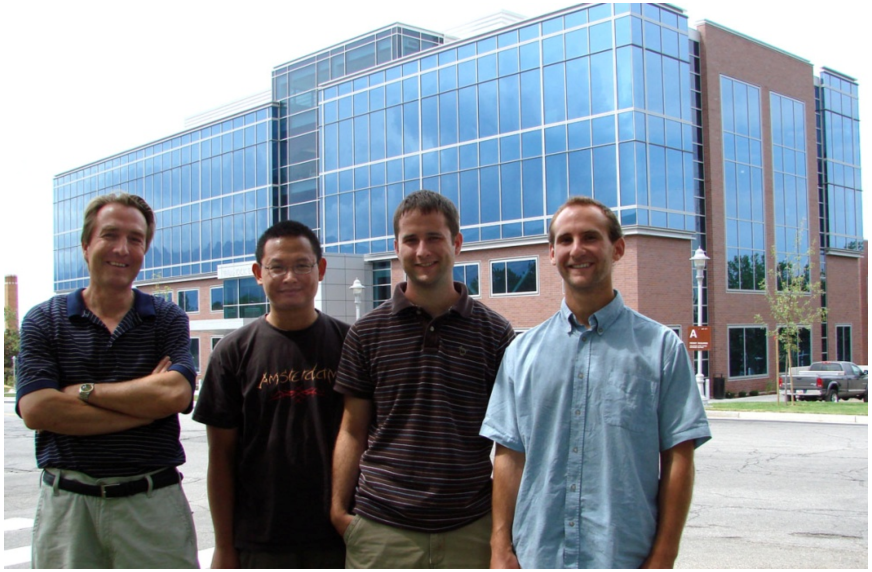
# Mapping Brain Changes Over Time during Development: Challenges, Limits and Potential

Guido Gerig
University of Utah
Scientific Computing and Imaging (SCI) Institute



# Outline

1. Imaging Technology for Pediatric Imaging
2. Analysis of structural MRI
3. Analysis of DTI
4. Multimodal MRI/DWI Analysis
5. Towards Longitudinal Analysis

# I: MR Imaging of Children

- Non-sedated neonates and children
  - Subject cooperation difficult
  - Motion problems
  - Safety issues
- Solutions:
  - MTRAs with special training
  - High-speed high-field imaging, high spatial resolution
  - Parallel Acquisition
  - Mock Scanner (Training)
  - Motion correction

Courtesy LeBihan 2005

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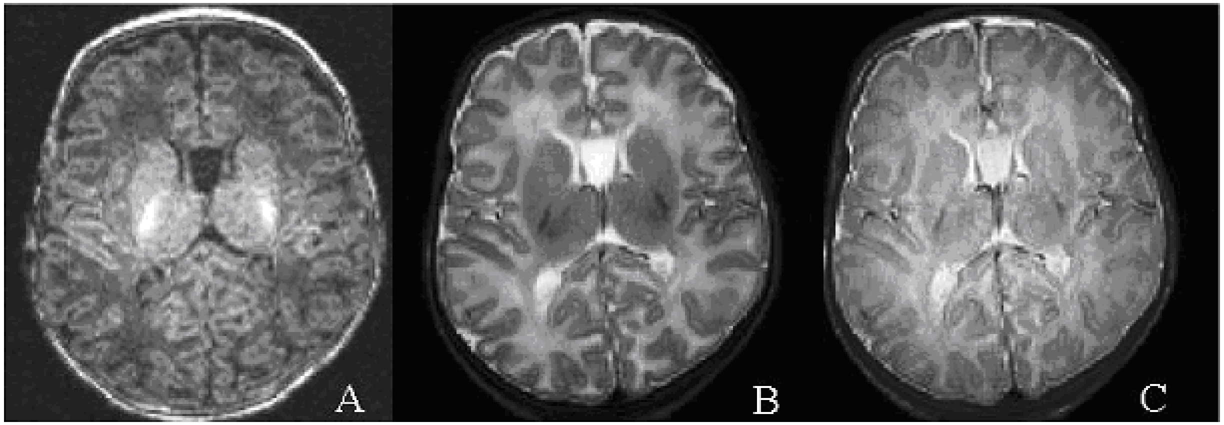
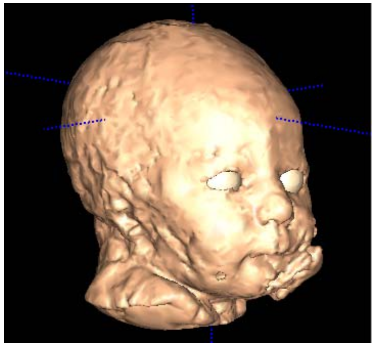
# High-Speed Imaging: Neonatal MRI at 3T

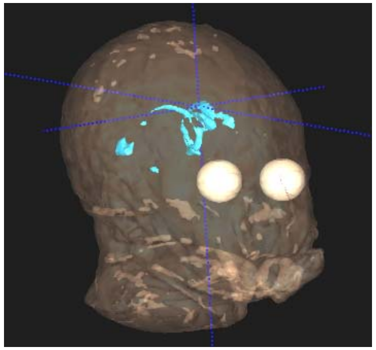


T1 3D MPRage or FLASH 1x0.9x0.9 mm3

FSE T2w 1.25x1.25x1.95mm3

FSE PDw 1.25x1.25x1.95 mm3





UNC Weili Lin: 3T Siemens Allegra

Scan Time: Structural MRI (T1 & SpinEcho): 8min, DTI: 4min -> 12 Min tot

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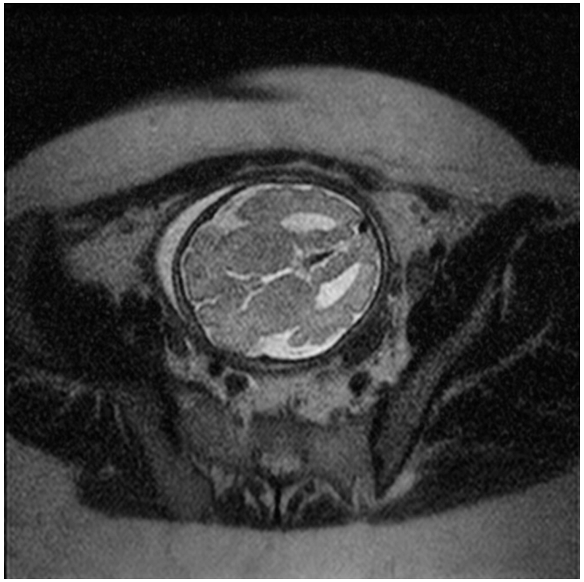
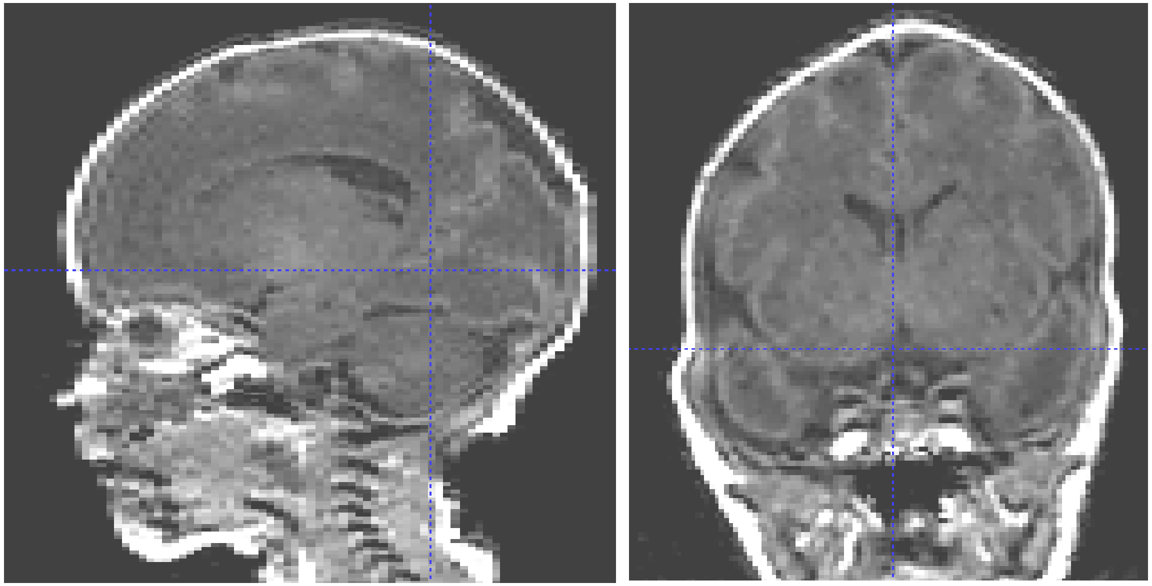
# Prenatal MRI / Premies



Julia Fielding, UNC
(intra-utero)

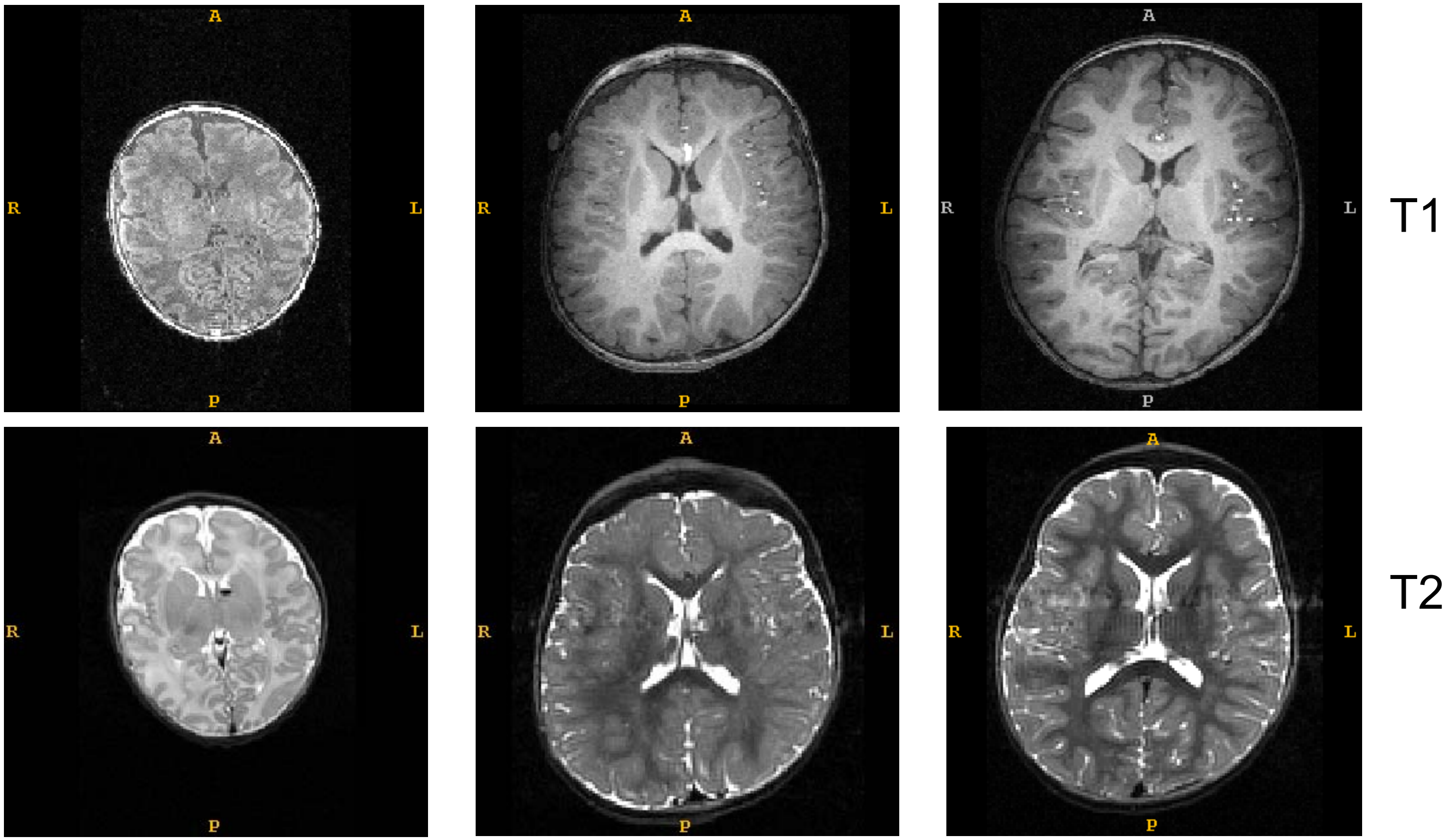


Petra Hueppi, Geneva and Harvard
(26 weeks premie)

# Training of infants: Mock Scanner

- Old MRI scanner used for practice sessions (pictures Yale Univ.)
- Subjects learn to remain still for up to 30 minutes
- Head tracking coupled with video presentation (Duke)

# High-Speed Imaging: Infant MRI at 3T



2 weeks 1 year 2 years

UNC Weili Lin: 3T Siemens Allegra

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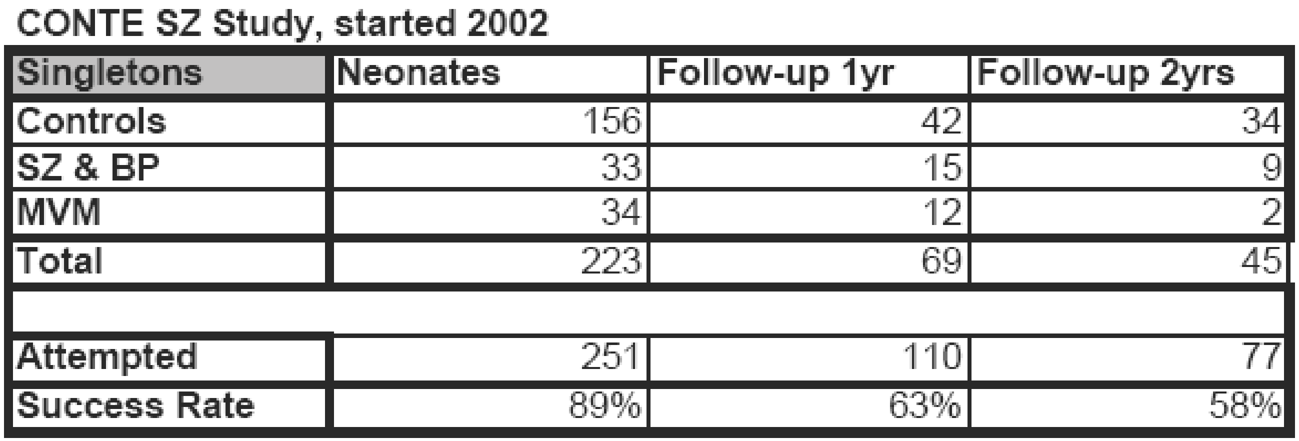
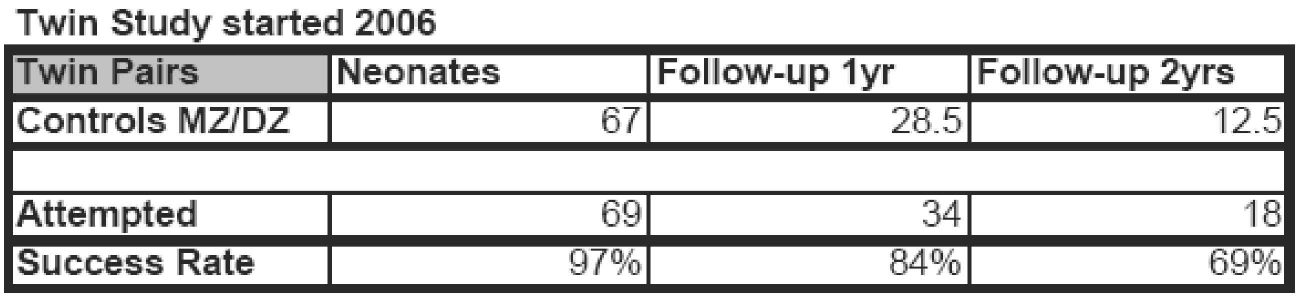
# Example: UNC Scan Success Rate

Siemens 3T Allegra, Weili Lin & team



CONTE SZ Study, started 2002

| Singletons | Neonates | Follow-up 1yr | Follow-up 2yrs |
|---|---|---|---|
| Controls | 156 | 42 | 34 |
| SZ & BP | 33 | 15 | 9 |
| MVM | 34 | 12 | 2 |
| Total | 223 | 69 | 45 |
| | | | |
| Attempted | 251 | 110 | 77 |
| Success Rate | 89% | 63% | 58% |



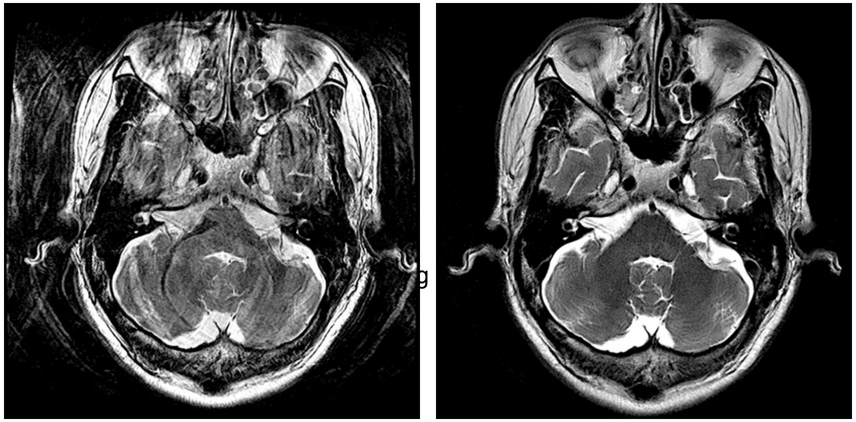
Twin Study started 2006

| Twin Pairs | Neonates | Follow-up 1yr | Follow-up 2yrs |
|---|---|---|---|
| Controls MZ/DZ | 67 | 28.5 | 12.5 |
| | | | |
| Attempted | 69 | 34 | 18 |
| Success Rate | 97% | 84% | 69% |

# New Technology: MRI Motion Correction

GE: PROPELLER* - Motion Correction Imaging (unique pattern of k-space filling that acquires data in radial "blades" rotating in sequence)

Siemens: Navigator pulse for online correction (Flash T1, courtesy of MGH ).



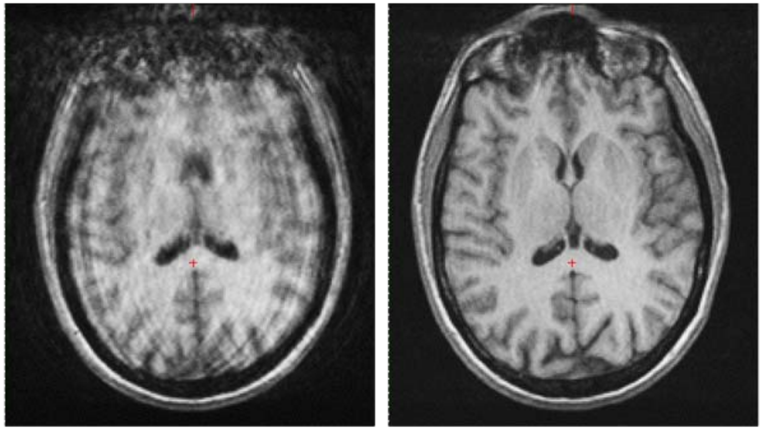
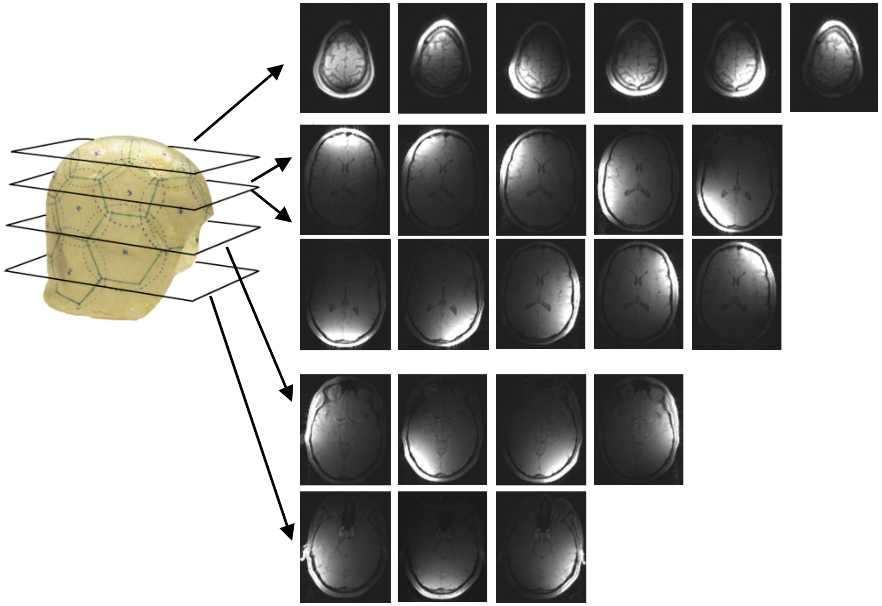
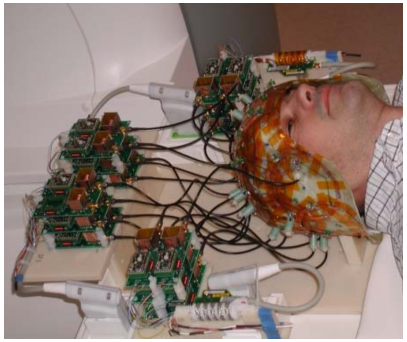
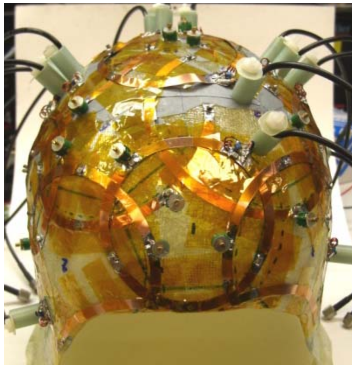


**Fig C 14** Slice through average of 3 FLASH scans without motion correction (left) and 3 FLASH scans with motion correction (right).

