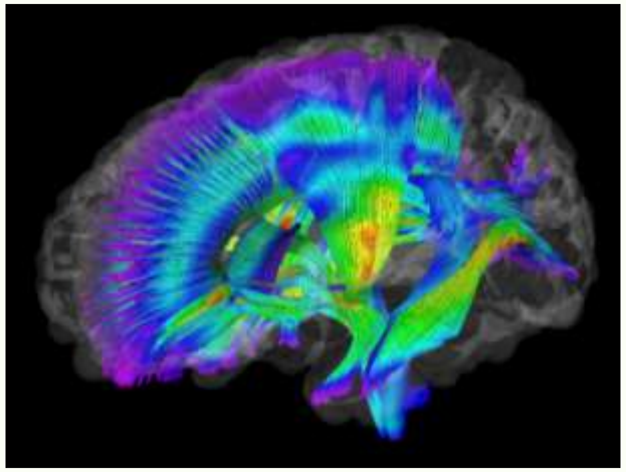
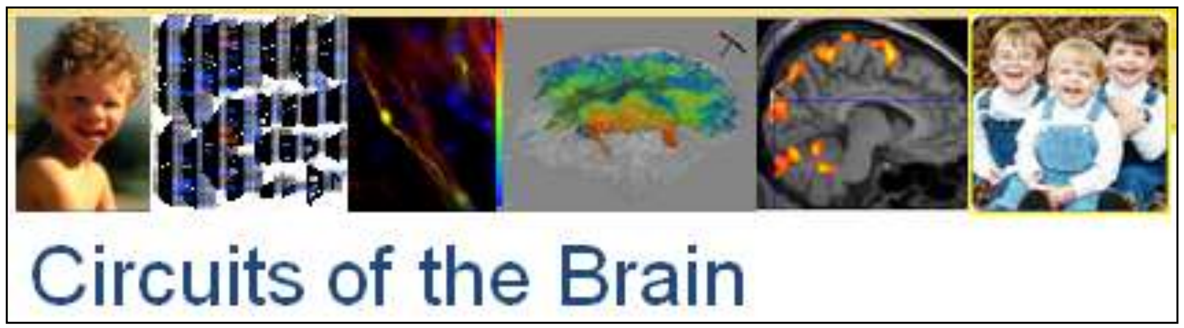
Modeling of early-infant brain growth using longitudinal data from diffusion tensor imaging.



Guido Gerig, Neda Sadeghi, PhD,
Marcel Prastawa, Tom Fletcher,
Clement Vachet
Scientific Computing and Imaging Institute
University of Utah
John H. Gilmore, UNC Chapel Hill
ACE-IBIS Team (Piven et al., UNC CH)

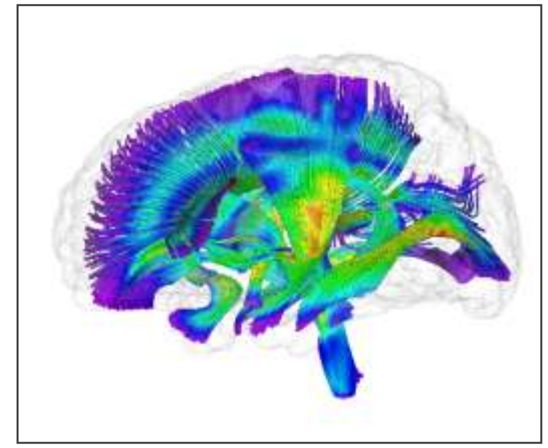
N. Sadeghi, M.W. Prastawa, P.T. Fletcher, J. Wolff, J.H. Gilmore, G. Gerig. **"Regional characterization of longitudinal DT-MRI to study white matter maturation of the early developing brain,"** In *NeuroImage*, Vol. 68, pp. 236--247. March, 2013. , DOI: 10.1016/j.neuroimage.2012.11.040 , PubMed ID: 23235270

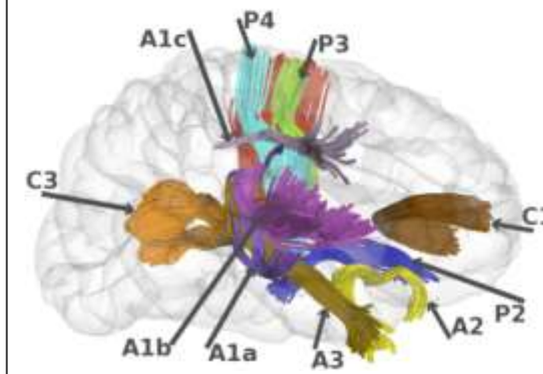


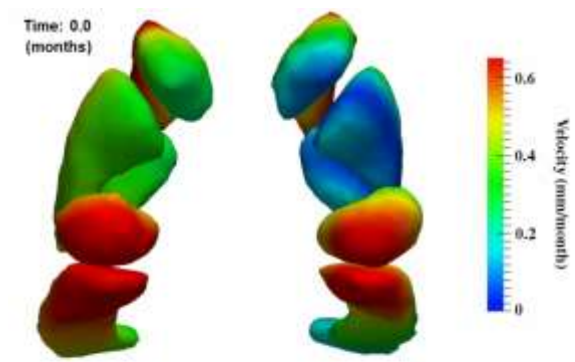
CAMID
COCAINE AFFECTS
MOTHER-INFANT DYADS

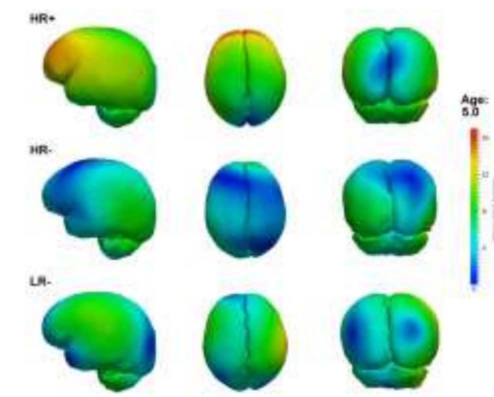
National Alliance for Medical Image Computing

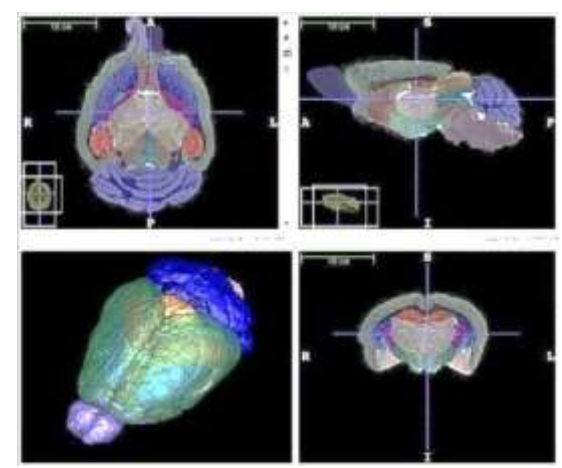
3D Slicer version 4.0

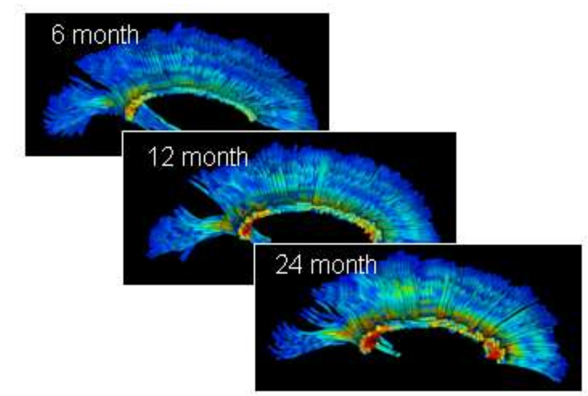


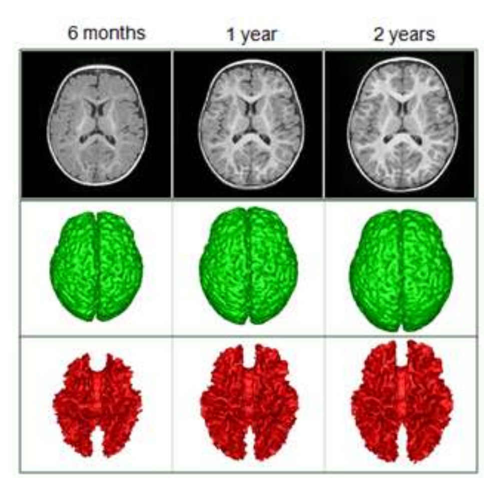


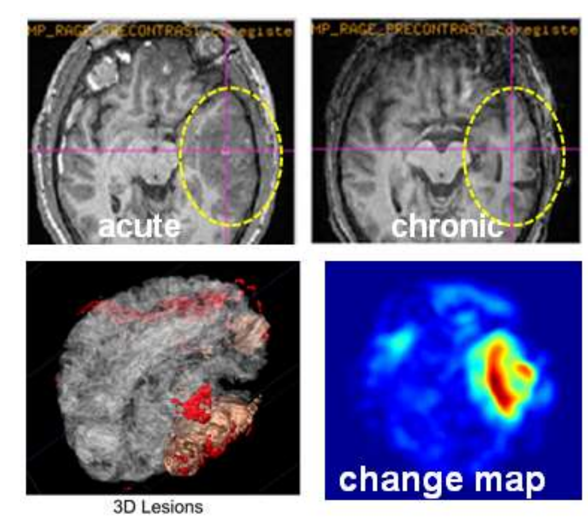










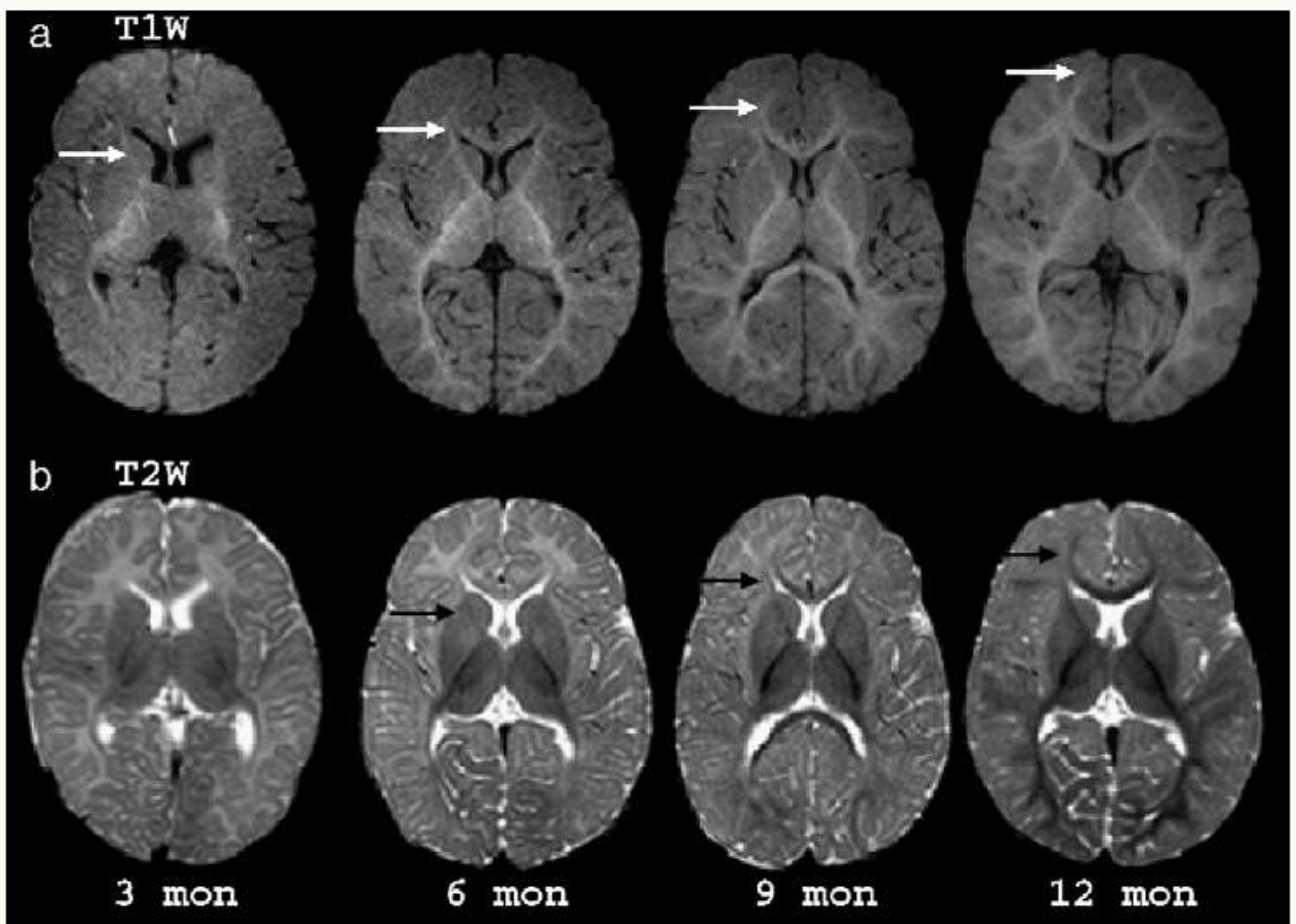


Pediatric Imaging

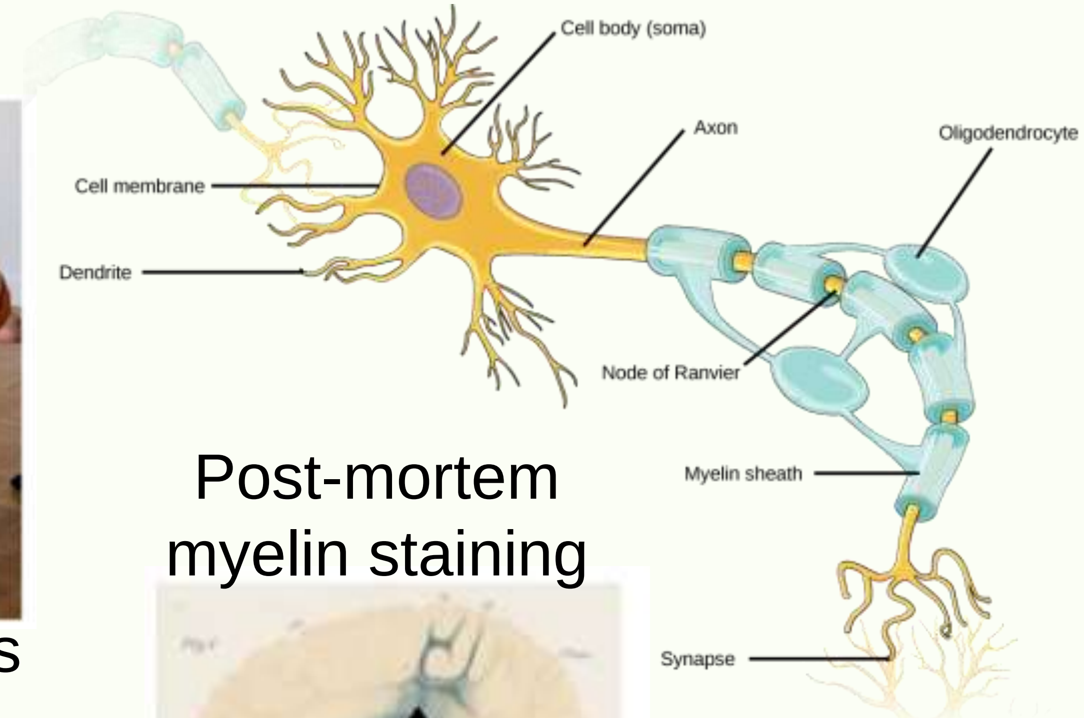
Birth | 3 mon | 6 mon | 1 year

Dubois

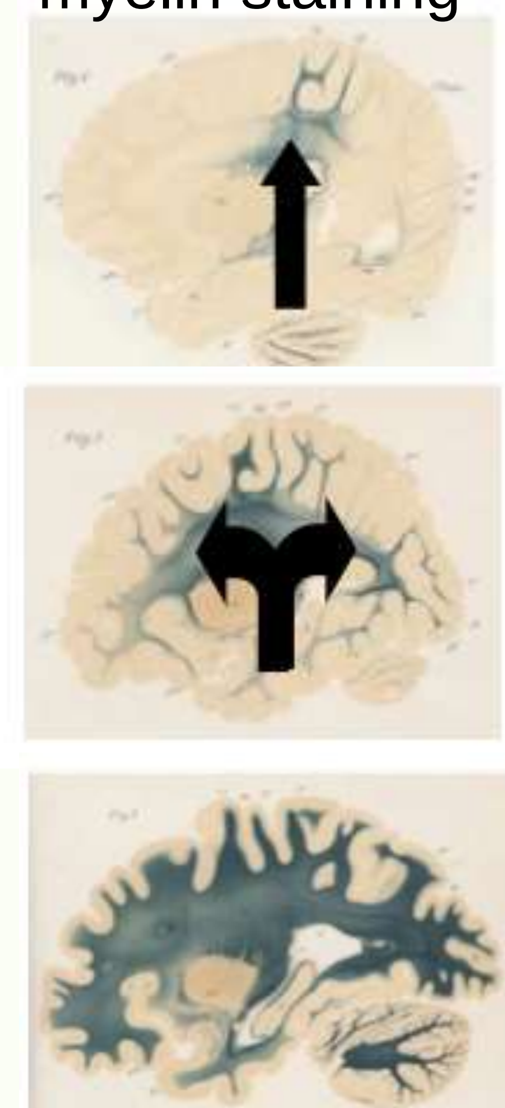
In vivo MRI



Paus et al. 2001

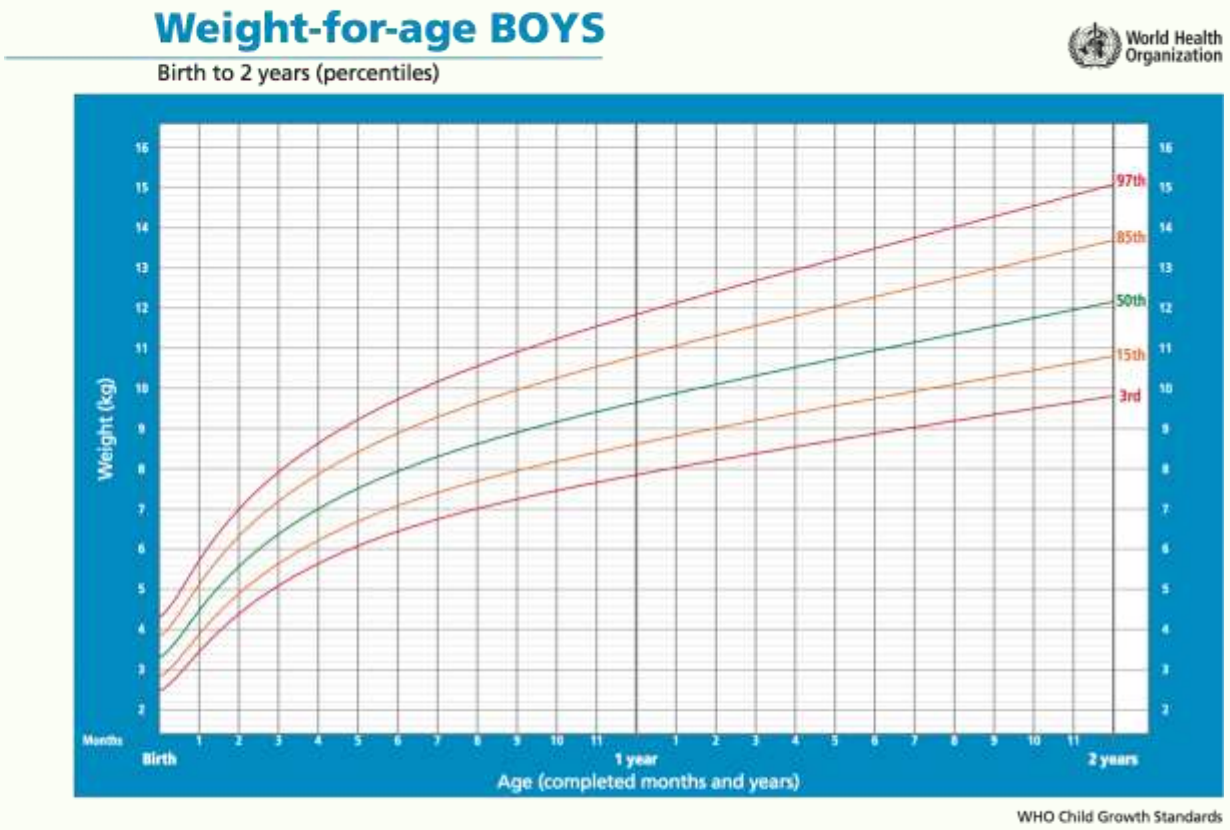


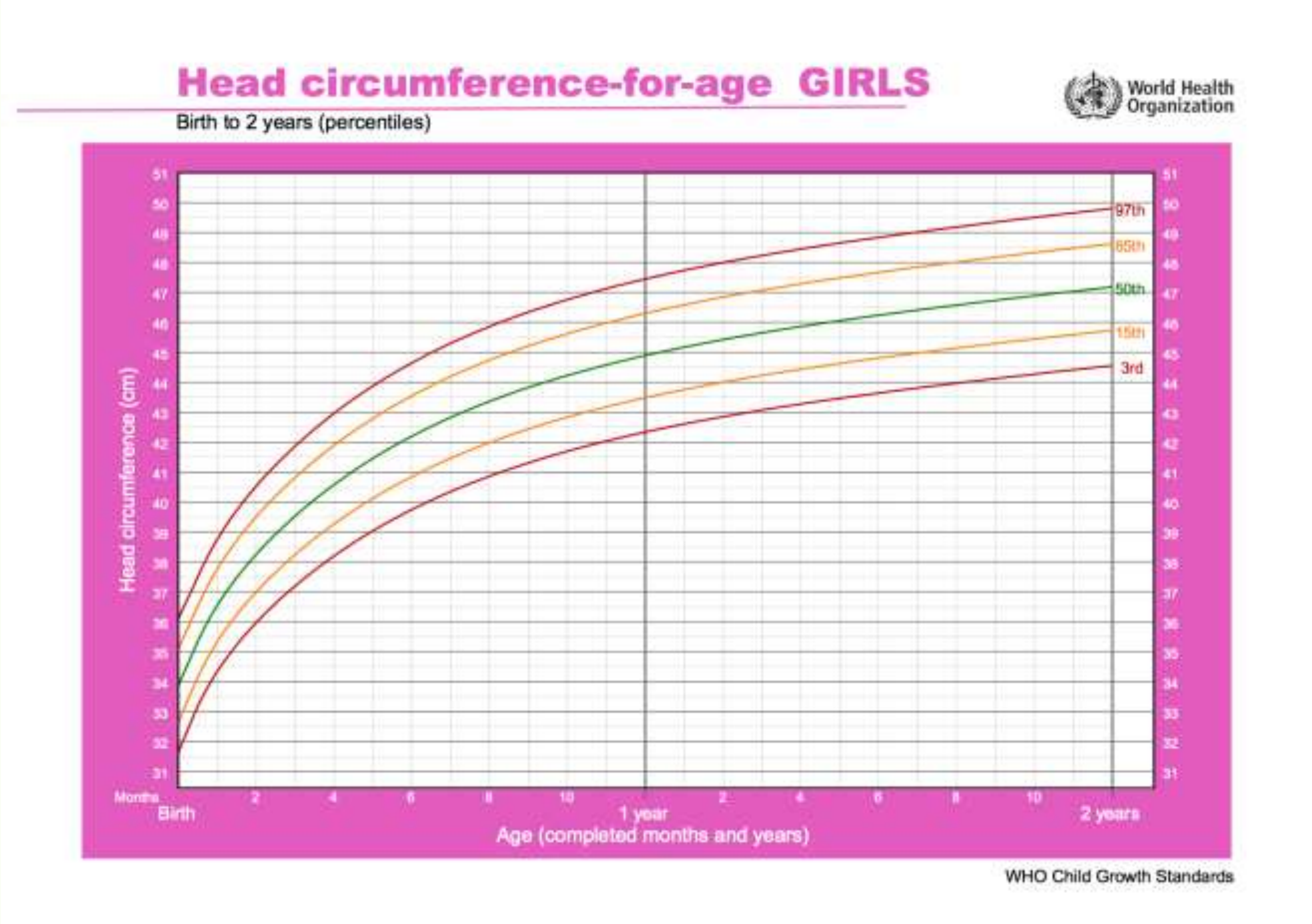
Post-mortem myelin staining



Flechsig 1920

Physical Measures





Spatiotemporal Modeling: Natural Task in Clinical Reasoning

Motivation:

- Development, degeneration, effects of therapeutic intervention are dynamic processes
- Personalized health care: Individual trajectories compared to expected “norm”
- Clinical terminology: Atypical, Monitoring
  - Departure from typical development, deviation from healthy
  - Typical but delayed growth patterns, catch-up, atypical development
  - Analysis of recovery for each patient
  - Predict onset of clinical symptoms
  - Monitor efficacy of treatment

→ **Focus on longitudinal design & longitudinal analysis**

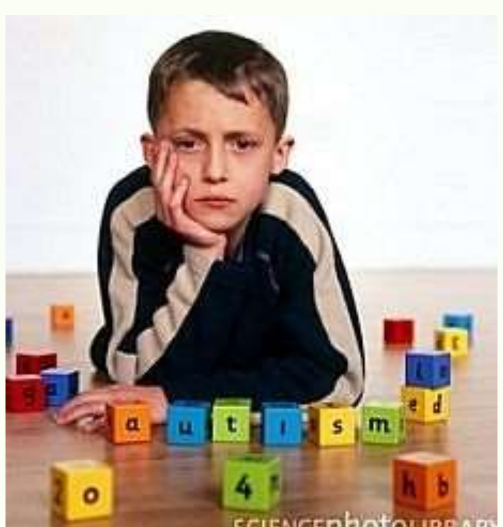
Why study early brain development?

Early childhood:
Origins of mental illnesses

(Autism, Schizophrenia, Depression, ...)

