Quantitative neuroimaging of human brain development

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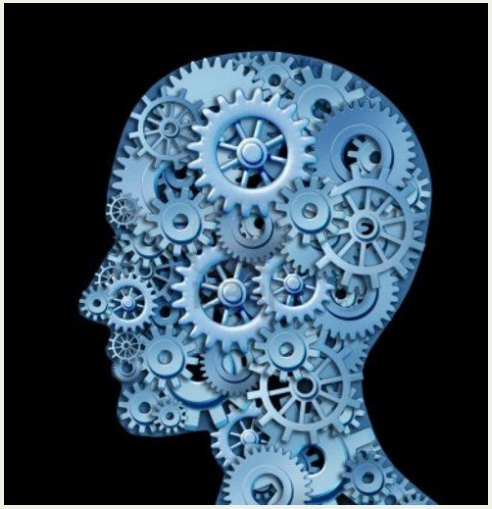
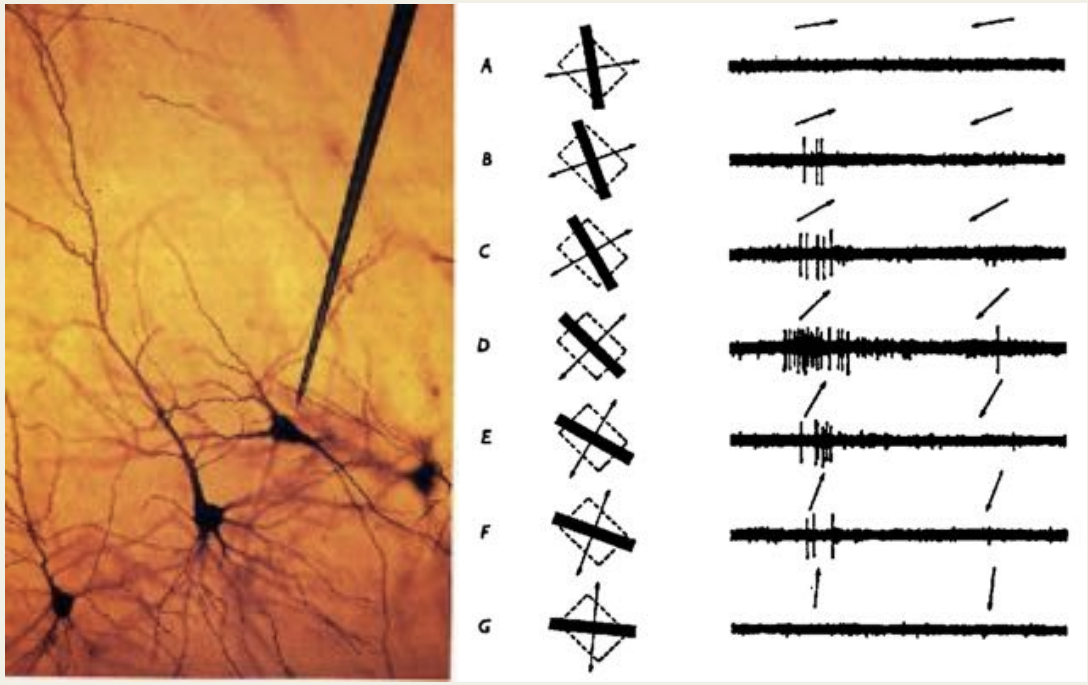
Cognition and the neuron doctrine

Cognitive function can be attributed to localized neural activity

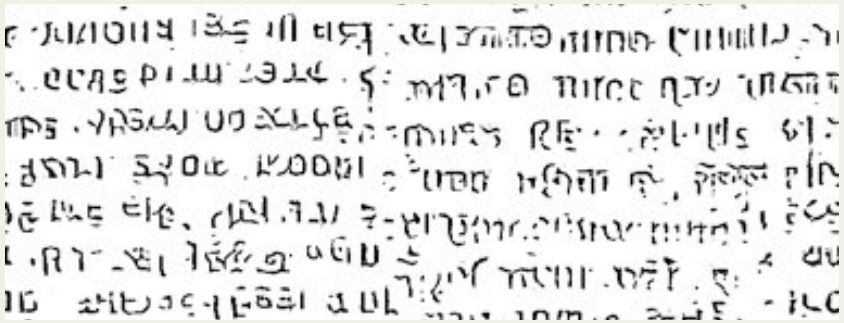


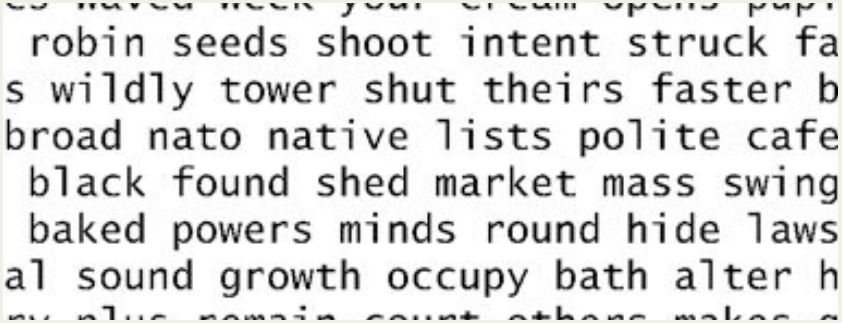


Hubel and Wiesel (1959 onward)

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).**



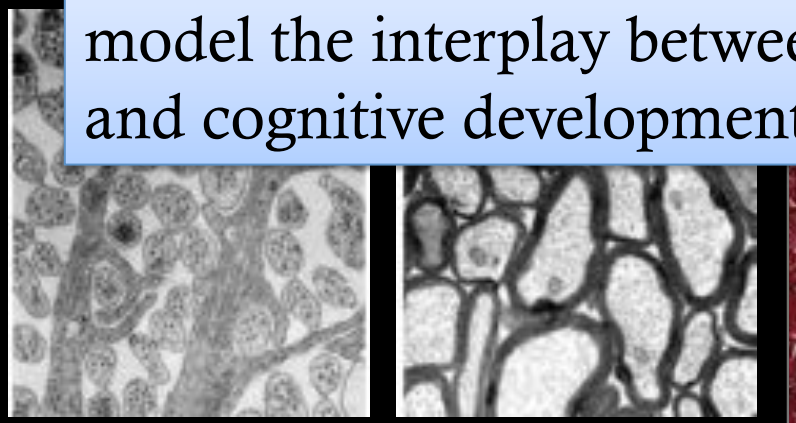


Portilla & Simoncelli, 2000

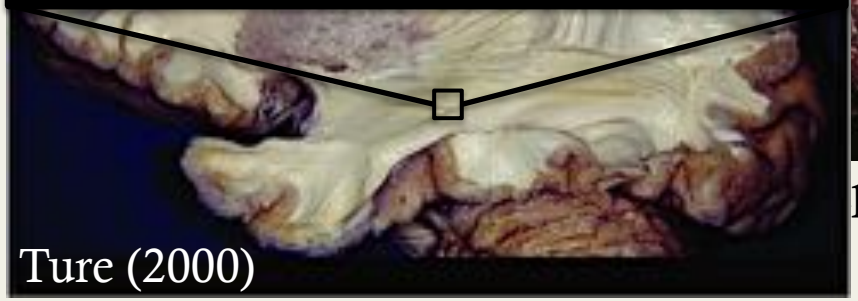
Cognitive development depends on tissue changes that occur over correspondingly long time-scales

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

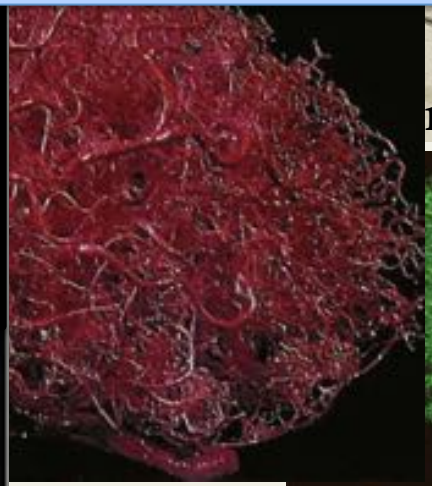
MRI can be used to quantify brain tissue properties and model the interplay between brain circuit development and cognitive development.



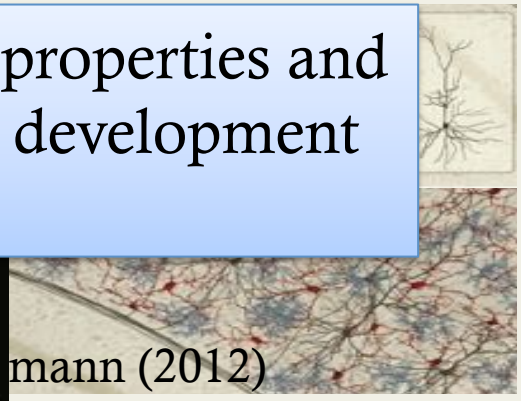
(LaMantia & Rakic, 1990)



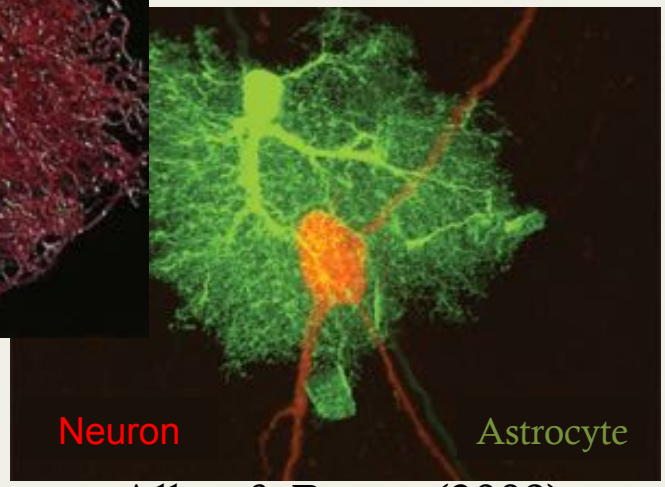
Ture (2000)



puzo (1998)



mann (2012)



Allen & Barres (2009)

Outline

1. From tractography to fascicles: Segmenting an individual's white matter.
2. Measuring white matter development with diffusion.
   - Inferring tissue properties from diffusion.
   - Cross-sectional versus longitudinal measurements.
   - Modeling the processes that underlie learning to read.
3. Quantitative MRI measurements of tissue volume and composition.
4. Combining multiple measurements to dissociate developmental processes.
   - Testing models of development.

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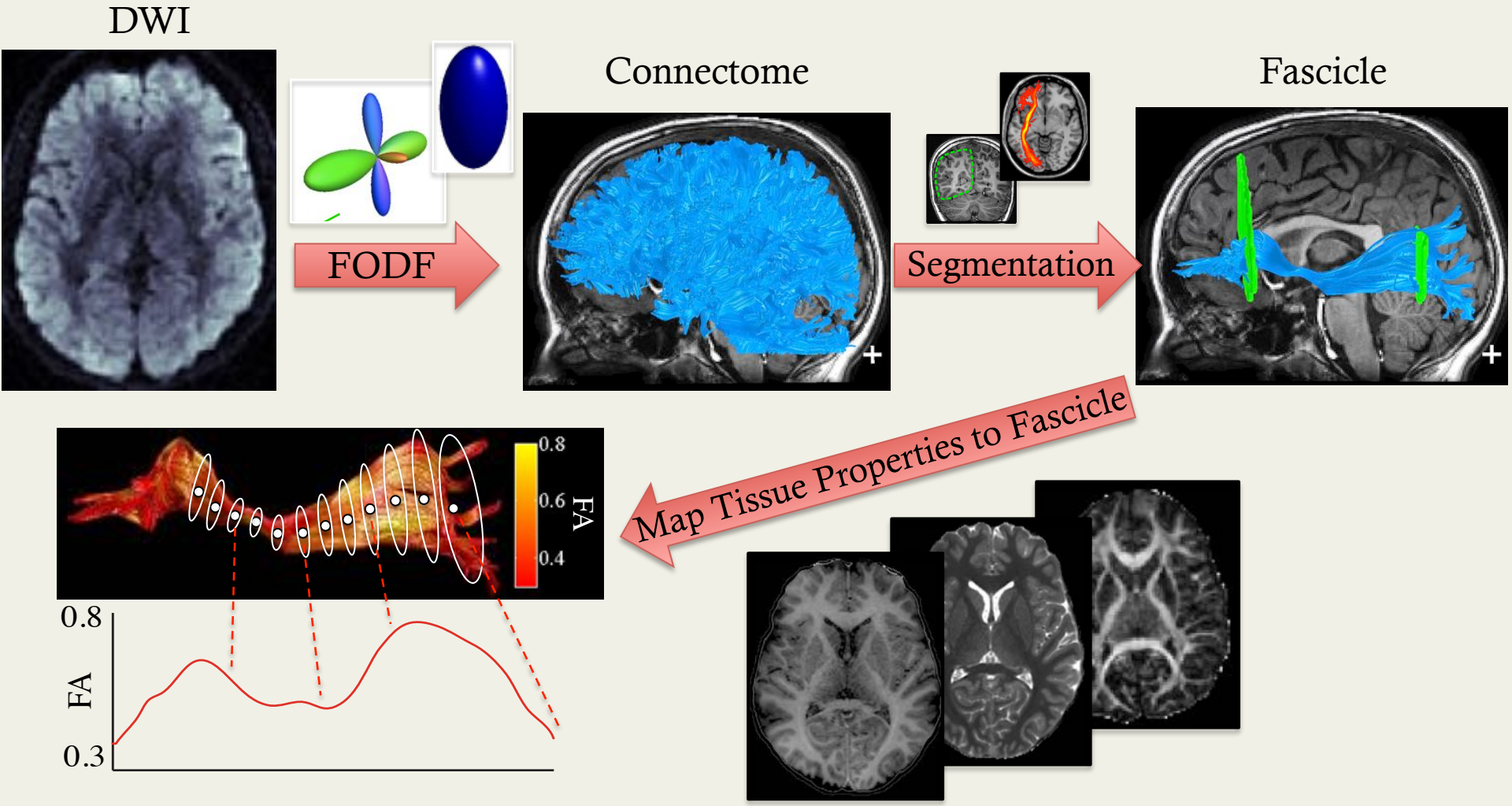
Automated fiber tract quantification (AFQ)



Yeatman et al. (*2012*), *PLoS ONE*.

Software available at: https://github.com/jyeatman

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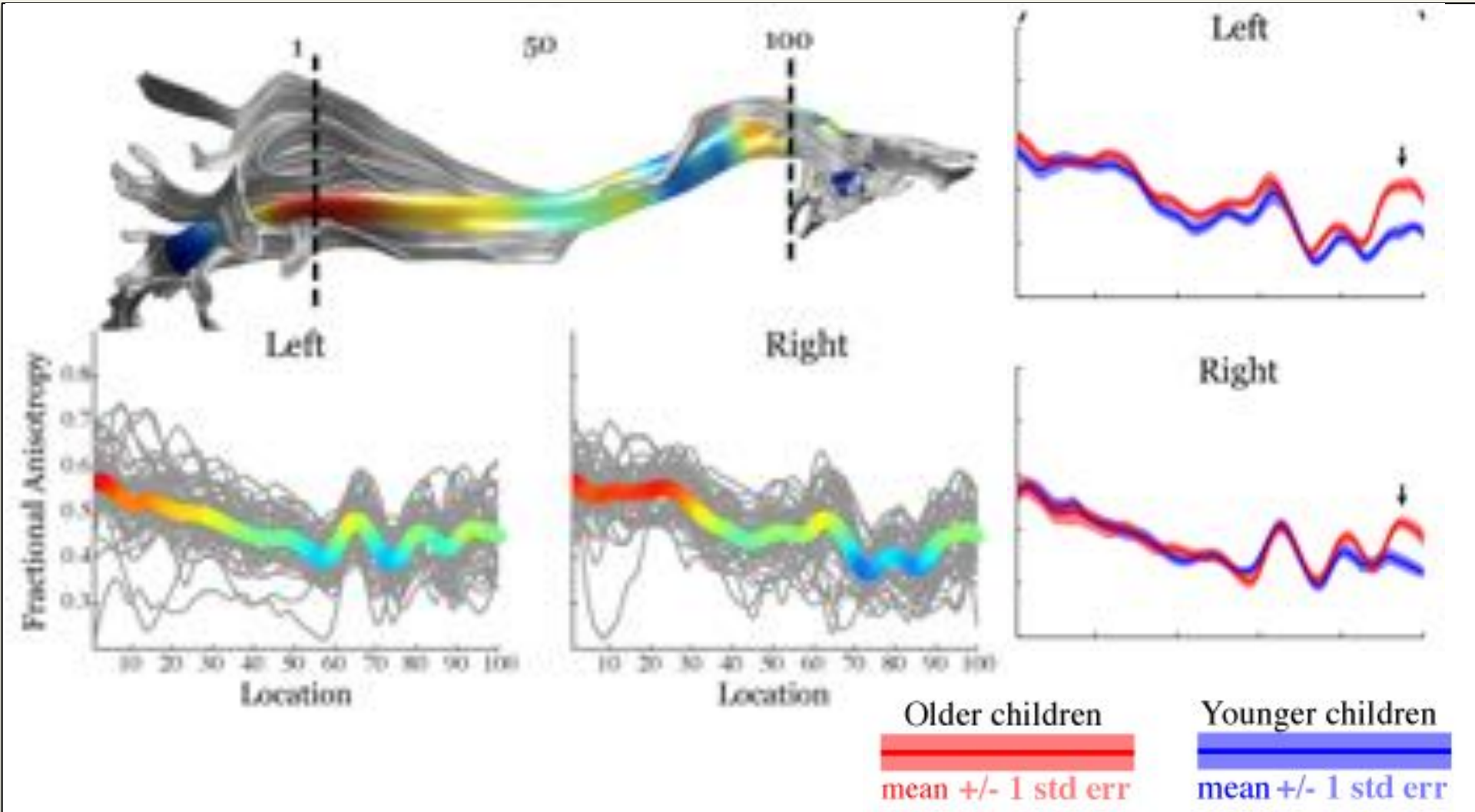


Yeatman et al. (*2012*), *PLoS ONE*. Software available at: https://github.com/jyeatman

