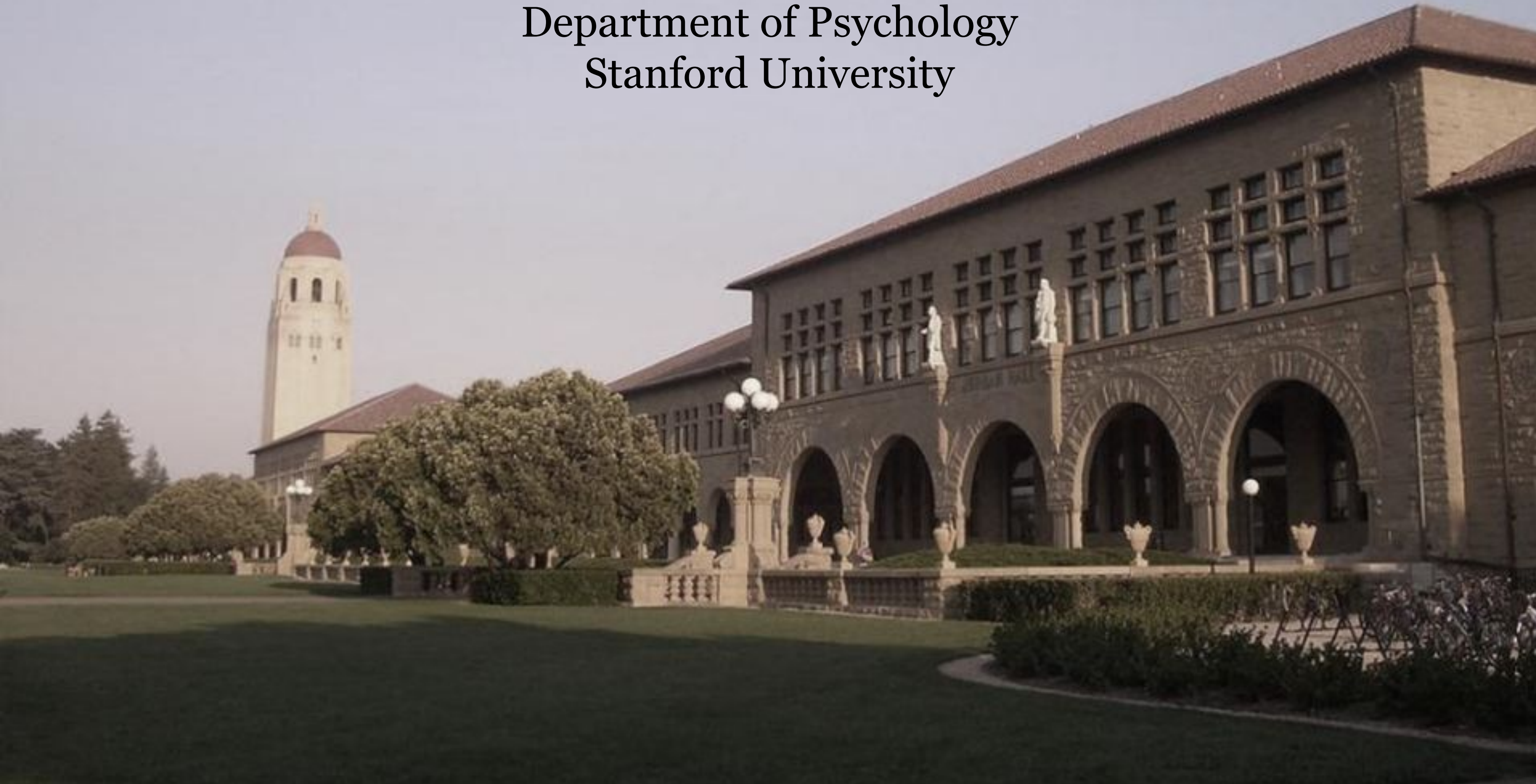
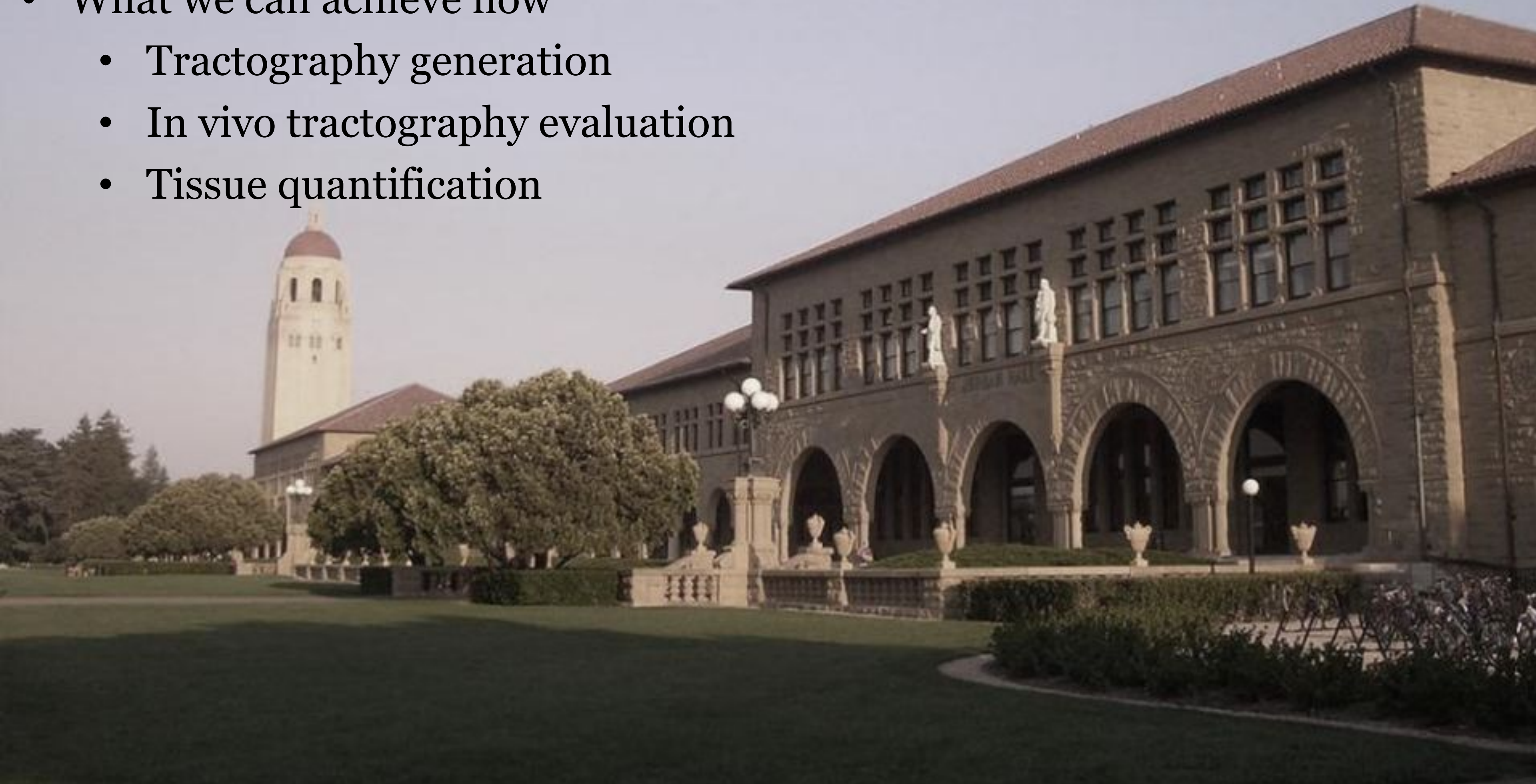
Rethinking tractography

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

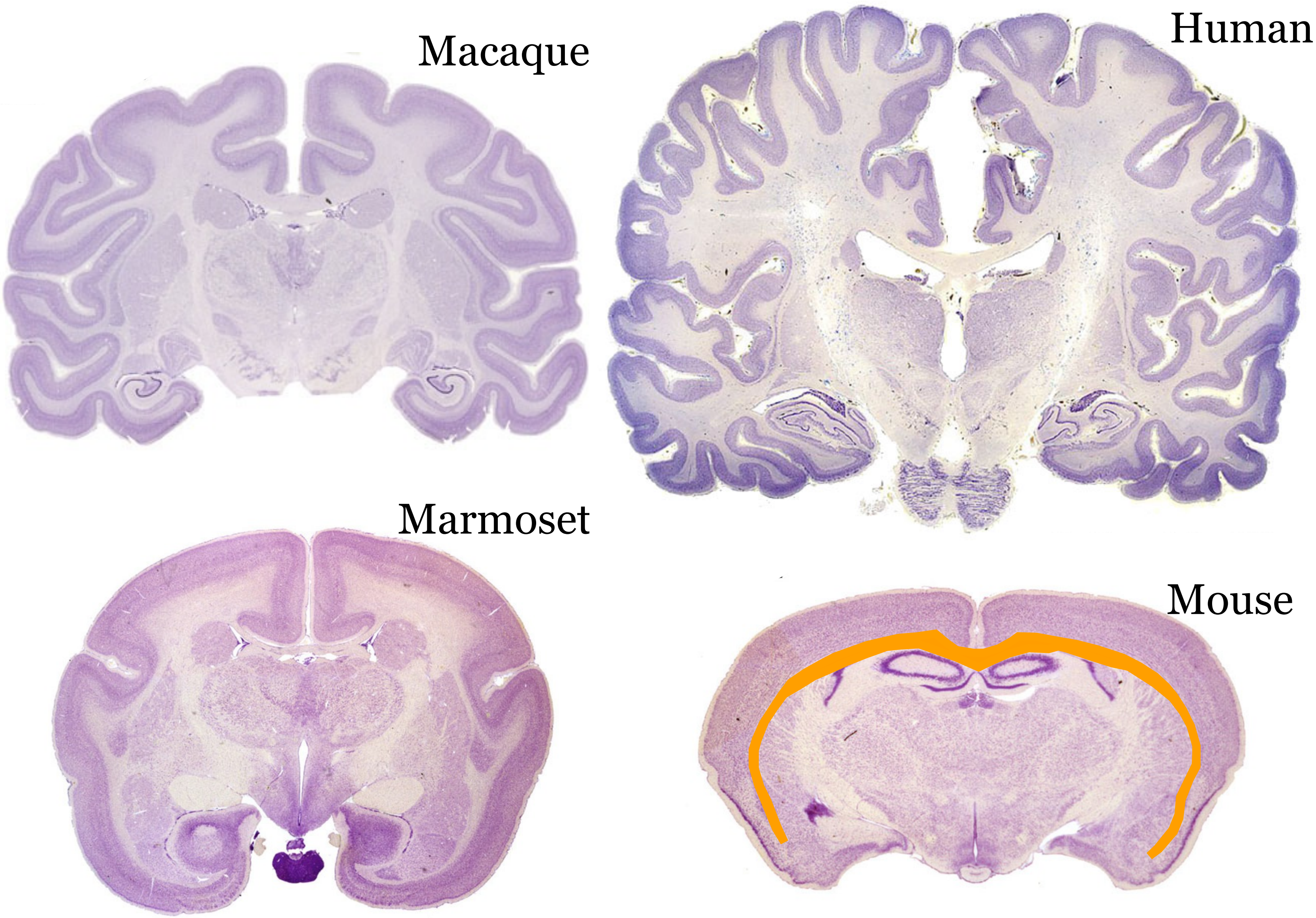


We can achieve a large-scale, quantified, human connectome in the next few years

- Quantitative white matter measurements in the living human brain
- What we can achieve now
  - Tractography generation
  - In vivo tractography evaluation
  - Tissue quantification



