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National Alliance for Medical Image Computing
http://na-mic.org

What is DTI, its use in research and clinical practice, and its future potential

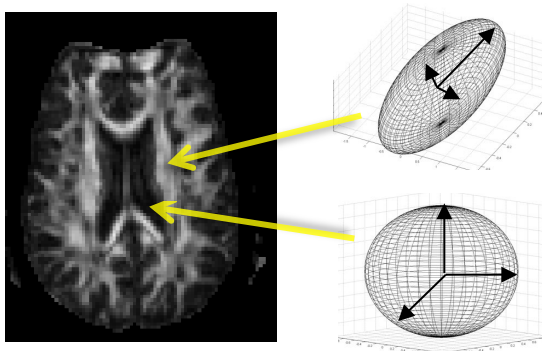
Martin Styner with thanks to many, many people
Departments of Computer Science and Psychiatry
UNC Neurodevelopmental Disorders Research Center
UNC Neuro Image Research and Analysis Lab

TOC

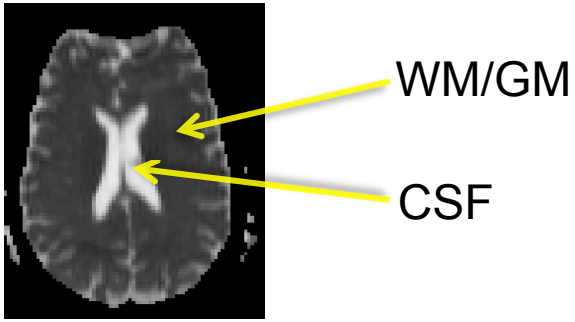
- Interpretation/validation of DTI properties
  - Rat spinal cord studies
- Validation of tractography
- What can DTI be used for? Many different applications…
  - Main part of the talk
- Future of DTI: looks bright…

DTI Properties (again)

Fractional Anisotropy (Tensor shape), 0..1



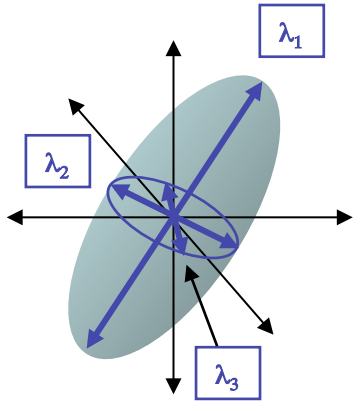
Mean Diffusion (Tensor volume)



Axial Diffusion

$$= \lambda_1 = \lambda_{||}$$

In WM: Diffusion parallel to axon



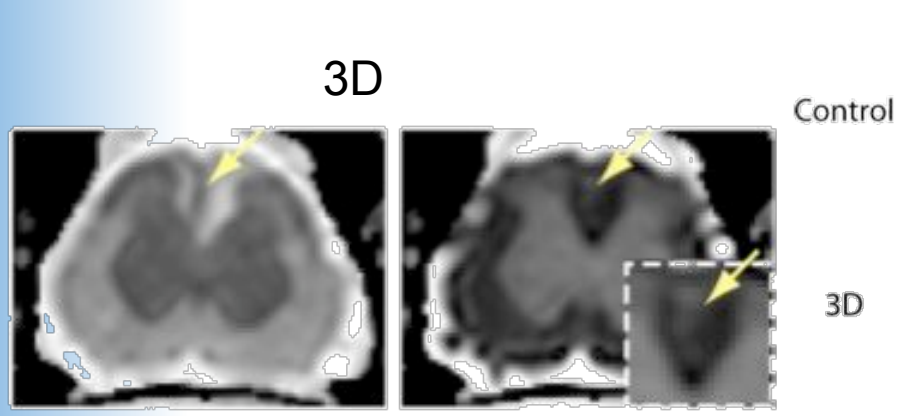
Radial Diffusion

$$= \frac{(\lambda_2 + \lambda_3)}{2} = \lambda_\perp$$

In WM: Diffusion orthogonal to axon

Spinal Cord Degeneration

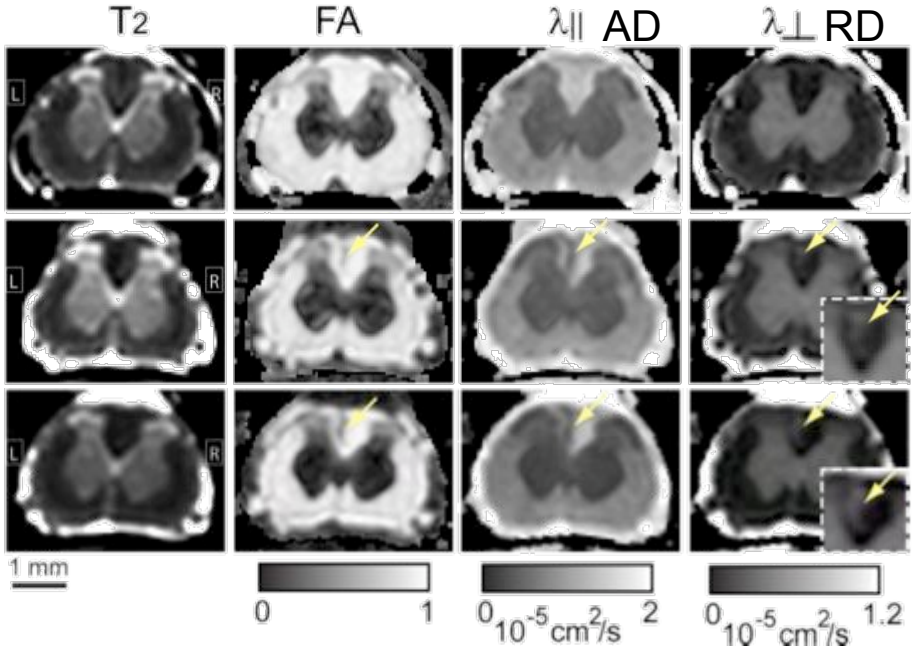
- DTI (AD/RD) & immunohistochemistry of Wallerian degeneration
- Unilateral L2–L4 dorsal axotomy in rat spine column
- DTI revealed dorsal lesion extending from lumbar to cervical cord



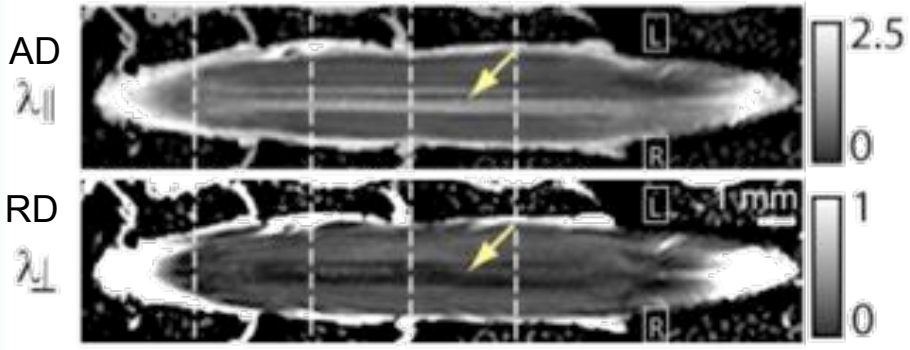
Neurobiology of Disease

Diffusion Tensor Magnetic Resonance Imaging of Wallerian Degeneration in Rat Spinal Cord after Dorsal Root Axotomy

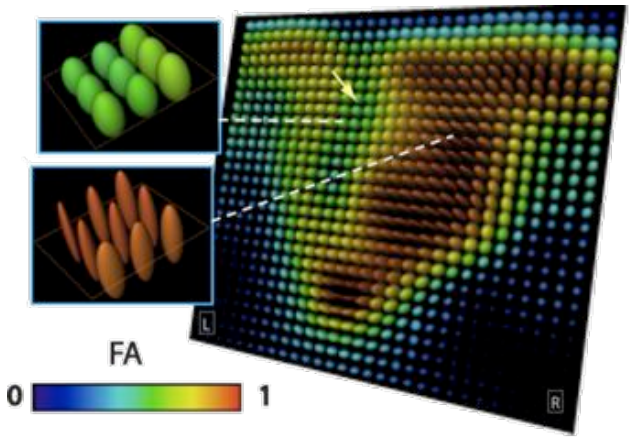
Jiangyang Zhang,[1] Melina Jones,[2] Cynthia A. DeBoy,[2] Daniel S. Reich,[1,2] Jonathan A. D. Farrell,[1,3,7] Paul N. Hoffman,[2,4] John W. Griffin,[2] Kazim A. Sheikh,[2] Michael I. Miller,[3,6] Susumu Mori,[1,7] and Peter A. Calabresi[2]



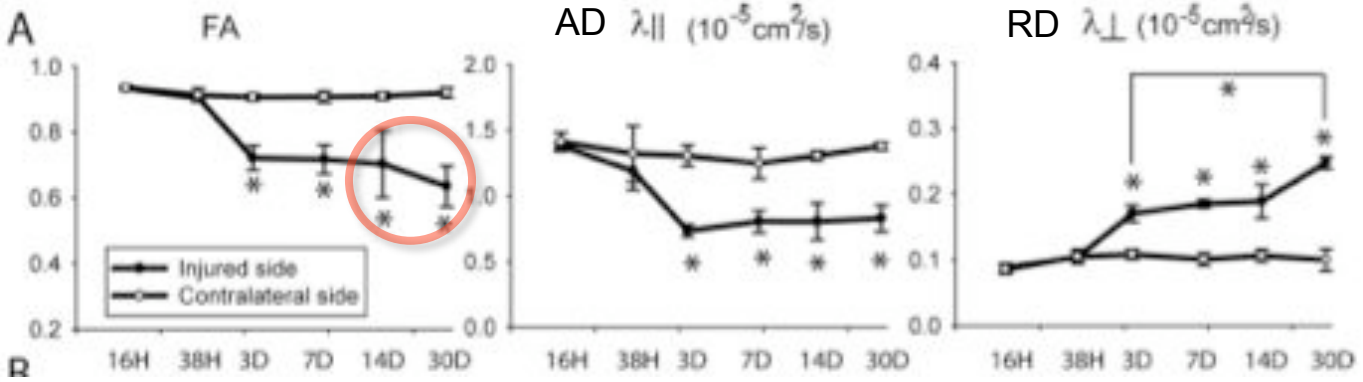
Spinal Cord Degeneration



Lesion at Day 3

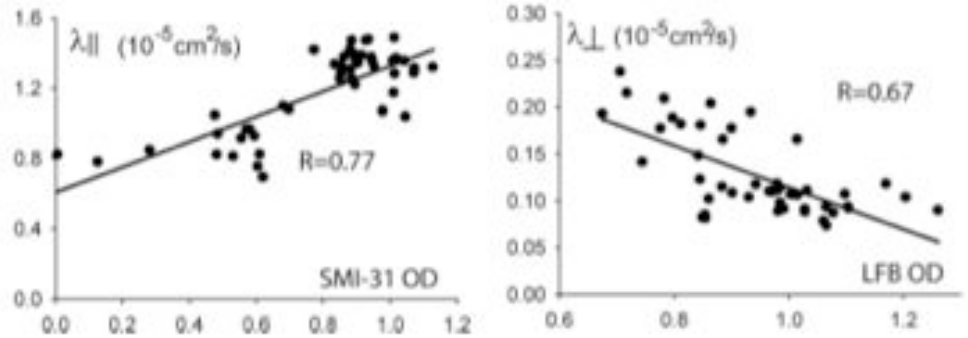


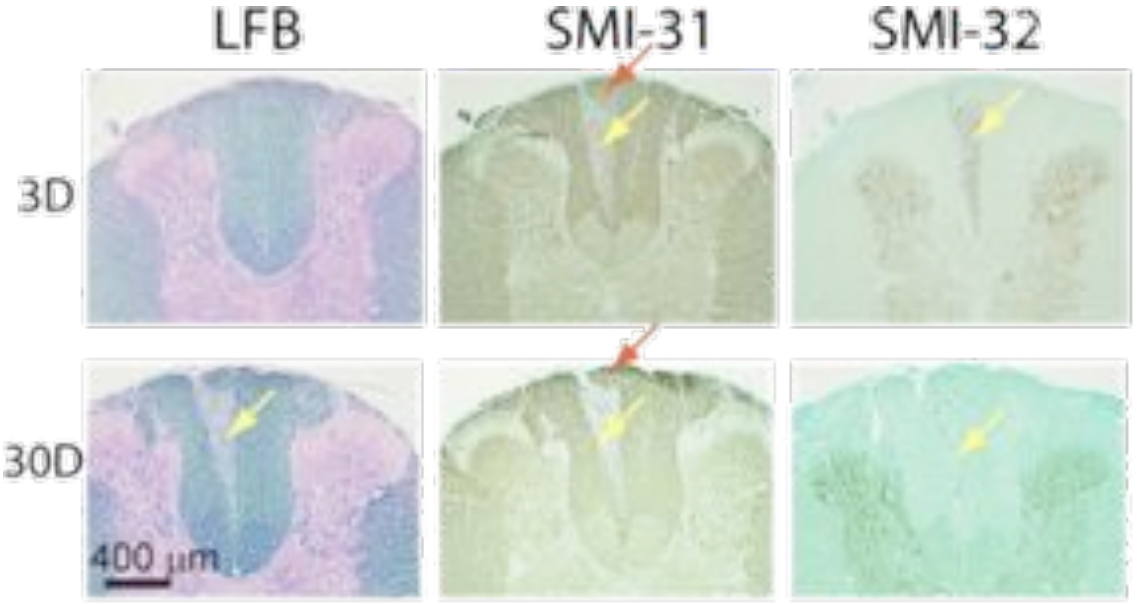
Day 30



Immunohistochemistry

- LFB: Myelin
- SMI : neurofilaments
  - 31: hyper-phosphylated
  - 32: hypo-phosphylated



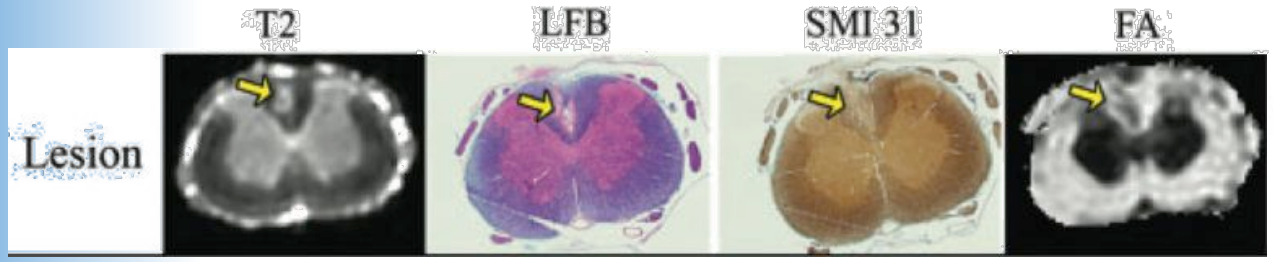


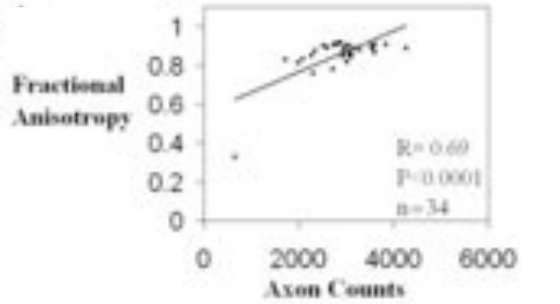
Spinal Cord Degeneration

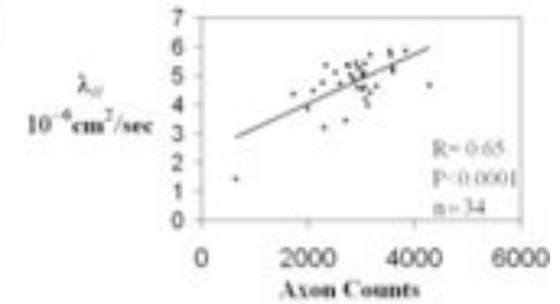
- Day 3 (as compared to unlesioned side)
  - DTI: significantly reduced AD and increased RD.
  - Immuno: Reduced phosphorylated, increased nonphosphorylated neurofilaments, swollen axons, myelin ovoids, no loss of myelin.
- Day 30 (as compared to day 3)
  - DTI: no reduction in AD but increase in RD
  - Immuno: Gradual clearance of myelin, no changes in neurofilament
- Conclusion:
  - DTI, AD/RD sensitive to axon degeneration
  - FA captures all effects, but cannot differentiate
  - Correlation of RD with myelin degeneration
  - Correlation of AD with loss of phosphorylated neurofilaments

