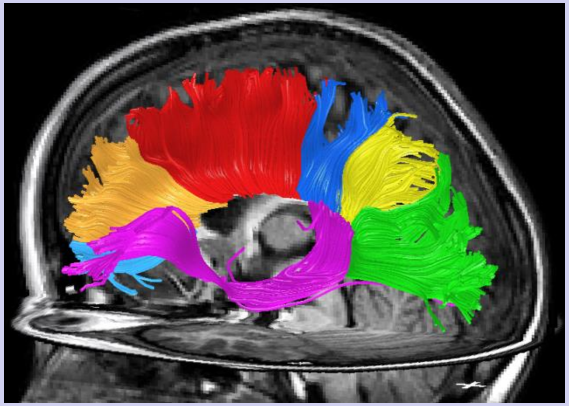
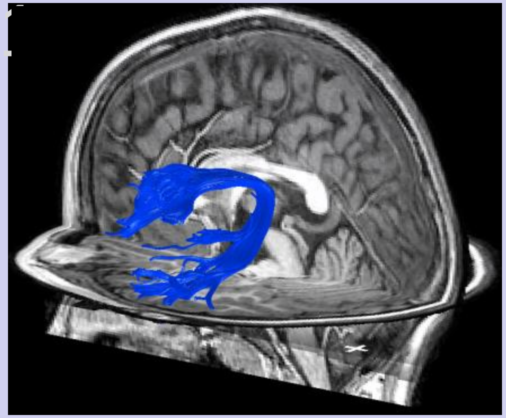
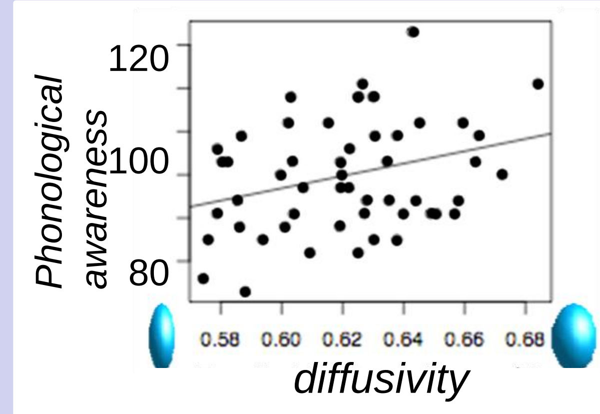






White matter pathways for language and reading in developmental and clinical populations

Dr. Michal Ben-Shachar

Department of English Literature and Linguistics

The Gonda Brain Research Center

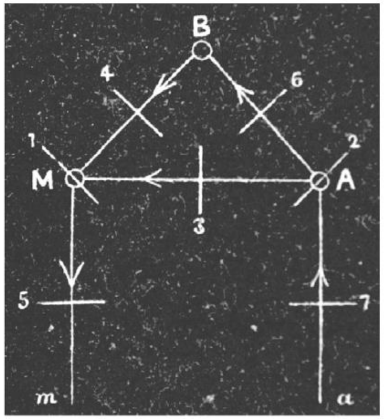
Bar Ilan University

Tradition of Excellence
Bar-Ilan University

המרכז הרב תחומי לחקר המוח
ע״ש לסלי וסוזן גונדה (גולדשמיד)
The Leslie and Susan Gonda (Goldschmied)
Multidisciplinary Brain Research Center

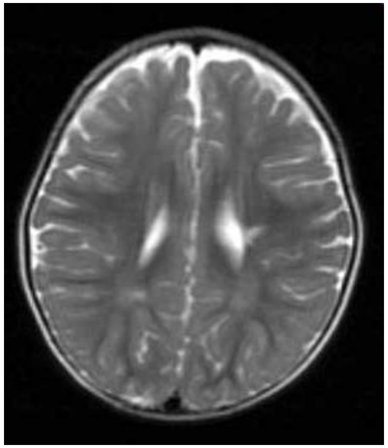
Why study white matter?

- When we study complex systems such as language and reading, connectivity is as important as cortical specialization

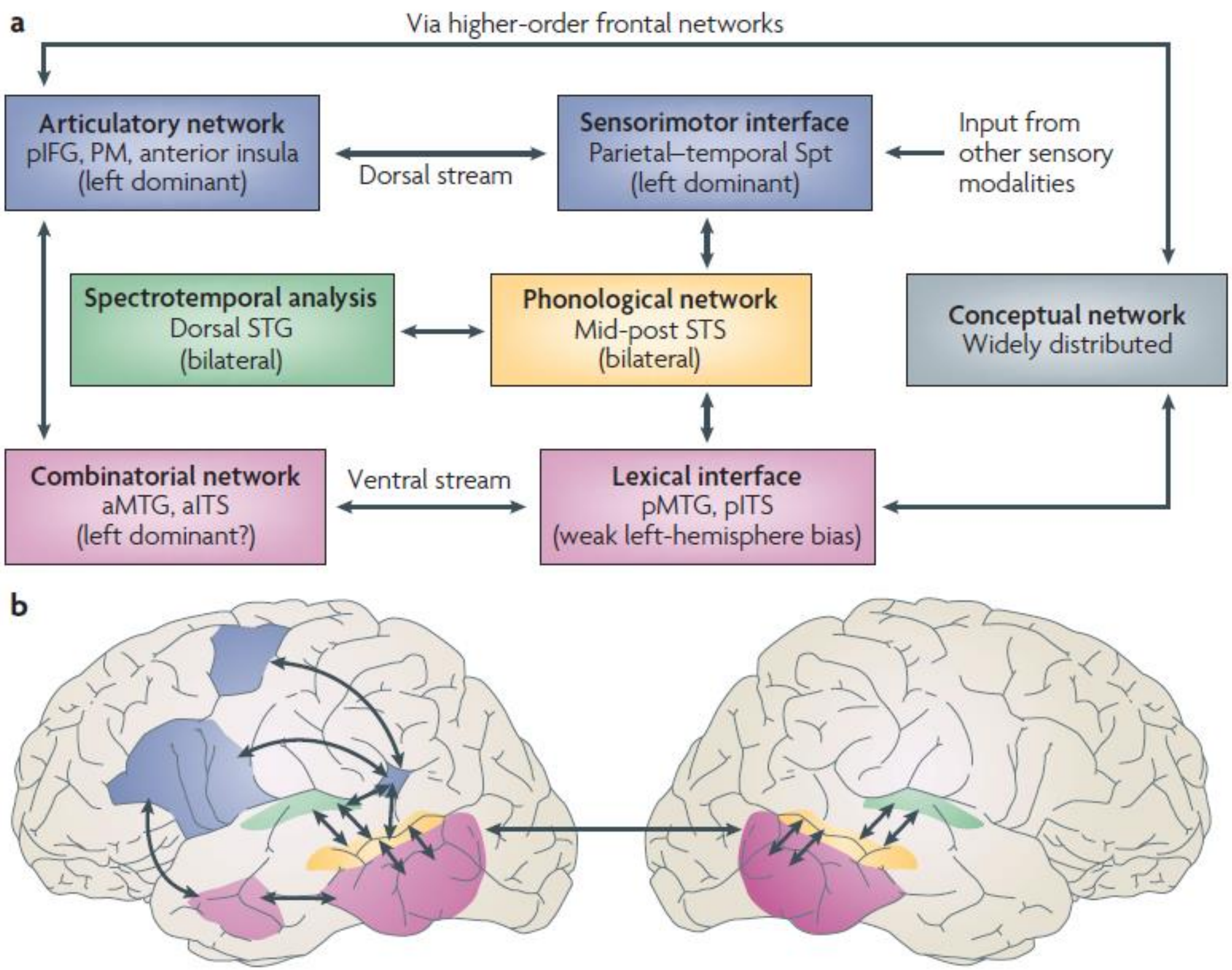


Wernicke, 1874
Lichtheim, 1885
Reproduced from:
Catani & Mesulam 2008

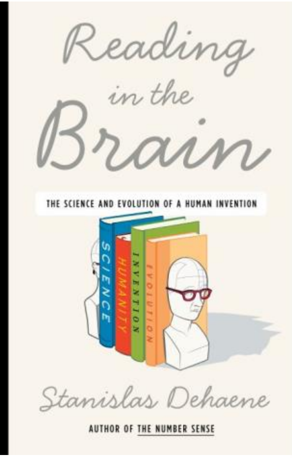
- White matter impairments underlie many developmental deficits (e.g., premature birth). Quantifying white matter properties in individuals is of major clinical interest to developmental neurology