Gray and white matter varies across species

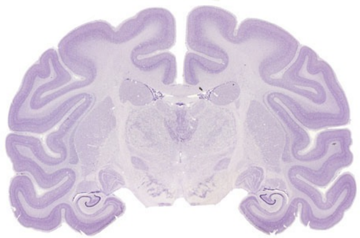


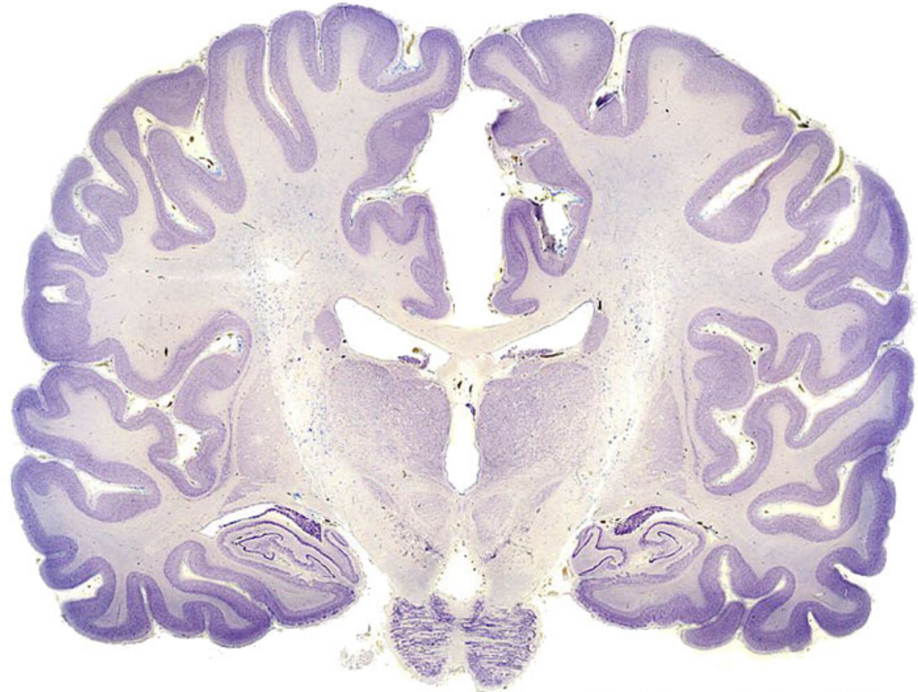
www.brainmuseum.org

White-matter matters more in humans

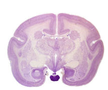
1 cm

Macaque

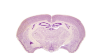




Marmoset



Mouse



www.brainmuseum.org

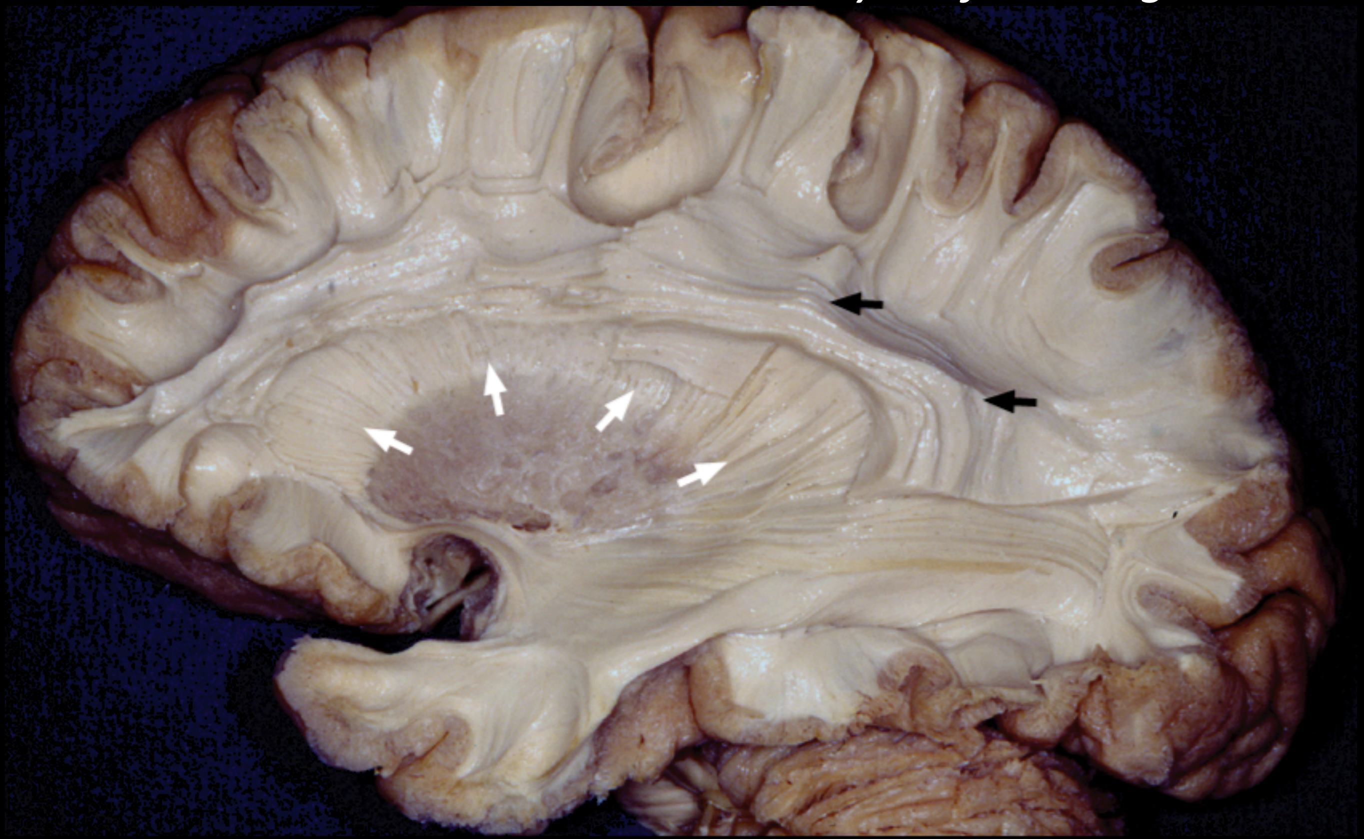
Why fascicles (tracts) matter

- 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

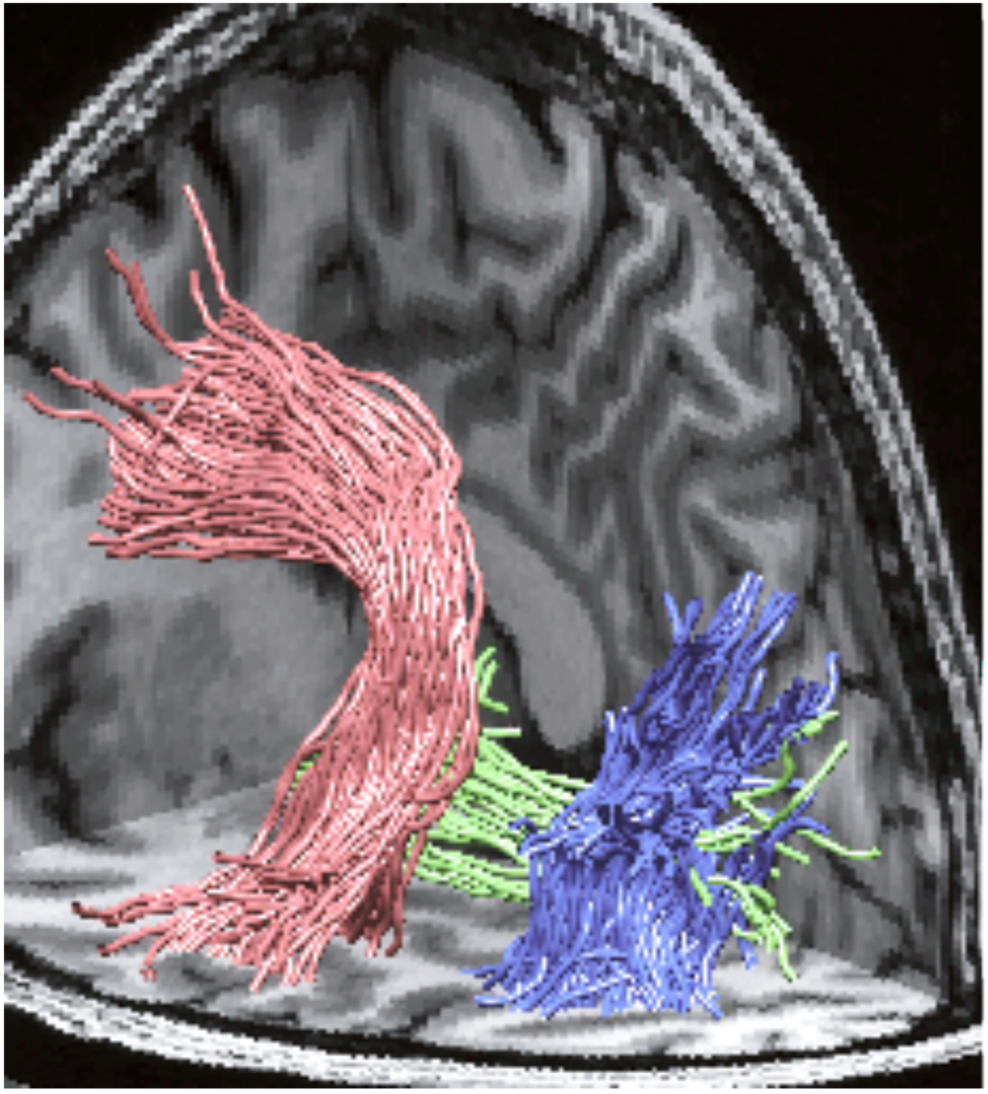


White matter quantitative assessment

- The tissue properties in these pathways influence many aspects of human health, cognition, and emotion
- Neurodegenerative diseases and traumatic brain injury damage these tracts

Example reviews

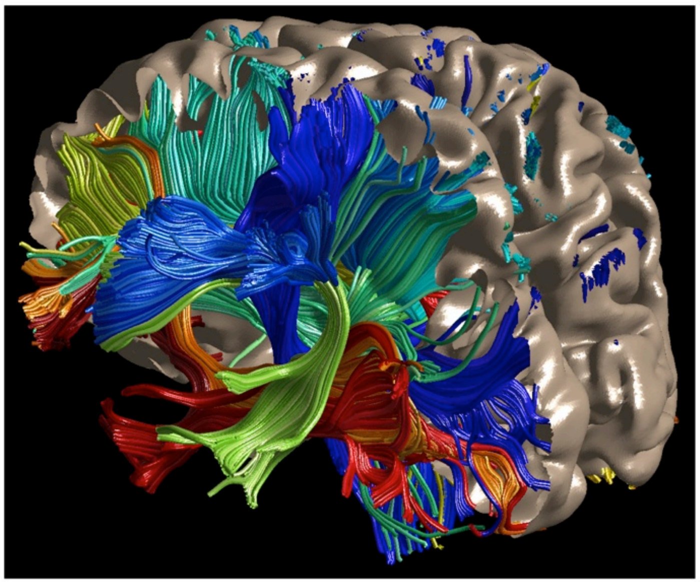
Psychiatric: Thomason and Thompson, Ann. Rev. Clin. Psych (2011)
Cognition: Fields, Trends Neurosci, (2008)
Reading: Wandell, Ann. Rev. Psych (2012)
TBI: Shenton, Brain Imaging and Behavior (2012)



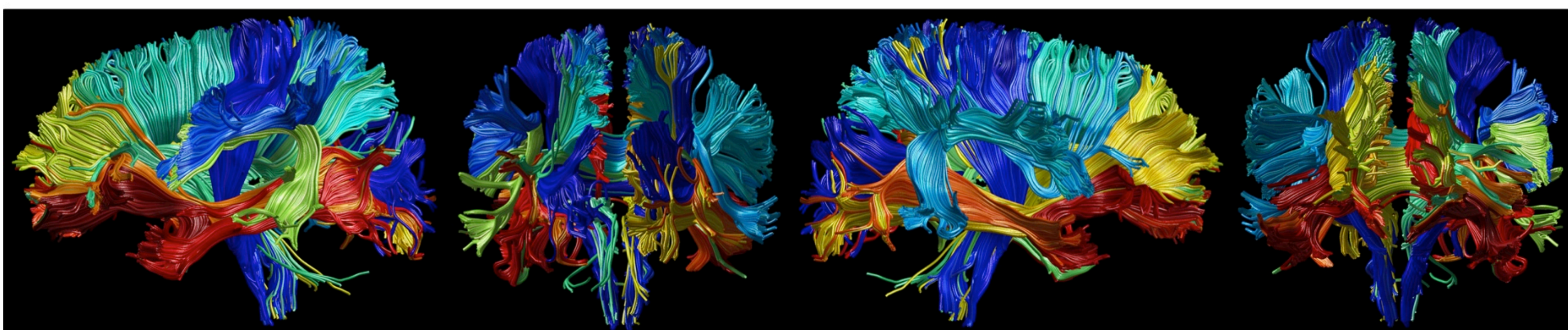
Basic tractography is successful

(Yeatman et al., *Nature Communications*, 2014)

Lifespan maturation and degeneration of human brain white matter



- Right Uncinate
- Left Cingulum Cingulate
- Right ILF
- Right Cingulum Cingulate
- Right Thalamic Radiation
- Left Arcuate
- Left Thalamic Radiation
- Post. Parietal Callosum
- Right Arcuate
- Left SLF
- Left Corticospinal
- Motor Callosum
- Left Uncinate
- Left ILF
- Orbitofrontal Callosum
- Left IFOF
- Right IFOF
- Ant. Frontal Callosum
- Temporal Callosum
- Sup. Frontal Callosum
- Right SLF
- Sup. Parietal Callosum
- Right Corticospinal
- Occipital Callosum

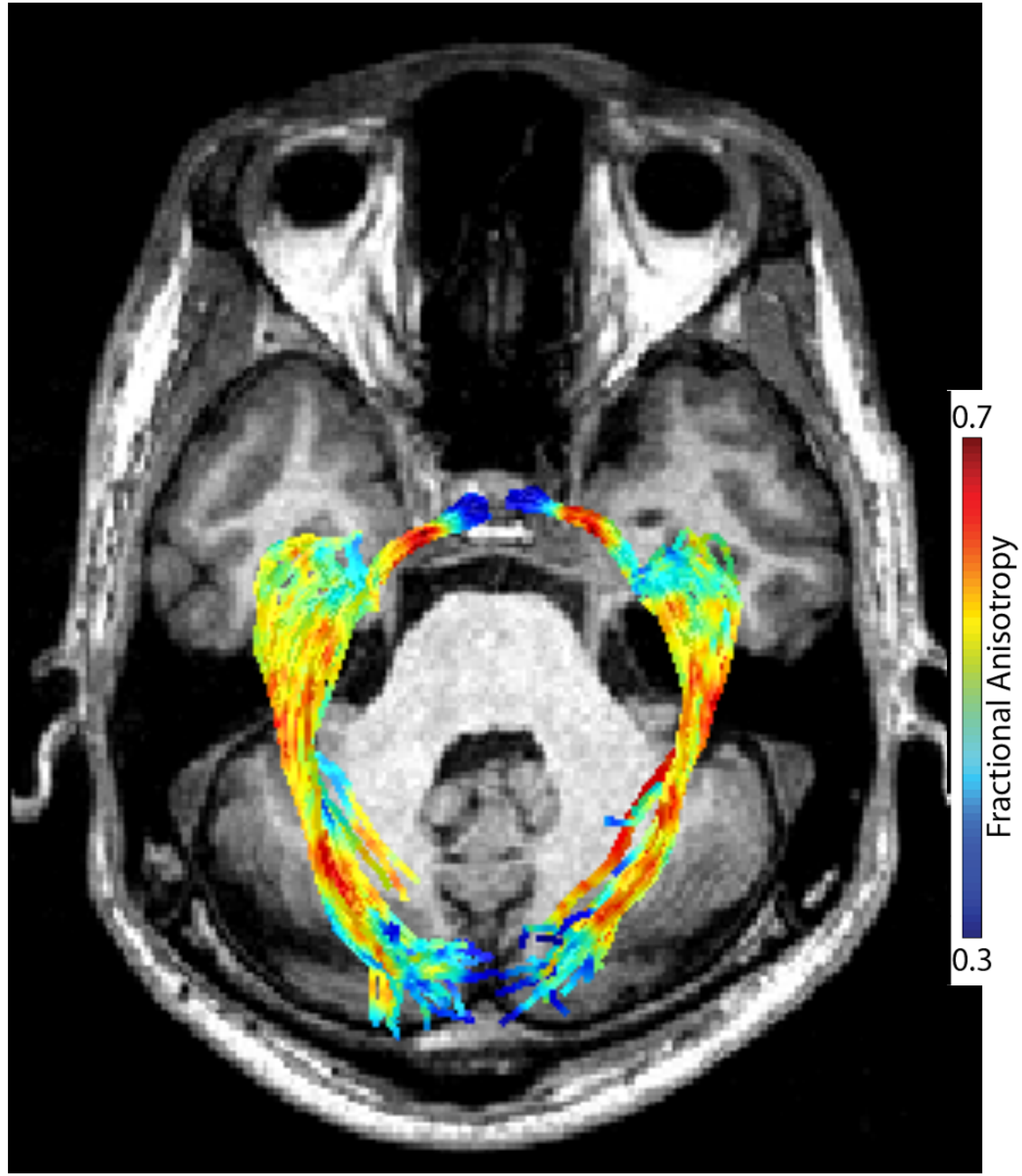


An example of what we might achieve

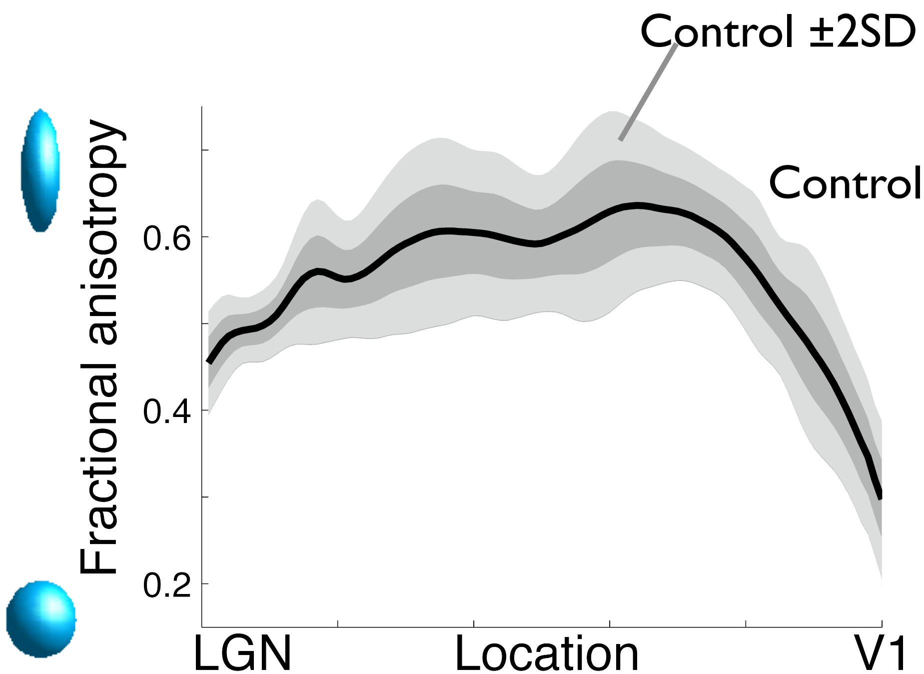
- A subject or patient with a retinal eye disease comes to the lab
- We want to know the consequences of retinal degeneration on cortical structures

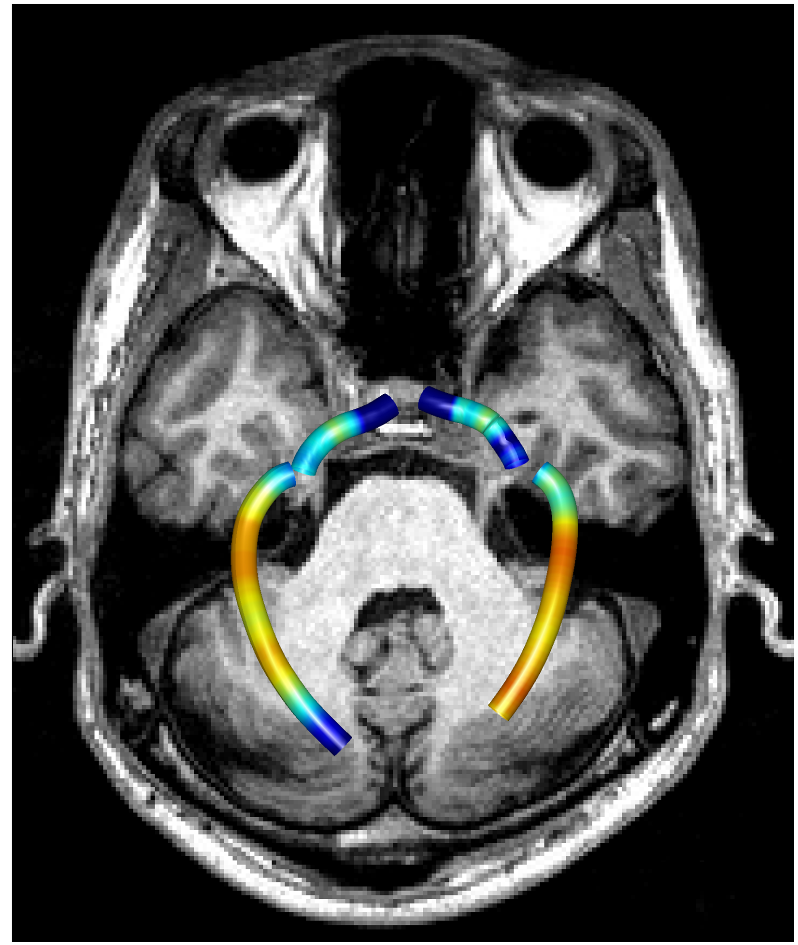
An example of what we might achieve

- Measure the subject's visual white matter
- Secure the data!
- Use validated computational tools for quality assurance and tissue estimation