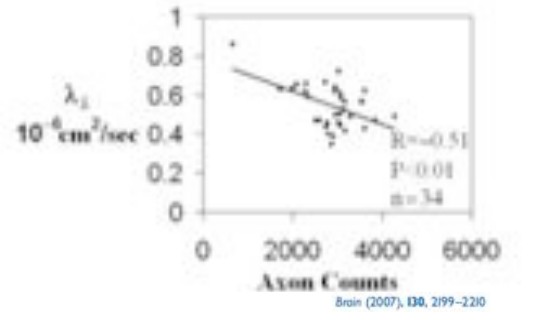
Demyelinating Lesions

- Rat model of autoimmune encephalomyelitis/MS
- Injection of cytokines (TNF-α, IFN-γ) or lipopolysaccharides => spinal cord lesions
- DTI & Immunohistochemistry
- FA, AD and RD correlate with axon counts and degenerating axon counts
- FA and T2-w intensity correspond to changes in myelin loss and axon phosphorylation









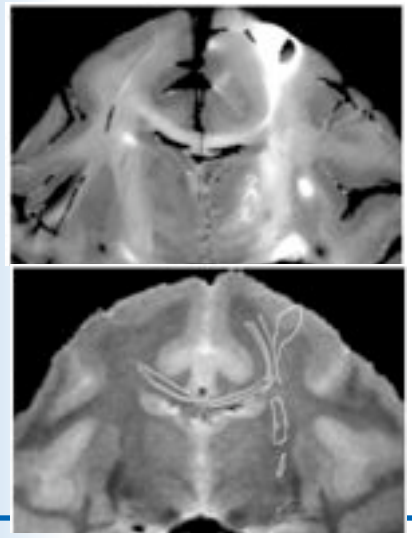
doi:10.1093/brain/awm122 Brain (2007), 130, 2199–2210

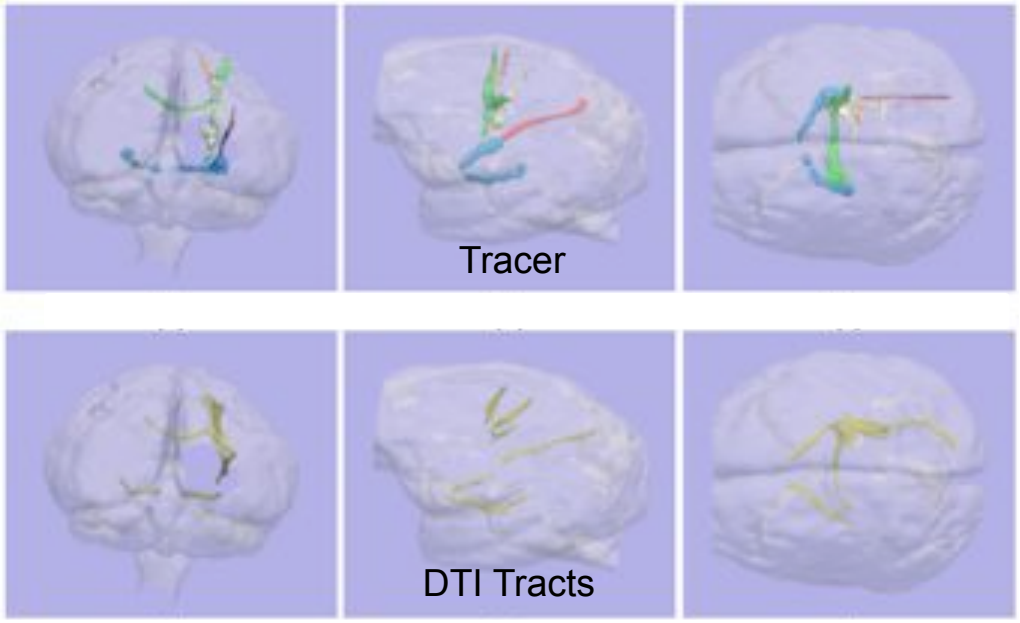
High resolution diffusion tensor imaging of axonal damage in focal inflammatory and demyelinating lesions in rat spinal cord

Cynthia A. DeBoy,[1] Jiangyang Zhang,[2] Sonny Dike,[3] Irina Shats,[3] Melina Jones,[1] Daniel S. Reich,[1,2] Susumu Mori,[2] Thien Nguyen,[1] Brian Rothstein,[4] Robert H. Miller,[4] John T. Griffin,[1,5] Douglas A. Kerr[1,3] and Peter A. Calabresi[1]

Validation of Tractography

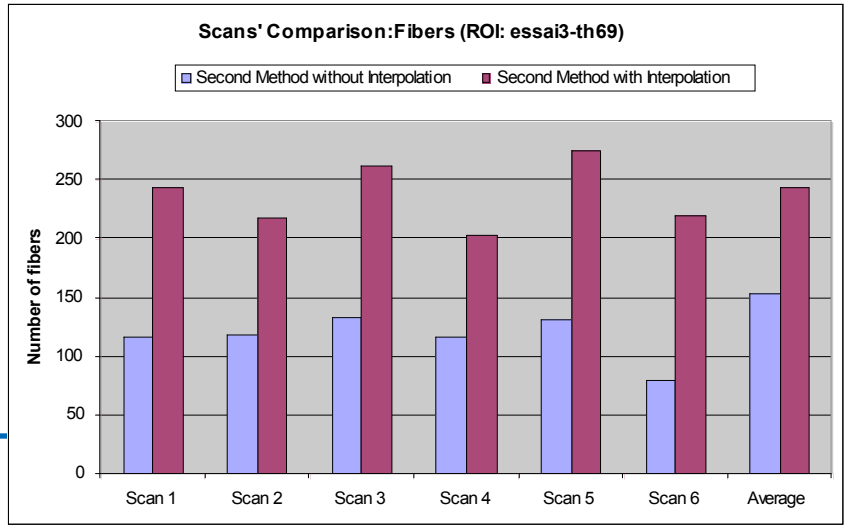
- Are results of DTI tractography anatomically correct? Yes and No…
- Many studies using synthetic ground truth & MRI phantoms show convincingly positive results
- In/Ex vivo: stimulation mapping, manganese imaging, tracer studies
  - Several performed in primates, Dauguet 2007 (NeuroImage)





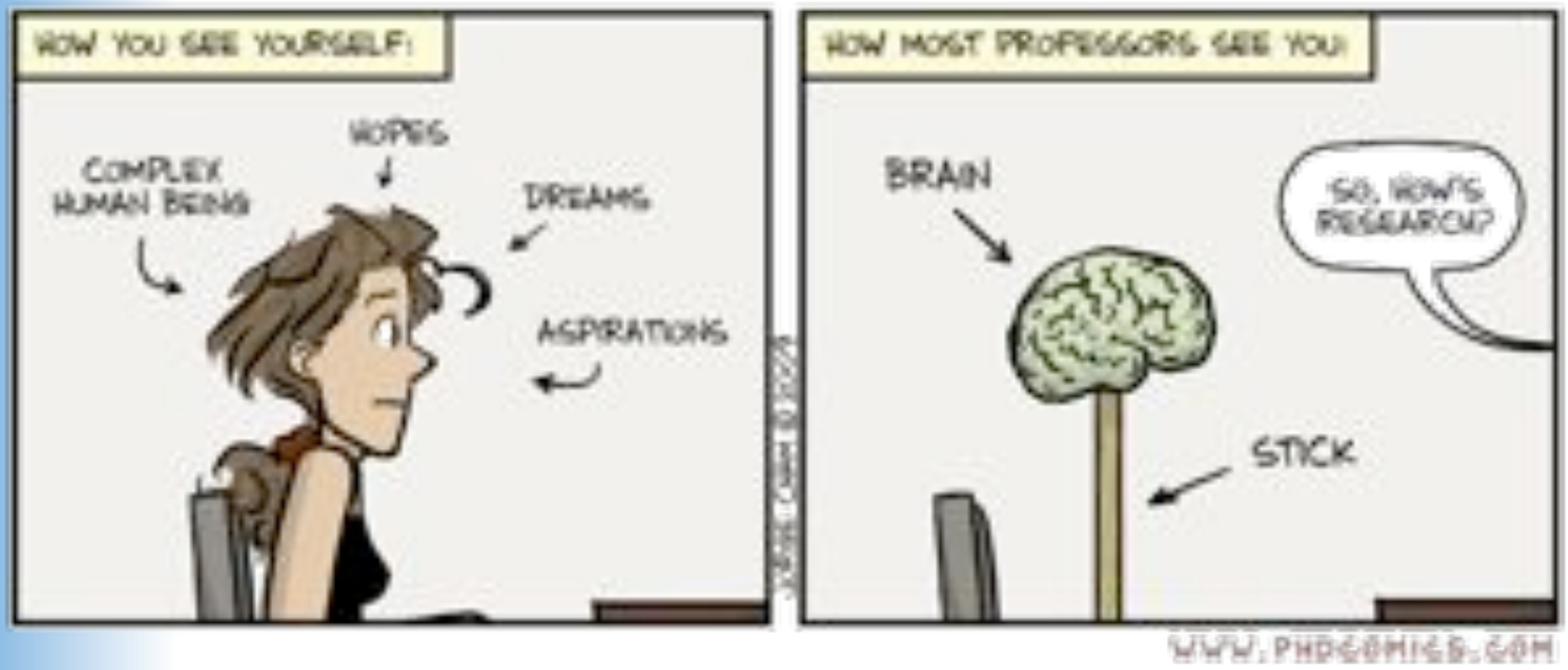
Validation of Tractography

- Good agreement for major fiber bundles
- Sensitivities to fiber crossings and small fiber bundles
  - Higher models of diffusion (Qball, DSI)
  - Anatomical knowledge via source and target selection
  - Novel tractography on DTI: multi-tensor or probabilistic tracking
- Overall convincing evidence for DTI tractography
  - Major fiber tracts are valid
  - #fibers highly variable!
  - Size of tracts variable!



Intermezzo

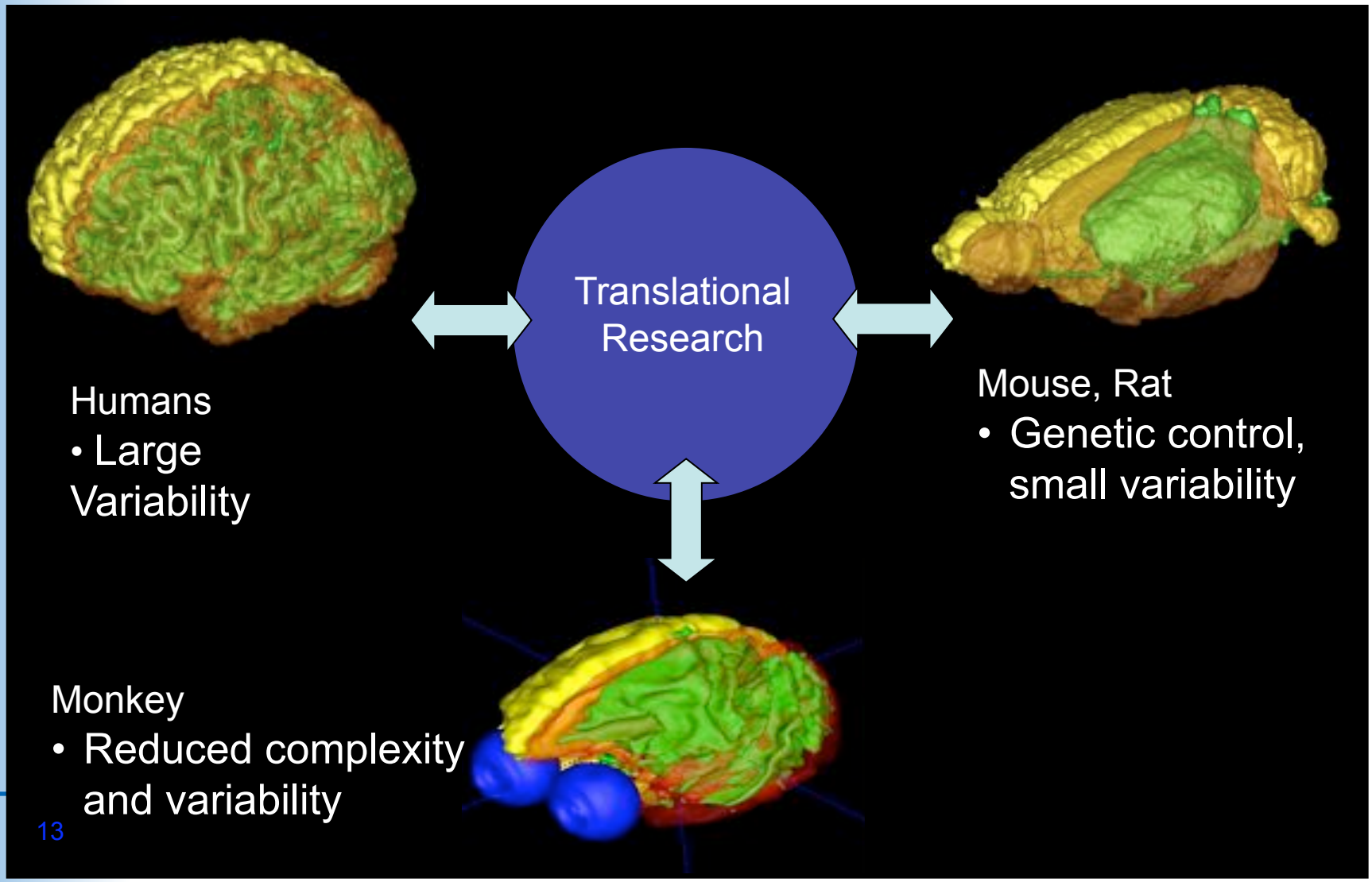
PhDcomics: Brain on a stick



Applications of DTI

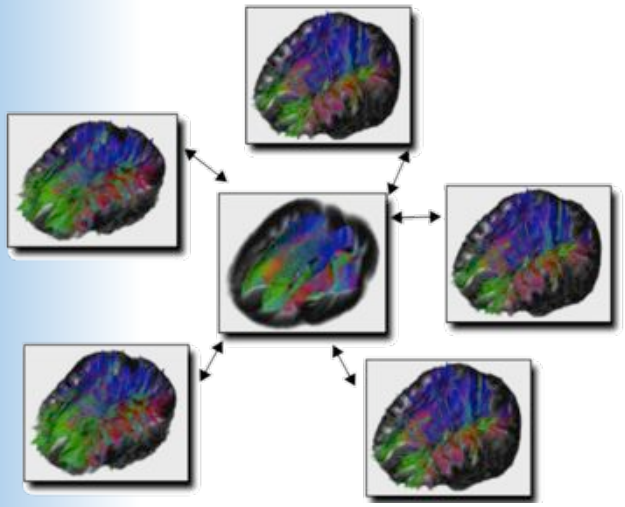
- General:
  - Atlases
  - Parcellation of striatum, thalamus
  - Segmentation of MS lesions
- Neoplasm, preoperative planning
- Demyelinating and neurodegenerative diseases
- Normal brain development and aging
- Congenital anomalies and diseases of white matter
- Traumatic brain injury
- Ischemia and stroke
- Epilepsy
- Dementia, schizophrenia, depression, autism

