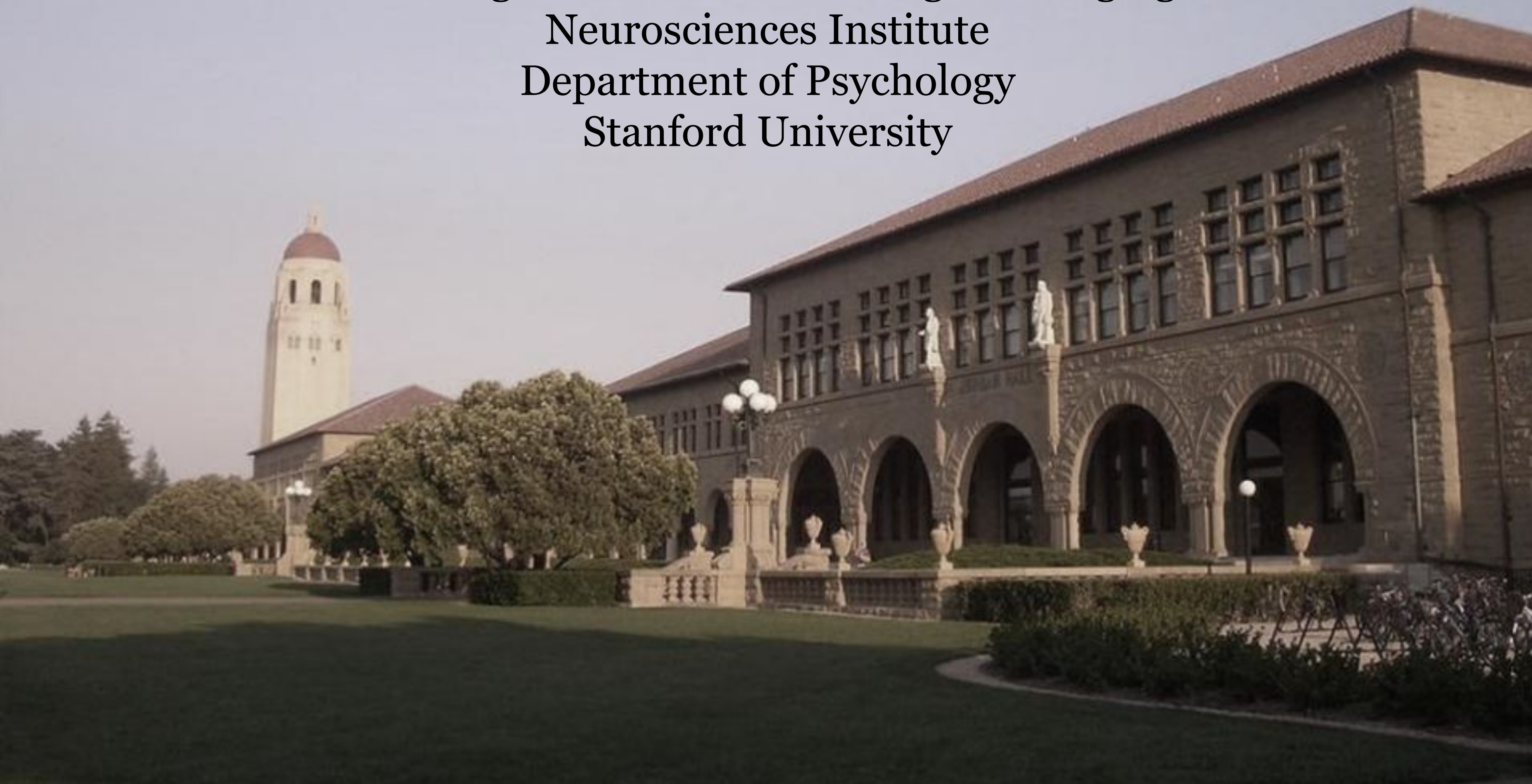
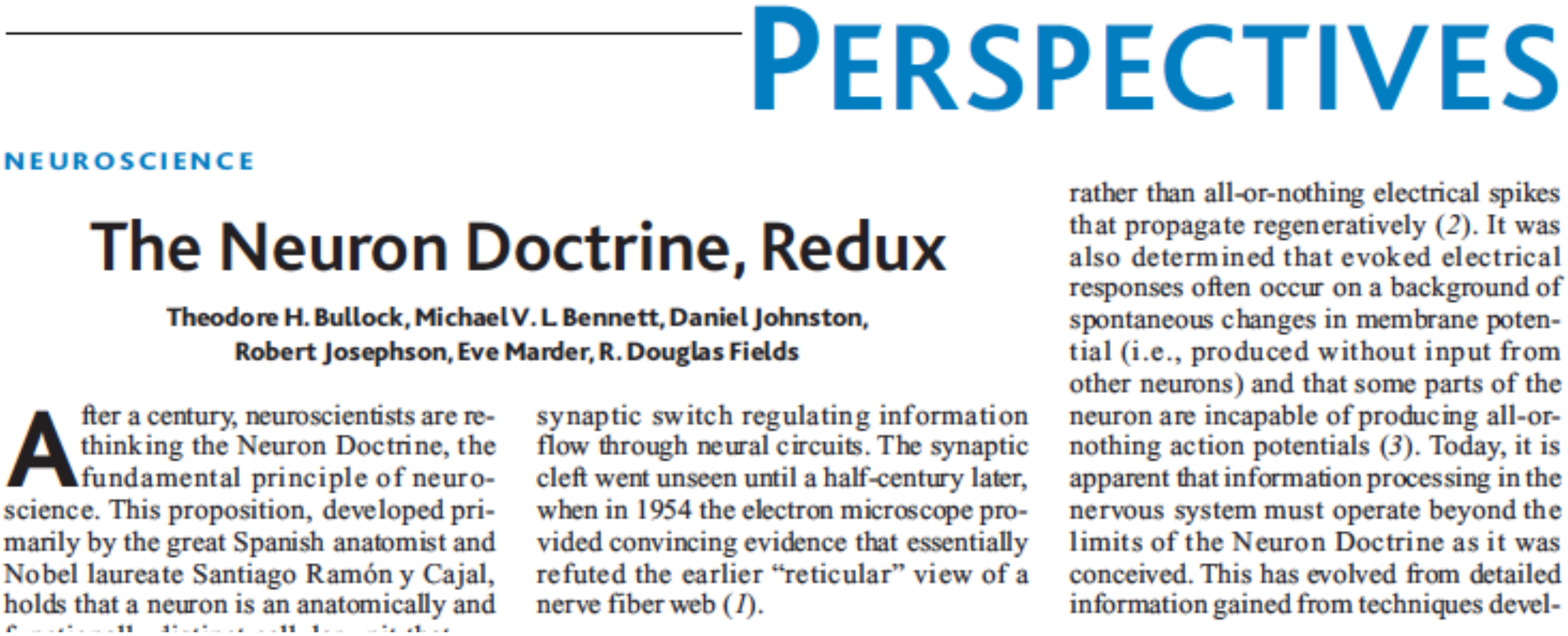
Mostly diffusion and tractography

Professor Brian Wandell
Center for Cognitive and Neurobiological Imaging (CNI)
Neurosciences Institute
Department of Psychology
Stanford University



Neuroscience is broadening its view of key brain functions

Bullock, Bennett, Johnston, Josephson, Marder, Fields
Science, 2005



PERSPECTIVES

NEUROSCIENCE

The Neuron Doctrine, Redux

Theodore H. Bullock, Michael V. L. Bennett, Daniel Johnston, Robert Josephson, Eve Marder, R. Douglas Fields

After a century, neuroscientists are rethinking the Neuron Doctrine, the fundamental principle of neuroscience. This proposition, developed primarily by the great Spanish anatomist and Nobel laureate Santiago Ramón y Cajal, holds that a neuron is an anatomically and

synaptic switch regulating information flow through neural circuits. The synaptic cleft went unseen until a half-century later, when in 1954 the electron microscope provided convincing evidence that essentially refuted the earlier "reticular" view of a nerve fiber web (*1*).

rather than all-or-nothing electrical spikes that propagate regeneratively (*2*). It was also determined that evoked electrical responses often occur on a background of spontaneous changes in membrane potential (i.e., produced without input from other neurons) and that some parts of the neuron are incapable of producing all-or-nothing action potentials (*3*). Today, it is apparent that information processing in the nervous system must operate beyond the limits of the Neuron Doctrine as it was conceived. This has evolved from detailed information gained from techniques devel-

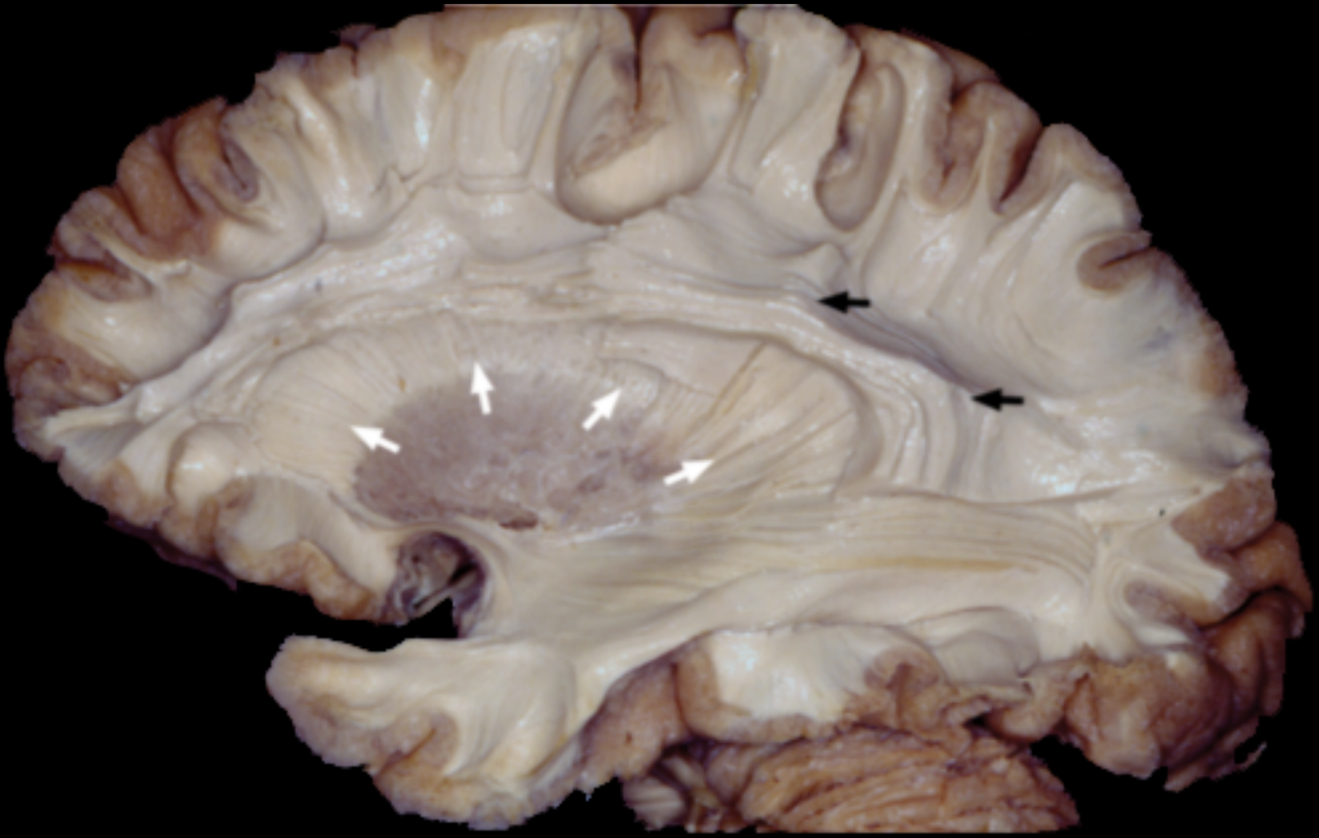
Human fascicles (tracts)

- There are many long-range connections
- These connections are not passive – they change their properties in response to use
- A system with active wires

Courtesy Professor Peggy Mason

Human fascicles (tracts)

- There are many long-range connections
- These connections are not passive – they change their properties in response to use
- A system with active wires



Courtesy Professor Ugur Ture

Types of Glia

Microglia (20%) scavenging for infections, plaques, damaged neurons; regulating healthy neurons

Astrocytes bring nutrients to neurons as well as surround and regulate synapses. (50%)

Oligodendrocytes produce myelin that insulates axons.

Schwann cells perform myelination duties in the body's peripheral nervous system.

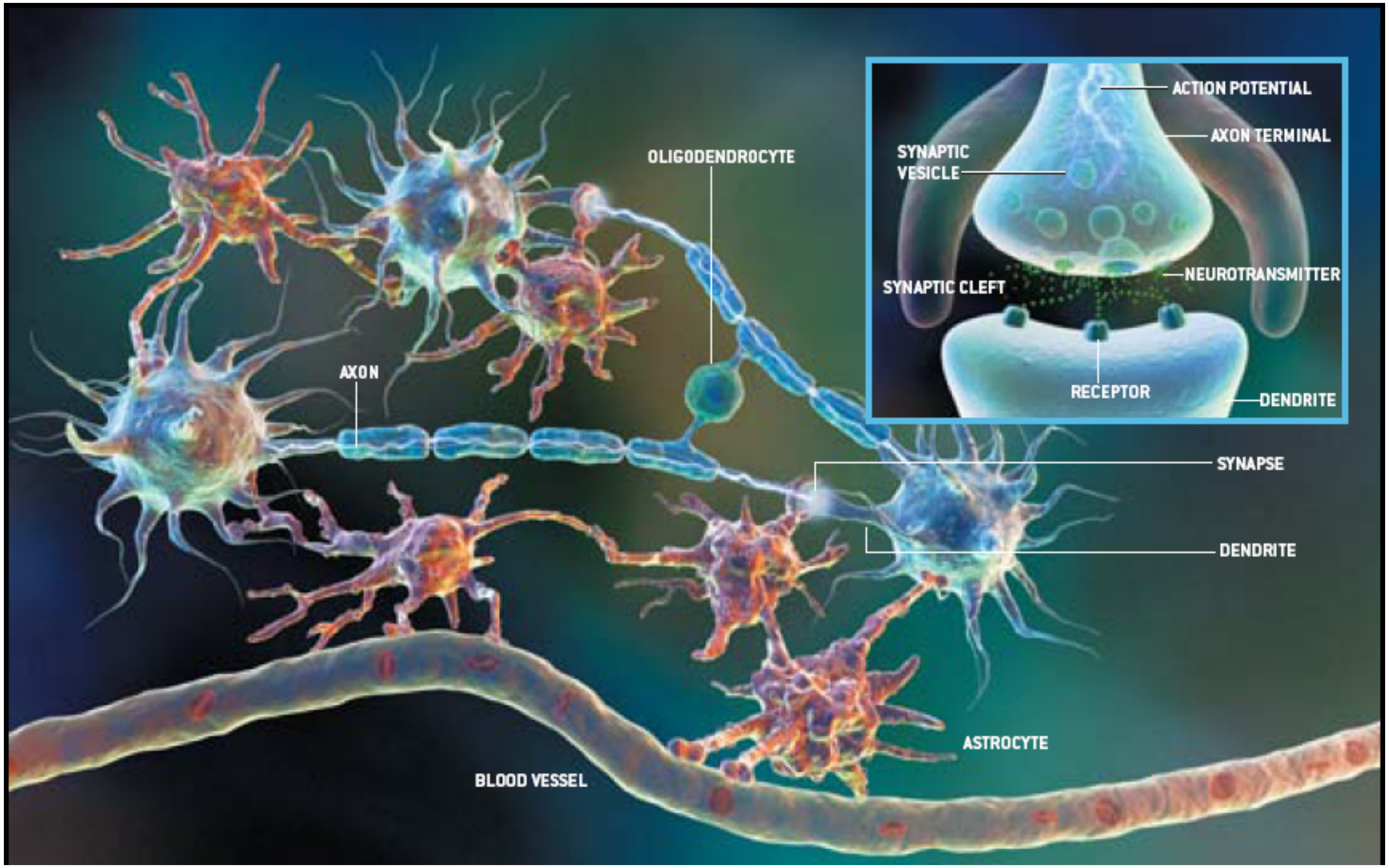
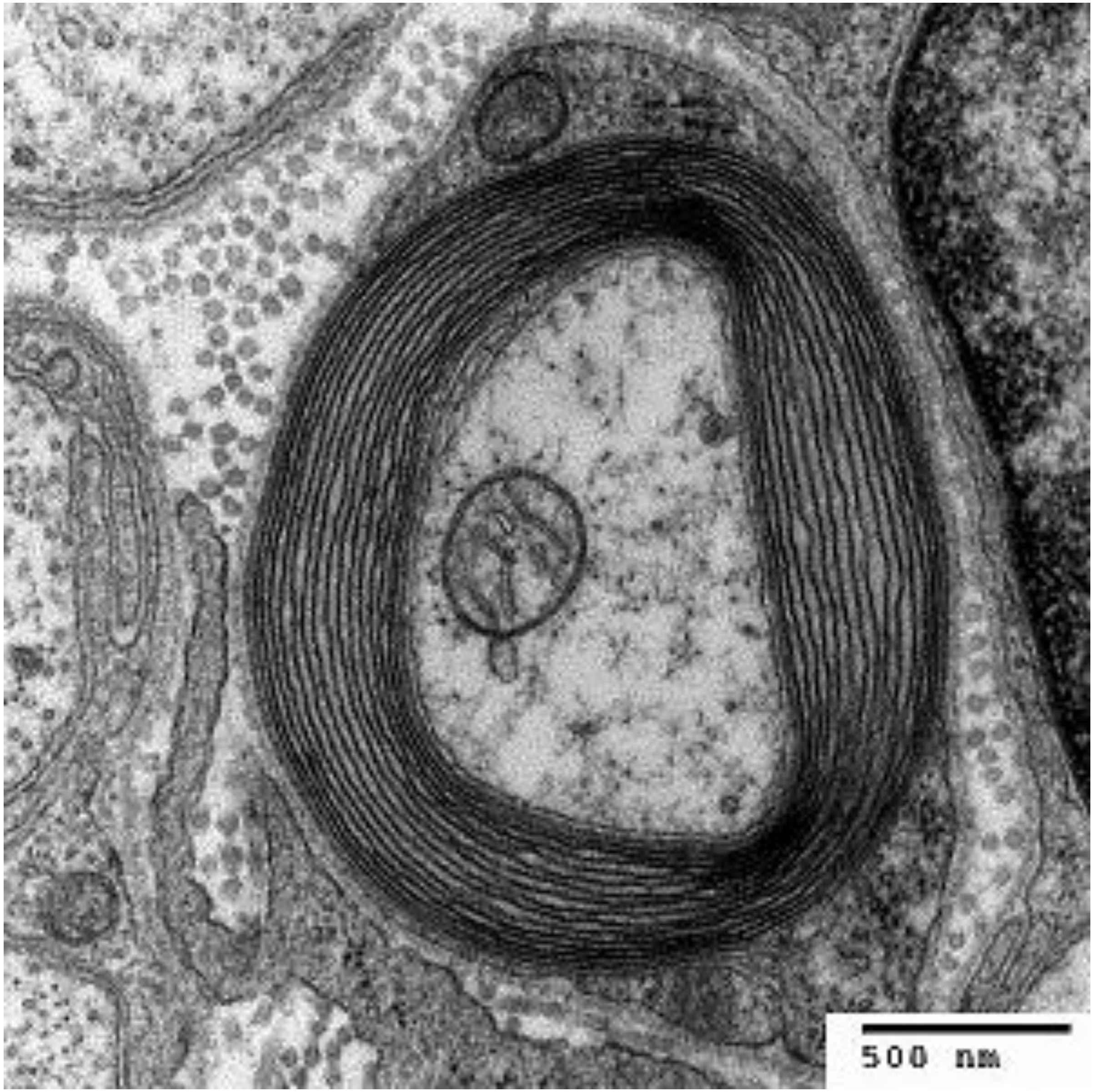


Image from
Wake, et al. Trends in Neurosciences
Volume 36, Issue 4, April 2013

An oligodendrocyte in the white matter

Electron micrograph showing the myelin sheath from an oligodendrocyte wrapping a single axons (cross-section)

Note the scale bar



McKenzie et al, Science (2014)

RESEARCH ARTICLE

SKILL DEVELOPMENT

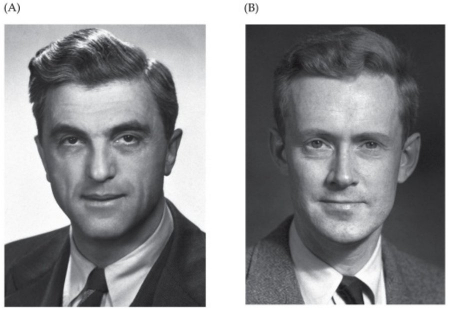
Motor skill learning requires active central myelination

Ian A. McKenzie,[1*] David Ohayon,[1*] Huiliang Li,[1] Joana Paes de Faria,[1]† Ben Emery,[2] Koujiro Tohyama,[3] William D. Richardson[1]‡

Myelin-forming oligodendrocytes (OLs) are formed continuously in the healthy adult brain. In this work, we study the function of these late-forming cells and the myelin they produce. Learning a new motor skill (such as juggling) alters the structure of the brain's white matter, which contains many OLs, suggesting that late-born OLs might contribute to motor learning. Consistent with this idea, we show that production of newly formed OLs is briefly accelerated in mice that learn a new skill (running on a "complex wheel" with irregularly spaced rungs). By genetically manipulating the transcription factor myelin regulatory factor in OL precursors, we blocked production of new OLs during adulthood without affecting preexisting OLs or myelin. This prevented the mice from mastering the complex wheel. Thus, generation of new OLs and myelin is important for learning motor skills.

Free induction decay

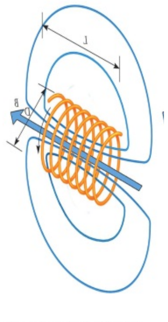
The free induction decay experiment



Functional Magnetic Resonance Imaging 2e, Figure 1.10

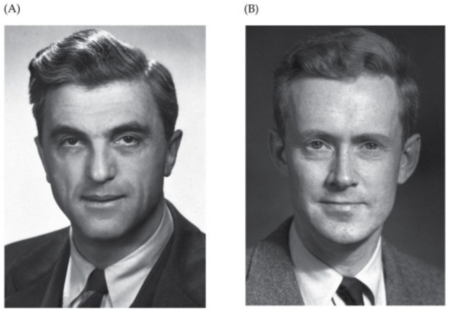
© 2009 Sinauer Associates, Inc.

Bloch **Purcell**



Beaker of water in a perfectly uniform magnetic field

The free induction decay experiment

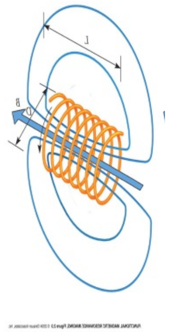


(A) (B)

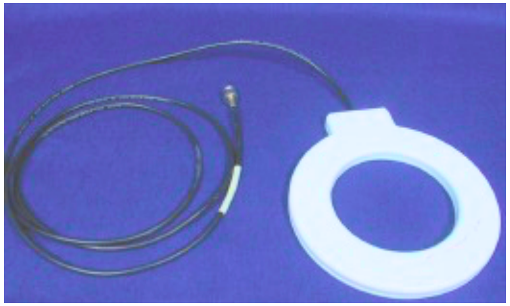
Functional Magnetic Resonance Imaging 2e, Figure 1.10

© 2009 Sinauer Associates, Inc.

Bloch **Purcell**

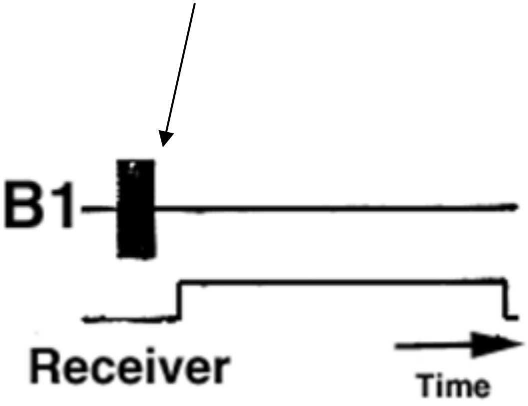


Coil

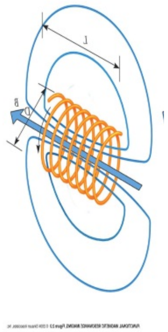


Beaker of water in a perfectly uniform magnetic field

RF signal excites spins



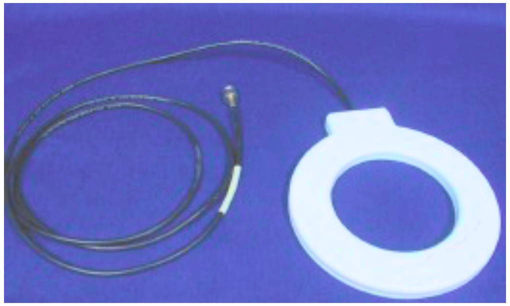
The free induction decay experiment

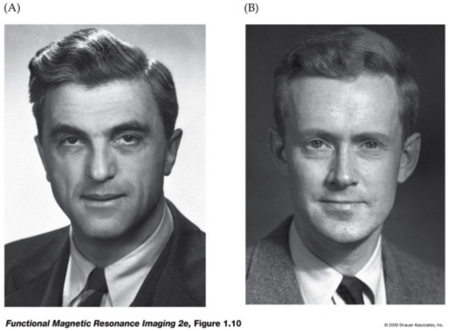


Beaker of water in a perfectly uniform magnetic field

RF signal excites spins

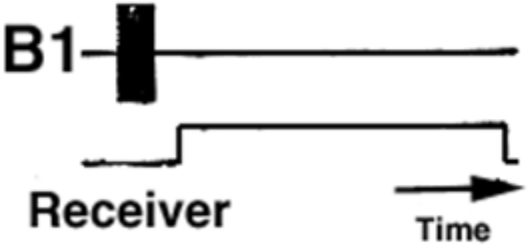
Coil



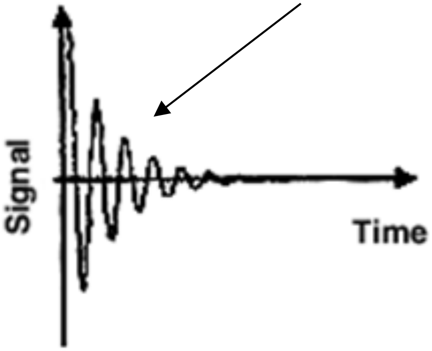


Functional Magnetic Resonance Imaging 2e, Figure 1.10

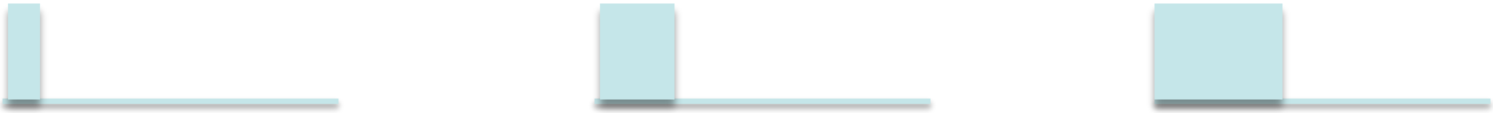
Bloch **Purcell**



Measured voltage signal



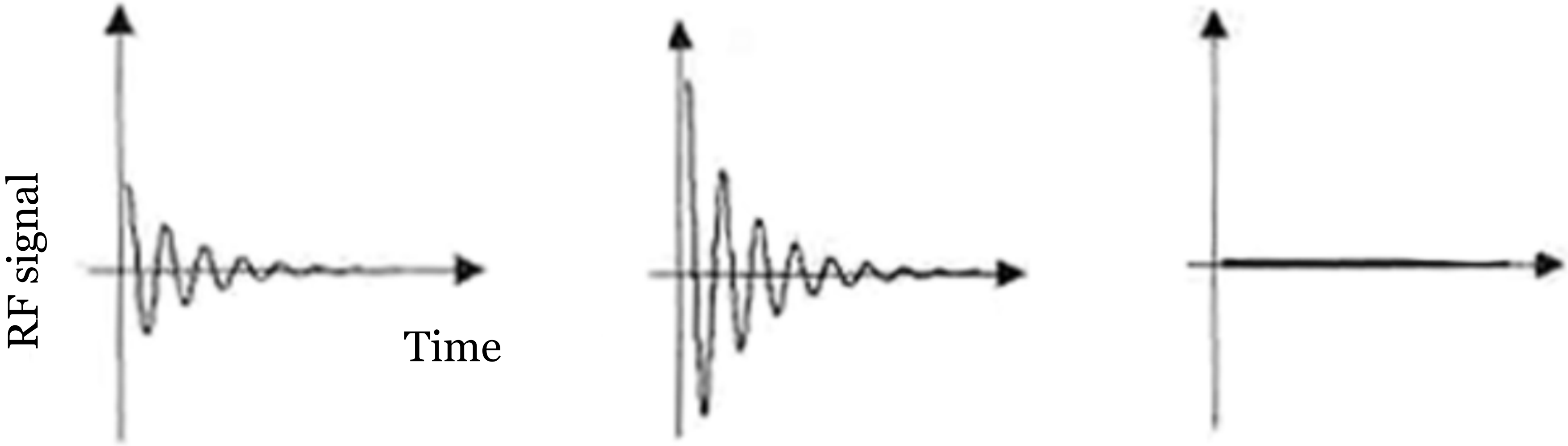
The FID signal depends on the B1 duration



Short duration RF pulse (B1)

Longer duration RF pulse

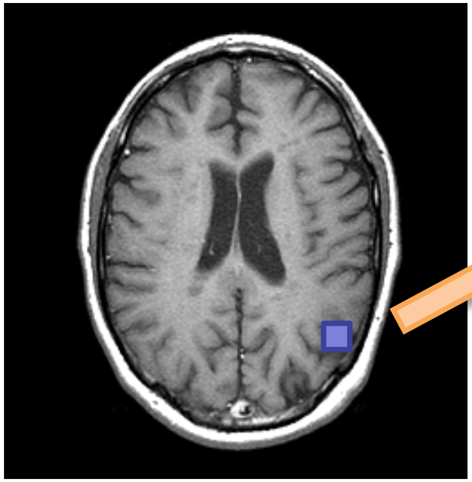
Even longer duration RF pulse

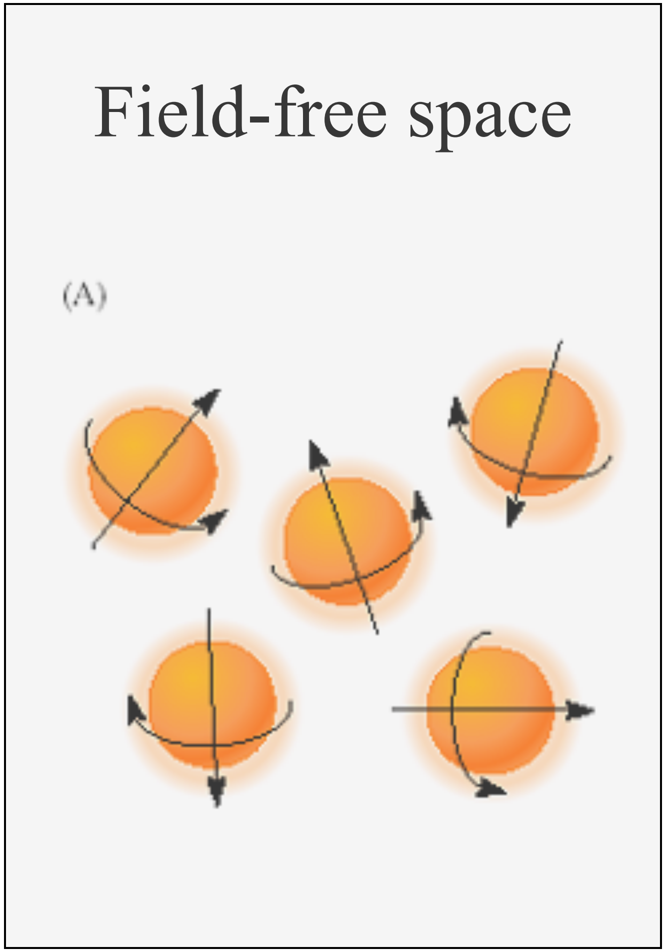


How can we explain this?