Find neuroimaging biomarkers (pre-symptomatic diagnosis)

Infant brain is highly plastic: Early intervention -> Improve life quality



Early Brain Development Studies

- John Gilmore, M.D.
  Principal Investigator
- Studies
- Investigators
- Image Analysis
- Progress/Publications
- Training Opportunities
- Links
- Contact Us

EDBS HOME

Early Brain Development Studies

Normal Controls

Twins

Mild Ventriculomegaly (MVM) (Brain)

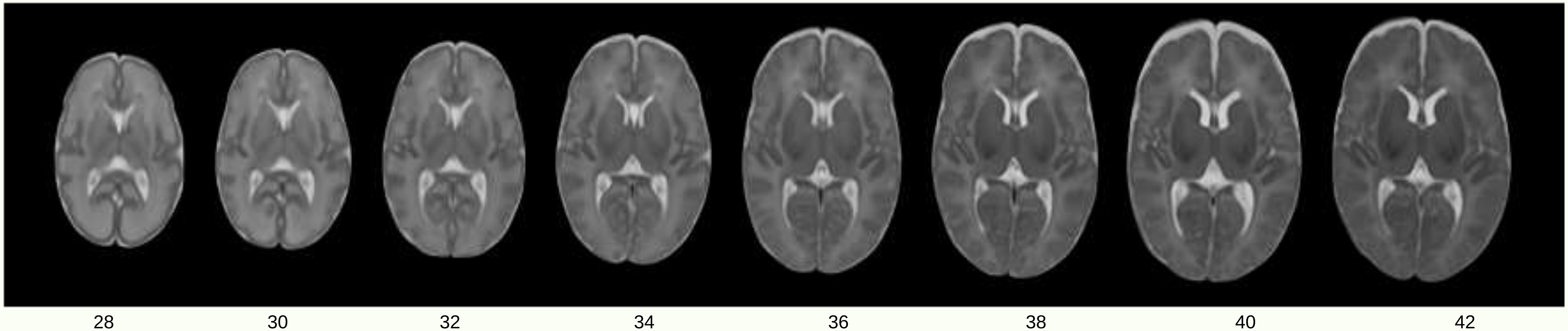
Babies of Mothers with Schizophrenia

Offsprings of cocaine-addicted mothers

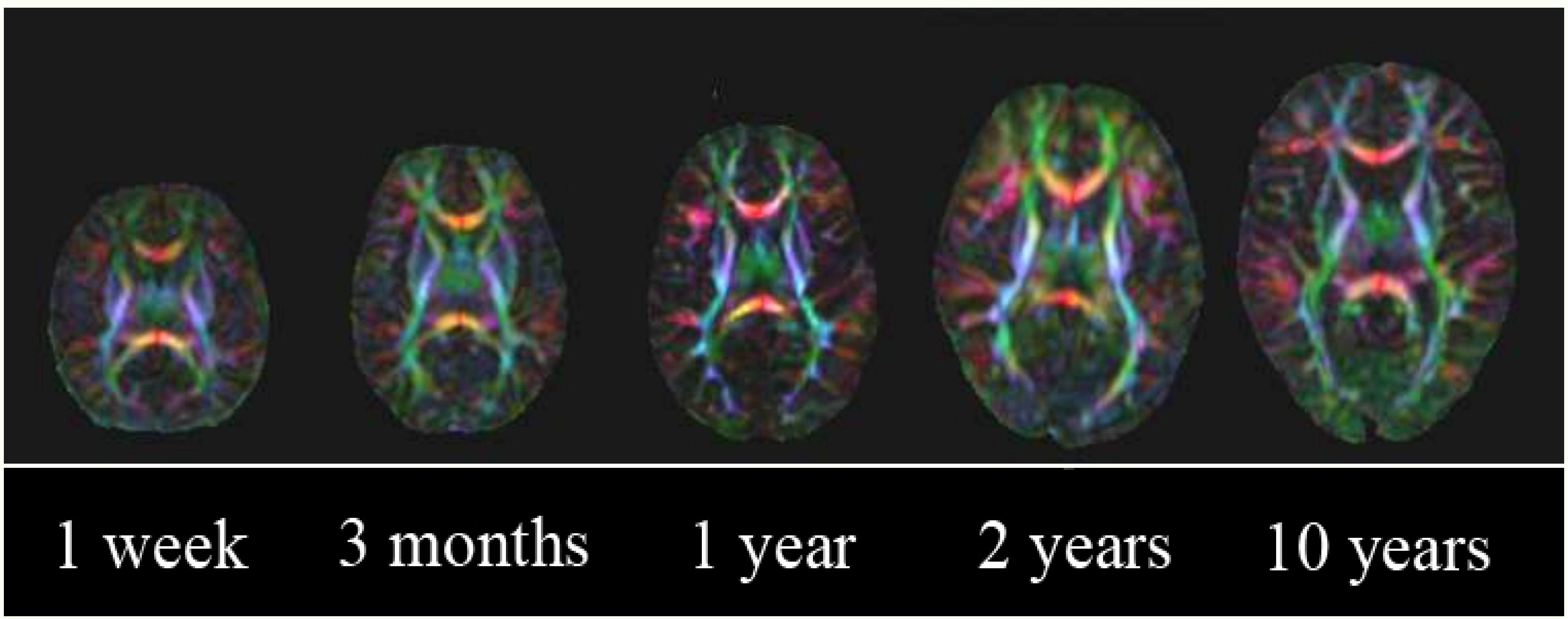
Neonatal Brain Development in High Risk Children (J. H. Gilmore, MD)

- Understanding rate and variability of normal development
- Detect differences from typical development
- Early diagnosis → early therapy → help families

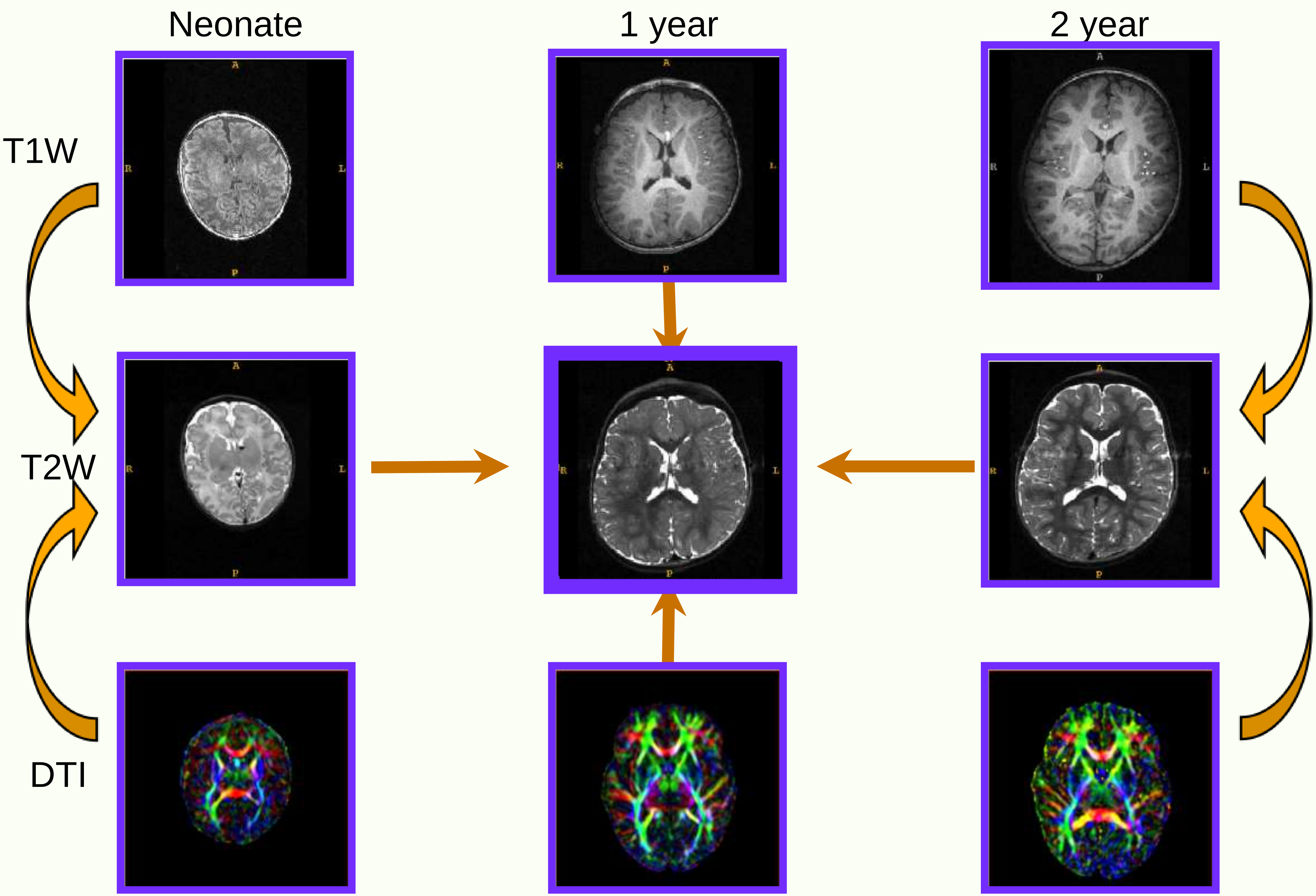
Longitudinal Imaging



A. Serag et al., Neuroimage, 2012

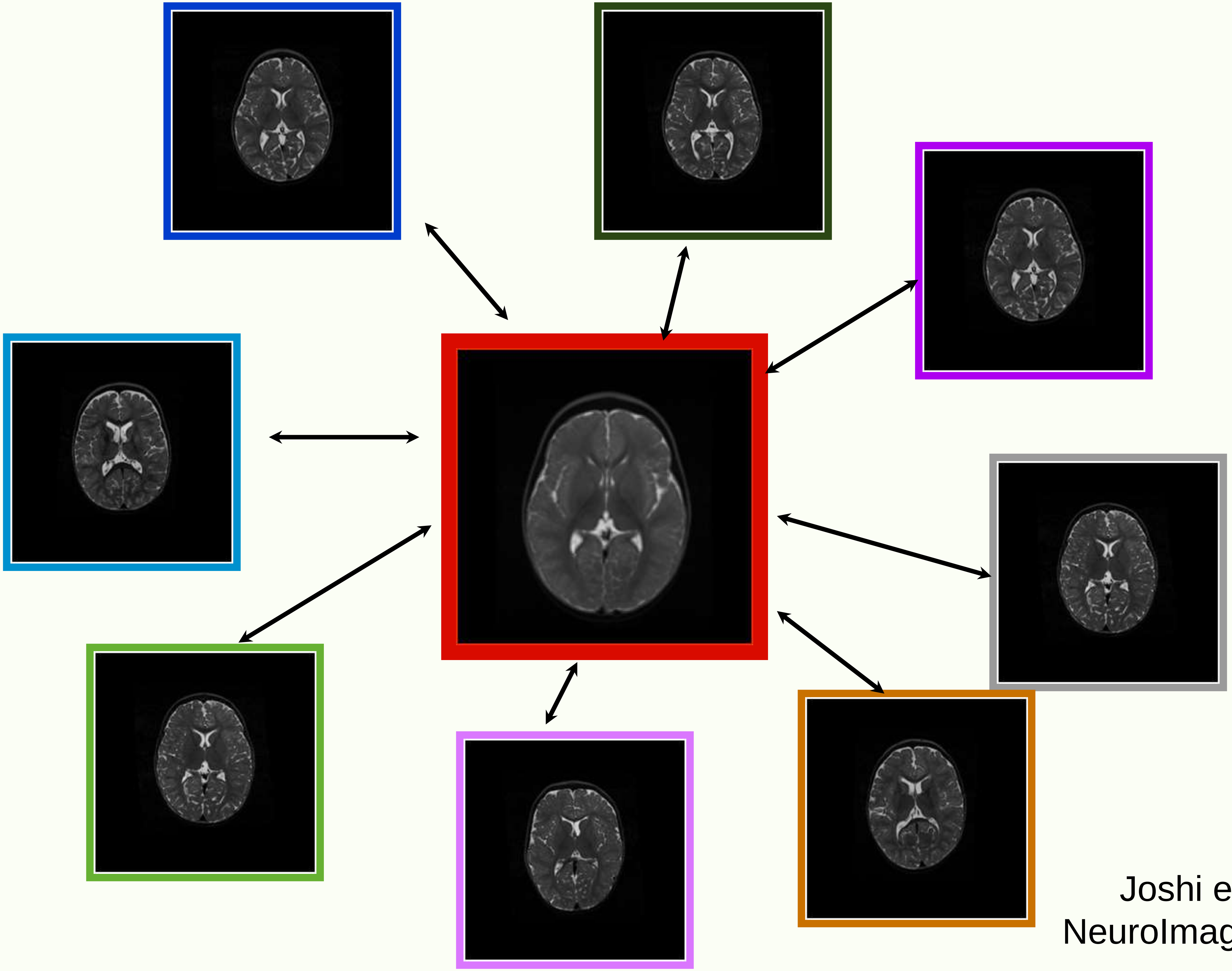


How to map multi-modality longitudinal data?



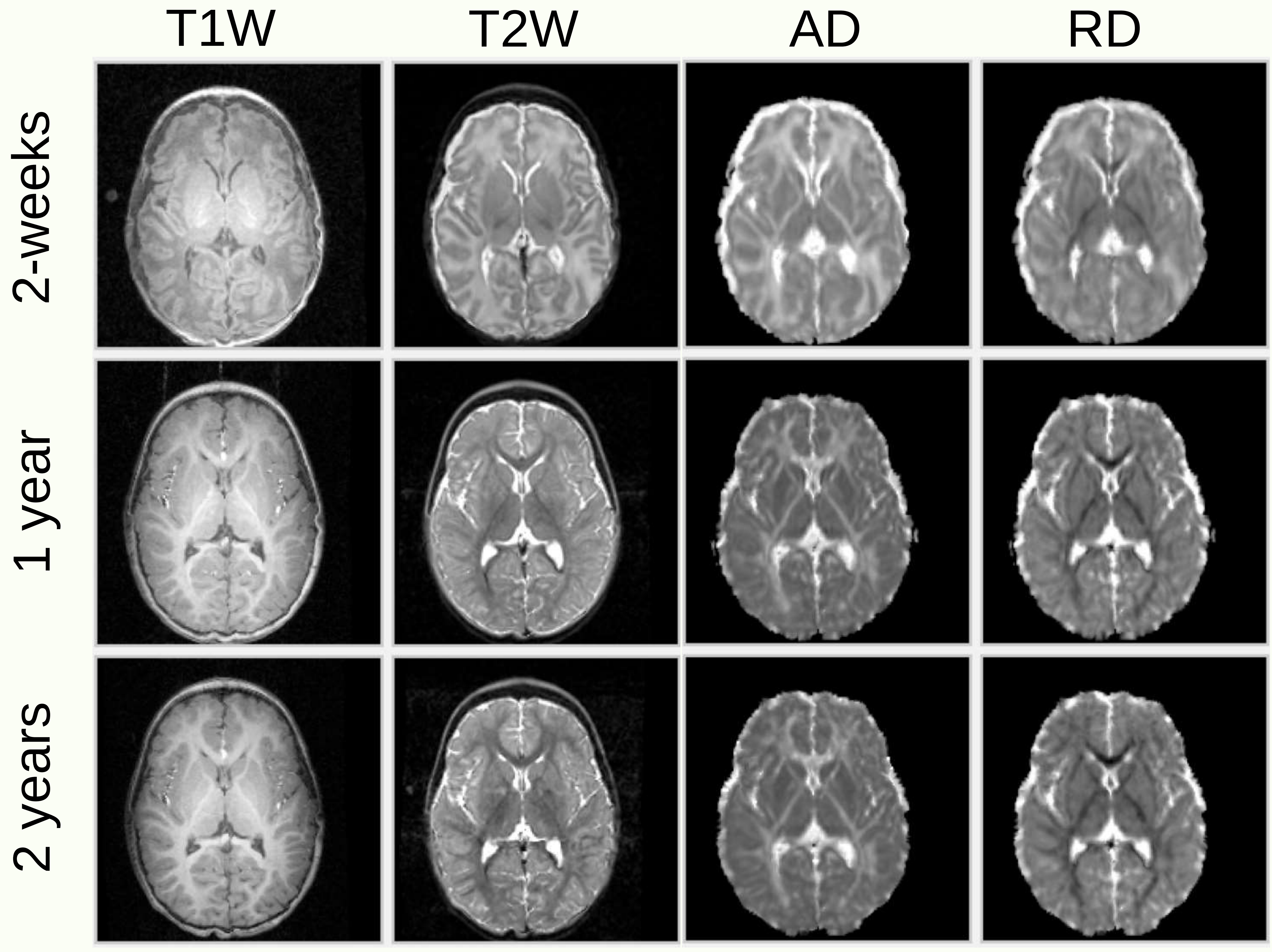
Sadeghi et al., SPIE 2010

Spatial normalization via atlas building of Subjects 1 year T2W scans



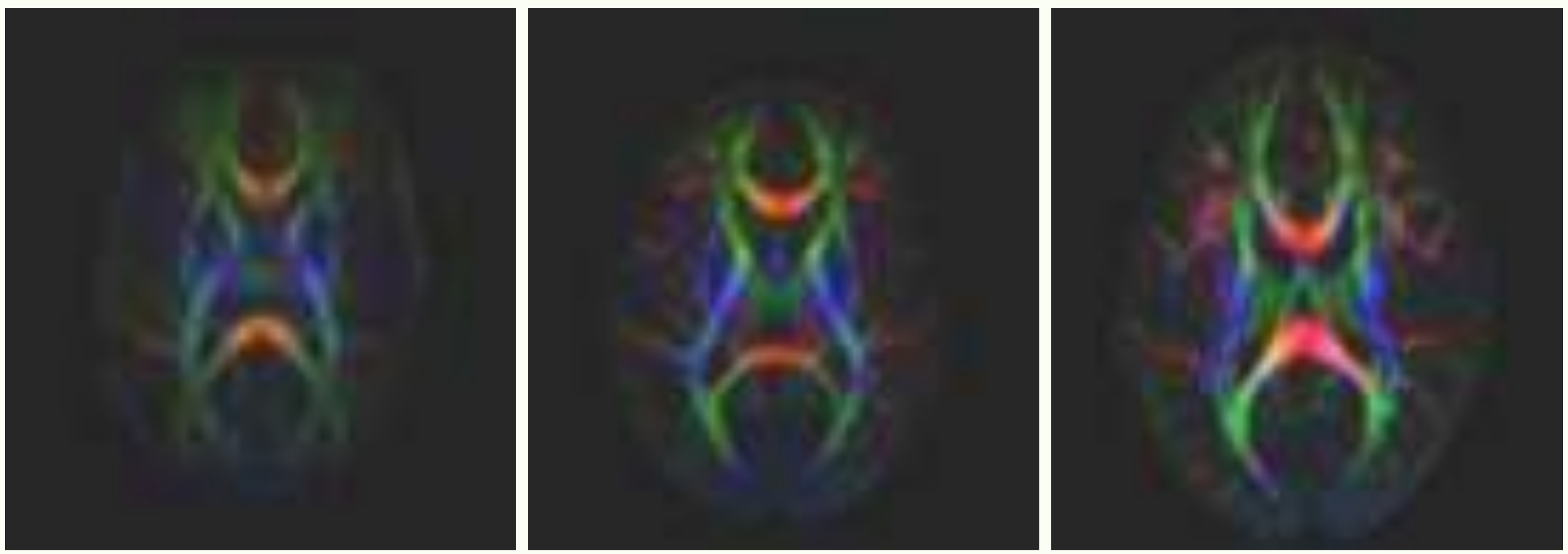
Joshi et al.
NeuroImage 2004

Multi-Modal Temporal Registration

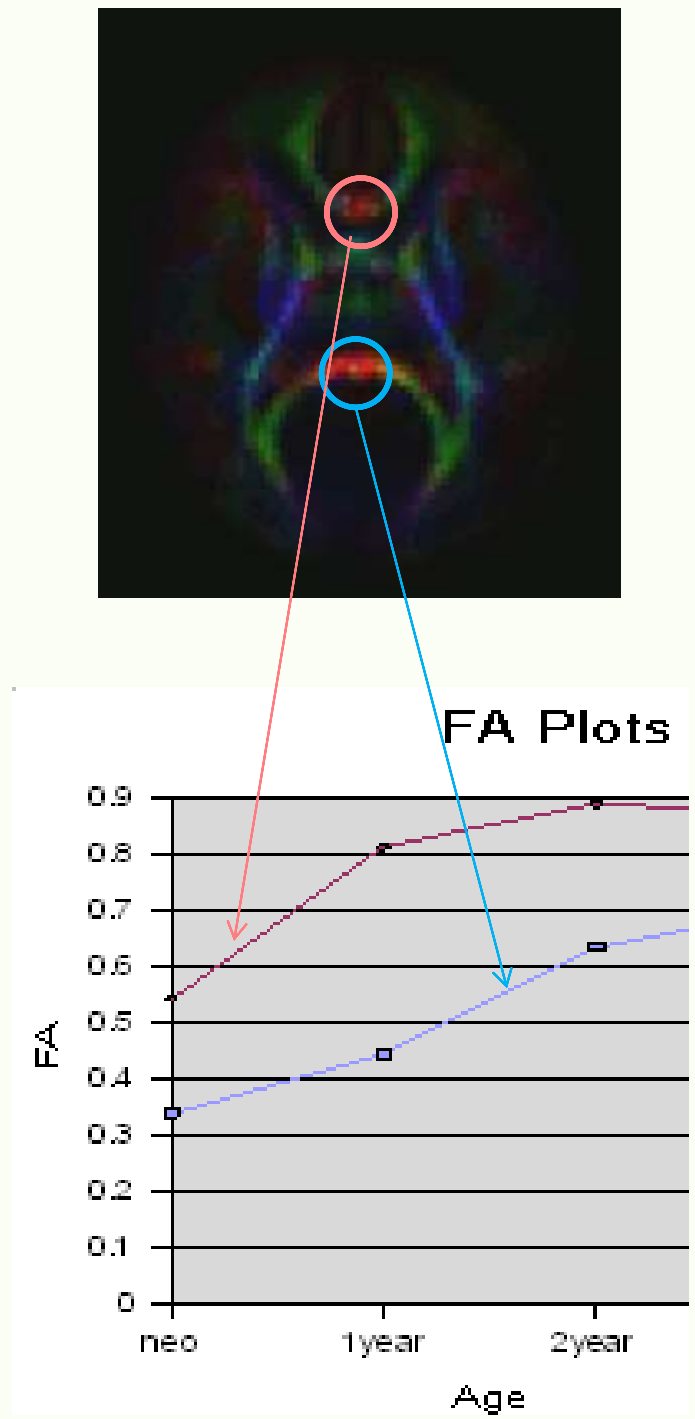


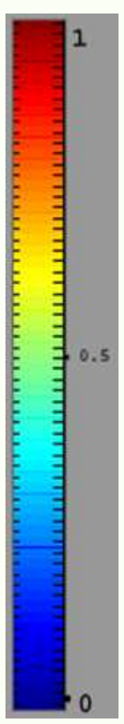
Longitudinal Diffusion Imaging

Neonate 1 year 2 years

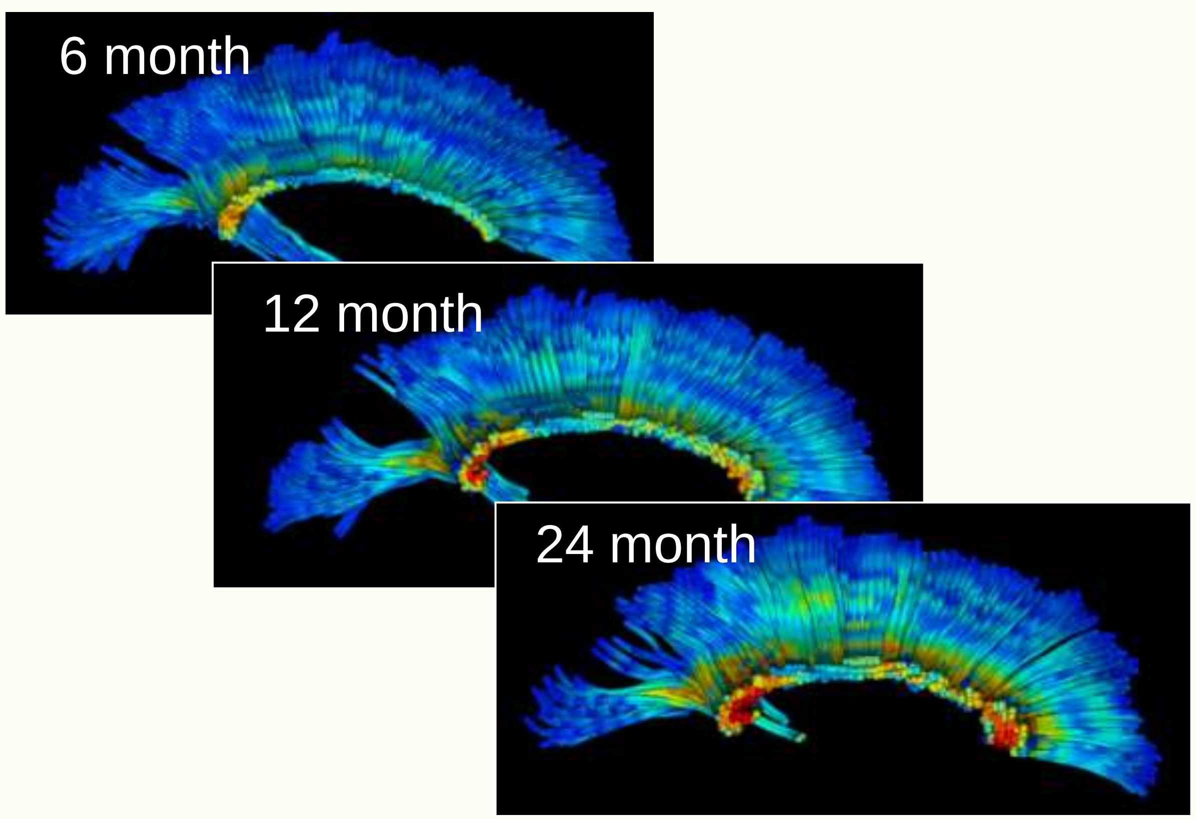


Cine



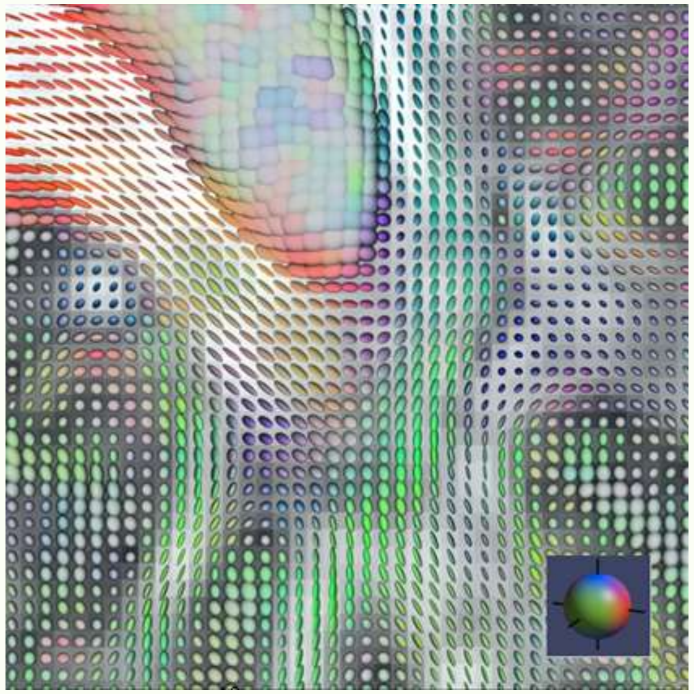


FA



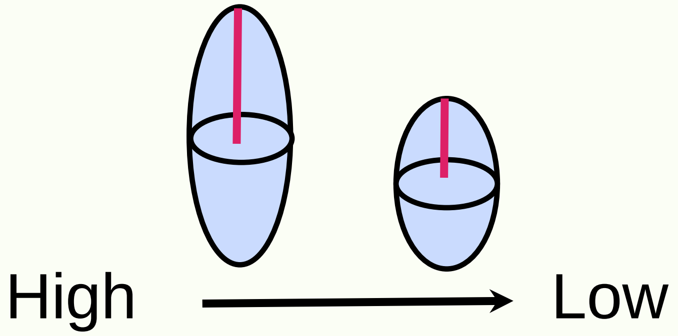
Autism infant study: ACE-IBIS, J. Piven PI

