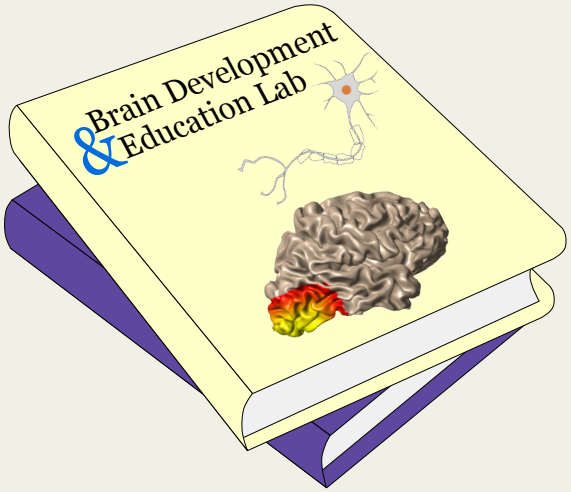
Models: From voxels, to fascicles, to brain development and cognition



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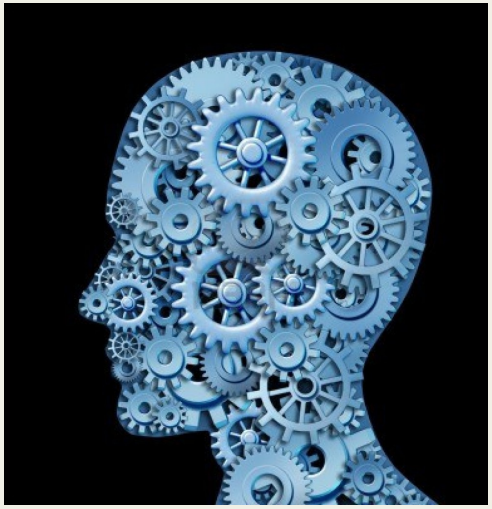
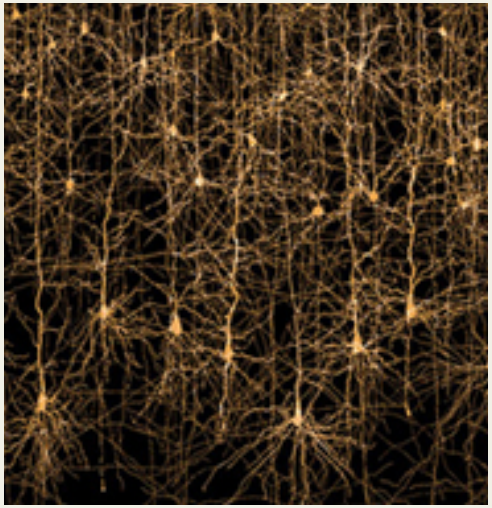
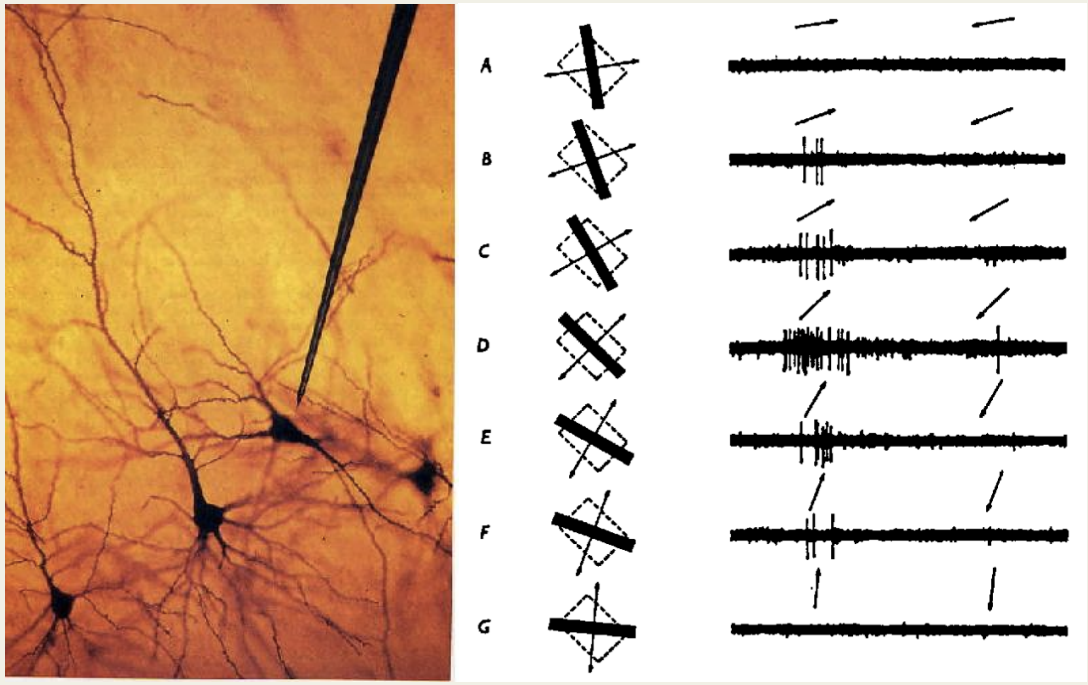
UNIVERSITY of WASHINGTON

Cognition and the neuron doctrine

Cognitive function can be attributed to localized neural activity



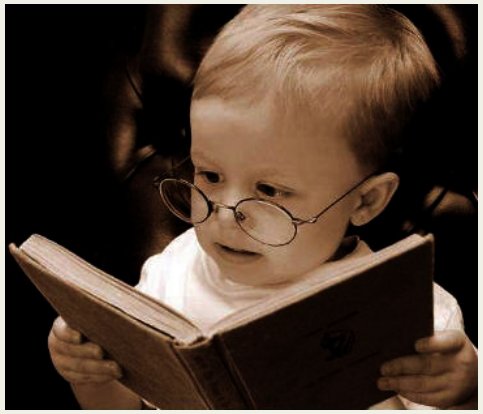


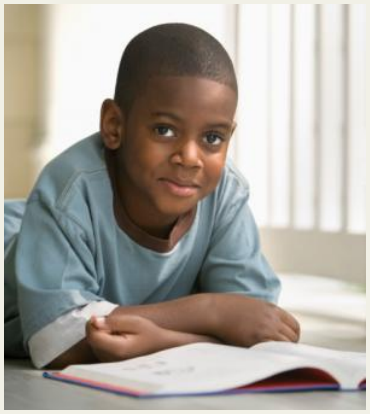


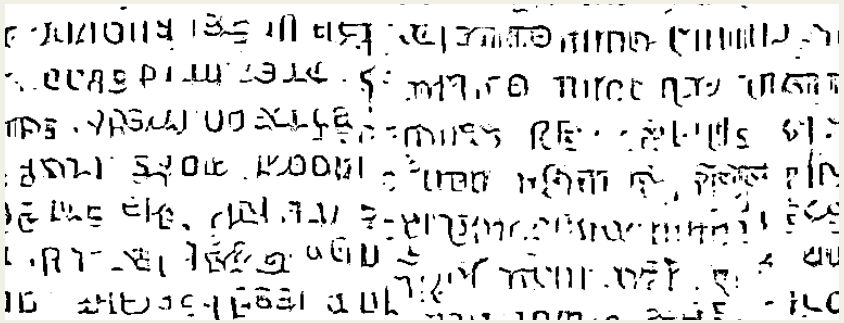
Hubel and Wiesel (1959 onward)

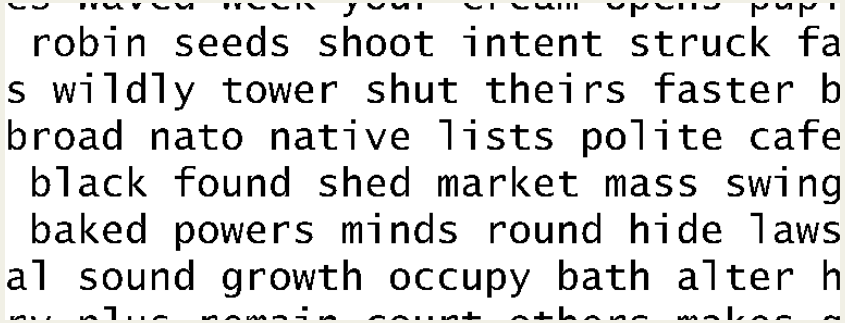
Developmental changes in behavior occur over much longer time scales

- For example ~10 years to become a skilled reader.
- Learning to read requires brain circuits to modify their structure in response to years of training **(Wandell & Yeatman, 2013).**









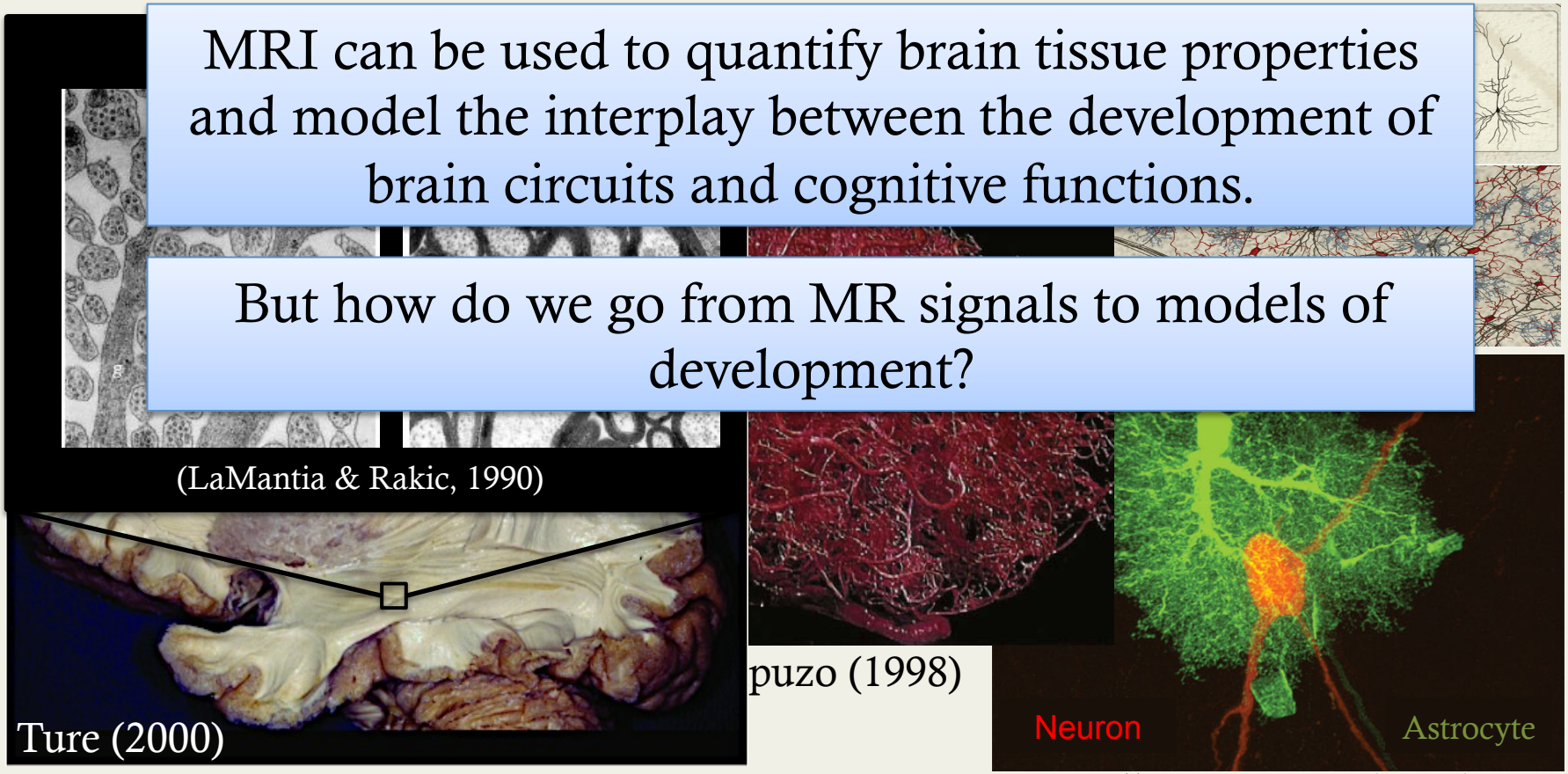
Portilla & Simoncelli, 2000

Cognitive development depends on tissue changes that occur over correspondingly long time-scales

- Understanding development requires measurements that are sensitive to changes in glia, axons, myelin and vasculature.

MRI can be used to quantify brain tissue properties and model the interplay between the development of brain circuits and cognitive functions.

But how do we go from MR signals to models of development?



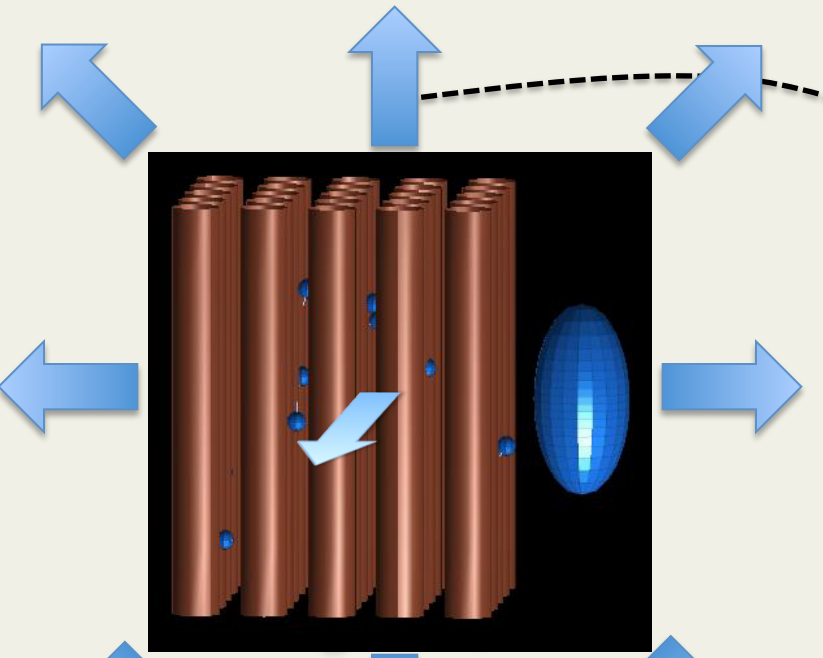
Outline

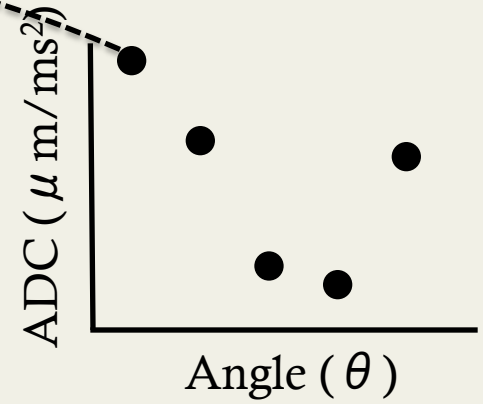
1. From diffusion to fascicles: Models of an individual's white matter.
2. Quantitative MRI measurements of tissue volume and composition.
3. Combining multiple measurements to dissociate developmental processes.
   - Testing models of development.

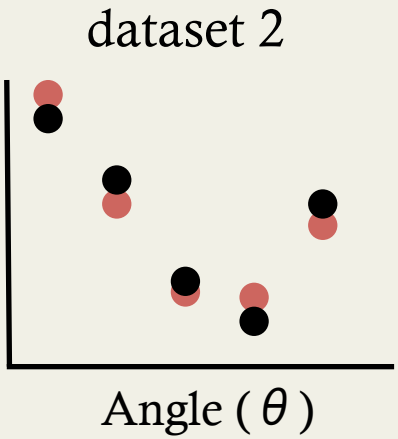
Outline

1. **From diffusion to fascicles: Segmenting an individual's white matter.**
2. Quantitative MRI measurements of tissue volume and composition.
3. Combining multiple measurements to dissociate developmental processes.
   - Testing models of development.