Source of the MR signal
Hydrogen nuclei (spins, protons)

An average person who weighs 150 lbs. contains approximately 5×10^{27} hydrogen nuclei (spins);





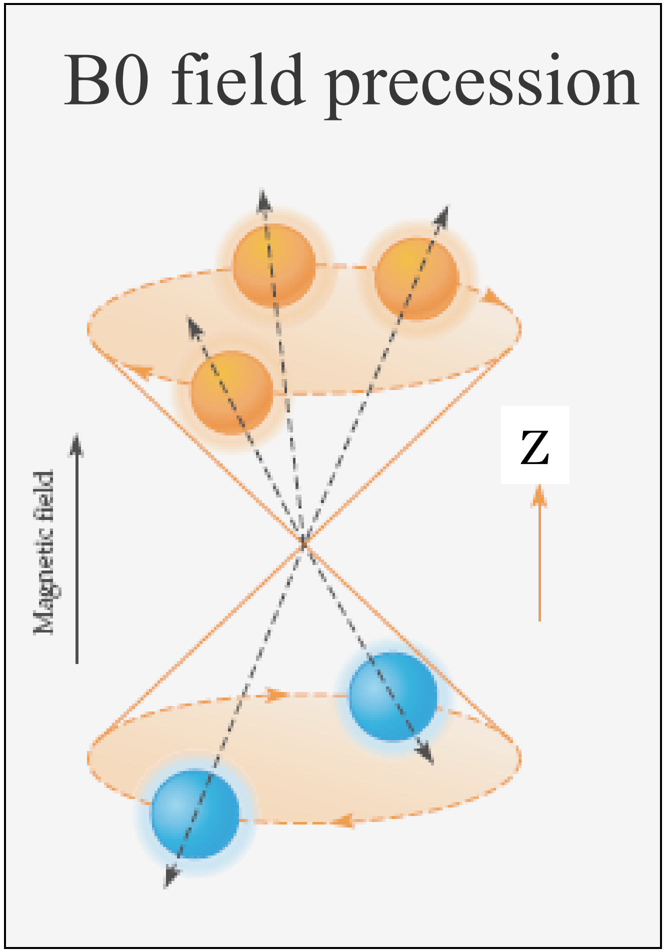
Functional Magnetic Resonance Imaging, Huettel et al. © Sinauer, 2004, 2009

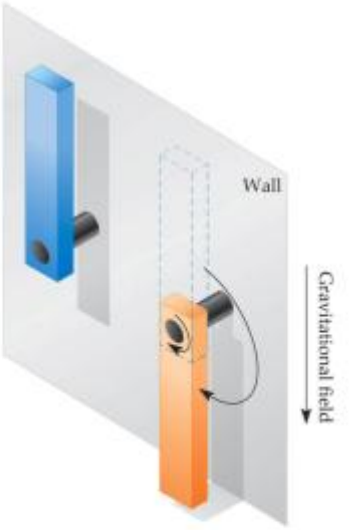
The FID signal: quantal descriptio

In the presence of the B0 field, the spins generally align with the field (Z-direction)

But they occupy one of two states: Parallel and anti-parallel

(mrTutMR explains how to calculate the percentage in each state)





Parallel

Anti-parallel

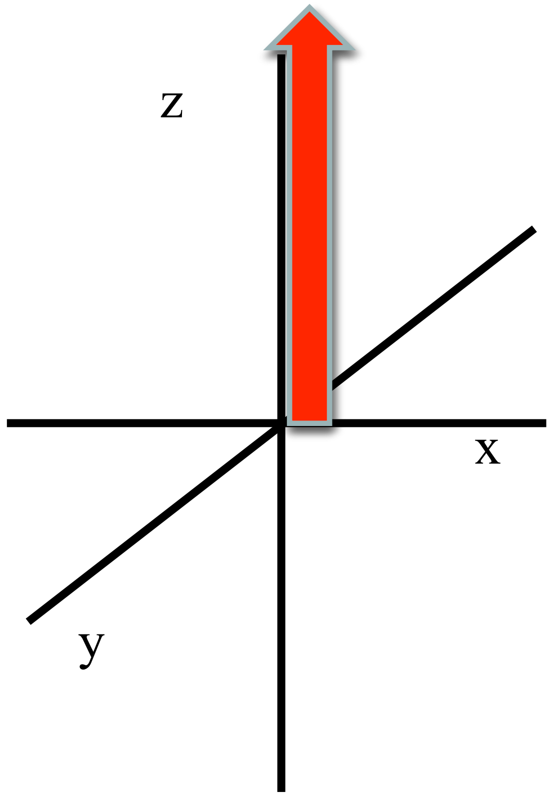
Functional Magnetic Resonance Imaging, Huettel et al. © Sinauer, 2004, 2009

The **bulk magnetization** is the sum of the spins

There are lots of spins in each voxel, and we measure the sum of these.

There is no xy-plane direction preference.

There is a z-direction preference because of the Bo field.

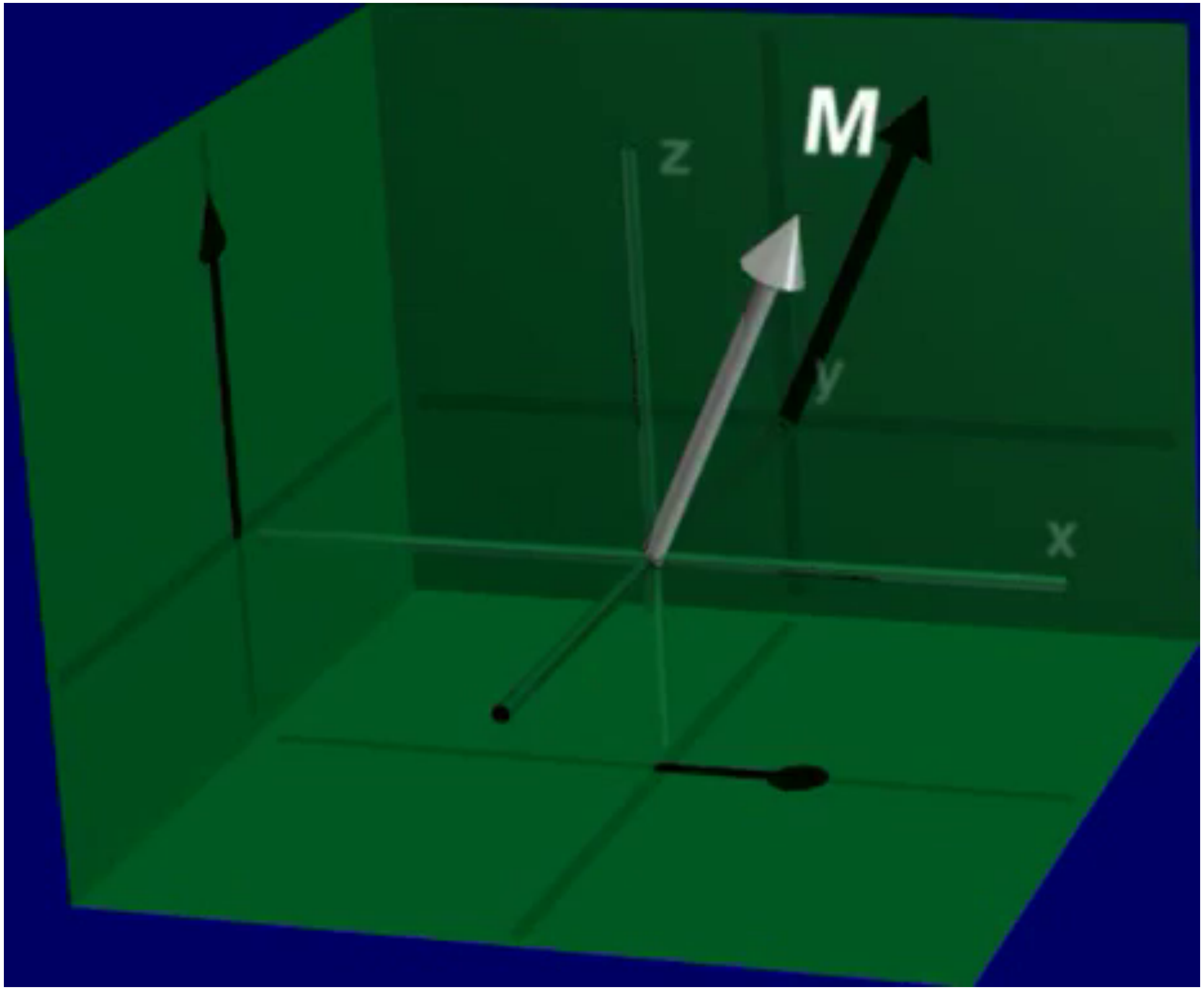


Functional Magnetic Resonance Imaging, Huettel et al. © Sinauer, 2004, 2009

Precession

When excited by an RF pulse, the bulk magnetization is modeled as spinning around the z-axis, like a top.

It has spin rate (frequency), an angle and a vector length

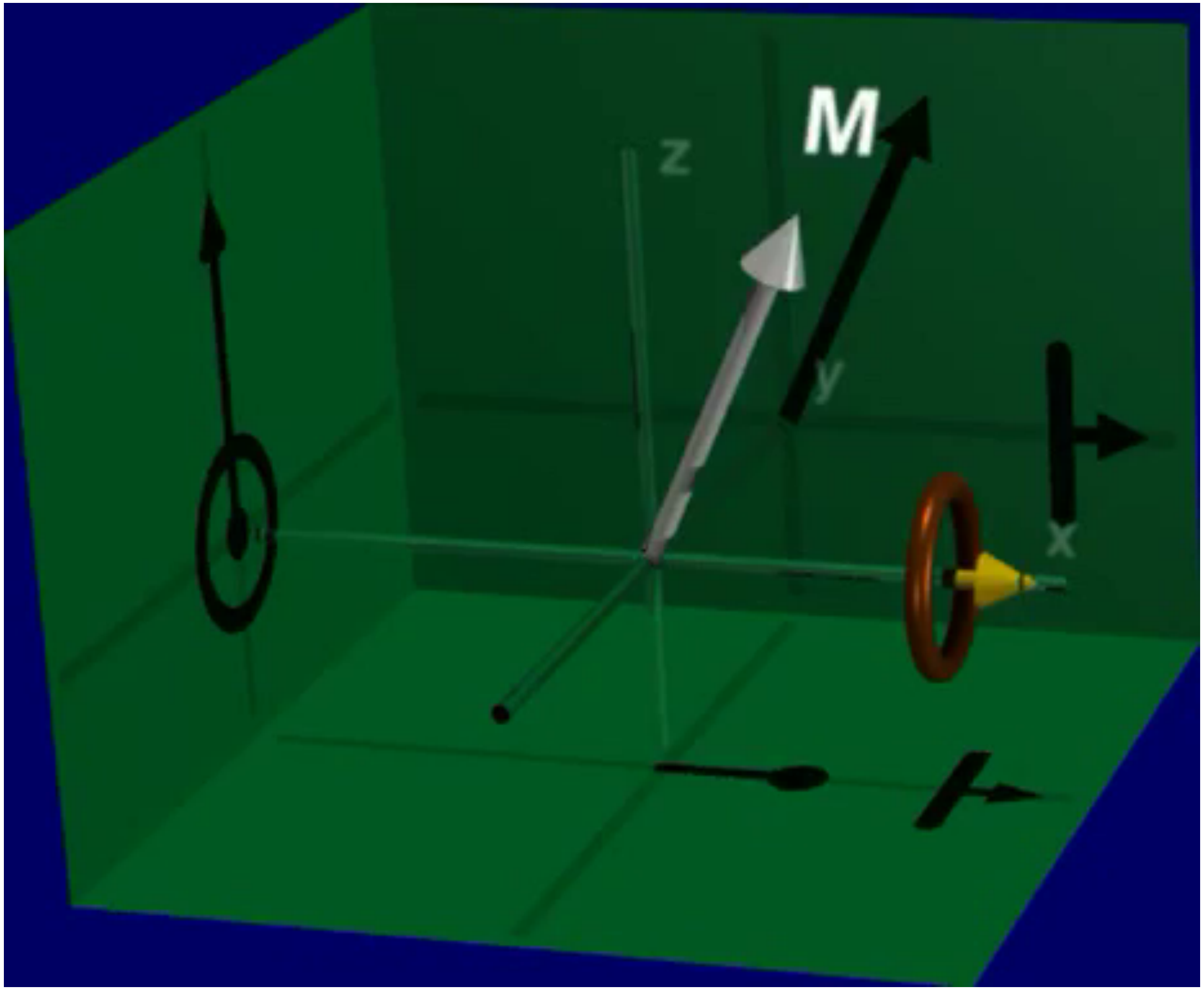


Play precess.avi

FID: The bulk (net) magnetization metaphor

An RF receive-coil measures the precessing bulk magnetization

The receive coil can be the same or different as the transmit (excite) coil

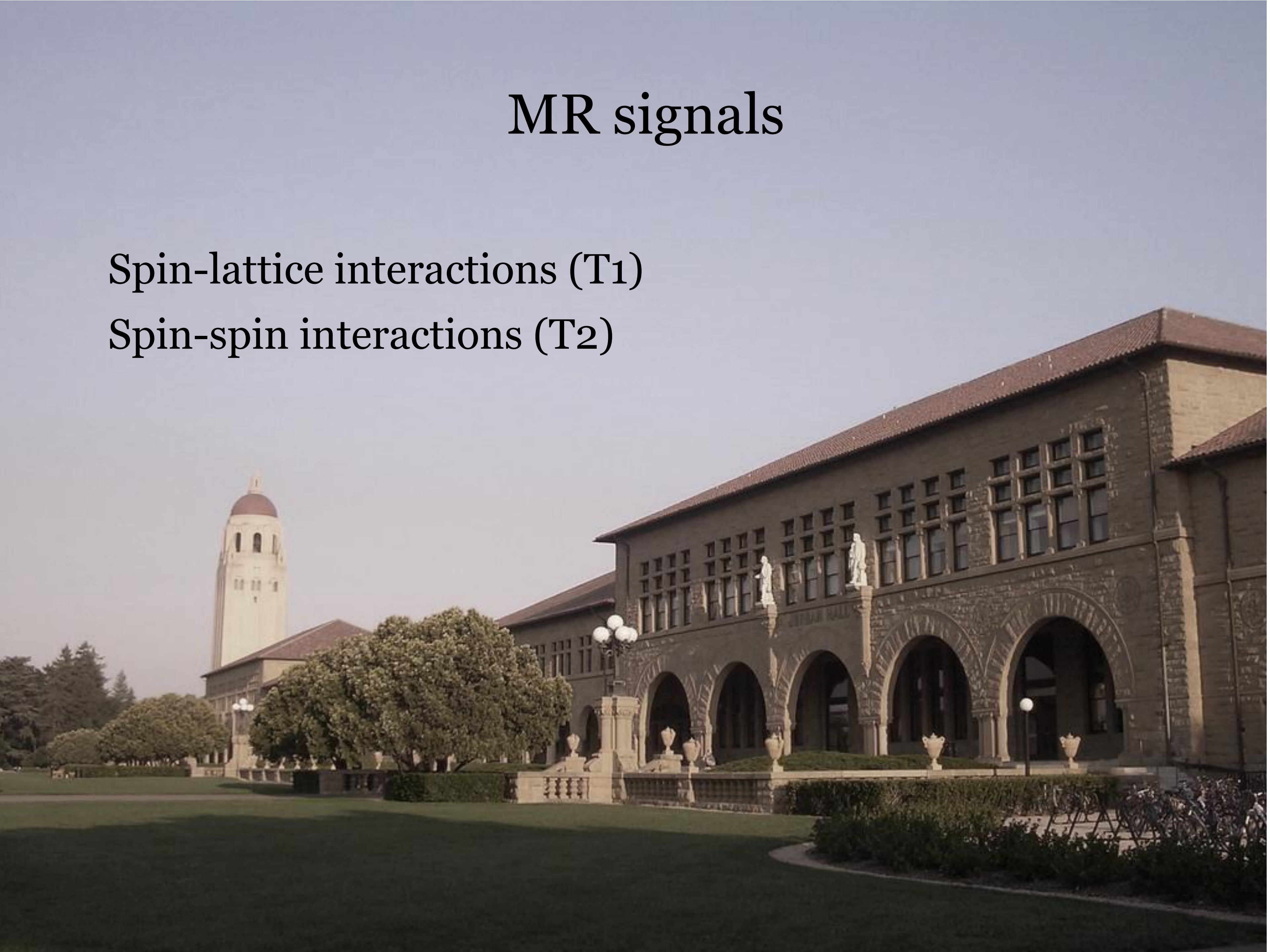


precess_coil_vec

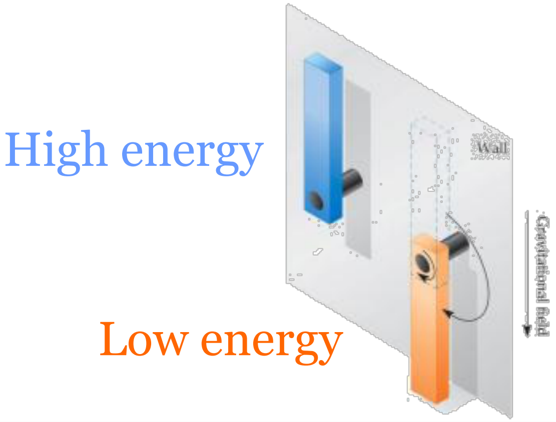
MR signals

Spin-lattice interactions (T1)

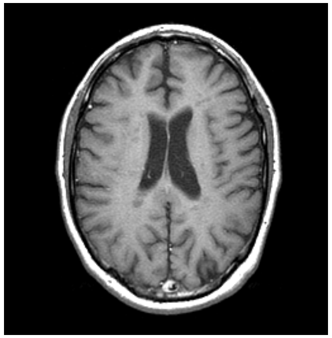
Spin-spin interactions (T2)

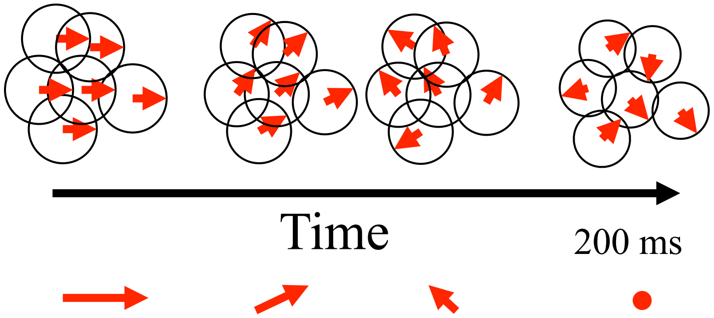


There are multiple mechanisms that can influence the bulk magnetization

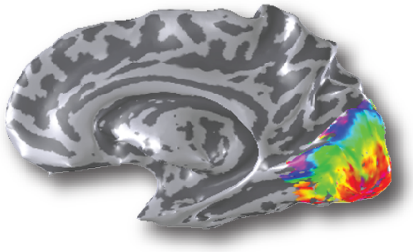


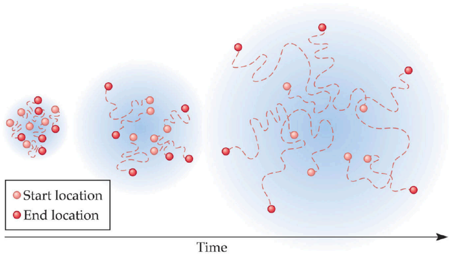
Anti-parallel spins give up energy to macromolecules (lattice) and return to lower parallel state
(T1)



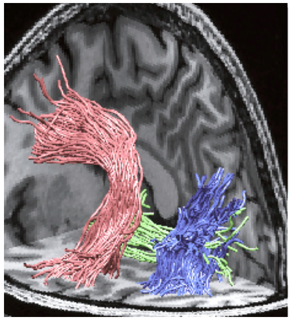


The spins dephase
(T2*)

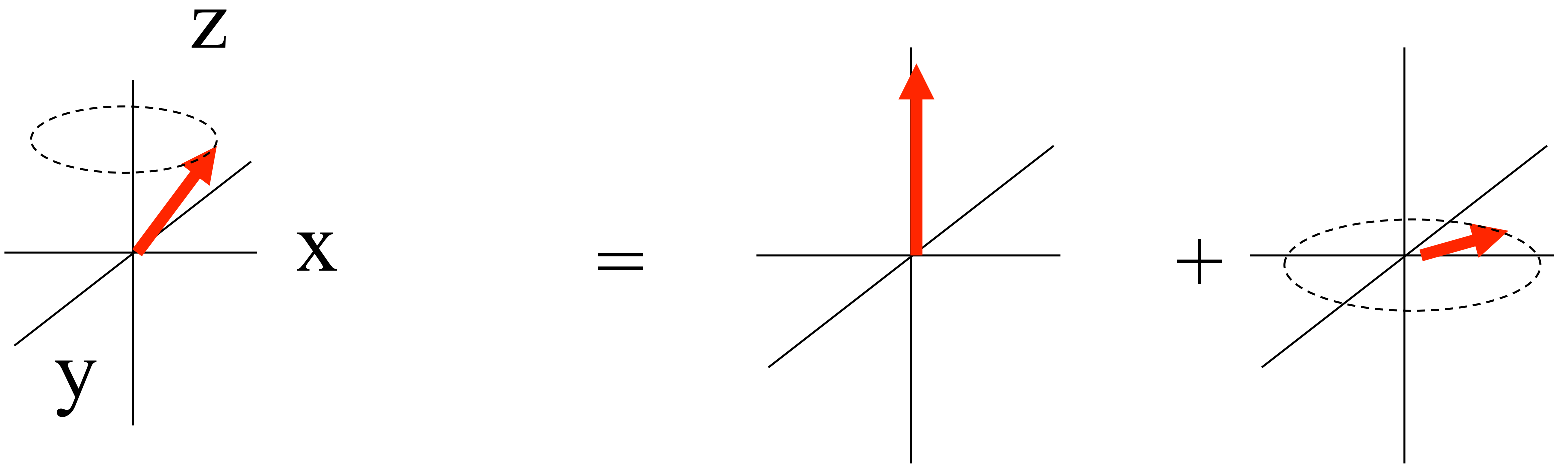




The spins move
(diffusion)



The bulk magnetization is the sum of two components



Precessing spin

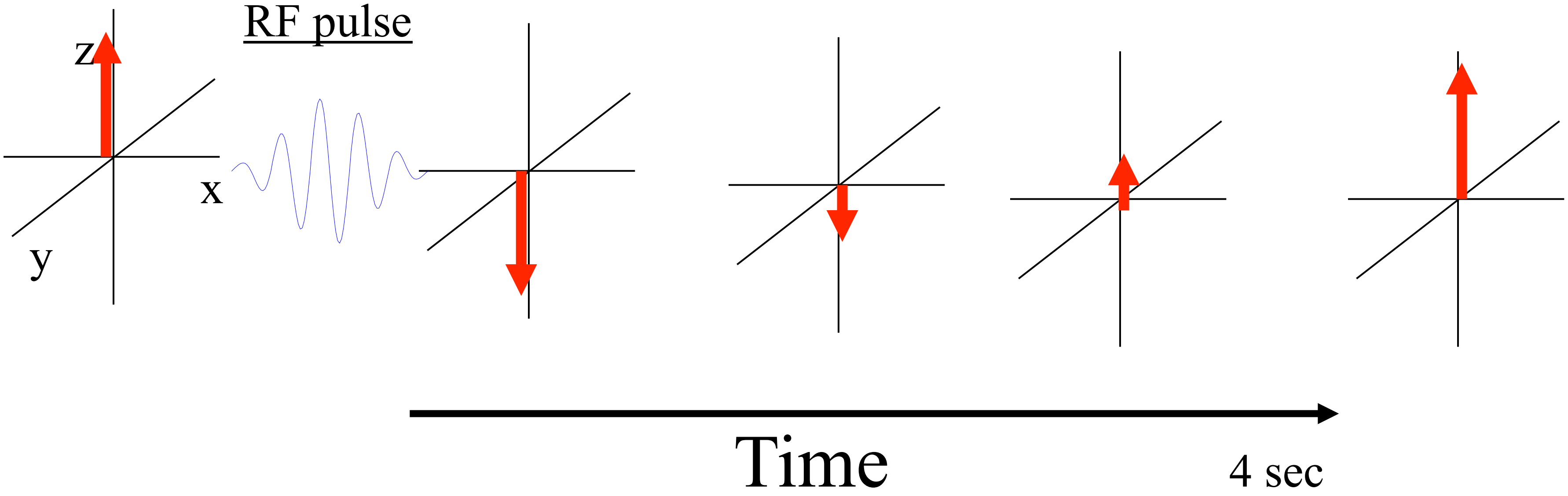
Longitudinal component

Transverse component

Longitudinal relaxation (T1)

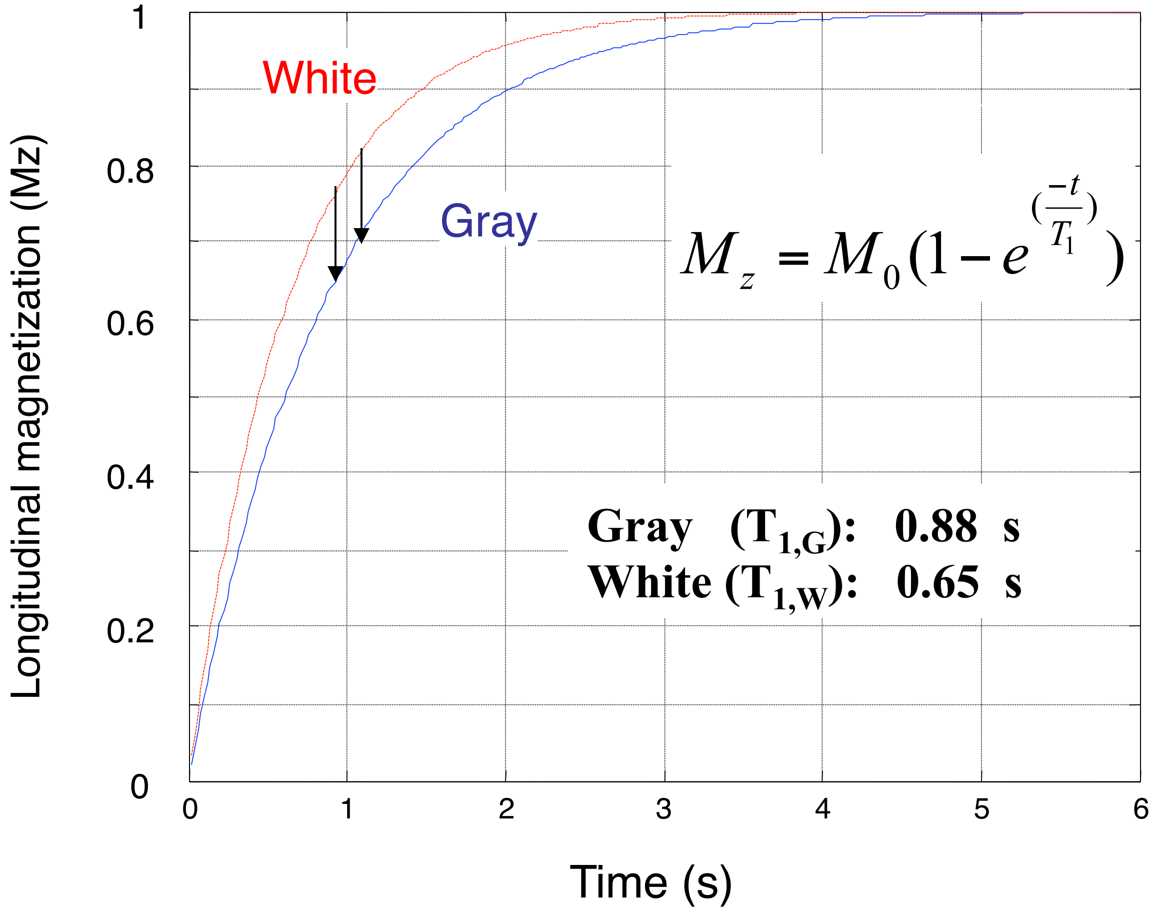
Suppose we apply a pulse that flips the bulk magnetization 180 deg. The longitudinal recovery follows an exponential time course, with a constant called T1

$$M_z = M_0(1 - e^{(\frac{-t}{T_1})})$$



Longitudinal relaxation rate depends on your neighborhood

The T1 values of water located in different brain tissue vary.
At 1.5T a good time to measure for contrast is around 0.8-1.2 sec following the RF pulse.



$$M_z = M_0(1 - e^{(\frac{-t}{T_1})})$$

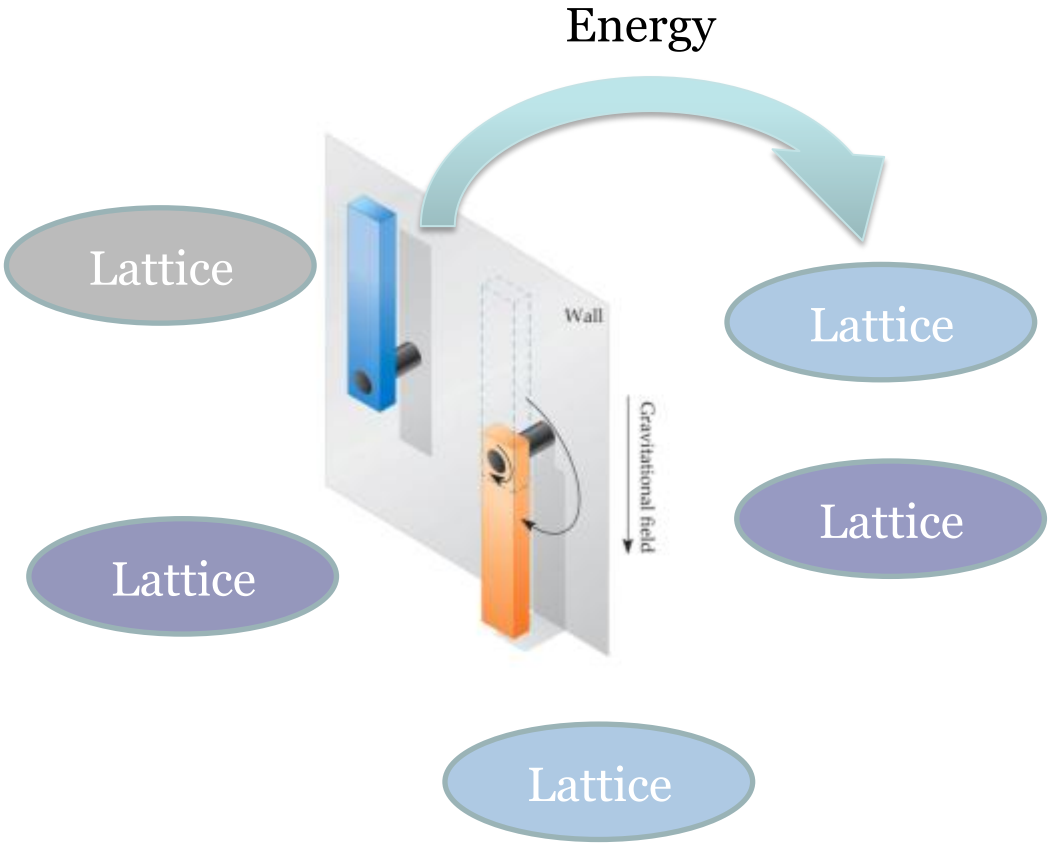
Gray (T$_{1,G}$): 0.88 s
White (T$_{1,W}$): 0.65 s

Analyzing spin-lattice exchange (T1)

Energy from anti-parallel spins is absorbed by the macromolecules in the environment (lattice)

How efficient is this energy exchange?

I am glad you asked.