Reproducible, open-source, scalable computations

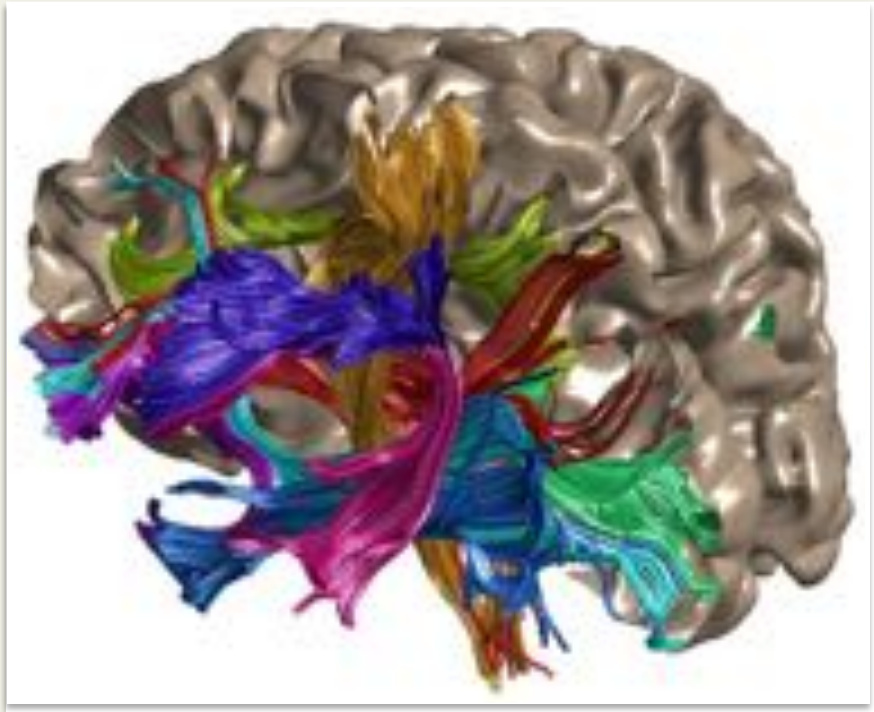
Reliability: Manual-automatic, r = 0.98

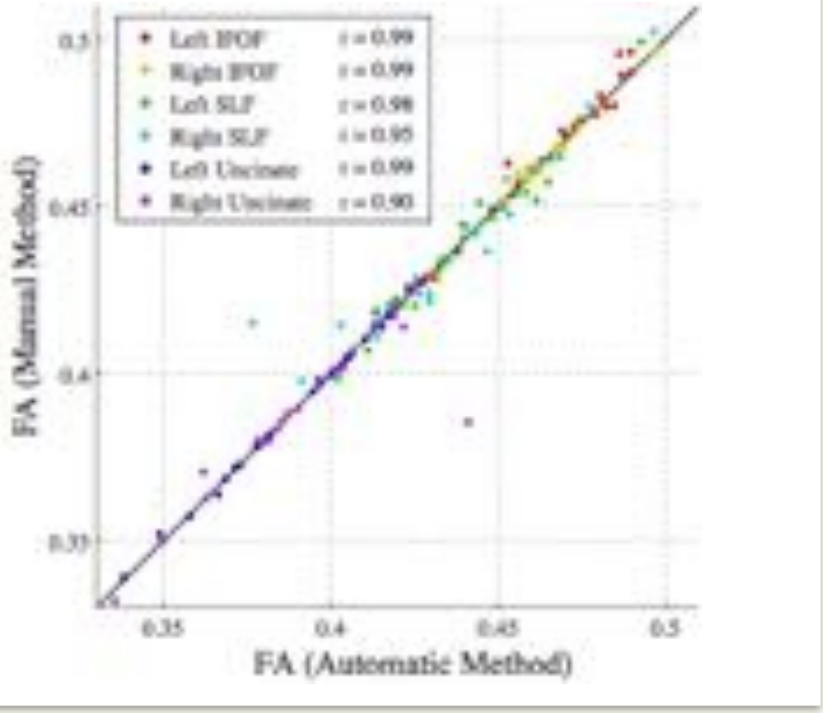
Reliability: Scan-rescan, r = 0.93

Wandell

Dougherty

Feldman





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

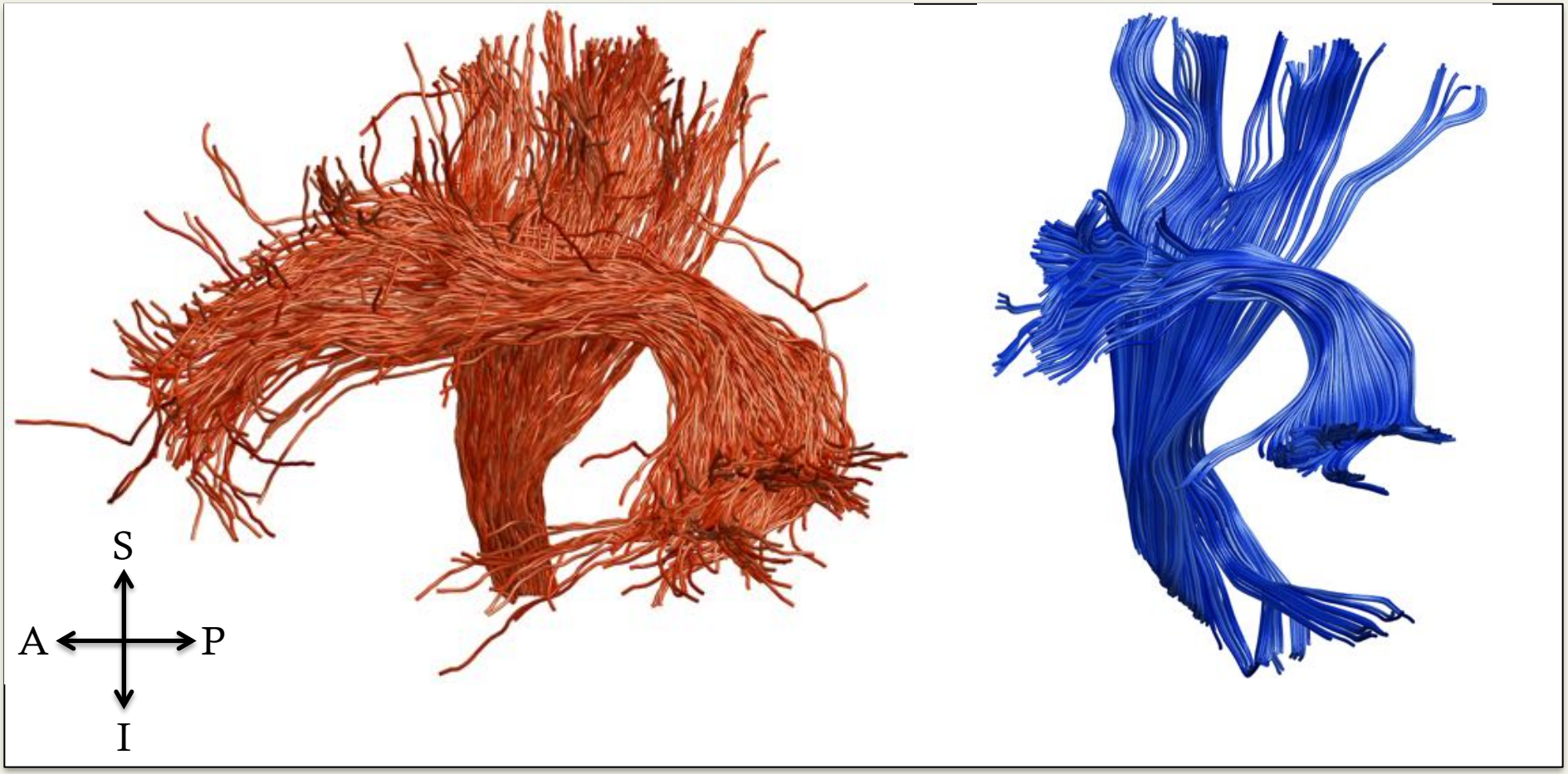
How might we select the optimal tractography algorithm to use with AFQ?

- 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

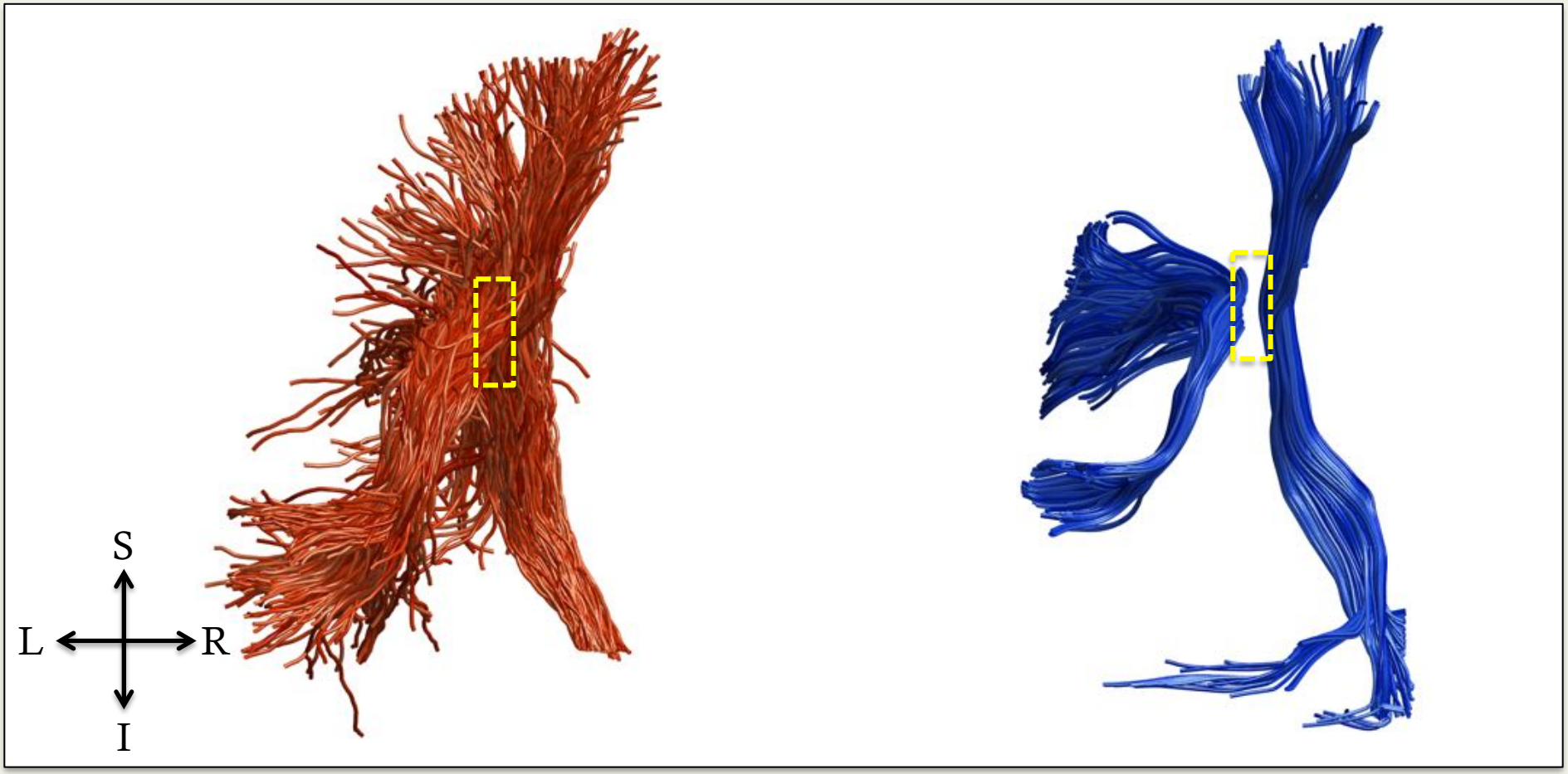
Tensor Model
Deterministic Tractography



The choice of algorithm has a substantial impact on the results

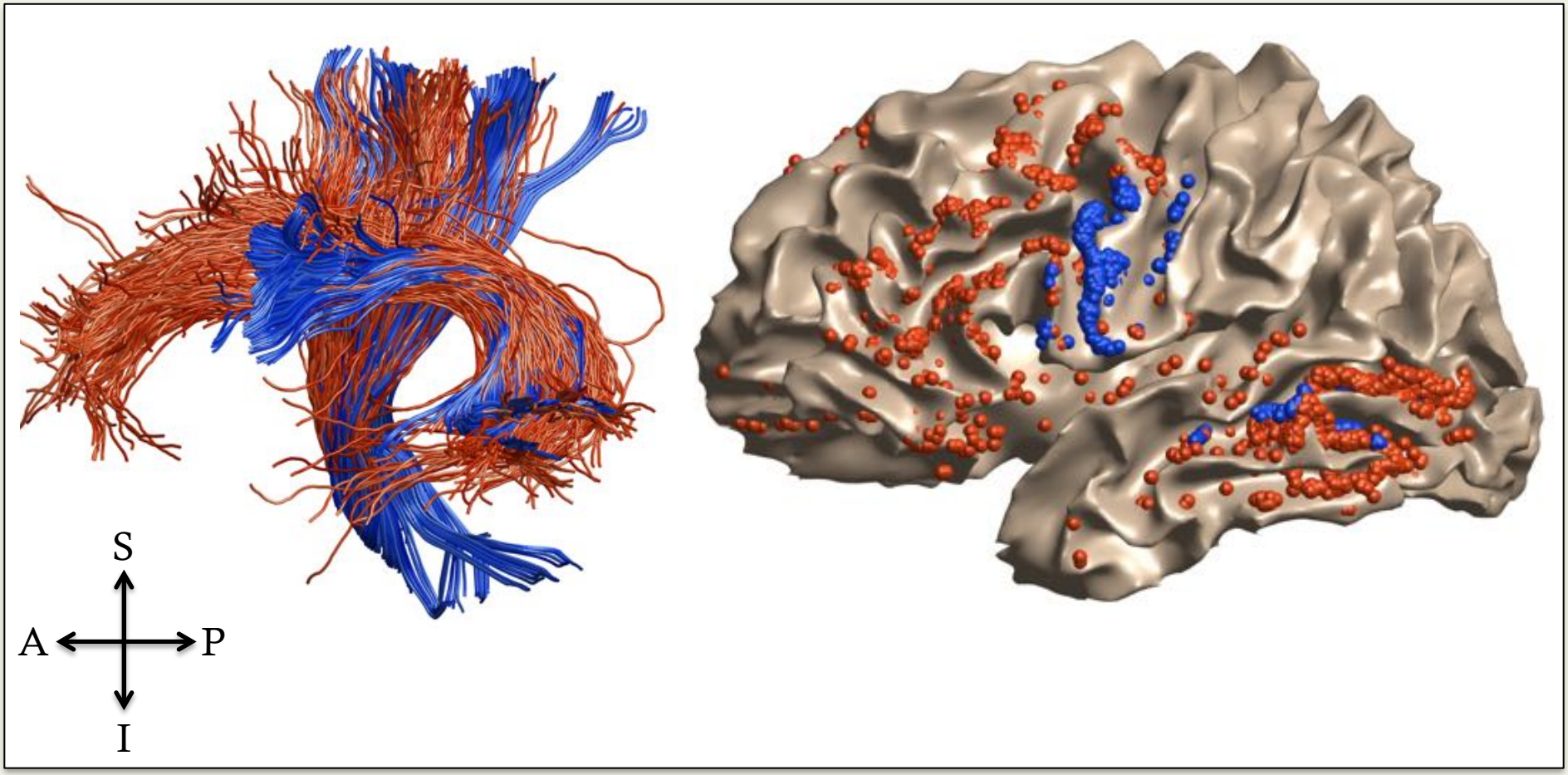
Spherical Deconvolution
Probabilistic tractography

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.



Summary: From tractography to fascicles

- AFQ will automatically identify 28 fascicles in an individual's brain and reliably quantify tissue properties along each fascicle.
- Results depend on selecting the appropriate diffusion model and tractography algorithm for your research question.

Outline

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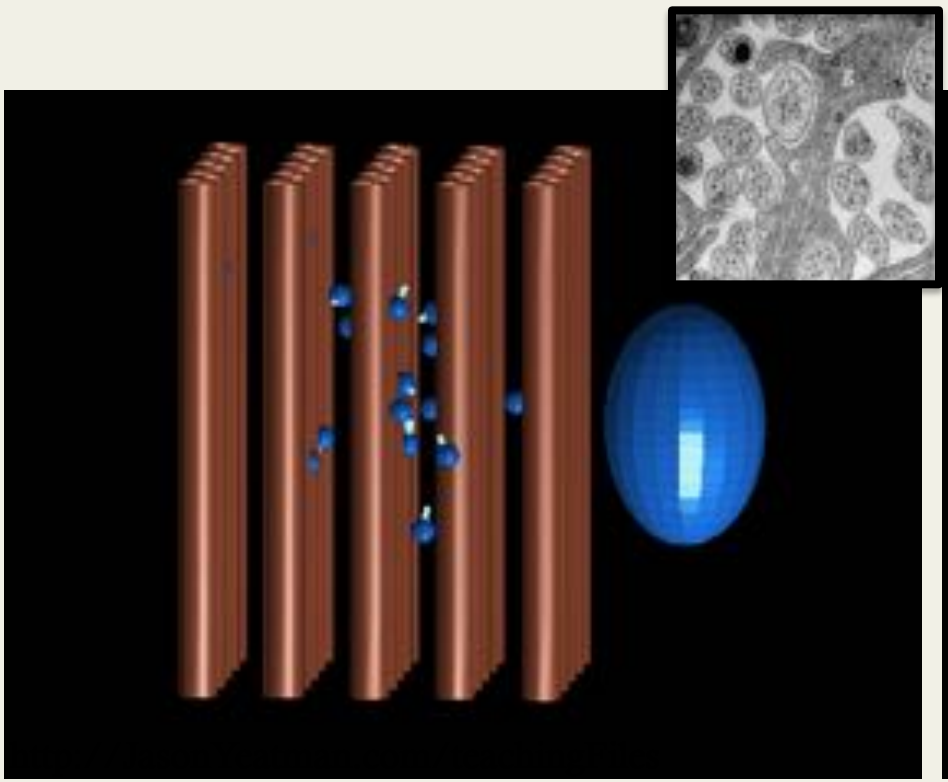
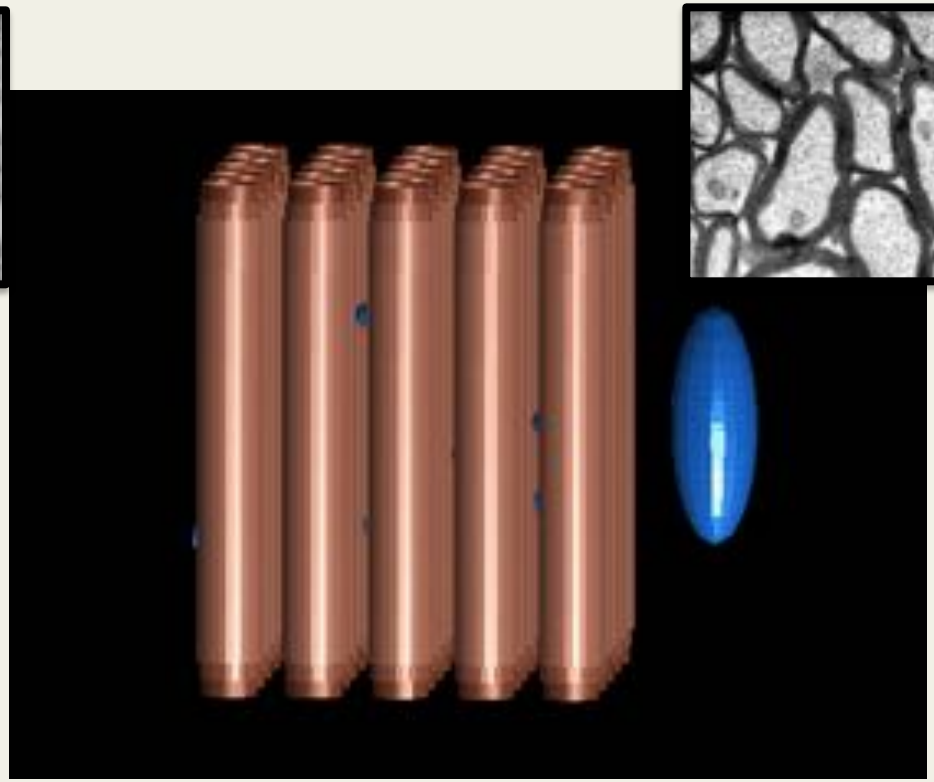
Inferring tissue biology from diffusion

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



Low Fraction Anisotropy (FA)
High Mean Diffusivity (MD)



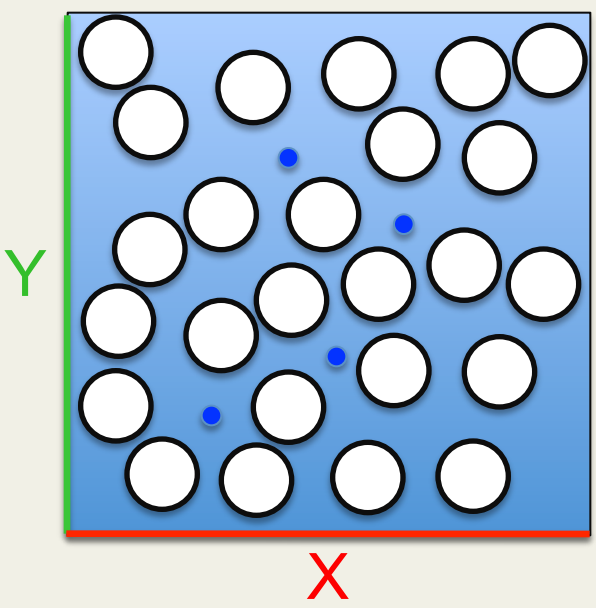
High Fraction Anisotropy (FA)
Low Mean Diffusivity (MD)

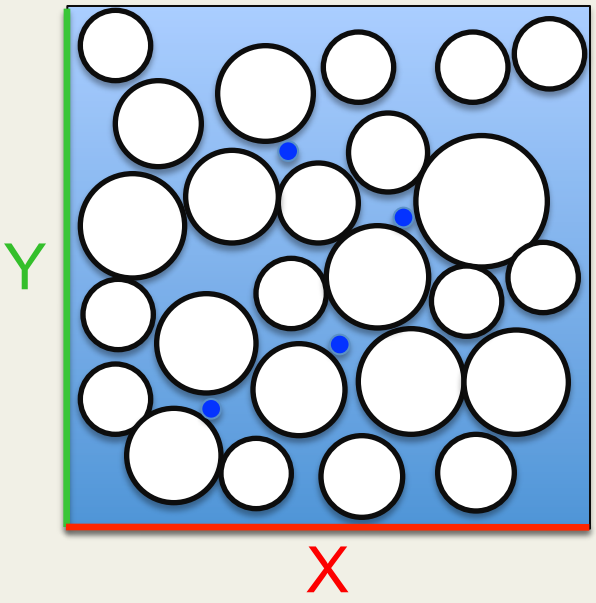
Wandell & Yeatman (2013); Stikov et al., (2011); Assaf & Pasternak (2008); Beaulieu (2002)

Inferring tissue biology from diffusion

In cases of parallel fibers (e.g., callosum), FA increases monotonically with fiber volume fraction (Stikov et al., 2011).