Building a wiring diagram with dMRI



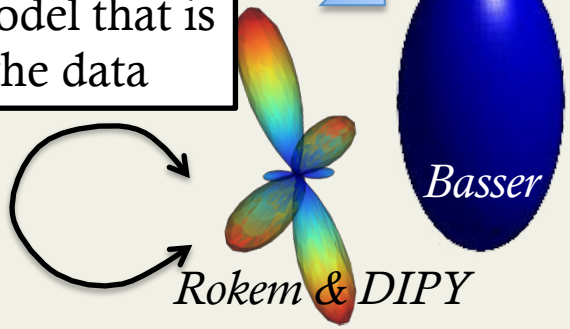




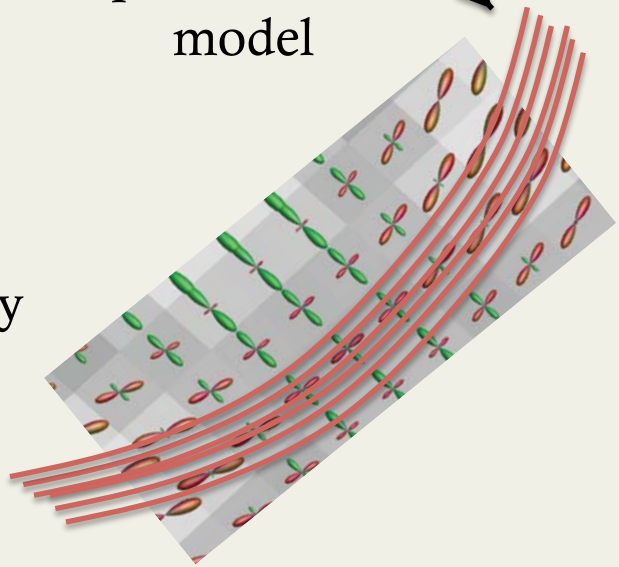
Fit diffusion model

Optimized fibers model

Choose the model that is the best fit to the data



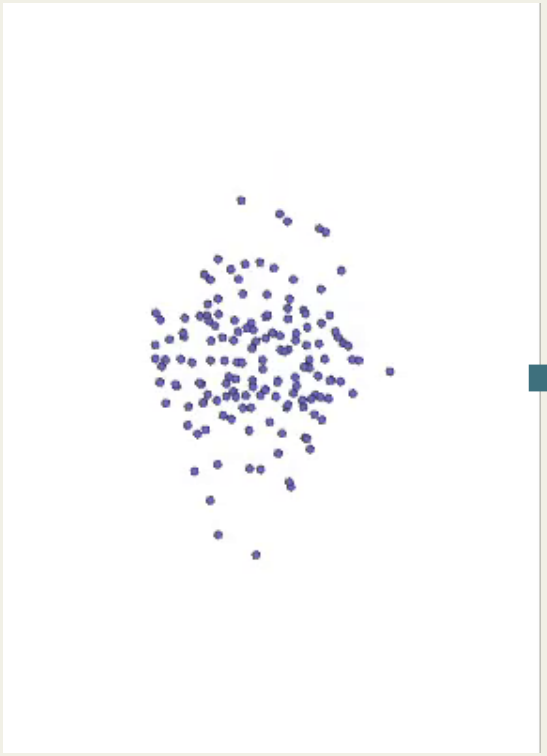
Tractography



Linear Fascicle Evaluation (LiFE) https://github.com/pestilli

Pestilli, Yeatman, Rokem, Kay & Wandell (2014), *Nature Methods*

Fitting a tensor model to diffusion measurements



$$\begin{pmatrix} \sigma_{xx} & \sigma_{xy} & \sigma_{xz} \\ \sigma_{yx} & \sigma_{yy} & \sigma_{yz} \\ \sigma_{zx} & \sigma_{zy} & \sigma_{zz} \end{pmatrix}$$

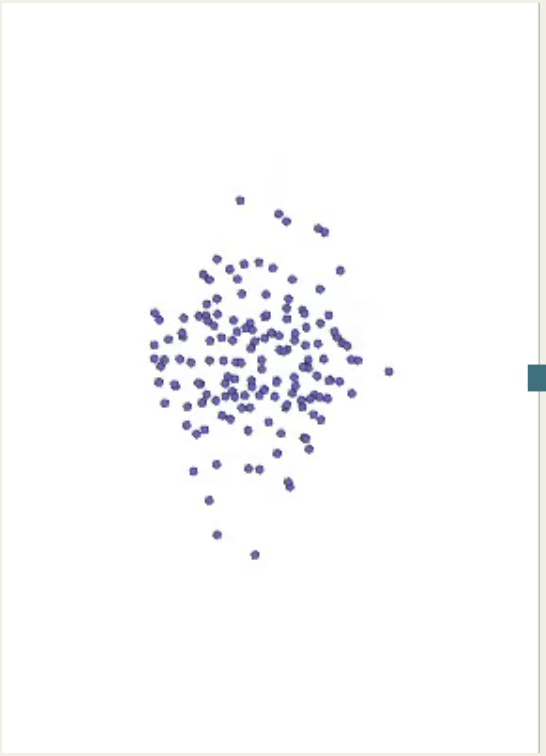
Diffusion signal measured in different directions

Diffusion tensor model: Predicts Gaussian diffusion in three dimensions

Visualization of tensor model: Ellipsoid

Rokem, Yeatman, Pestilli, Kay, Mezer, Van der Walt and Wandell, (2014), *PLoS ONE*

Fitting a tensor model to diffusion measurements

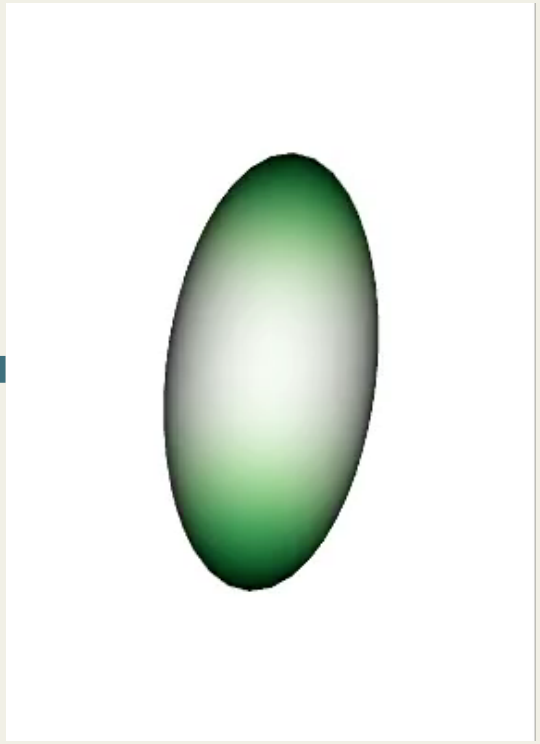


Diffusion signal measured in different directions

Predict diffusion measures from tensor model

$$\begin{pmatrix} \sigma_{xx} & \sigma_{xy} & \sigma_{xz} \\ \sigma_{yx} & \sigma_{yy} & \sigma_{yz} \\ \sigma_{zx} & \sigma_{zy} & \sigma_{zz} \end{pmatrix}$$

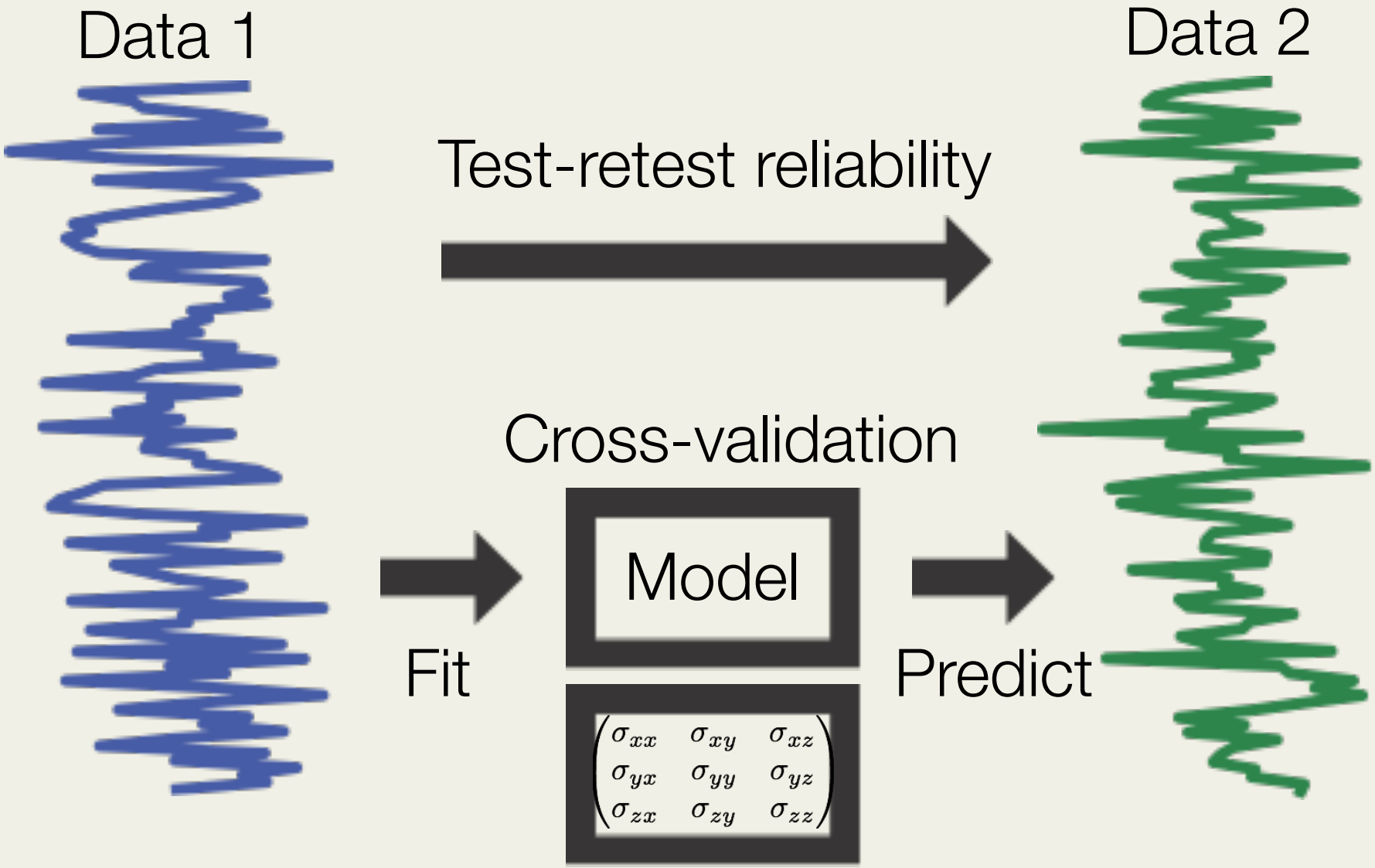
Diffusion tensor model: Predicts Gaussian diffusion in three dimensions



Visualization of tensor model: Ellipsoid

Rokem, Yeatman, Pestilli, Kay, Mezer, Van der Walt and Wandell, (2014), *PLoS ONE*

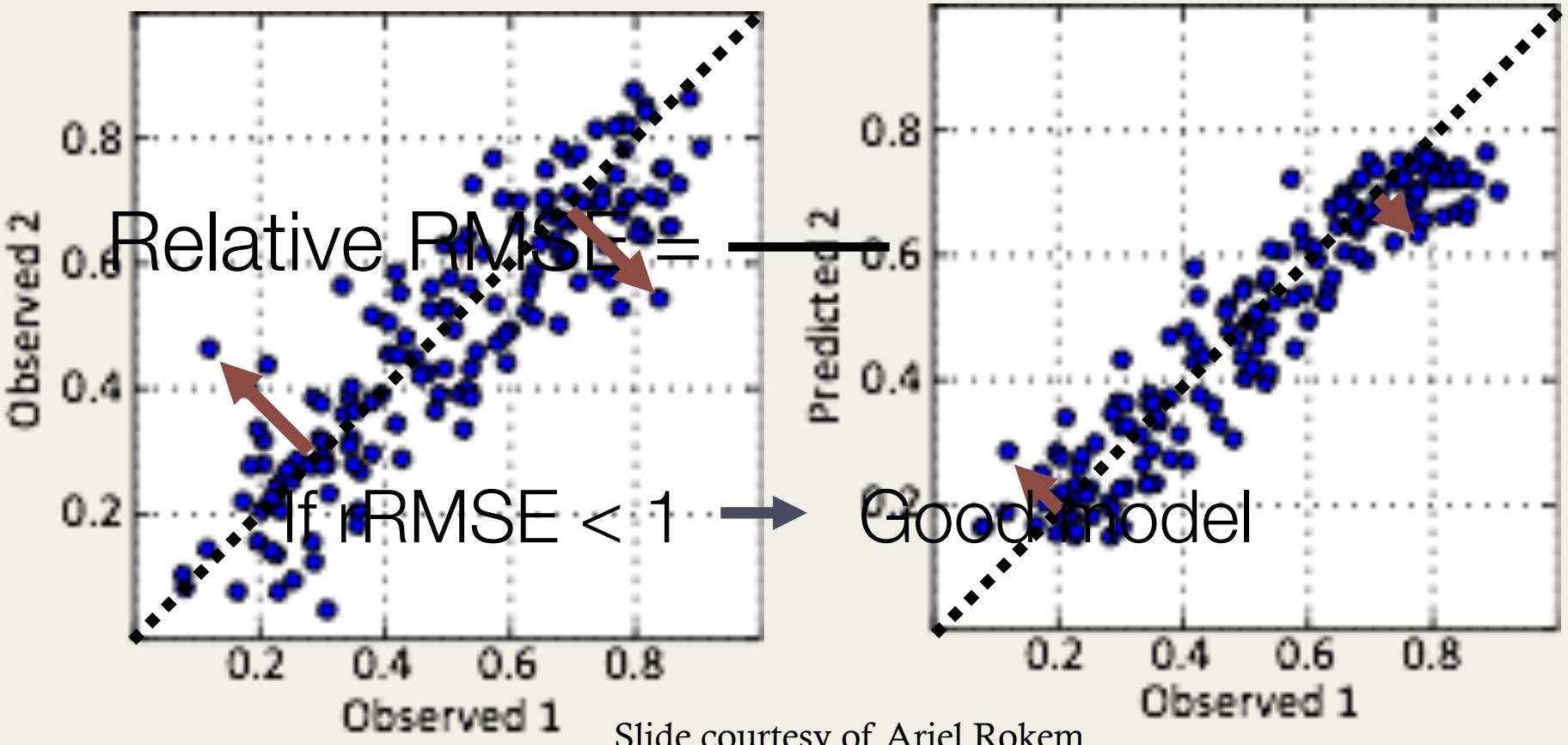
Evaluating the tensor mdoel



Evaluating tensor model with cross validation

Data => data

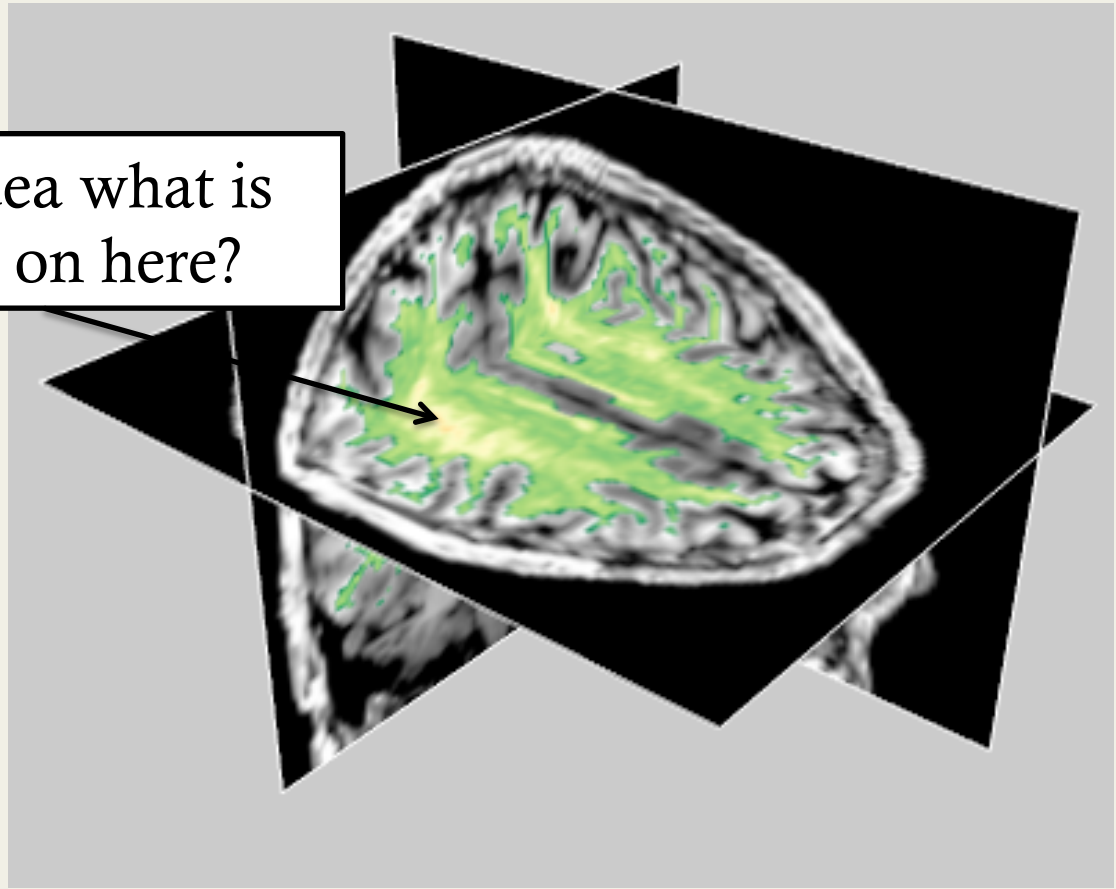
Model => data



Slide courtesy of Ariel Rokem

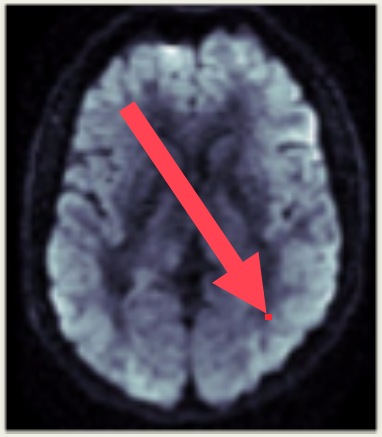
Rokem, Yeatman, Pestilli, Kay, Mezer, Van der Walt and Wandell, (2014), *PLoS ONE*

The tensor model is a good fit through much of the brain

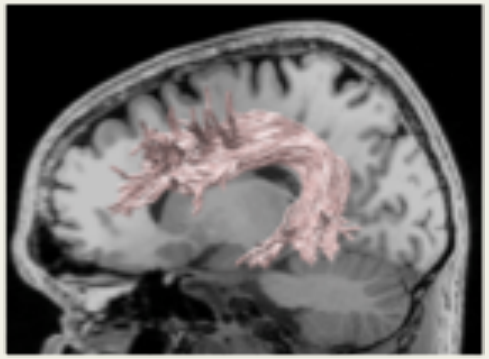


Rokem, Yeatman, Pestilli, Kay, Mezer, Van der Walt and Wandell, (2014), *PLoS ONE*
http://nipy.org/dipy/examples_built/kfold_xval.html#example-kfold-xval