Current pathway-based models of the language systems



Hickok and Poeppel 2007



A modern vision of the cortical networks for reading

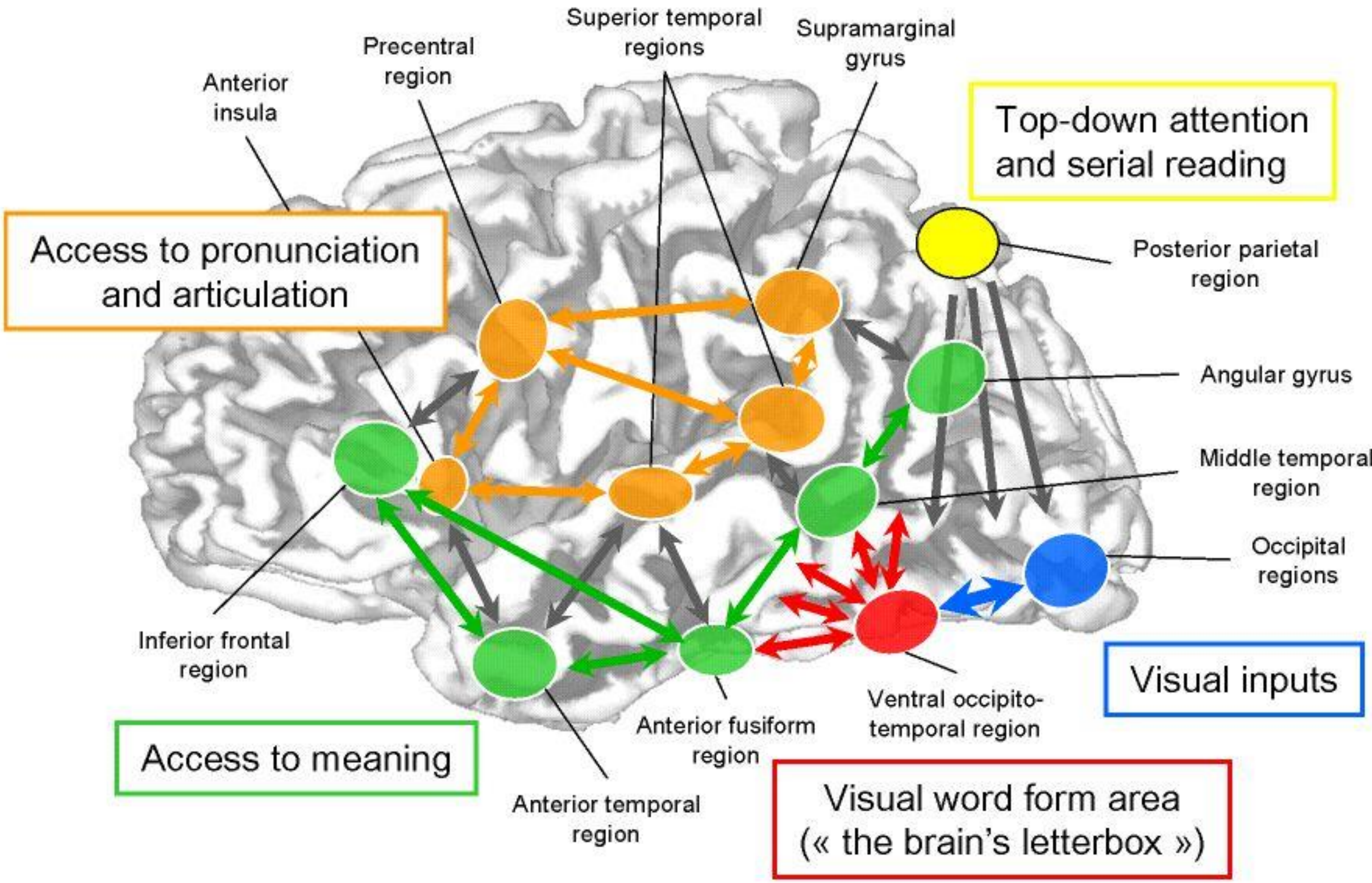
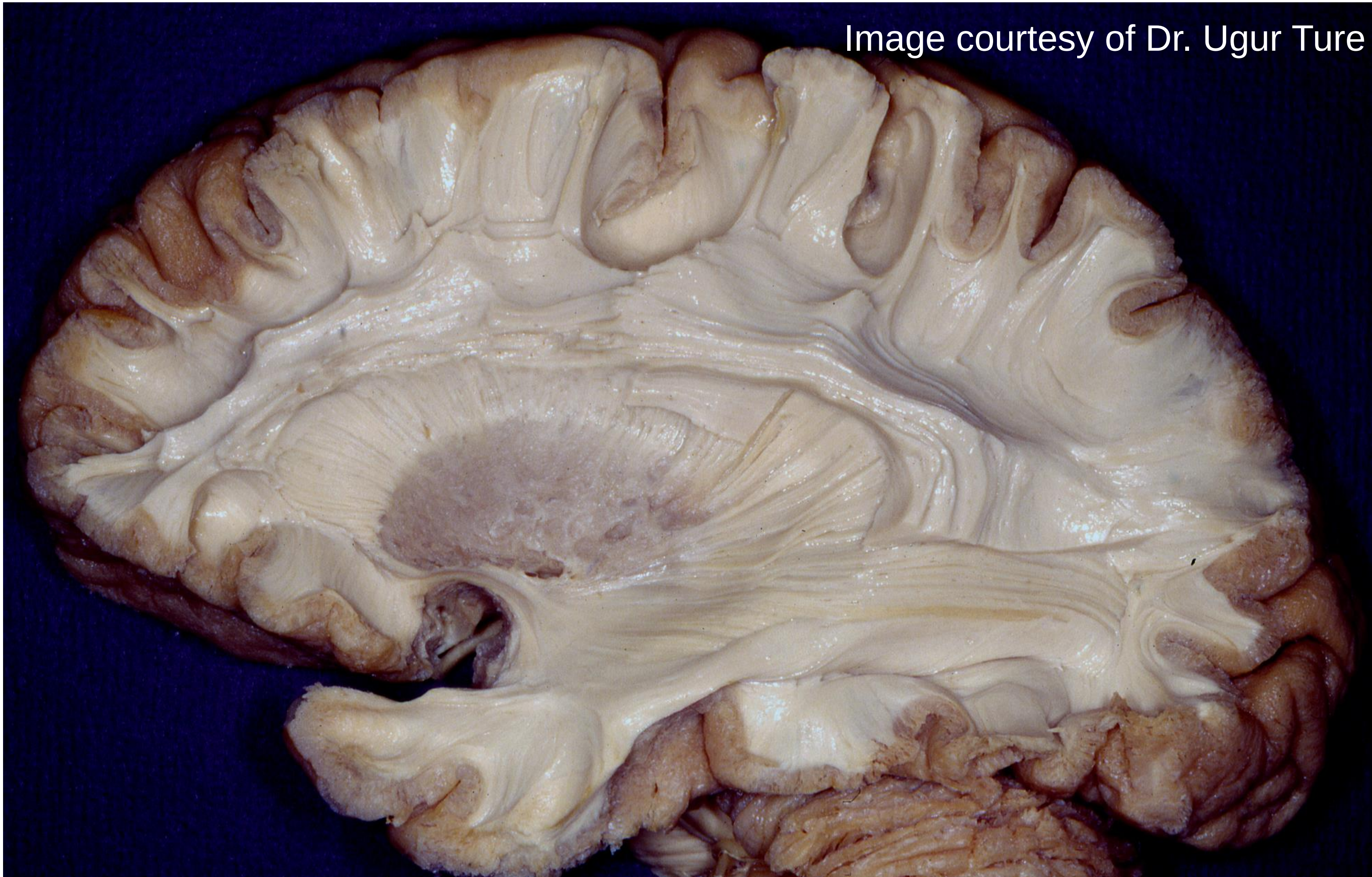
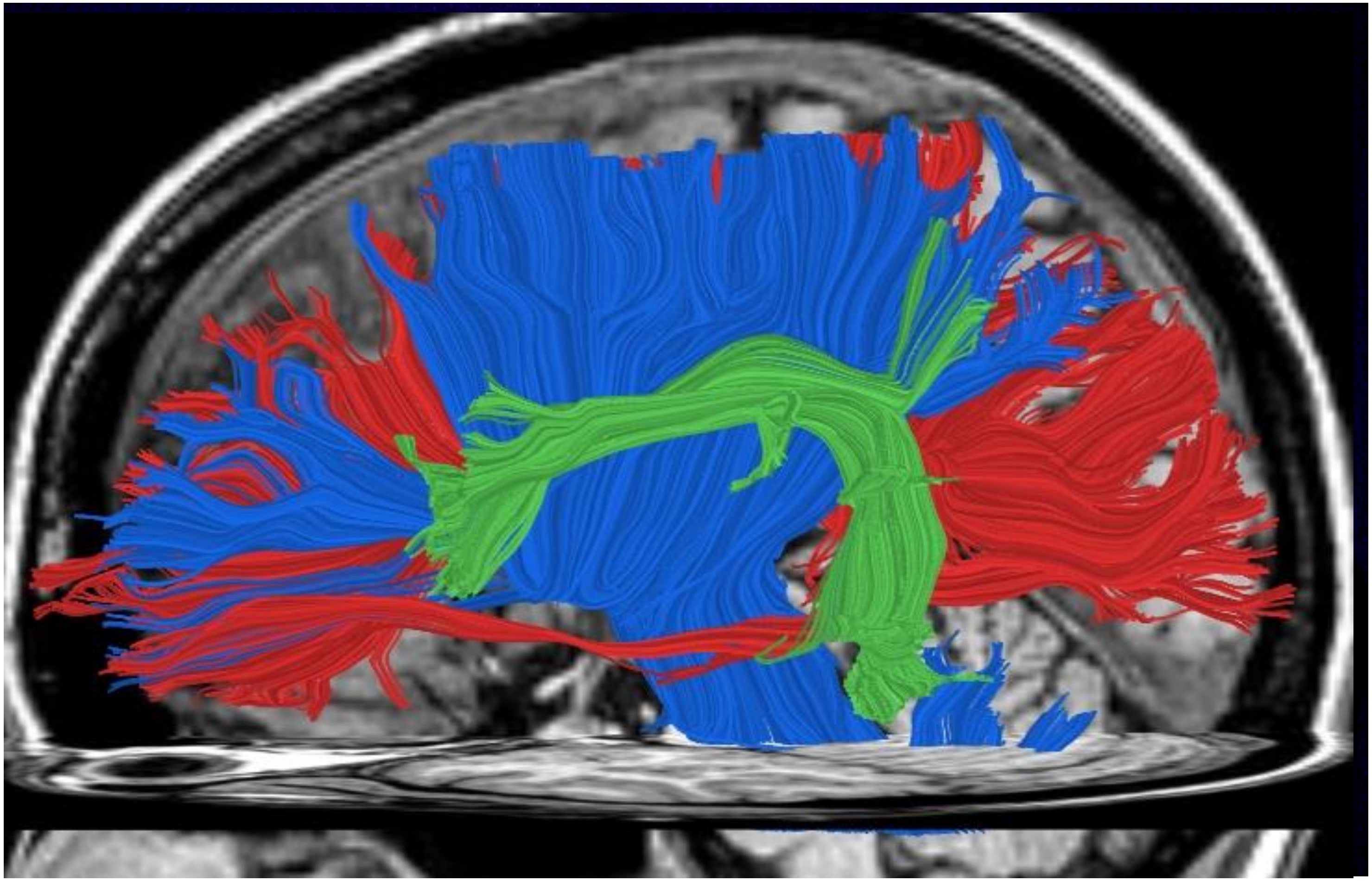


Figure 2.2. The classical neurological model of reading (top) is now replaced by a parallel and "bushy" model (bottom).The left occipito-temporal "letterbox" identifies the visual form of letter strings. It then distributes this invariant visual information to numerous regions, spread over the left hemisphere, that encode word meaning, sound pattern, and articulation. All the regions in green and orange are not specific to reading: they primarily contribute to spoken language processing. Learning to read thus consists of developing an efficient interconnection between visual areas and language areas. All connections are bidirectional. Their detailed organization is not yet fully known – in fact, cortical connectivity is probably much richer than suggested in this diagram.

