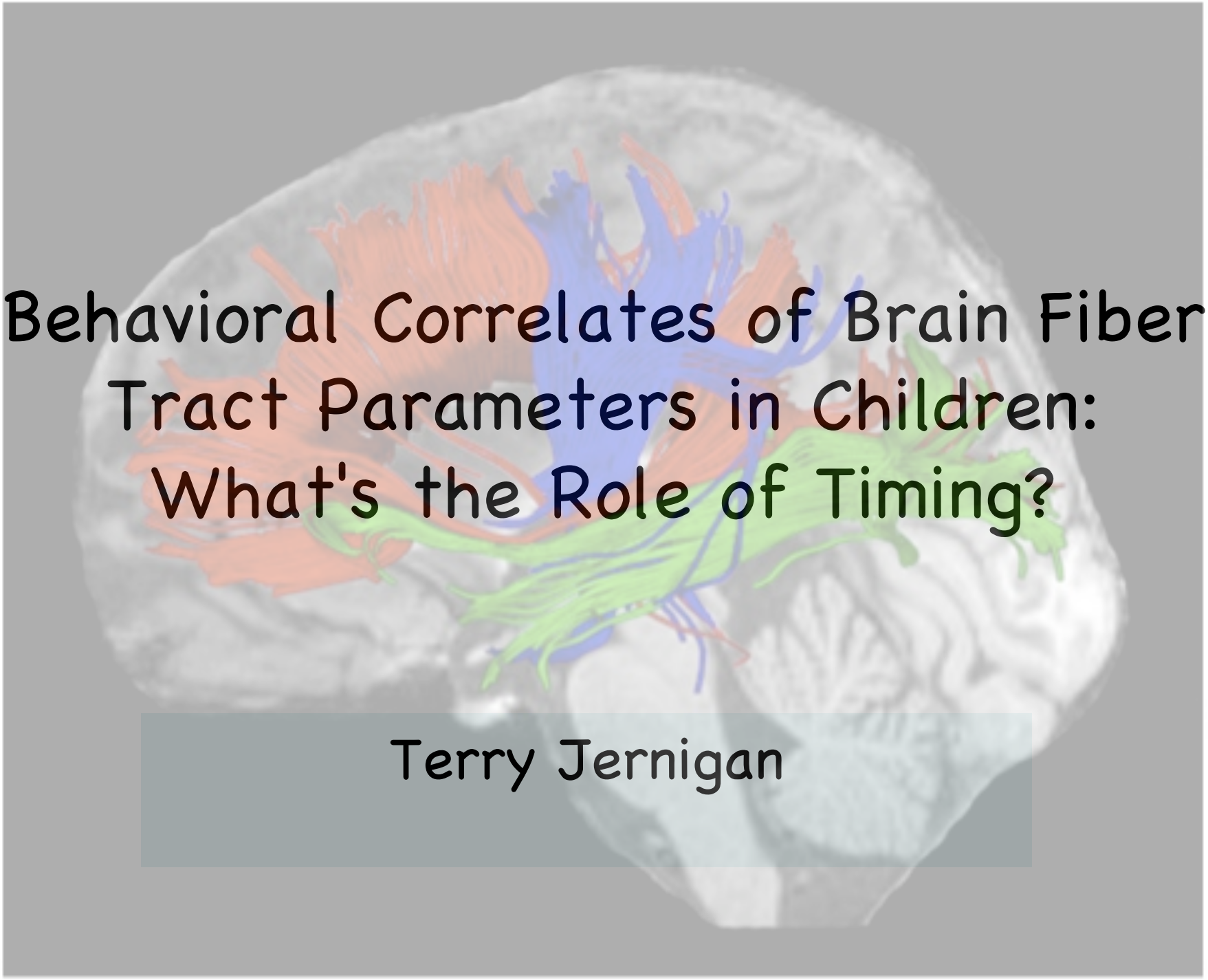


Behavioral Correlates of Brain Fiber Tract Parameters in Children: What's the Role of Timing?

Terry Jernigan

Old View of Human Brain Structure

- Although myelination of fibers occurs rapidly over the first few years of life...
- brain structure is "adult-like" at approximately age 5 (i.e., growth is essentially complete).
- Brain morphology is stable during late childhood, adolescence and adulthood.
- Regressive changes of old age begin after 60.

"Brain structure is adult at approximately age 5."

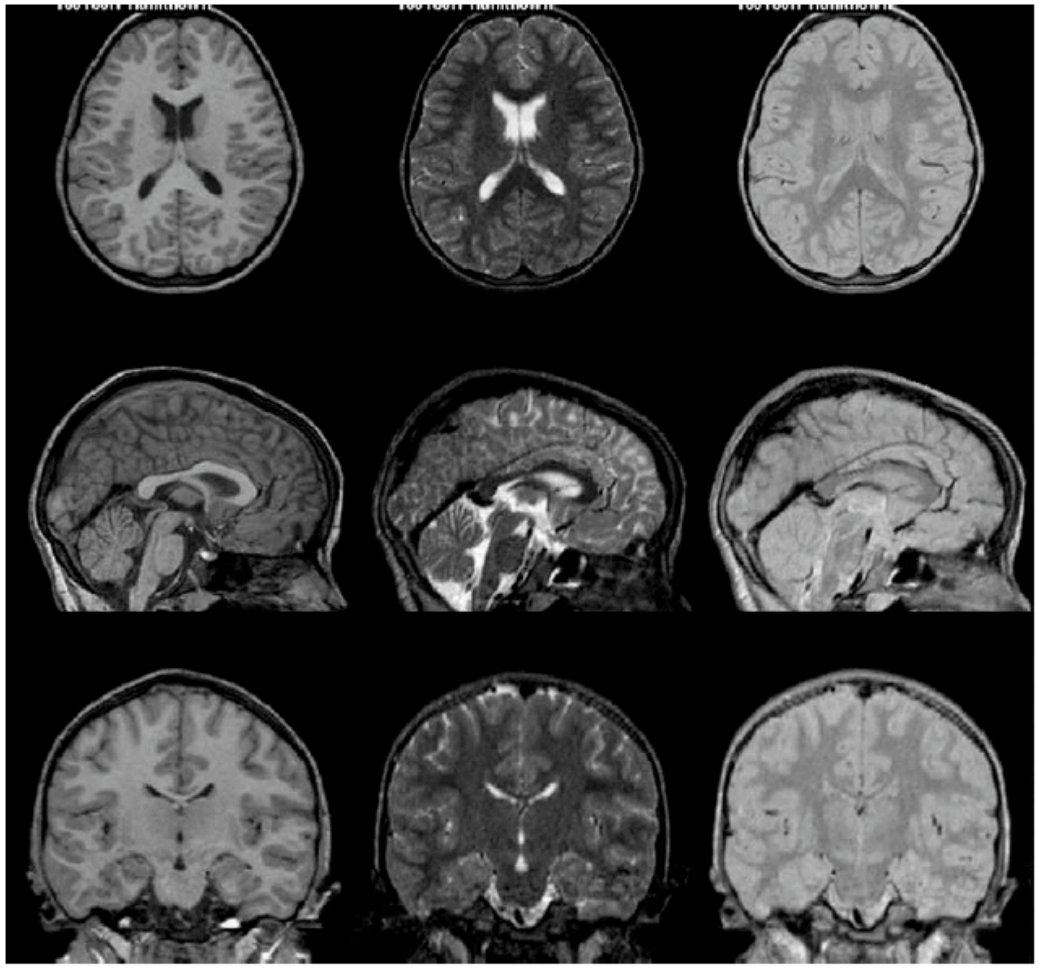
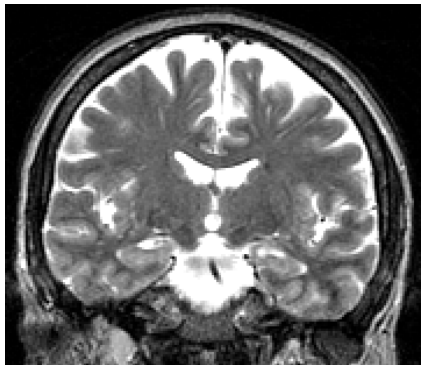


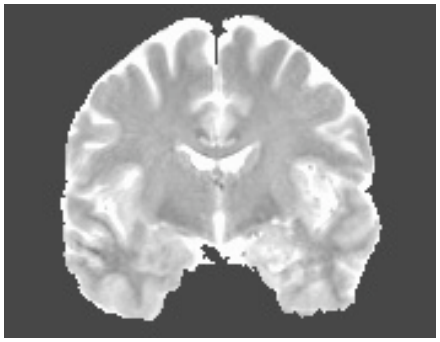
Fig. 1. Objective 1 sample data (T1W/T2W/PDW).

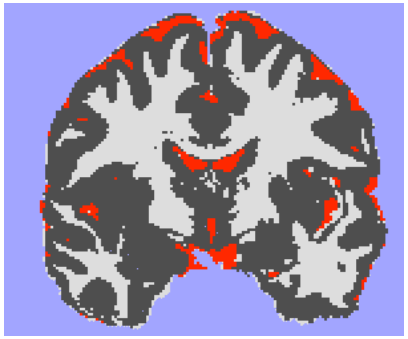
Structural MRI of young child from NIH Brain Development Study

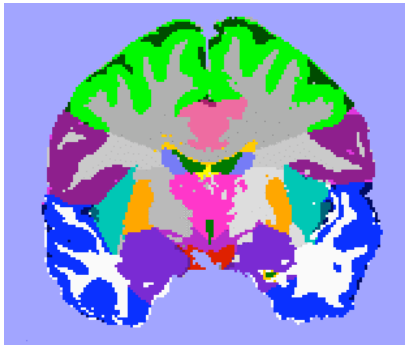
Image Analysis for Brain Morphometry

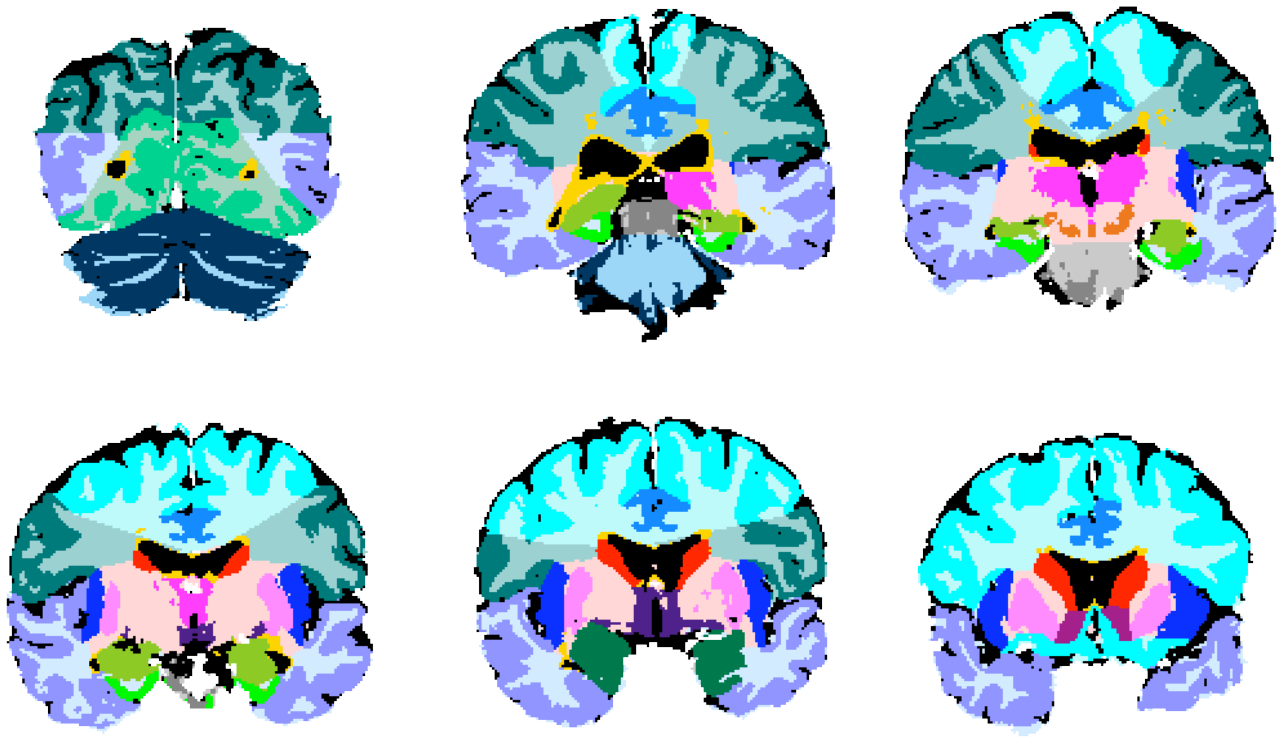
- Stripping (Isolation of Brain Areas)
- Bias Correction to Reduce Signal Inhomogeneity
- Tissue Segmentation
- Anatomical Segmentation (Within-Tissue Segmentation)











Cerebral Lobes

- Frontal Cortex/White
- Temporal Cortex/White
- Parietal Cortex/White
- Occipital Cortex/White

Cerebellum

- Cortex/White

Subcortical Regions

- White Matter
- Basomesial Diencephalon
- Caudate Nucleus
- Lenticular Nucleus
- Nucleus Accumbens
- Thalamus
- Substantia Nigra

