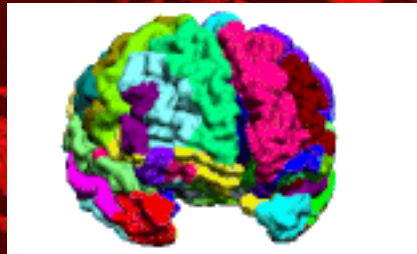




White Matter Development in at-risk children and typical controls



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4.7.2016

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Nebraska
Lincoln

Reading: a complex cognitive process



source: <http://casamento.culturamix.com/relacionamento-2filhos/como-estimular-o-bebe-a-falar>

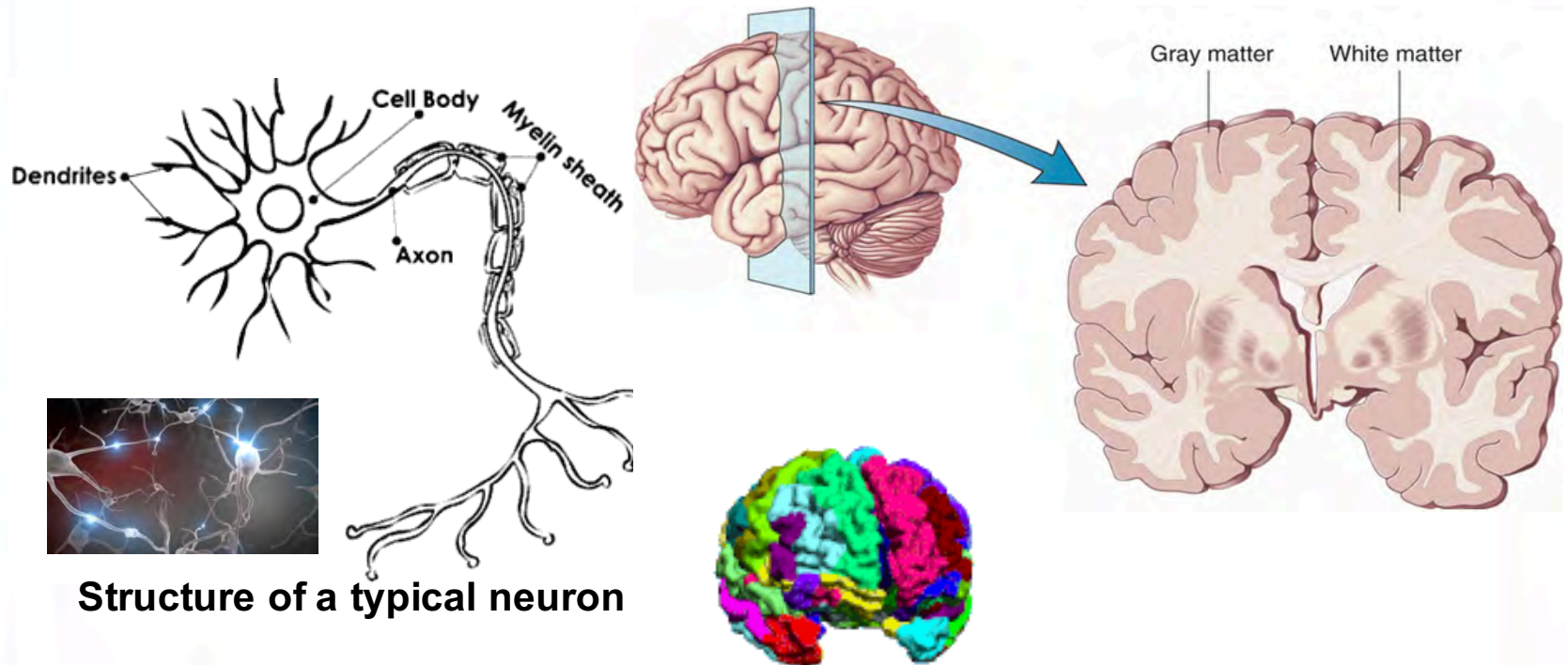


= k - aaaa - t =



Brain: a complex organ

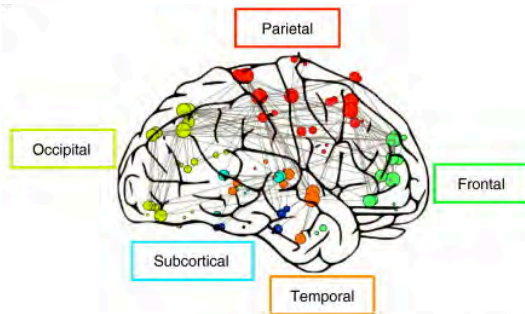
- Newborn babies' brain 100 billions neurons (nerve cells).
- A baby forms 700 new neural connections per second in the first year of life.



Structure of a typical neuron

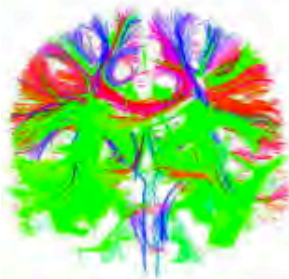
Gray matter and White matter

- Gray matter – numerous cell bodies (functional sites)
- White matter – myelinated axon tracts (structural connections)



TRENDS in Cognitive Sciences

- Gray matter – brain function

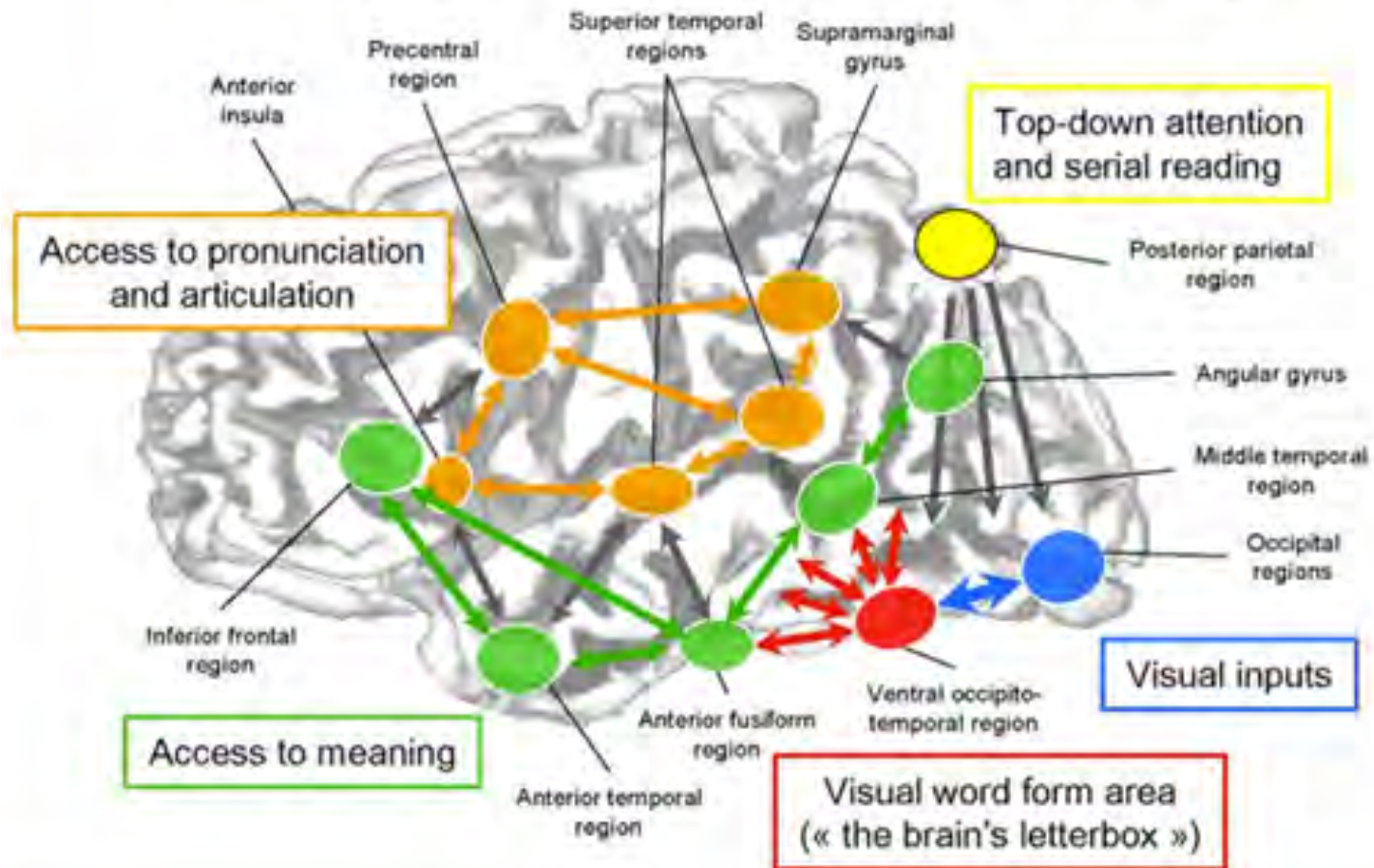


Anatomical connectivity



- White matter – rapid nerve impulse conduction

What happens in our brains as we read?



What is developmental dyslexia?

- Developmental Dyslexia (DD) is a brain-based type of learning disability that specifically impairs a person's ability to read.
 - Word decoding
 - Lack of fluency
 - Poor reading comprehension
- It affects 5-17% of all children.
- DD has been genetically linked to at least four candidate susceptibility genes (DYX1C1, KIAA0319, DCDC2 and ROBO1). *[Galaburda et al. 2006, Meng et al. 2005, Paracchini et al. 2006, Skiba et al. 2011]*
- Children with a family history of DD have a 34%-56% chance of developing DD.

What causes developmental dyslexia?