Examining white matter anatomy: Post mortem dissection



We can now estimate fascicles in living humans



Water diffusion probes white matter structure

Water diffusion is faster along the fascicle

Longitudinal Diffusivity ($\mu m^2/ms$)

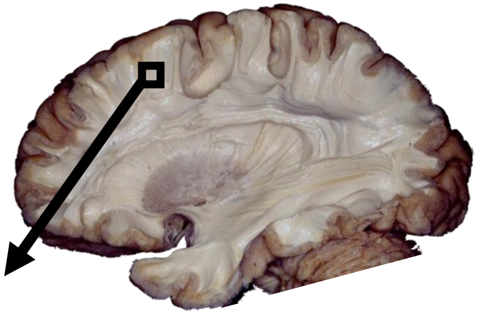
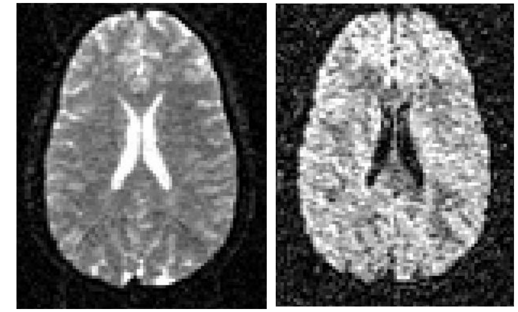


Image courtesy of George Bartzokis

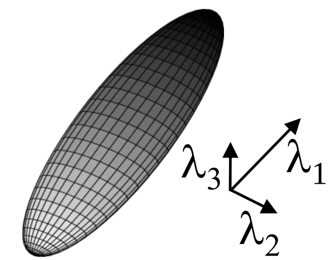
Radial Diffusivity ($\mu m^2/ms$)

Water diffusion is slower perpendicular to the fascicle

Diffusion Tensor Imaging: reminder



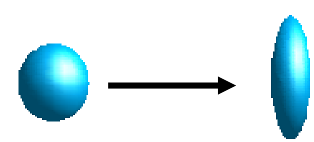
- Acquire images with a standard MRI scanner (1.5T/3T/..)
- Sequence sensitized to diffusing water molecules



- Measure diffusion in multiple directions
- Model diffusion in each voxel as a tensor (ellipsoid)

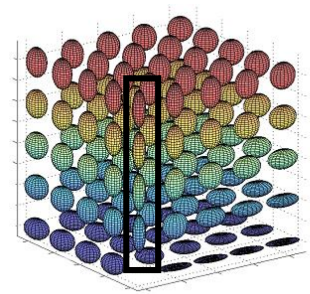
$$FA = \sqrt{\frac{3}{2}}\sqrt{\frac{\sum_{i=1,2,3}(\lambda_i-\bar{\lambda})^2}{\sum_{i=1,2,3}\lambda_i^2}}$$

- Summarize tensor shape: FA

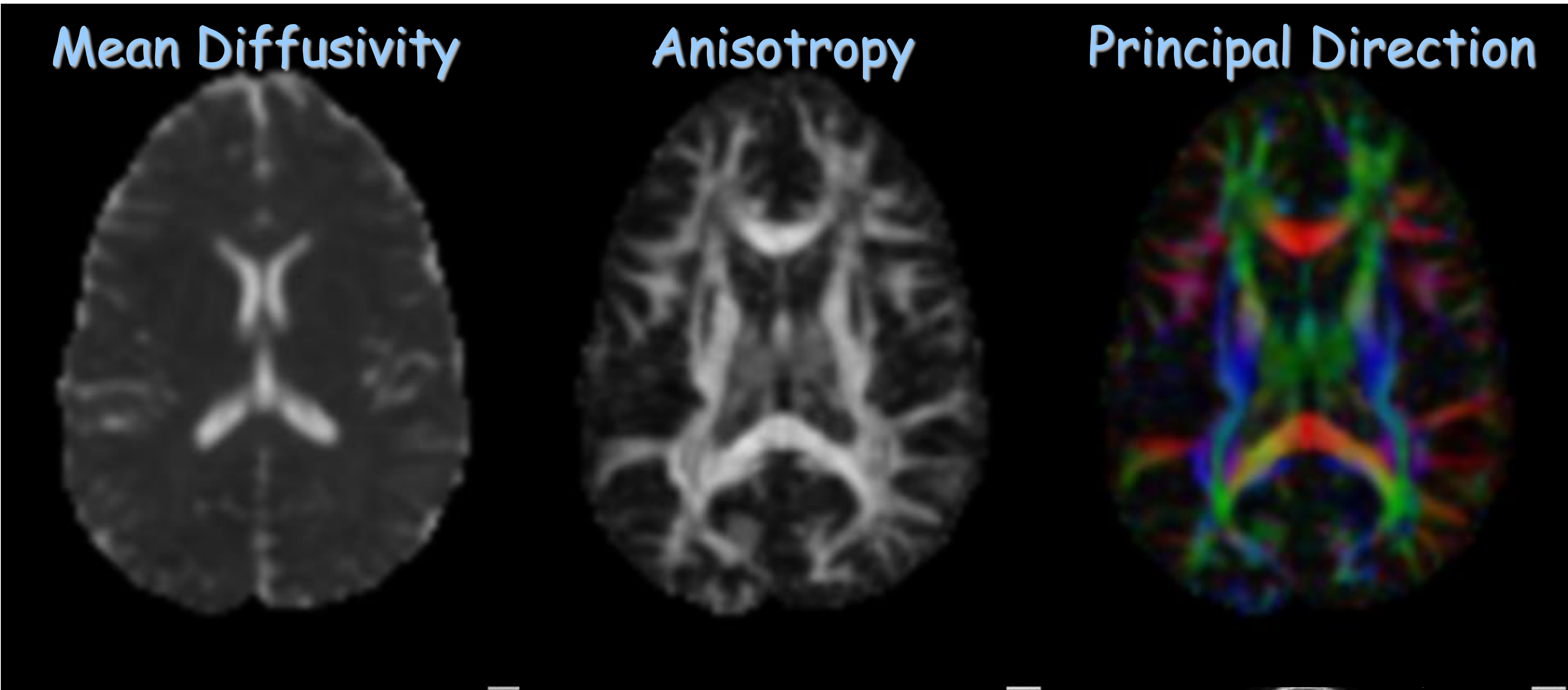


$0 \leq FA \leq 1$

- Follow principal diffusion direction to reconstruct fiber bundles

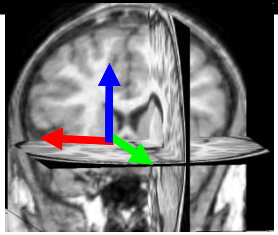


DTI reveals White Matter Structure

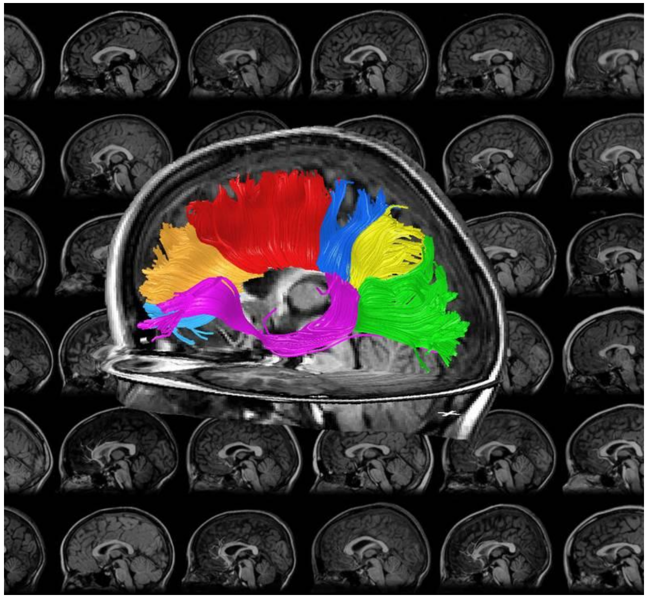


MD (um^2/msec)

