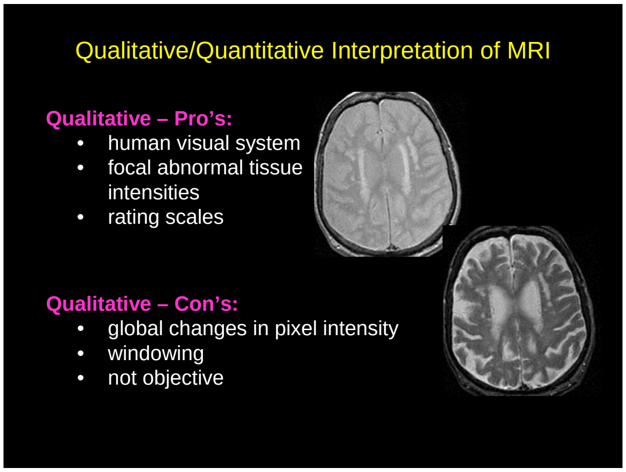
Alternatively:
$SNR = \mu_{brain} / SD_{outside} = 200/2.1 = 95$
(should be 1/1.91 of above because μ/SD ~ 1.91)

When citing SNR, state which denominator you used.

Head coil should have SNR > 50:1

Surface coil should have SNR > 100:1

Source: Joe Gati, personal communication, via Jody Culham



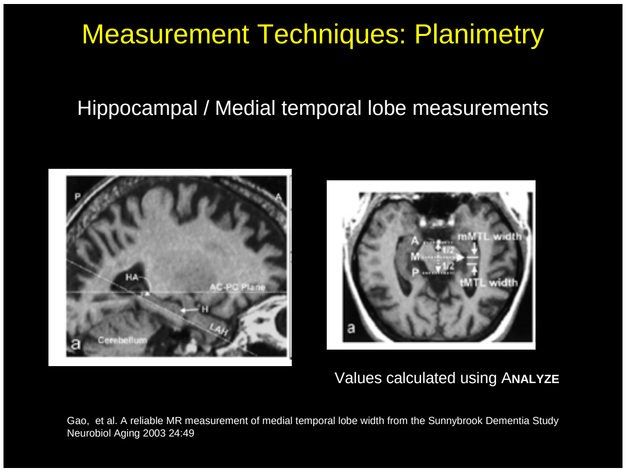
Qualitative/Quantitative Interpretation of MRI

Qualitative – Pro's:

- human visual system
- focal abnormal tissue intensities
- rating scales

Qualitative – Con's:

- global changes in pixel intensity
- windowing
- not objective

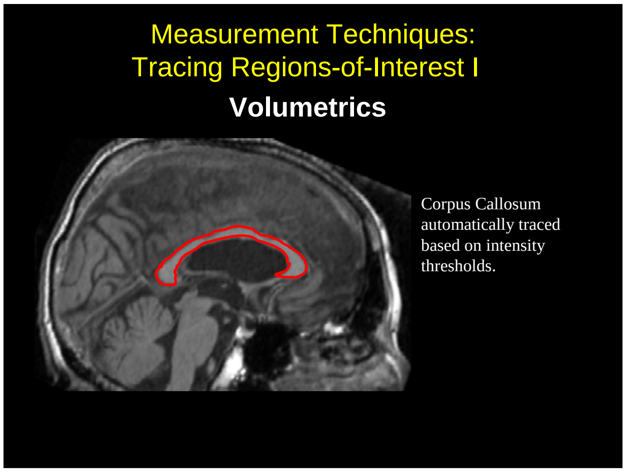


Measurement Techniques: Planimetry

Hippocampal / Medial temporal lobe measurements

Values calculated using ANALYZE

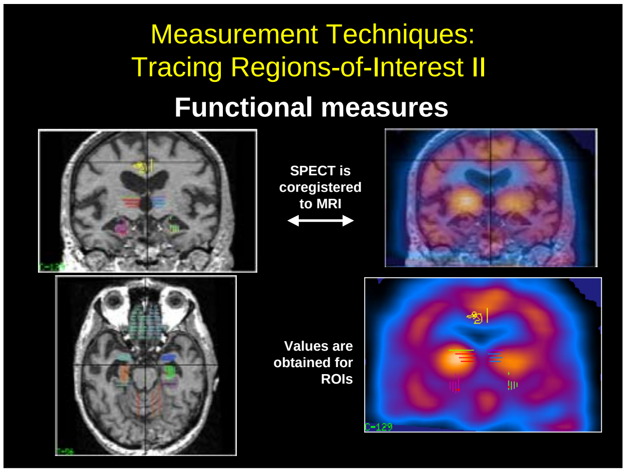
Gao, et al. A reliable MR measurement of medial temporal lobe width from the Sunnybrook Dementia Study Neurobiol Aging 2003 24:49



Measurement Techniques: Tracing Regions-of-Interest I

Volumetrics

Corpus Callosum automatically traced based on intensity thresholds.



Measurement Techniques: Tracing Regions-of-Interest II

Functional measures

SPECT is coregistered to MRI

Values are obtained for ROIs

Measurement Techniques: Tracing Regions-of-Interest III

Issues

Precision: Operator must be well-trained

But:
even the best operator can be misled by the image and trace the wrong thing - more on that with DTI

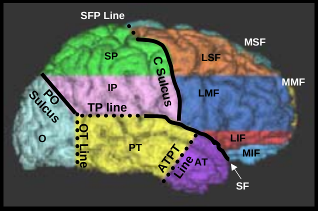
Reliability: Imperative to demonstrate
(e.g., Intra/Interclass correlations)

But:
It may take a long time, but you know exactly what you are measuring!

Measurement Techniques: Parcellation Semi-automatic

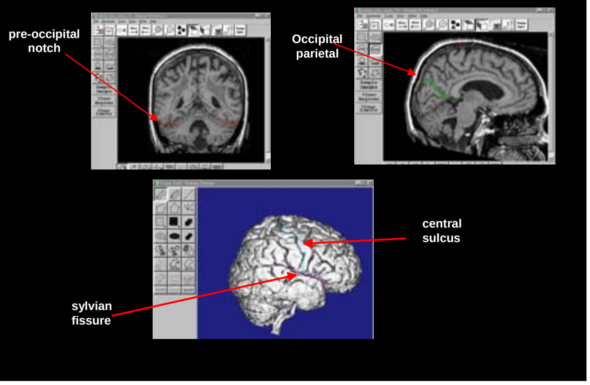
SABRE

Semi-Automated Brain Region Extraction
Dade, et al, 2004 Neuroimage



Regions defined on T1-weighted image that has been resliced into isotropic voxels, and reoriented in ACPC plane

Measurement Techniques: Parcellation Semi-automatic

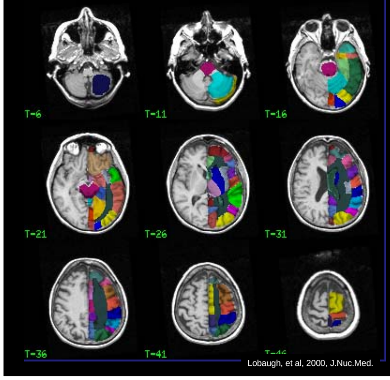


Measurement Techniques: Parcellation

Successful manual and semi-automatic parcellation /ROI protocols

- **NEED:** High inter- and intra-rater reliability
- **NEED:** Training and test sets of representative images
- Can take a long time
- “Reasonable” to high levels of precision

Measurement Techniques: Automatic Parcellation

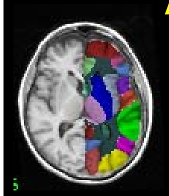


Lobaugh, et al, 2000, J.Nuc.Med.