- The exact causes of dyslexia are still not completely clear, but anatomical and brain imagery studies show differences in the way the brain of a person with dyslexia develops and functions.
- Currently up to seven theories that try to explain DD
 - The most popular one: The phonological theory [Ramus et al. 2003]
 - The general magnocellular theory (includes rapid auditory processing theory, visual theory, and cerebellar theory) [Ramus et al. 2003]
 - The double-deficit theory [Vukovic et al. 2004, 2006]
- Towards a multidimensional model [Ramus et al. 2013]
 - Phonological skills versus phonological representations
 - Towards a general multimodal (verbal and visual) deficit

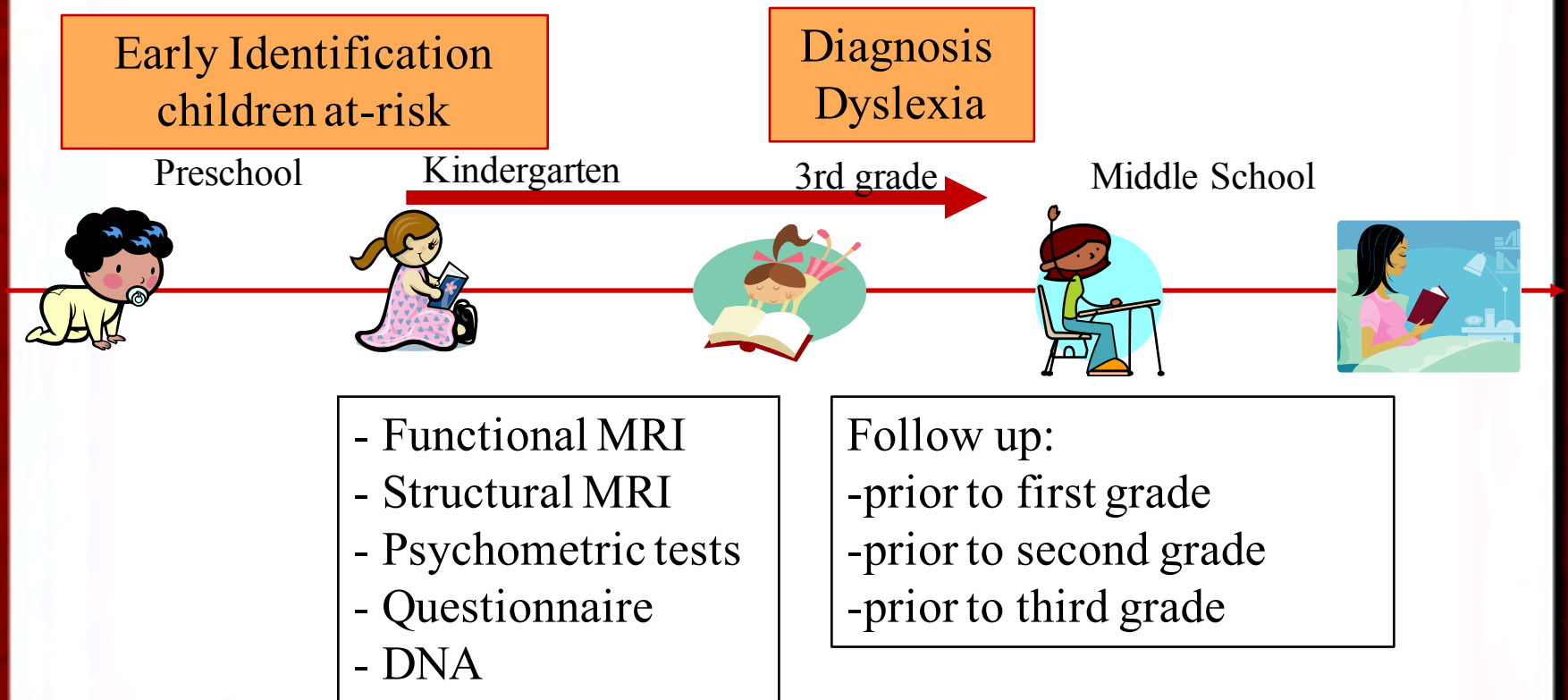
Diagnosis of developmental dyslexia

- Most children who struggle to read are not recognized until third grade, though some are identified earlier. Many more go undetected until much later.
- Strong psychological and clinical implications which start long before reading failure. Years of self-doubt and self-recrimination may erode a person's self-esteem, making them less able to tolerate the challenges of school, work, or social interactions and more stressed and anxious (low self-esteem, depression).
- No medications available for dyslexia yet.
- Early identification and customized remediation programs may reduce child stress, parental stress, improved overall family dynamic.

The "Dyslexia Paradox"

- To date, the earliest that DD can be reliably diagnosed is in second/third grade and most children exhibit enduring reading impairments throughout adolescence and into adulthood [*Francis & Shaywitz et al. 1996, Juel et al. 1988, Torgesen & Buress et al. 1998*].
- Intervention studies are most effective in kindergarten and first grade. When “at risk” beginning readers receive intensive instruction, 56% to 92% of at-risk children across six studies reached the range of average reading ability [*Torgesen et al. 2004*].

The BOston Longitudinal Dyslexia (BOLD) Study



Psychometric Measures:

- Clinical Evaluation Language Fundamentals –Preschool 2
- Comprehensive Test Of Phonological Processing
- Grammar And Phonology Screening Test
- York Assessment for Reading for Comprehension
- Rapid Automatized Naming and Rapid Alternating Stimulus Test
- Kaufman Brief Intelligence Test 2
- Year 2: Word reading (timed/untimed), passage comprehension, fluency, spelling, letter knowledge

Psychophysics Measures:

- RAP (tones and environmental sounds)
- Rise Time perception

Questionnaires :

- Development
- Home literacy
- SES

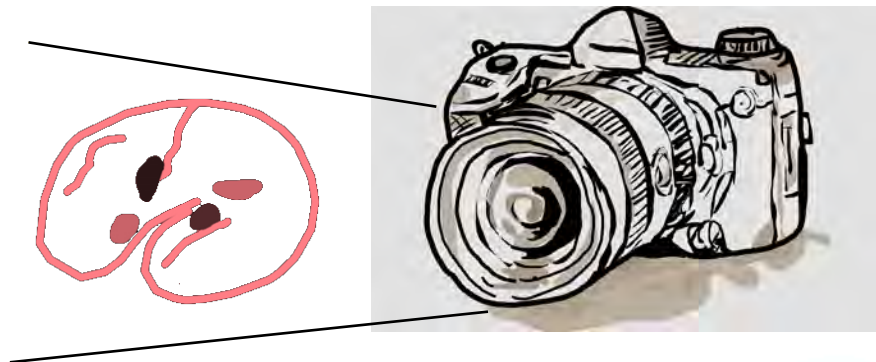
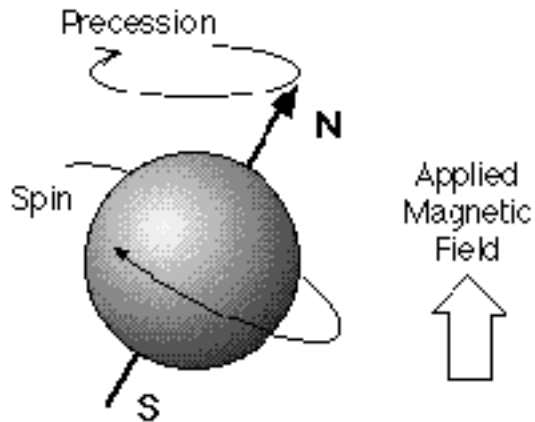
Tasks used in the MRI scanner :

- Phonological Processing
- Rapid auditory processing
- Executive functioning
- Reading Fluency

Structural brain
differences
(gray matter
volume, DTI)

Magnetic Resonance Imaging (MRI)

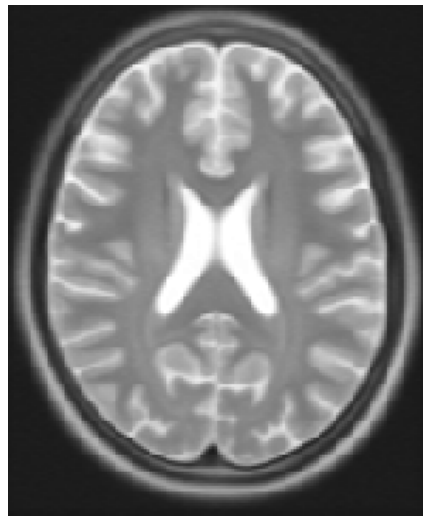
- Human body is made up of $\sim 63\%$ water.
- MRI system utilizes hydrogen atoms.