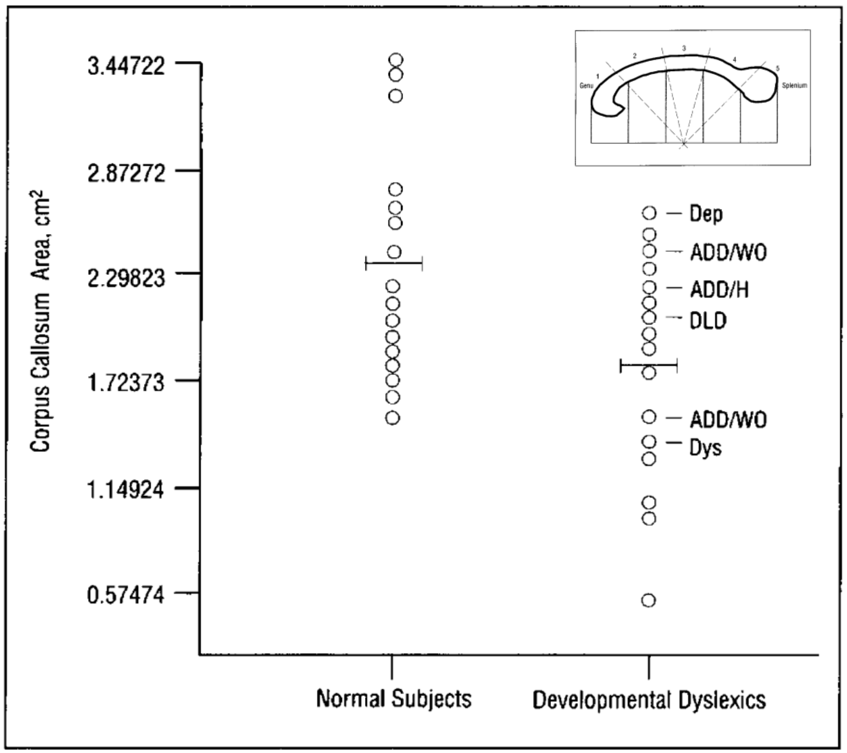
FA: Dimensionless



DTI of reading pathways



Pre-DTI literature: Corpus callosum is different in dyslexia



Hynd et al., 1995

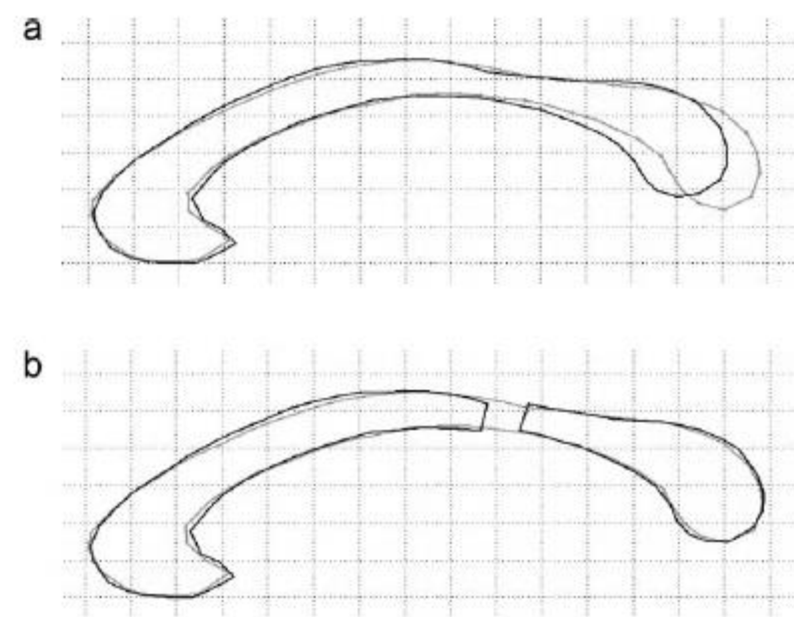
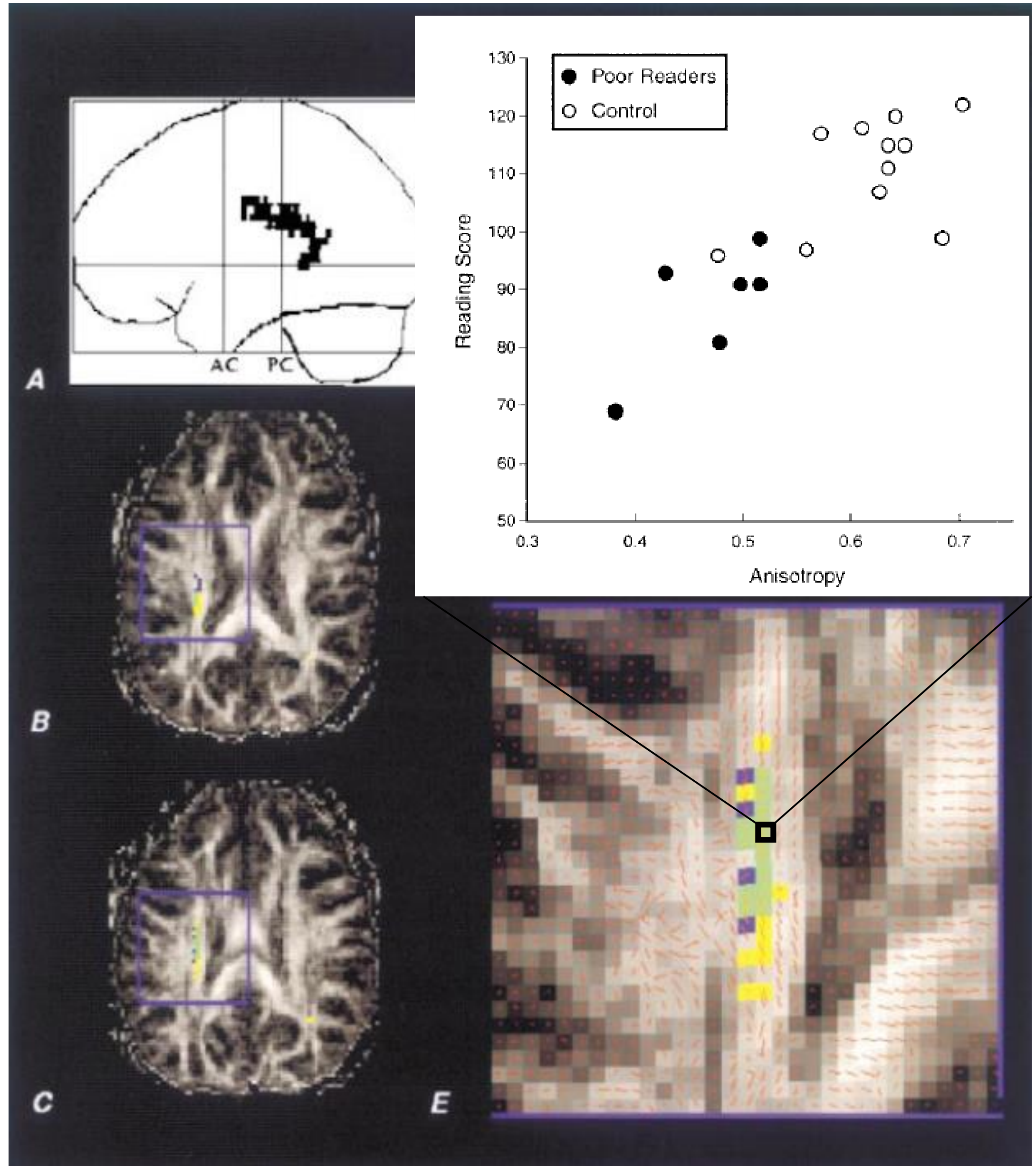


Fig. 4. Comparing the control (shown in grey) and dyslexic (shown in black) average CC shapes (prototypes) (a). The dyslexic prototype is cut into two pieces that are aligned separately at rostrum and splenium (b). The posterior midbody region in the dyslexic subjects is significantly shorter than in the control subjects.

Von Plessen et al., 2002

First DTI-dyslexia study:
Poor readers have lower FA in a temporo-parietal white matter region (Klingberg et al. 2000)



Neuron, Vol. 25, 493–500, February, 2000, Copyright ©2000 by Cell Press

Microstructure of Temporo-Parietal White Matter as a Basis for Reading Ability: Evidence from Diffusion Tensor Magnetic Resonance Imaging

Torkel Klingberg,*§ Maj Hedehus,† Elise Temple,*
Talya Salz,*‡ John D. E. Gabrieli,*†
Michael E. Moseley,† and Russell A. Poldrack*

Why is there no group difference reported in the callosum using voxel based DTI methods?