Pro’s:
Easy - draw the ROI one time

Con’s:
Not subject-specific:
Anatomy may not precisely match the template

Measurement Techniques: Automatic Parcellation

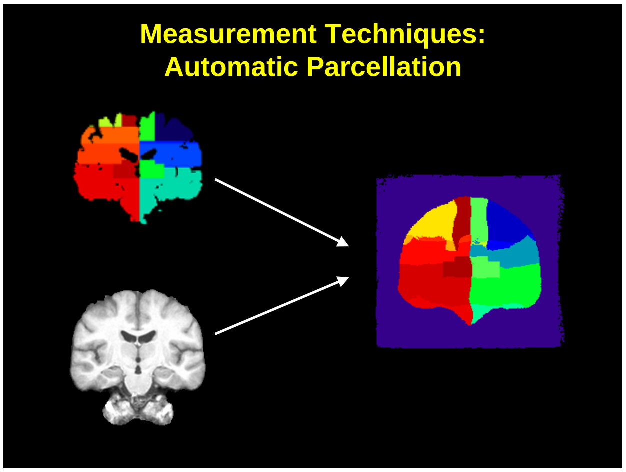


“Compromise”

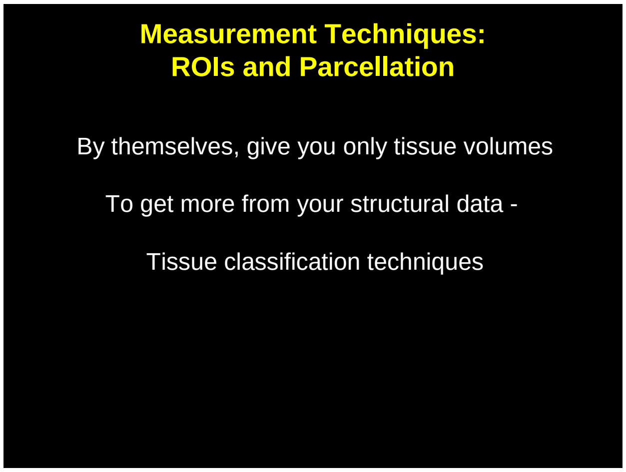
Make the subject fit the template

High-resolution nonlinear deformation to template.

Move template back to individual subject space.



Measurement Techniques: Automatic Parcellation

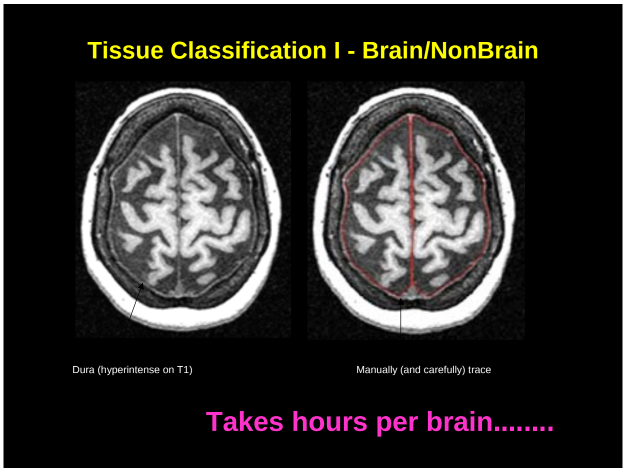


Measurement Techniques: ROIs and Parcellation

By themselves, give you only tissue volumes

To get more from your structural data -

Tissue classification techniques

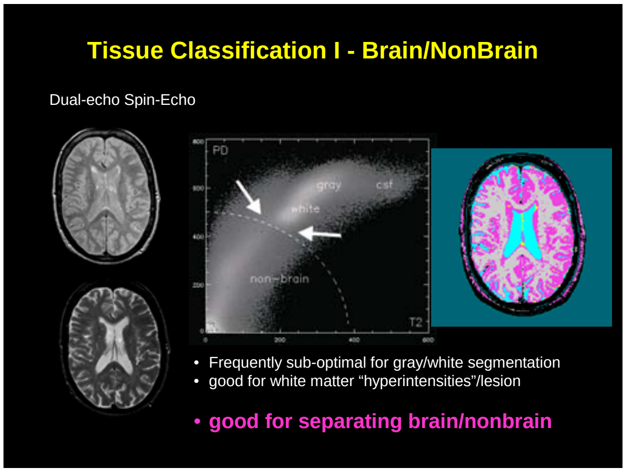


Tissue Classification I - Brain/NonBrain

Dura (hyperintense on T1)

Manually (and carefully) trace

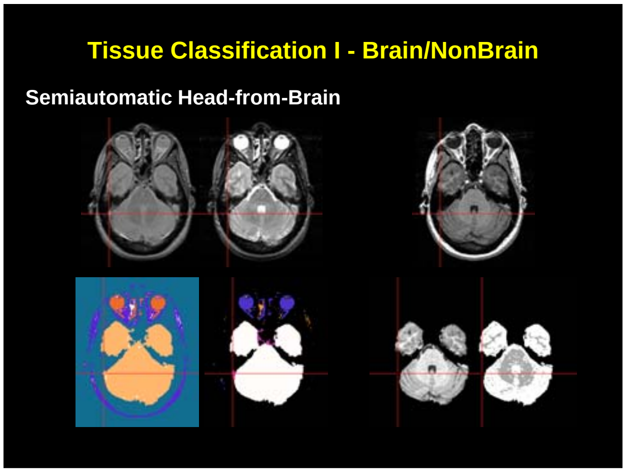
Takes hours per brain........



Tissue Classification I - Brain/NonBrain

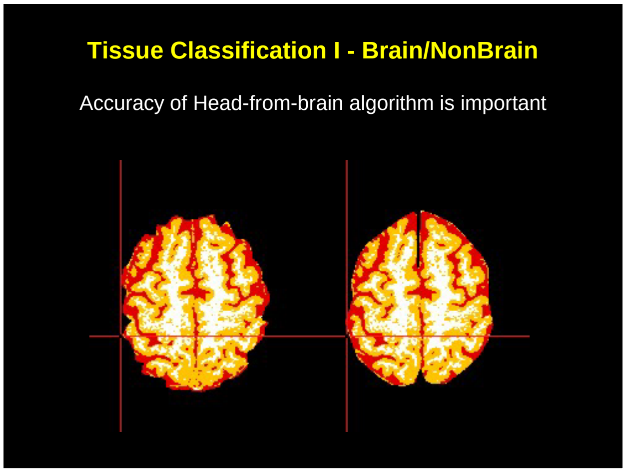
Dual-echo Spin-Echo

- Frequently sub-optimal for gray/white segmentation
- good for white matter “hyperintensities”/lesion
- **good for separating brain/nonbrain**



Tissue Classification I - Brain/NonBrain

Semiautomatic Head-from-Brain

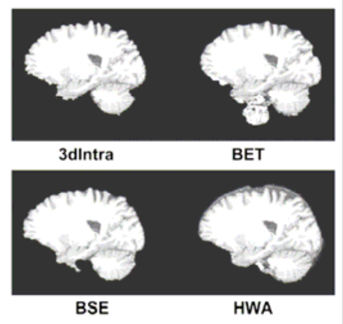


Tissue Classification I - Brain/NonBrain

Accuracy of Head-from-brain algorithm is important

Tissue Classification I - Brain/NonBrain

Accuracy of Head-from-brain algorithm is important



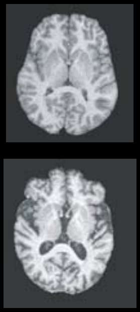
Different algorithms may be more appropriate for some images than others

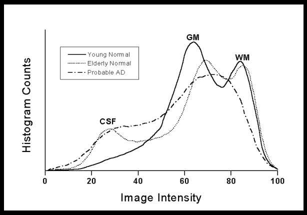
TEST them out !!!