# Most Recent: Parallel Acquisition and matrix coils

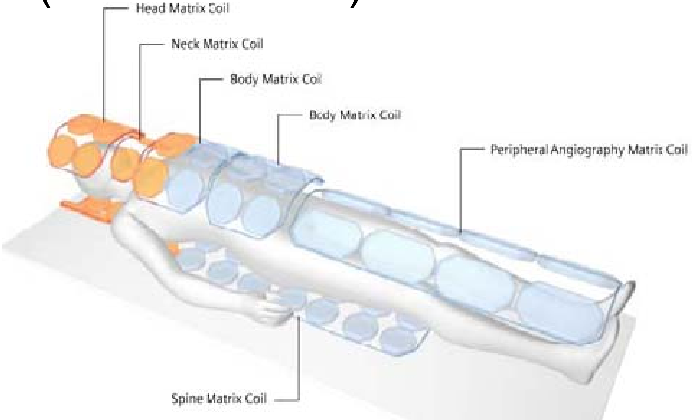






**23 channel prototype array at 1.5T – Gram Wiggins and Larry Wald, MGH**

Parallel imaging & matrix coils (here Siemens)



We've lightened the load.

Our Body Matrix ultra lightweight coil weighs only 950 grams (2.1 lbs). That's ten times lighter than the industry average in 3T. So it's significantly more comfortable, especially for very sick

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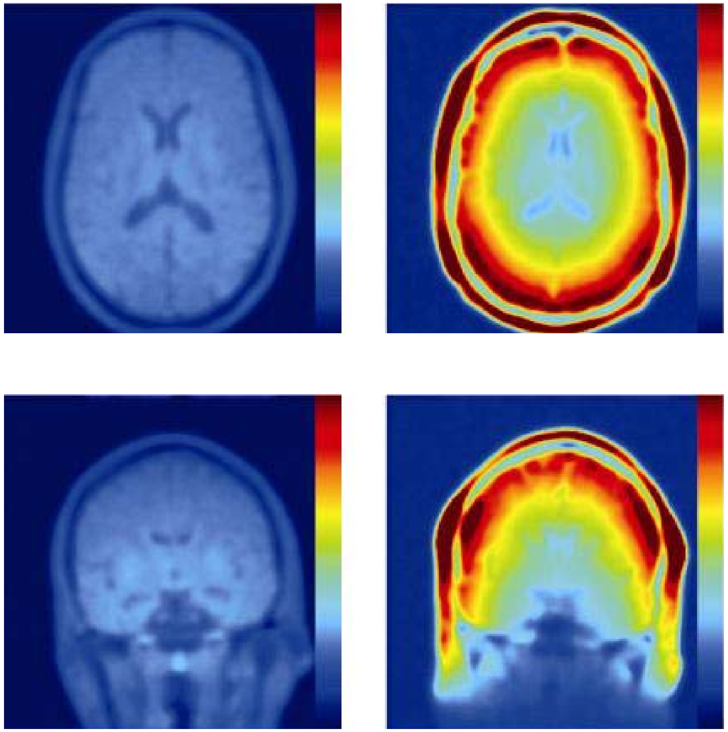
# 23 channel array for 1.5T

**SNR Maps**
Grad. Echo

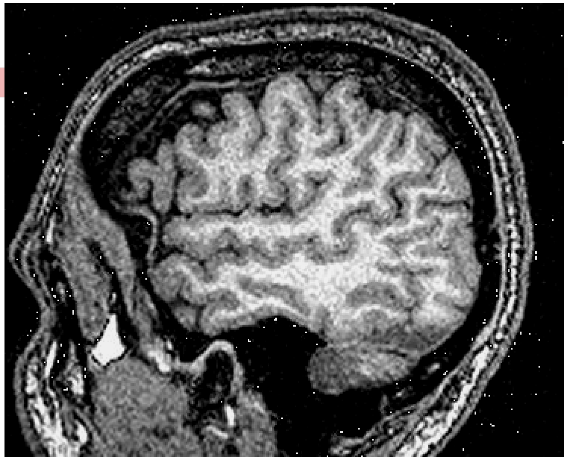
Normalized to volume coil average (=1.0)

SNR gain:
- 4 fold in cortex
- 1.75x in corpus callosum

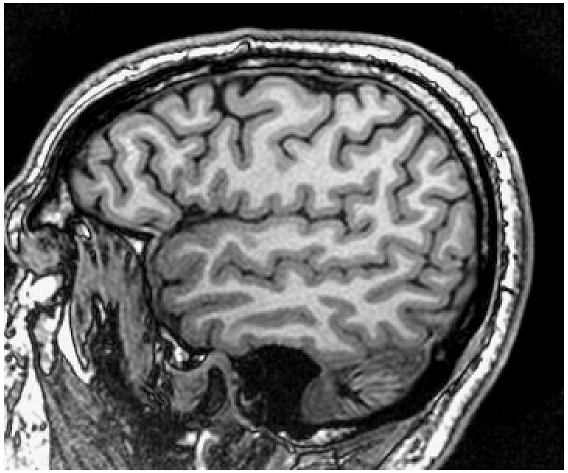


Siemens volume coil

23 channel array



Volume coil



23 Channel “Bucky”

Courtesy Bruce Rosen, MGH

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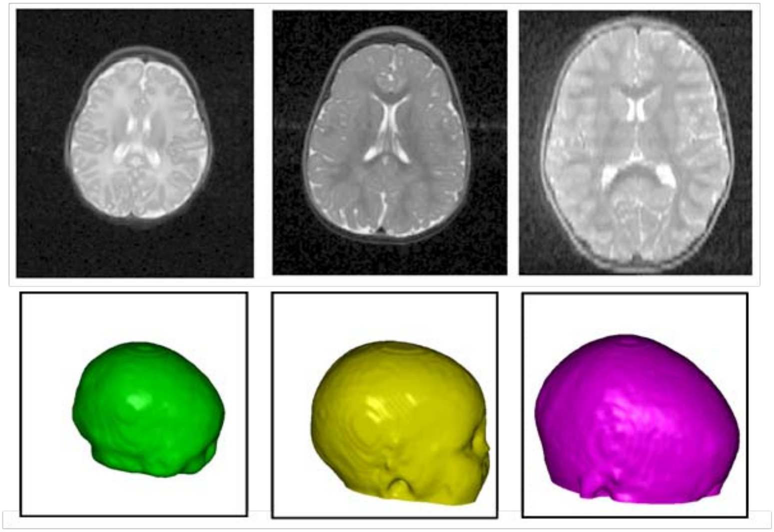
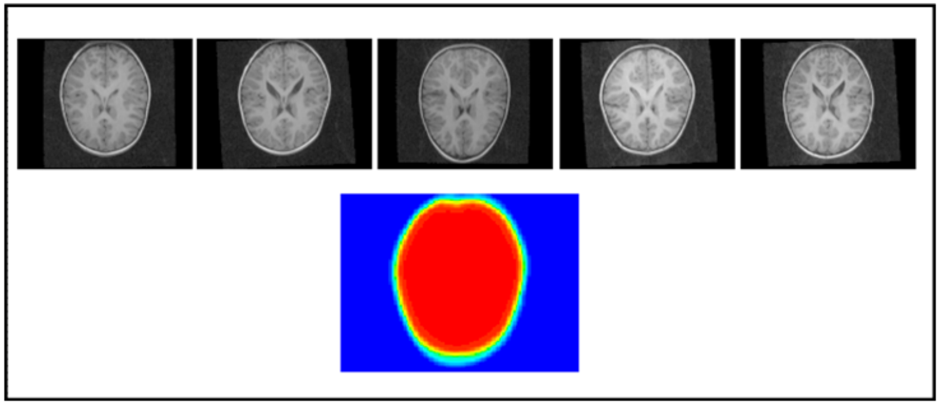
# UNC – MGH Project: Modeling Head Shapes for Infant Coil Design



Statistical modeling of head shapes for infant matrix coils: Collaboration with Larry Wald, MGH and W. Lin, UNC



Example: 95% head and brain size for 2yr group.

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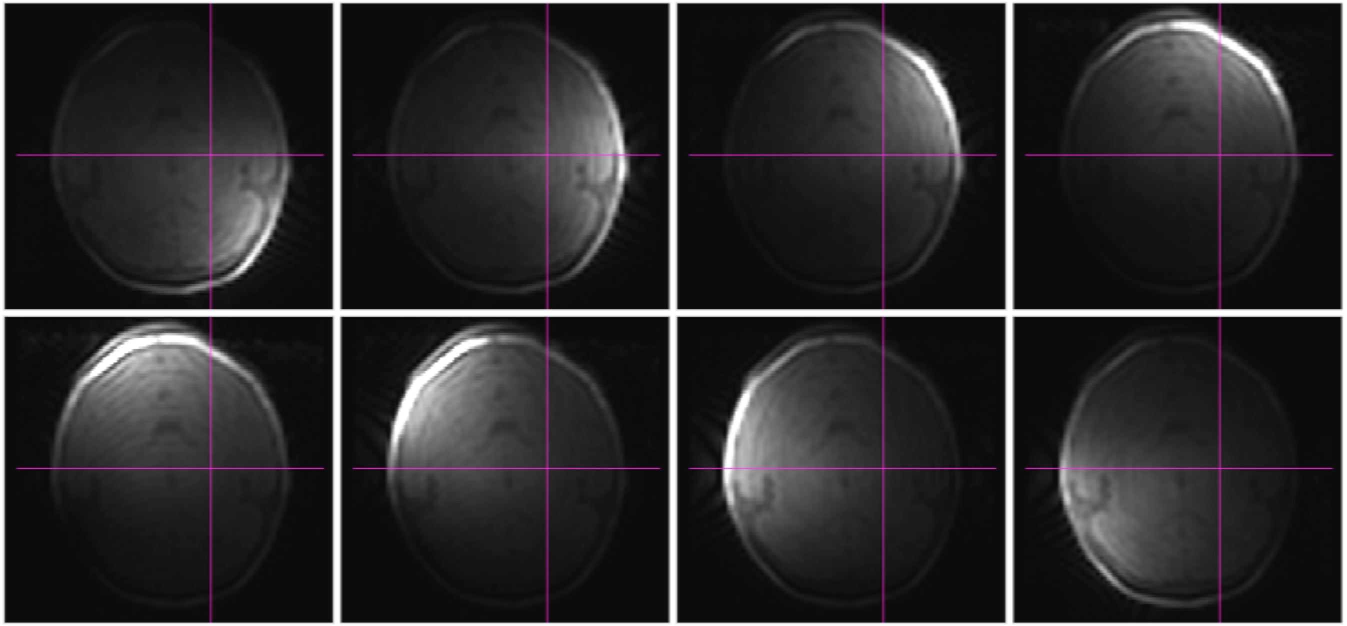
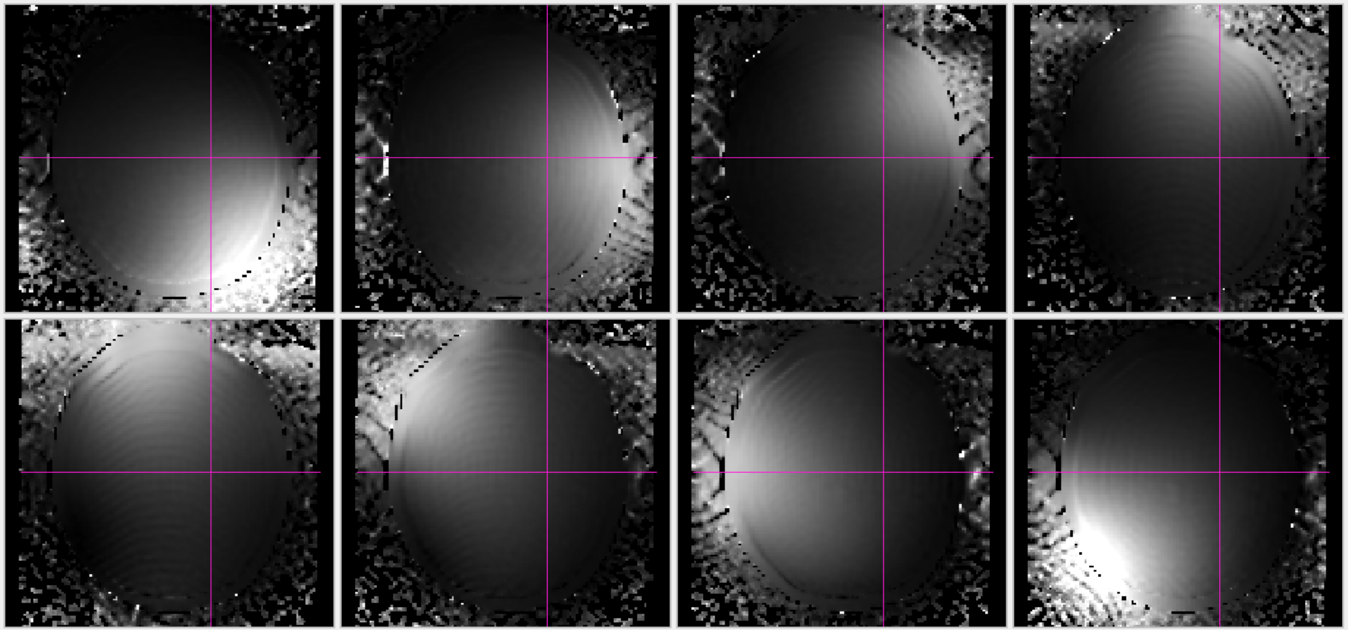
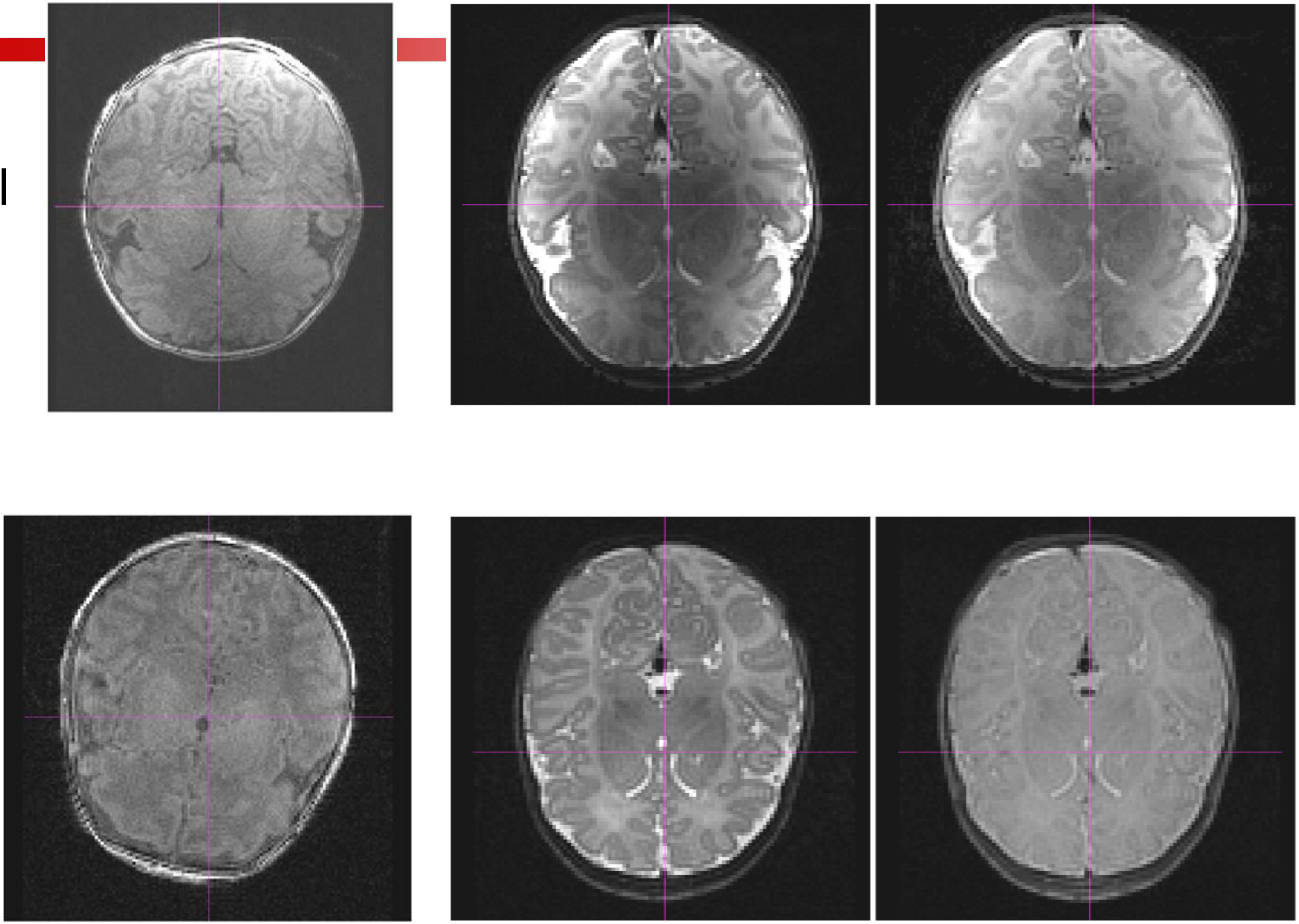
Profile PD images