Project on Scientific Transparency (PoST)





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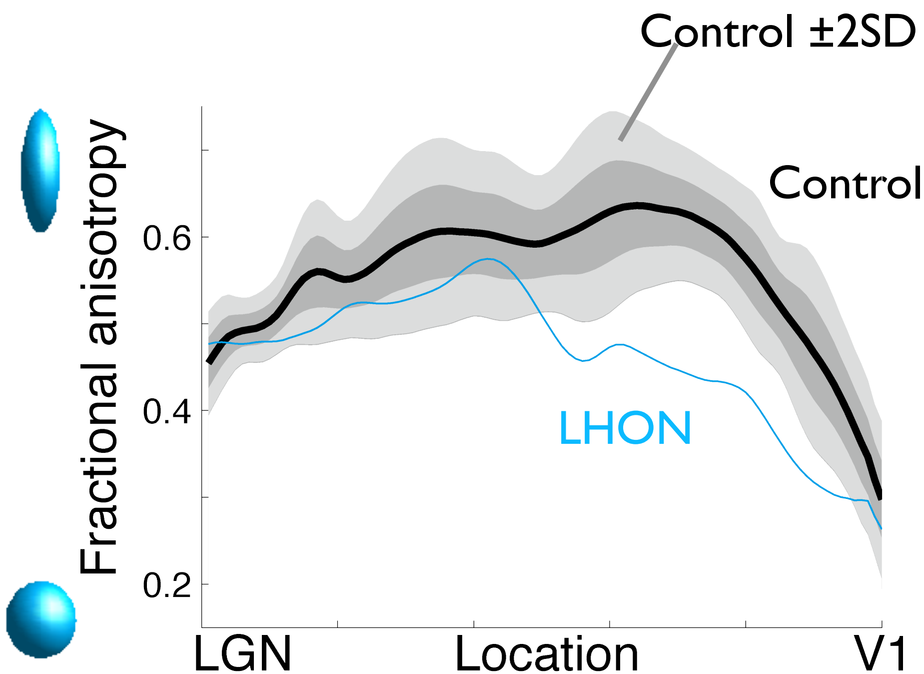
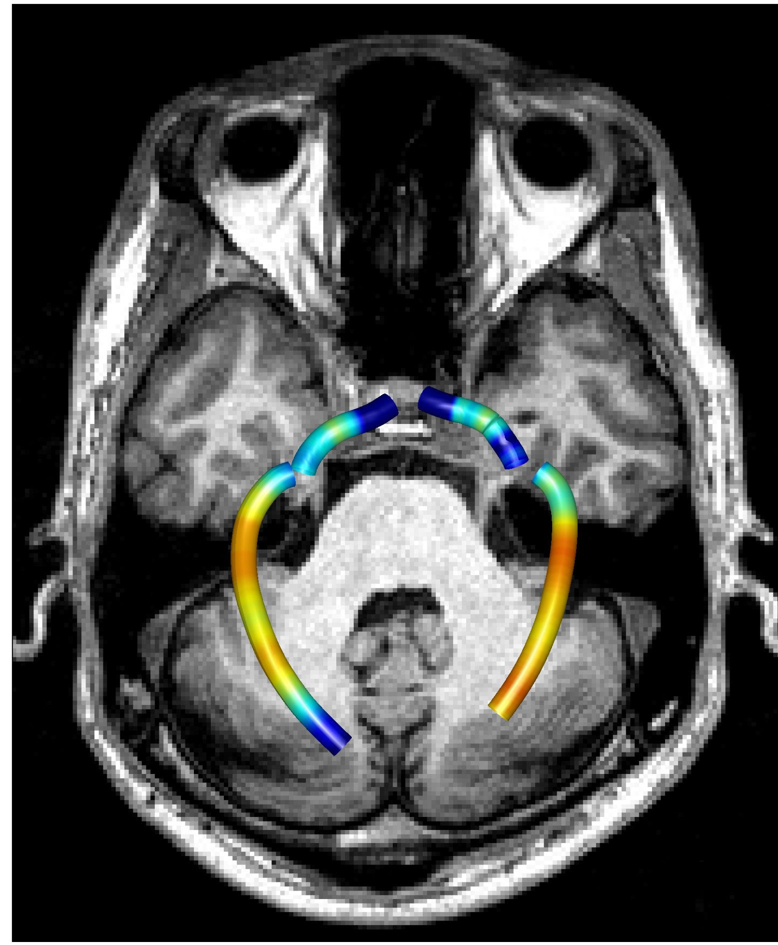
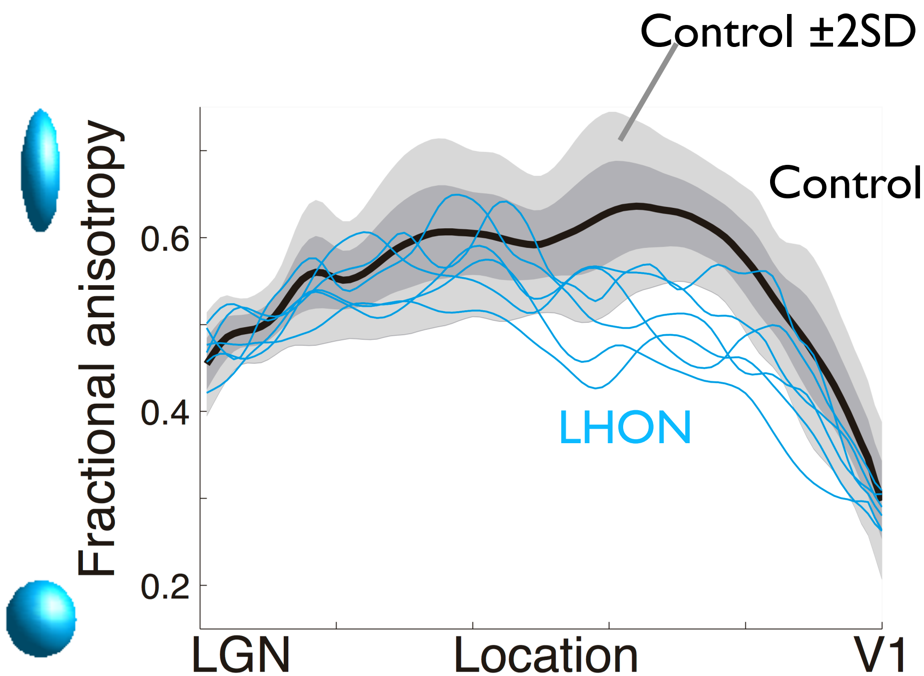
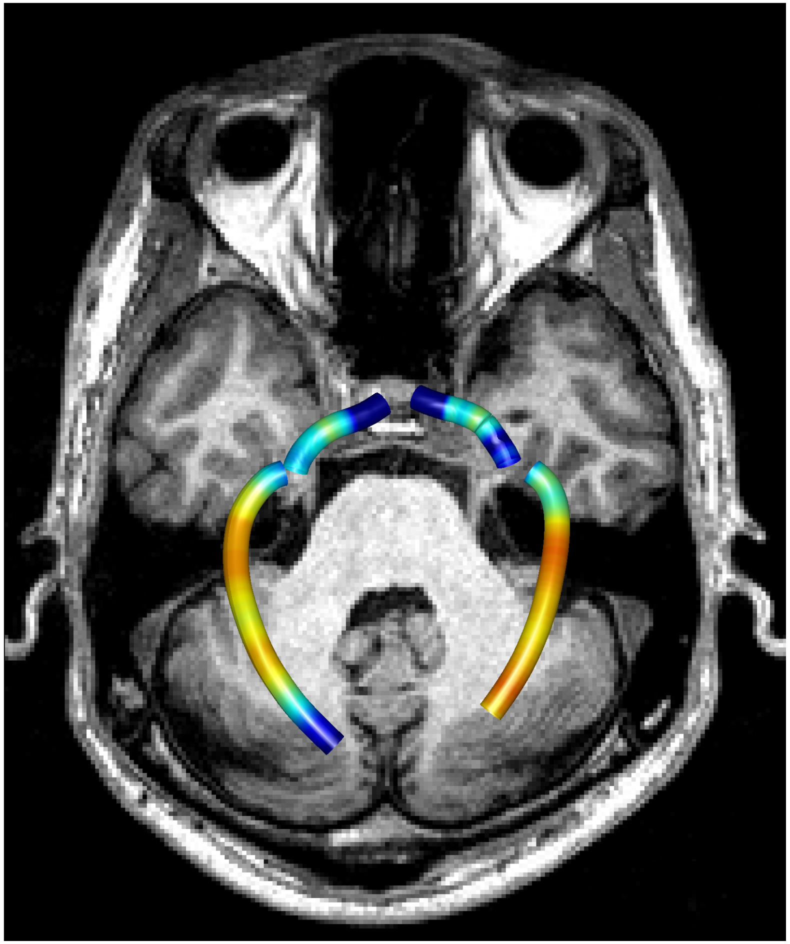




Leber's hereditary optical neuropathy

Project on Scientific Transparency (PoST)





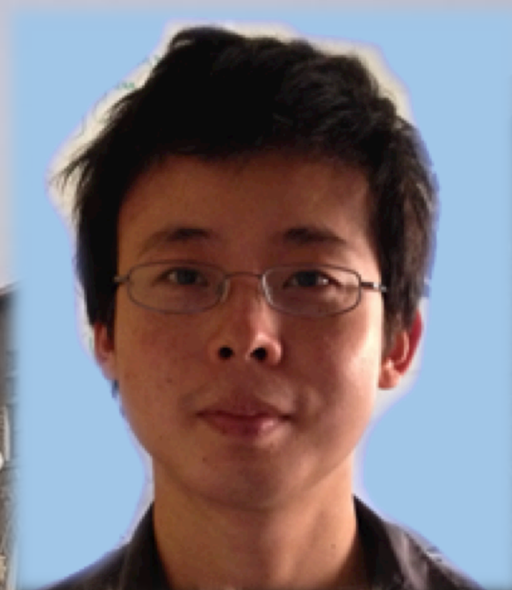
Leber's hereditary optical neuropathy

Linear Fascicle Evaluation

Pestilli et al., September, 2014, *Nature Methods*

Franco Pestilli

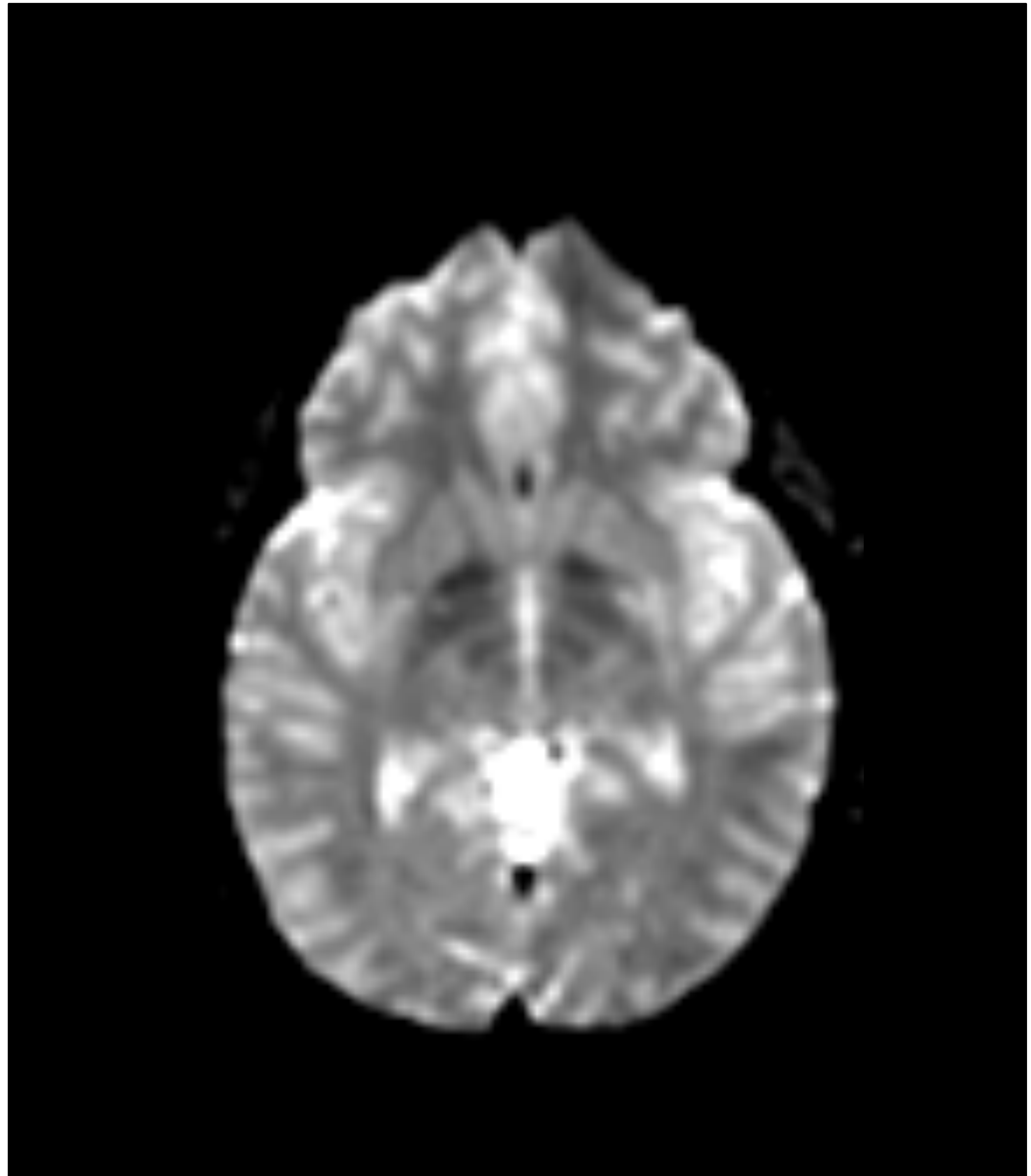
Hiromasa Takemura



Non-diffusion MR image

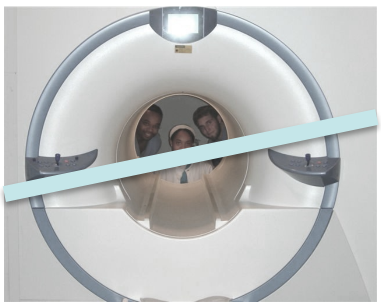
Dark means large
signal attenuation
High ADC