Linear Fascicle Evaluation (LiFE): Validating tractography



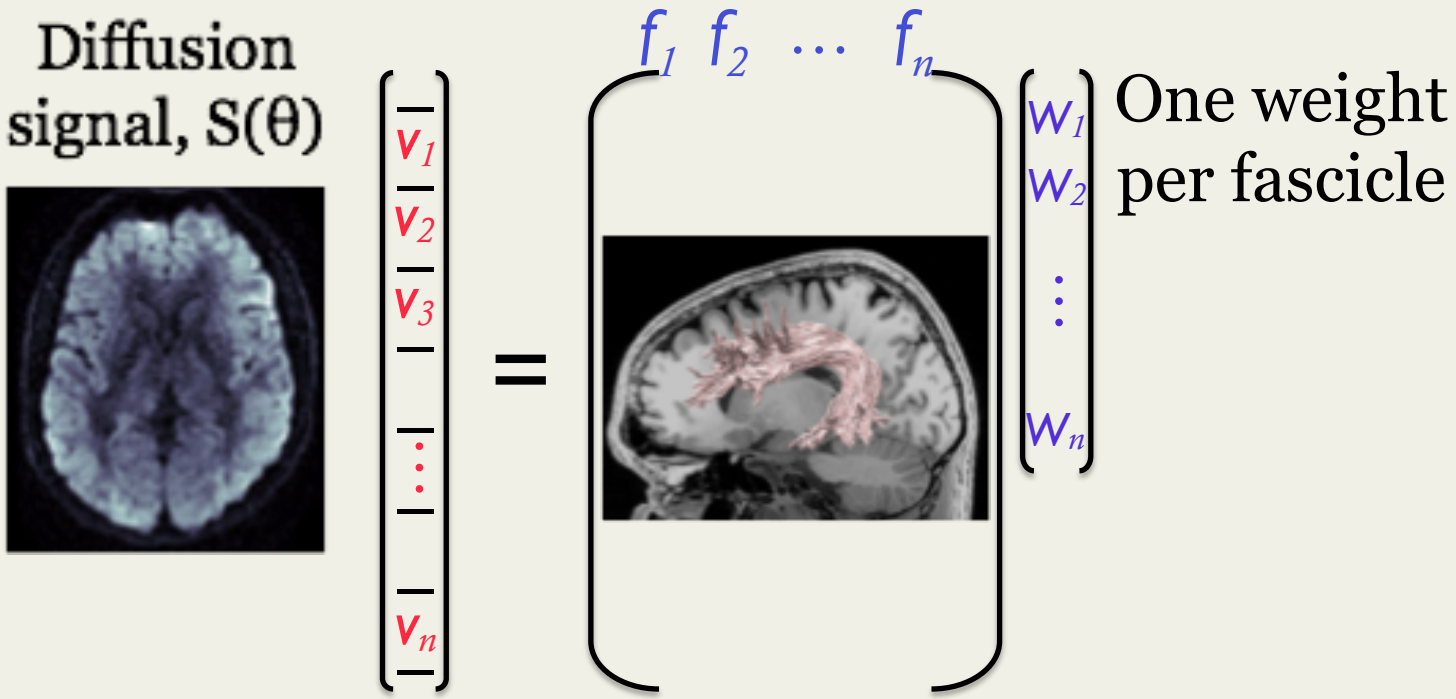
Voxel signal = Fascicle 1 + Fascicle 2 + Fascicle 3 + Fascicle 4



Slides courtesy of Franco Pestilli

Linear Fascicle Evaluation (LiFE): Validating tractography

Validation: Eliminate fascicles with zero weight

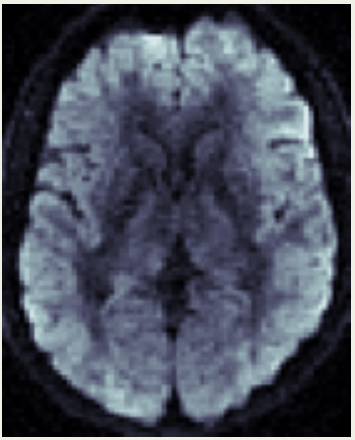


Linear Fascicle Evaluation (LiFE) https://github.com/pestilli

Pestilli, Yeatman, Rokem, Kay & Wandell (2014), *Nature Methods*

Automated fiber tract quantification: Segmenting an individual's white matter

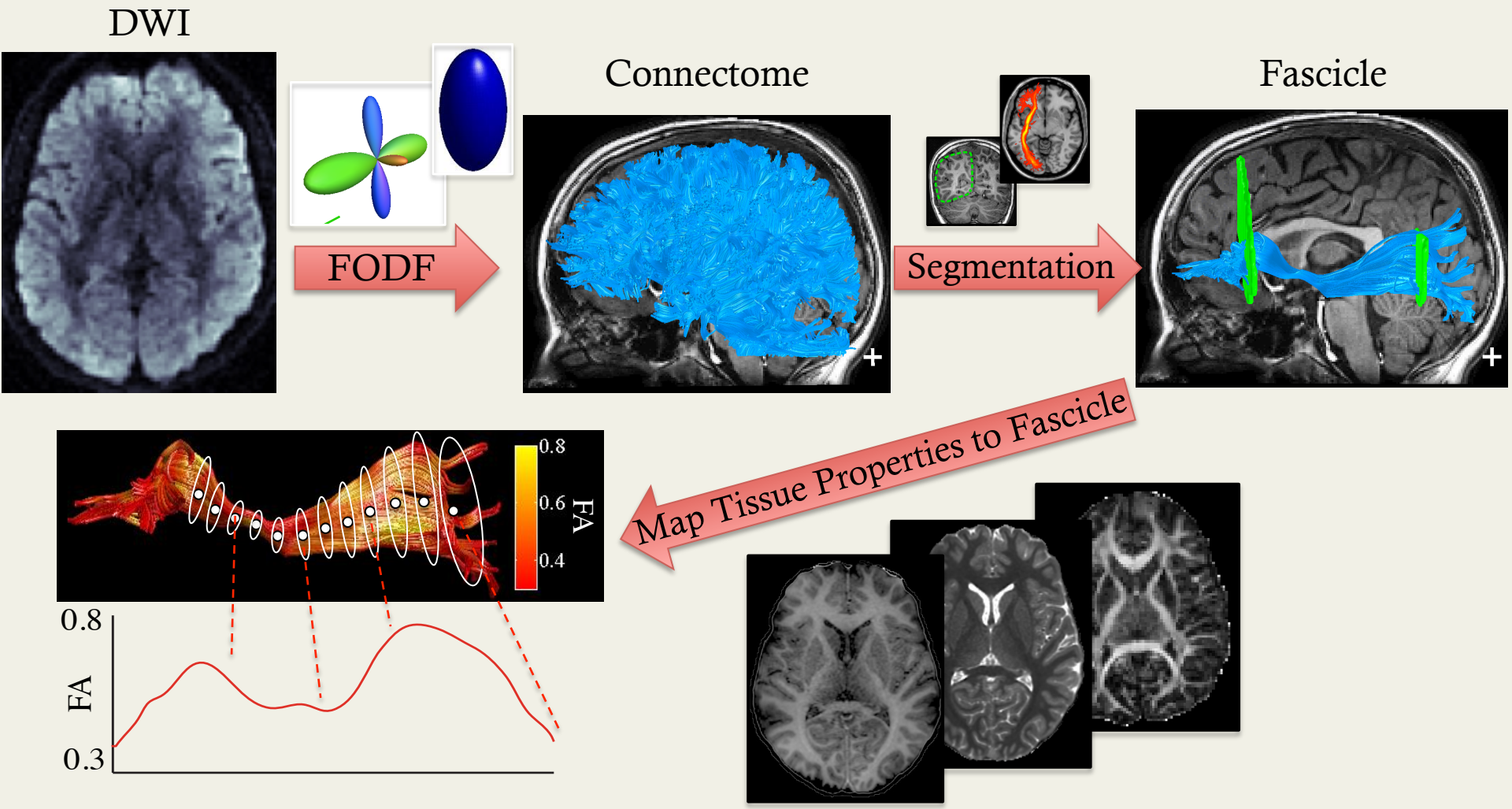
DWI



The goal of all this modeling is to generate accurate estimates of an individual's white matter connections

Yeatman et al. (*2012*), *PLoS ONE* -- Software available at: https://github.com/YeatmanLab/AFQ

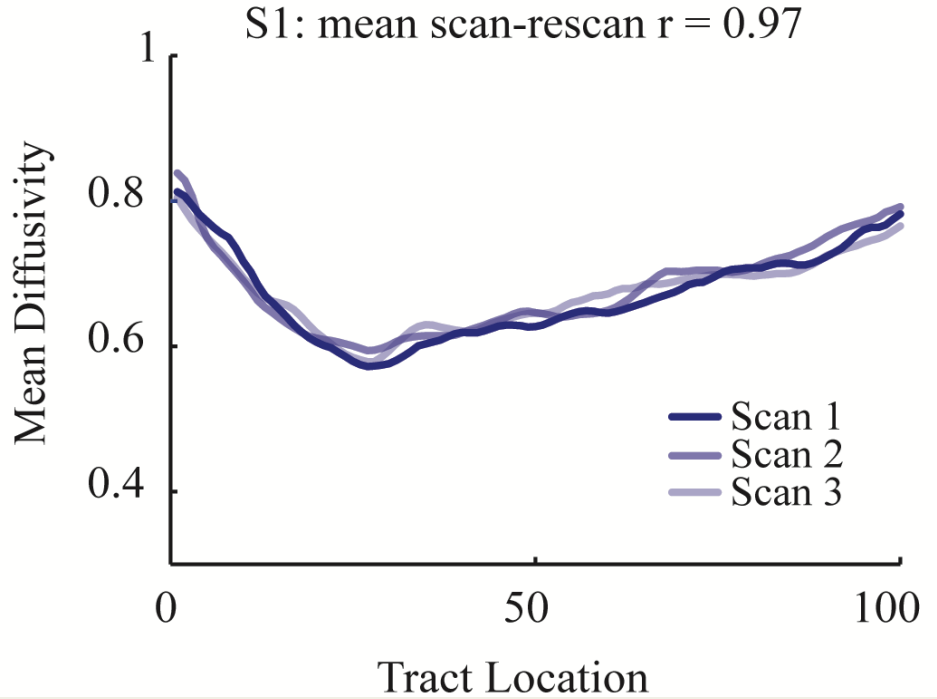
Automated fiber tract quantification: Segmenting an individual's white matter

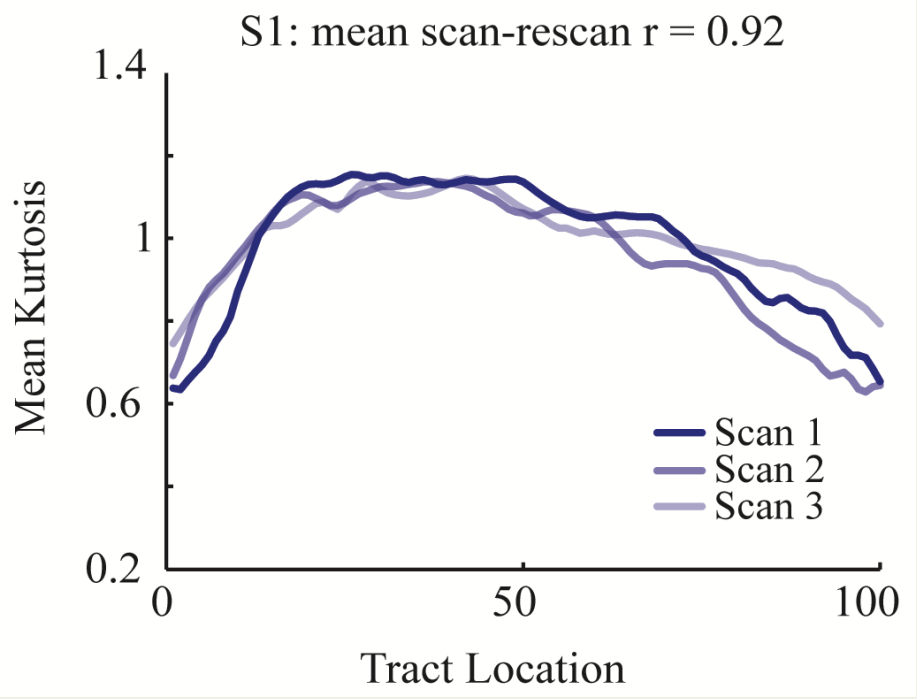


Yeatman et al. (*2012*), *PLoS ONE* -- Software available at: https://github.com/YeatmanLab/AFQ

So with all this work, how well do we do?

- Measures of white matter microstructure are **highly** reliable.





Arcuate Fasciculus – dMRI acquisition: 32 directions b=800; 64 directions b=2000

Yeatman et al. (*2012*), *PLoS ONE* -- Software available at: https://github.com/YeatmanLab/AFQ

How might we select the optimal tractography algorithm to use with AFQ?

- Consider two use cases:
  - Clinical data collected on children with traumatic brain injury versus Human Connectome Project data.
- What might be the pros and cons to using a tensor model with deterministic tractography versus spherical deconvolution with probabilistic tractography?

The choice of algorithm has a substantial impact on the results

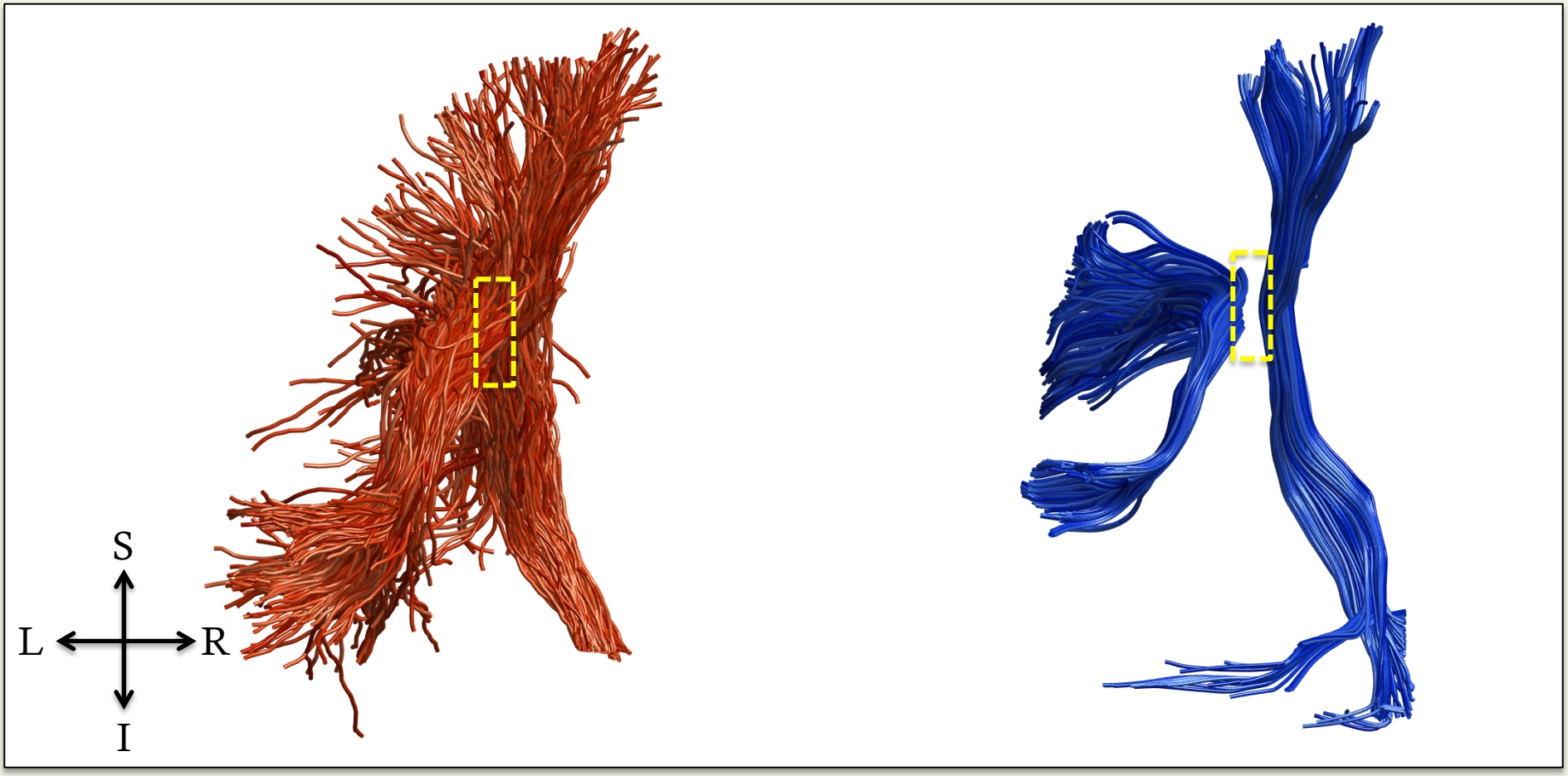
Spherical Deconvolution
Probabilistic tractography