Fenneme-Notestine et al.,
Human Brain Mapp 2006, 27:99

Tissue Classification II - GM-WM-CSF

T1-weighted SPGR



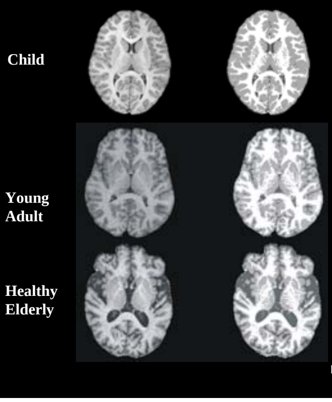


T1-weighted better for gray/white/CSF

Sub-optimal for white matter “hyperintensities”/lesion

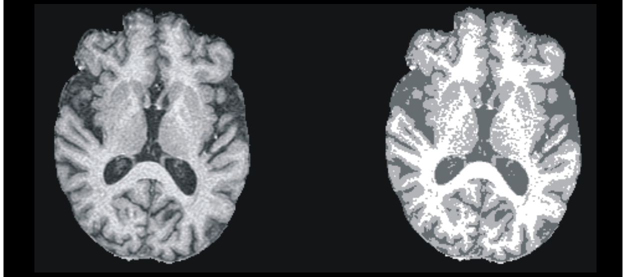
Kovacevic et al. Neuroimage,2002

Tissue Classification II - GM-WM-CSF



Kovacevic et al. Neuroimage,2002

Tissue Classification II - GM-WM-CSF

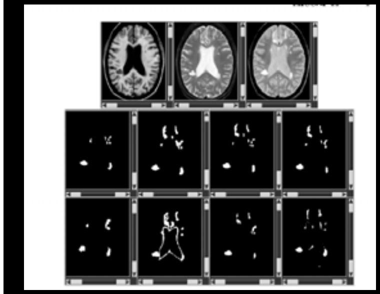


Healthy Elderly

Kovacevic et al. Neuroimage,2002

Tissue Classification III - T2 Hyperintensities

Inter-rater reliability is practically non-existent across institutions



The results of the automated method are compared with lesion delineations by human experts, showing a high total lesion load correlation.

When the degree of spatial correspondence between segmentations is taken into account, considerable disagreement is found, both between expert segmentations, and between expert and automatic measurements.

Van Leemput et al, IEEE Trans Med Imag 2001

from Zijdenbos, 98

Tissue Classification IV - Voxel-based

Allows direct comparisons of MR images

Requires image registration

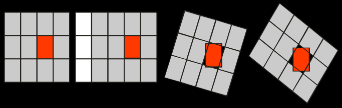
Image Registration

Moving an image from one space to another

Requires:

A transformation matrix -

How far does each voxel have to move?
Does it shift or rotate or change size or all of the above?



An interpolation scheme -

voxels do not always "move" into a space that is exactly the same size as the starting point

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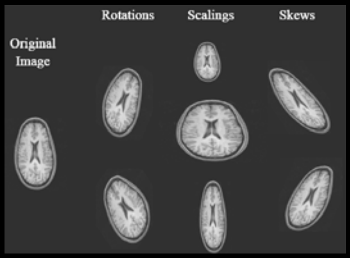
Image Registration

Affine transformation

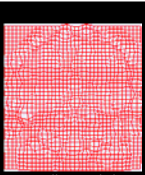


Source: Mark Jenkinson, 2005, ISMRM educational session

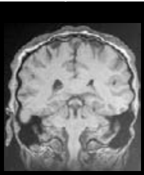
Nonlinear Deformations

To make this brain match

This template brain



Apply a nonlinear deformation
to the template



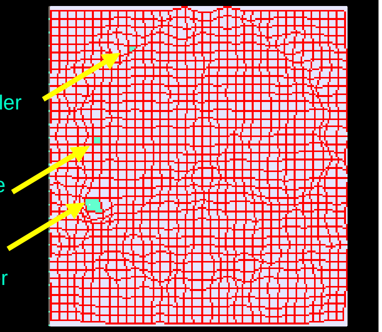
Fei Lu, WashStateU

Nonlinear Deformations

No longer a square grid

Some local regions are a different size from original -

Change in local volume



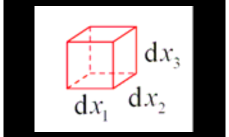
smaller

same

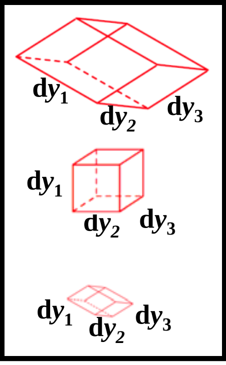
larger

Jacobian: a measure of relative volume change

x (original)



y (transformed)



Ratio of **dx/dy**

dx/dy > 1.0

dx/dy = 1.0

0 < dx/dy< 1.0

Jacobian: a measure of relative volume change

Ratio of **dx/dy**

>1.0

=1.0

<1.0

For any physically admissible deformation:

The volume of the deformed element must be positive: No matter how much you deform a solid, you can't make material disappear.

Therefore, all physically admissible displacement fields must satisfy *J>0.*

If a material is ***incompressible***, its volume remains constant. This requires *J=1*.

After A. F. Bower, BrownUniv

Jacobian: a measure of relative volume change

Ratio of **dx/dy**

>1.0

=1.0

<1.0

Interpreting the Jacobian:

All the shrinkages are in the range from 0 to 1.0;

All the expansions are free to be anything >1.0

So... frequently, jacobian results are log-transformed for analysis/display:

- **$\log(J>1.0) \Rightarrow > 0.0$**
- **$\log(J=1.0) \Rightarrow = 0.0$**
- **$\log(J<1.0) \Rightarrow < 0.0$**

Tissue Classification IV - Voxel-based

Allows direct comparisons of MR images

Within & across individuals:

Ashburner & Friston – Neuroimage, 2000

- Spatial transformation of image to template -
- Segment – Extract gray matter (**priors**)
- Smooth – “local tissue concentration”
- “Modulate” by the jacobian (optional)
- Stats

Within individual

Fox et al. – e.g., Lancet 2001

Global atrophy:

Rigid body registration

Image subtraction –

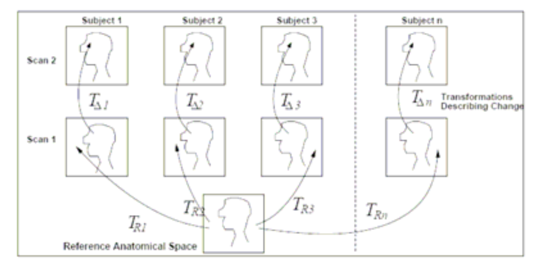
Local atrophy:

Nonlinear registration

Magnitude of deformation

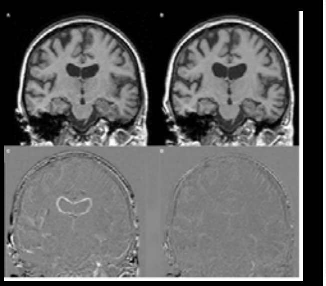
Jacobian: a measure of relative volume change

Measuring change over time

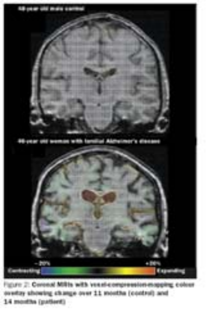


Studholme, et al, MICCAI, 2002

Tissue Classification IV - Voxel-based



rigid-body non-linear



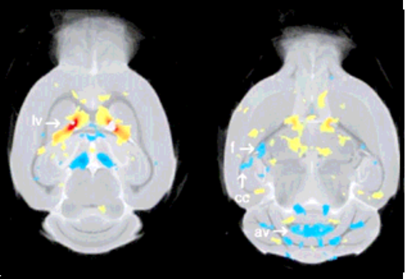
Fox, et al, Lancet 2001

Tissue Classification IV - Voxel-based

If you have ...
really high-resolution images,
with good SNR,
and a good nonlinear registration algorithm....

you can easily determine the amount of deformation required to move one group of images into another, or the voxel-wise volumetric differences

(it helps to have brains that don’t differ much, but we’ve been working with human brain images as well...)