$$FVF = 0.883*FA^2 - 0.082*FA + 0.074$$

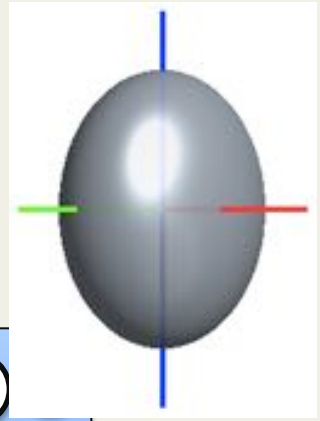




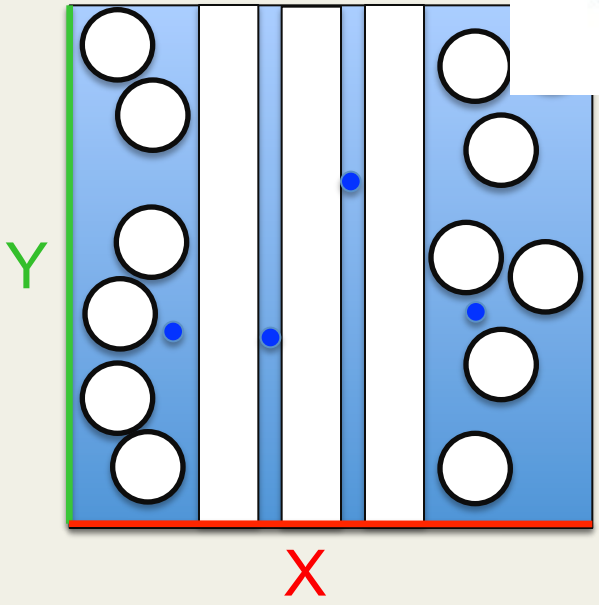
Inferring tissue biology from diffusion

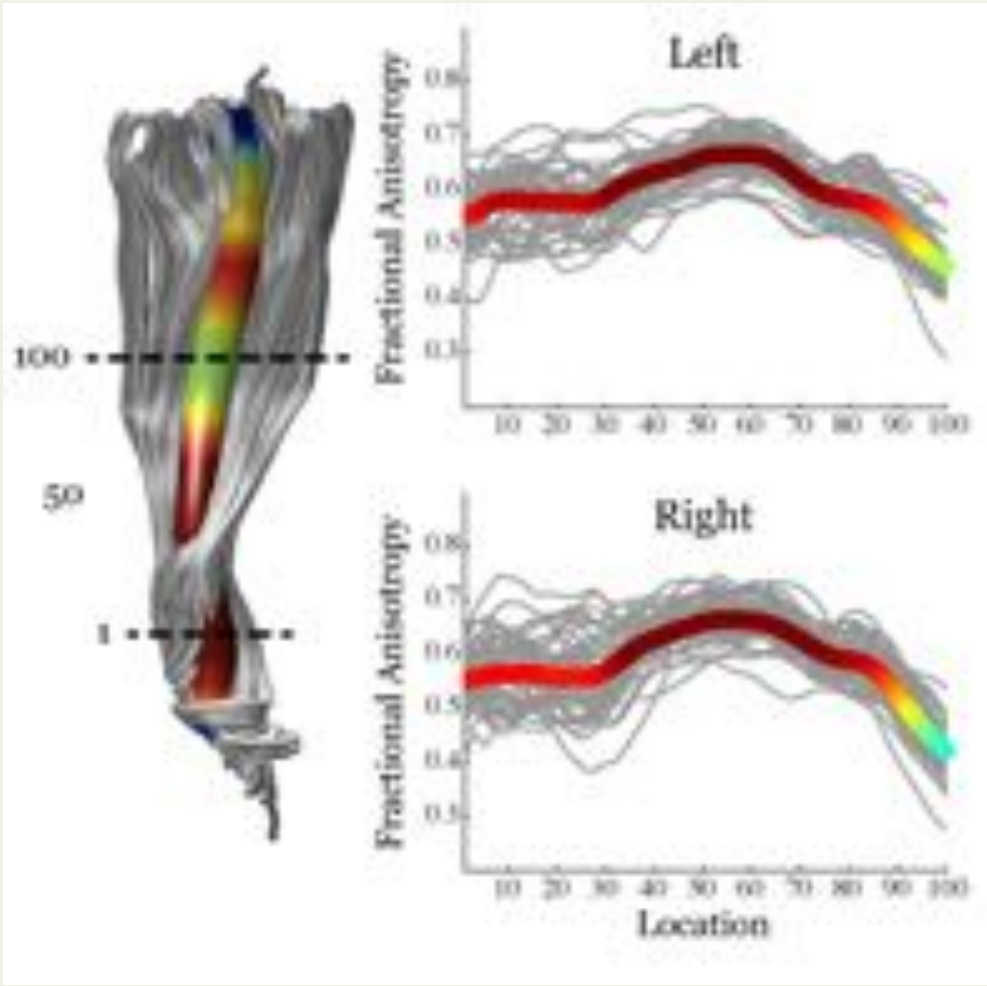
All bets are off in cases of crossing fibers!

Low FA



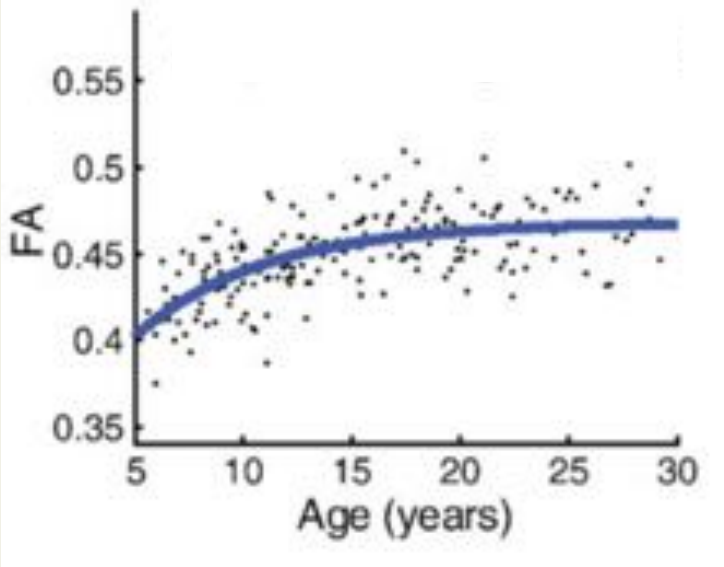
Crossing Fibers

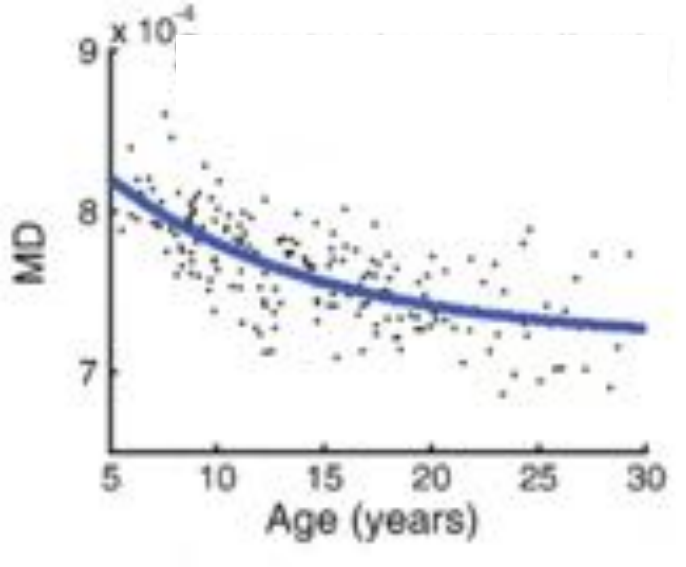


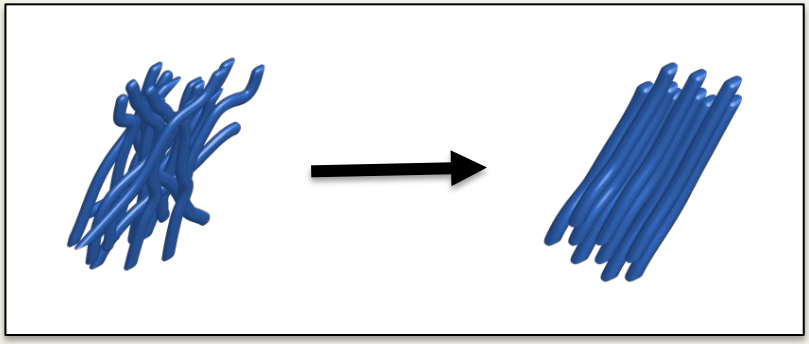


What can diffusion tell us about development?

Maturation of the arcuate fasciculus (cross sectional)



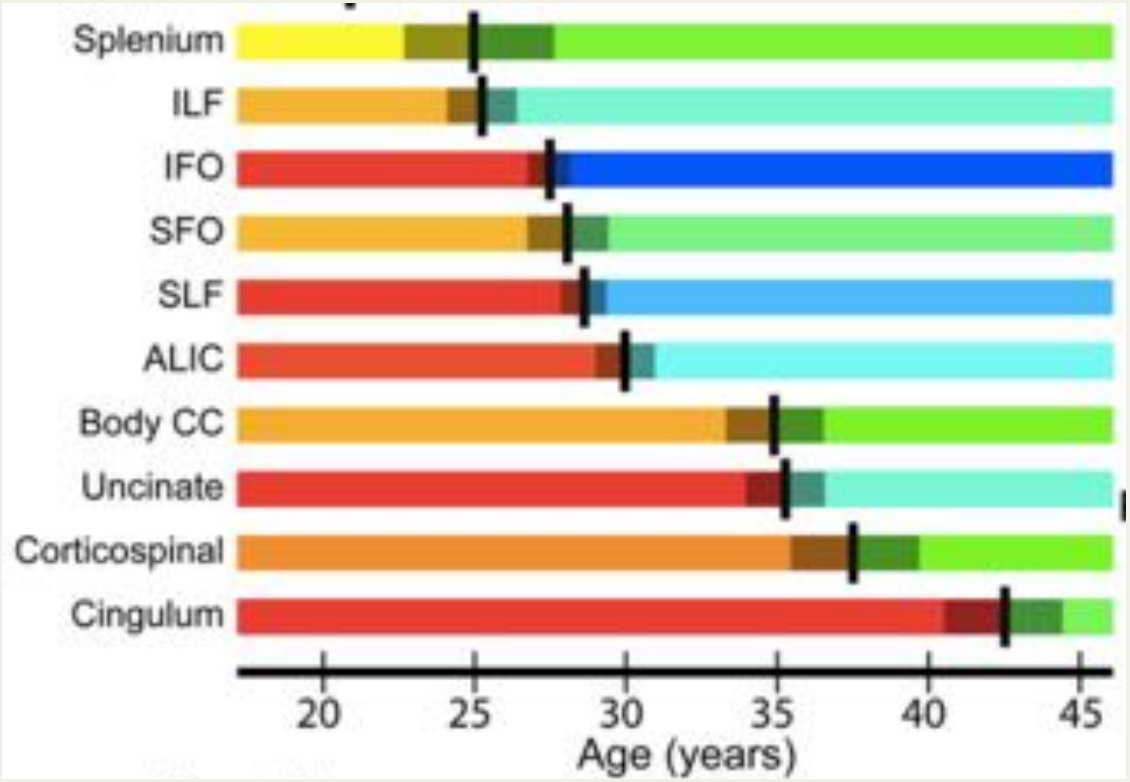




Lebel et al., Neuroimage, 2008, 2012.

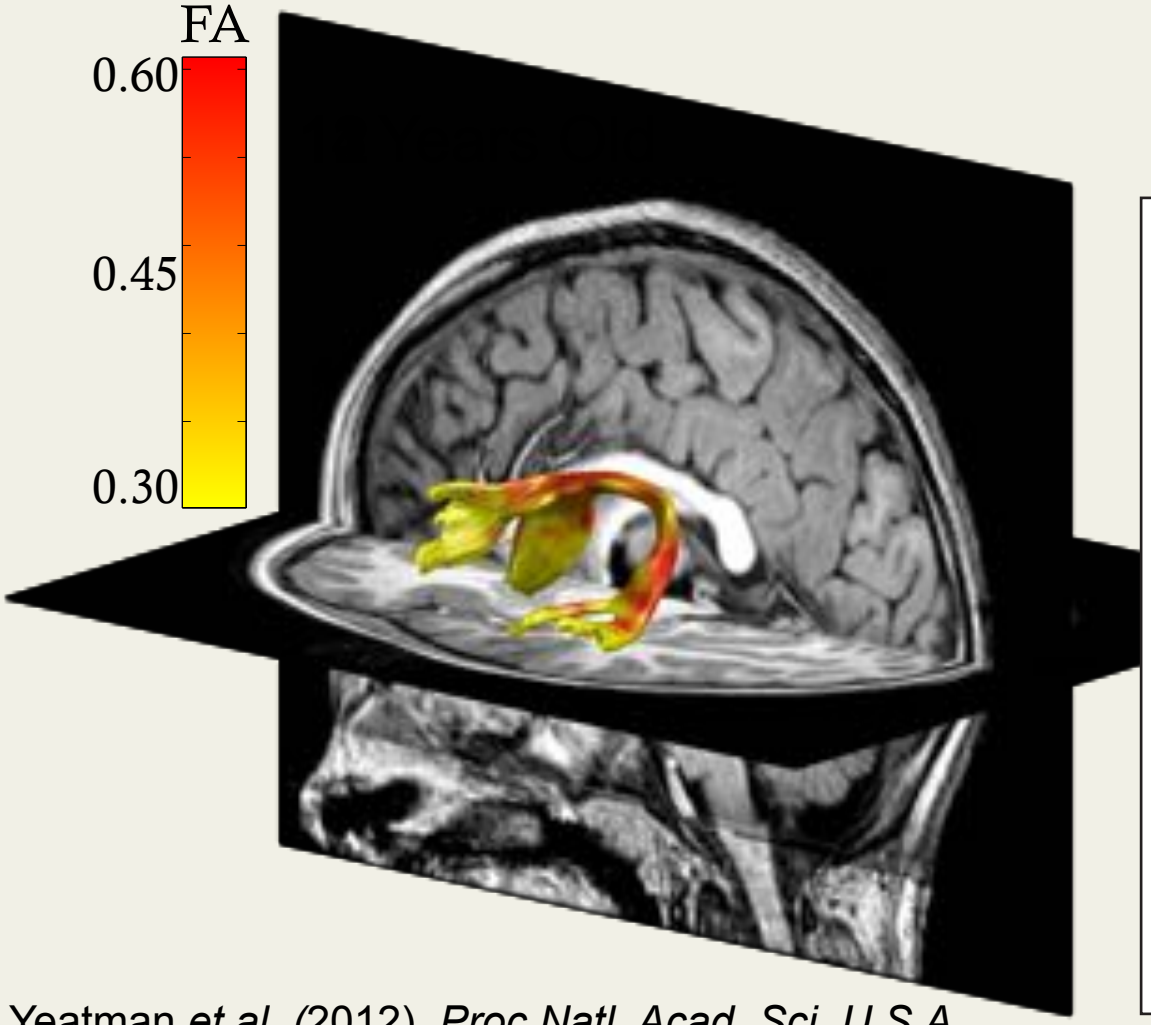
A few important points

- White matter maturation continues into young adulthood.
- Average rate and time of maturation varies among tracts.
- Do we expect each individual to follow this time-course?

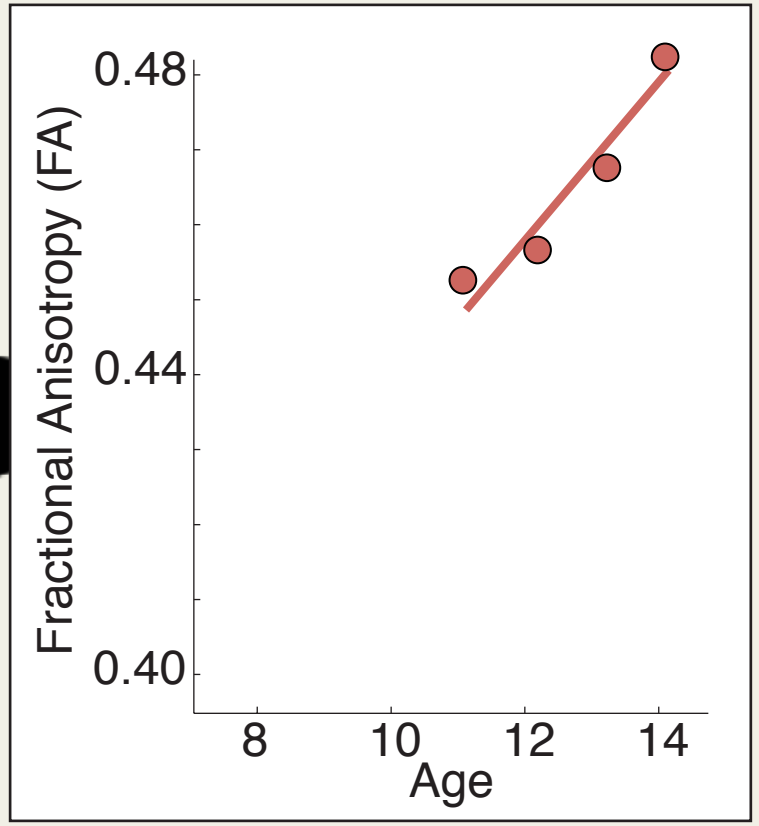


Lebel et al., Neuroimage, 2008, 2012.

Measuring arcuate fasciculus development in an individual (longitudinal)