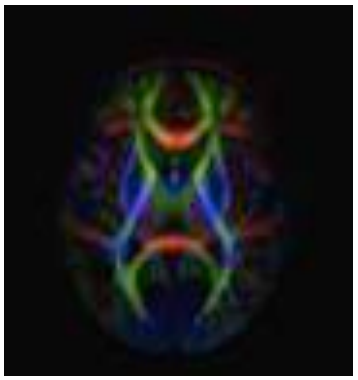
DTI is Translational



DTI Population Atlases

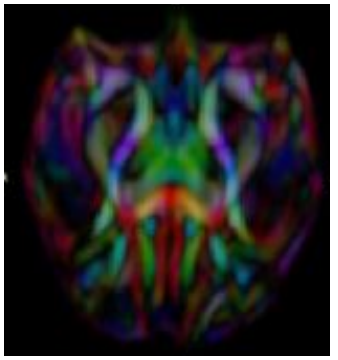
- Definition of standard space
- SNR increase
- Better tractography



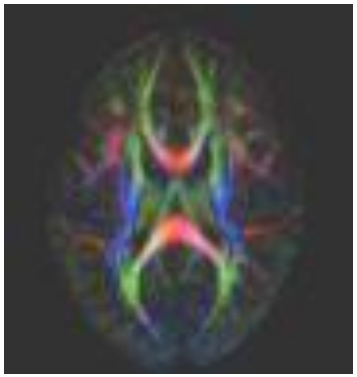


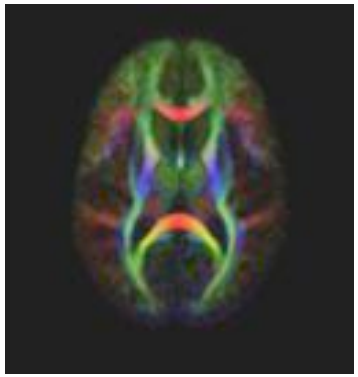
Neonate

1 year



Rhesus (15mo)

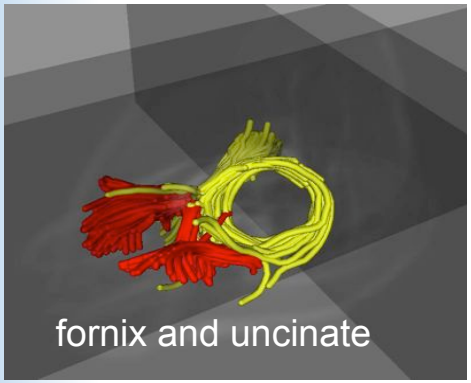


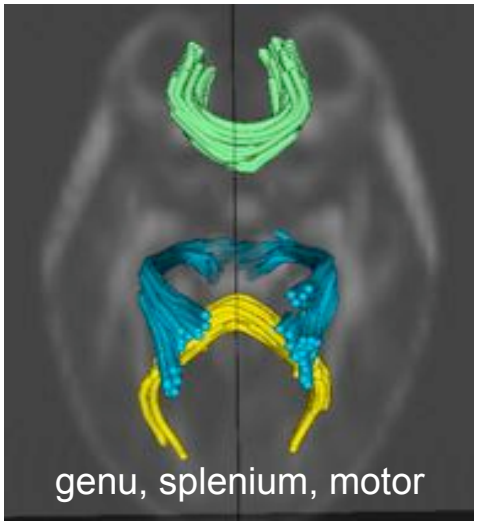


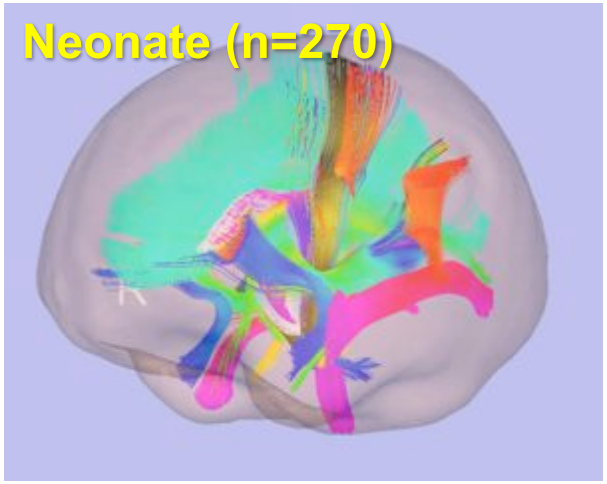
2 year

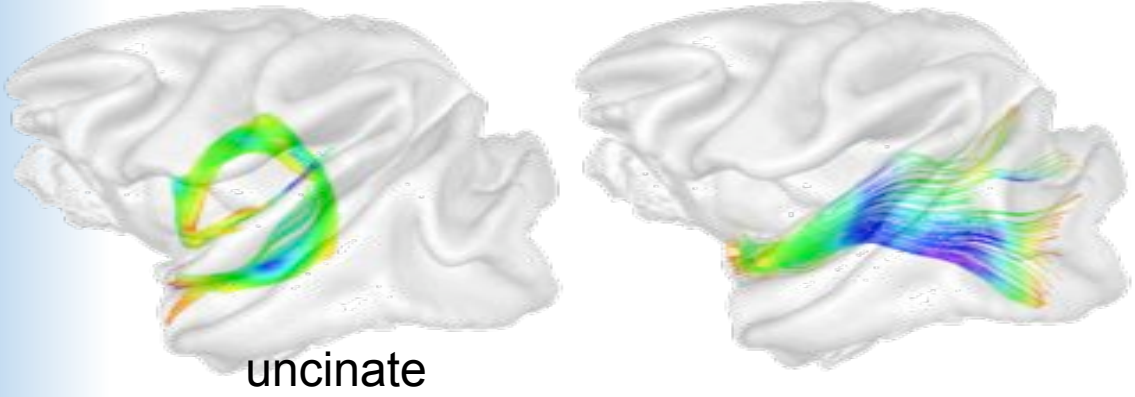
Adult

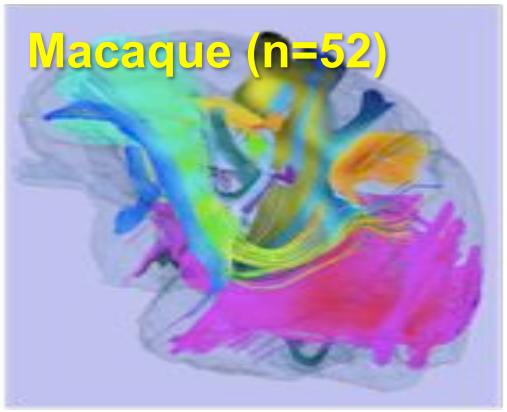
Fiber tracts in Atlas





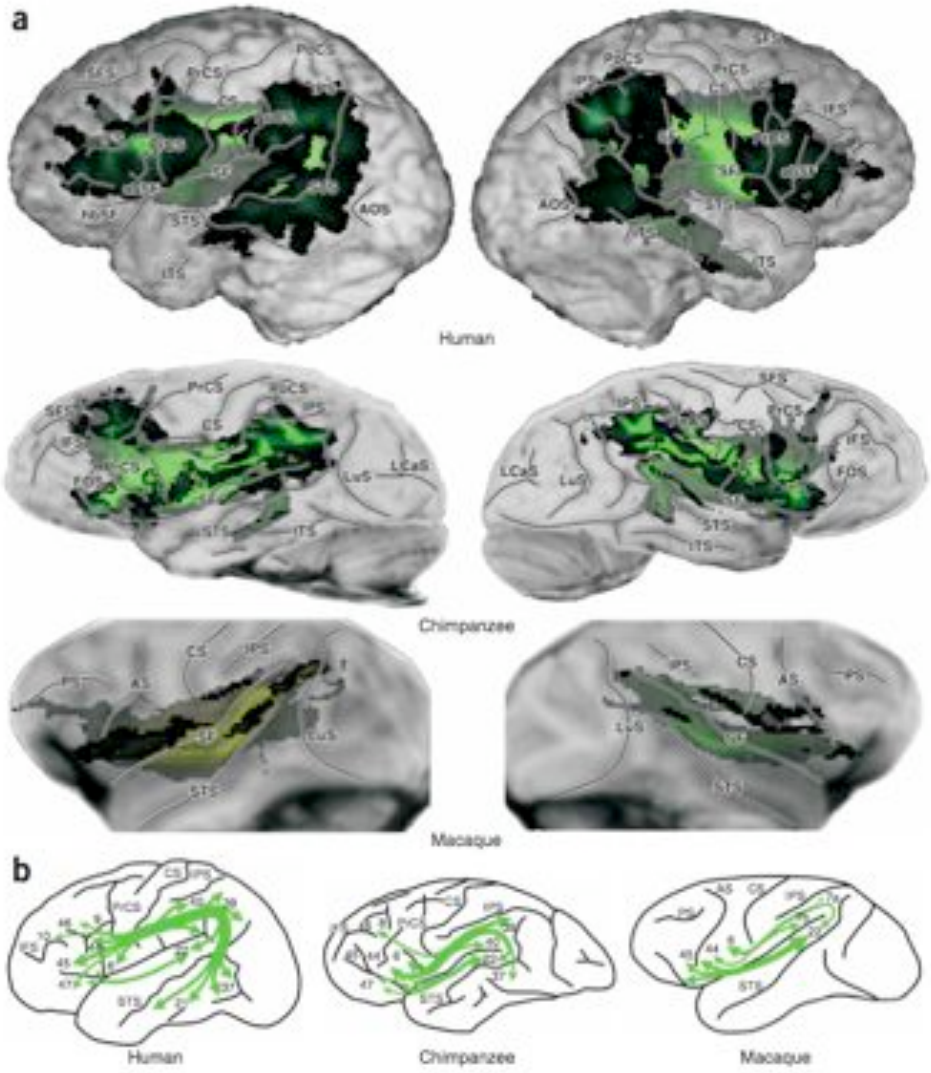




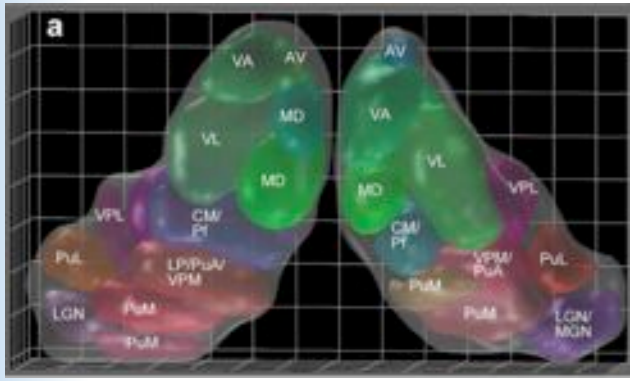


Brain Evolution

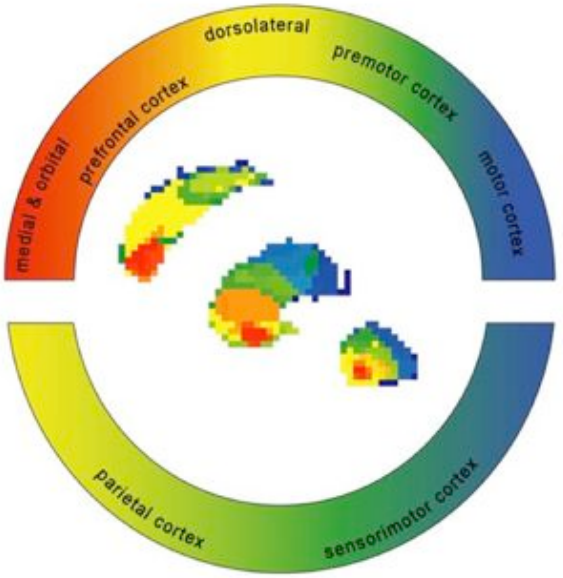
- Arcuate fasciculus, associated with language/ expression
  - Temporal lobe projection absent/smaller in non-human primates
- Rilling, 2008 Nature Neuroscience
- Probabilistic tractography