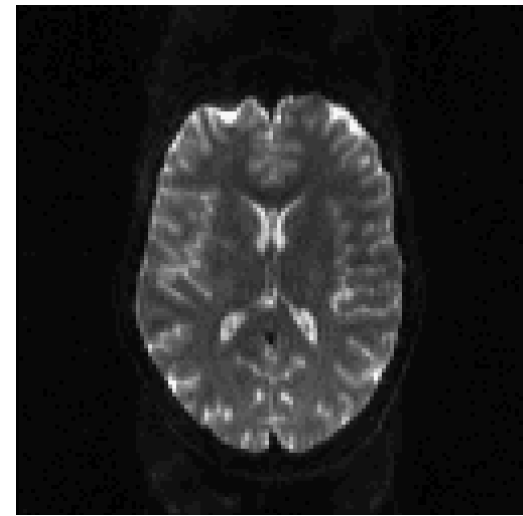
Various MRI signals



T1



T2

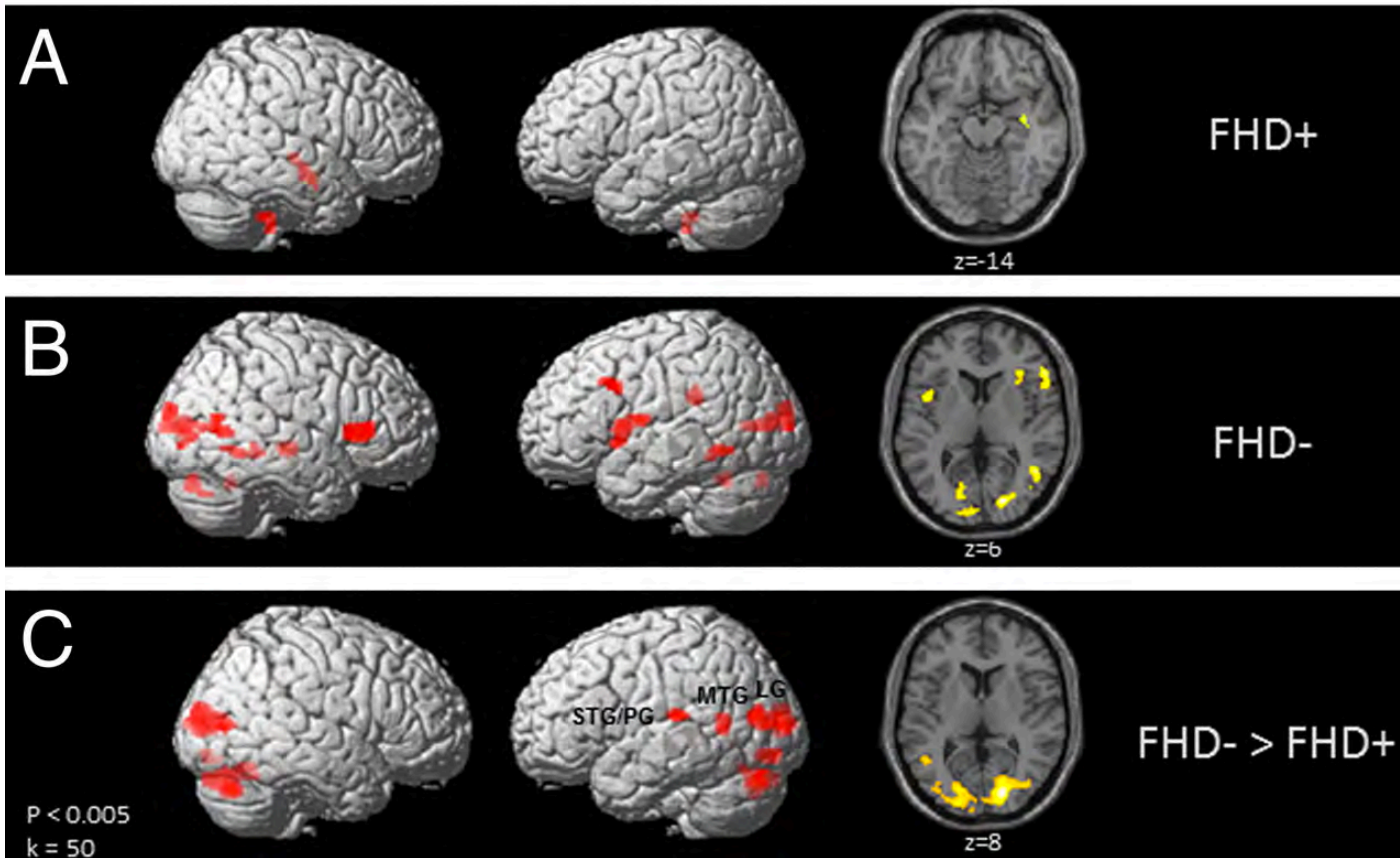


Diffusion

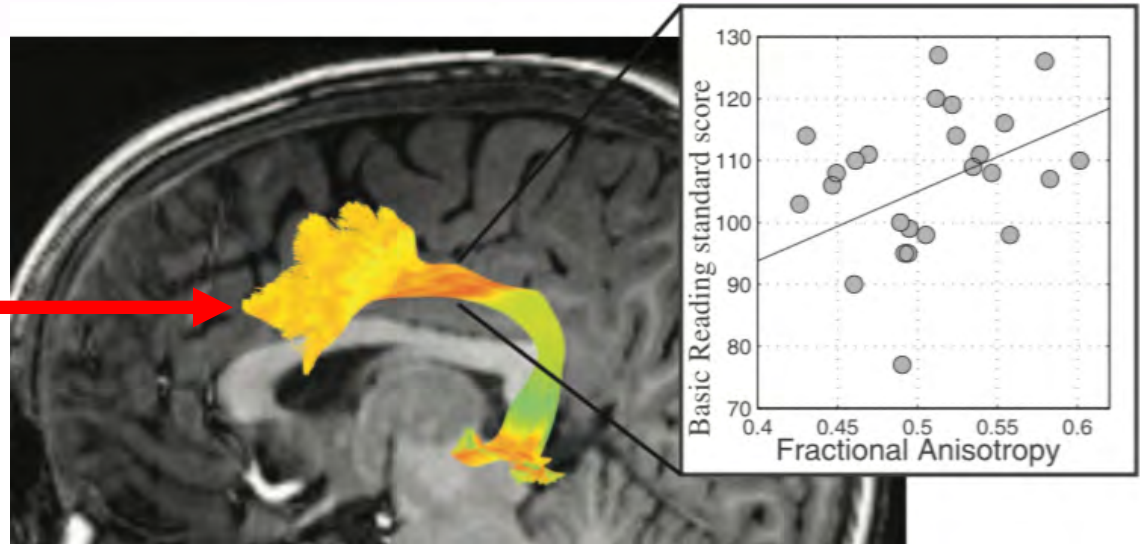
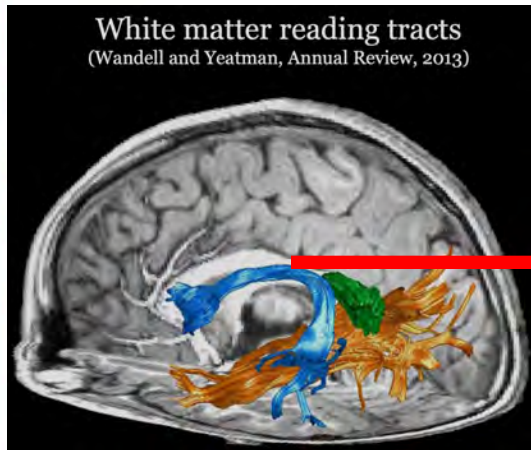
Gray matter alterations in at-risk children

FSM > VM

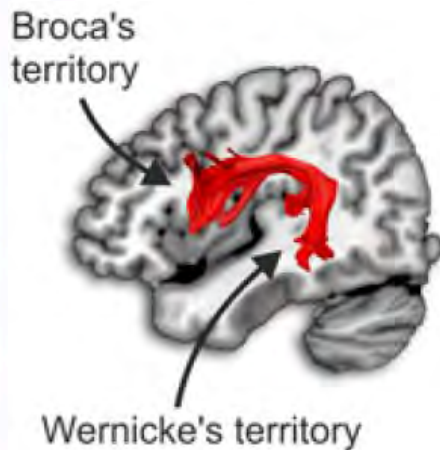
[Raschle et al., 2012]



White matter related to reading



[Yeatman *et al.*, 2012]



- White matter diffusion anisotropy in the temporo-parietal region positively correlates with reading ability.
- Arcuate Fasciculus (AF) tract (in Red)

White matter integrity in at-risk children?

- Does white matter integrity differences between individual at-risk for dyslexia and typical controls exist before reading onset?
- How is white matter development in at-risk children and typical controls?
- Can our imaging findings help us to predict later reading abilities?
- Why some at-risk children became good readers and the others became poor readers? (brain mechanism?)

Materials and Methods

- 78 healthy, native English-speaking children (45 FHD+, 33 FHD-)
- Among them, 45 children had at least one scan and composed a longitudinal cohort.
- 45 children (23 FHD+, 22 FHD-)
- None of the participants had any history of neurological or psychological symptoms, head injuries, visual problems or hearing loss.

Cross-sectional cohort

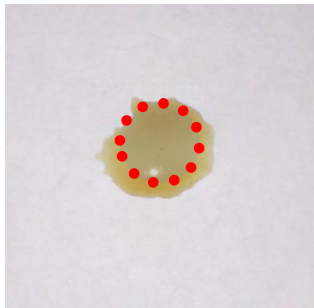
- 78 children were divided into three developmental groups. Children who recognized fewer than 9 single words were regarded as pre-readers. Children had either entered kindergarten or 1st /2nd grade were regarded as beginning readers. Children had entered 3rd/4th/5th grade were regarded as fluent readers. 45 children (age range: 59-150 months, 24 boys, 21 girls) who had at least one first-degree relative with a clinical diagnosis of DD were classified as FHD+ (with a family history of DD). 33 children (age range: 60 - 134 months 18 boys/15 girls) who had no first-degree relatives with DD or reading difficulties were classified as FHD- (without a family history of DD).

Longitudinal cohort

- Of the 78 children, 45 had more than one scan point and formed the longitudinal cohort (FHD-: $n = 22$, mean age at the first data point: 80 months 10 boys/12 girls; FHD+: $n = 23$, mean age at the first data point: 81 months 13 boys/10 girls), with a total of 103 scans (see Table S2). None of the participants had any history of neurological or psychological symptoms, head injuries, visual problems or hearing loss. The study was approved by the Institutional Review Board at Boston Children's Hospital. Written informed consent was obtained from each participant's parents and verbal assent was obtained from each participant.

Diffusion process

- Water molecules move through and within tissue
 $D = x^2/(2t)$, t is the time and x^2 is the mean squared displacement
- Faster or slower depending on the tissue properties

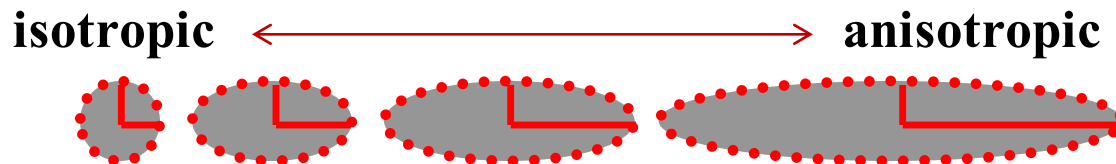


Coffee drop on
a piece of
B5 printing paper



Coffee drop on
a piece of
tissue paper

- Anisotropy: diffusion rate depends on direction



Diffusion Weighted MR Imaging

Diffusion weighted imaging (DWI) is a form of MR imaging based upon measuring the random Brownian motion of water molecules within a voxel of tissue.