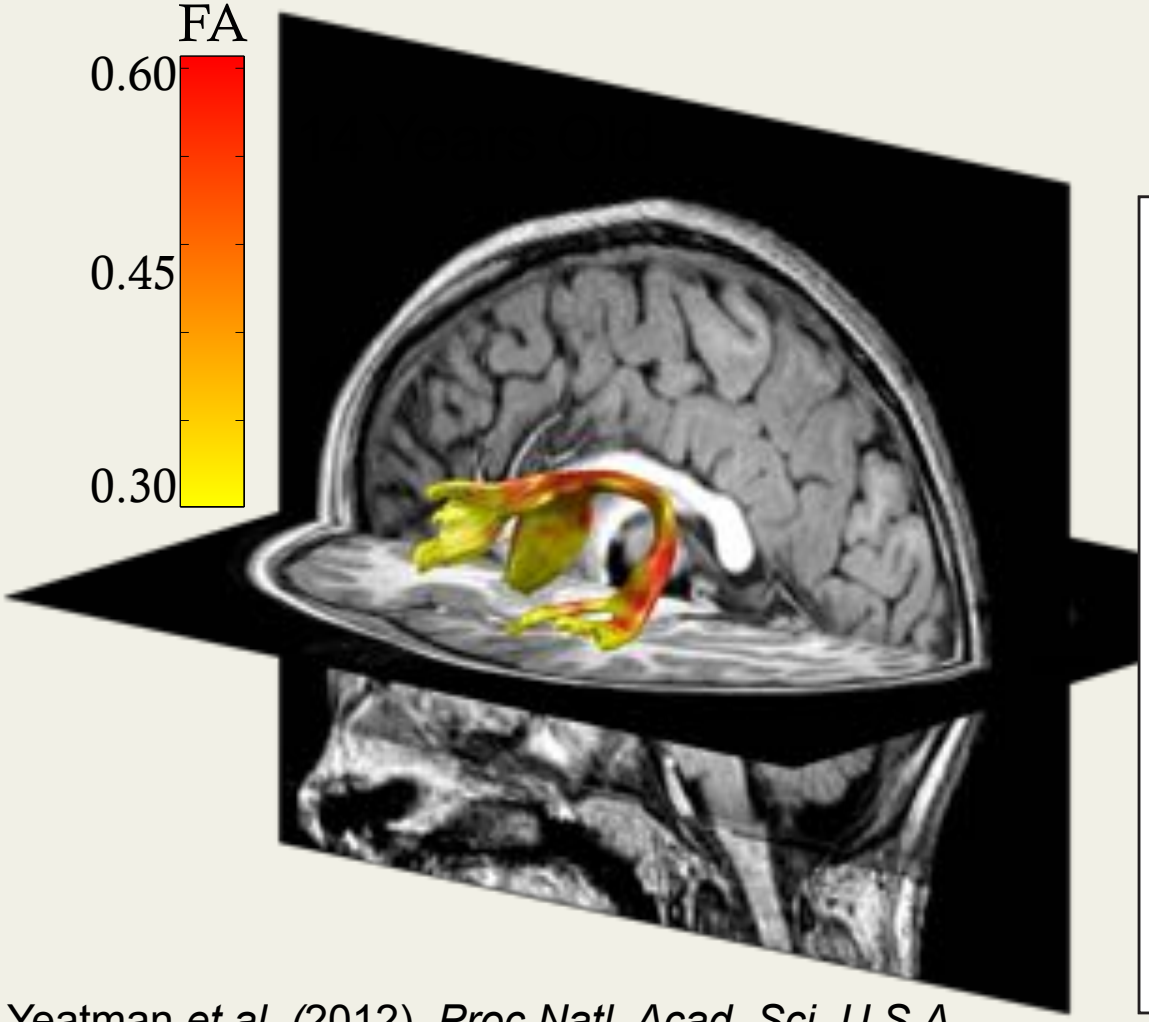


FA=b*(Age)+c



Yeatman *et al.* (2012). *Proc Natl. Acad. Sci. U.S.A.*

Rates of white matter development vary substantially among children



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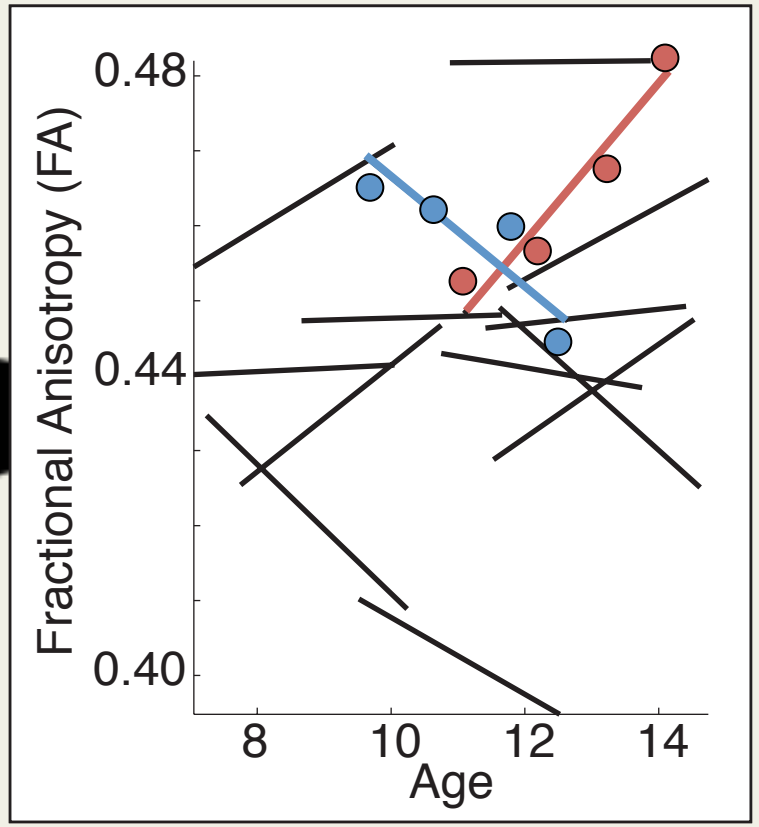
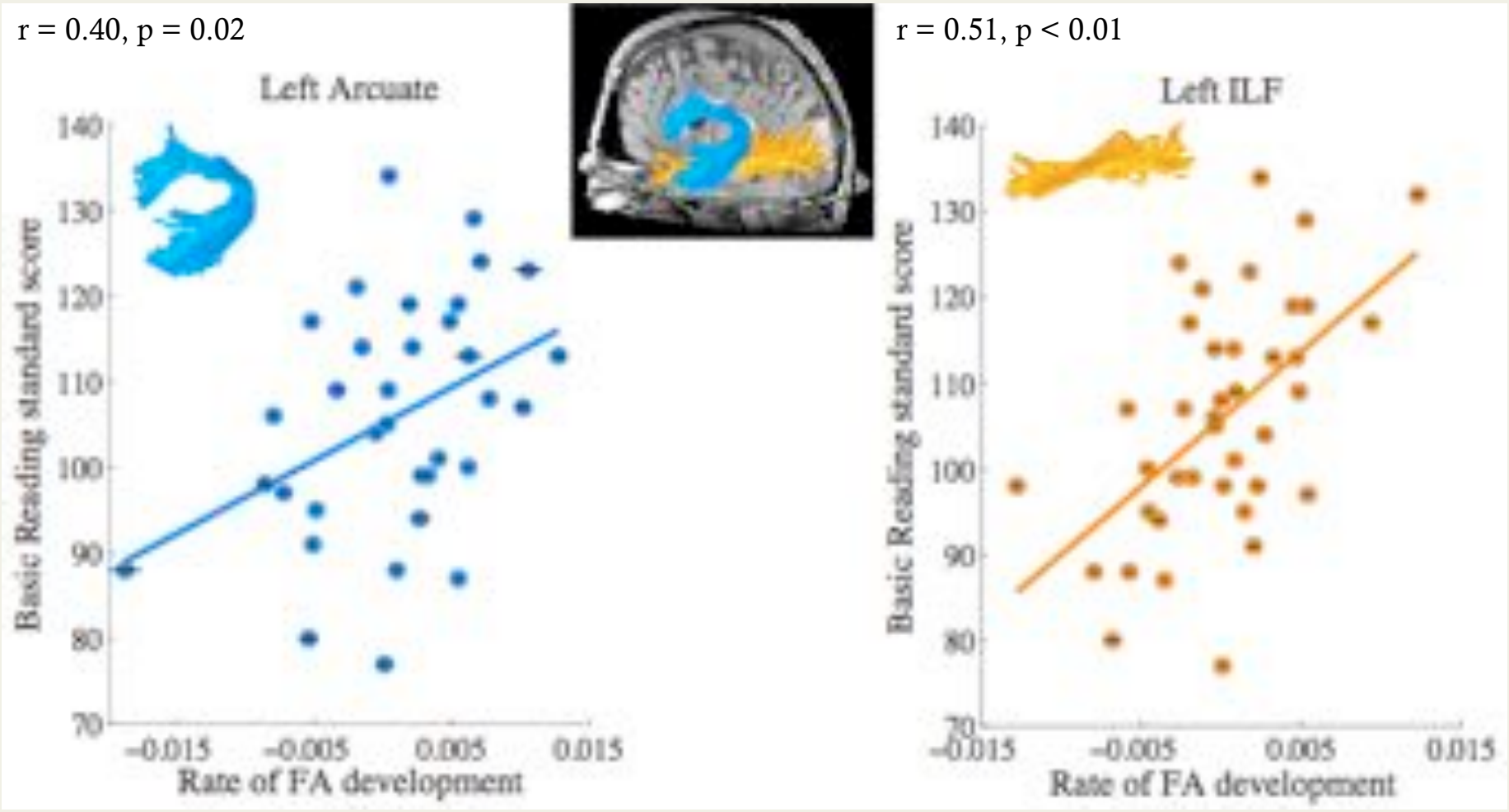


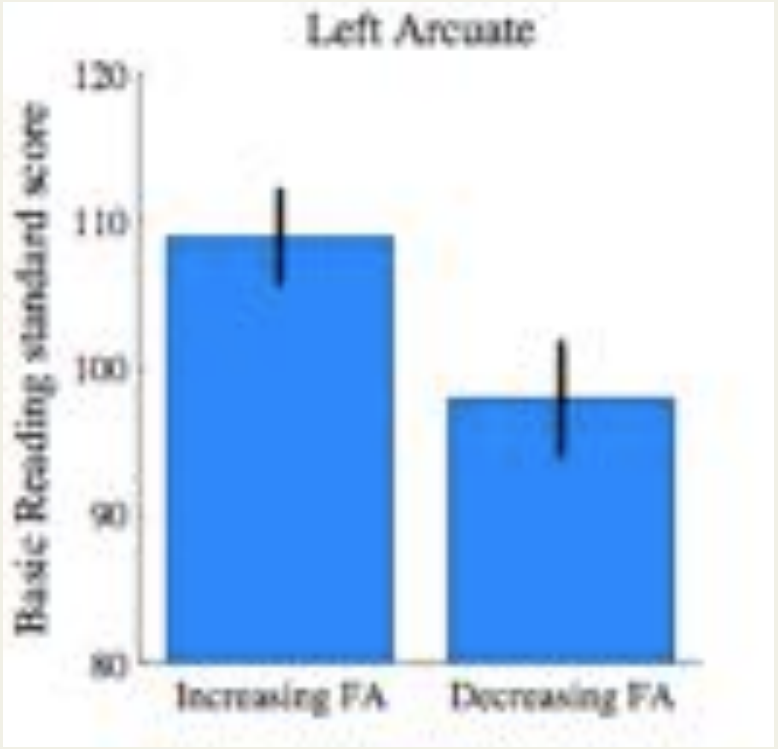
Yeatman *et al.* (2012). *Proc Natl. Acad. Sci. U.S.A.*

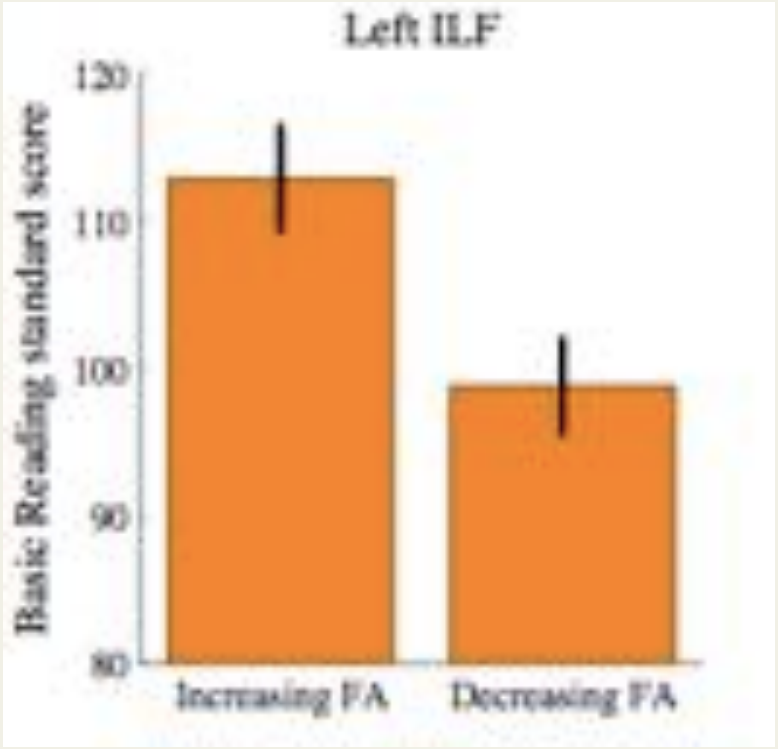
The rate of white matter development correlates with reading skill



Yeatman *et al. (*2012). *Proc Natl. Acad. Sci. U.S.A.*

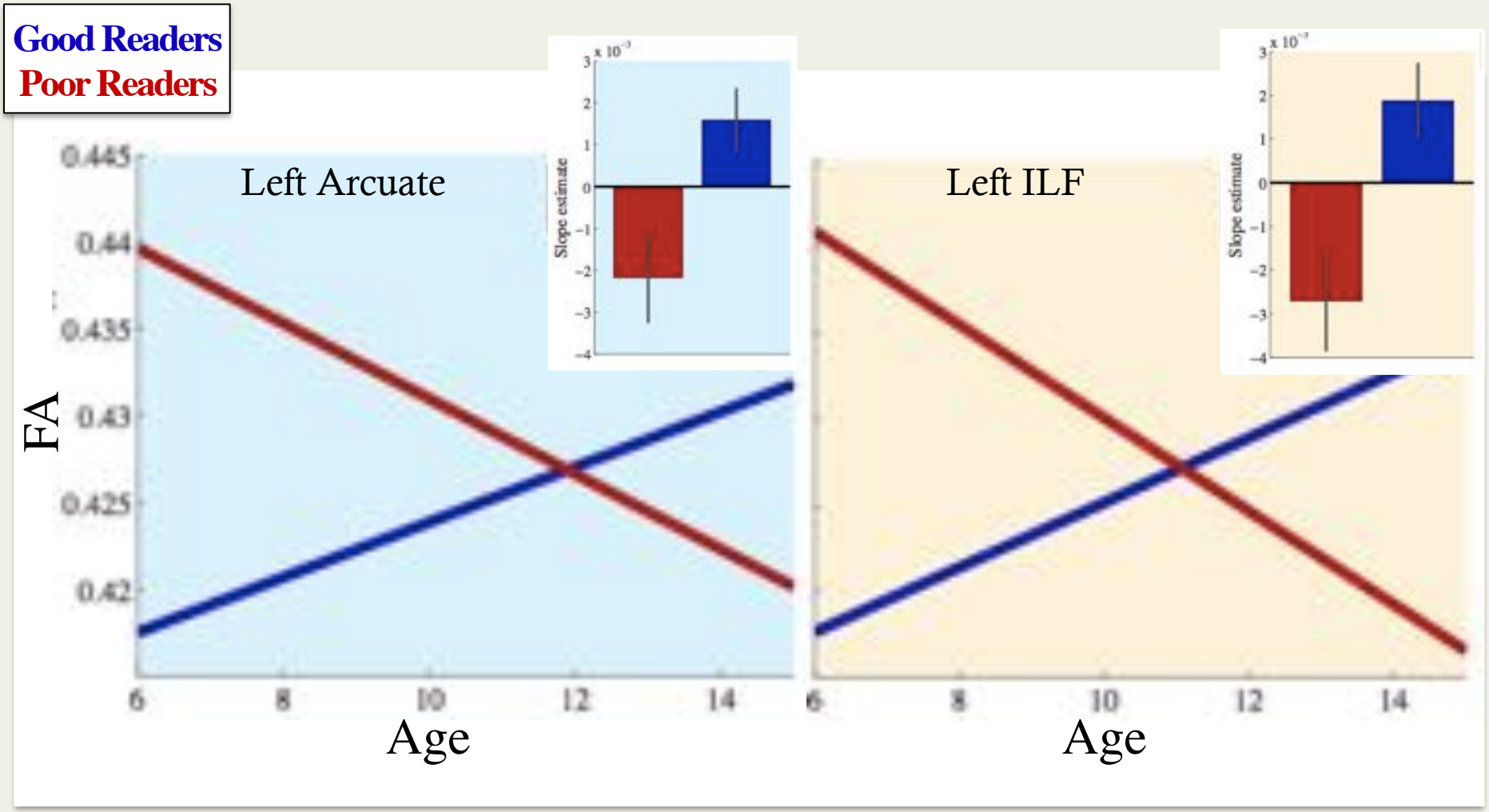
Children with positive growth rates have superior reading skills





Yeatman *et al. (*2012). *Proc Natl. Acad. Sci. U.S.A.*

Good versus poor readers show divergent developmental trajectories



Yeatman *et al.* (2012). *Proc Natl. Acad. Sci. U.S.A.*

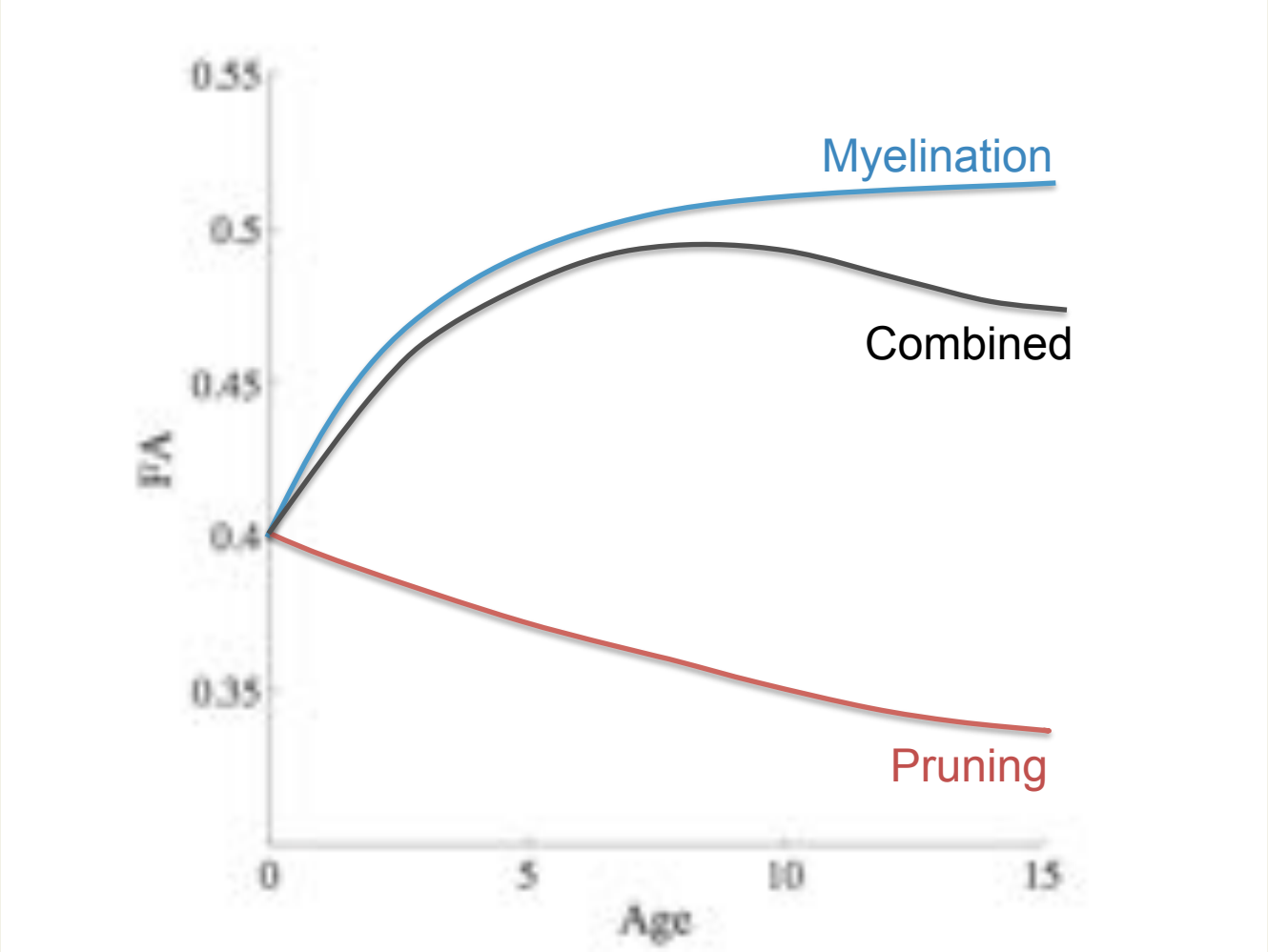
What might be the biology underlying the observed diffusion changes?

Myelination and pruning of axons during development

- Myelination increases during childhood.
  - Speeds signal conduction and increases bandwidth.
  - Is influenced by the level of electrical activity of an axon (Barres & Raff, 1993, *Nature*).
  - Increases the diameter of an axon -> increase in FVF.
- Number of axons decreases after birth (pruning).
  - 3.5x axons in the callosum at birth than in adulthood.
  - Underused axons are pruned away.
  - Decreases the space occupied by axons -> decrease in FVF.

LaMantia & Rakic (1990). *J. Neurosci.* LaMantia & Rakic (1994). *J. Comp. Neurol*.

Dual process account of the joint development of white matter and reading skills



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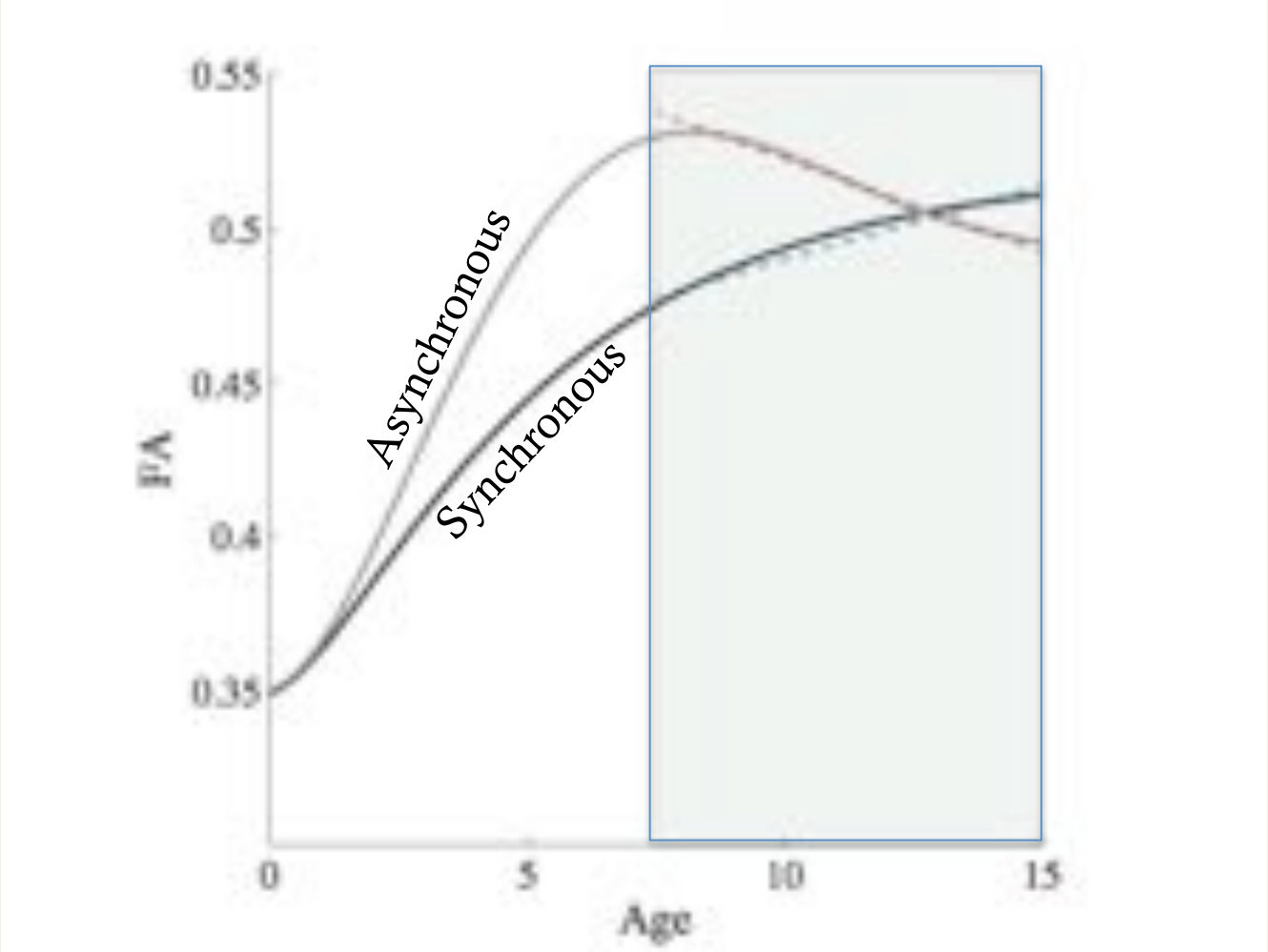

Yeatman *et al. (*2012). *Proc Natl. Acad. Sci. U.S.A.*

Summary: Measuring development with diffusion

- Diffusion is highly sensitive to tissue changes and can inform hypotheses about biological mechanisms.
- The rate and timing of white matter maturation varies substantially among children.
- The dynamics of an individual's white matter development predicts their acquisition of skilled reading.
- Hypothesis: Differences between good and poor readers reflect timing of myelination and pruning.
  - Caveat: Many other factors affect the diffusion process!