Energy

Lattice

Lattice

Lattice

Lattice

Lattice

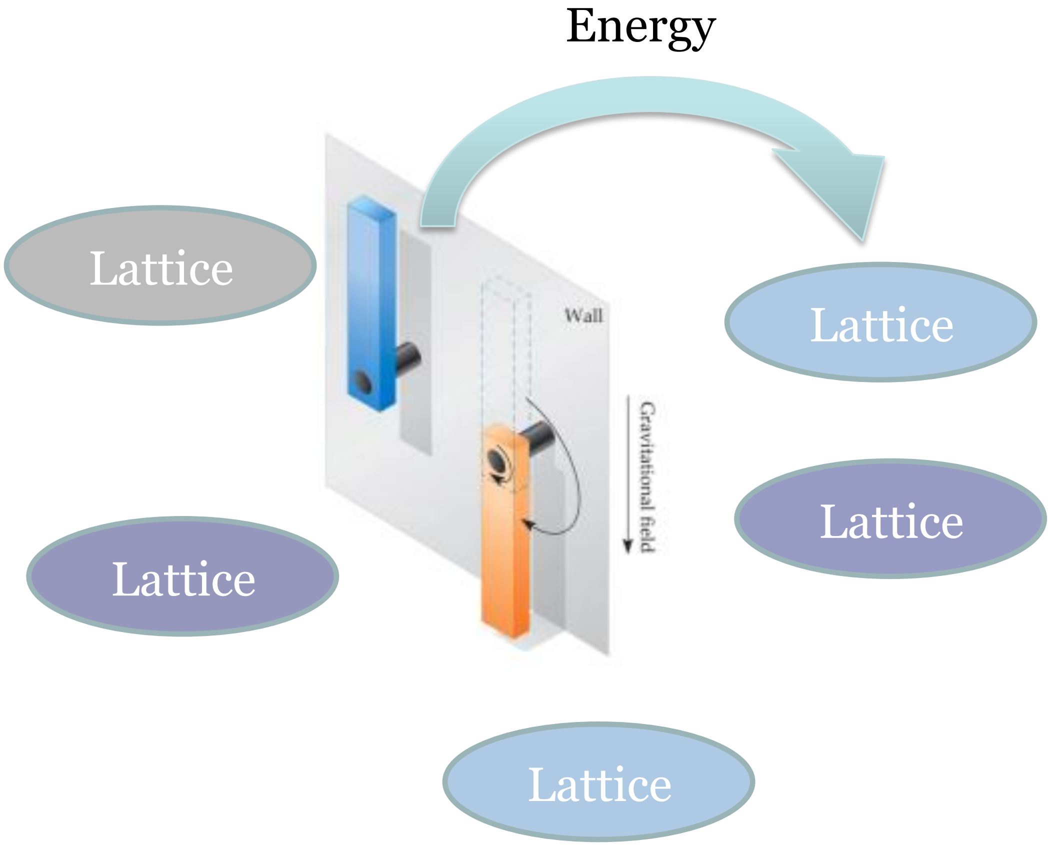
Analyzing spin-lattice exchange (T1)

(Mezer et al., 2014)

Spin-lattice energy exchange rate (T1) depends on

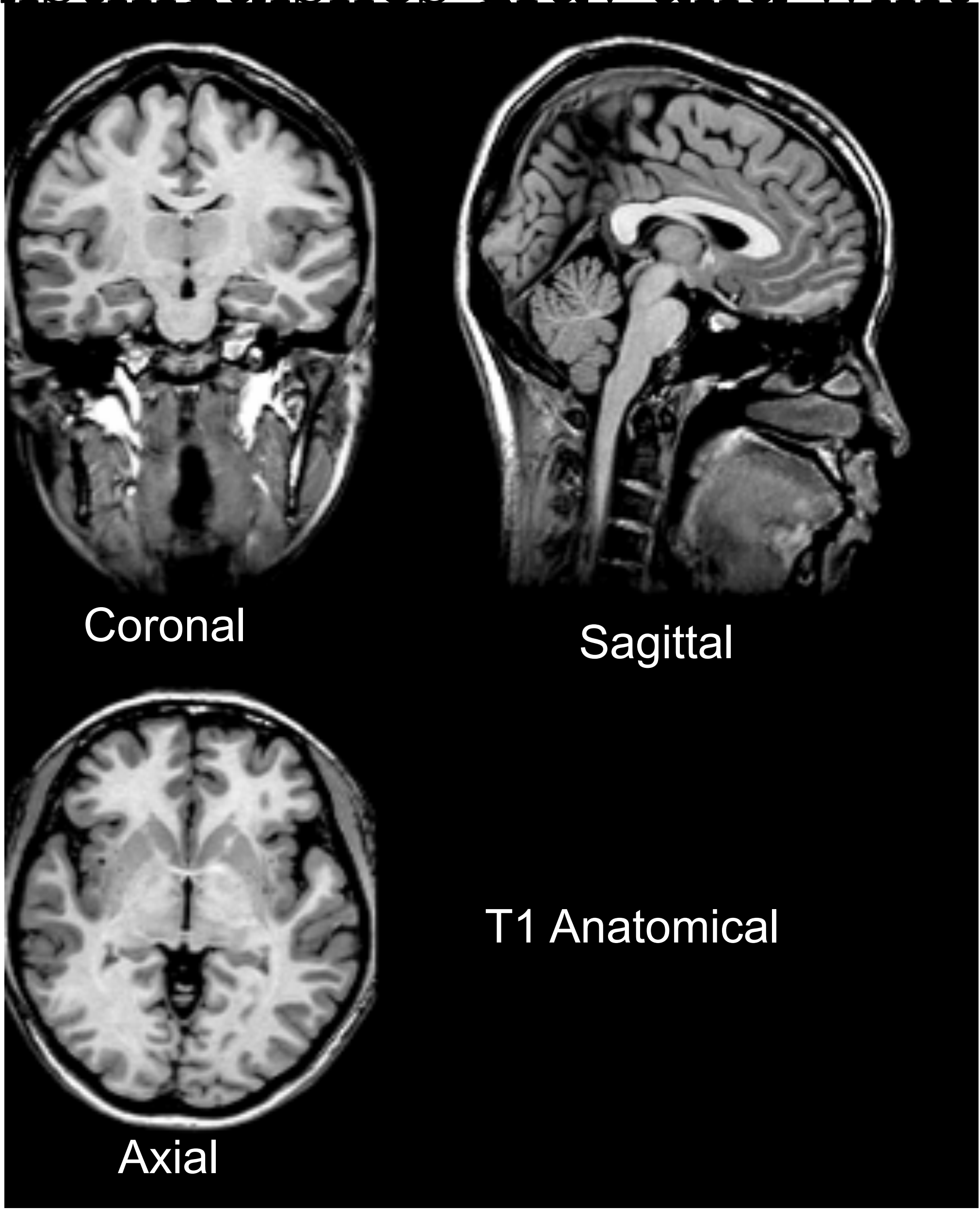
- How many macromolecules are in the lattice
- The type of macromolecules

If you could measure this in the brain, these are pretty good things to know (noninvasively)



The T1-contrast distinguishes gray and white

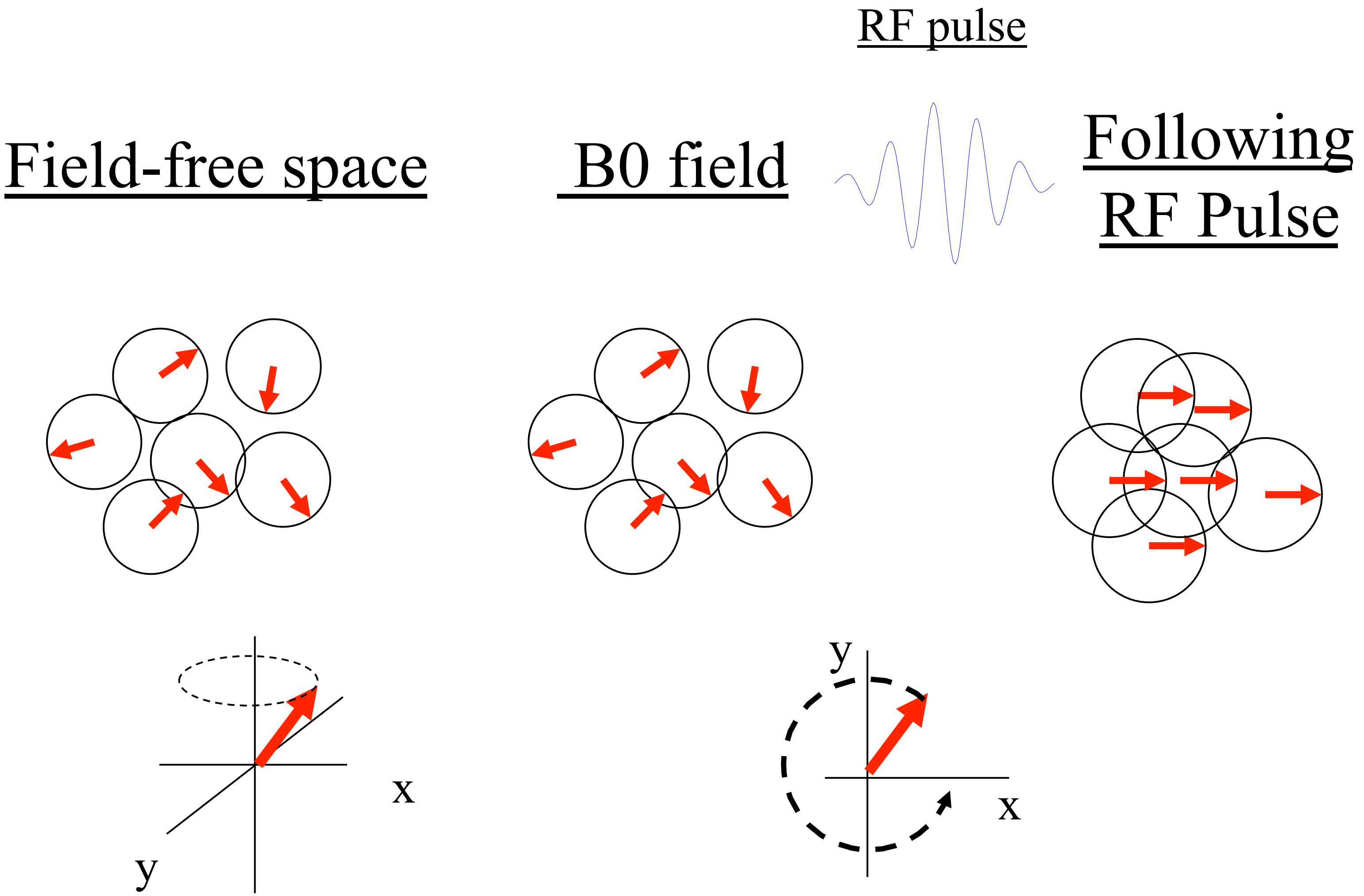
T1-weighted images are typically used for understanding gray matter atrophy, or ventricular enlargement



The T2* signal and functional MRI

Blood Oxygen Level Dependent
(BOLD) signals

Transverse magnetization



RF pulse

Field-free space

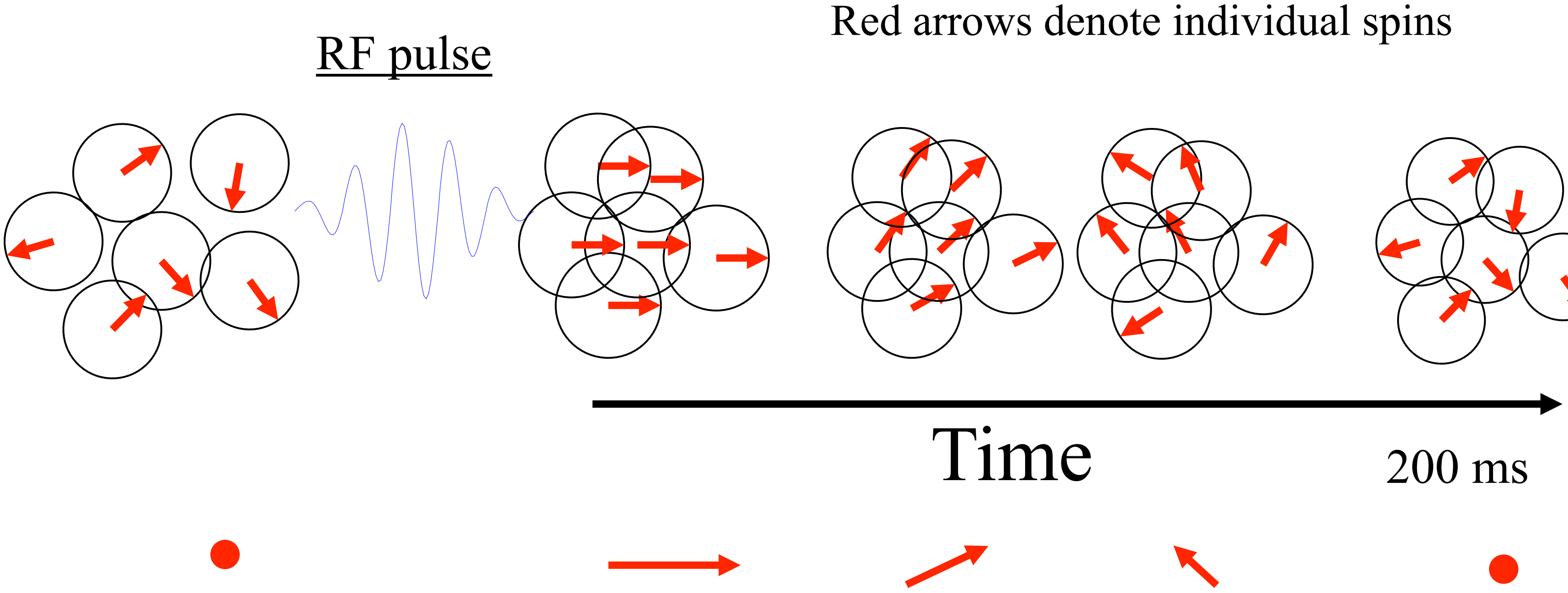
B0 field

Following RF Pulse

Transverse relaxation: T2 (and T2*)

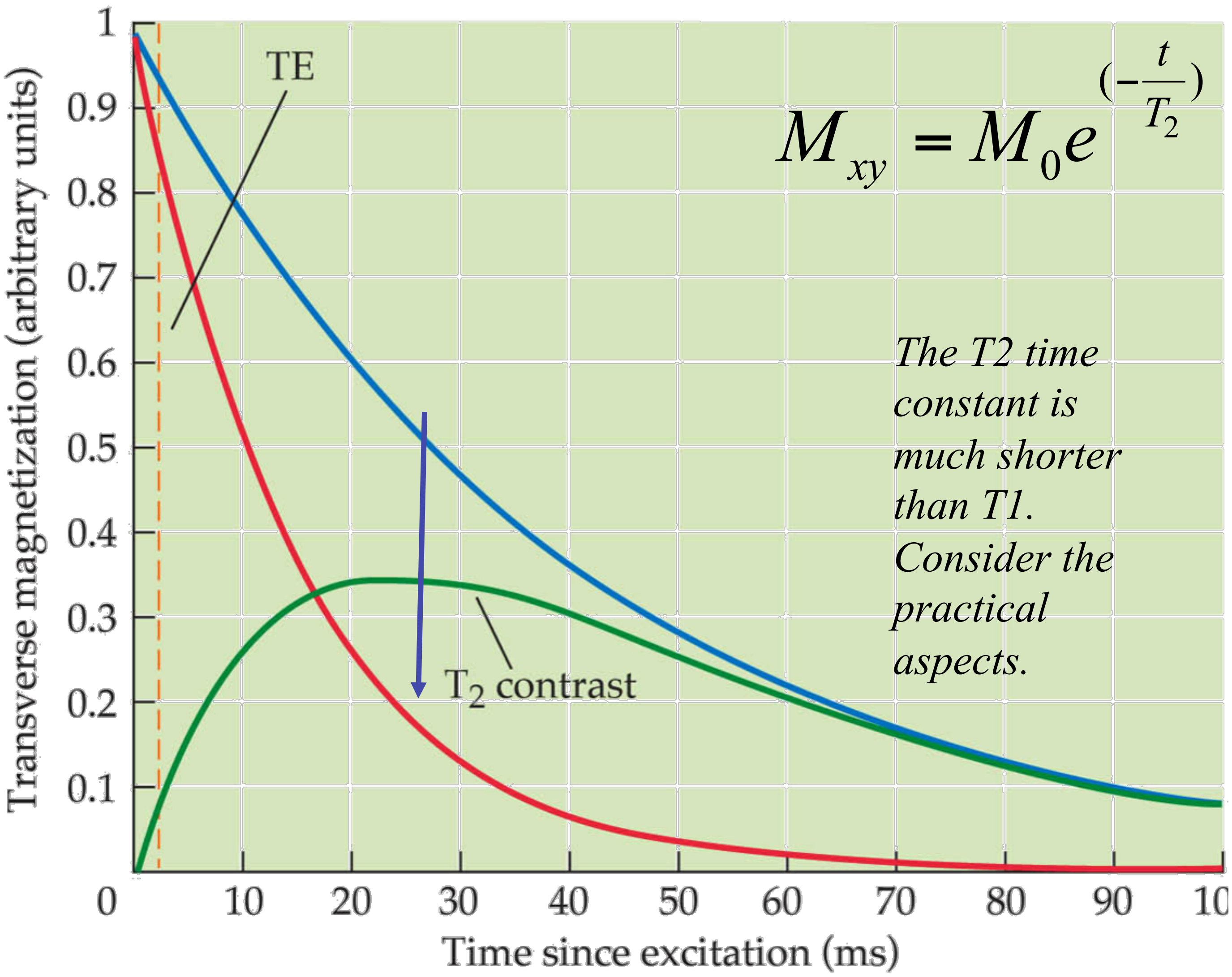
Bulk transverse magnetization follows an exponential recovery with a time constant called T2

$$M_{xy} = M_0 e^{(-\frac{t}{T_2})}$$



Selection of delay for T2 contrast

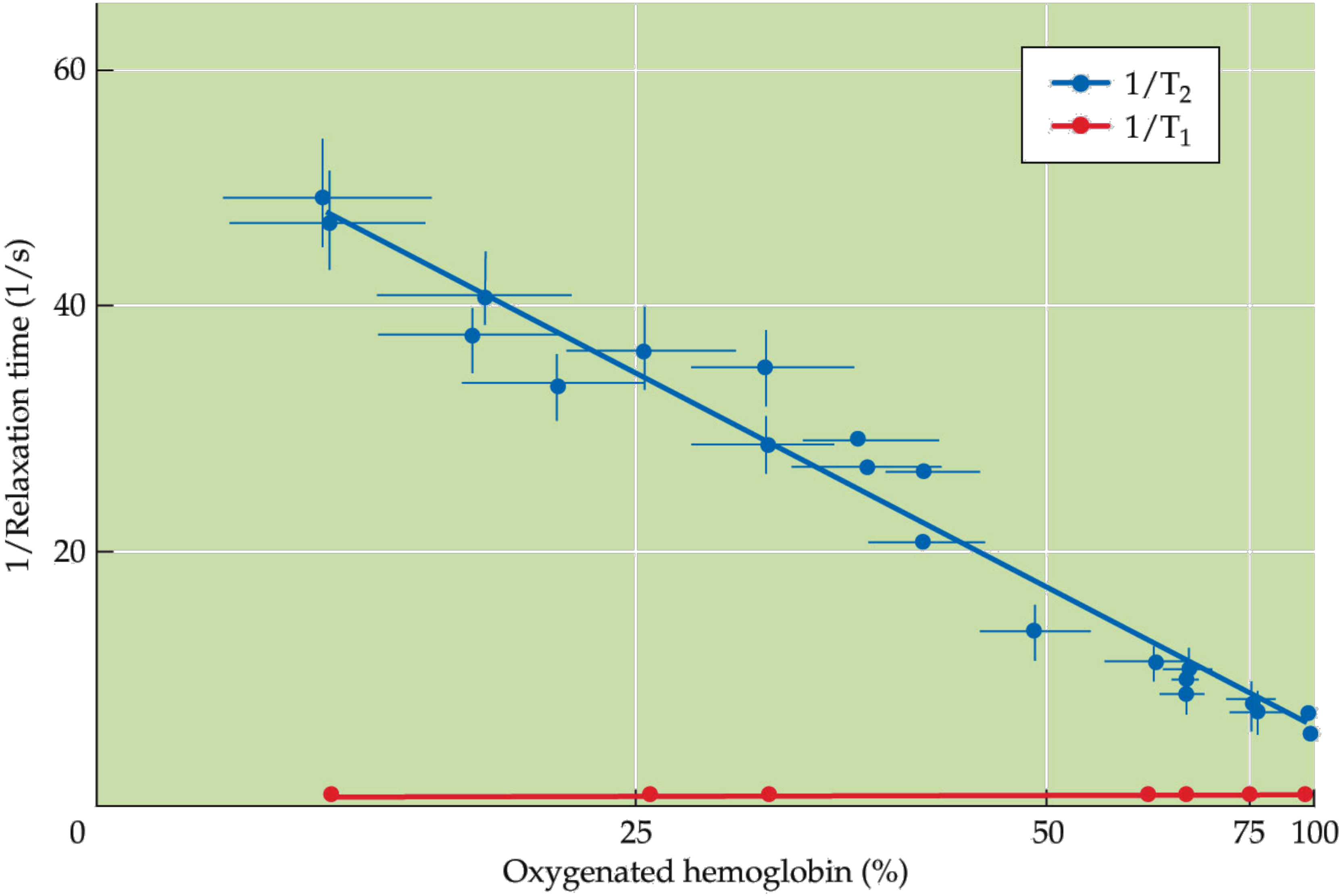
(After Huettel et al., Functional Magnetic Resonance Imaging)



$$M_{xy} = M_0 e^{\left(-\frac{t}{T_2}\right)}$$

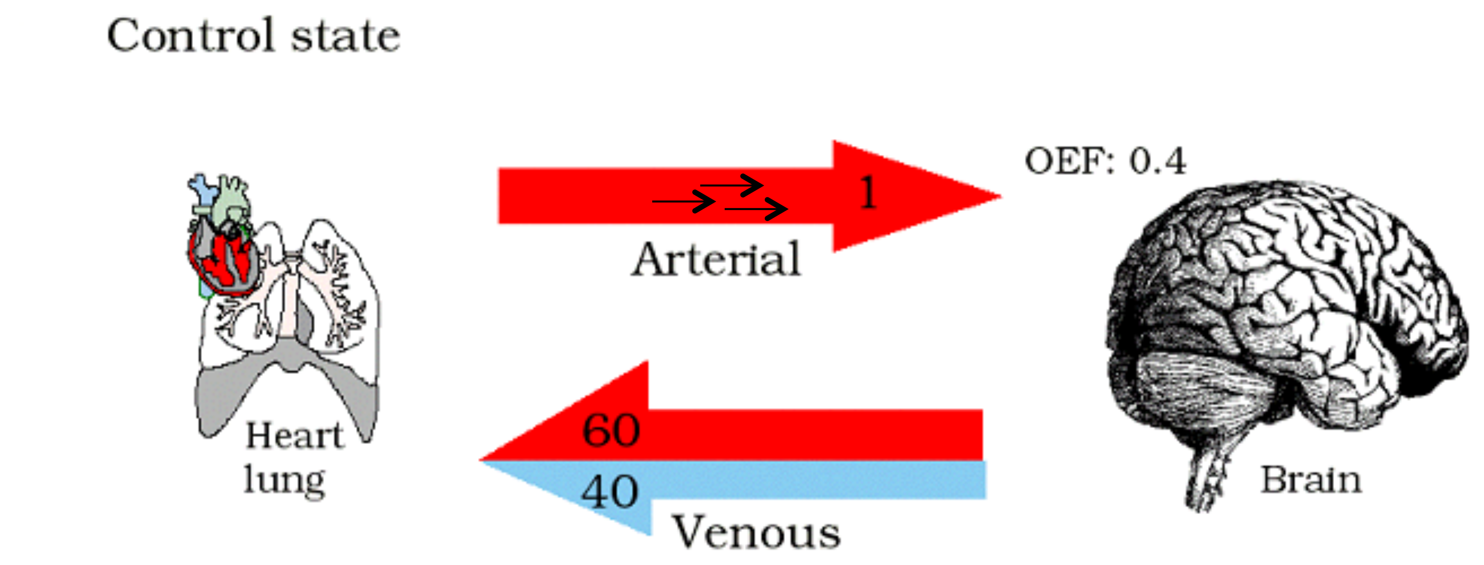
The T2 time constant is much shorter than T1. Consider the practical aspects.

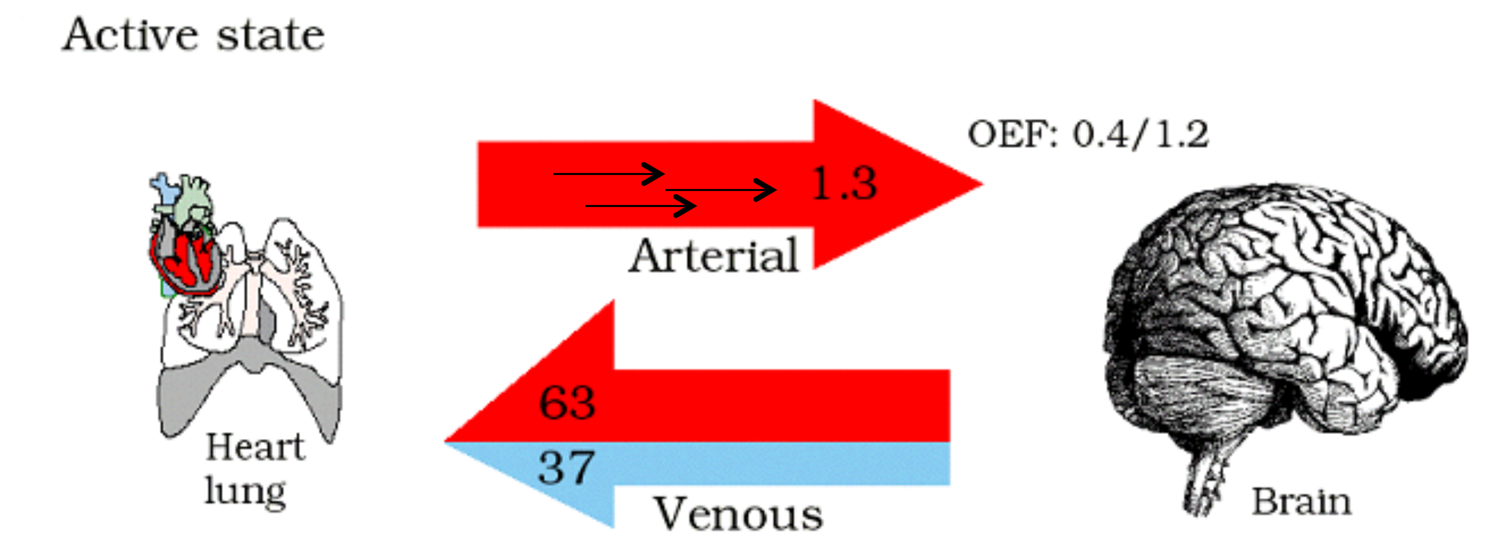
Blood oxygenation effects T2 but not T1



***Functional Magnetic Resonance Imaging* 2e, Figure 7.1**

Blood oxygenation increase is localized

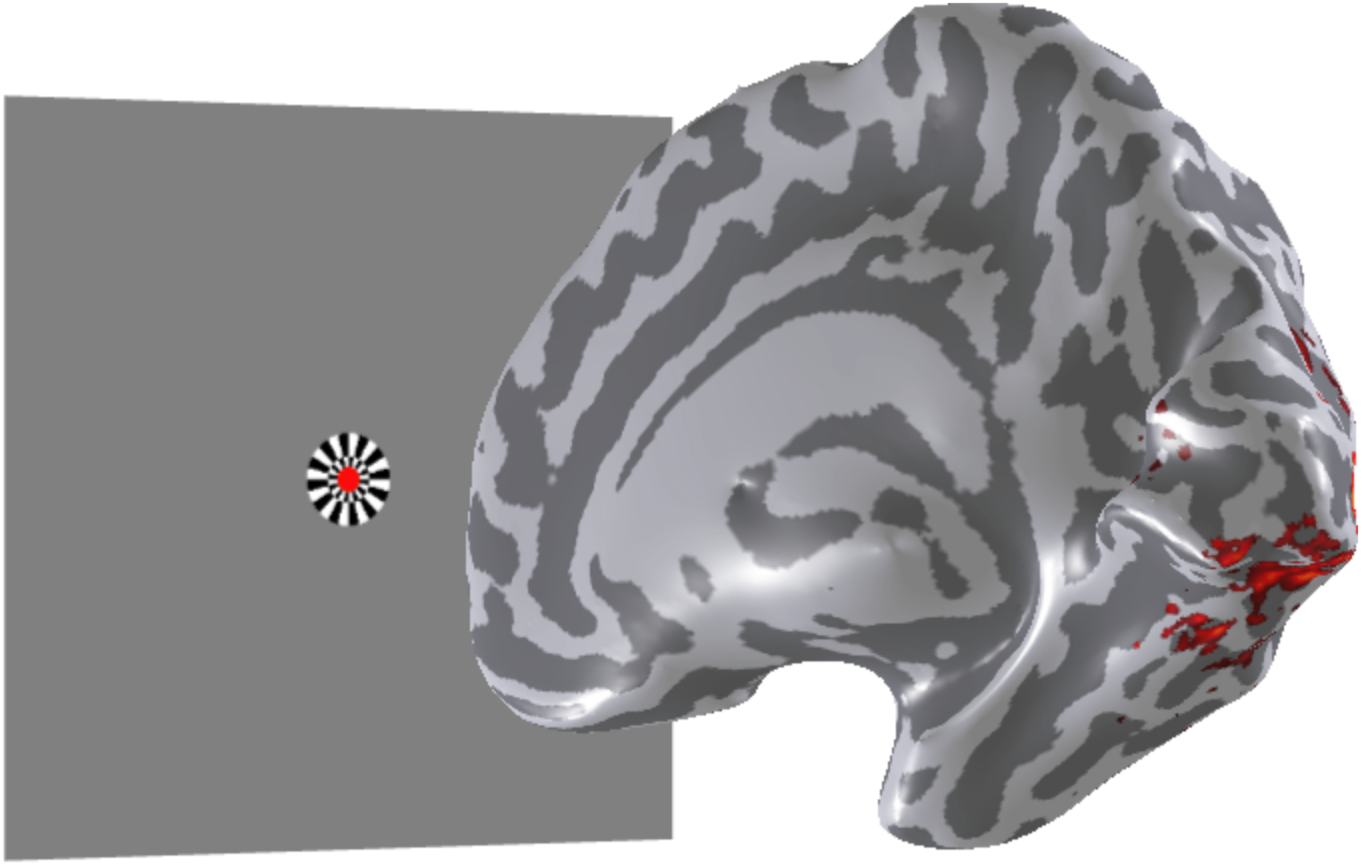




Sokolow
Raichle
Fox

Human eccentricity mapping with fMRI

(Engel et al., 1994,1997; Sereno; DeYoe; Others)



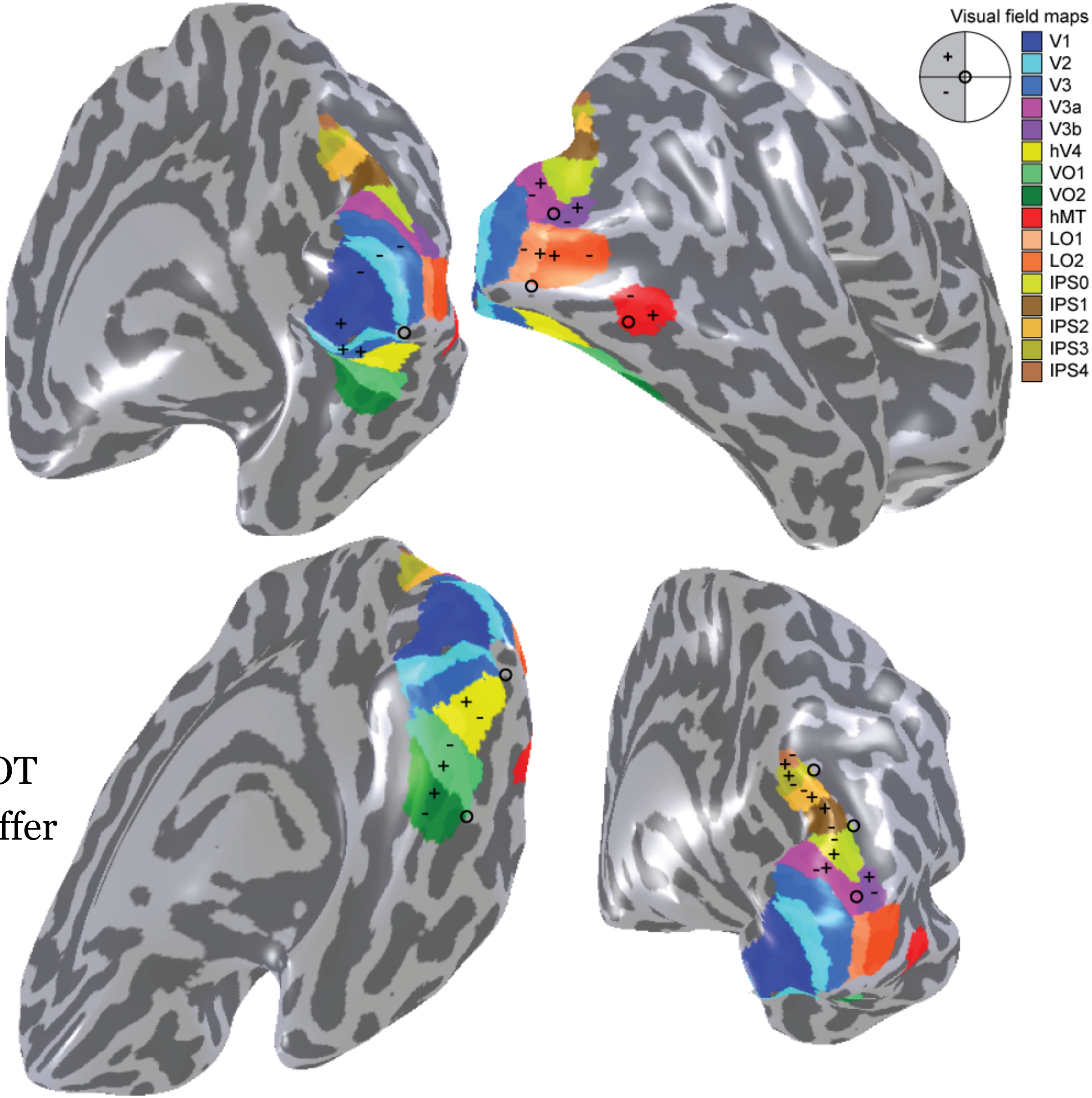
More than twenty visual field maps

Wandell, Dumoulin, Brewer
(2007) **Neuron**

Wandell and Winawer
(2011) **Vision Research**

Wang et al.
(2014) **Cerebral Cortex**

- Tile the occipital lobe
- Extend into IPS and VOT
- Response properties differ



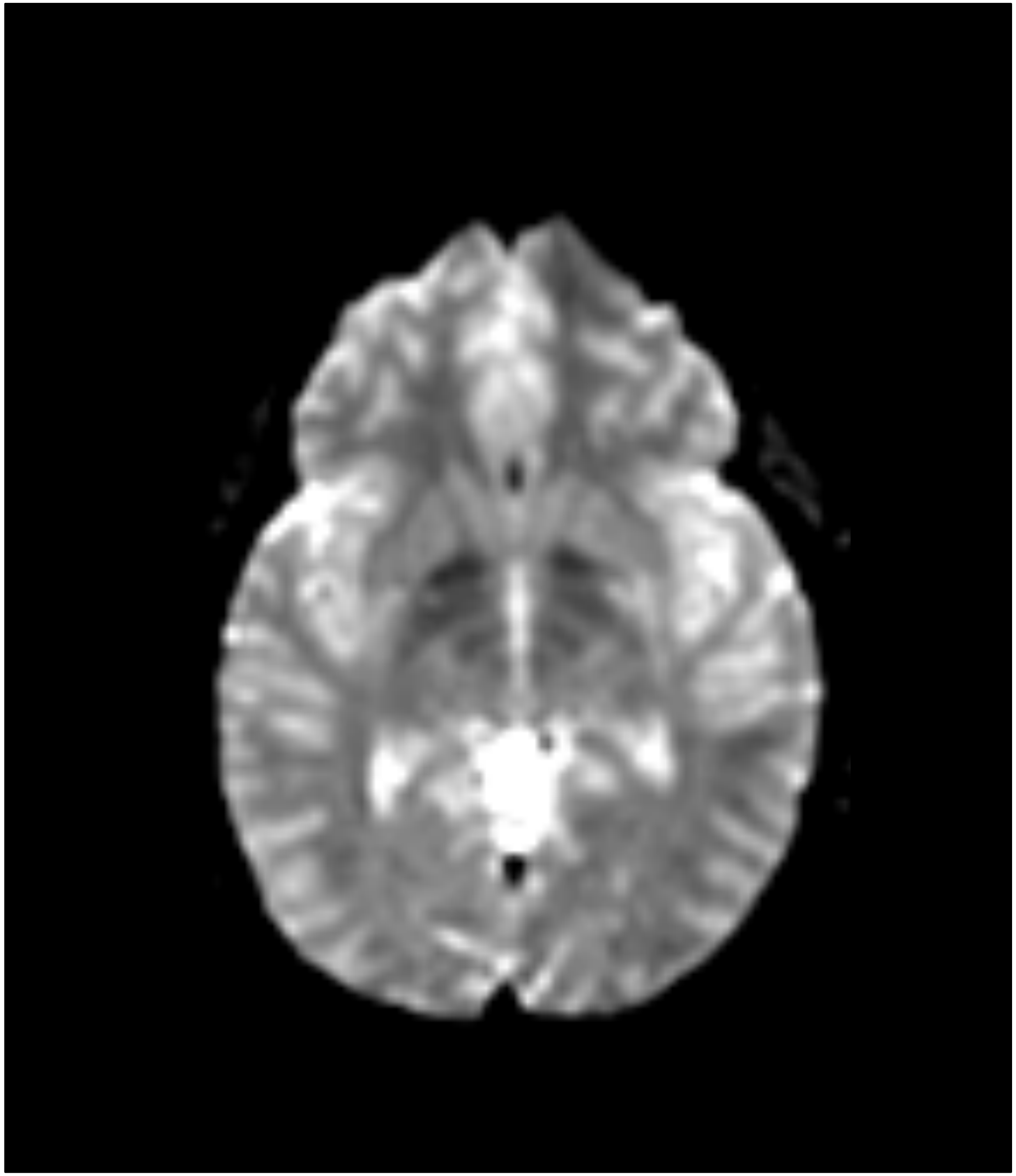
Diffusion weighted imaging tutorial

- Measuring the diffusion signal

Bob
Dougherty

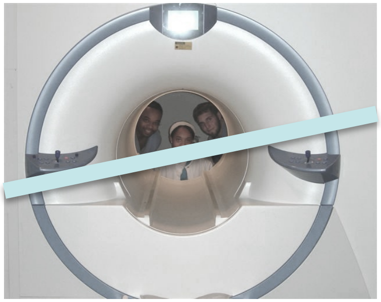
Non-diffusion MR image

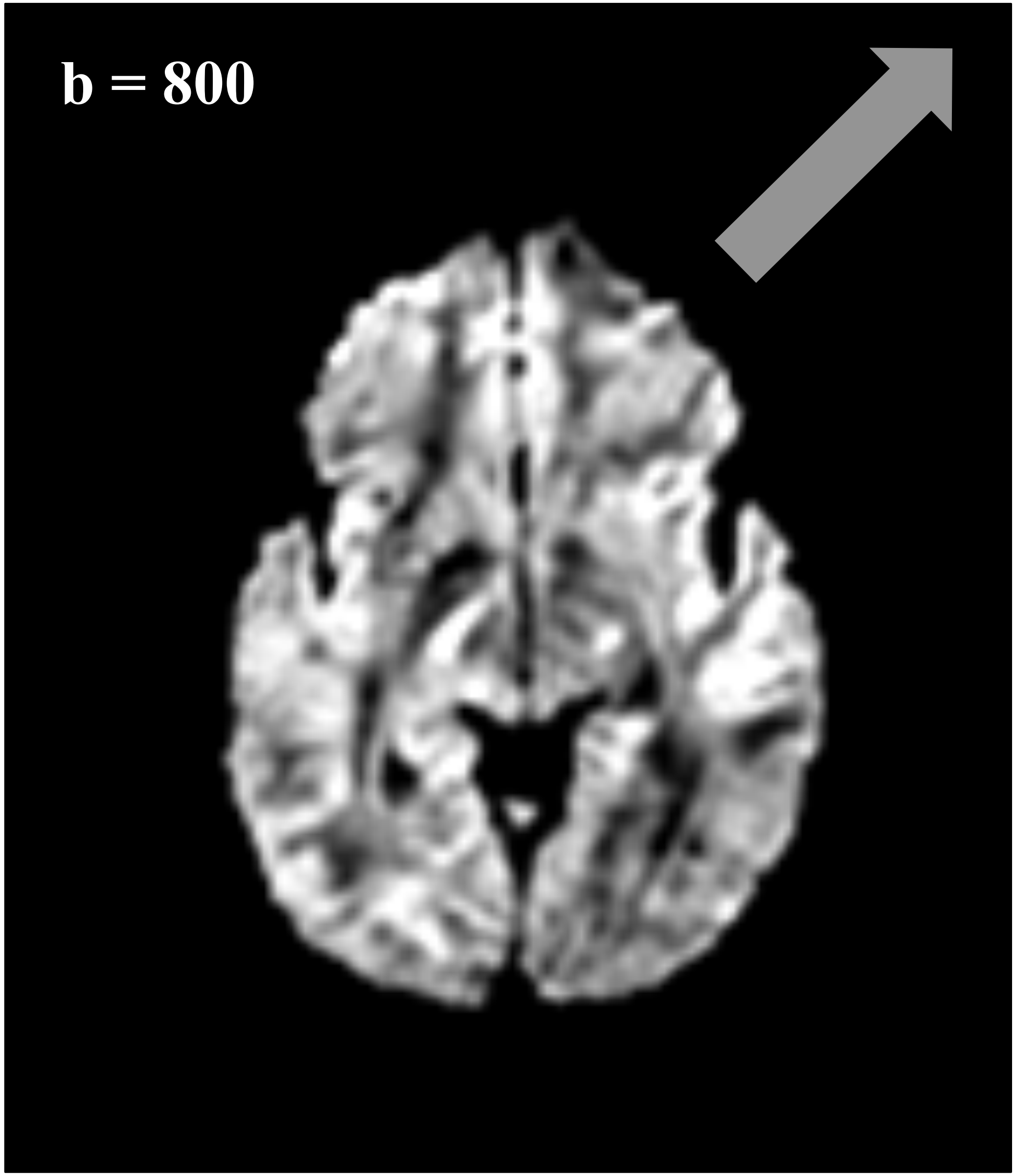
Dark means large
signal attenuation
High ADC