- Quantitative measurement:

$$S = S_0 \cdot e^{-b \cdot D}$$

S_0 : signal intensity without diffusion weighting

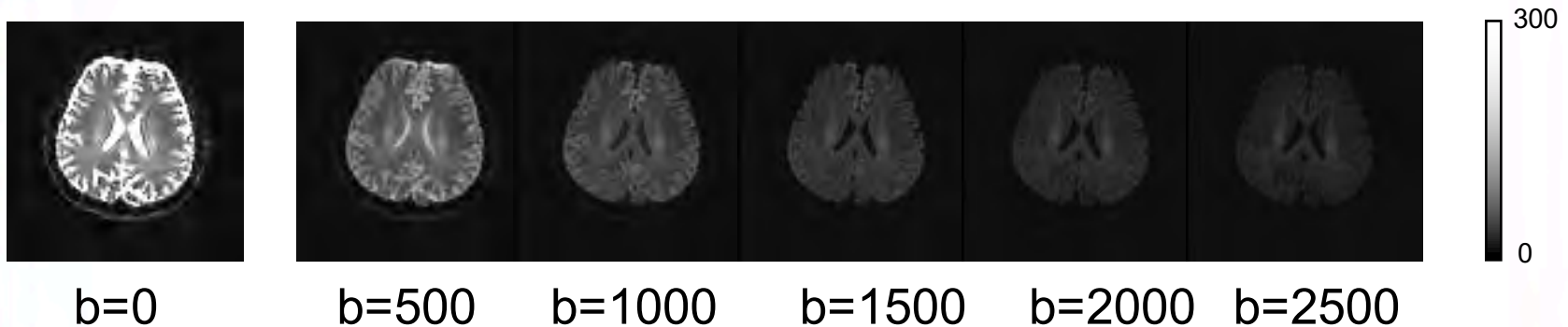
S: signal intensity with diffusion weighting

b: diffusion gradient

D: diffusion coefficient

b-value

Mean DWI (50 directions)



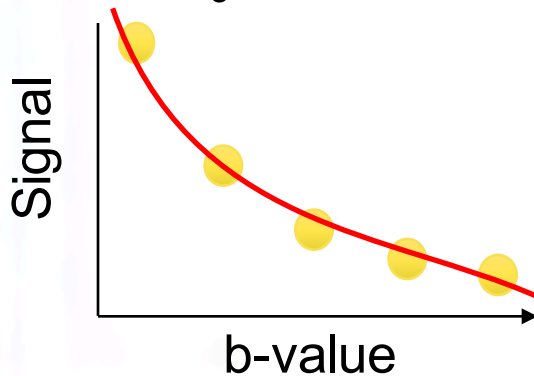
b-value: can change diffusion related signal attenuation. Higher b-value increases sensitivity to diffusion.

The optimum diffusion-weighting (also called b-value) for the brain is roughly between 700 and 1300 s/mm² with a b-value of 1000 s/mm² being most common.

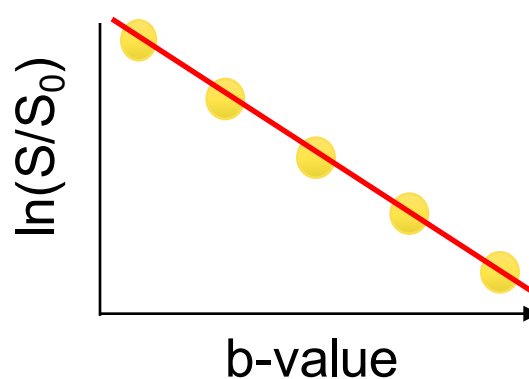
Gaussian distribution of diffusion

- If diffusion weighted signal comes from free diffusion, gradient magnetic pulse would decay DW signal mono-exponentially with b-value:
 - Diffusivity across b-value decreases linearly
 - Diffusion coefficient across b-value is constant

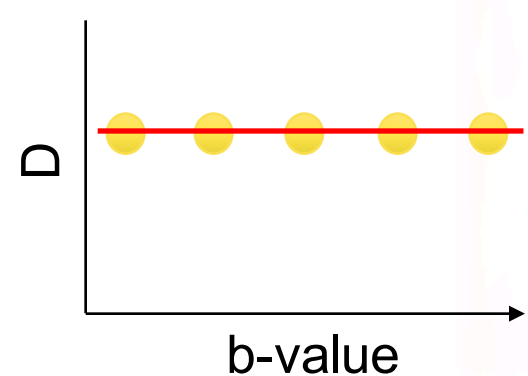
$$S = S_0 \cdot e^{-bD} \rightarrow$$



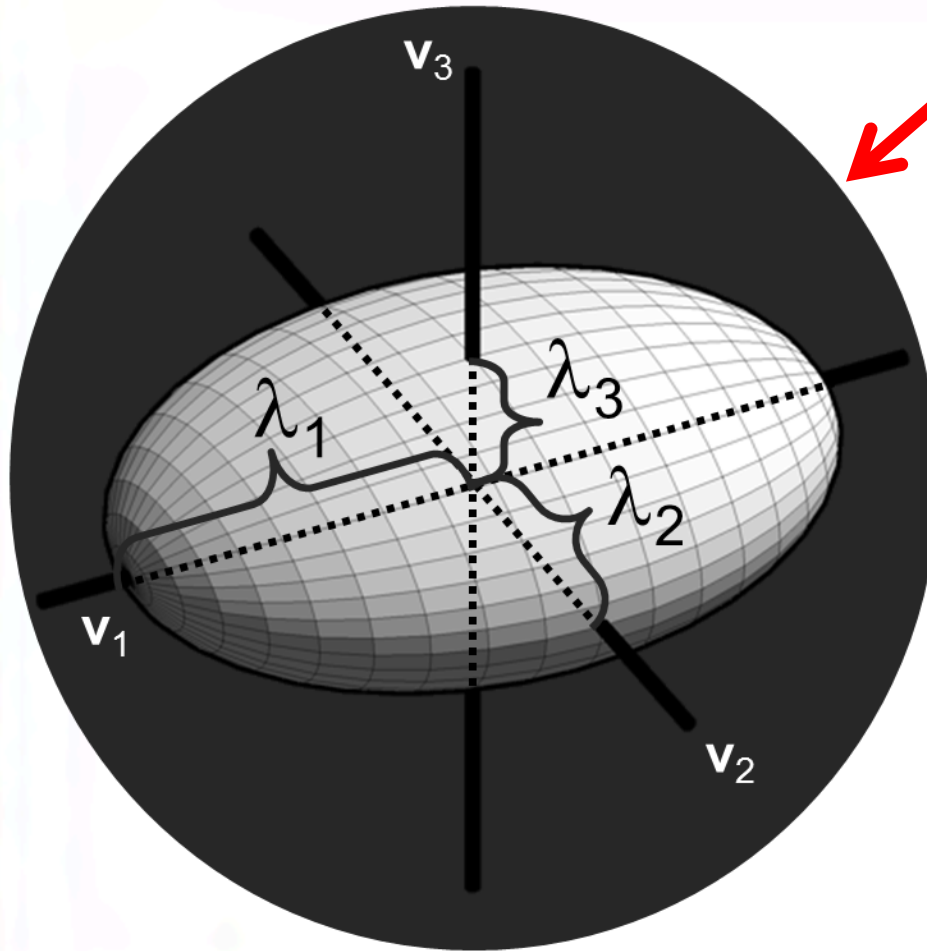
$$-bD = \ln(S/S_0) \rightarrow$$



$$D = \ln(S/S_0) / -b$$



Diffusion Tensor Imaging



$$D = \ln(S/S_0) / -b$$

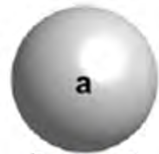
D is a “square, symmetric, positive-definite matrix”.

$$\bar{D} = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{bmatrix}$$

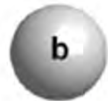
$$\overline{D}_{diag} = \begin{bmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{bmatrix}$$

Quantitative measures of diffusion

Fractional anisotropy (FA)



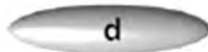
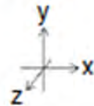
$$\begin{bmatrix} 8 & 0 & 0 \\ 0 & 8 & 0 \\ 0 & 0 & 8 \end{bmatrix}$$



$$\begin{bmatrix} 4 & 0 & 0 \\ 0 & 4 & 0 \\ 0 & 0 & 4 \end{bmatrix}$$



$$\begin{bmatrix} 6 & 0 & 0 \\ 0 & 3 & 0 \\ 0 & 0 & 3 \end{bmatrix}$$



$$\begin{bmatrix} 8 & 0 & 0 \\ 0 & 2 & 0 \\ 0 & 0 & 2 \end{bmatrix}$$



$$\begin{bmatrix} 10 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}$$



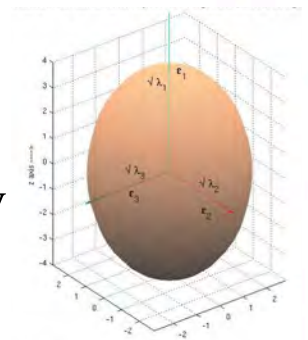
$$\begin{bmatrix} 3.25 & 3.90 & 0 \\ 3.90 & 7.75 & 0 \\ 0 & 0 & 1 \end{bmatrix}$$

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

FA range from 0 – 1

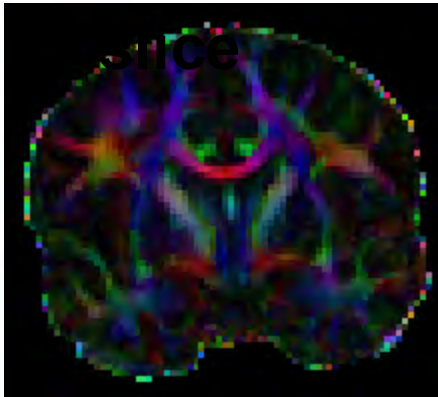
FA= 0 → Diffusion is spherical (i.e. isotropic, gray matter)