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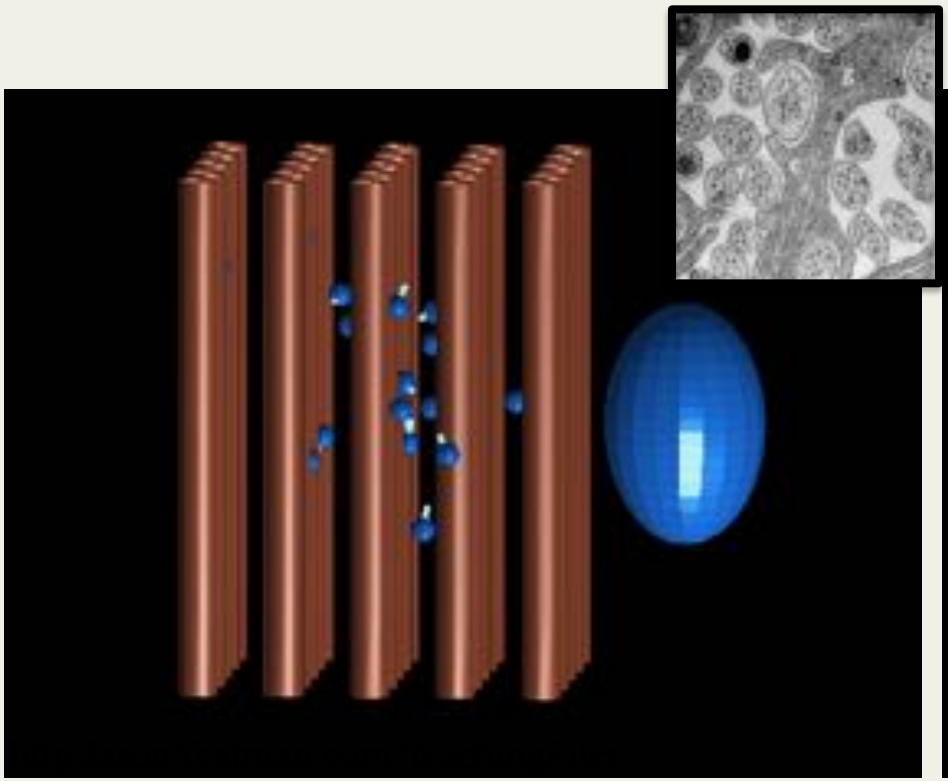
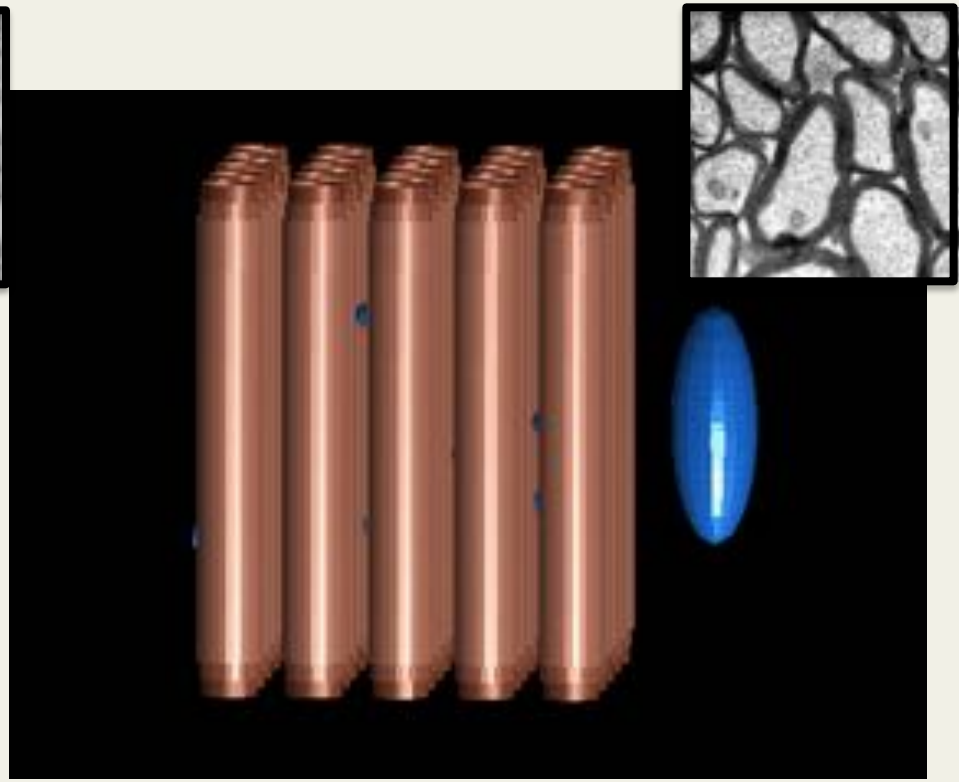
Diffusion is affected by many biological properties not only myelin and axon density

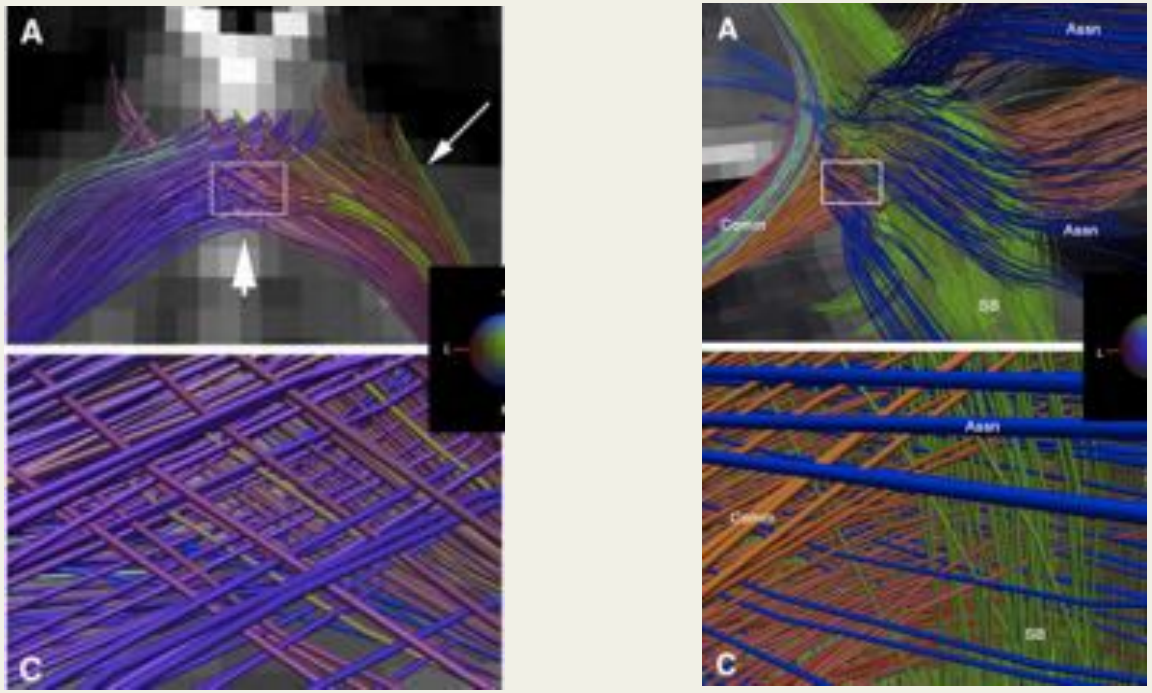




Wandell & Yeatman (2013); Stikov et al., (2011); Assaf & Pasternak (2008); Beaulieu (2002)

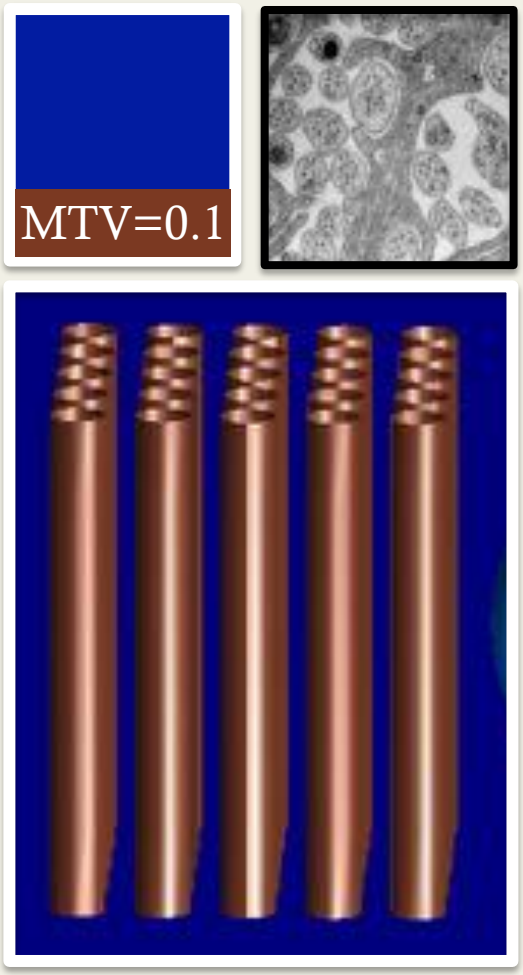
Diffusion is affected by many biological properties not only myelin and axon density

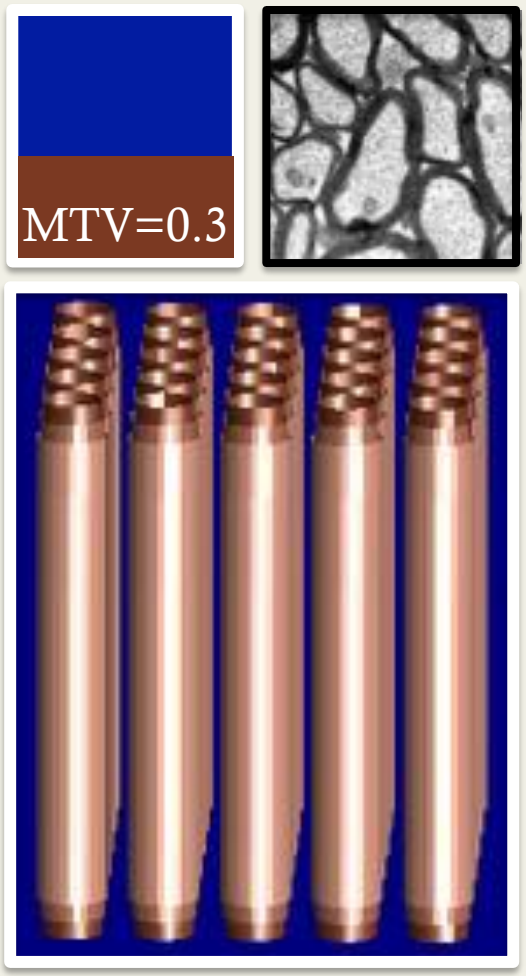
- It's amazing that water diffusion correlates with behavior (e.g., Klingberg et al., 2000).
- The relationship between water diffusion and tissue biology is not straightforward (Beaulieu, 2002).



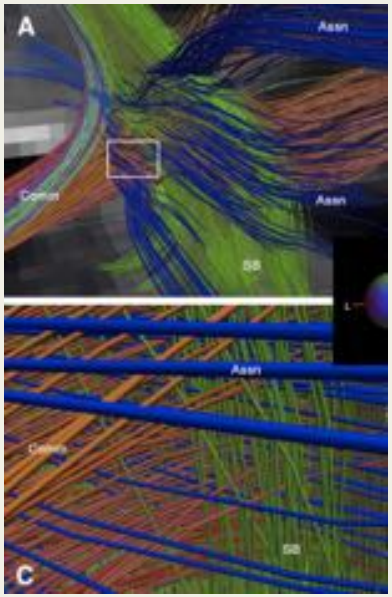
Wedeen et al., (2008, 2012)

Quantitative MRI measurements of tissue volume and composition





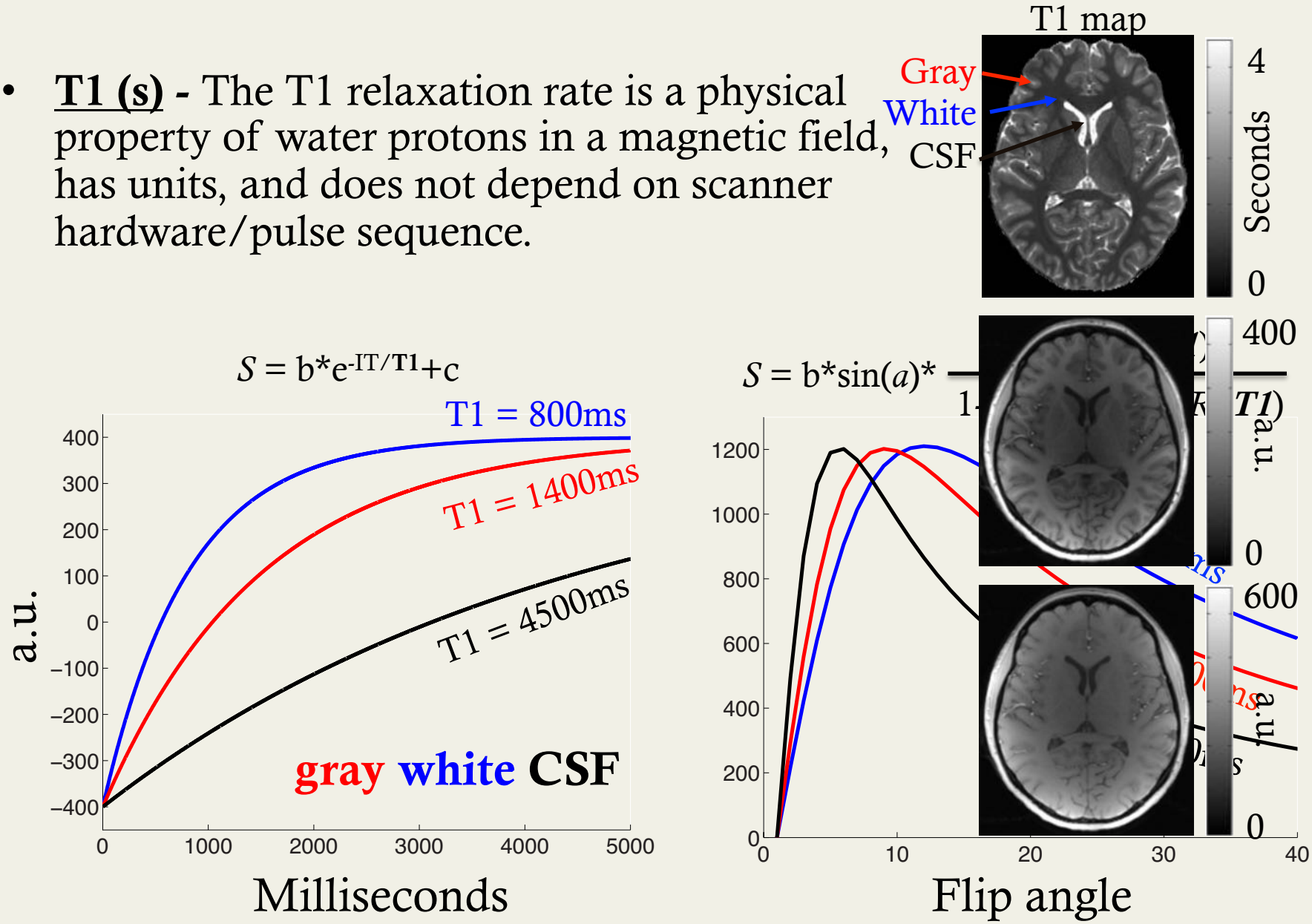
Aviv Mezer



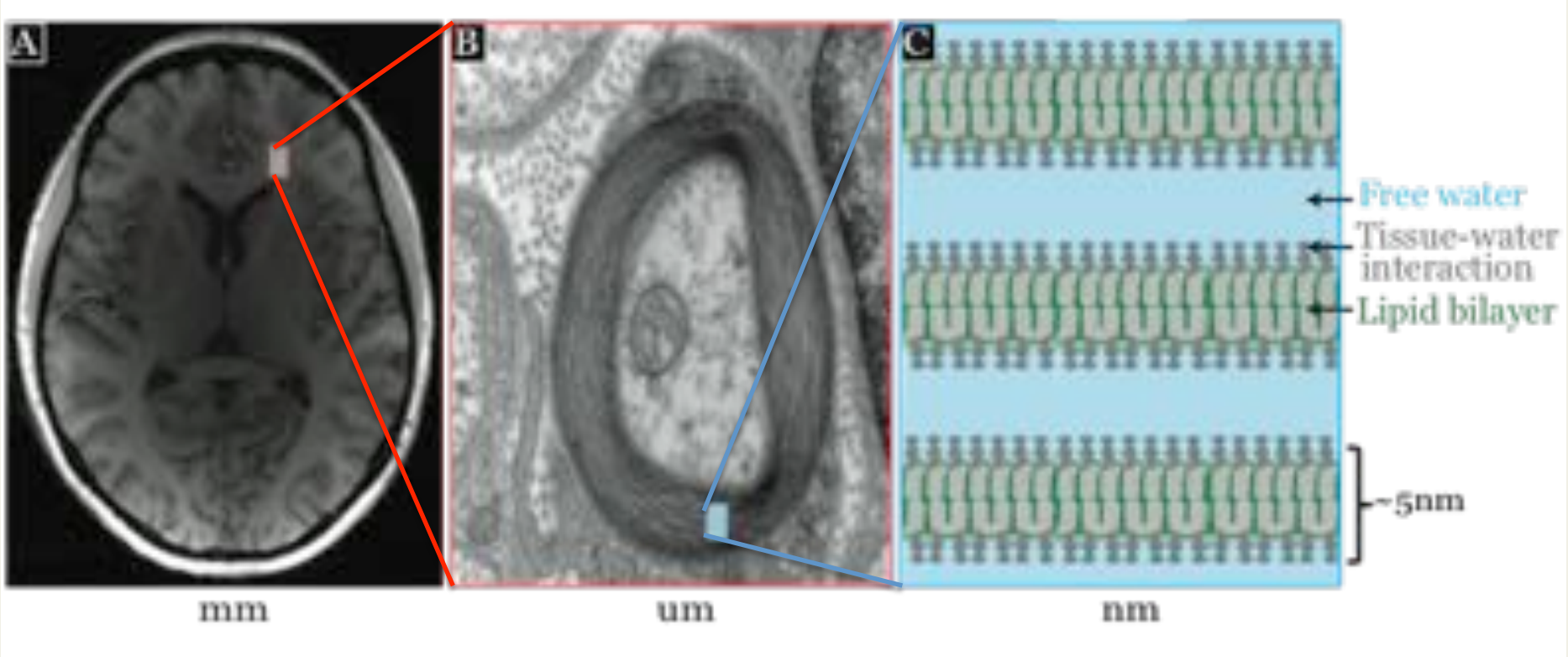
Mezer, Yeatman et al. (*2013*), *Nature Medicine*

What does "quantitative MRI" mean?

- **T1 (s)** - 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.