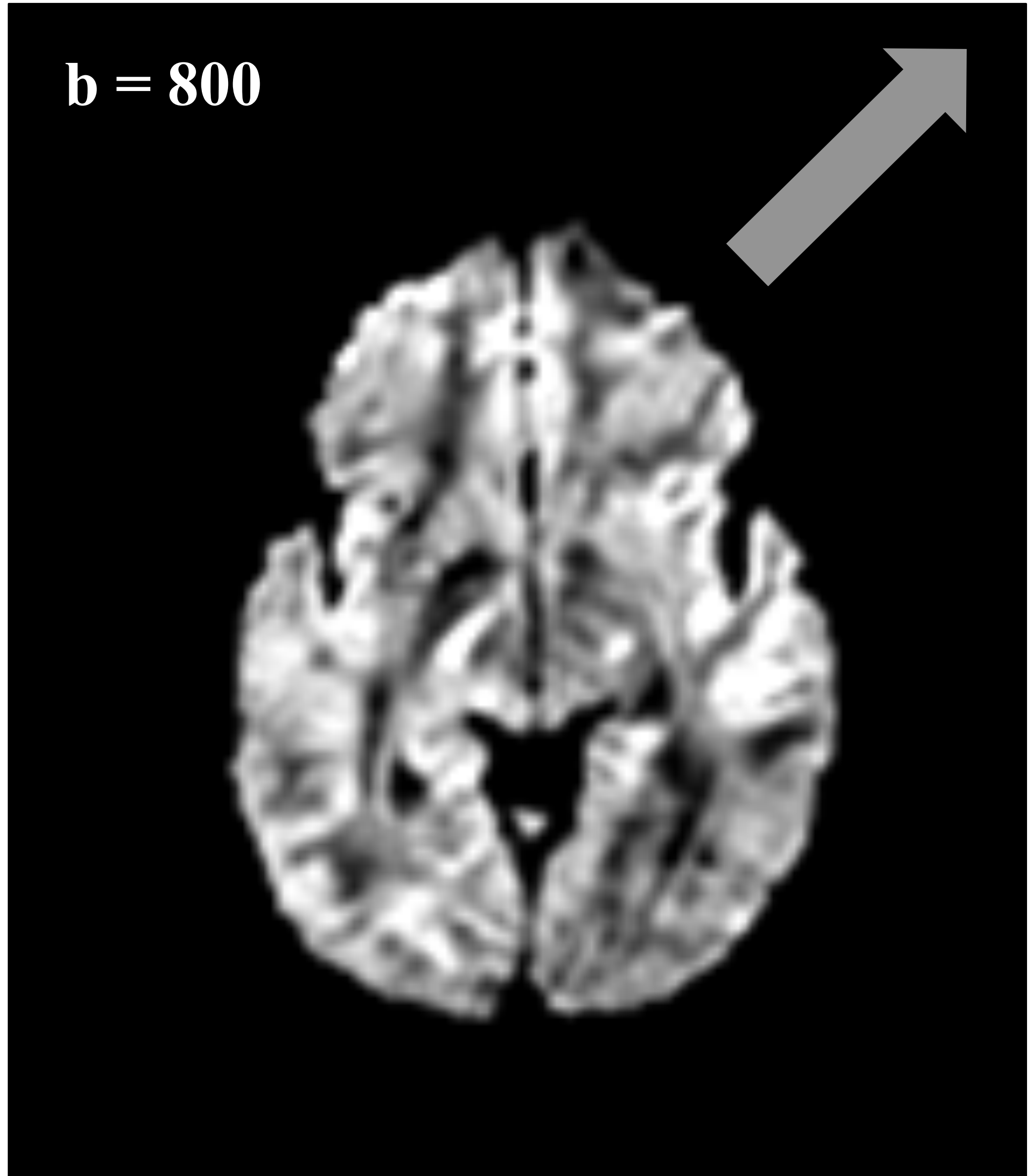
b = 0



Diffusion weighting: Directions

Dark means large signal attenuation
High ADC





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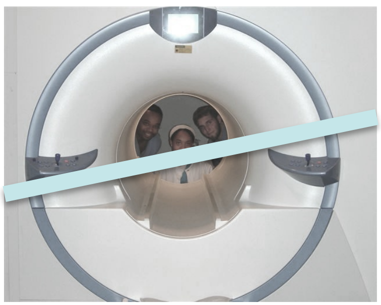
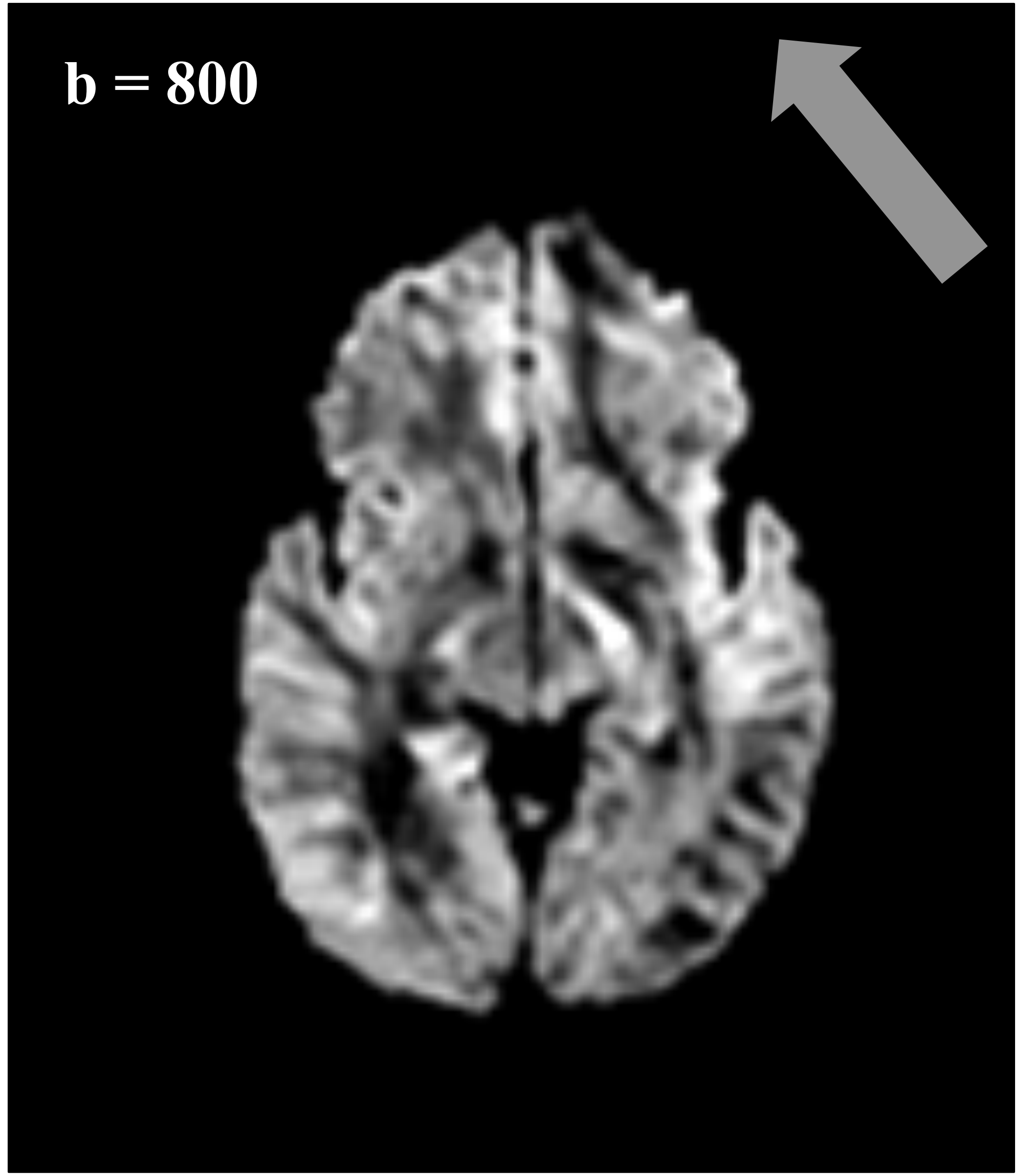
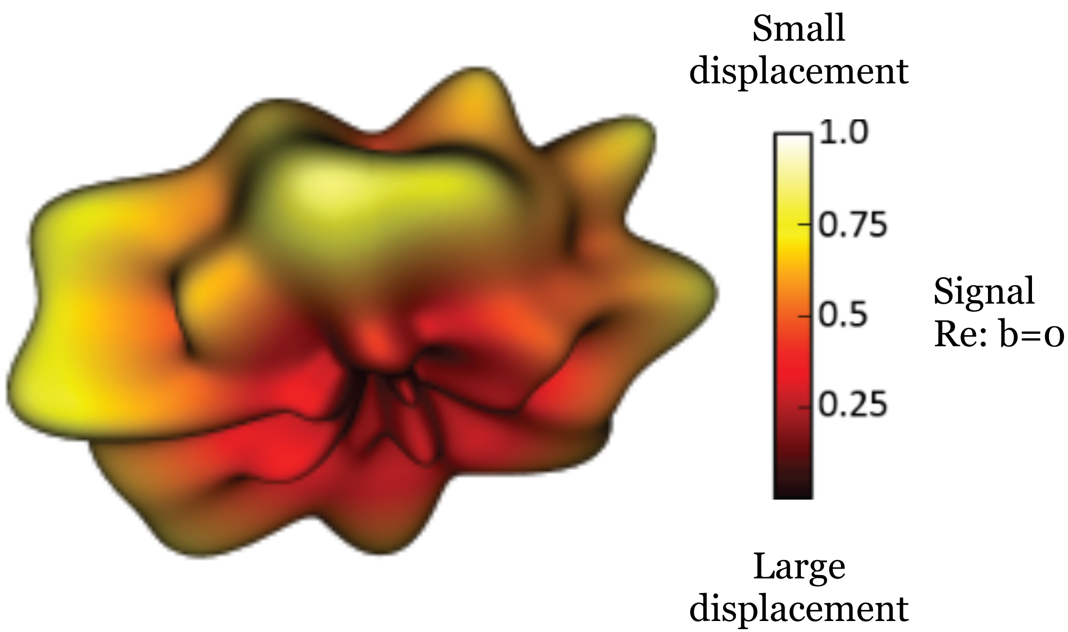




Diffusion signals in different directions

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

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



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

Diffusion signals in different directions

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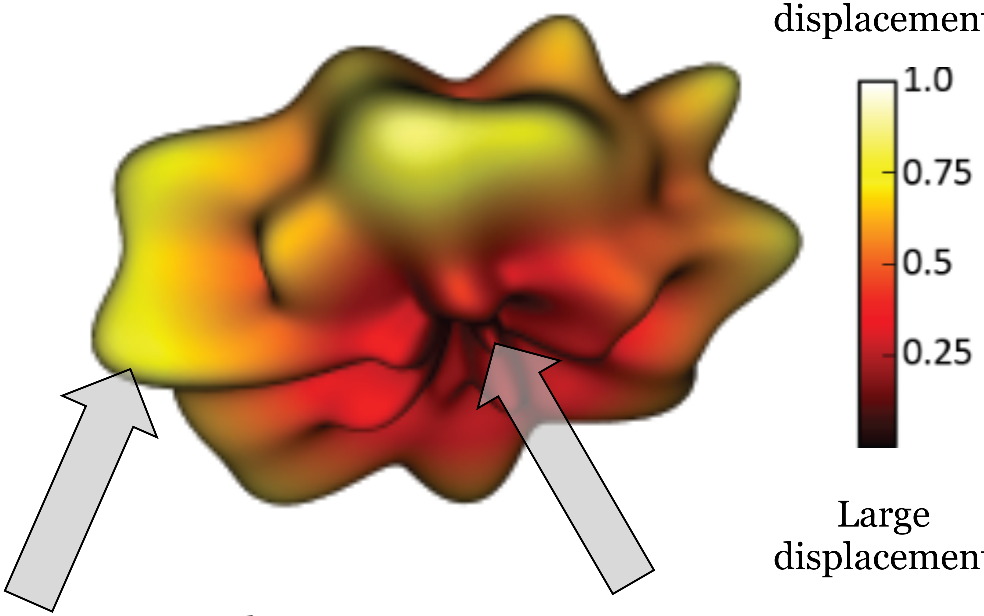


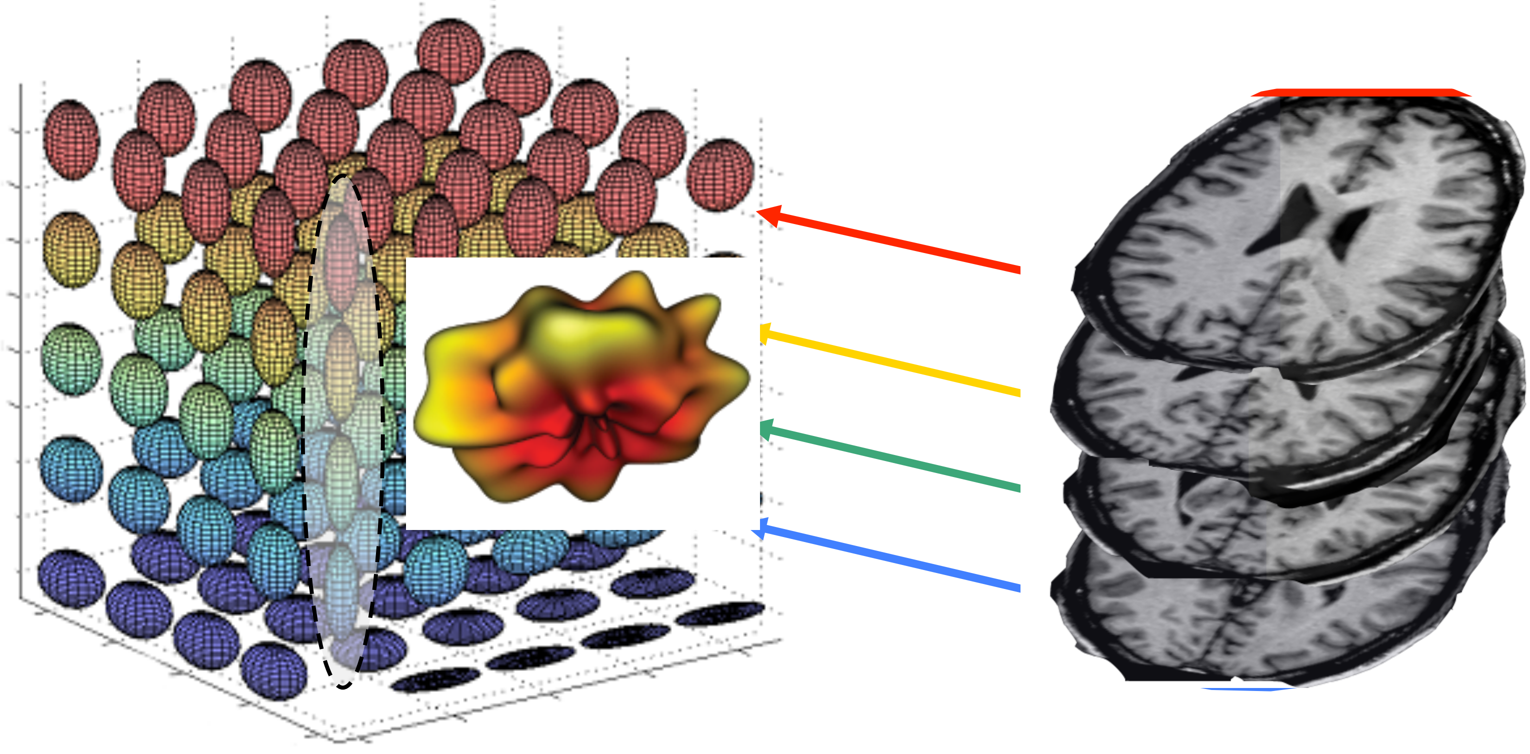
The measured diffusion signal in a direction, θ, is related to the apparent diffusion coefficient in that direction, D(θ)