FA= 1 → Diffusion is tubular (i.e. anisotropic)

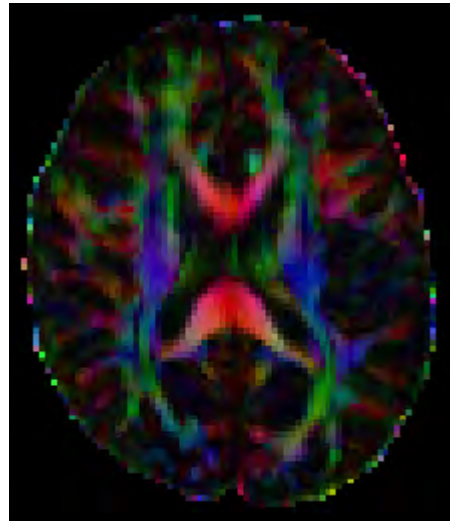


Visualization: Color FA

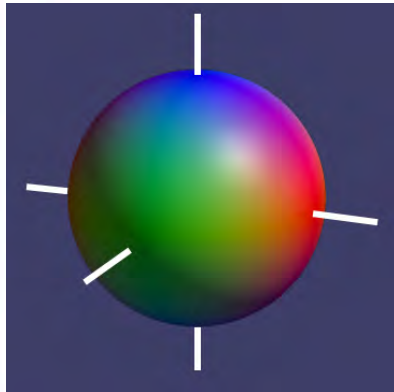
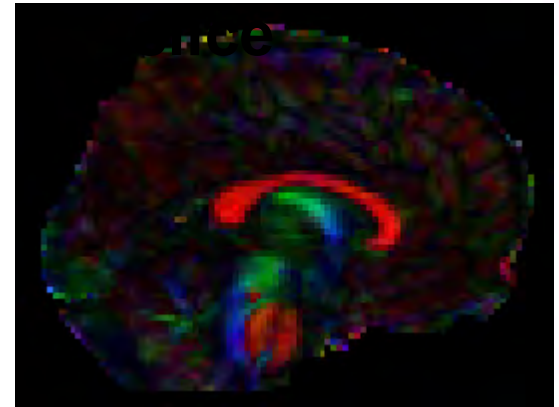
Coronal



Axial slice



Sagittal



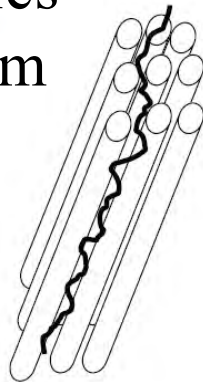
R = $|\mathbf{e}_1 \cdot \mathbf{x}|$ --- Red indicates directions in the X axis: right to left or left to right.

G = $|\mathbf{e}_1 \cdot \mathbf{y}|$ --- Green indicates directions in the Y axis: posterior to anterior or from anterior to posterior.

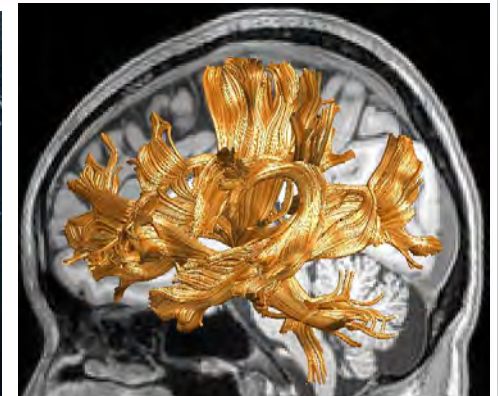
B = $|\mathbf{e}_1 \cdot \mathbf{z}|$ --- Blue indicates directions in the Z axis: foot-to-head direction or vice versa

Whole-brain Tractography

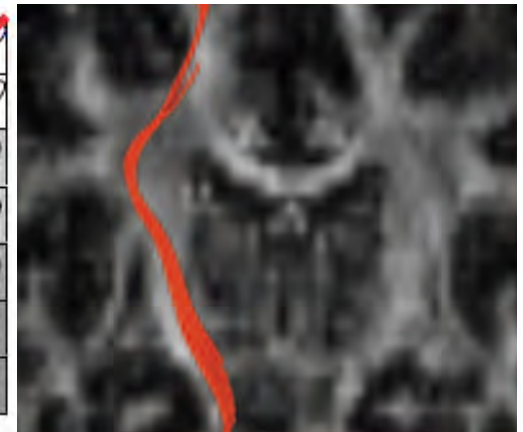
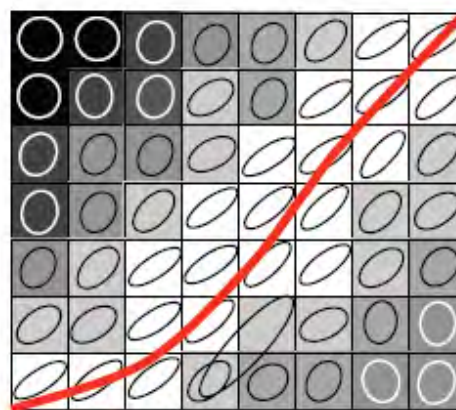
- Infer where fiber tracts are.
- Voxels are connected based upon similarities in the maximum diffusion direction.



<http://fieremans.diffusion-mri.com/phd/PhDch2.html>



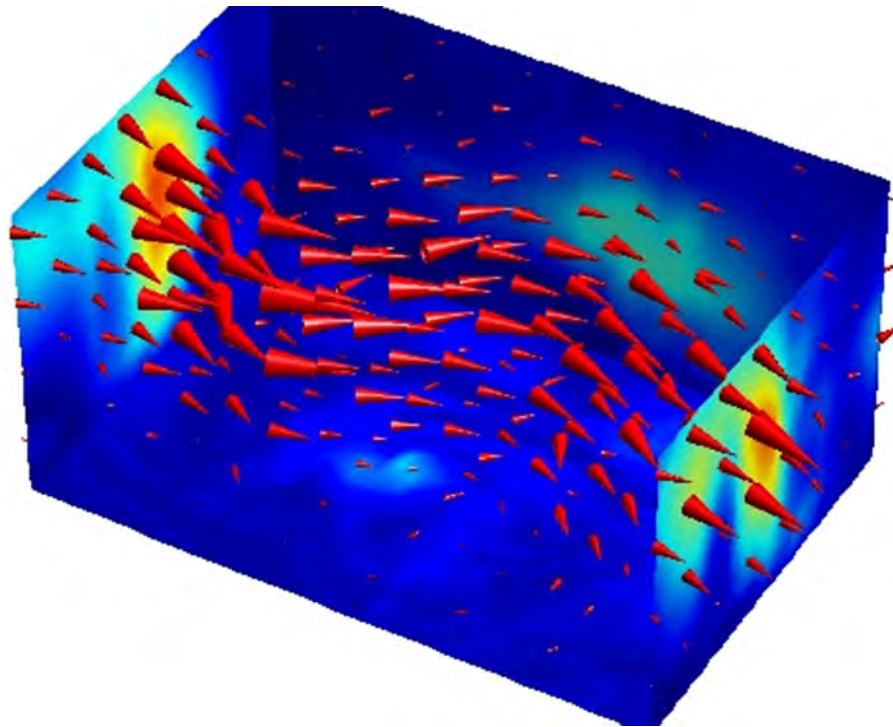
Tractography from my own DWIs



Johansen-Berg et al.
Ann Rev. Neurosci 32:75-94 (2009)

Tractography Basis

- Fluid Dynamics (visualization of flow field)



Deterministic Tractography

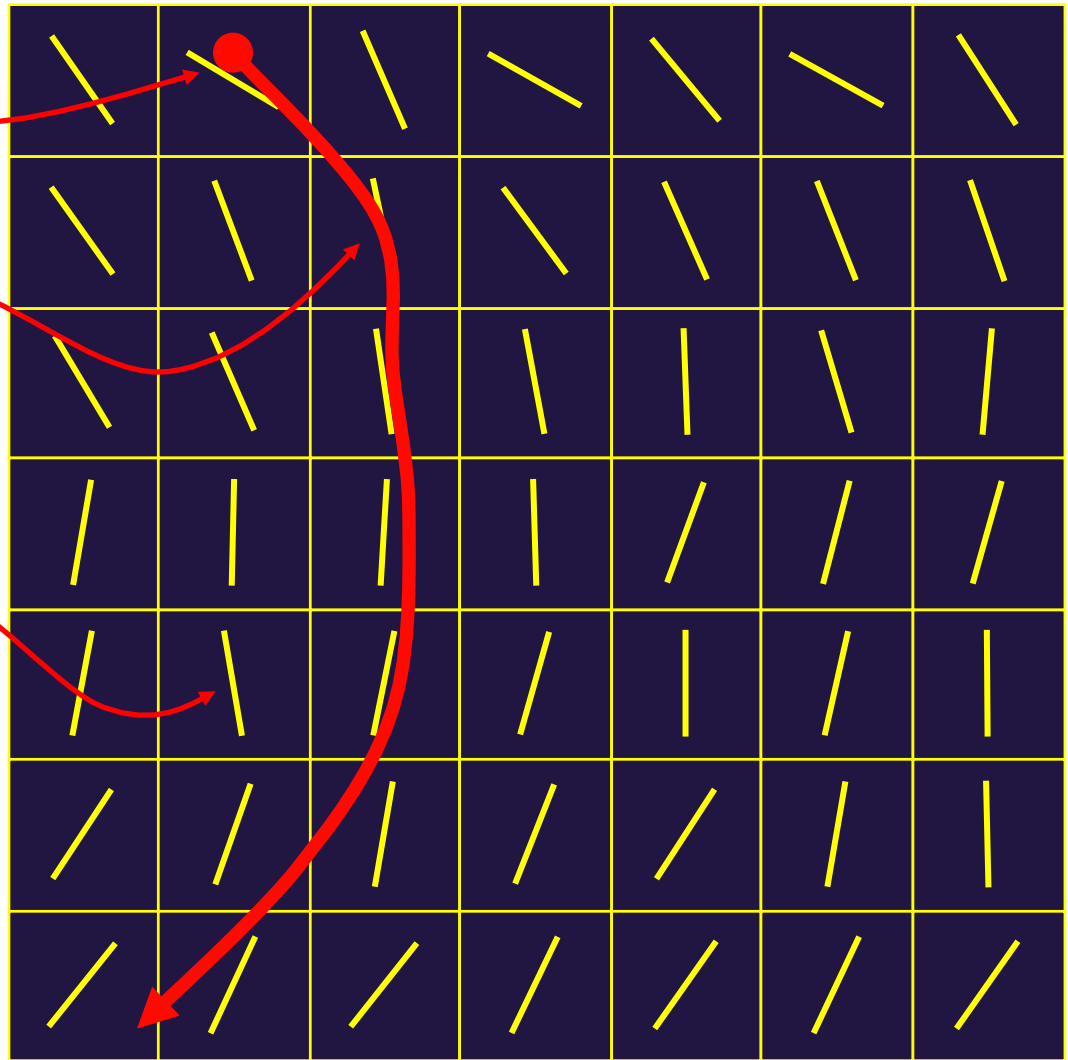
- Uses vector field associated with grid of principle directions
- Requires
 - Seed points (s)
 - Stopping criteria
 - FA too low
 - Directions not aligned (curvature too high)
 - Leave region of interest/volume
- Different algorithm: FACT, TEND, Tensorline, ConTrack, Gtrack, Level-Set