Diffusion parameters



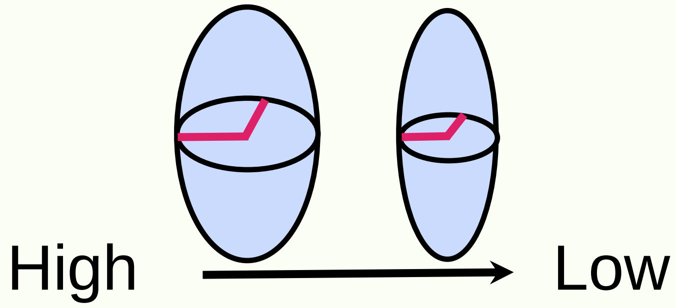
Axial Diffusivity

$$AD = \lambda_1$$



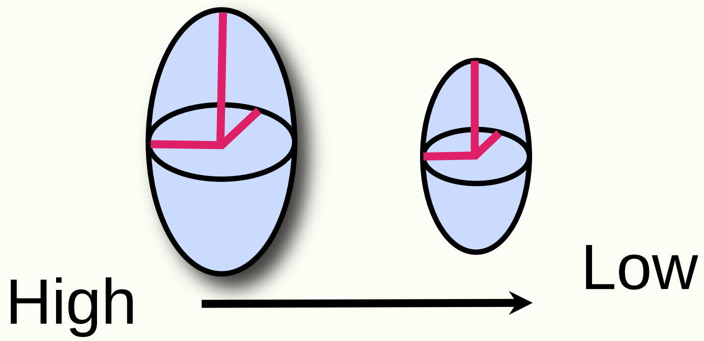
Radial Diffusivity

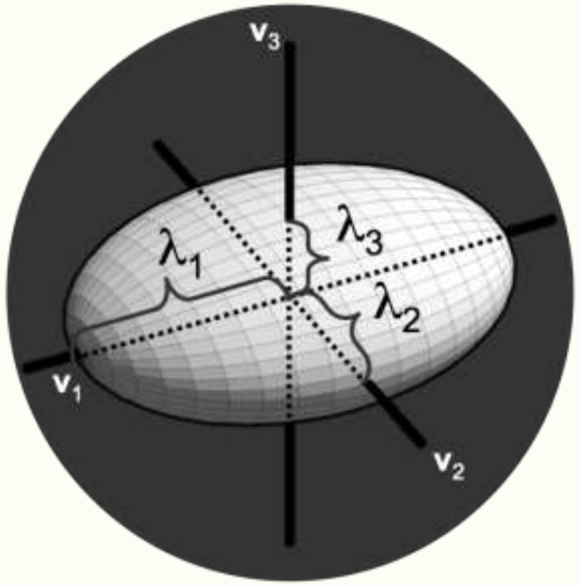
$$RD = \frac{\lambda_2 + \lambda_3}{2}$$



Mean Diffusivity

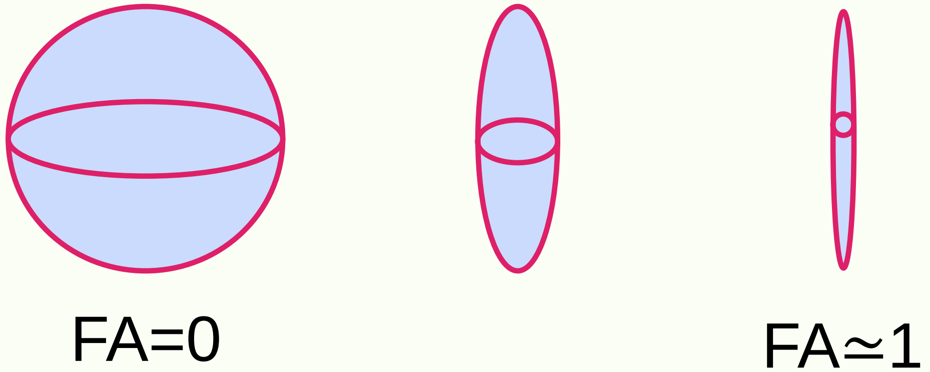
$$MD = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3}$$



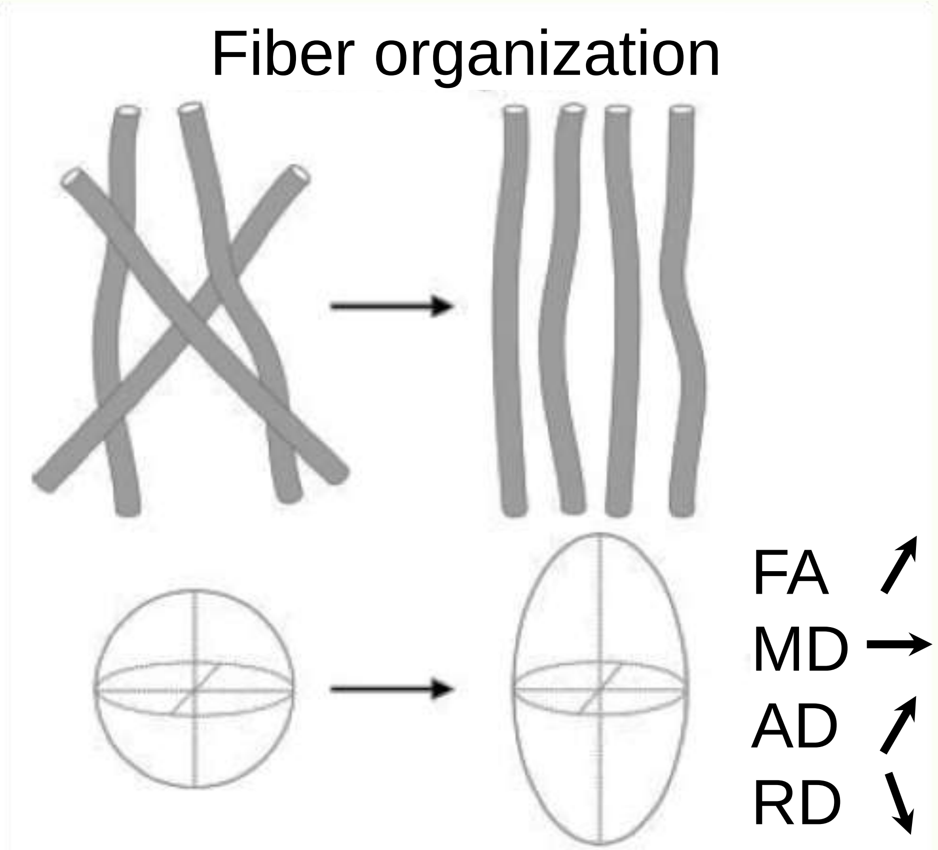


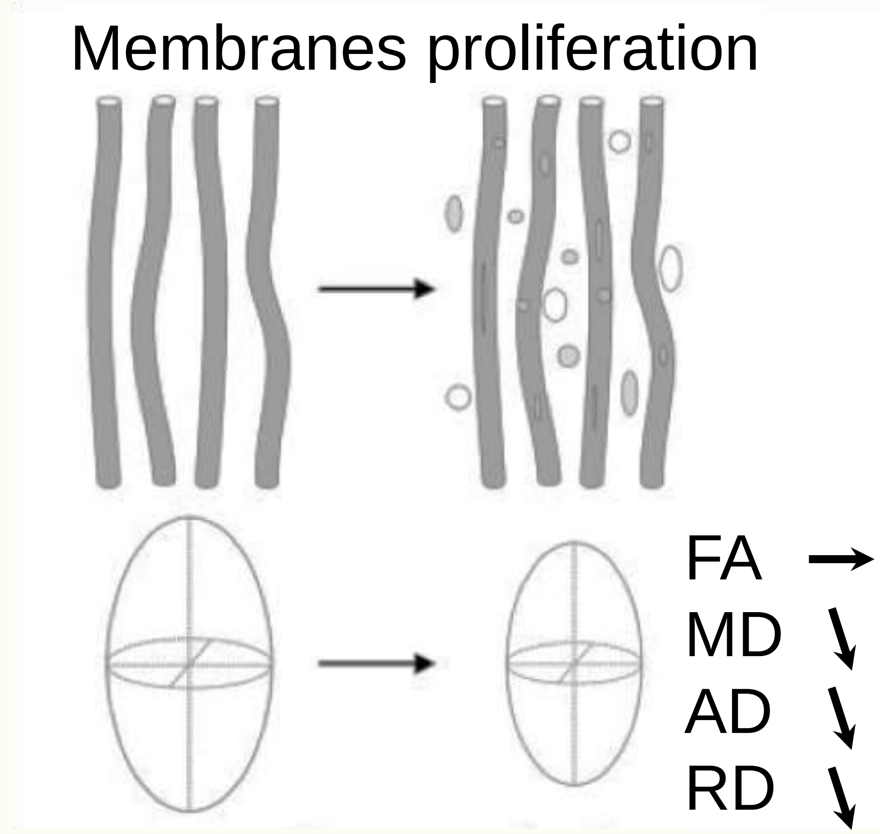
Fractional Anisotropy

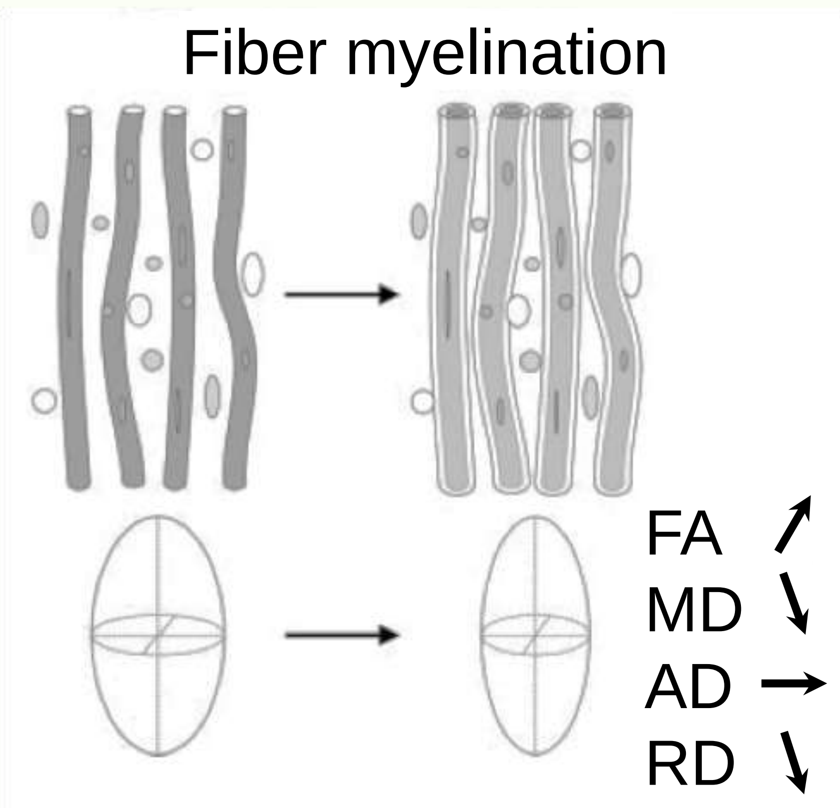
$$FA = \sqrt{\frac{1}{2}}\frac{\sqrt{(\lambda_1 - \lambda_2)^2 + (\lambda_1 - \lambda_3)^2 + (\lambda_2 - \lambda_3)^2}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}$$



Diffusion changes as white matter matures







Observation:

Increasing or decreasing measures with age:

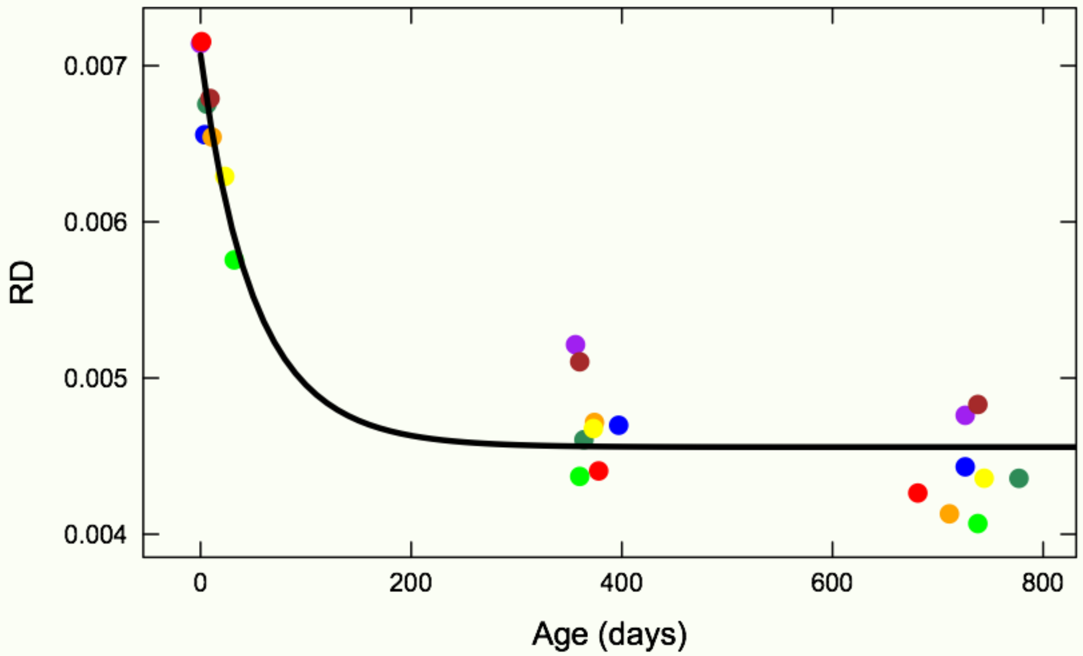
↑ : FA (also volume, T1w)

↓ : MD, AD, RD (also T2w)

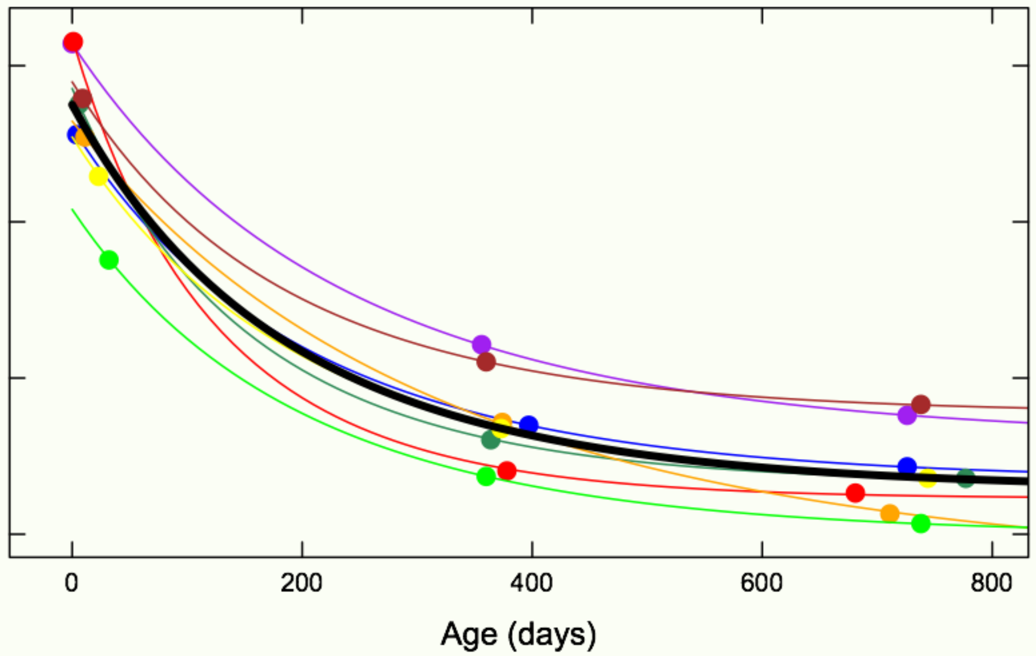
Dubois et al, Human Brain Mapping, 2008

True Longitudinal Analysis: Data and Model

Regression of Longitudinal Data



Longitudinal Modeling of Longitudinal Data

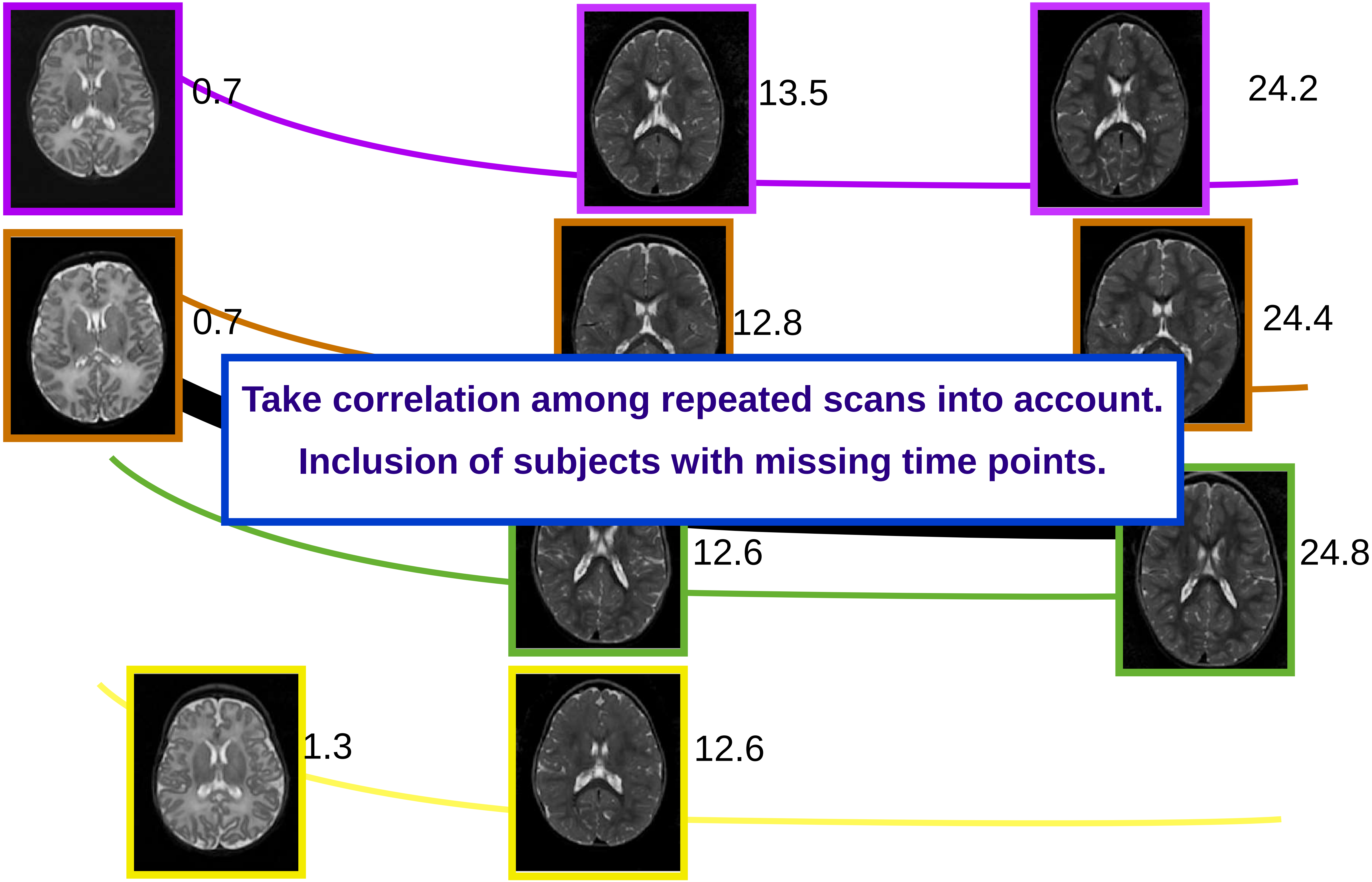


Regression is not an appropriate model of longitudinal data, the growth trajectory is not representative of individual trajectories

→ Mixed Effect Models

Sadeghi et al., ISBI 2012, NeuroImage 2013

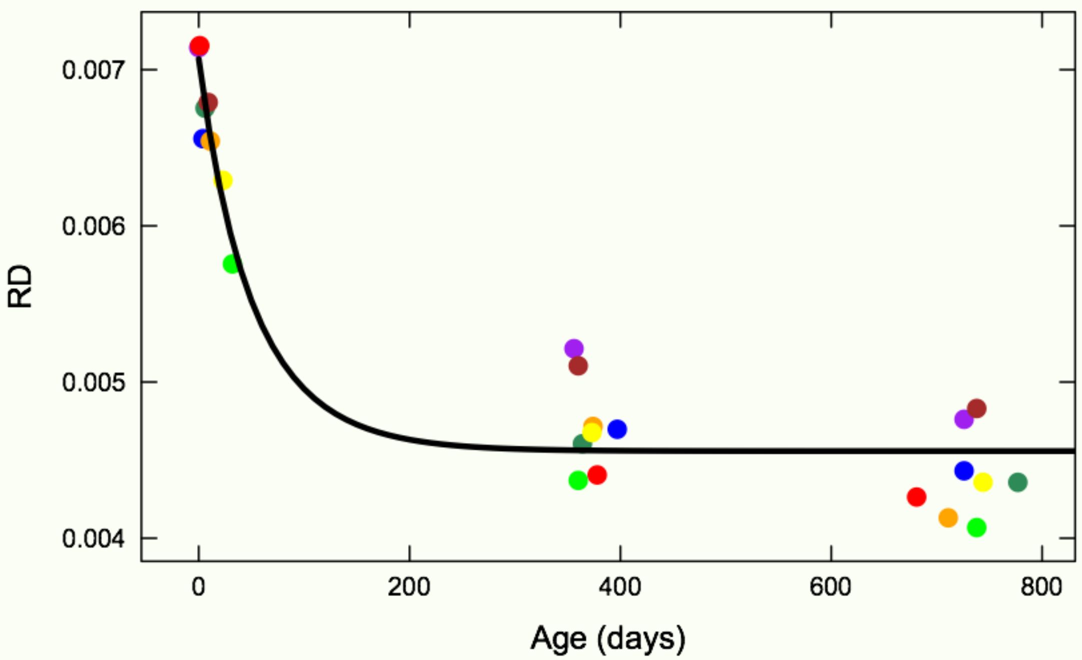
Contribution: Jointly model individual and group trajectories



Take correlation among repeated scans into account.

Inclusion of subjects with missing time points.