ADC – apparent diffusion coefficient

Tractography

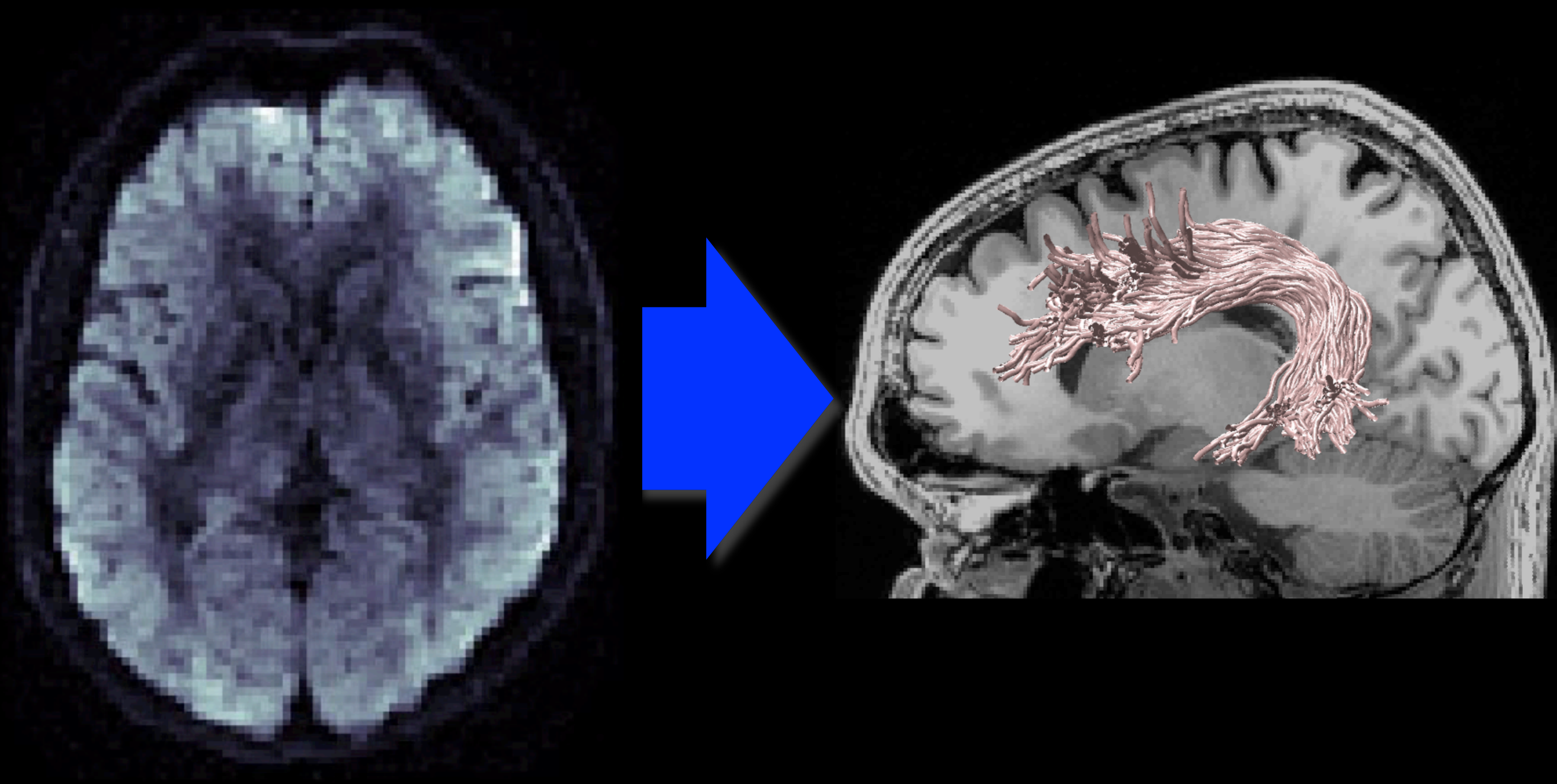
Use the local (voxel) diffusion measurements to estimate white matter tracts

Diffusion data are surfaces

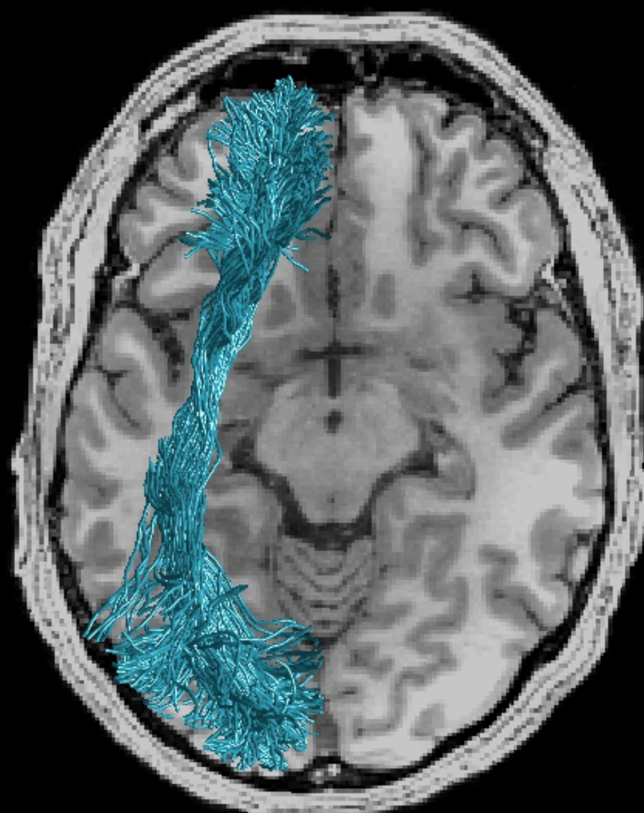


Tractography

Estimate fascicles from diffusion data



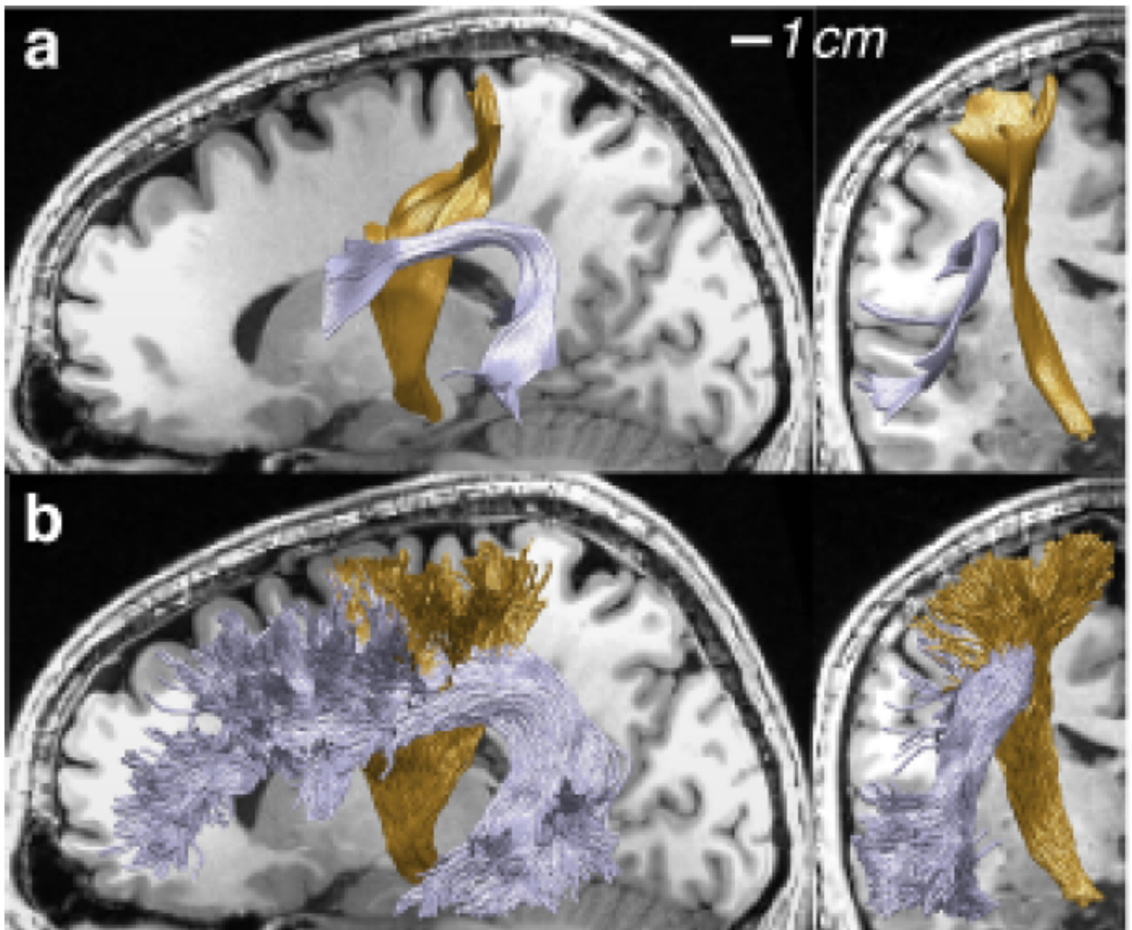
White matter fascicles are generated by step-wise sampling of local diffusion information

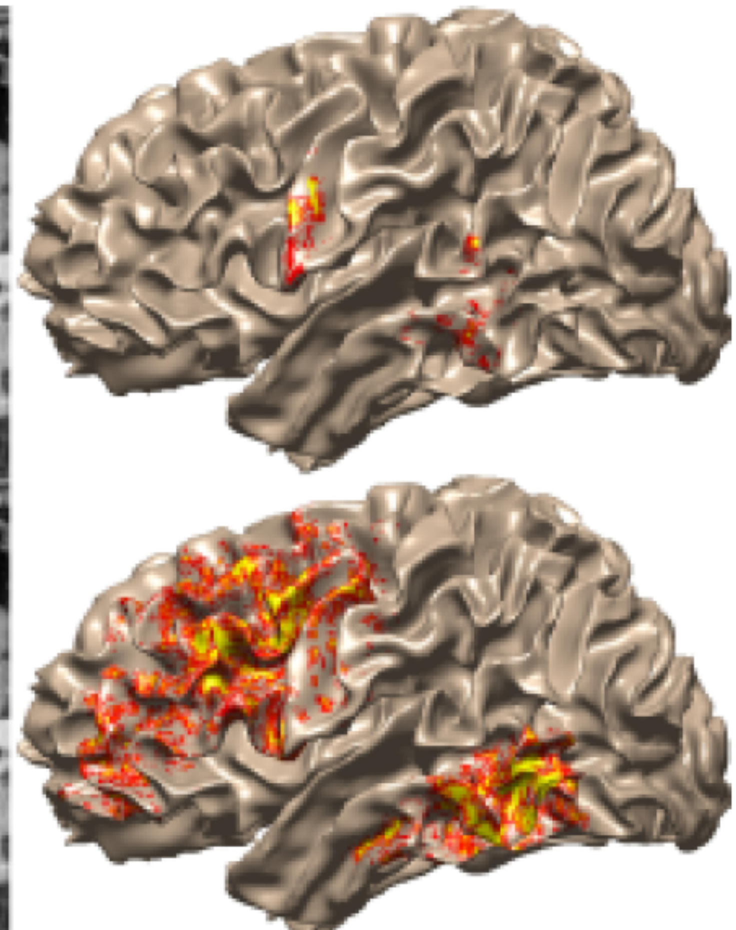


Left IFOF

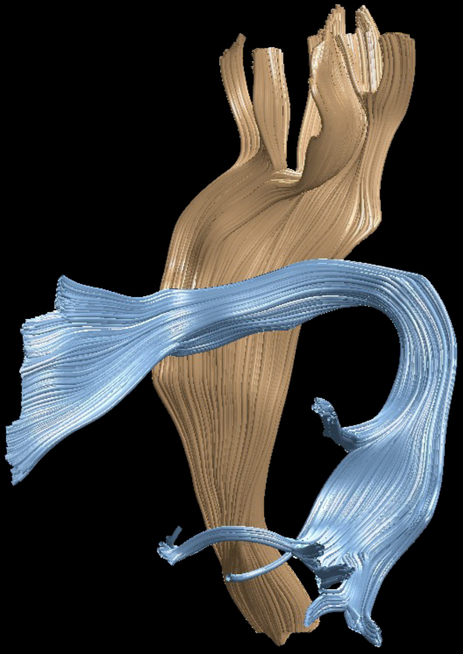
150 Directions, 2 mm^3, B=2000 projected on a 1 mm^3 T1 anatomical image

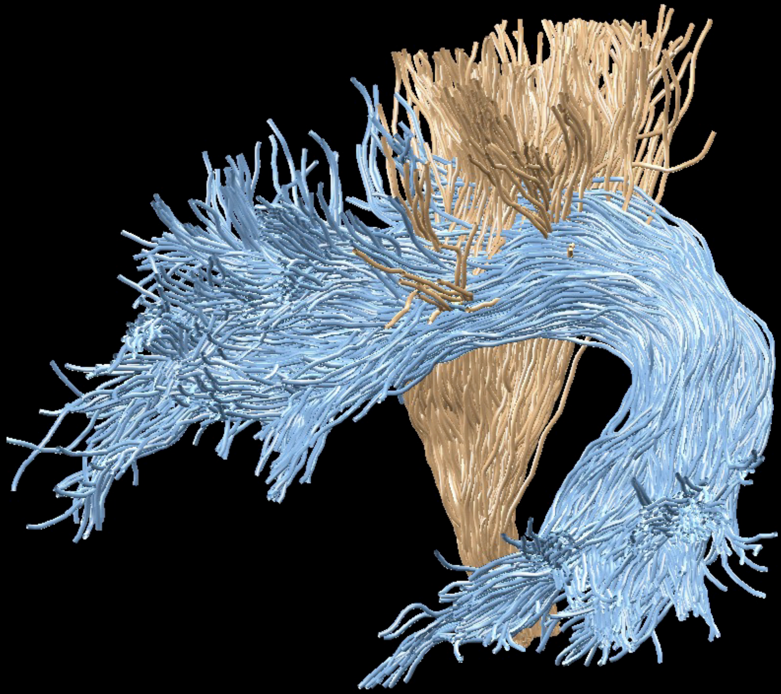
Different tractography methods and parameters make different predictions





Which connectomes should we study?





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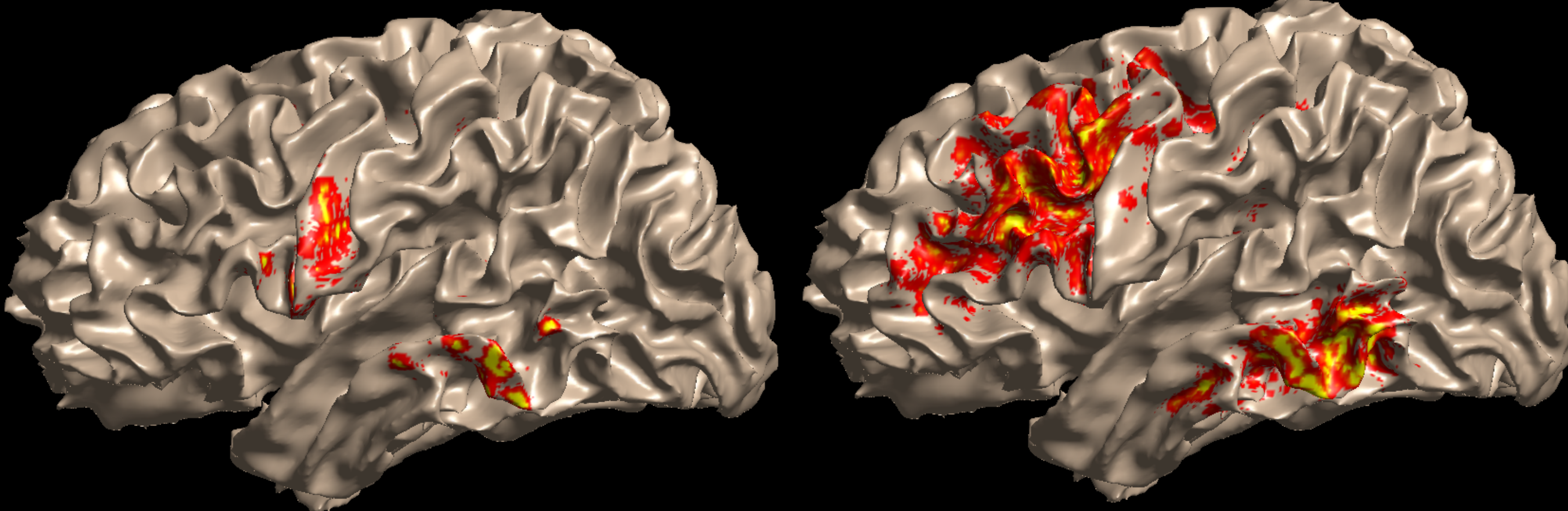
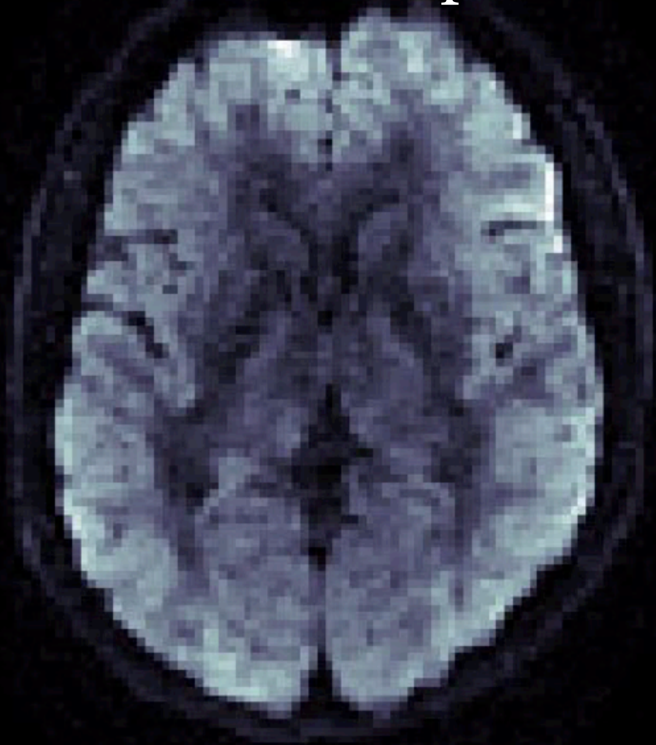
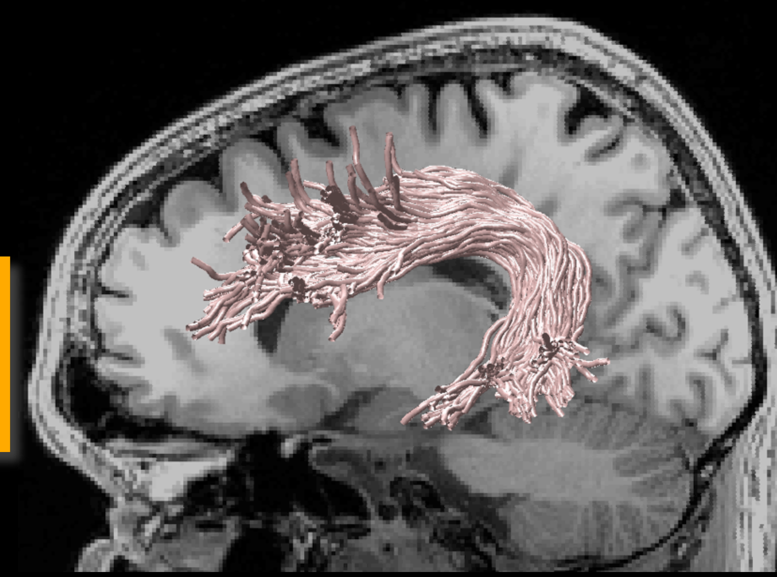