Tensor Model
Deterministic Tractography

The choice of algorithm has a substantial impact on the results

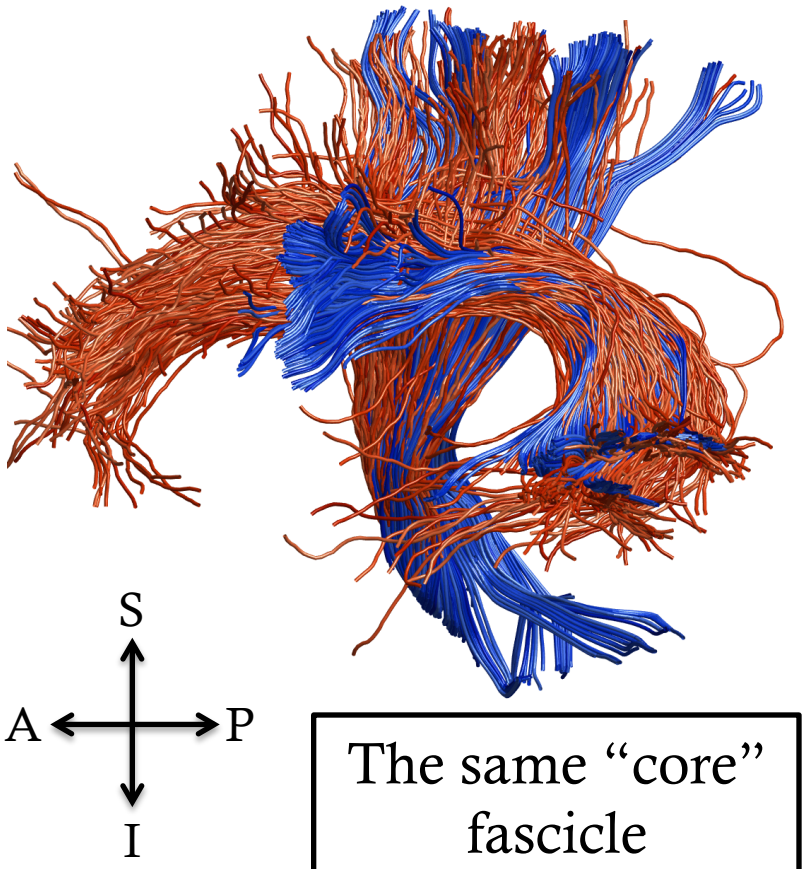
Spherical Deconvolution
Probabilistic tractography

Tensor Model
Deterministic Tractography

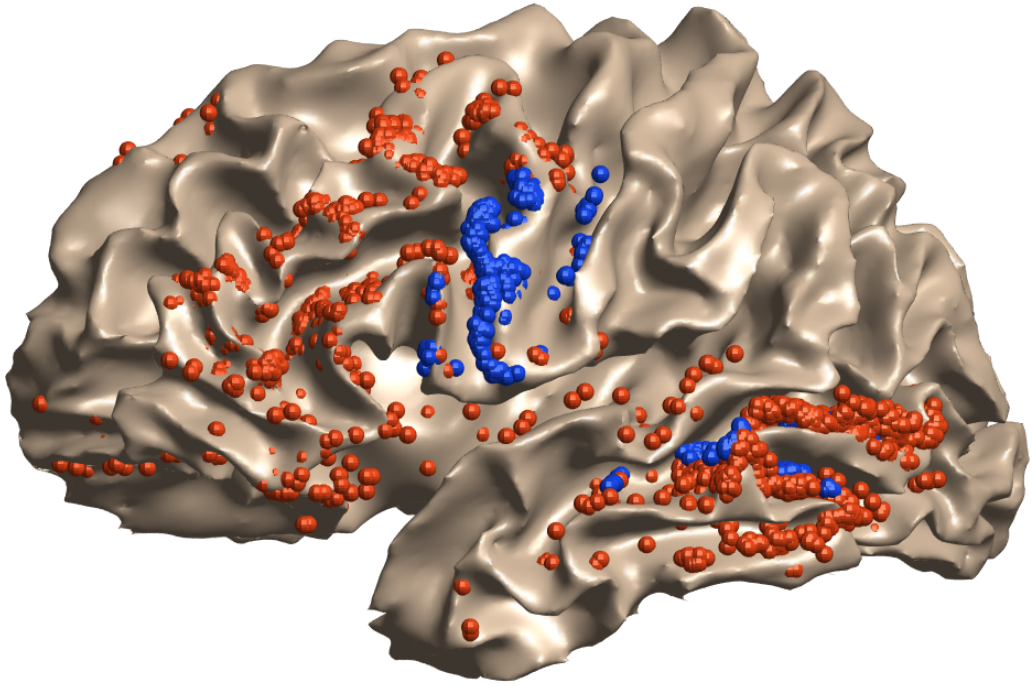


The core of the fascicle is consistent but the cortical endpoints differ

- Select the appropriate algorithm based on the goals of the study.
- Test the fit of the fascicles to the diffusion measurements.
  - Remember that tractography is a model



The same "core" fascicle



Substantially different endpoints

Summary: From diffusion to fascicles

- Based on diffusion measurements we can fit a model of the fascicles that pass through a voxel and quantify the fit of the model with cross-validation.
  - http://nipy.org/dipy/examples_built/kfold_xval.html#example-kfold-xval
- Inferences about brain connectivity depend on selecting the appropriate diffusion model and tractography algorithm for your research question.
  - Fascicles are themselves a model and we should use cross-validation to test how well they predict the data.
  - https://github.com/pestilli

Outline

1. **From diffusion to fascicles: Segmenting an individual's white matter.**
2. Quantitative MRI measurements of tissue volume and composition.
3. Combining multiple measurements to dissociate developmental processes.
   - Testing models of development.

Outline

1. From tractography to fascicles: Segmenting an individual's white matter.
2. **Quantitative MRI measurements of tissue volume and composition.**
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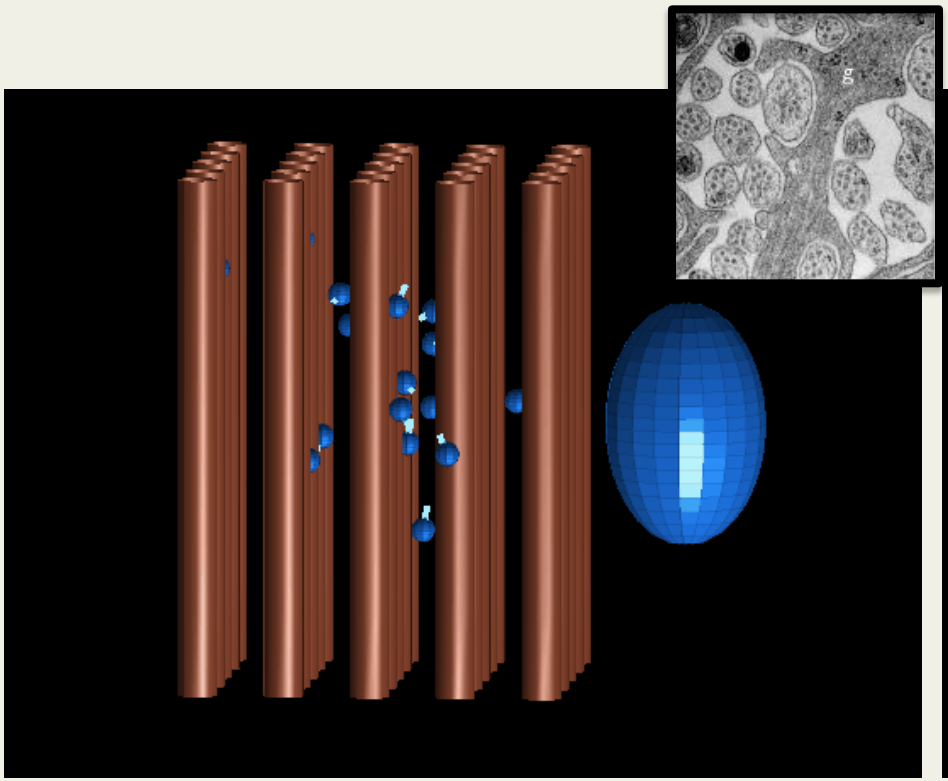
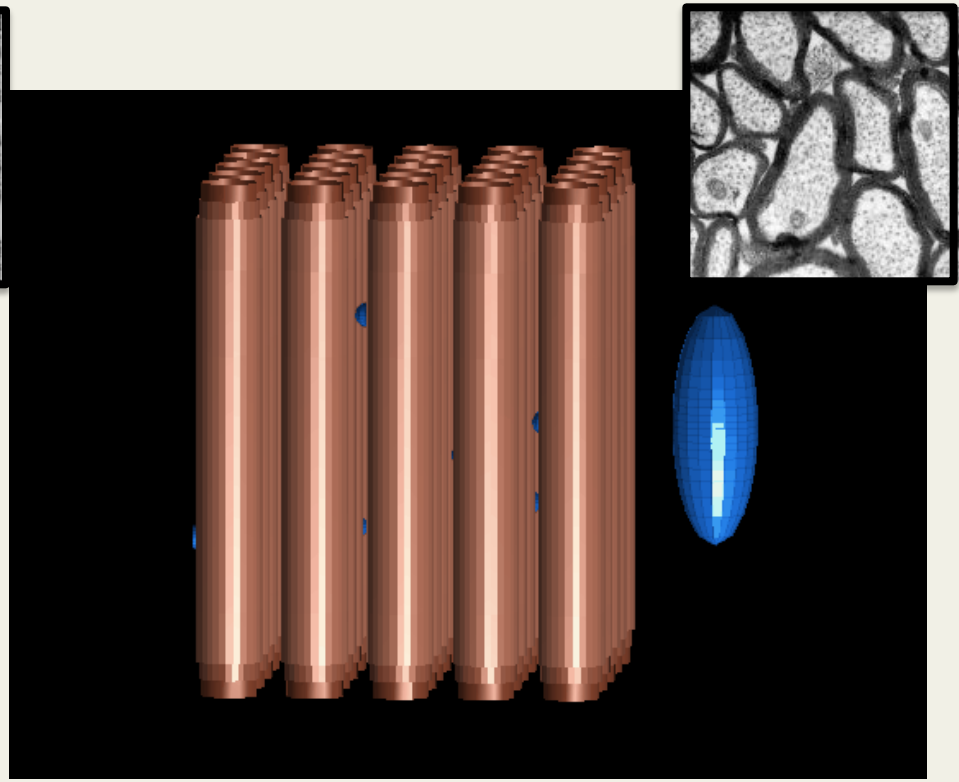
   - Testing models of development.

Inferring tissue biology from diffusion

- Diffusion is very sensitive to tissue changes and can help generate hypotheses about potential biological processes.



High Mean Diffusivity (MD)

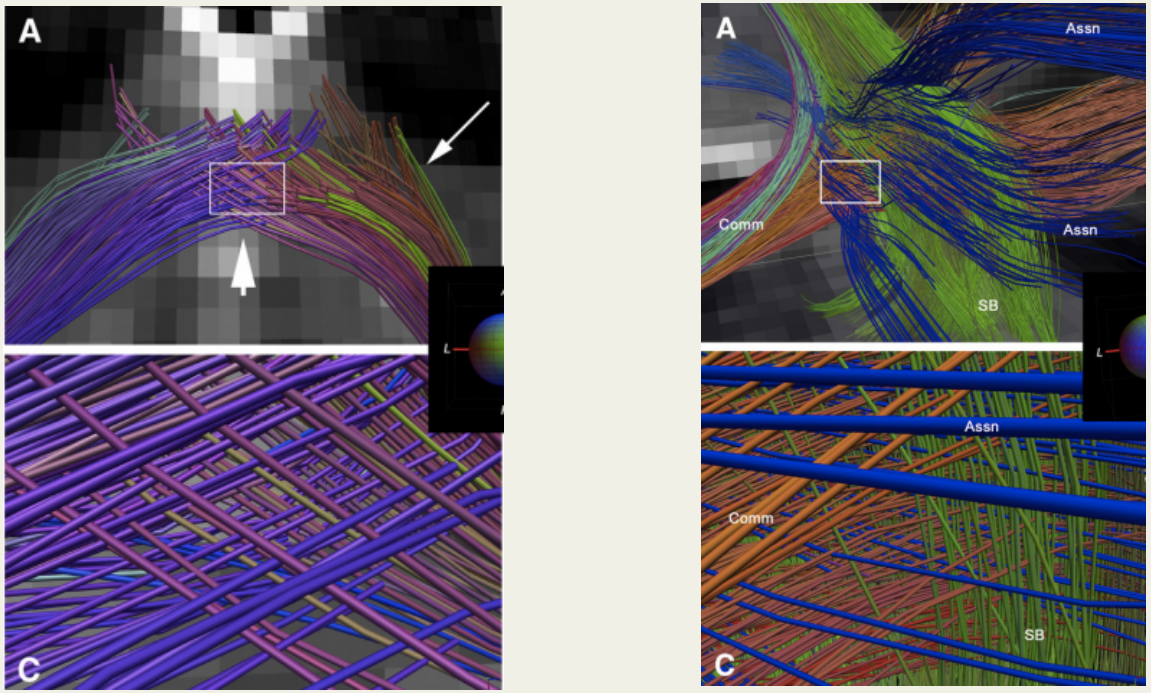


Low Mean Diffusivity (MD)

Wandell & Yeatman (2013); Stikov et al., (2011); Assaf & Pasternak (2008); Beaulieu (2002)

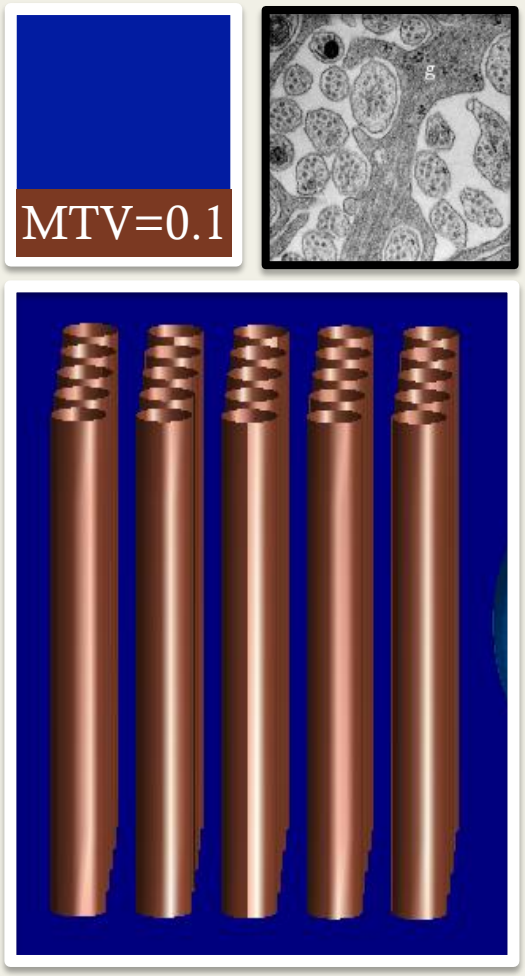
Diffusion is affected by many tissue properties

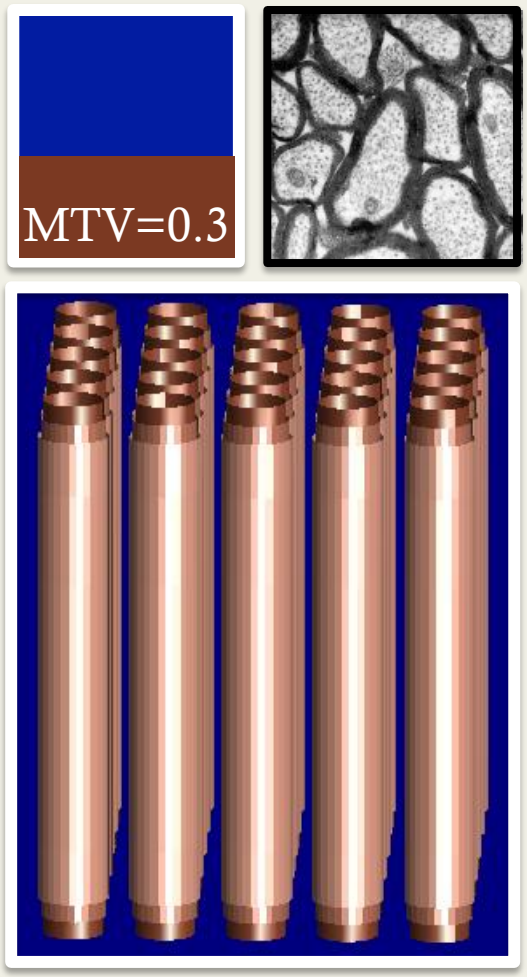
- It's amazing that water diffusion correlates with behavior (e.g., Klingberg et al., 2000).
- The relationship between water diffusion and tissue biology is not straightforward (Beaulieu, 2002; Jones, Knosche & Turner 2013).
- Additional measurements modalities will be help constrain our models.