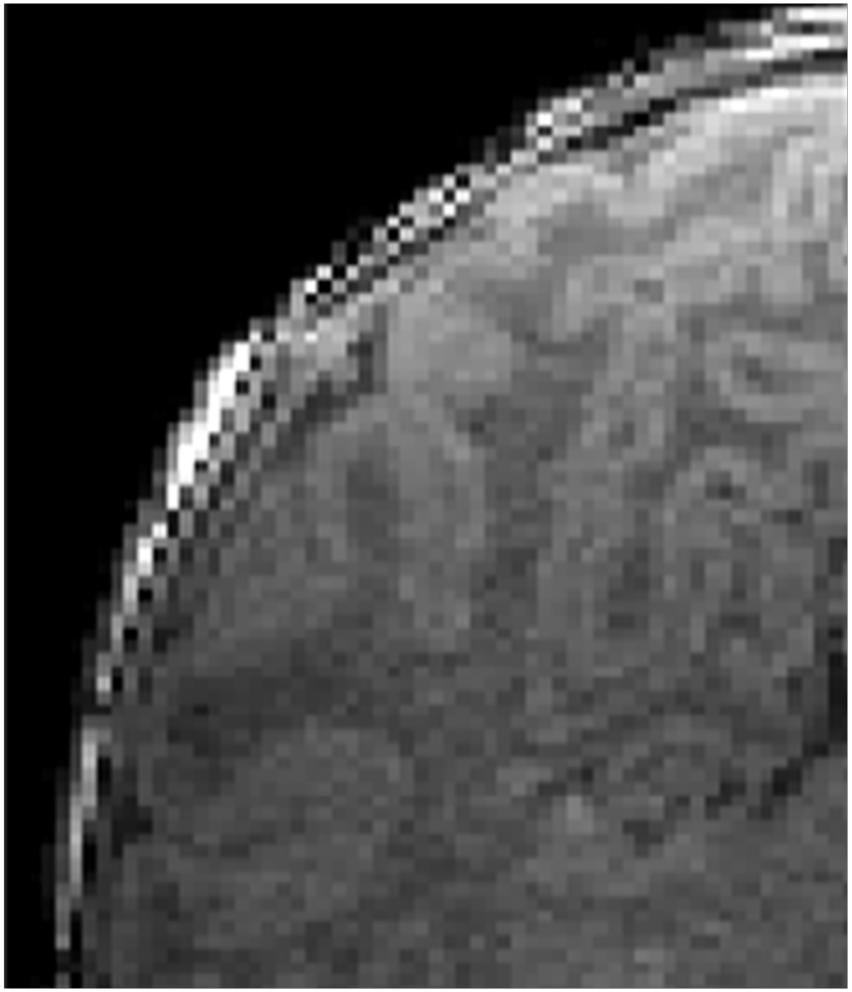


Profile PD normalized images → Coil Sensitivity Profiles



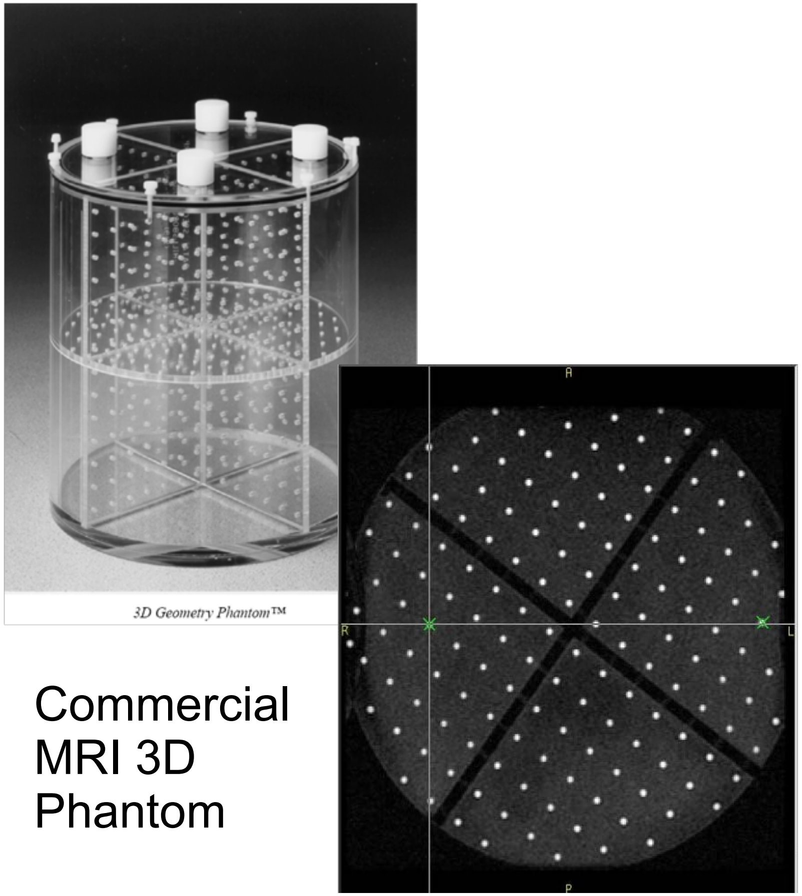

T1
T2
PD
Parallel coil
Volume coil

## T1 Parallel coil



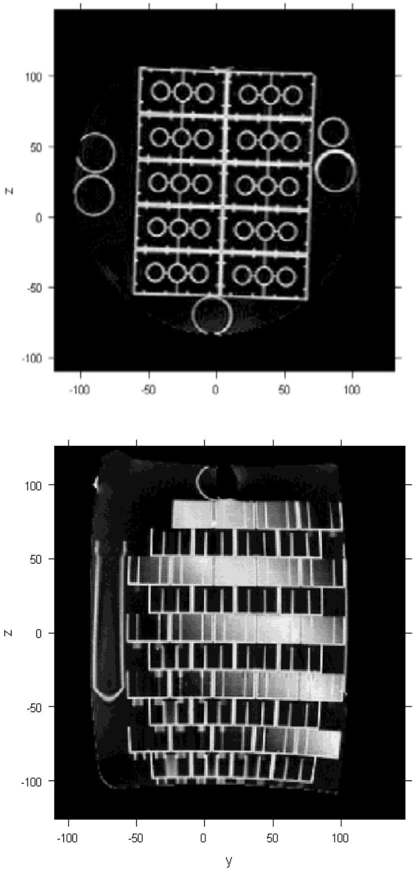
## T1 Volume coil

# Images used for Measurements: Calibration

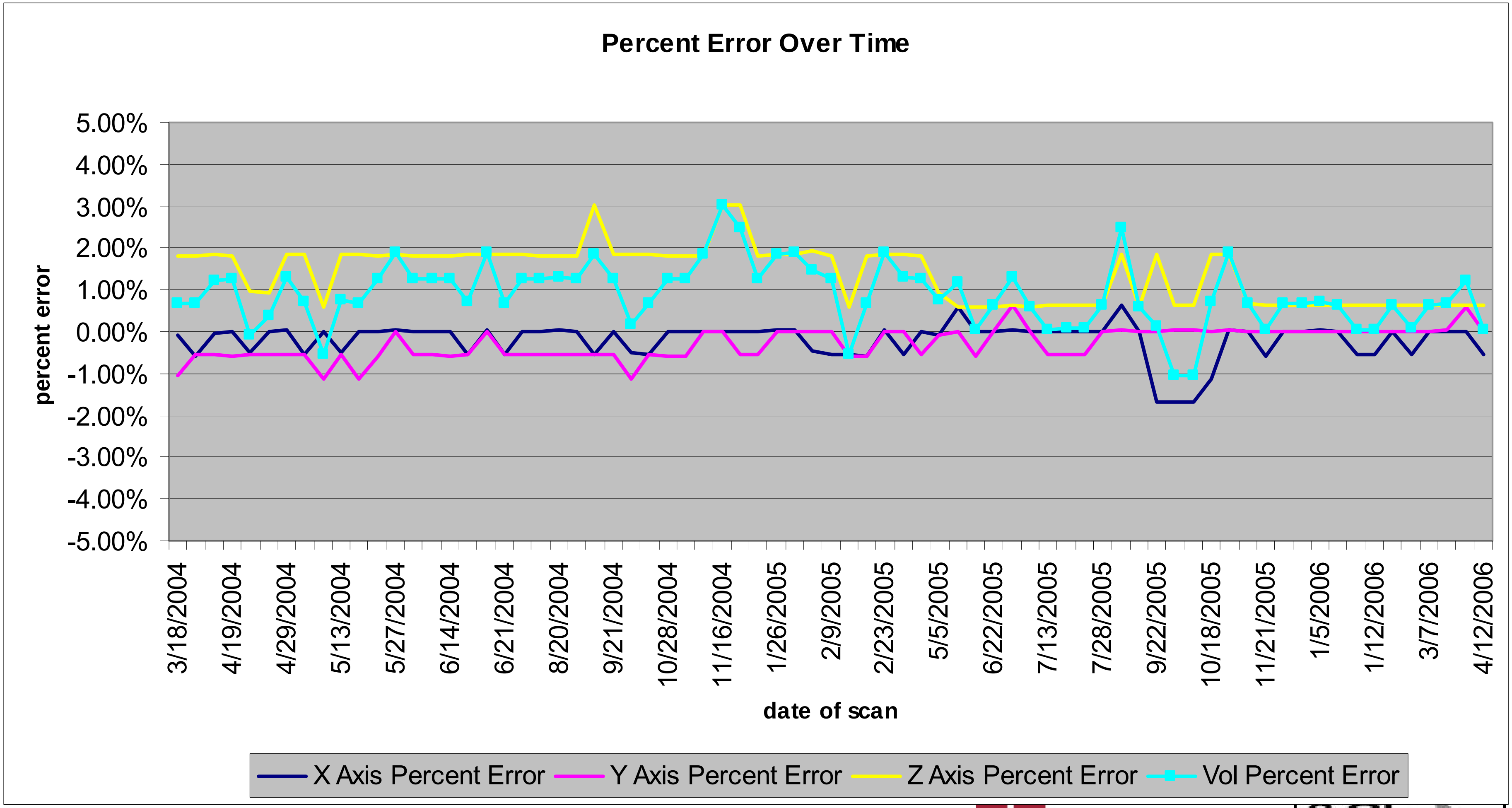


Commercial
MRI 3D
Phantom

Fonov et al., MNI



# Example Duke: BIAC BIRN scanner calibration



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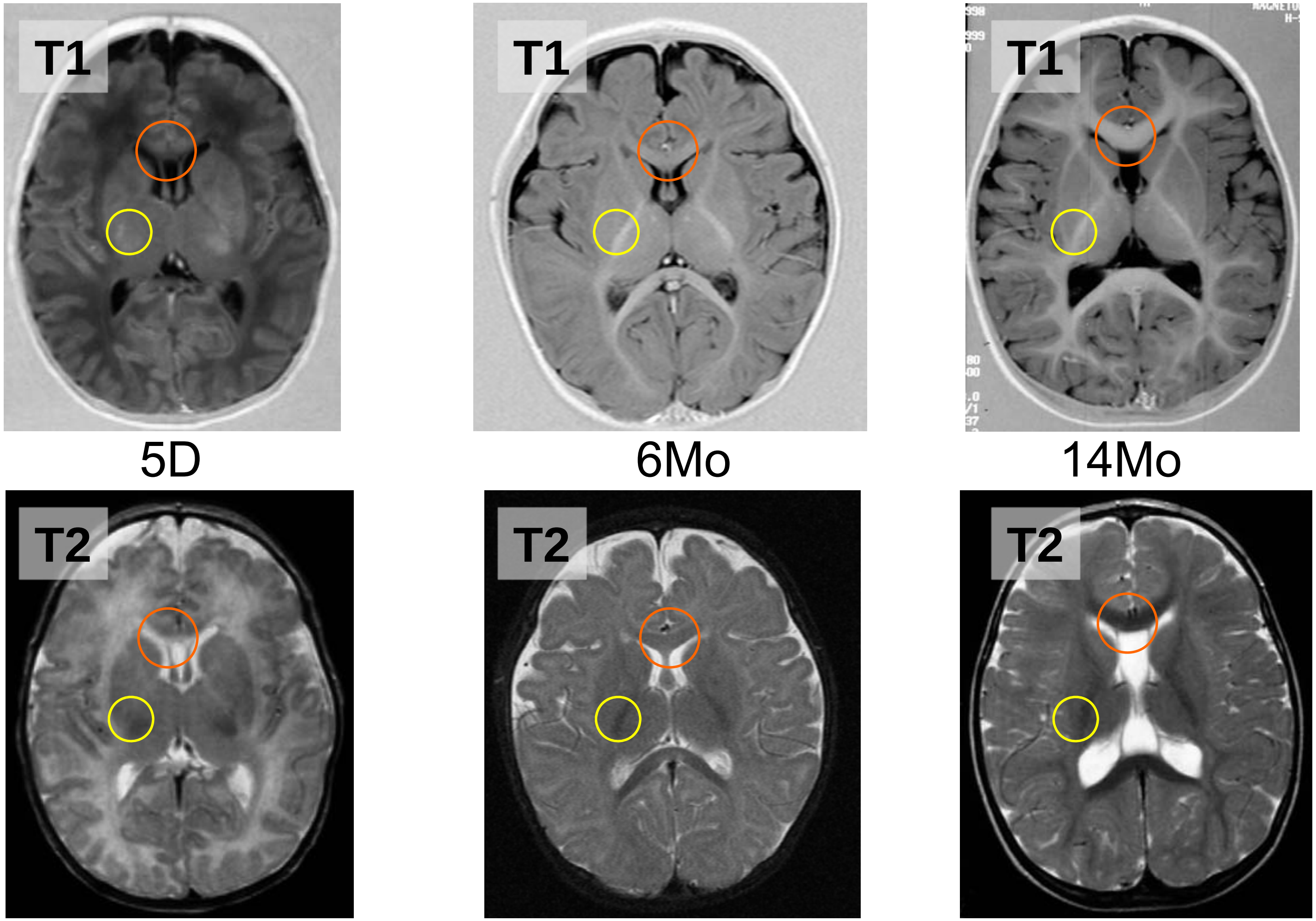
# 2. Structural MRI

# Contrast changes in early development



5D 6Mo 14Mo

5D 6Mo 14Mo

🟧 Myelinated during 1st yr

🟨 Early myelination

Courtesy Keith Smith, UNC Radiology

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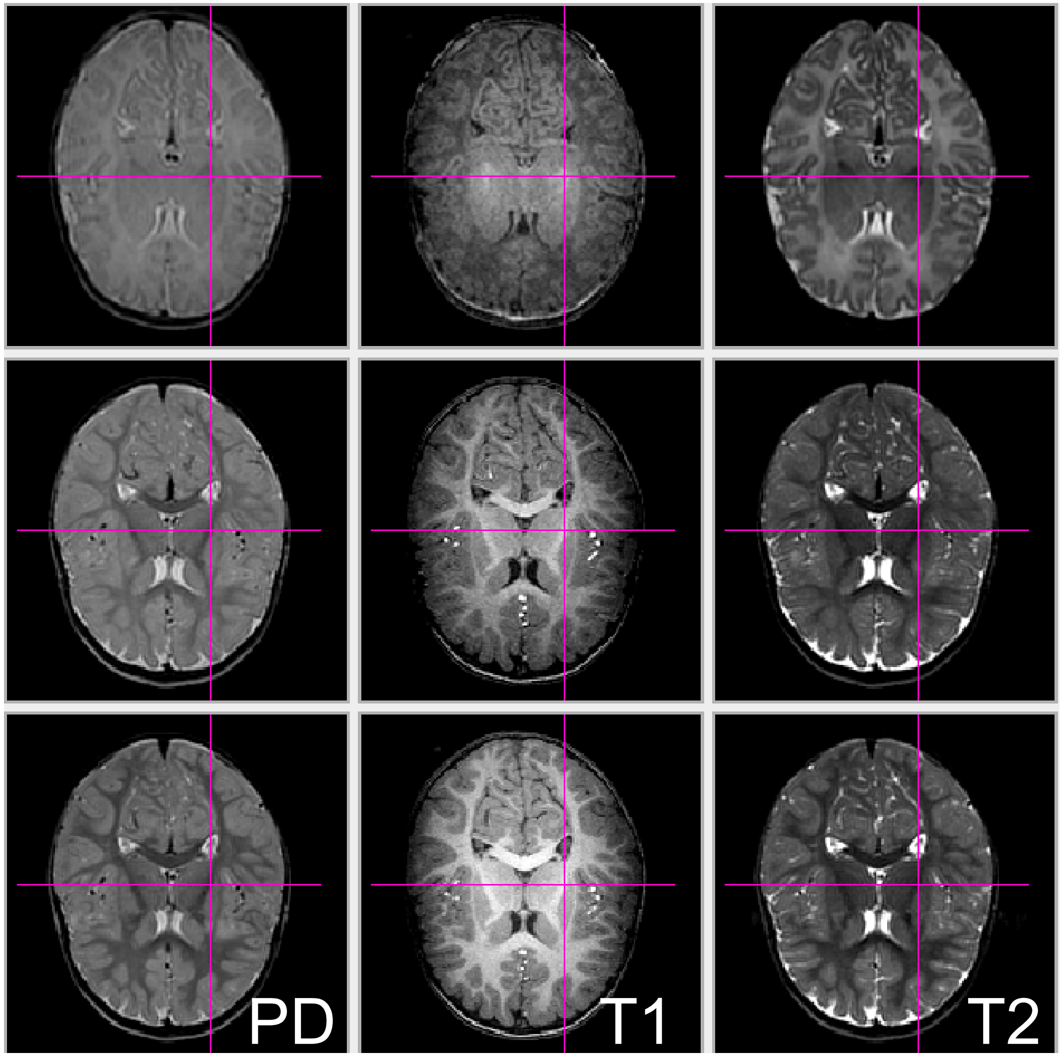
# Contrast changes in early development



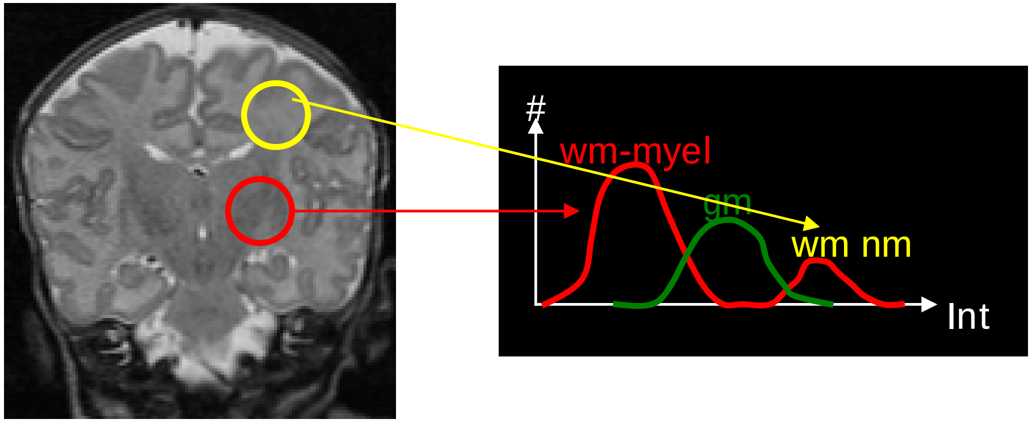
neonate

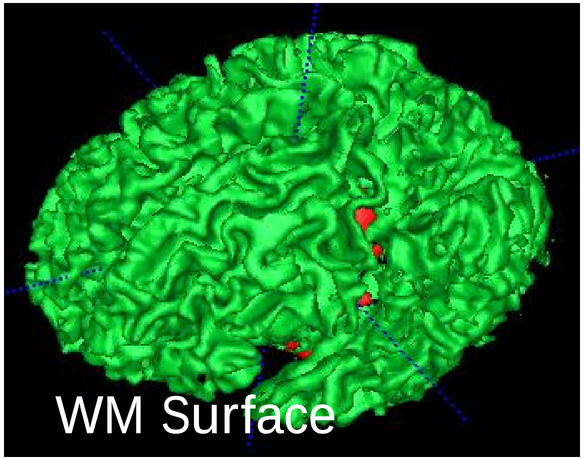
1 year

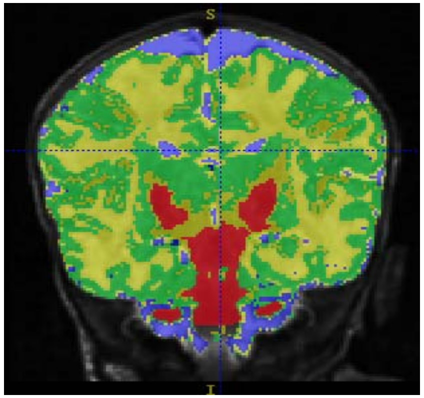
2 years

UNC/Utah infant neuroimaging study

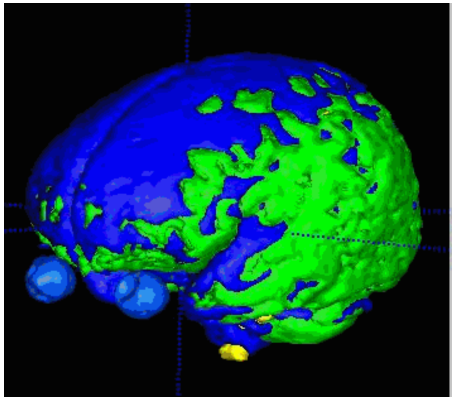
# Neonatal MRI Segmentation

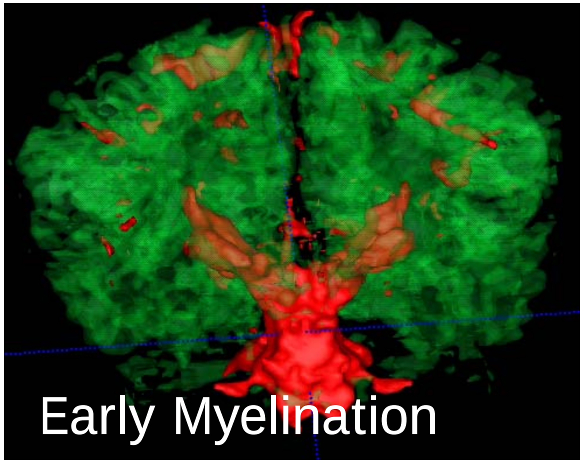






- 🟦 csf
- 🟨 nWM
- 🟩 gm
- 🟥 mWM





Marcel Prastawa, John H. Gilmore, Weili Lin, Guido Gerig, Automatic Segmentation of MR Images of the Developing Newborn Brain, (MedIA). Vol 9, October 2005, pages 457-466

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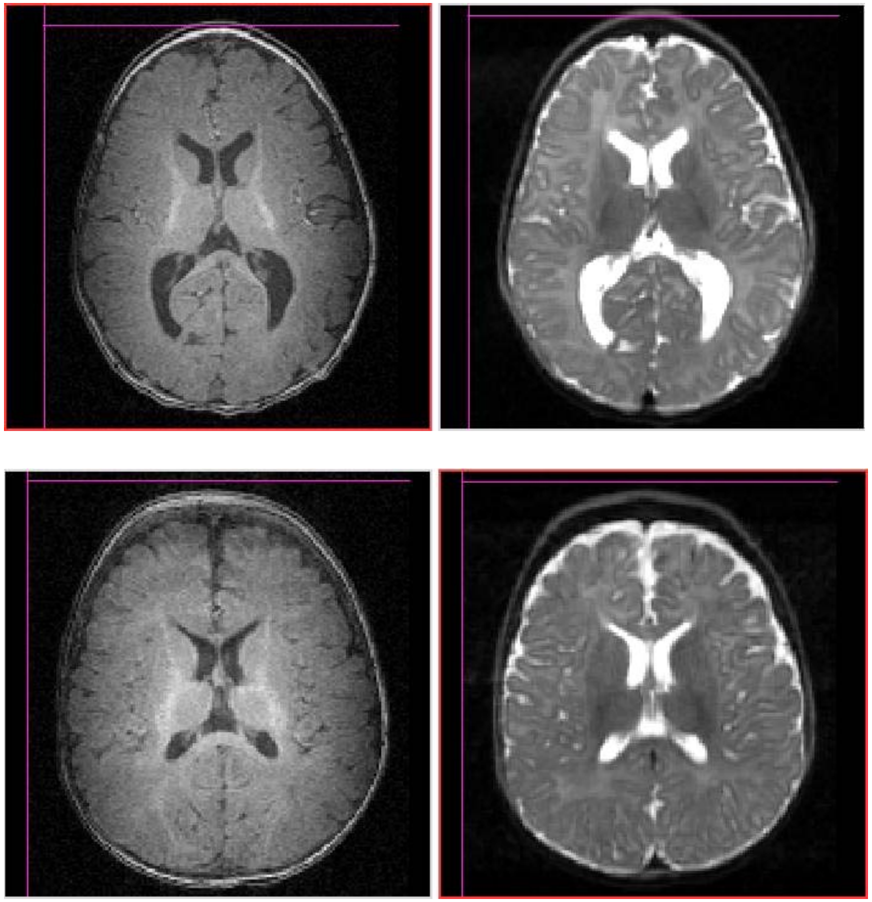
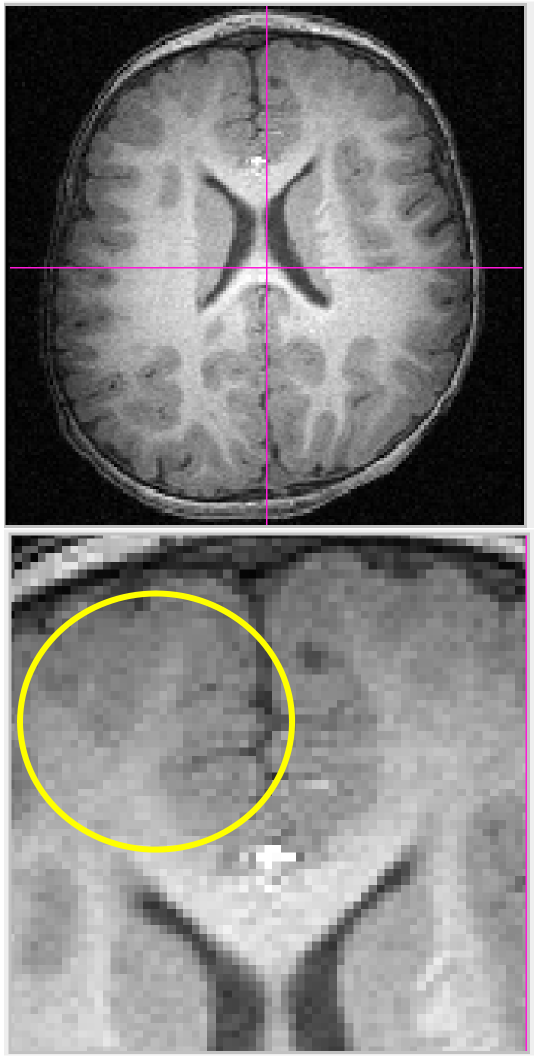
# 4 and 6 month old subjects