Seed point(s)

**Move marker in
discrete steps and
find next direction**

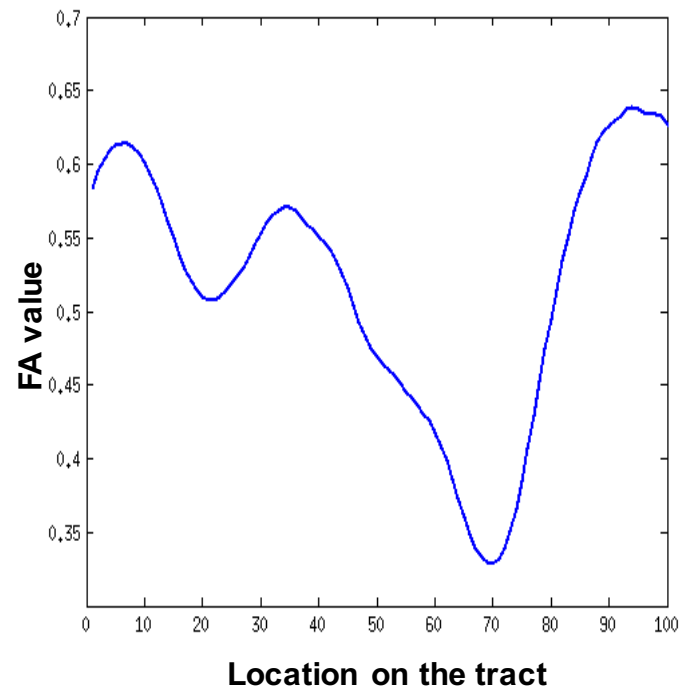
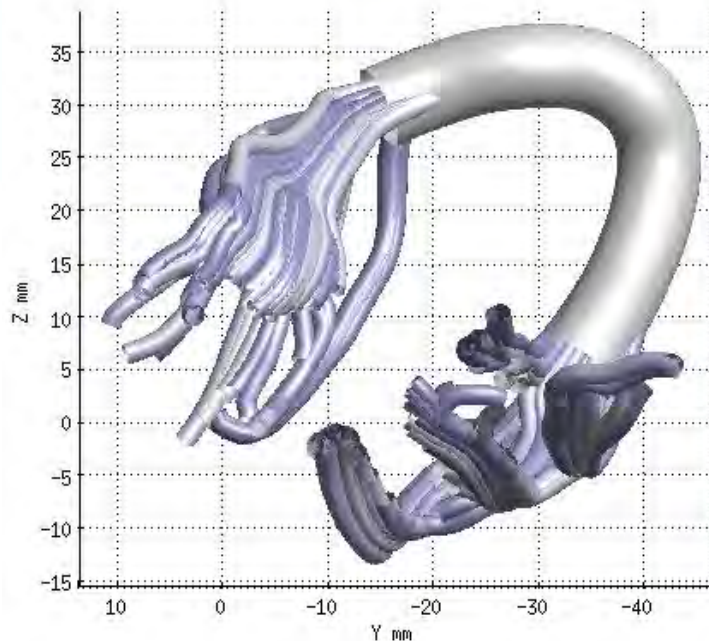
**Direction of
principle eigen
value**



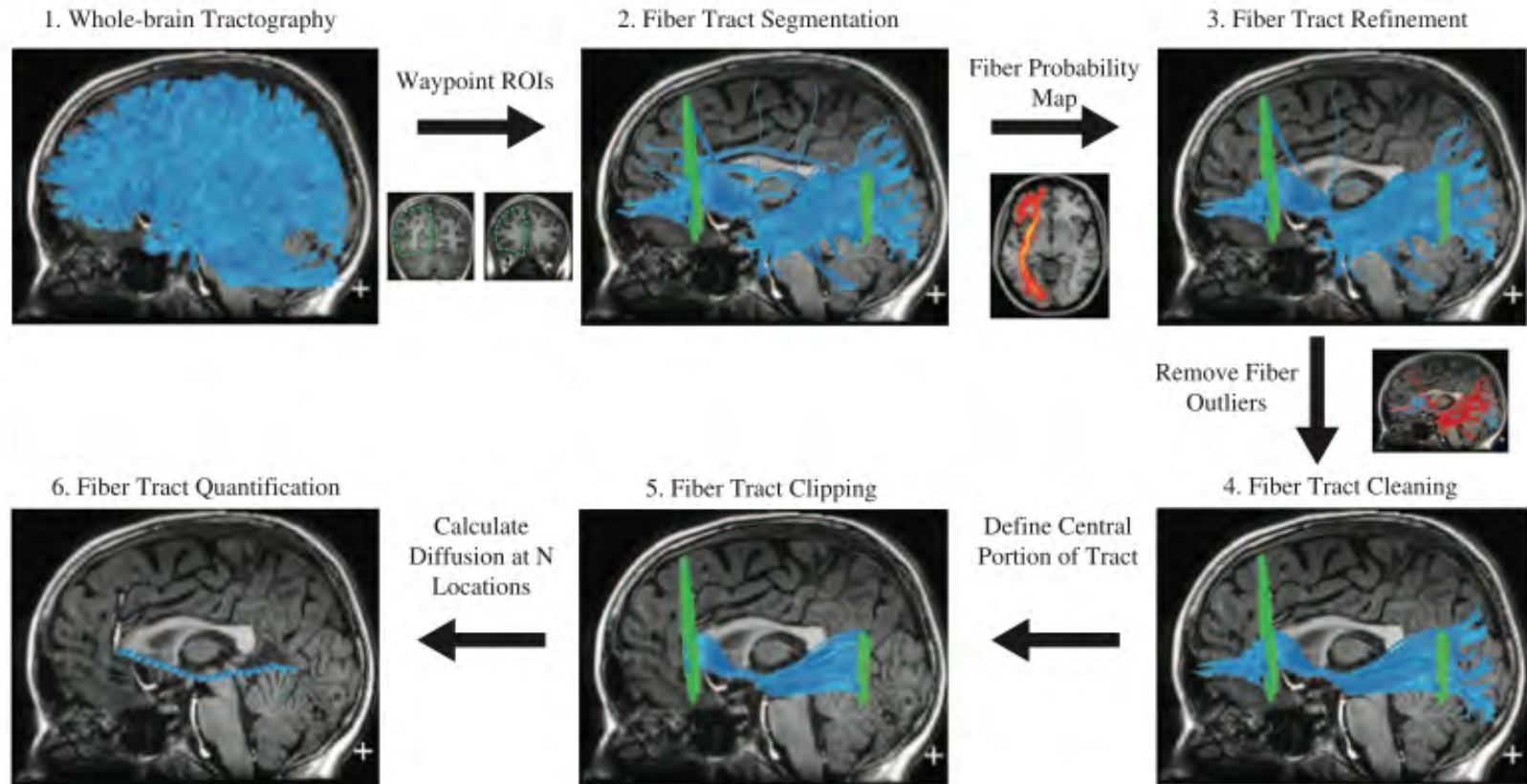
Tract Profiles of White Matter Properties: Automating Fiber-Tract Quantification

Jason D. Yeatman^{1,2*}, Robert F. Dougherty², Nathaniel J. Myall³, Brian A. Wandell^{1,2}, Heidi M. Feldman^{3,4}