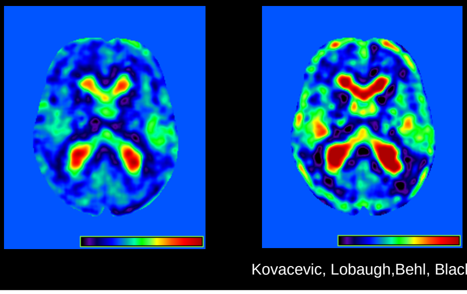
Chen, Kovacevic, Lobaugh et al, Neuroimage 2006,29:99

Tissue Classification IV - Voxel-based

Using the Jacobian to measure change over time

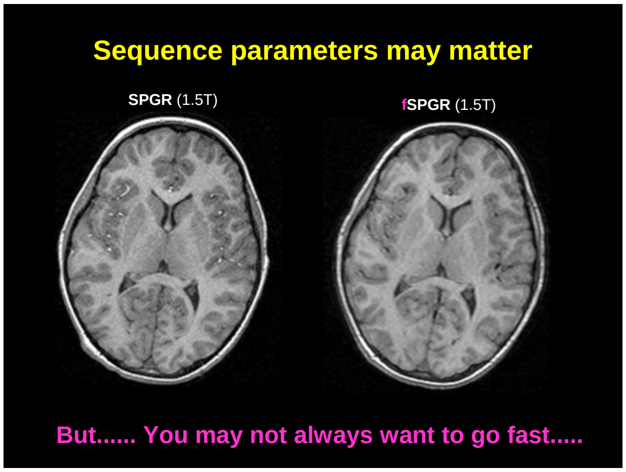
Voxel-based analysis: Where is the maximal change?

Treated Untreated



Kovacevic, Lobaugh,Behl, Black in prep

Sequence parameters may matter

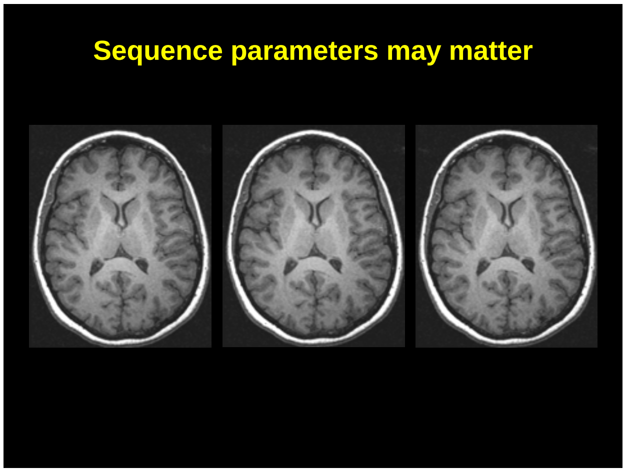


Sequence parameters may matter

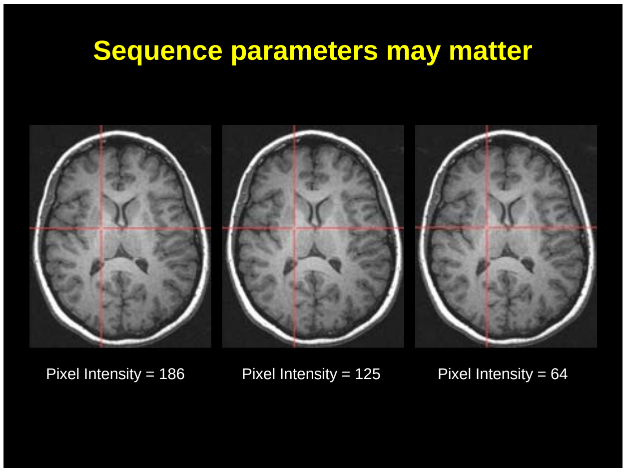
SPGR (1.5T)

fSPGR (1.5T)

But...... You may not always want to go fast.....



Sequence parameters may matter

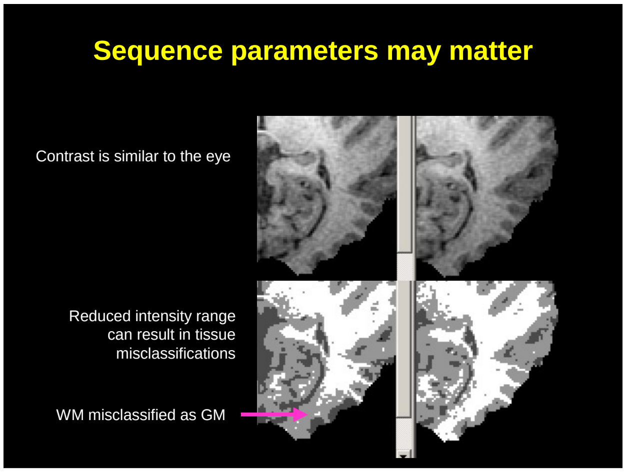


Sequence parameters may matter

Pixel Intensity = 186

Pixel Intensity = 125

Pixel Intensity = 64

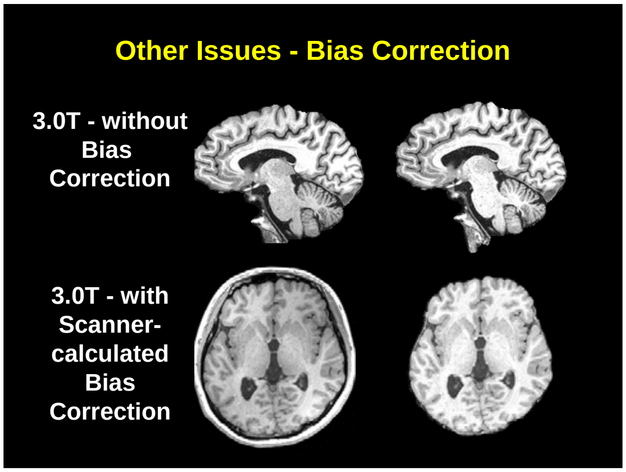


Sequence parameters may matter

Contrast is similar to the eye

Reduced intensity range can result in tissue misclassifications

WM misclassified as GM



Other Issues - Bias Correction

3.0T - without Bias Correction

3.0T - with Scanner-calculated Bias Correction

Causal patterns in brain research
What is a Network?

A Collection:

an accumulation of objects gathered for study, comparison, or as a hobby

A System:

a group of independent but interrelated elements comprising a unified whole

A Network:

an interconnected **system** of things or people; a complex, interconnected group or system

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Causal patterns in brain research
What is a Network?

So…

A network REQUIRES a system,

And a system MAY be a network,

And a collection MAY be a system or a network

But you don't know that a collection is part of a system that is part of a network

UNTIL YOU MEASURE IT.

Causal patterns in brain research
What is a Network?

But if you don't know that a collection of regions form a system that is part of a network

until you measure it…

You DEFINITELY don't know how INTACT any network is until you measure *that* -

QUANTITATIVE MRI - qMRI

Causal patterns in brain research
Going beyond connectivity analyses

Using Quantitative MRI to Characterize Connectivity

- Brain connectivity can be affected by disease and normal processes (e.g., development, aging):
  - **neuronal loss/addition**,
  - **myelination/demyelination**
  - **Inflammation**
  - **axonal loss**
  - **edema**

Using Quantitative MRI
to Measure Connectivity

- Quantitative MR sequences focus on measuring biophysical and biochemical properties of tissue.
- Attempt to identify underlying physical parameters of tissues being imaged
- Move beyond "image intensity"

Nonquantitative/Semiquantitative	Quantitative
T1-weighted (e.g., SPGR)	T1 mapping (e.g., inversion recovery)
T2-weighted (e.g., Spin Echo, T2flair)	Quantitative T2 (e.g., CPMG)
Diffusion-weighted (e.g., DWI)	Diffusion-tensor (DTI)
Magnetization transfer (e.g, MTR)	Magnetization transfer (e.g, qMT)
	Magnetic resonance spectroscopy (MRS)

Quantitative imaging takes longer!!