Linear Fascicle Evaluation (LiFE)

Compare how well different models and algorithms do in predicting the original data



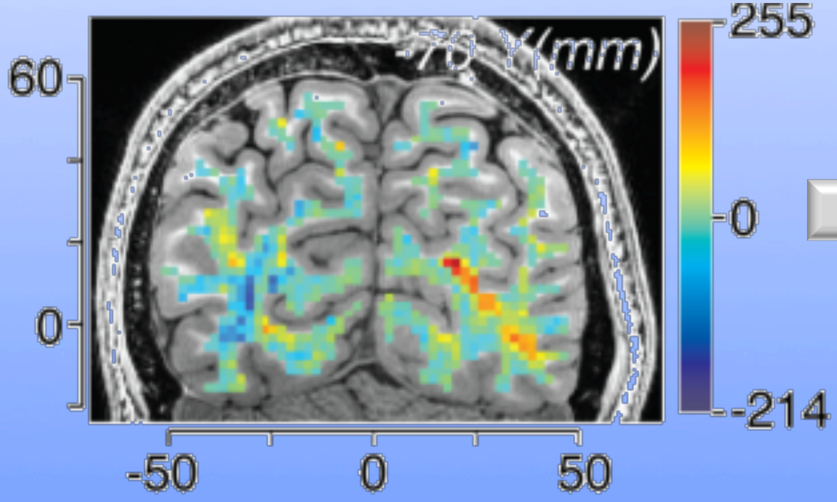


Pestilli et al., *Nature Methods*, 2014

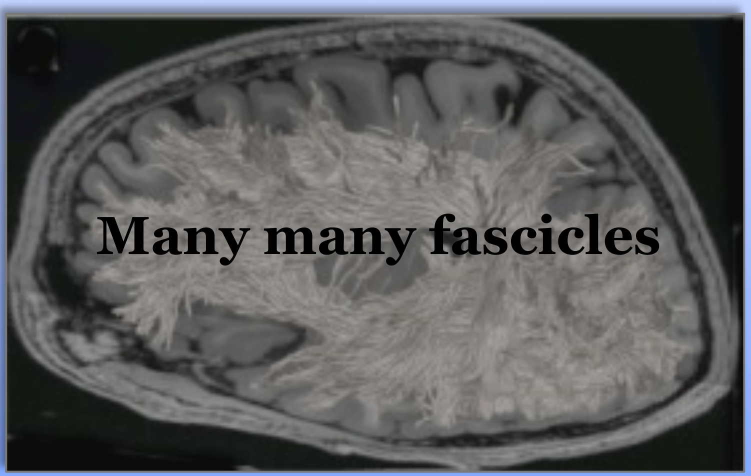
1. Stages of LiFE

Use tractography to generate a candidate connectome

First data set



Candidate connectome



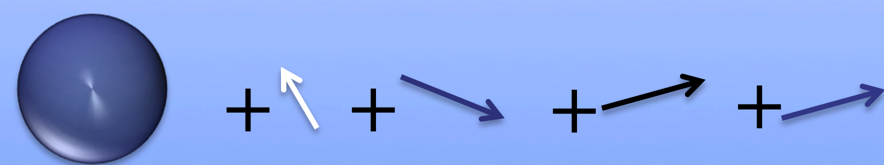
2. Stages of LiFE

Set up diffusion predictions for each voxel

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

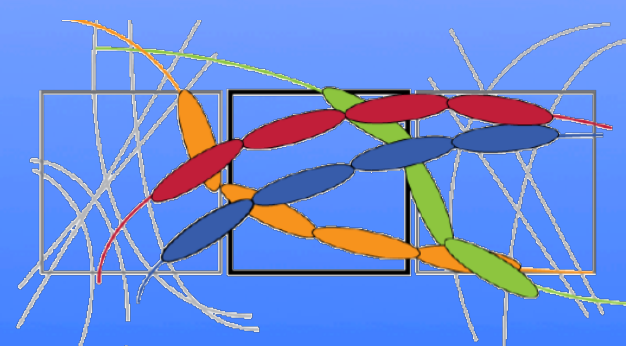
isotropic
weights
fascicles

Use the standard fascicle diffusion model to predict the diffusion signal in each voxel



Bal
l

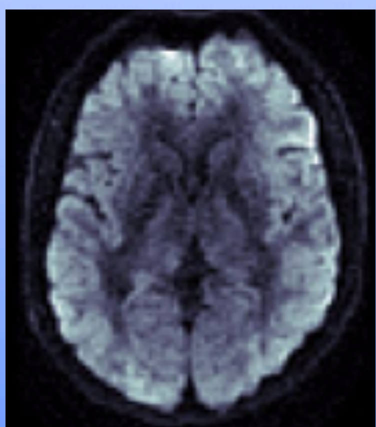
Stick
s



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

$10^7 \times 10^6$

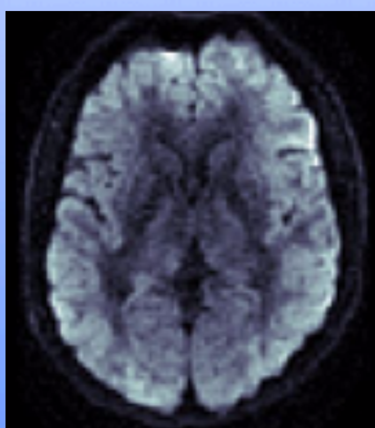
w_f

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

3. Stages of Life

Solve for the fascicle weights

Diffusion signal, $S(\theta)$



$S(\theta)$

v1
v2
⋮
vN

=

Each column is the prediction of a fascicle

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

$10^7 \times 10^6$

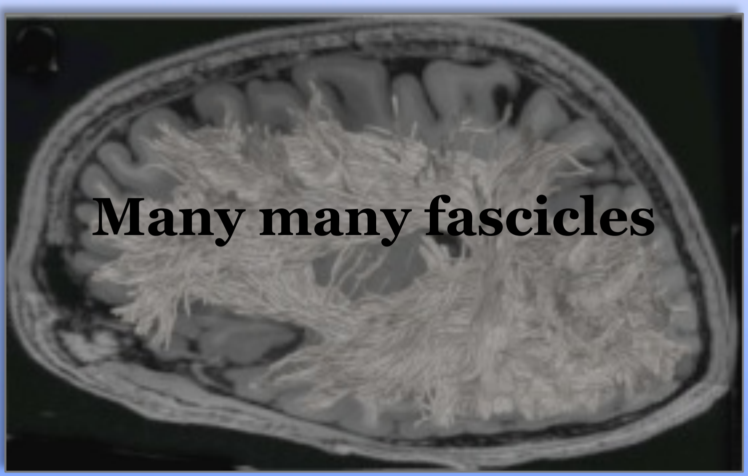
w_f

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

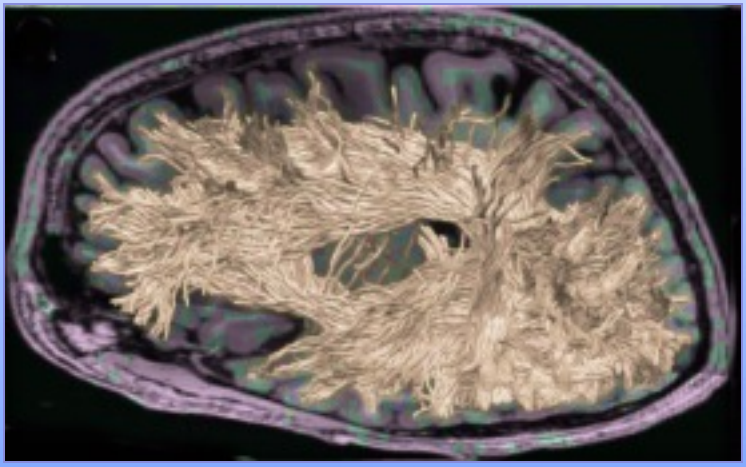
4. Stages of LiFE

Eliminate zero weight fibers (false alarms)

Candidate connectome

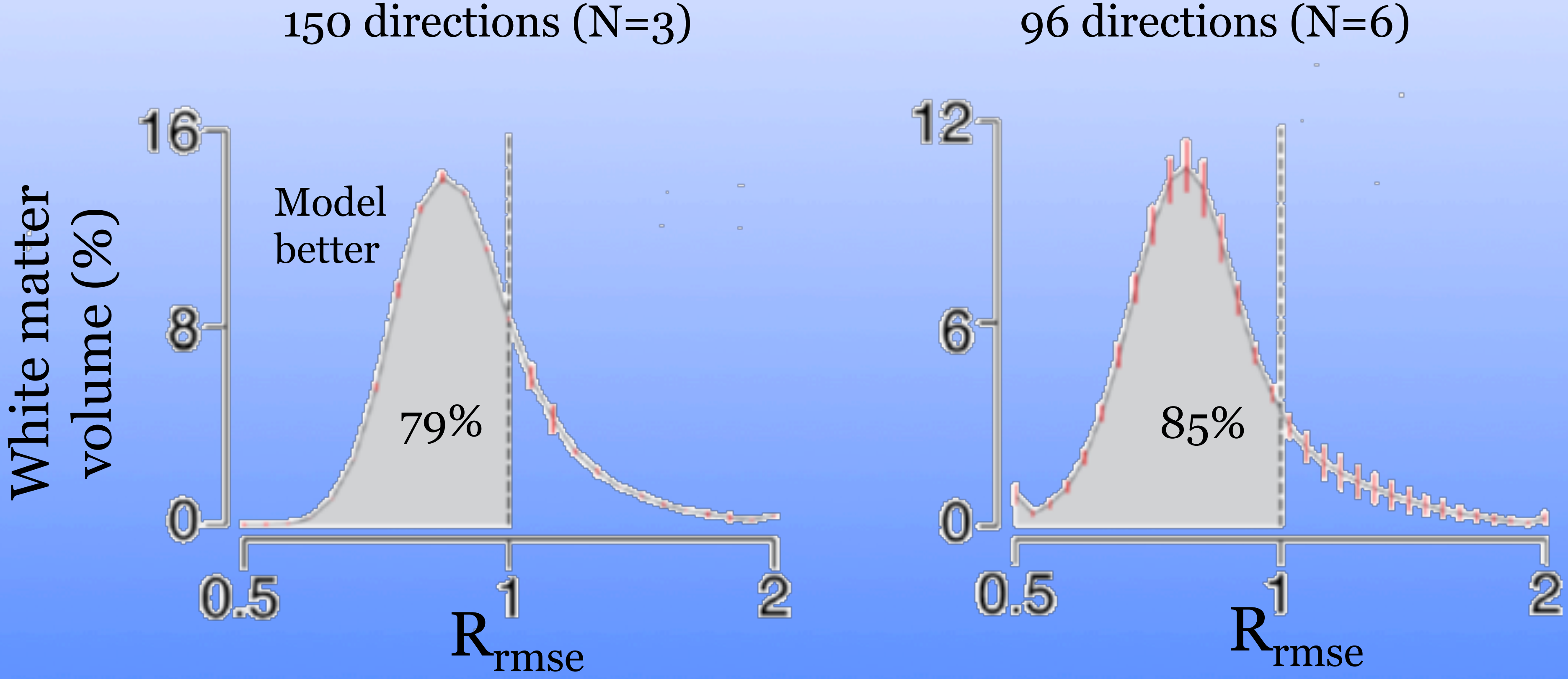


Optimized connectome



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

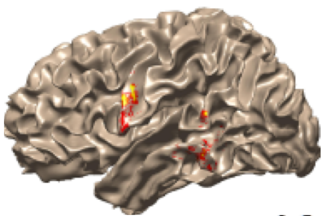
(b=2000 data shown)

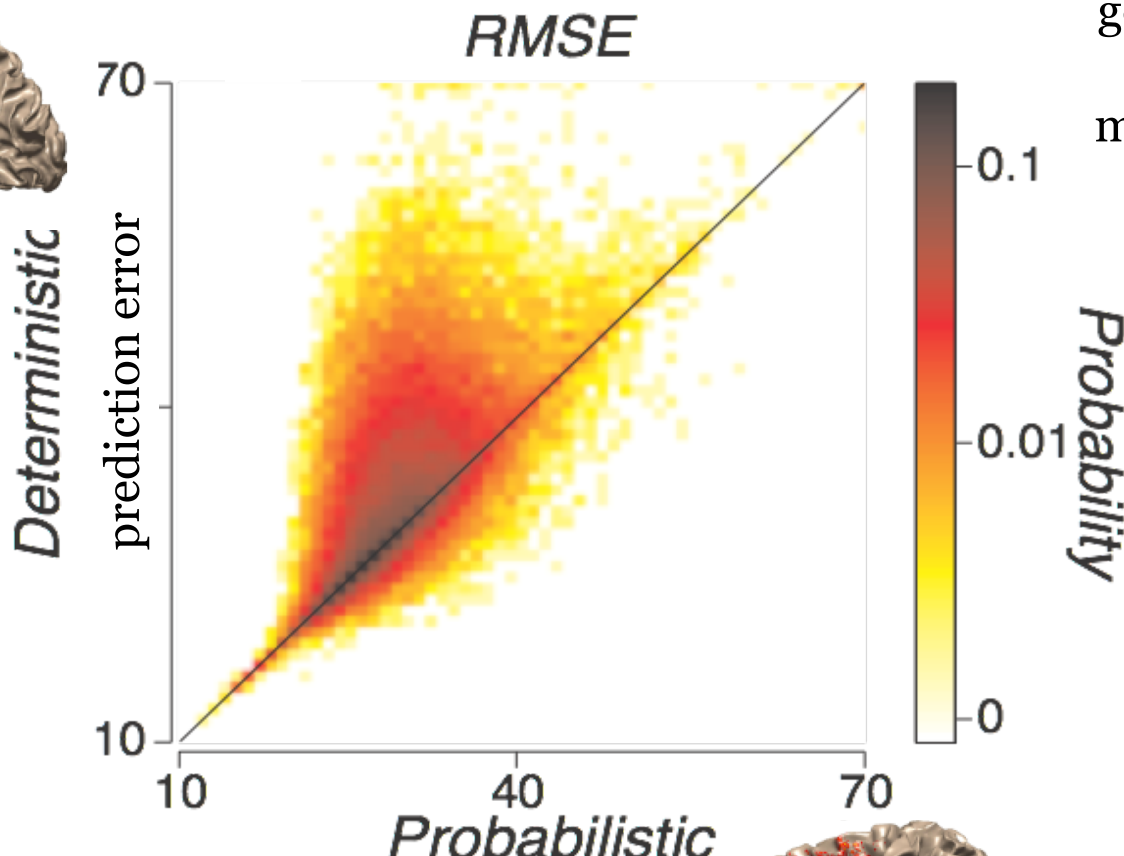


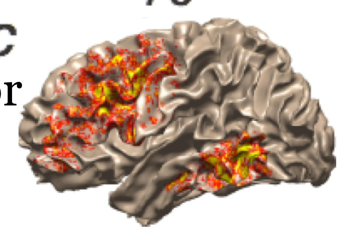
R_{rmse} = Ratio of model error to reliability error

Statistical inference

Which connectomes is supported by the data?





