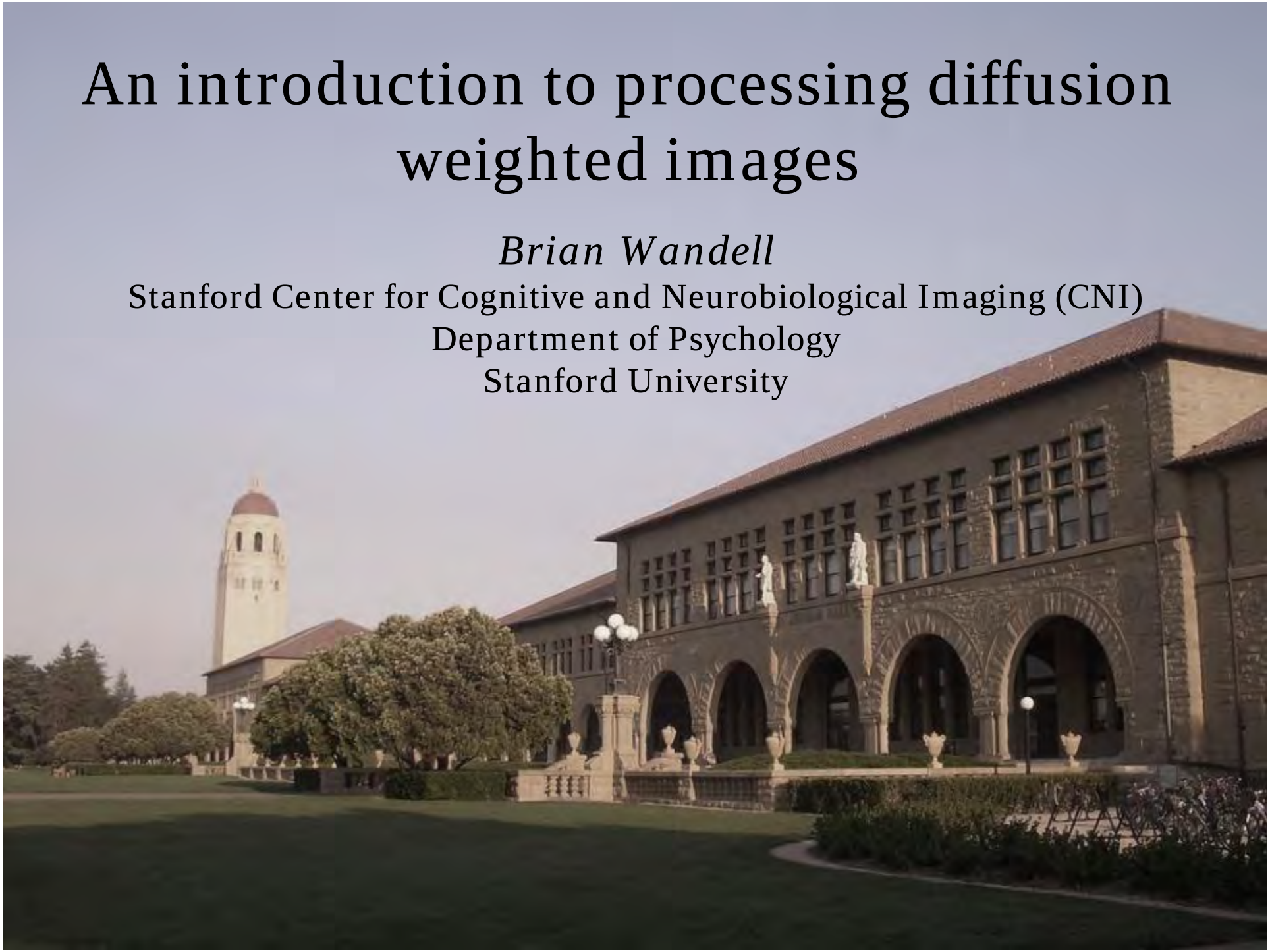
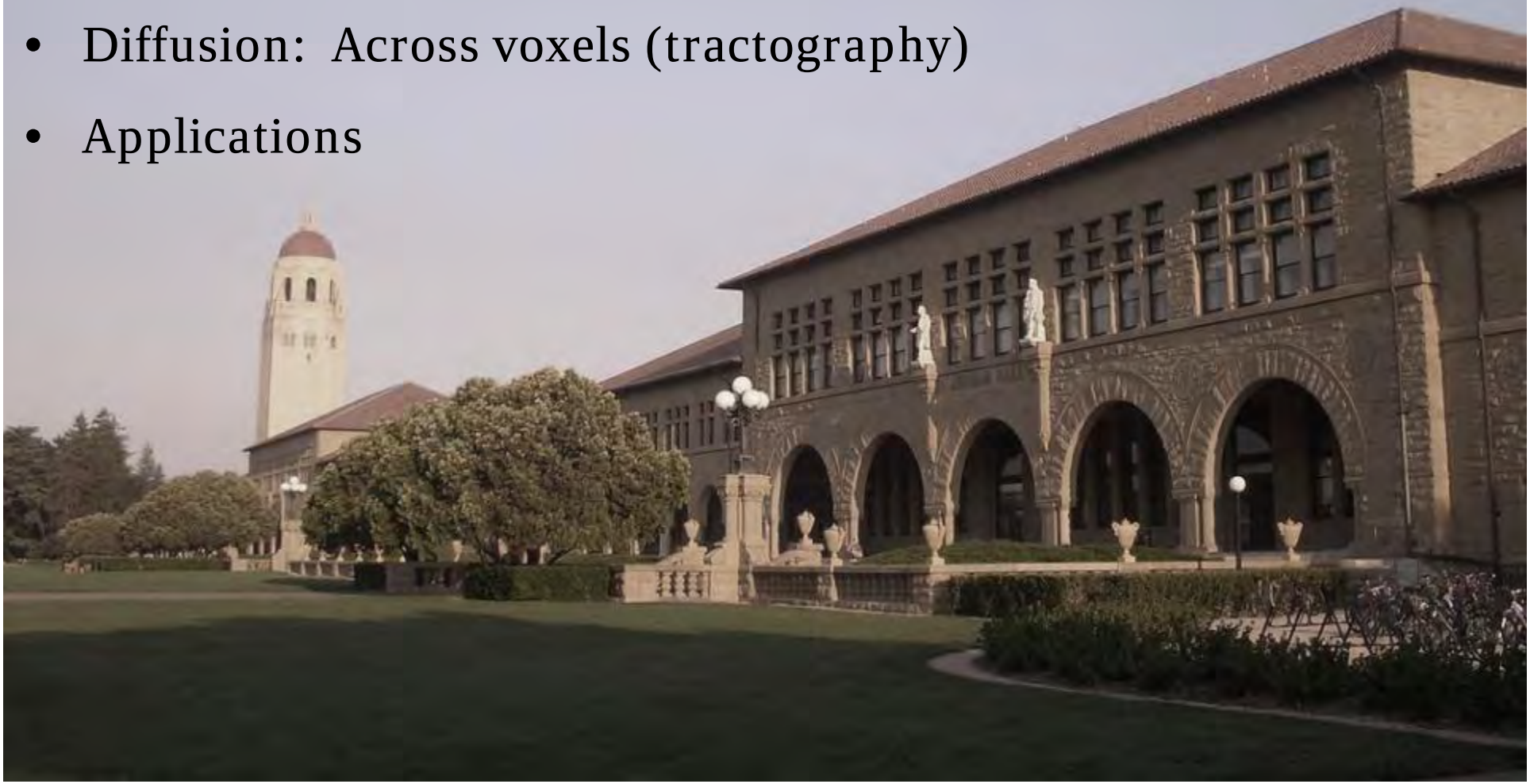
An introduction to processing diffusion weighted images

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



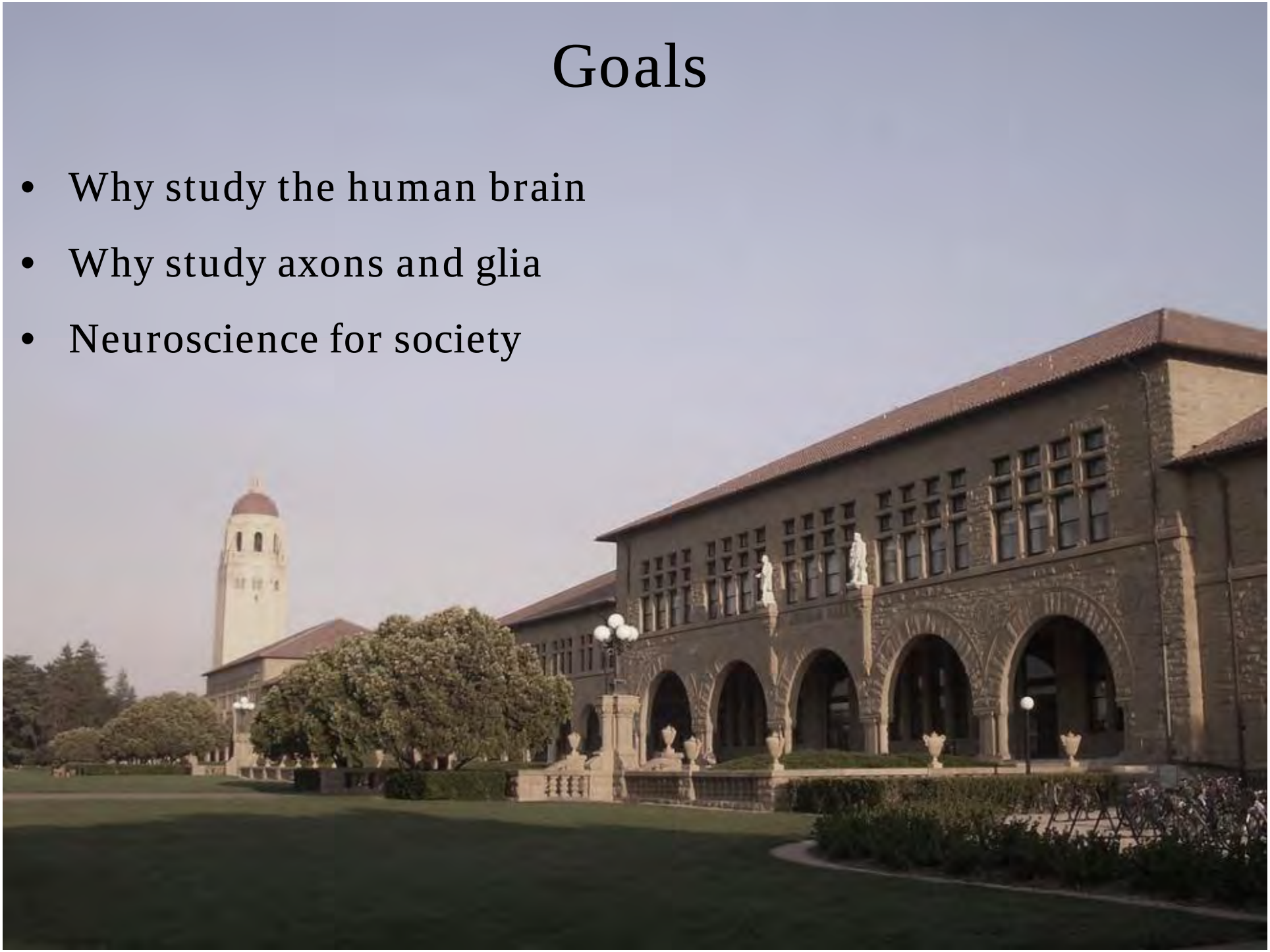
Overview

- What are the neuroscience issues
- Diffusion: Within the voxel
- Diffusion: Across voxels (tractography)
- Applications

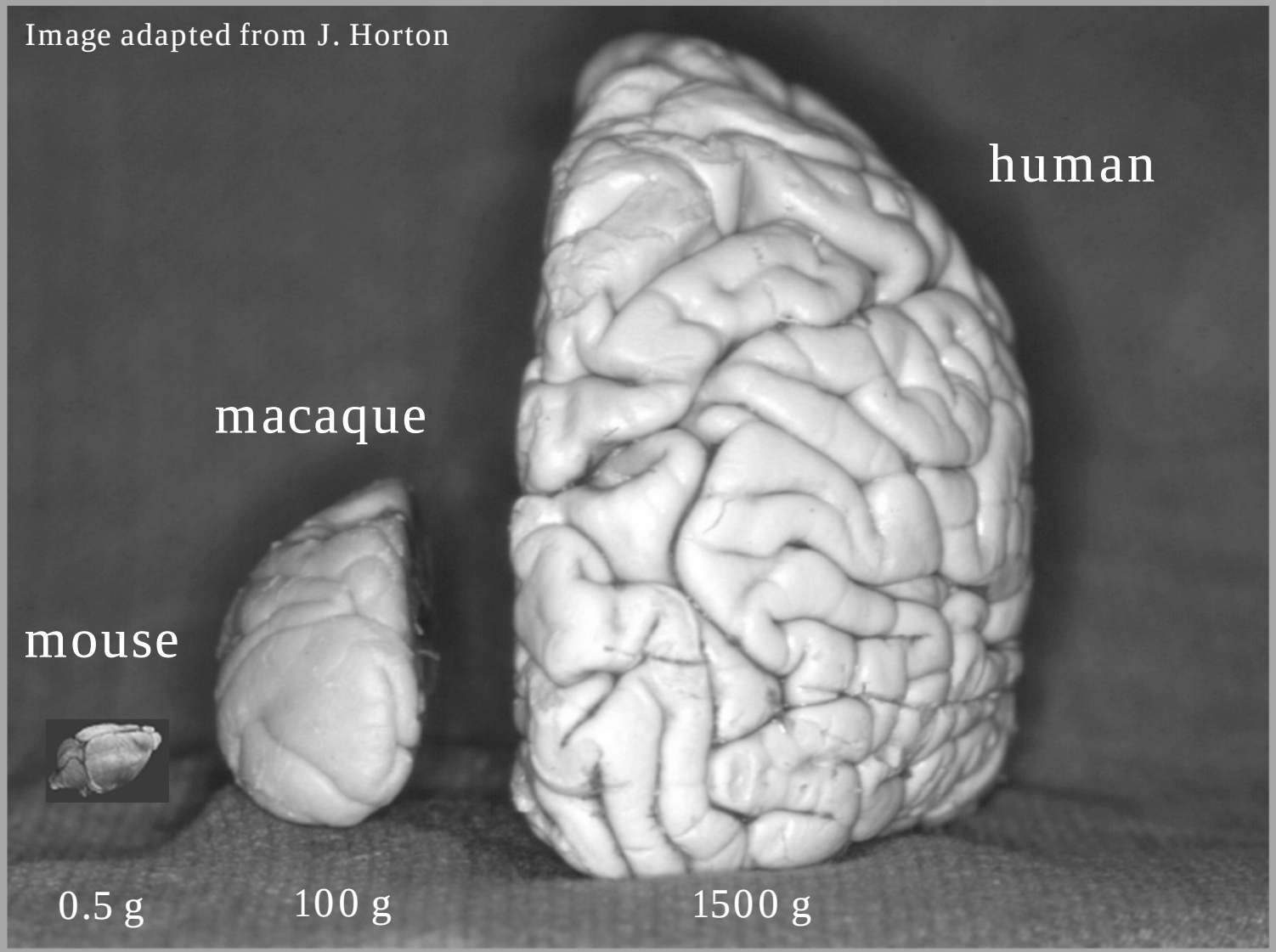


Goals

- Why study the human brain
- Why study axons and glia
- Neuroscience for society

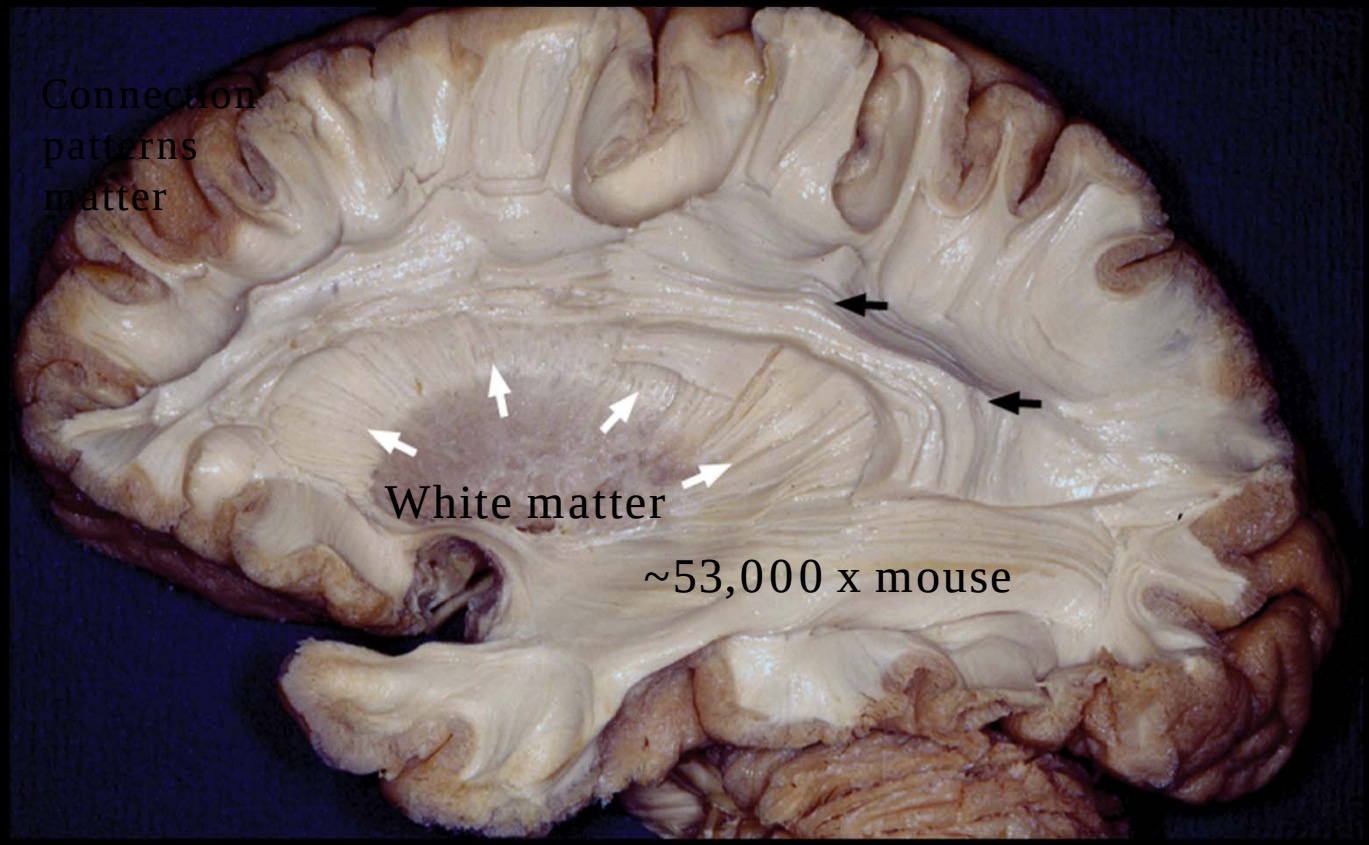


The human brain



Human brain characteristics

- Neuron cell bodies in cortex
- Long-range axons in white matter
- A system with active wires that develop and whose properties correlate with visual skills (e.g., sight word efficiency)

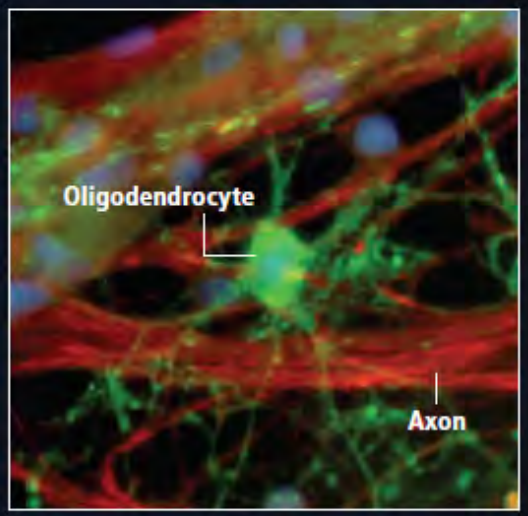


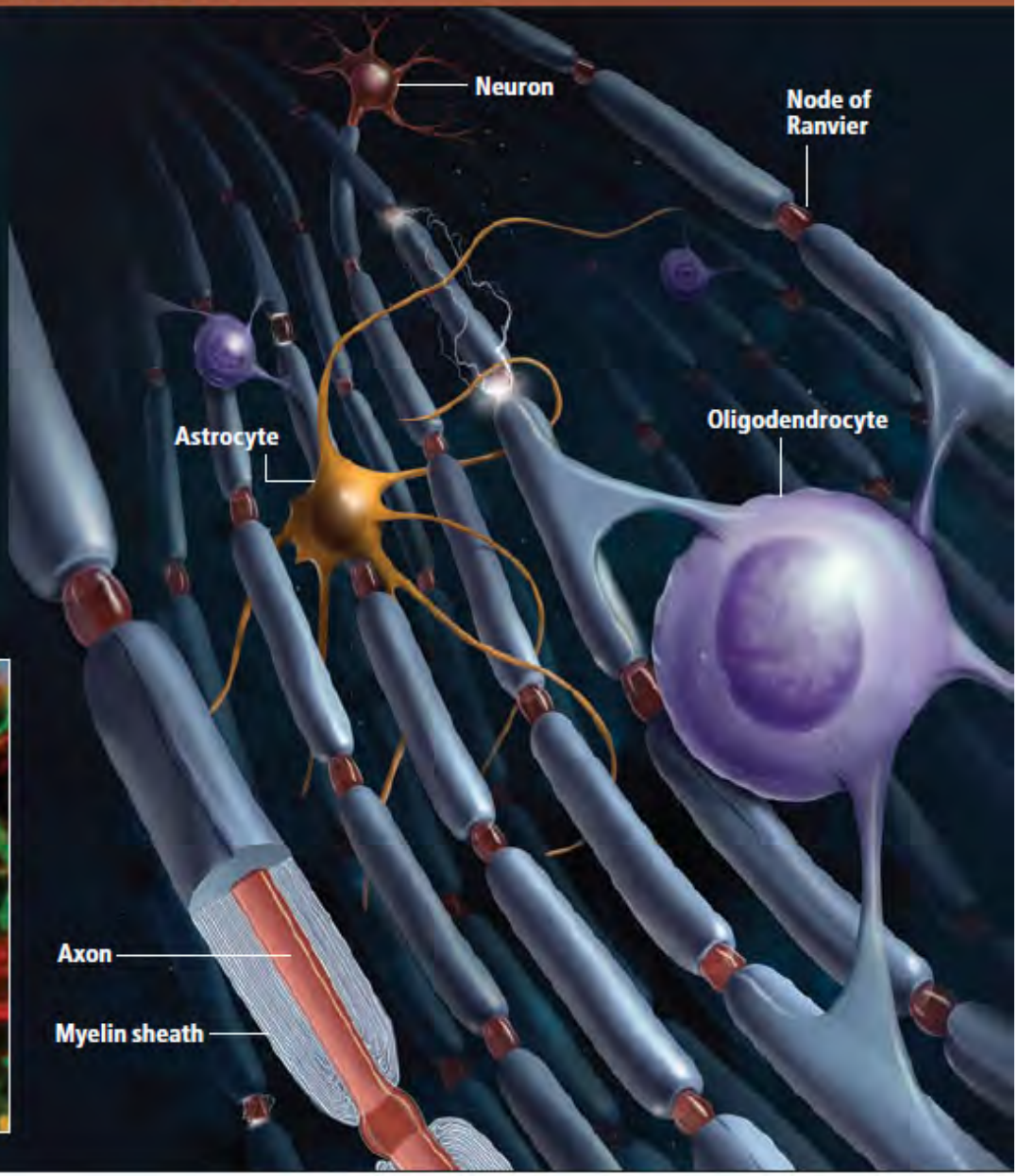
Courtesy Professor Ugur Ture

R. Douglas Fields

MYELIN FORMATION

Long axons insulated with myelin carry signals between neurons faster than unmyelinated axons. Oligodendrocyte cells manufacture the fatty membrane and wrap the axon with 10 to 150 layers. Different factors can stimulate the myelination process; often astrocyte cells "listen in" on the signals traveling along axons and relay chemical messages to the oligodendrocytes. Below, a microscope shows axons in red being wrapped.

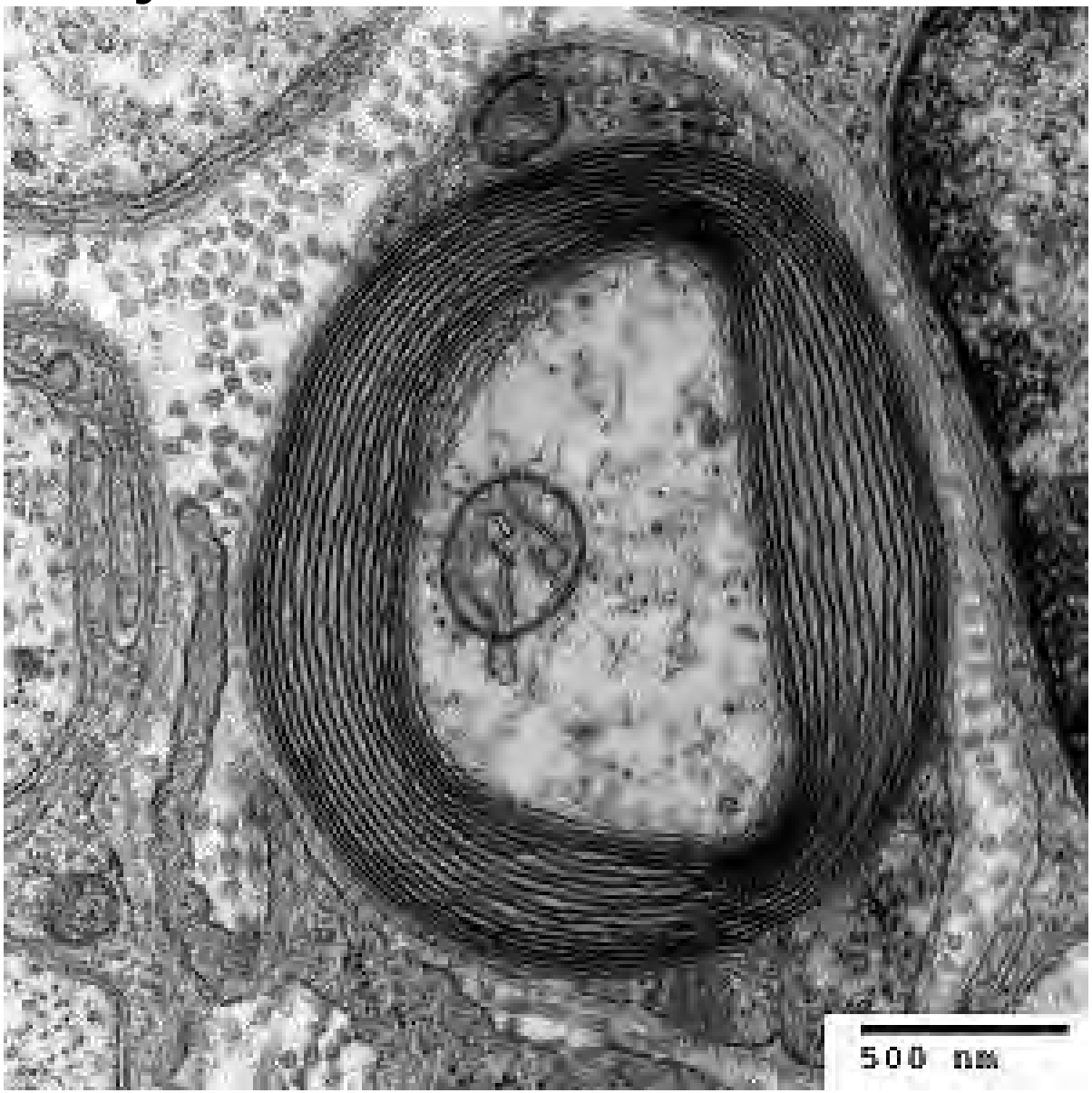




An oligodendrocyte in the white matter

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

Note the scale bar



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.