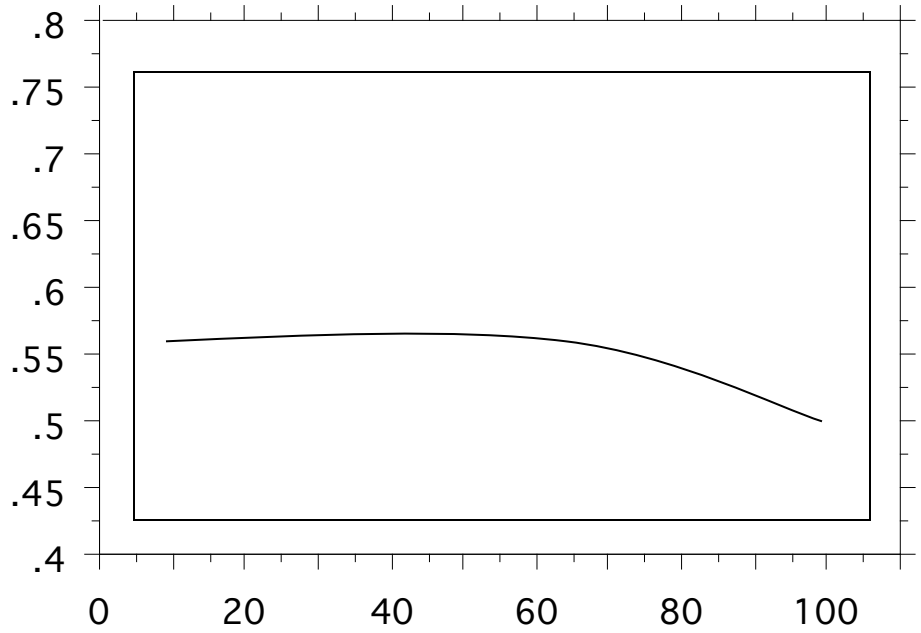
Other Structures

- Insular Cortex
- Cingulate Cortex
- Hippocampus
- Amygdala
- Parahippocampal Gyrus
- White Matter w/ Elevated Signal

Predictions Based on Conventional Views of Brain Morphology

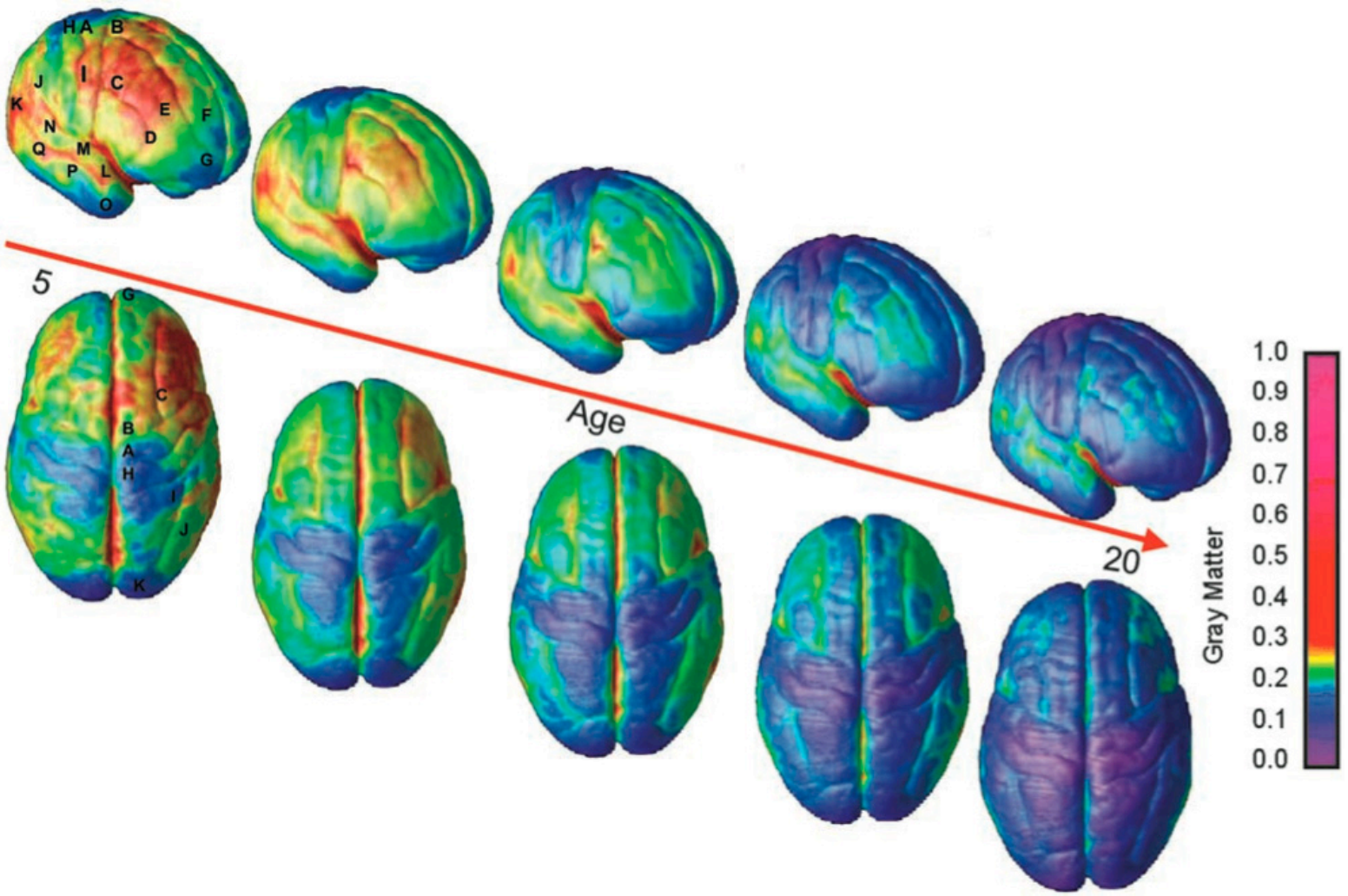
- Adult brain structure in school-aged children.
- Stable brain morphological characteristics across childhood, adolescence, and adult years.
- Atrophy of some brain structures in old age.

Age-Related Alterations of Normalized Cerebral Gray Matter Volume



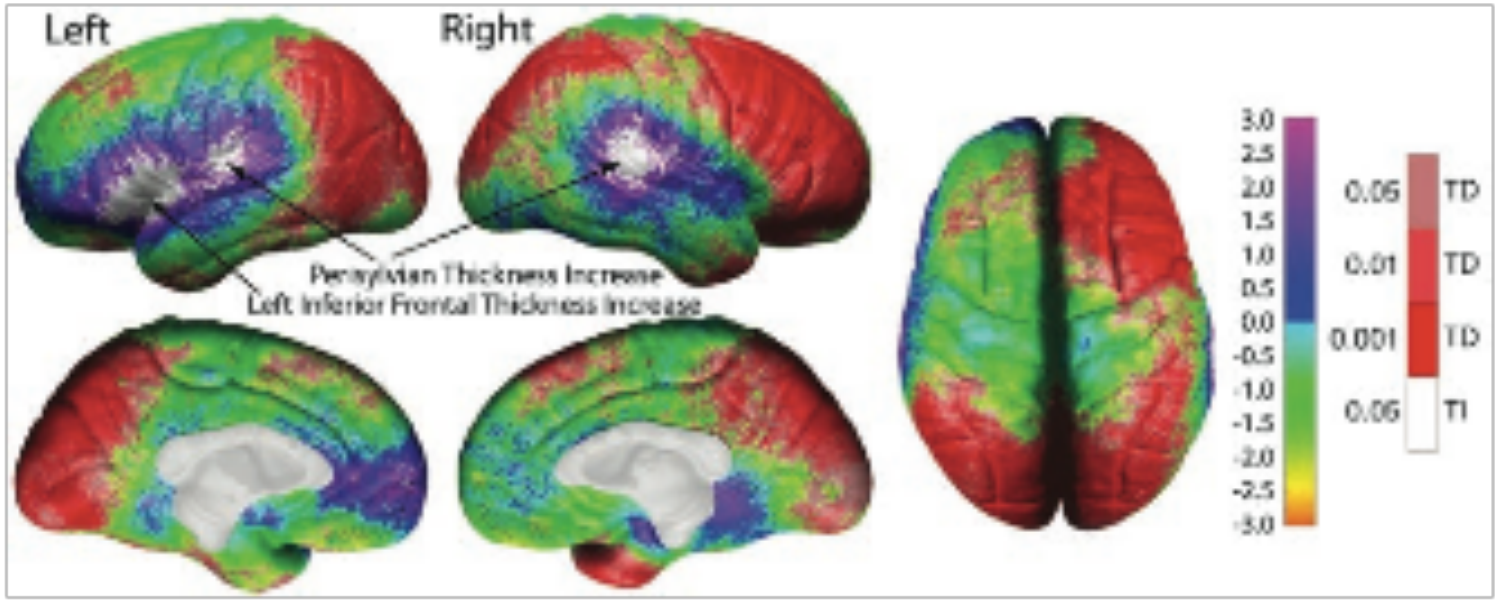
Mapping of Cortical Thinning with Longitudinal MRI Data

Gogtay et al., PNAS, 2004



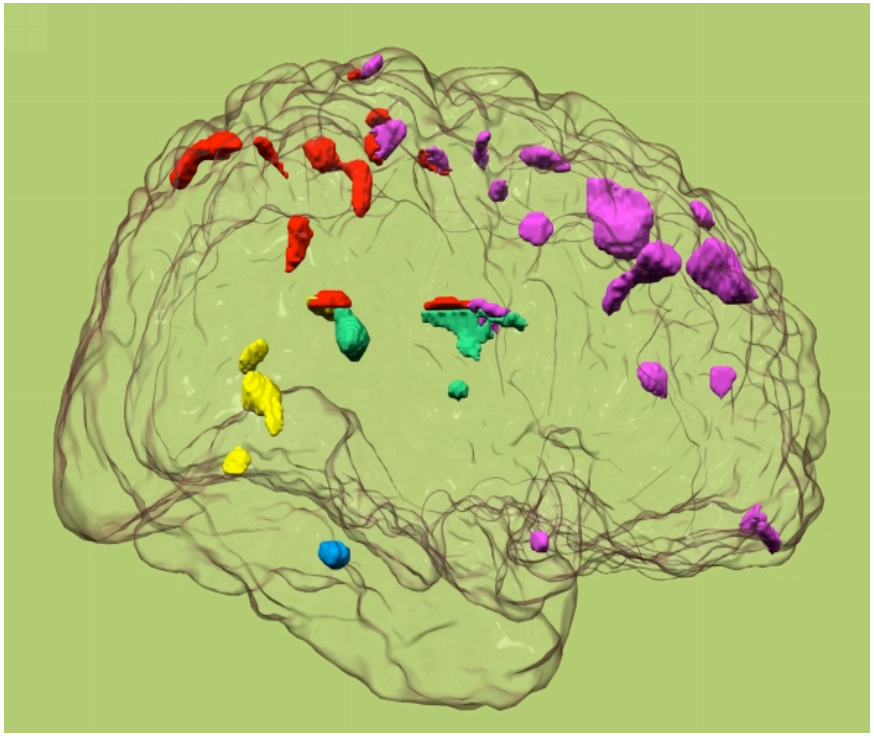
Longitudinal Mapping of Cortical Thickness and Brain Growth in Normal Children

(Sowell et al.,J. Neurosci., 2004)

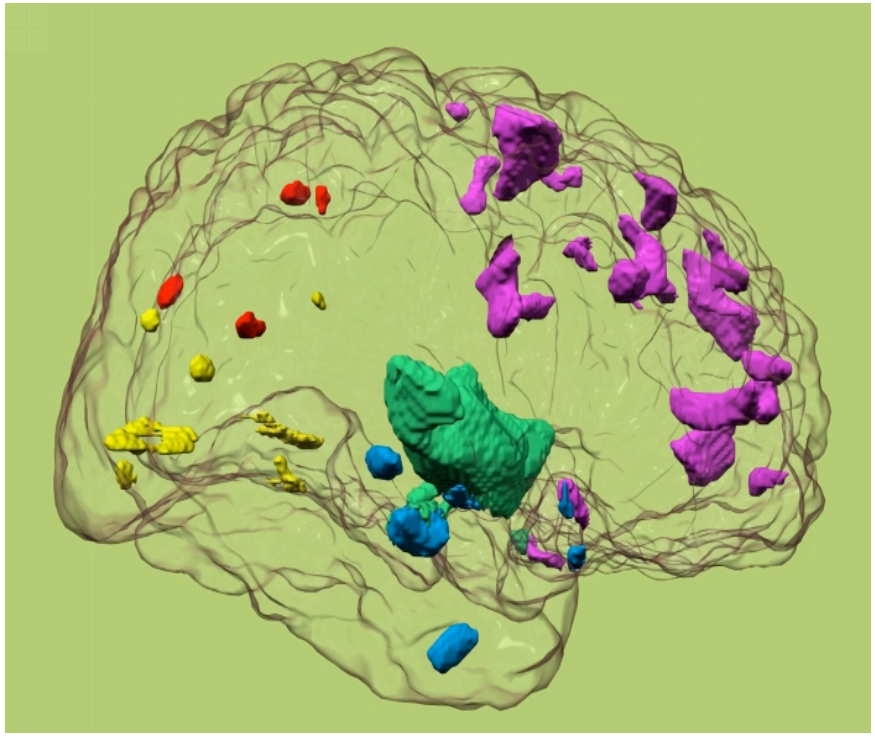


Widespread cortical thinning, and focal areas of cortical thickening observed longitudinally in children over 2 years, from 7 to 9.