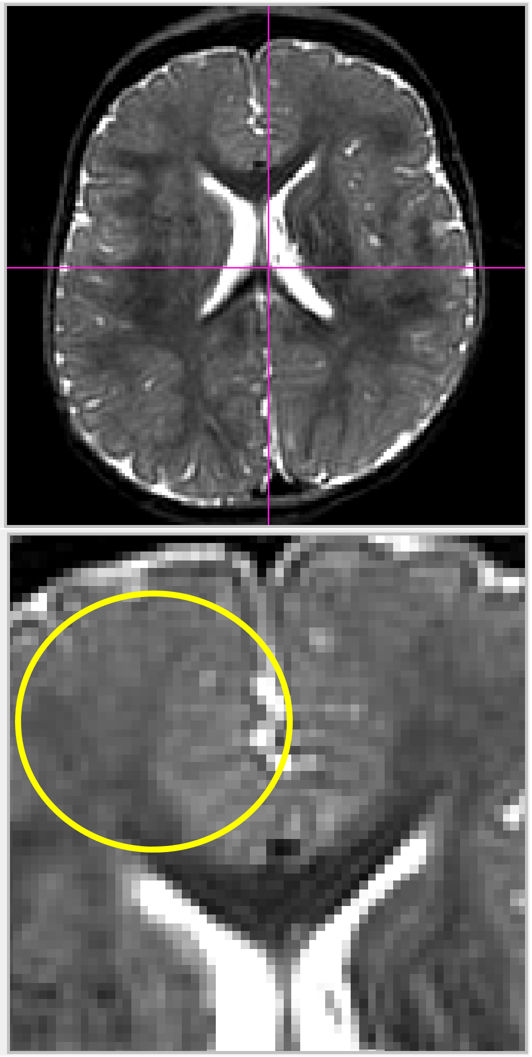
Intermediate stage of contrast flip between white and gray, with no differentiation in T1w at 4-6 mt and in T2 at 6-8 mt.

T1 and T2 are not in sync w.r.t. tissue contrast

# Challenge in Segmentation of 1years olds



T1w axial and zoomed

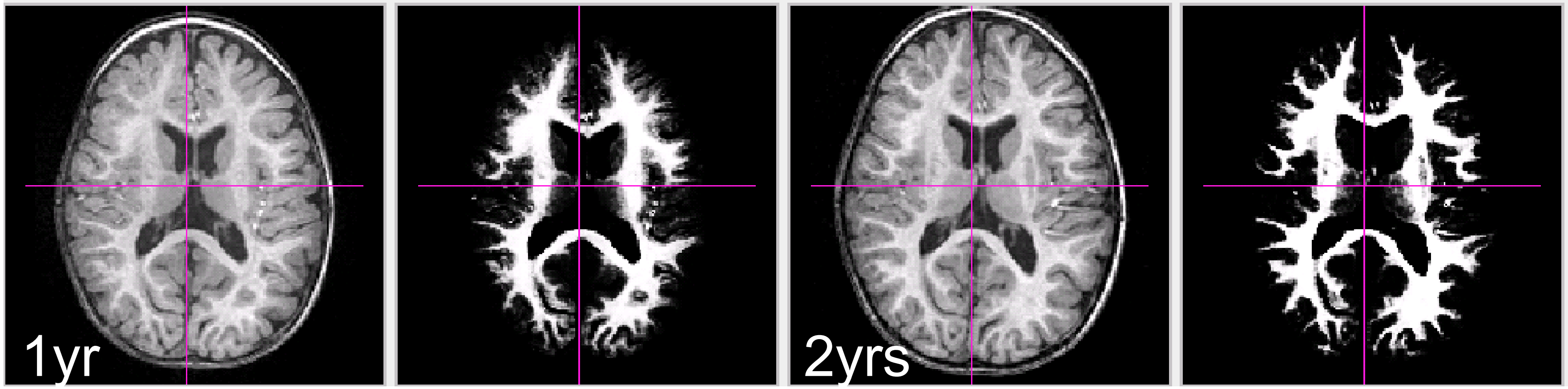


T2w axial and zoomed

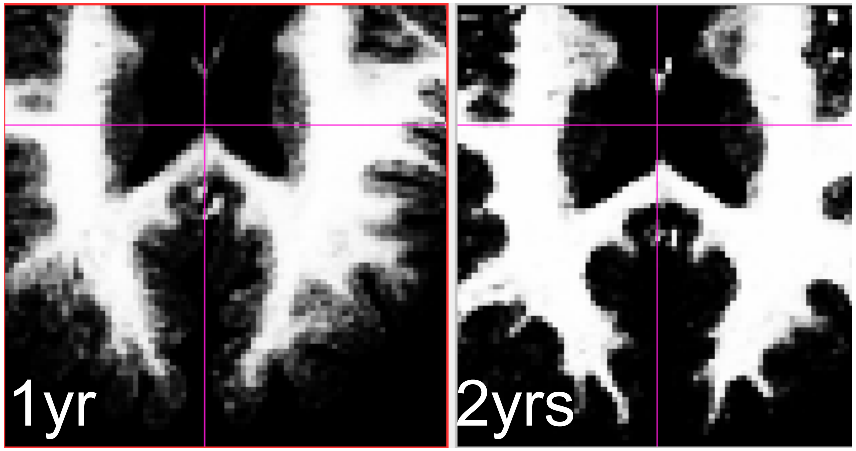
Difficulties for tissue segmentation:

- Strong bias inhomogeneity
- Gradual degree of myelination decreasing from central to peripheral regions
- Very low contrast in cortical white/gray
- T2 lags behind T1 in its ability to depict wm contrast and therefore even shows less contrast.

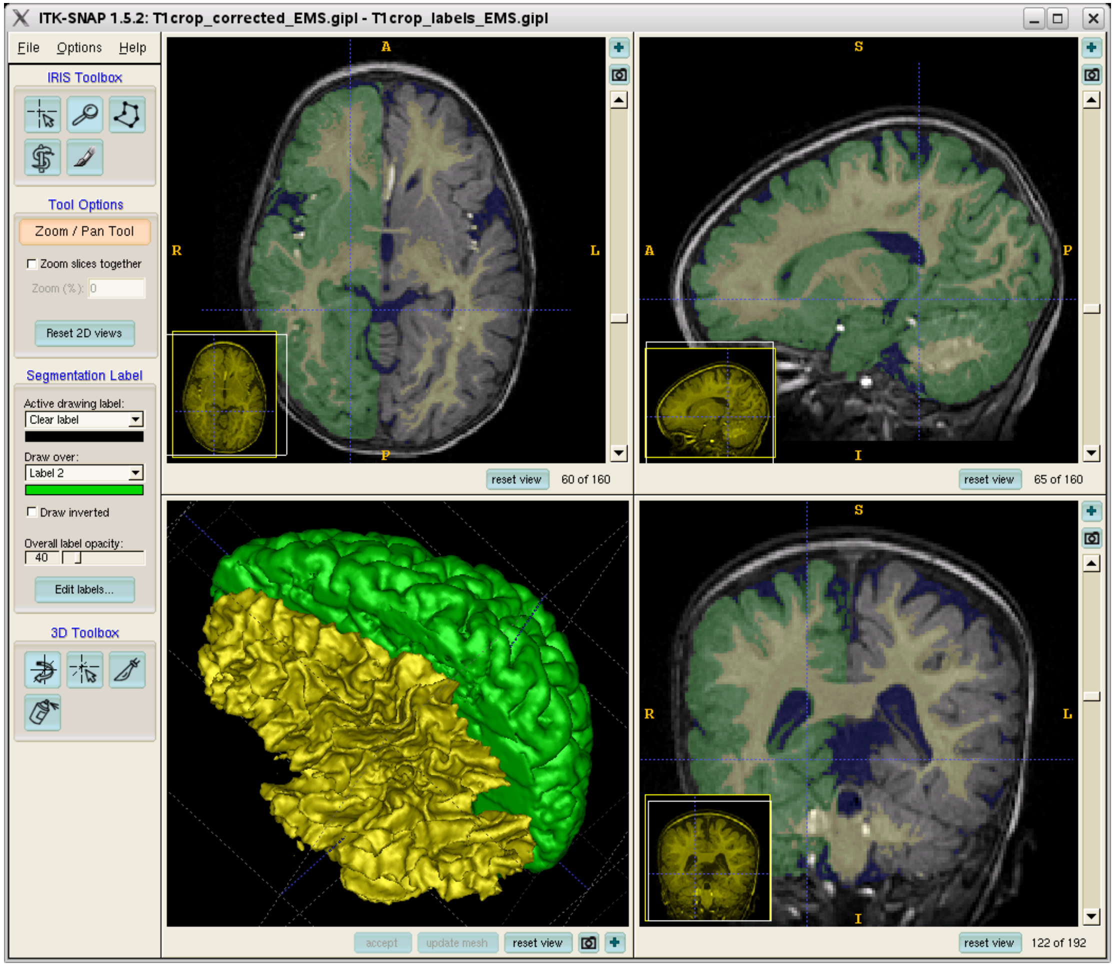
# Follow-up: Hi-res T1 (Weili Lin, UNC)



T1 MRI of same child at 1yr and 2yrs with wm probability maps: wm/gm boundary more fuzzy at 1yr.



# Brain Segmentation 1year old



ITK-SNAP 1.5.2: T1crop_corrected_EMS.gipl - T1crop_labels_EMS.gipl

☐ Zoom slices together

Zoom (%): 0

Active drawing label: Clear label

Draw over: Label 2

☐ Draw inverted

Overall label opacity: 40

60 of 160

65 of 160

122 of 192

- Advanced version of expectation-maximization segmentation (M. Prastawa)
- Prior: Age-specific atlas
- Nonlinear registration of atlas to subject
- Robust, nonparametric clustering
- Parametric bias field correction

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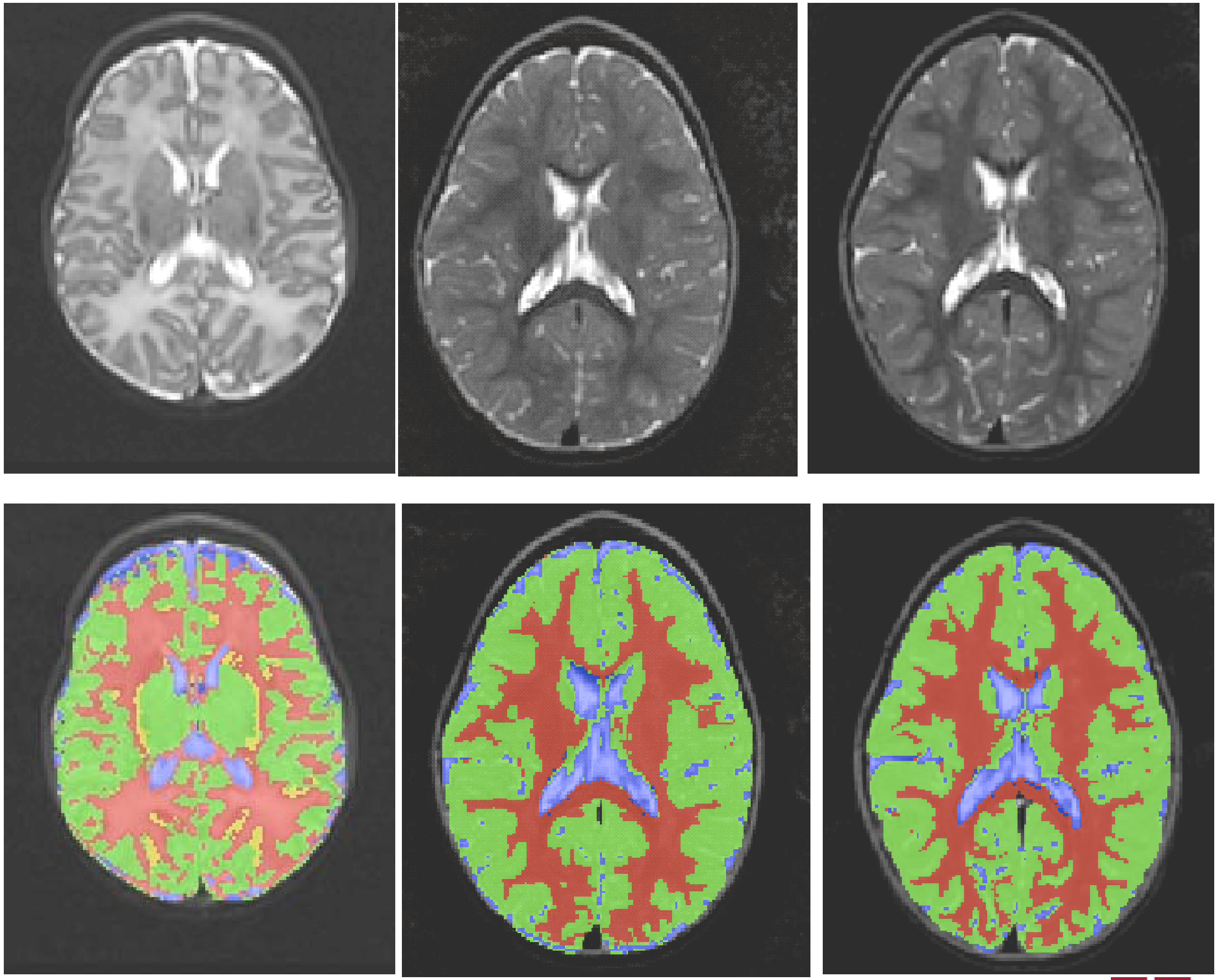
# Current Solution: Individual Tissue Segmentation at each time point



0.7 months 13.4 months 24.2 months

Segmentation procedures:

Prastawa et al.,

Warfield et al.,

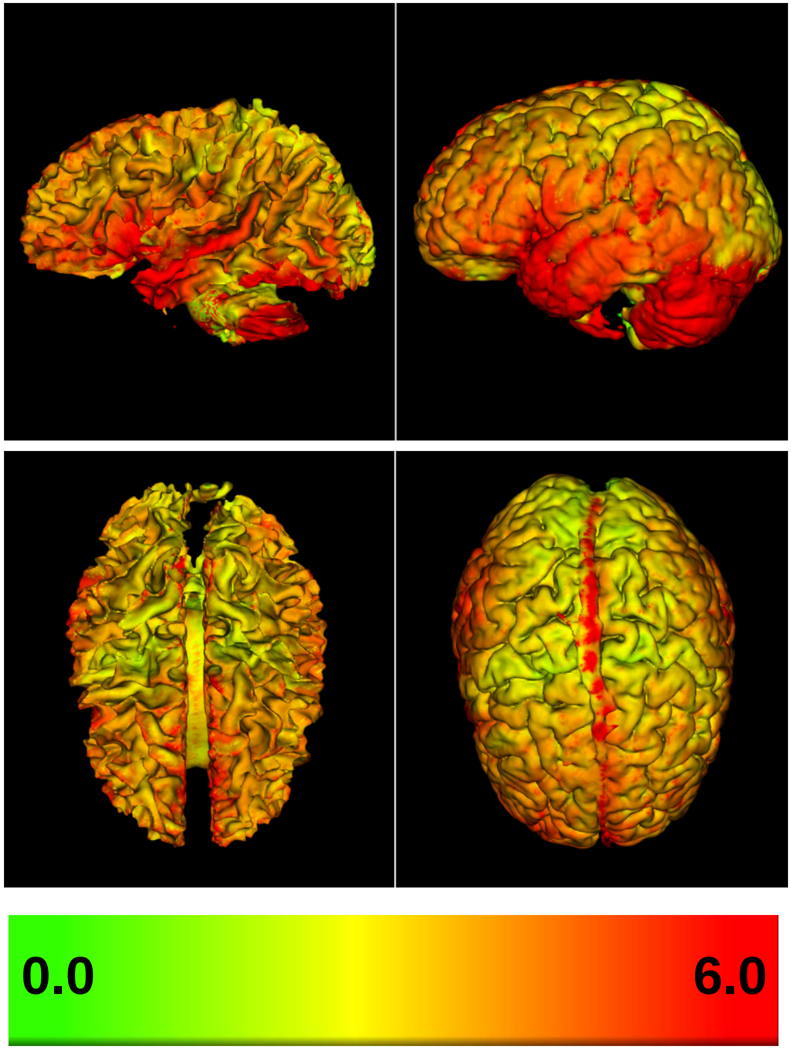
Rueckert/Aljabar et al.