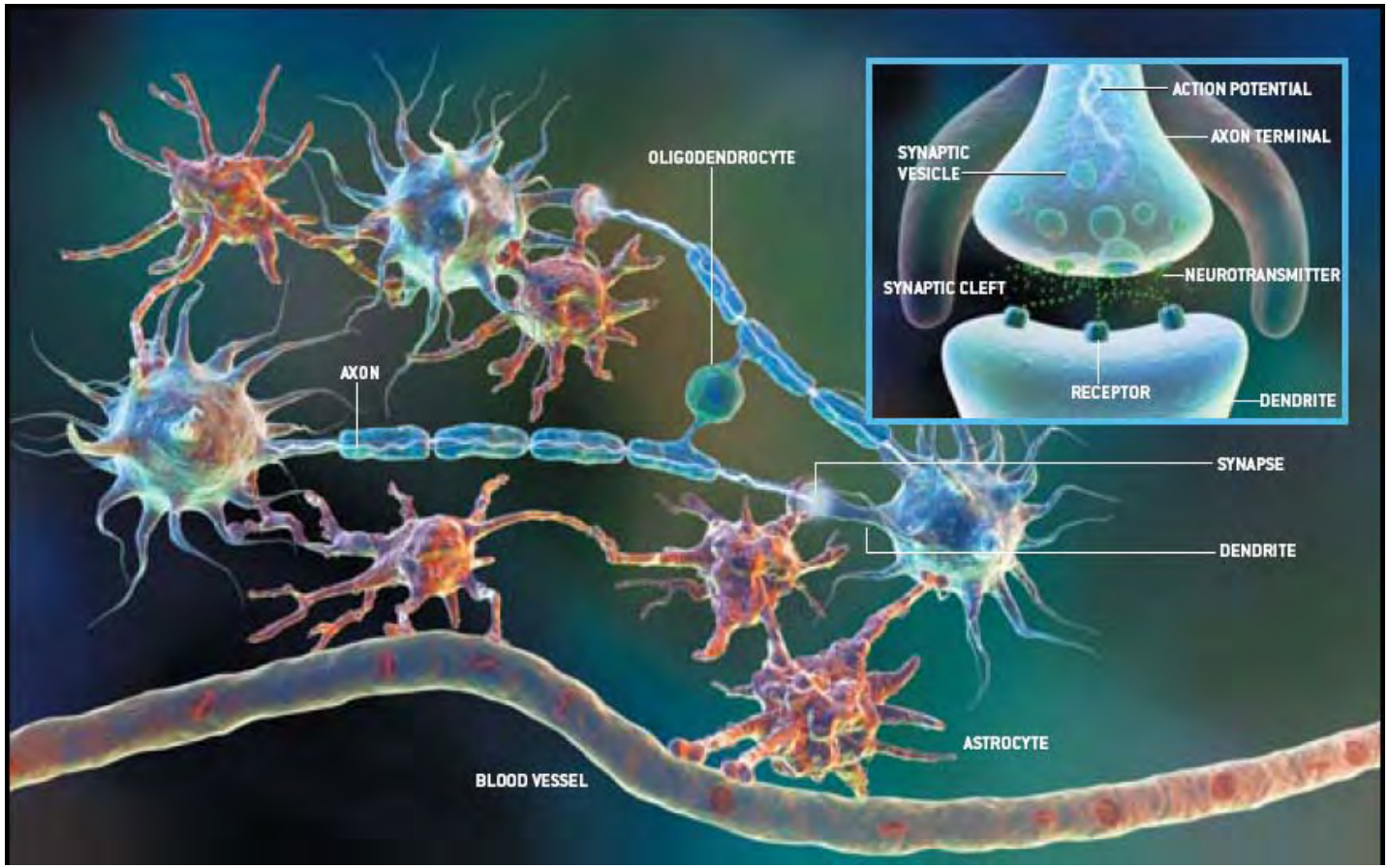


Image from
Wake, et al. Trends in Neurosciences
Volume 36, Issue 4, April 2013

Neuroscience is broadening its view

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-

Diffusion imaging is providing new understanding

Sagi, Tavor, Hofstetter, Tzur=Moryosef, Blumenfeld-Katrzir, Assaf
Neuron, 2012

Learning in the Fast Lane: New Insights into Neuroplasticity

Yaniv Sagi,[1,2] Ido Tavor,[1,2] Shir Hofstetter,[1] Shimrit Tzur-Moryosef,[1] Tamar Blumenfeld-Katzir,[1] and Yaniv Assaf[1,*]
[1]Department of Neurobiology, George S. Wise Faculty of Life Sciences, Tel Aviv University, Tel Aviv 69978, Israel
[2]These authors contributed equally to this work
*Correspondence: assafyan@post.tau.ac.il
DOI 10.1016/j.neuron.2012.01.025

Abstract

Using diffusion tensor imaging (DTI), an MRI-based framework, we examined subjects before and after a spatial learning and memory task. Microstructural changes (as reflected by DTI measures) of limbic system structures (hippocampus and parahippocampus) were significant after only 2 hr of training. This observation was also found in a supporting rat study. We conclude that cellular rearrangement of neural tissue can be detected by DTI, and that this modality may allow neuroplasticity to be localized over short timescales.

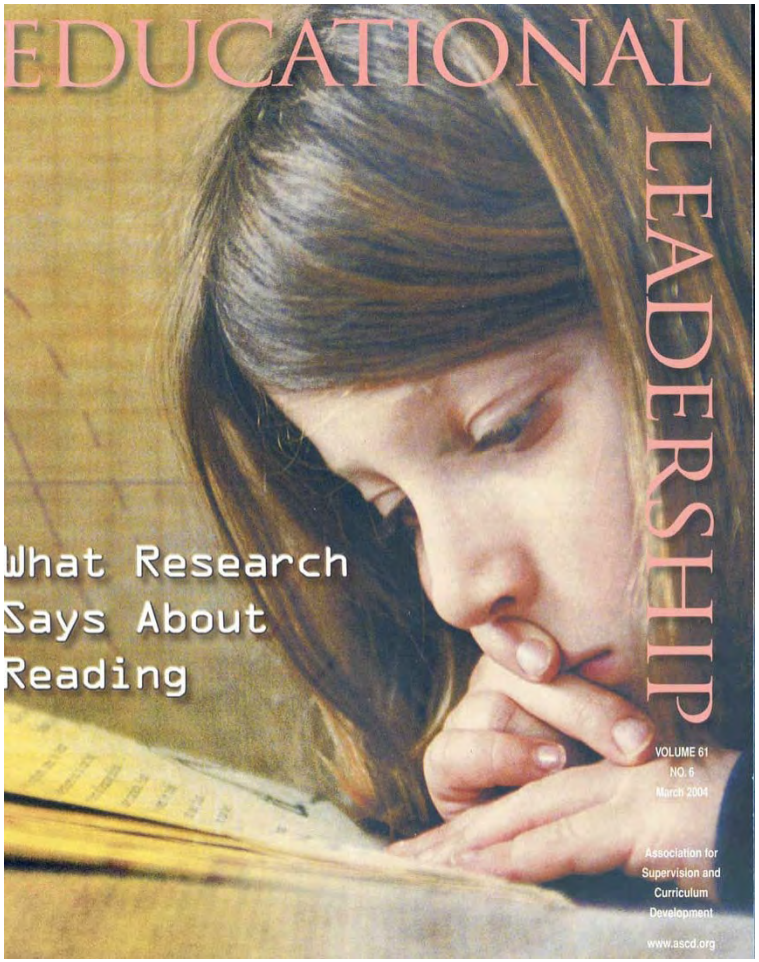
Neuroscience for Society

Wandell and Yeatman, CONB, 2013

- Some behaviors, such as psychological tests of performance during brief trials, may be best understood by measuring synaptic activity or spikes.

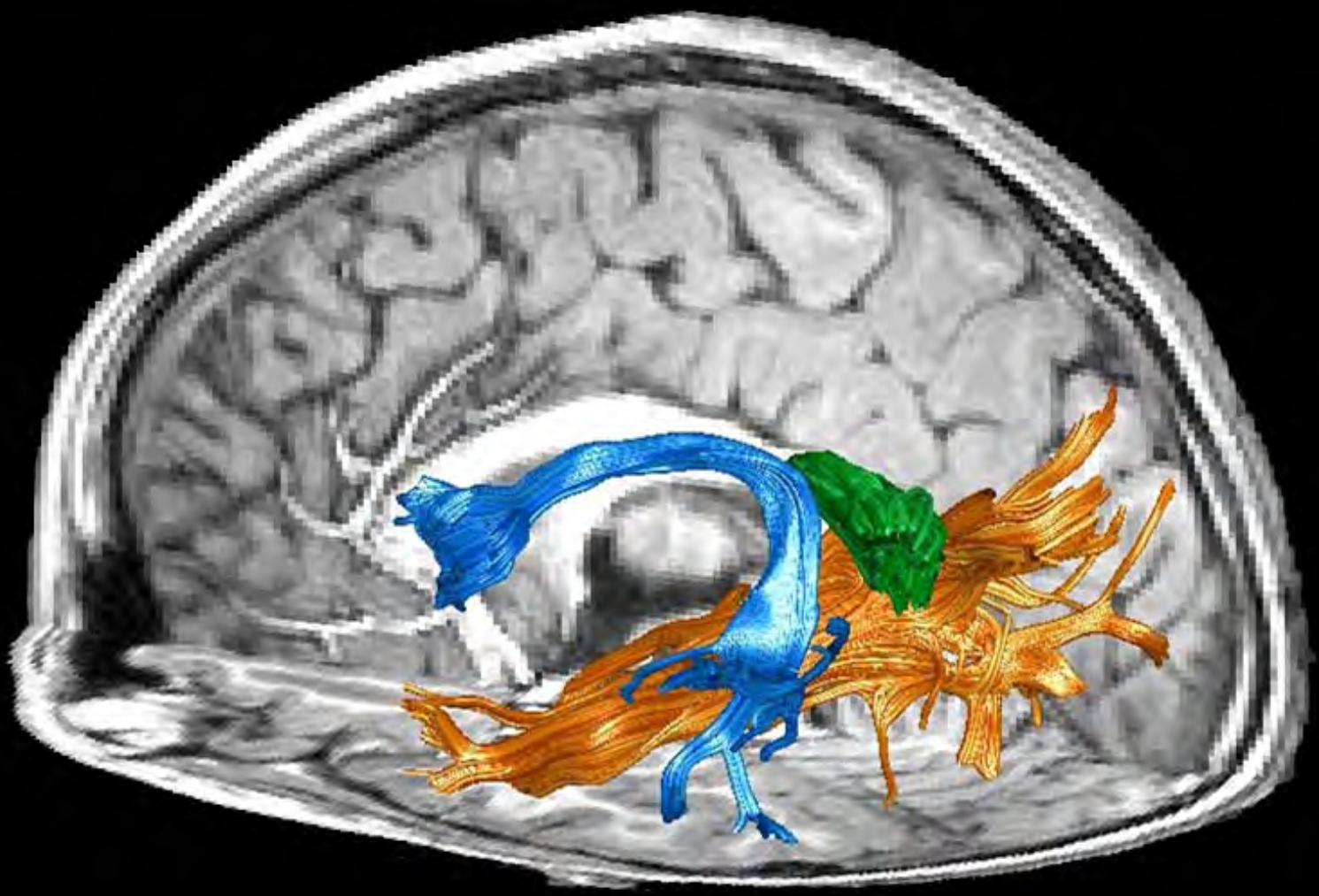
- Other important behaviors - learning to read or to regulate emotions - take place over longer time periods. These skills may depend on biological processes such as cell development, growth and pruning of dendritic arbors, the proliferation and activity of glia.

- Scientists need to account for the entire range of processes to understand circuit function in health and disease.



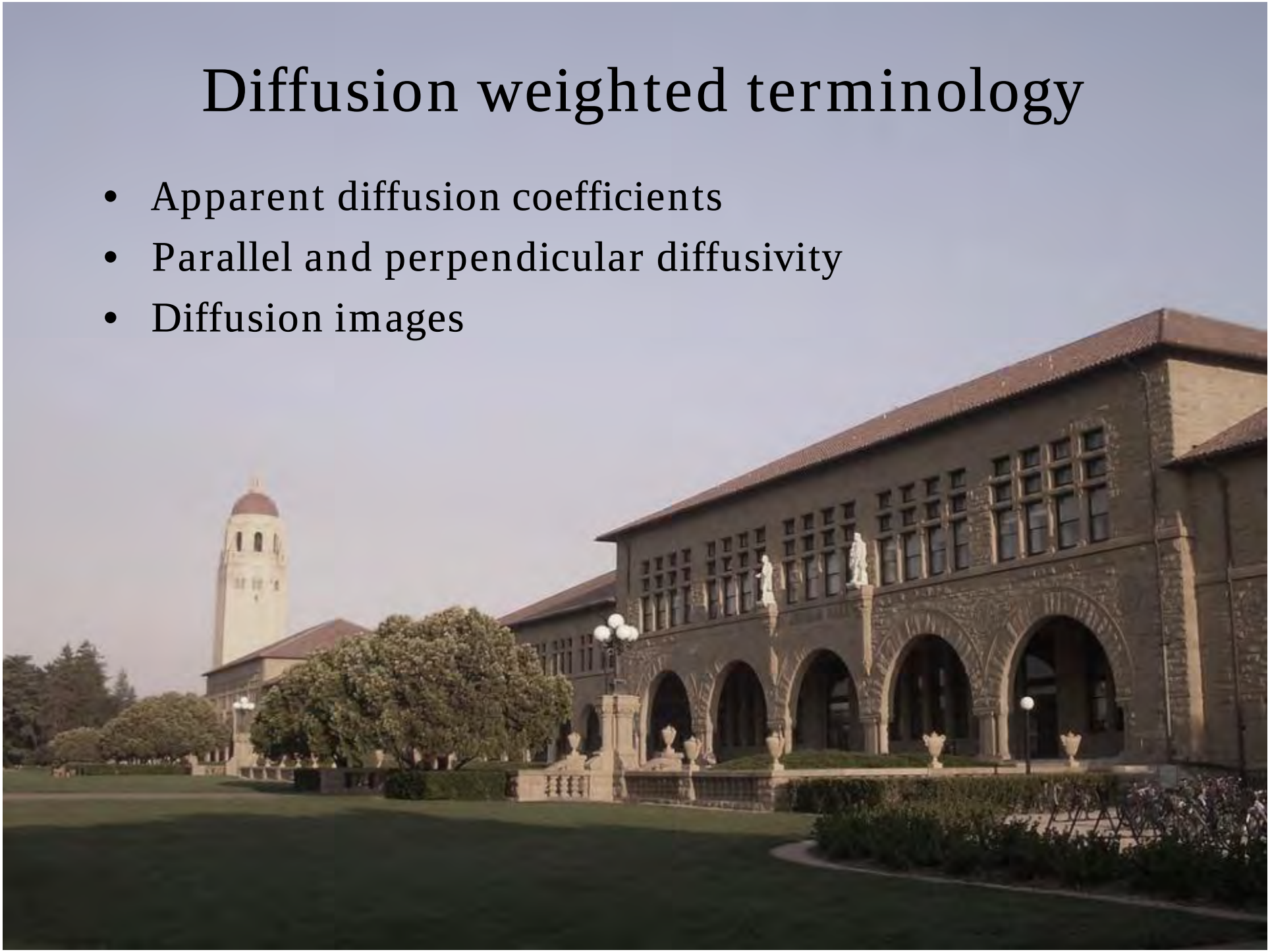
White matter reading tracts

(Wandell and Yeatman, Annual Review, 2013)



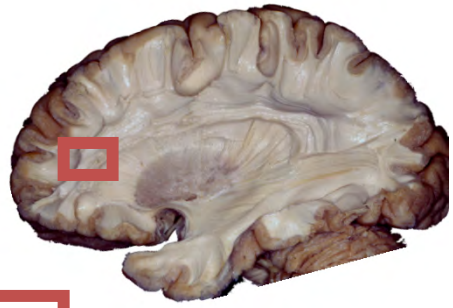
Diffusion weighted terminology

- Apparent diffusion coefficients
- Parallel and perpendicular diffusivity
- Diffusion images



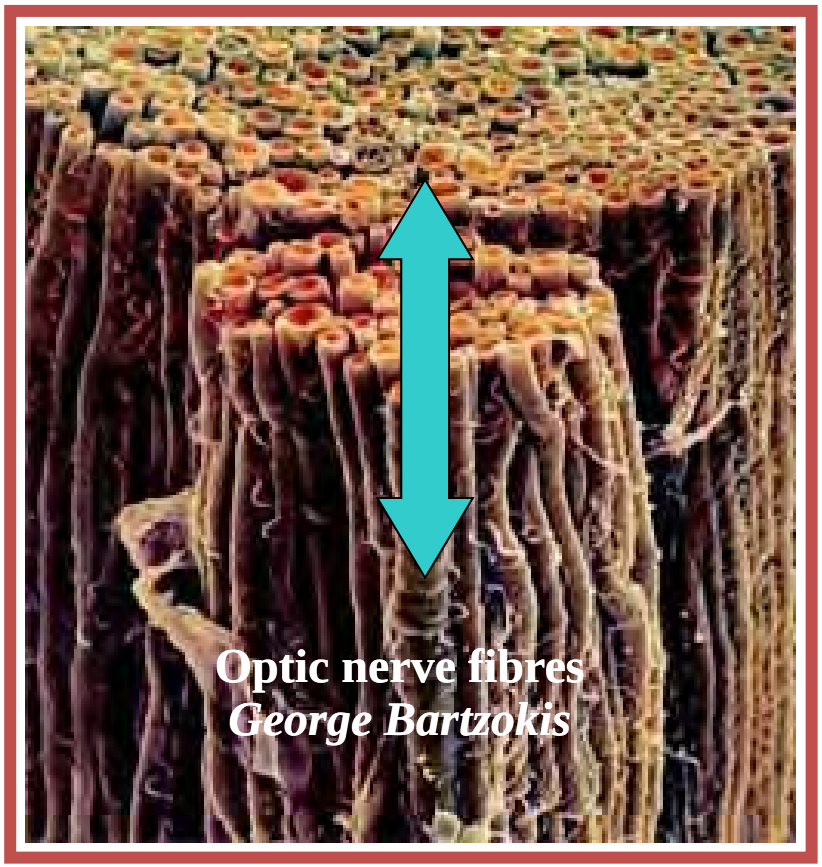
Diffusion probes brain microscopic structure

Parallel diffusivity ($\mu m^2/ms$)



Given a b-value and gradient direction, we measure **Apparent Diffusion Coefficient (ADC)**

Along the principal direction of axons, within the cytoskeleton, water displacement is large and signal is low



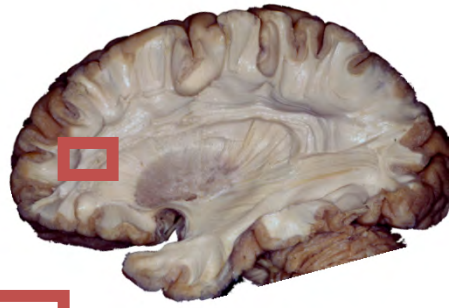
5 um

Equivalent names

- Parallel, axial, longitudinal, principal diffusion direction (PDD)

Diffusion probes brain microscopic structure

Perpendicular diffusivity ($\mu m^2/ms$)



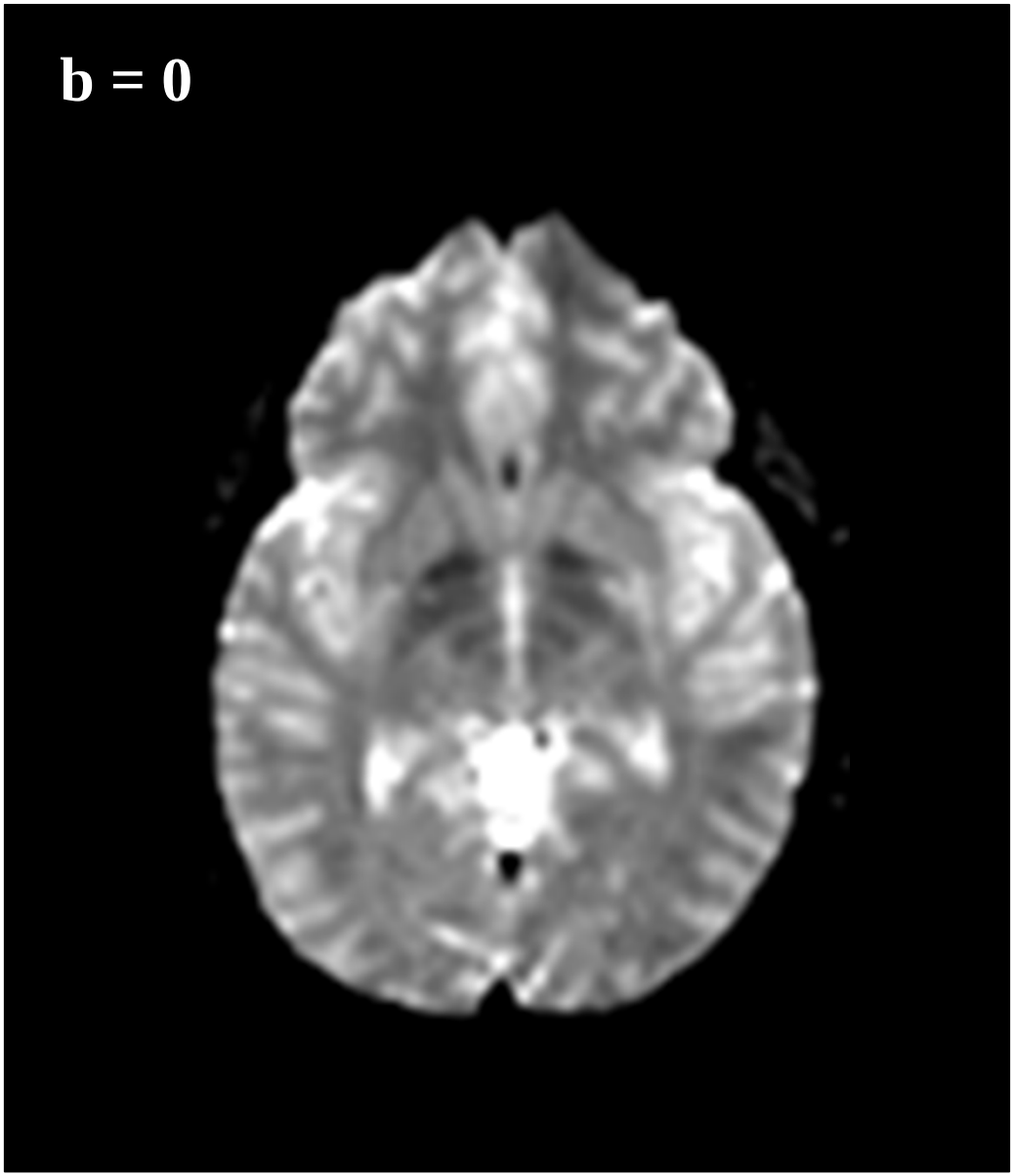
Perpendicular to the principal direction of axons, bi-lipid membranes limit water displacement so the signal is higher