Changes in Brain Structure in Maturing Young People

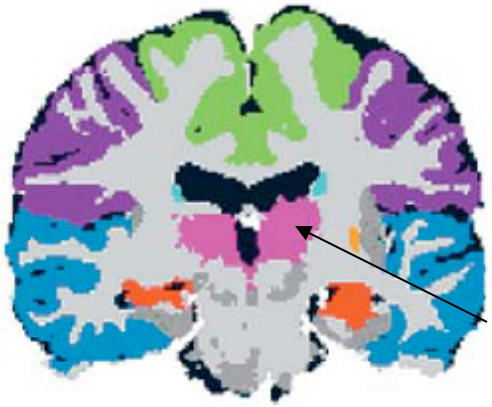


Childhood to Adolescence
(Sowell et al, NeuroImage, 1999)



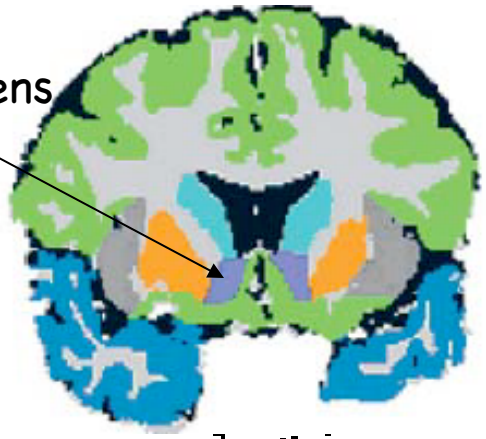
Adolescence to Adulthood
(Sowell et al, Nature Neuroscience, 1999)

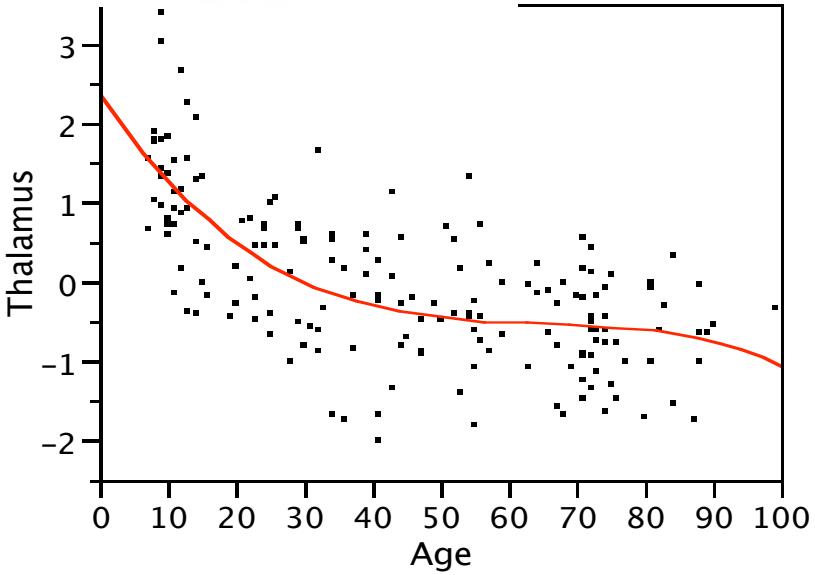
Age-Associated Alterations of Volumes of Subcortical Nuclei

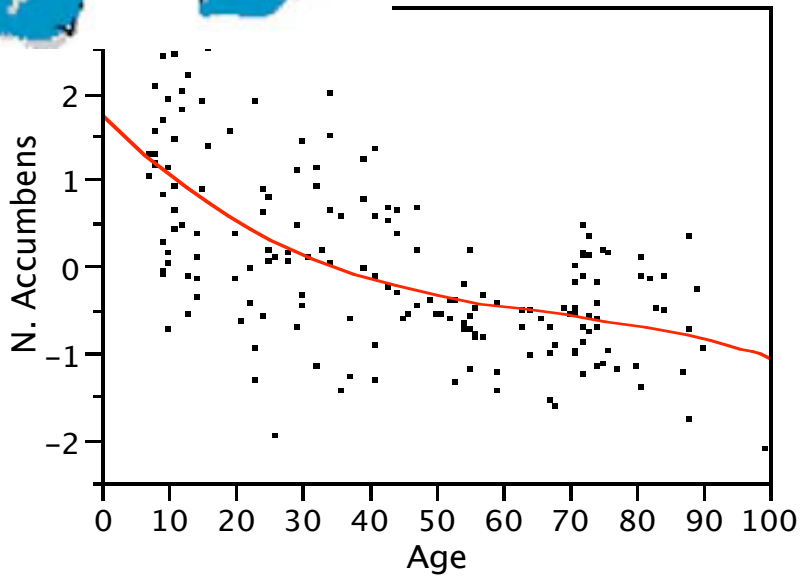


Thalamus

N.Accumbens

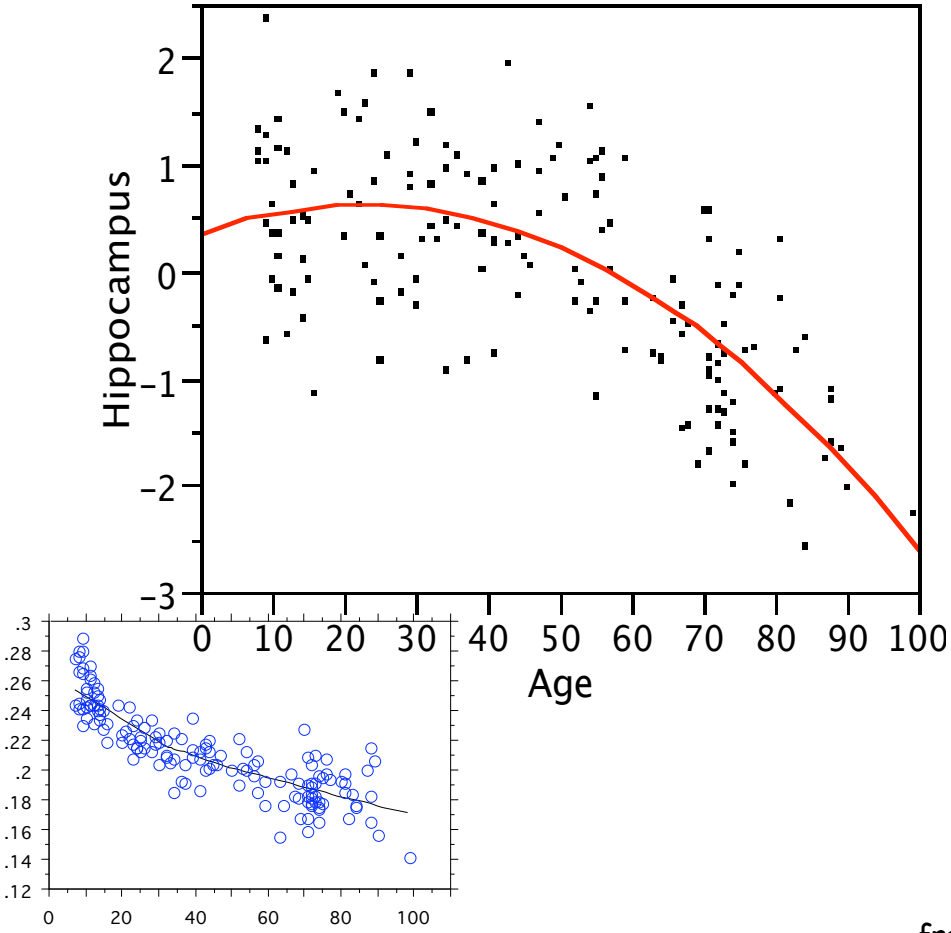


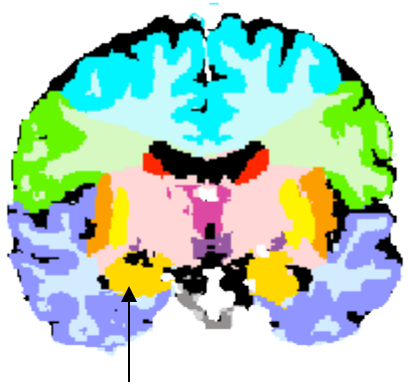


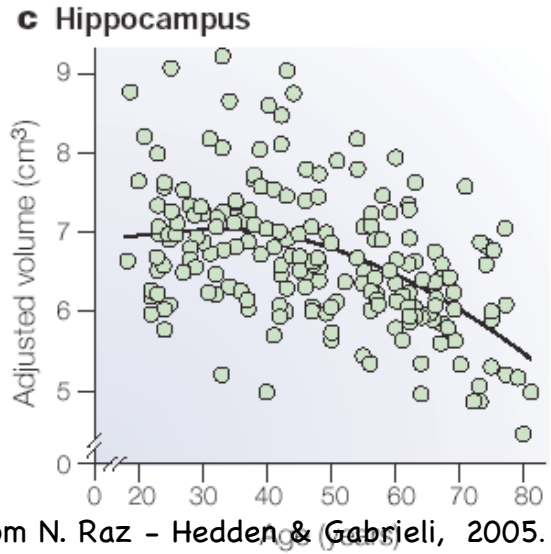


Curvilinear Age-Function for Hippocampal Volume

(Jernigan & Gamst, 2005)



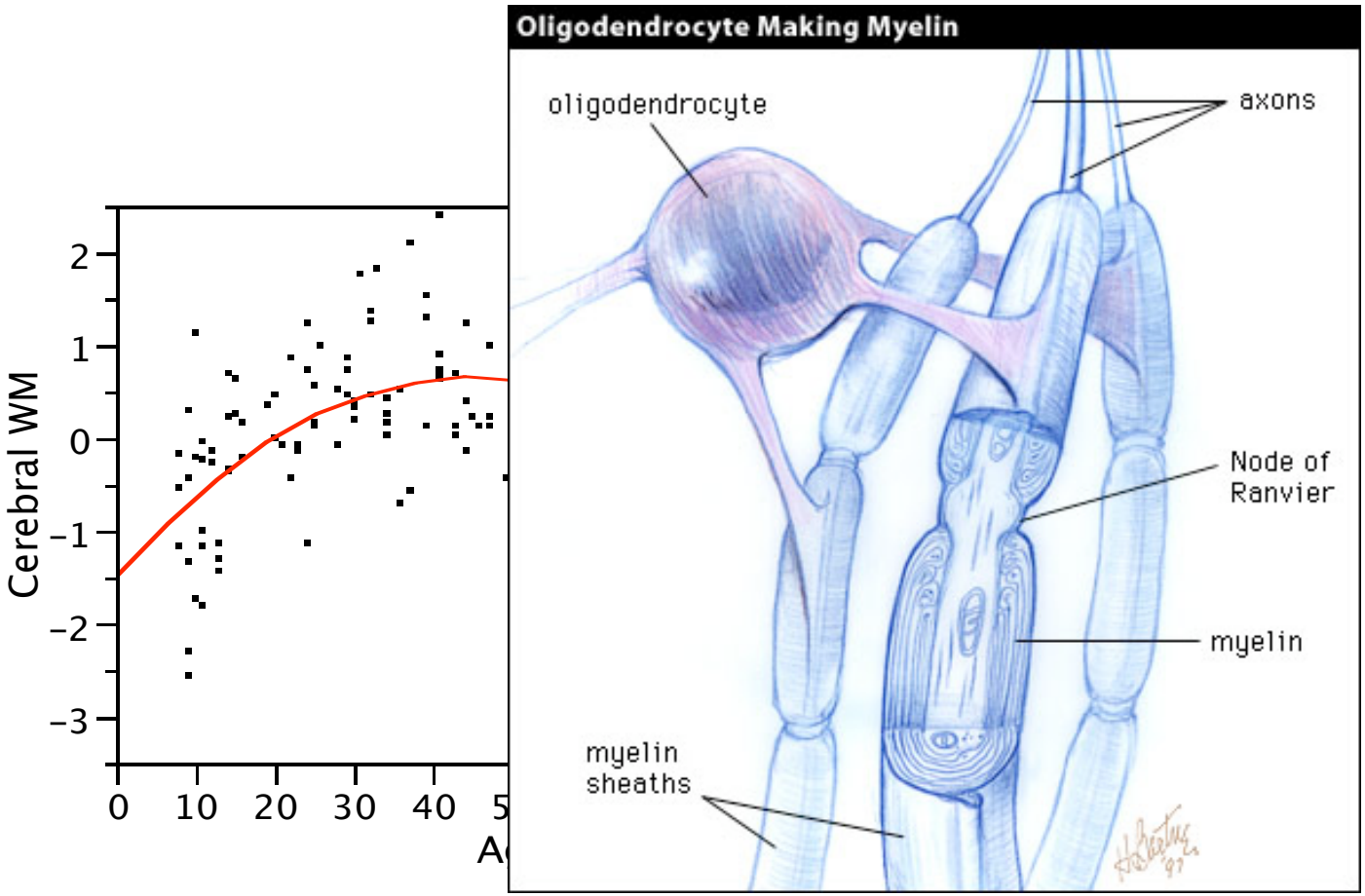




from N. Raz - Hedden & Gabrieli, 2005.