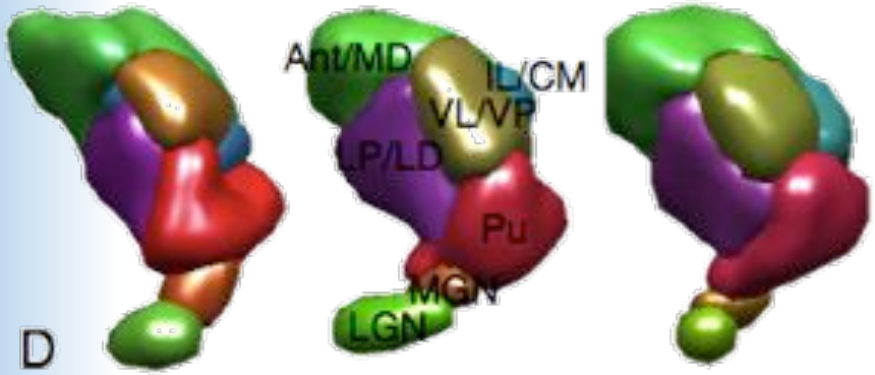
DTI based Segmentation



Tuch 2003



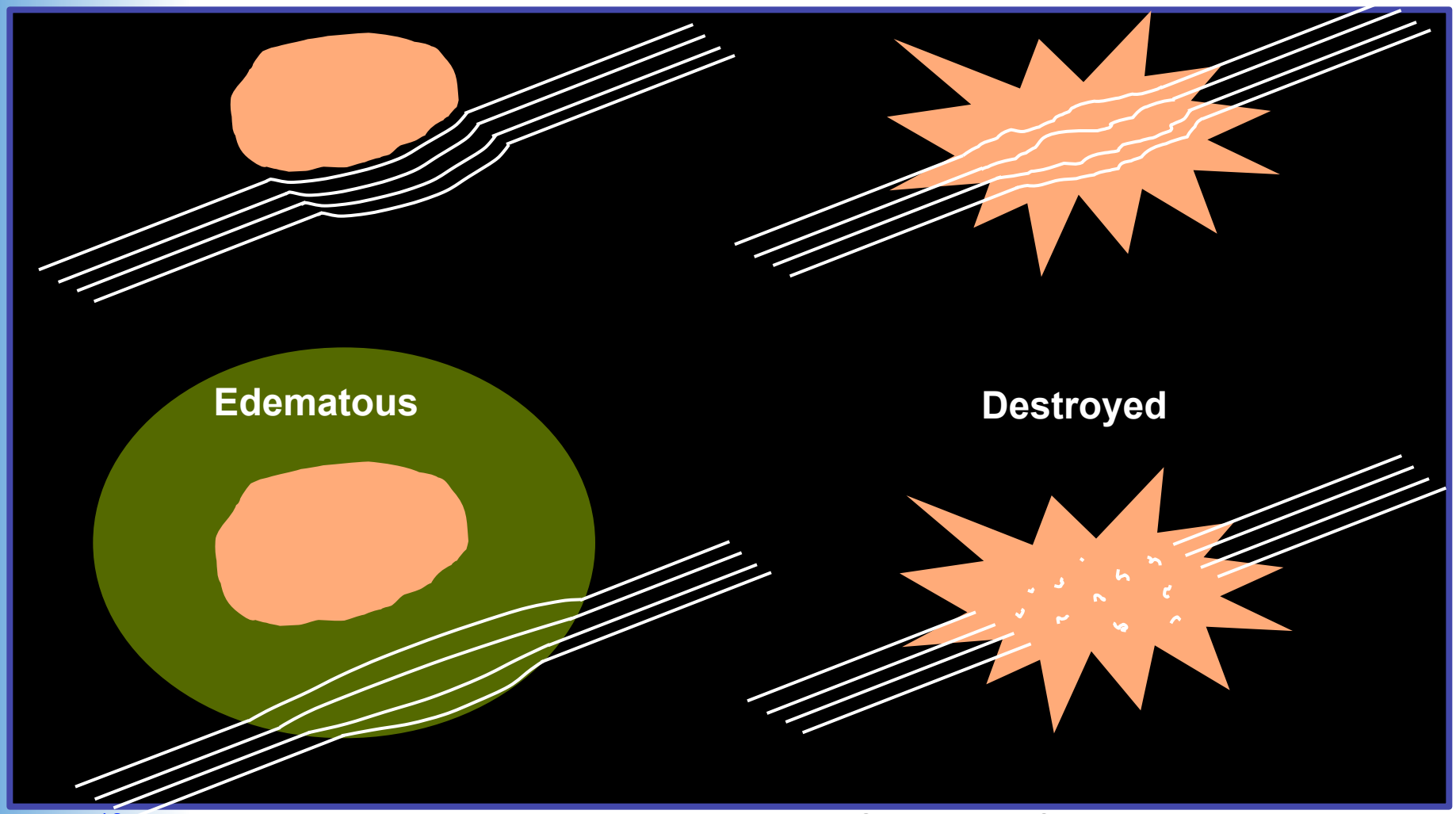
DTI based clustering of thalamus



Striatal subdivision
Via cortical connectivity
Draganski, 08 J Neuroscience

Ziyan and Westin, MICCAI 08

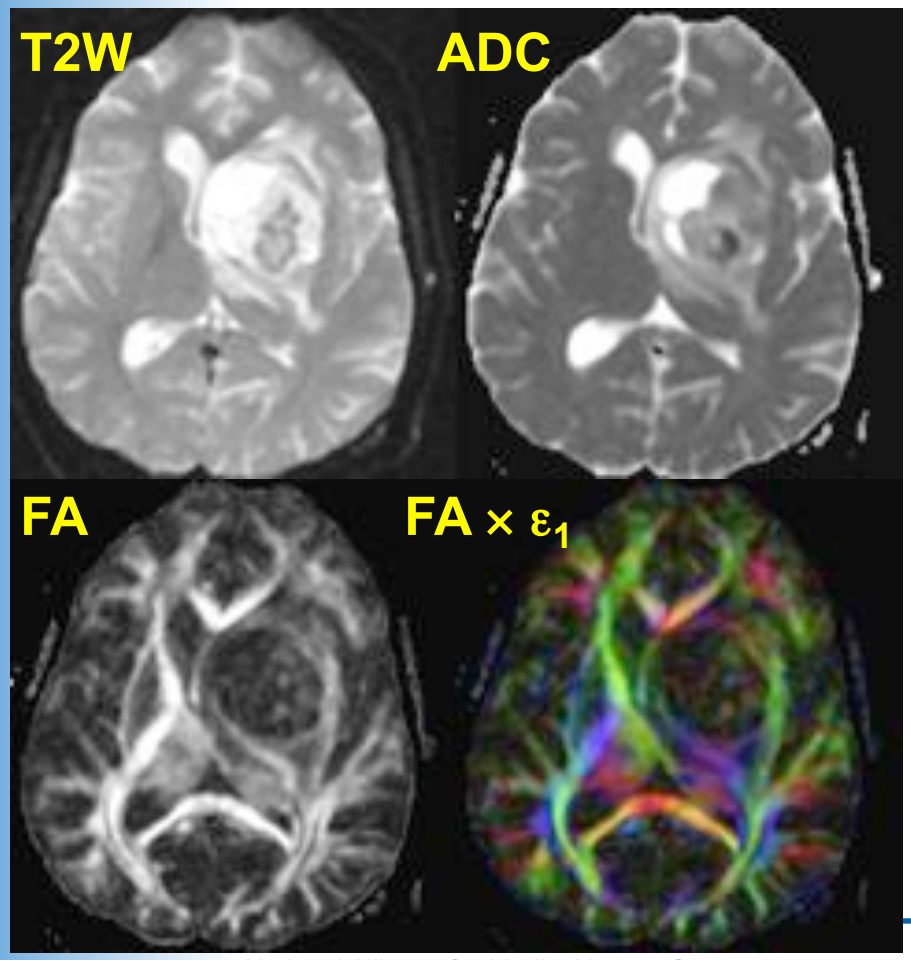
DTI: Cerebral Neoplasms



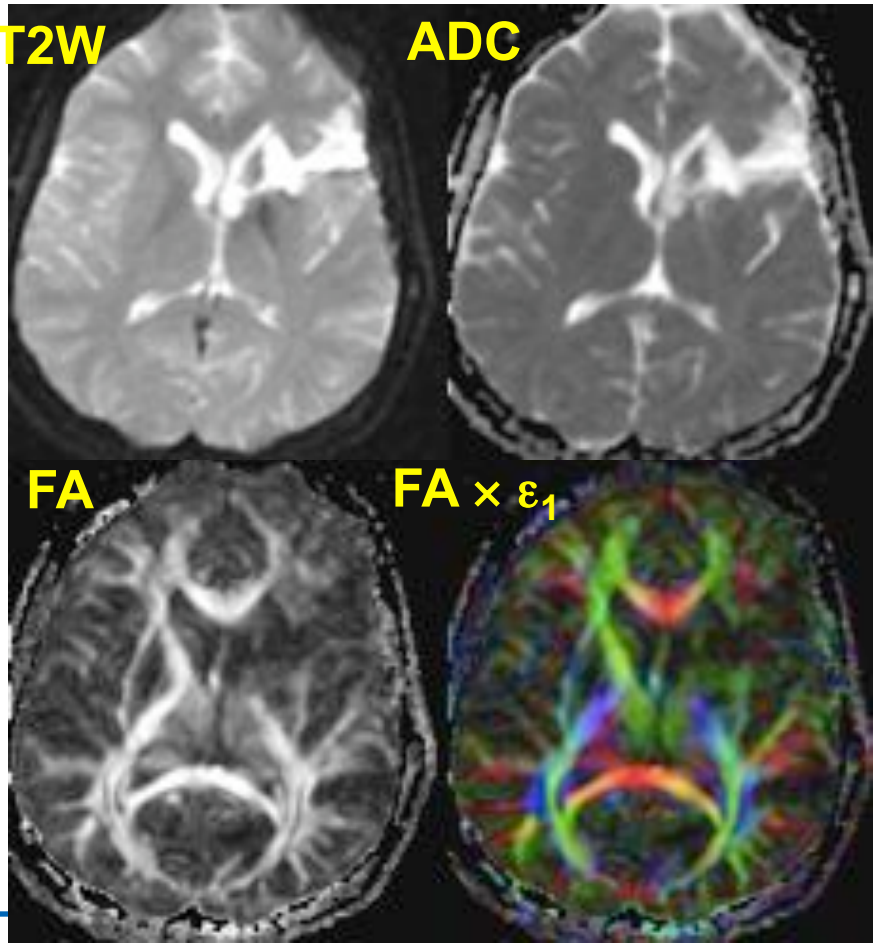
Courtesy of AL Alexander

Pilocytic Astrocytoma

Preop

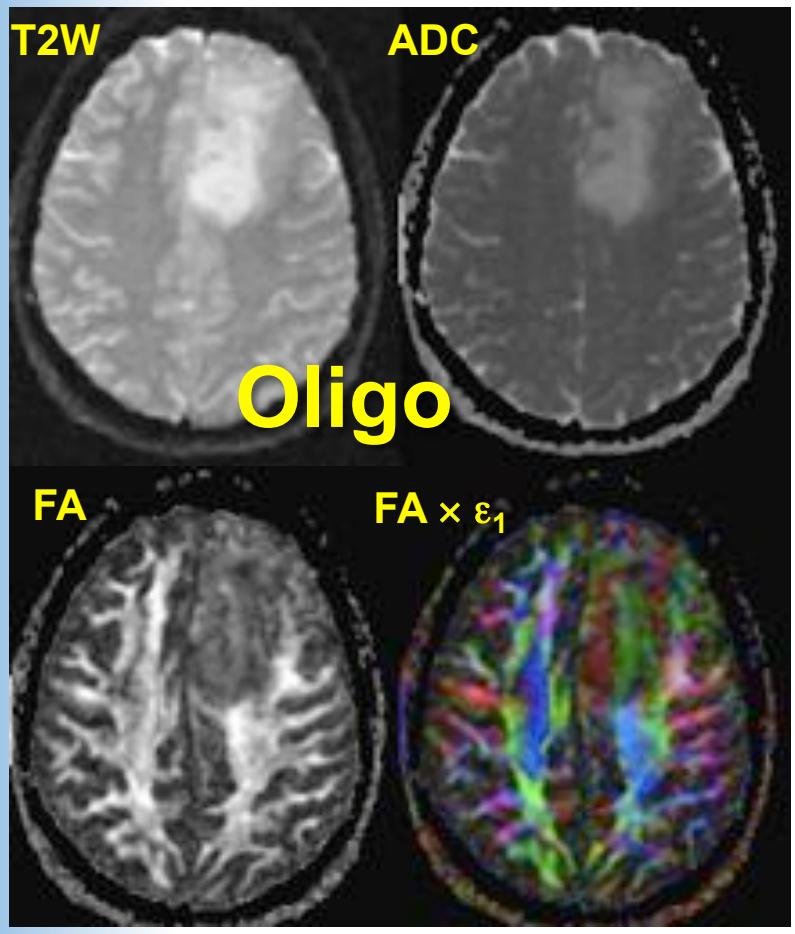


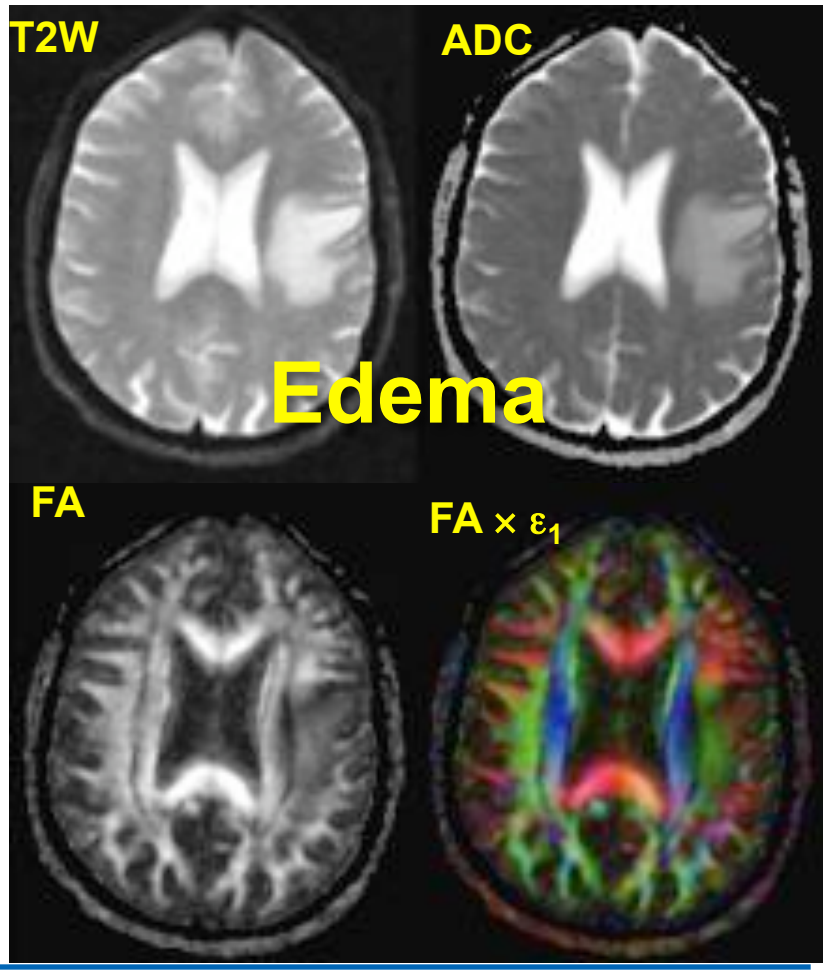
Postop



Courtesy of AL Alexander

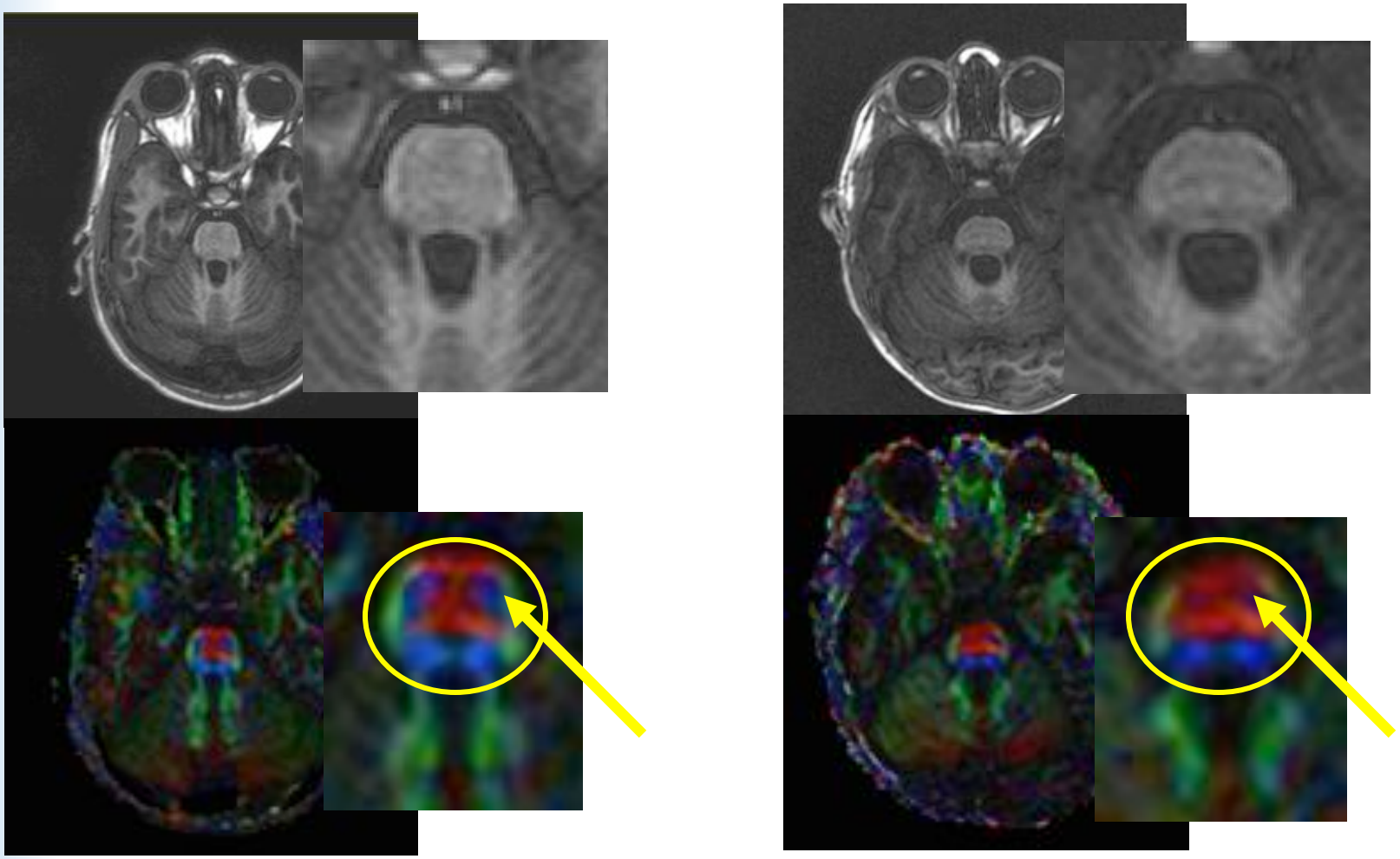
Tract Infiltration





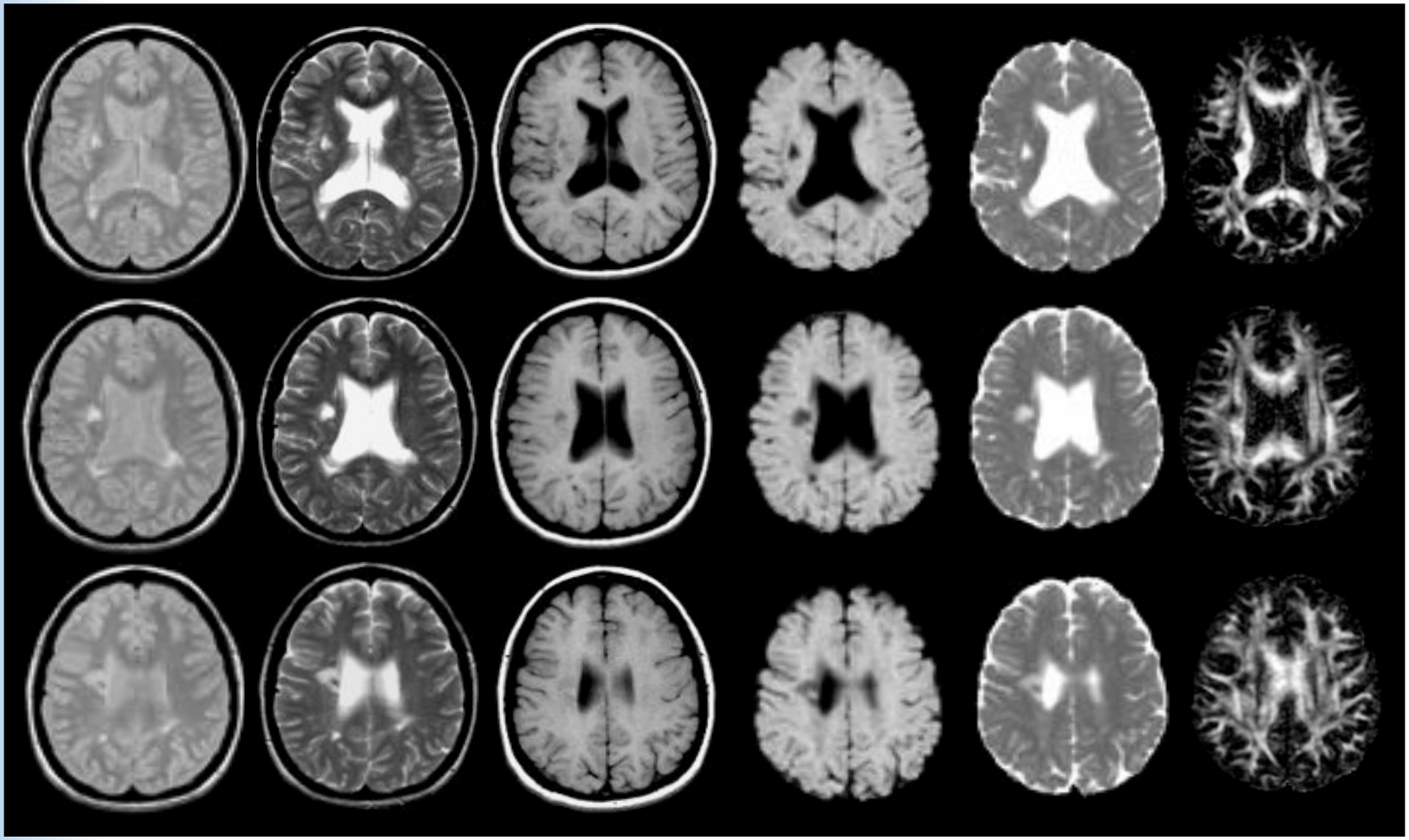