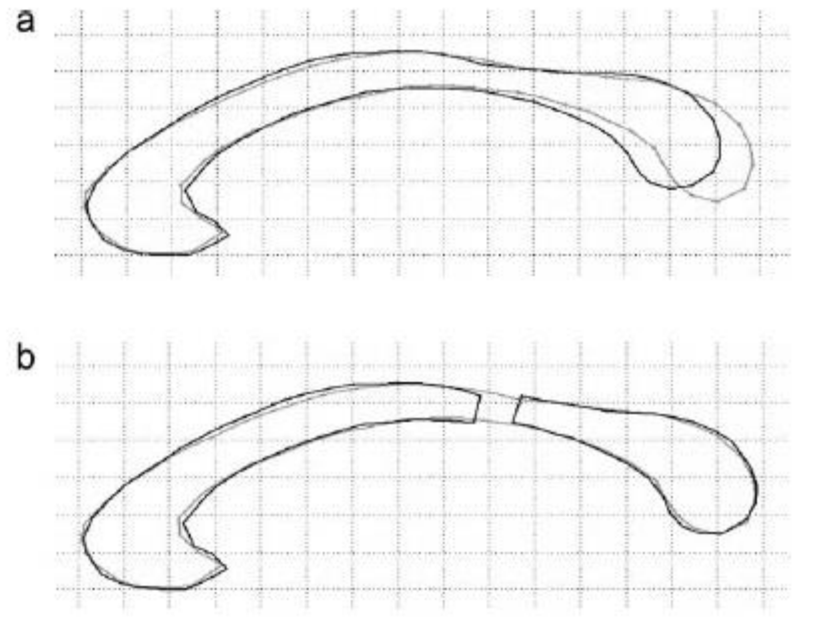
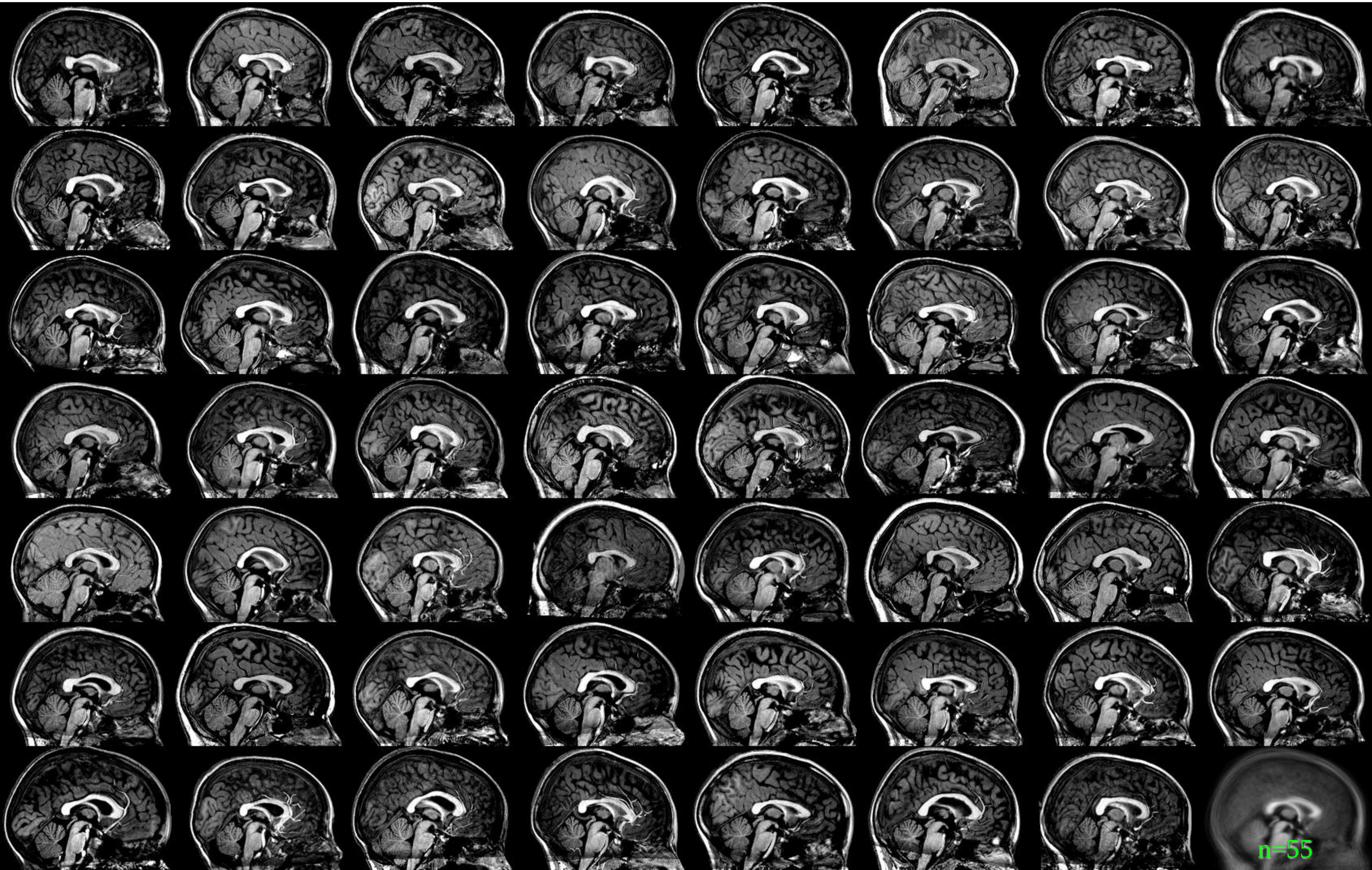


Fig. 4. Comparing the control (shown in grey) and dyslexic (shown in black) average CC shapes (prototypes) (a). The dyslexic prototype is cut into two pieces that are aligned separately at rostrum and splenium (b). The posterior midbody region in the dyslexic subjects is significantly shorter than in the control subjects.

Von Plessen et al., 2002

CC shape variability

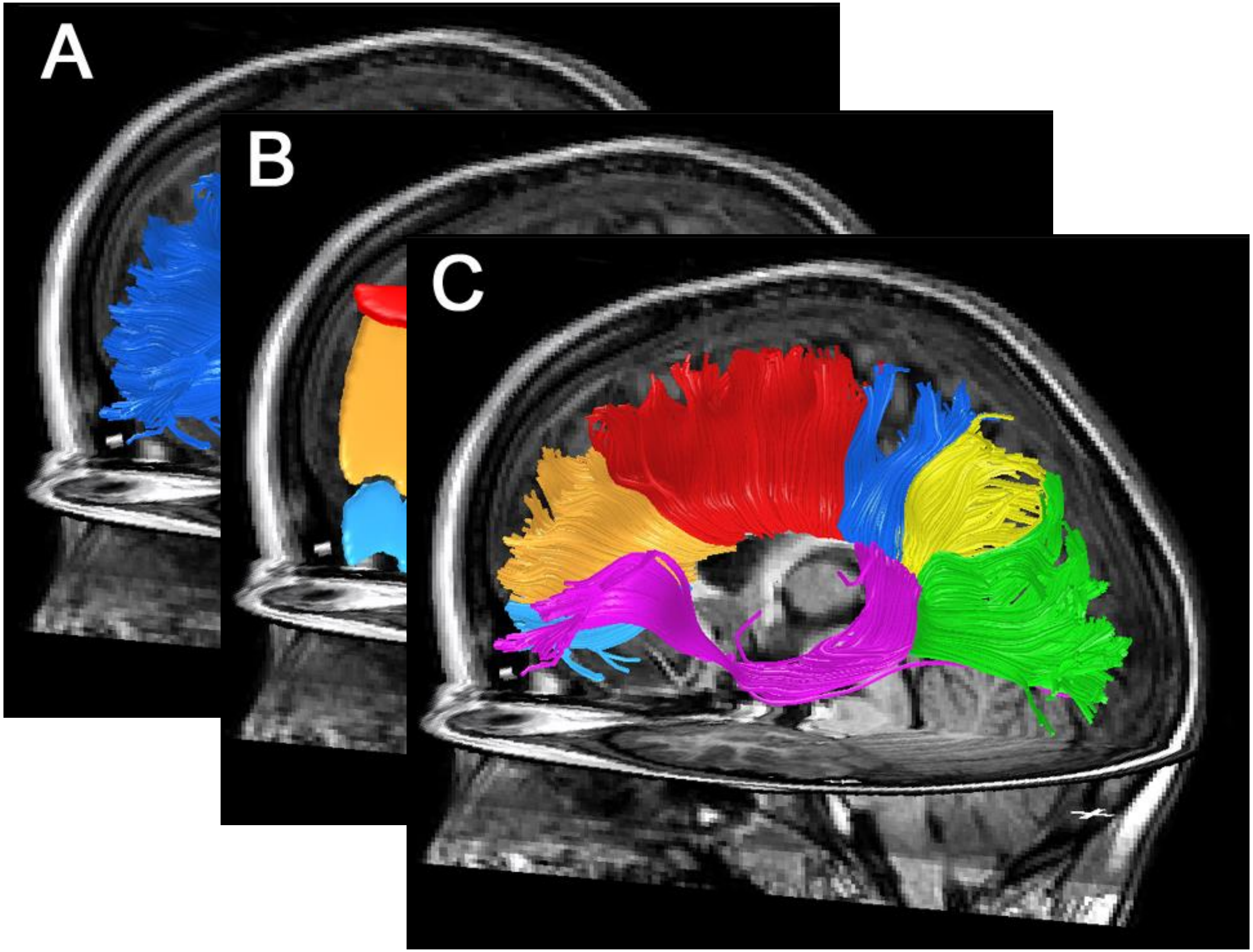


Segmentation by projection zones

Generate a large set of fibers that pass through the callosum

Find the intersections with WM ROIs that correspond to cortical divisions (Huang et al., 2004)

'Stain' the fibers according to the ROI.

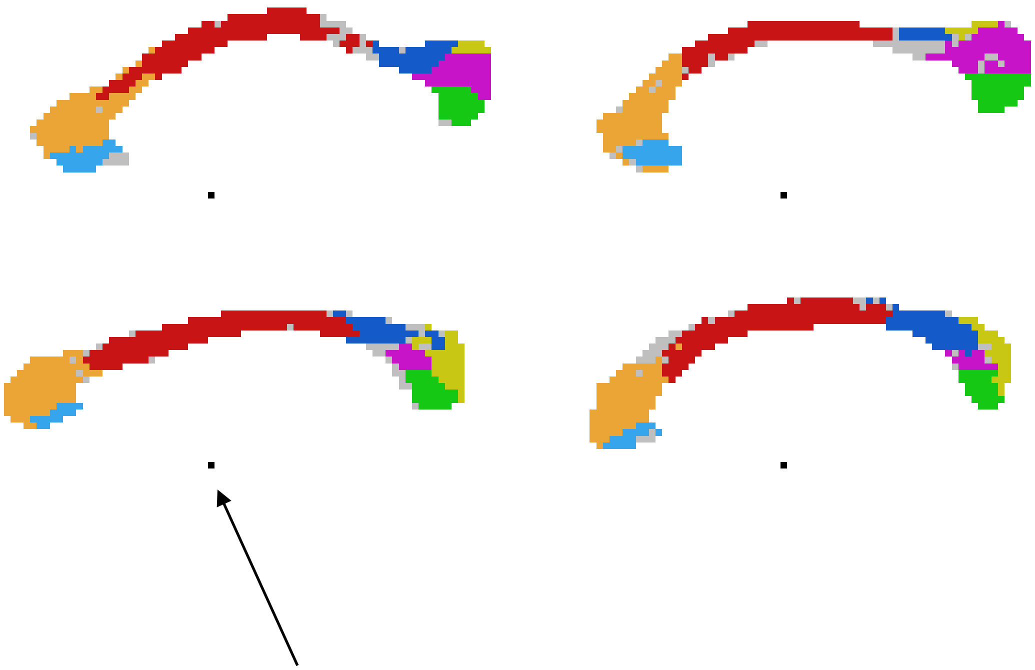


Segmented fibers

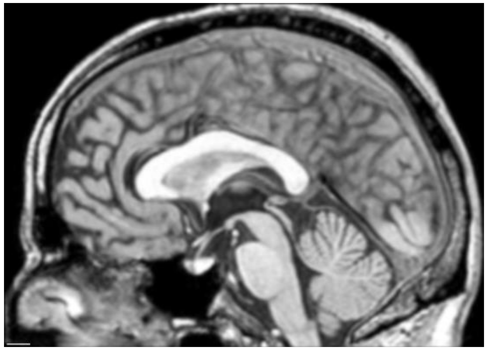
Dougherty, Ben-Shachar et al., PNAS 2007