Why don't young brains appear atrophied?

White Matter Growth Associated with Post-natal Proliferation of Oligodendrocytes and Myelin Deposition



Summary

- During the first 2-3 decades of life, age-related tissue alterations, presumably related to brain maturation, can be observed with morphometry.

- Though the first evidence came in the form of apparent changes in the morphology of gray matter structures, it was suspected that much of the change was directly, or indirectly, related to continuing myelination and fiber tract development.

- However, until recently, further investi ract maturation was limited by the lack of s ite matter structure with existing MR met

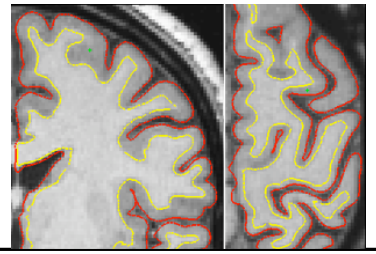
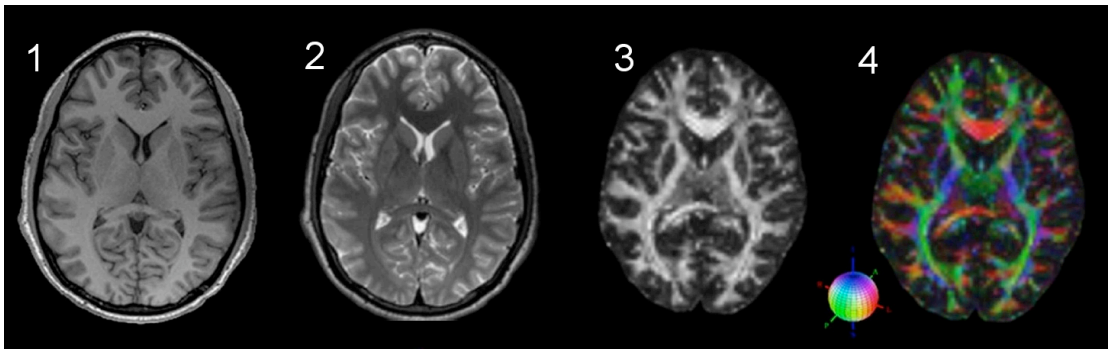


Figure 5. Coronal (left) and horizontal (right) slices of the left hemisphere with gray/white (yellow) and pial surfaces (red) overlaid.

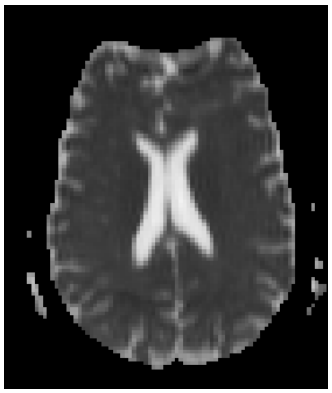
Diffusion Tensor Imaging



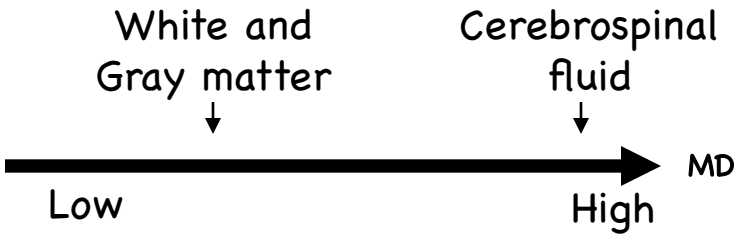
- Measures diffusion (motion) of protons in water molecules.
- Direction of proton motion within a voxel can be described by a "tensor".
- Proton diffusion tends to be relatively isotropic in gray matter.
- The linear structure of fiber tracts constrains proton diffusion and produces **anisotropy**.

White Matter Diffusion Properties

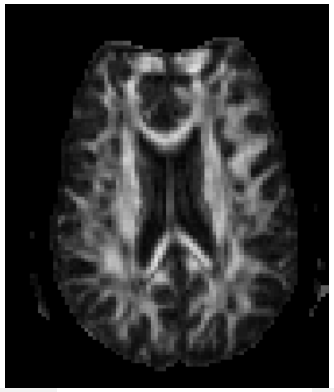
Apparent Diffusion Coefficient
Tensor size

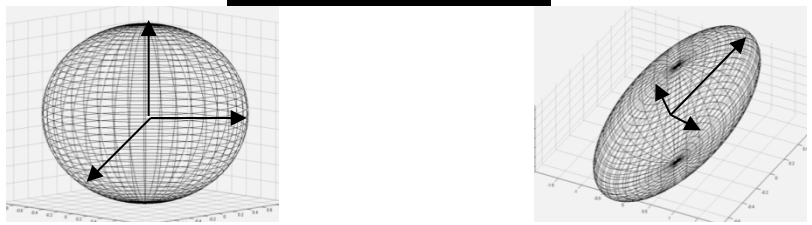


Mean diffusivity



Fractional Anisotropy
Tensor shape

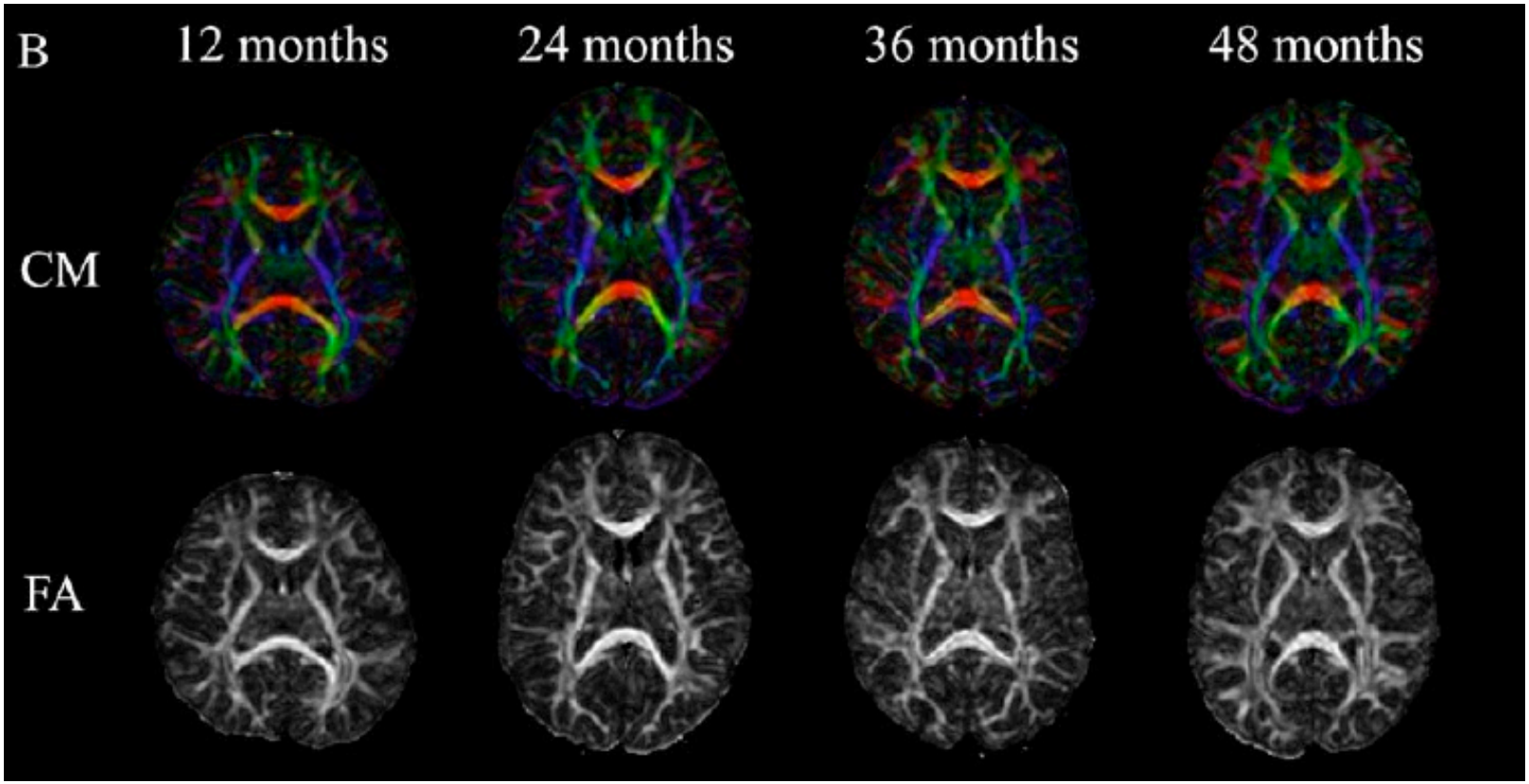




Slide borrowed from Guido Gerig

Fiber Tract Development Observable with DTI

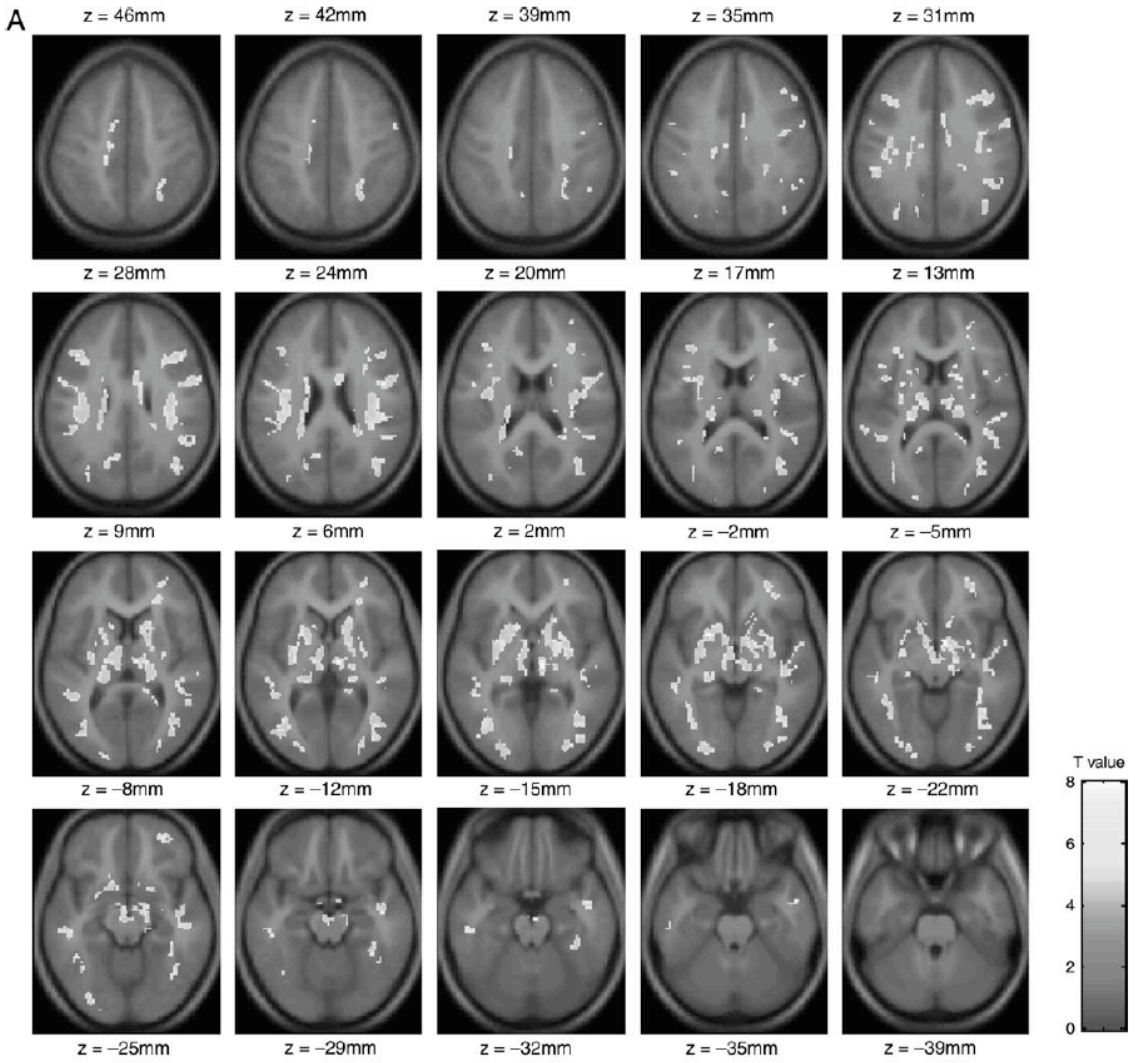
(from Hermoye et al., 2006)