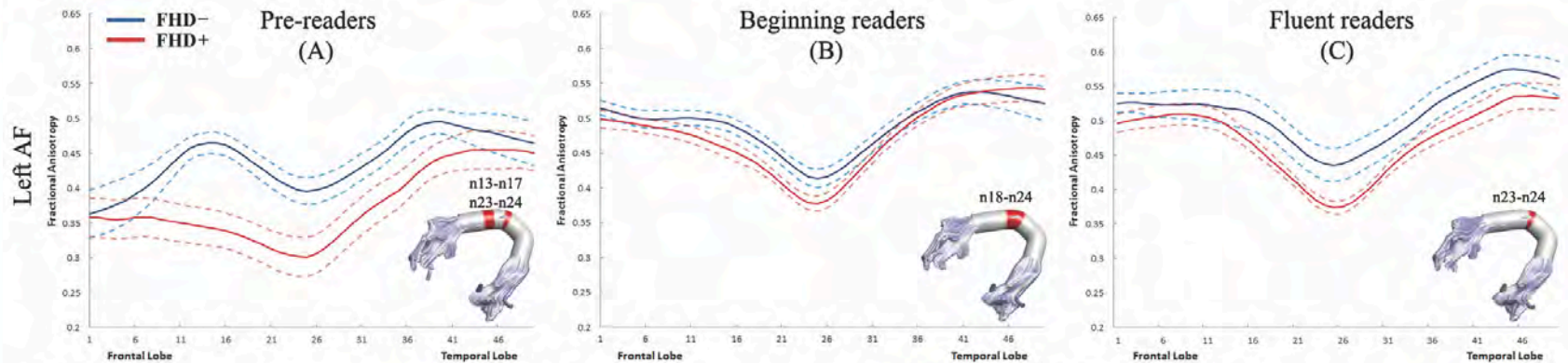
1 Department of Psychology, Stanford University, Stanford, California, United States of America, **2** Stanford Center for Cognitive and Neurobiological Imaging, Stanford University, Stanford, California, United States of America, **3** Stanford University School of Medicine, Stanford, California, United States of America, **4** Division of Neonatal and Developmental Medicine, Department of Pediatrics, Stanford University School of Medicine, Stanford, California, United States of America



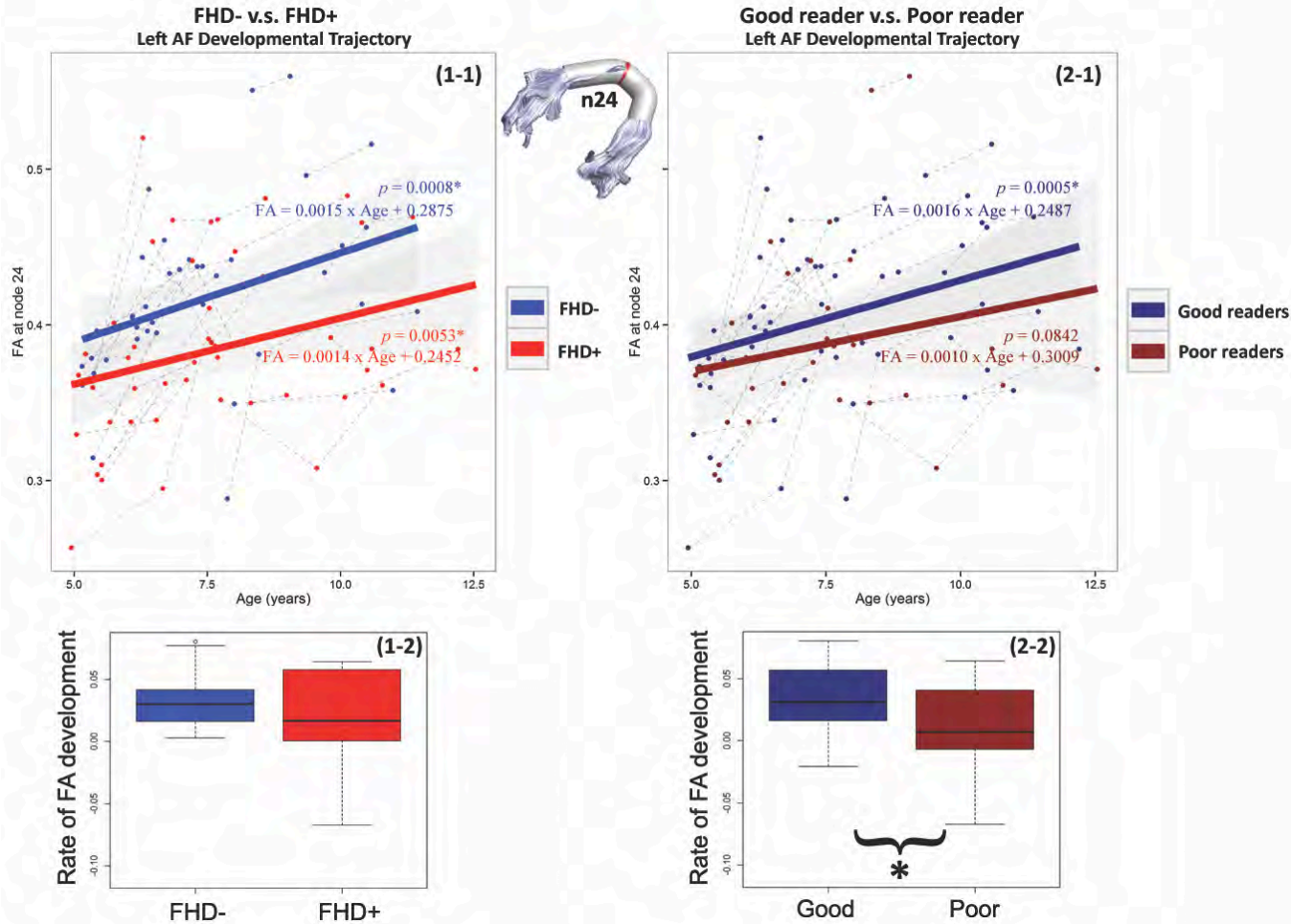
Automated Fiber Quantification (AFQ)