🟩 GM

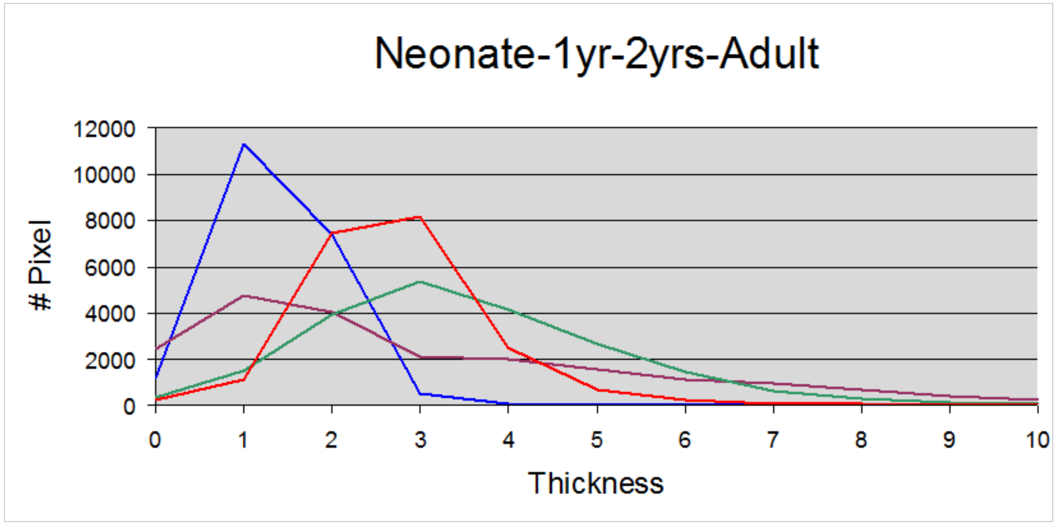
🟥 WM

🟦 CSF

# Cortical Thickness Analysis



Cortical thickness in mm



| | **Mean:** |
|---|---|
| — Neonate | 1.37 mm |
| — 1yr | 3.10 mm |
| — 2yrs | 3.60 mm |
| — Adult | 2.75 mm |

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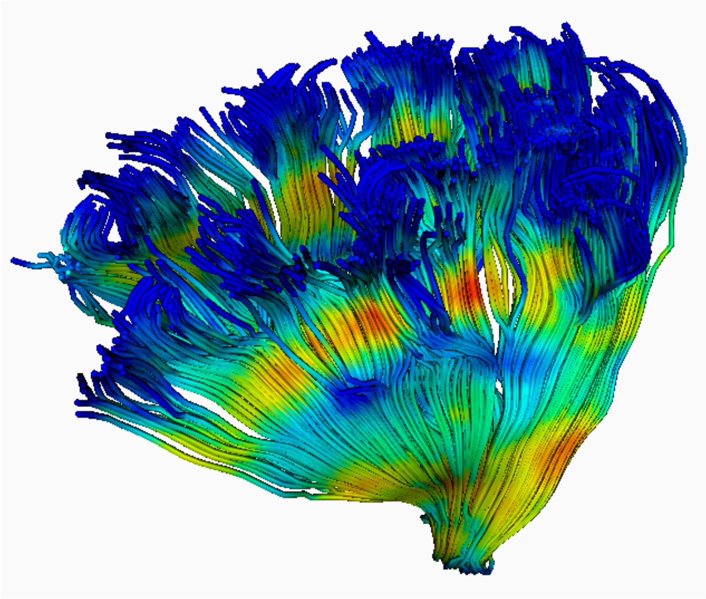
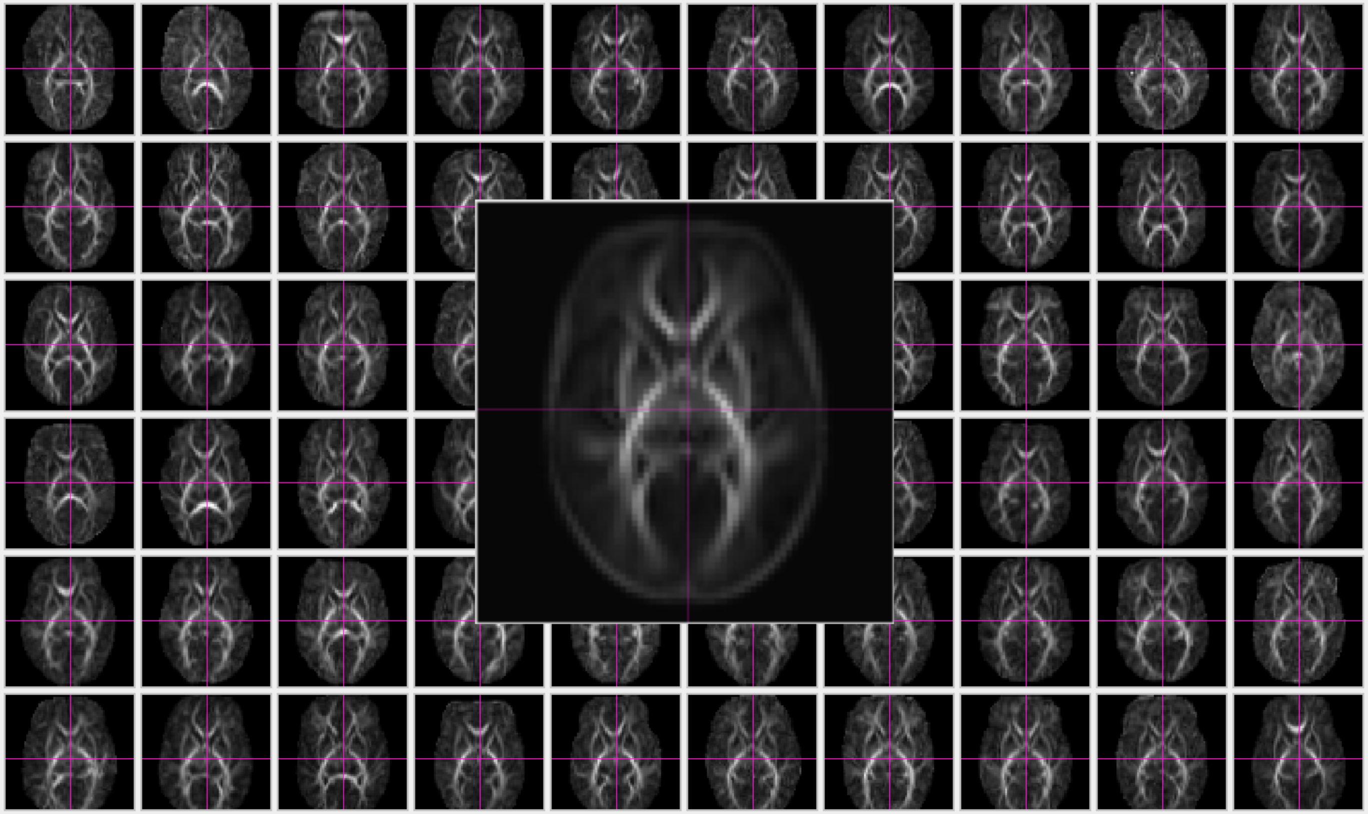
# 3. DTI in Infants



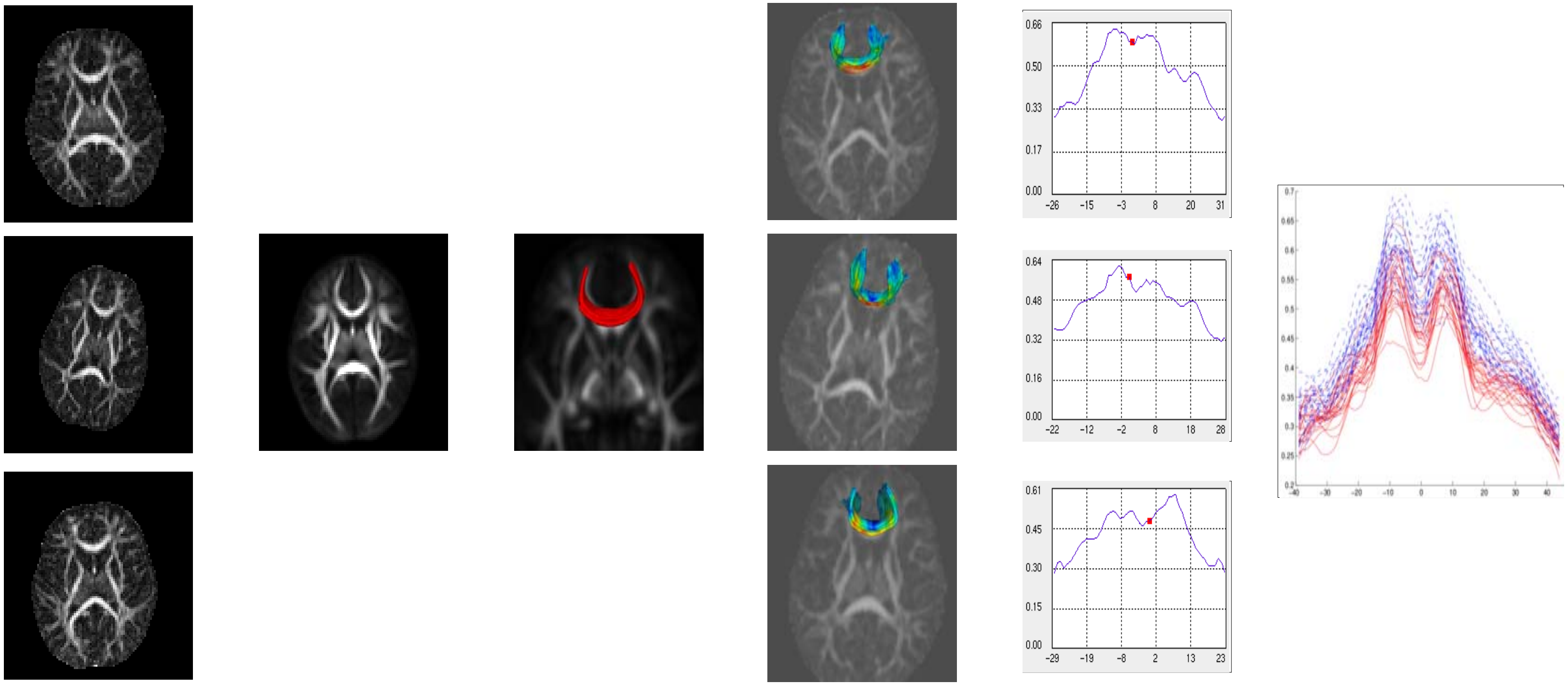
# Population-based analysis of fiber tracts

Example: 150 neonate DTI mapped to unbiased atlas



Casey Goodlett, Sarang Joshi, Sylvain Gouttard, Guido Gerig, SCI Utah (MICCAI'06, MICCAI'08, NeuroImage (in press)

# Concept: Group statistics of fiber tracts



Images

Atlas

Atlas
Tract

Mapped
Tracts

Sampled
Functions

Functional
Statistics

Goodlett et al., MICCAI’08, NeuroImage in print

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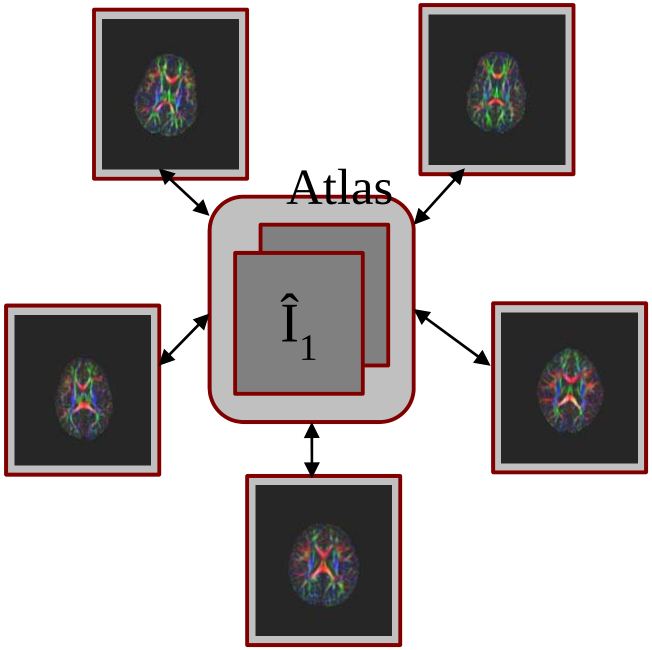
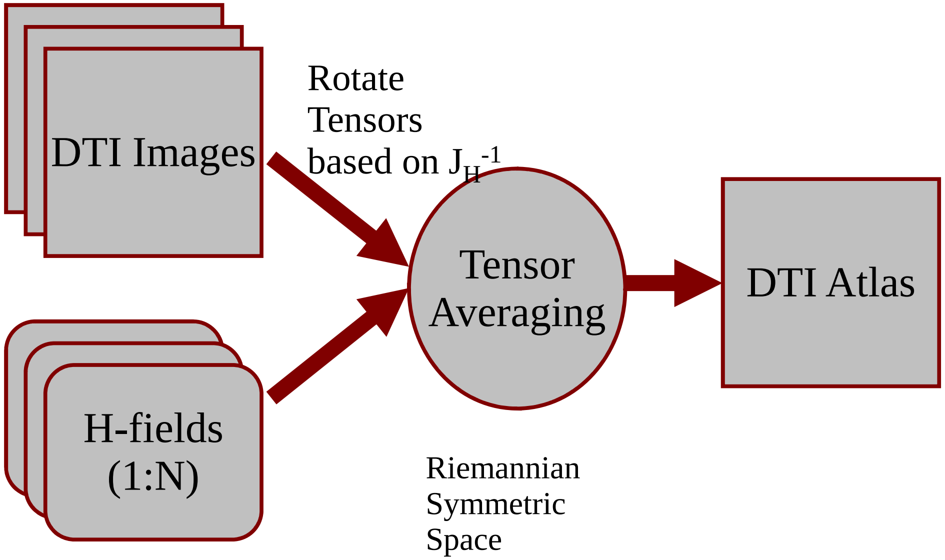
# Atlas Building





DTI Images

Rotate Tensors based on $J_H^{-1}$

H-fields (1:N)

Tensor Averaging

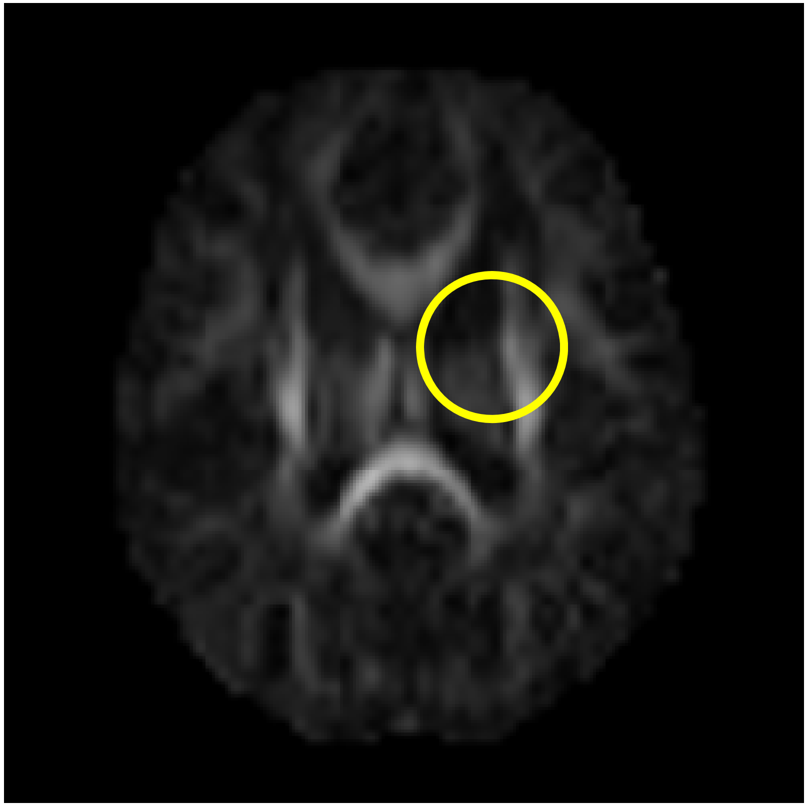
DTI Atlas

Riemannian Symmetric Space

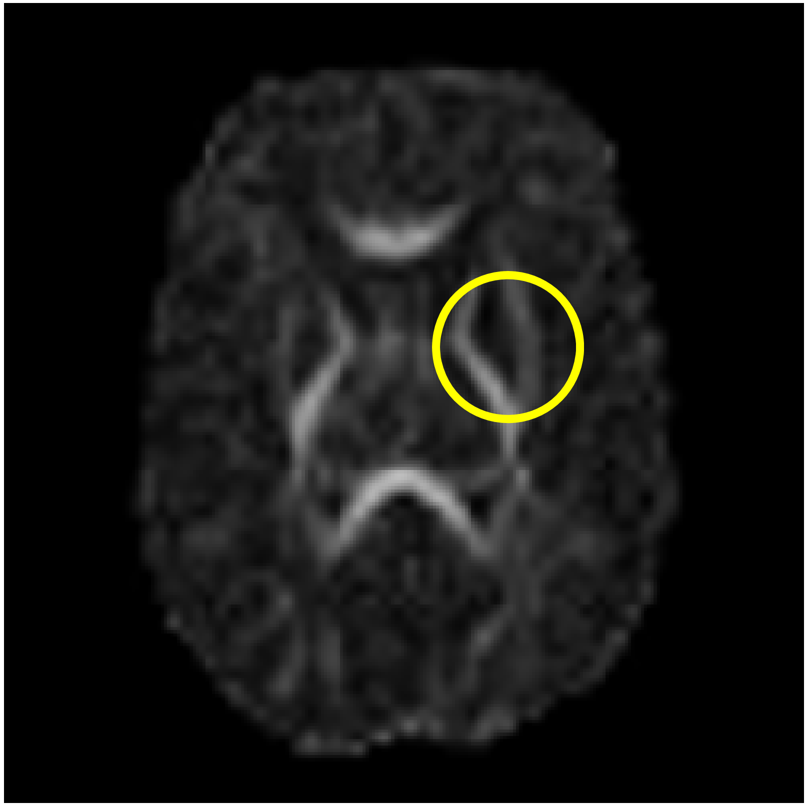
**Challenges:**

- Linear vs. nonlinear registration (Gee et al., Joshi et al., Goodlett et al., ..)
- Reorientation of tensors (Alexander, Jones)
- Interpolation of DWI or tensors (Fletcher, Arsigny, Westin&Kindlman)

# Co-registration of image sets



Not registered



Linear registration (affine)

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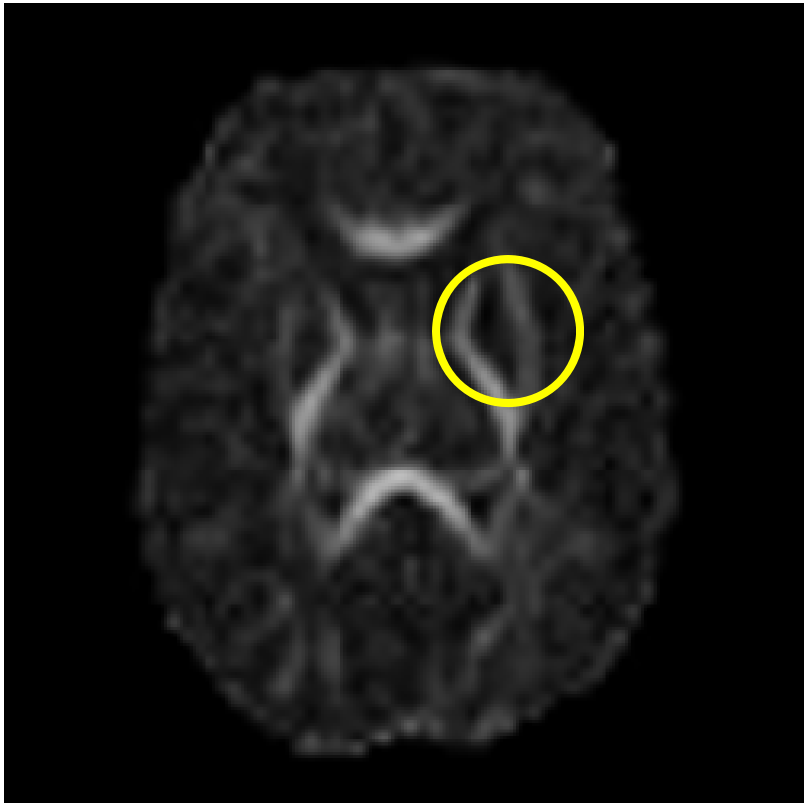
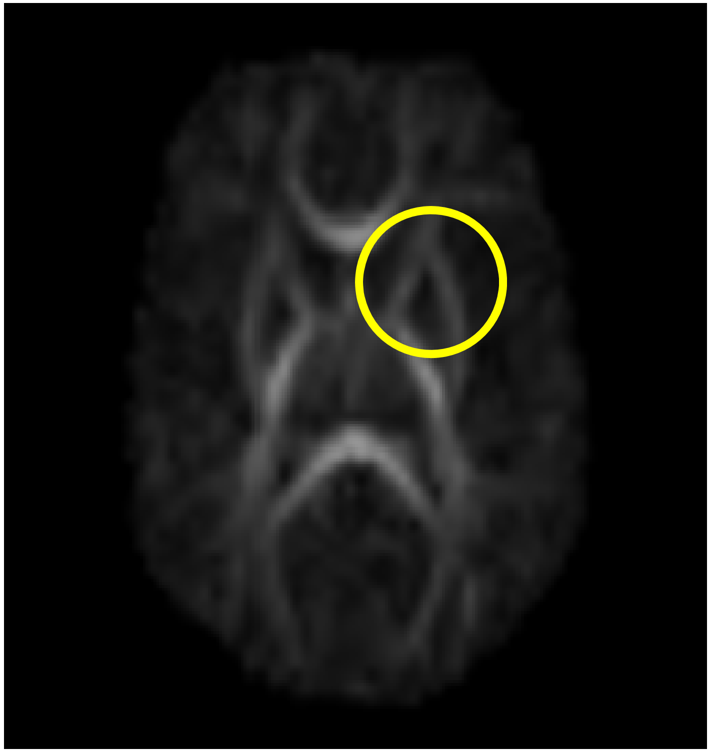
# Co-registration: From linear to nonlinear

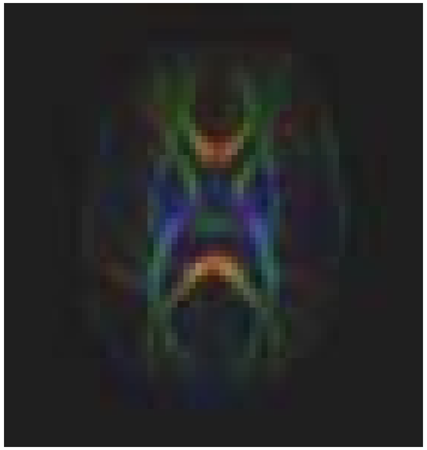


Linear registration (affine)

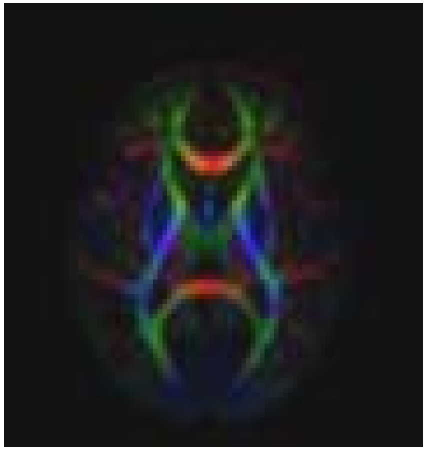


Nonlinear registration (fluid)

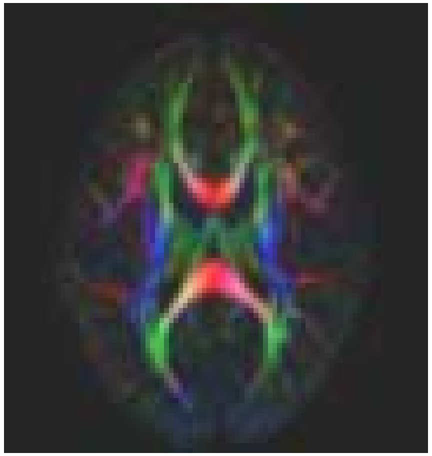
# Application: Neurodevelopmental Statistical Atlases