Segmentation of the callosum

Find the location where these fibers pass through the callosum



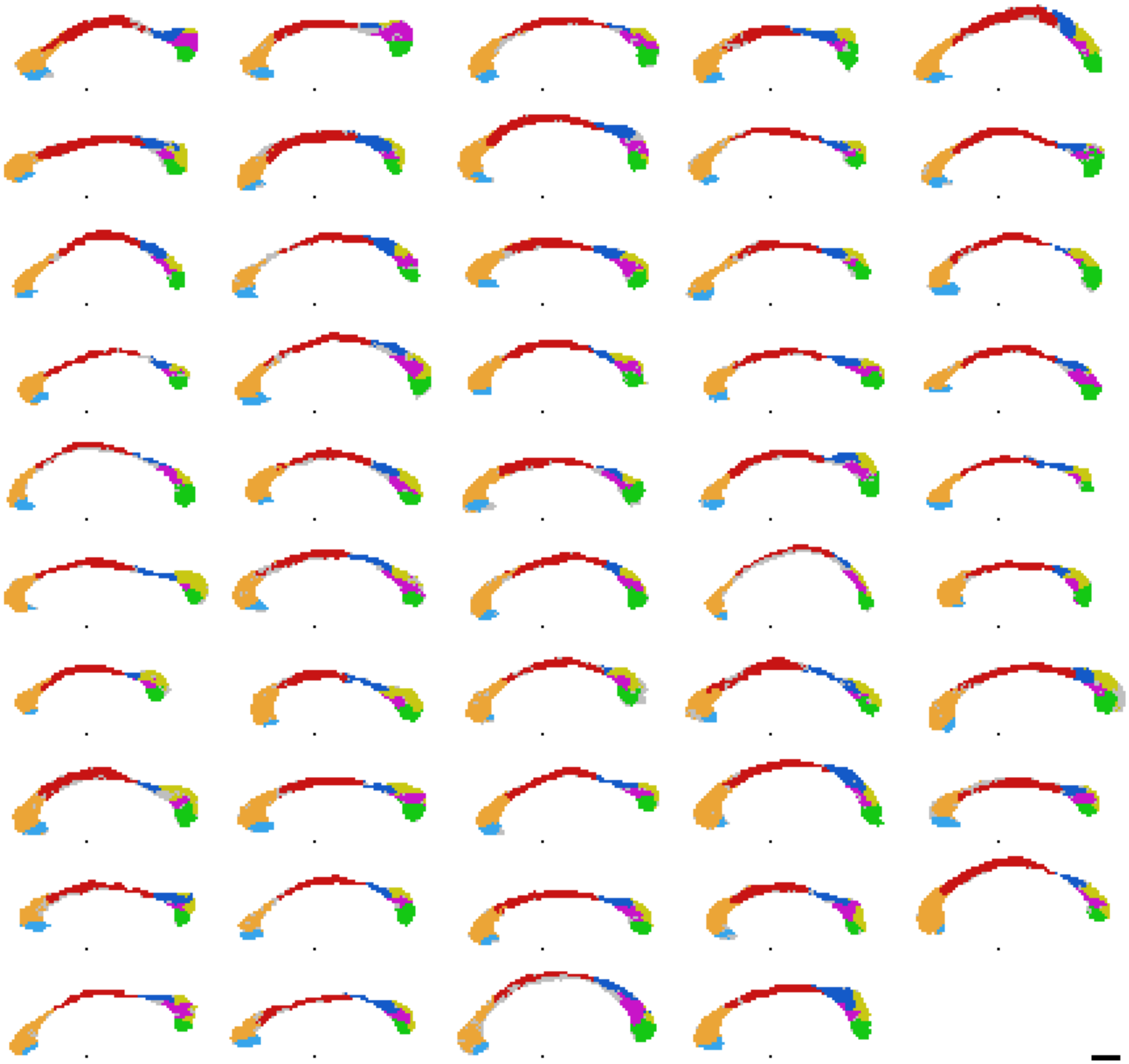
Anterior commisure

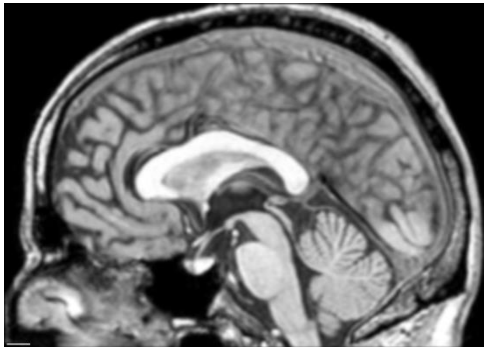


Projection zones

- Occipital
- Temporal
- Posterior Parietal
- Superior Parietal
- Superior Frontal
- Anterior Frontal
- Orbital Frontal
- Indeterminate

Shapes differ, segmentation is possible, N=49 children

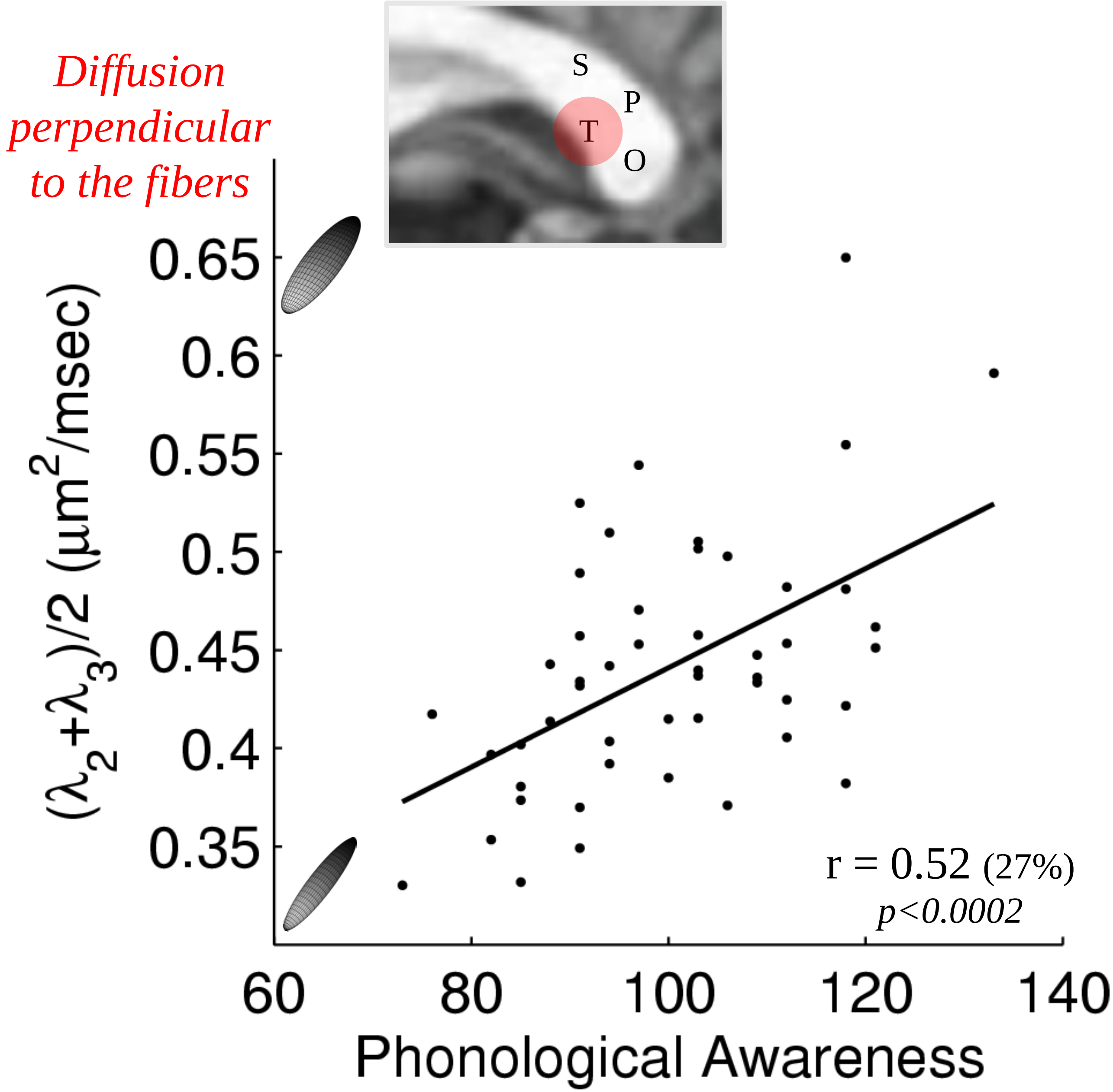




Projection zones

- Occipital
- Temporal
- Posterior Parietal
- Superior Parietal
- Superior Frontal
- Anterior Frontal
- Orbital Frontal
- Indeterminate