Courtesy of AL Alexander

Cerebral Palsy

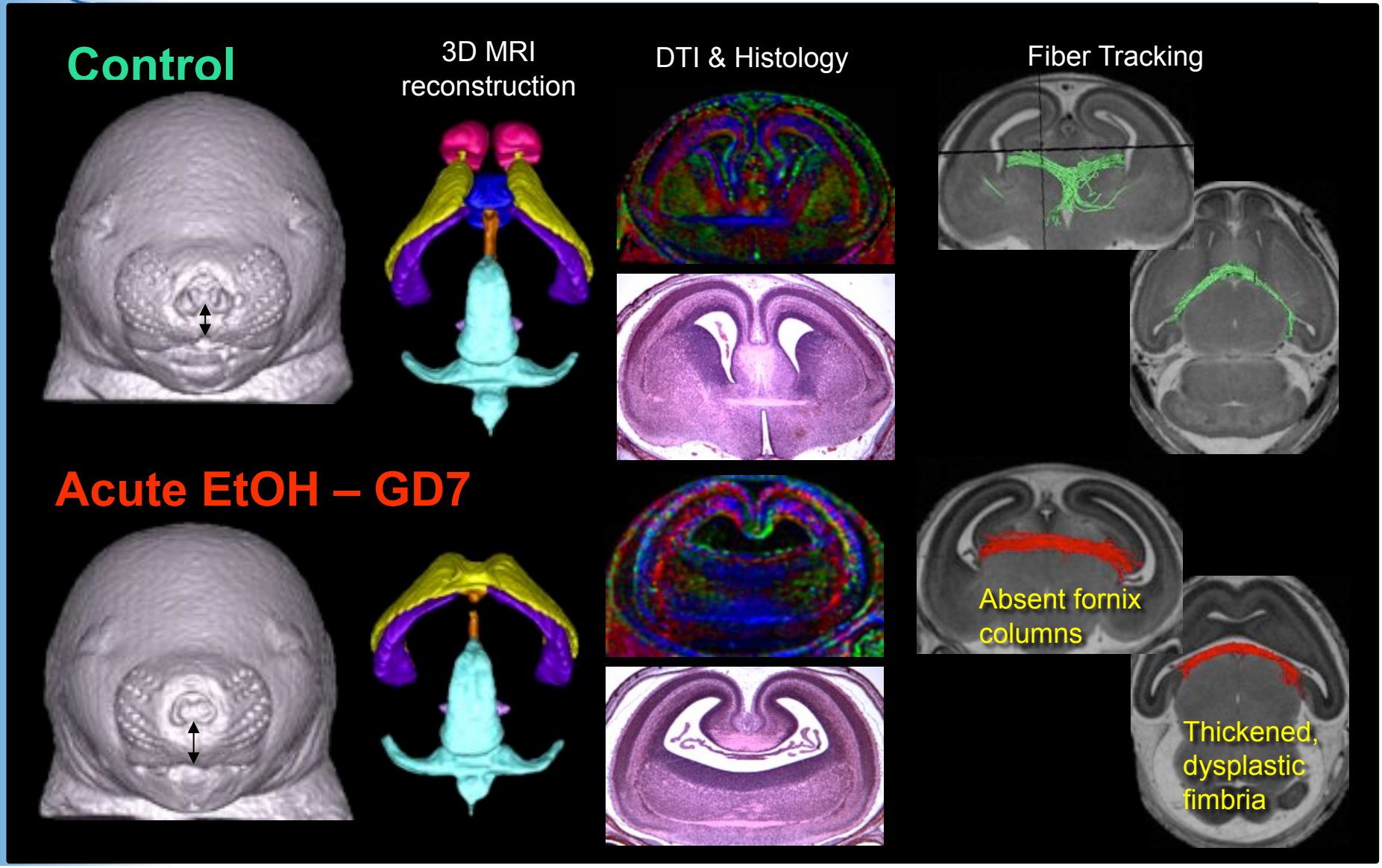


Courtesy of Susumu Mori

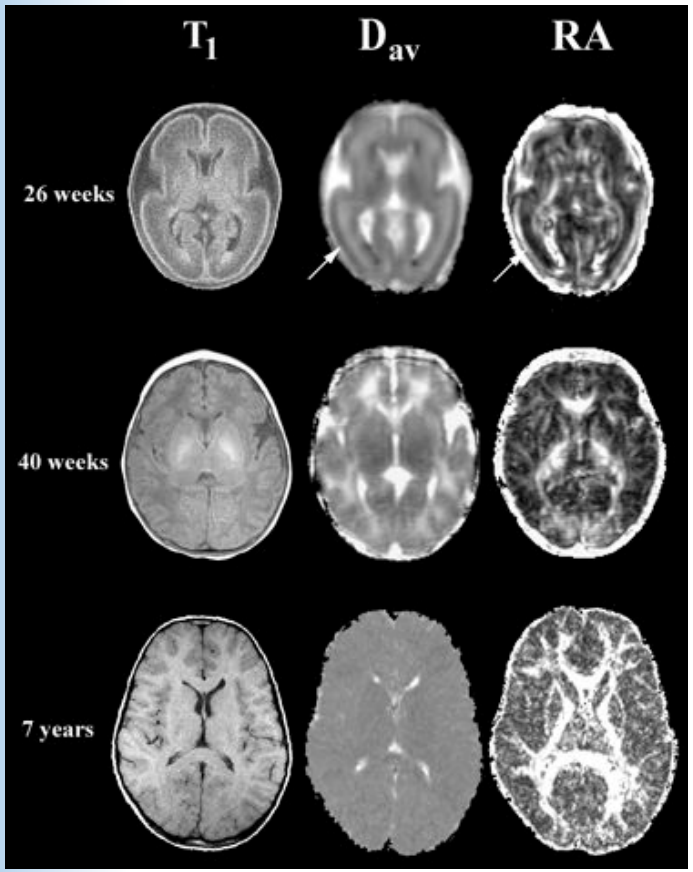
Multiple Sclerosis



Fetal Alcohol Syndrome

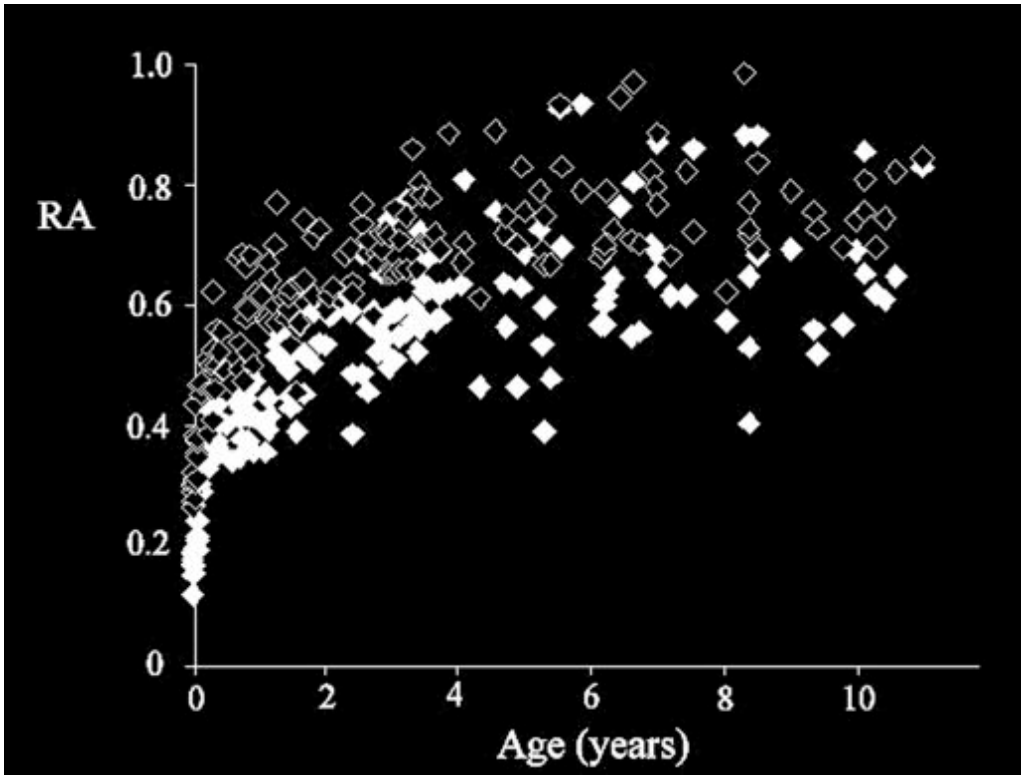


Normal Brain Development



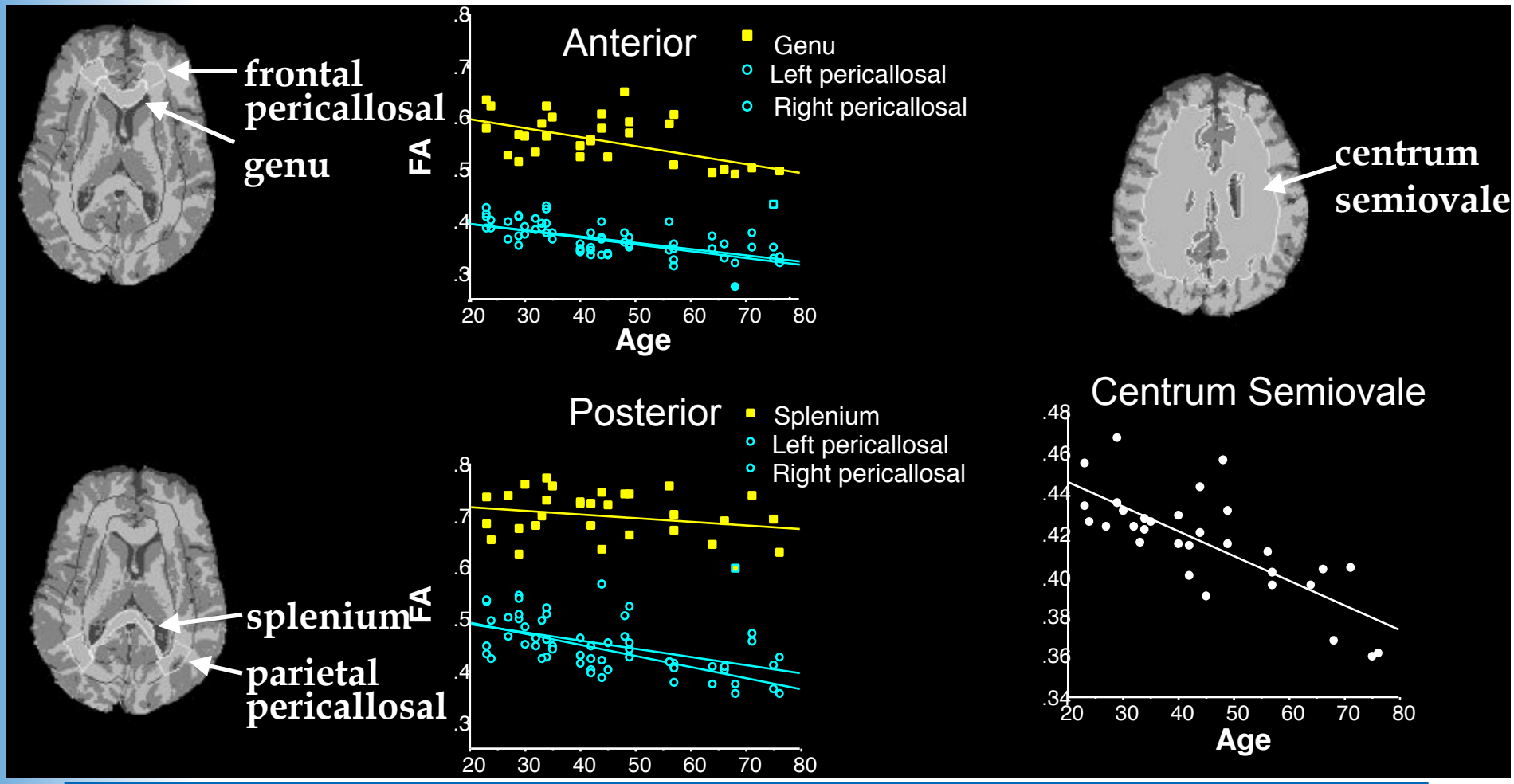
Courtesy P Hueppi
Univ Geneva

$$RA = \frac{\sqrt{(\lambda_1 - \langle D \rangle)^2 + (\lambda_2 - \langle D \rangle)^2 + (\lambda_3 - \langle D \rangle)^2}}{\sqrt{3}\langle D \rangle}$$



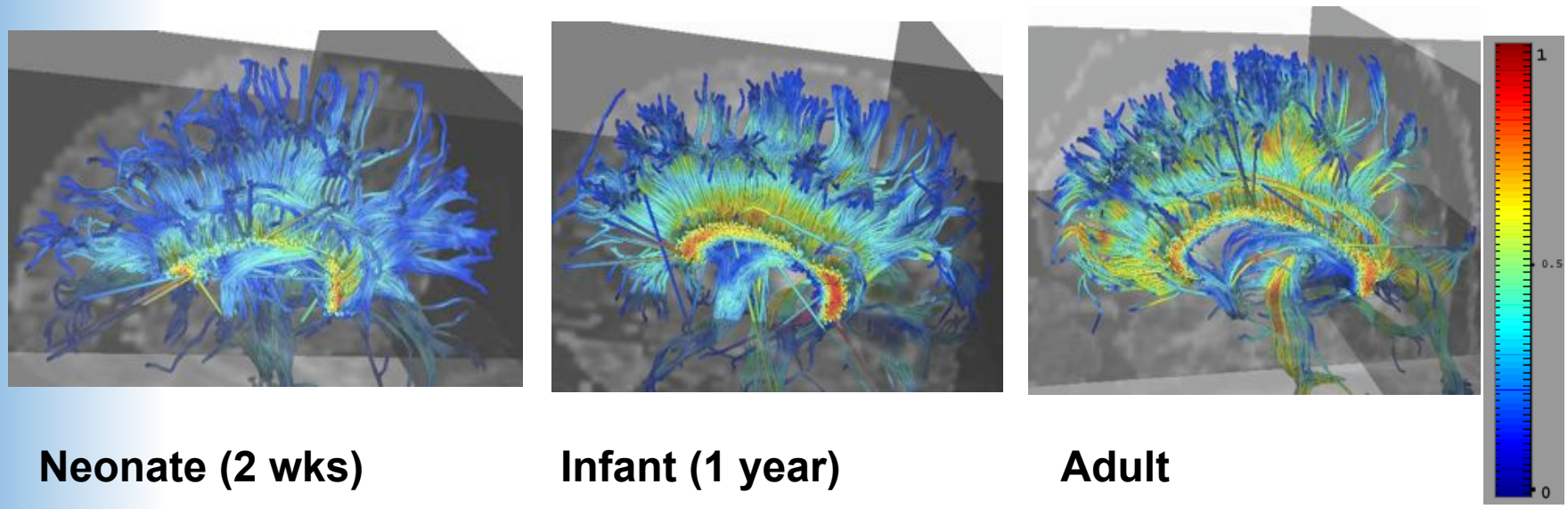
Courtesy J. Neil
Washington Univ., St. Louis

WM Anisotropy Changes with Age



Courtesy K. Lim, Univ. Minn.