Other names

- Perpendicular, radial, transverse

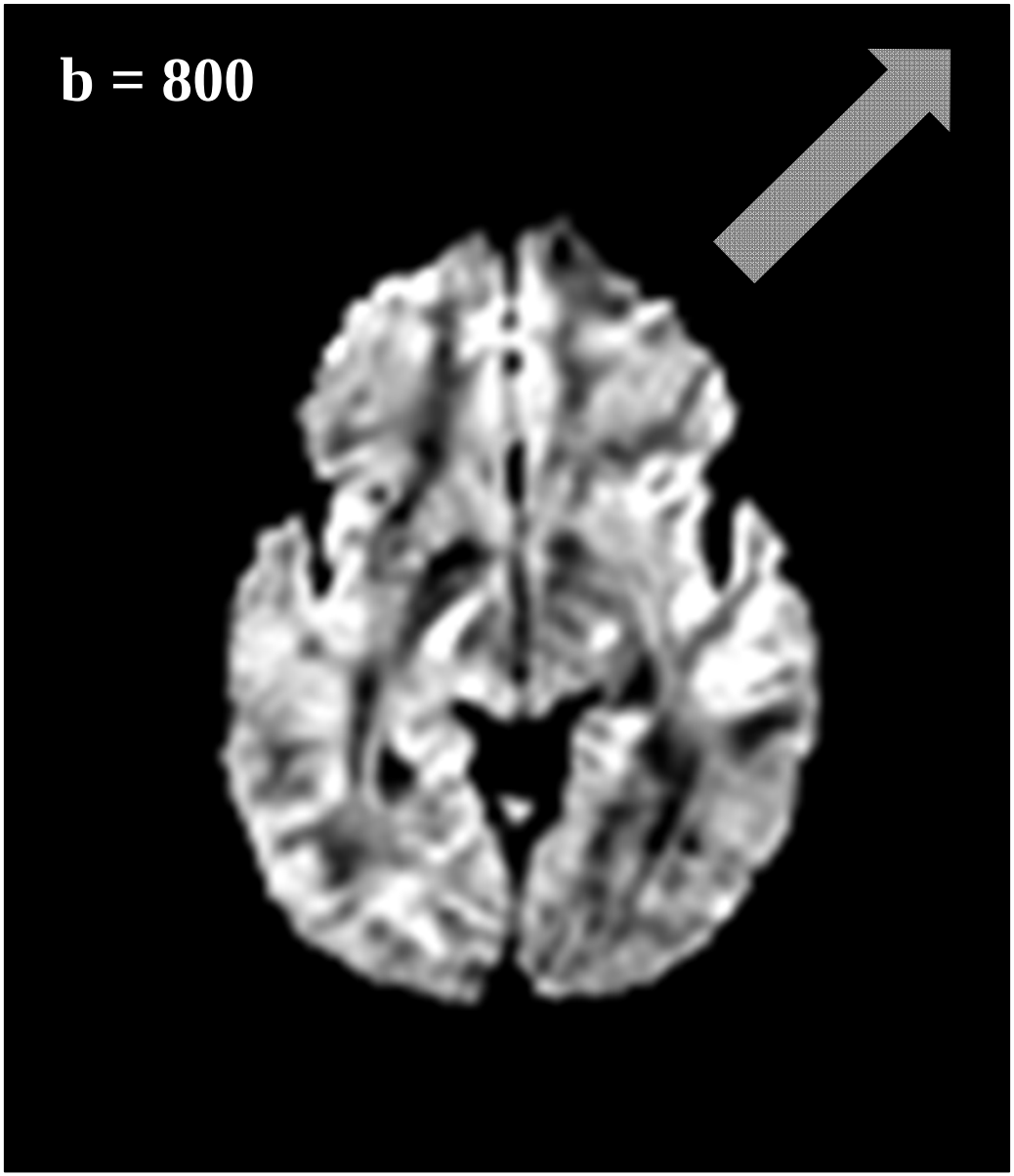
Non-diffusion MR image

Dark means large signal attenuation
High ADC



Diffusion weighting: Directions

Dark means large signal attenuation
High ADC



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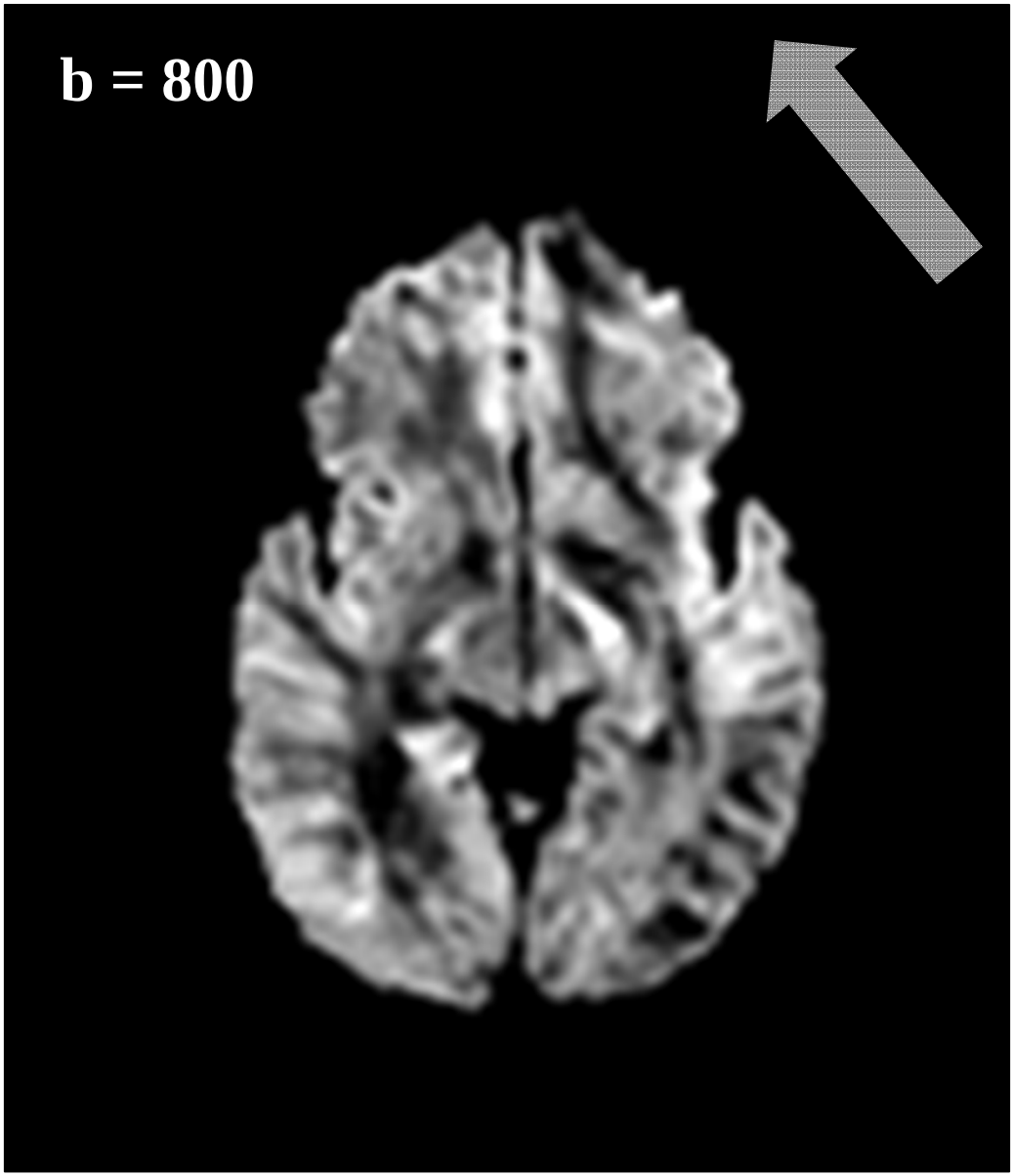
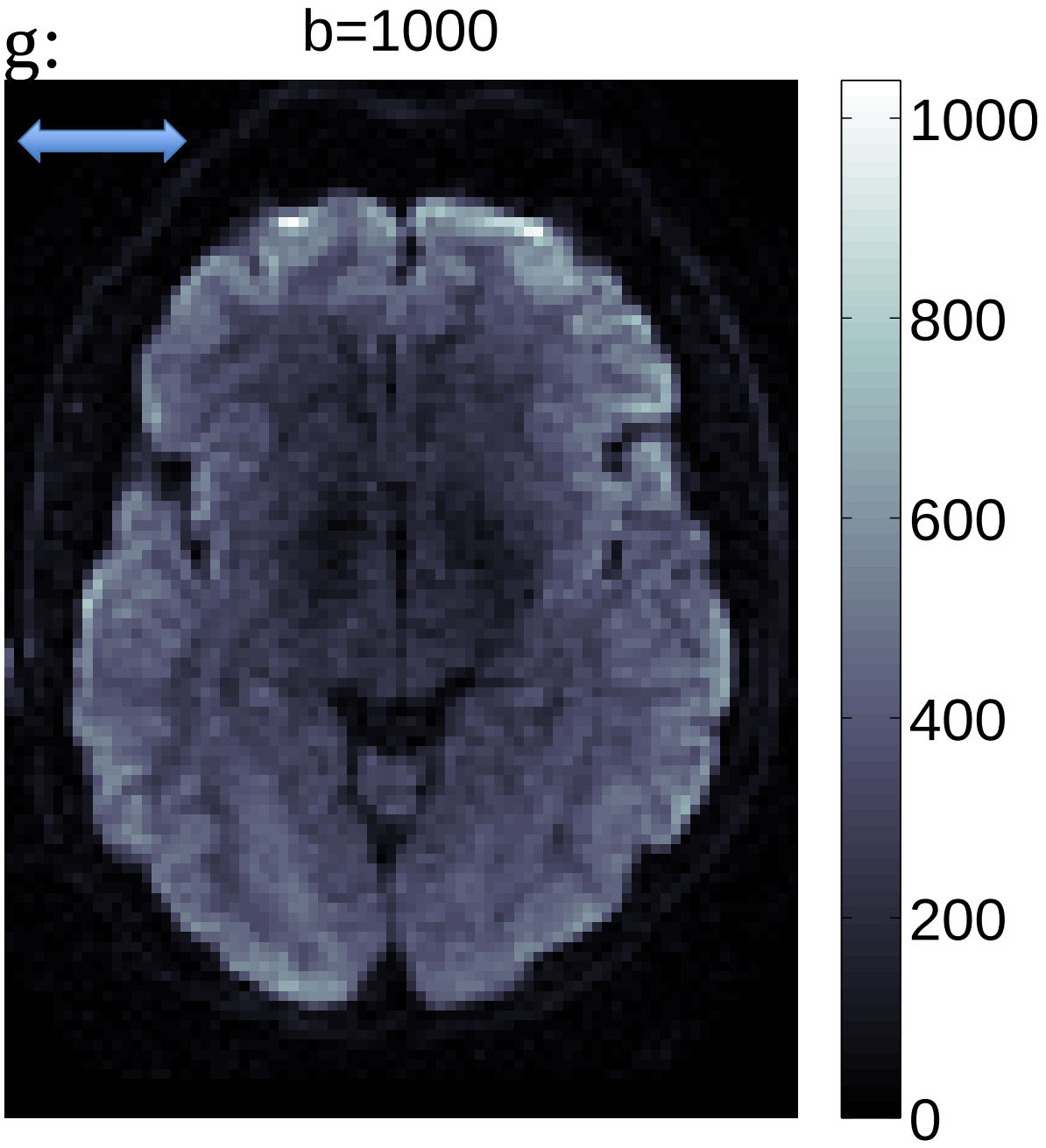
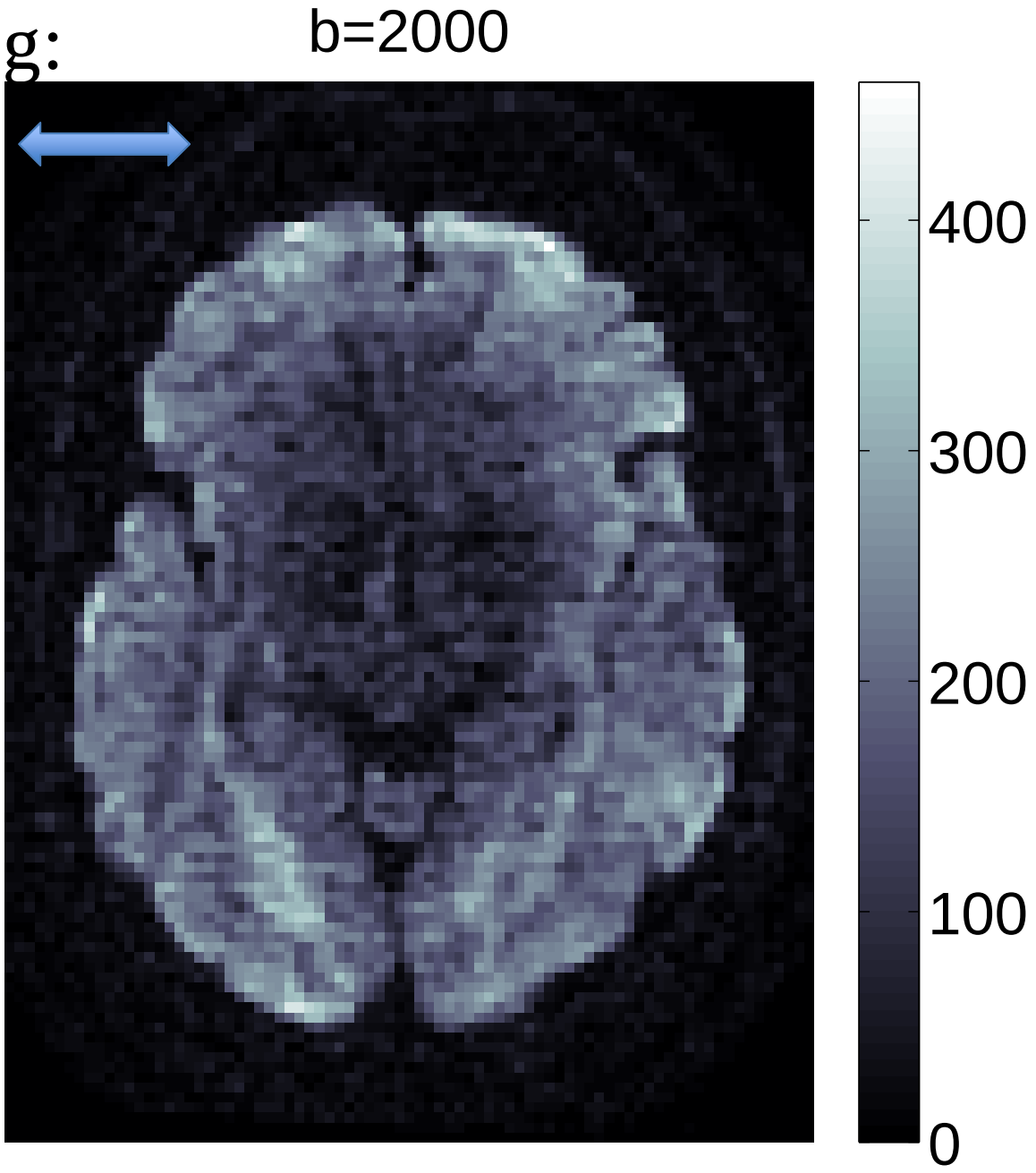


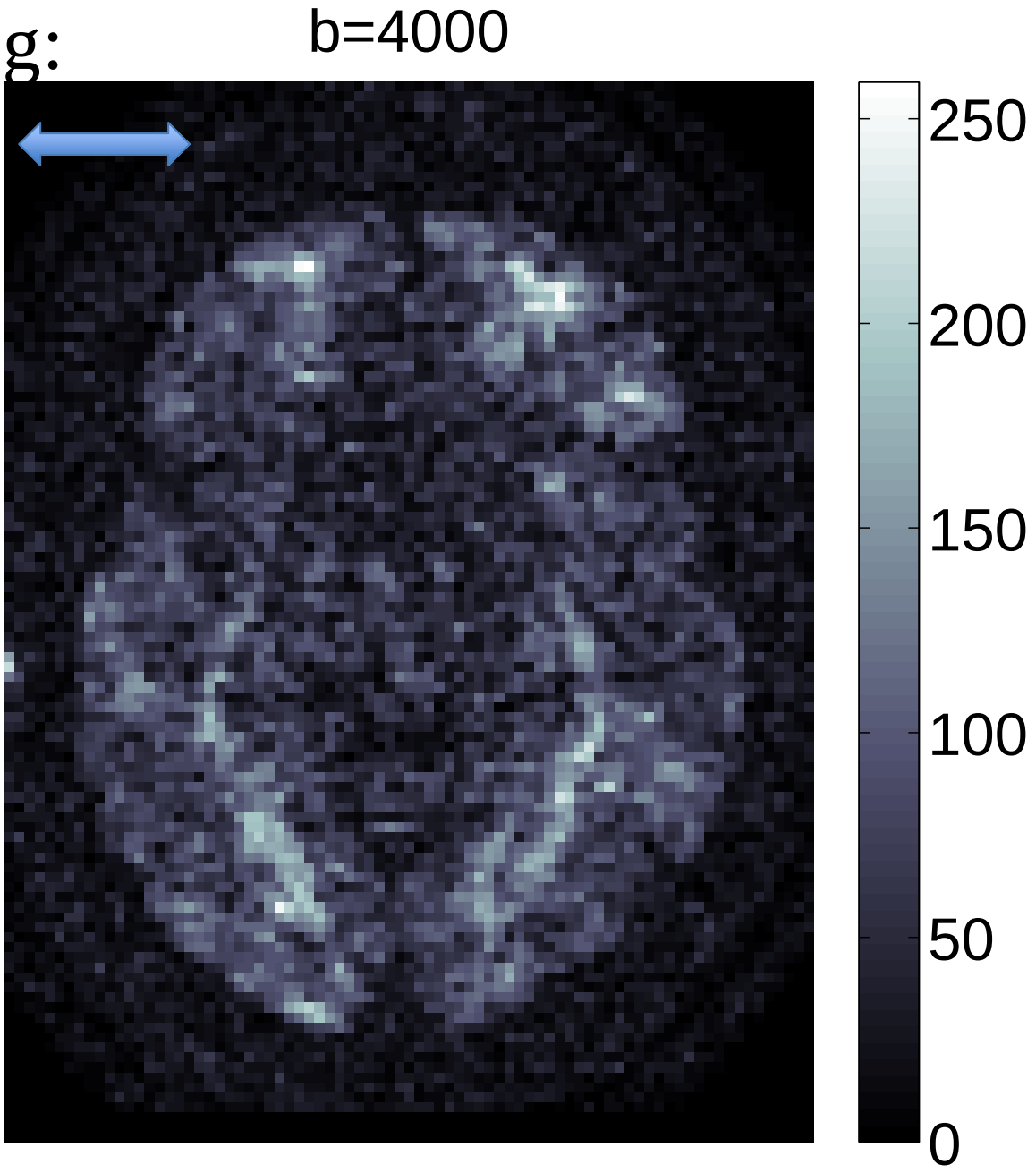
Diffusion-weighting: b-values



Diffusion-weighting: b-values



Diffusion-weighting:
b-values



Modeling the diffusion signal

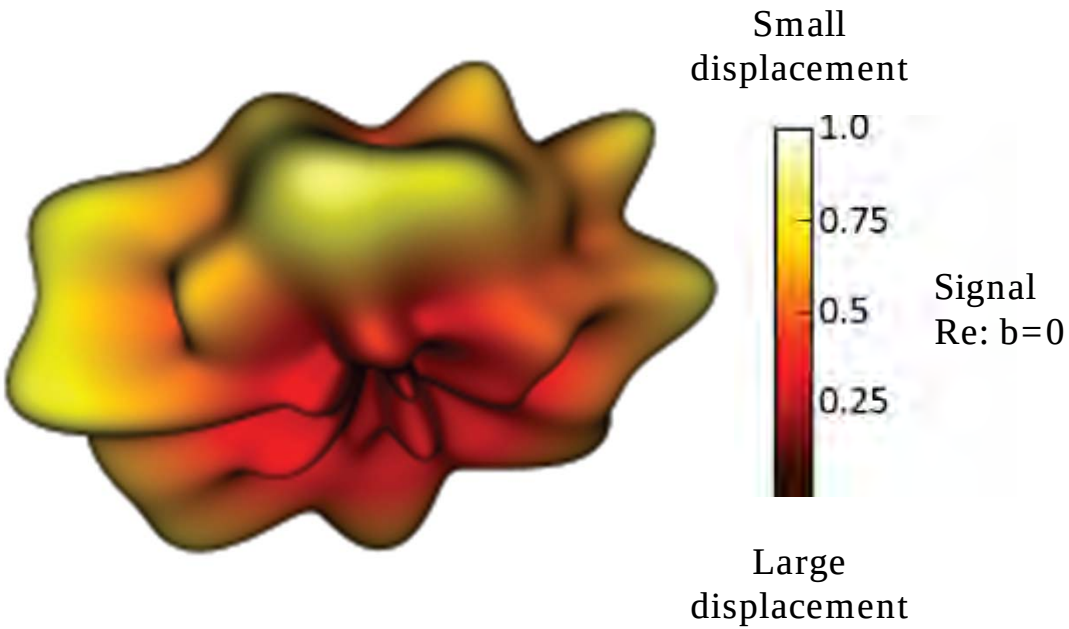
- The diffusion signal data in 3-space
- The diffusion tensor model (DTM)
- The ball-and-stick model (SFM)

Diffusion data analysis

High angular resolution diffusion imaging (HARDI)

MRI diffusion signal

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



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

Diffusion data analysis

High angular resolution diffusion imaging (HARDI)

MRI diffusion signal

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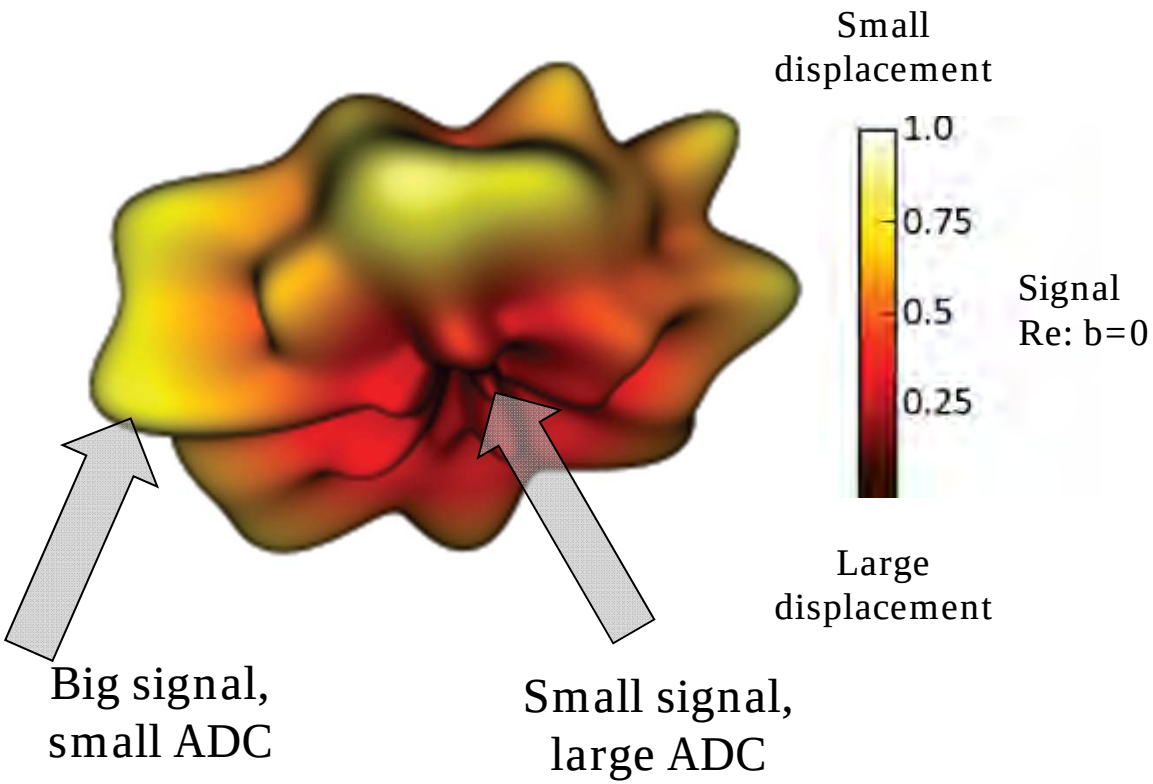


The measured diffusion signal in a direction, θ, is related to the apparent diffusion coefficient in that direction, D(θ)

Diffusion tensor model (DTM)

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

Stejskal-Tanner

Model the diffusion term using a quadratic form

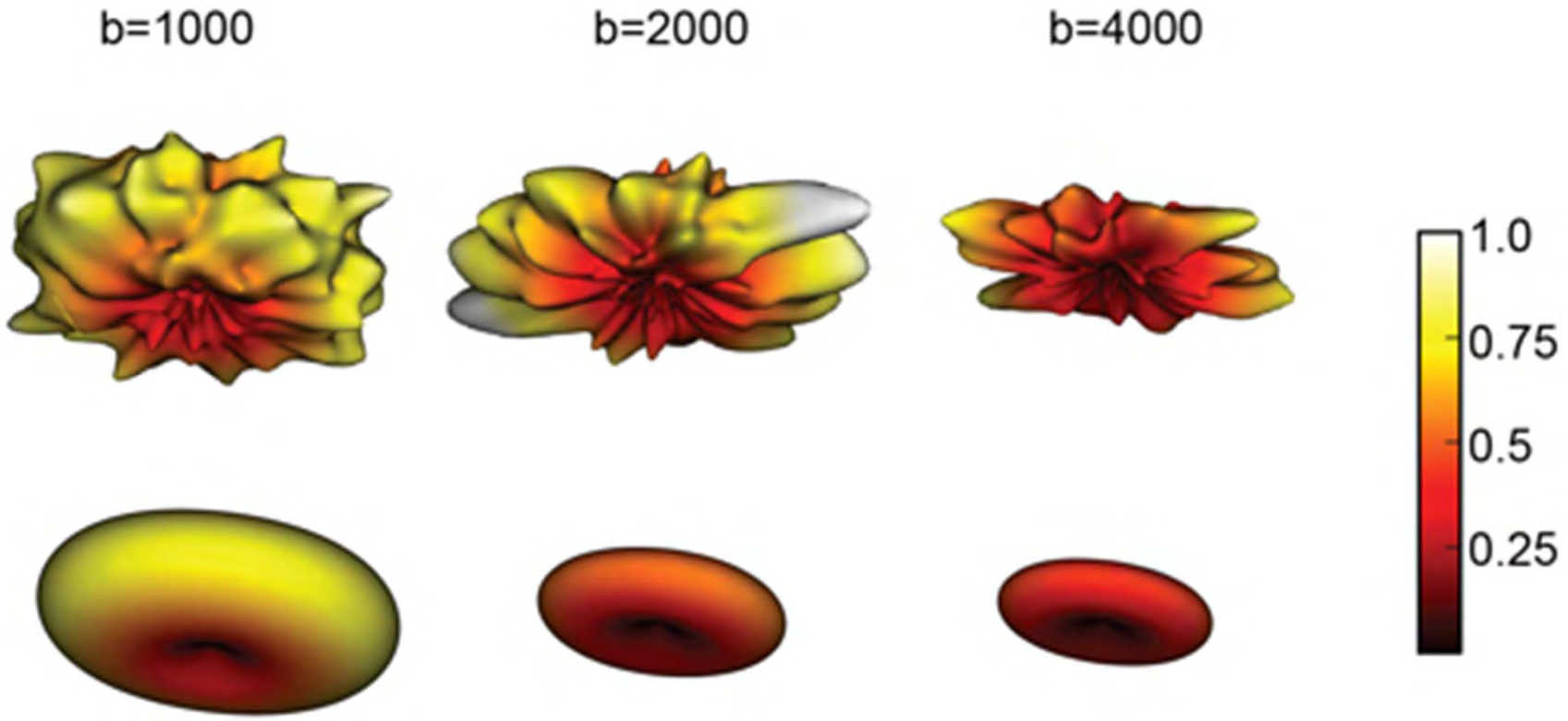
Basser, Pierpaoli

$$D(\theta) = \theta^t Q \theta$$

$$Q = A^t A$$

One way to model the signal is state a formula for diffusion in different directions (Gaussian)

Diffusion tensor model

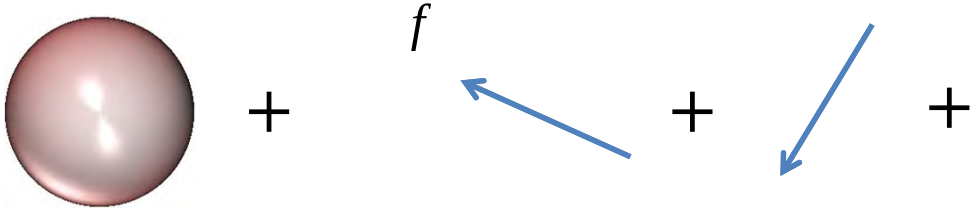


Signal re: b=0

The ball and stick model

Predicts the **voxel diffusion signal** with a model of the sum of fascicles plus isotropic diffusion