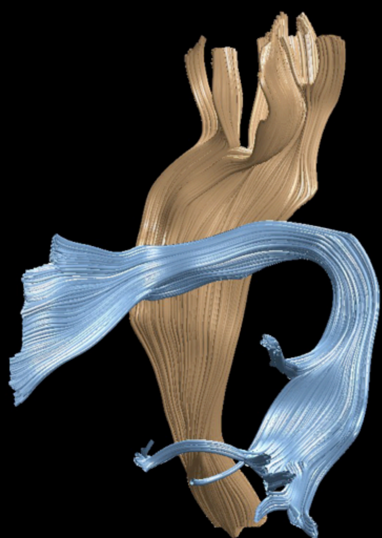


To date, we generally find that probabilistic models predict the data more accurately

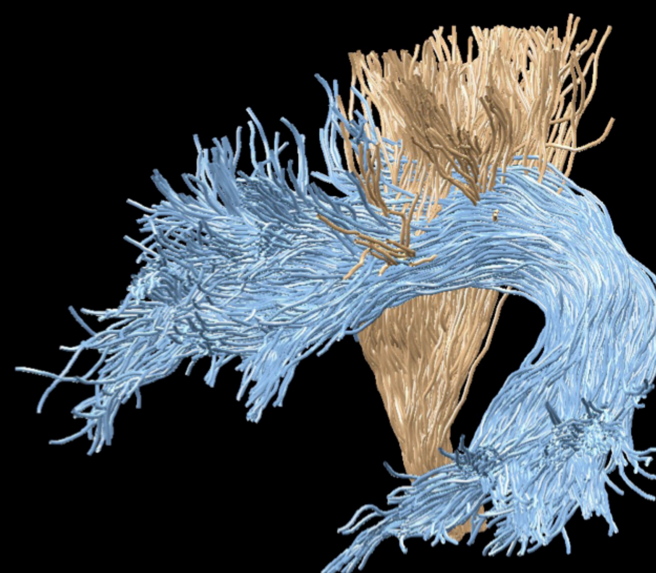
Pestilli et al., Nature Methods, 2014

Which connectomes should we study?

Deterministic



Probabilistic √



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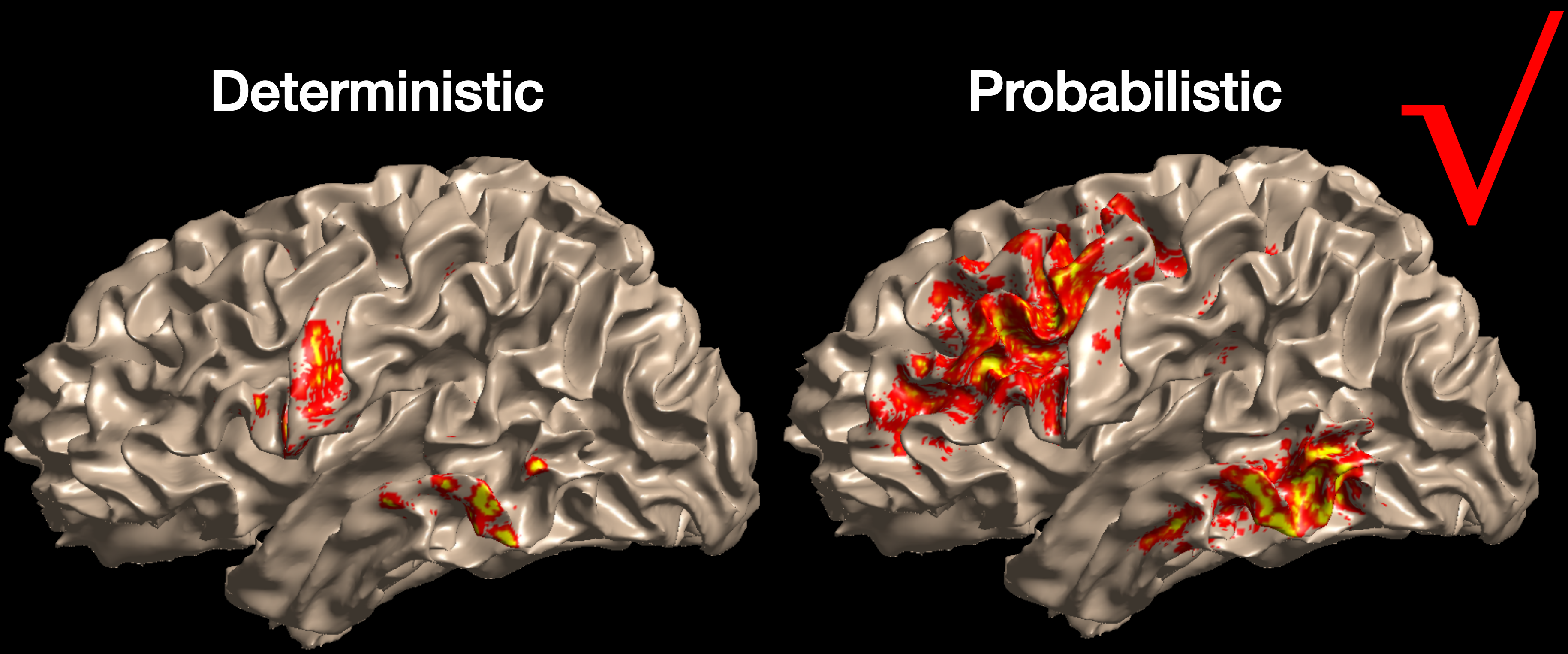


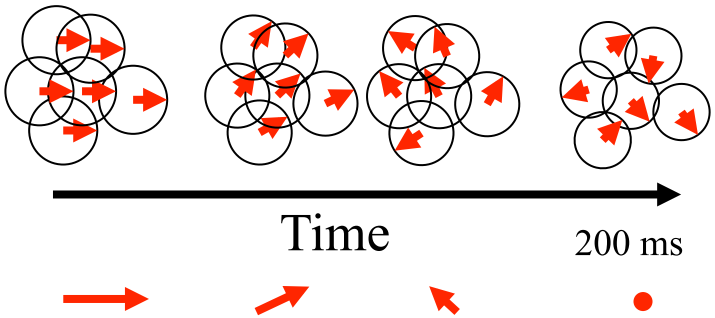
Quantitative MRI of the fascicle tissue

(Mezer et al., *Nature Medicine*, 2013)

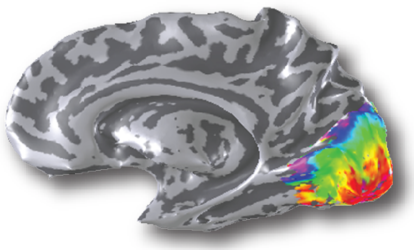
- What tissue properties change?
- T1, Macromolecular tissue volume (MTV), and Surface interaction rate (SIR)
- Single patient diagnosis

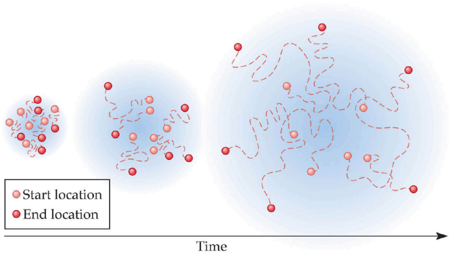
Aviv Mezer **Jason Yeatman**

There are multiple types of MR mechanisms

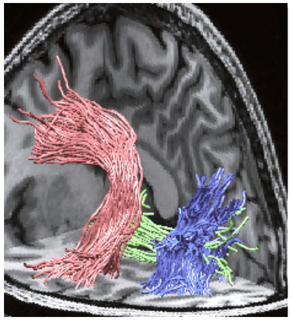


The spins dephase
(T2*)

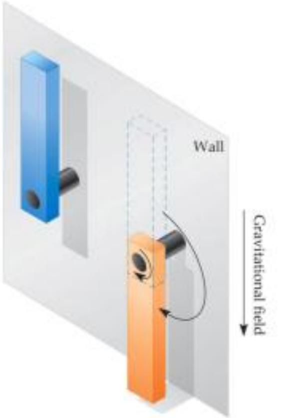




The spins move
(diffusion)



High energy



Low energy

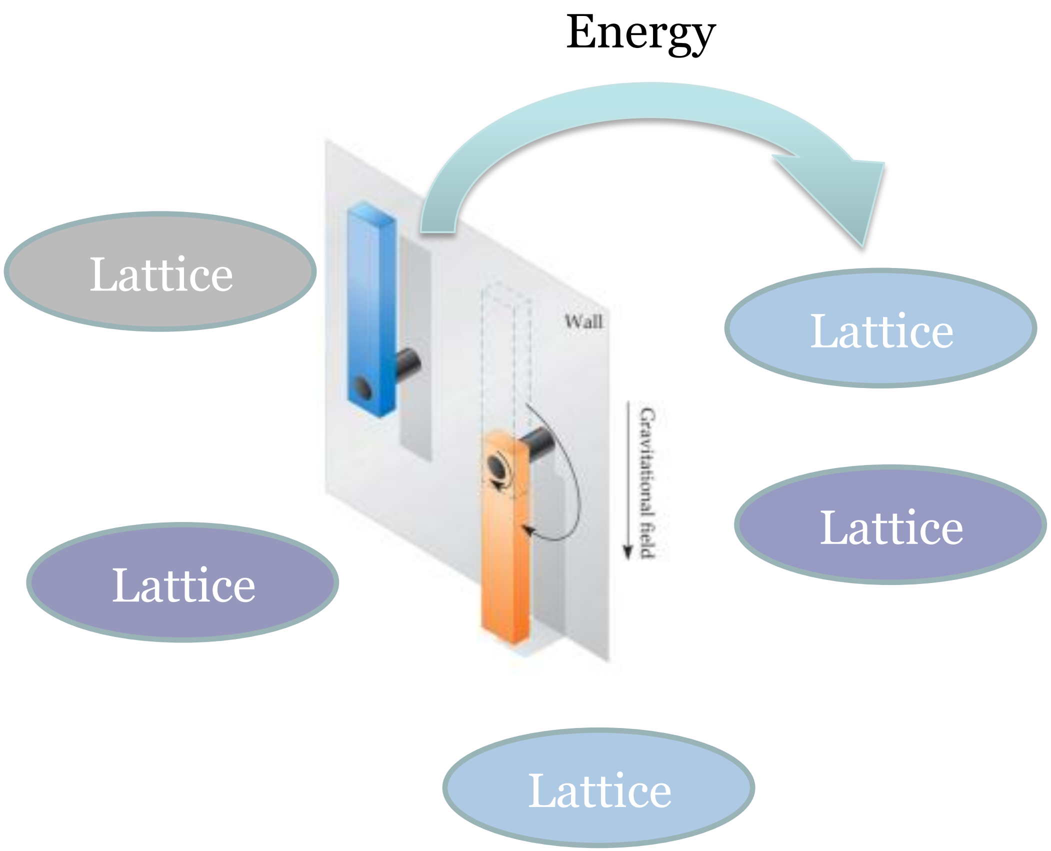
Anti-parallel spins give up energy to macromolecules (lattice) and return to lower parallel state
(T1)

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.

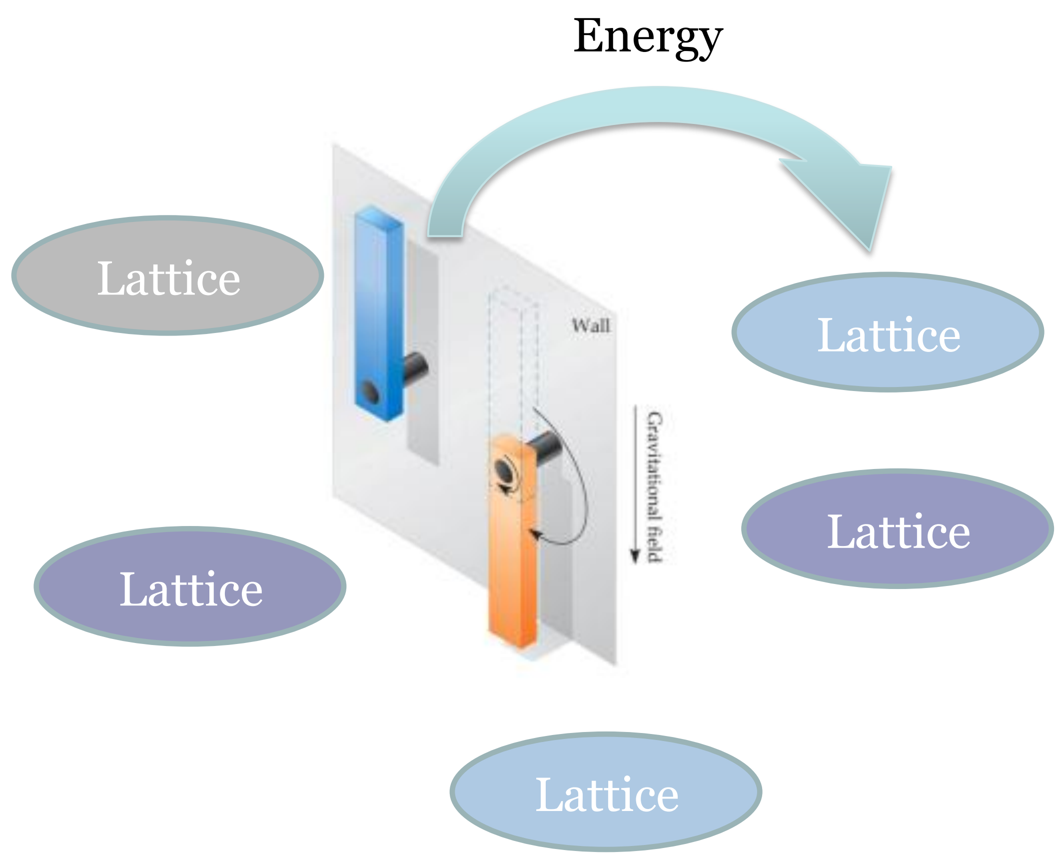


Analyzing spin-lattice exchange (T1)

Spin-lattice energy exchange rate (T1) depends on

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

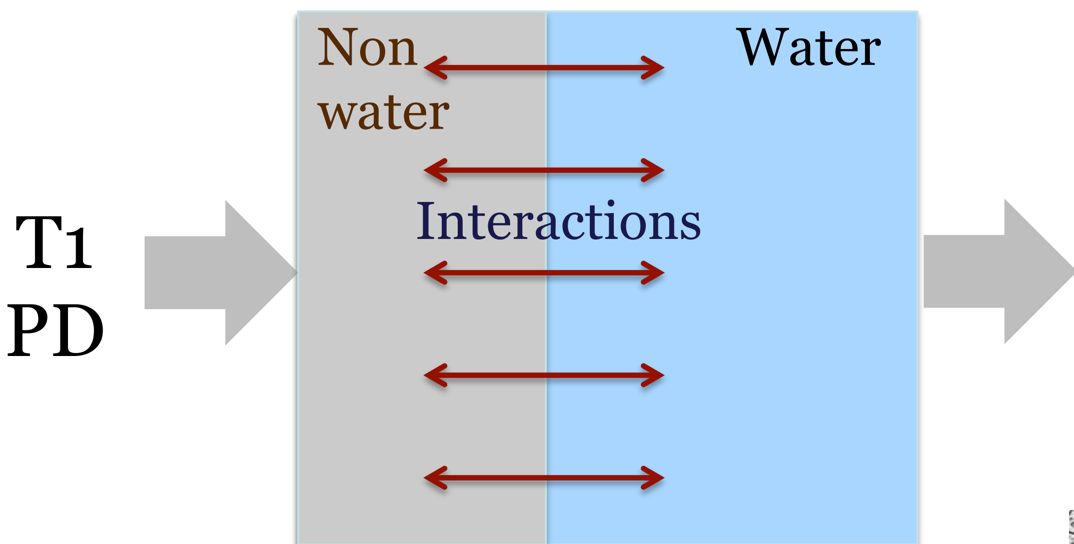
If you could measure this in the brain, these are pretty good things to know (noninvasively)