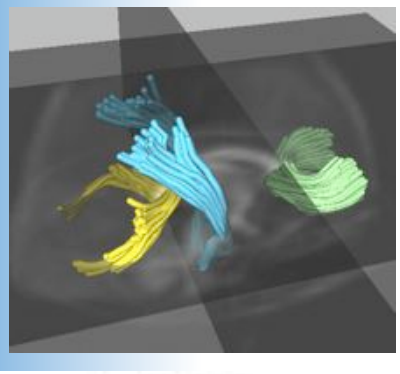
Corpus Callosum Tracts: Study of Early Development

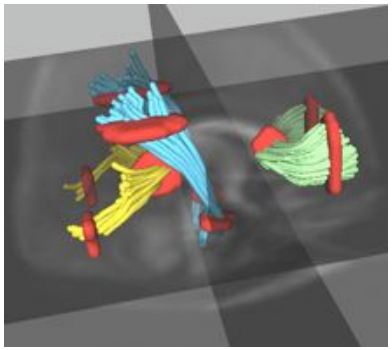


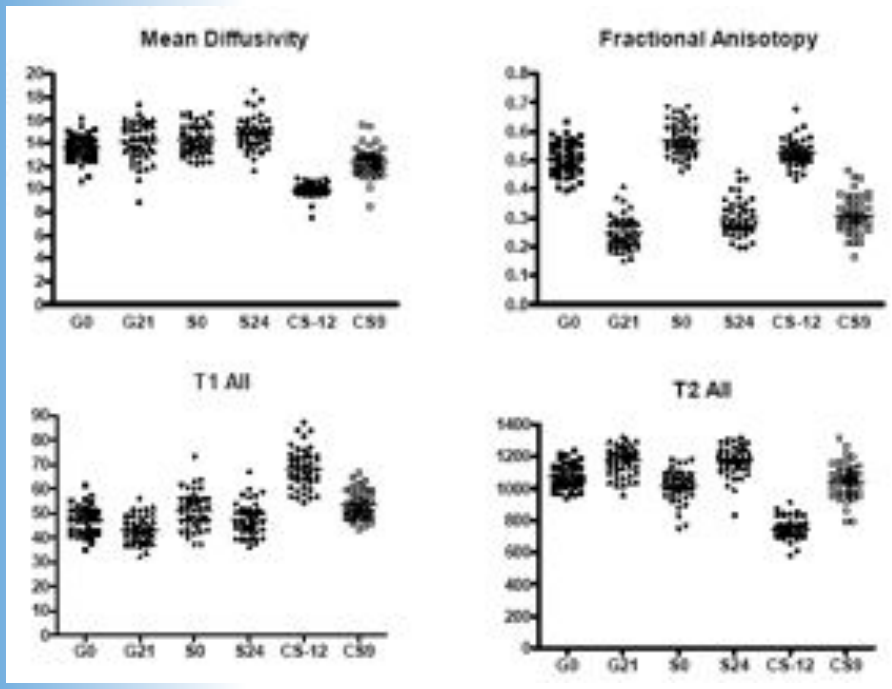
Neonate (2 wks) **Infant (1 year)** **Adult**

Corpus callosum: Commissural bundles, color coding of FA (0=blue, 1=red)

Early postnatal development of white matter on neonates







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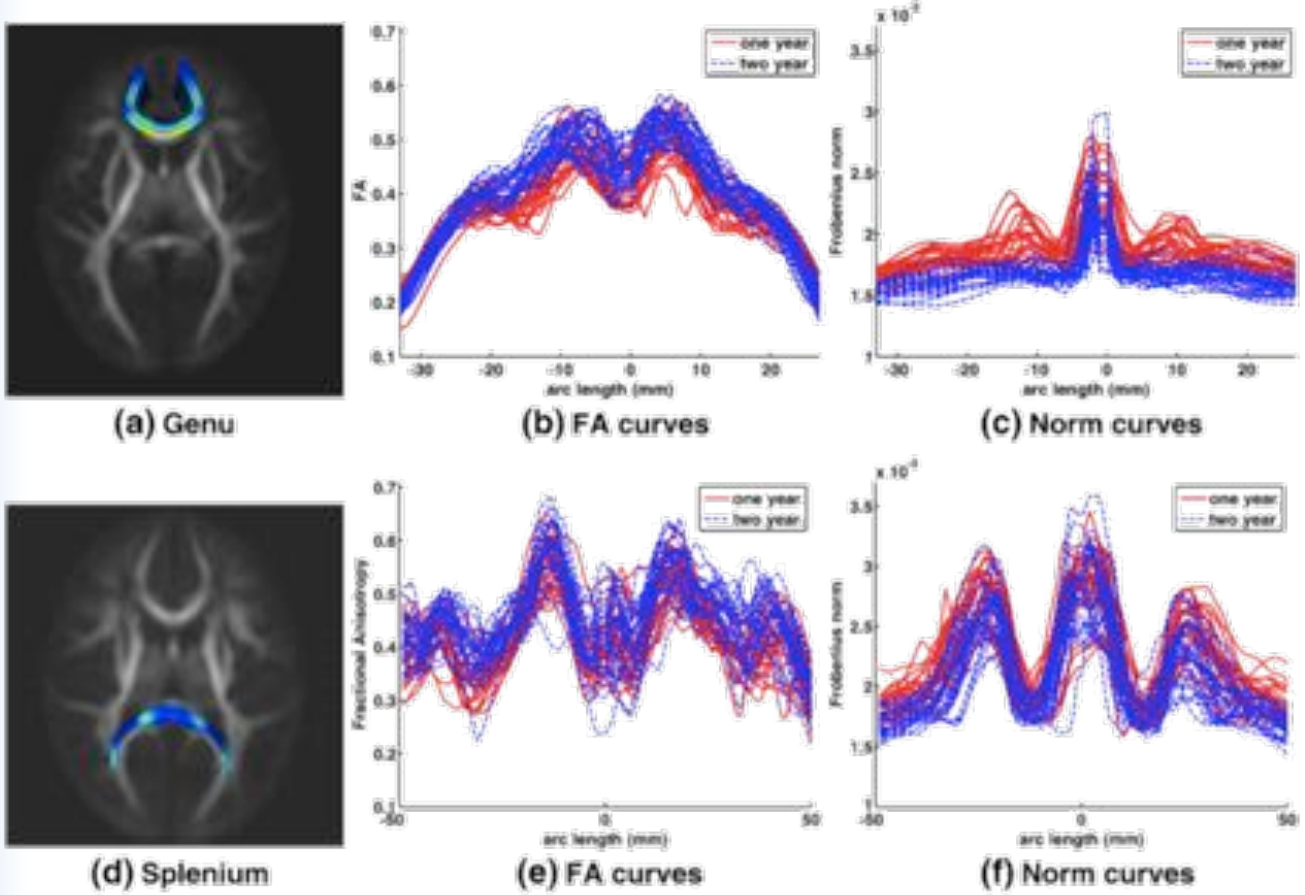
Analysis of white matter in healthy controls (N=47)

Myelination and axon elimination:

- FA center >> peripheral
- FA splenium > genu
- MD splenium & genu > intcaps
- T1w splenium & genu < intcaps