Diffusion weighting: Directions

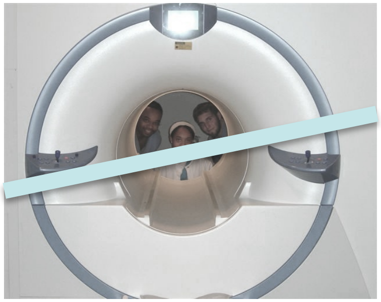
Dark means large signal attenuation
High ADC

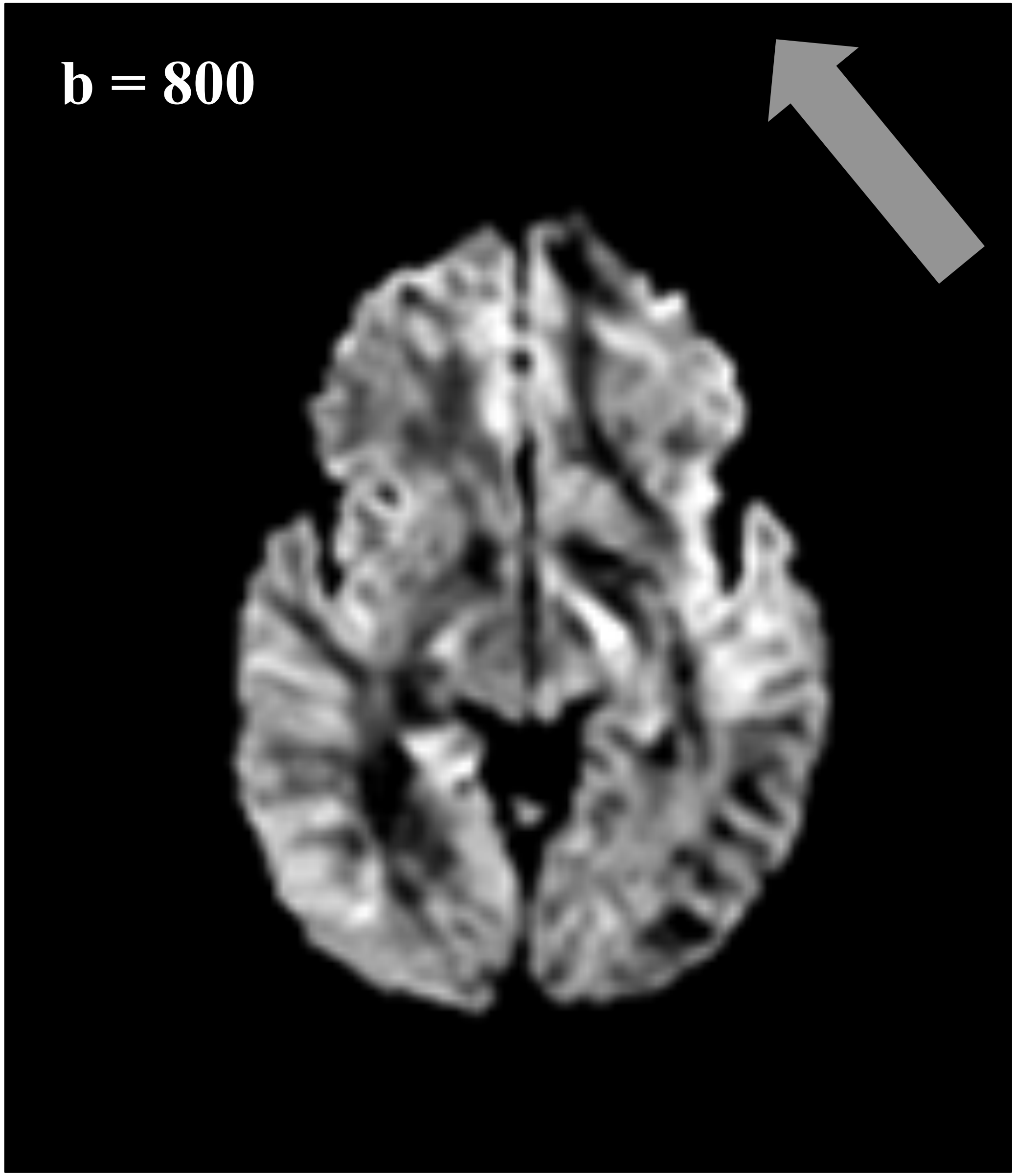




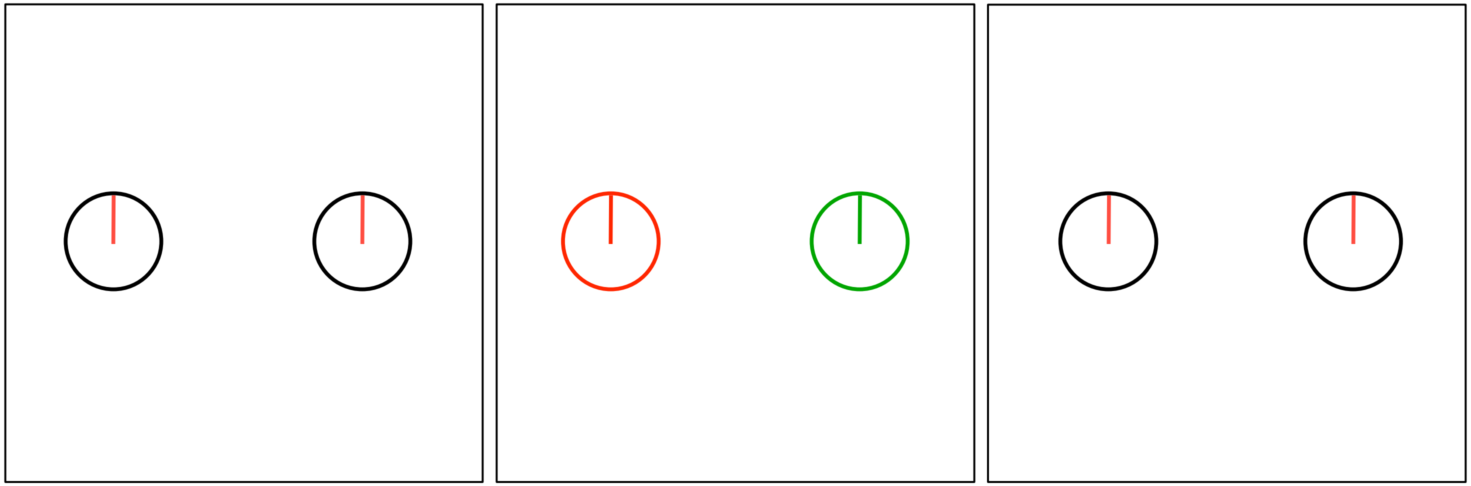
Diffusion weighting: Directions

Dark means large signal attenuation
High ADC

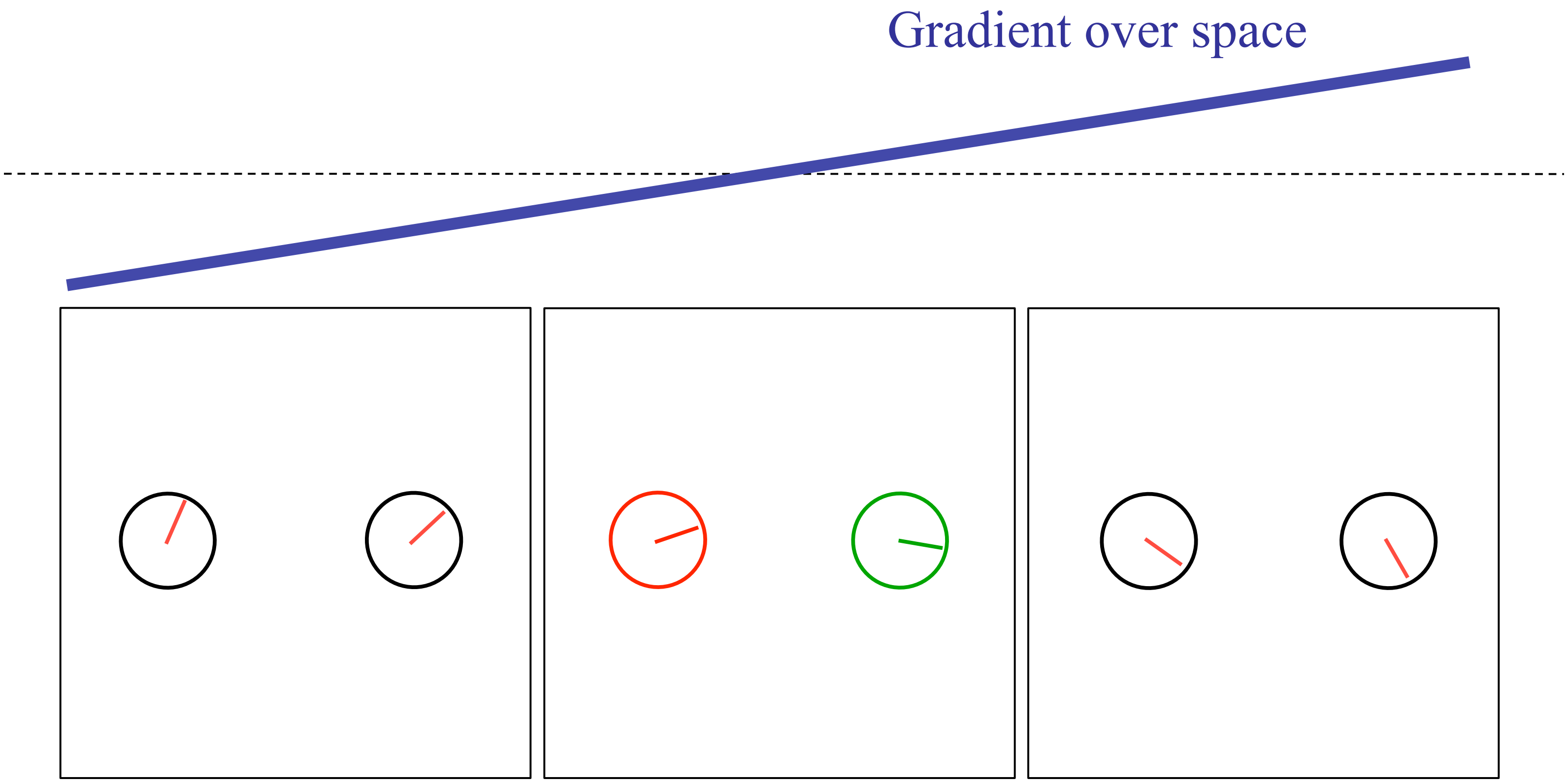




Protons Precessing in Phase



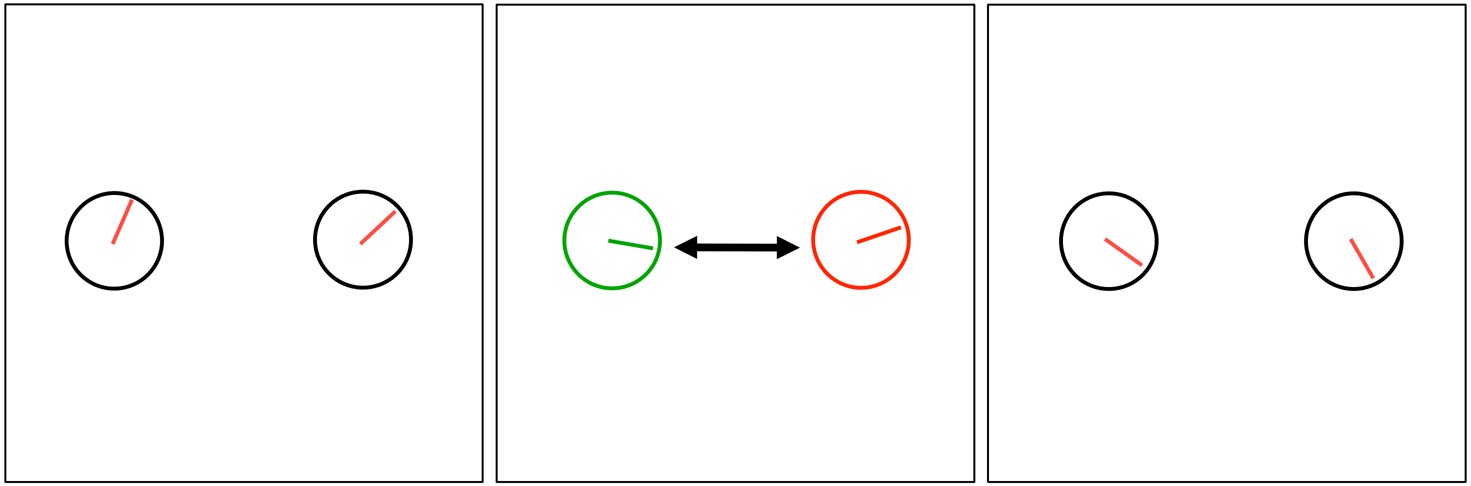
Diffusion Weighting: First Pulse



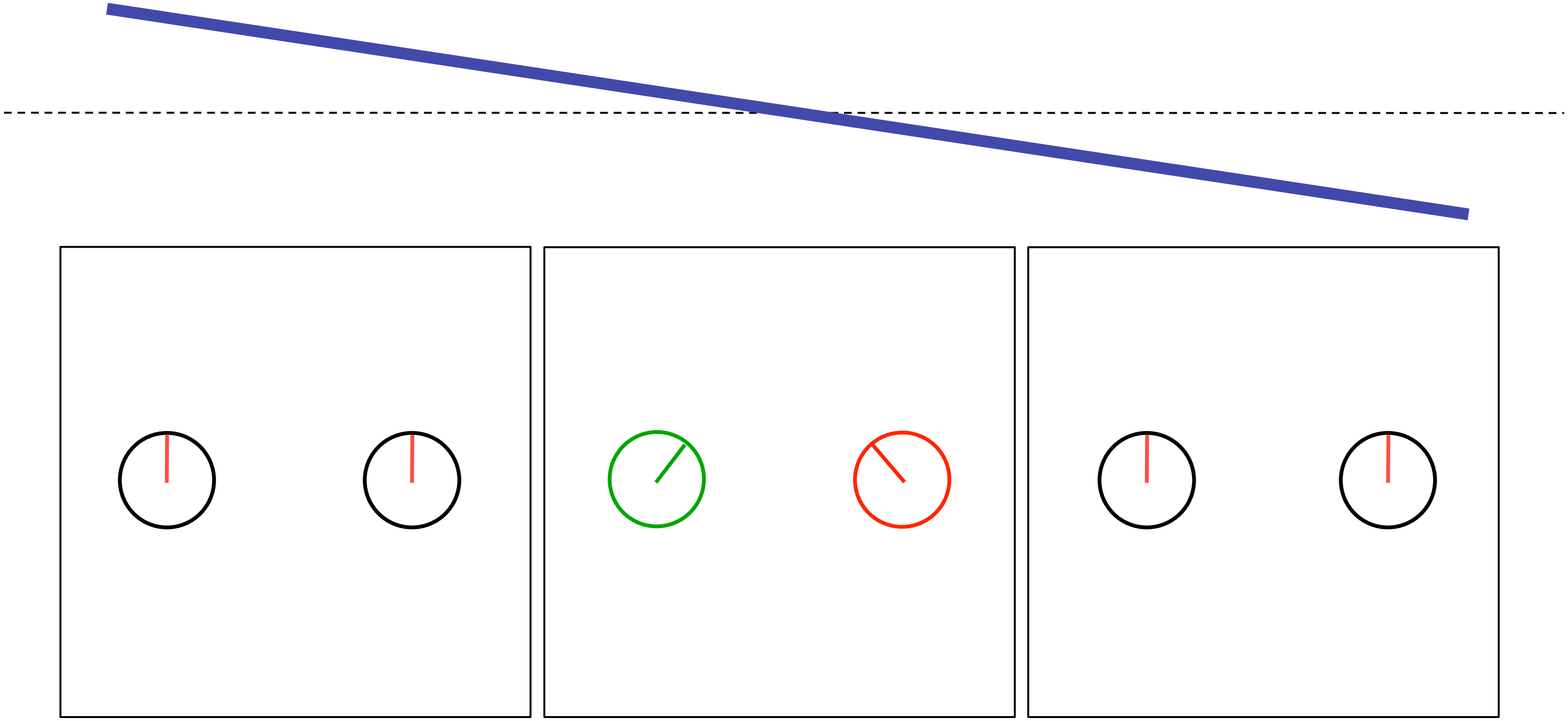
Slower
(local field is lower)

Faster
(local field is higher)

Time to Diffuse



Diffusion Weighting: Second Pulse



Gradient over space

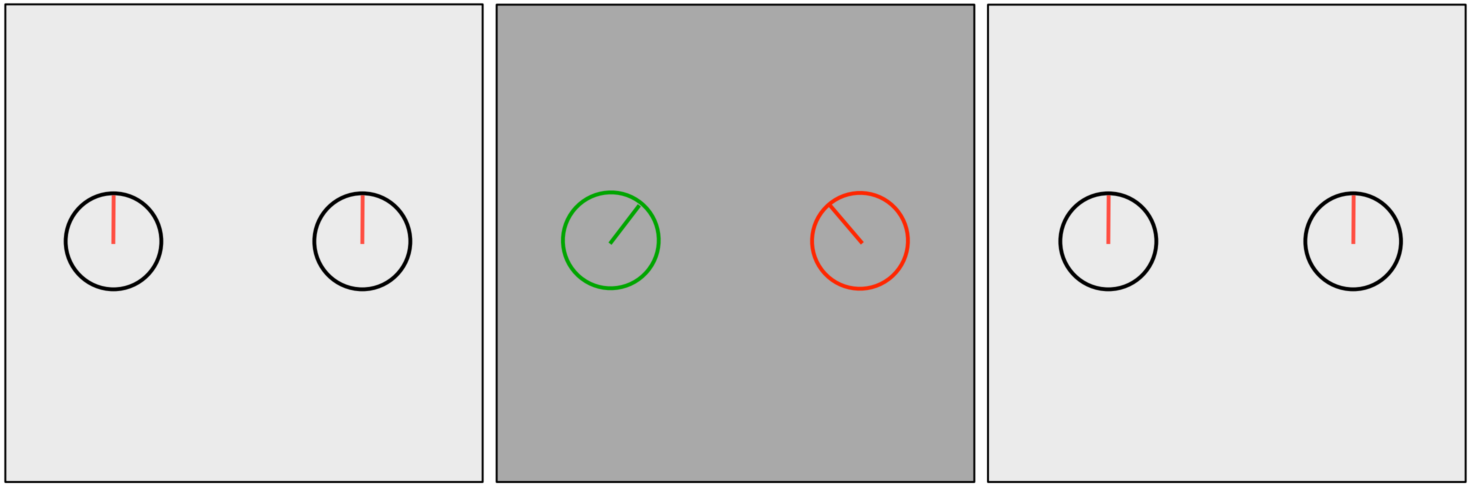
Faster
(local field is higher)

Slower
(local field is lower)

Reduced signal from spin dephasing

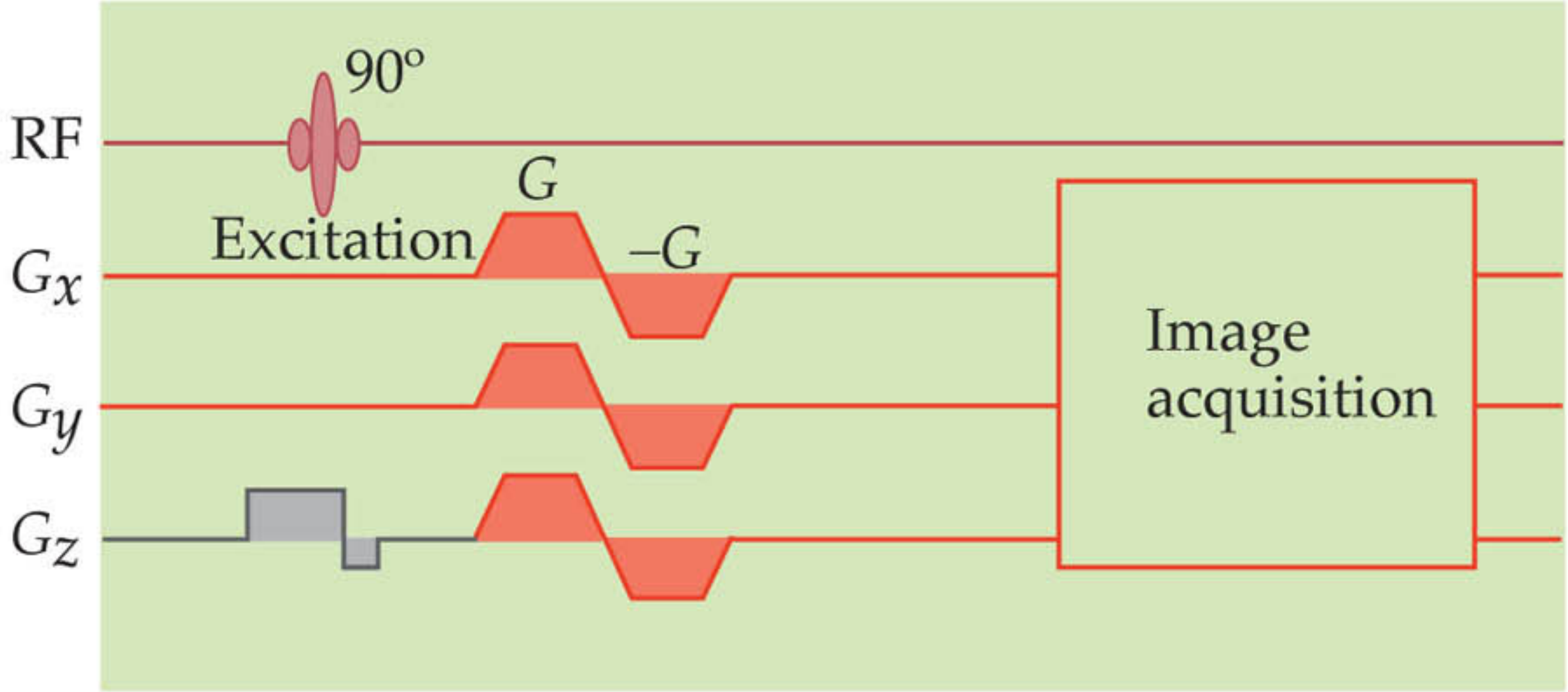
E. O. Stejskal and J. E. Tanner (1965)

Signal attenuation = exp(-b * ADC)



Signal from spins that that diffused is lower because the spins are not aligned (incoherent)

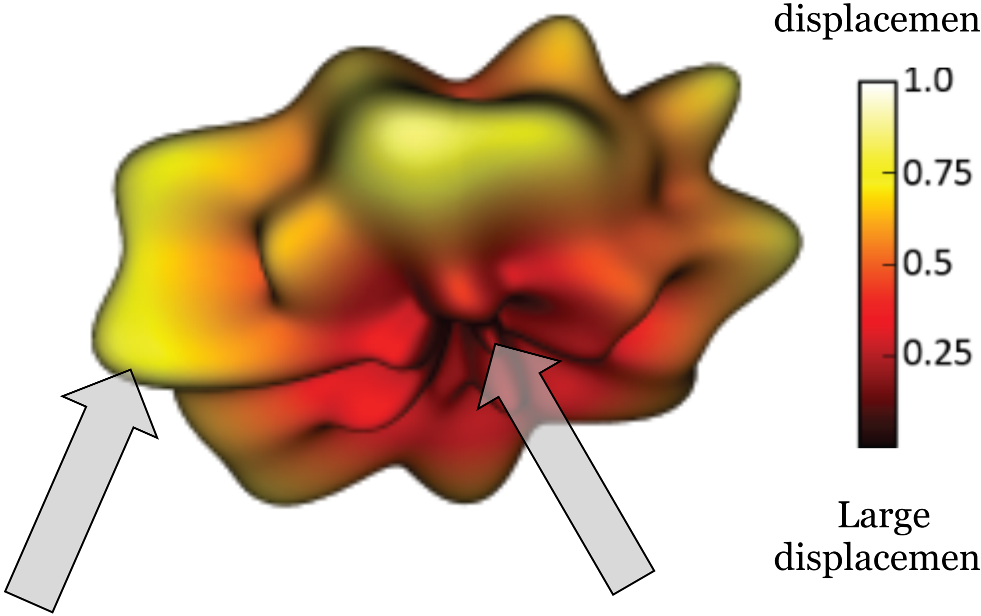
Pulse sequences for diffusion-weighted imaging (Huettel et al.)



FUNCTIONAL MAGNETIC RESONANCE IMAGING, Figu

Diffusion orientation distribution function (ODF)

$$S(\theta) = S_0\, e^{-bD(\theta)}$$



Small
displacement

Large
displacement

Signal
Re: b=0

Big signal,
small ADC

Small signal,
large ADC

The measured diffusion signal in a direction, θ, is related to the apparent diffusion coefficient in that direction, D(θ)

ADC – apparent diffusion coefficient

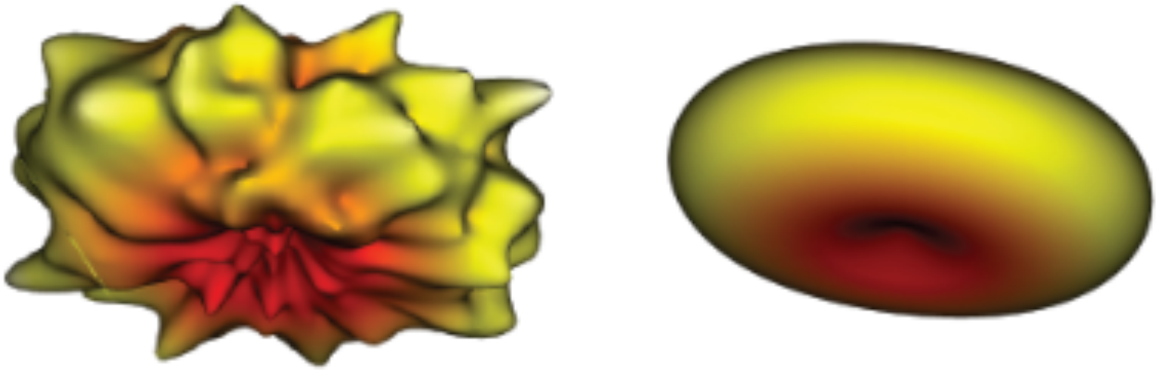
Modeling the diffusion signal

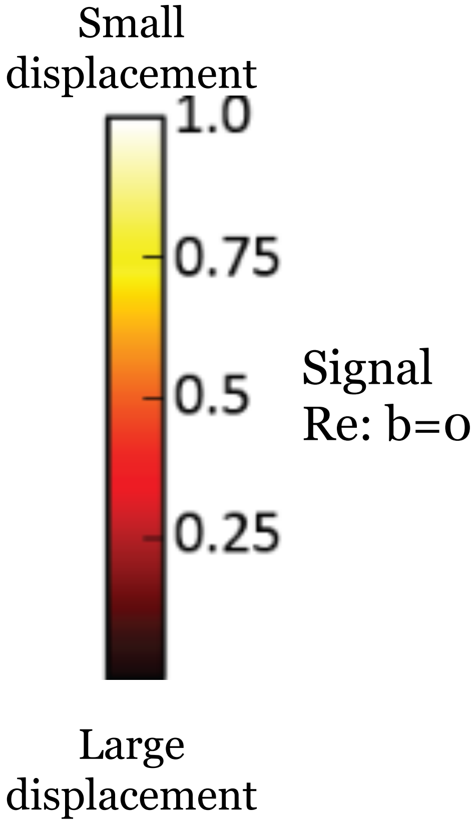
- The diffusion tensor model (DTM)
- The ball-and-stick model (SFM)

Ariel
Rokem

Diffusion tensor model (DTM)

Predicts the **voxel diffusion signal** with a phenomenological equation, motivated by Gaussian diffusion
(Basser, Pierpaoli, 1996)