Modeling and calibration of the MRI signal yields quantitative measures of tissue

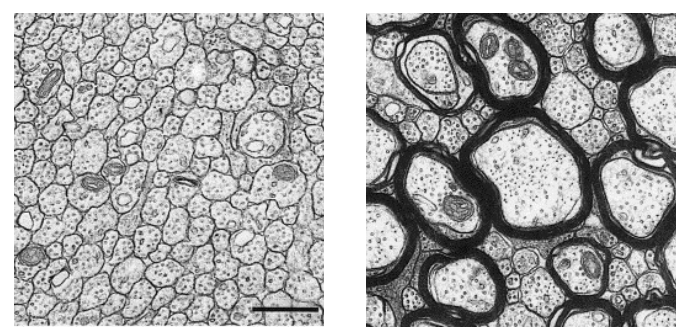
Mezer et al., Nature Medicine (2013)

Quantitative
biophysical modeling



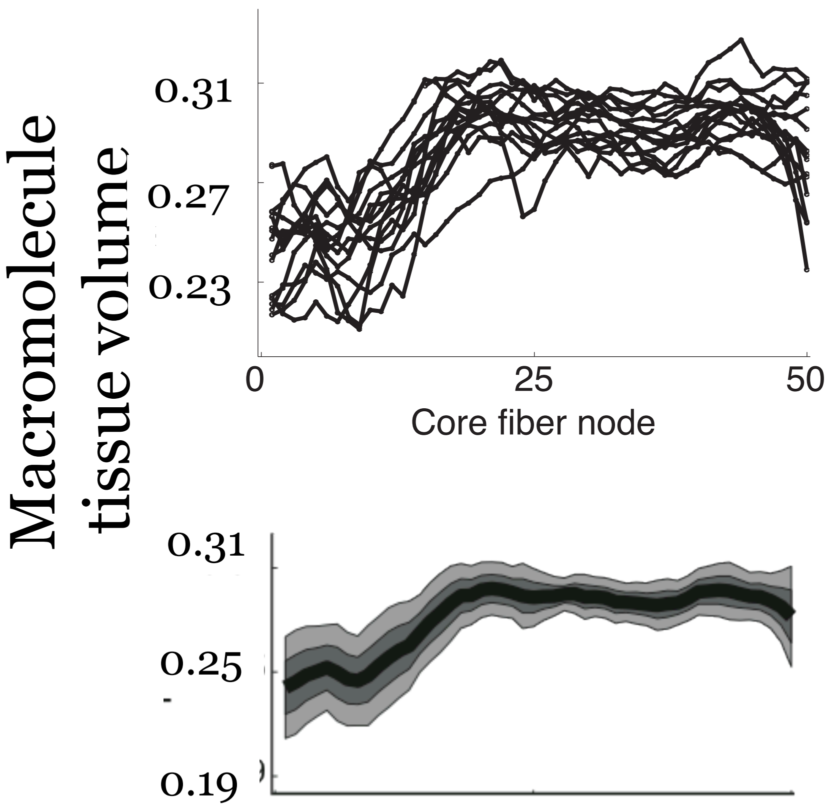
Macromolecule tissue volume (MTV)

Surface interaction ratio (SIR)

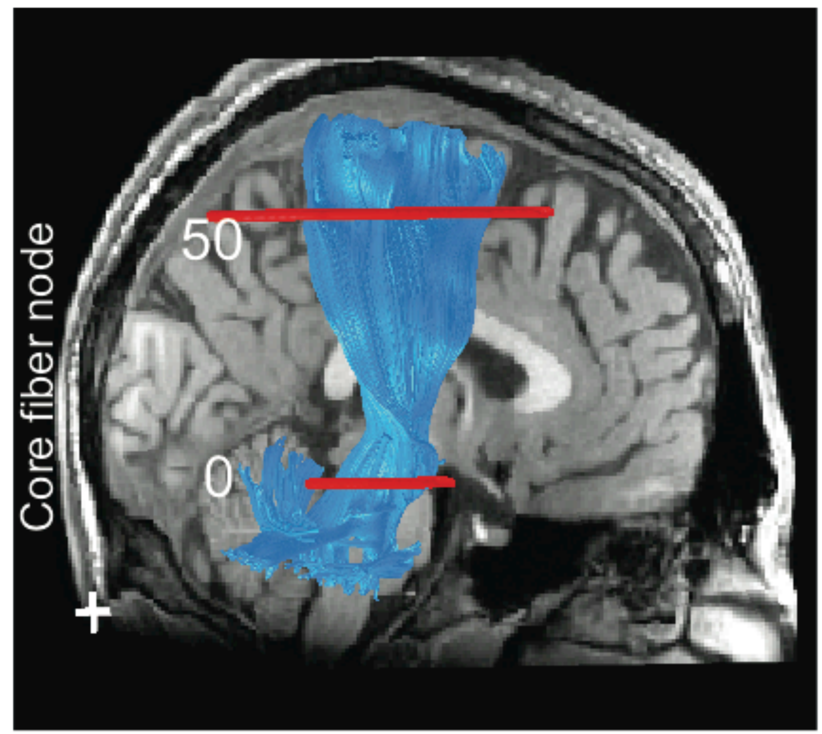


Single subject measures and multiple sclerosis

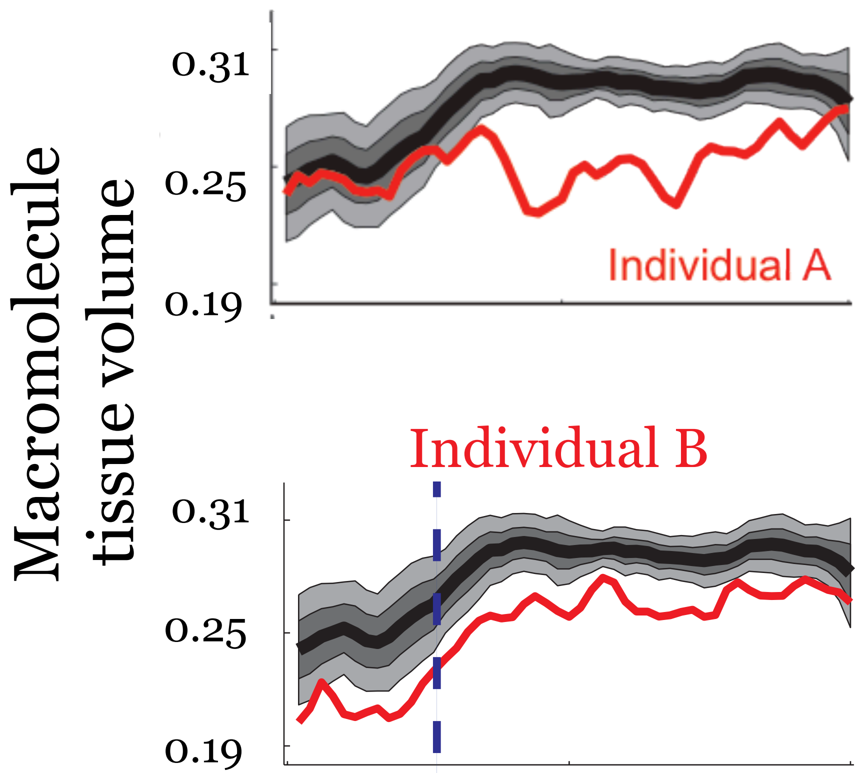
Control distribution



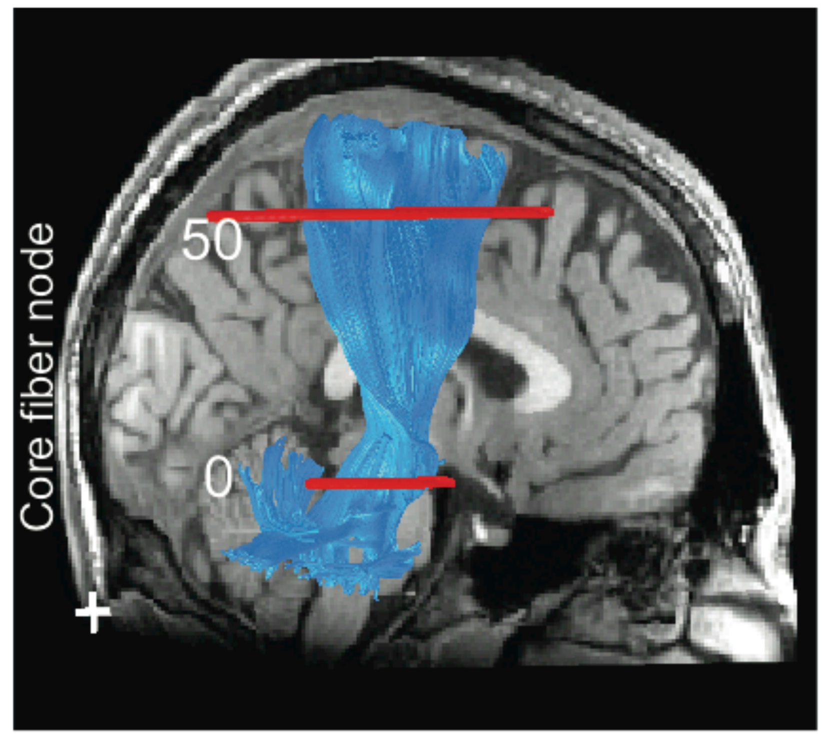
Cortical spinal track



Single subject measures (MS)



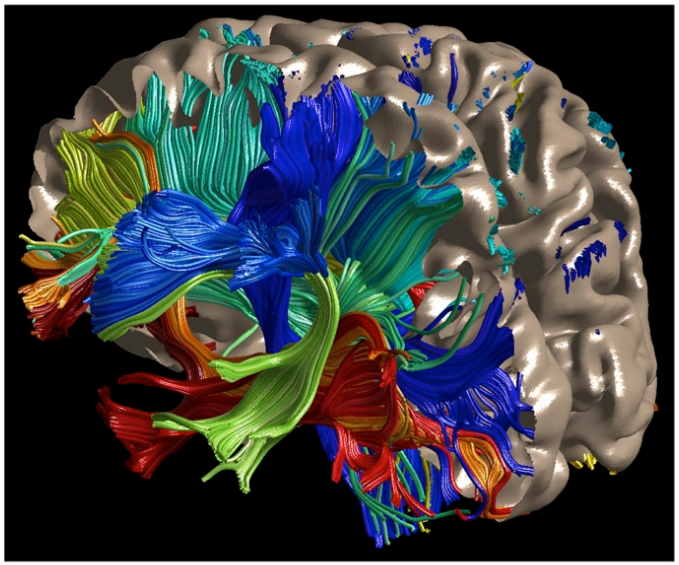
Cortical spinal track



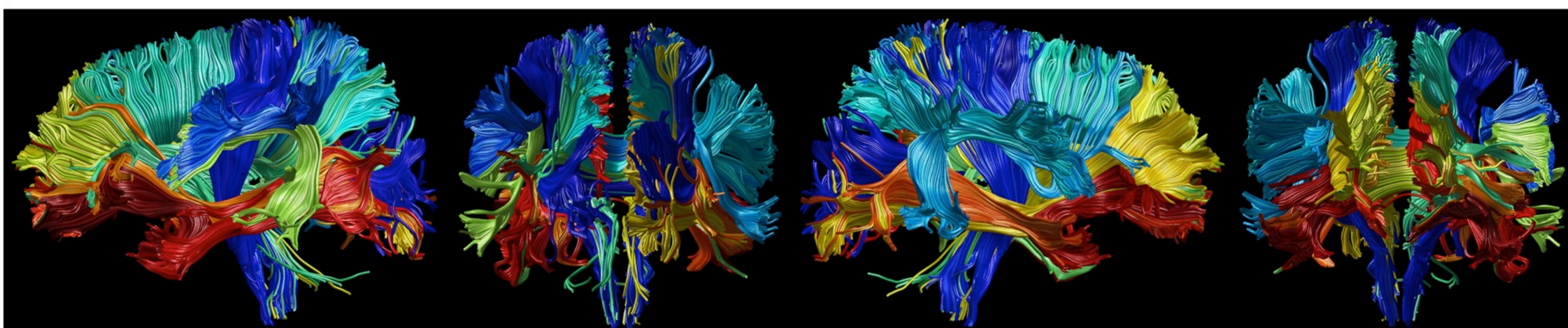
Tissue development from 7-85 years

(Yeatman, Wandell, Mezer, 2014, *Nature Communications*)

(N=120), Technology development



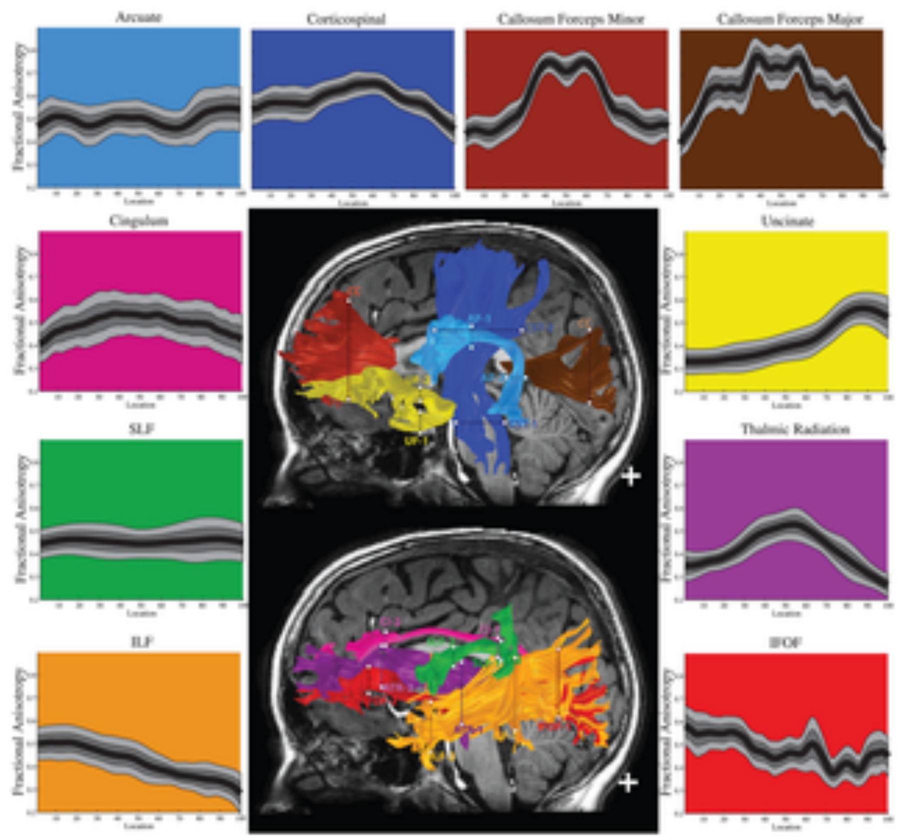
Right Uncinate	Left Uncinate
Left Cingulum Cingulate	Left ILF
Right ILF	Orbitofrontal Callosum
Right Cingulum Cingulate	Left IFOF
Right Thalamic Radiation	Right IFOF
Left Arcuate	Ant. Frontal Callosum
Left Thalamic Radiation	Temporal Callosum
Post. Parietal Callosum	Sup. Frontal Callosum
Right Arcuate	Right SLF
Left SLF	Sup. Parietal Callosum
Left Corticospinal	Right Corticospinal
Motor Callosum	Occipital Callosum



Conclusions

- Diffusion-weighted imaging, tractography, AFQ, and LiFE identify the major tracts in individual subjects

- These methods provide means of testing hypotheses about fascicles and their tissue properties on datasets from individual subjects



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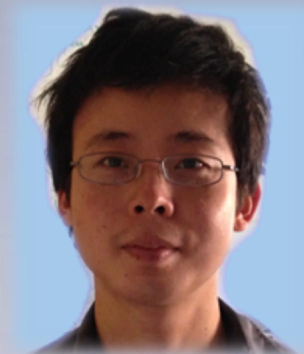

Jason Yeatman

Shumpei Ogawa

Aviv Mezer

Ariel Rokem