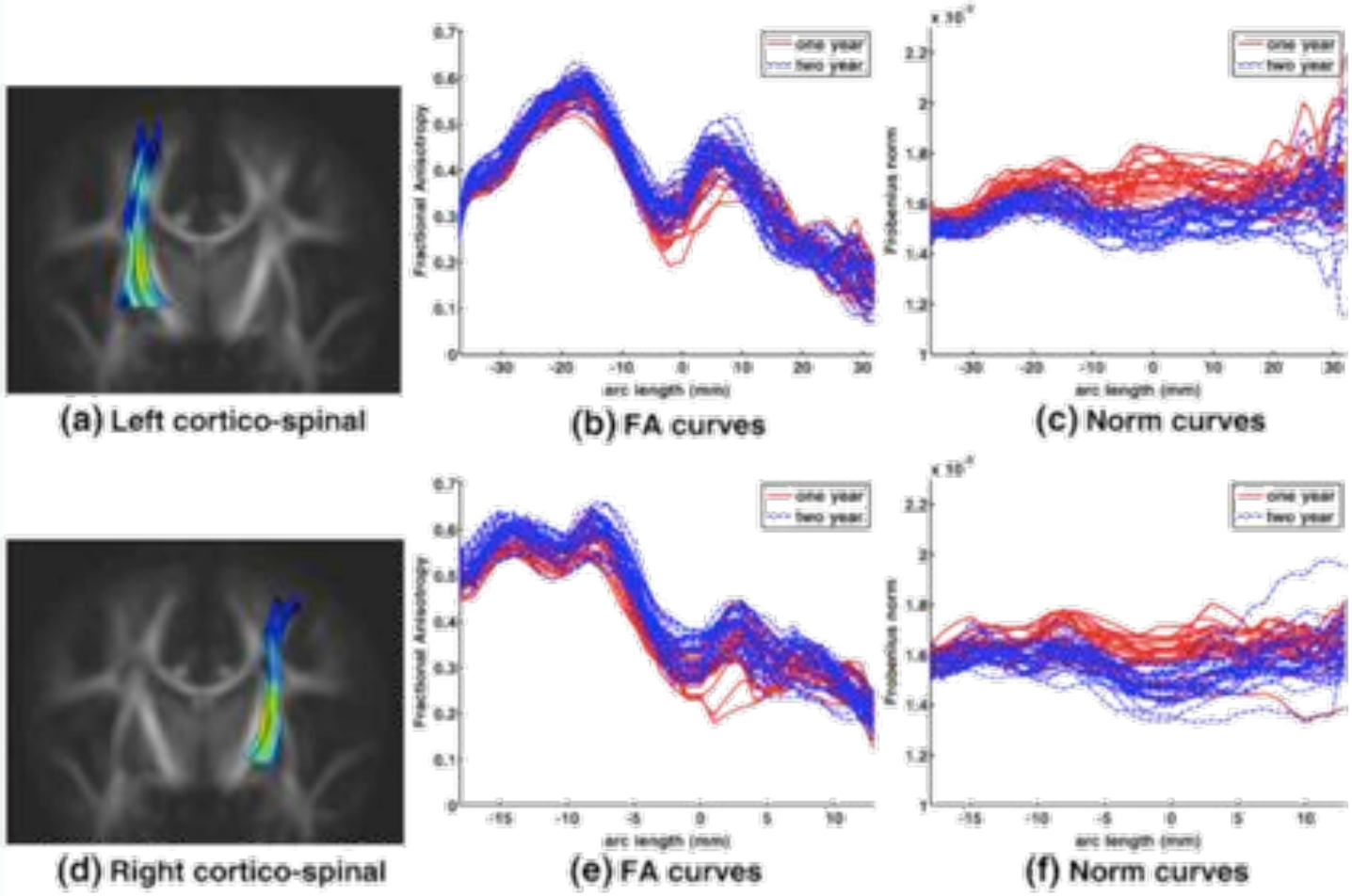
Gilmore 2007 AJNR

1-2 year old: CC Tracts



Goodlett 2009 NeuroImage

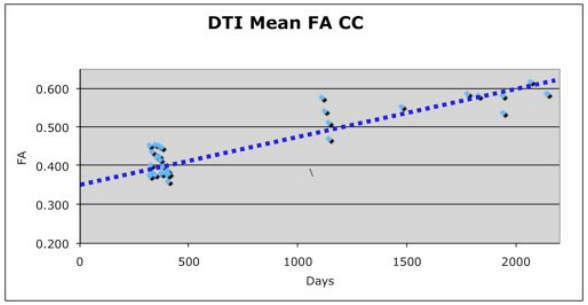
Left Motor Tract

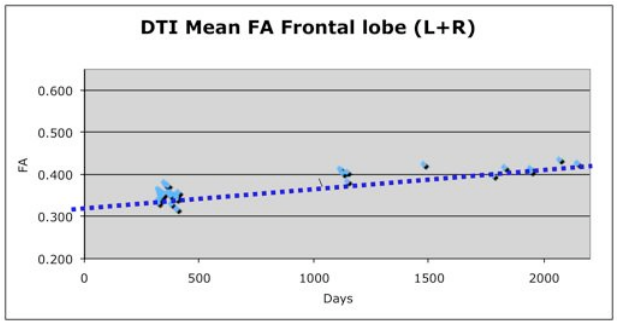


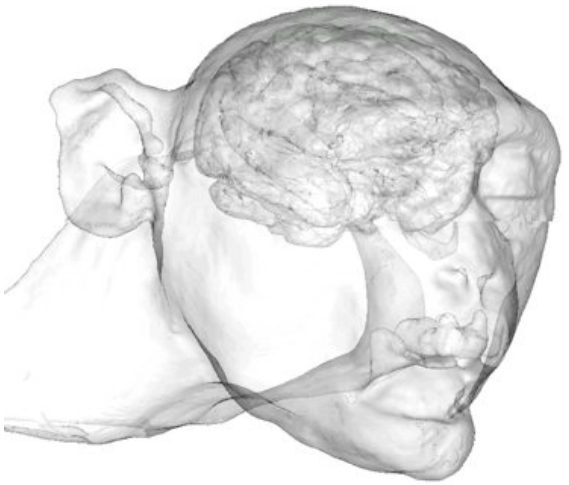
Goodlett 2009 NeuroImage

Monkey Brain Studies

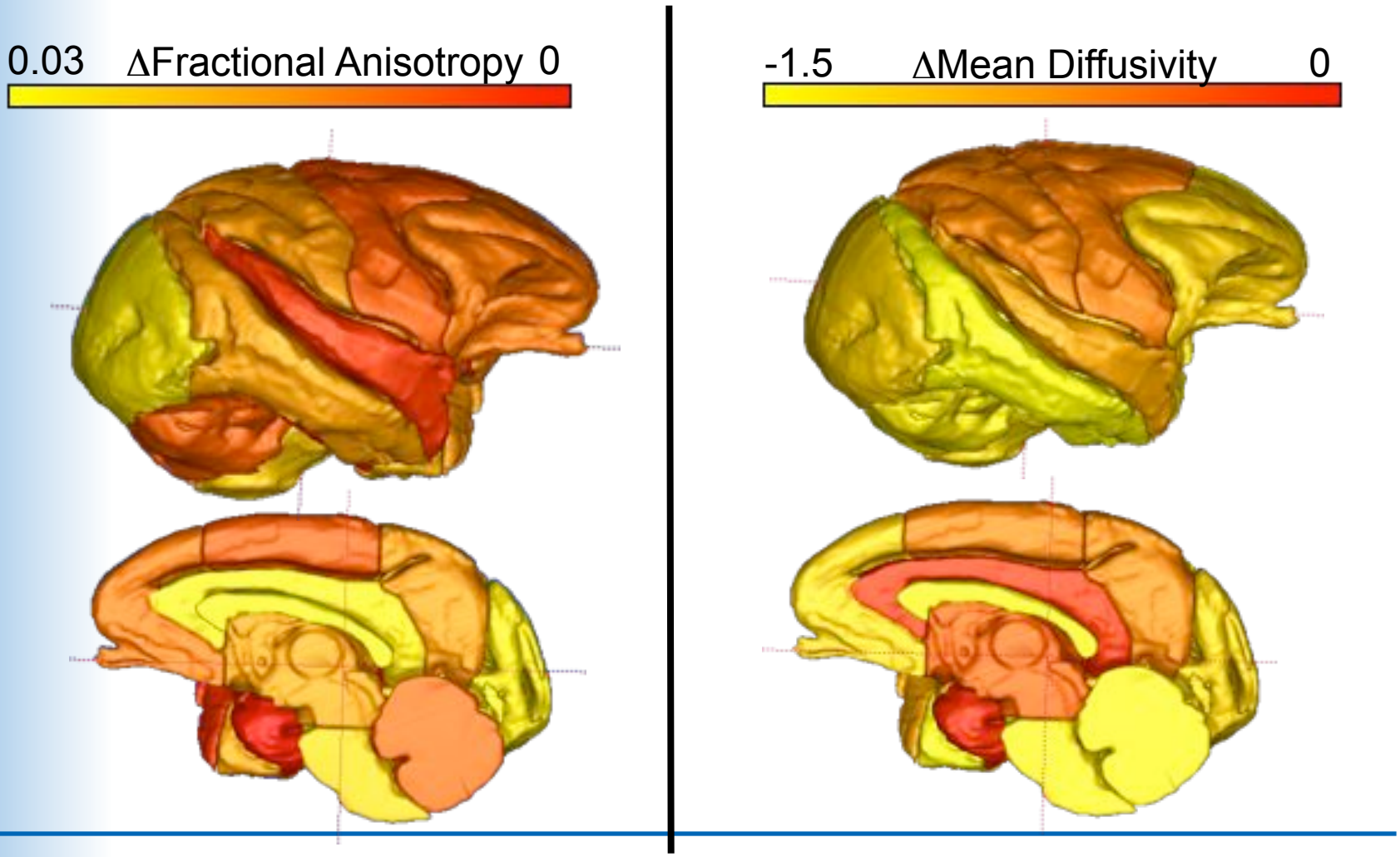
- Harlow Primate Lab @ UWisc / Yerkes @ Emory
- Studies: Intrauterine exposure (Flu, LPS), abuse
- Understanding brain development & environment
- Regression with age



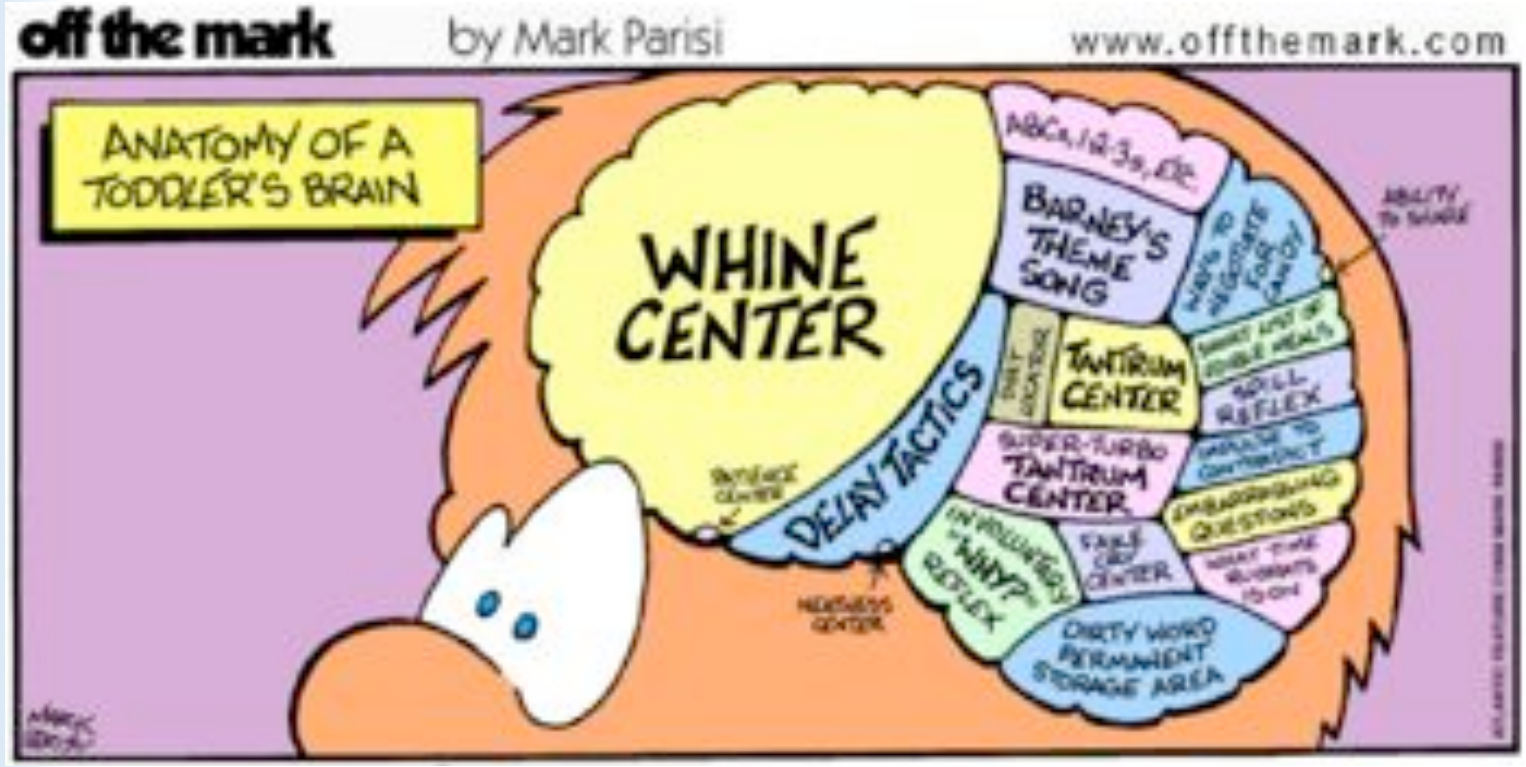




DTI Comparison ΔFA vs ΔMD
Y 1 – Y5



How the brain of a toddler really looks like …



Krabbe Leukodystrophy

- Rare, lethal genetic leukodystrophy
  - Autosomal recessive pattern (not X-linked)
  - Worldwide: 1 in 80,000 births.
  - Isolated communities: 6 per 1,000 births
- Deficiency in galactosylceramidase enzyme
  - **Buildup of undigested fats affects myelin sheath**
  - Imperfect growth and development of myelin
  - Severe degeneration of mental and motor skills
- Lorenzo's Oil featured similar leukodystrophy
- Normal at birth, symptoms usually start 2-6 mts
- Fever, uncontrollable crying, seizures, vomiting, spasticity, paralysis, blind, finally death within 2y
- Juvenile- and adult-onset cases rare

NATIONAL INSTITUTES OF HEALTH
THE DANA FOUNDATION

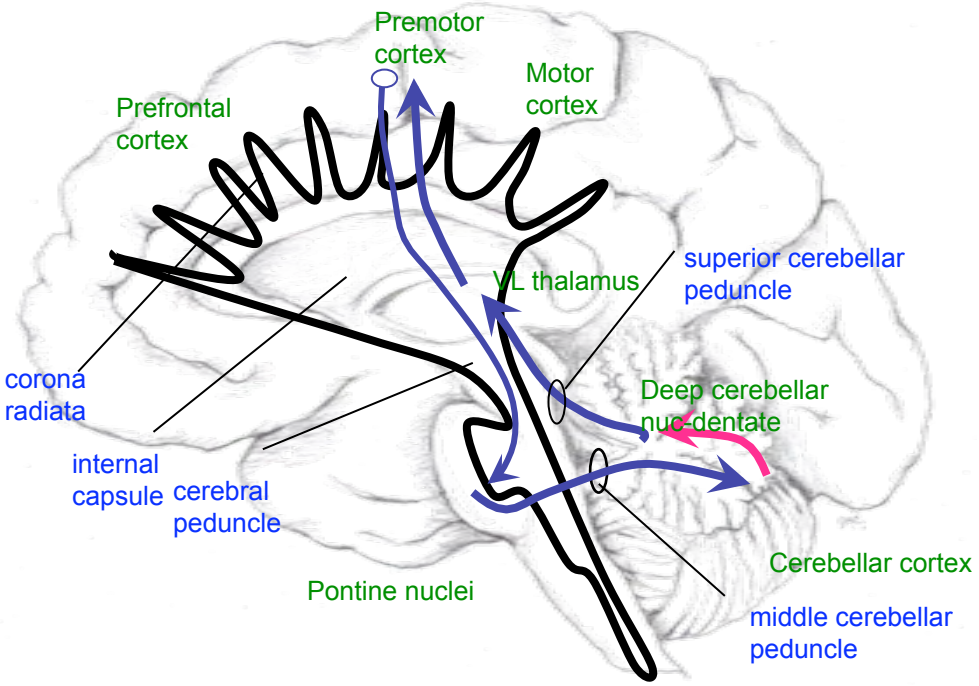
Diffusion Tensor Imaging Detects Abnormalities in the Corticospinal Tracts of Neonates with Infantile Krabbe Disease

Escolar 2009 AJNR

Krabbe: Treatment

- Therapy (Maria Escolar, UNC), Therapy @ Duke
  - Myeloablative chemotherapy followed by stem cell transplantation from umbilical-cord blood
  - Treatment at Birth, no effect at symptomatic stage
  - Treated kids show differences in motor abilities
  - Survival rate depends on survival of therapy (15 of 17 ~ 88%)
- New Krabbe's screening with enzyme test
  - New York started August 2006
  - Parents often wait
- DTI: Assessing damage at birth via DTI
  - Illustration of damage to parents? Diagnosis?
  - Prediction of developmental outcome for motor abilities
- Here: Prelim data of project