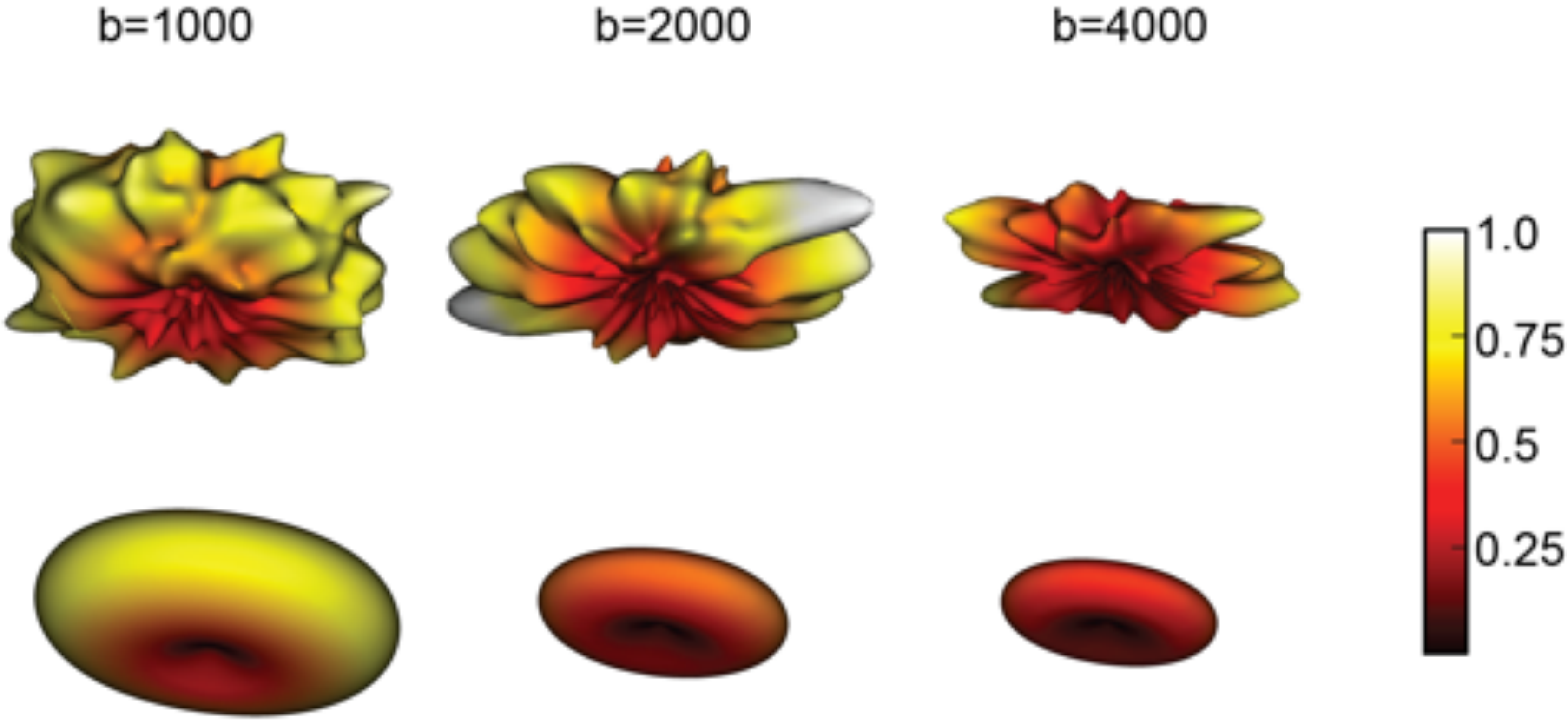




$$S(\theta) = S_0\, \mathrm{e}^{-bD(\theta)} \longleftarrow D(\theta) = \theta^t Q \theta$$

$$Q = A^t A$$

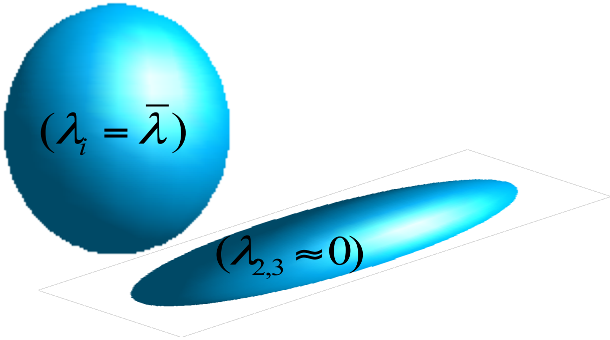
Diffusion tensor model fits



Signal re: b=0

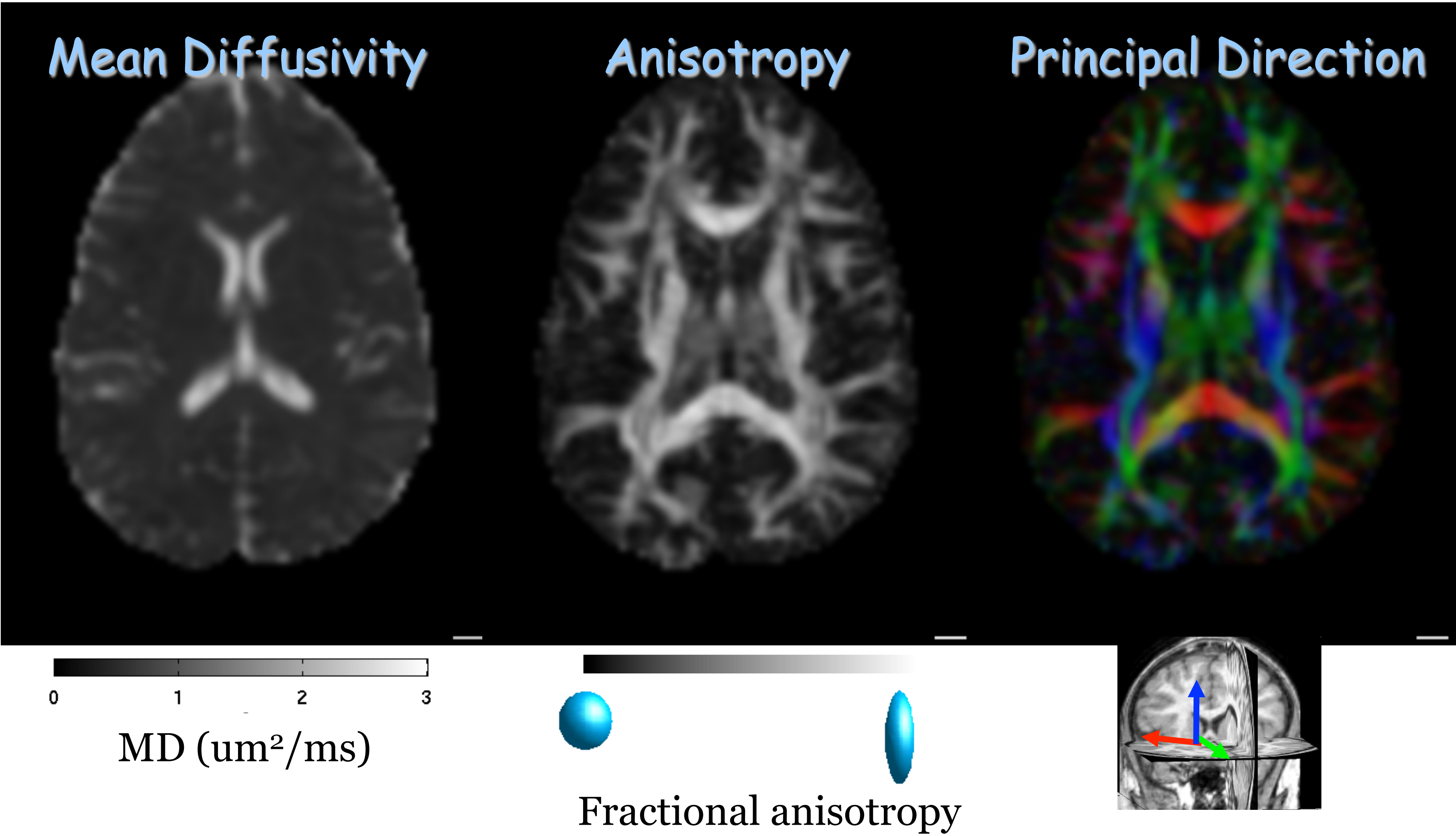
Summary measures of the DTM

(Basser & Pierpaoli, 1996)



Axial diffusivity (AD)	λ_1
Radial diffusivity (RD)	$\frac{\lambda_2 + \lambda_3}{2}$
Mean diffusivity (MD)	$\bar{\lambda} = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3}$
Fractional anisotropy (FA, dimensionless)	$\sqrt{\frac{3}{2}}\sqrt{\frac{(\lambda_1 - \bar{\lambda})^2 + (\lambda_2 - \bar{\lambda})^2 + (\lambda_3 - \bar{\lambda})^2}{\lambda_1{}^2 + \lambda_2{}^2 + \lambda_3{}^2}}$

DTI analyzes white matter structure

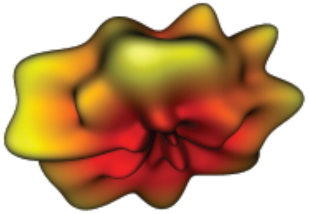


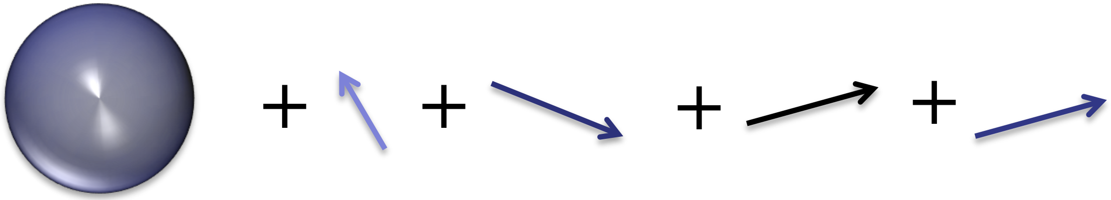
The sparse fascicle model (SFM)

Frank (2002), Behrens et al. (2003)

Predicts the diffusion signal with an isotropic diffusion term (**ball**) plus a weighted sum of anisotropic terms (**sticks**) that are meant to summarize oriented fibers

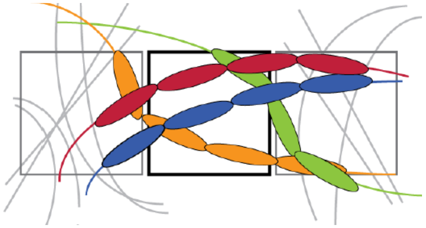
$$S(\theta) = \underset{\uparrow\ \text{isotropic}}{w_0 D_0} + \sum_f \underset{\uparrow\ \text{weights}}{w_f}\, e^{\overset{\text{fascicles}\ \nwarrow}{-bD_f(\theta)}}$$





Ball

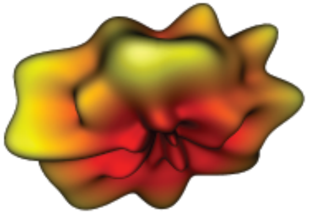
Sticks

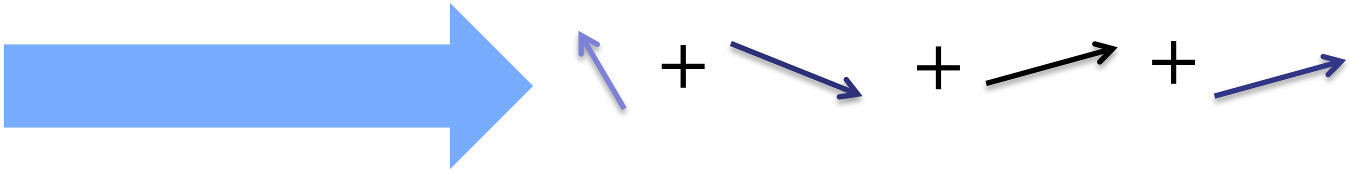


From diffusion data to fiber orientations

Orientation distribution function (ODF)

Fiber orientation distribution (FOD)



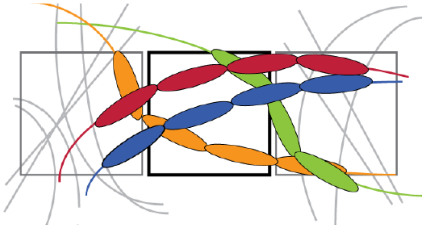


ARD/Probtrackx
(Behrens et al., 2007)

Constrained spherical deconvolution (CSD)
(Tournier et al., 2007)

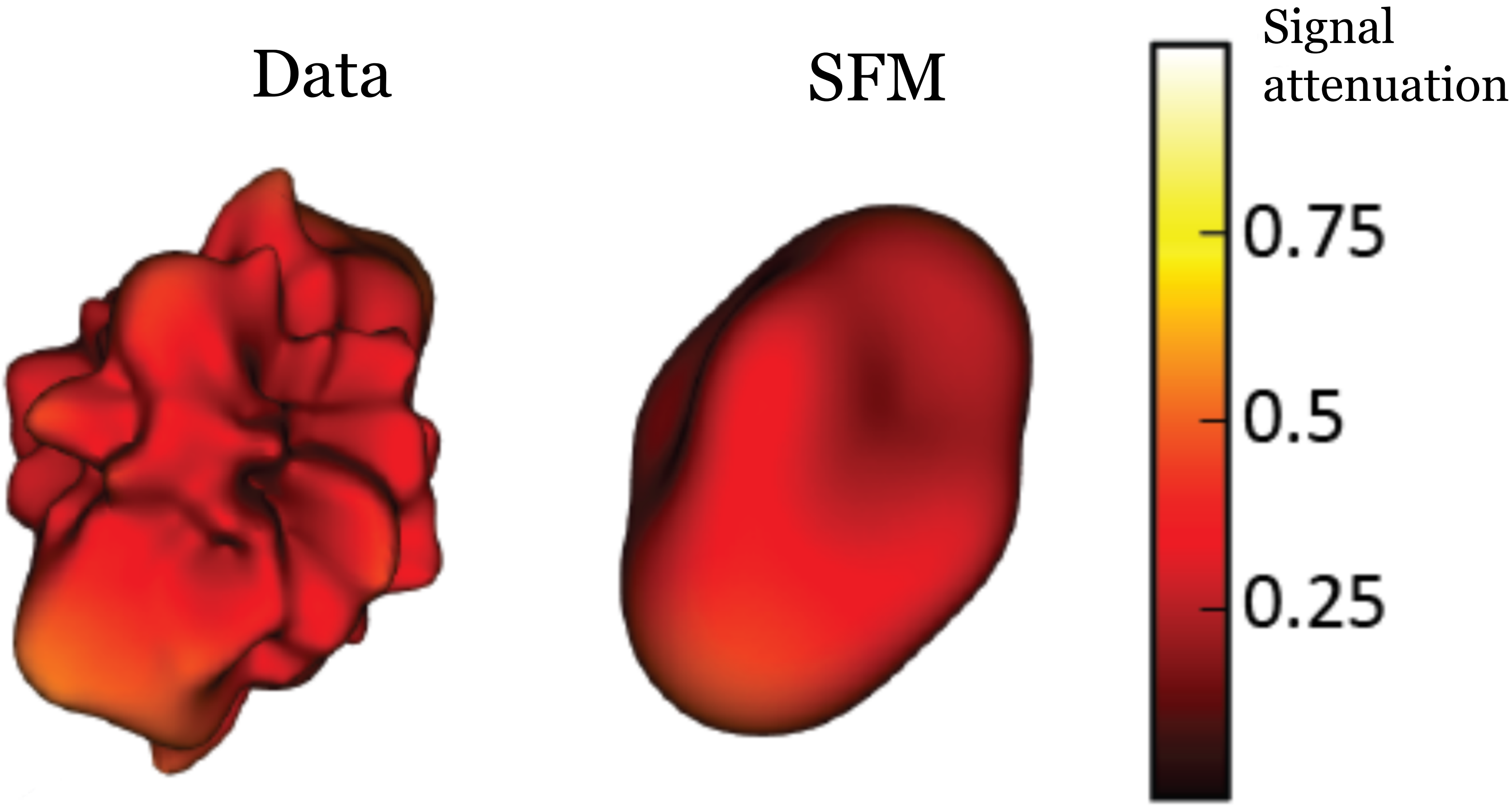
Sparse Fascicle Model
(Rokem, 2015)

Others



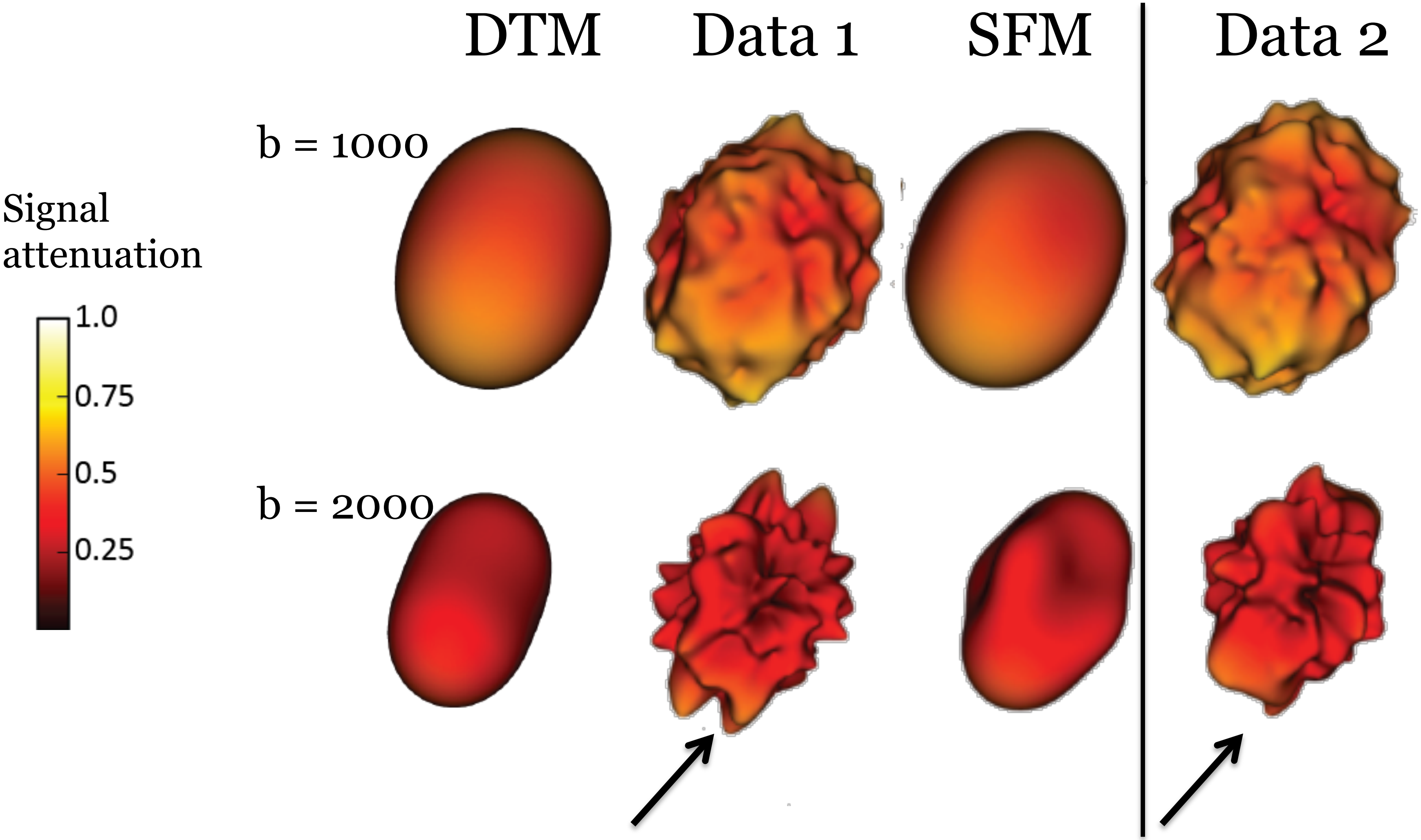
Sparse fascicle model (SFM)

(Rokem et al. 2015)



SFM uses a sparseness constraint on the sticks (fascicles)
Related to mrTrix, but no intermediate spherical harmonics

Evaluating models using cross-validation
(Rokem et al., 2015)

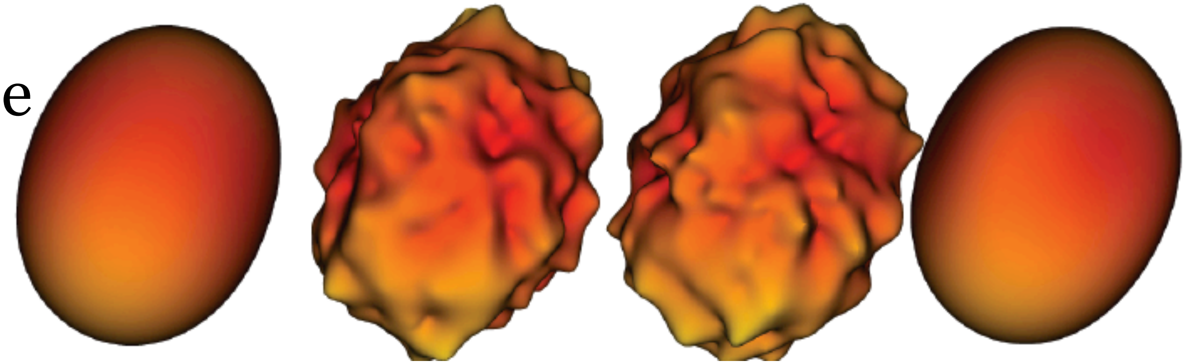


Evaluating models using cross-validation
(Rokem et al., 2015)

DTM Data 1 Data 2 SFM

Low b-value

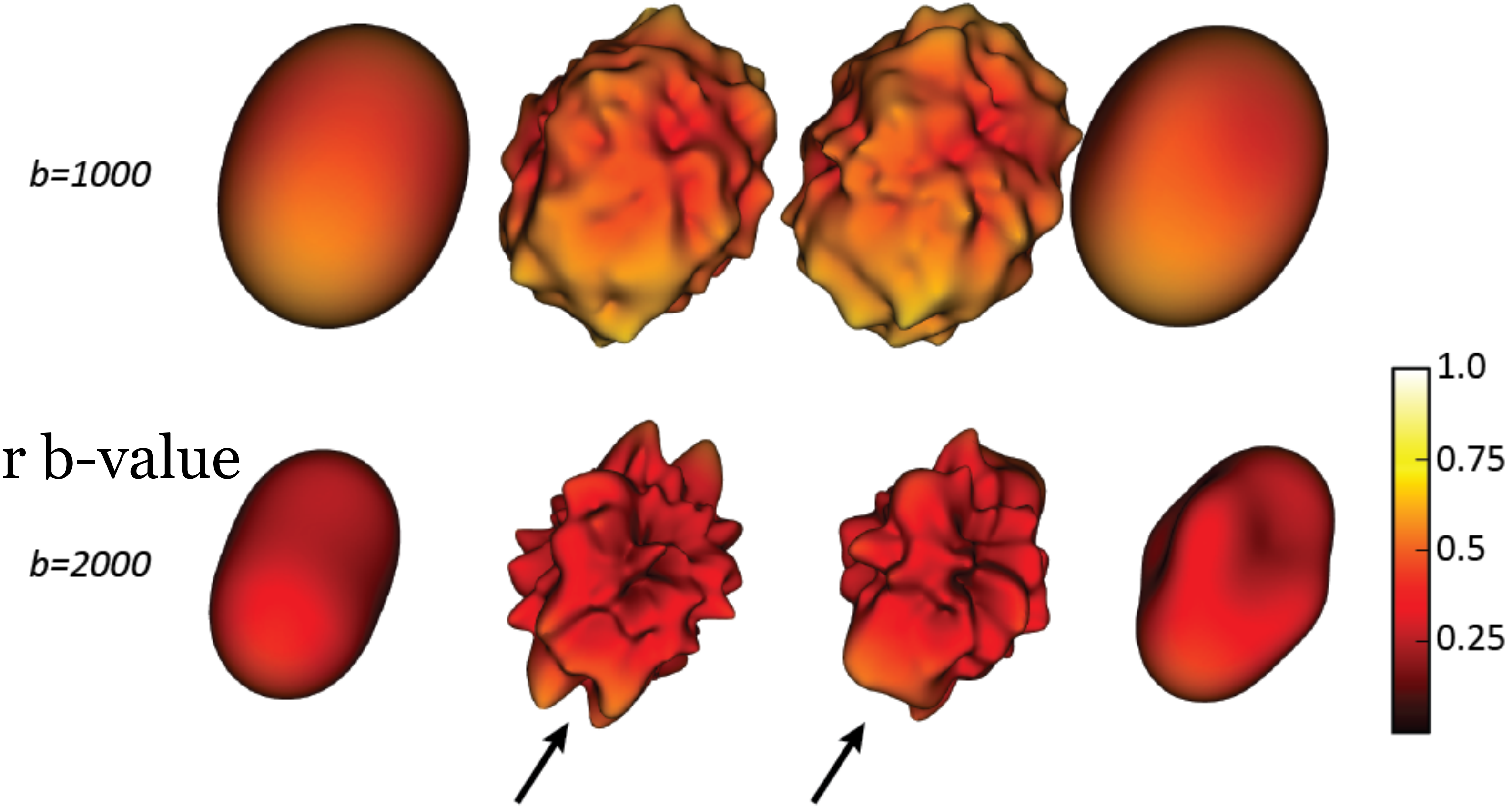
b=1000

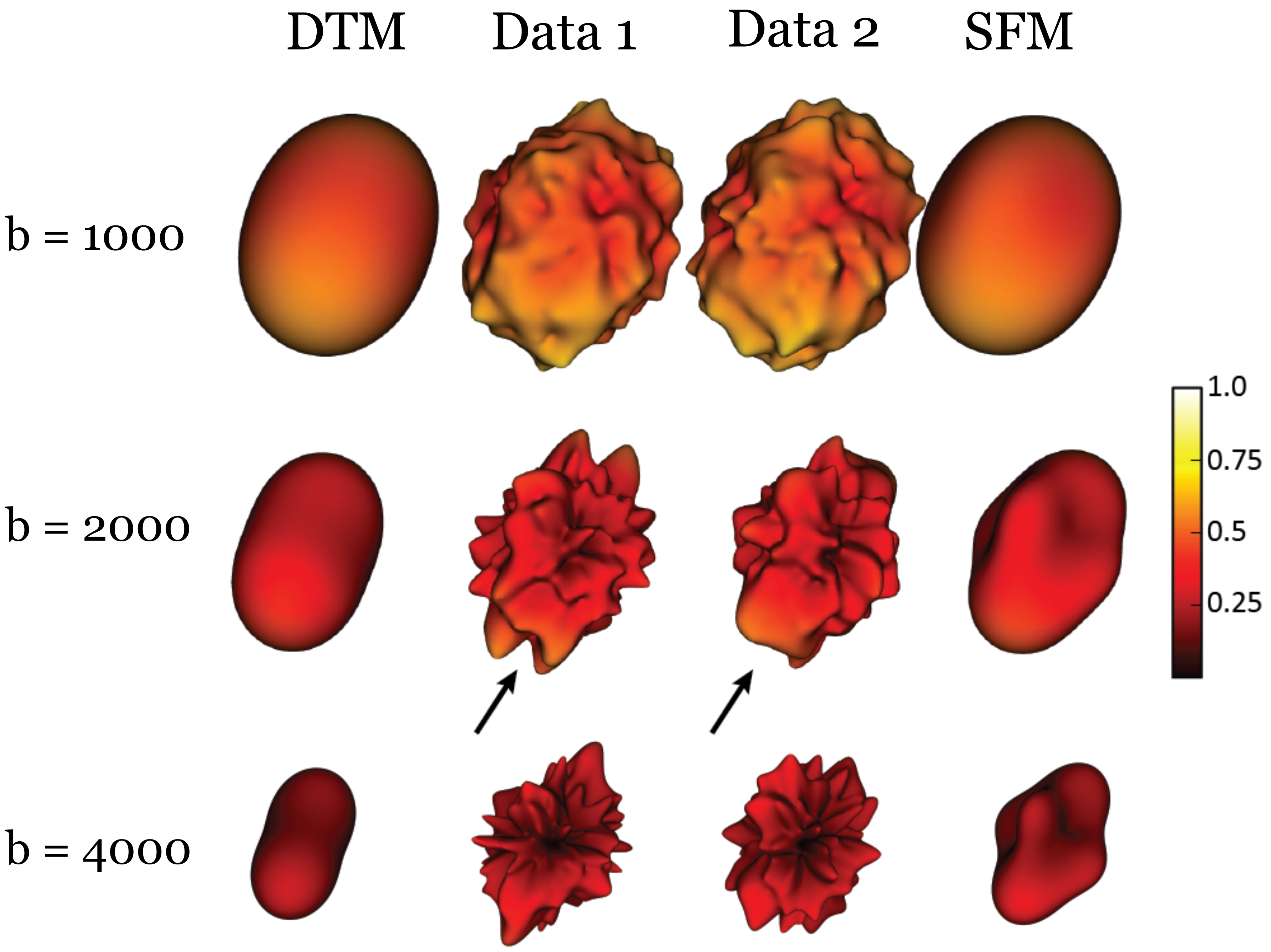


Evaluating models using cross-validation
(Rokem et al., 2015)

DTM Data 1 Data 2 SFM

Higher b-value




DTM
Data 1
Data 2
SFM
b = 1000
b = 2000
b = 4000
1.0
0.75
0.5
0.25

Evaluating models using cross-validation (Rokem et al., 2015)

Two data sets, one b-value, many directions, same session

Fit the model to these data

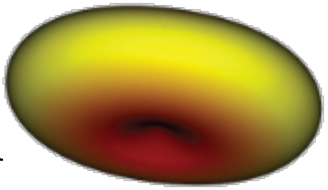
Data set 1

Measure prediction error with these data

Data set 2

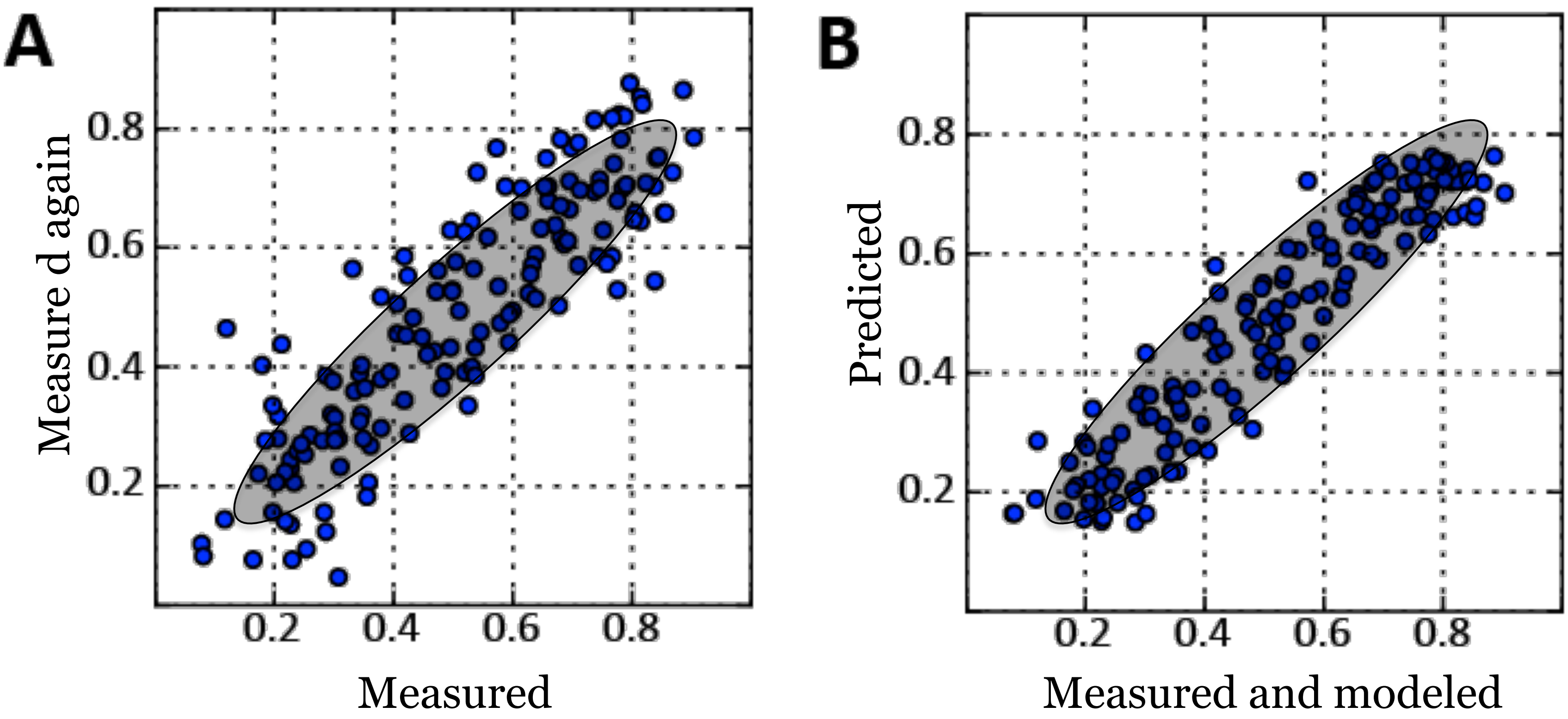
(In the old days, we used to call this testing the model on an independent data set)