Radial diffusivity in temporal segment correlates with phonological awareness



Dougherty et al., PNAS 2007

Clinical application: premature birth

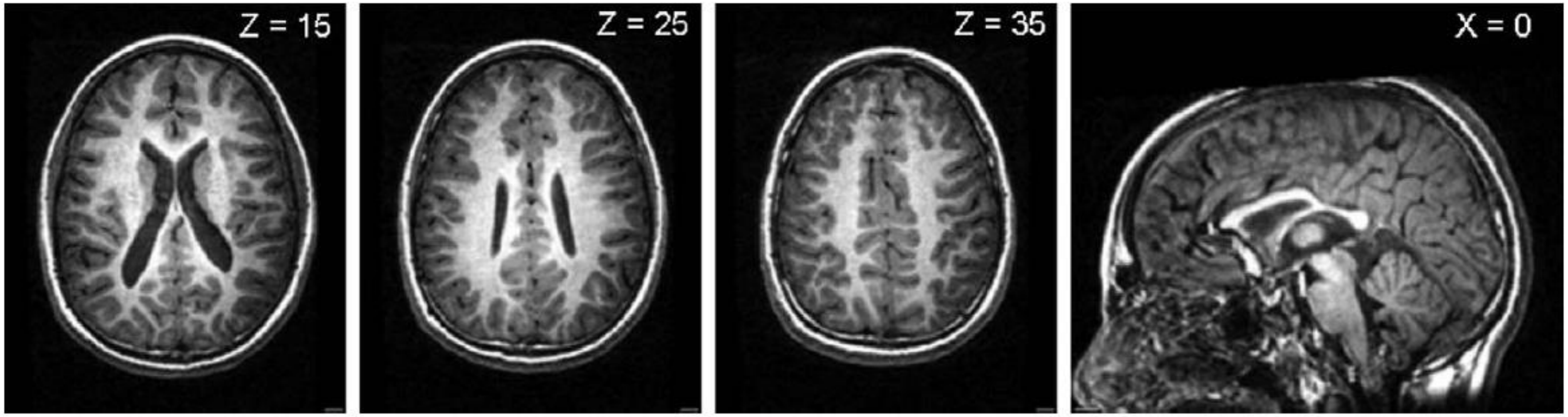
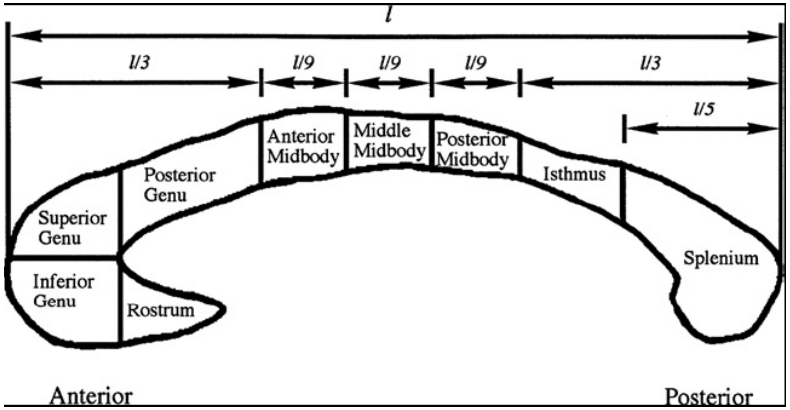


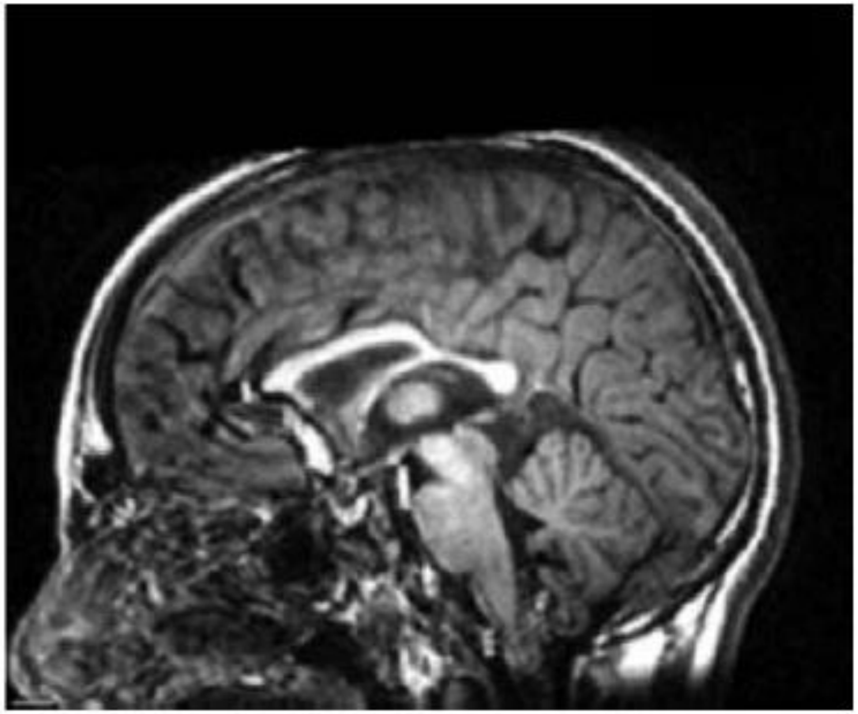
Figure 1. Three axial slices and 1 sagittal slice from the T1-weighted magnetic resonance imaging scan of the participant born prematurely.

12-year-old boy, born at 25 weeks gestation, weighing 768 g at birth

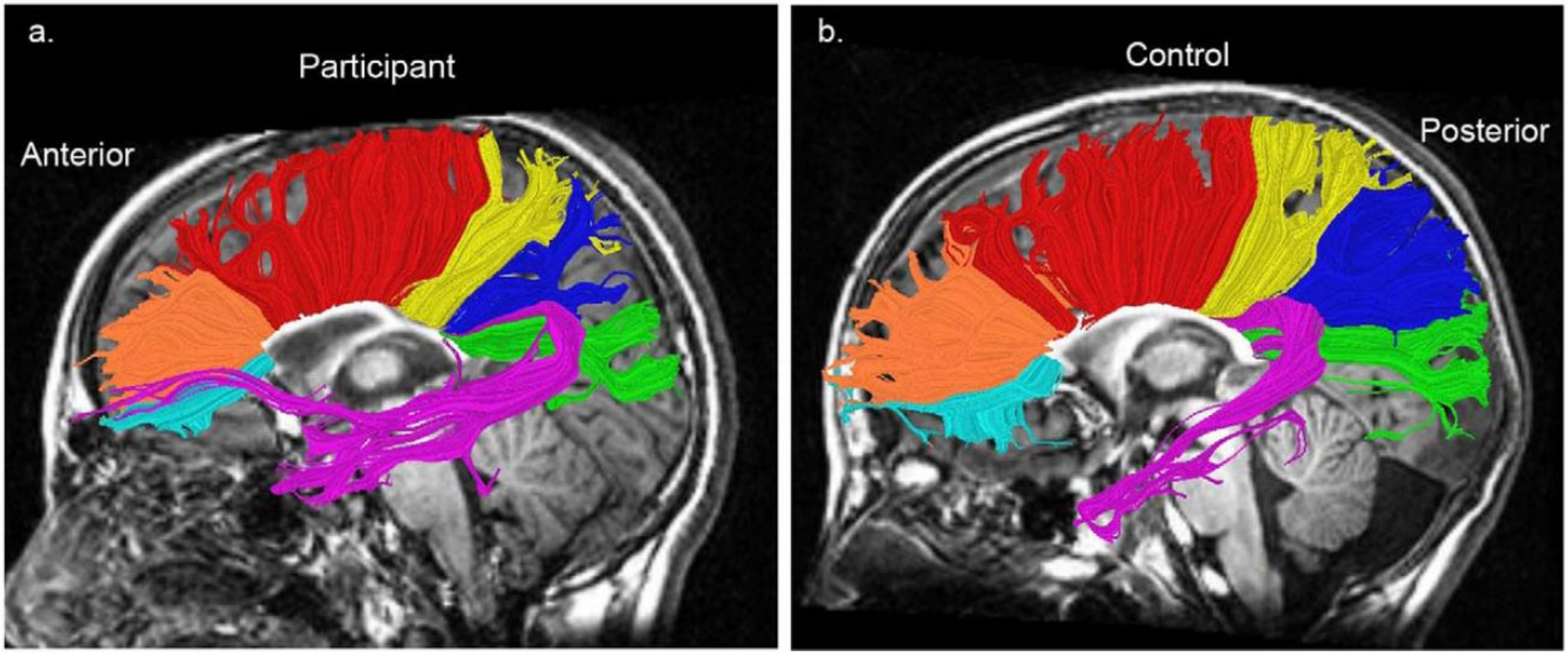
Yeatman, Ben-Shachar, Bammer and Feldman, Journal of Child Neurology 2009

Which callosal fibers are implicated?