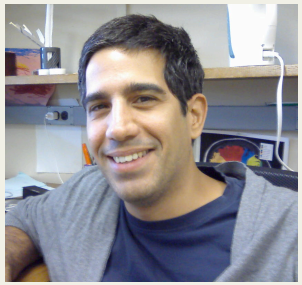


Wedeen et al., (2008, 2012)

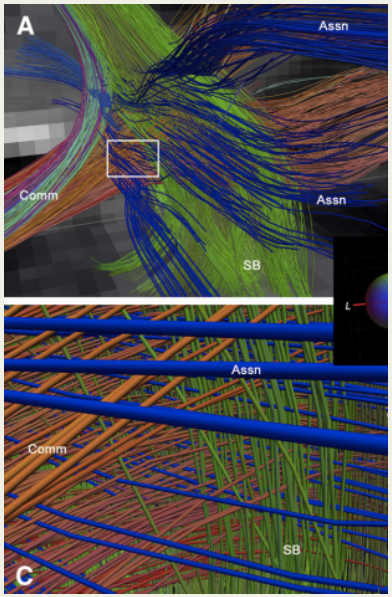
Quantitative MRI measurements of tissue volume and composition







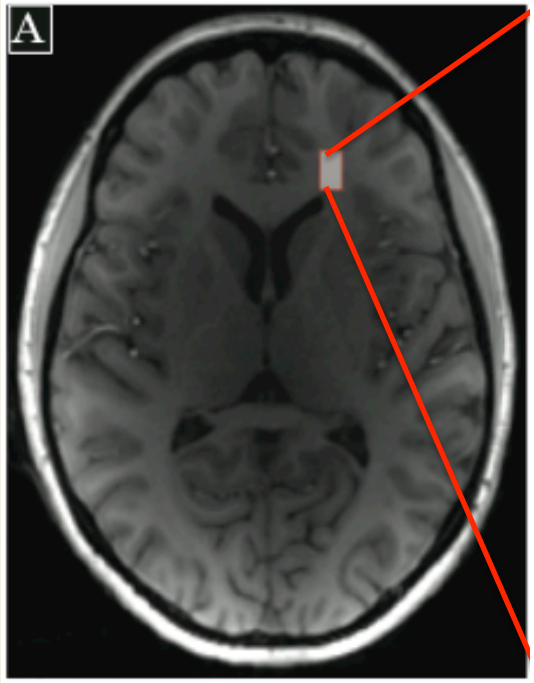
Aviv Mezer

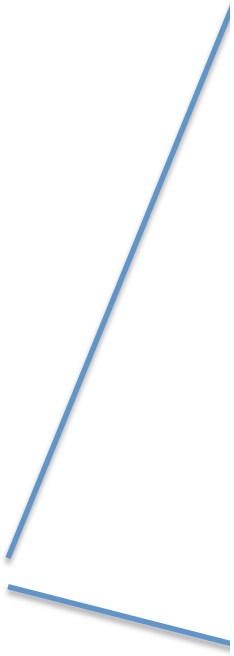


Mezer, Yeatman et al. (*2013*), *Nature Medicine*

In vivo histology with quantitative MRI

Aviv Mezer
Hebrew University

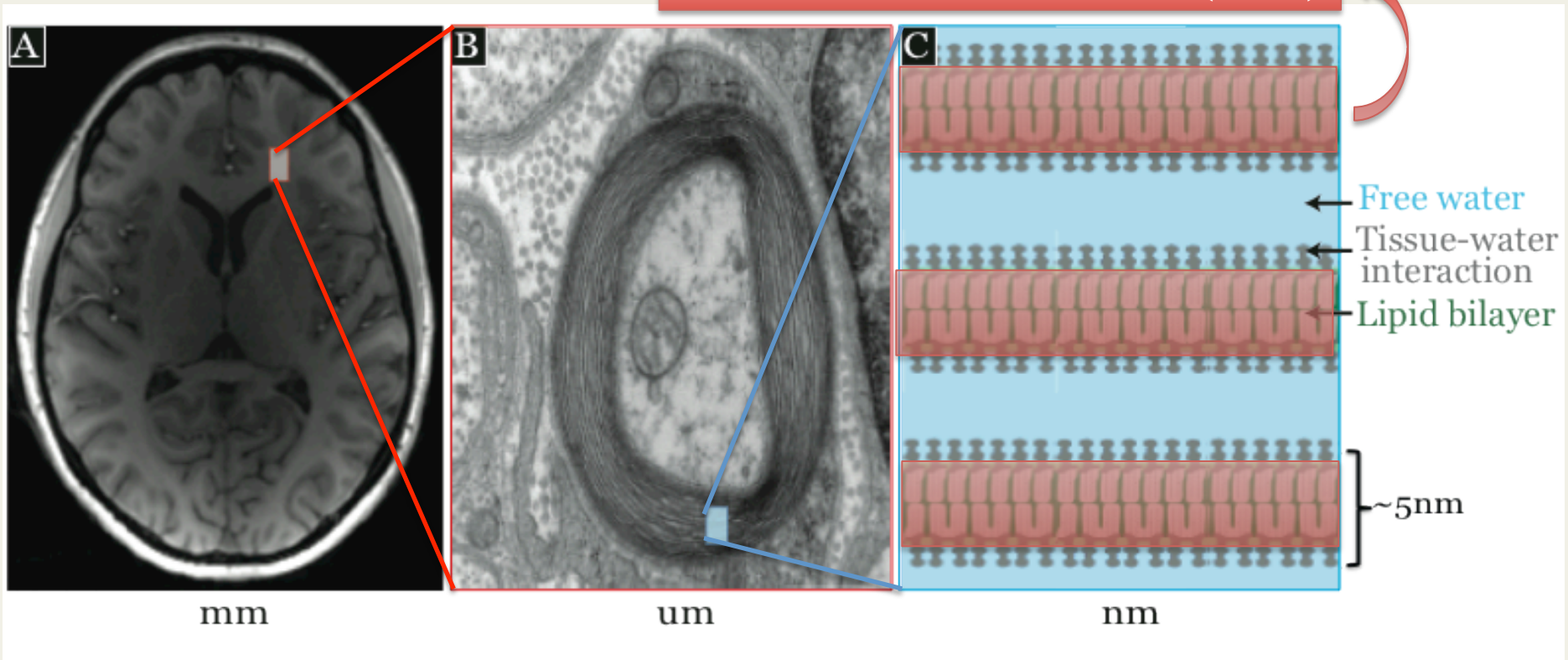




Mezer, Yeatman et al. (2013), *Nature Med*; Yeatman, Wandell & Mezer (2014) *Nature Comm*

In vivo histology with quantitative MRI

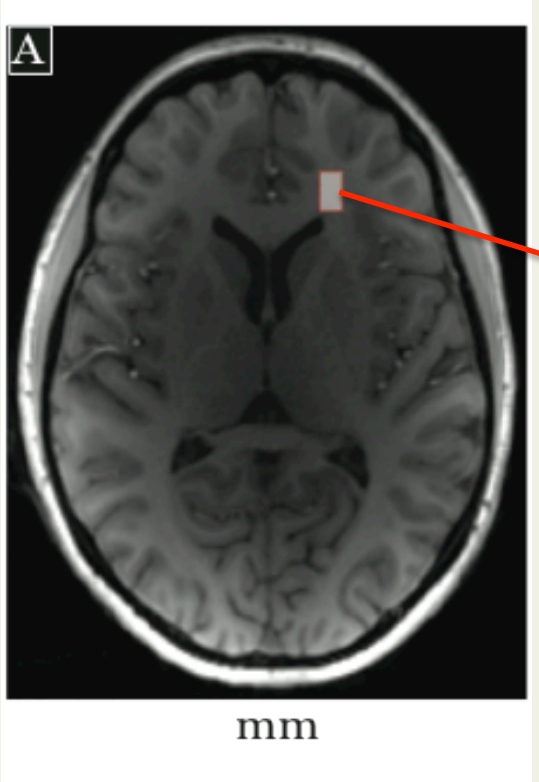
- MR signals (T1) from water protons change when the protons interact with membranes.
- T1 image intensity depends on the **amount** and **composition** of tissue in each voxel a



Mezer, Yeatman et al. (2013), *Nature Med*; Yeatman, Wandell & Mezer (2014) *Nature Comm*

In vivo histology with quantitative MRI

- MR signals (T1) from water protons change when the protons interact with membranes.
- T1 image intensity depends on the **amount** and **composition** of tissue in each voxel as well as scanner biases.



coil gain | scan parameters | tissue properties

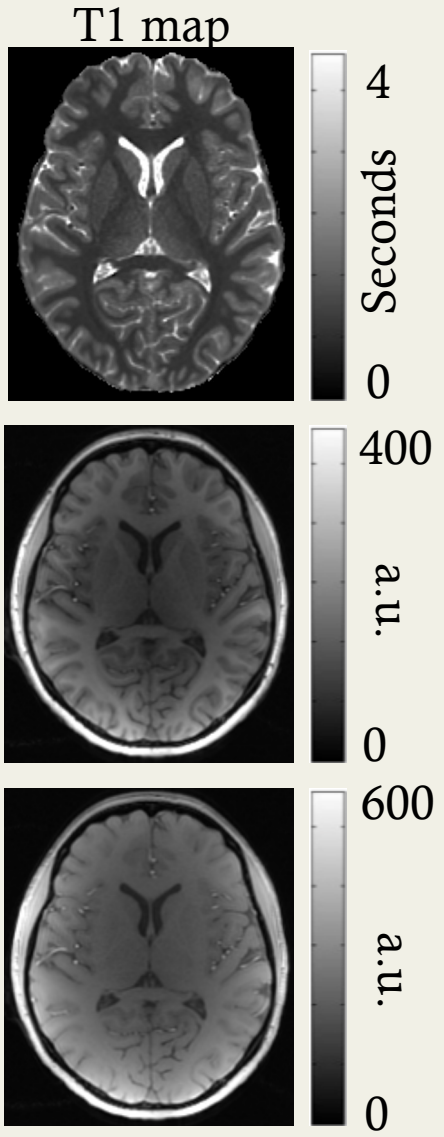
$$\text{Image intensity} = f(\cancel{g, c,} T1, MTV)$$

In the white matter T1 relaxation rate is principally driven by myelin content (Stuber et al., 2014).

Mezer, Yeatman et al. (2013), *Nature Med*; Yeatman, Wandell & Mezer (2014) *Nature Comm*

What does “quantitative MRI” mean?

- **<u>T1 (s)</u> -** The T1 relaxation rate is a physical property of water protons in a magnetic field, has units, and does not depend on scanner hardware/pulse sequence.



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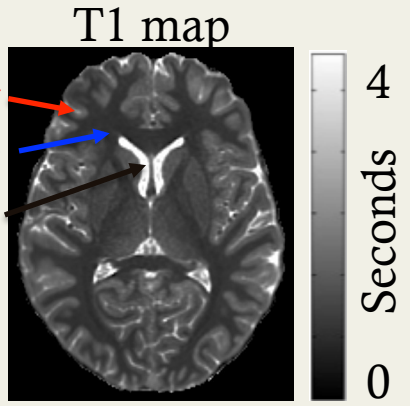
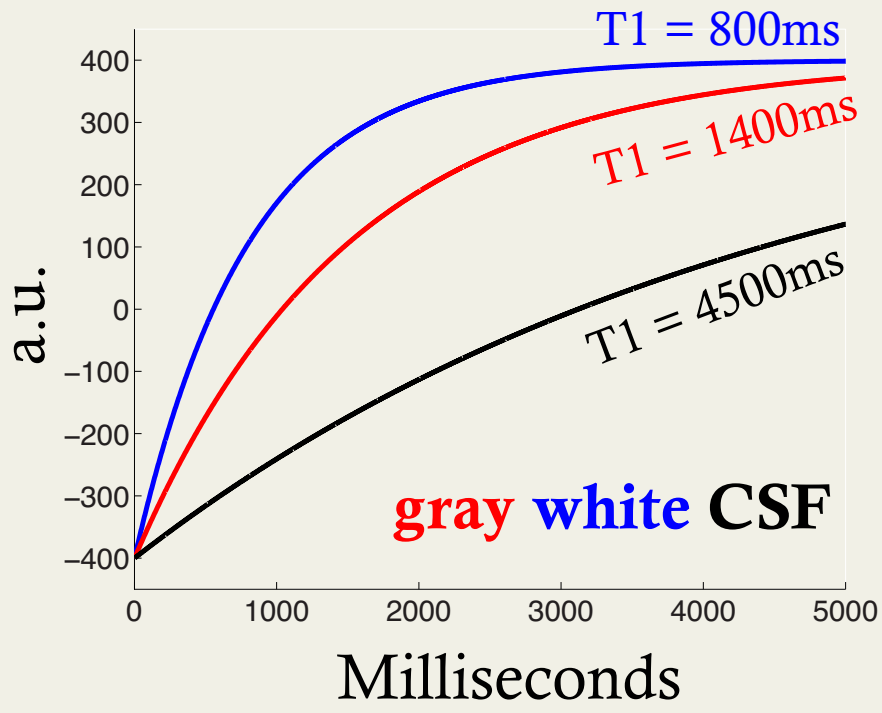
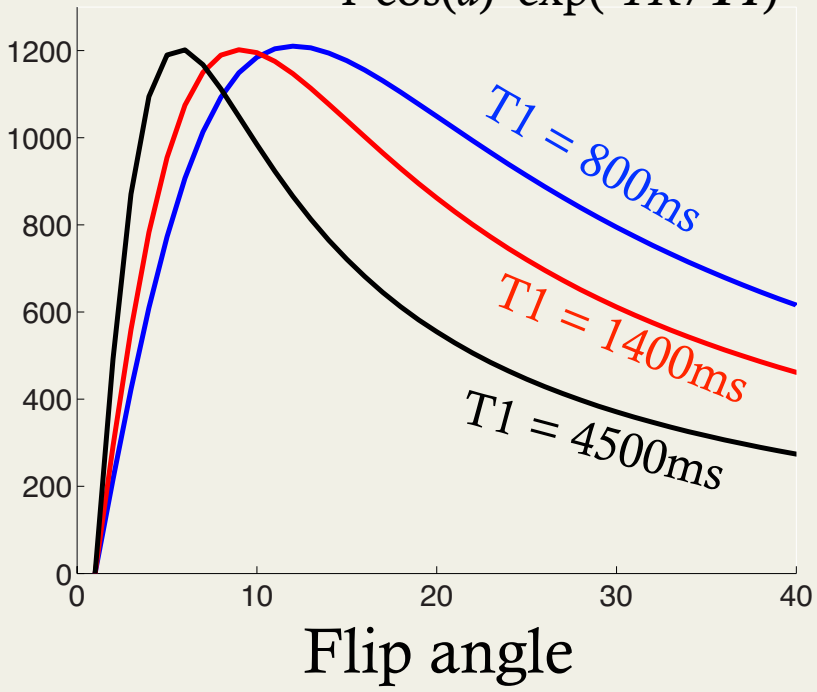


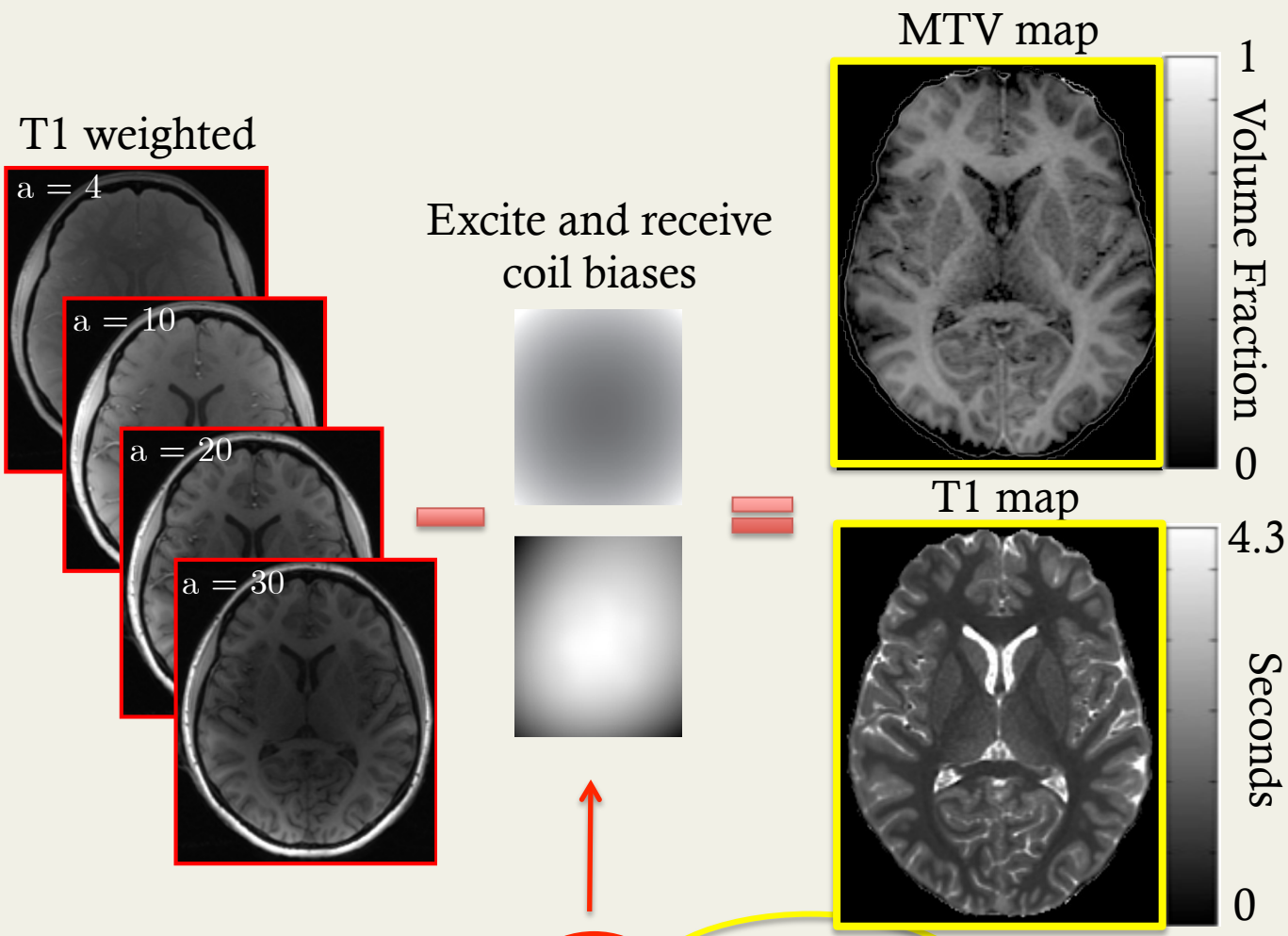
$S = b*e^{-IT/T1}+c$



$$S = b*\sin(a)*\frac{1-\exp(-TR/T1)}{1-\cos(a)*\exp(-TR/T1)}$$



From images to quantitative tissue maps



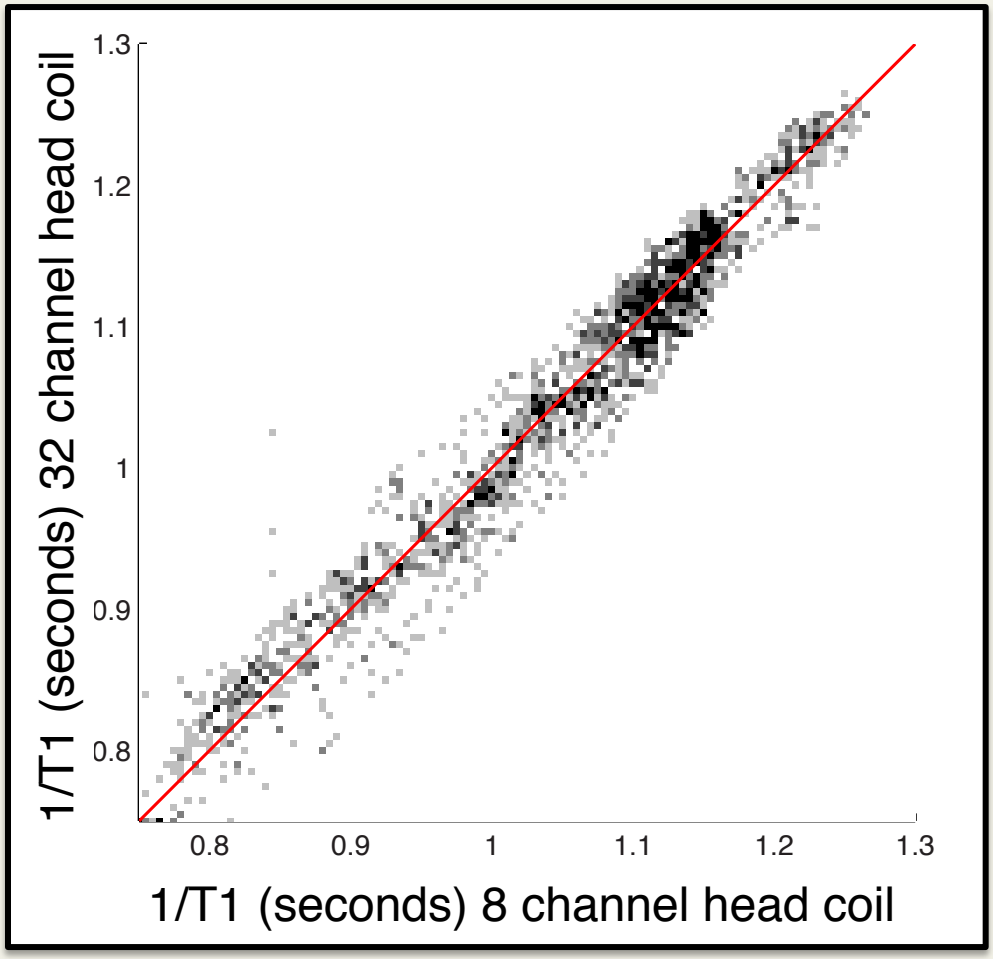
MTV quantifies the volume of tissue versus water in a voxel.