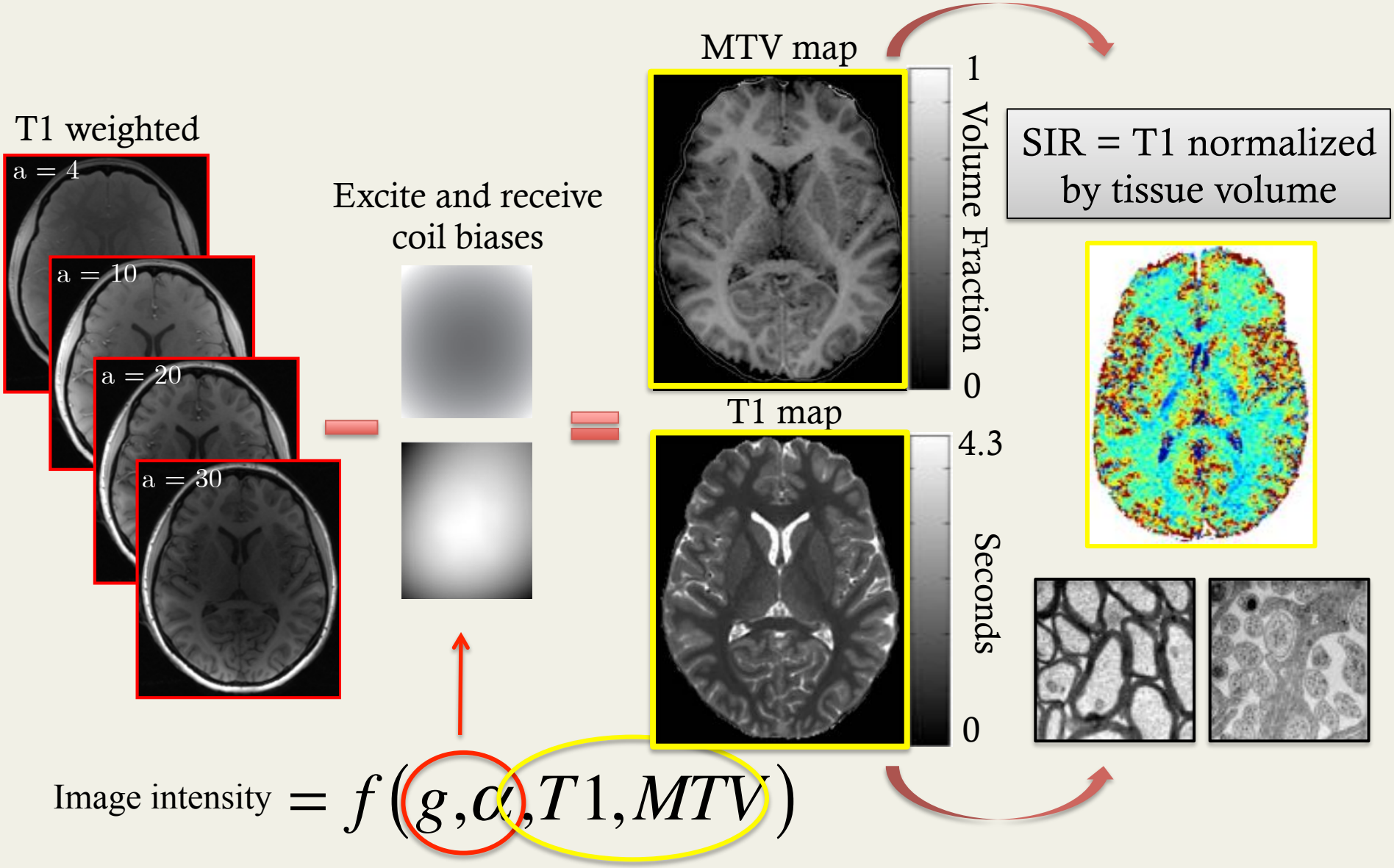


- MR signals (T1) from water protons change when the protons interact with membranes.
- T1 image intensity depends on the amount and composition of tissue in each voxel as well as scanner biases.



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

From images to quantitative tissue maps



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

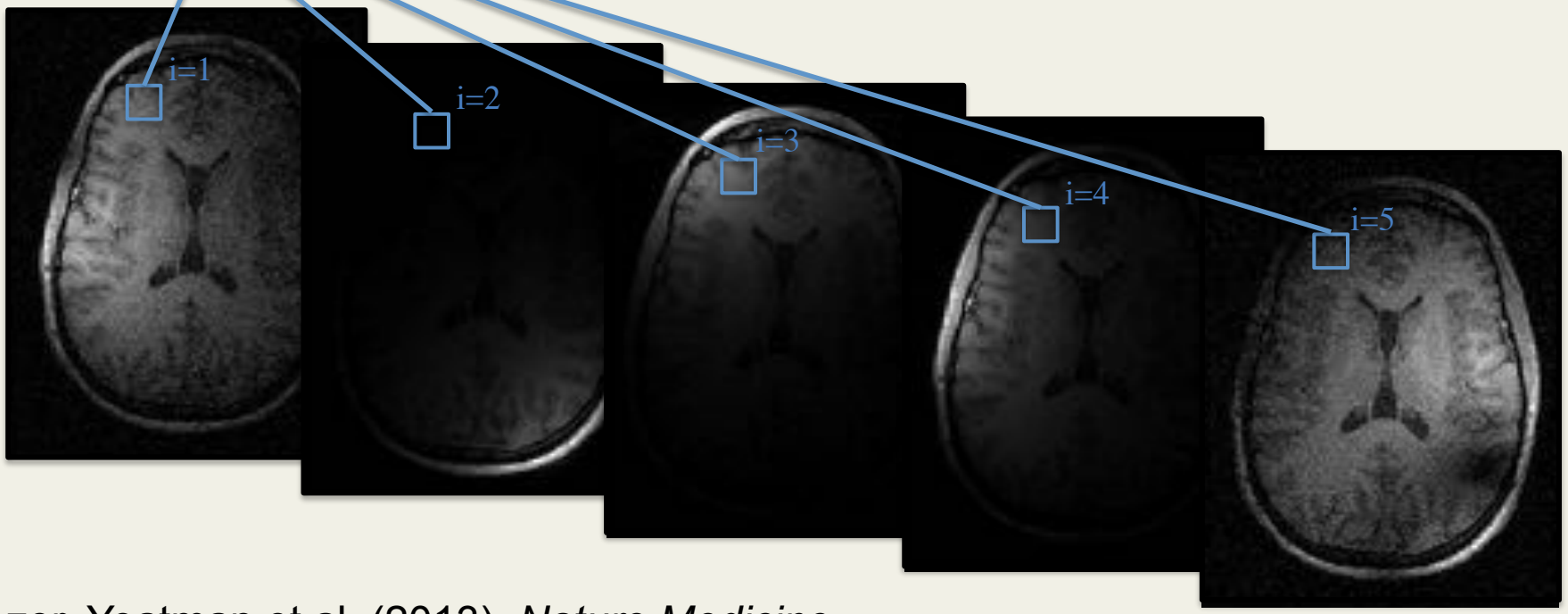
Removing bias and computing MTV

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

$$g_i * (1 - MTV)$$

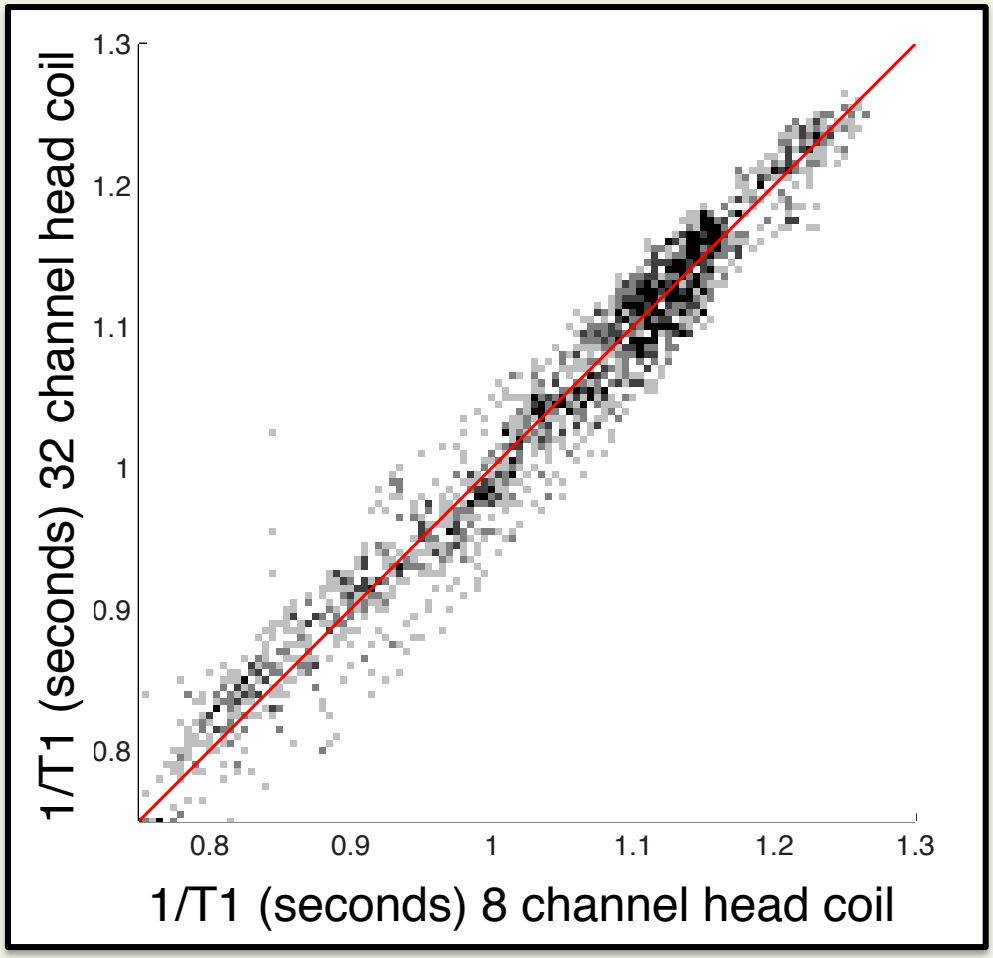
Solve for the each coil's gain function to uncover the true MTV value

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



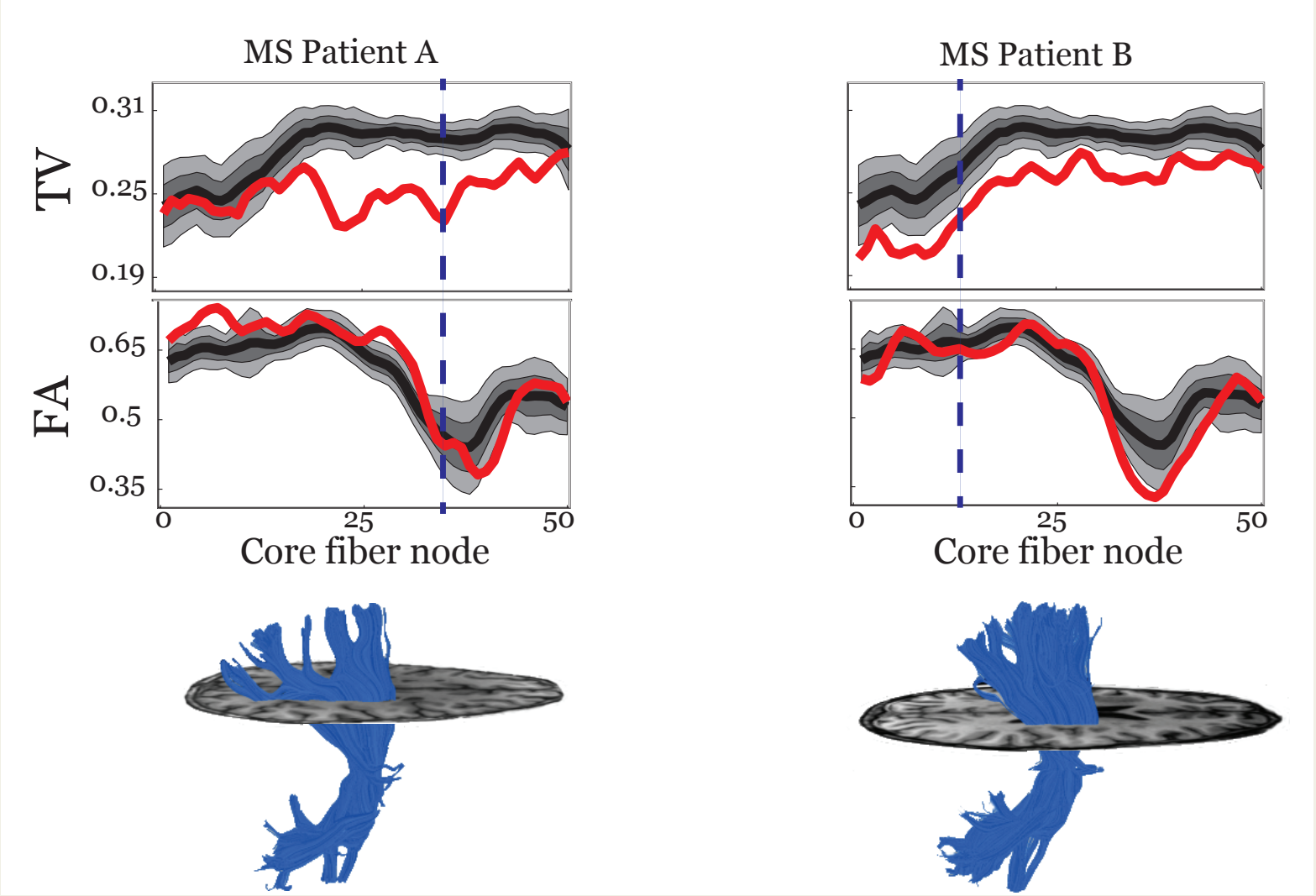
Mezer, Yeatman et al. (2013), *Nature Medicine*

Quantitative MRI measures are independent of scanner hardware



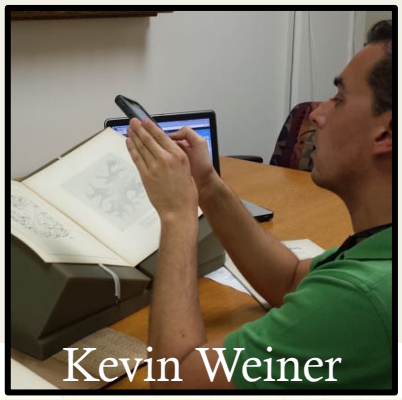
Yeatman, Wandell & Mezer, (2014). *Nature Communications*

Single patient disease detection

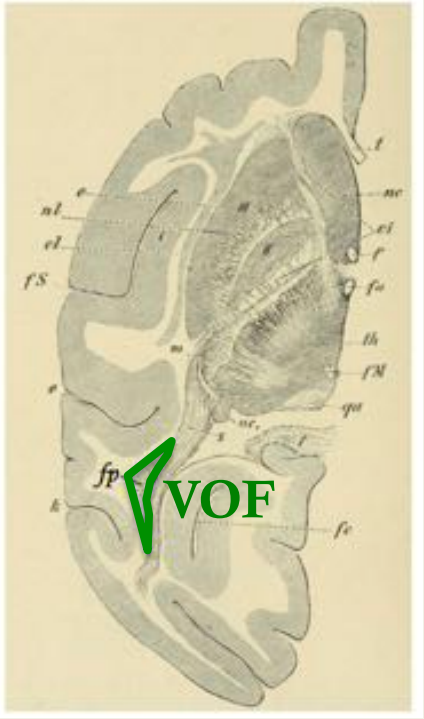


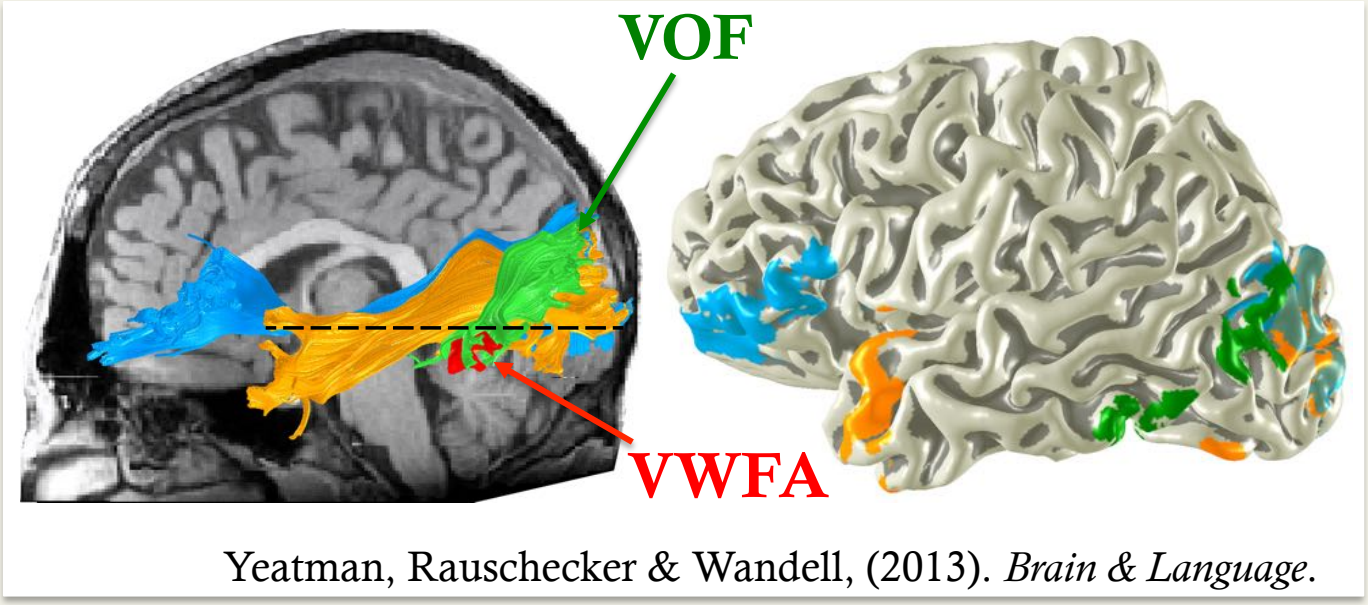
Mezer, Yeatman et al. (2013), *Nature Medicine*

In vivo histology with quantitative T1



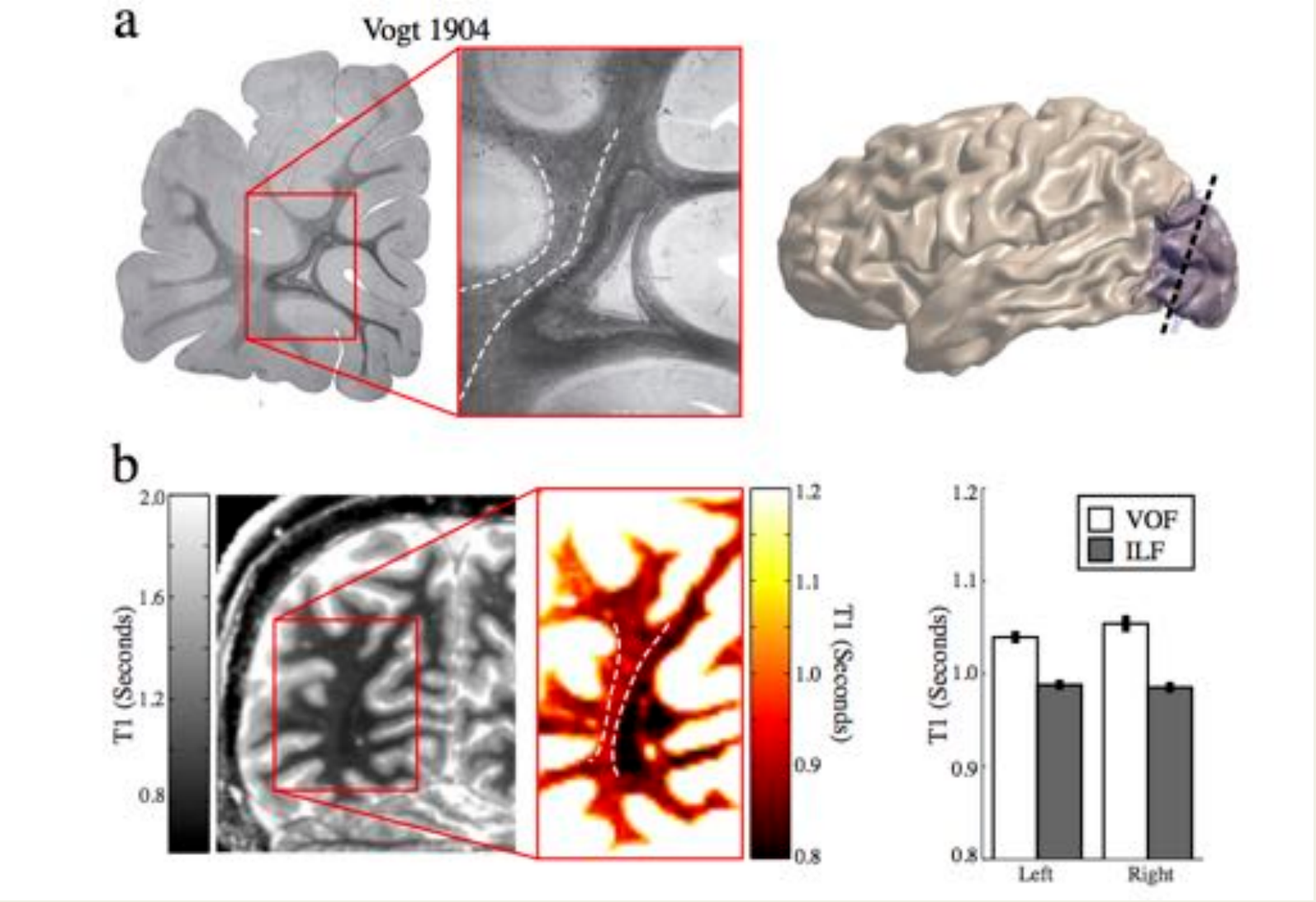
- The vertical occipital fasciculus (VOF) connects the dorsal and ventral visual streams and terminates in the VWFA.