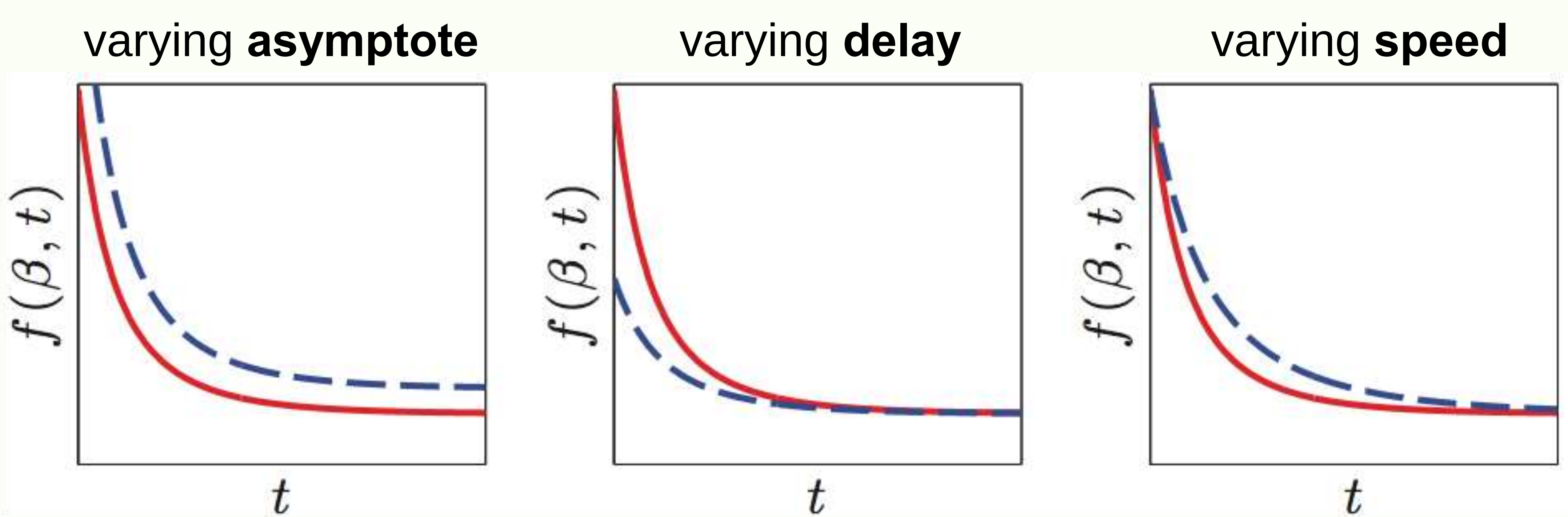
Modeling nonlinear change via Gompertz function



$$y = \textbf{asymptote}\ \exp(-\textbf{delay}\ \exp(-\textbf{speed}\ t))$$

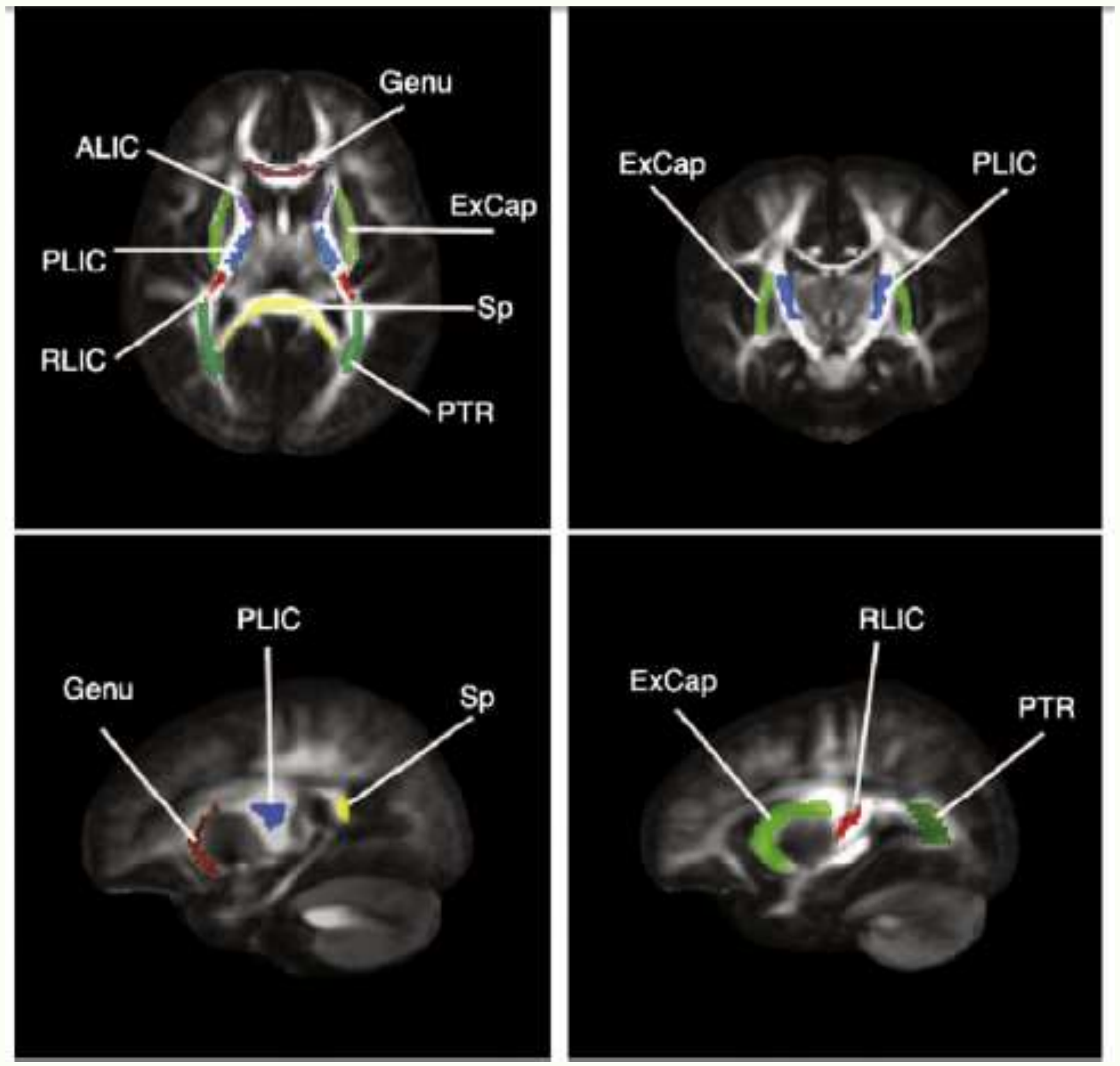
$$y = f(\beta, t) = \beta_1 \exp\{-\beta_2 {\beta_3}^t\}$$

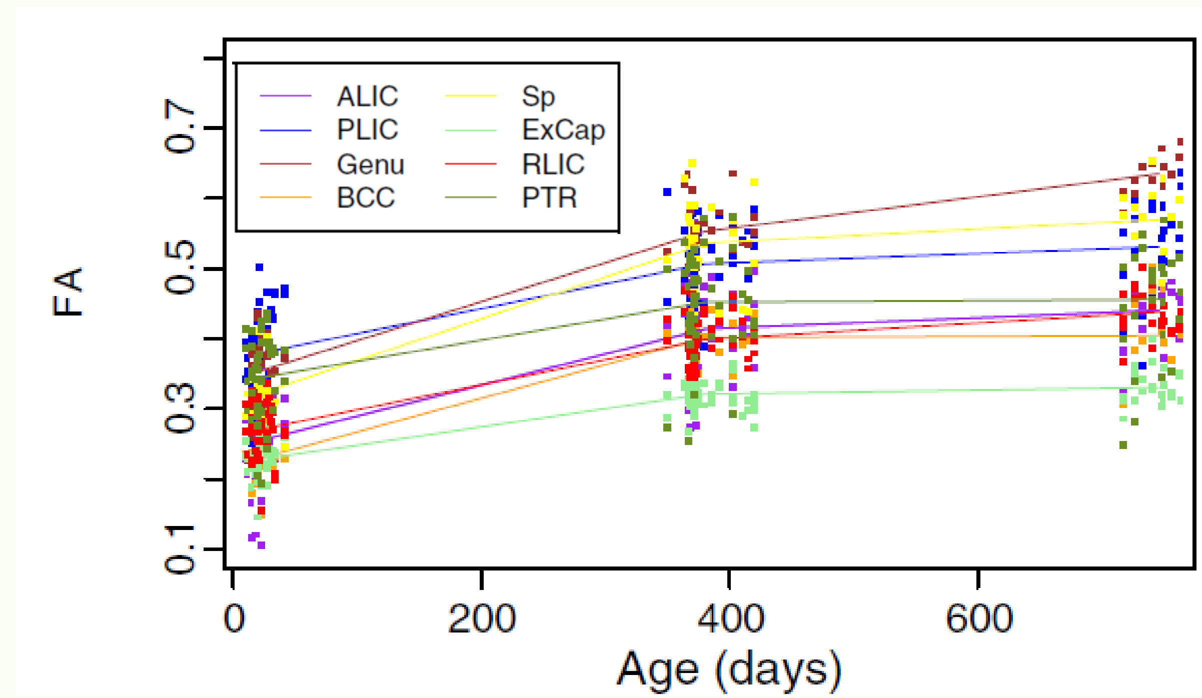
$$\beta_3 = exp(-speed)$$

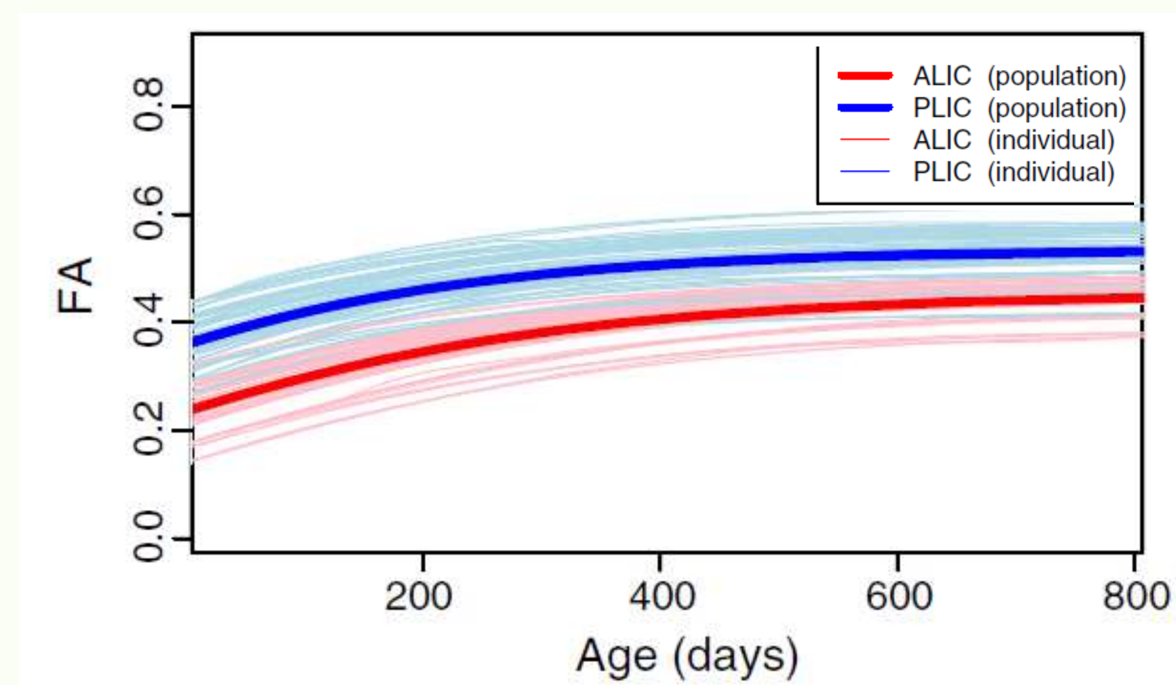


Sadeghi et al., Asilomar 2010

Longitudinal analysis of DTI: Nonlinear mixed-effect modeling

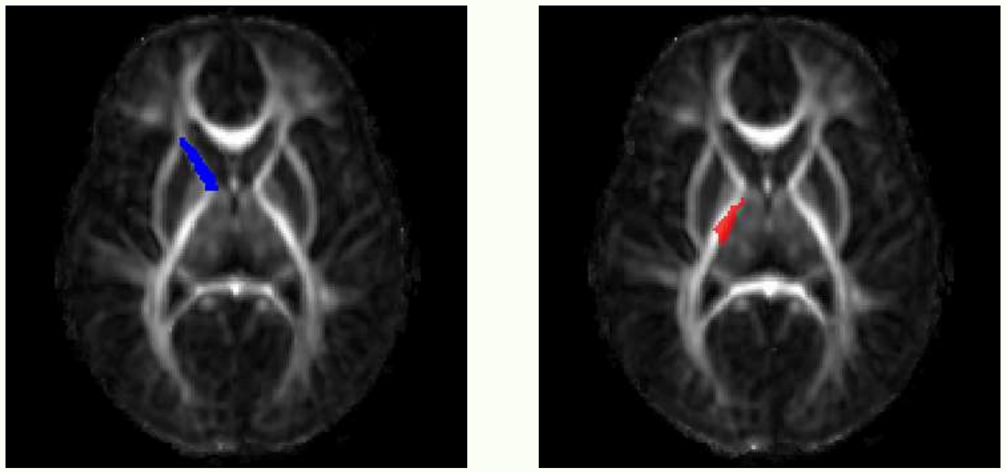




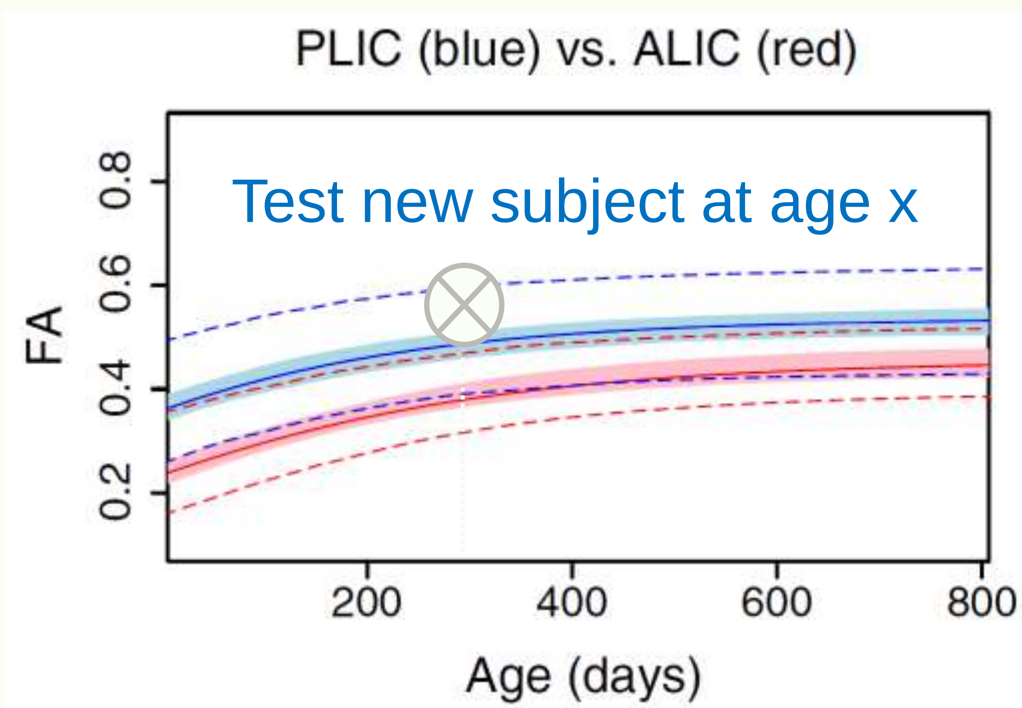


Sadeghi et al., Neuroimage 2013

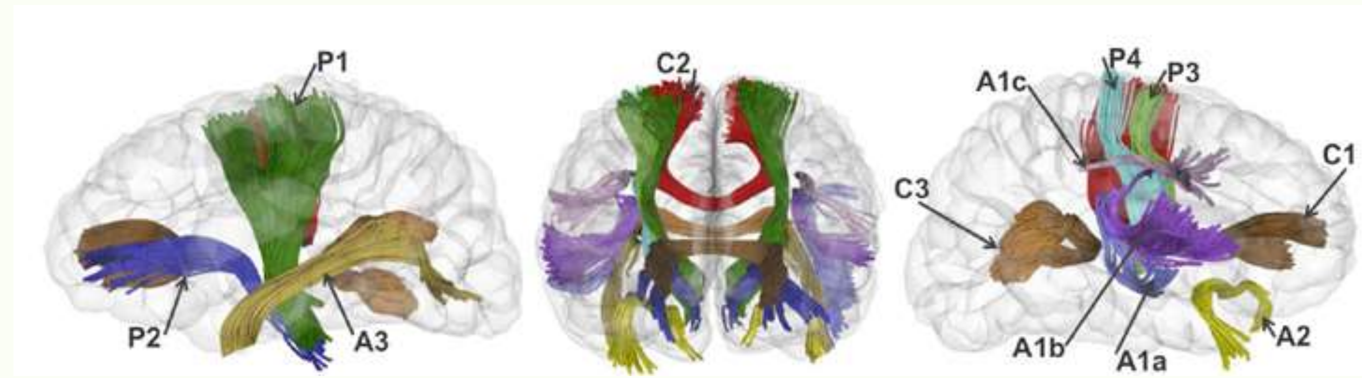
Longitudinal analysis of DTI: NLME Normative Infant WM Brain Atlas

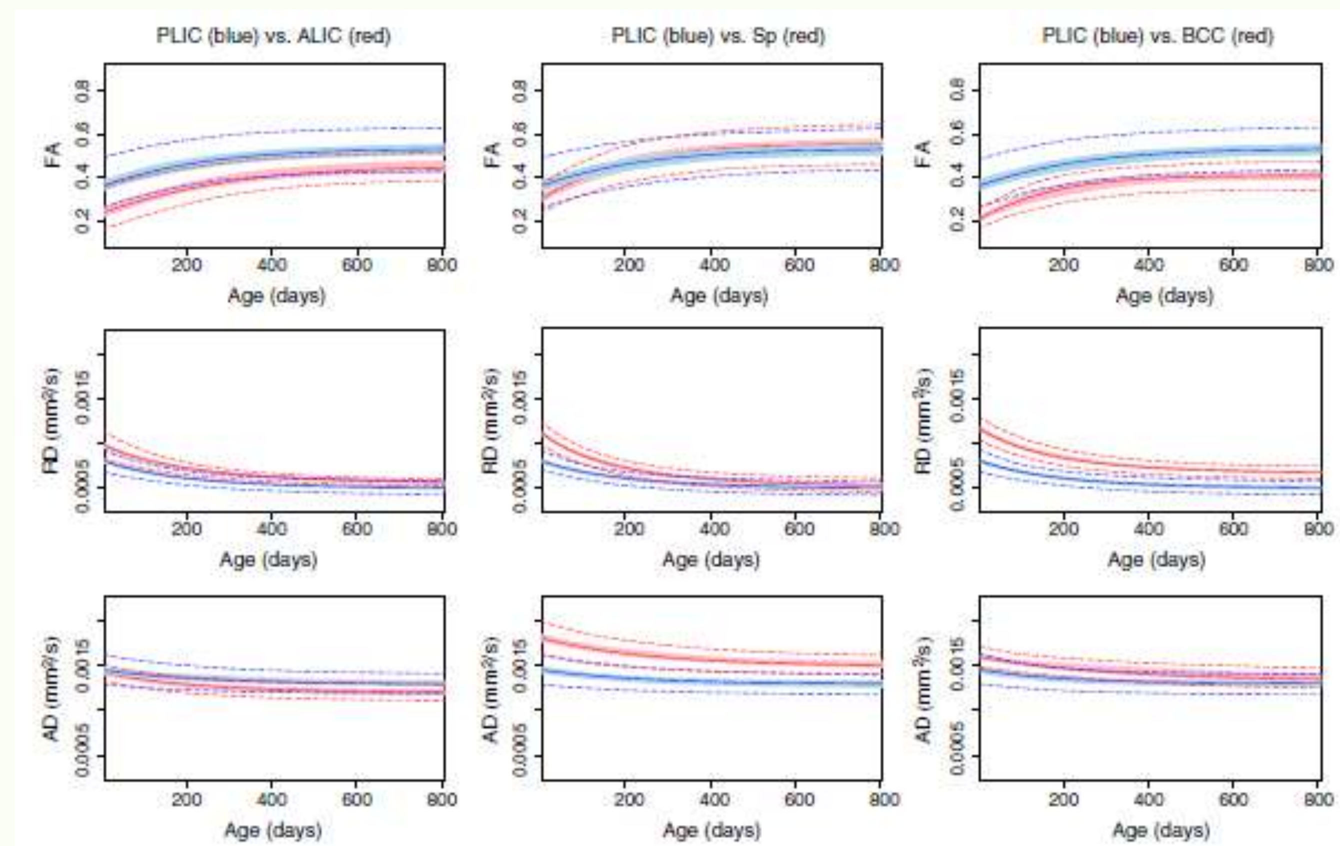


ALIC vs. PLIC, $p < 0.001$



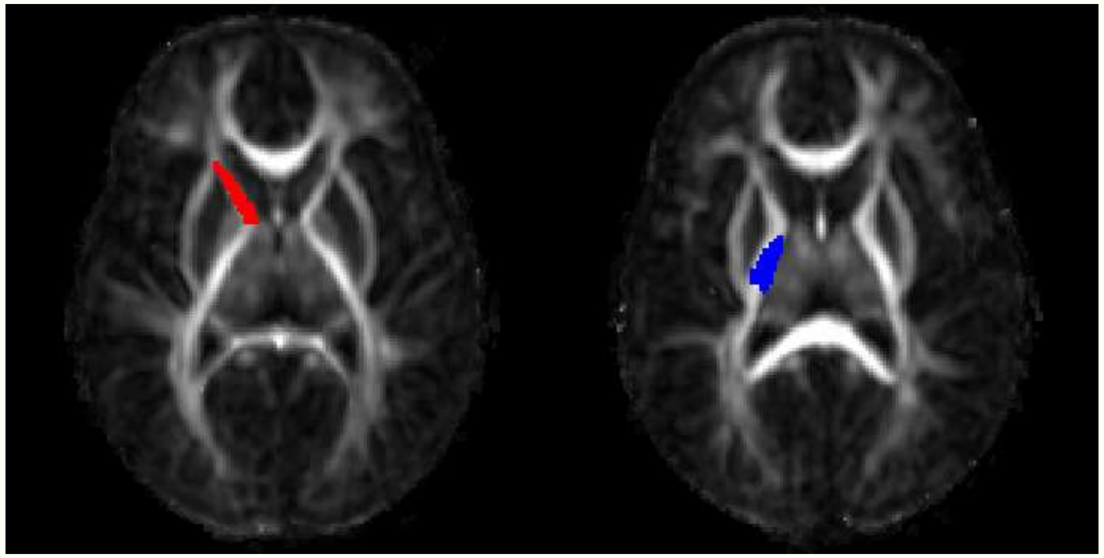
Shaded intervals: 95% Conf. Mean
Dashed: 95% Predicted intervals for trajectories





Geng et al., Neuroimage ‘12, Sadeghi et al., Neuroimage ‘13

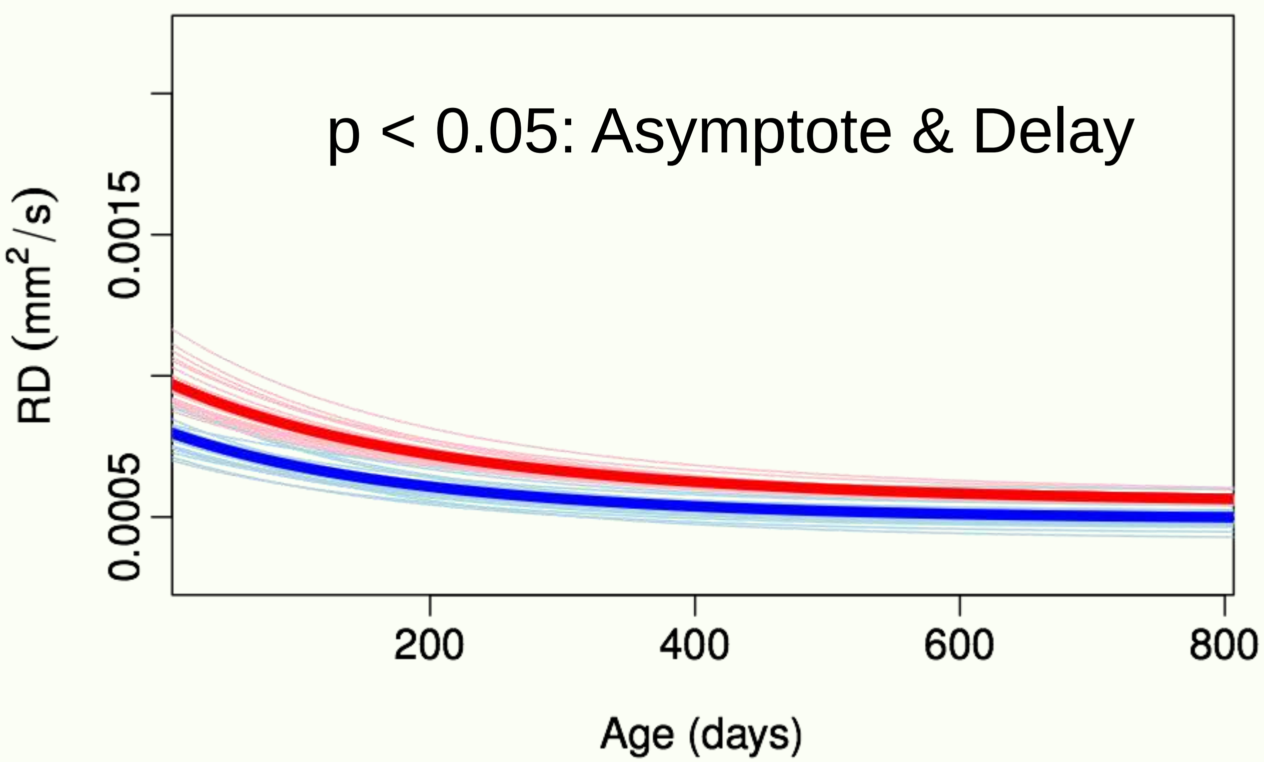
Regional Comparison

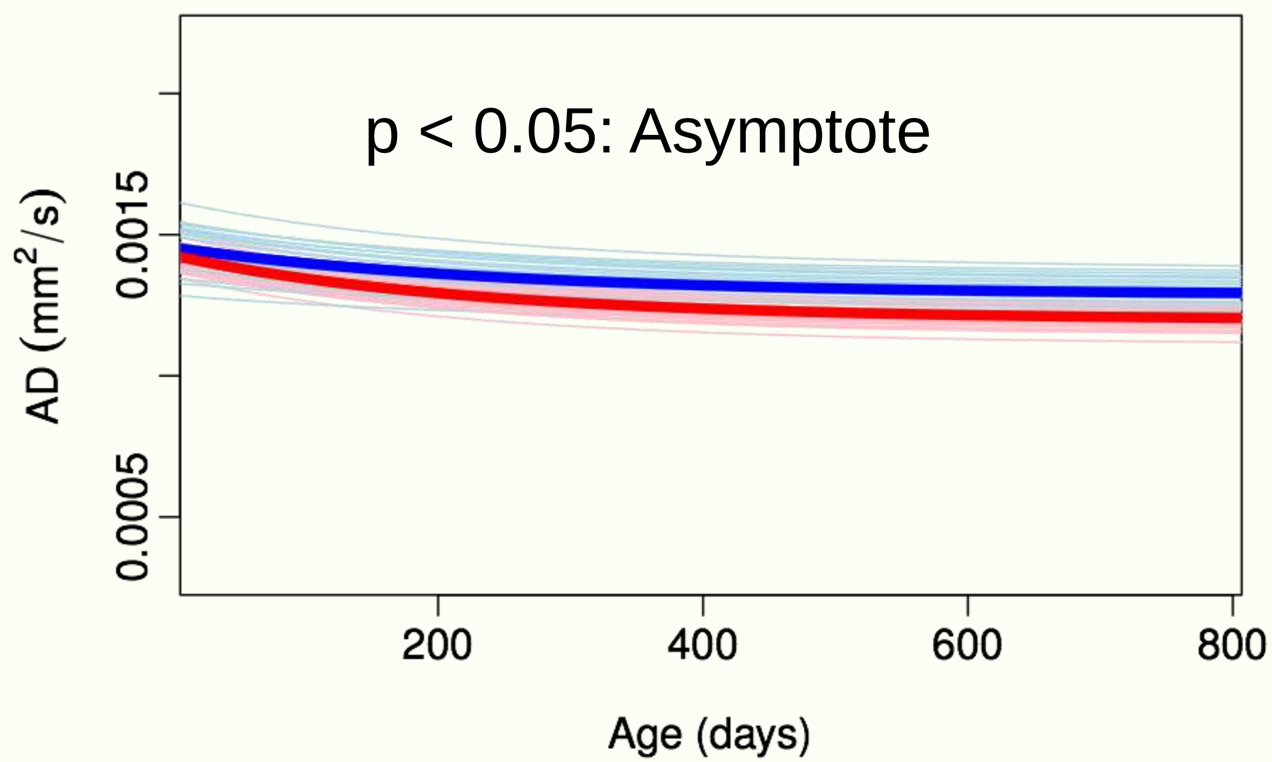


$$\hat{\beta} \sim \mathcal{N}\left(\beta, \sigma^2 \left[\sum_{i=1}^{M} \hat{X}_i V_i^{-1} \hat{X}_i\right]^{-1}\right)$$