DTM predicts the independent data more accurately than assuming replication



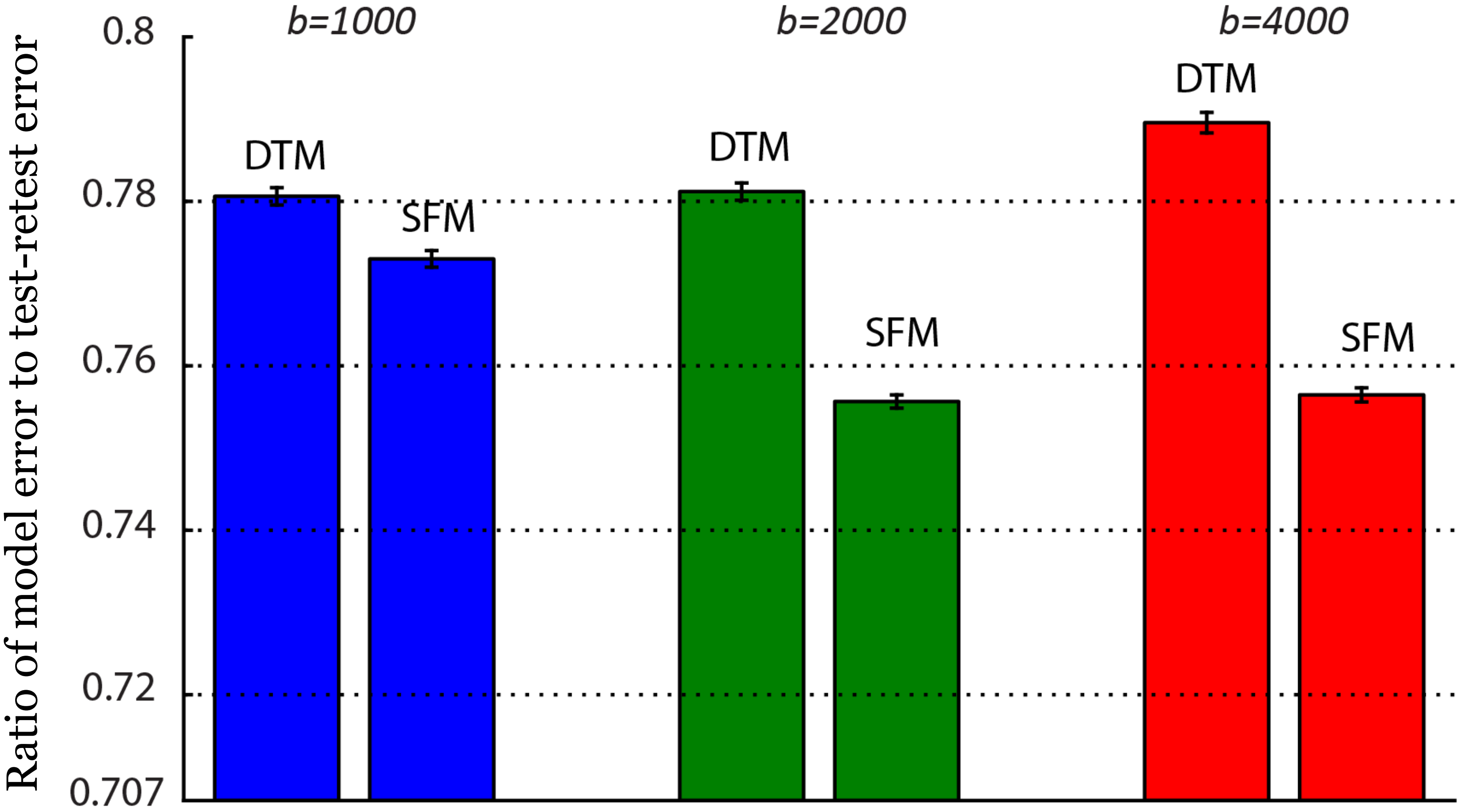
Replication

Prediction



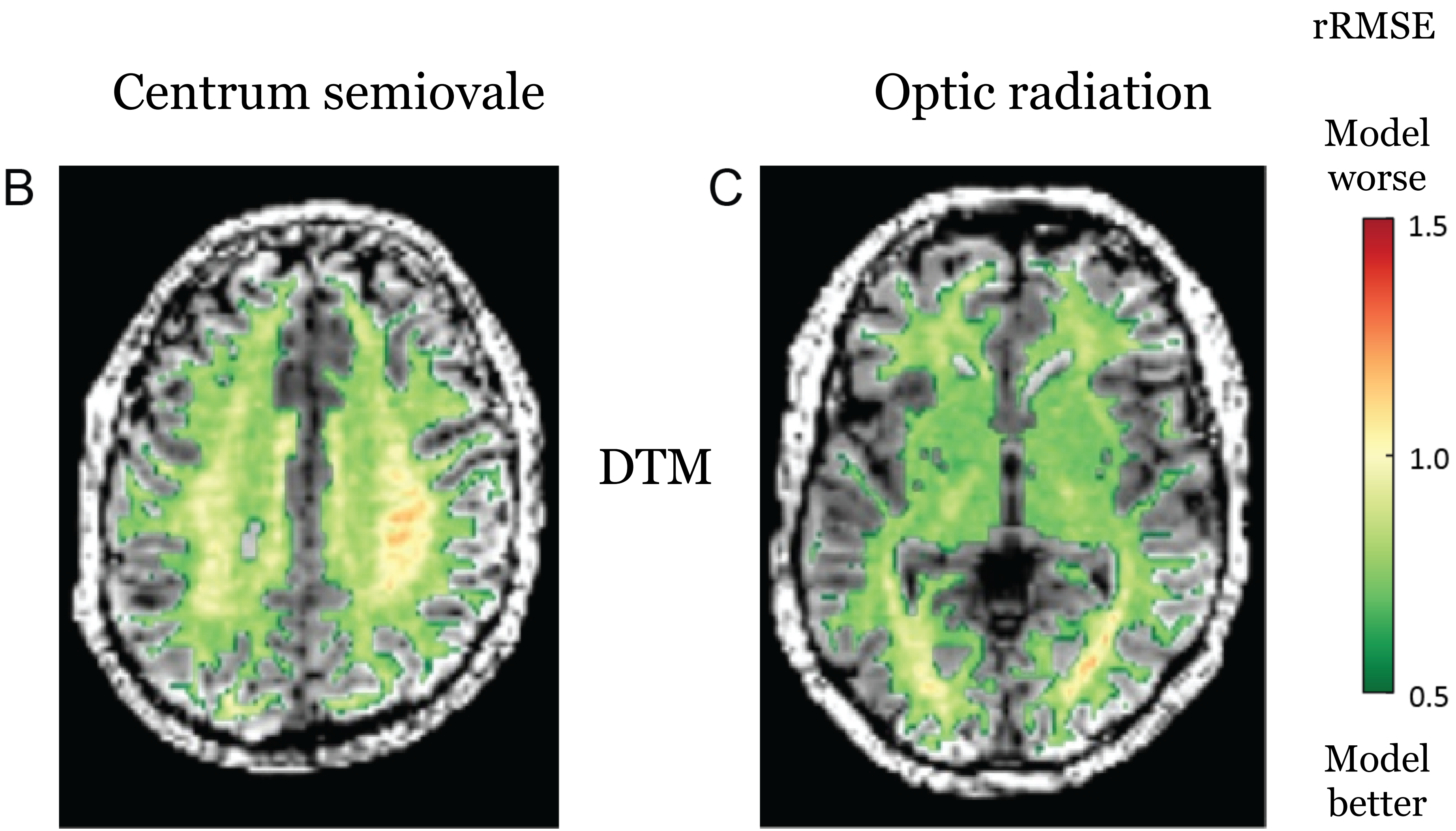
The SFM is slightly better (whole brain analysis)

Both are very good, and just short of best possible performance



Best possible = $\frac{1}{\sqrt{2}}$

SFM outperforms DTM in ~10% of the voxels (b = 4000)


Centrum semiovale

Optic radiation

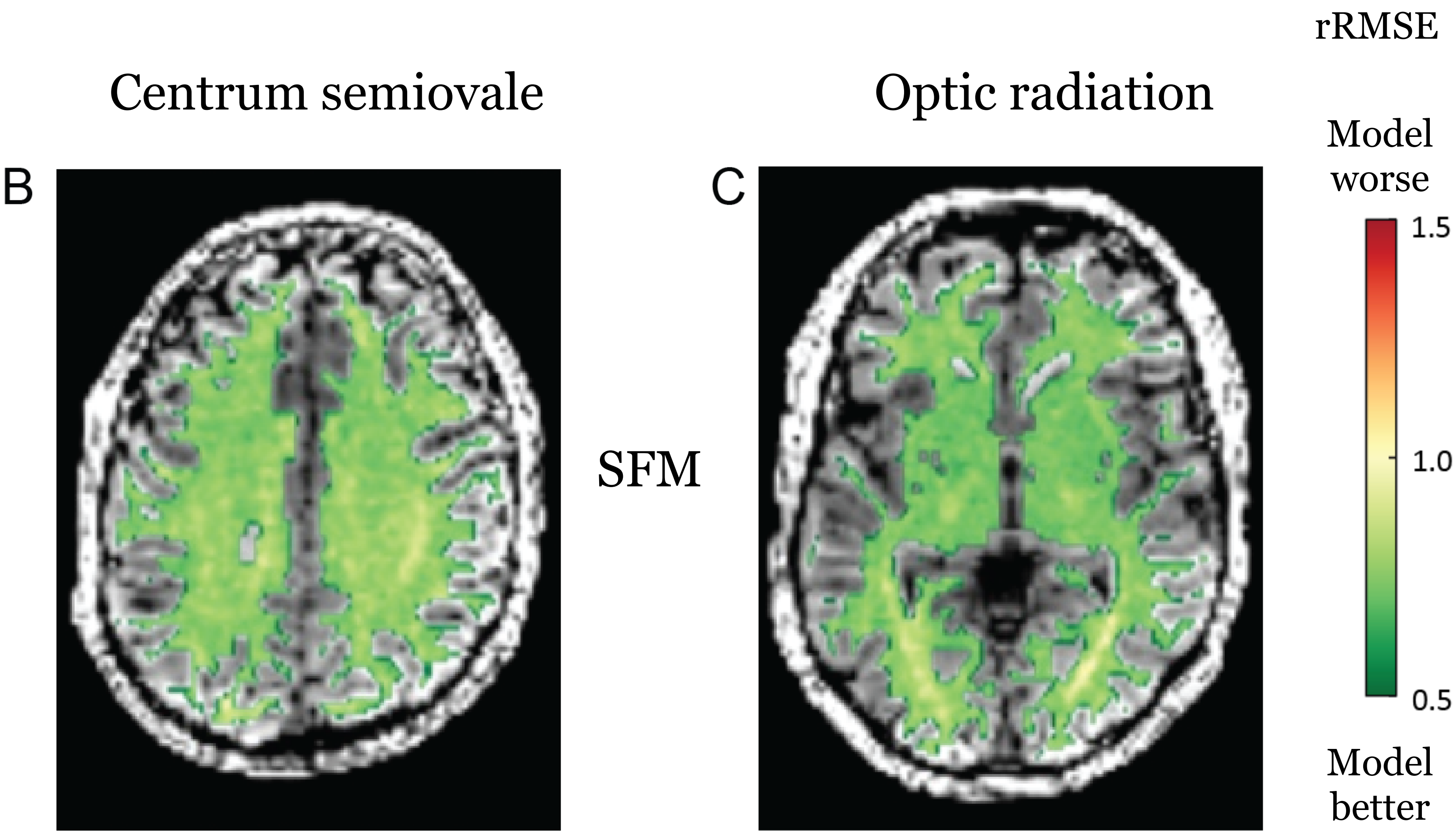
DTM

rRMSE

Model worse

Model better

In a few regions, the SFM outperforms DTM ~10% of the voxels (b = 4000)



Summary

If your goal is to provide a mathematical model of the diffusion signal in each voxel then:

- DTM and SFM are both excellent descriptions of the diffusion data; much better than test-retest reliability
- The summary statistics of the DTM (e.g., FA, RD, AD, MD) are useful for voxel-wise experimental comparisons
- In a few brain regions the SFM is better
- **BUT:** The principal diffusion direction of the DTM is not a good estimate of local axonal direction

References

Moseley, Cohen et al. 1990 Radiology
Origins of white matter diffusion

Le Bihan, Mangin, Poupon et al. 2001 Journal of Magnetic Resonance Imaging
A nice early review

Basser et al., 1994 – Biophysical Journal
Good opening sentence: “This paper describes a new NMR imaging modality-MR
diffusion tensor imaging.”

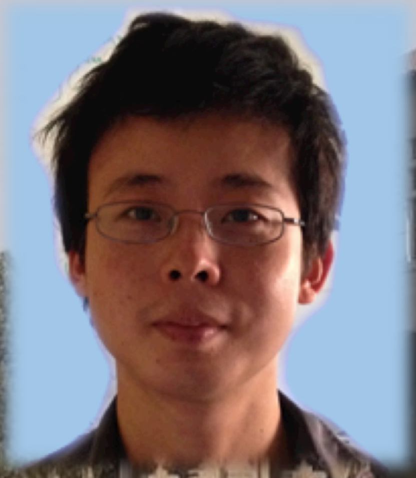
Basser and Pierpaoli – 1996,
Journal of Magnetic Resonance Imaging
Introduces FA and univariate statistics for DTM

Klingberg et al., 2000, Neuron
First application to human cognition

Linear Fascicle Evaluation

- Tractography
- Linear Fascicle Evaluation (LiFE)

Franco Pestilli



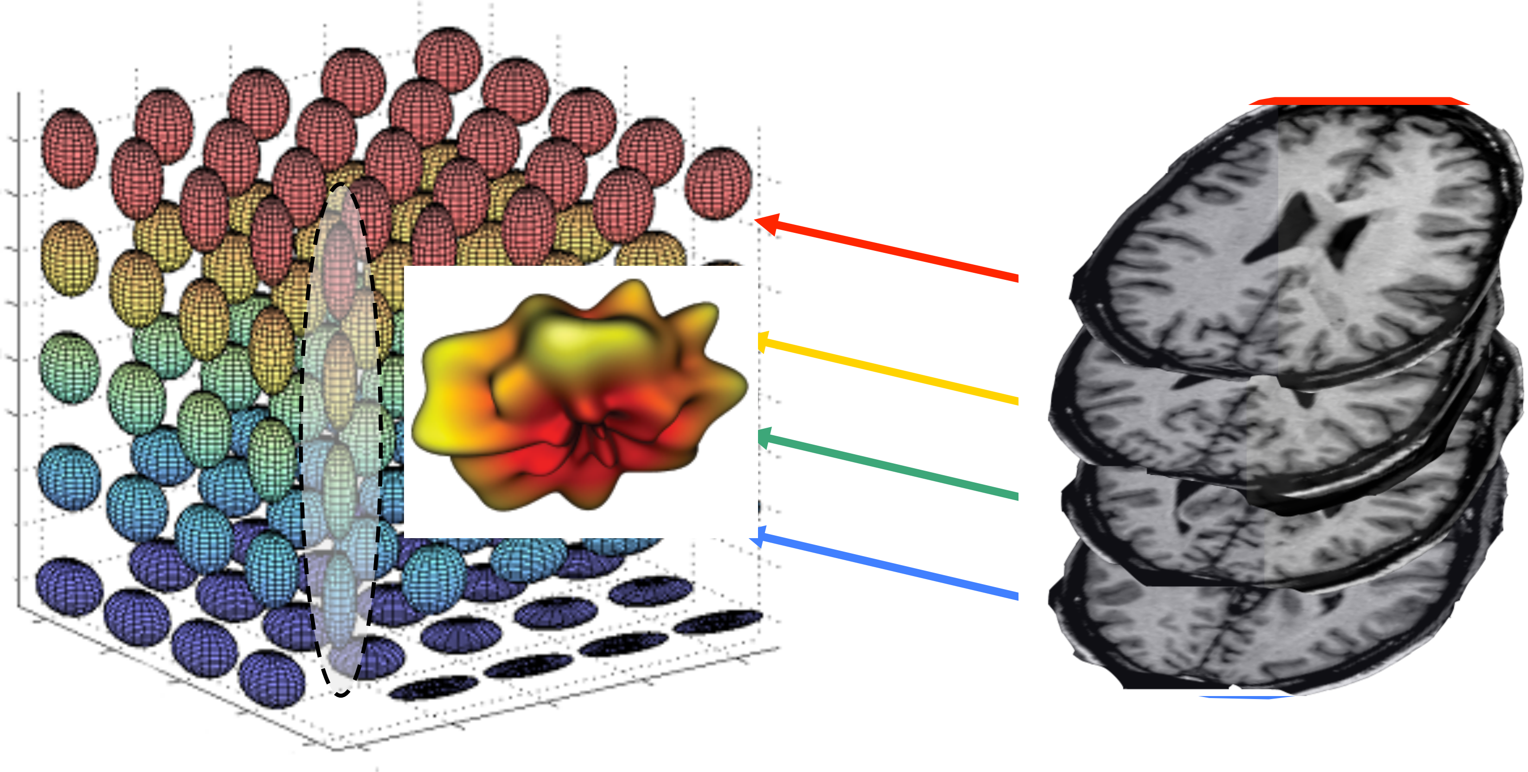
Hiromasa
Takemura

Jason Yeatman

Tractography

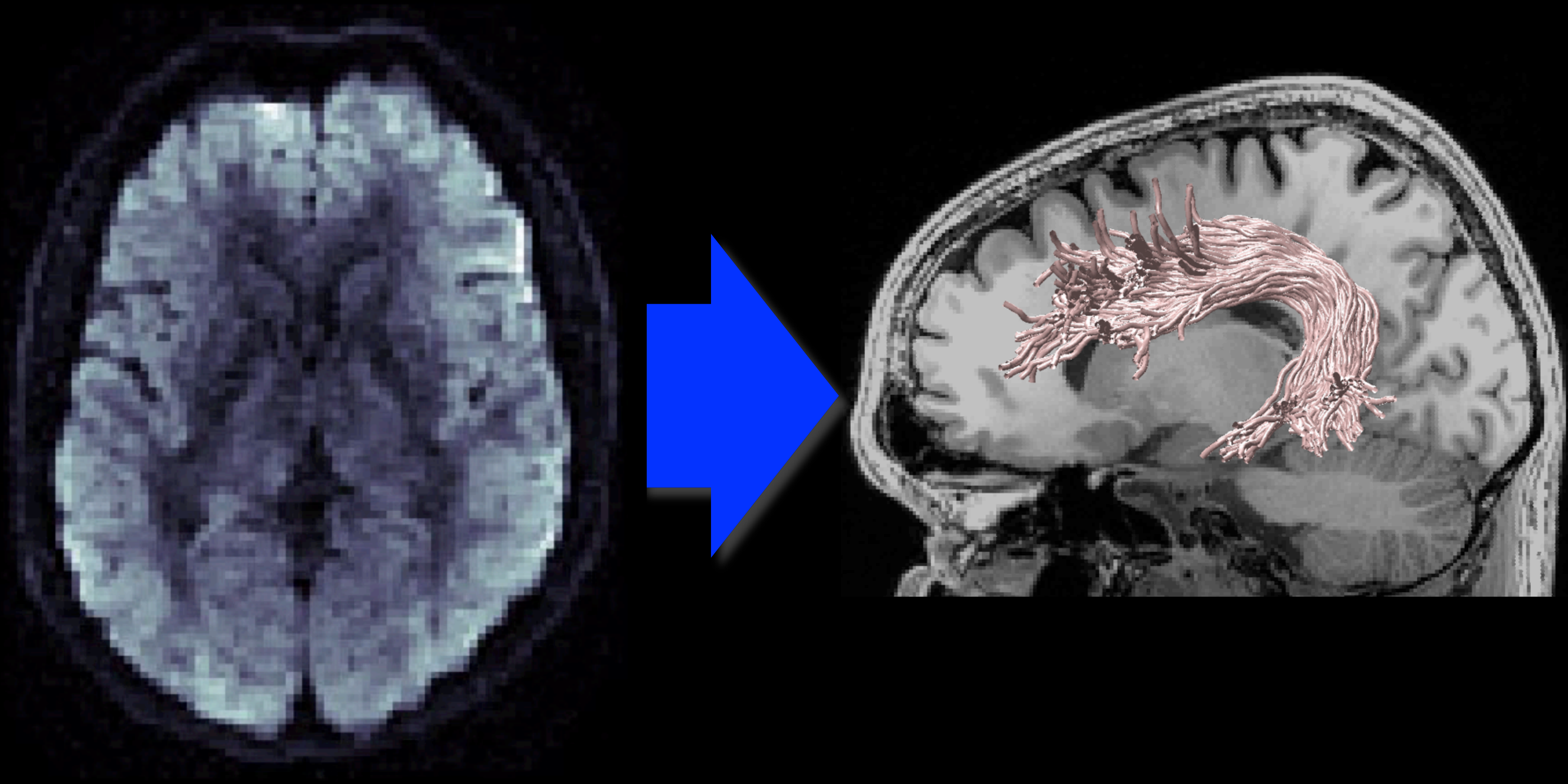
Use the local (voxel) diffusion measurements to estimate white matter tracts

Diffusion data are surfaces

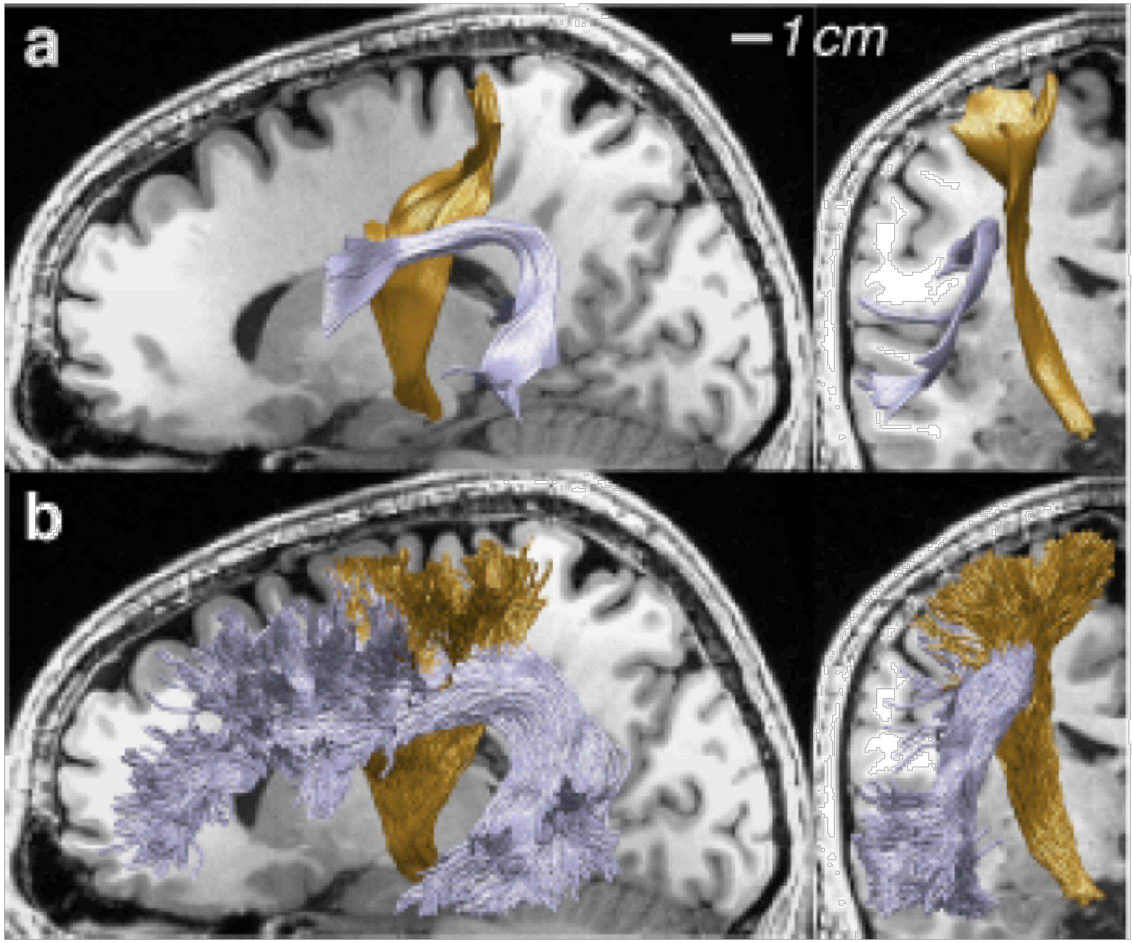


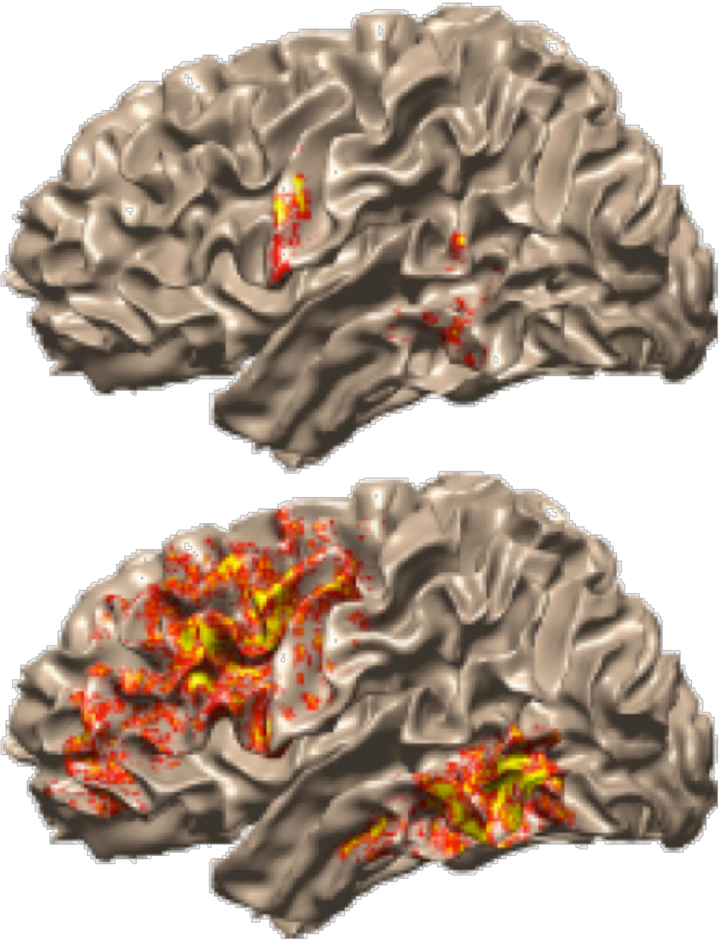
Tractography limitations

Estimate fascicles from diffusion data



Different tractography methods and parameters make different predictions

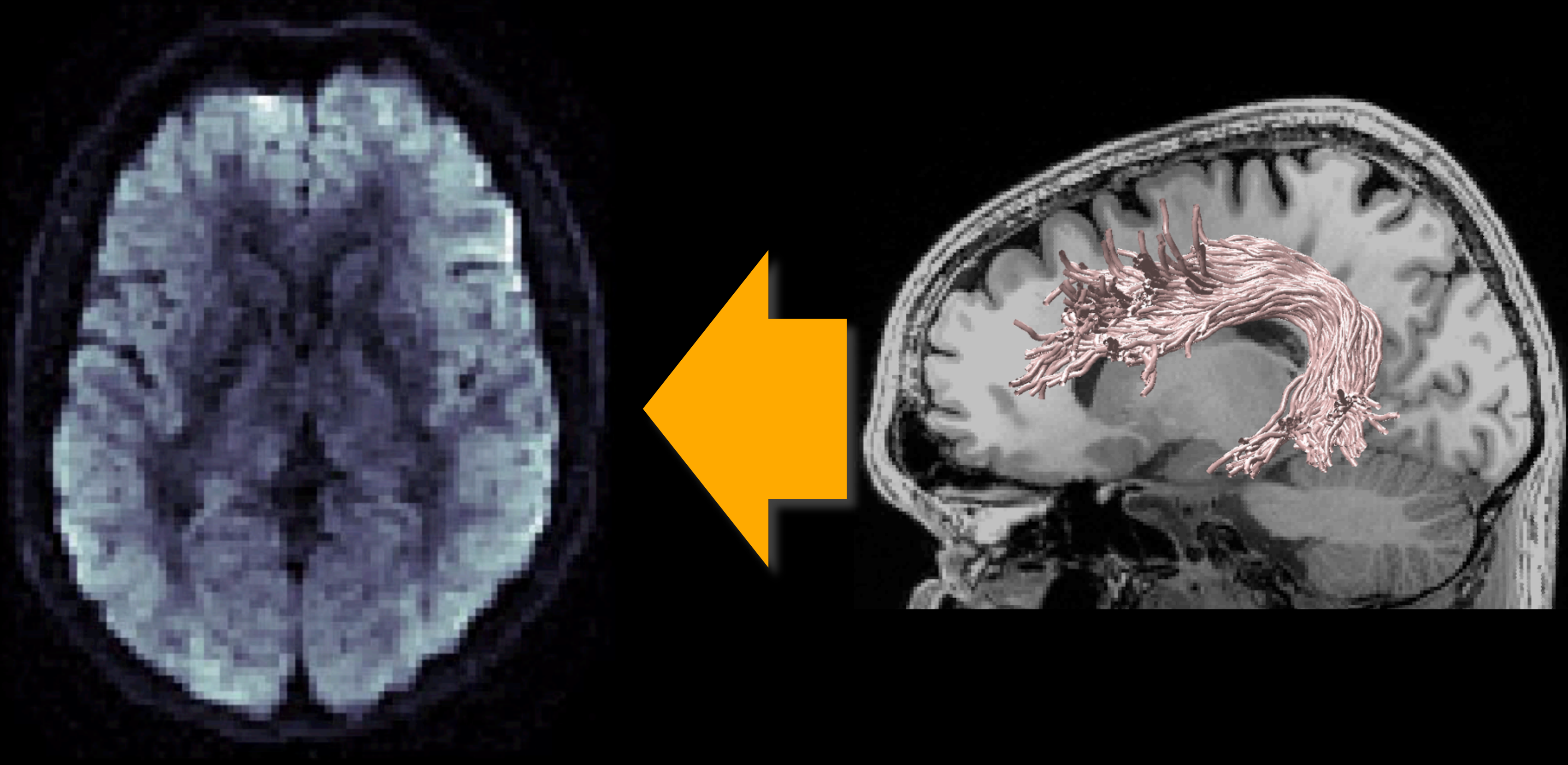




Linear Fascicle Evaluation (LiFE)

Predict diffusion data from fascicles

Compare how well different models and algorithms do



2. Stages of LiFE

Set up diffusion predictions for each voxel

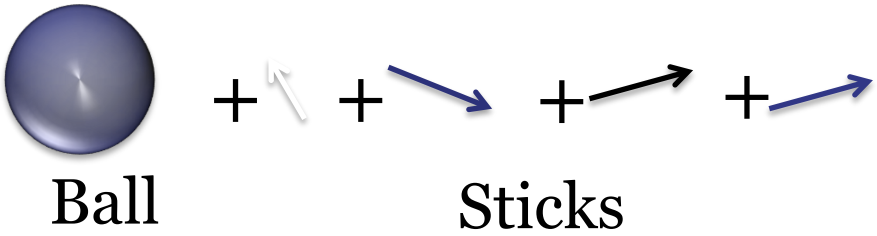
$$S(\theta) = w_0 D_0 + \sum_f w_f e^{-bD_f(\theta)}$$

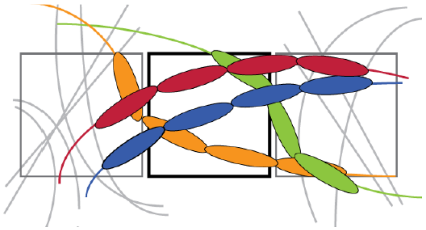
isotropic

weights

fascicles

In each voxel use the conventional fascicle diffusion model to predict the diffusion signal from the candidate connectome

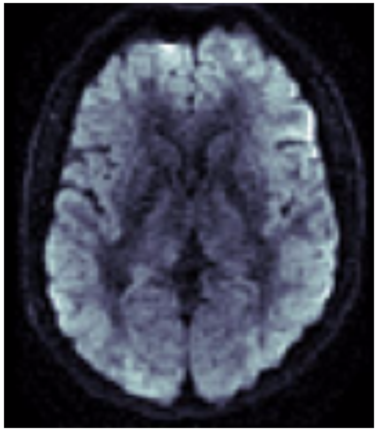


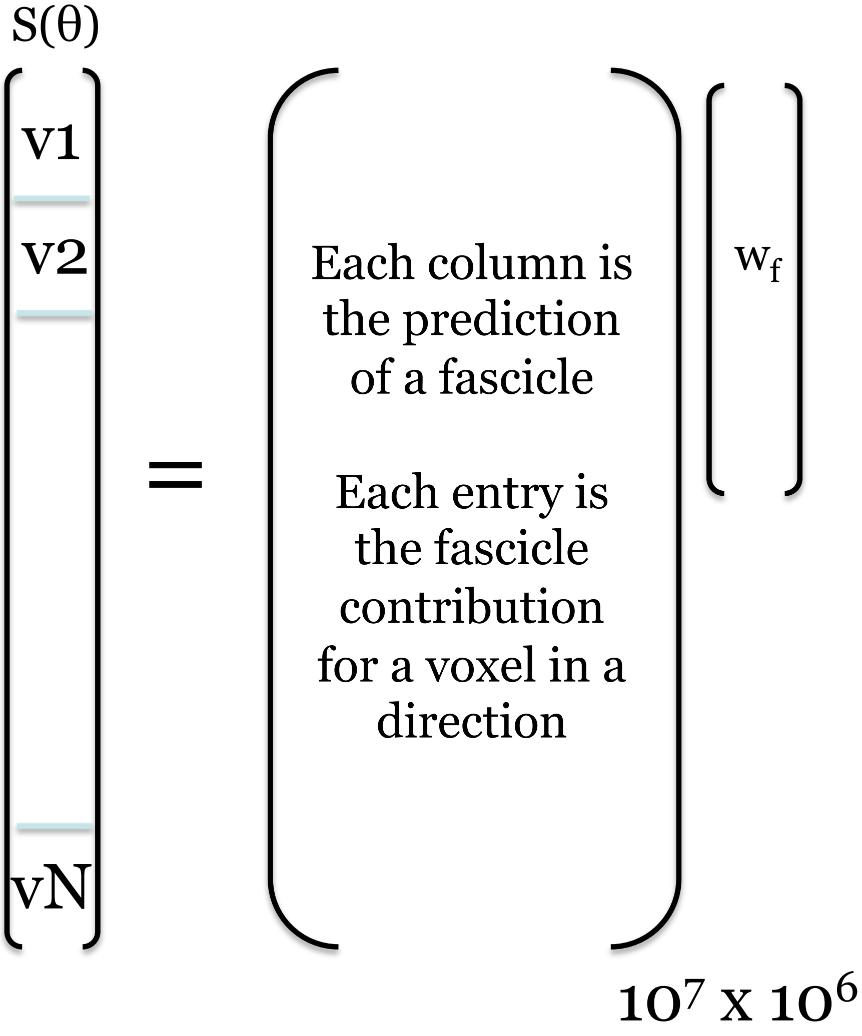


3. Stages of Life

Solve for the fascicle weights

Diffusion signal, S(θ)





S(θ)

v1

v2

vN

=

Each column is the prediction of a fascicle

Each entry is the fascicle contribution for a voxel in a direction

w_f

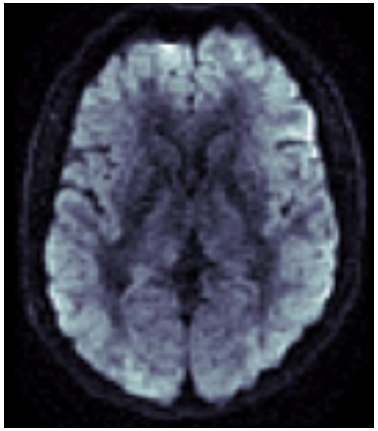
$10^7 \times 10^6$

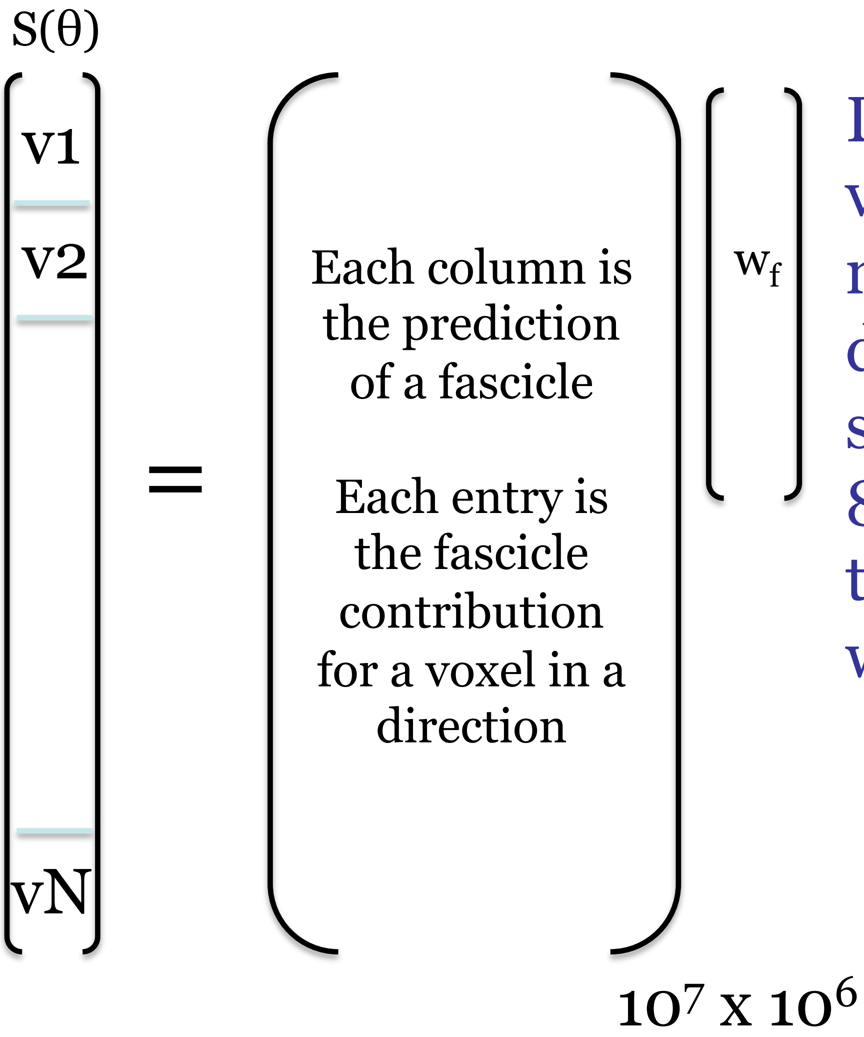
Solve for a non-negative weight for each fascicle (least-squares)

3. Stages of Life

Solve for the fascicle weights

Diffusion signal, S(θ)





Each column is the prediction of a fascicle

Each entry is the fascicle contribution for a voxel in a direction

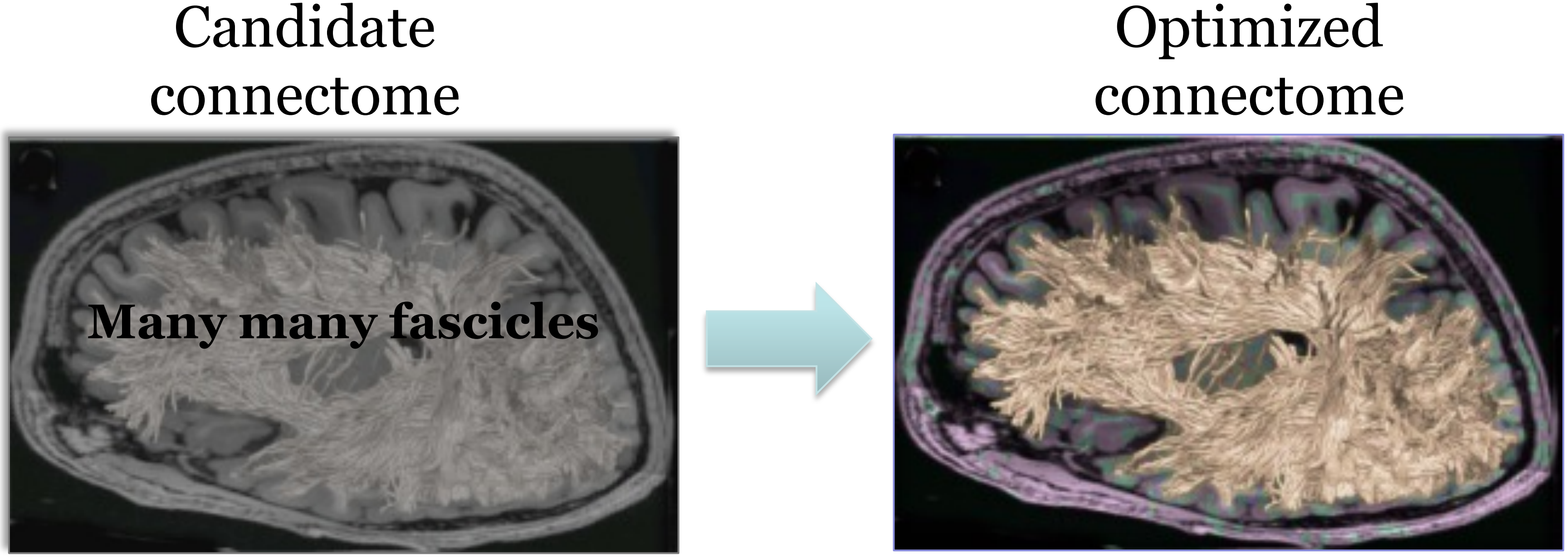
w_f

10^7 x 10^6

Depending on voxel size, number of directions, and so forth, about 80% of typical tractography weights are zero.