Quantitative MR sequences

Magnetization Transfer –

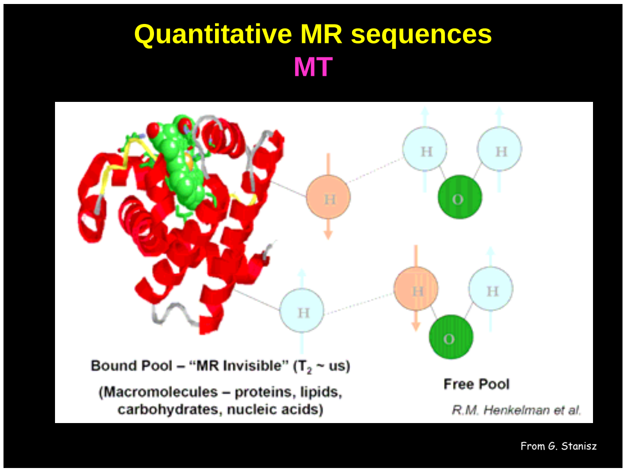
- T2 of protein matrices, cell membranes too short to see typically
- MT - indirectly observe magnetization exchange between semi-solid macromolecular protons and water protons.
- Rate of exchange related to **myelination/demyelination**
- Success in MS and dementia (MNI)

Quantitative T2 imaging -

- T2 decay: multicomponential
- increase # of echoes: finer measurement of T2 decay curve
- Can decompose the decay curve to identify that part related to **myelin/non-myelin** components

Diffusion Tensor imaging -

- Sensitive to water motion in the voxel -
- Restricted motion typically seen in regions with fibre bundles
- Tensor calculations: Fractional Anisotropy, Mean Diffusivity
- **Indirect measure of myelinated status**



Quantitative MR sequences
MT

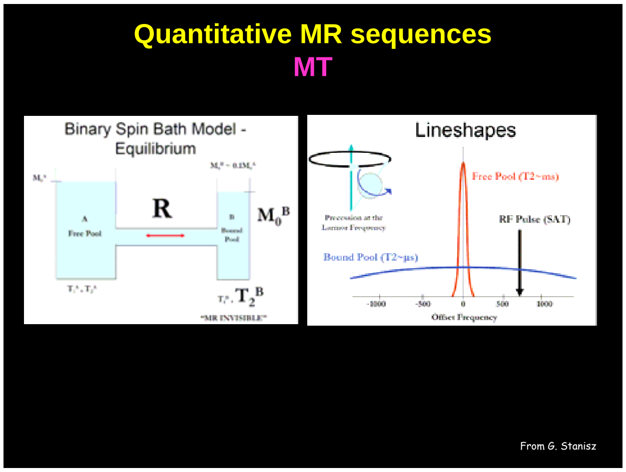
Bound Pool – "MR Invisible" (T_2 ~ us)

(Macromolecules – proteins, lipids, carbohydrates, nucleic acids)

Free Pool

R.M. Henkelman et al.

From G. Stanisz

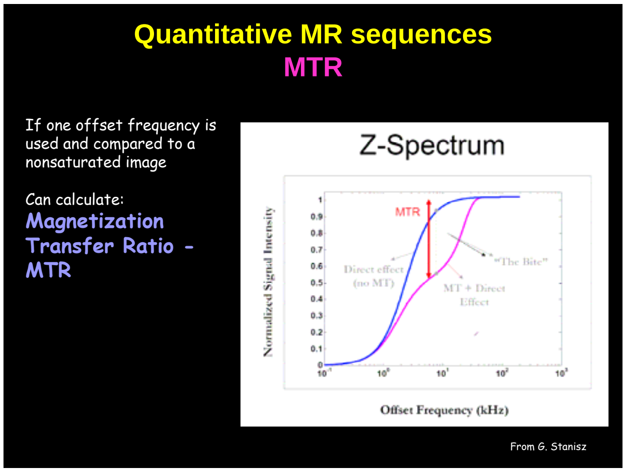


Quantitative MR sequences
MT

Binary Spin Bath Model - Equilibrium

Lineshapes

From G. Stanisz



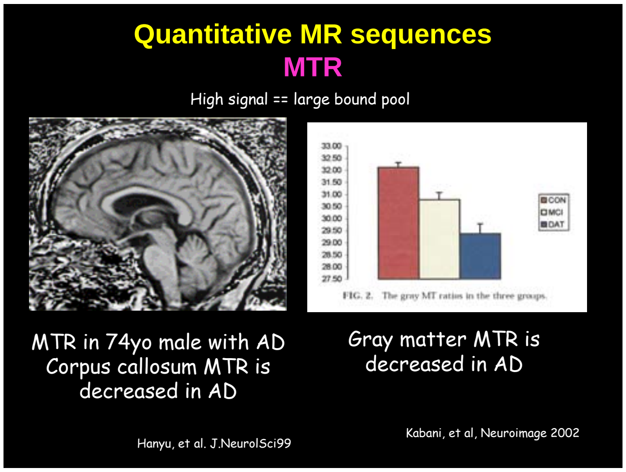
Quantitative MR sequences
MTR

If one offset frequency is used and compared to a nonsaturated image

Can calculate:
Magnetization Transfer Ratio - MTR

Z-Spectrum

From G. Stanisz



Quantitative MR sequences
MTR

High signal == large bound pool

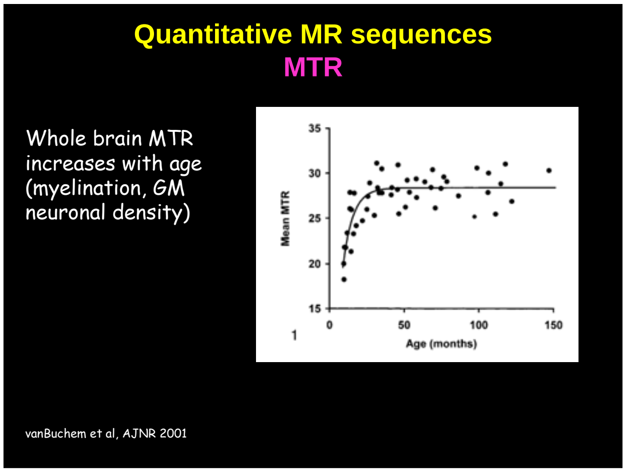
FIG. 2. The gray MT ratios in the three groups.

MTR in 74yo male with AD Corpus callosum MTR is decreased in AD

Gray matter MTR is decreased in AD

Hanyu, et al. J.NeurolSci99

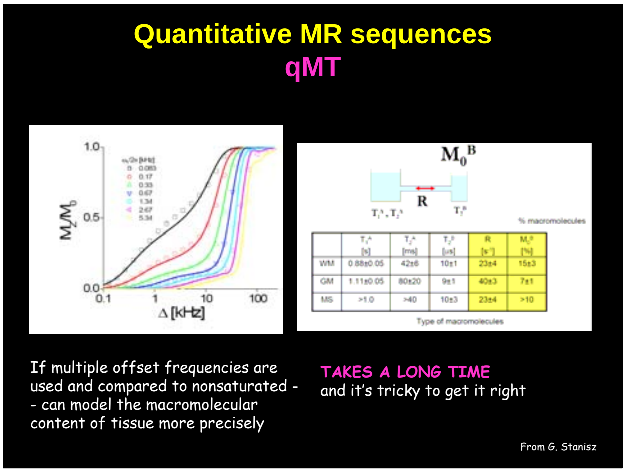
Kabani, et al, Neuroimage 2002



Quantitative MR sequences
MTR

Whole brain MTR increases with age (myelination, GM neuronal density)

vanBuchem et al, AJNR 2001



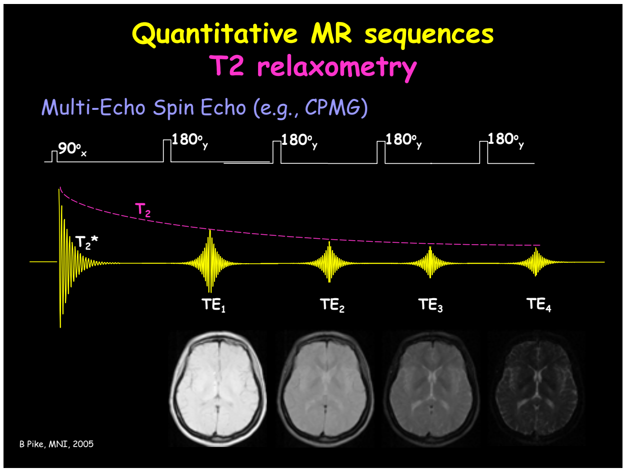
Quantitative MR sequences
qMT

	T_1^A [s]	T_2^A [ms]	T_2^B [µs]	R [s^{-1}]	M_0^B [%]
WM	0.88±0.05	42±6	10±1	23±4	15±3
GM	1.11±0.05	80±20	9±1	40±3	7±1
MS	>1.0	>40	10±3	23±4	>10