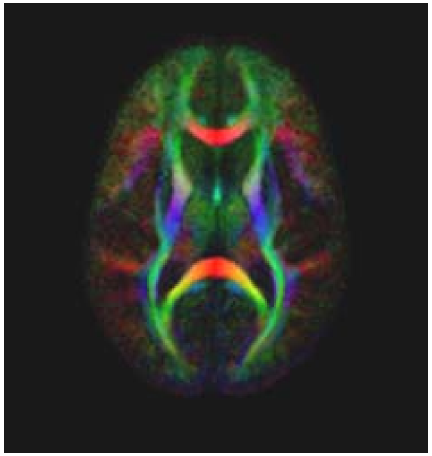
Neonate (N=95)



1 year (N=25)

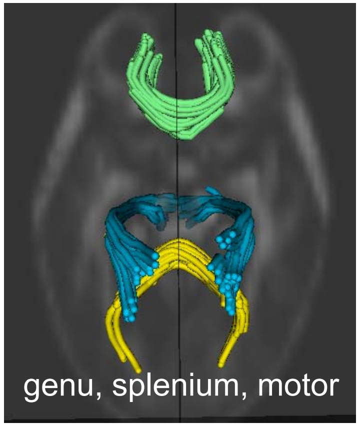


2 year (N=25)

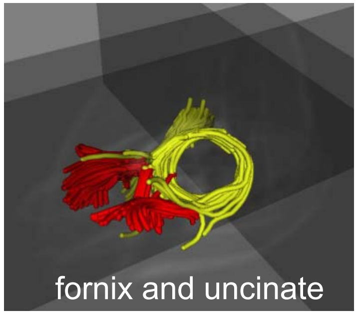


Adult (N=24)

Collaborative research on studying the early developing brain with John H. Gilmore and Weili Lin, UNC Chapel Hill

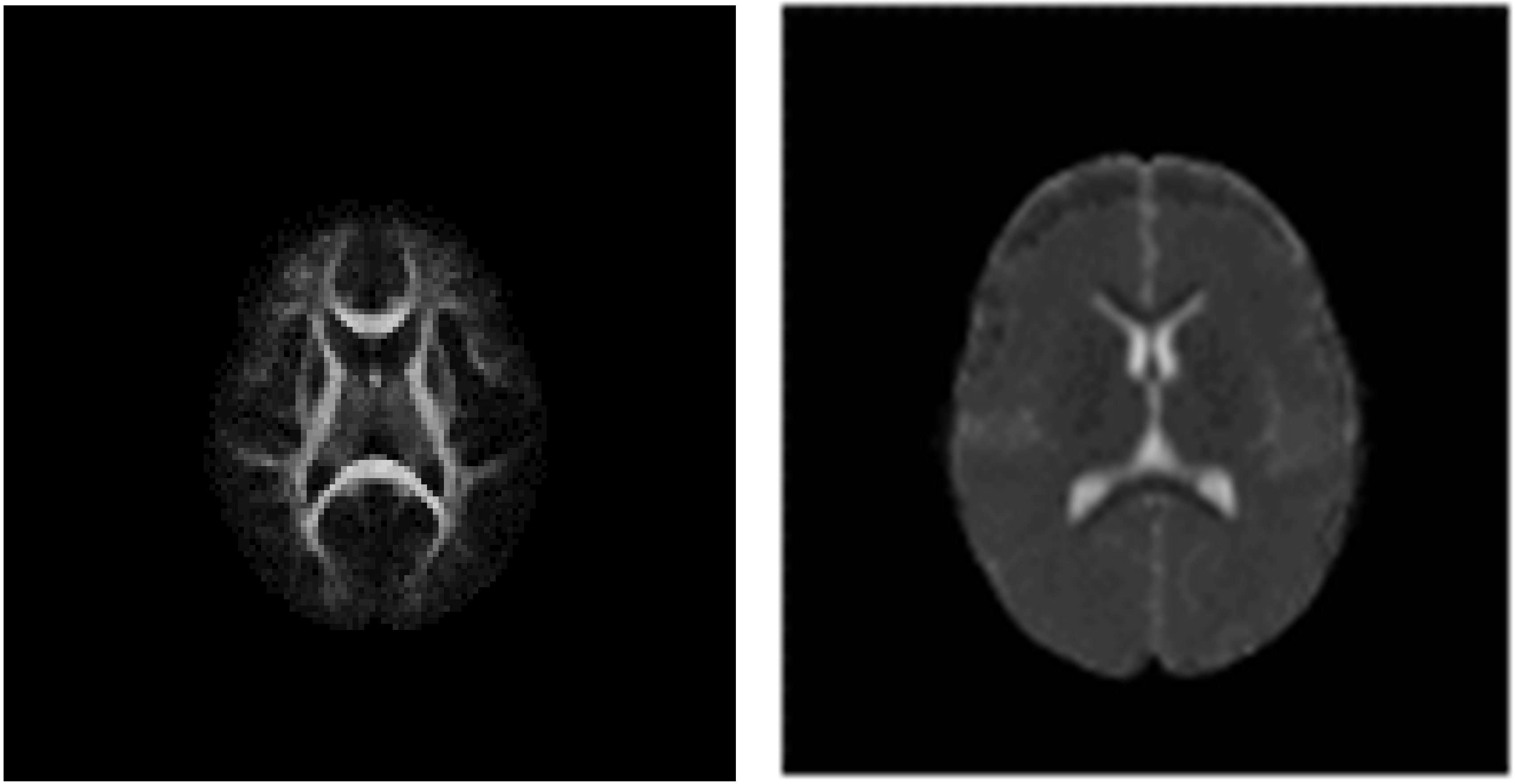


genu, splenium, motor

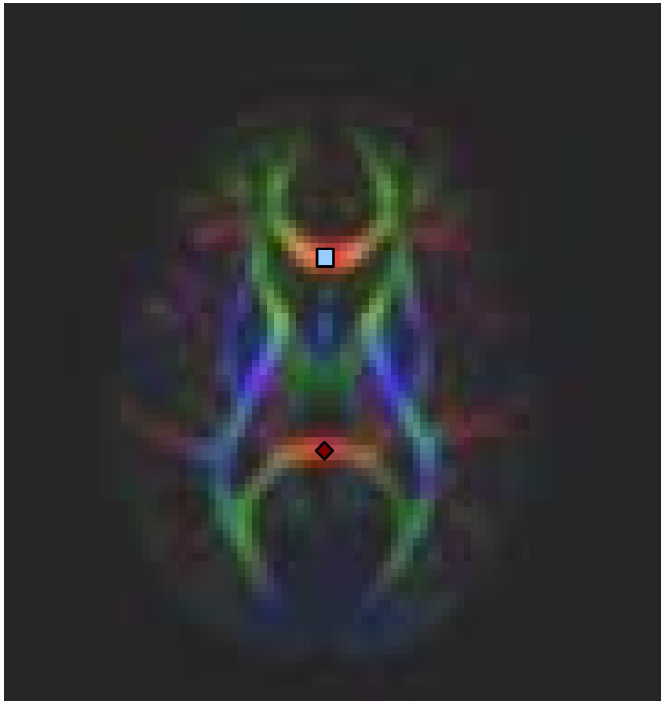


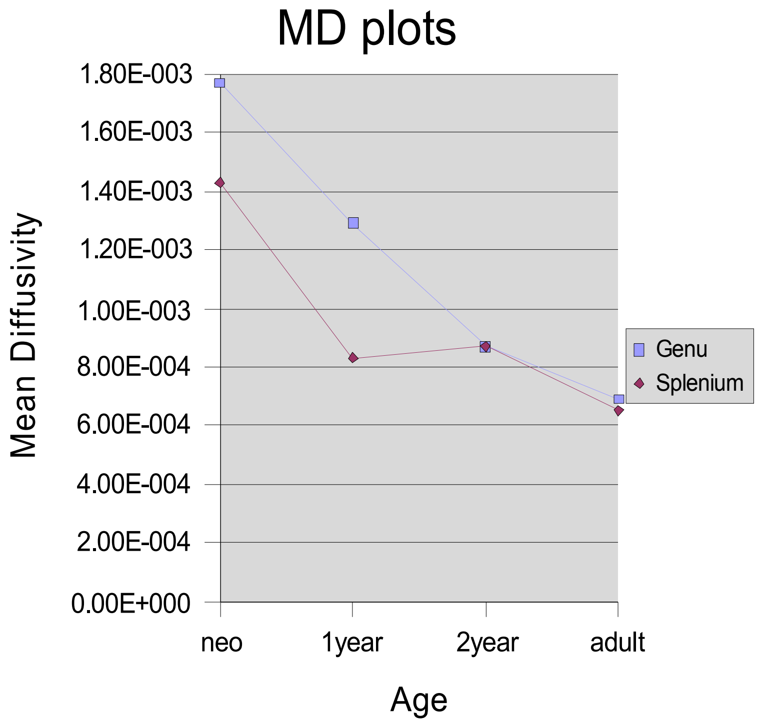
fornix and uncinate

# Neurodevelopmental atlas

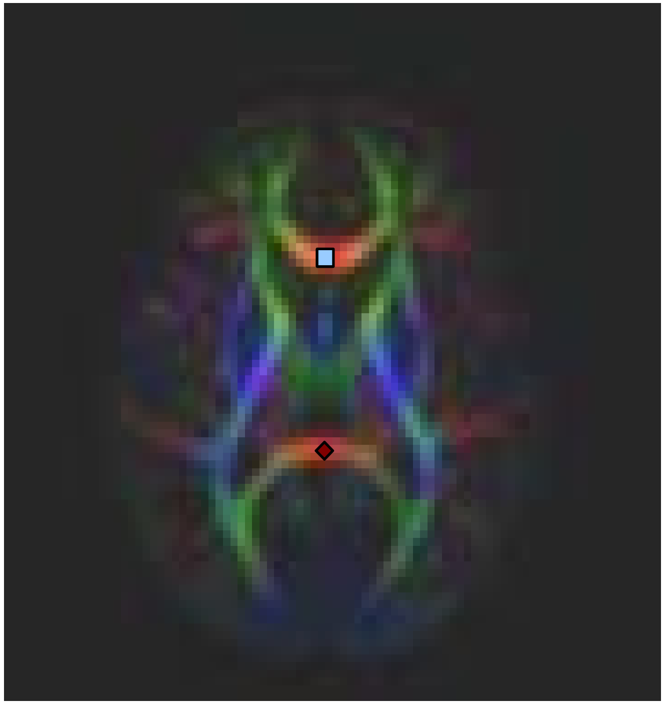


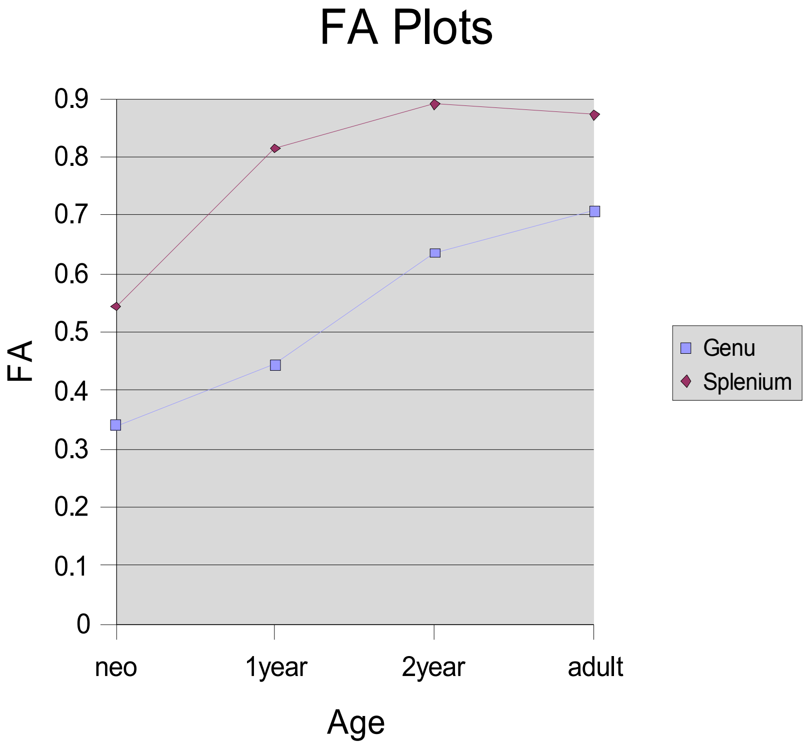
# Sample Quantitative Statistics



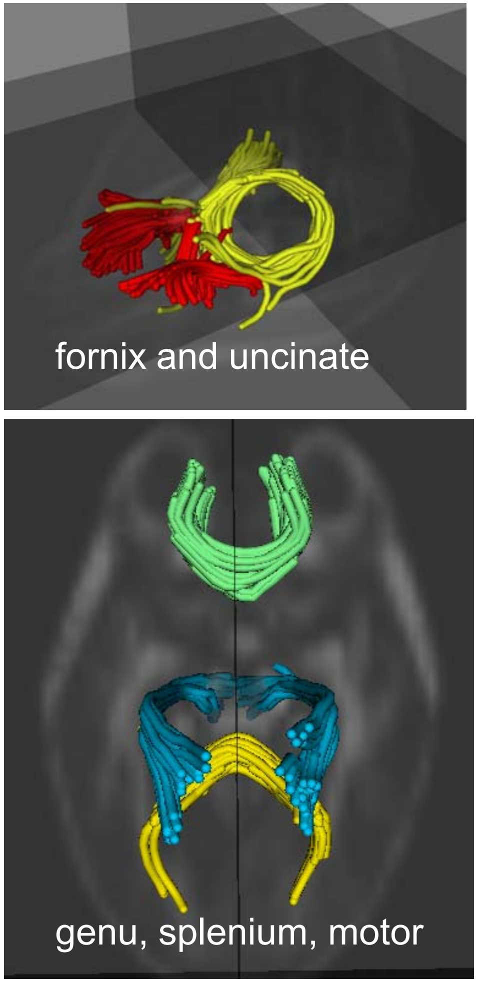


# Sample Quantitative Statistics

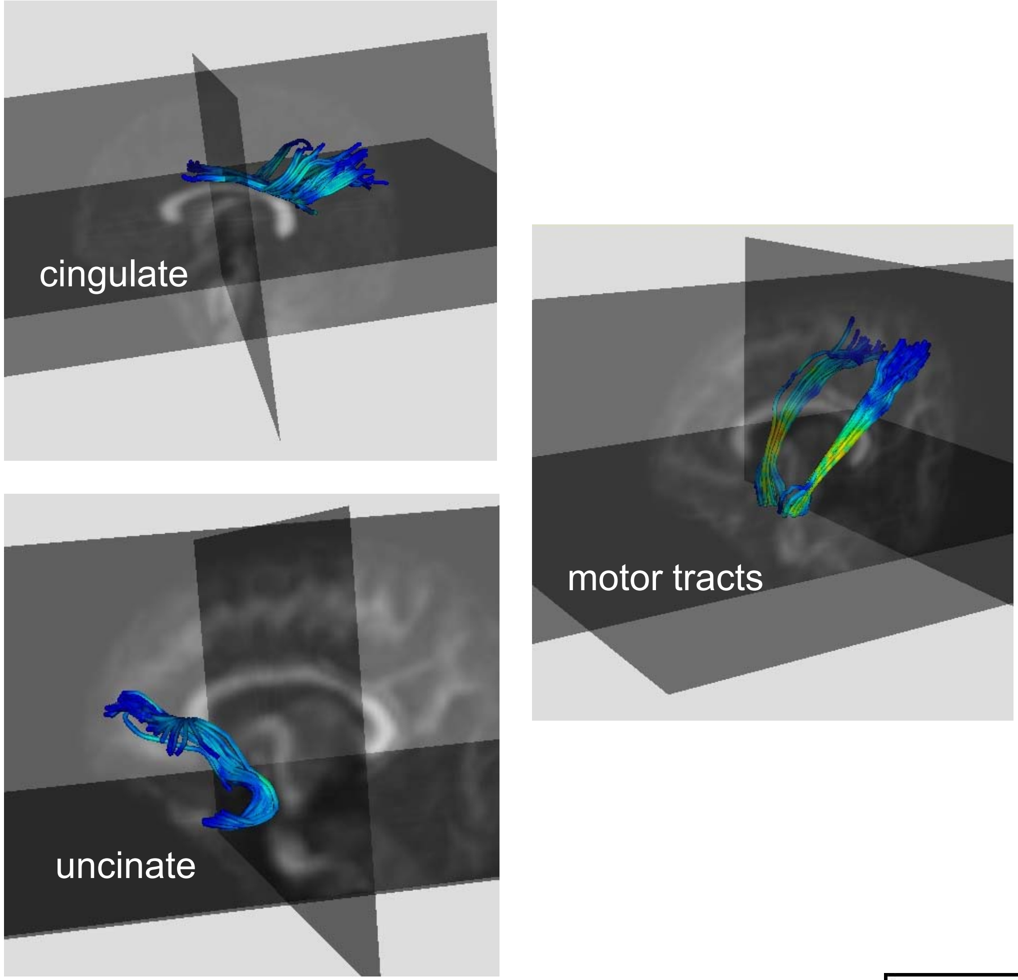




# Fiber Tractography via Atlases



Neonate atlas DTI



1yr atlas DTI

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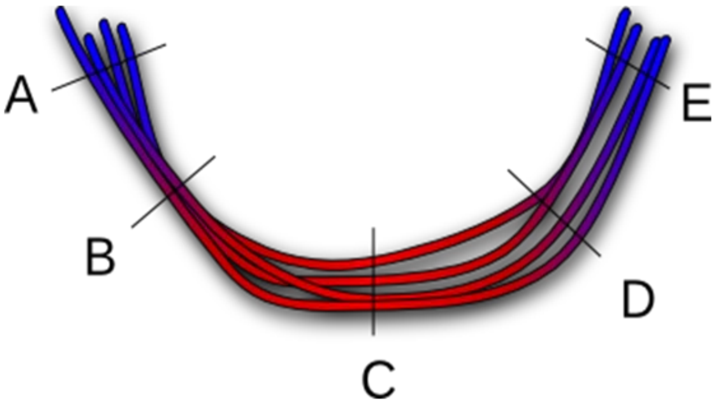
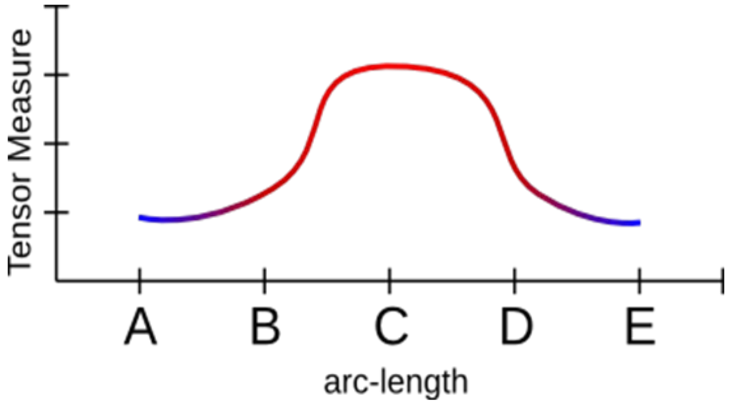
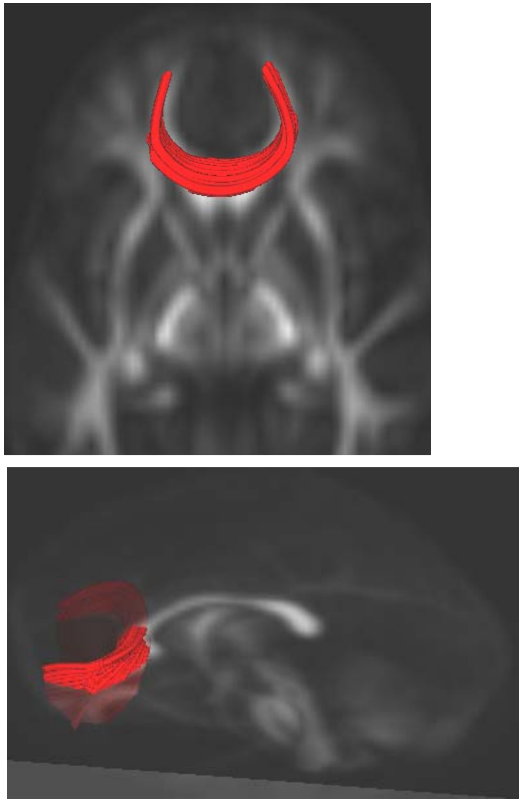
# Tract Parametrization and Analysis