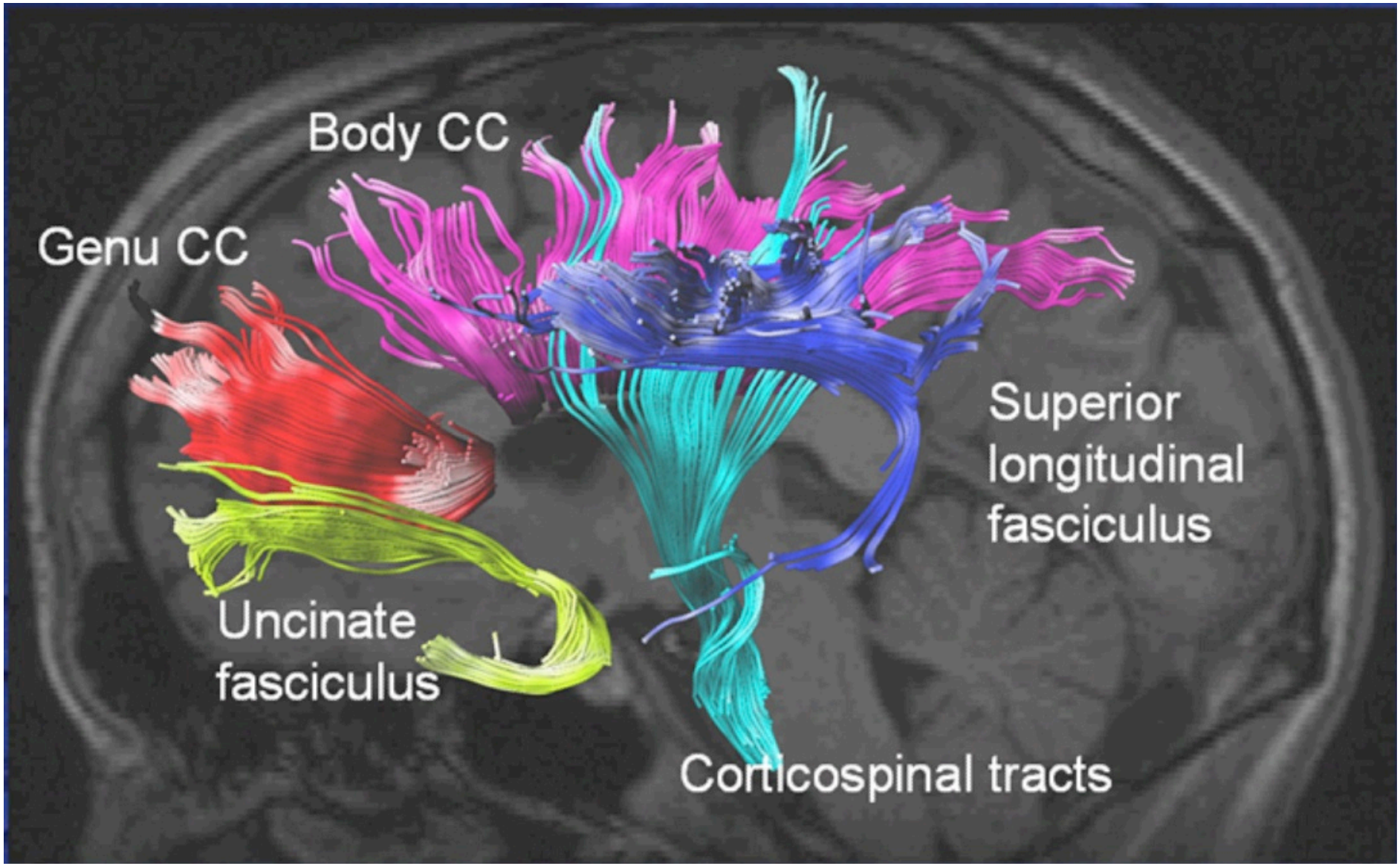


"White Matter Development During Childhood and Adolescence: A Cross-sectional Diffusion Tensor Imaging Study"

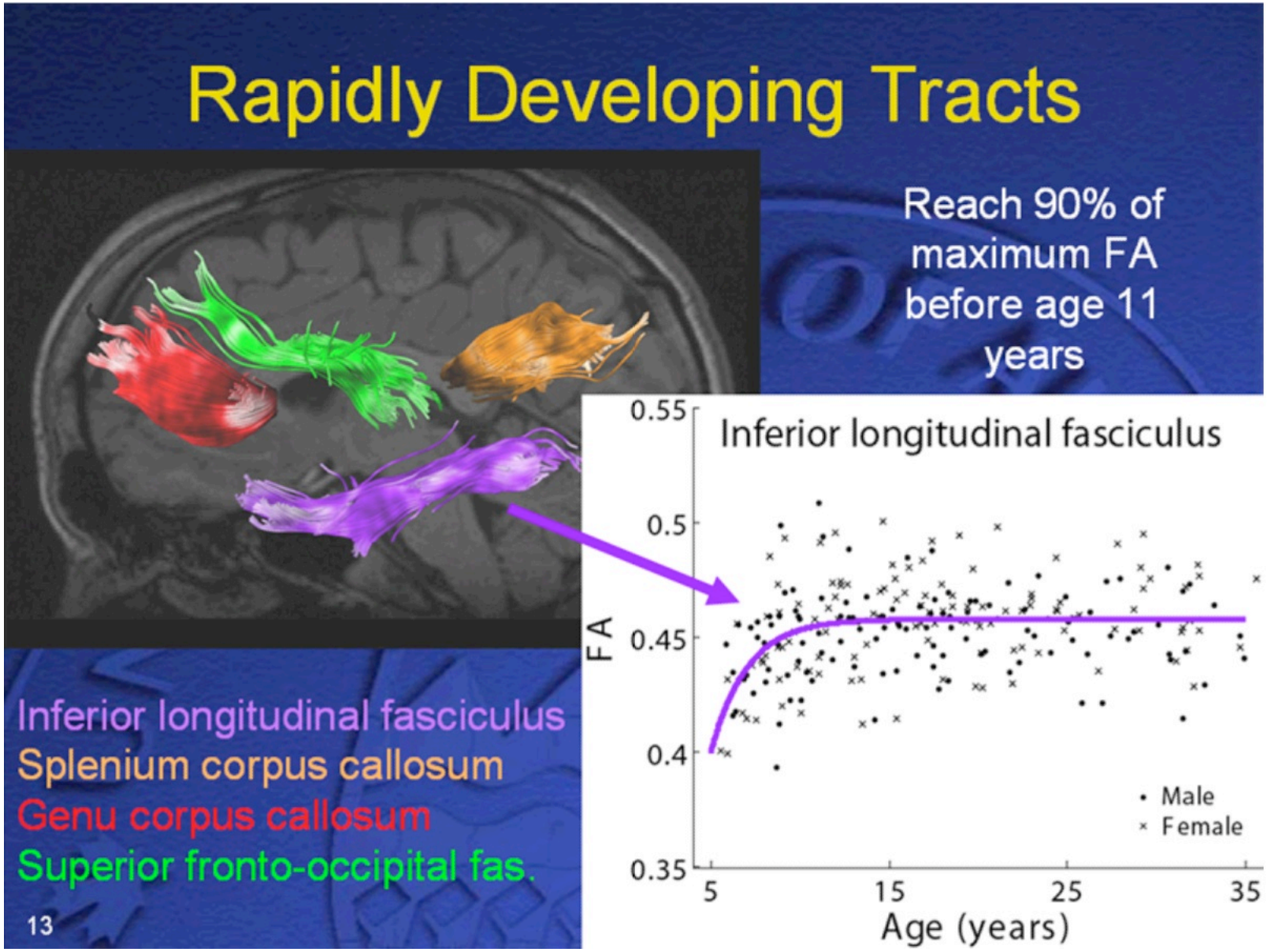
(Barnea-Goraly et al., Cerebral Cortex, 2005)

Age effects on fractional anisotropy (FA) in 6-19 year old subjects

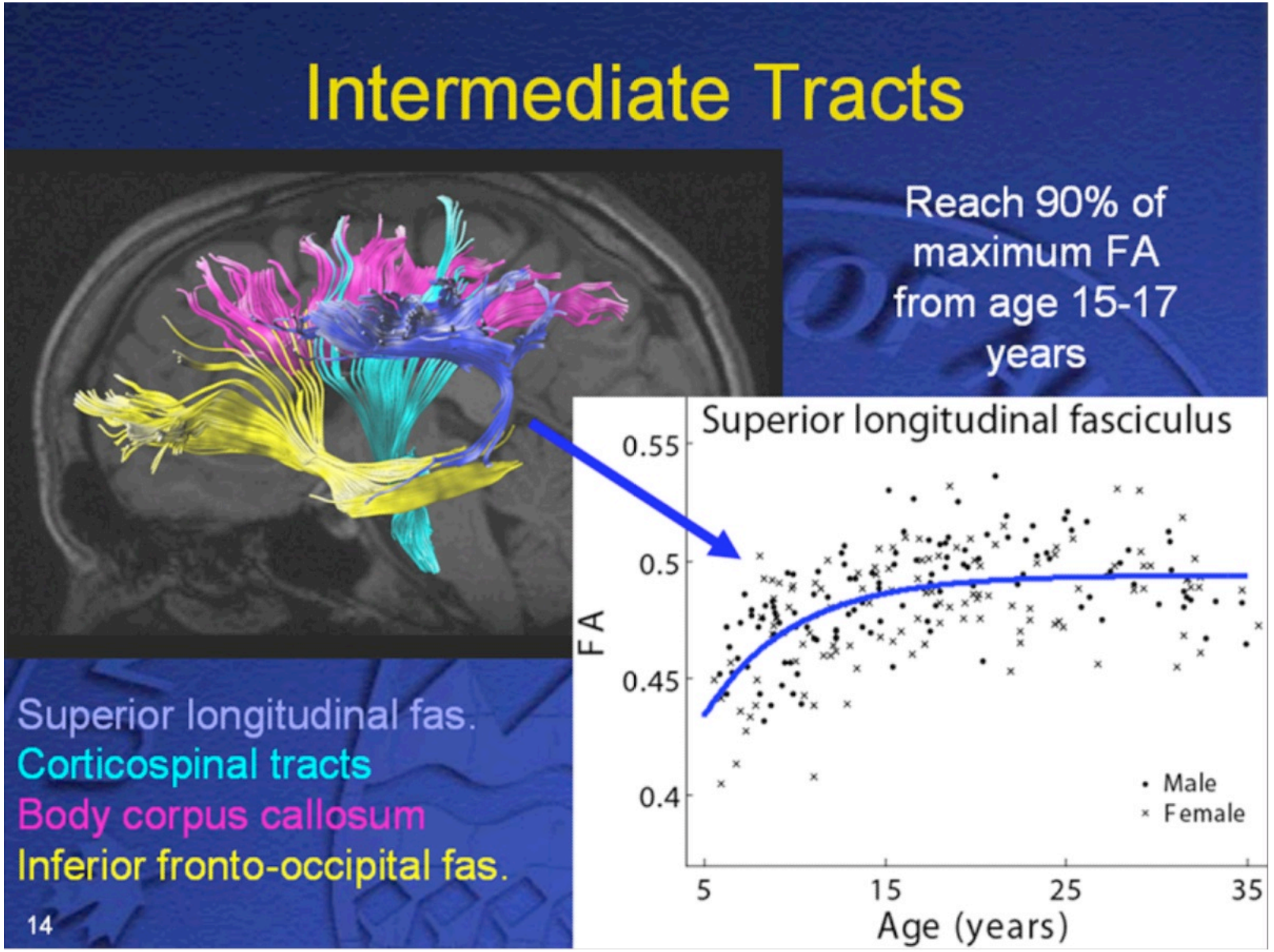




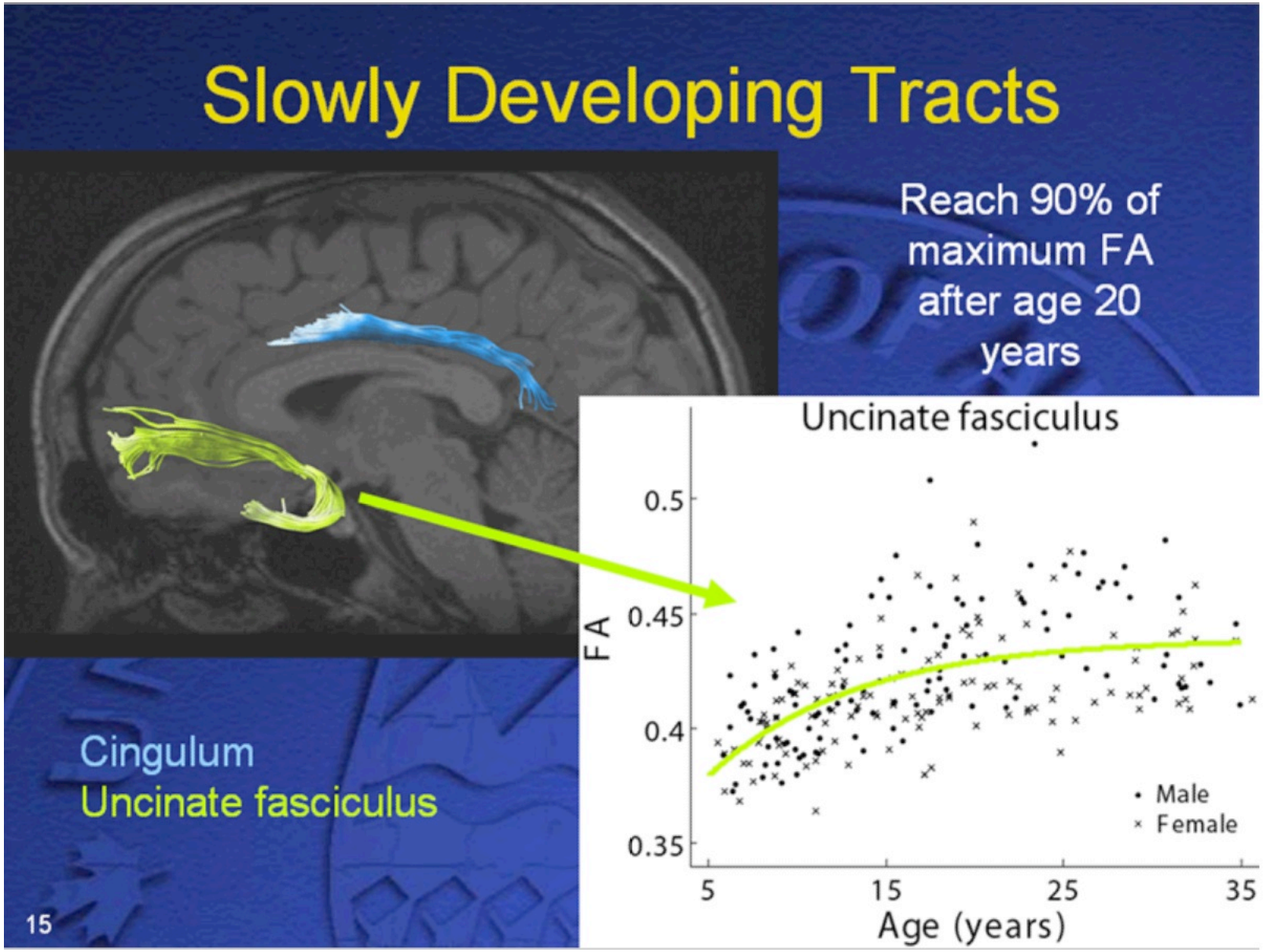
Lebel et al., 2007 ISMRM Meeting



Lebel et al., 2007 ISMRM Meeting



Lebel et al., 2007 ISMRM Meeting



Lebel et al., 2007 ISMRM Meeting

"Absolute eigenvalue diffusion tensor analysis for human brain maturation"