Yeatman, Rauschecker & Wandell, (2013). *Brain & Language*.

In vivo histology with quantitative T1



Yeatman, Weiner, Pestilli, Rokem, Mezer & Wandell (2014). PNAS

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).
  - Surface interaction rate (**SIR**) is sensitive to changes in molecular composition.
- Quantitative MRI measurements are independent of the specific scanner hardware and pulse sequence.
  - Opens up new diagnostic applications.

Outline

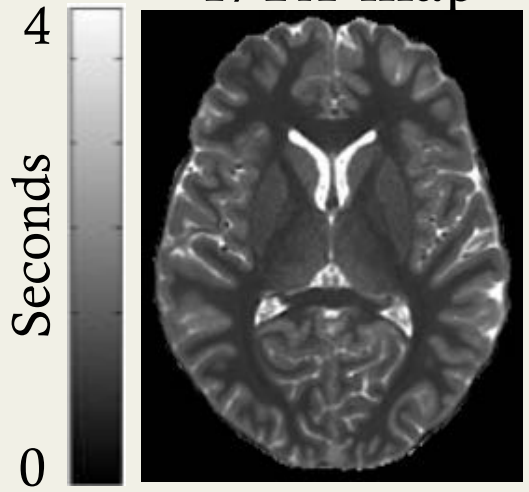
1. From tractography to fascicles: Segmenting an individual's white matter.
2. Measuring white matter development with diffusion.
   - Inferring tissue properties from diffusion.
   - Cross-sectional versus longitudinal measurements.
   - Modeling the processes that underlie learning to read.
3. Quantitative MRI measurements of tissue volume and composition.
4. **Combining multiple measurements to dissociate developmental processes.**
   - **Testing models of development.**

In vivo histology: Combining measures to model brain tissue

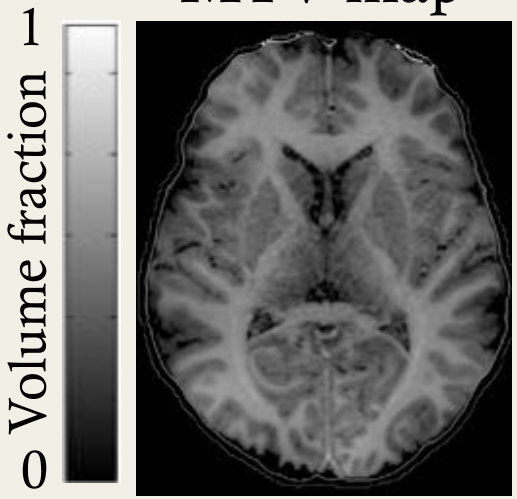
- What can we learn about development with qMRI:
  - Do different types of tissue have distinct maturational time-courses (e.g., myelin vs. astrocytes)?
  - Which properties of the white matter are related to behavior?
  - Can we model how properties of the white matter affect cortical computation (i.e.,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

In vivo histology:
Combining measures to model brain tissue

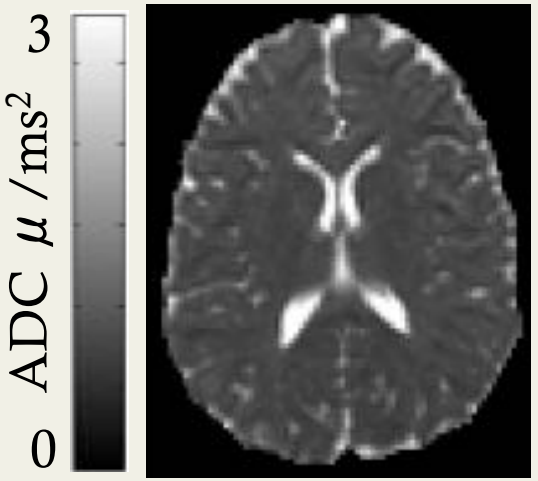
T1 map
1/R1 map



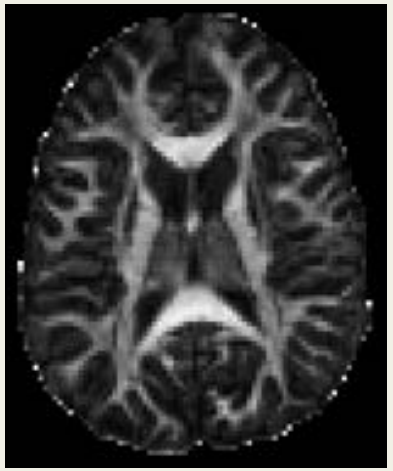
MTV map



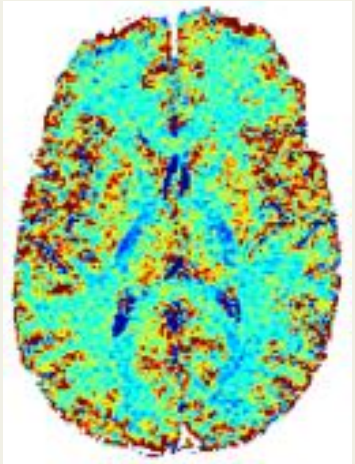
Diffusivity



FA

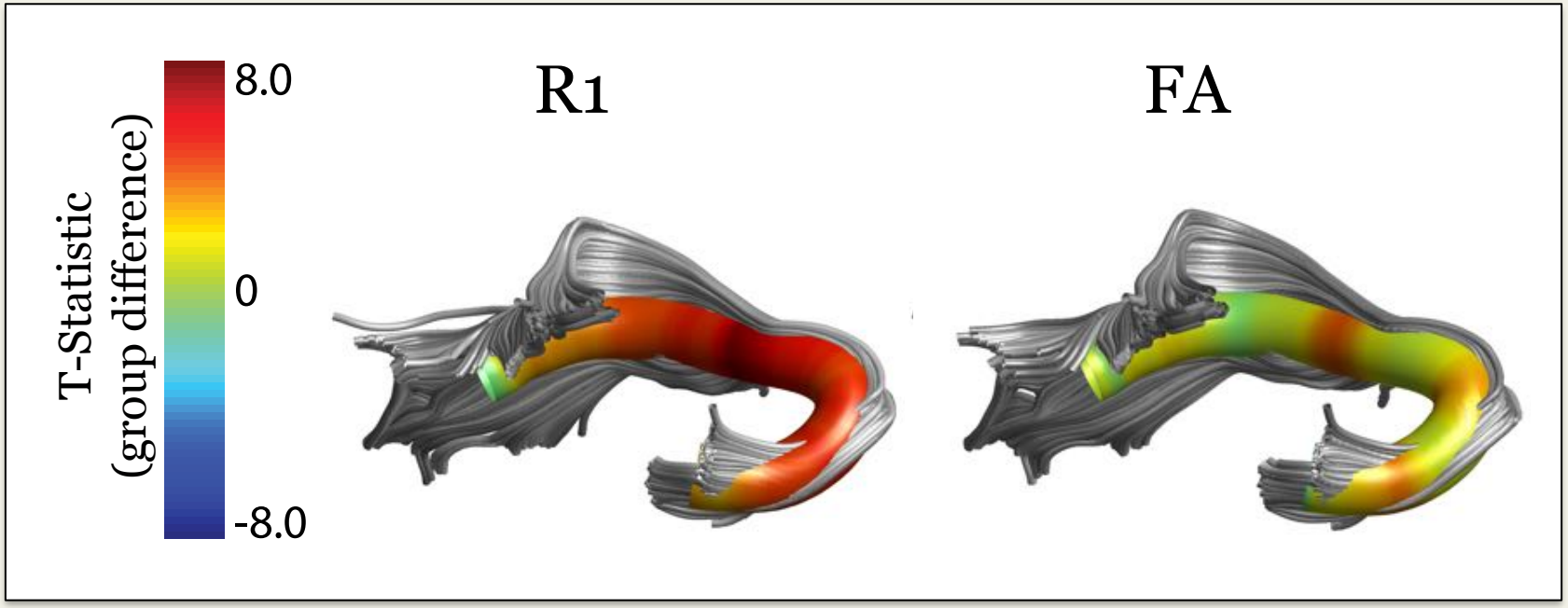


SIR



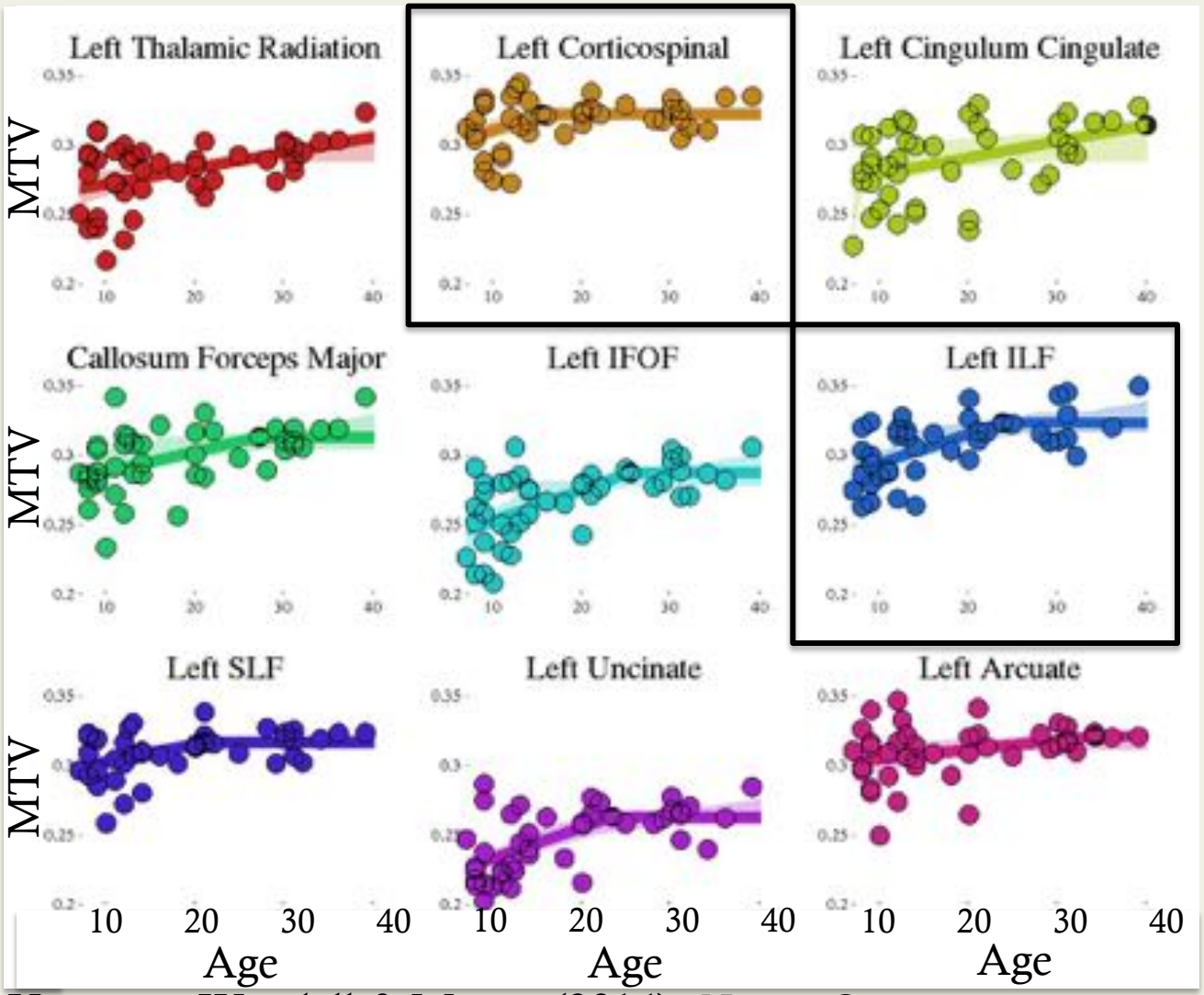
Fascicle development measured with diffusion vs. R1

- FA varies substantially along the length of a tract. This is due to geometric properties not changes in myelin.
- In terms of R1 but not FA, growth rates are consistent along the tract length.

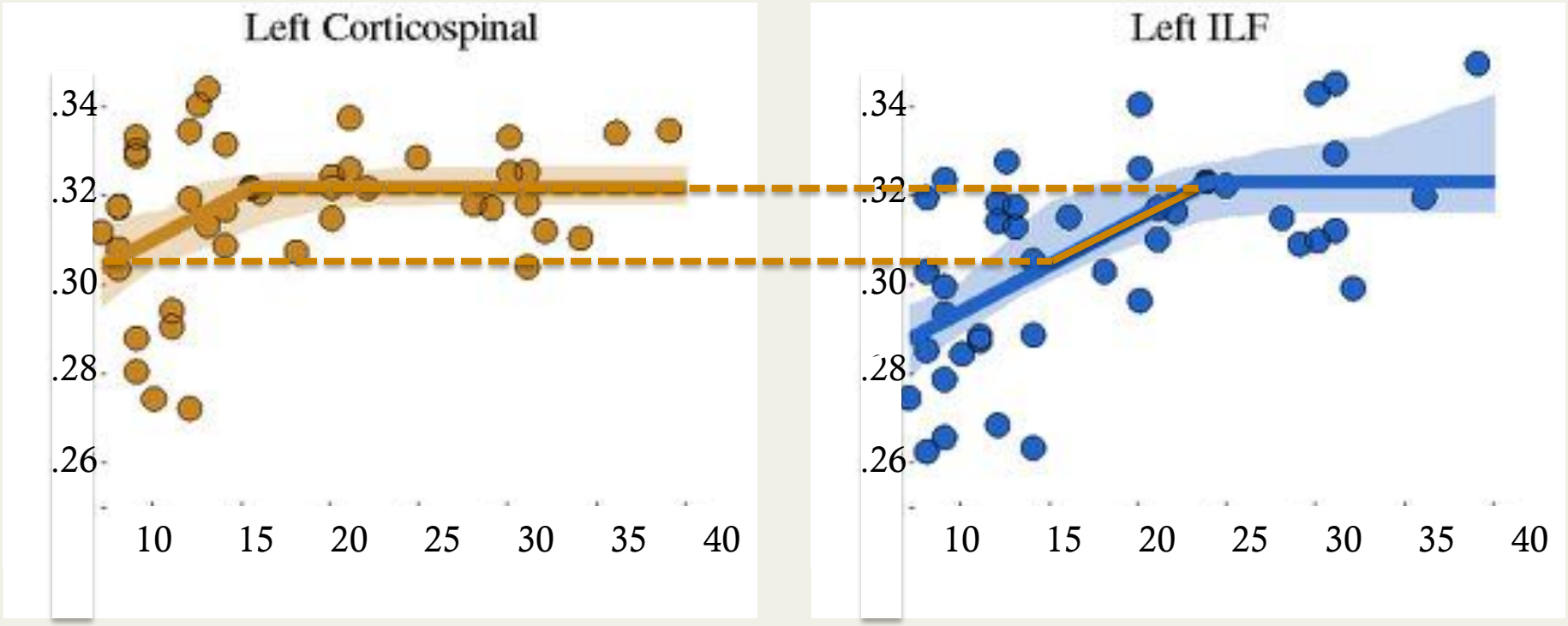


Yeatman, Wandell & Mezer, (2014). *Nature Communications*

Measuring the creation of new tissue in the developing brain



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



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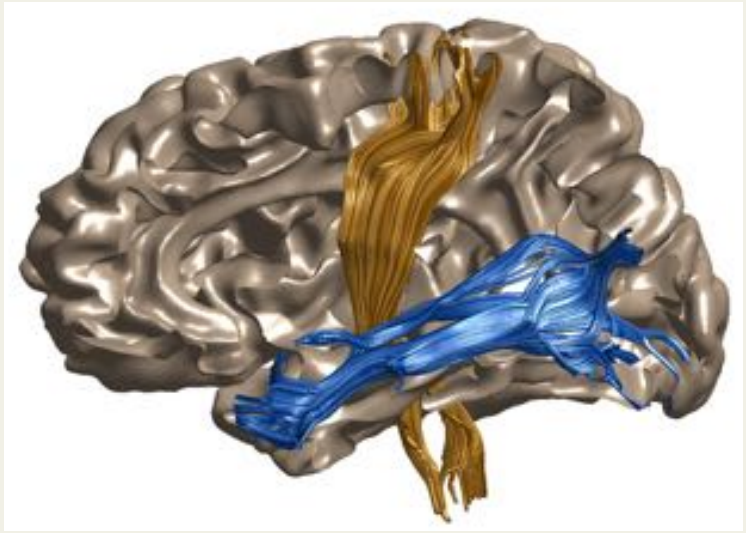
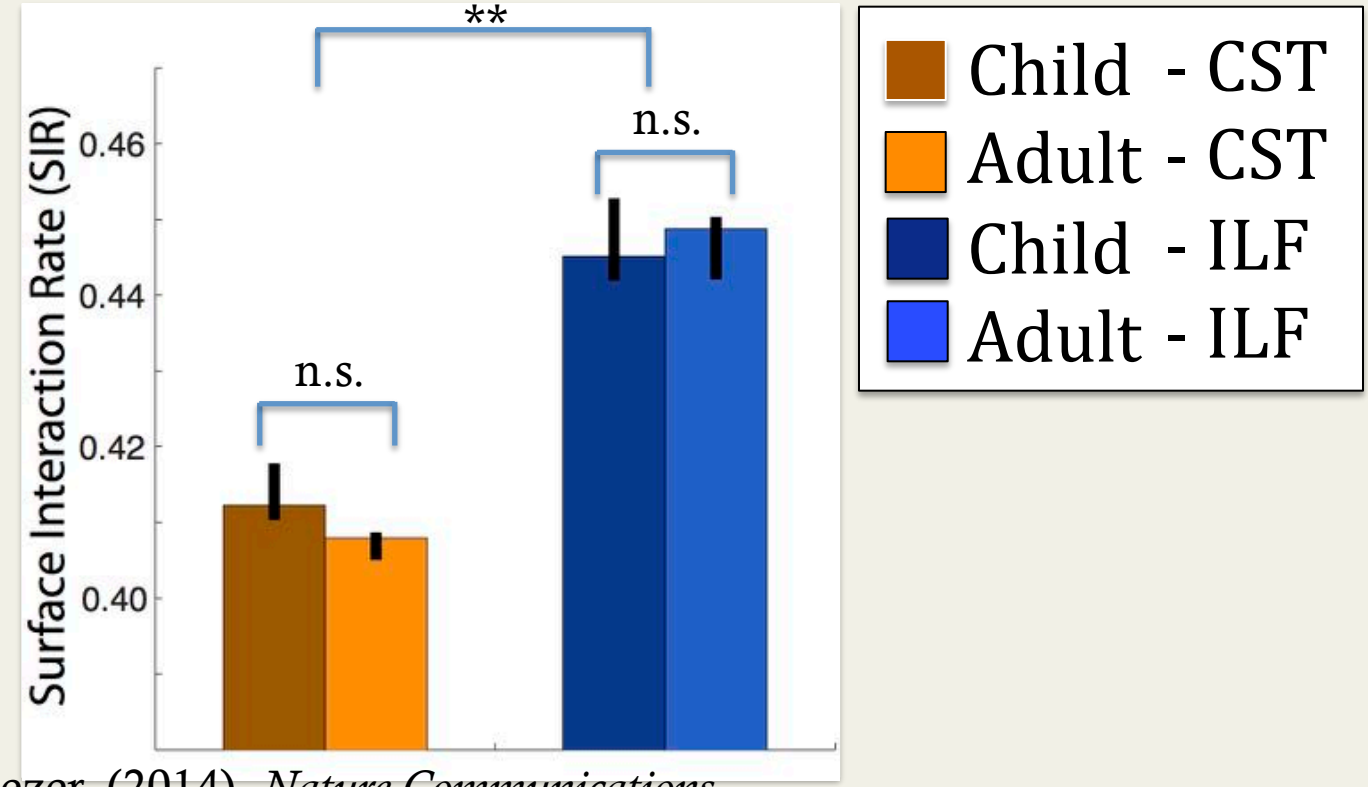
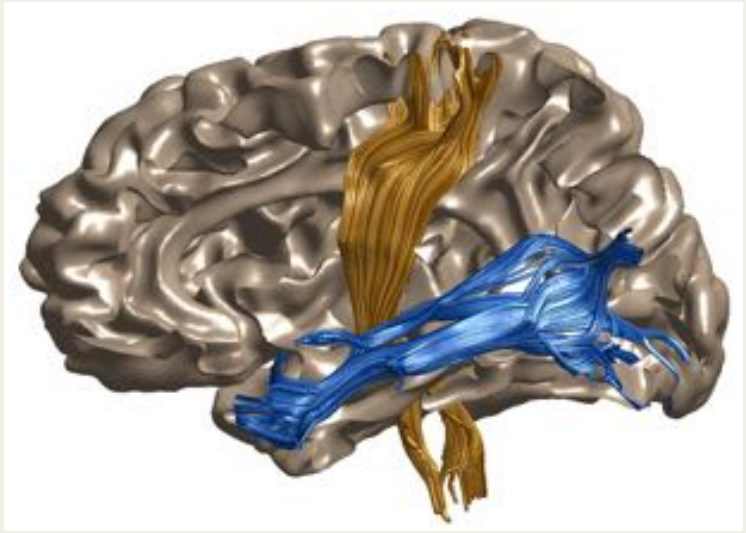
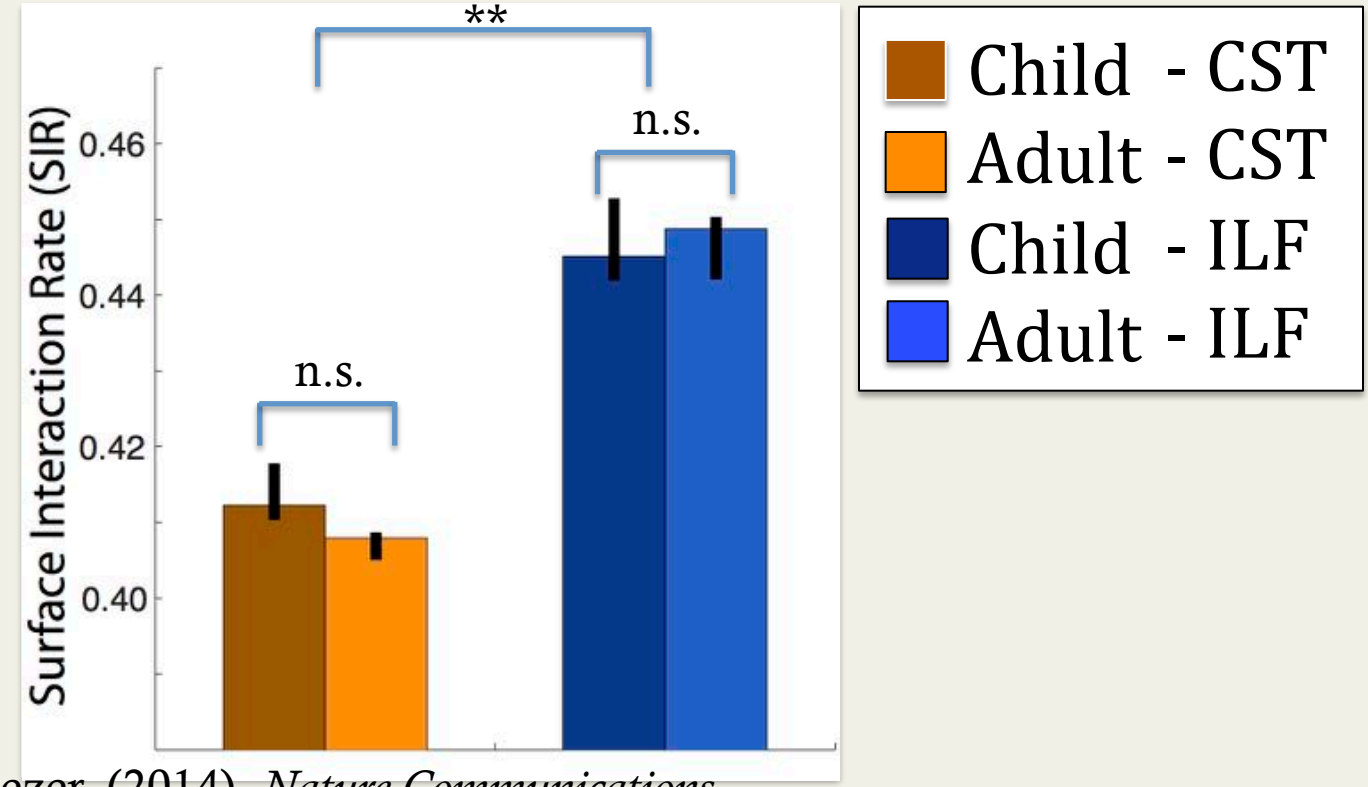