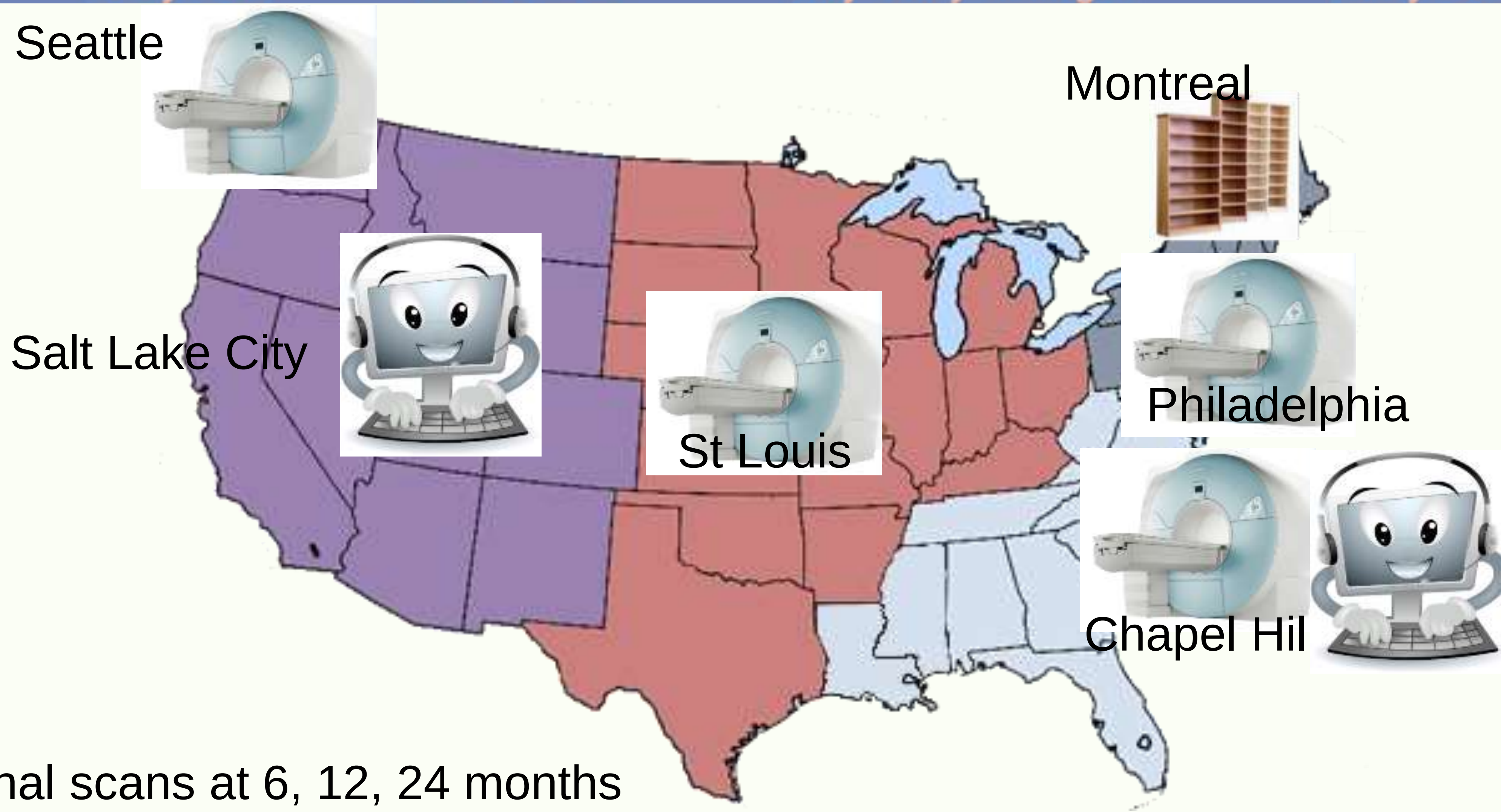
$$\hat{X}_i = \frac{\partial f_i}{\partial \beta^T}\Big|_{\hat{\beta},\hat{b}_i} \qquad V_i = I + \hat{Z}_i \hat{\Sigma}_i \hat{Z}_i^T$$

$$\hat{Z} = \frac{\partial f}{\partial b^T}\Big|_{\hat{\beta},\hat{b}}$$

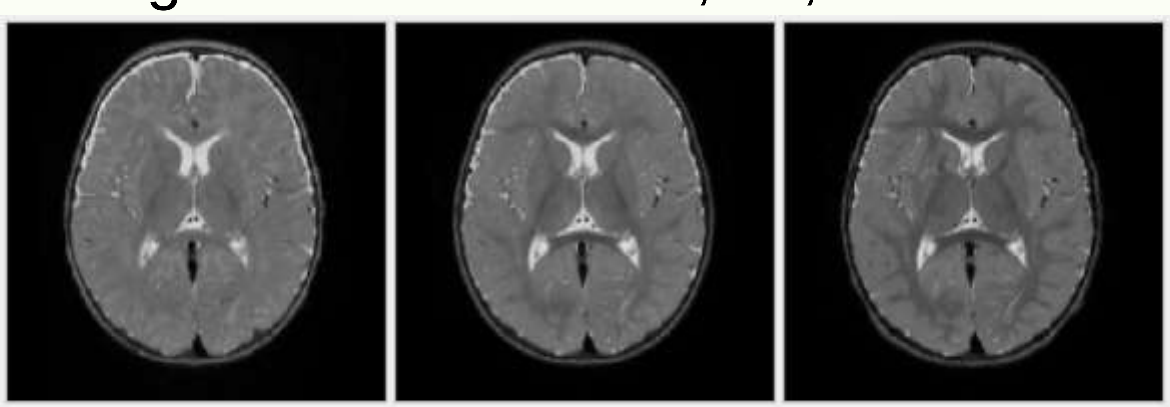




Sadeghi et al., MICCAI workshop 2011
Sadeghi et al., NeuroImage 2013



Longitudinal scans at 6, 12, 24 months

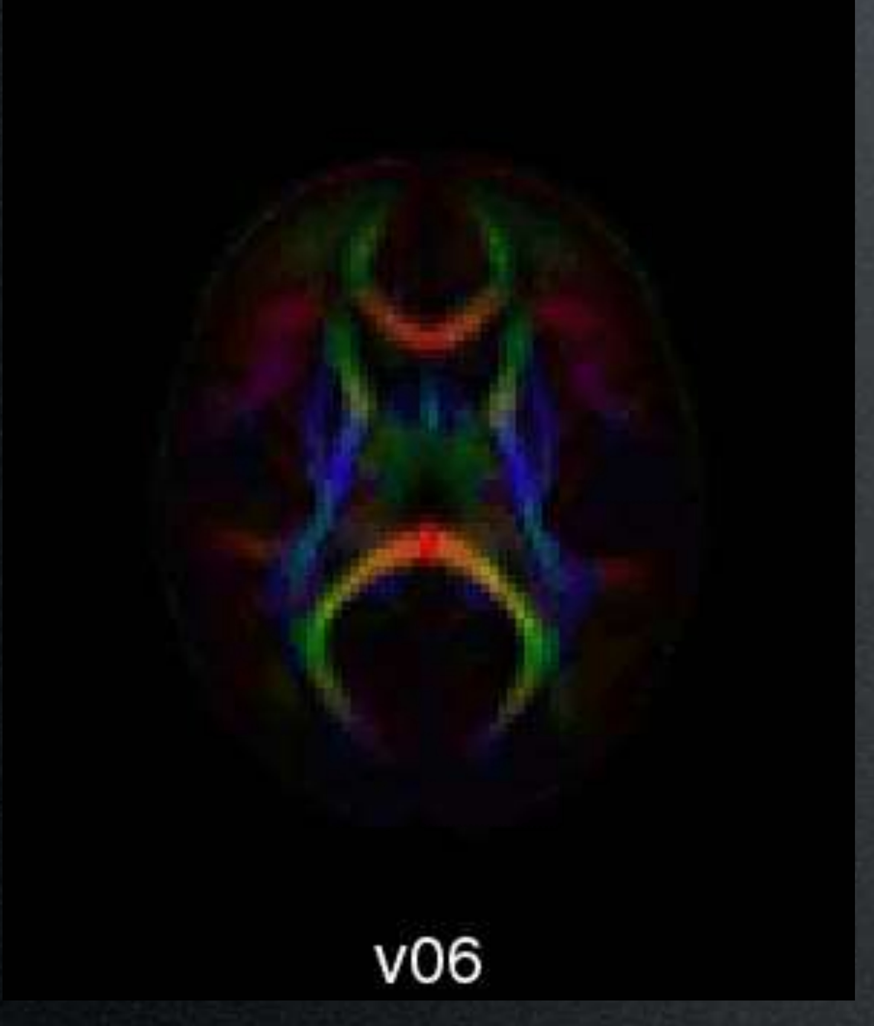


Goal: Pre-diagnostic imaging biomarkers

PI: Dr. Joe Piven, UNC

DTI atlas building

- Generated combined v06-v12-v24 DTI atlas:
  - June: 750 data points
  - September: 978 data points



Processed DTI: ‘data point’ information

IBIS dataset:

- Nb data points: 958
- Nb subjects: 481

Fragile X, “relative”: excluded

Visit Label:

- v06: 351
- v12: 349
- v24: 258

Gender:

- F: 357
- M: 601

Visit cohort:

- 6-month recruit: 554
- 12-month recruit: 92
- Control: 304
- IBIS 2 high risk: 8

Cohort risk:

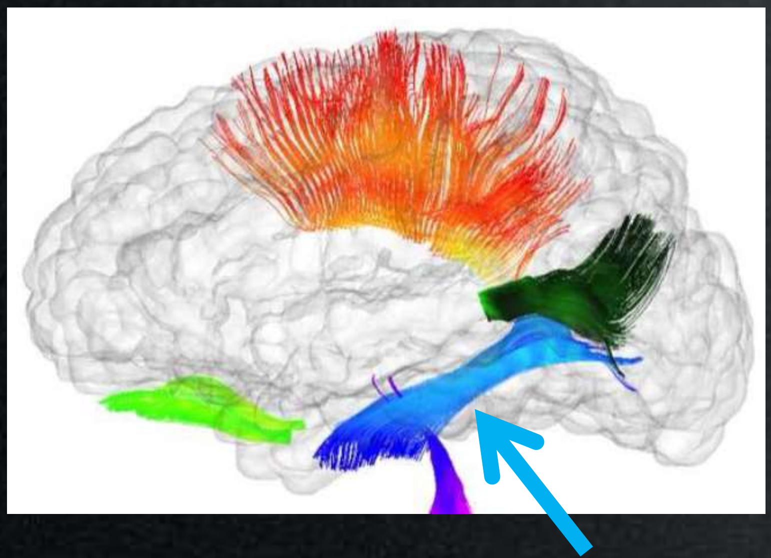
- HR: 654
- LR: 304

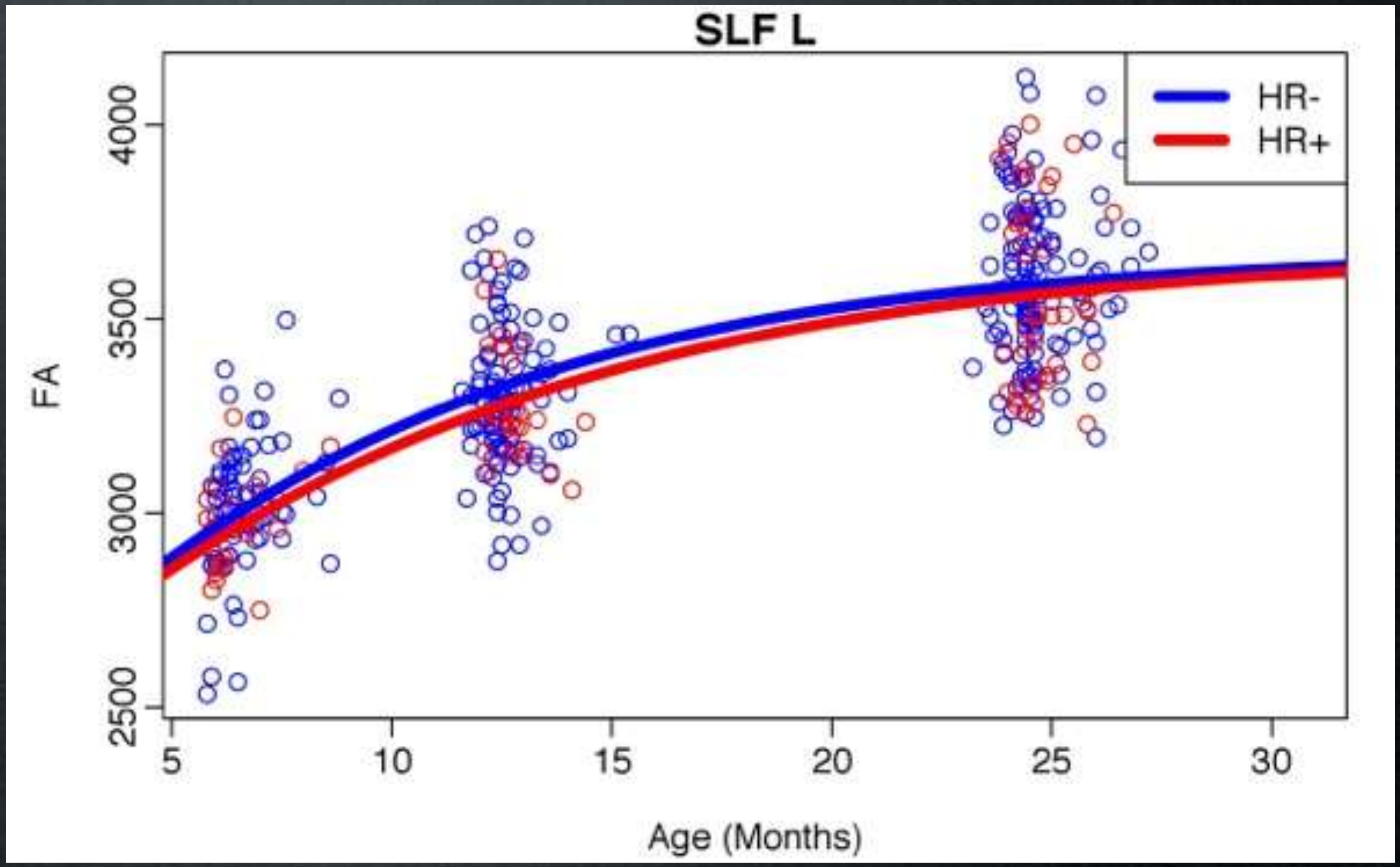
Cohort risk ADOS:

- HR+: 103
- HR-: 347
- LR+: 6
- LR-: 168
- unknown: 334

Longitudinal modeling
(HR+ vs HR-)

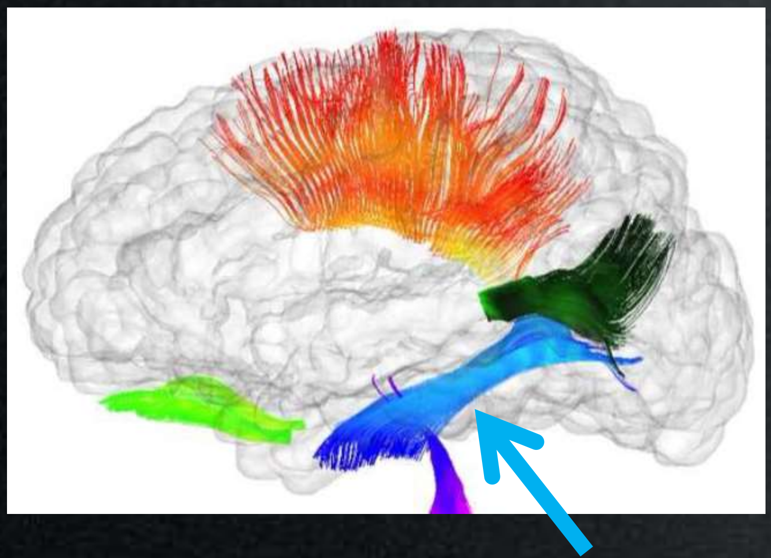
- Non-significant FA group difference for Superior Longitudinal Fasciculus Left

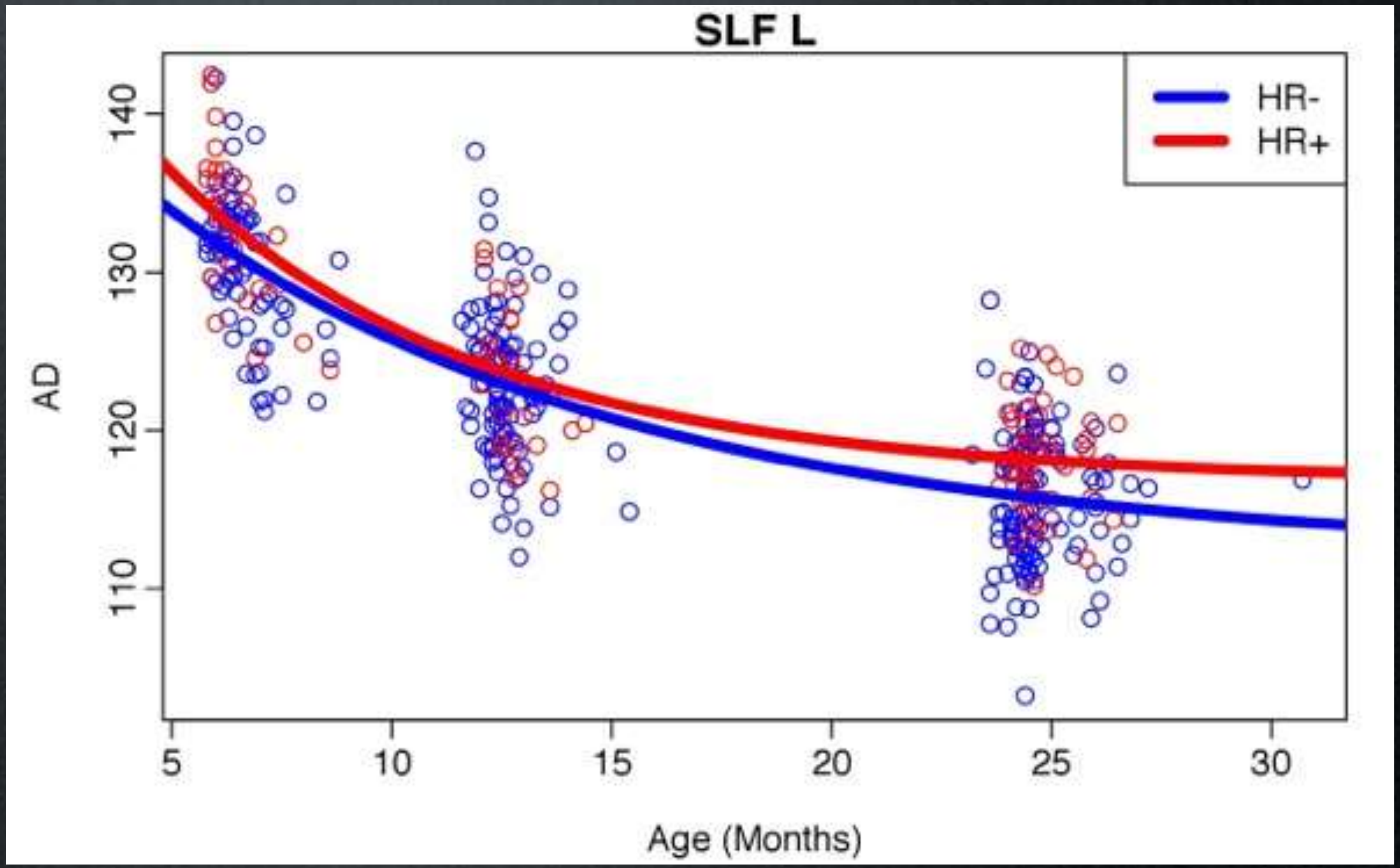




Longitudinal modeling
(HR+ vs HR-)

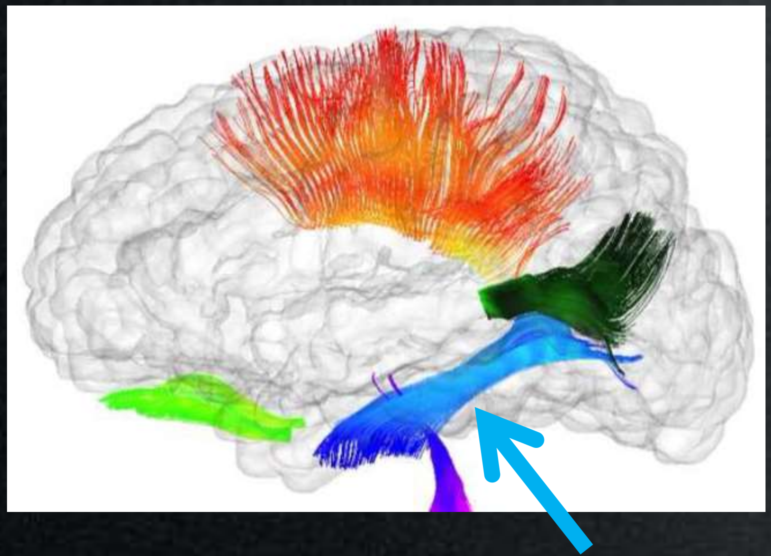
- Significant **AD** group difference on **asymptote** for Superior Longitudinal Fasciculus Left ($p < 0.002$)