In the white matter T1 relaxation rate is principally driven by myelin content (Stuber et al., 2014).

$$\text{Image intensity} = f\left(g, \alpha, T1, MTV\right)$$

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

Quantitative MRI measures are independent of scanner hardware



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

Summary: Quantitative MRI

- MRI can be used to quantify many important properties of the tissue.
  - Volume of tissue macromolecules (**MTV**).
  - **T1** relaxation rate is sensitive to myelin (Stuber et al., 2014).
- Quantitative MRI measurements are independent of the specific scanner hardware and pulse sequence.
  - Opens up new diagnostic applications.

Outline

1. From tractography to fascicles: Segmenting an individual's white matter.
2. **Quantitative MRI measurements of tissue volume and composition.**
3. Combining multiple measurements to model brain development.

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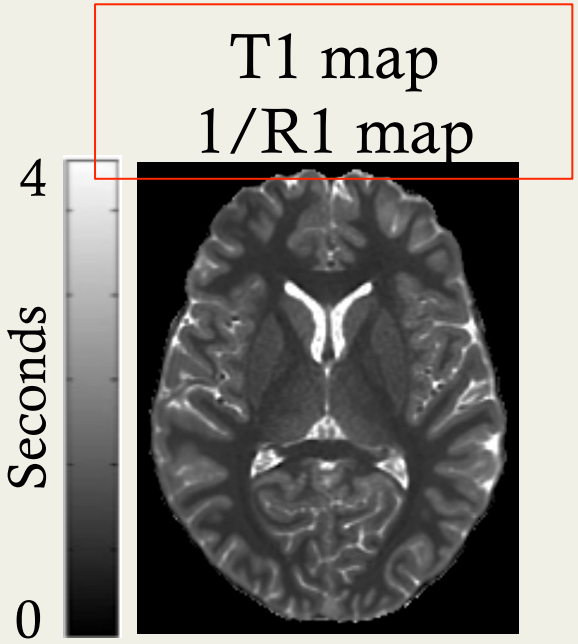
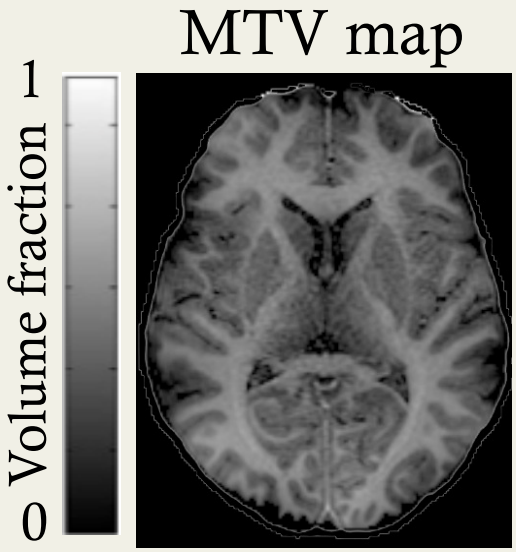
1. From tractography to fascicles: Segmenting an individual's white matter.
2. Quantitative MRI measurements of tissue volume and composition.
3. **Combining multiple measurements to model brain development.**

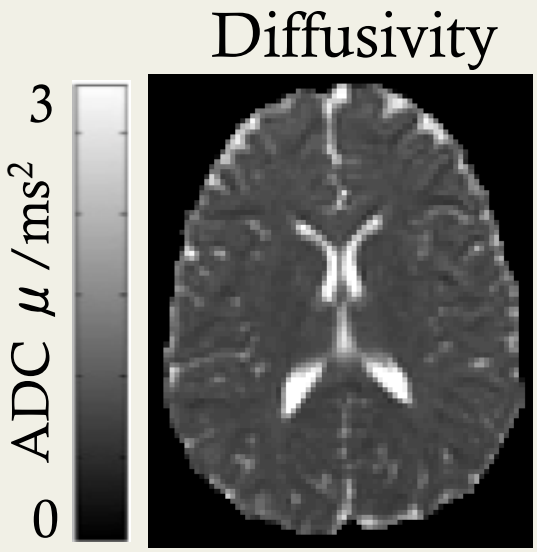
In vivo histology: Combining measures to model brain tissue

- What can we learn about development with qMRI:
  - Do different types of tissue have distinct maturational time-courses (e.g., myelin vs. astrocytes)?
  - Which properties of the white matter are related to behavior?
  - Can we model how properties of the white matter affect cortical computation (i.e., why do white matter measures predict behavior)?

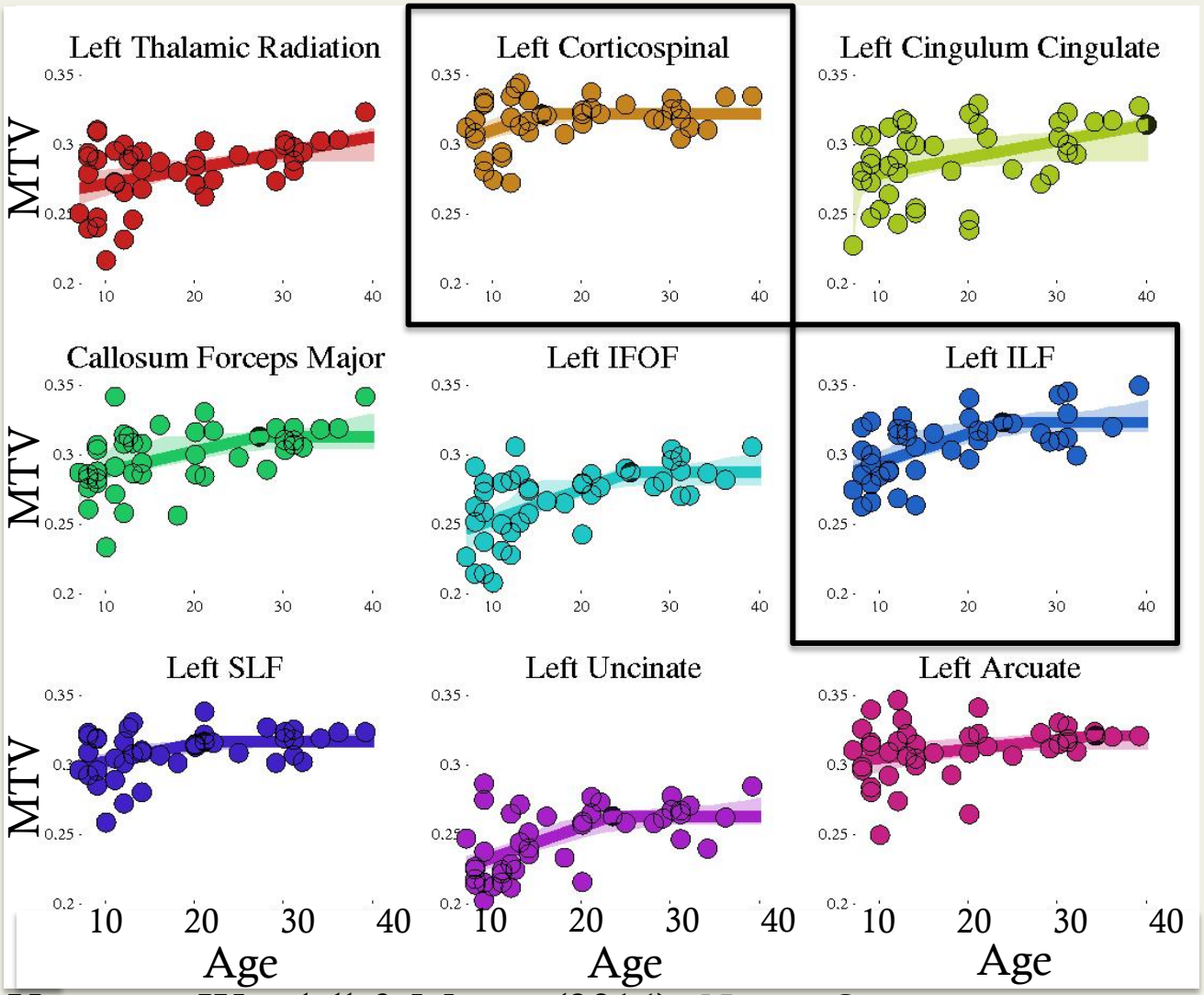
In vivo histology:
Combining measures to model brain tissue

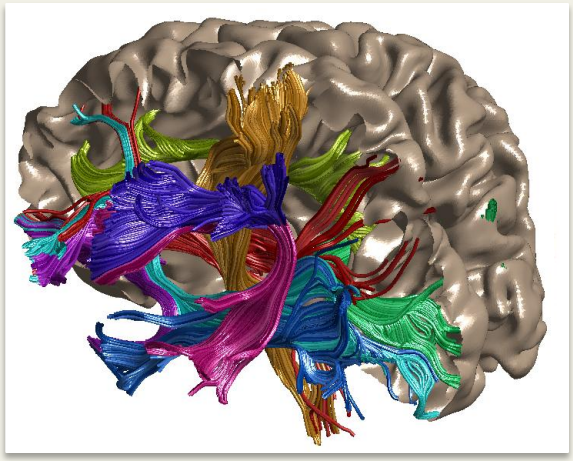


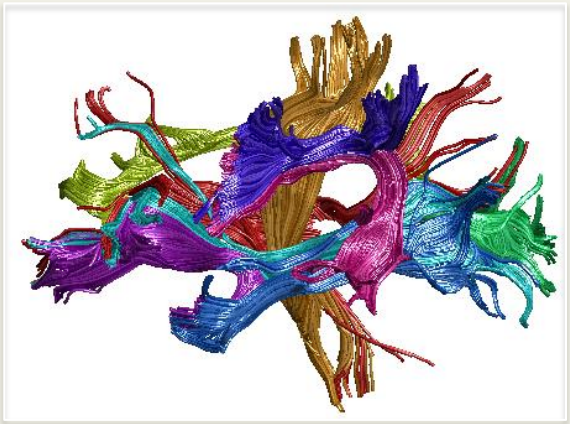




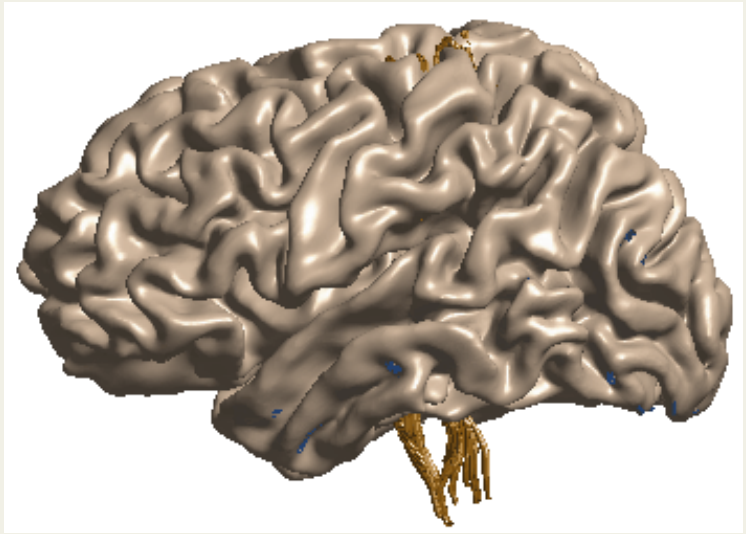
Measuring the creation of new tissue in the developing brain