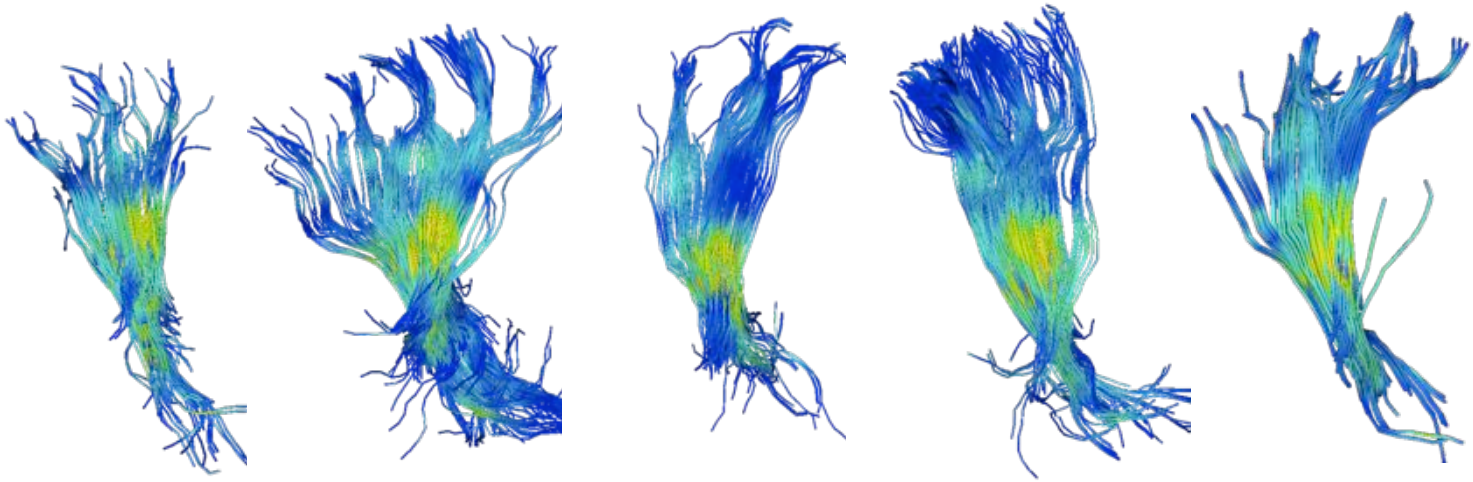
Motor Related Fibertracts



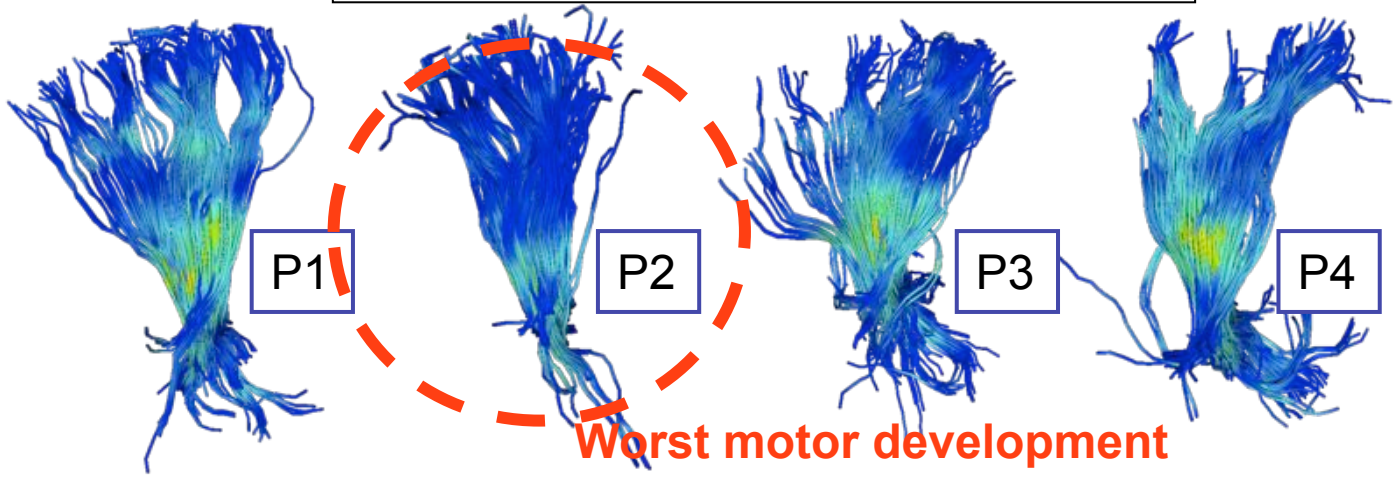
Courtesy of Jim Fallon

- Left and right hemispheric Cortico-spinal tracts

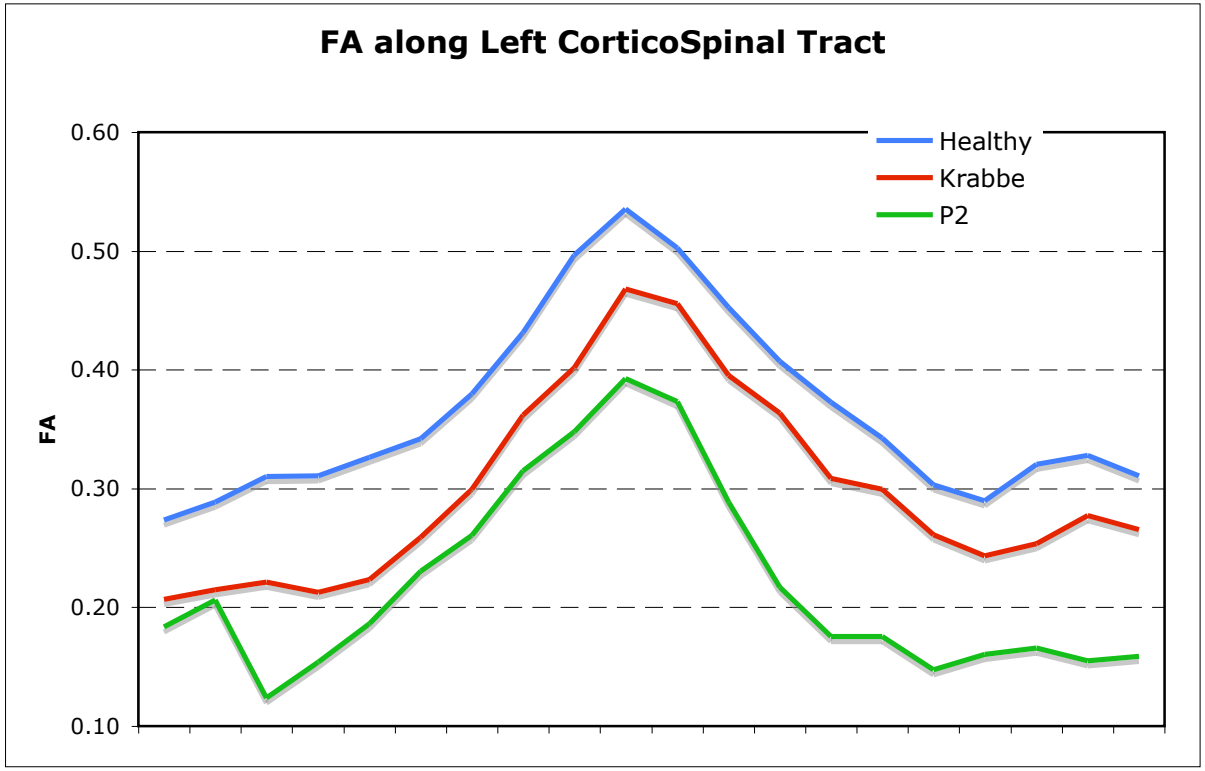
Controls - Left Internal Capsule Tracts



Krabbe's - Left Internal Capsule Tracts

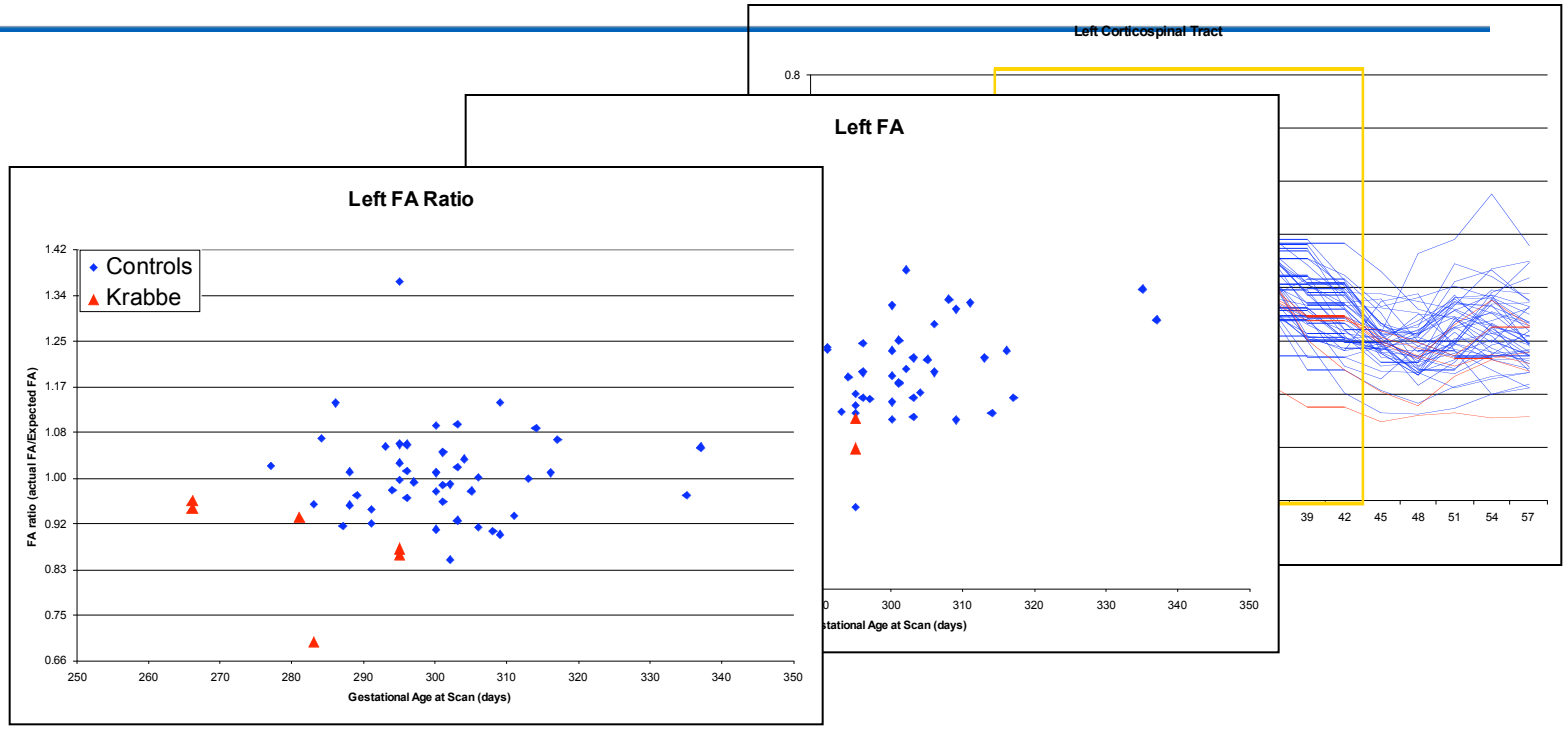


FA Statistics along Fibers



Statistics over 6 Krabbe, 53 Healthy neonate babies

FA Stats Center Region



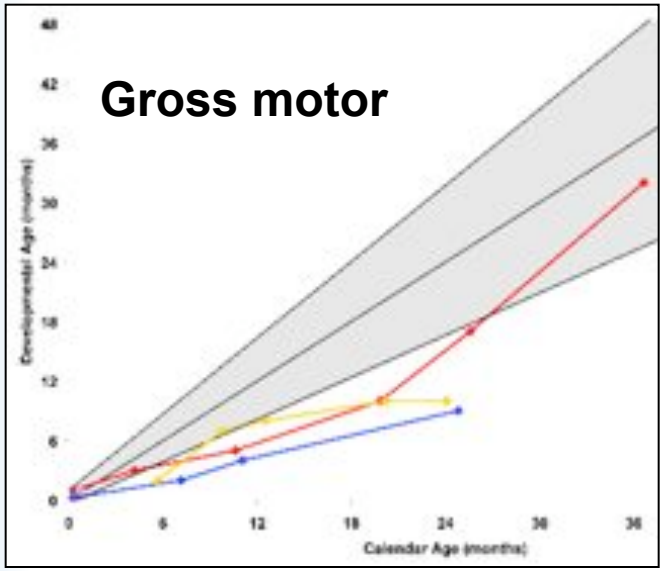
- Center region selection => Mean FA computation
- FA ratio = FA divided by expected FA given gestational age at birth, at scan, birth weight, gender

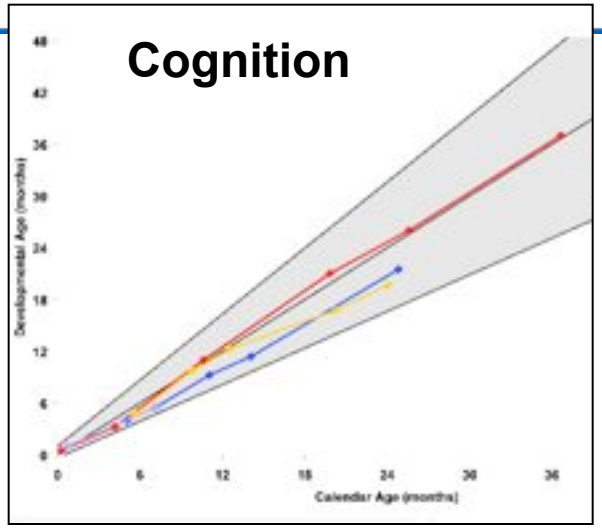
Outcome Correlation

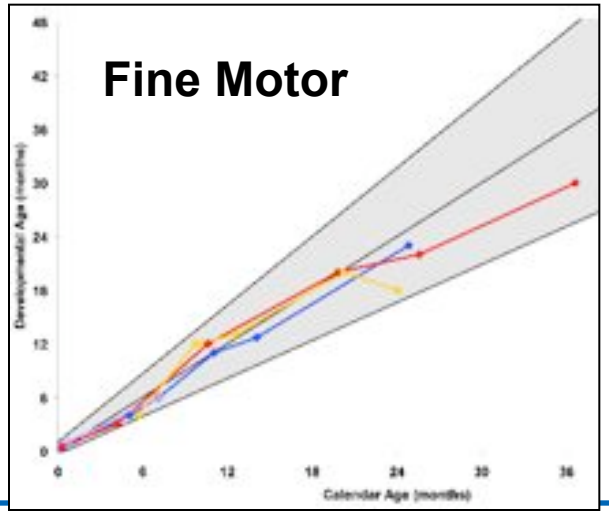
FA Ratio at Baseline

0.70 0.91

0.89 0.84







Conclusion Krabbe

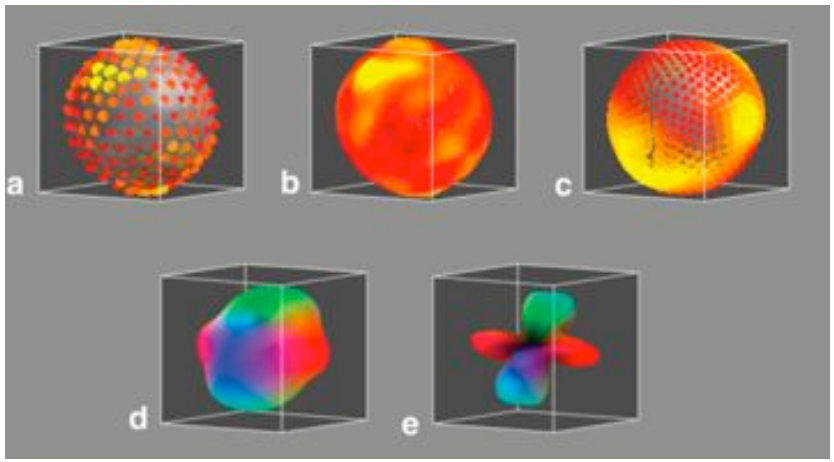
- Correlation of DTI with outcome after treatment
- Current investigation:
  - Natural history of development with DTI
  - Can DTI predict, when symptoms will arise if untreated?

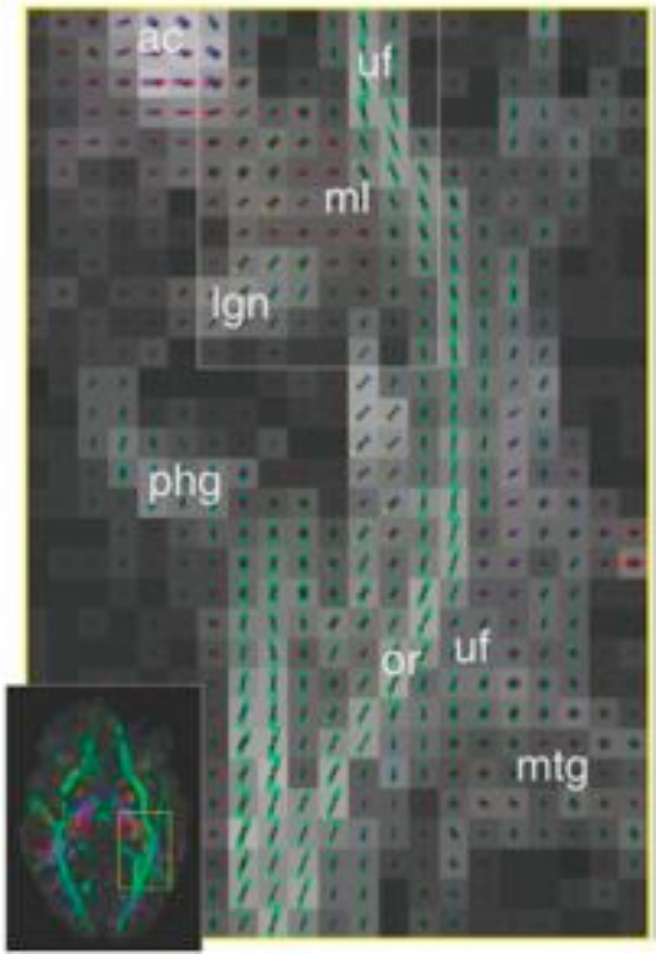
Future of DTI

- Highly valuable MR based modality
  - Many applications
  - Considerable validation (though more is needed)
- What's next?
  - Higher order of diffusion representation
  - Improved tractography algorithms
  - Network analyses
  - Need for automatic, blackbox processing

Higher Order Diffusion Representations

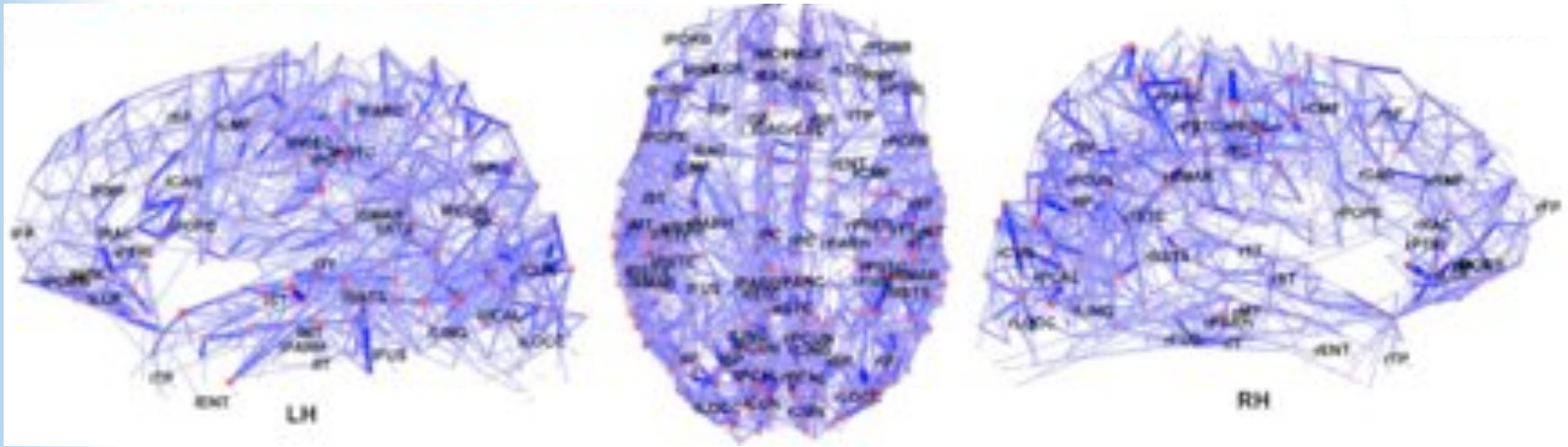
- Active field of research since 2003
  - Qball, Tuch
  - DSI, Van Wedeen
- No real clinical tools yet
  - Next evolutionary stage for DTI?





Network Analyses

- Structural network using diffusion spectral imaging
- Combination with functional imaging (resting state, event driven)
- Main issue: stability, clinical application
- Hagmann 2008 PLOS Biology



Blackbox Processing

- DTI property images (FA, MD, AD, RD) clinically useful
- But tractography application lag behind in clinical use
- Current processing is
  - Mostly interactive
  - Significant training in DTI necessary
- Need for automatic blackbox tools
  - No technical training needed
  - Adequate in presence of pathology
  - Includes analysis framework

The last slide

- We love DTI!
- And there are many reasons why, as shown in this talk…
- Thanks!