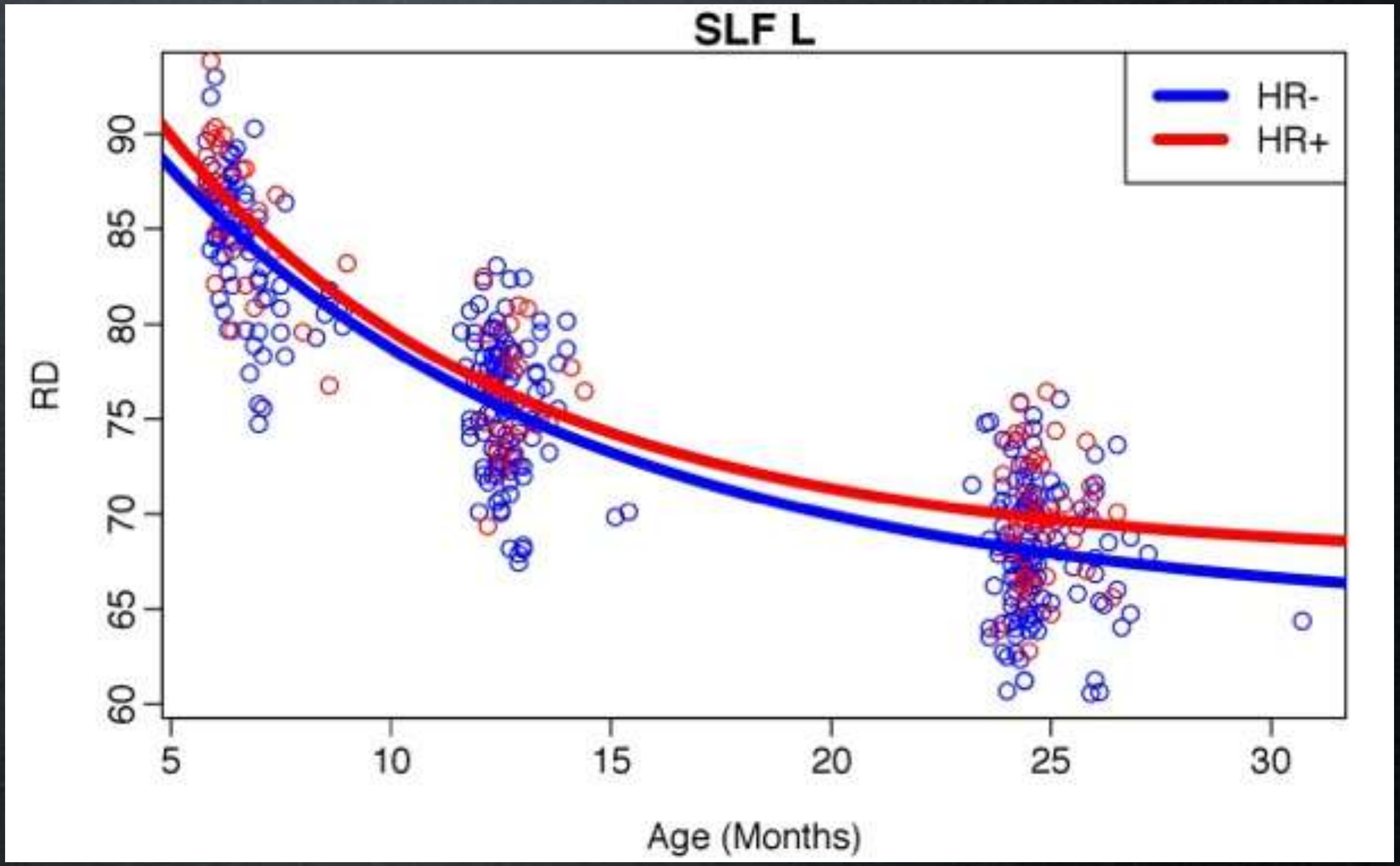




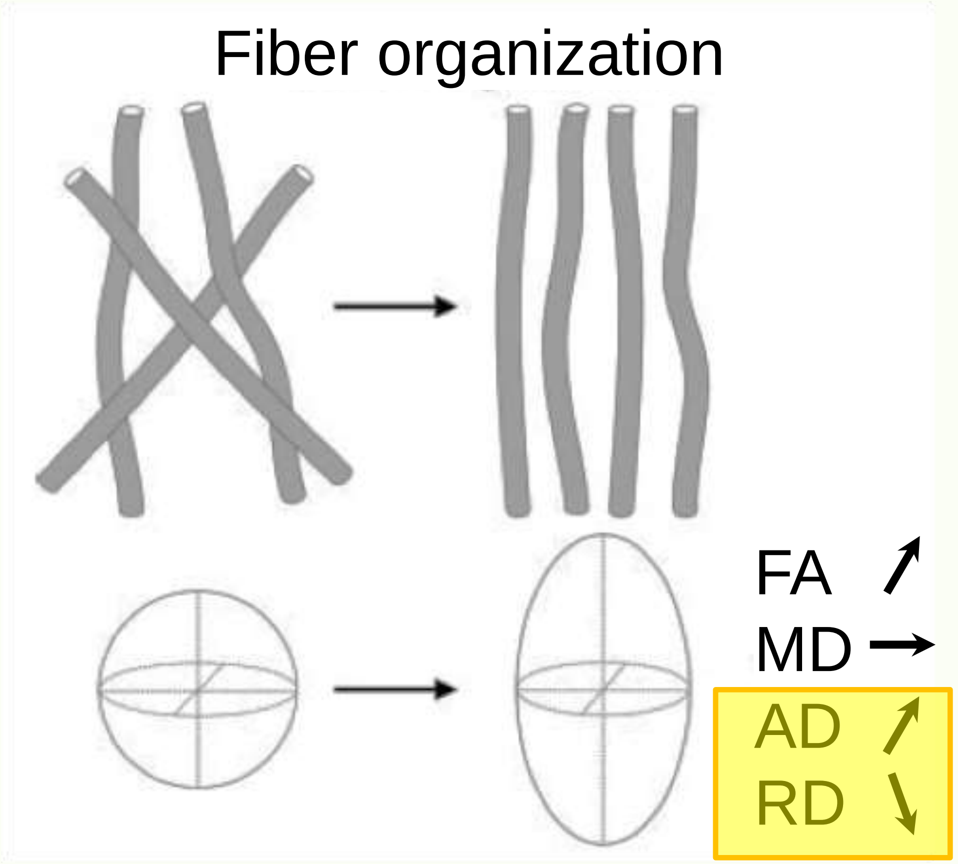
Longitudinal modeling
(HR+ vs HR-)

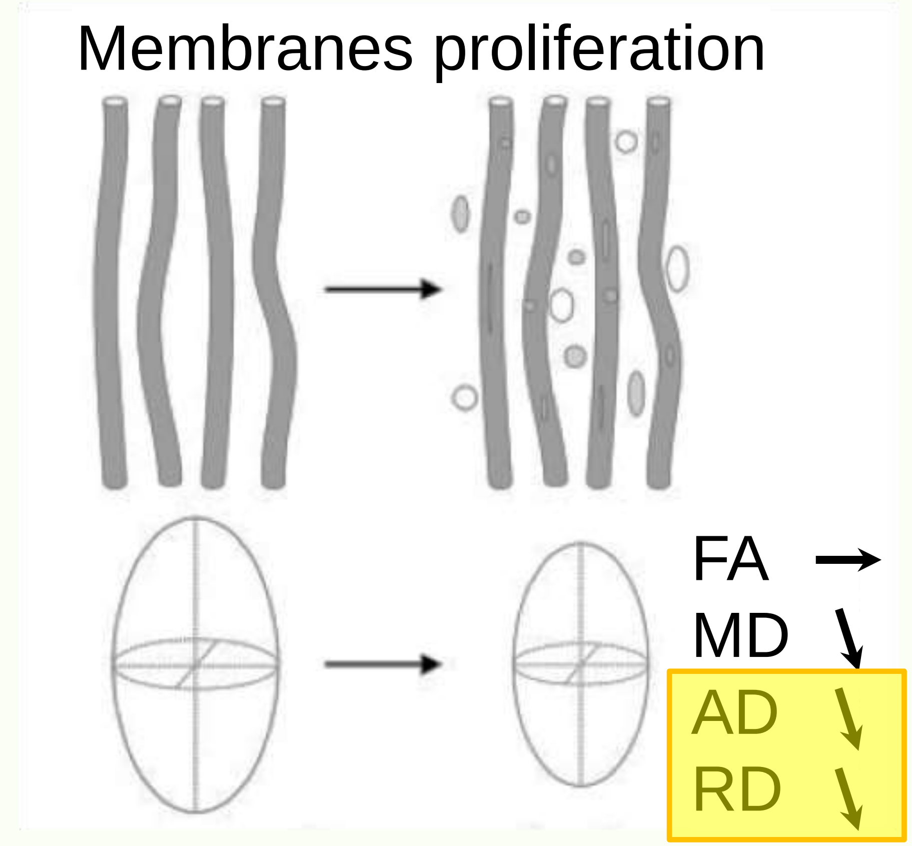
- Significant **RD** group difference on **asymptote** for Superior Longitudinal Fasciculus Left ($p < 0.04$)

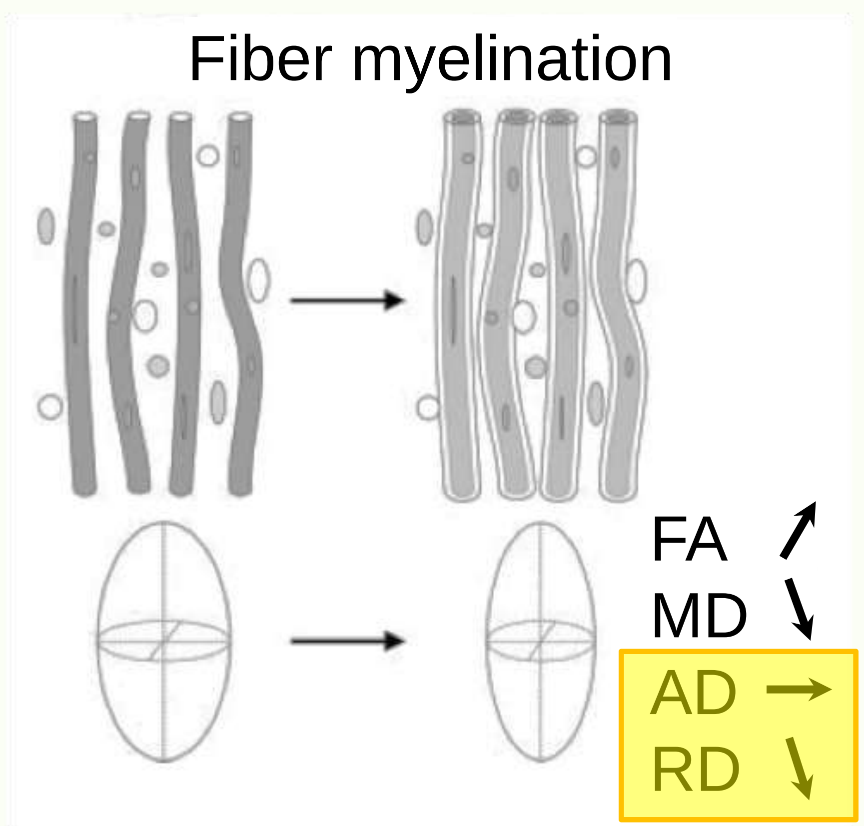




Diffusion changes as white matter matures







Observation:

Increasing or decreasing measures with age:

↑ : FA (also volume, T1w)

↓ : MD, AD, RD (also T2w)

Dubois et al, Human Brain Mapping, 2008

Study: Brain scans detect early signs of autism

[Link to CBS News]

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The American Journal of Psychiatry, VOL. 169, No. 6
ARTICLES | June 01, 2012

Differences in White Matter Fiber Tract Development Present From 6 to 24 Months in Infants With Autism

Jason J. Wolff, Ph.D.; Hongbin Gu, Ph.D.; Guido Gerig, Ph.D.; Jed T. Elison, Ph.D.; Martin Styner, Ph.D.; Sylvain Gouttard, M.S.; Kelly N. Botteron, M.D.; Stephen R. Dager, M.D.; Geraldine Dawson, Ph.D.; Annette M. Estes, Ph.D.; Alan C. Evans, Ph.D.; Heather C. Hazlett, Ph.D.; Penelope Kostopoulos, Ph.D.; Robert C. McKinstry, M.D., Ph.D.; Sarah J. Paterson, Ph.D.; Robert T. Schultz, Ph.D.; Lonnie Zwaigenbaum, M.D.; Joseph Piven, M.D.; the IBIS Network

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UCNIA

Computational tools for quantitative image analysis

Researchers See Differences in Autism Brain Development as Early as 6 Months

Scientists created 3D images of major brain pathways in infants at high risk for developing autism. [Credit: UNC]

The defining features of autism—hampered communication, social challenges and repetitive actions—may not become obvious until after a baby's first birthday. But the changes in brain development that underlie these behaviors may be detectable much earlier. In a new study, researchers found clear differences in brain communication pathways starting as early as 6 months and continuing through 2 years of age in children who were later diagnosed with autism spectrum disorder (ASD). The findings appear online today in the *American Journal of Psychiatry*.

Study Suggests Pre-Autism Brain Differences In Six Month Olds

February 18, 2012

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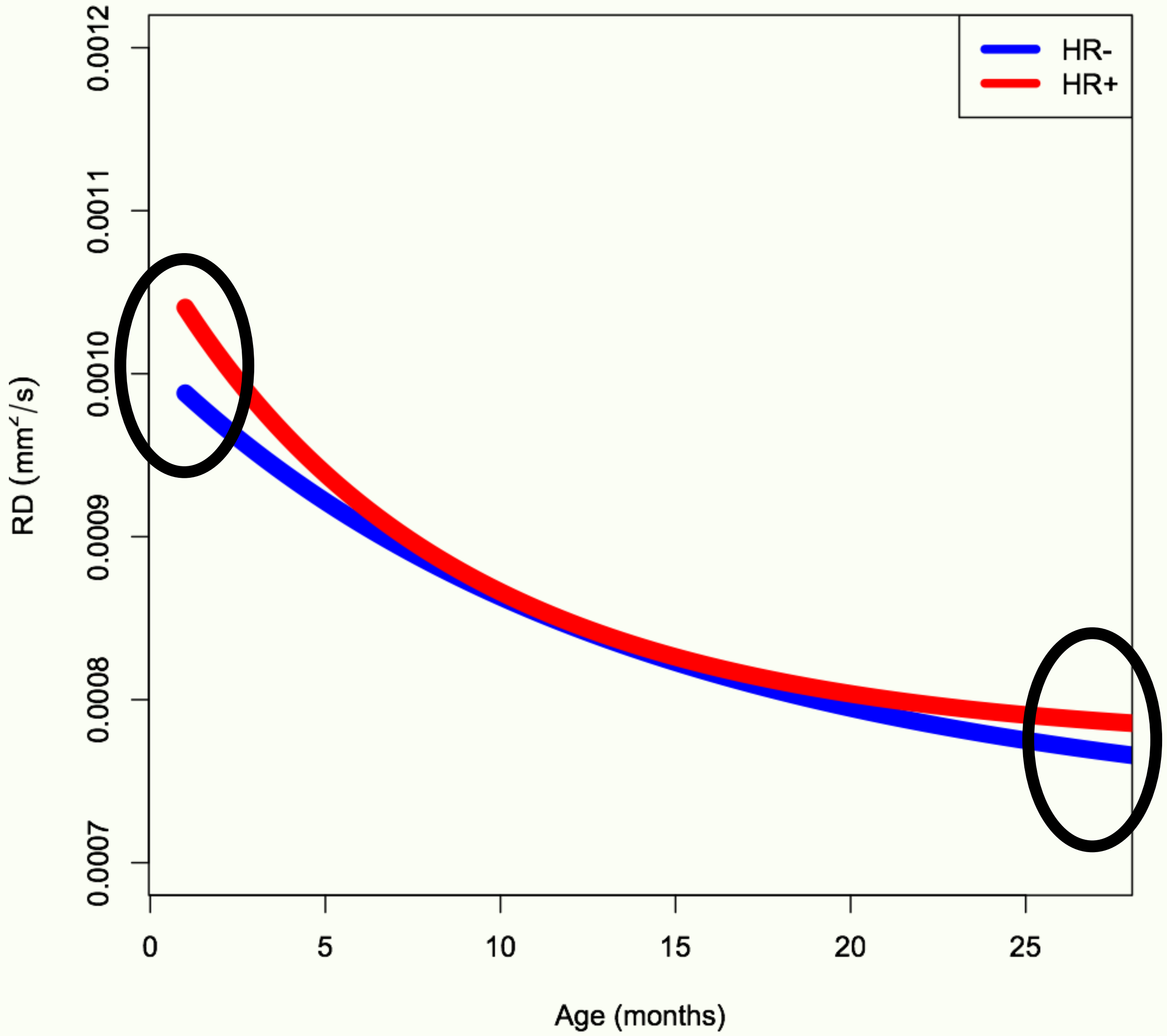
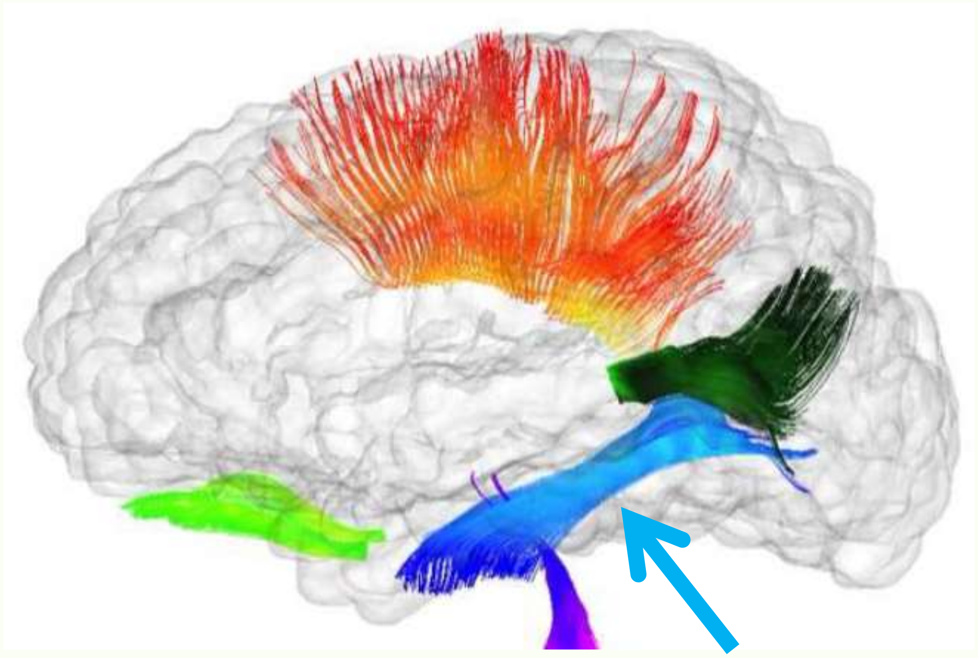
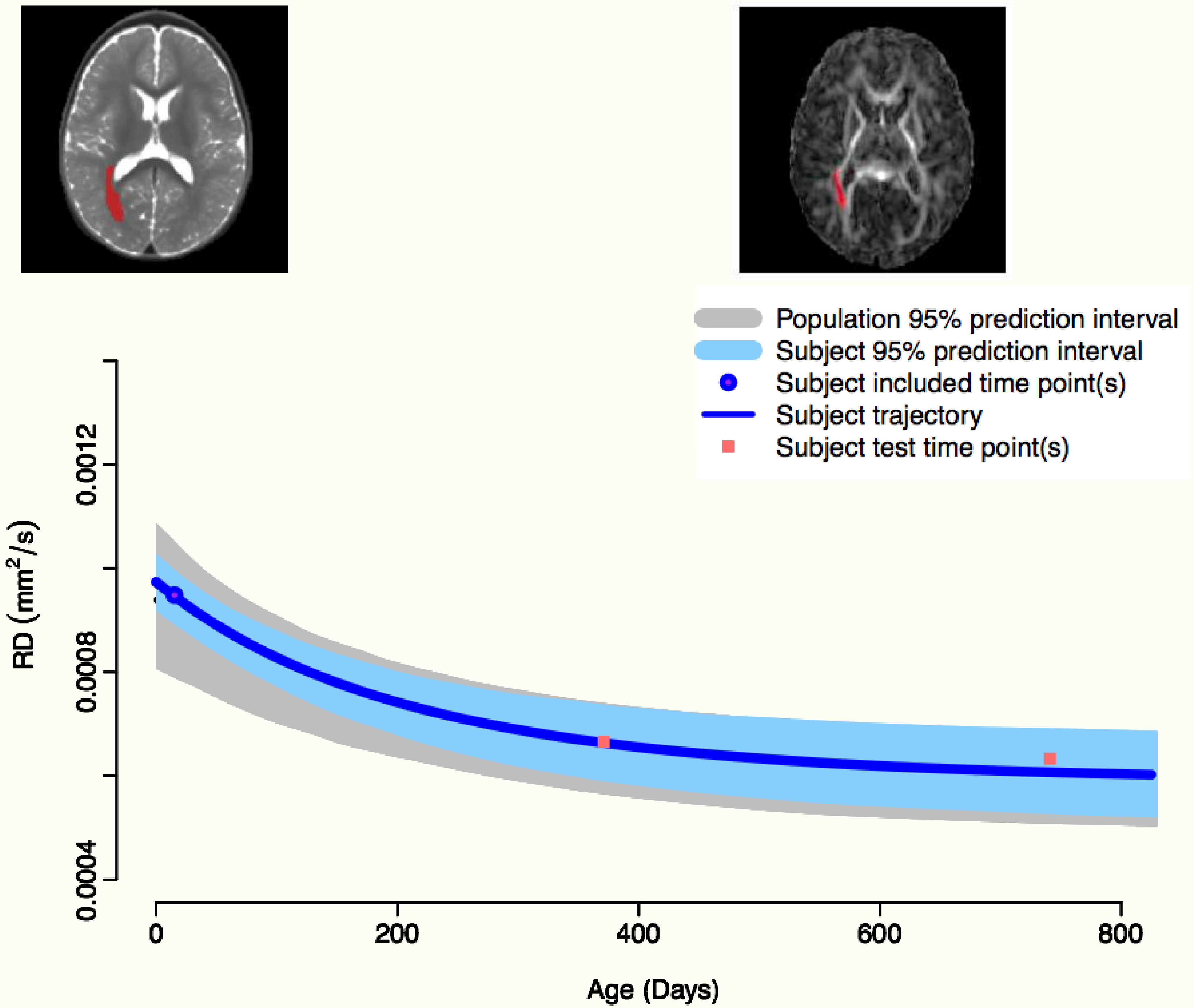
Population Trajectory Comparison : DTI



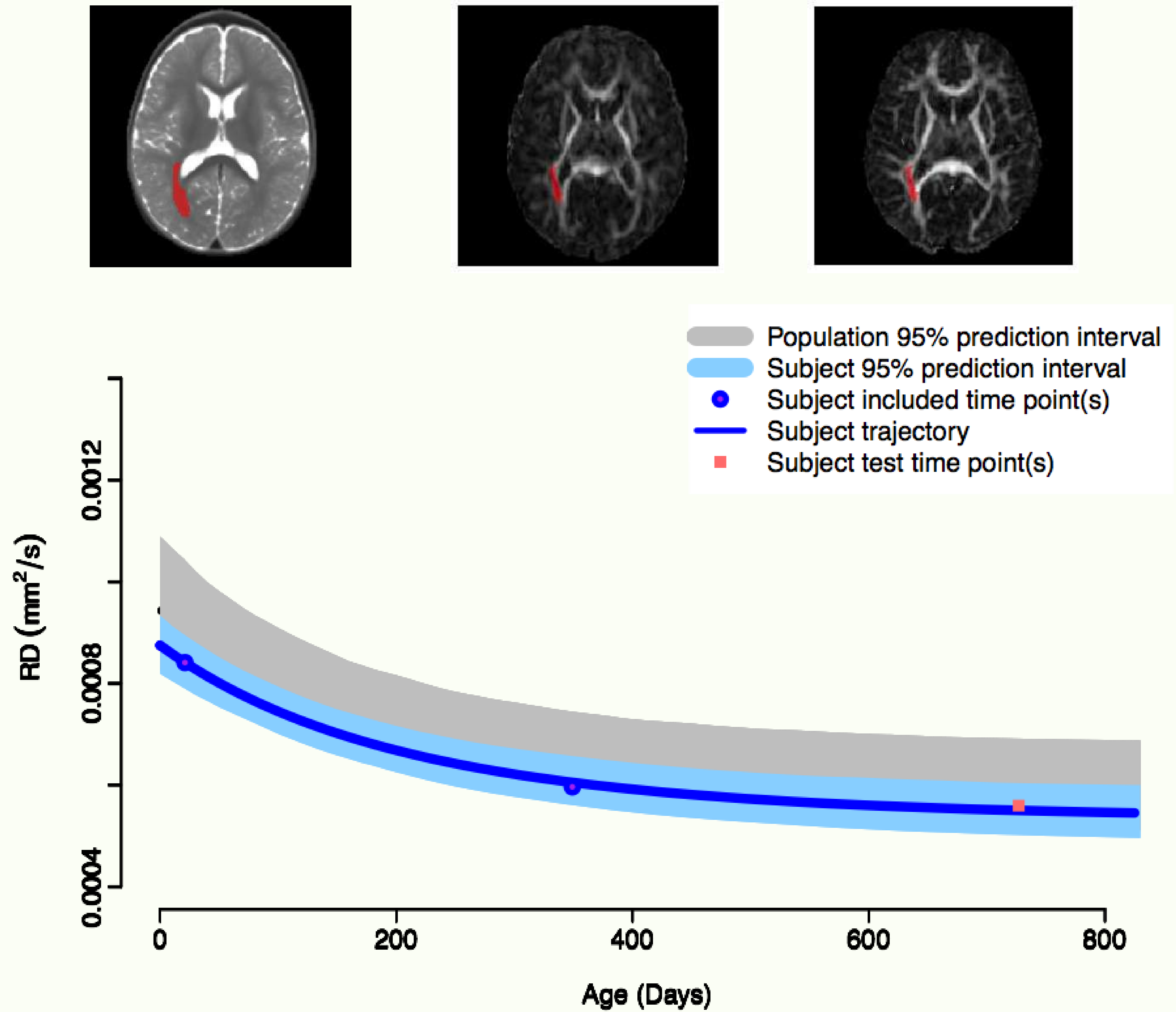


Hypothesis testing on DTI RD:
ILF: Speed & Asymptote ($p < 0.05$)

Can we predict **individual** status/category at year 2 given image measurements only at 6 month? (DWI as prediagnostic biomarker).