(Suzuki et al., NMR in Biomedicine, 2003)

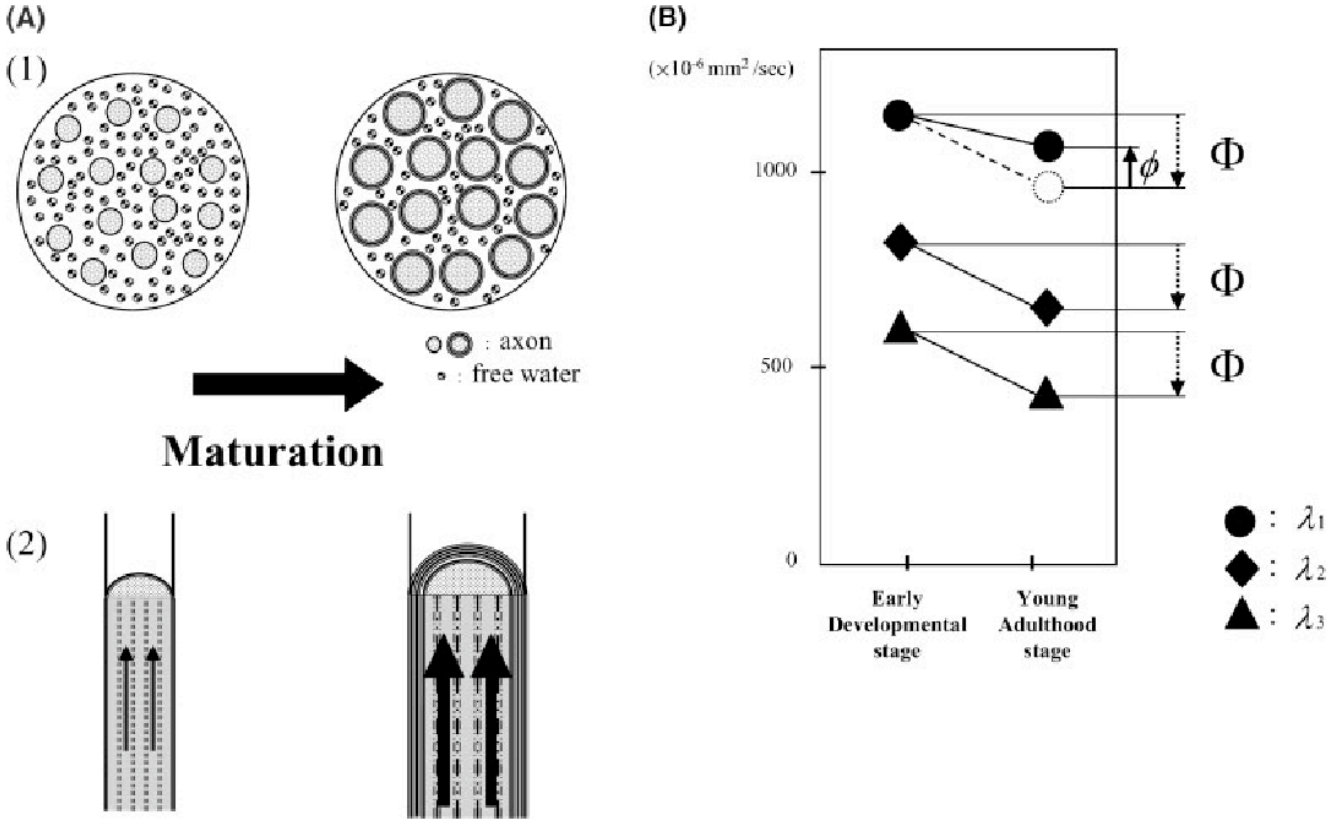
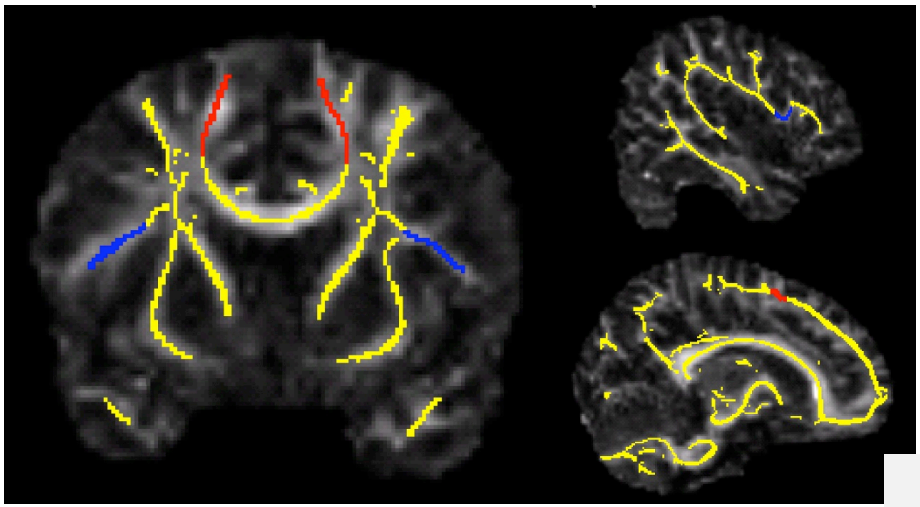
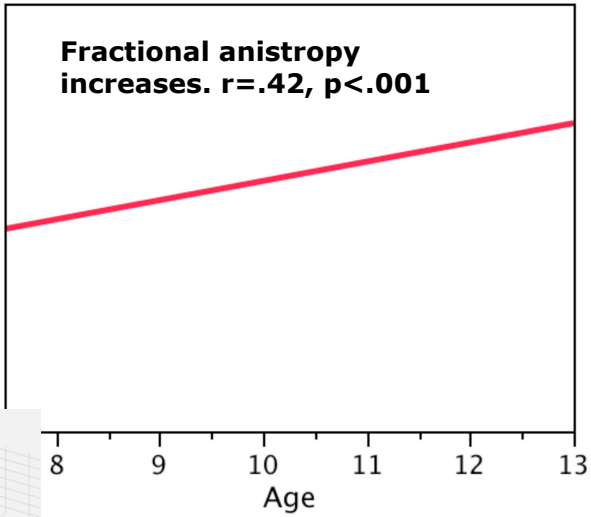


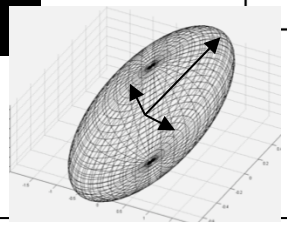
Figure 1. Schema showing micro-environmental alterations during myelination period and their relationship to characteristic changes in eigenvalue. (A) Schematic presentation of maturational changes, the characteristics of which include (1) decline in free extra axonal water and (2) increase in axoplasmic flow. (B) Alteration in diffusion characteristics clearly corresponds to the maturational changes in micro-environment. While all eigenvalues decline according to the decline in free extra-axonal water (Φ), the largest eigenvalue showed fractional increase due to increase in axoplasmic flow (ϕ)

Fibre Tracts Show Protracted Course of Maturation During Childhood

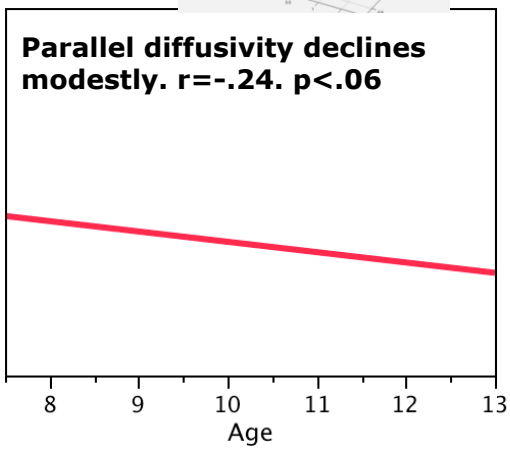
Evidence from DRCMR Study of Brain Development

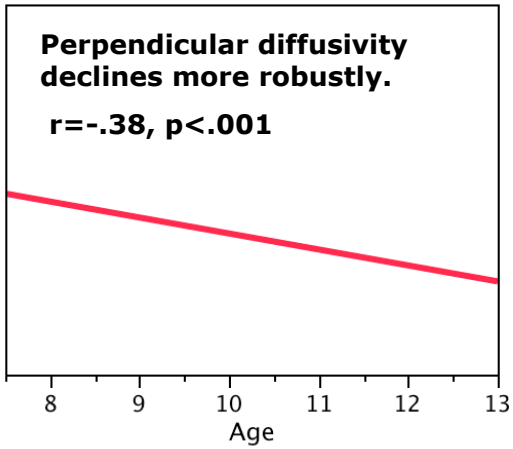






- We studied sixty-five typically developing children, 7 - 13 years of age.
- As predicted, global fractional anisotropy increased with age in the principal fibre tracts (colored areas).





Summary

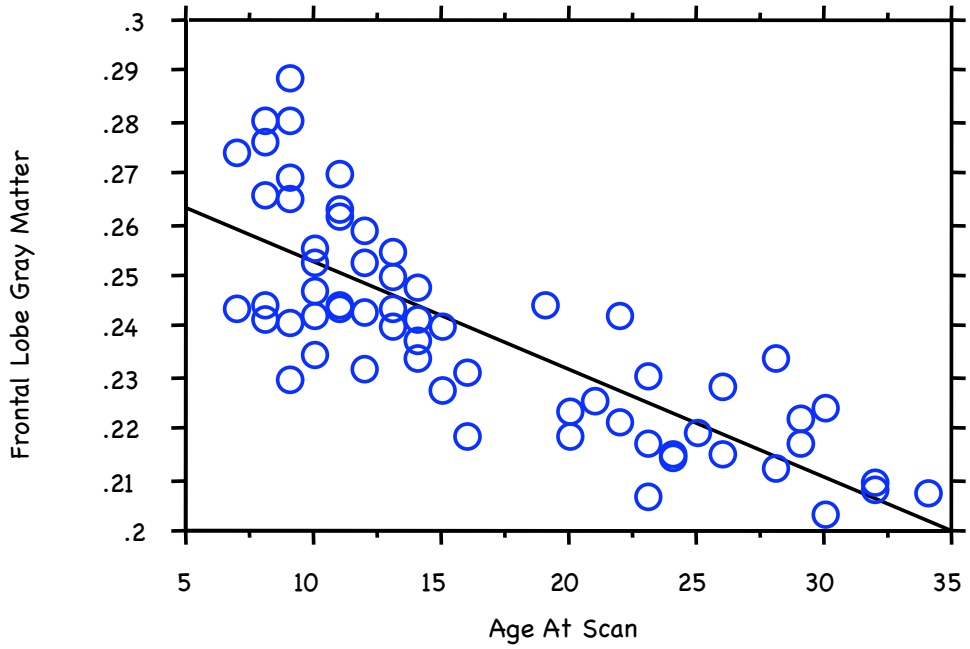
- Although the changes may be visually subtle, when examined closely, the brain exhibits a complex pattern of age-associated tissue alterations well into adulthood.

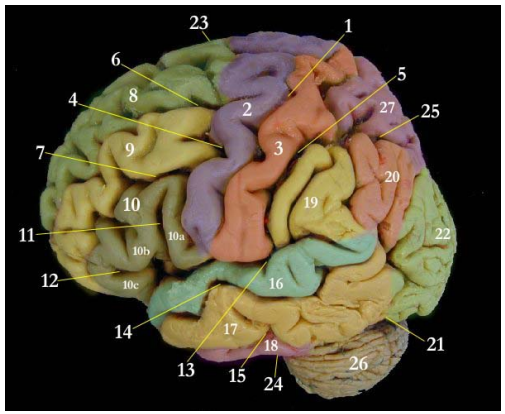
- We are just beginning to understand the biology and the role that these dynamic changes play in evolving mental functions.