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

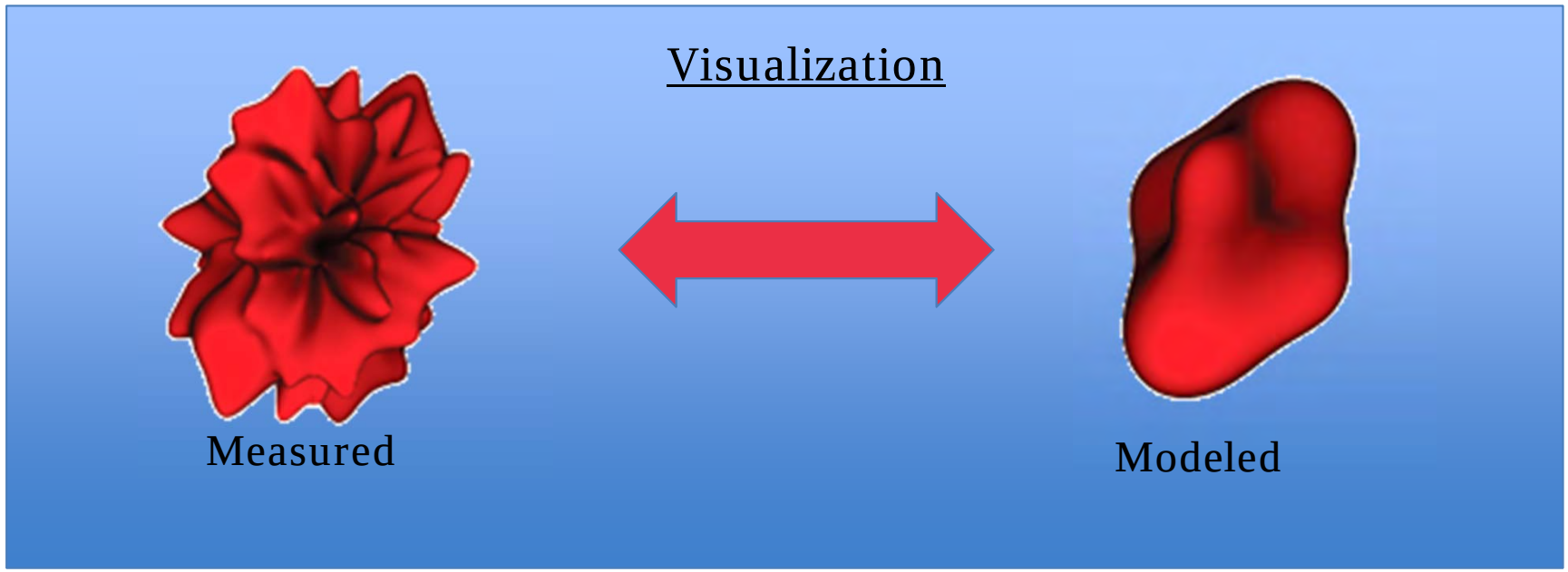


Ball Sticks

Larry Frank (2002)
Tim Behrens (2003)

The ball and stick model

Predicts the **voxel diffusion signal** with a model of the sum of fascicles plus isotropic diffusion

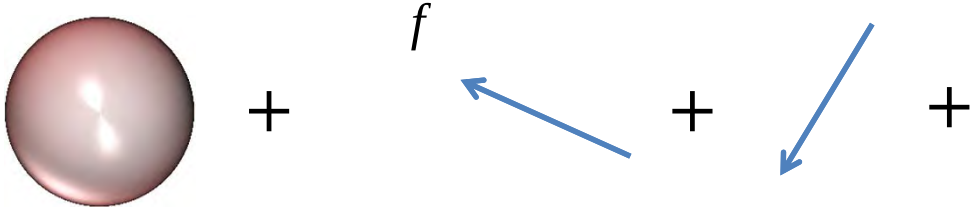


Sparse fascicle model (SFM)

Ariel Rokem and I call it this because

- BS model seemed like a bad idea
- We estimate the fascicles using a linear method with a sparseness constraint

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



Ball Sticks

Same idea as in spherical deconvolution; different estimation method

Summary

- DTM is a phenomenological description of the diffusion signal (like spherical harmonics)
- The ball and stick model (SFM) uses concepts that are evoke biological structures

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

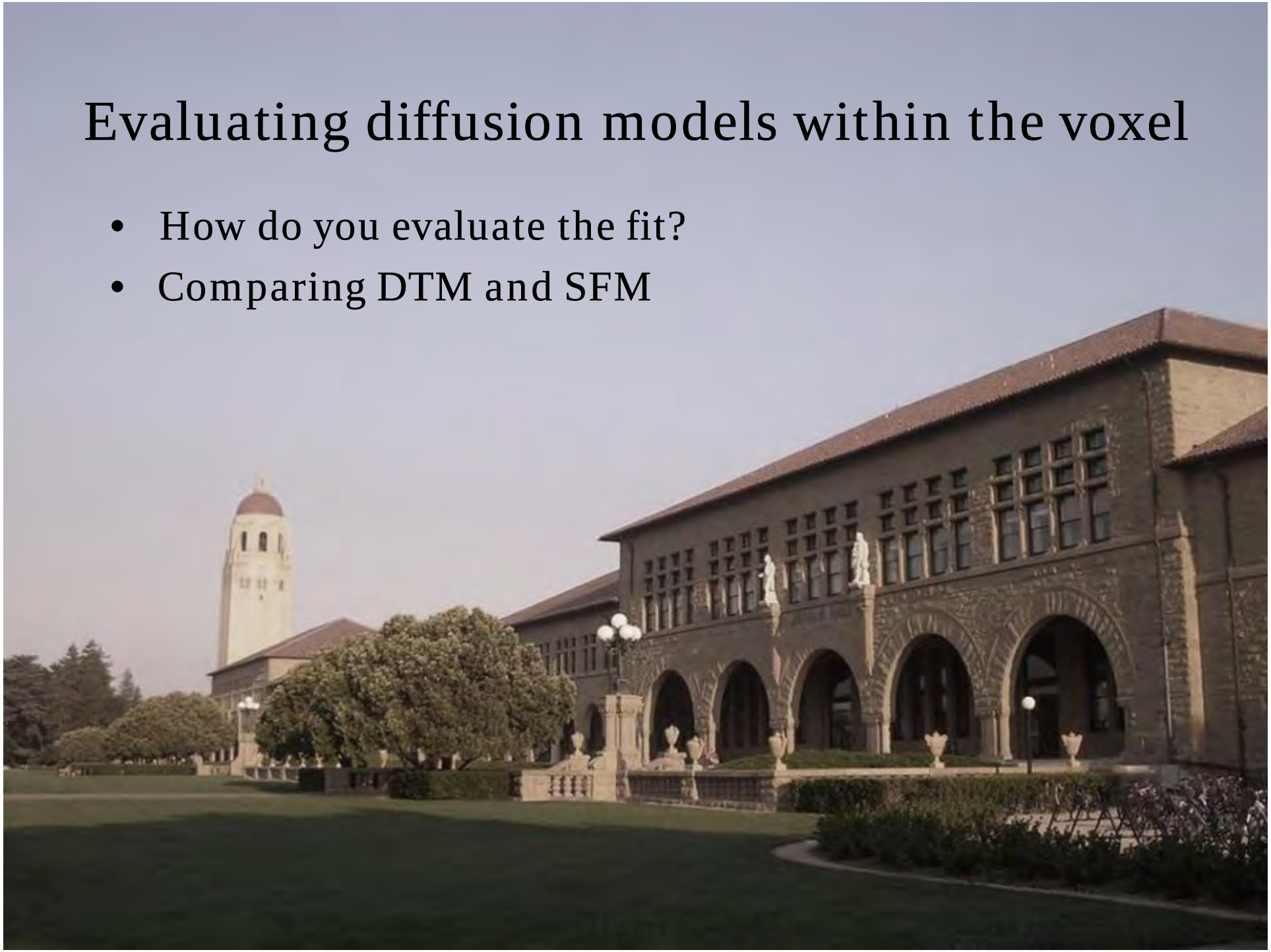
Basser et al., 1994 – Biophysical Journal
Good opening sentence: “This paper describes a new NMR imaging modality-MR diffusion tensor imaging.”

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

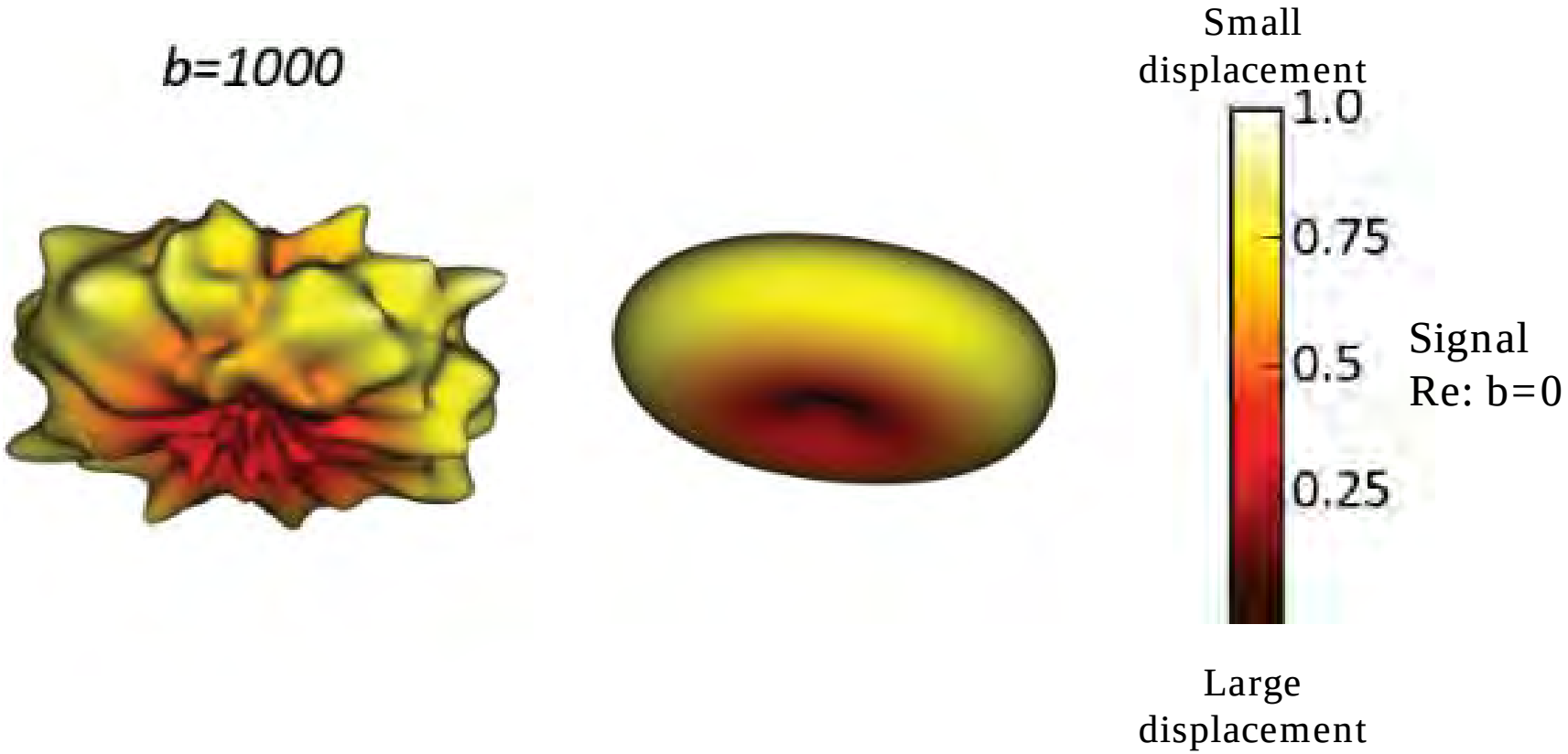
Evaluating diffusion models within the voxel

- How do you evaluate the fit?
- Comparing DTM and SFM



Diffusion tensor model (DTM)

Predicts the **voxel diffusion signal** with
a **phenomenological** equation,
motivated by **Gaussian** diffusion.



Cross-validation assessment

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

Fit the model to these data

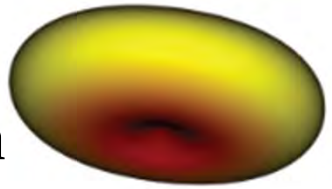
Data set 1

Measure prediction error with these data

Data set 2

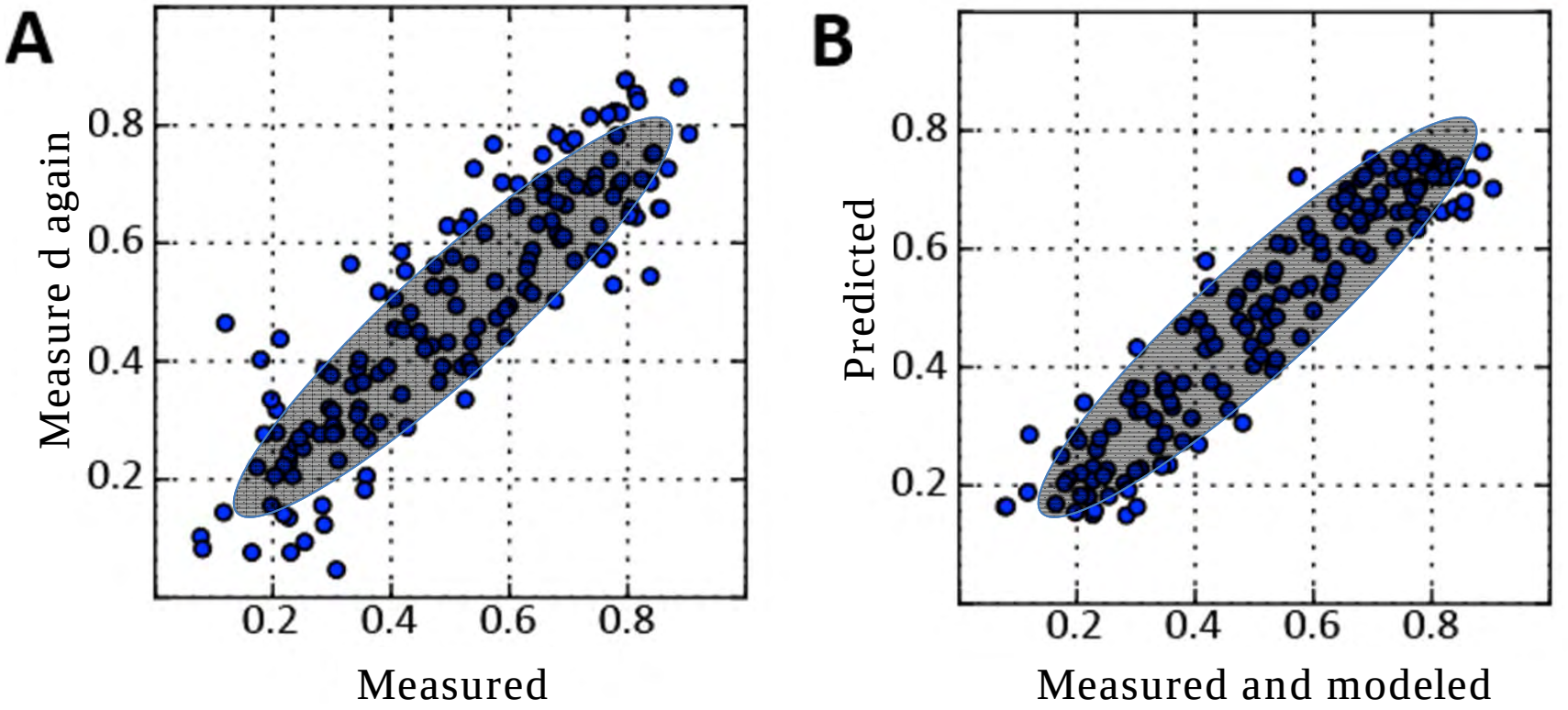
(In the old days, we used to call this testing the model on an independent data set)

DTM predicts the independent data more accurately than assuming replication



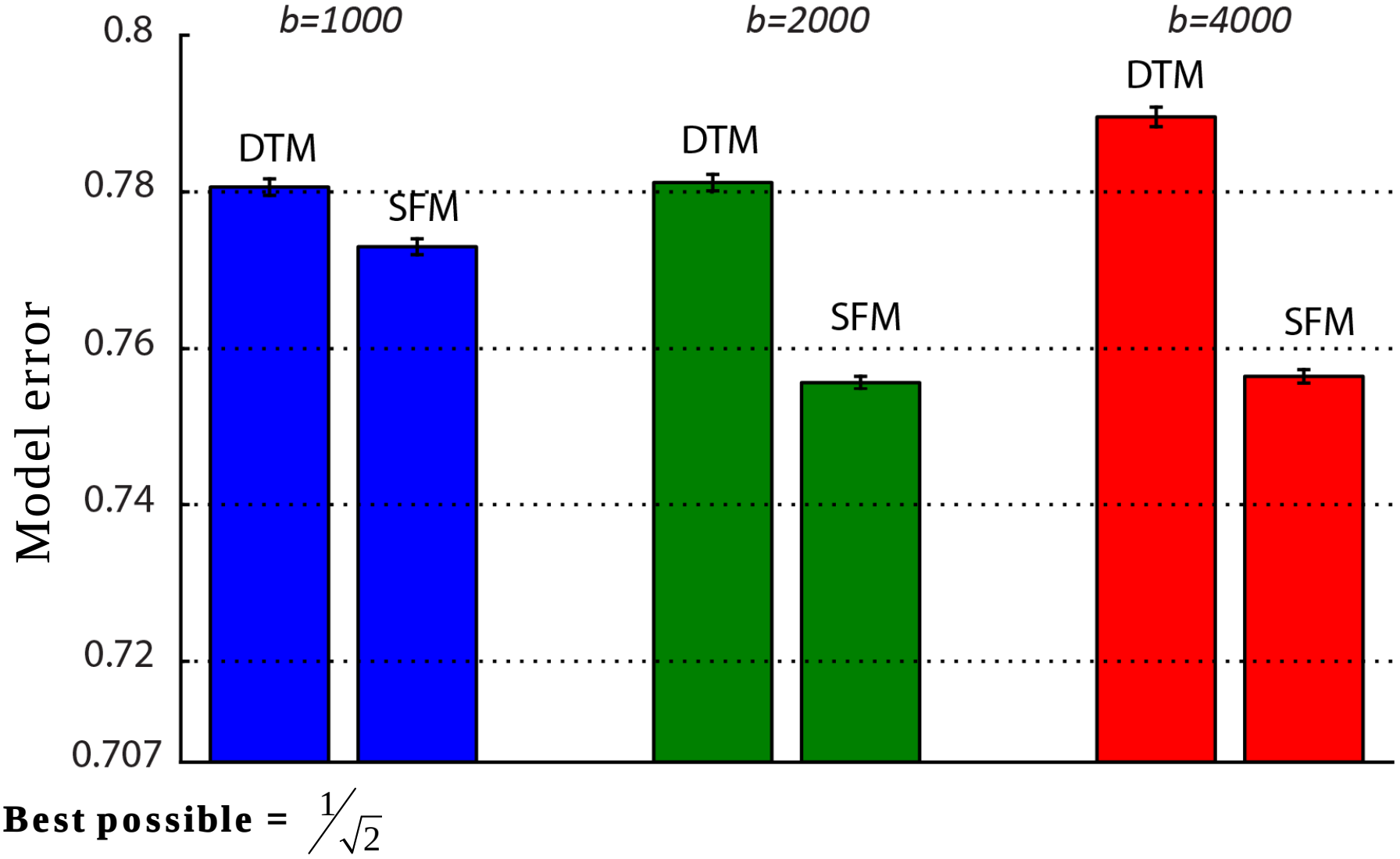
Replication

Prediction



The SFM is slightly better (whole brain analysis)

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

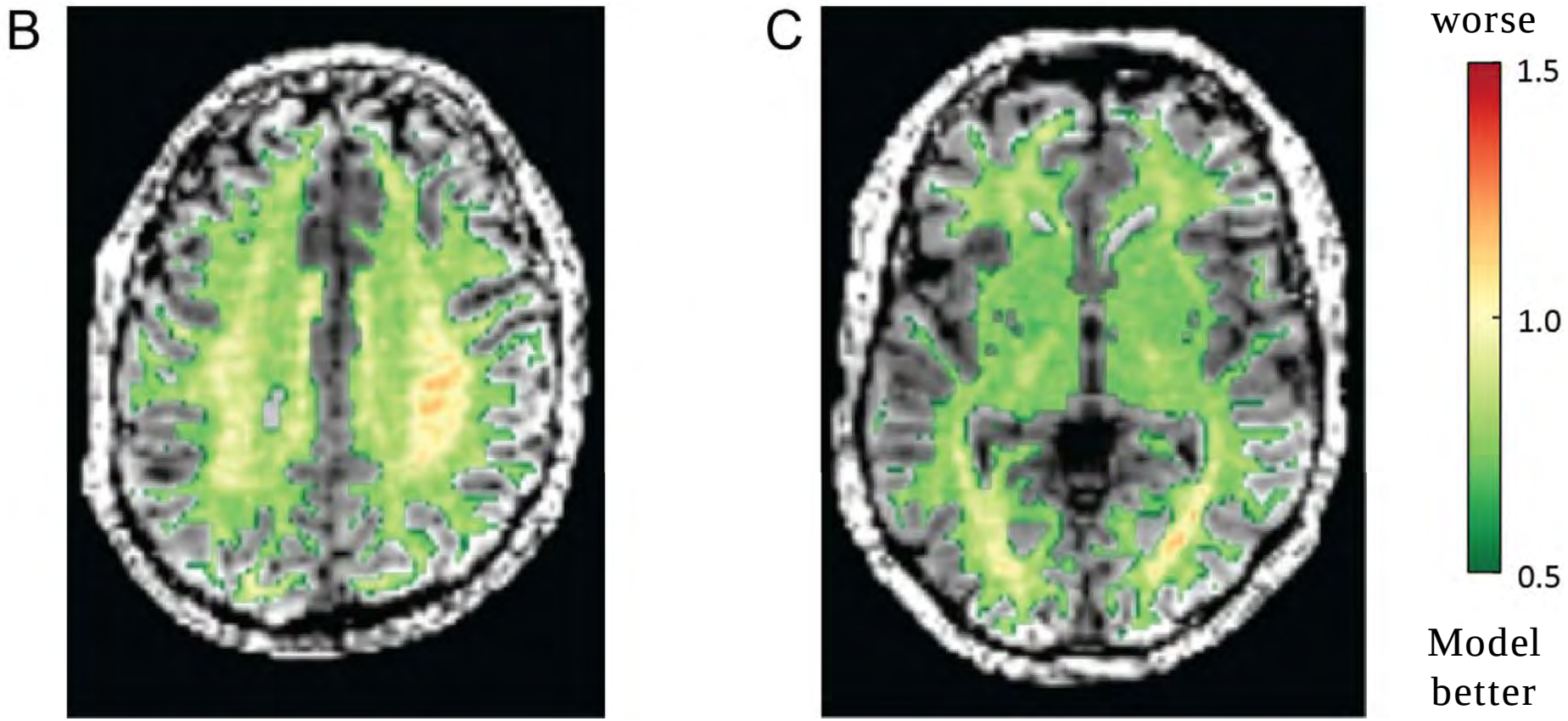


Best possible = $1/\sqrt{2}$

DTM errors are localized in a few regions (b = 4000)

Centrum semiovale

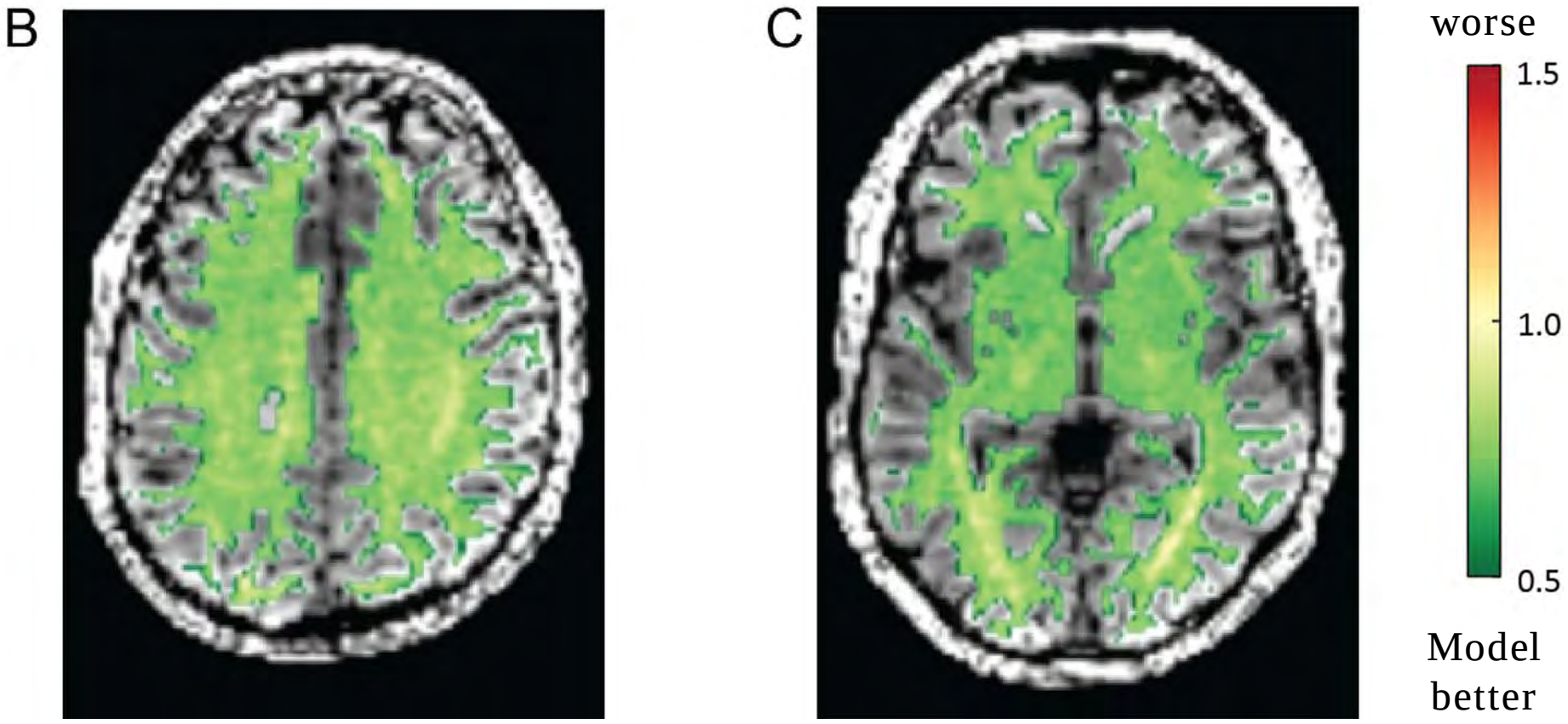
Optic radiation



SFM outperforms DTM in these regions (b = 4000)

Centrum semiovale

Optic radiation



Summary

- We have excellent quantitative models of the diffusion signal within a voxel
- The model fits are more reliable predictors of independent measurements than the data; use them for tractography
- People should stop whining about diffusion data.