Population 95% prediction interval
Subject 95% prediction interval
Subject included time point(s)
Subject trajectory
Subject test time point(s)
RD (mm²/s)
0.0004
0.0008
0.0012
0
200
400
600
800
Age (Days)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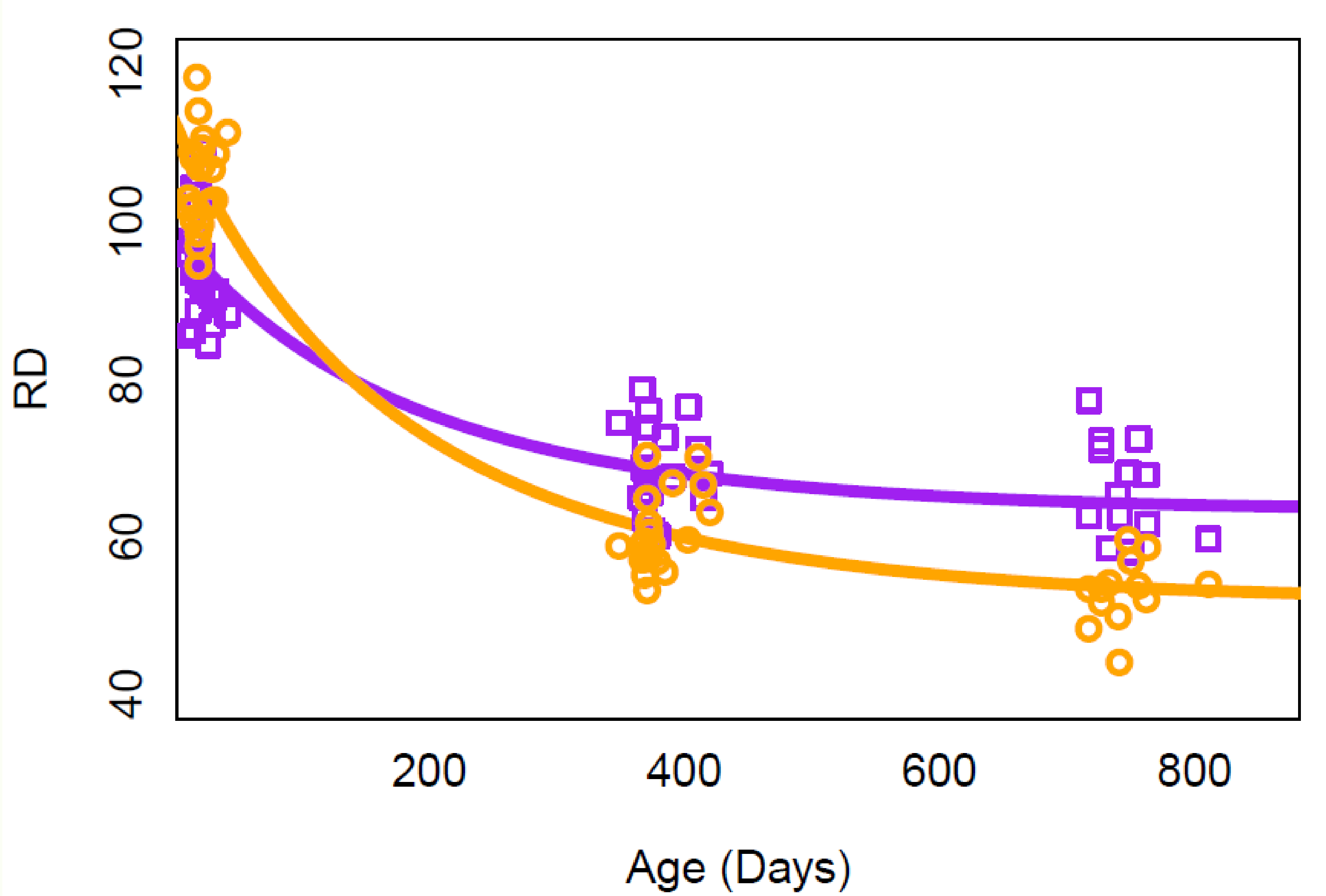
RD (mm²/s)
0.0004
0.0008
0.0012
0
200
400
600
800
Age (Days)

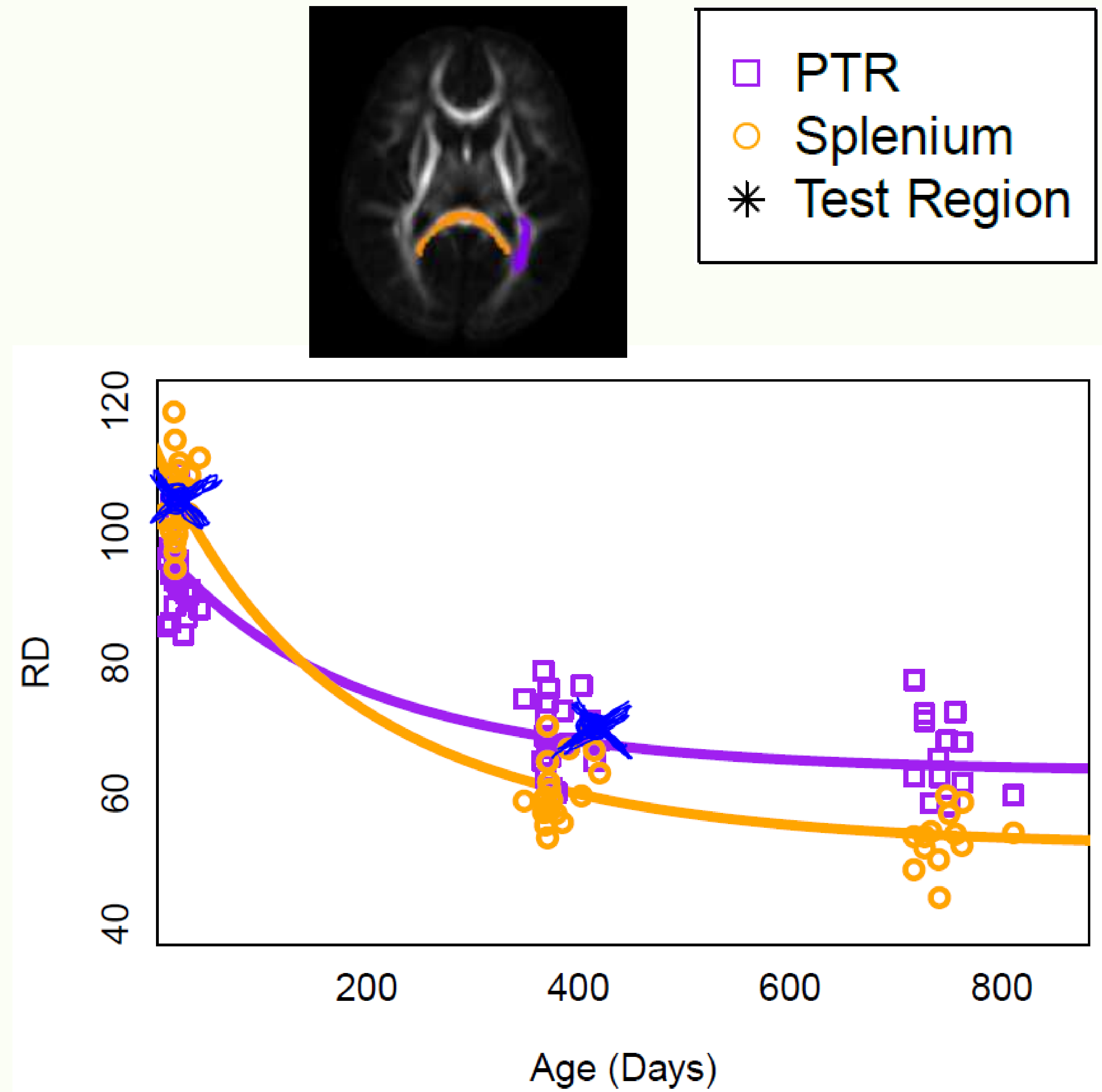
Classification / Prediction of Category

- Two class case: Controls versus patients, e.g.
- Building of models for each class
- Testing new individual on <u>both</u> models
- Classify into model with higher likelihood = Prediction of Class



Preliminary Example: PTR vs. Splenium

- Looking at the test region's first time point, it seems that it would be <u>splenium</u>.
- Second time point is more similar to <u>PTR</u>.
- Illustrates that analysis at single time points can easily lead to contradictory results.



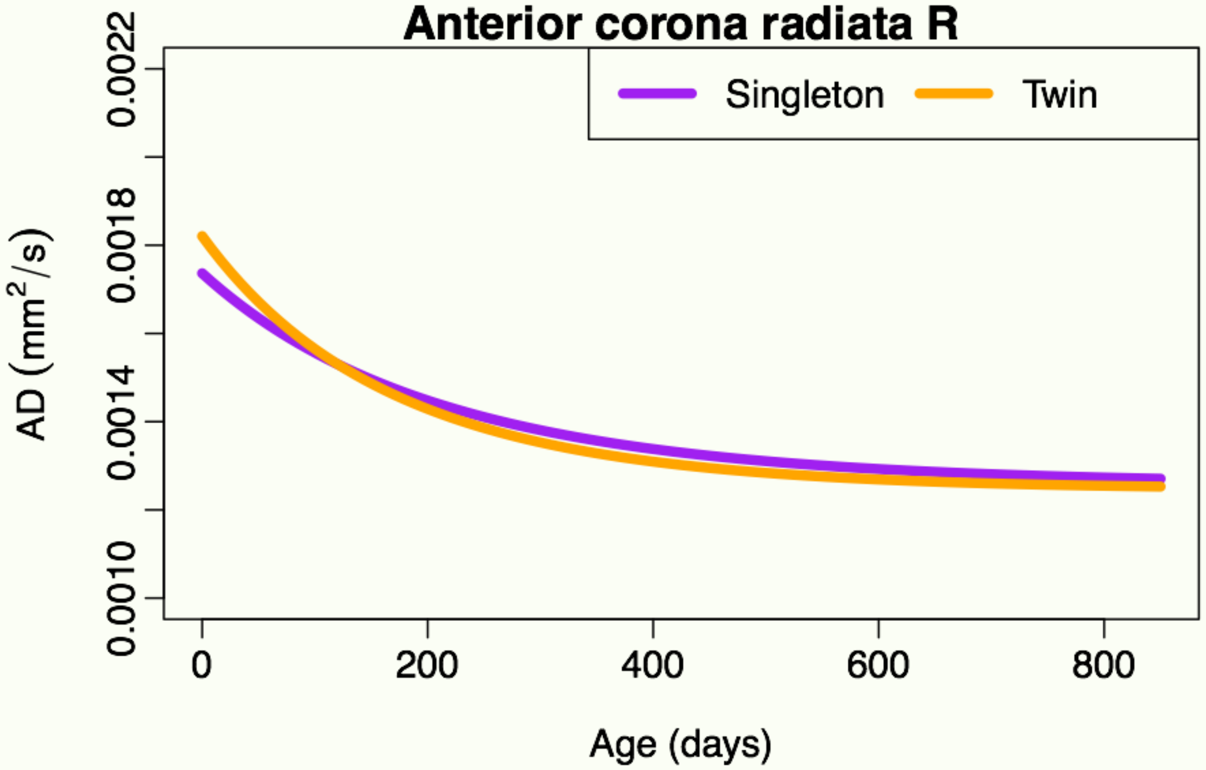
And the winner is? **PTR**

Twin Study (UNC Gilmore)

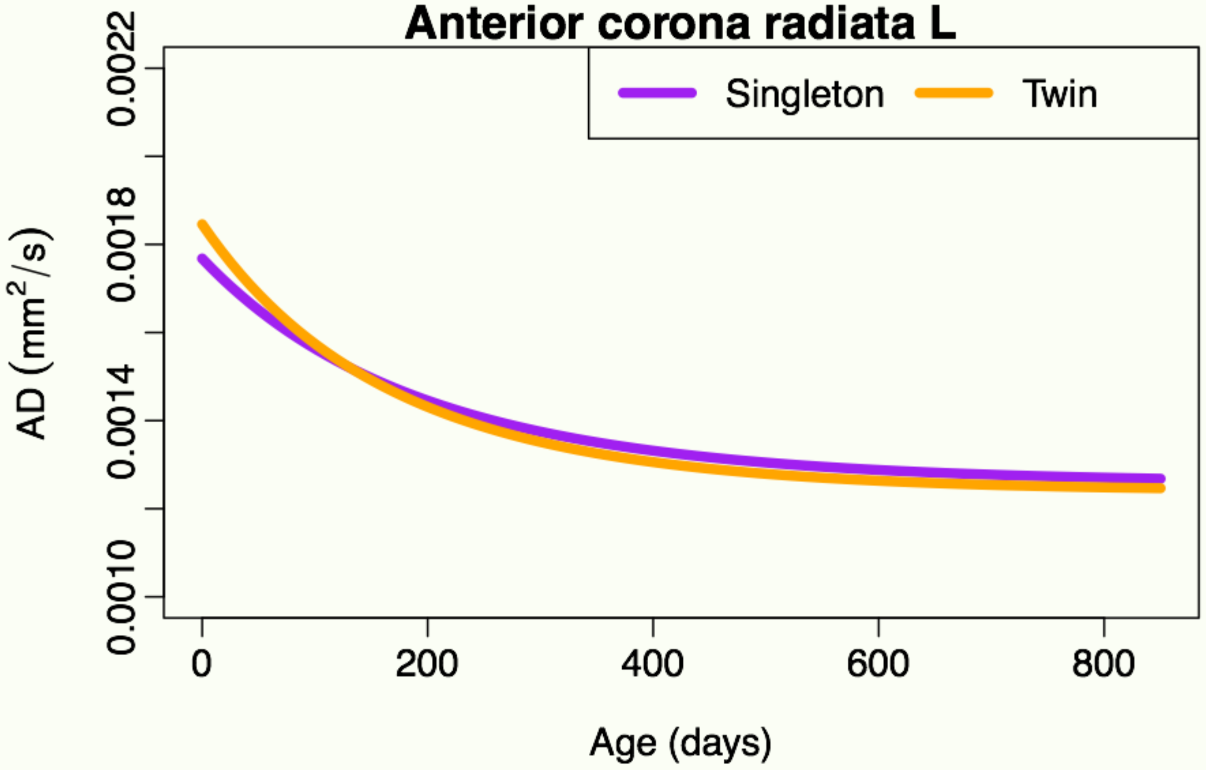
Motivation: Is early development in twins same as in singletons?

	Neonate	1 year	2 year	Total
Singletons	23	22	14	59
Twins	69	65	35	179
Total	92	97	49	238

Singletons vs. Twins Developmental Trajectories



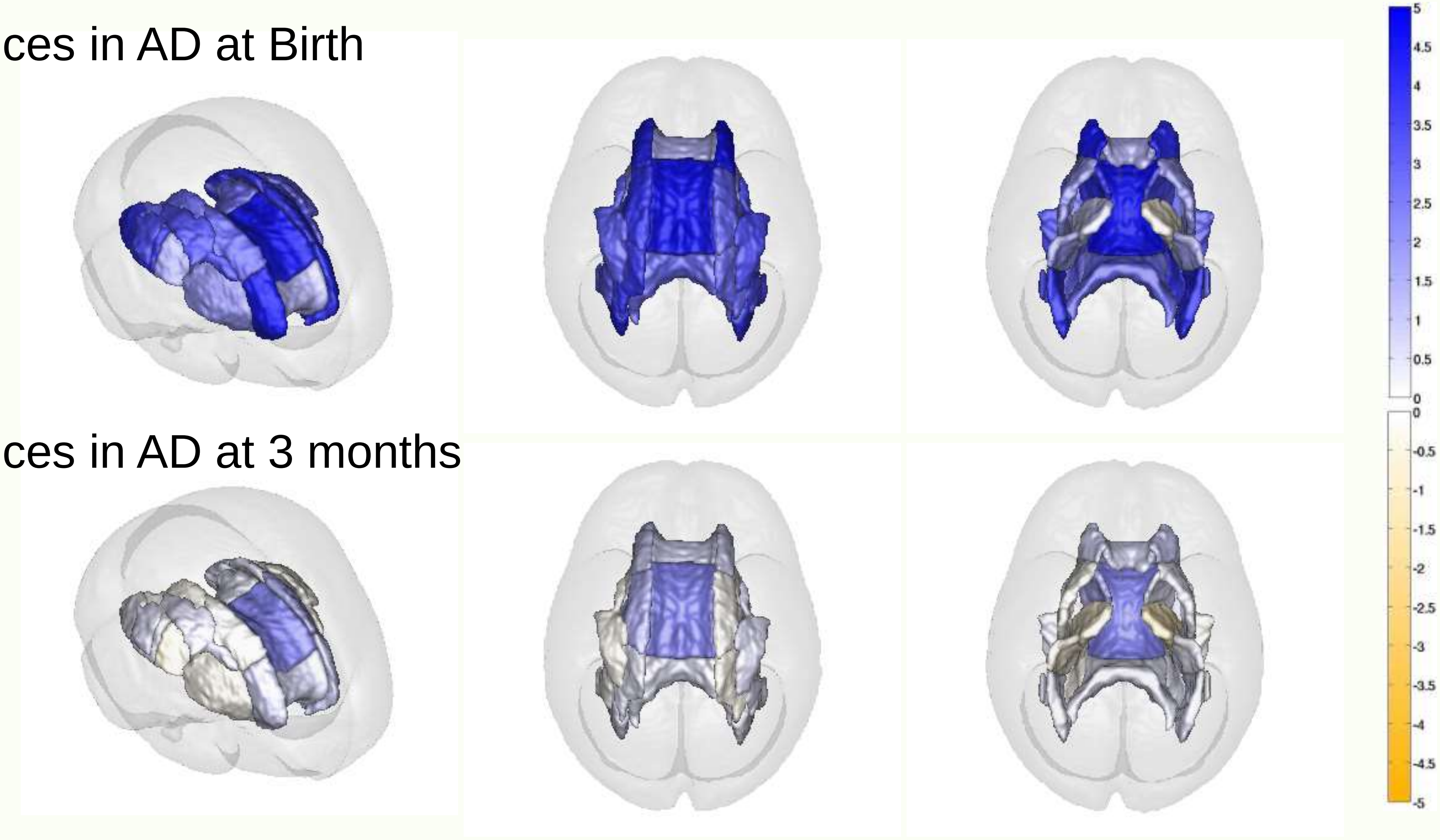
Hypothesis Testing:
Delay Parameter < 0.05



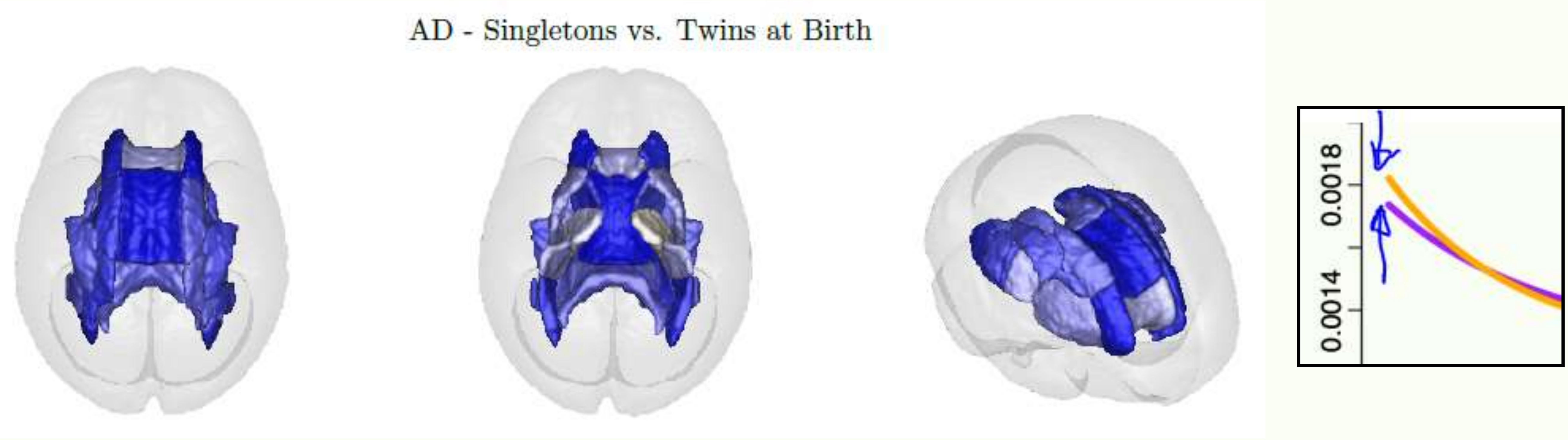
Singletons vs. Twins

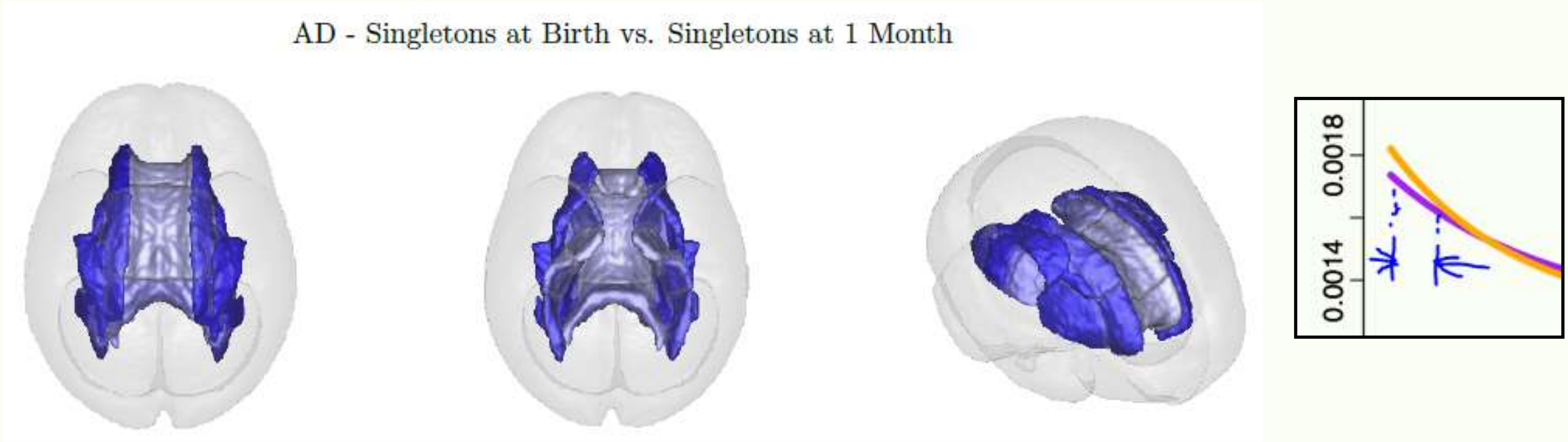
Differences in AD at Birth

Differences in AD at 3 months



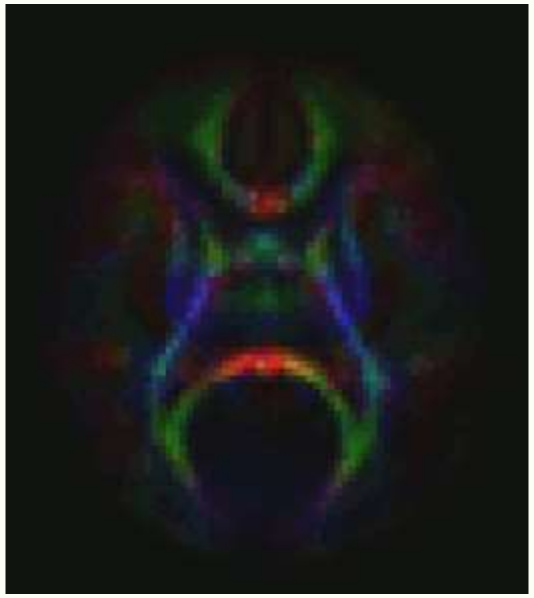
Question: Could this difference be explained by slightly delayed development of twins?