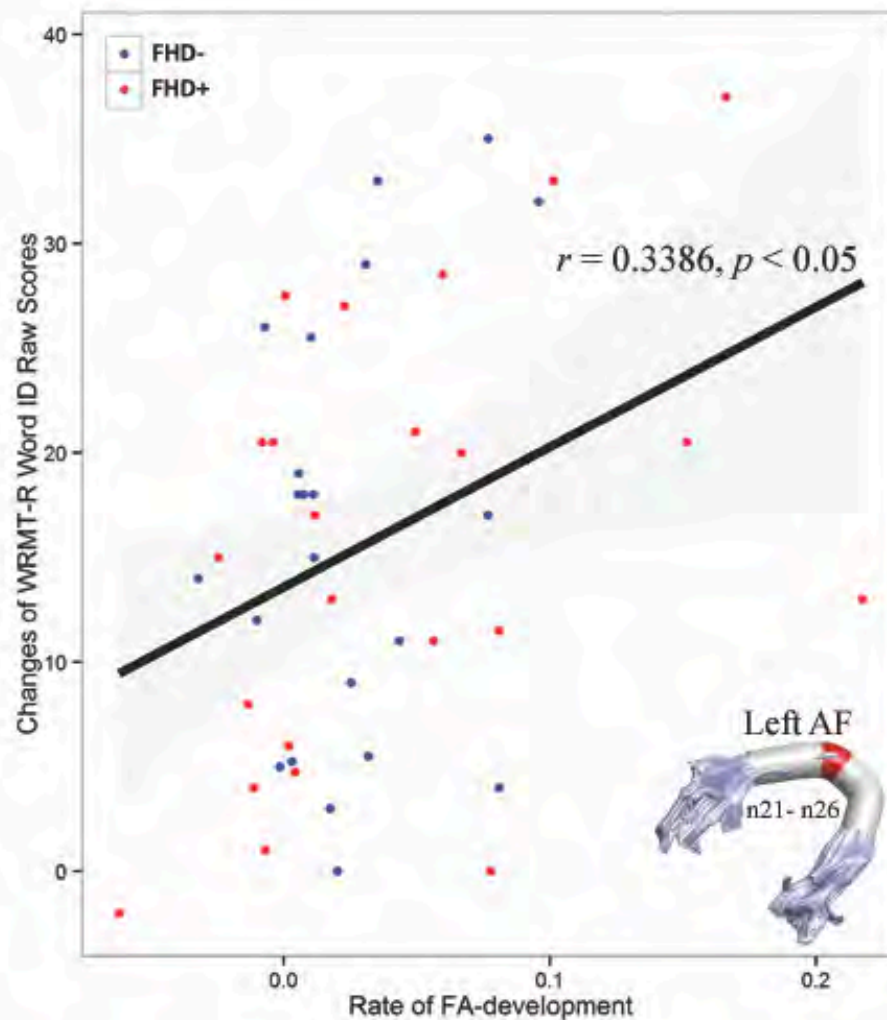
Cross-sectional findings



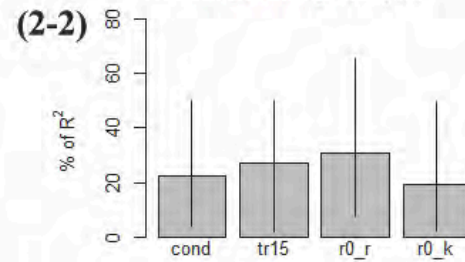
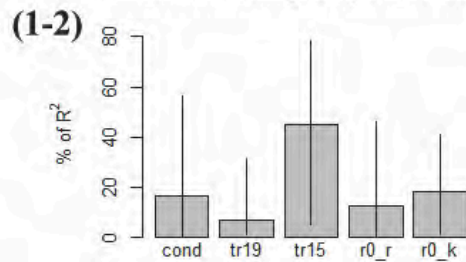
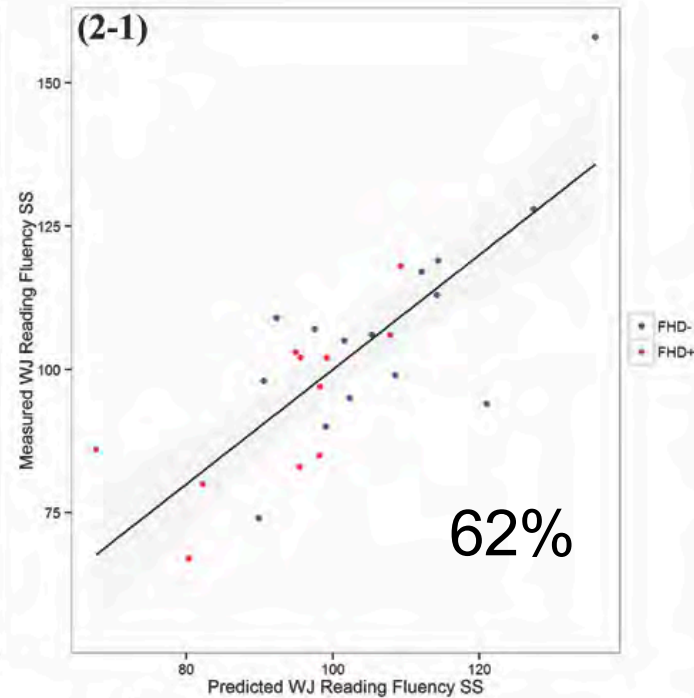
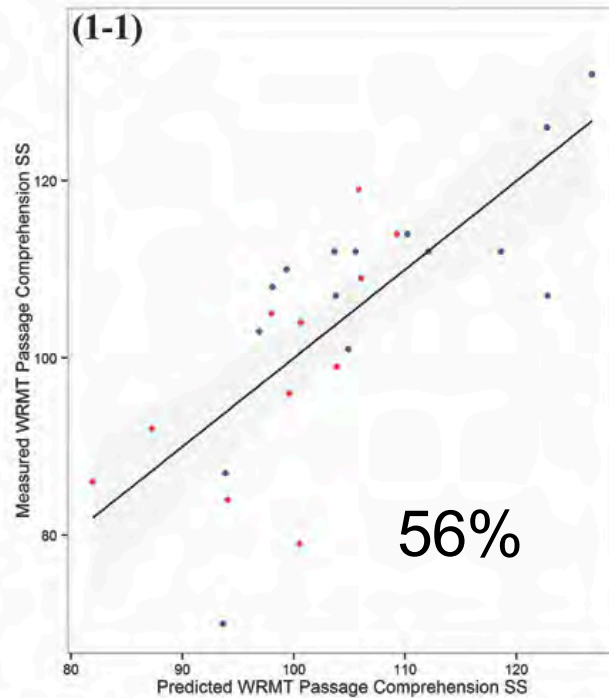
Longitudinal findings



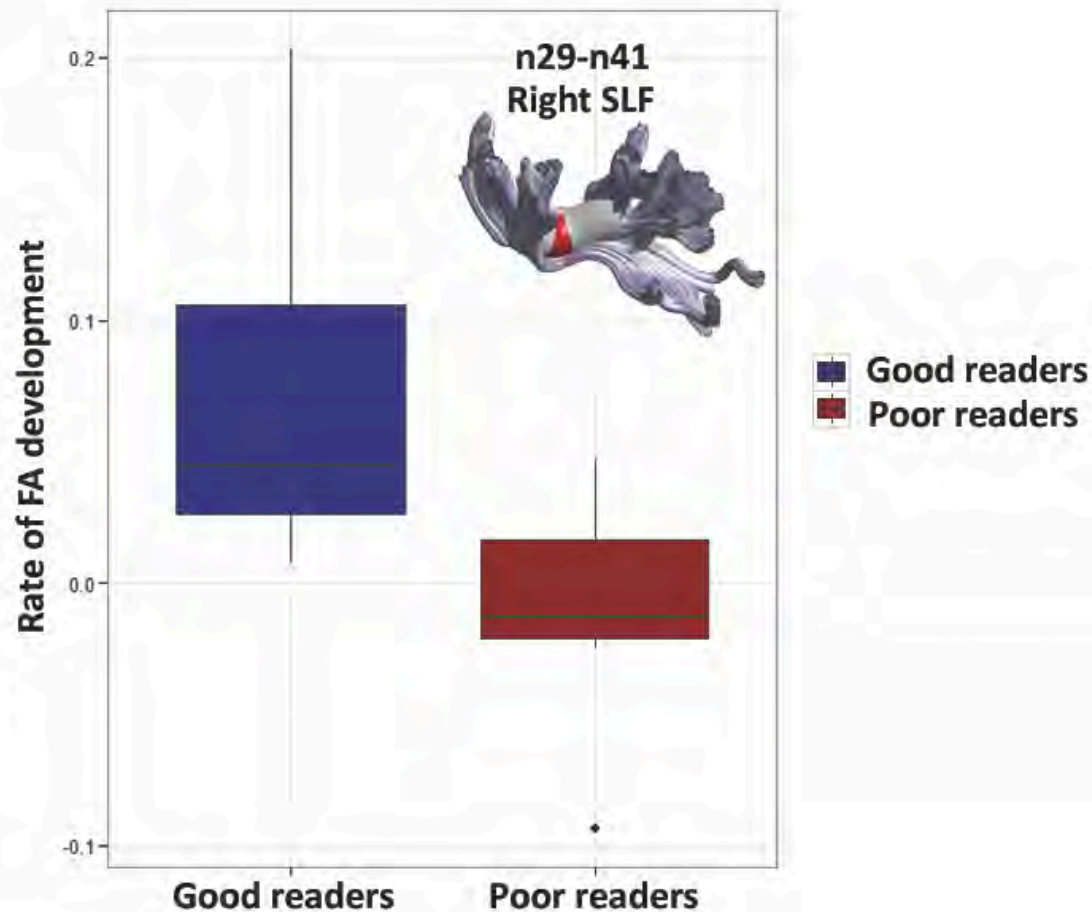
Brain-Behavior relationship



Predication of later reading abilities



Protective factor/Compensatory



Discussion

- Tract-specific white matter alterations predate reading onset. FHD+ children showed lower FA in the temporo-parietal segment of AF.
- Interestingly, the section along the AF showing lower FA in FHD+ children reduced in size over the course of brain development, which suggests that white matter alterations in the AF in FHD+ children remain capable of plastic changes through brain development, most likely as a result of postnatal factors such as home literacy environments and quality of reading instruction.

Discussion

- Slower FA-development in the temporo-parietal segment of the left AF can lead to insufficient transmission between reading-related functional regions, which might indirectly lead to subsequent poor reading development.
- The maturation of white matter pathway plays an important role in atypical and typical reading development.

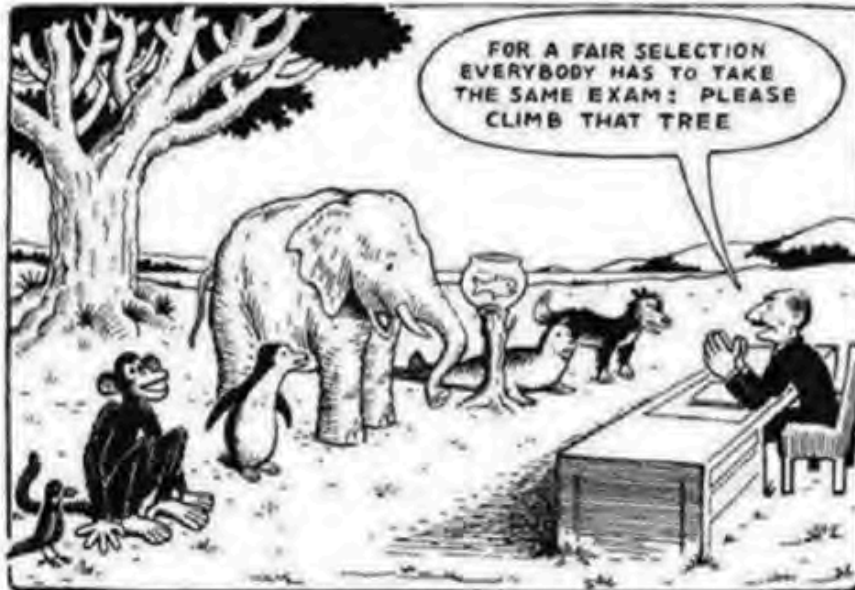
Discussion

- A subset of FHD+ children who developed into good readers show faster white matter development in the right superior longitudinal fasciculus compared to those FHD+ children who developed into poor readers, suggesting a potential right-hemispheric compensatory mechanism for DD.

Discussion

- White matter maturation from the pre-reading to the fluent reading stage in the longitudinal cohort combined with familial risk and psychometric measures at the pre-reading stage best predicts later reading abilities, emphasizing the importance of considering white matter development as a dynamic variable when examining typical and atypical reading development and its brain correlates.

Benefits from our research findings



Our Education System

"Everybody is a genius. But if you judge a fish by its ability to climb a tree, it will live its whole life believing that it is stupid."

- Albert Einstein

- Changes in educational policies (early IEPs; design and implementation of customized curriculums for children at-risk).
- Maximizing use of 'intellectual potential' and maximizing the joy to learn to read.
- One-on-one early literacy development program

Future directions

- Dissociation of prenatal versus postnatal influences. Thus, in order to understand the entire process of white matter development, it is necessary to collect longitudinal data starting from as early as infancy and continuing through late adolescence.
- The resilient brain (protective factors, critical periods) – help us to predict who will benefit from intervention.

Take away points

- Children with a family history of dyslexia (direct relatives, for example, parents or siblings) demonstrated less white matter integrity in the left hemisphere than healthy typical controls, indicating abnormalities in brain structure predate reading onset. This finding suggests that teacher might want to know the family history of dyslexia for a child in order to help identify children at-risk for dyslexia even before they learn to read.

Take away points

- Longitudinal analysis revealed that faster white matter development in subsequent good versus poor readers, highlighting the importance of white matter pathway maturation in the development of typical and atypical reading skills.

Take away points

- Imaging data combined with behavioral measures best predict reading outcomes. The earlier a child gets help to remediate their reading difficulties, the better the outcome will be. Thus, this finding indicates imaging data can really help teachers to identify children at-risk for dyslexia so that these children will receive individualized education programs earlier even before reading onset.

Take away points

- Among those children who have a family history of dyslexia, some of those who later had no reading difficulty showed faster white matter development in the right hemisphere than those who later had reading difficulties, suggesting a potential compensation mechanism in the right side of the brain.
- Our findings suggest that Individualized education program policy shall allow school and teachers to use neuroimaging data as part of the evidence to request special education service for children at-risk for dyslexia.

Acknowledgements

Funding source: NICHD (1R01HD065762-03), P.I. Dr. Nadine Gaab