Relationships to Behavior

What is the significance of individual difference variability?

Sowell, Delis, Stiles & Jernigan, 2001



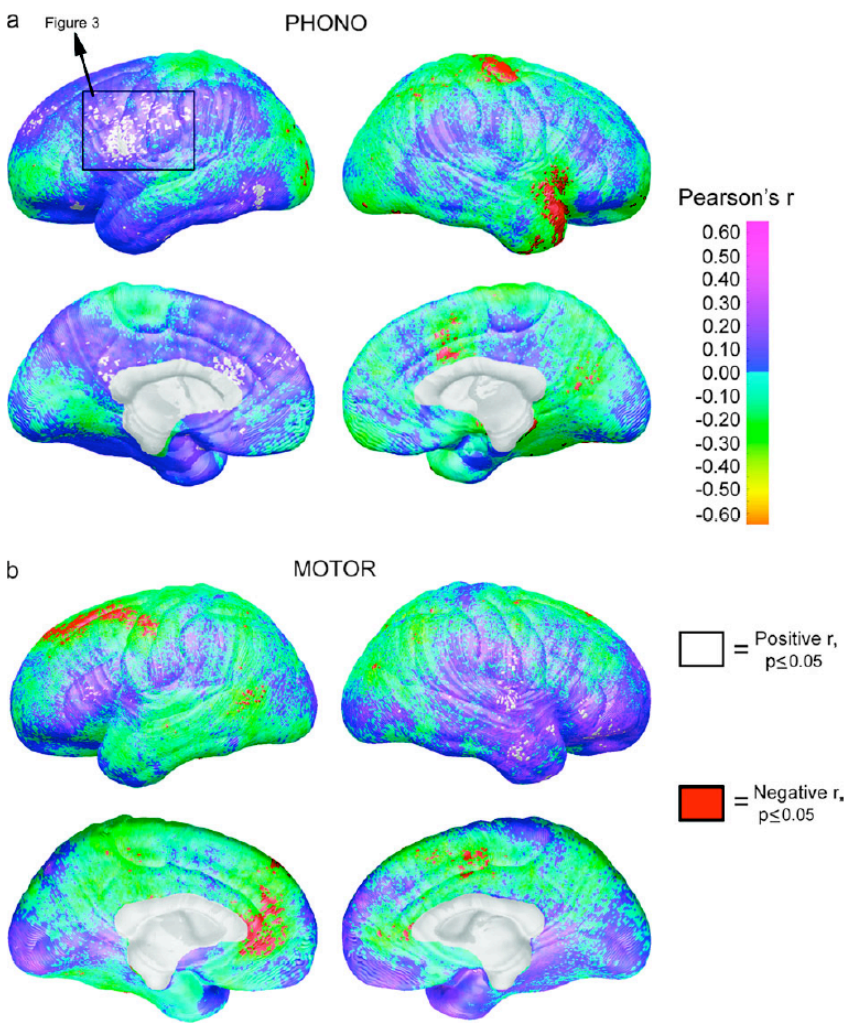


Better memory retrieval was correlated with thinner (more mature) frontal cortex.

Normal Developmental Changes in Inferior Frontal Gray Matter Are Associated with Improvement in Phonological Processing: A Longitudinal MRI Analysis

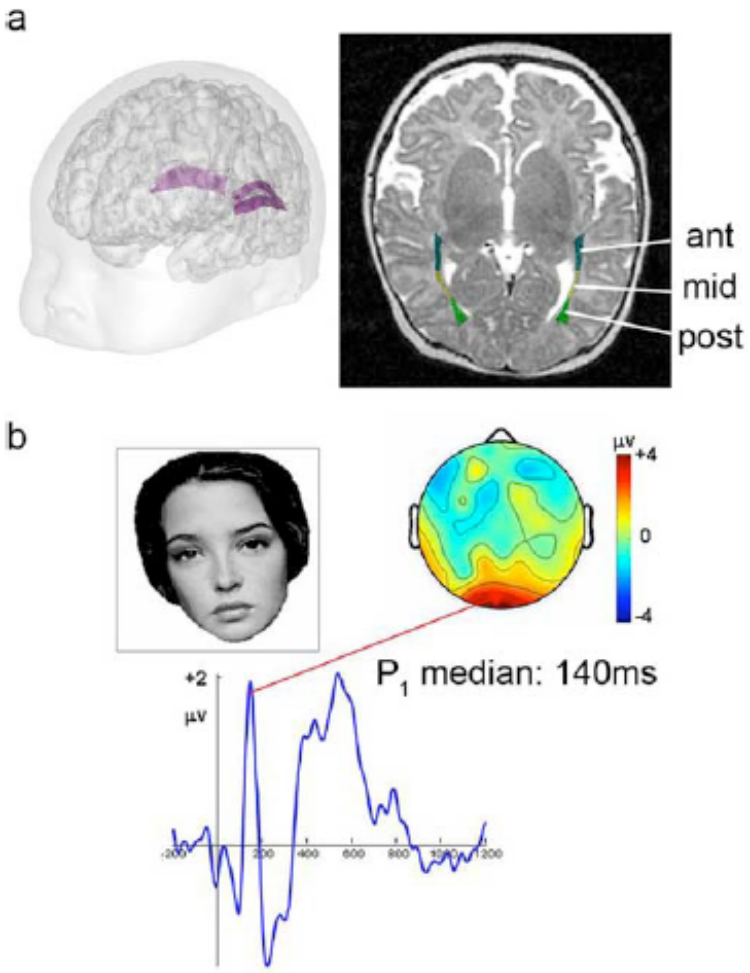
(Lu et al., Cerebral Cortex, 2007)

Thickening inferior frontal cortex and thinning dorsal prefrontal cortex exhibit distinct functional correlates in the same children across the age range from 7-9.



Microstructural Correlates of Infant Functional Development: Example of the Visual Pathways

(Dubois et al., J. Neurosci, 2008)



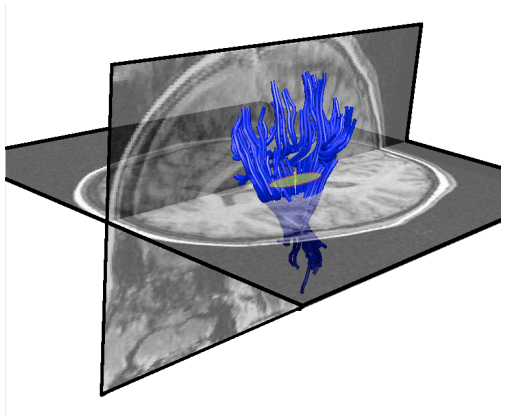
Latency of the P1 component of the Visual Evoked Potential correlated with FA in the optic radiations, independent of chronological age, in 5 - 17 week old infants.

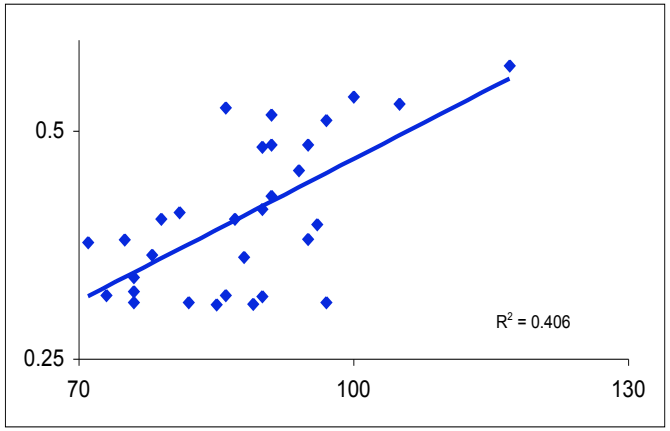
"Double Dissociation" in Correlation Patterns

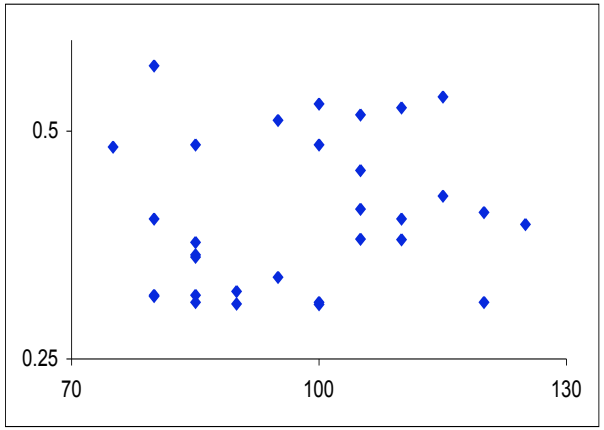
Standardized Word ID

Standardized Digit Recall

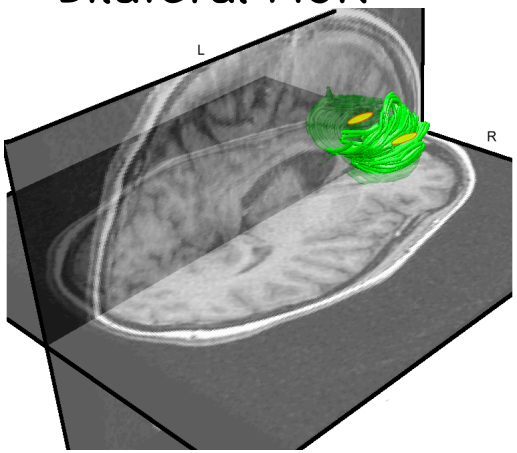
Left SCR

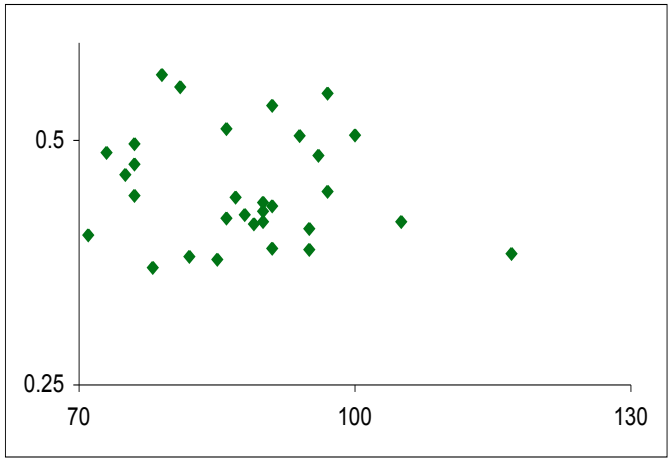


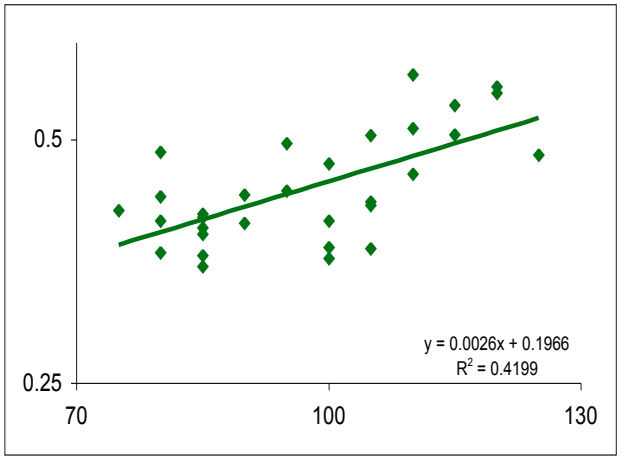




Bilateral ACR







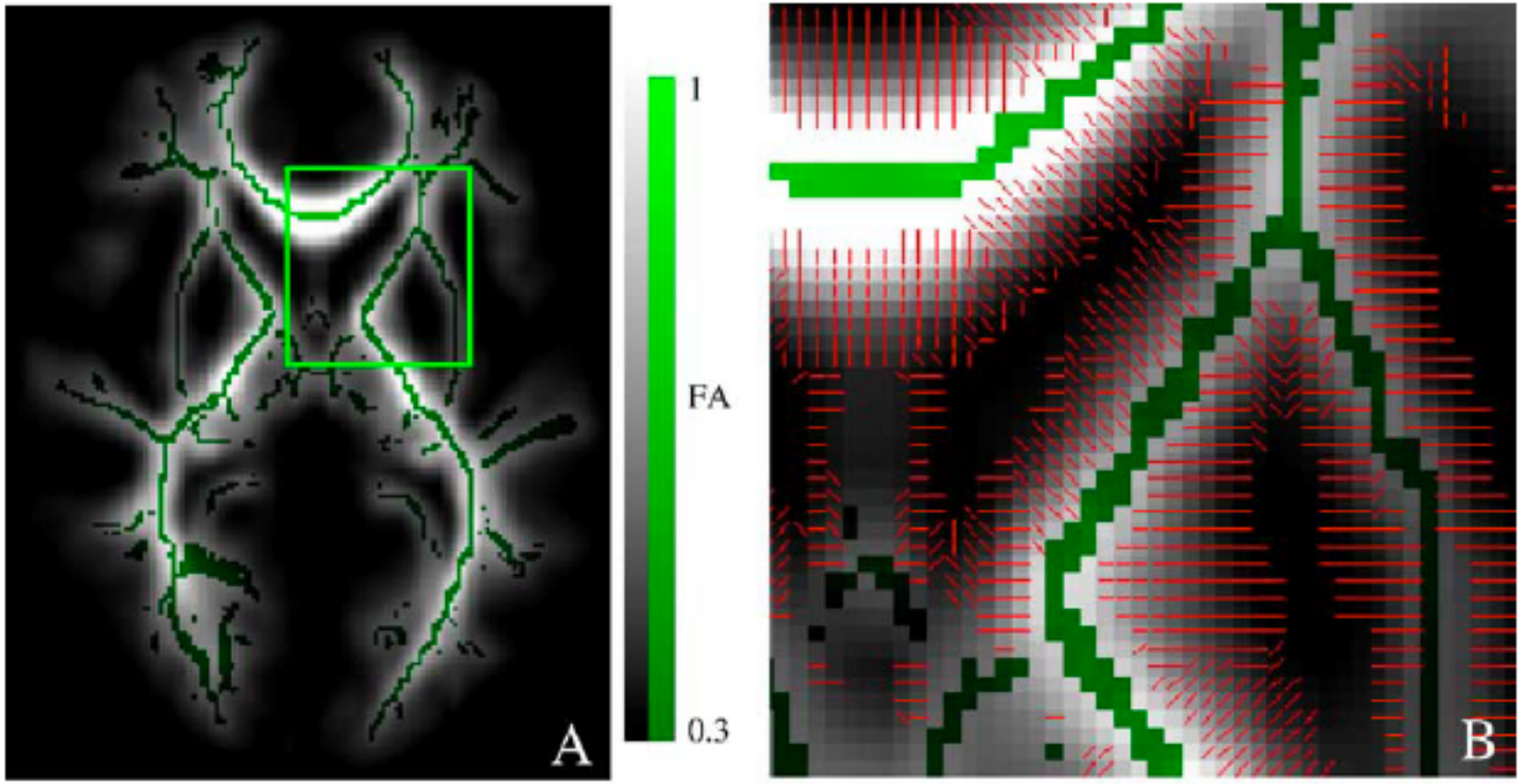
Niogi, S. & McCandliss, B.D.(2006) *Neuropsychologia*