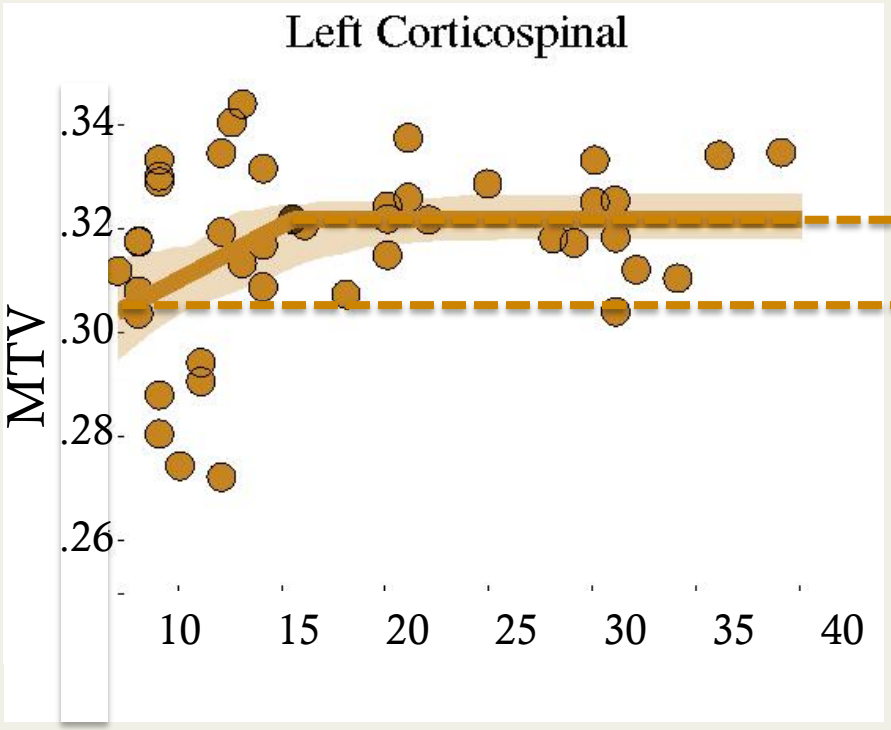


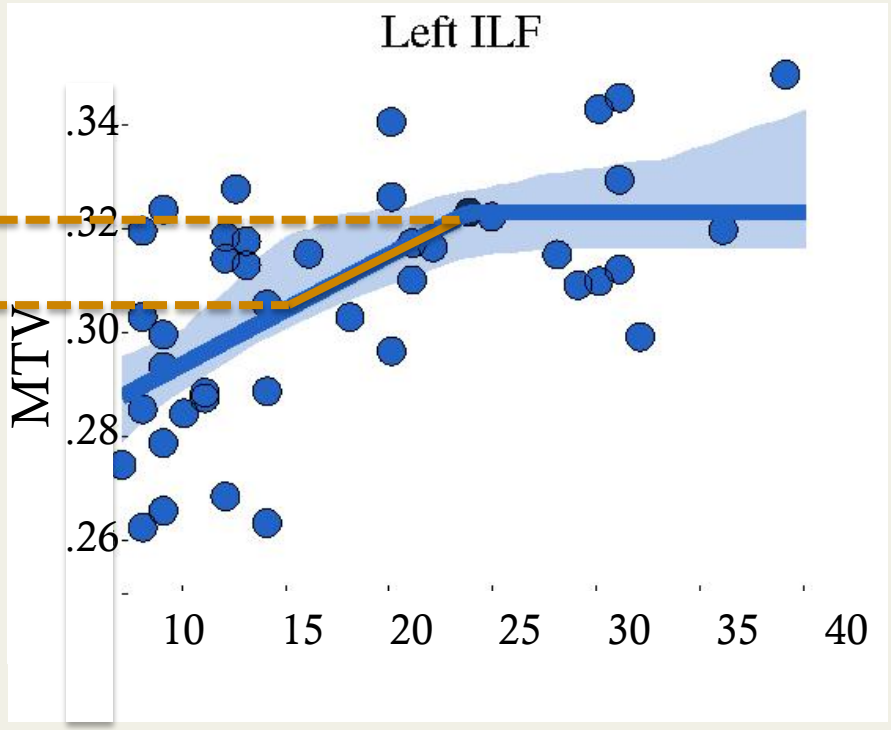




Yeatman, Wandell & Mezer, (2014). *Nature Communications*

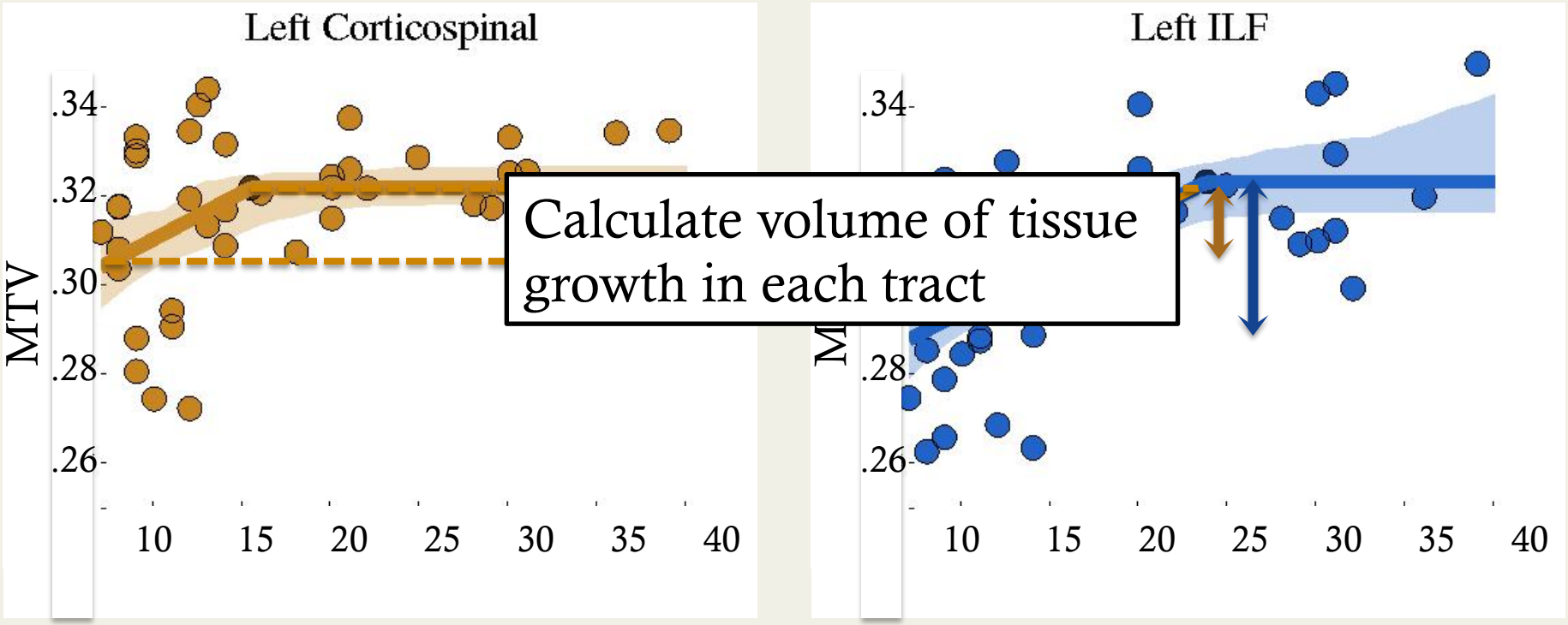






Yeatman, Wandell & Mezer, (2014). *Nature Communications*

Does each qMRI parameter measure the same underlying biological properties?
Can we detect multiple developmental processes in the white matter?



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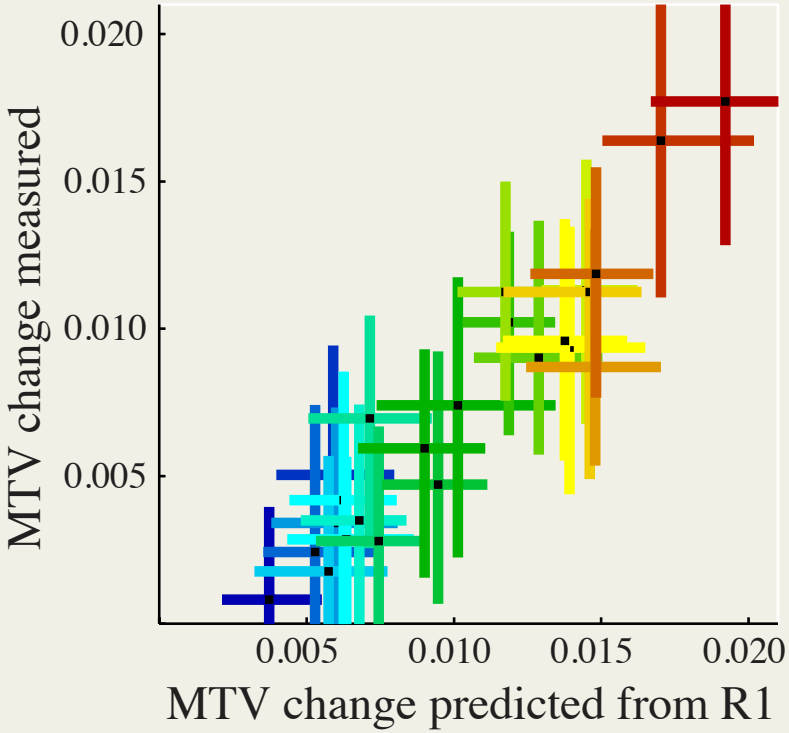

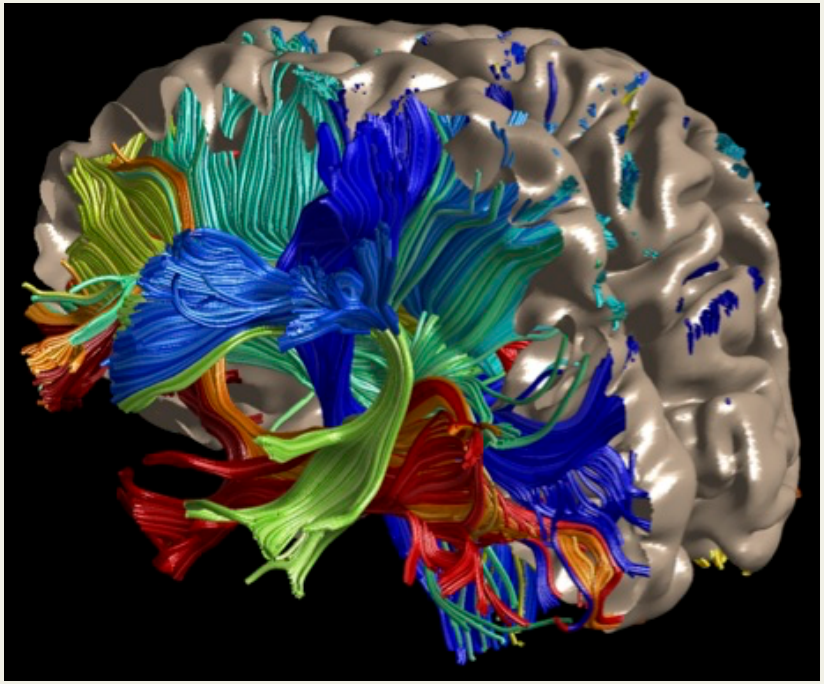

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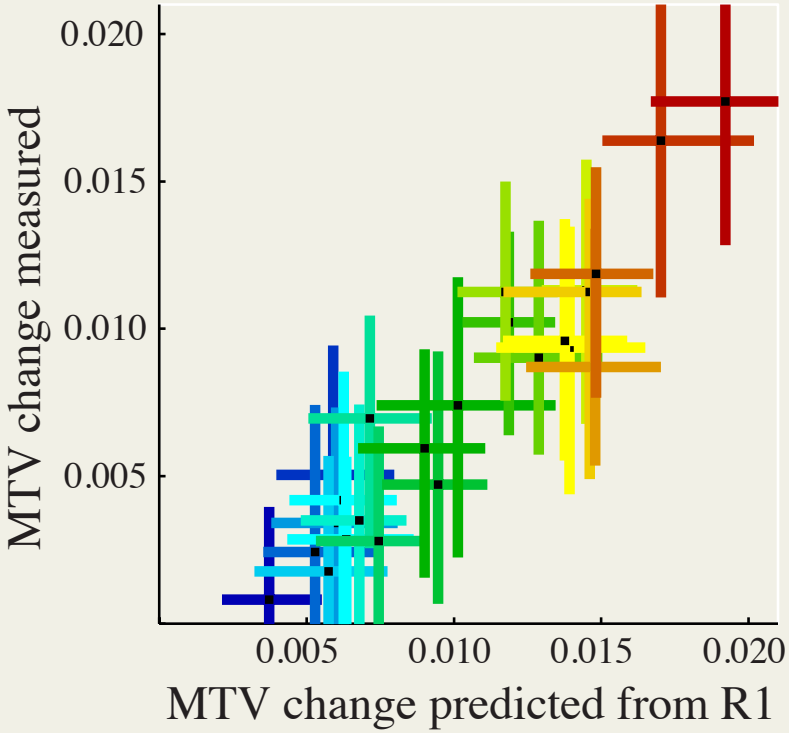
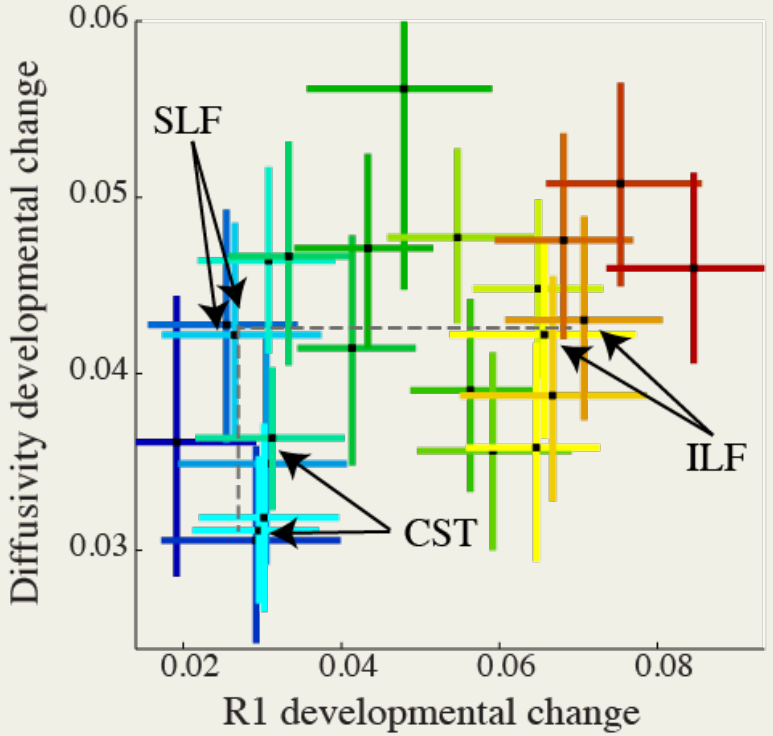


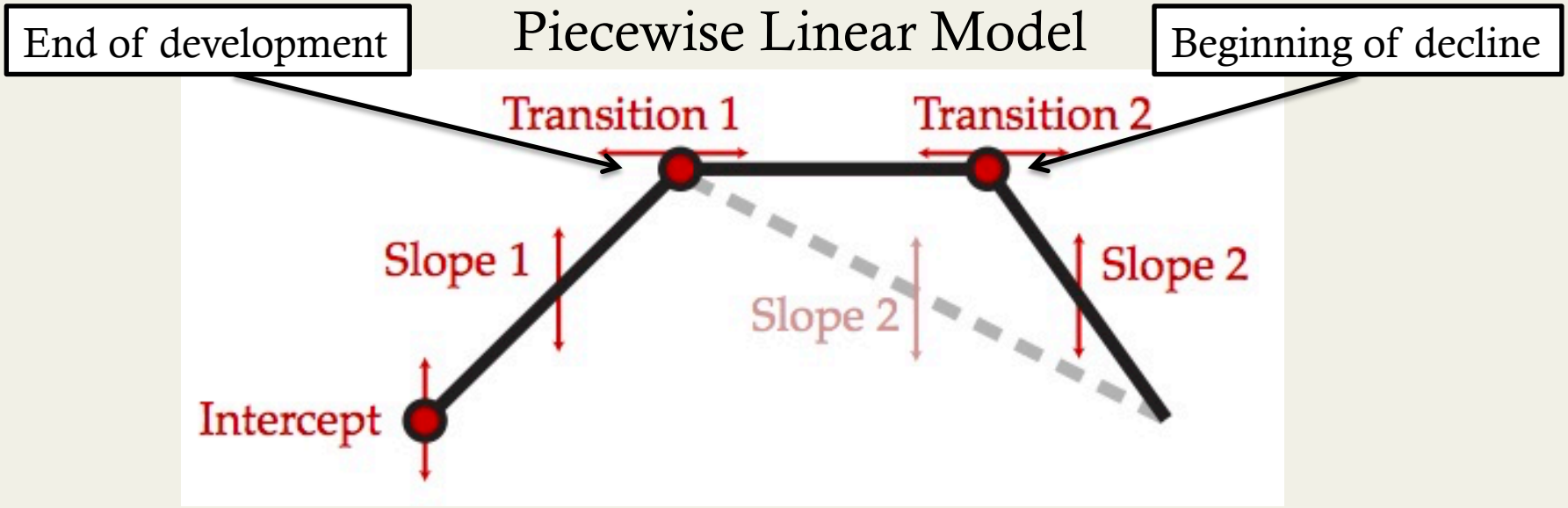


- R1 and MTV are sensitive to the same developmental processes.
- Diffusion is sensitive to independent processes.

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

Last-in-first-out hypothesis: Late developing brain regions are more susceptible to degenerative processes.

- Are the last regions to develop, the first to degenerate?
  - Important implications for models of aging and disease.
- How might we test this hypothesis?
  - Implement a model and test the fit to the data



https://github.com/yeatmanlab/lifespan piecewiseFit.m, piecewiseEval.m

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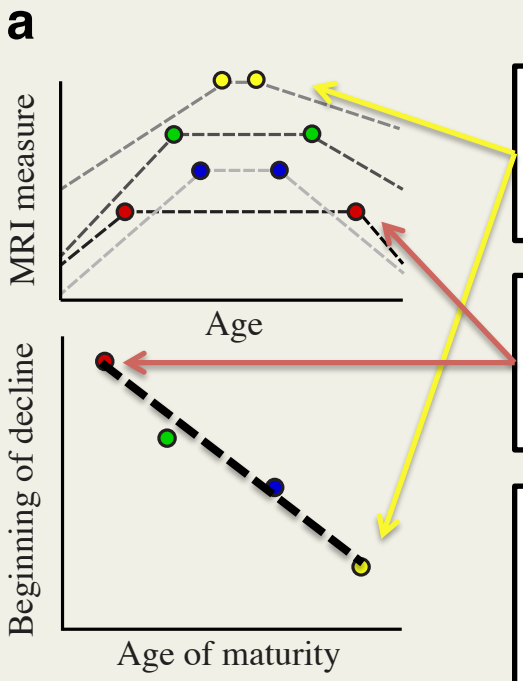


Prediction 1: Tracts that develop **late** decline **early**

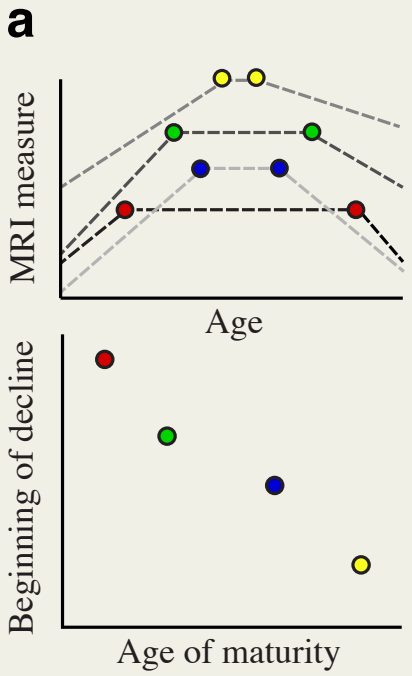
Prediction 2: Tracts that develop **early** decline **late**

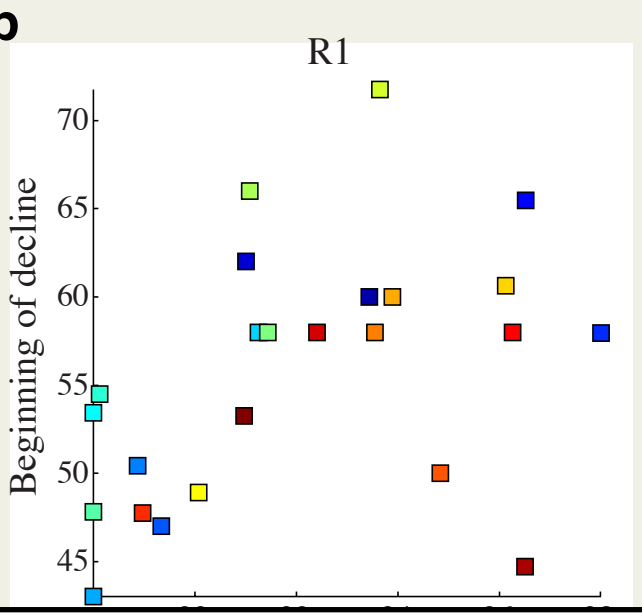
Prediction 3: Negative correlation between the two transition points

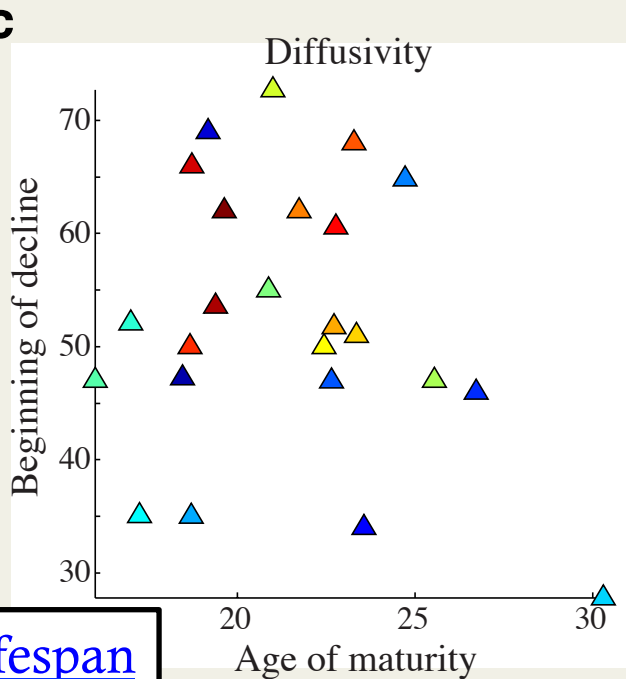
https://github.com/yeatmanlab/lifespan piecewiseFit.m, piecewiseEval.m

Last-in-first-out hypothesis: Late developing brain regions are more susceptible to degenerative processes.