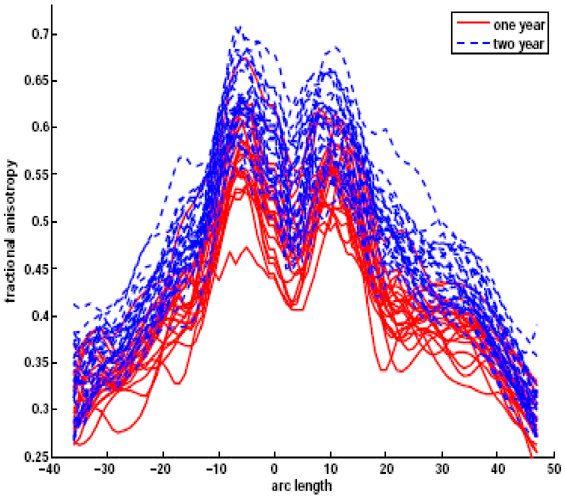




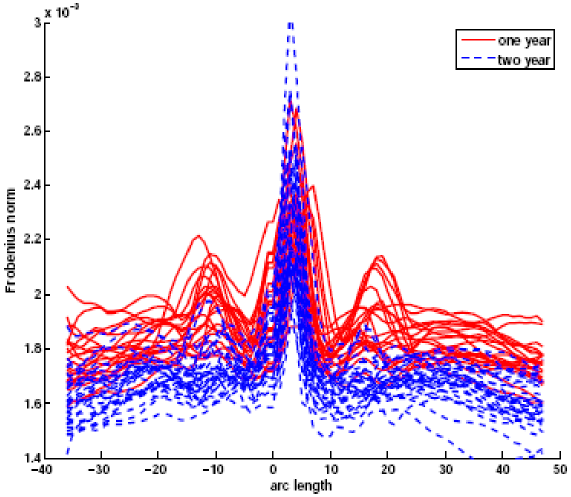
Corouge et al. *Fiber tract-oriented statistics for quantitative diffusion tensor MRI analysis*. Medical Image Analysis 2006.
FiberViewer software - http://www.ia.unc.edu/dev/

# Pediatric Example: Genu Tract 1-2yrs





(b) All FA curves



(c) All norm curves

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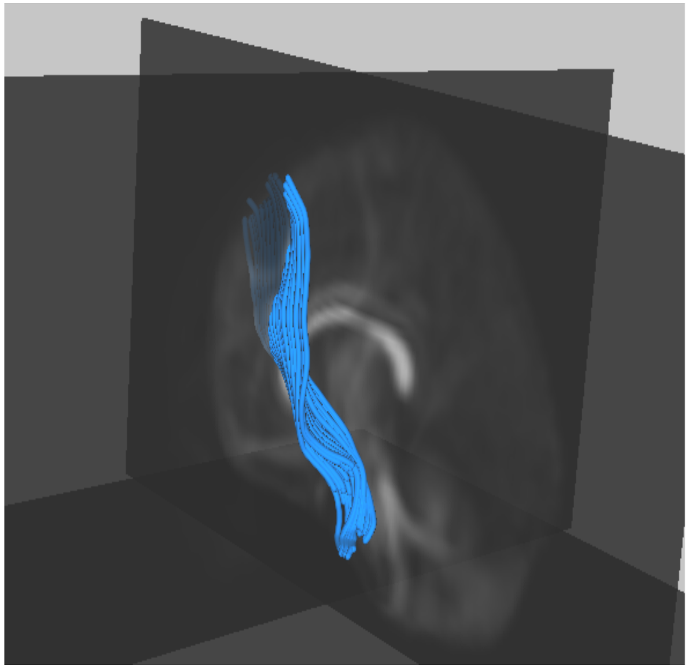
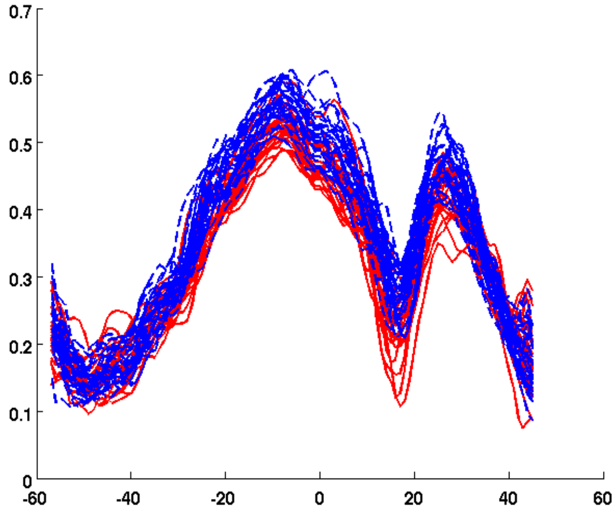
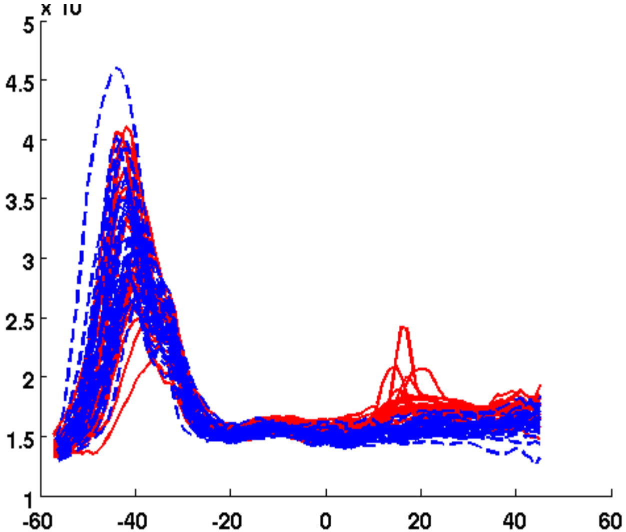
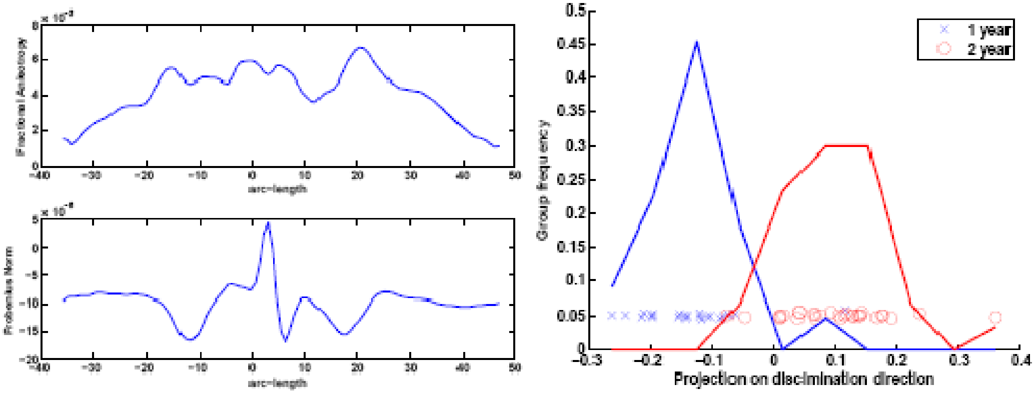
# Pediatric Example – Left motor tract



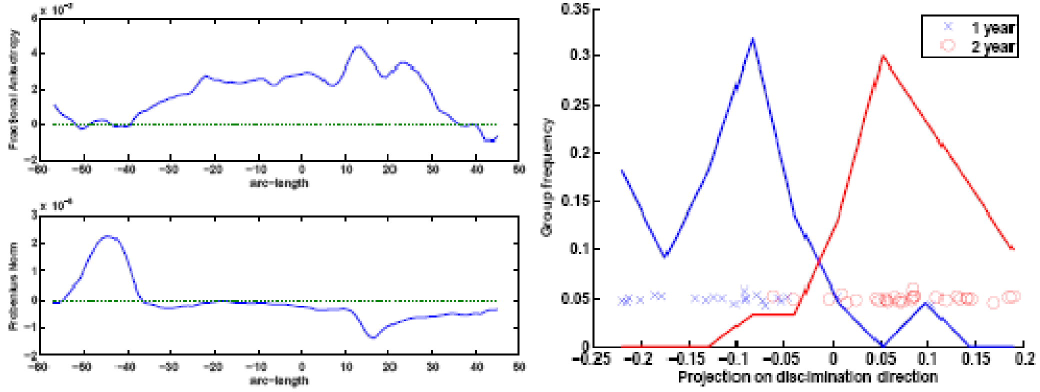




# Statistical analysis of tracts as 1-D curves: Functional data analysis (FDA)



(a) Genu discriminant functions (b) Data functions projected on FLD



(c) Motor tract discriminant functions (d) Data functions projection on FLD

“Group Statistics of DTI Fiber Bundles Using Spatial Functions of Tensor Measures” Casey Goodlett, P. Thomas Fletcher, John Gilmore, and Guido Gerig, MICCAI 2008, NeuroImage (in press)

Hypothesis testing and discriminant analysis on first k PCA modes (Hotelling T^2)
→ Type and Location of group differences.

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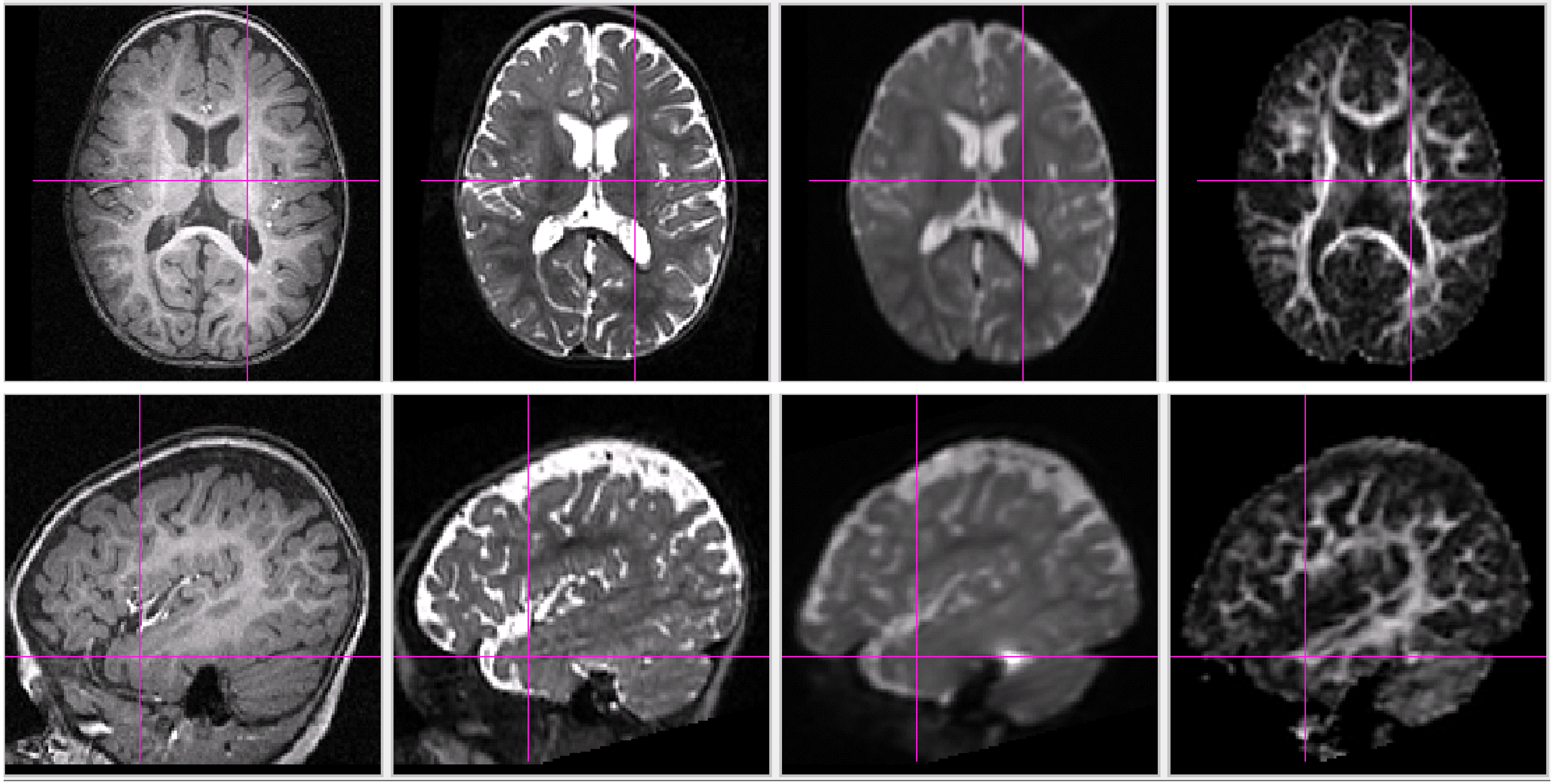
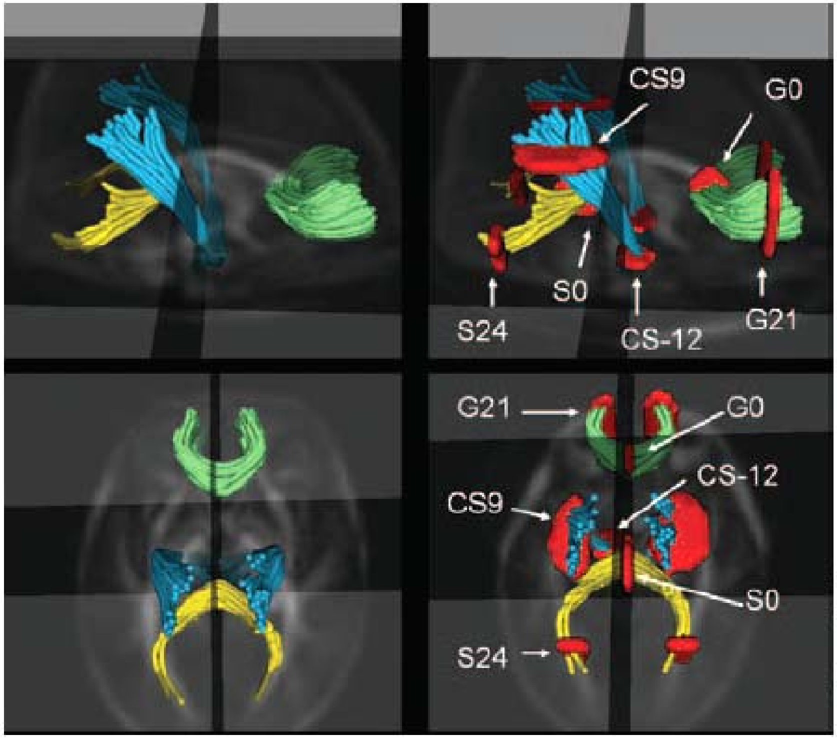
# DTI is part of multi-modal MRI protocol

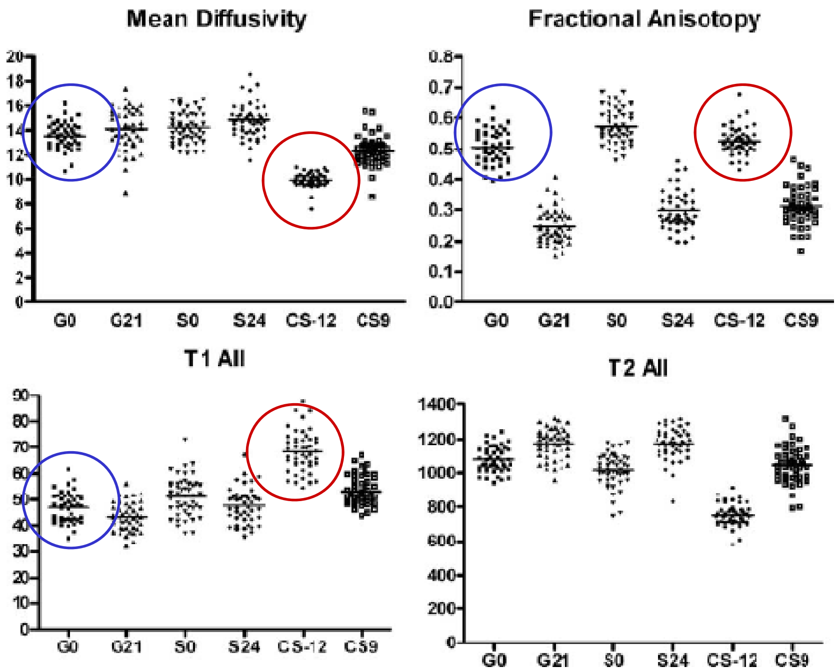


T1 MPRage. T2 3D TSE, MD, FA (2yrs old. Weili Lin, UNC)

# Quantitative Tractography to study early wm development



John H. Gilmore et al., Early Postnatal Development of Corpus Callosum and Corticospinal White Matter Assessed with Quantitative Tractography, AJNR Nov. 2007



- FA does not explain degree of myelination and structuring
- Combined use of DTI, T1w and T2w

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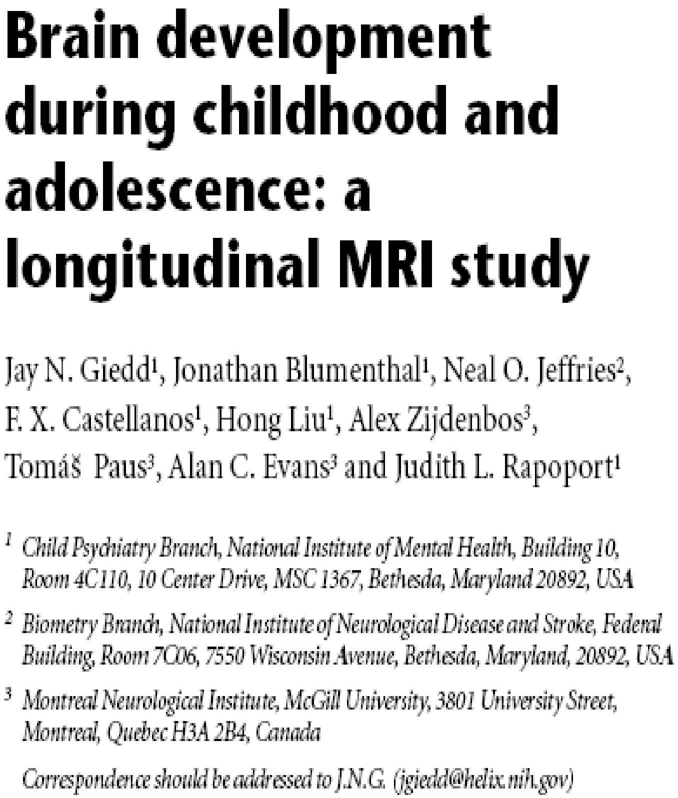
# 5. Towards Longitudinal Analysis

# Fallacy of global versus local analysis: Nonlinear growth of human brain



## Brain development during childhood and adolescence: a longitudinal MRI study

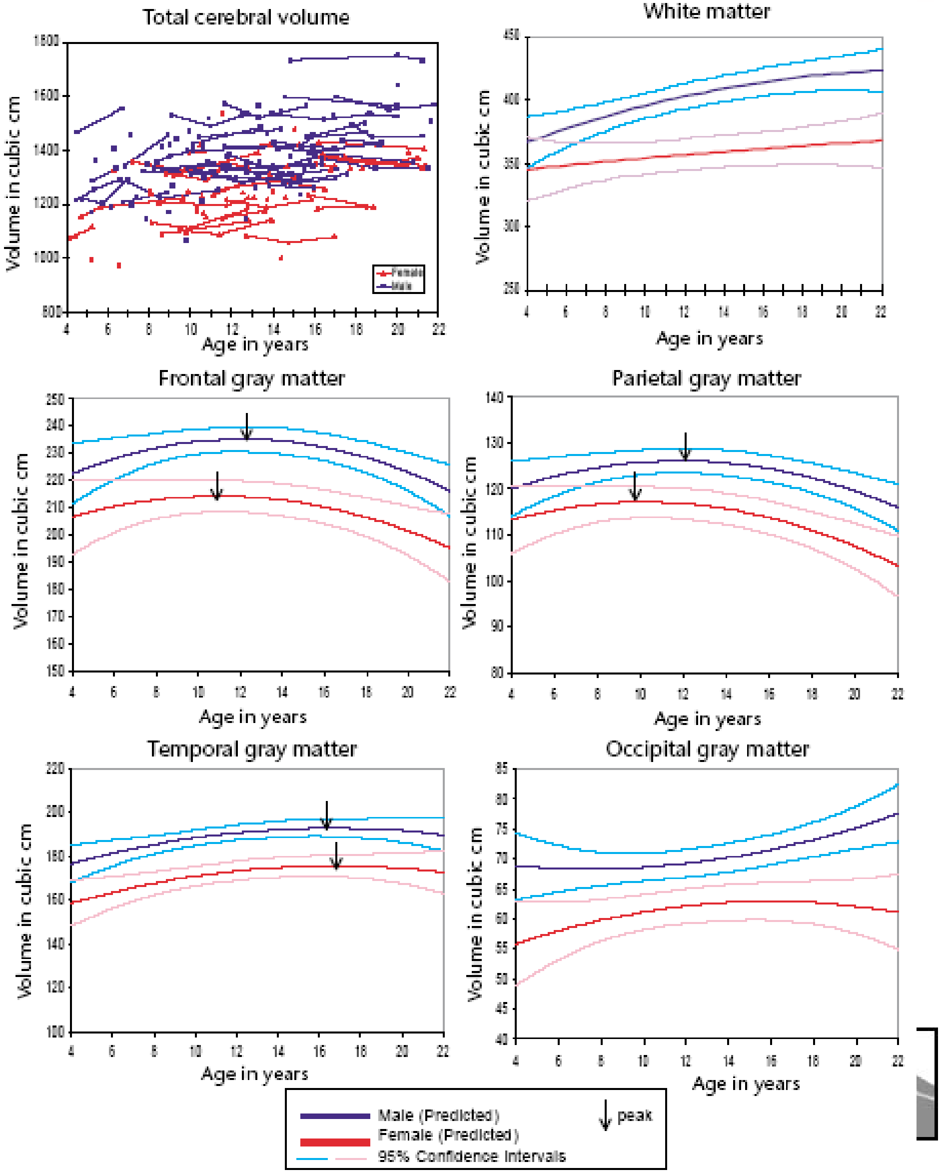
Jay N. Giedd[1], Jonathan Blumenthal[1], Neal O. Jeffries[2], F. X. Castellanos[1], Hong Liu[1], Alex Zijdenbos[3], Tomáš Paus[3], Alan C. Evans[3] and Judith L. Rapoport[1]