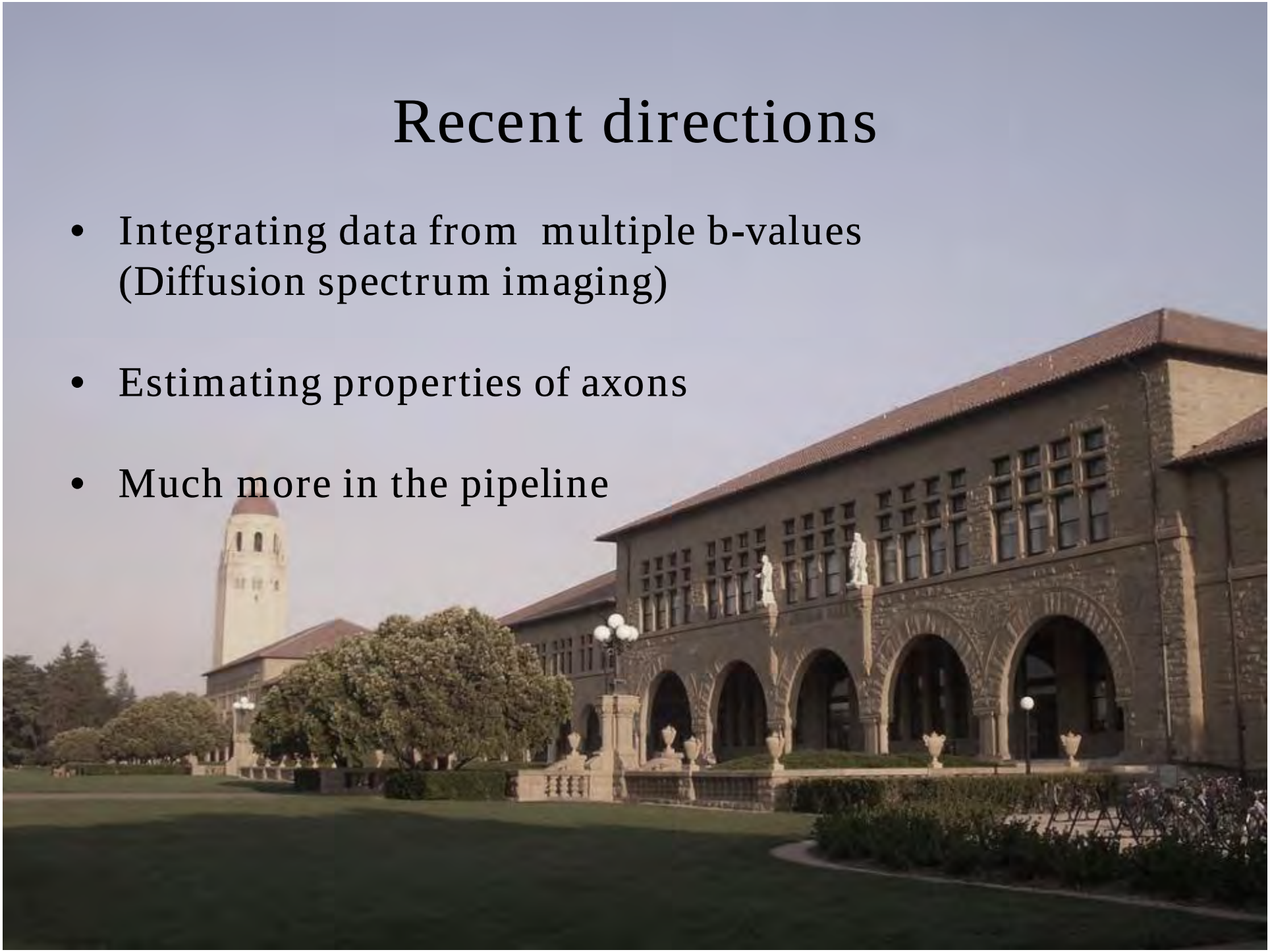
References

Frank, L.R., 2001. Anisotropy in high angular resolution diffusion-weighted MRI. Magn Reson Med 45, 935–9.

Frank, L.R., 2002. Characterization of anisotropy in high angular resolution diffusion-weighted MRI. Magn Reson Med 47, 1083–99.

Recent directions

- Integrating data from multiple b-values (Diffusion spectrum imaging)
- Estimating properties of axons
- Much more in the pipeline



Summary diffusion measures

- Once you have a model, it is natural to produce summary measures

- For the DTM, the Principal diffusion direction (PDD) and fractional anisotropy (comparing eigenvalues) have been convenient
  BEWARE

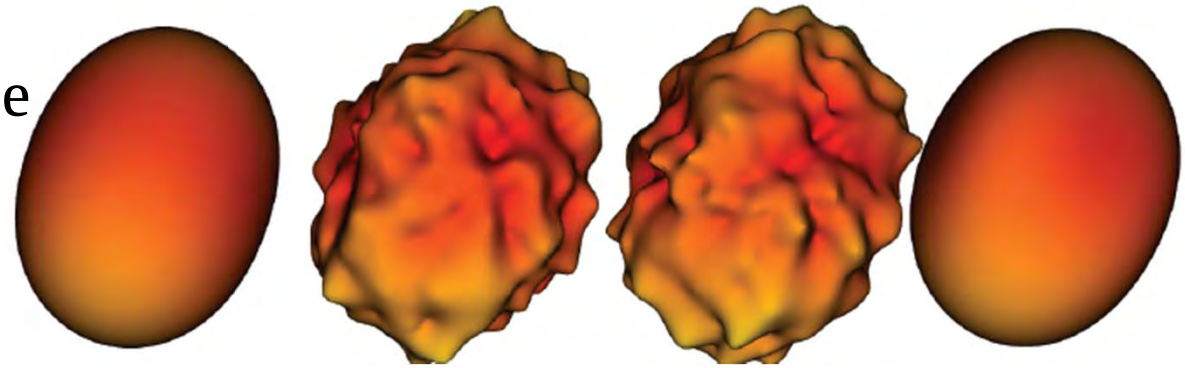
- For the SFM (ball and stick), no standard has emerged but Dell'Aqua et al. (2007) have proposed useful univariate measures

Models and data replication

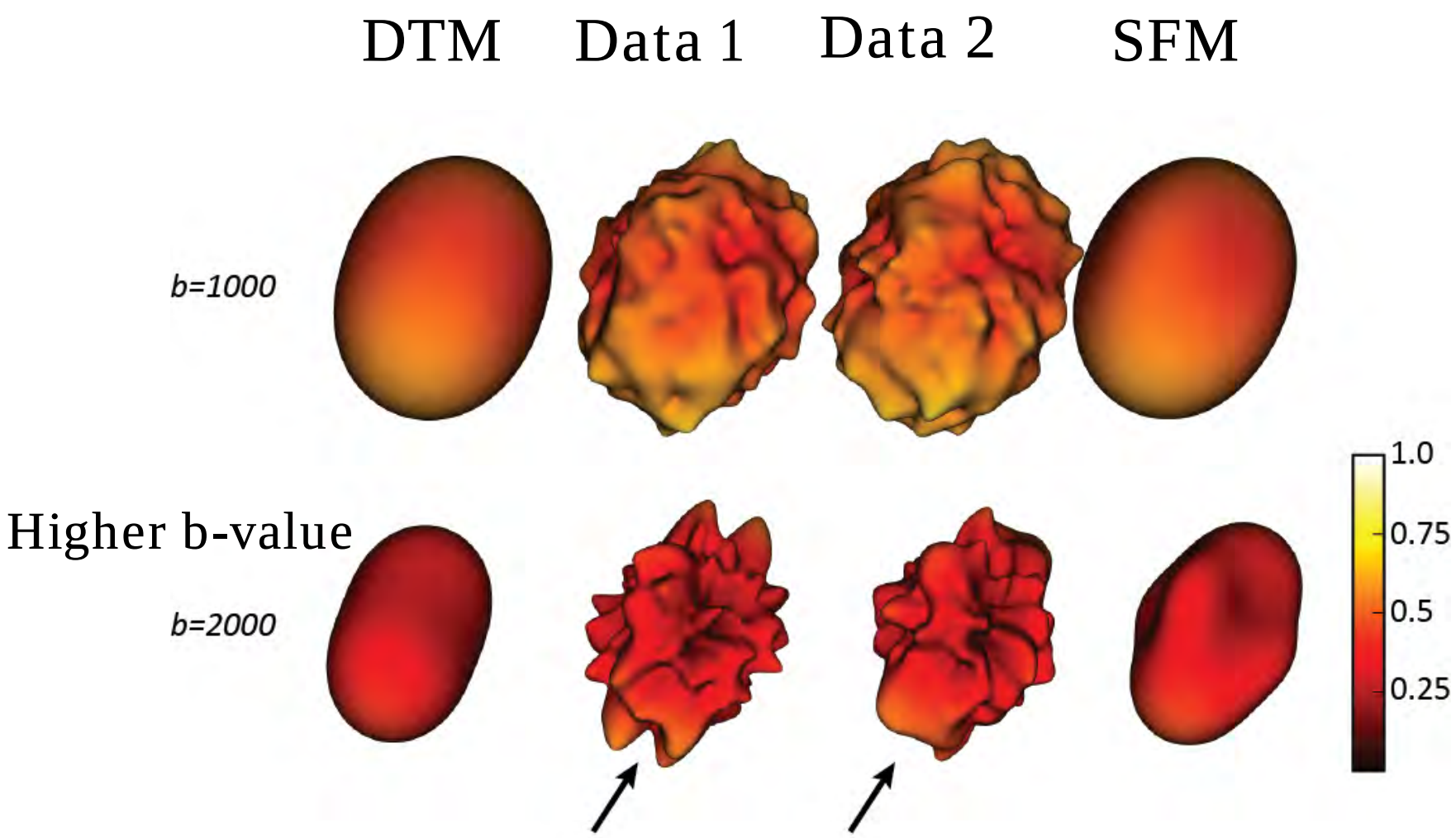
DTM Data 1 Data 2 SFM

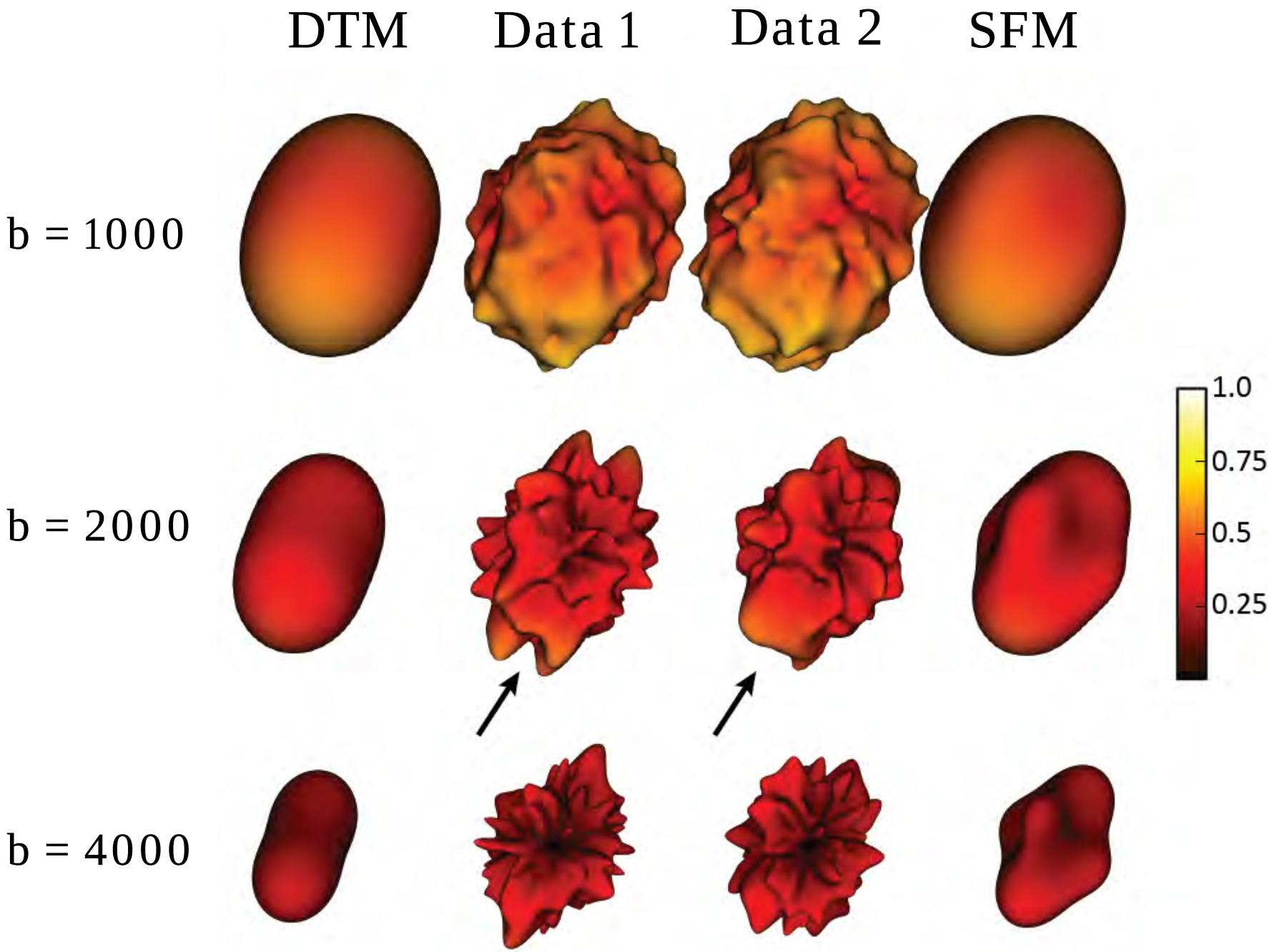
Low b-value

b=1000



Models and data replication




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

Quantitative MRI rising

Magnetic Resonance in Medicine 00:000–000 (2008)

AxCaliber: A Method for Measuring Axon Diameter Distribution from Diffusion MRI

Yaniv Assaf,[1*] Tamar Blumenfeld-Katzir,[1] Yossi Yovel,[1] and Peter J. Basser[2]

The diameter of a myelinated nerve axon is directly proportional to its conduction velocity, so the axon diameter distribution helps determine the channel capacity of nervous transmission along fascicles in the central (CNS) and peripheral nervous

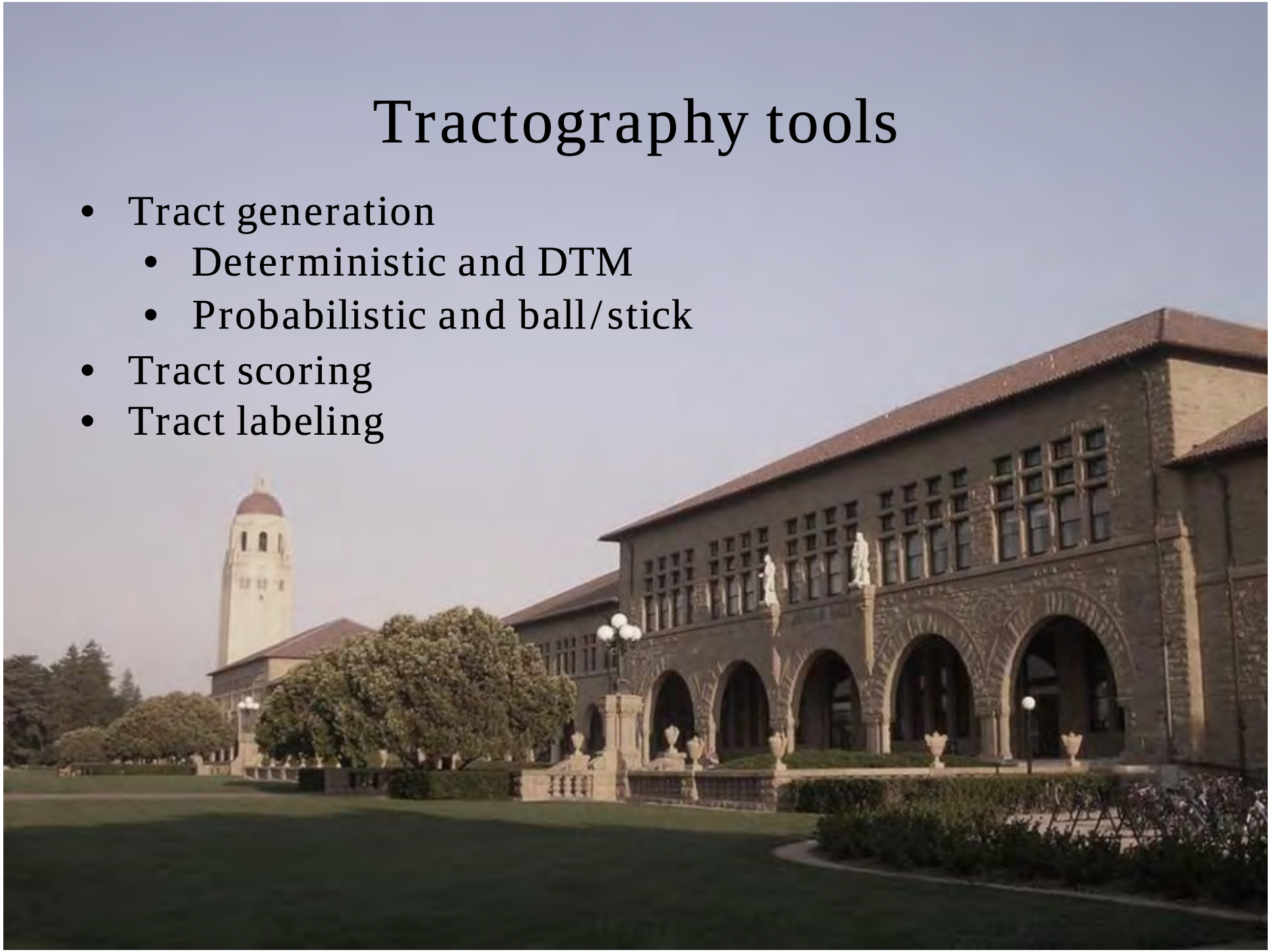
ment and in health and disease. For instance, it is hypothesized that in amyotrophic lateral sclerosis (ALS) large diameter axons (type A-alpha) are damaged selectively (8,9), while in autism small-diameter axons are maldevel-

Once you think about varying b-level, go nuts people. Ask yourself: What are the implications of varying diffusion time and b-level?

Assaf and colleagues fit a model based on assumptions about the intra-axonal diffusion of water

Tractography tools

- Tract generation
  - Deterministic and DTM
  - Probabilistic and ball/stick
- Tract scoring
- Tract labeling



Tract generation and visualization packages

http://www.nitrc.org/

Central source

MRI studio – http://www.mristudio.org

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/

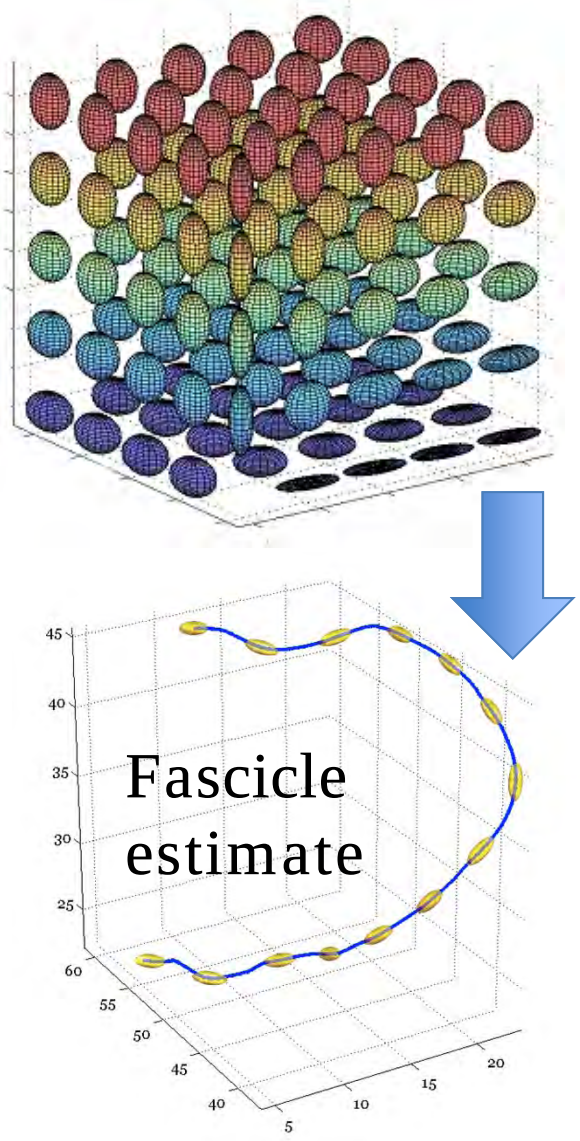
MRtrix - http://brain.org.au/software/mrtrix/

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

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

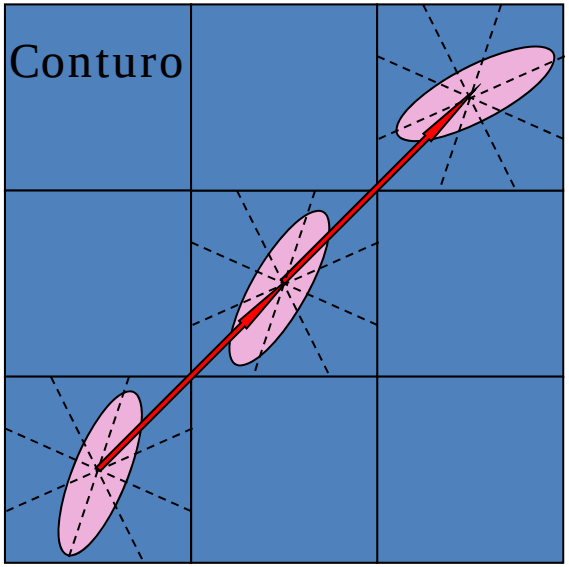
Early deterministic tractography

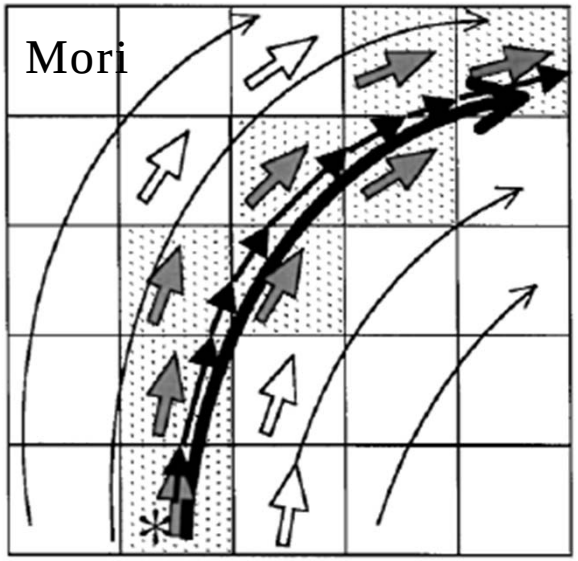
- Summarize each voxel with a DTM
- Follow voxels (bi-directional) in PDD direction
- Stopping rule (e.g., tensor becomes round)
- Rinse and repeat
- Significant implementation differences



Tracking fibers in the human brain
(Mori et al., 1999; Conturo et al, 1999)

- Summarize each voxel with a DTM
- Follow voxels (bi-directional) in PDD direction
- Stopping rule (e.g., tensor becomes round)
- Rinse and repeat
- Significant implementation differences





Limitations of deterministic methods

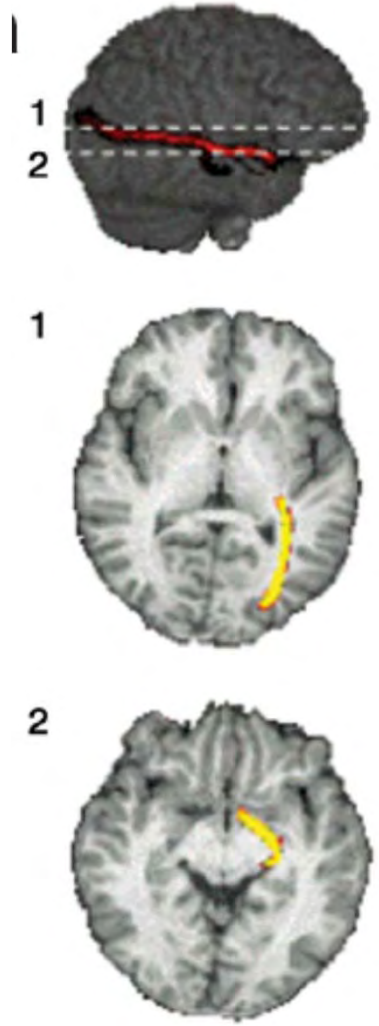
- Don’t account for noise and uncertainty
- Greedy: Uses the local (voxel) diffusion measurements to estimate global white matter tracts; never measures the whole solution
- Validation

nature neuroscience

Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging

T E J Behrens[1,2,4], H Johansen-Berg[1,4], M W Woolrich[1,2], S M Smith[1], C A M Wheeler-Kingshott[3], P A Boulby[3], G J Barker[3], E L Sillery[1], K Sheehan[1], O Ciccarelli[3], A J Thompson[3], J M Brady[2] & P M Matthews[1]

- Use the ball and stick model for local diffusion
- Repeatedly trace a path, choosing directions at each step from a probability distribution of angles determined by local diffusion data
- Stopping rule: No strong direction in local data



(Fig 1a)

nature neuroscience

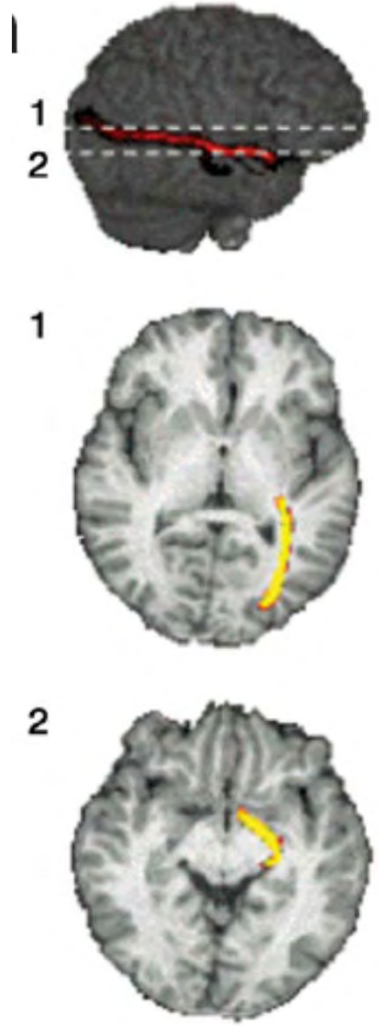
Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging

T E J Behrens[1,2,4], H Johansen-Berg[1,4], M W Woolrich[1,2], S M Smith[1], C A M Wheeler-Kingshott[3], P A Boulby[3], G J Barker[3], E L Sillery[1], K Sheehan[1], O Ciccarelli[3], A J Thompson[3], J M Brady[2] & P M Matthews[1]

- Given a seed in region A, evaluate connection strength to region B as

The number of fibers between the regions A and B divided by the total number of fibers from A