Study of Individual Differences in Task Performance in 65 7-13 year old children

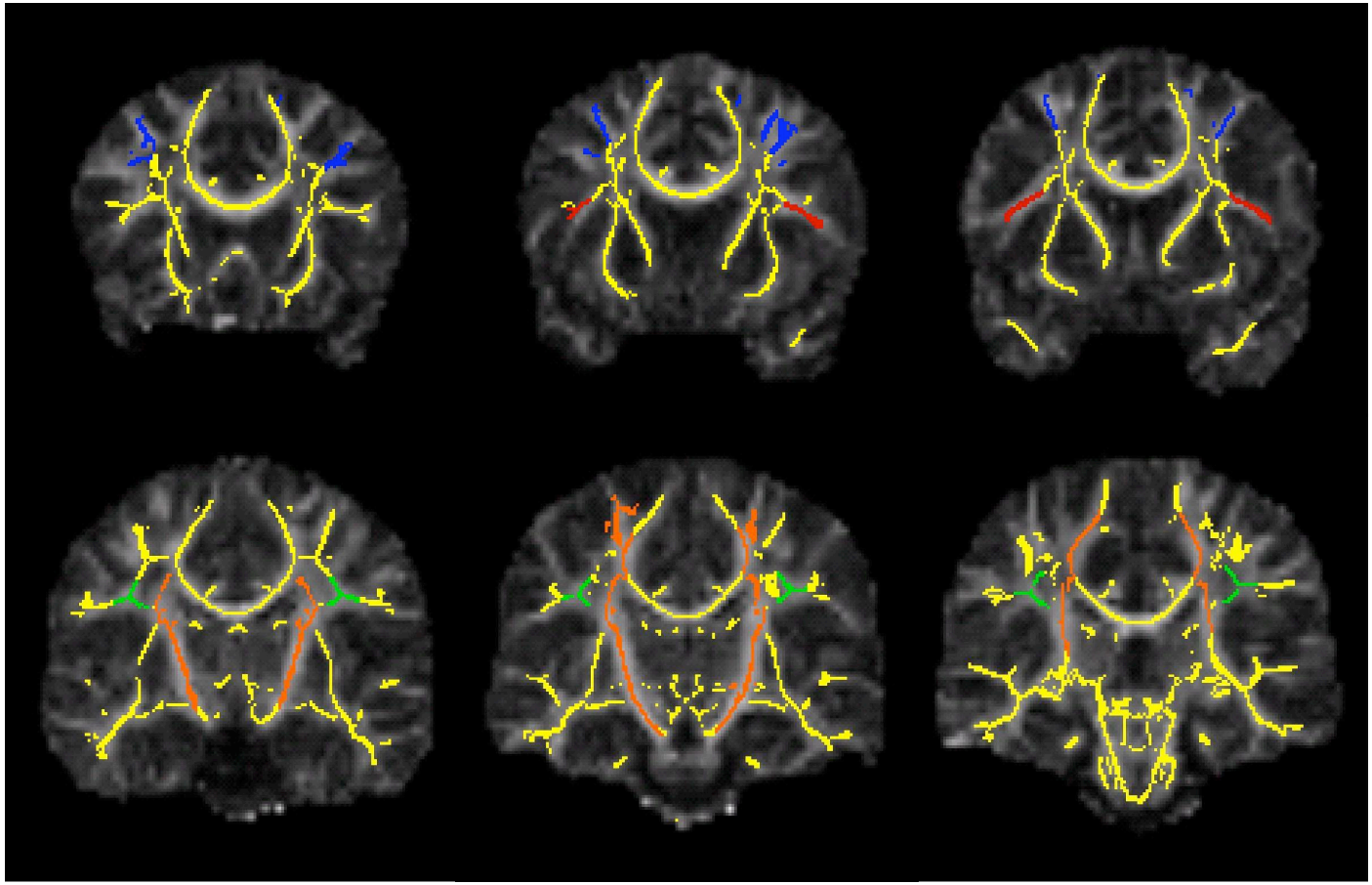
- Danish school children
- Mean age 10.1 years
- 36 girls, 29 boys
- sMRI, DTI, cognitive testing

Computational Morphometry: Tract-Based Spatial Statistics

(Smith et al., NeuroImage, 2006)



4 ROIs for Study of Danish School Children



Corticospinal Tract

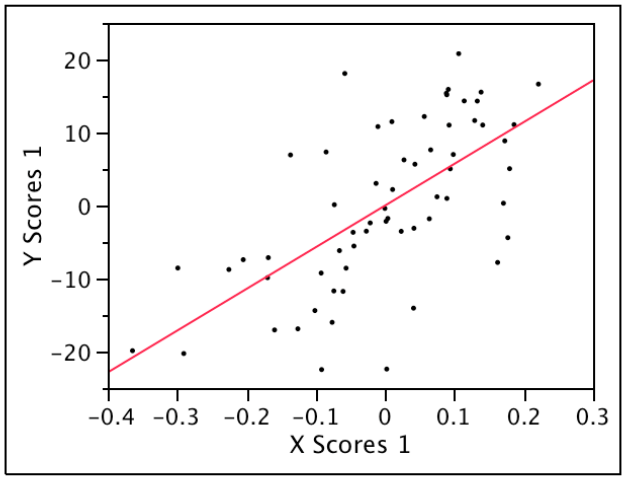
Superior Longitudinal Fasciculus

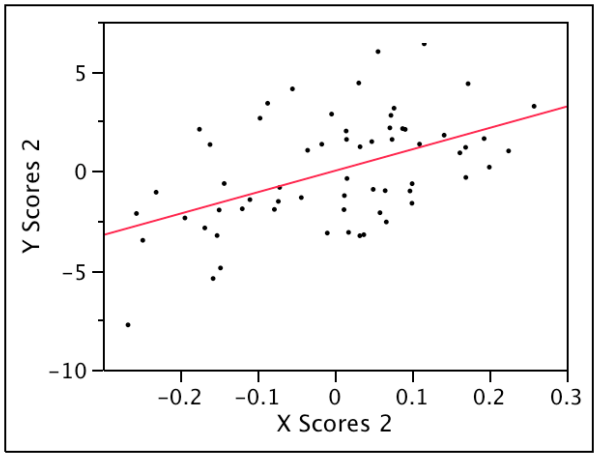
Dorsolateral Prefrontal Ctx

Inferior Frontal Gyrus

Partial Least Squares Analysis Predicting Behavioral Measures with FA in 4 ROIs

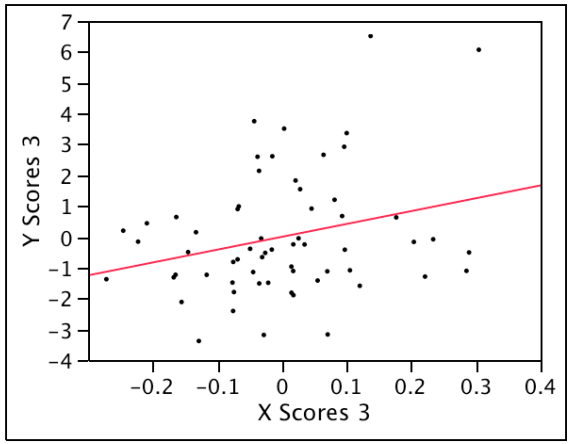
- Behavioral Measures (Y)
  - Choice Reaction Time
  - Response Inhibition (SSRT)
  - Spatial Working Memory
  - Verbal Fluency





↑ Performance ← ↑ Tract FA

Verb Flu > SSRT ← DLPFC,SLF FA > IFG FA



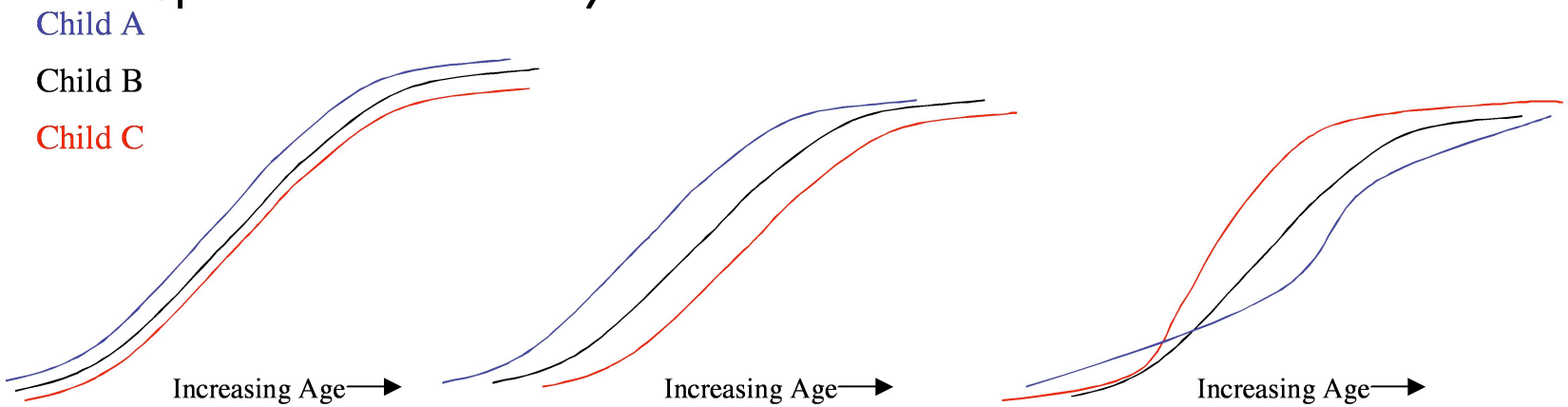
↑ Choice RT Performance ← Corticospinal Tract FA > DLPFC,IFG

Summary of Results of Danish Study

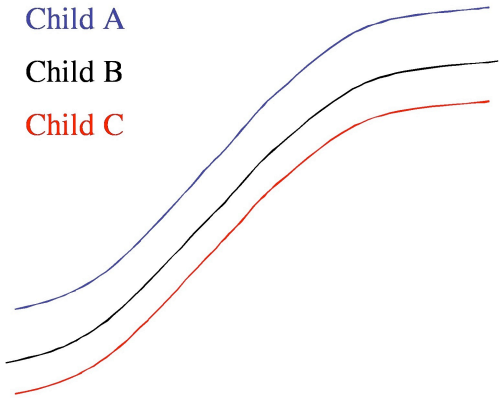
- Significant age effects were observed for all behavioral and all tract FA measures.
- Independent of age and global effects, individual differences in behavioral profiles were mirrored by individual differences in tract FA profiles.

How do we interpret these associations?

Do the relationships in children reflect the effects of developmental variability?



Low phase variability **High phase variability** **Shape variability**



Variable asymptotes

New TDLC Supported Pilot Study of 6-10 year old children

- Children studied at baseline and follow-up with cognitive measures of temporal (and spatial, linguistic, numerical) processing, sMRI, DTI, and MEG.
- In the interval, they will participate in a behavioral intervention program aimed at improving rapid auditory processing.

Behavioral Correlates of DTI Parameters in Children: The role of timing

To what extent are these related to:

- increased speed of conduction within the fiber tracts?
- individual differences in the phase of biological development of the fiber tracts?
- temporal sequence of development of different tracts (and associated neural systems)?

Conclusions

- There is evidence that biological development of brain tissues continues throughout childhood and adolescence.
- The biological changes can be linked to individual differences in behavior in developing children.
- Little is presently known about the meaning of these associations – e.g., about the roles of genes, experience, and other environmental factors.

Thanks