- There is no relationship between the age of maturation and the age of degeneration for R1 or diffusivity.
- We can reject the Last-in-first-out hypothesis.



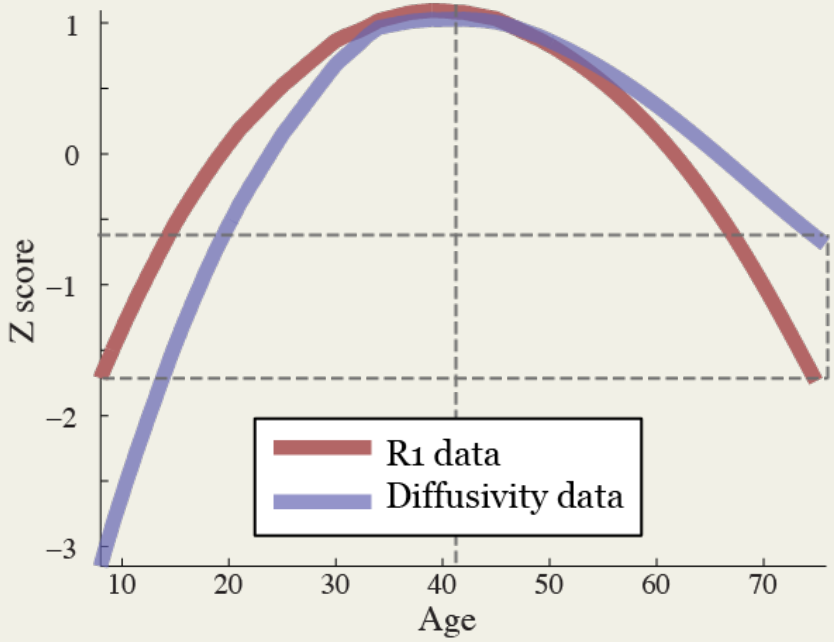


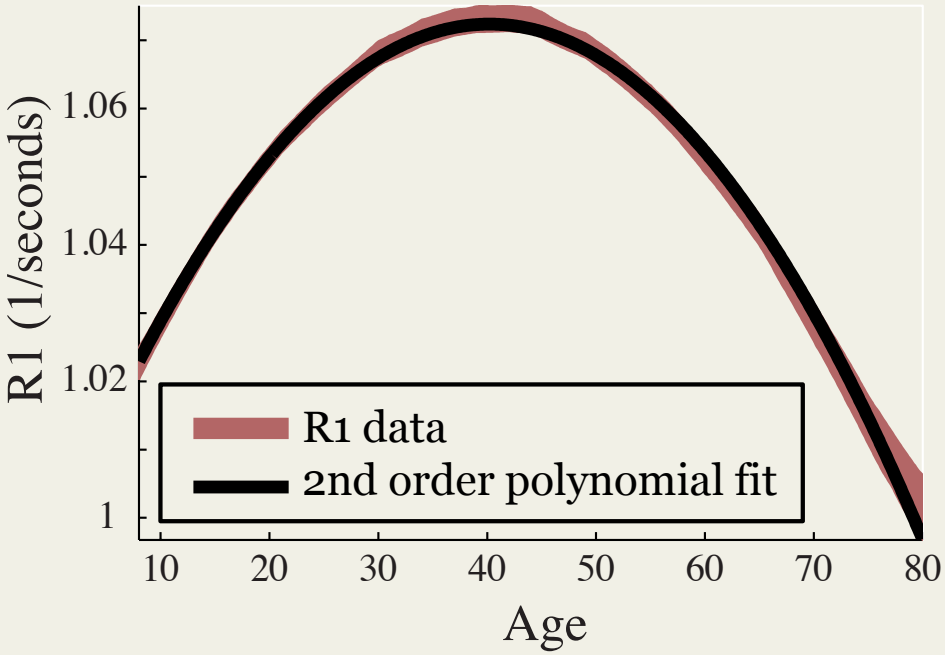


https://github.com/yeatmanlab/lifespan
nc_Figure6.m

https://github.com/yeatmanlab/lifespan piecewiseFit.m, piecewiseEval.m

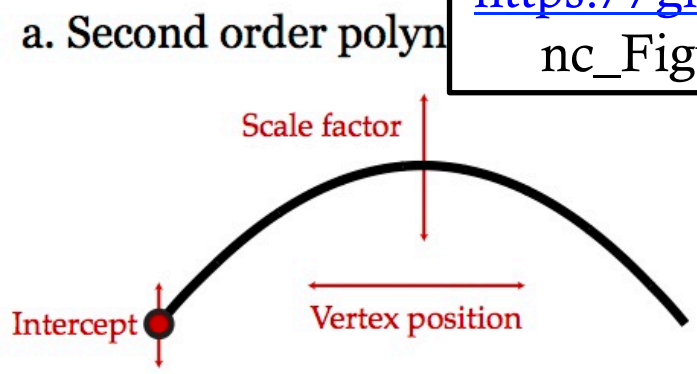
Symmetry hypothesis: The amount of growth predicts the amount of decline

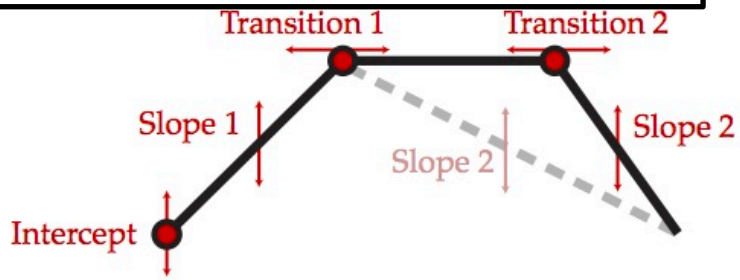


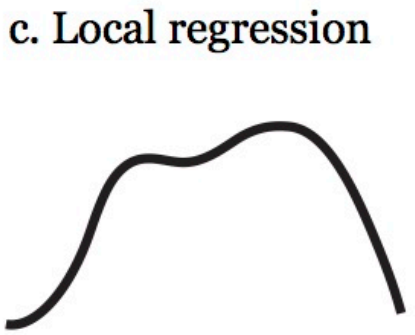


https://github.com/yeatmanlab/lifespan

nc_Figure4.m nc_Figure5.m







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

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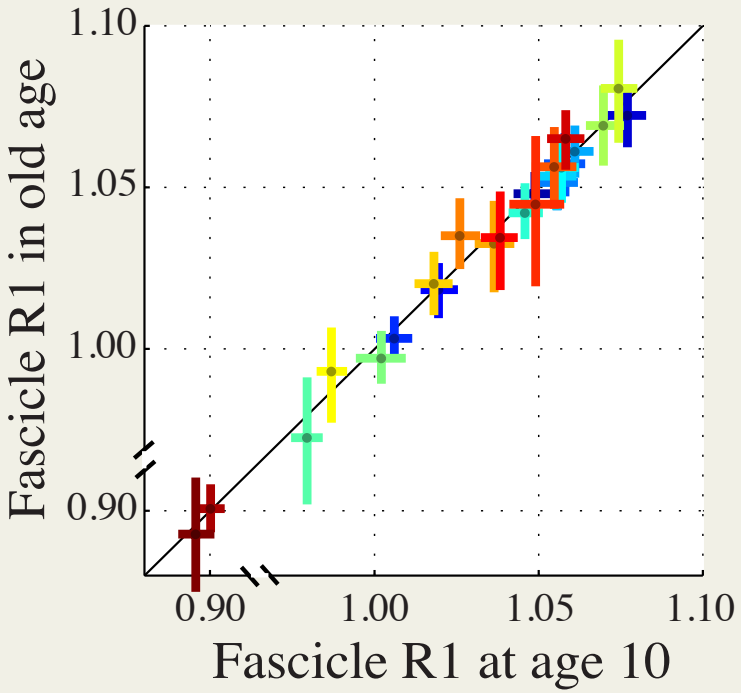
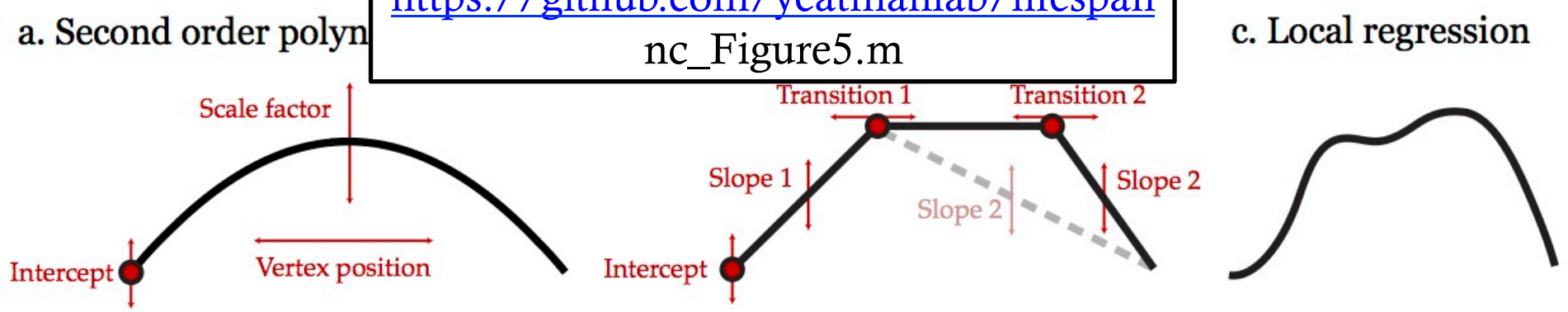


1. Testing the prediction of the parabolic model: Lifespan changes should be symmetric.
2. Growth of myelin during development predicts degeneration during aging.

https://github.com/yeatmanlab/lifespan
nc_Figure5.m

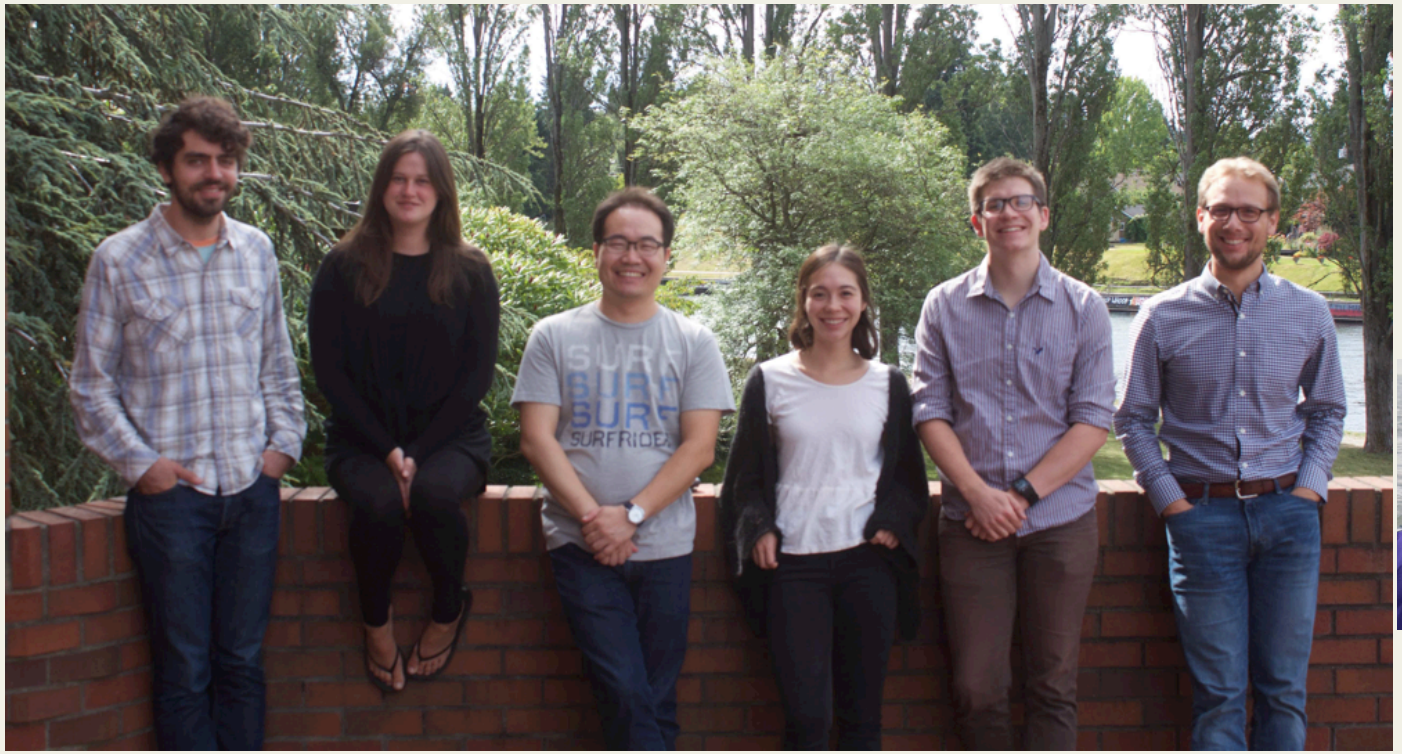


Yeatman, Wandell & Mezer, (2014). *Nature Communications*

Summary

- The time-courses of R1 and diffusion changes demonstrate that multiple biological processes drive changes in the white-matter over the lifespan.
  - qMRI can dissociate different tissue changes.
- There is not a systematic relationship between the **age** of maturation and degeneration
  - Last-in-first out does not fit the data
- A symmetric model predicts R1 changes over the lifespan.
  - Models provide insight into mechanisms and generate testable perditions.
- We can define, test and interpret models at the level of voxels, tracts and lifespan maturation.

Thank you!



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University of Washington

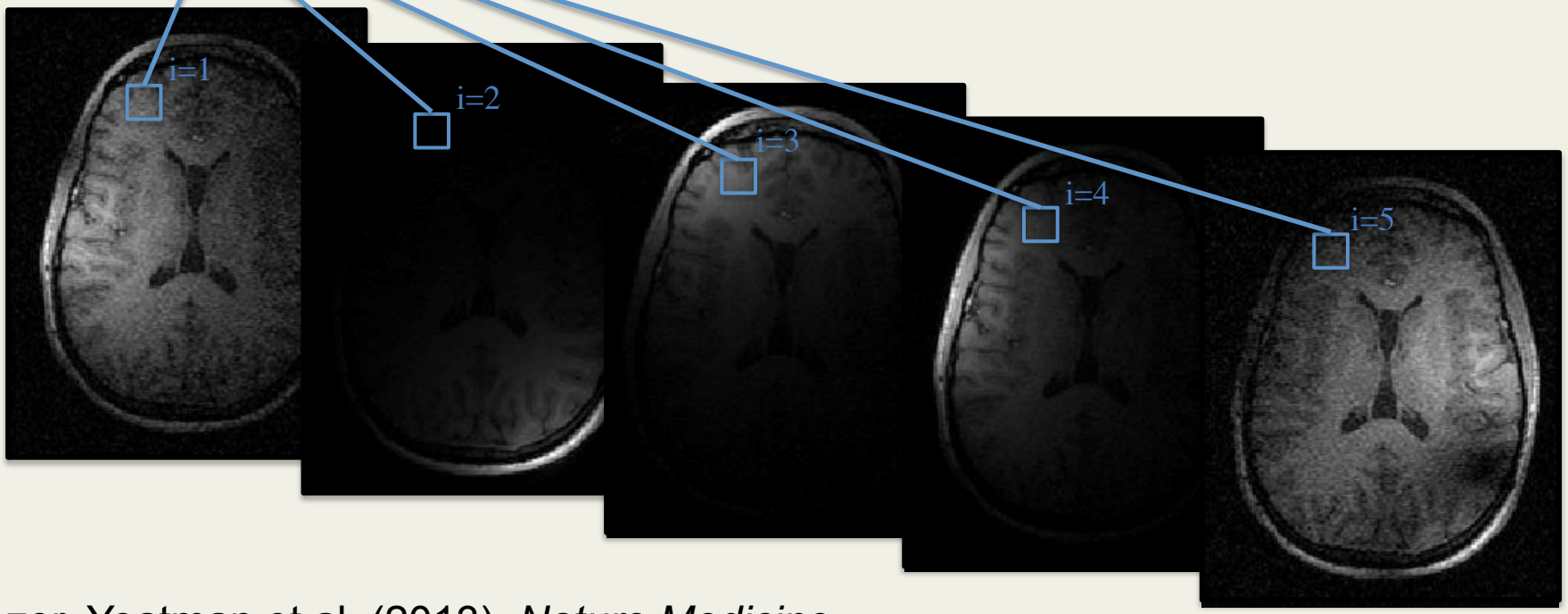
Removing bias and computing MTV

Each coil sees the same underlying MTV value but has its own gain function

$$g_i * (1 - MTV)$$

Solve for the each coil's gain function to uncover the true MTV value

$$\min_{g_i} \{ \sum (MTV_i - MTV)^2 \}$$



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