If multiple offset frequencies are used and compared to nonsaturated - - can model the macromolecular content of tissue more precisely

TAKES A LONG TIME
and it's tricky to get it right

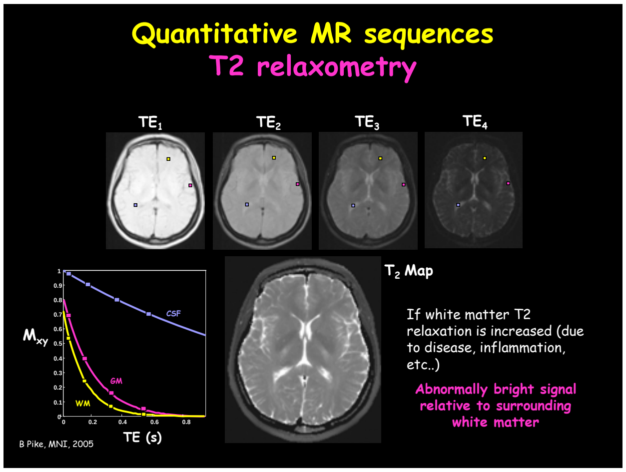
From G. Stanisz



Quantitative MR sequences
T2 relaxometry

Multi-Echo Spin Echo (e.g., CPMG)

B Pike, MNI, 2005

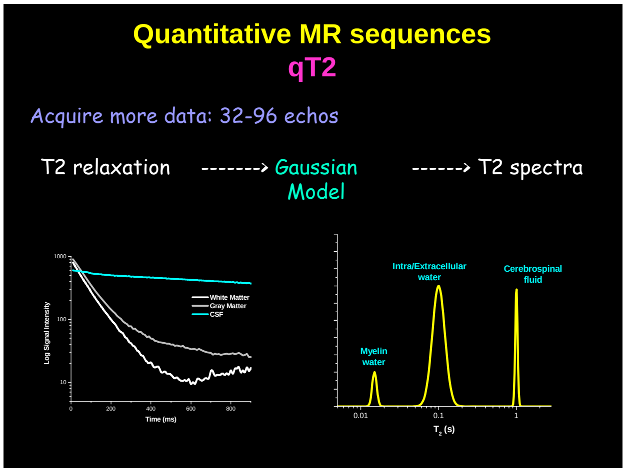


Quantitative MR sequences
T2 relaxometry

If white matter T2 relaxation is increased (due to disease, inflammation, etc..)

Abnormally bright signal relative to surrounding white matter

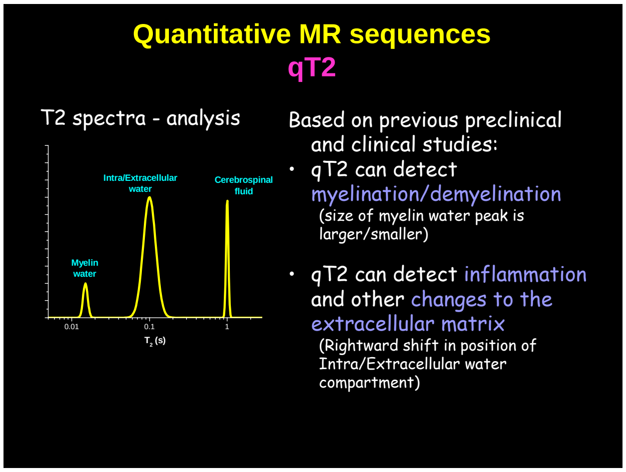
B Pike, MNI, 2005



Quantitative MR sequences
qT2

Acquire more data: 32-96 echos

T2 relaxation -------> Gaussian Model ------> T2 spectra

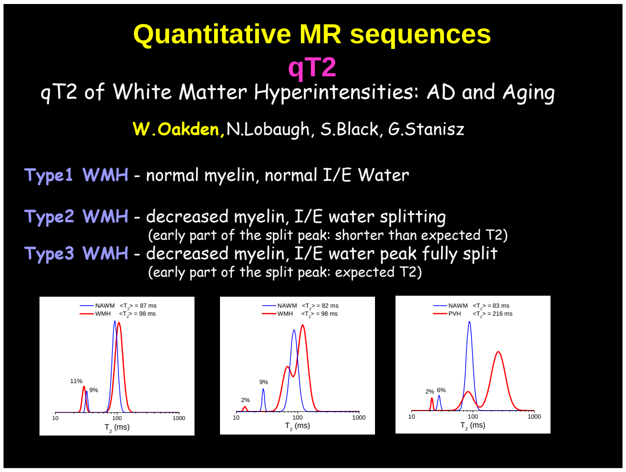


Quantitative MR sequences
qT2

T2 spectra - analysis

Based on previous preclinical and clinical studies:

- qT2 can detect myelination/demyelination (size of myelin water peak is larger/smaller)
- qT2 can detect inflammation and other changes to the extracellular matrix (Rightward shift in position of Intra/Extracellular water compartment)



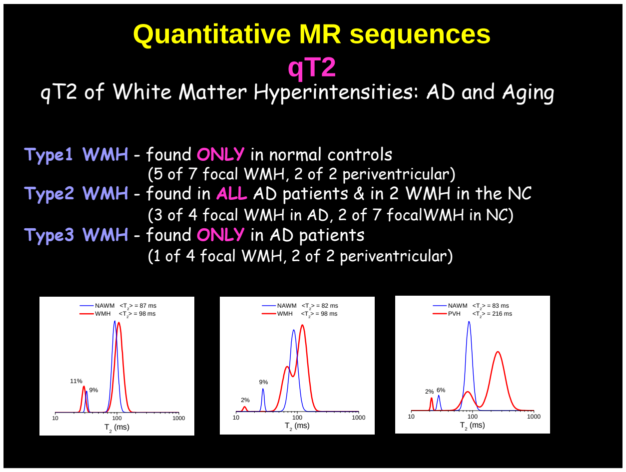
Quantitative MR sequences
qT2

qT2 of White Matter Hyperintensities: AD and Aging

W.Oakden, N.Lobaugh, S.Black, G.Stanisz

Type1 WMH - normal myelin, normal I/E Water

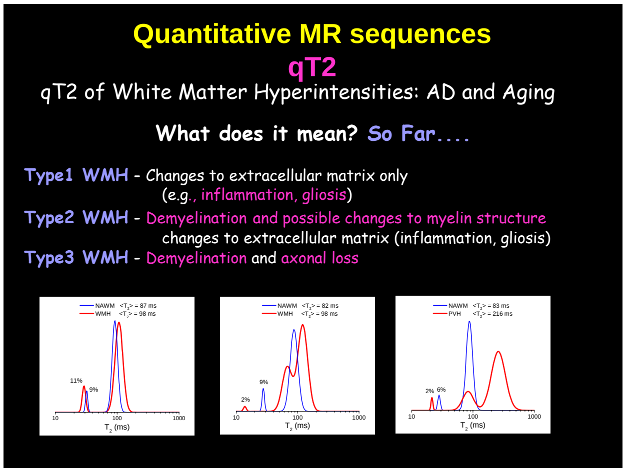
Type2 WMH - decreased myelin, I/E water splitting
(early part of the split peak: shorter than expected T2)
Type3 WMH - decreased myelin, I/E water peak fully split
(early part of the split peak: expected T2)



Quantitative MR sequences
qT2

qT2 of White Matter Hyperintensities: AD and Aging

Type1 WMH - found ONLY in normal controls
(5 of 7 focal WMH, 2 of 2 periventricular)
Type2 WMH - found in ALL AD patients & in 2 WMH in the NC
(3 of 4 focal WMH in AD, 2 of 7 focalWMH in NC)
Type3 WMH - found ONLY in AD patients
(1 of 4 focal WMH, 2 of 2 periventricular)