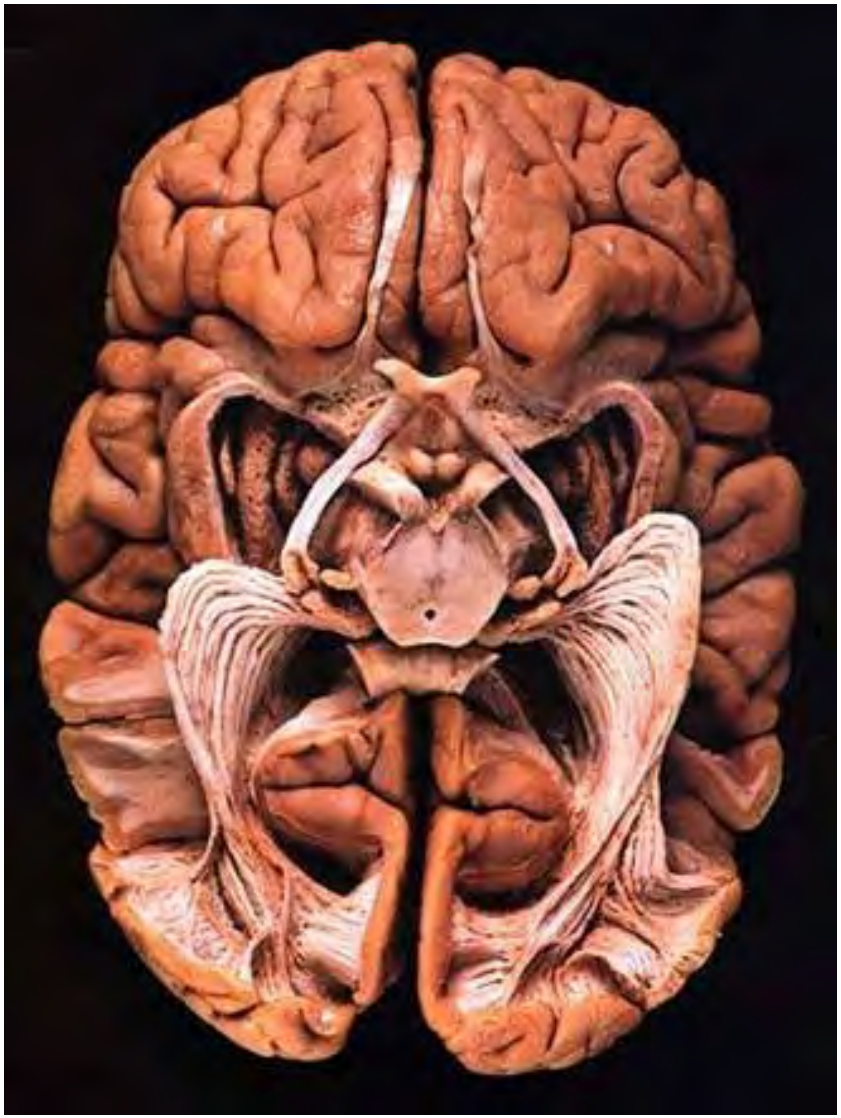
See Sherbondy et al., 2008A for a discussion of the implications of this rule for symmetry and independence

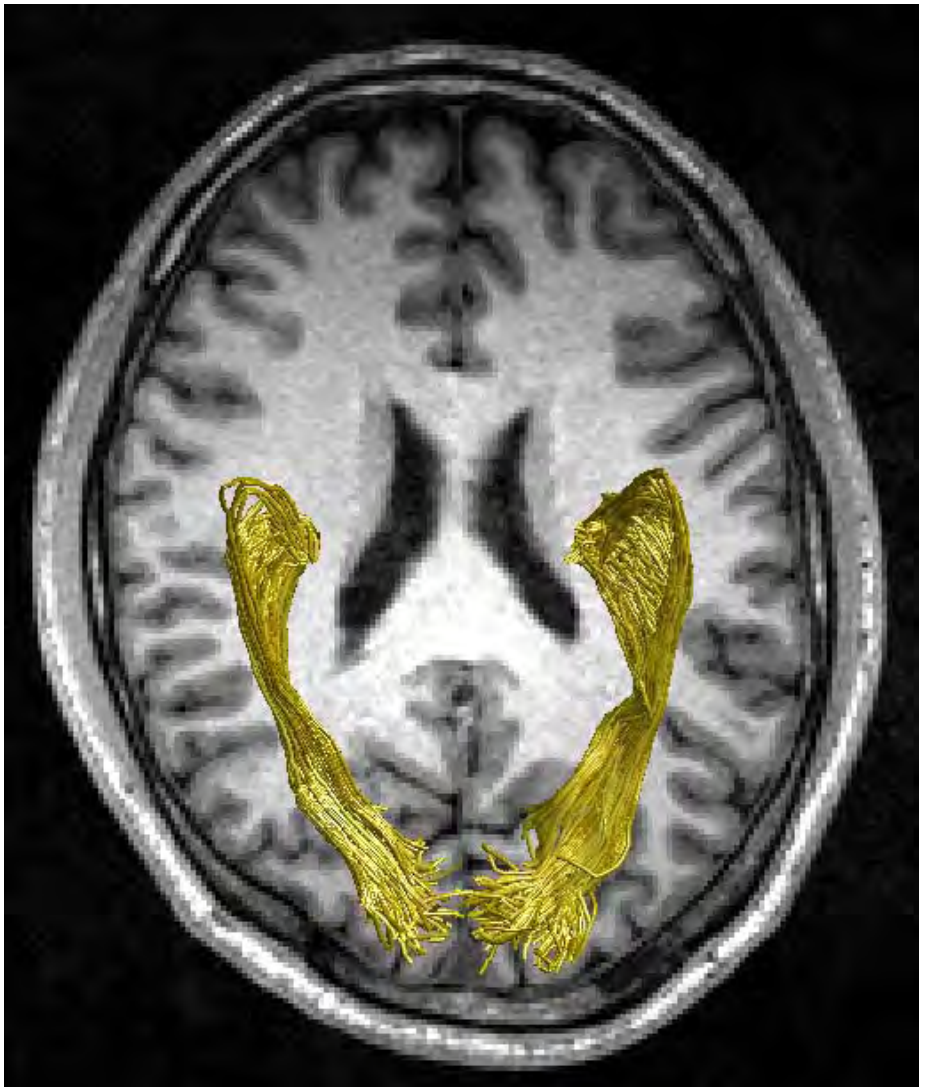


(Fig 1a)

Separating tract discovery and evaluation

(Contrack, Sherbondy et al., 2008A,B)





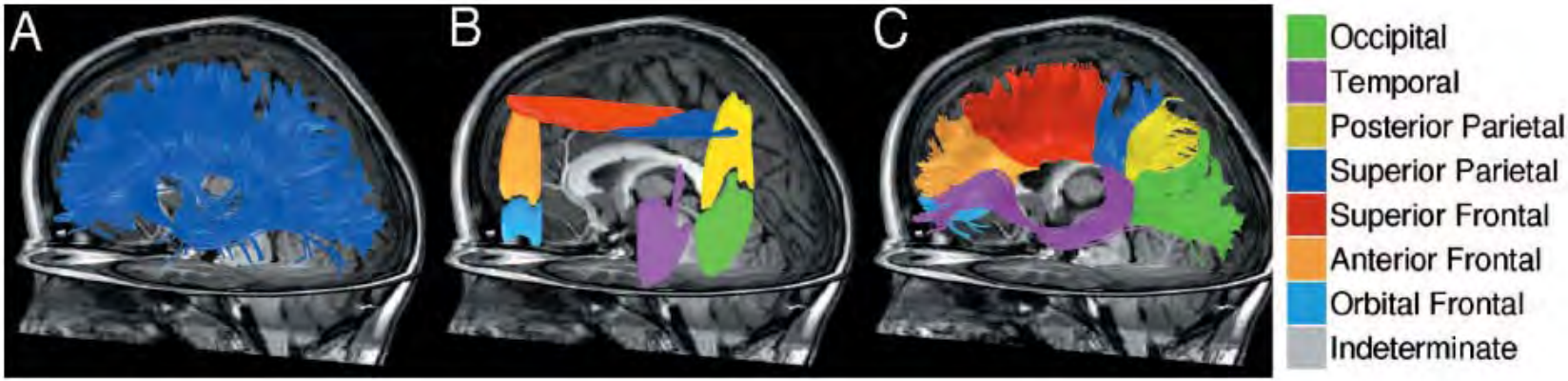
Tract identification

NeuroImage

www.elsevier.com/locate/ynimg
NeuroImage 36 (2007) 630–644

Reproducibility of quantitative tractography methods applied to cerebral white matter

Setsu Wakana,[a,b] Arvind Caprihan,[c] Martina M. Panzenboeck,[d] James H. Fallon,[d] Michele Perry,[e] Randy L. Gollub,[f] Kegang Hua,[a] Jiangyang Zhang,[a] Hangyi Jiang,[a,b] Prachi Dubey,[a] Ari Blitz,[b] Peter van Zijl,[a,b] and Susumu Mori[a,b,*]

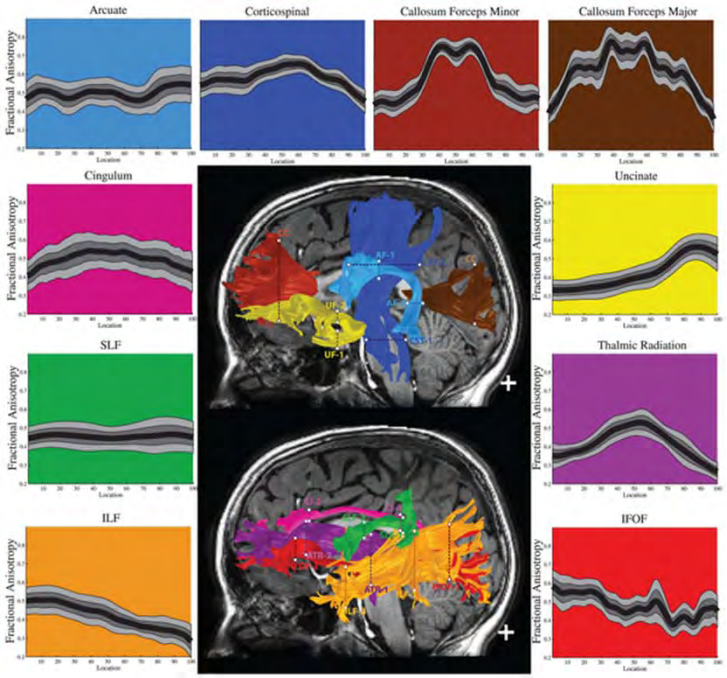


Dougherty et al., 2007, PNAS

Tract segmentation and identification

Automated Fiber Quantification

Yeatman et al., 2012



https://github.com/jyeatman/AFQ

TRACULA

Yendiki A et al., 2011

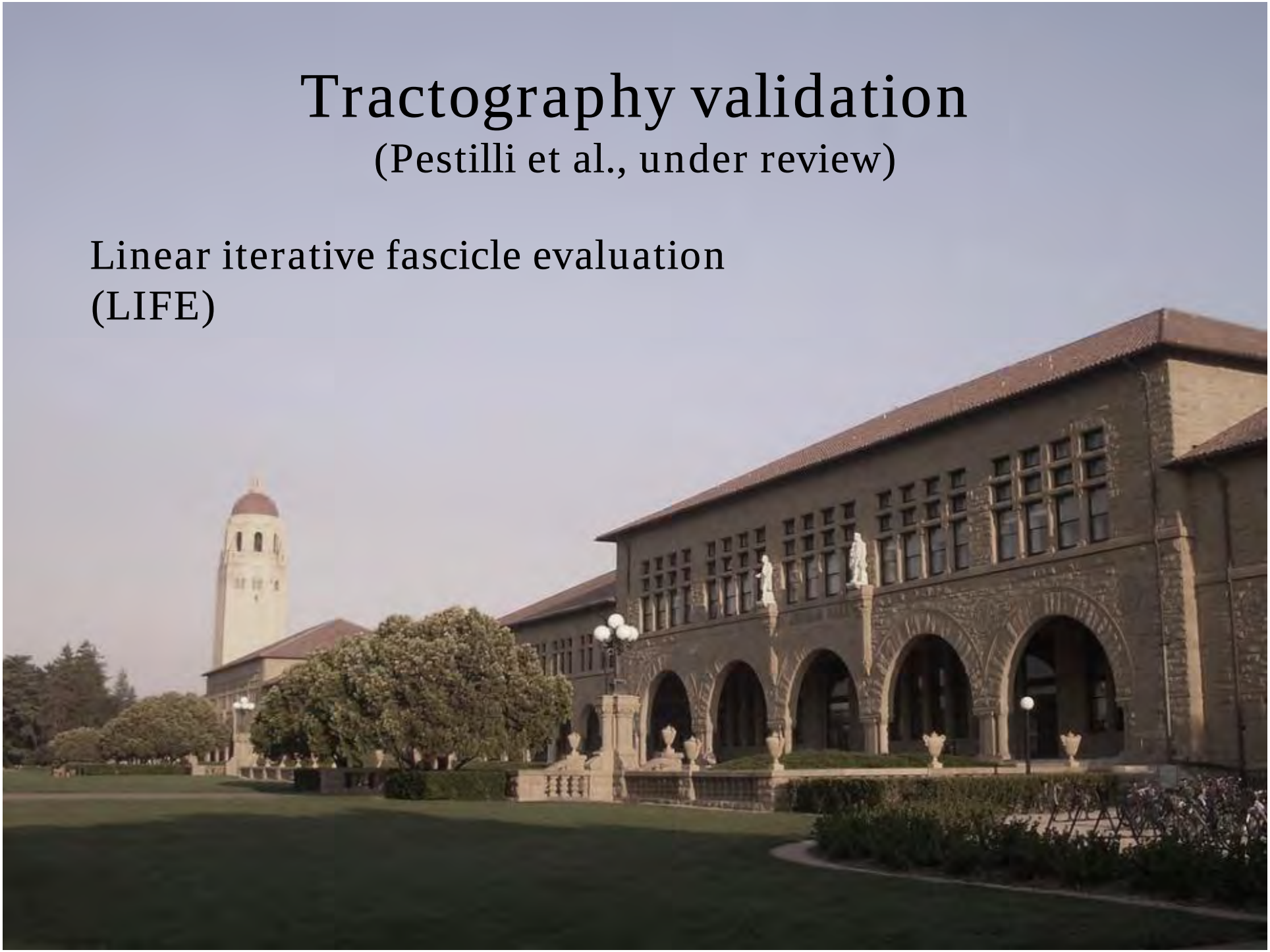
https://surfer.nmr.mgh.harvard.edu/fswiki/Tracula

Summary

- There are high quality tools for tract generation
- Visualization is important for understanding the tracts
- The tool set is evolving and expanding to include segmentation, and measurements along tracts (tractometry)

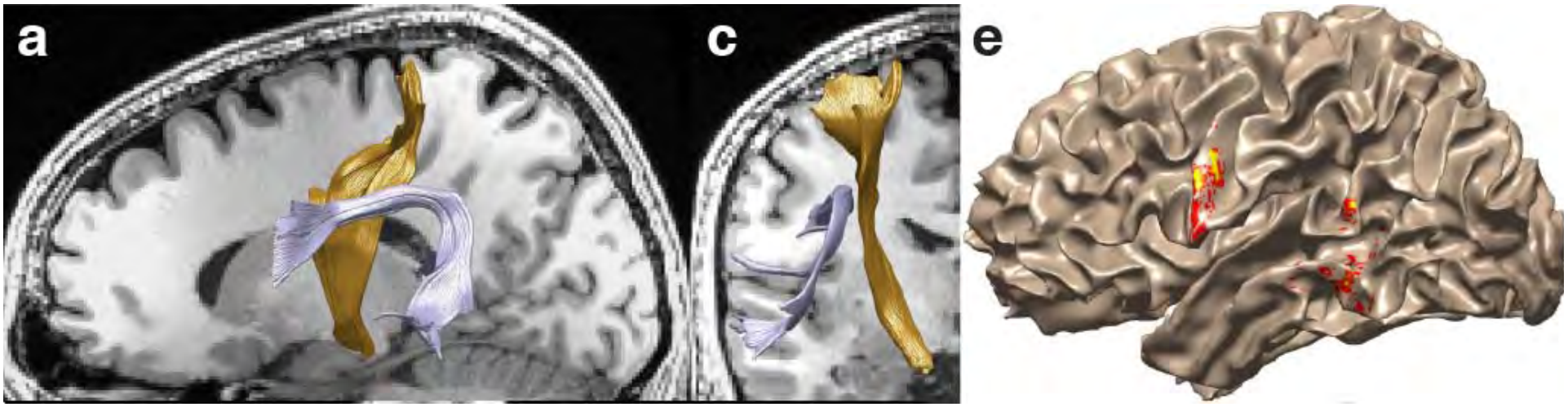
Tractography validation
(Pestilli et al., under review)

Linear iterative fascicle evaluation
(LIFE)



Tractography algorithms differ

Mrtrix, L=2, deterministic



Tractography algorithms differ

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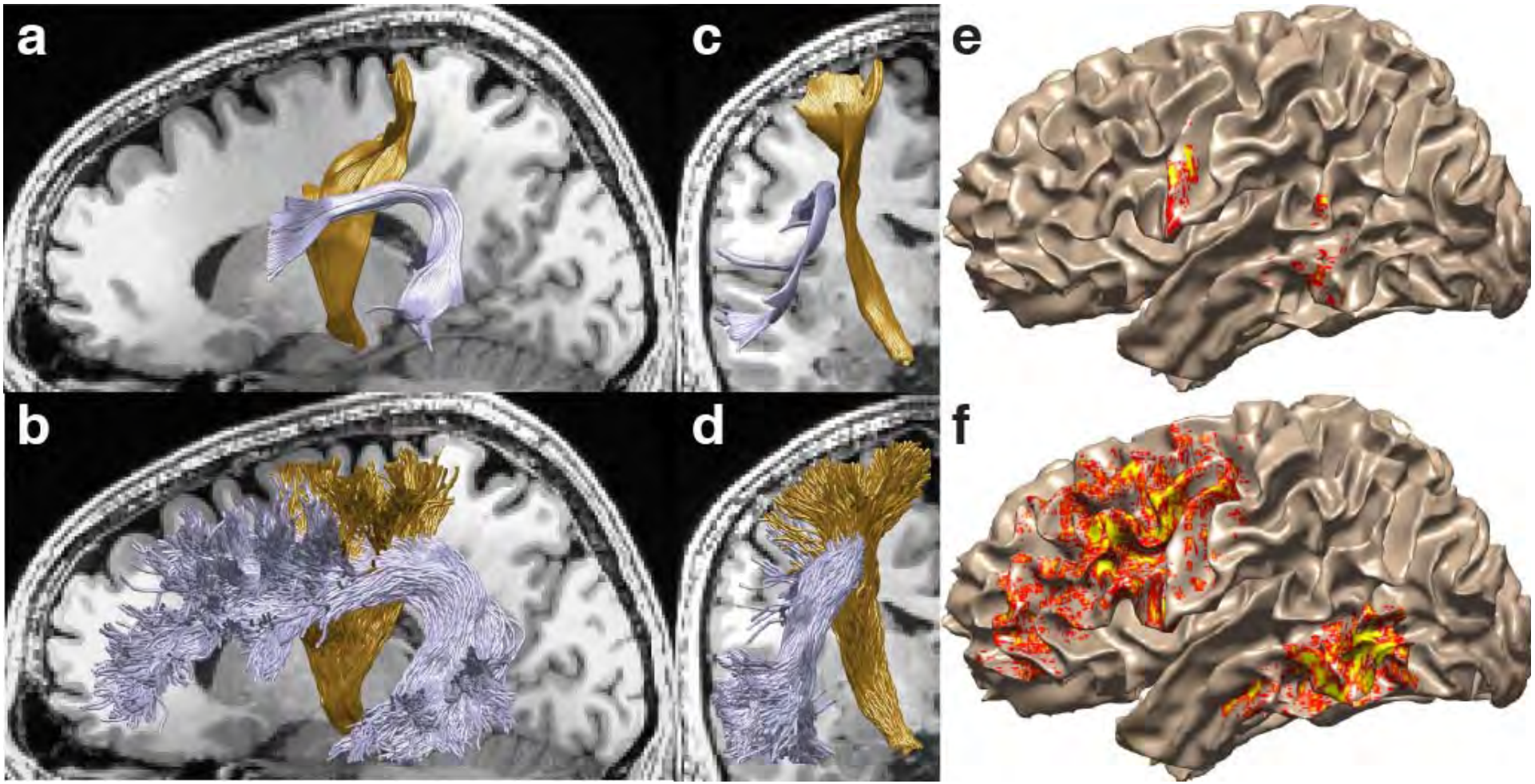


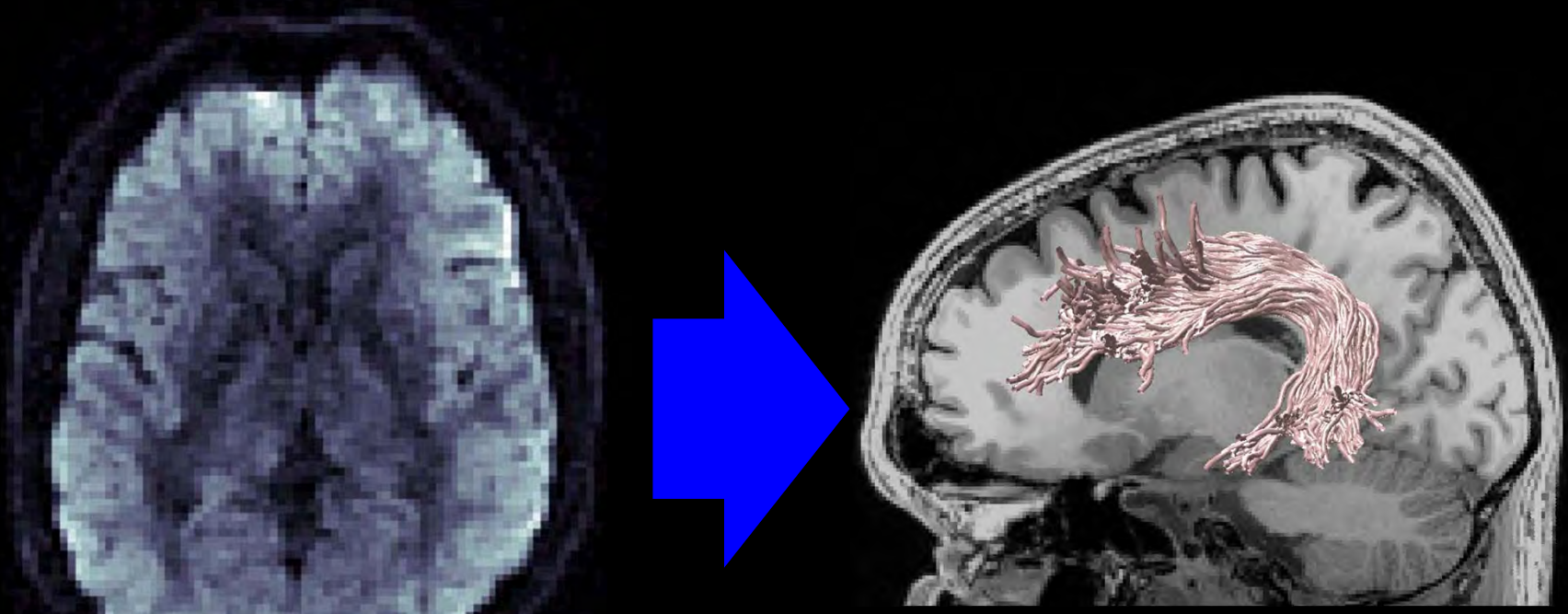
Mrtrix, L=8, probabilistic

Validation principles

- Evaluates data at hand; these subjects and this instrument
- Measures individual tracts in individual subjects
- Specifies strength of evidence, not probability of existence
- Compares connectome solutions

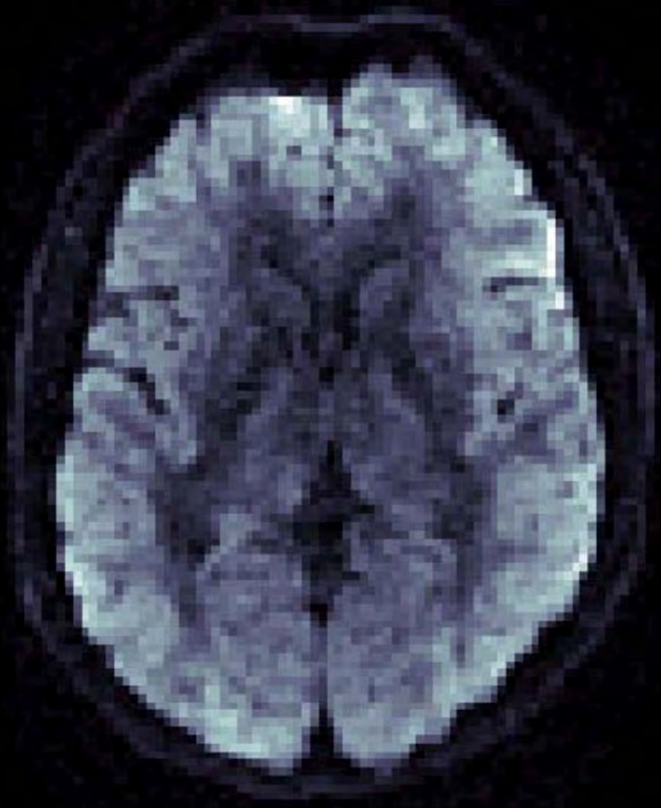
Tractography

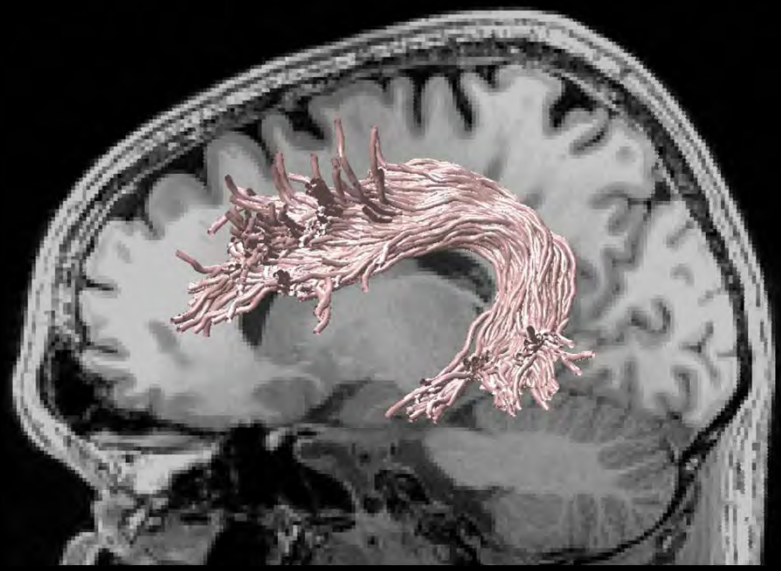
Estimate fascicles from diffusion data



Tractography validation

Linear iterative fascicle evaluation (LIFE, Pestilli et al.)