4. Stages of LiFE

Eliminate zero weight fibers (false alarms)

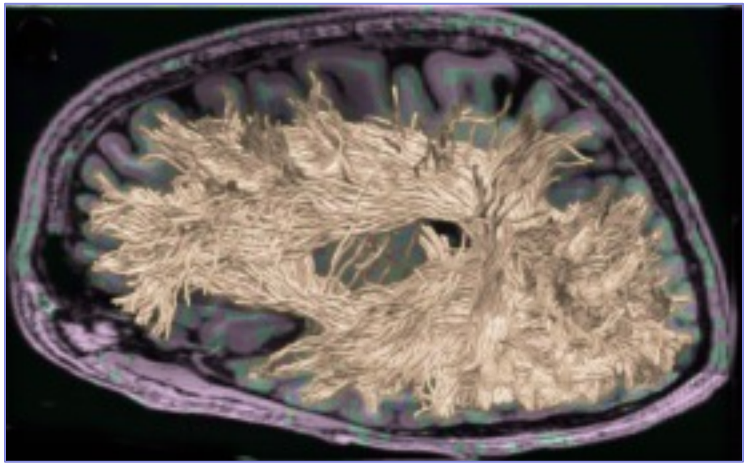


Solving a system of linear equations
(non-negative least-squares)

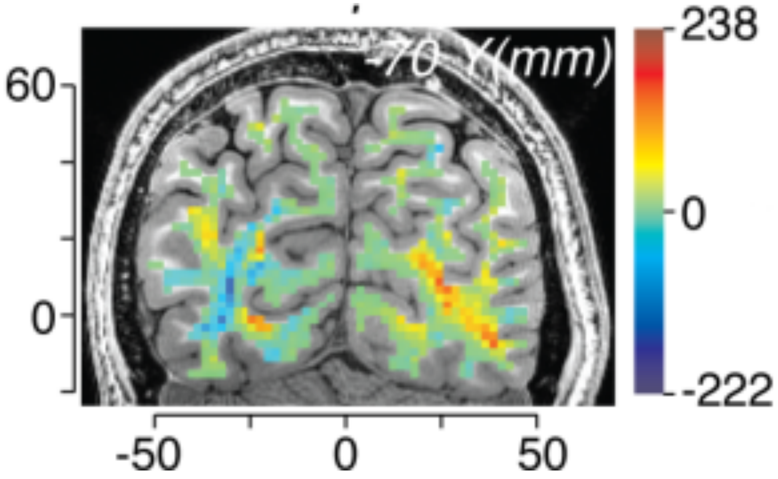
5. Stages of LiFE

Predict diffusion signal

Optimized connectome and weights



Prediction

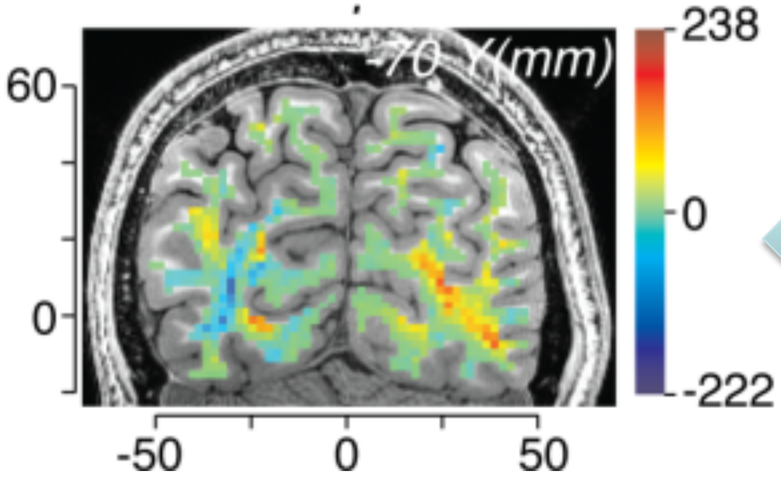


Big matrix multiplication

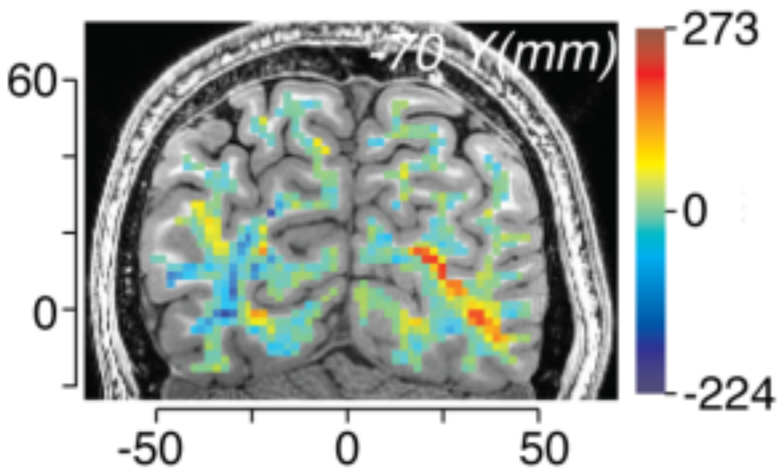
6. Stages of LiFE

Cross-validation error between predicted and 2nd data set

Prediction



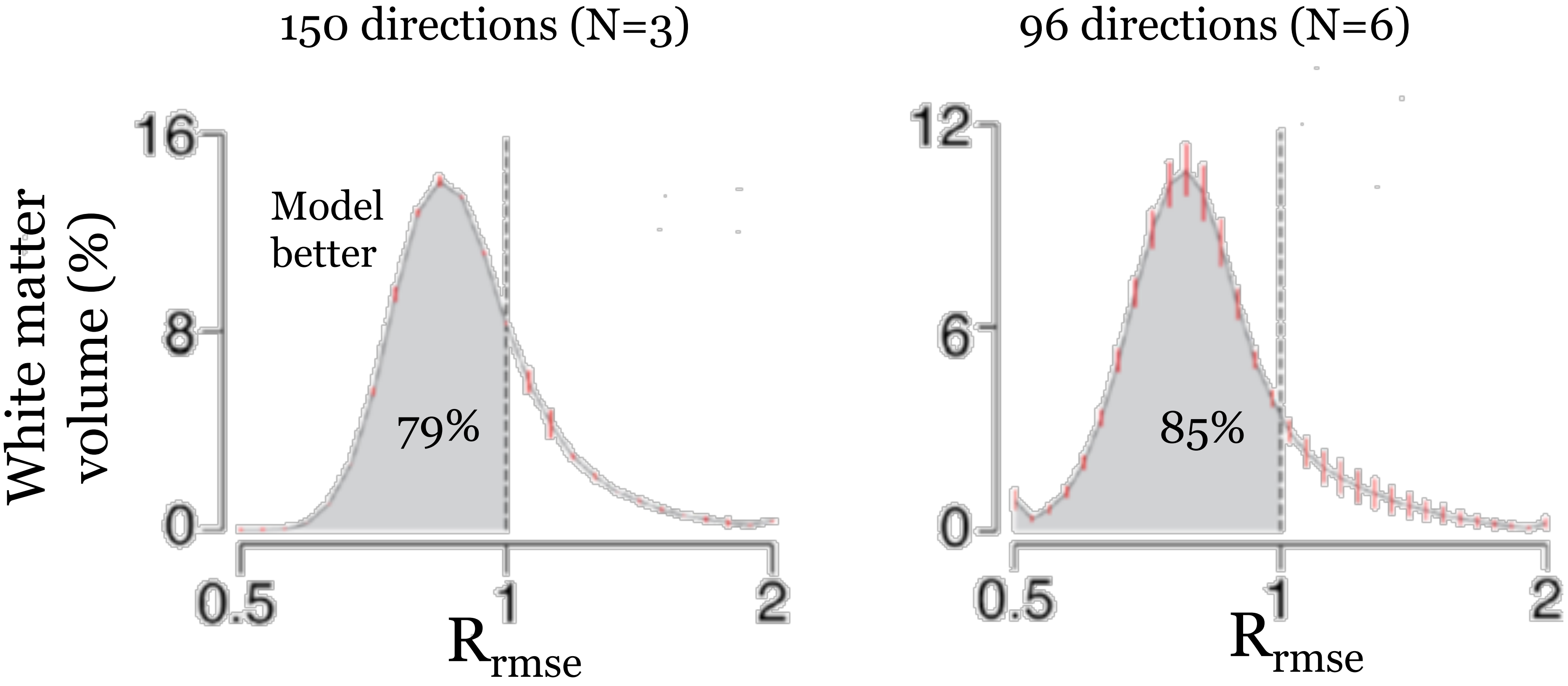
Second data set



Subtraction and root mean square error

The optimized connectome predicts diffusion data slightly better than test-retest reliability

(b=2000 data shown)



150 directions (N=3)

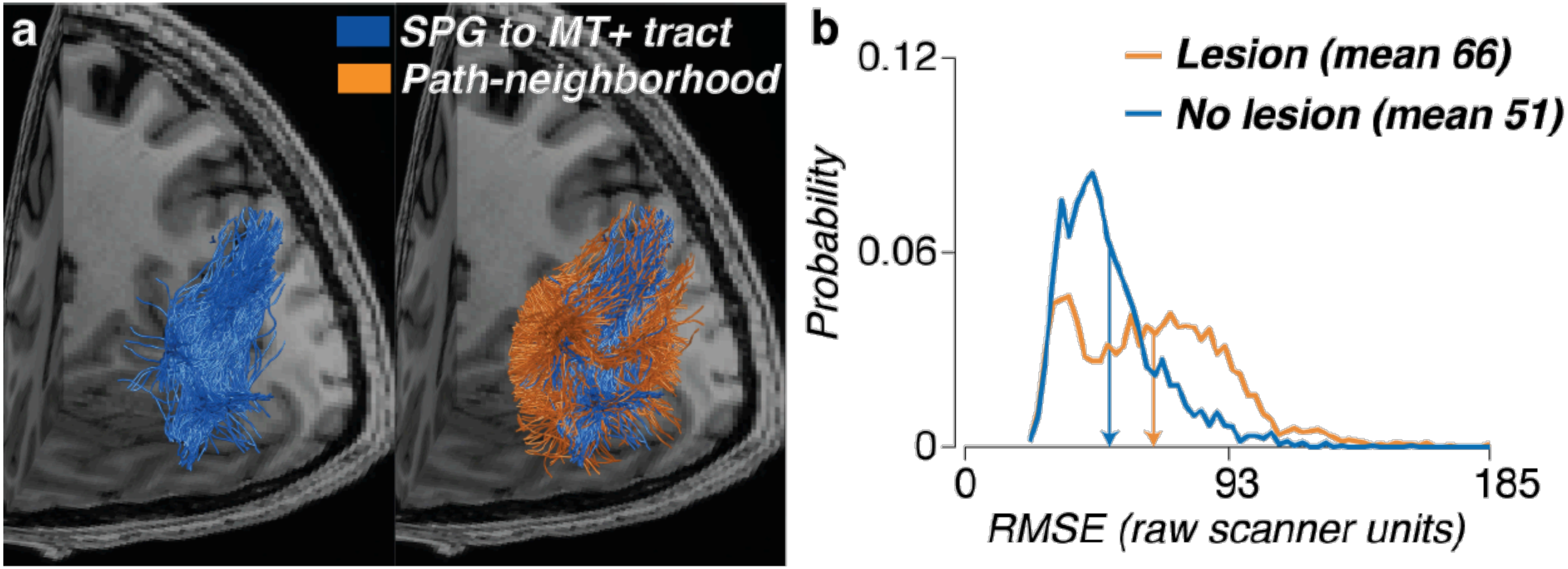
96 directions (N=6)

R_{rmse} = Ratio of model error to reliability error

Methods for hypothesis testing

Path-neighborhood (Wedeen)

Earth Mover's Distance on error distribution (Guibas)



Partial list of tractography and visualization software

http://www.nitrc.org/

Central source

MRI studio – http://www.mristudio.org

FiberTools (Reisert)

FMRIB

- PROBTRACK
  http://users.fmrib.ox.ac.uk/~behrens/fdt_docs/fdt_probtrack.html
- Tract Based Spatial Statistics
  http://users.fmrib.ox.ac.uk/fsl/fslwiki/TBSS

TrackVis - http://www.trackvis.org

DSI studio - http://dsi-studio.labsolver.org/

MRtrix - http://brain.org.au/software/mrtrix/

Exploredti - http://www.exploredti.com/

Camino - http://cmic.cs.ucl.ac.uk/camino/

mrDiffusion - https://github.com/vistalab/vistasoft

Building a model of the circuit for seeing words

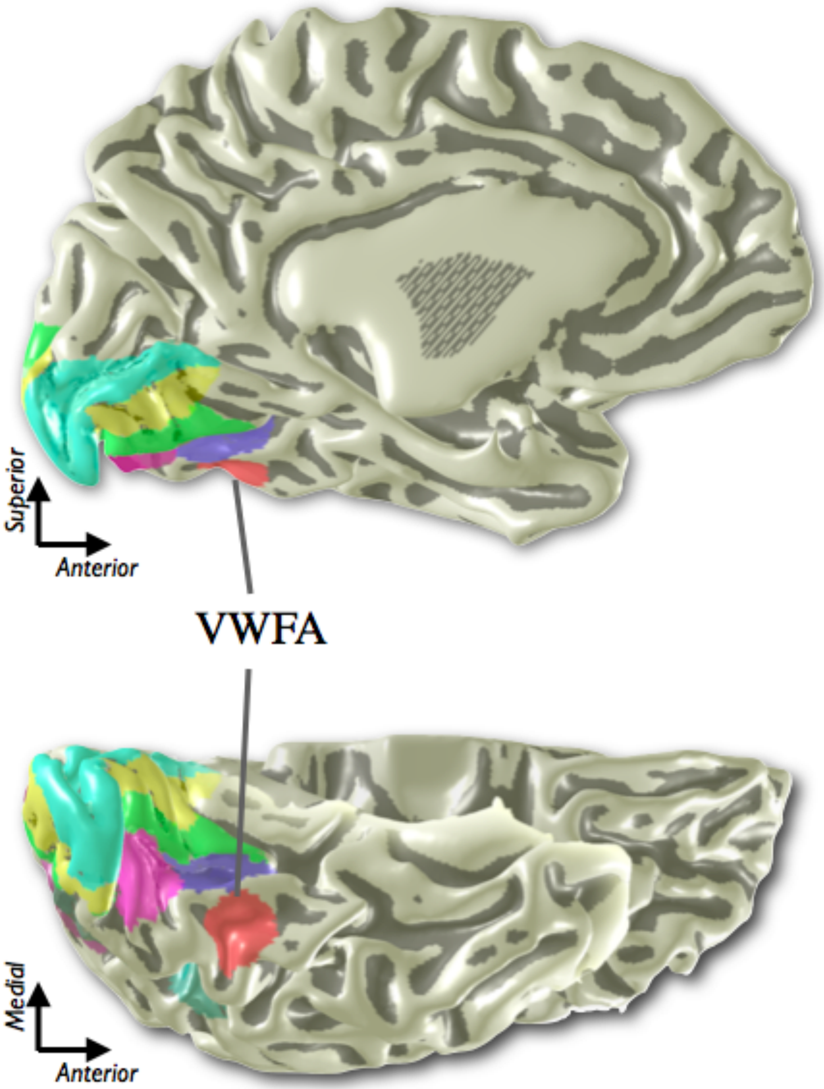
- White matter tissue properties predict how well children can quickly recognize words

Michal Ben-Shachar

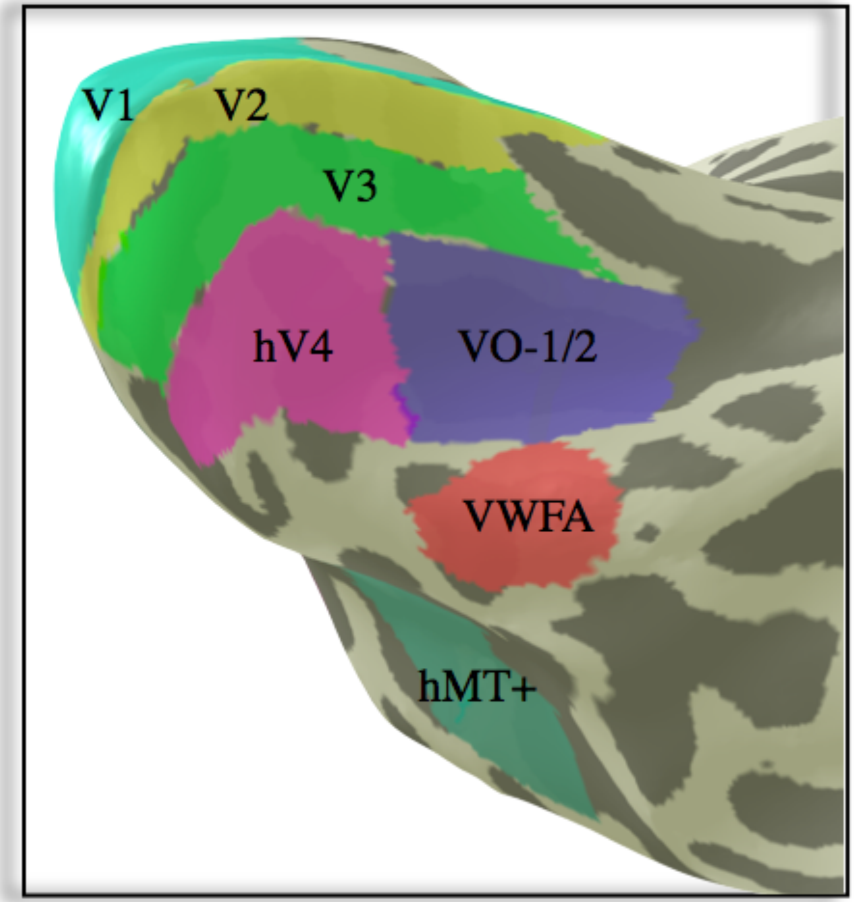
Jason Yeatman

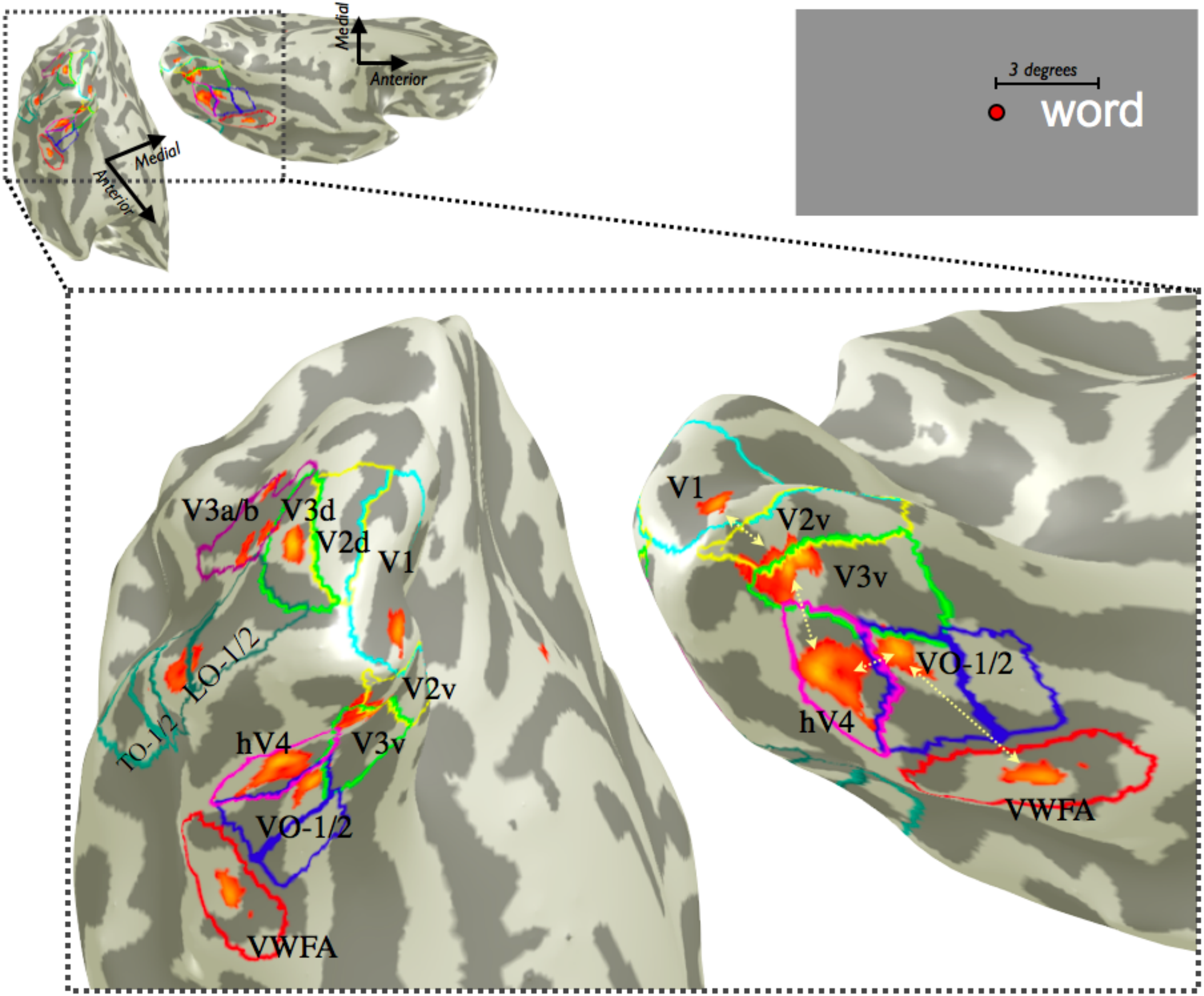
Andreas Rauschecker

Locating reading circuits and maps



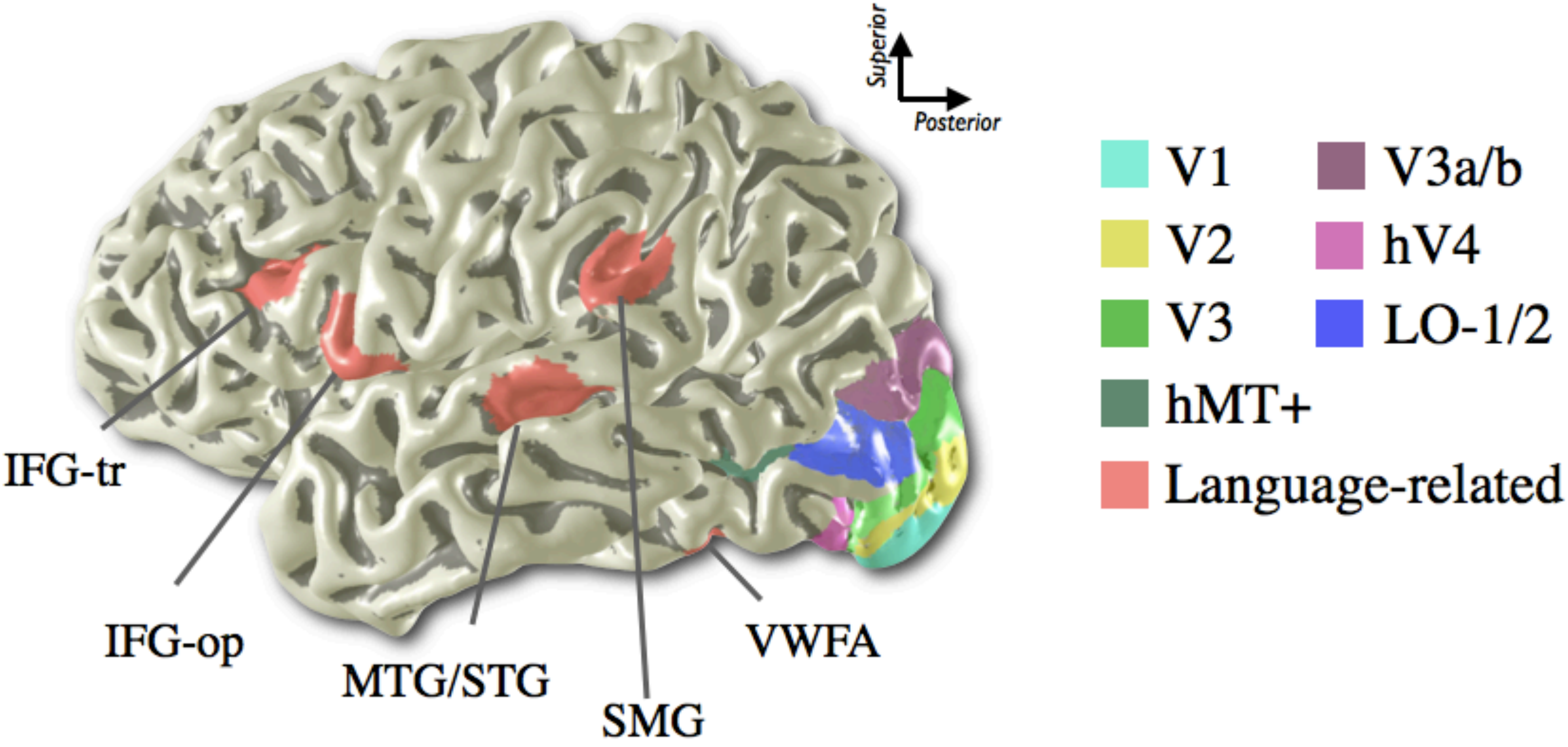
VWFA - essential for reading, but not unique to reading




Medial
Anterior
Medial
Anterior
3 degrees
word
V3a/b
V3d
V2d
V1
LO-1/2
TO-1/2
V2v
hV4
V3v
VO-1/2
VWFA
V1
V2v
V3v
hV4
VO-1/2
VWFA

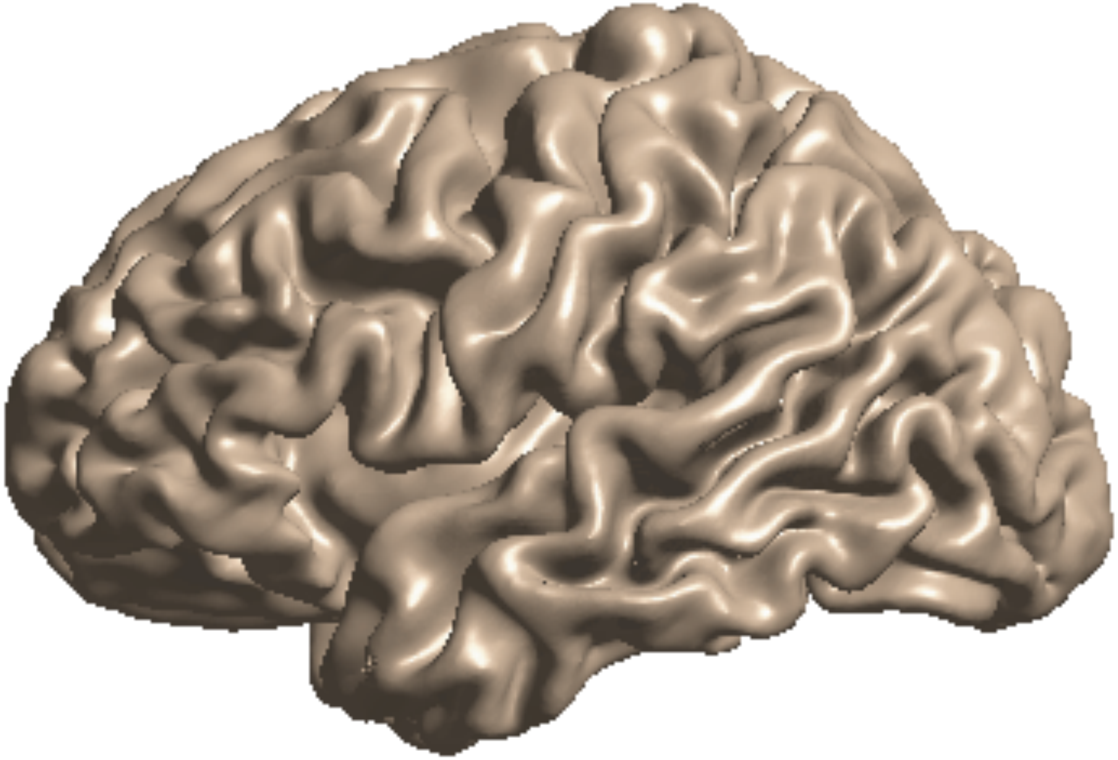
The cortical reading network

Learning to See Words
B.A. Wandell, A. Rauschecker and
J. Yeatman (2012).
Annual Review of
Psychology Vol. 63, pp.31-53.