Quantitative MR sequences
qT2

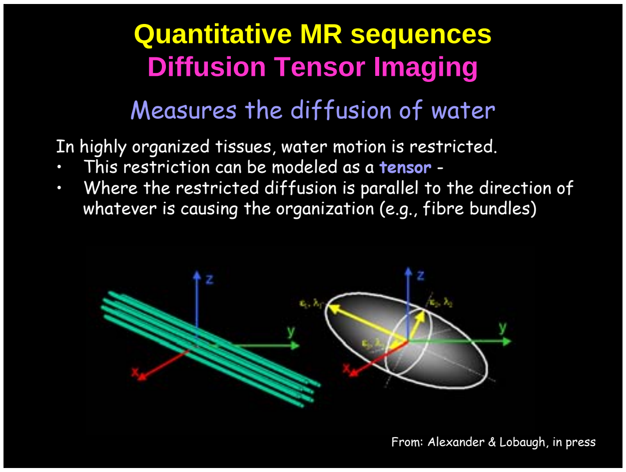
qT2 of White Matter Hyperintensities: AD and Aging

What does it mean? So Far....

Type1 WMH - Changes to extracellular matrix only
(e.g., inflammation, gliosis)

Type2 WMH - Demyelination and possible changes to myelin structure
changes to extracellular matrix (inflammation, gliosis)

Type3 WMH - Demyelination and axonal loss



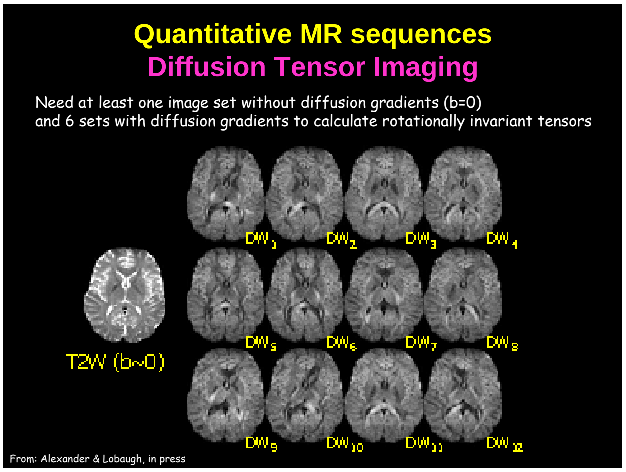
Quantitative MR sequences
Diffusion Tensor Imaging

Measures the diffusion of water

In highly organized tissues, water motion is restricted.

- This restriction can be modeled as a **tensor** -
- Where the restricted diffusion is parallel to the direction of whatever is causing the organization (e.g., fibre bundles)

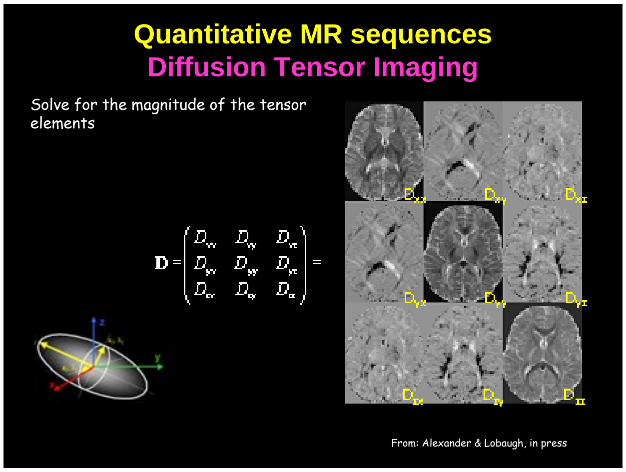
From: Alexander & Lobaugh, in press



Quantitative MR sequences
Diffusion Tensor Imaging

Need at least one image set without diffusion gradients (b=0)
and 6 sets with diffusion gradients to calculate rotationally invariant tensors

From: Alexander & Lobaugh, in press

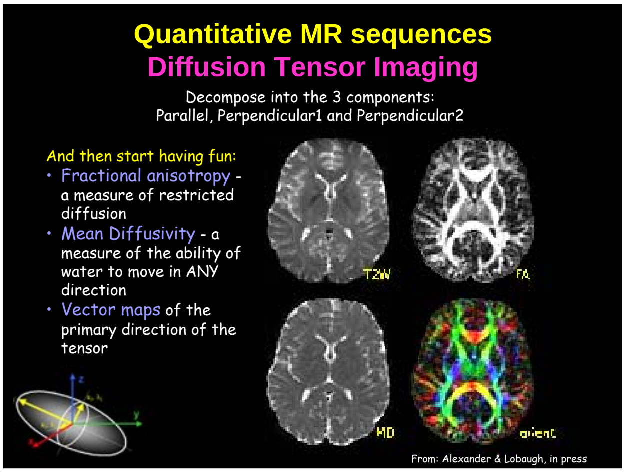


Quantitative MR sequences
Diffusion Tensor Imaging

Solve for the magnitude of the tensor elements

$$\mathbf{D} = \begin{pmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{pmatrix} =$$

From: Alexander & Lobaugh, in press



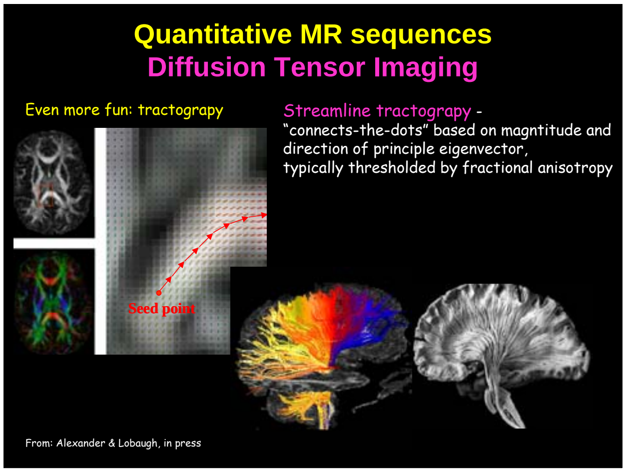
Quantitative MR sequences
Diffusion Tensor Imaging

Decompose into the 3 components:
Parallel, Perpendicular1 and Perpendicular2

And then start having fun:

- Fractional anisotropy - a measure of restricted diffusion
- Mean Diffusivity - a measure of the ability of water to move in ANY direction
- Vector maps of the primary direction of the tensor

From: Alexander & Lobaugh, in press

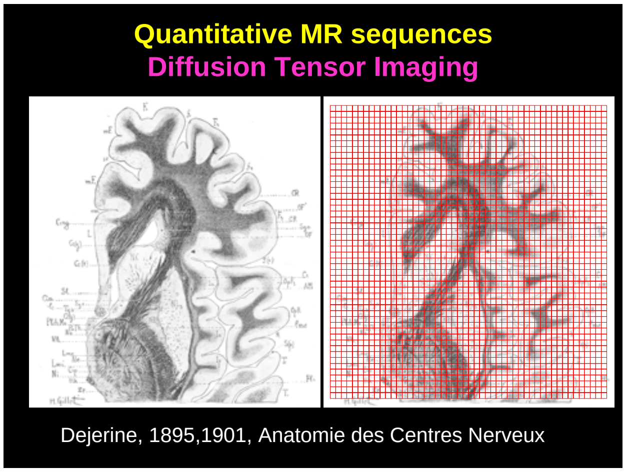


Quantitative MR sequences
Diffusion Tensor Imaging

Even more fun: tractograpy

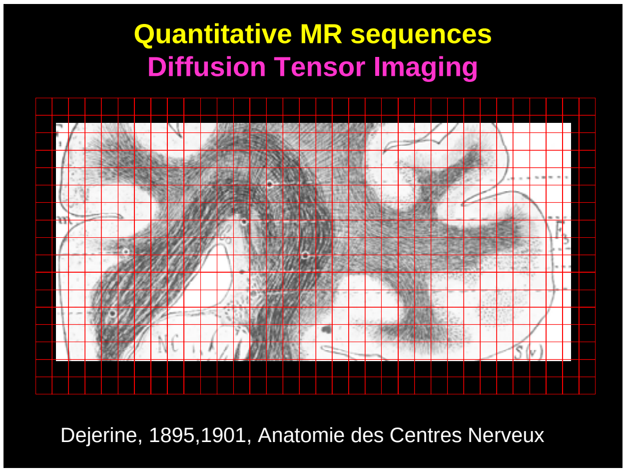
Streamline tractography -
"connects-the-dots" based on magntitude and direction of principle eigenvector, typically thresholded by fractional anisotropy