[1] *Child Psychiatry Branch, National Institute of Mental Health, Building 10, Room 4C110, 10 Center Drive, MSC 1367, Bethesda, Maryland 20892, USA*

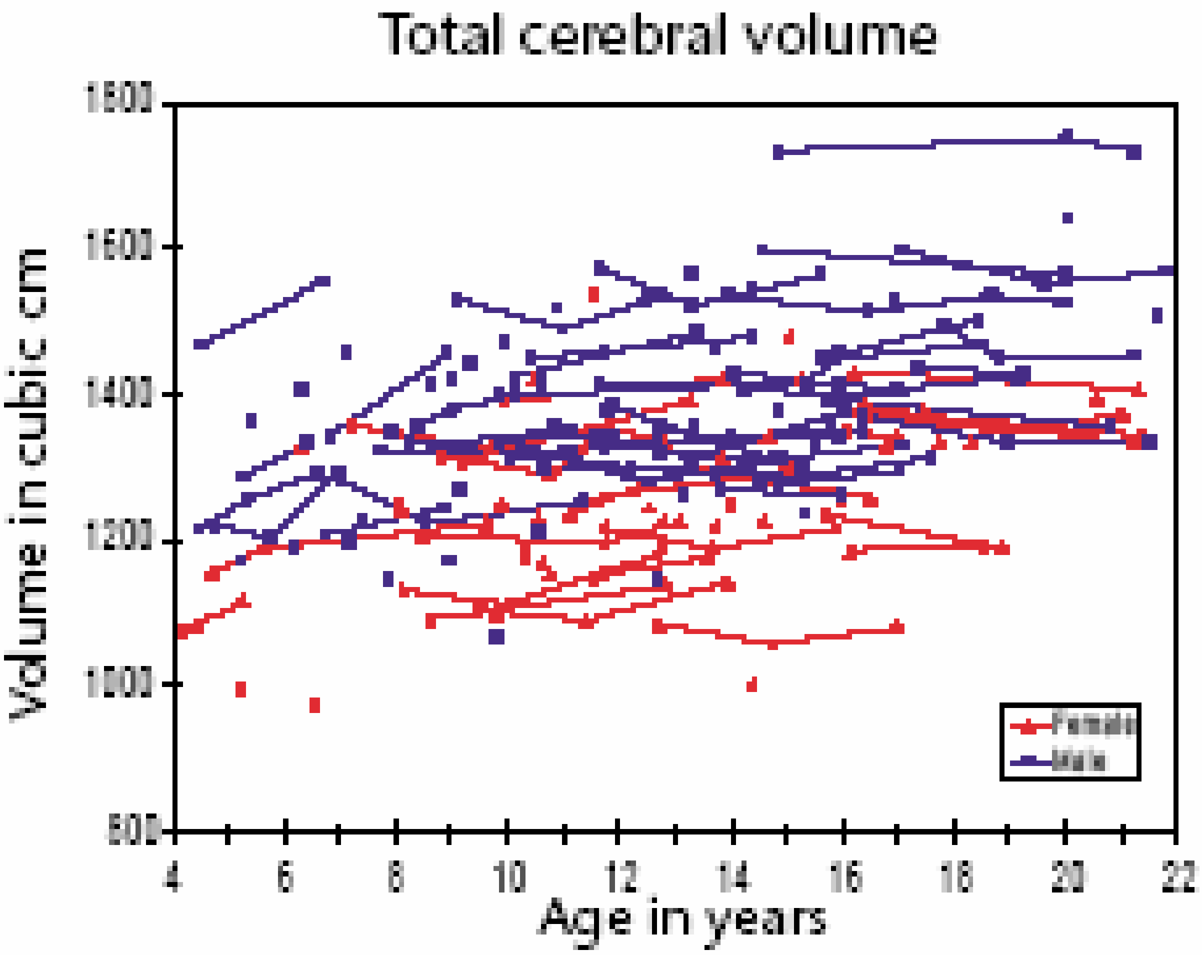
[2] *Biometry Branch, National Institute of Neurological Disease and Stroke, Federal Building, Room 7C06, 7550 Wisconsin Avenue, Bethesda, Maryland, 20892, USA*

[3] *Montreal Neurological Institute, McGill University, 3801 University Street, Montreal, Quebec H3A 2B4, Canada*

*Correspondence should be addressed to J.N.G. (jgiedd@helix.nih.gov)*



# Longitudinal Study Design: Normative NIH Brain Study



**Challenges:**

- Mixed Cross-sectional and longitudinal design
- Missing data (1, 2 or 3 data points per subject)

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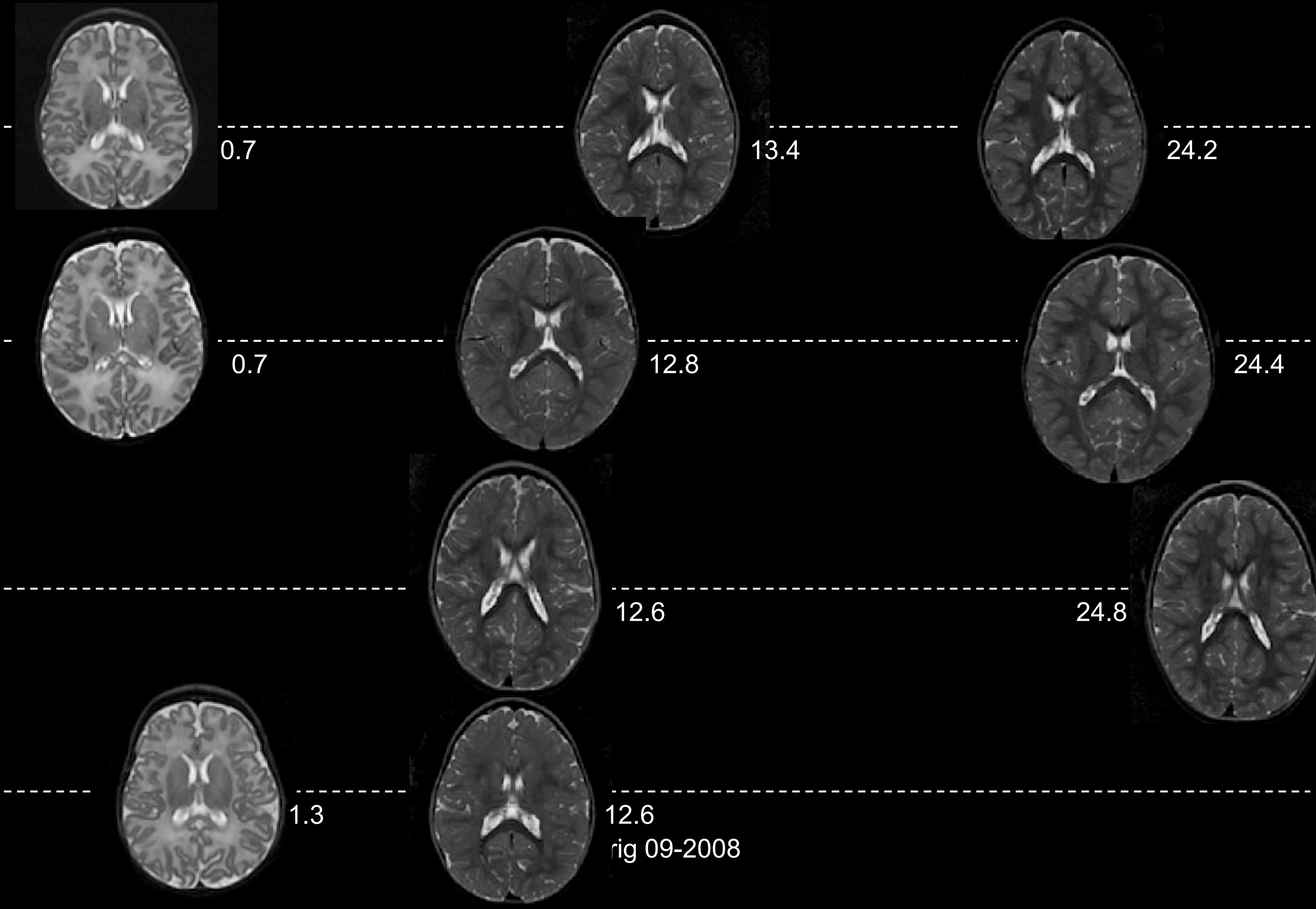
# Longitudinal changes of MR images of population



rig 09-2008

# Properties of data

- Correlation, similarity between repeated MR scans
- Missing Data
- Unbalanced spacing, different time points
- Correlation between tissues, inter-subject variance, etc.
- Multivariate features: Dimensionality
- Regression not suitable

# Challenge: Multivariate Longitudinal data analysis

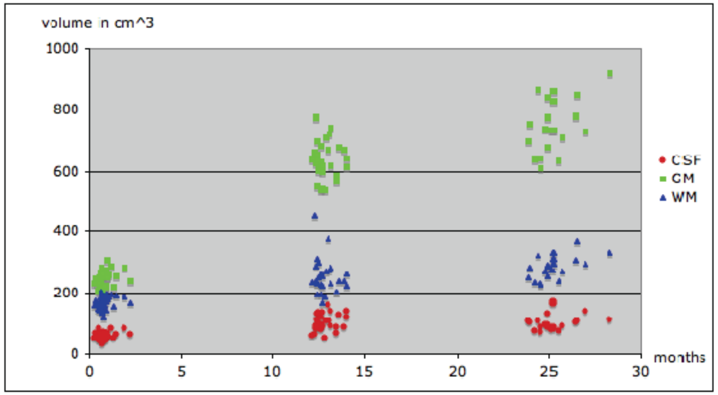


**Figure 2.** Scatter plot of our WM, GM, CSF data versus time. An illustration of irregular data that has uneven sampling at time axis for different subjects. CSF: red dot, GM: green box, WM: blue triangle.

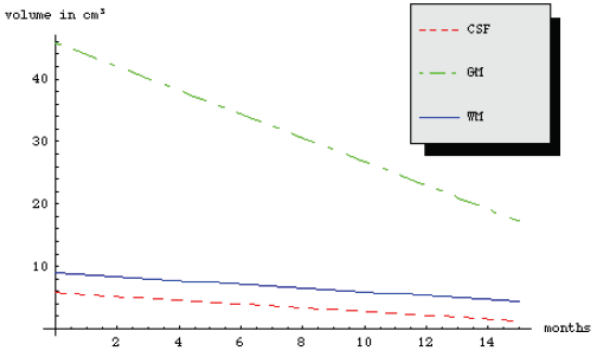


**Figure 7.** Derivatives of the parametric growth curves of three brain tissues. CSF: red dash line, GM: green dot-dash line, and WM: blue solid line.

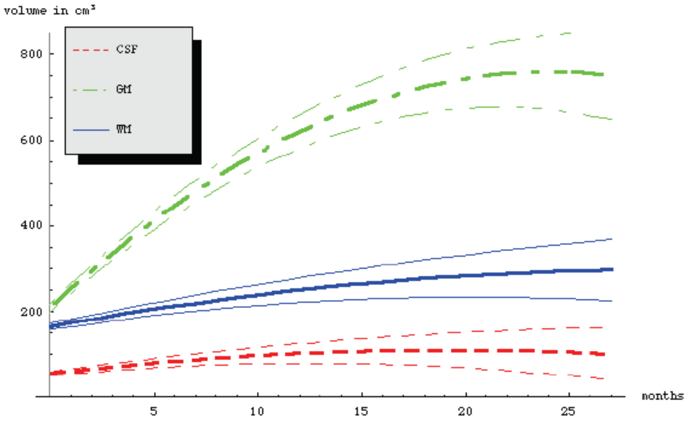


**Figure 4.** 95 % confidence interval of the growth curves of three brain tissues. CSF: red dash line, GM: green dot-dash line, and WM: blue solid line.

Multivariate Longitudinal Statistics for Neonatal-Pediatric Brain Tissue Development, Sh. Xu, M. Styner, J.H. Gilmore, G. Gerig, SPIE 2008

Multivariate Nonlinear Mixed Model to Analyze Longitudinal Image Data: MRI Study of Early Brain Development, Shu Xu et al., MMBIA 2008

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# Challenge: Multivariate Longitudinal data analysis

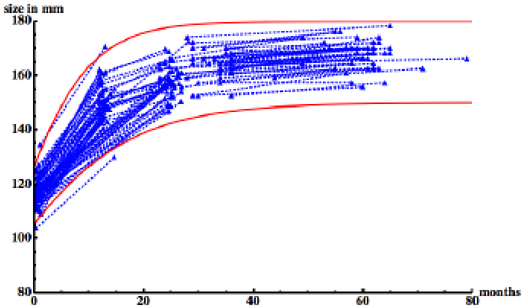

Figure 2. Illustration of individual growth trends. A spaghetti plot that connects repeated measurements of the same individual is shown. The two red upper and lower bound curves are generated by varying $\beta_1$ and $\beta_3$ only and with fixed $\beta_2$, which indicates population variance can be captured by varying only $\beta_1$ and $\beta_3$.

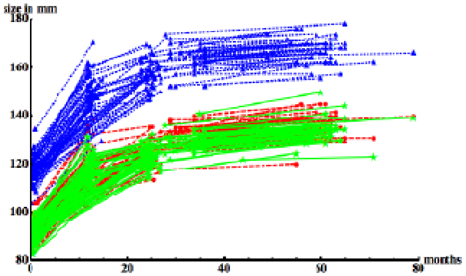

Figure 3. Illustration of individual growth trends. A spaghetti plot that connects repeated measurements of the same individual is shown. Multiple features that describe the three dimensional head size derived from each MRI brain image of neonates and young children is illustrated. X dimension: red dots connected by dashed lines; Y dimension: blue triangles connected by dotted lines; Z dimension: green stars connected by solid lines.

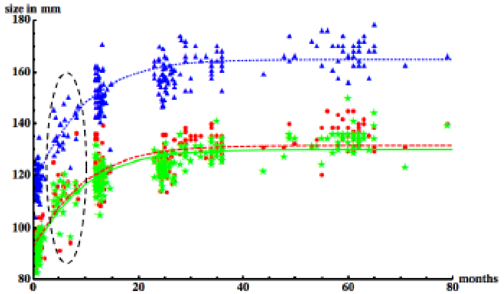

Figure 4. Population growth trajectories of head size dimension X, Y, Z plotted against the original data points ranged from age 0 to around 6 years old. A third population of 22 infants aged from 4 to 8 months old (in black dashed circle) are also plotted to validate the soundness of the average growth estimation. Symbols are the same as those in Fig. 3.

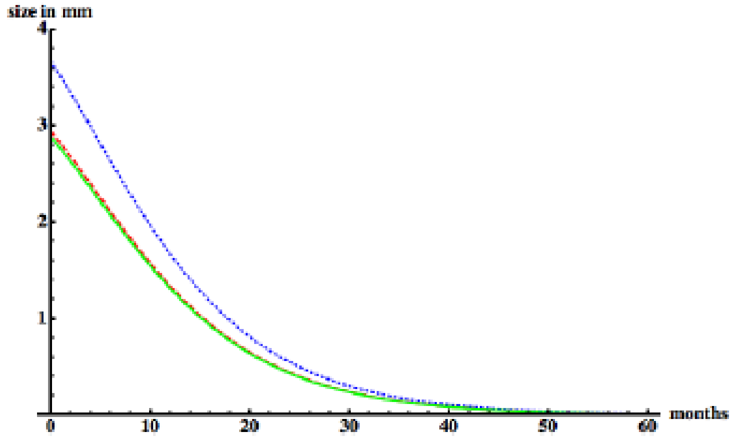

Figure 5. Growth rates of head size dimension X, Y, Z between birth to around 6 years old. X dimension: dashed red lines; Y dimension: dotted blue lines; Z dimension: solid green lines.

Multivariate Longitudinal Statistics for Neonatal-Pediatric Brain Tissue Development, Sh. Xu, M. Styner, J.H. Gilmore, G. Gerig, SPIE 2008

Multivariate Nonlinear Mixed Model to Analyze Longitudinal Image Data: MRI Study of Early Brain Development, Shu Xu et al., MMBIA 2008

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# Summary

Key topics related to imaging of early development:

- Imaging itself is great challenge
- Continuous contrast, size, shape changes:
  - Challenge for image registration
  - Challenge for image segmentation (thin cortex, very low contrast of subcortical structures)
  - Contrast flip wm/gm in anatomical images
- Myelination: Appearance changes within tissue: Should not affect registration!
- Longitudinal studies: Requires study of temporal changes rather then cross-sectional differences

# Conclusions

- **Pediatric Imaging & Image Analysis:**
  - Amazing progress of imaging technology
  - Image processing tools newly developed
  - Wealth of new results
  - Fascinating research area: Full of discoveries
  - **Potential impact: Better understanding → early detection → therapy**
- **Research field needs:**
  - Multidisciplinary research: Biology, anatomy, medicine, CS, statistics
  - Link between MRI findings and underlying neurobiology
  - Sharing of data and analysis tools
- **Fundamental computational and statistical problems:**
  - Everything changes: Contrast, size, shape, appearance
  - Statistics of growth of images and structures: 4D statistical atlases
  - (Longitudinal) multivariate statistics of imaging features & patient parameters

# Acknowlegements

Clinical Research Partners:

- Joseph Piven (UNC)
- John H. Gilmore (UNC)
- Janet Lainhart (Utah)
- Weili Lin (UNC)

Computer Science Partners:

- Sarang Joshi (Utah)
- Tom Fletcher (Utah)
- Marcel Prastawa (Utah)
- Sylvain Gouttard (Utah)
- Casey Goodlett (Utah)
- Shu Xun (UNC)
- Martin Styner (UNC)
- Ron Kikinis (SPL Harvard)

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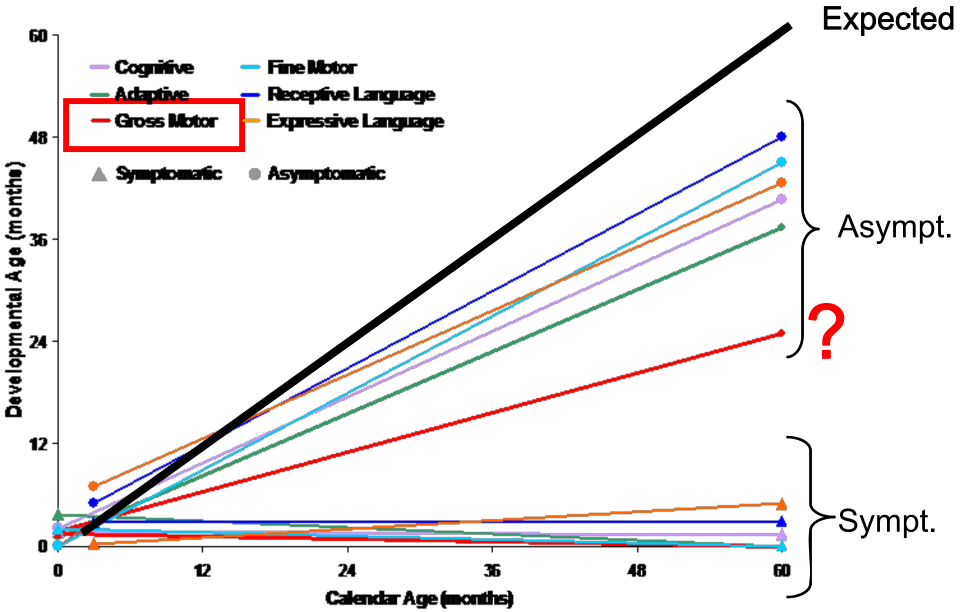
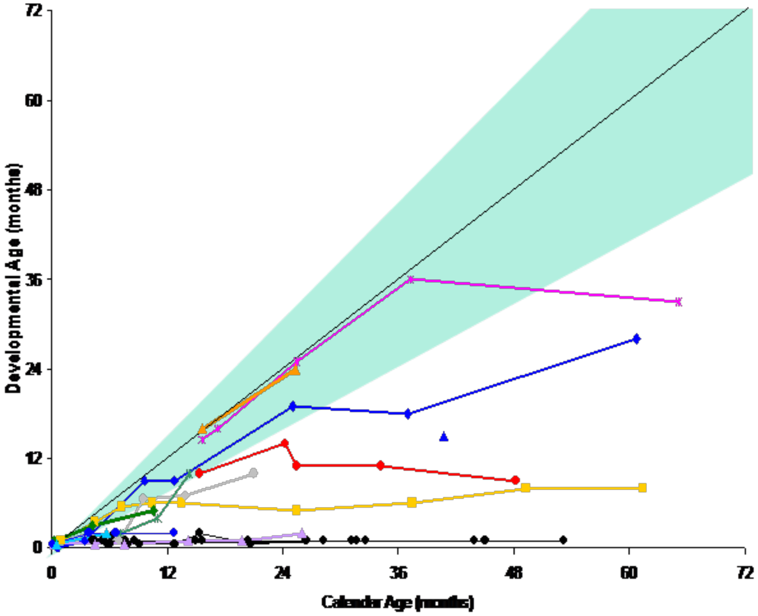
# Developmental Trajectory: Krabbe's

## Behavioral Phenotypes



Description of behavioral phenotypes are instrumental in understanding the disease's process and its impact in neurological function.

## Gross Motor



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

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