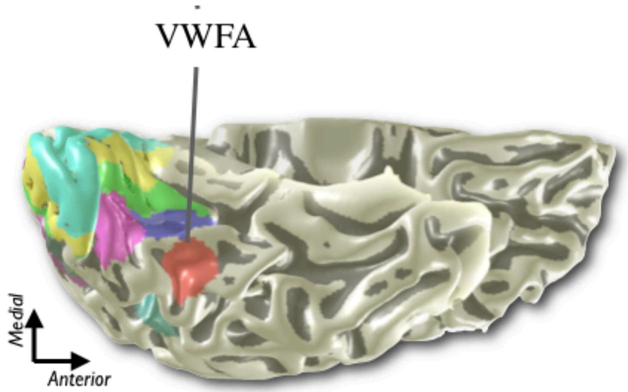


Seeing the white matter reading tracts

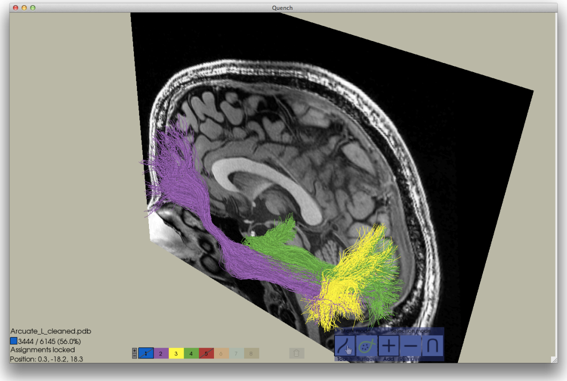
(Yeatman et al., 2011)



Intermediate summary



- Reading requires quickly and accurately identifying forms (seeing words)
- The cortex learns to do this using the VWFA, a region located in ventral temporal cortex, amidst a set of visual field maps



Arcuate_L_cleaned.pdb
3444 / 6145 (56.0%)
Assignments locked
Position: 0.3, -18.2, 18.3

- White matter development (arcuate, ILF) predicts reading development

Data management for reproducible research

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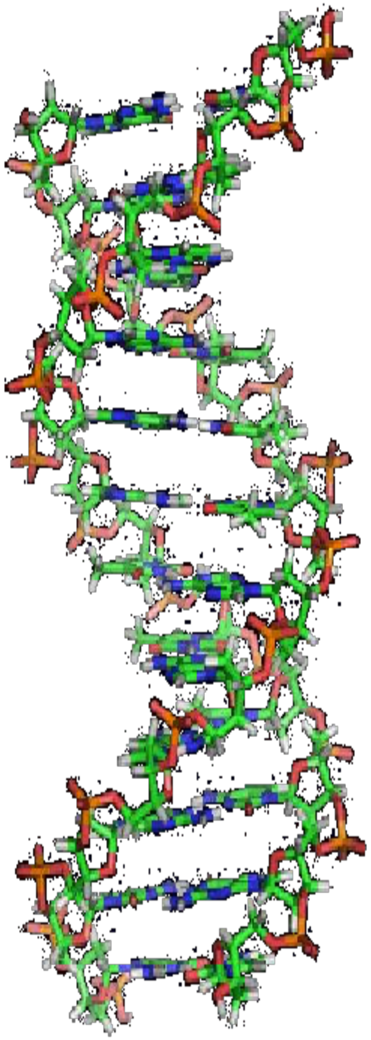
Disclosure: Flywheel.io

Replication is often impractical

- Neuroscience has entered an era of ‘big science’ in which replication is impractical

  - ☐ **Example 1:**
    Analyses of 320 subjects with autism, each measured using MRI, at 3 time points over four years
  - ☐ **Example 2:**
    Structural MRI of 50 illiterate adults flown in from the Amazon rain forest



Reproducible research is within reach

Replication means obtaining the data again, usually by independent investigators using similar methods, equipment and protocols

Many big science experiments are too expensive and time-consuming to replicate

Reproducible means that starting with the data gathered by the scientists, we can confirm the derived results (e.g., statistics, summary curves and images, numerical relationships)

Proper tools enable scientists to achieve reproducibility much more often

Reproducible Research

Computational reproducibility is not an afterthought—it is something that must be designed into a project from the beginning. **One does need to develop a whole set of programming and research disciplines** with the end result in mind and stick with them.

Donoho

Scientific data management tools

- Reproducible research requires **scientific data management** tools **Disclosure: Flywheel.io**

- These should be an expected part of any important scientific experiment

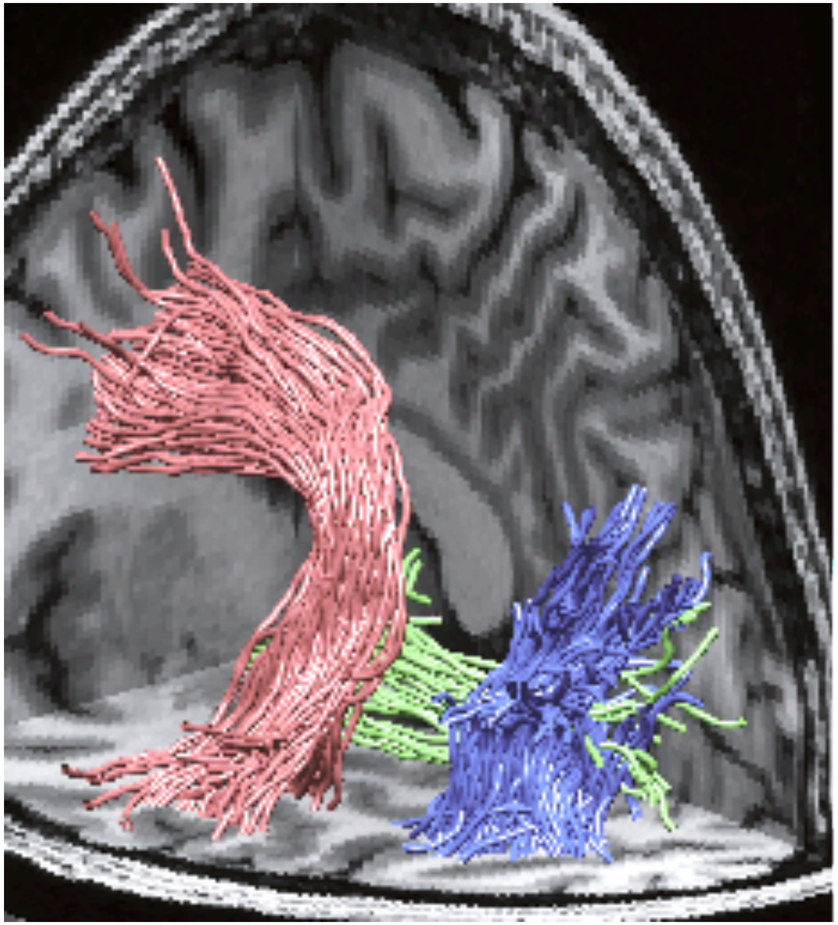
- For reproducible research the tools should simplify both

  - Data sharing
  - Computational sharing

Scientific goals of the project

Personalized neuroscience

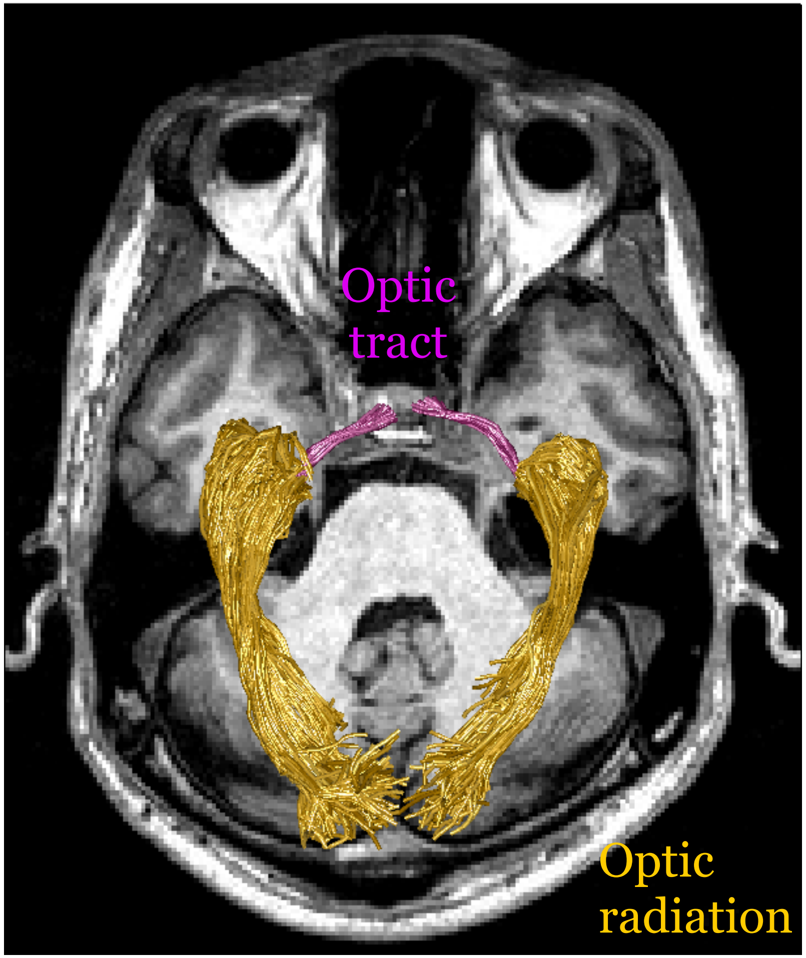
An opportunity that derives from a combination of data management and the quest for reproducible research



A motivating example

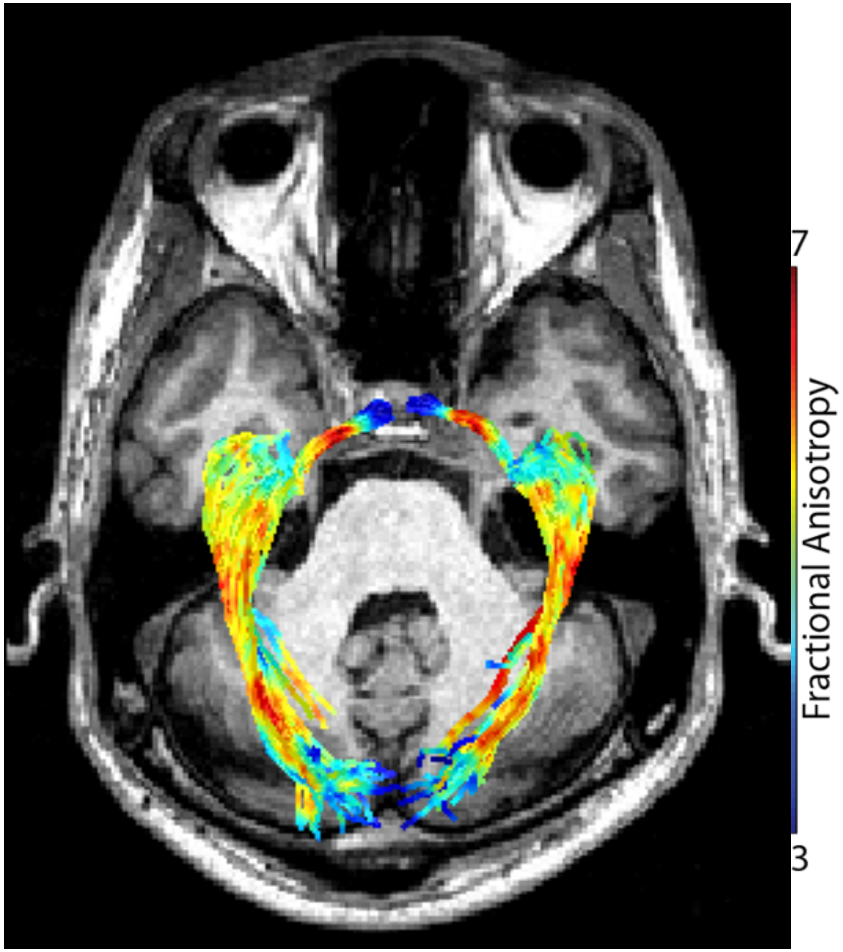
- A subject or patient with a retinal eye disease comes to the lab

- We want to know the consequences of retinal degeneration on cortical structures

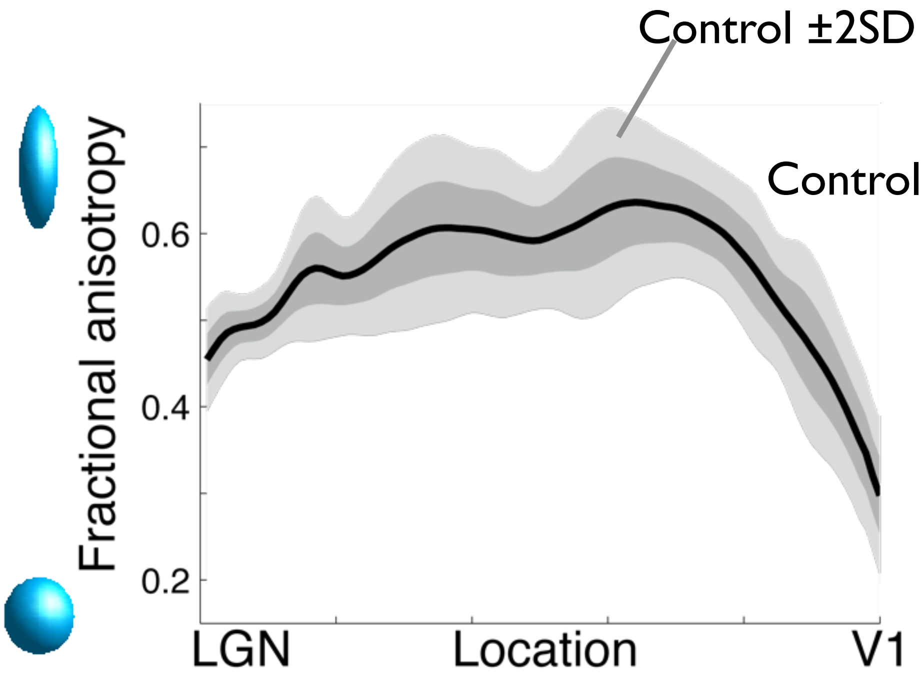


A motivation example

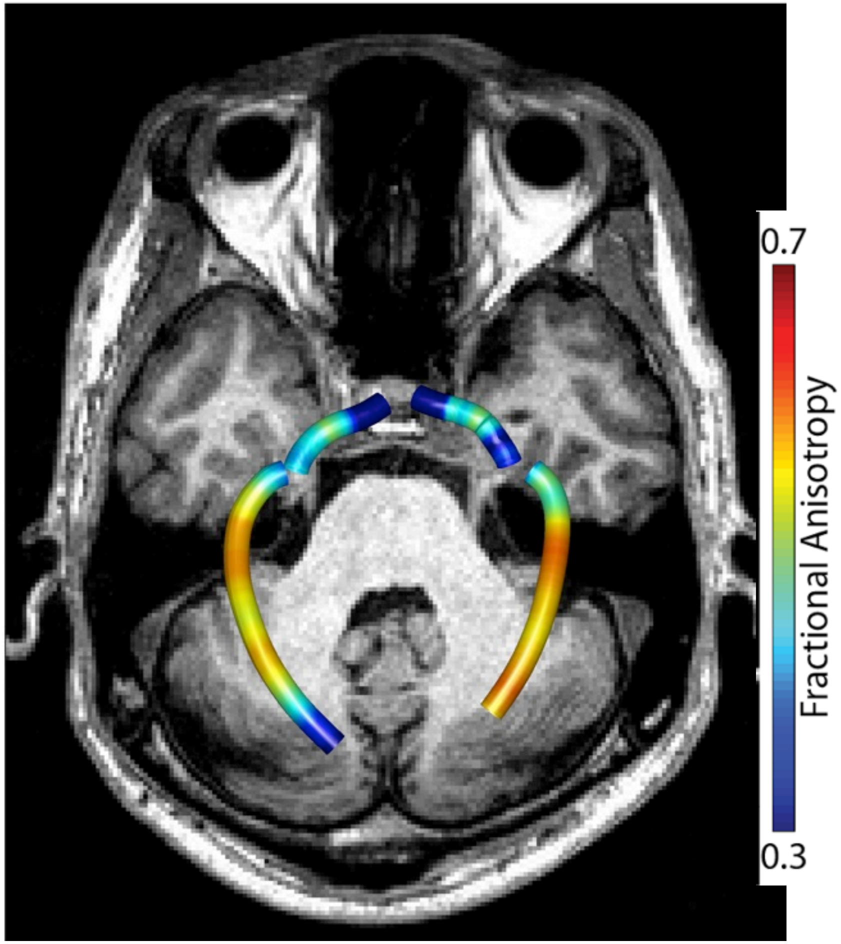
- Measure the subject’s visual white matter and secure the data!
- Use validated computational tools for quality assurance
- Use open-source software for tract identification, tissue estimation and comparison with other populations



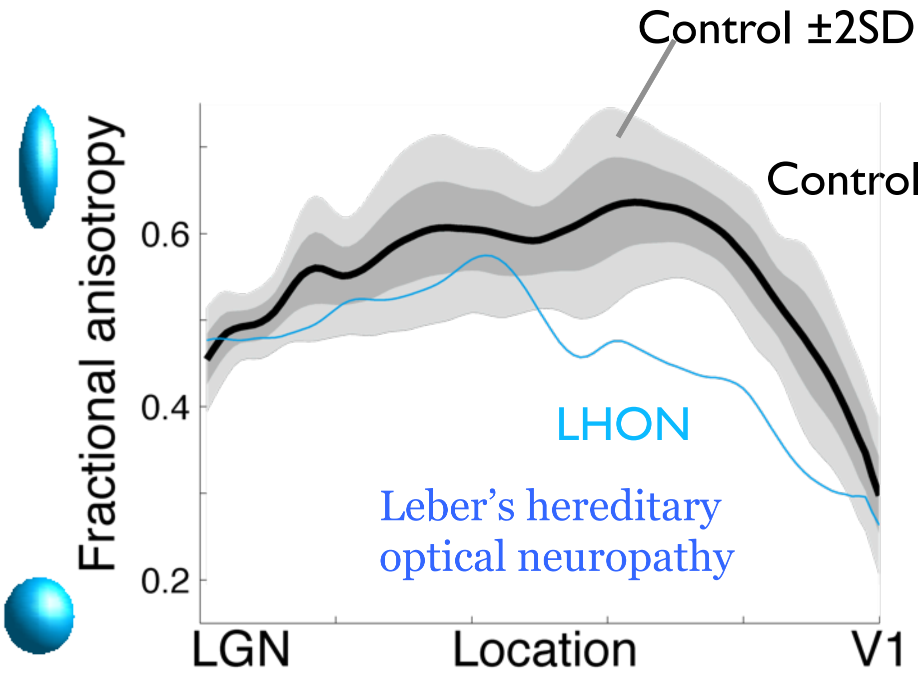
Use databases to find controls



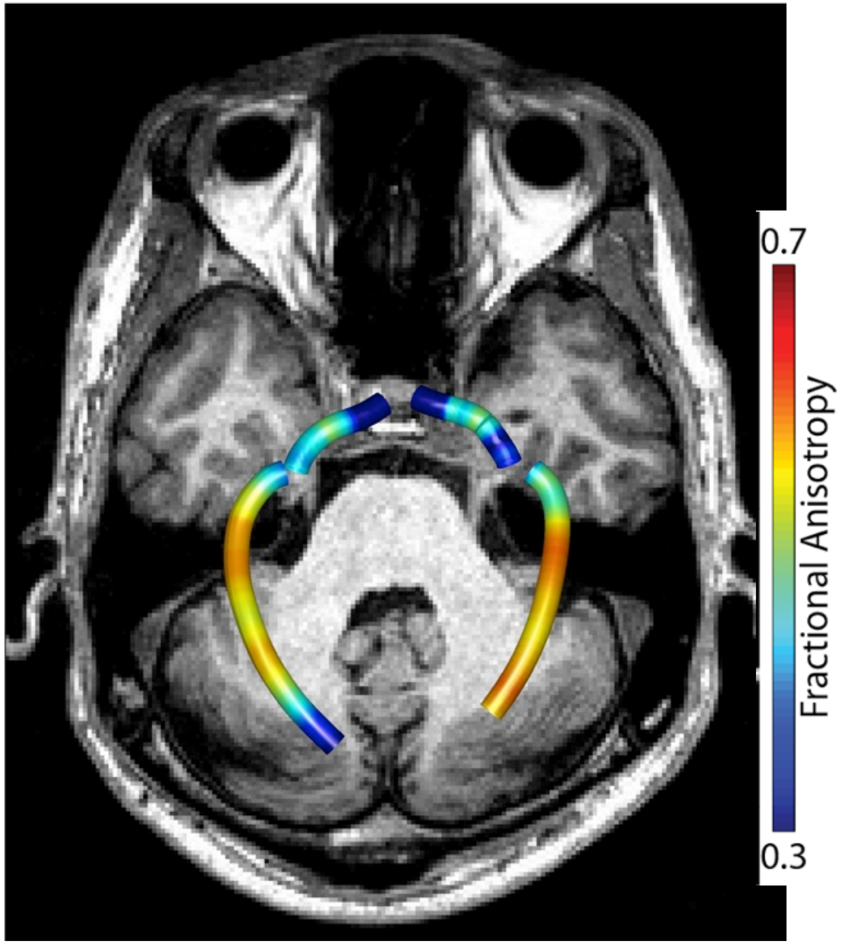
The expectation based on data acquired and stored in the SDM



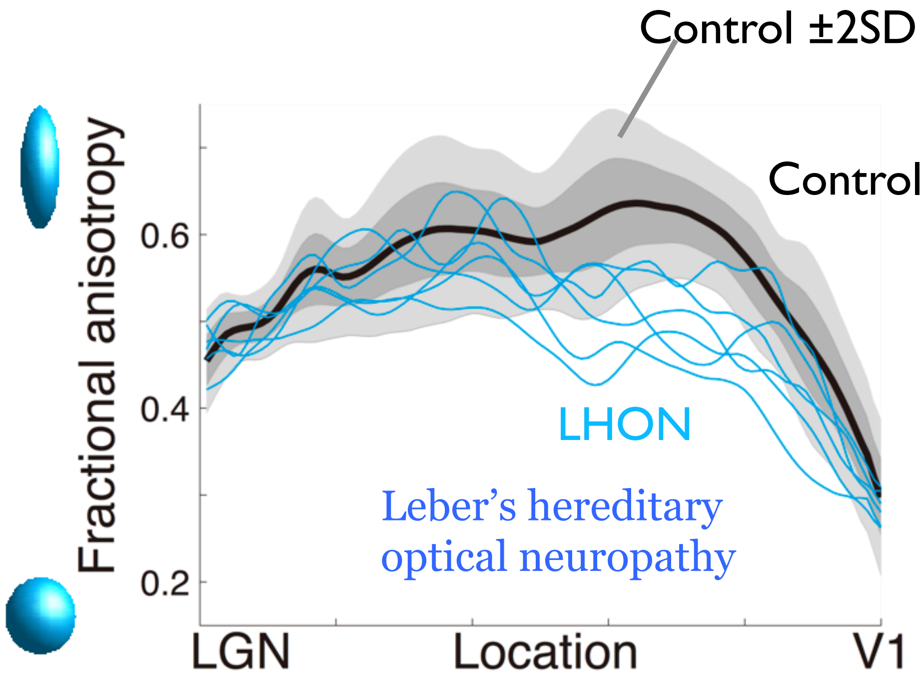
Compare your subject with the distribution and think

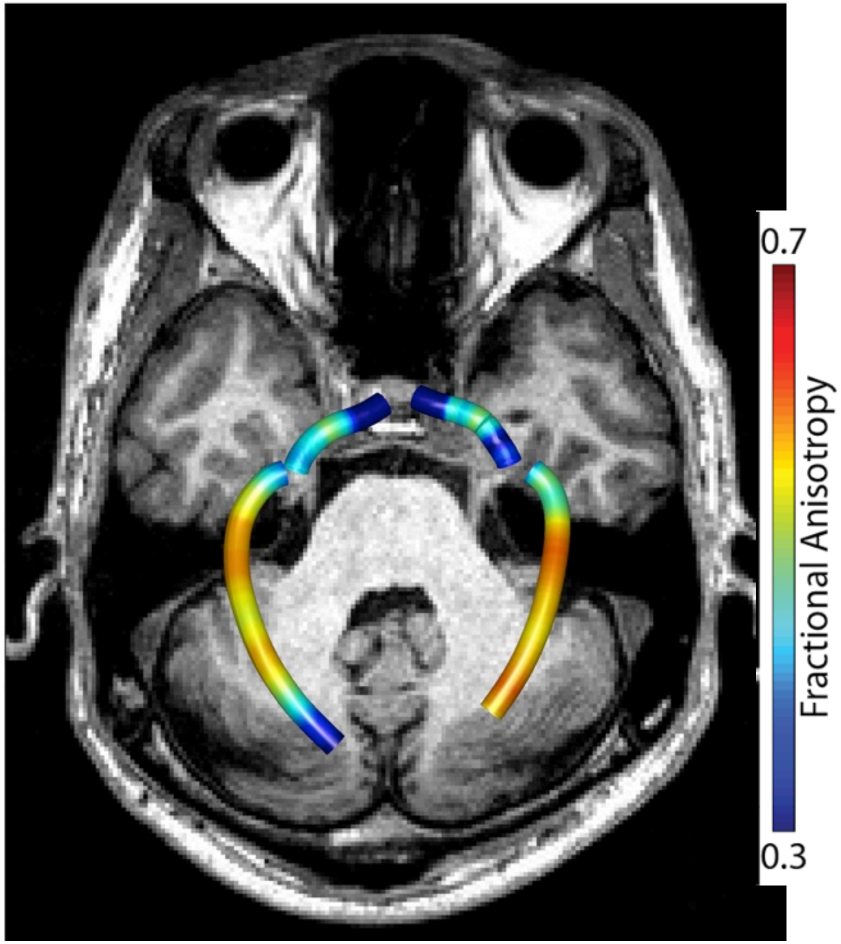


This subject compared to the expectation



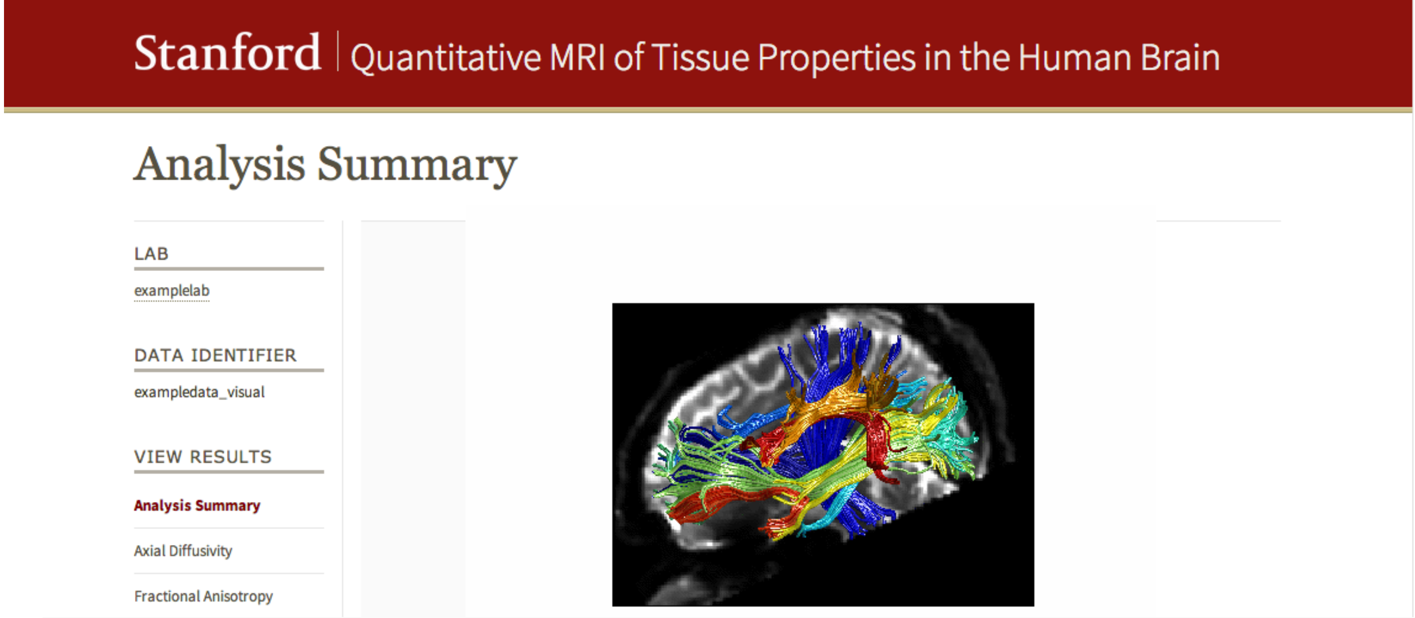
Data science and statistics issues





Each subject with the disease has some variation and we would like to know, and track each one over time

We are building computational tools that automate the comparison of individual patients with groups of matched controls



Stanford | Quantitative MRI of Tissue Properties in the Human Brain

Analysis Summary

LAB

examplelab

DATA IDENTIFIER

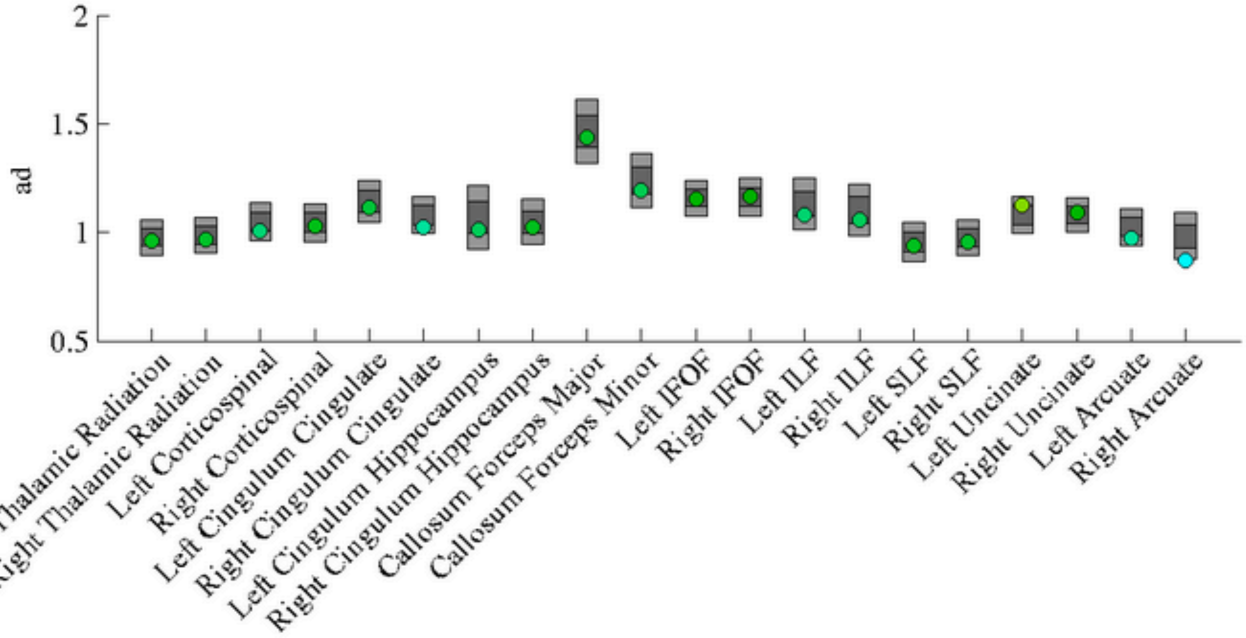
exampledata_visual

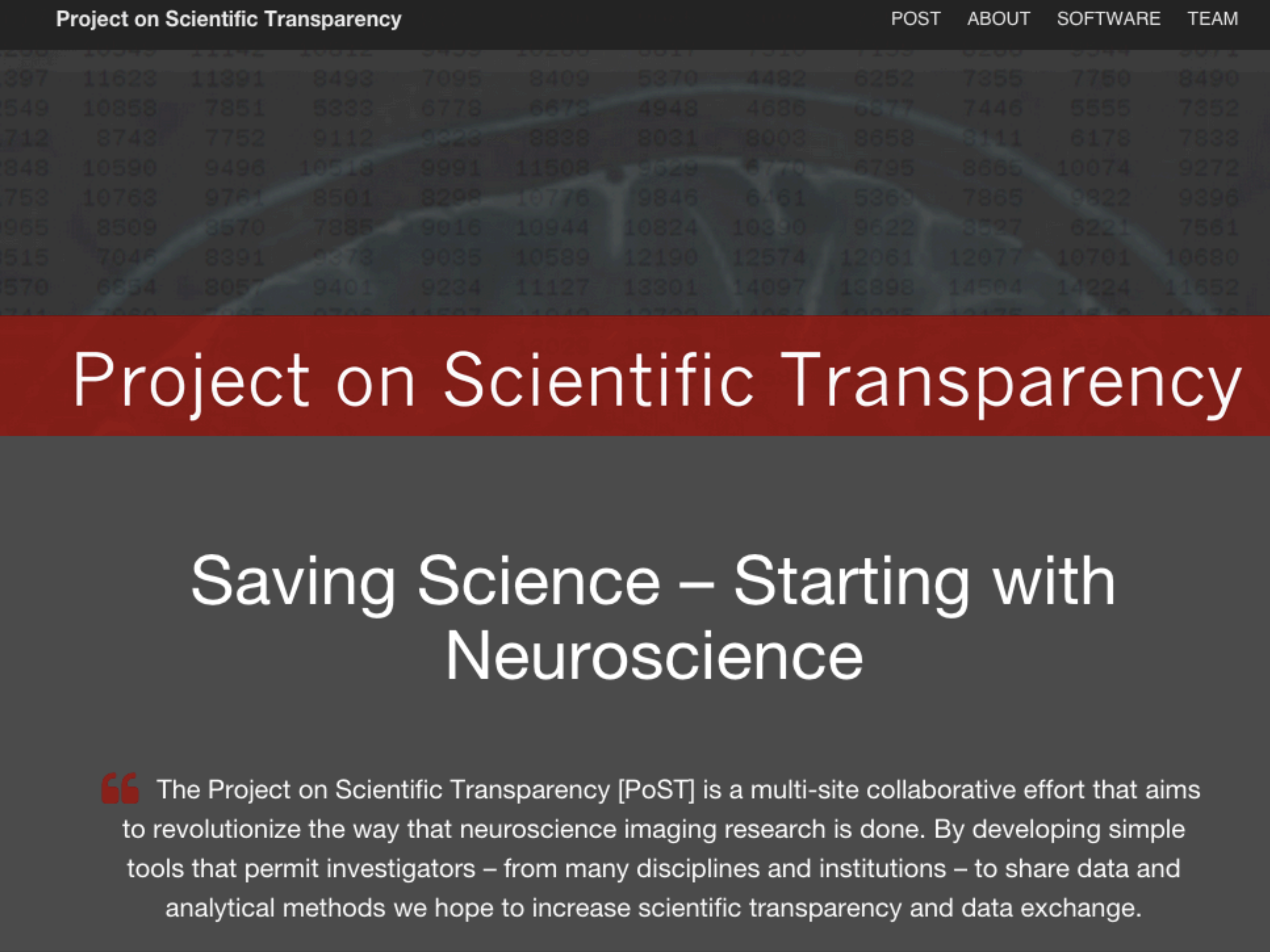
VIEW RESULTS

Analysis Summary

Axial Diffusivity

Fractional Anisotropy





Project on Scientific Transparency

POST ABOUT SOFTWARE TEAM

Project on Scientific Transparency

Saving Science – Starting with Neuroscience

> The Project on Scientific Transparency [PoST] is a multi-site collaborative effort that aims to revolutionize the way that neuroscience imaging research is done. By developing simple tools that permit investigators – from many disciplines and institutions – to share data and analytical methods we hope to increase scientific transparency and data exchange.

- Maps and models
- White matter methods
- Reading

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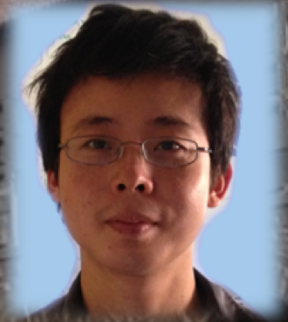

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