From: Alexander & Lobaugh, in press



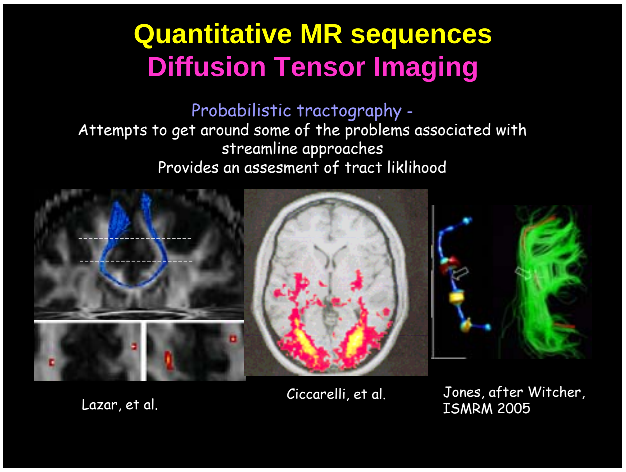
Quantitative MR sequences
Diffusion Tensor Imaging

Dejerine, 1895,1901, Anatomie des Centres Nerveux



Quantitative MR sequences
Diffusion Tensor Imaging

Dejerine, 1895,1901, Anatomie des Centres Nerveux



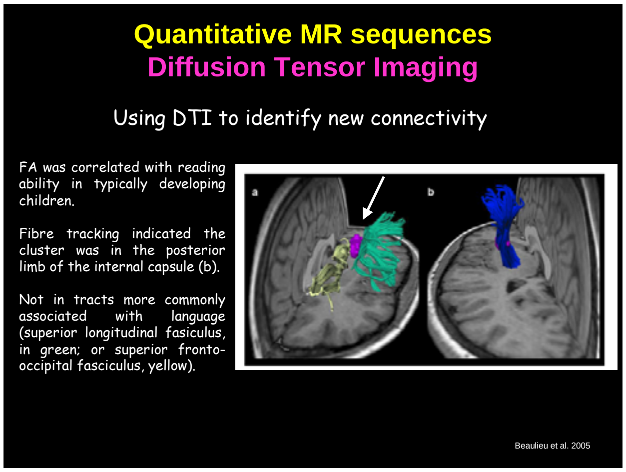
Quantitative MR sequences
Diffusion Tensor Imaging

Probabilistic tractography -
Attempts to get around some of the problems associated with streamline approaches
Provides an assesment of tract liklihood

Lazar, et al.

Ciccarelli, et al.

Jones, after Witcher, ISMRM 2005



Quantitative MR sequences
Diffusion Tensor Imaging

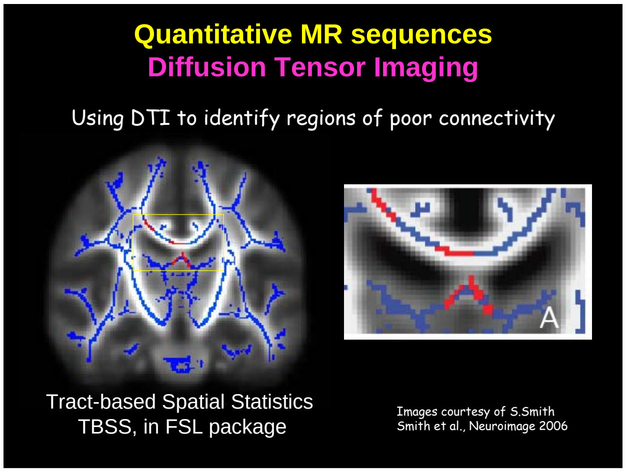
Using DTI to identify new connectivity

FA was correlated with reading ability in typically developing children.

Fibre tracking indicated the cluster was in the posterior limb of the internal capsule (b).

Not in tracts more commonly associated with language (superior longitudinal fasiculus, in green; or superior fronto-occipital fasciculus, yellow).

Beaulieu et al. 2005

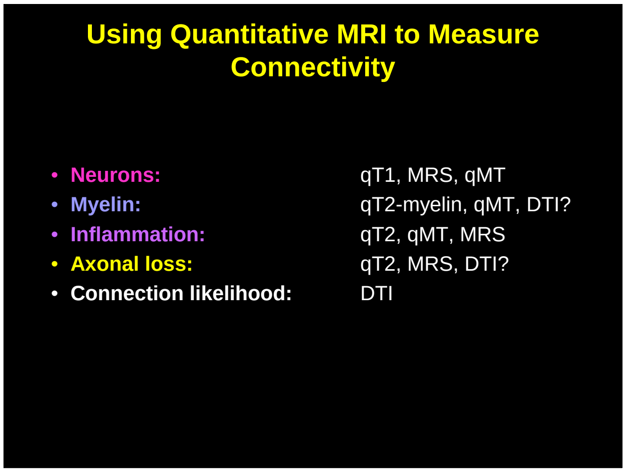


Quantitative MR sequences
Diffusion Tensor Imaging

Using DTI to identify regions of poor connectivity

Tract-based Spatial Statistics
TBSS, in FSL package

Images courtesy of S.Smith
Smith et al., Neuroimage 2006



Using Quantitative MRI to Measure Connectivity

Neurons:	qT1, MRS, qMT
Myelin:	qT2-myelin, qMT, DTI?
Inflammation:	qT2, qMT, MRS
Axonal loss:	qT2, MRS, DTI?
Connection likelihood:	DTI

Quantitative MR sequences
Sensitivity vs. Specificity

Sensitivity <---------------- **TO** ----------------> **Specificity**

Magnetization Transfer: MTR	qMT: size of macromolecular pool, exchange
T2 relaxometry: Estimated T2	qT2: estimated T2, myelin water fraction, I/E water fraction location
Diffusion tensor: FA,diffusivity	Diffusion: Beyond the tensor (fibre tracking - connectivity)
Potentially identify **"that"** there differences in tissue microstructure	Potentially identify **"what kind"** of differences are in tissue microstructure

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Using Quantitative MRI to Measure Connectivity
Conclusions

It is possible to obtain reasonable semi-quantitative data relevant to brain function from standard clinical sequences

Major issues:

- robust algorithms
- artifact, reproducibility, variations in scanner operation
- best way to examine serial scans – separating registration error from true tissue change

Fully quantitative sequences take advantage of ability to measure biophysical properties more precisely.

But what about Blobology

"To our disappointment," the scientists wrote last month in The Biological Bulletin, "we have not found any evidence that any of the blobs are the remains of gigantic octopods, or sea monsters of unknown species."

But maybe, just maybe... they are part of a large and interesting functional neural network whos actions can be charcterized using qMRI

Full story at
http://www.collisiondetection.net/mt/archives/000923.html

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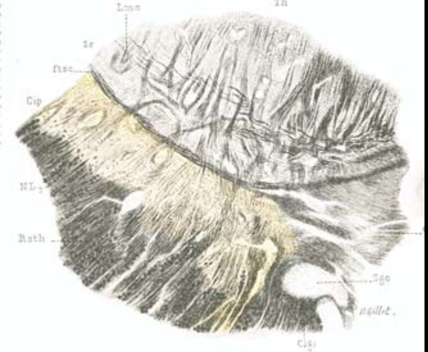
qMRI is a challenge, but it's fun....



Dejerine, 1901