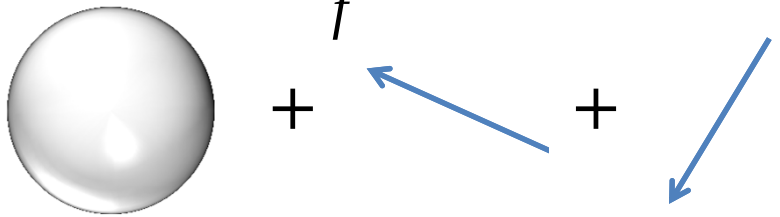
Compare how well different models and algorithms do

Fascicle contributions

- Each fascicle makes a contribution to the diffusion signal for each voxel it passes through
- The contribution depends on the fascicle orientation
- The fascicles contributions are weighted (size, length)

In each voxel, the fascicles are the sticks

$$S(\theta) = w_0 D_0 + \sum_f w_f D_f(\theta)$$



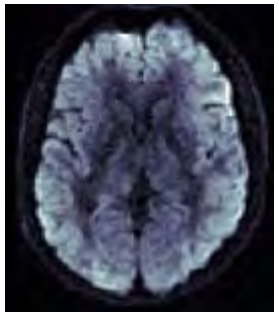
Set up the non-negative LS equations

- The system of linear equations is biggish

  rows -
  100 directions x
  100,000 voxels

  cols -
  1,000,000
  fascicles

Diffusion signal, S(θ)



$$S(\theta) = \begin{bmatrix} v1 \\ v2 \\ \\ \\ vN \end{bmatrix} = \begin{pmatrix} \text{Each column is the prediction of a fascicle} \\ \\ \text{Each matrix entry is the contribution from a voxel in a direction} \end{pmatrix} \begin{bmatrix} \\ \\ \end{bmatrix}$$

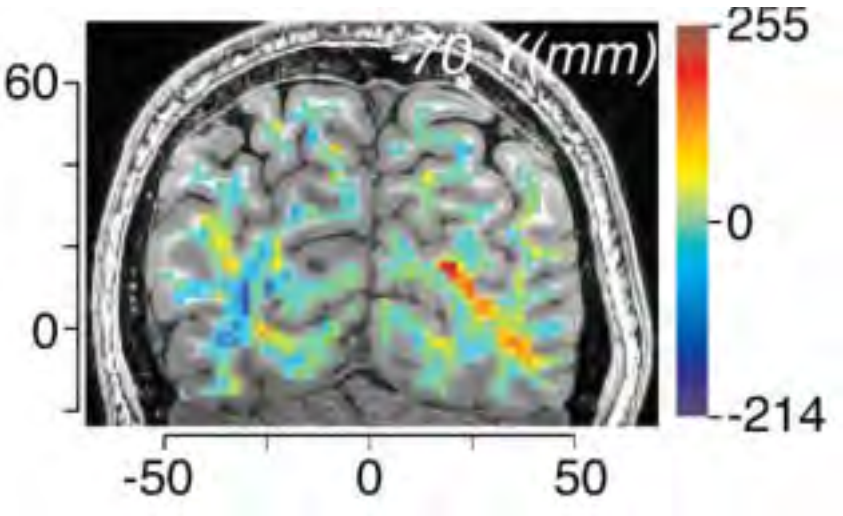
Weight for each fascicle

Or

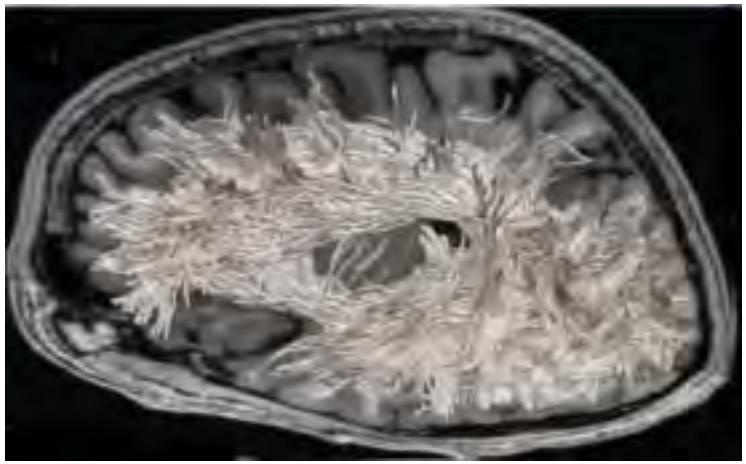
(smoothly varying weights along the length)

Compare measurements and connectome predictions

First data set



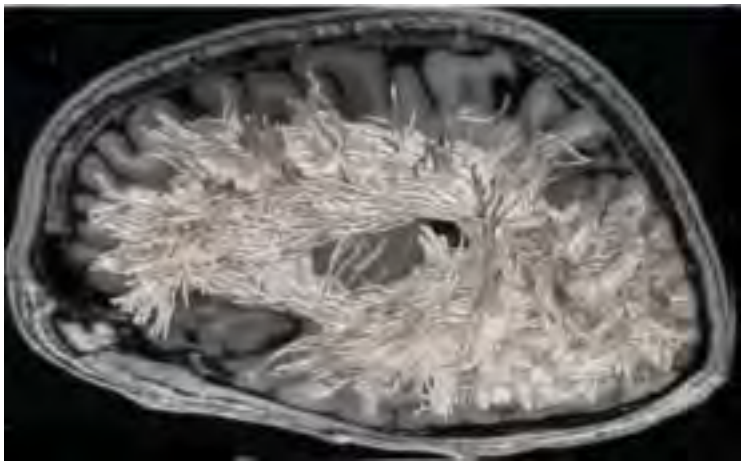
Connectome



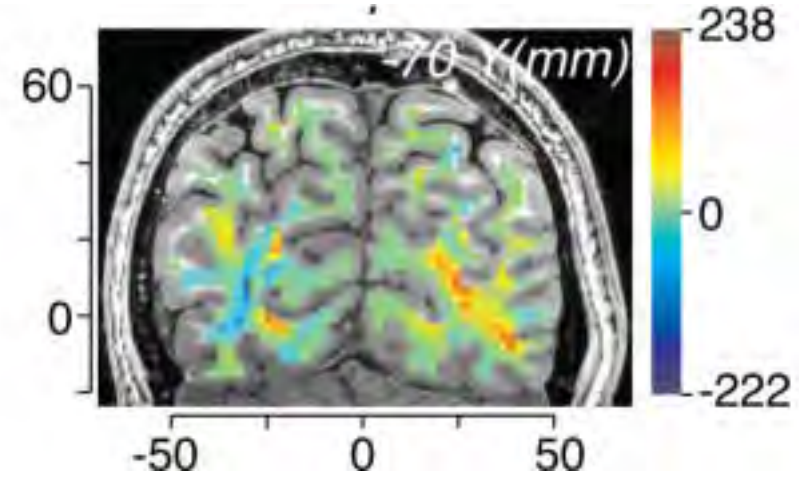
Solving a big system of linear equations
(non-negative least-squares)

Compare independent measurements with connectome predictions

Connectome



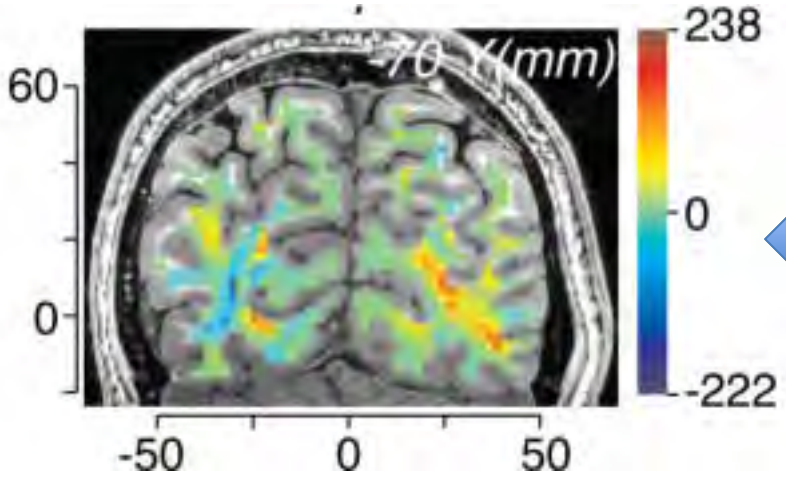
Prediction



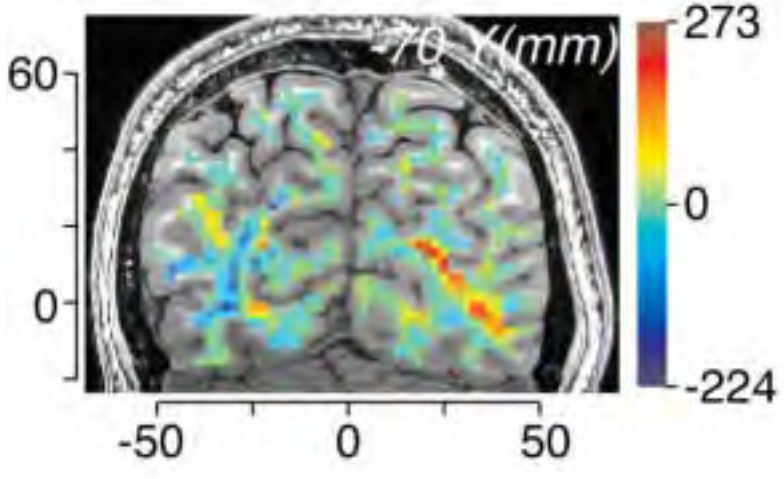
Big matrix multiplication

Compare independent measurements with connectome predictions

Prediction

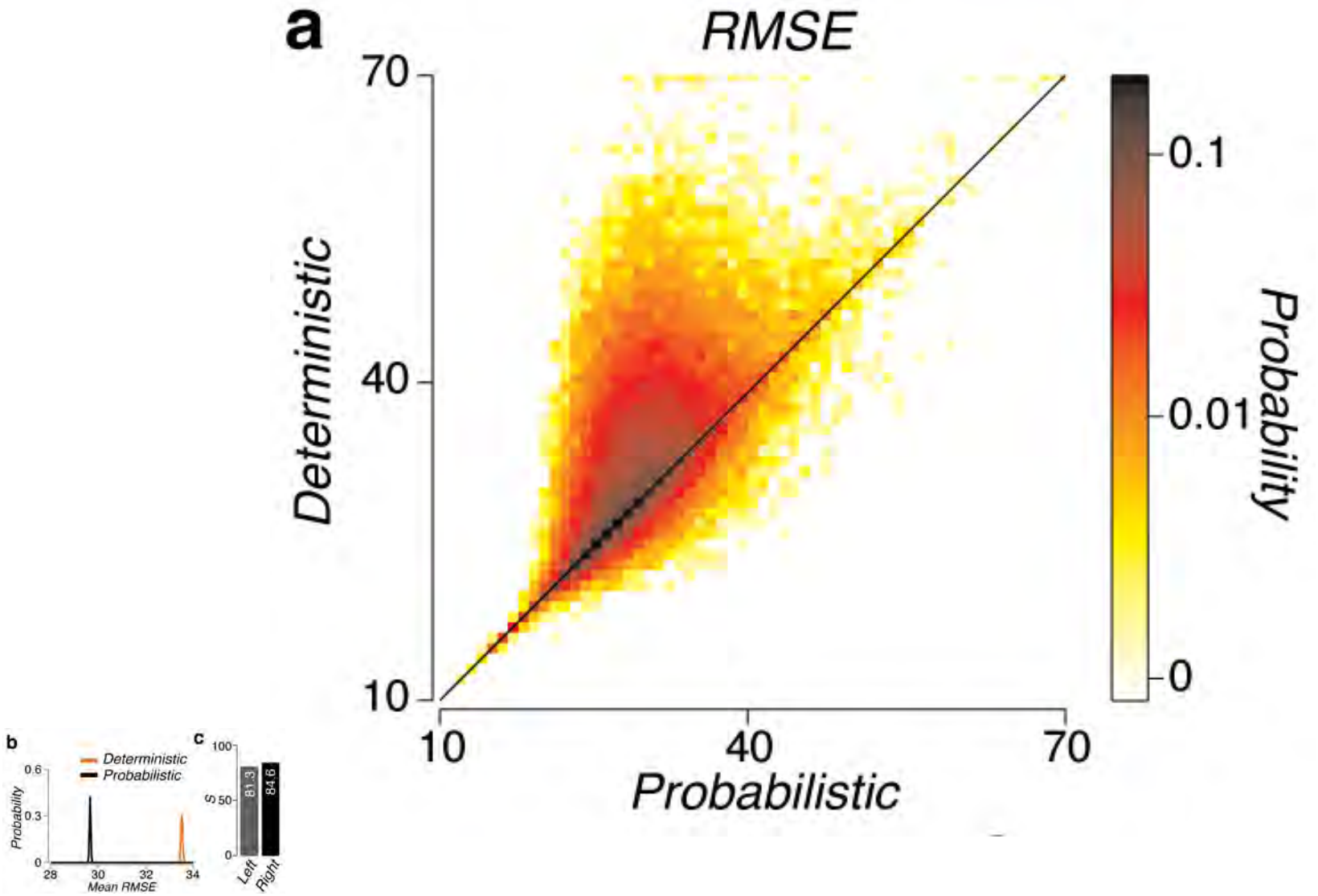


Second data set

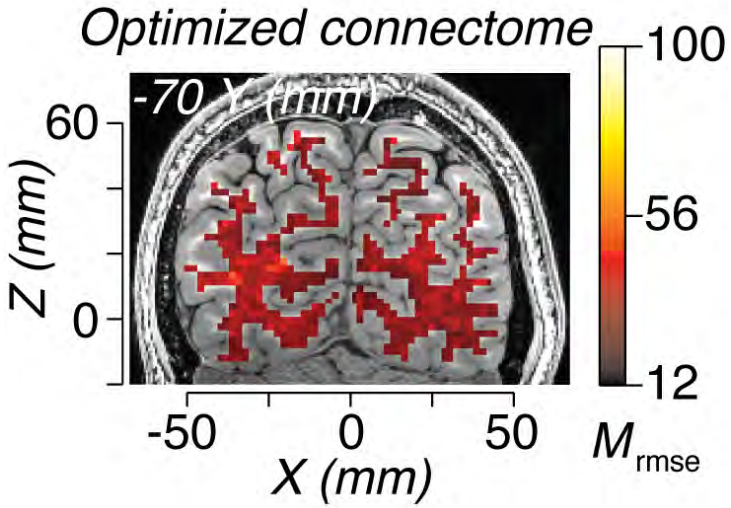


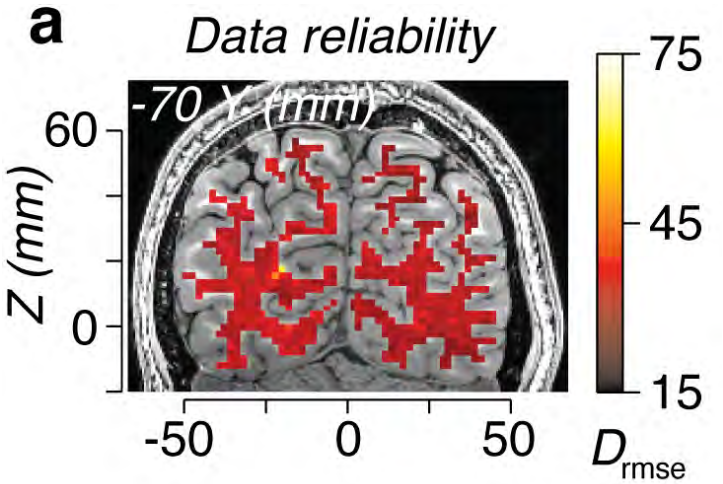
Subtraction and root mean square error

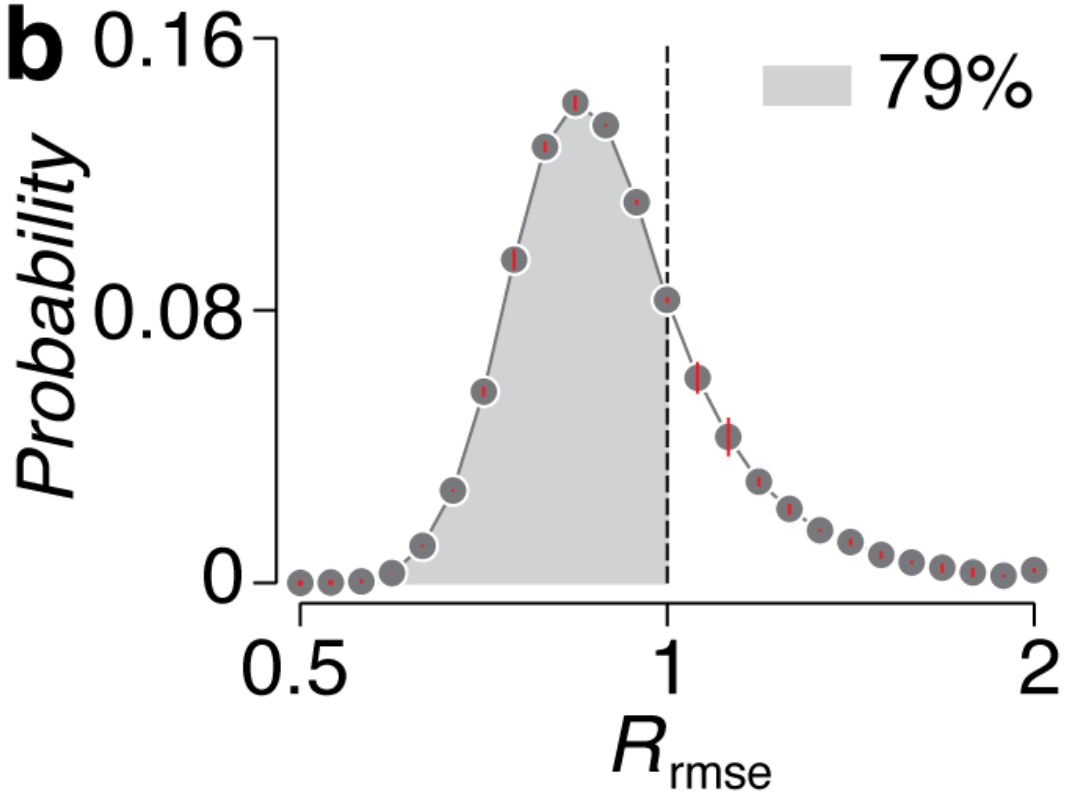
Scatter density histogram comparing two MRtrix parameters



On average, the connectome predicts an independent data set a little better than replication





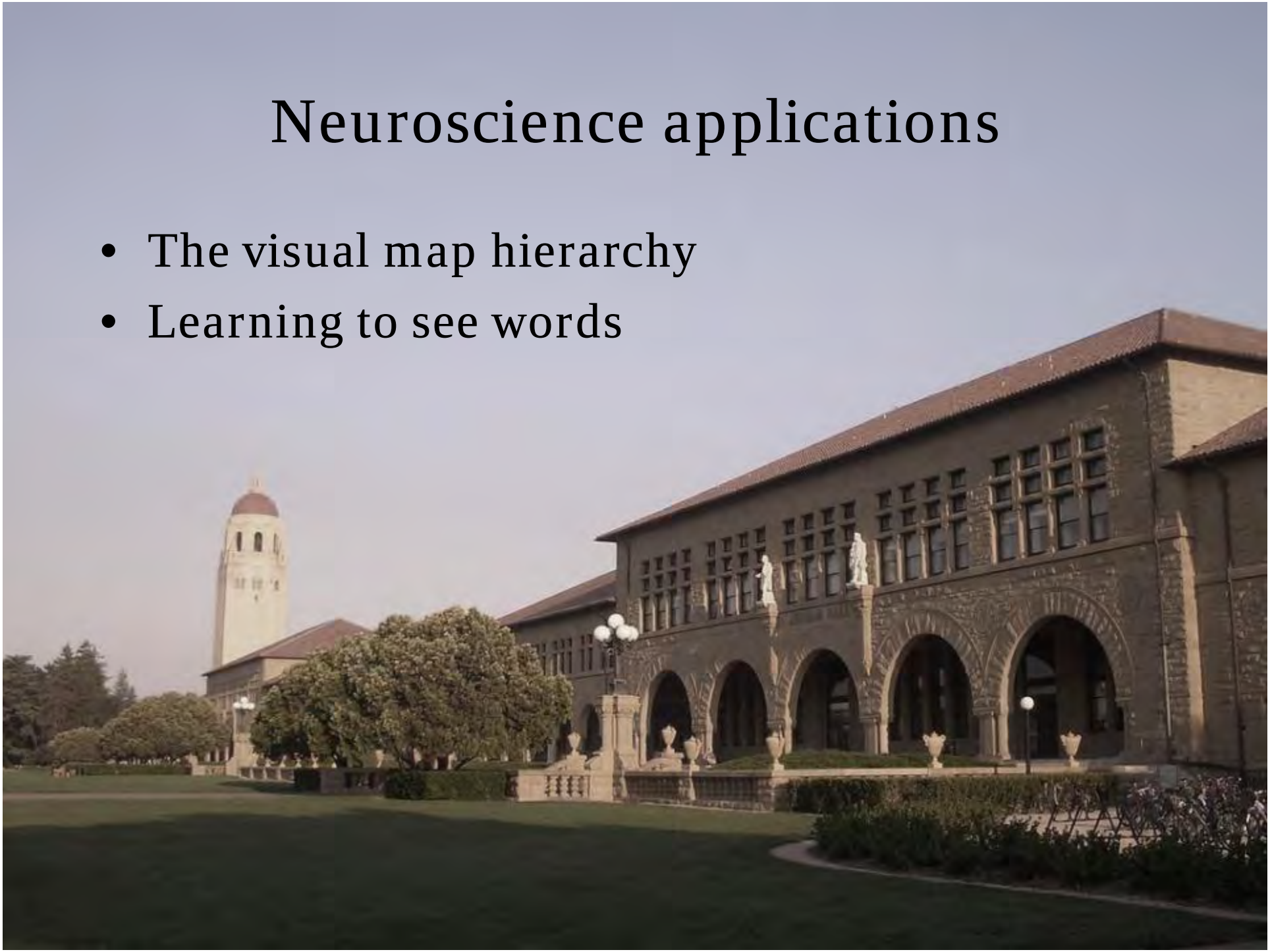


Summary

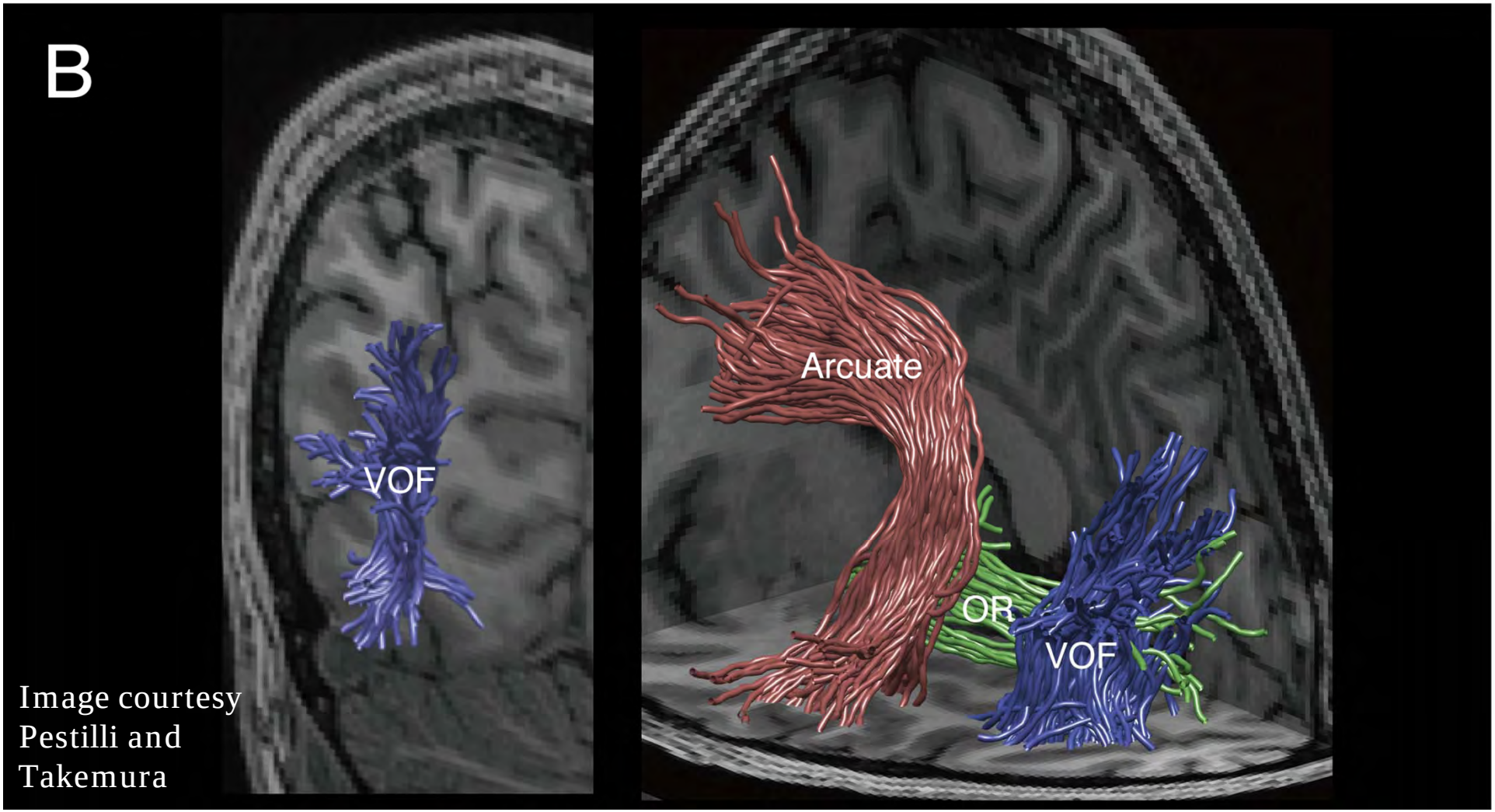
- Validation methods should enable us to test hypotheses about human tracts using the internal validation of the data at hand

Neuroscience applications

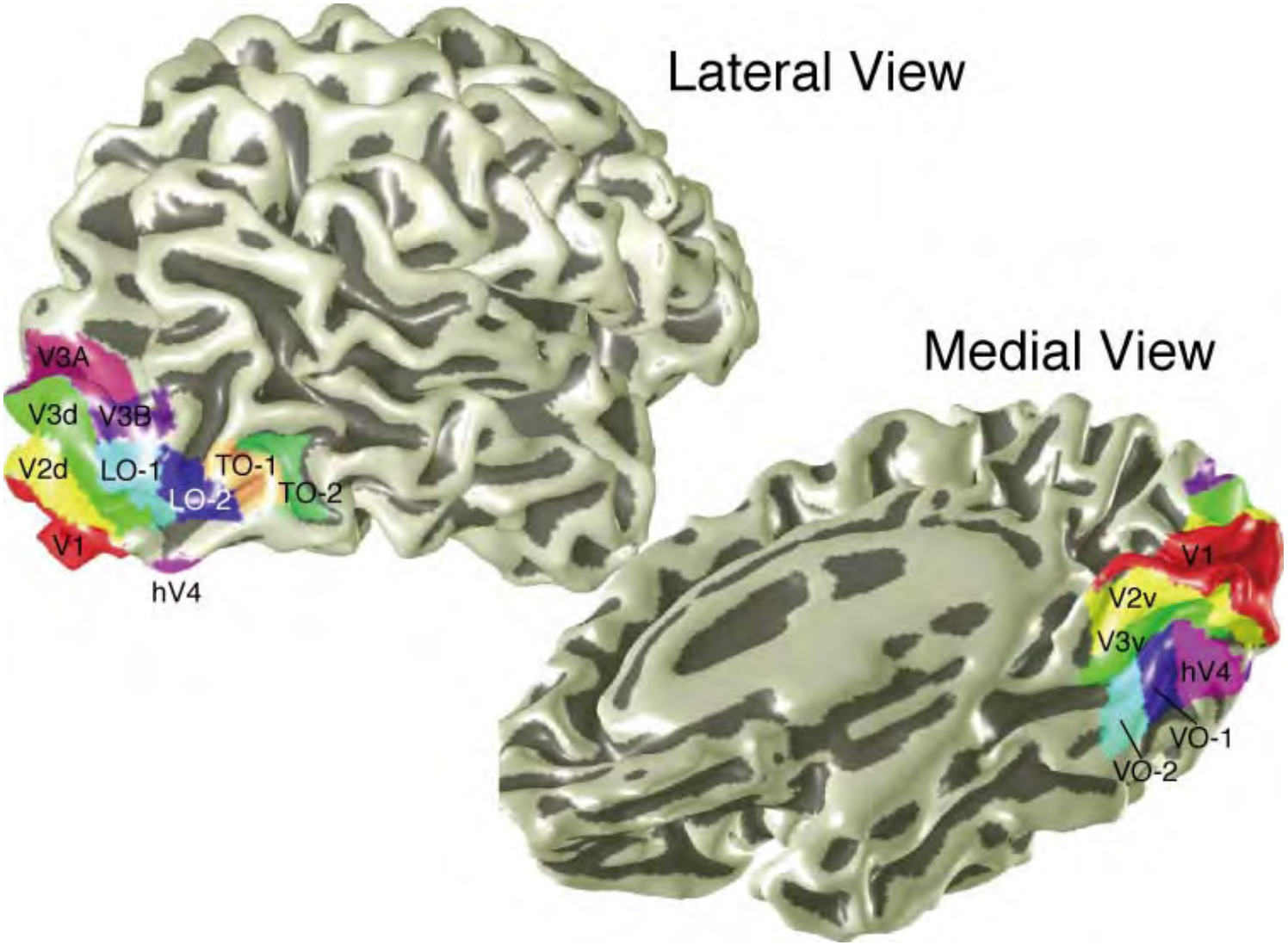
- The visual map hierarchy
- Learning to see words