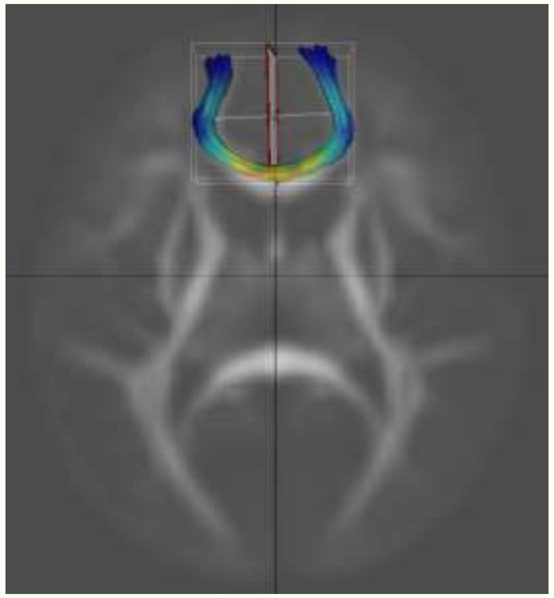


In progress: Longitudinal Tract-Based Modeling

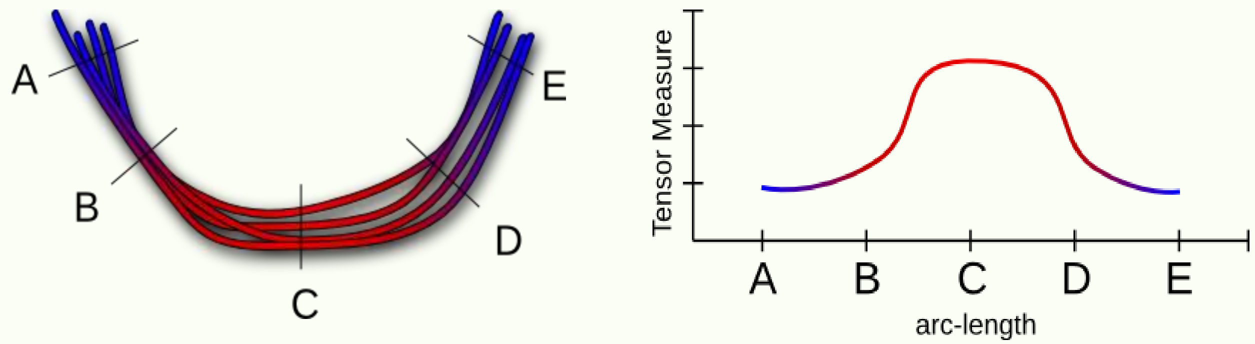
Cine



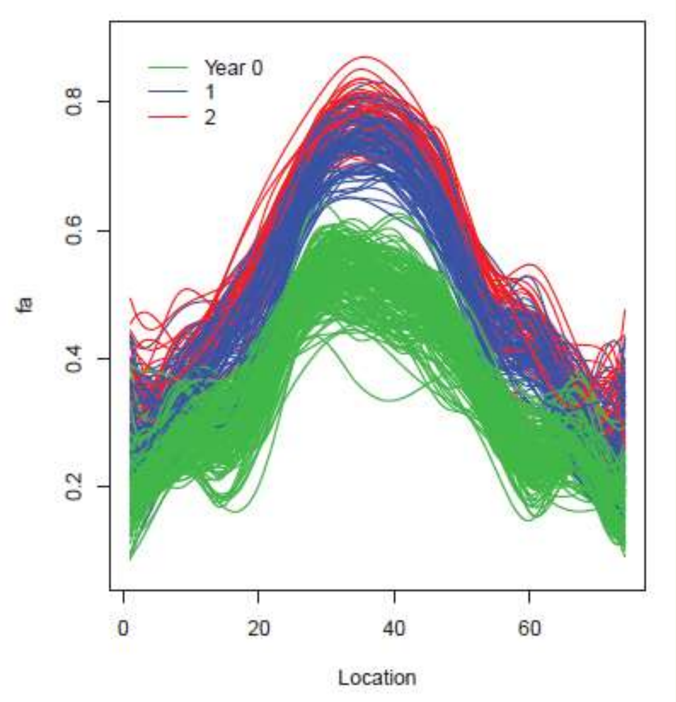
Genu Tract

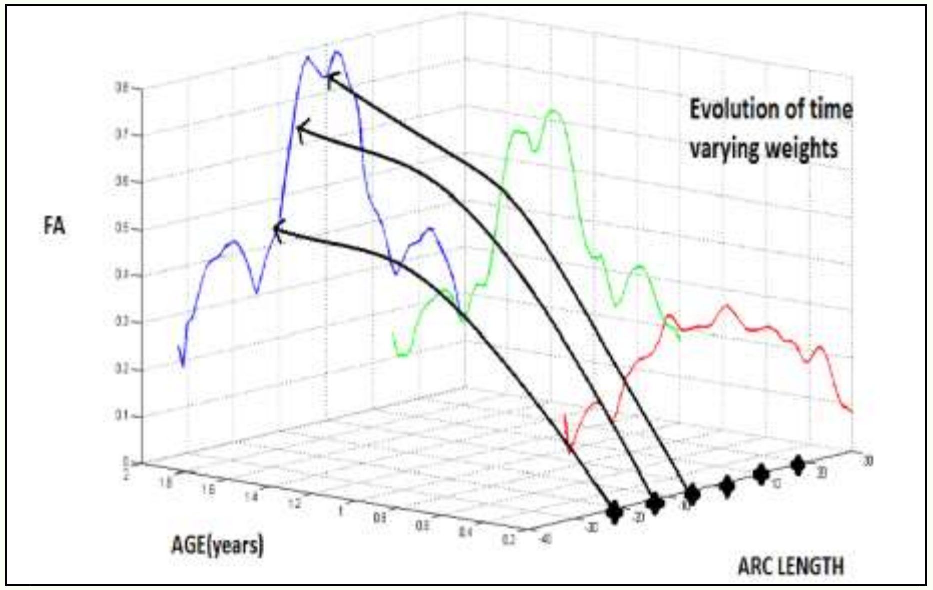


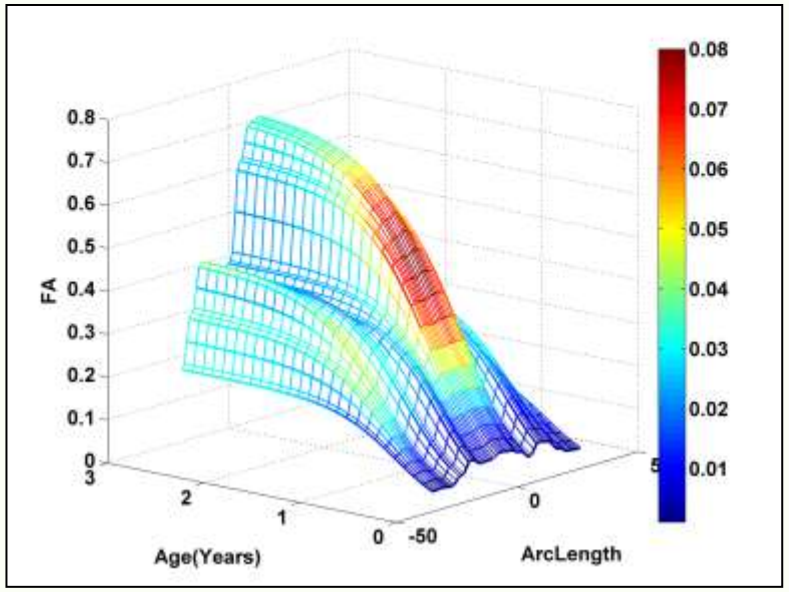
Parametrization by arc length



Spatio-temporal statistical tract model





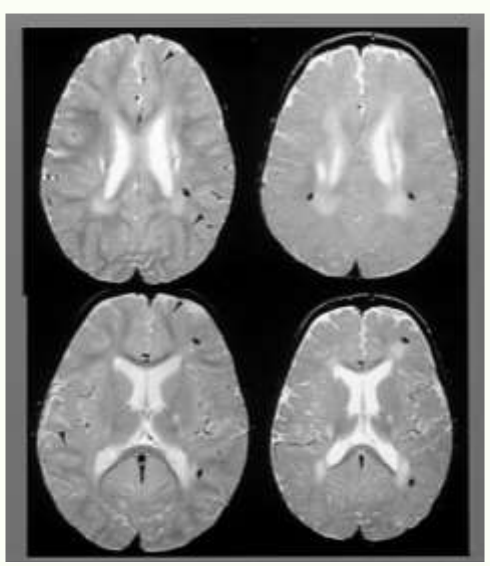


Corouge et al., '06, Goodlett et al, '09, Sharma et al., ISBI '12, '13

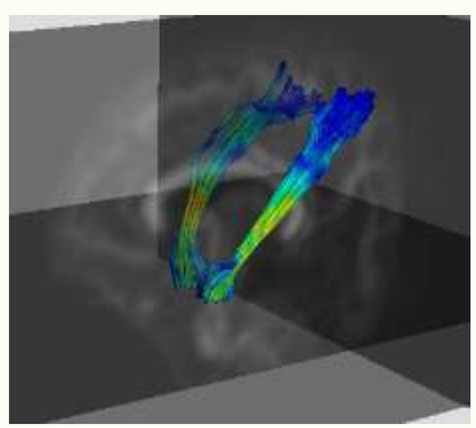
Application: Infantile Krabbe's Disease

- Rare disease
- Demyelination in CNS & PNS
- Progressive neurological deterioration
- Symptoms before 6mt
- **Fatal before age 2**

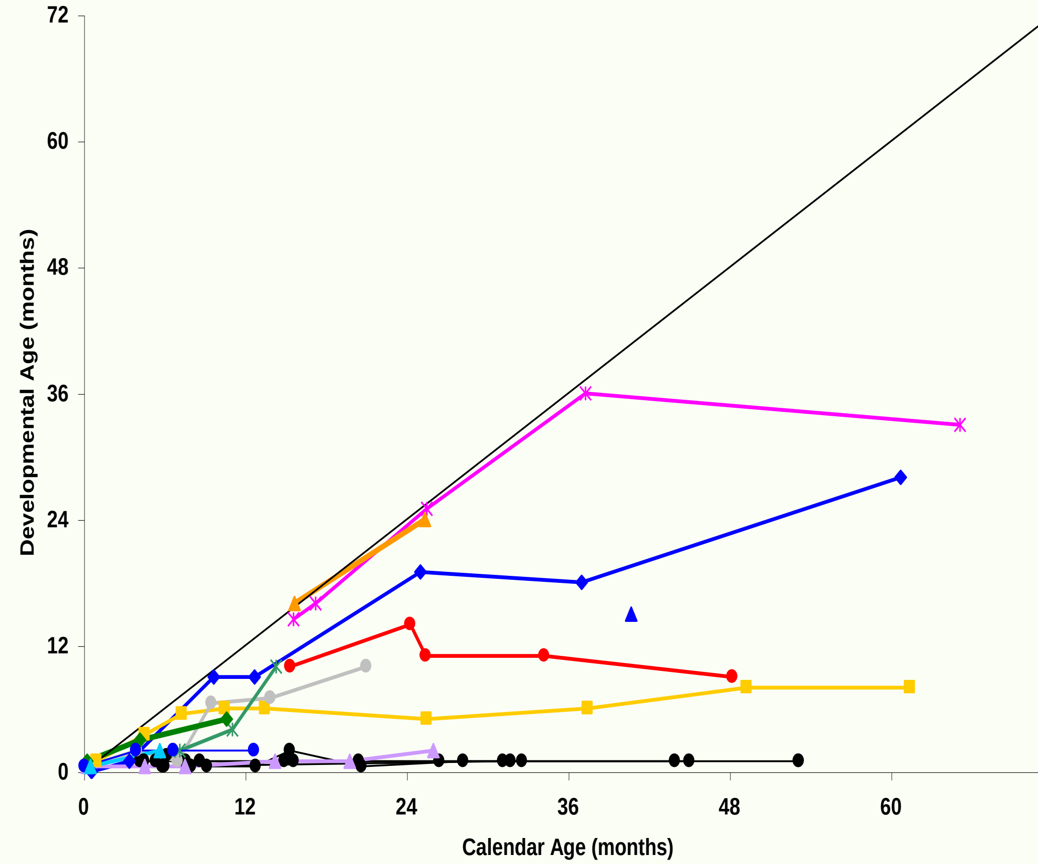
UCBT



Motor Tract



Gross Motor Scores



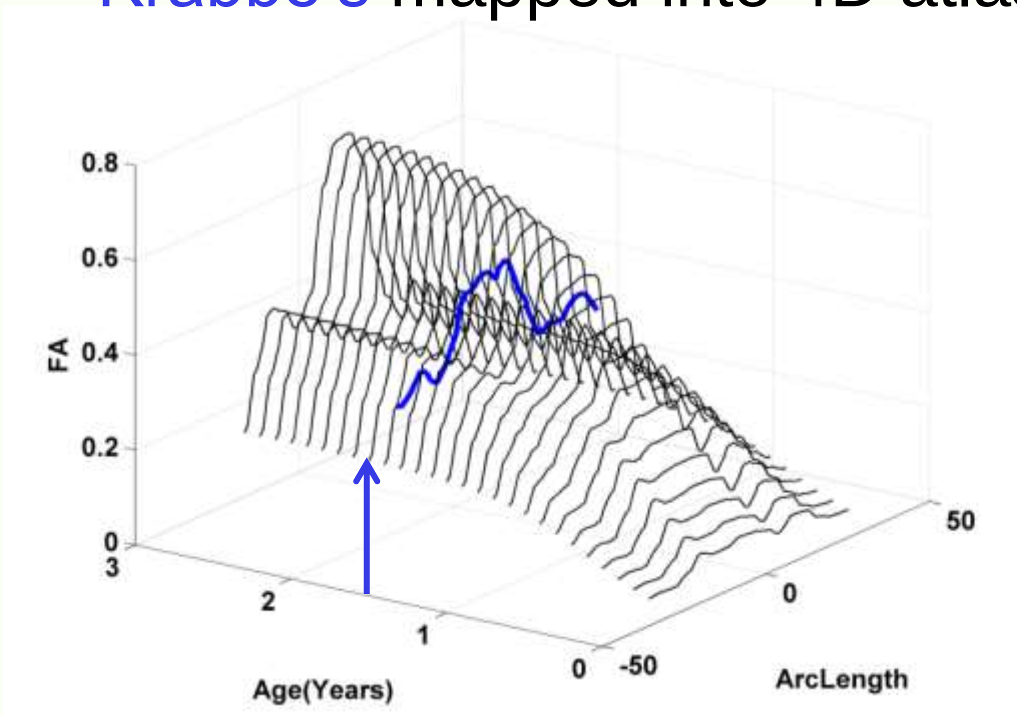
Scores for treated (colors) versus nontreated subjects (dark):

Notion of normative model/atlas: Describe patients relative to population statistics of healthy development.

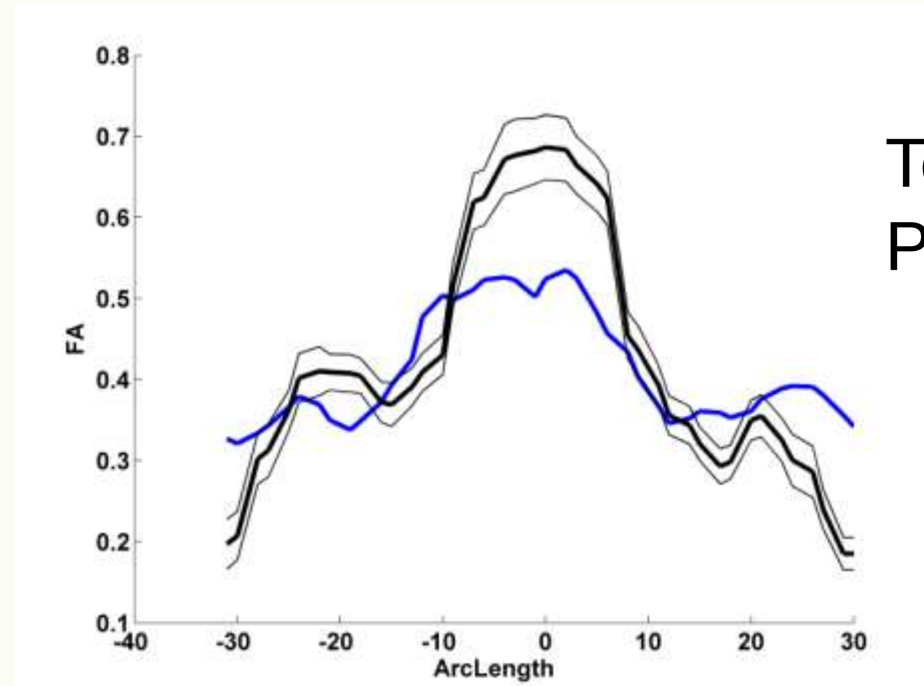
Dr. Maria Escolar, Pediatrics, Pittsburgh

Compare Individual Patient to Atlas

Krabbe's mapped into 4D atlas

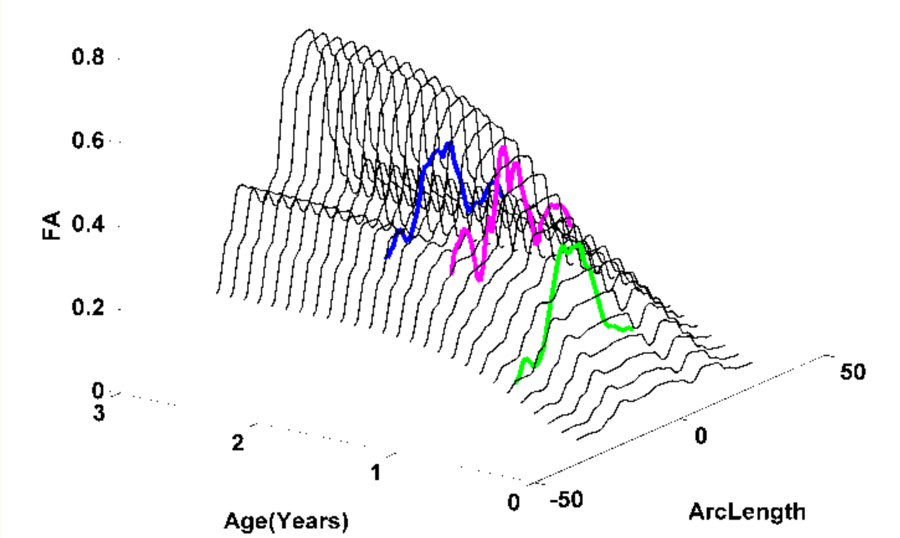


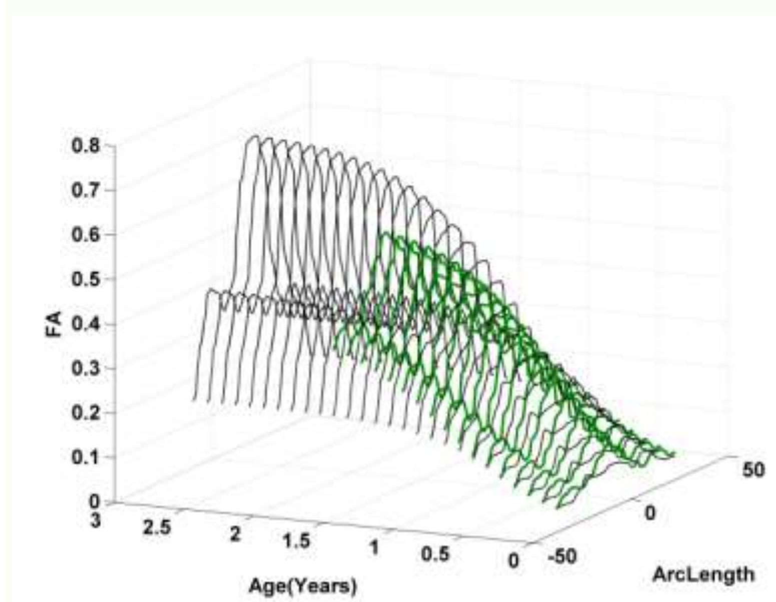
Time slice of atlas and Krabbe's subject

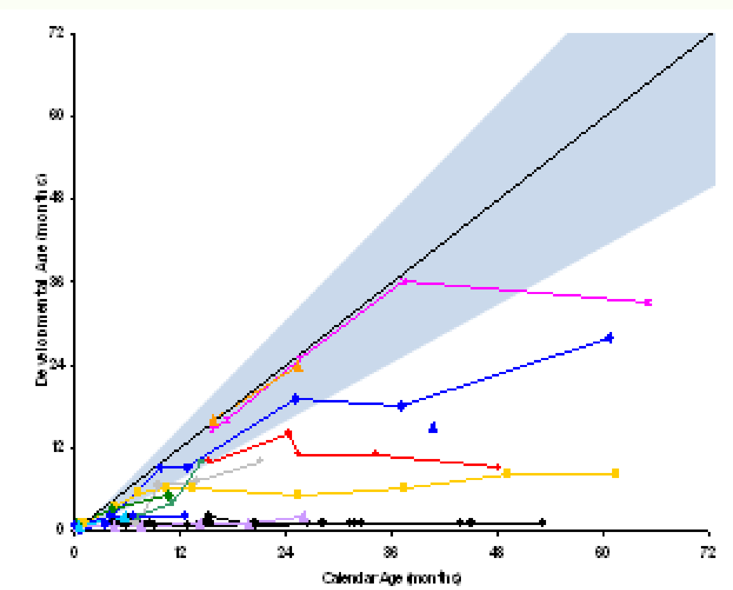


Testing:
P<0.001

4D Krabbe's versus 4D atlas

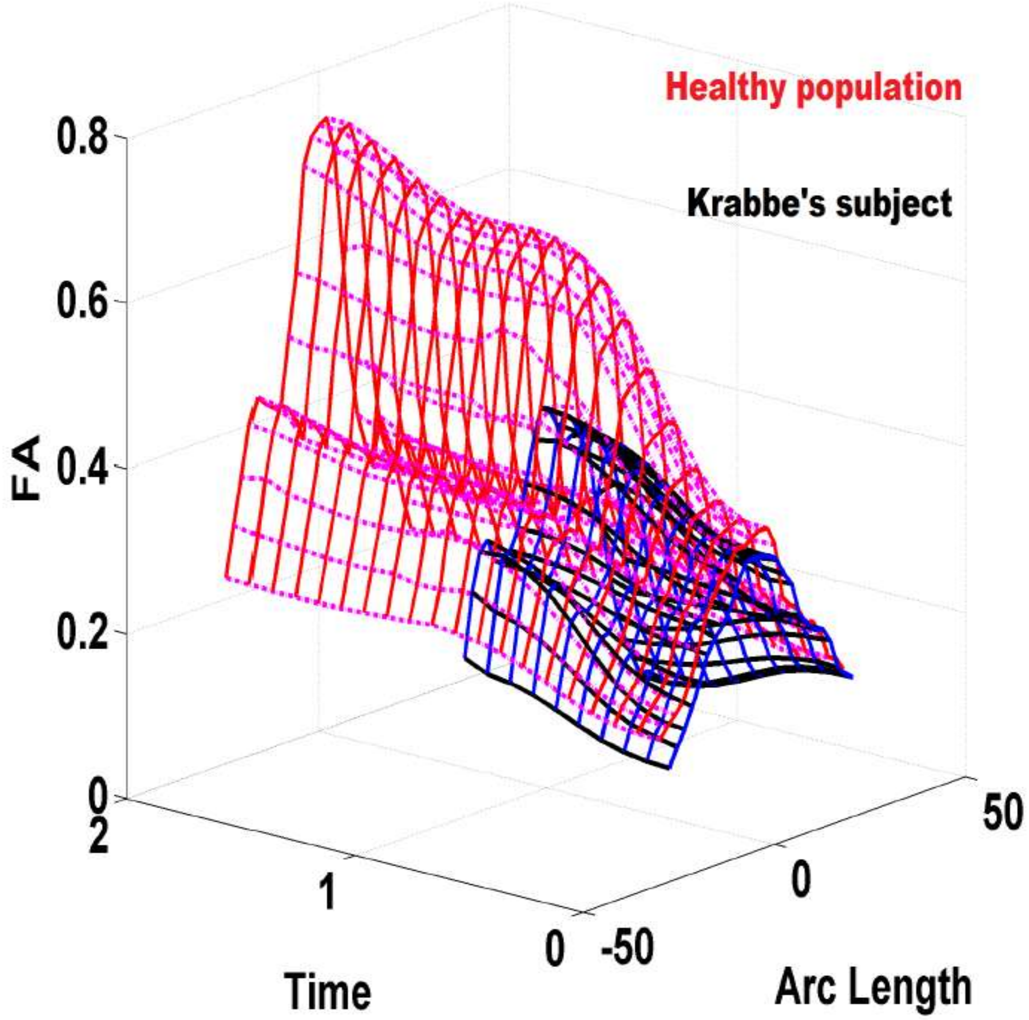




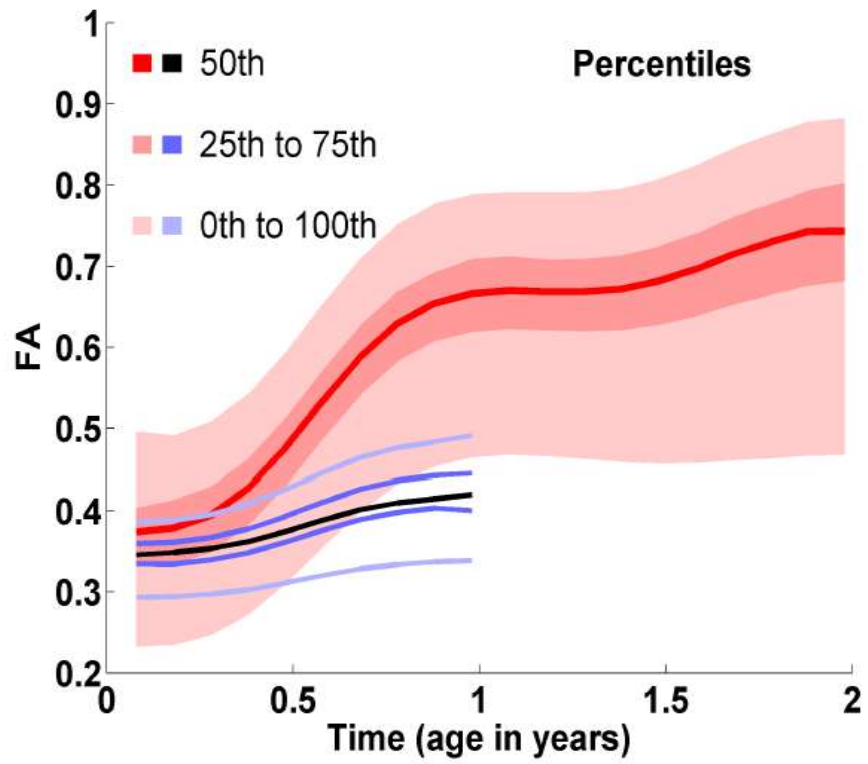


Subject-specific Analysis

- Krabbe's disease affects myelin of the nervous system.
- Degenerative in nature, often fatal without early therapy.



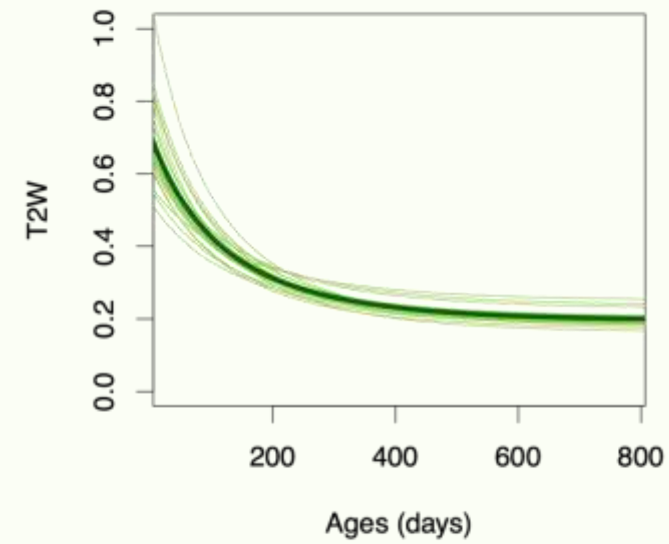
Normative FA trajectory wrt a single Krabbe's subject.

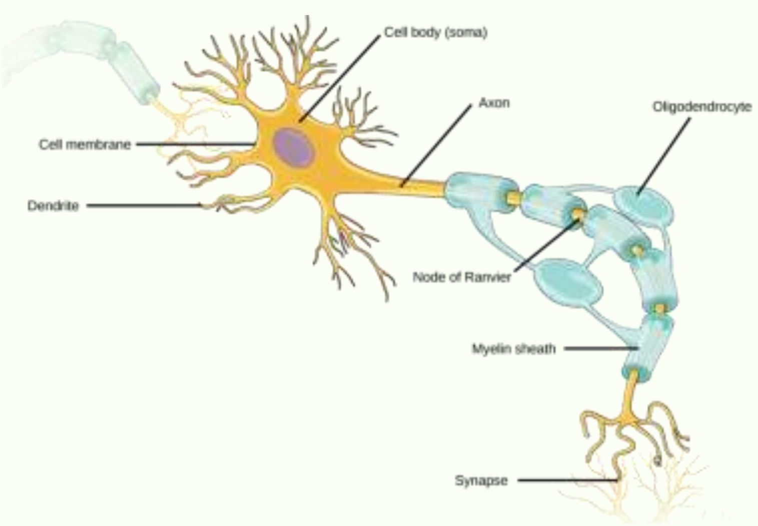


FA quartiles for a single tract location along time.

Conclusions 4D DTI

- Growth is <u>nonlinear</u> (DTI, volume, circumf., T1/T2 MRI) ->nonlin. model.
- NLME: Modeling of individual trajectories & fixed effects.
- RD and AD seem more sensitive than FA (*Sadeghi, Neuroimage '13*).
- Longitudinal imaging seems key for subject-specific prediction modeling.
- Tbd:
  - Integration of region/tract diffusivities into connectivity analysis
  - Inclusion of behavioral/diagnostic features into the model
  - Still more effort in data QC and corr.





Acknowledgements

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- **NIH-NIBIB**: 2U54EB005149-06 , NA-MIC: National Alliance for MIC
- **NIH (NICHD) 2 R01 HD055741-06**: ACE-IBIS (Autism Center)
- **NIH NIBIB 1R01EB014346-01**: ITK-SNAP
- **NIH NINDS R01 HD067731-01A1**: Down's Syndrome
- **NIH P01 DA022446-011:** Neurobiological Consequences of Cocaine Use

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- **UofU SCI Institute**: Imaging Research Team
- **Insight Toolkit ITK**