Yeatman, Wandell & Mezer, (2014). *Nature Communications*

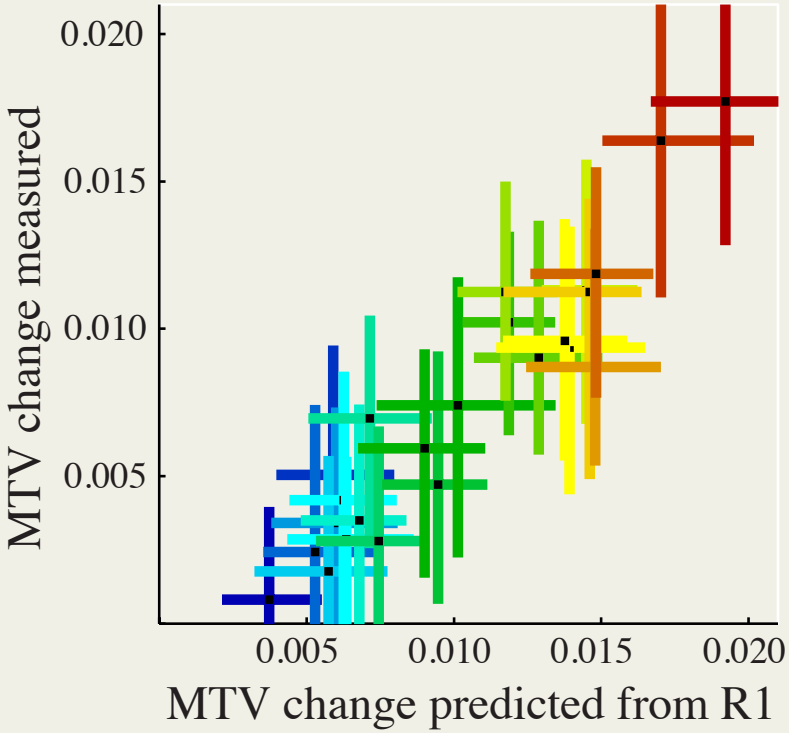


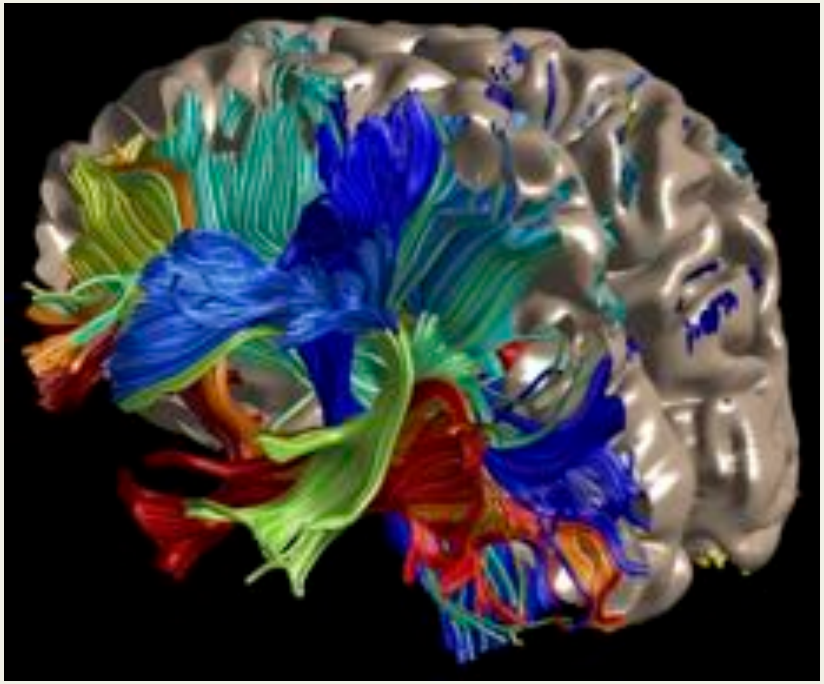


Yeatman, Wandell & Mezer, (2014). *Nature Communications*

Does each qMRI parameter measure the same thing?

Can we detect multiple developmental processes in the white matter?





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

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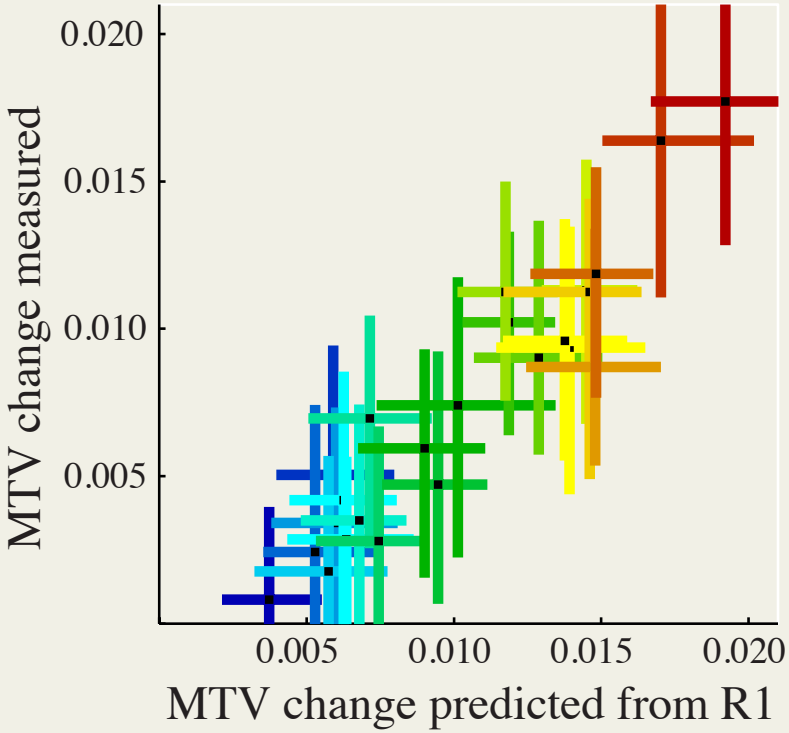
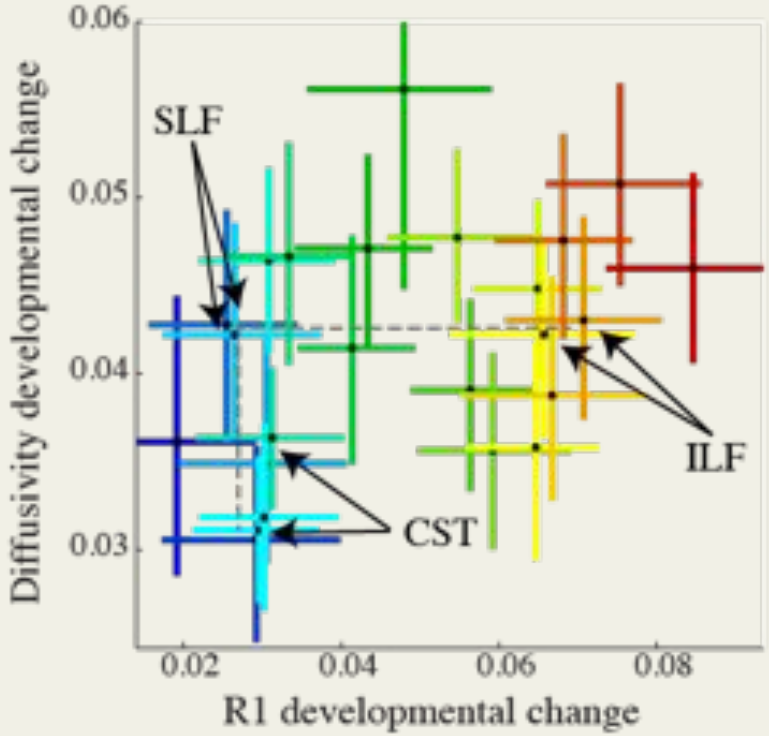
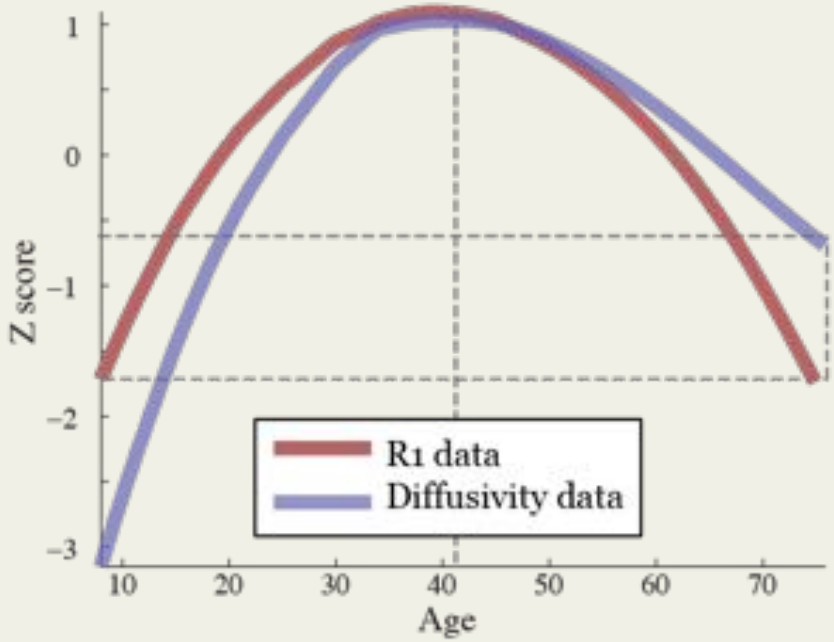


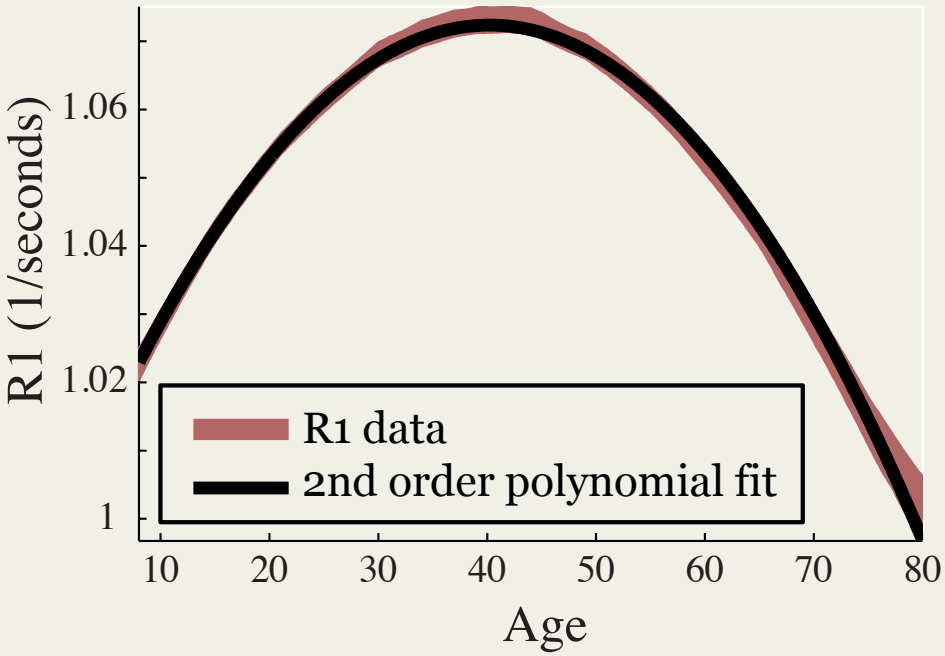


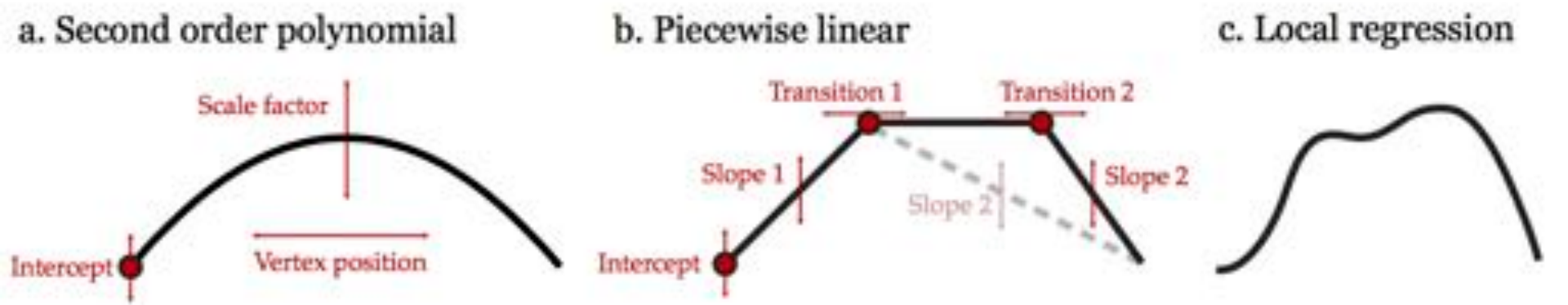
- R1 and MTV are sensitive to the same developmental processes.
- Diffusion is sensitive to independent processes.

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

Looking forward: Modeling brain development

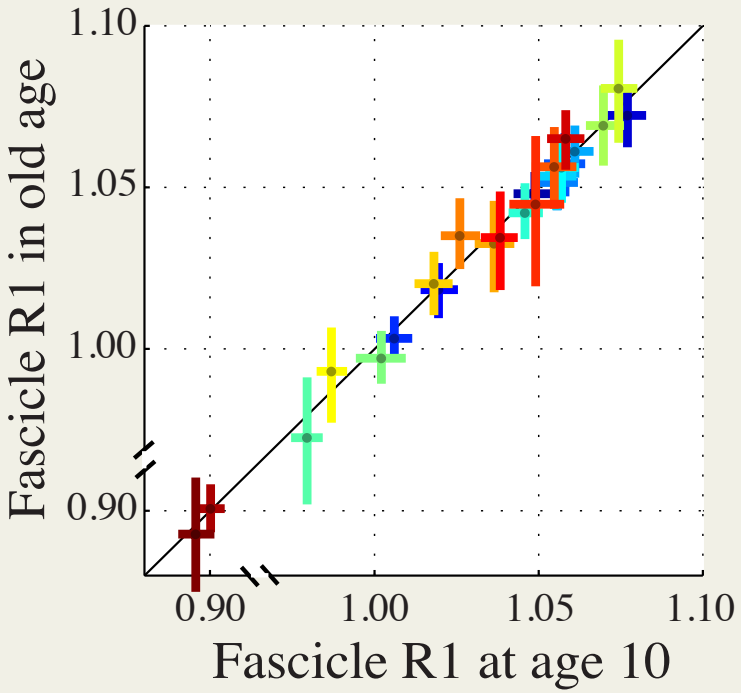




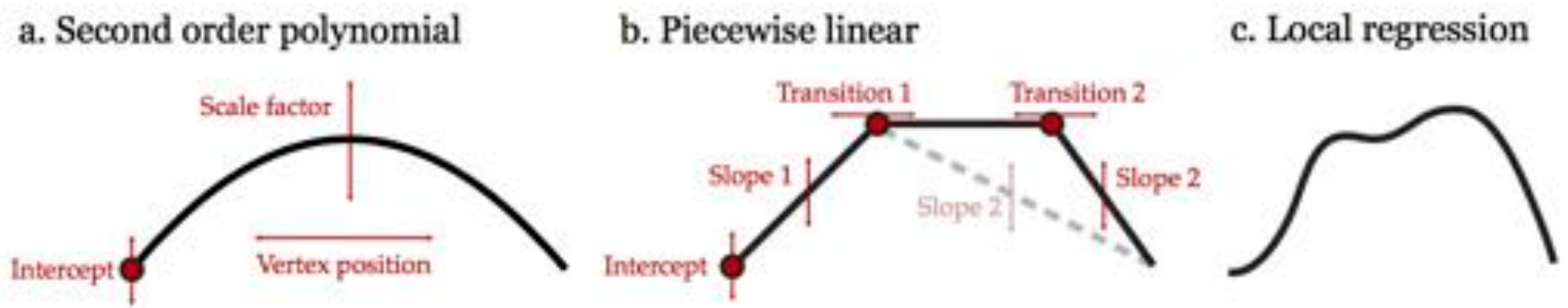


Yeatman, Wandell & Mezer, (2014). *Nature Communications*

Looking forward: Modeling brain development



1. Testing the prediction of parabolic model: Lifespan changes should be symmetric.
2. Do we expect this to be true for every individual?



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.
- A symmetric model predicts R1 changes over the lifespan.
  - Models provide insight into mechanisms and generate testable perditions.
- How might we develop a model that integrates measures of tissue properties, cortical computation and behavior?

Thank You!

Brian Wandell

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Aviv Mezer

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Heidi Feldman

Ariel Rokem

Michal Ben-Shachar

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