Vertical occipital fasciculus (Yeatman et al., 2012)



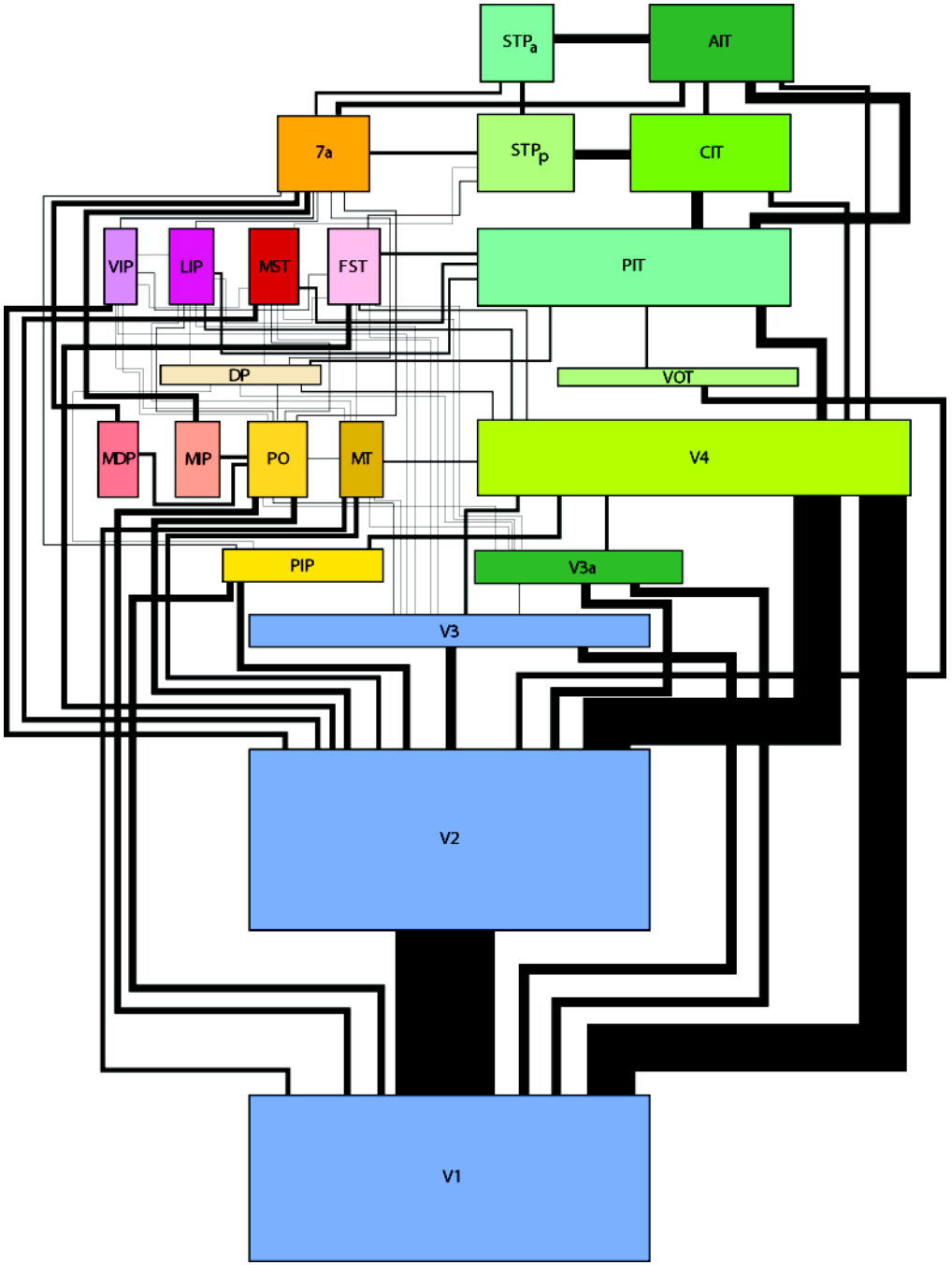
Visual field maps in humans



Wandell and Winawer (2011) *Vision Res*

Macaque field map organization

Felleman and Van Essen (1991),
Annotated by
Wallish and Movshon (2008)

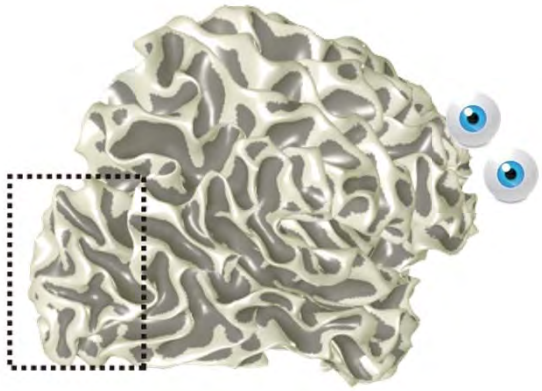


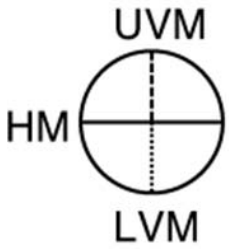
Human diagram

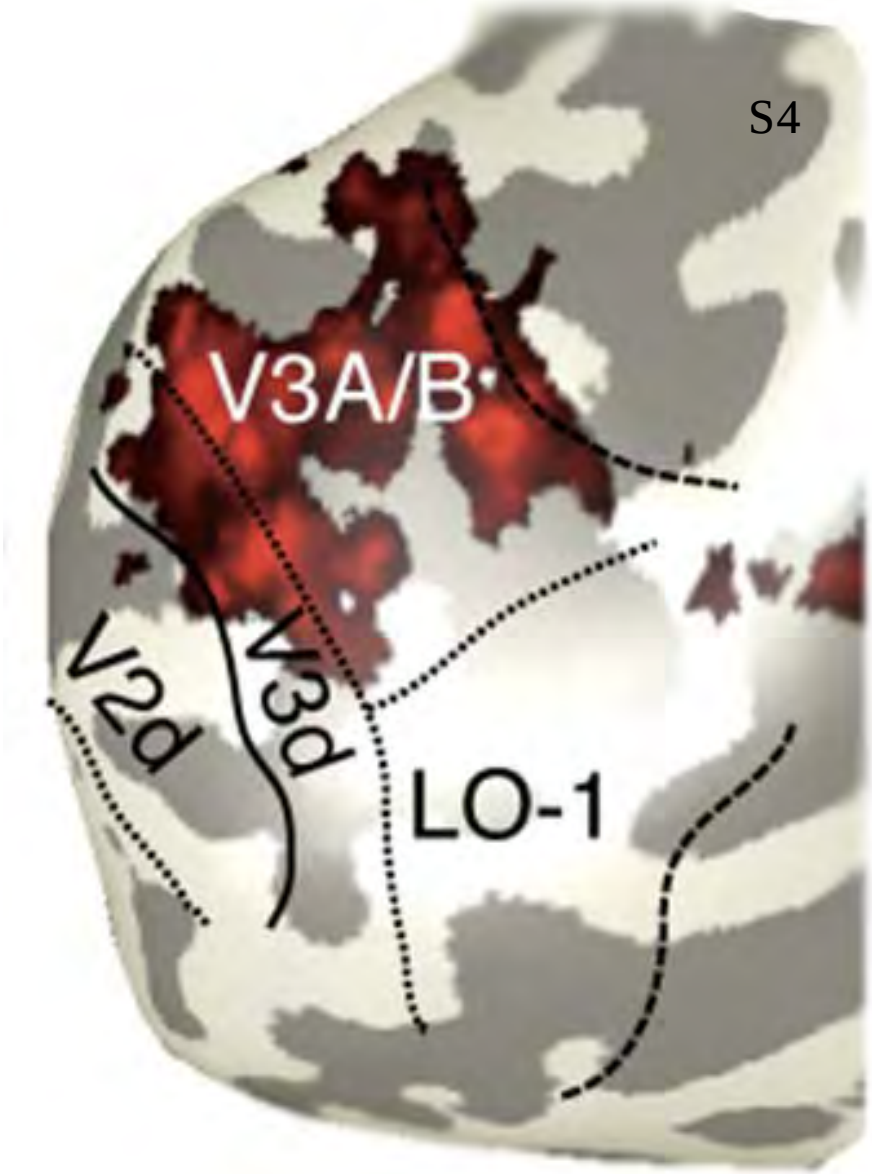
V3 is much bigger (75% of V2)
V3A is accompanied by V3B
hV4 position

What about dorsal-ventral segregation

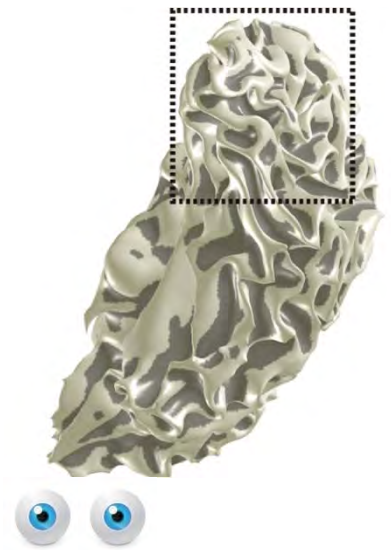
Dorsal VOF endpoints

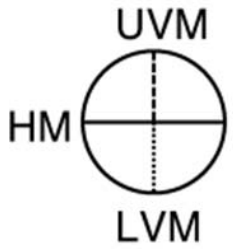


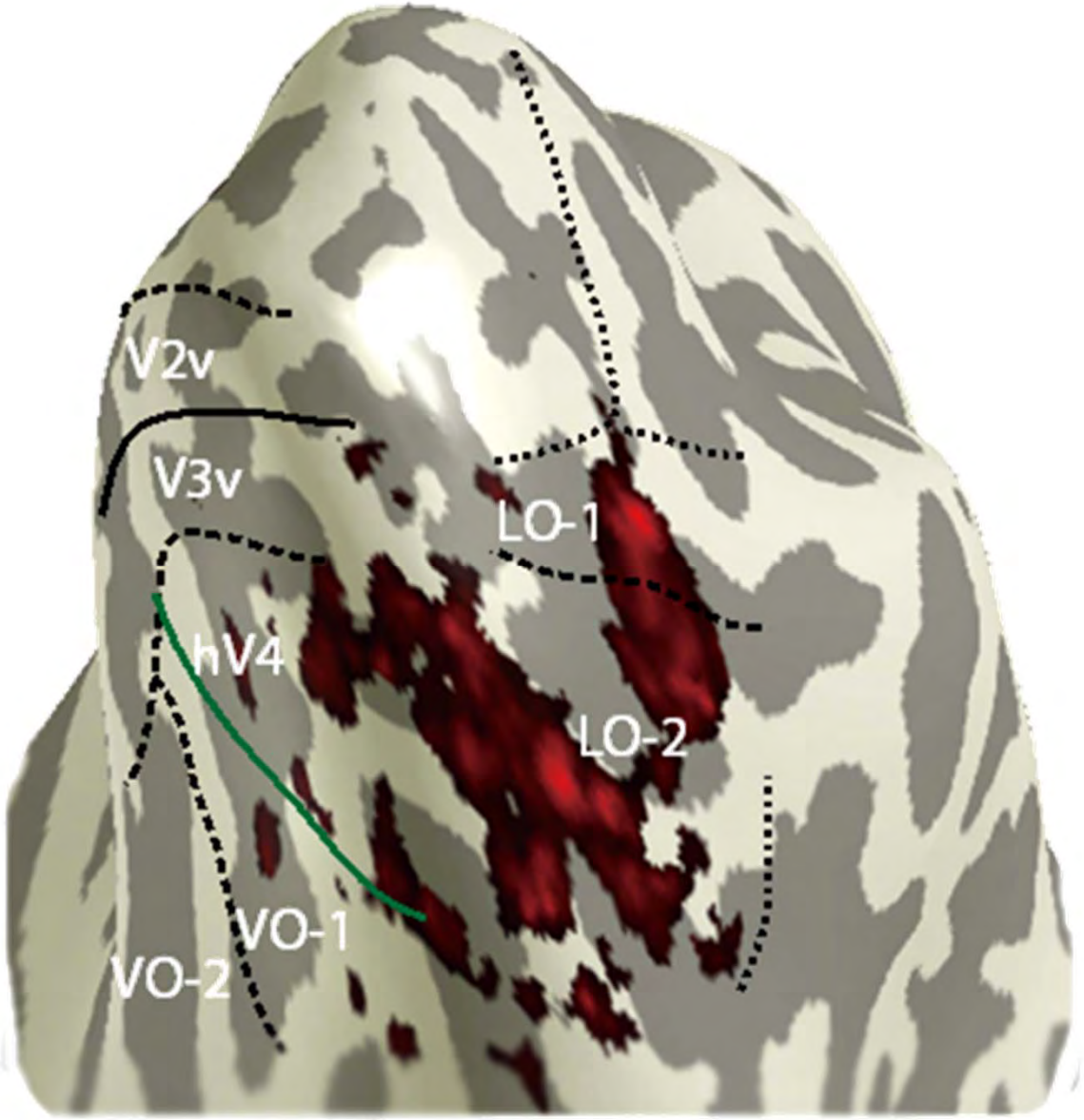




Ventral VOF endpoints

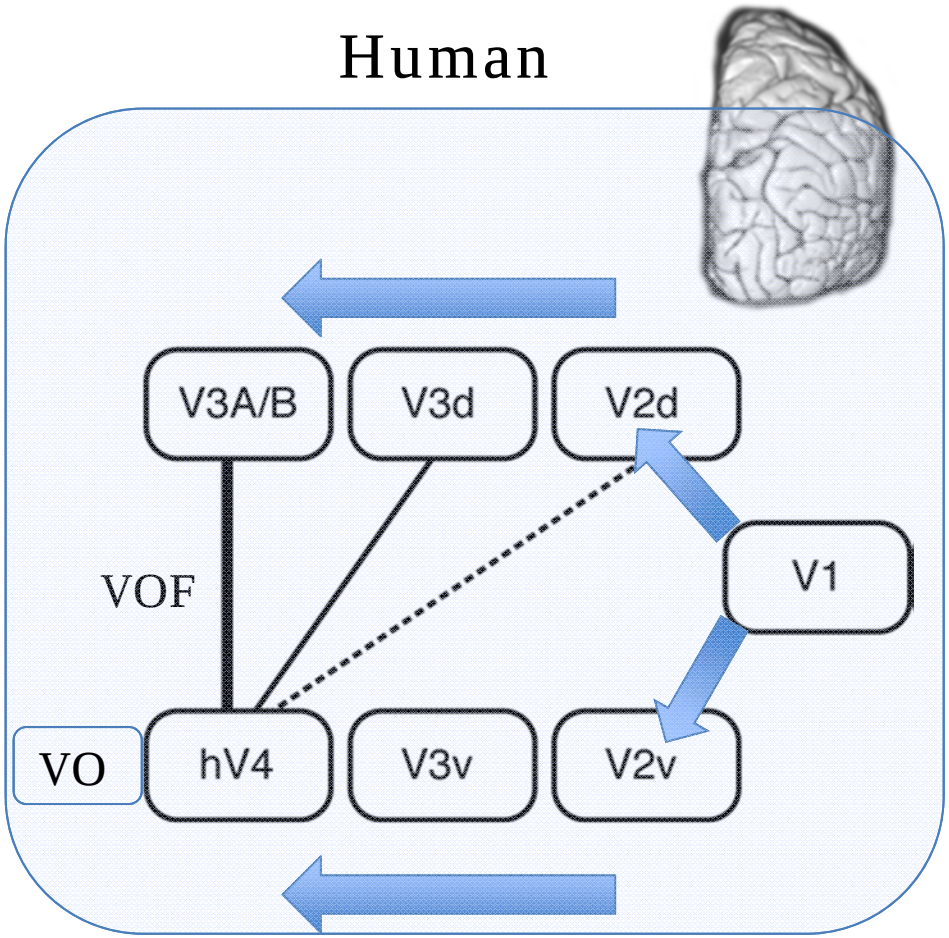




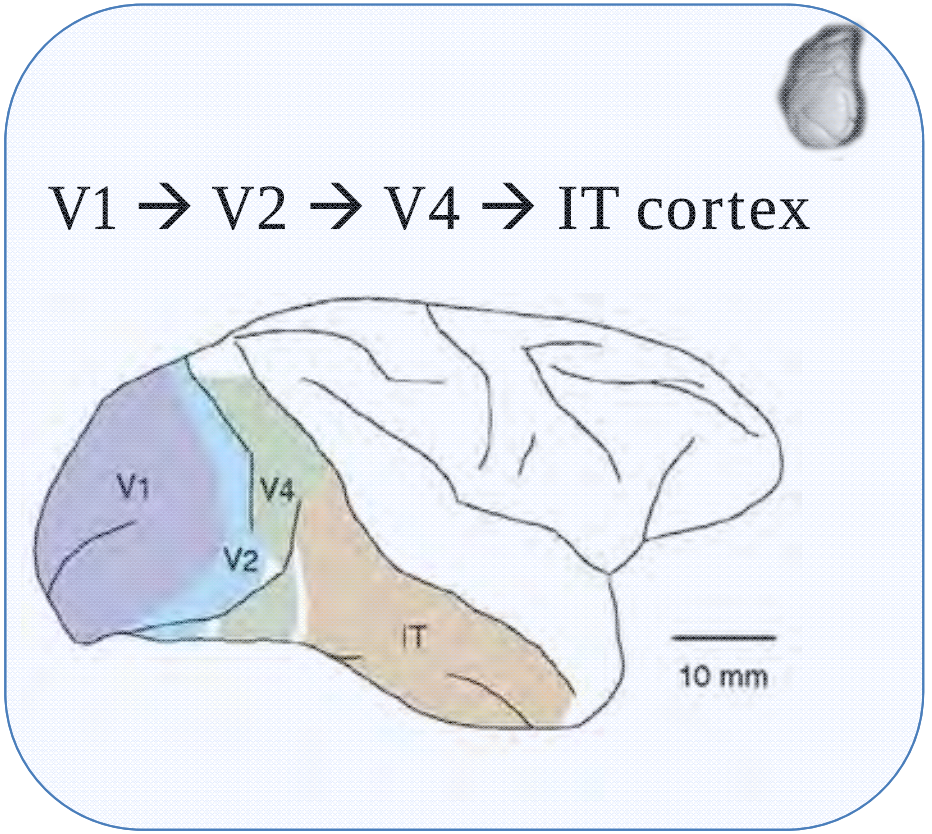


Rethinking the human wiring diagram

Human



Macaque electrophysiology



DiCarlo and Cox, 2007

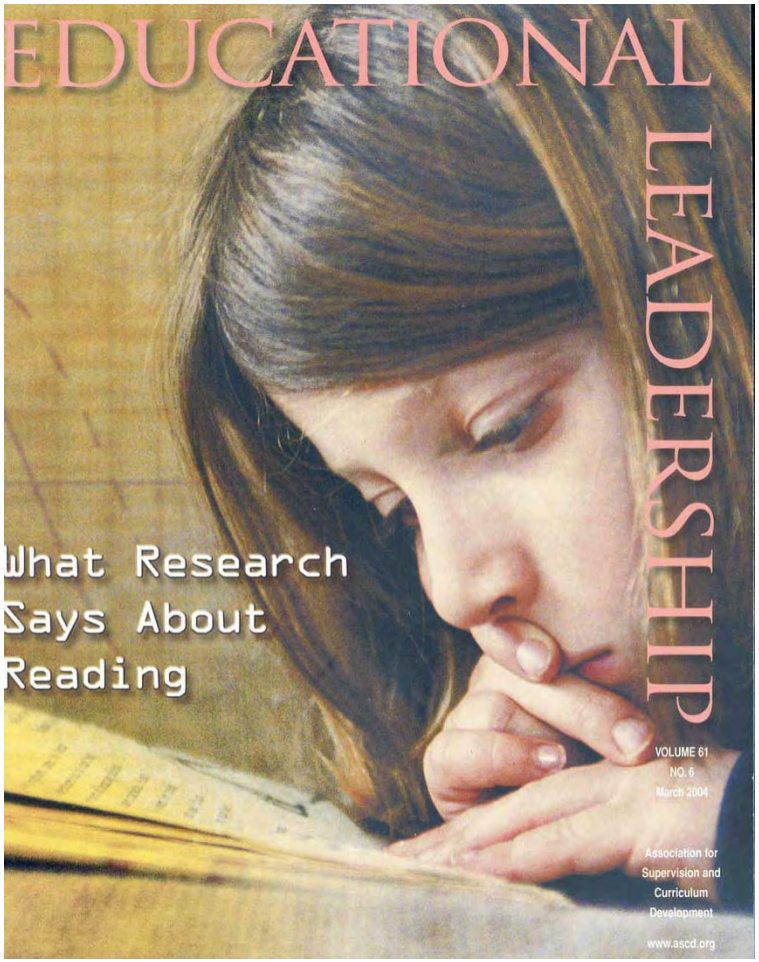
Neuroscience for Society

Wandell and Yeatman, CONB, 2013

- Some behaviors, such as psychological tests of performance during brief trials, may be best understood by measuring synaptic activity or spikes.

- Other important behaviors - learning to read or to regulate emotions - take place over longer time periods. These skills may depend on biological processes such as cell development, growth and pruning of dendritic arbors, the proliferation and activity of glia.

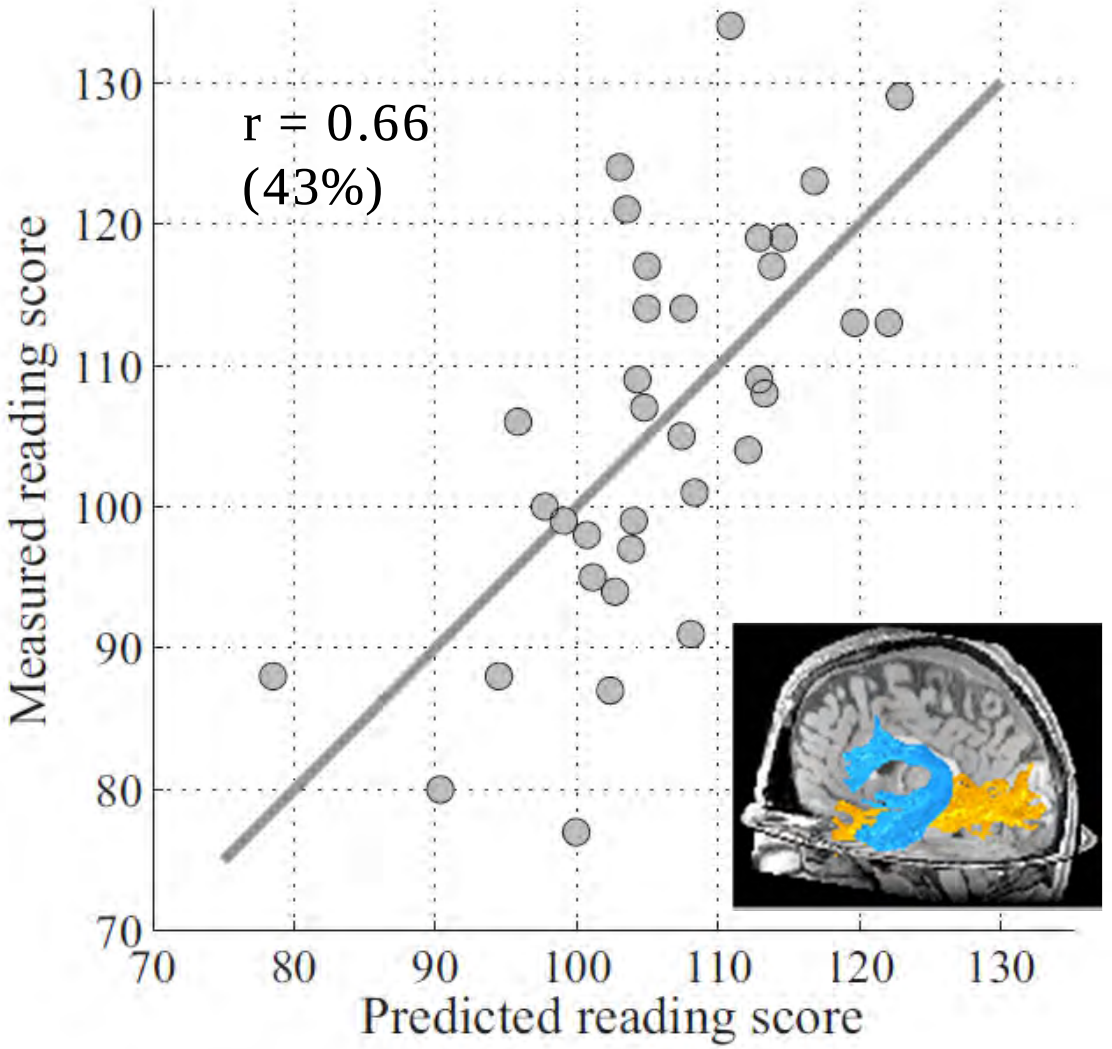
- Scientists need to account for the entire range of processes to understand circuit function in health and disease.



Predicting reading scores from white matter maturity

(Yeatman et al., PNAS, 2012)

- With very simple models based on diffusion data, we predict reading skill
- The predictions are statistically significant, but not yet useful



(From white matter diffusion data)

See work by Gabrieli and Hoeft groups

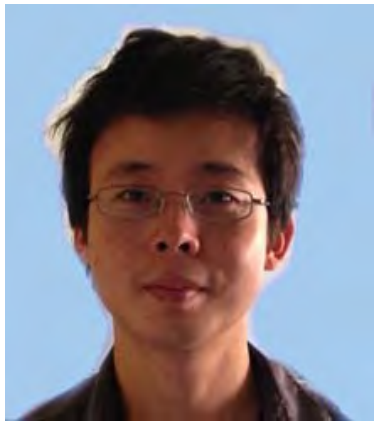
Thank you!

Stanford Psychology

B. Dougherty
J. Winawer
A. Mezer
M. Perry
K. Kay

Ariel Rokem

Franco Pestilli



Hiromasa Takemura

Jason Yeatman