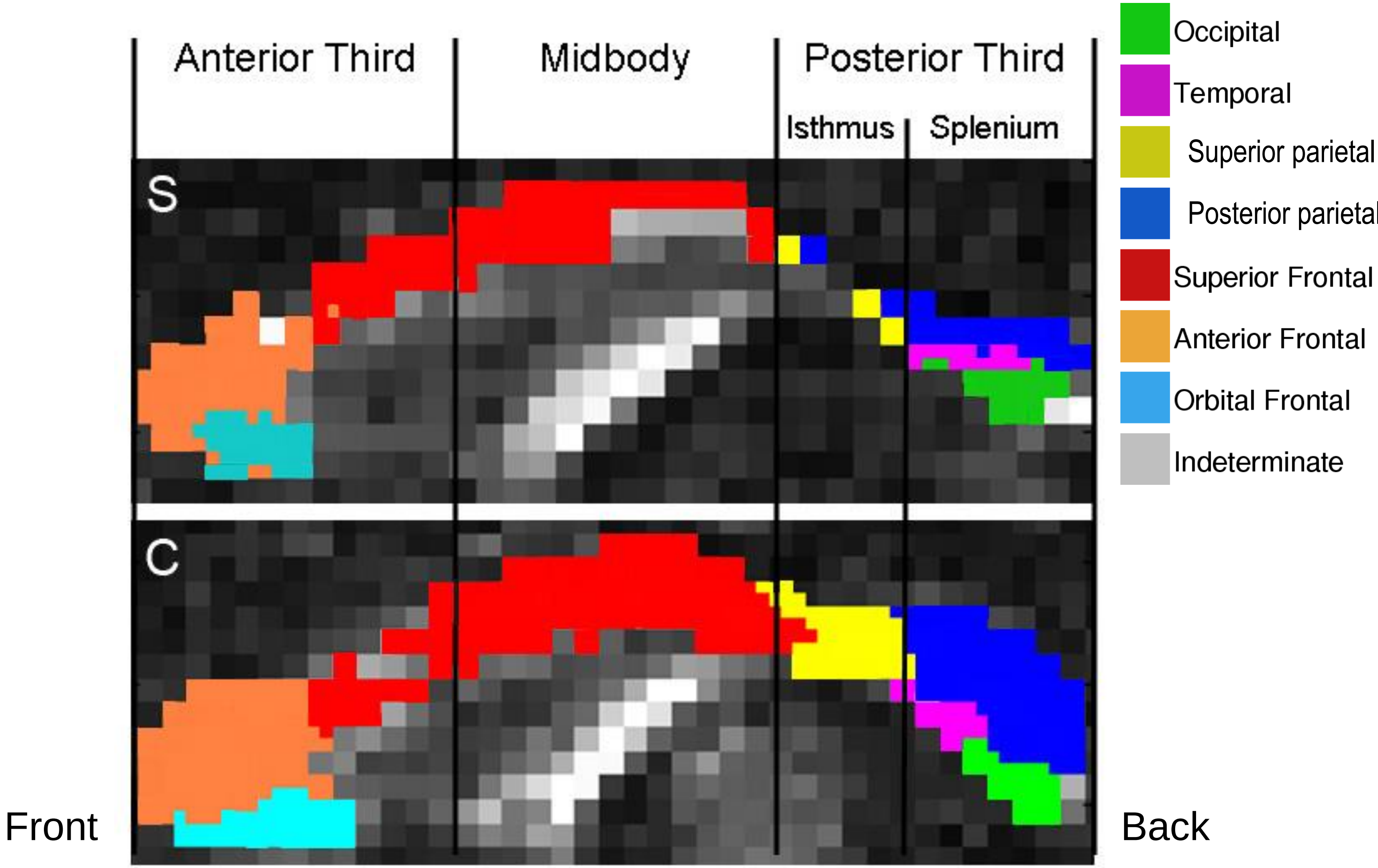


Individual tract-based segmentations

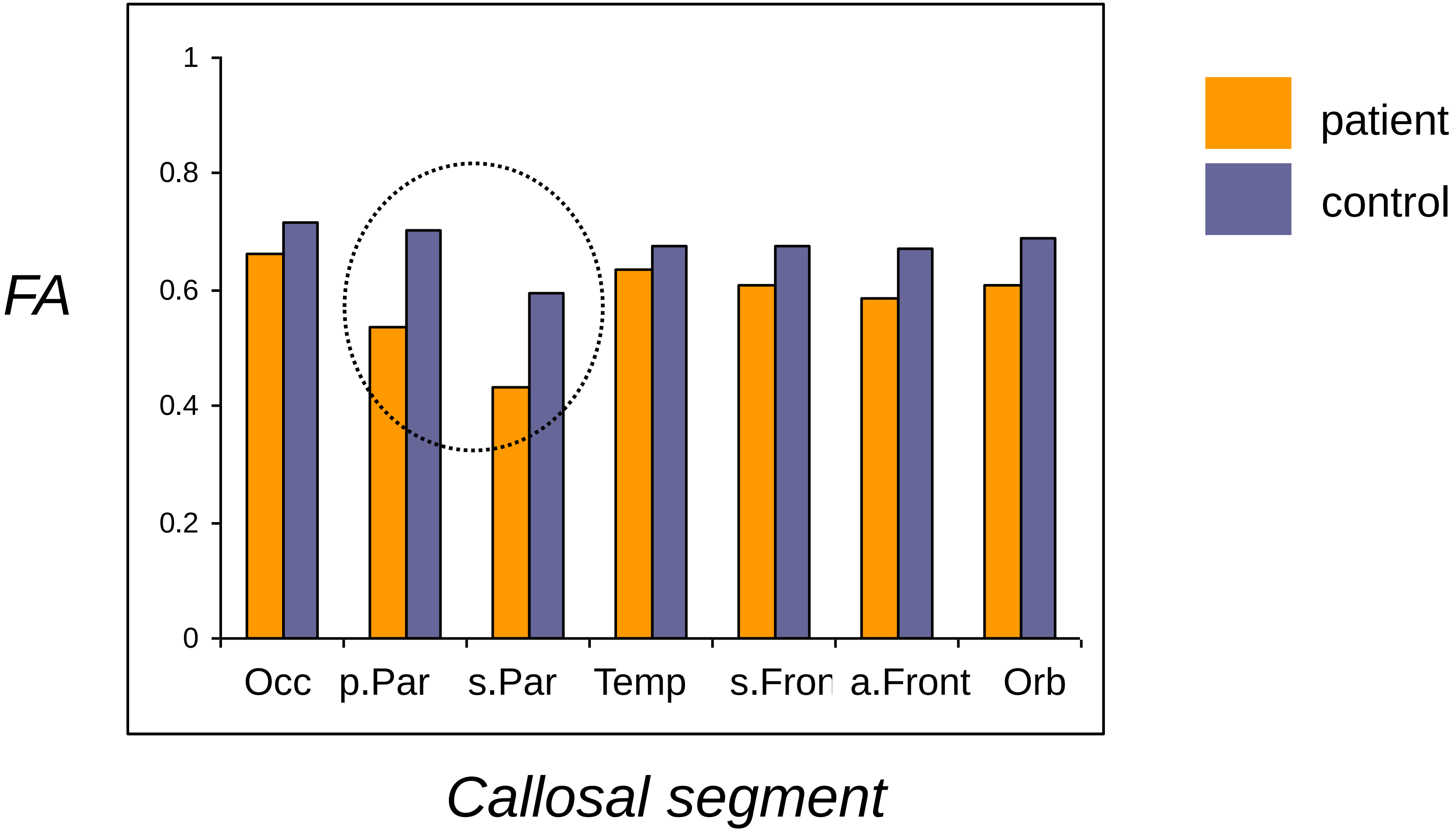


Yeatman, Ben-Shachar, Bammer and Feldman, Journal of Child Neurology 2009

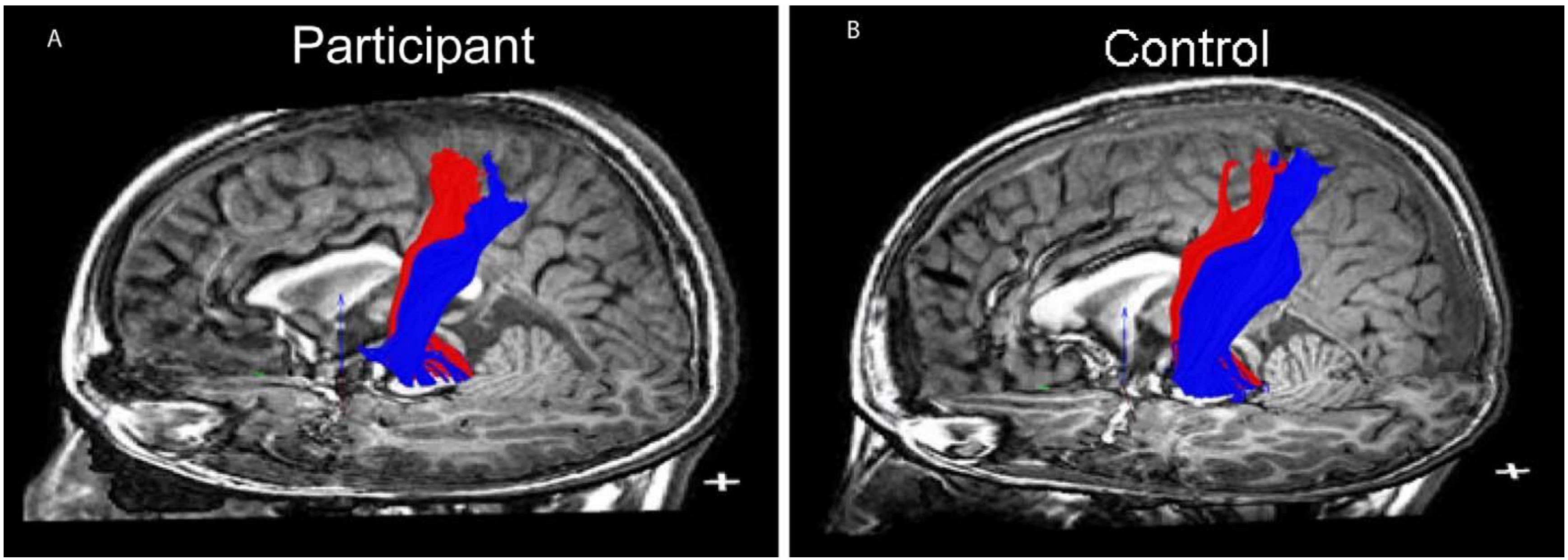
Which callosal tracts are affected?



Quantitative comparison



No reduction in FA in Corona Radiata



FA in participant:

Left CST	0.678
Right CST	0.702
Left SST	0.667
Right SST	0.657

FA in control:

Left CST	0.568
Right CST	0.595
Left SST	0.628
Right SST	0.572

Premature birth: missing arcuate

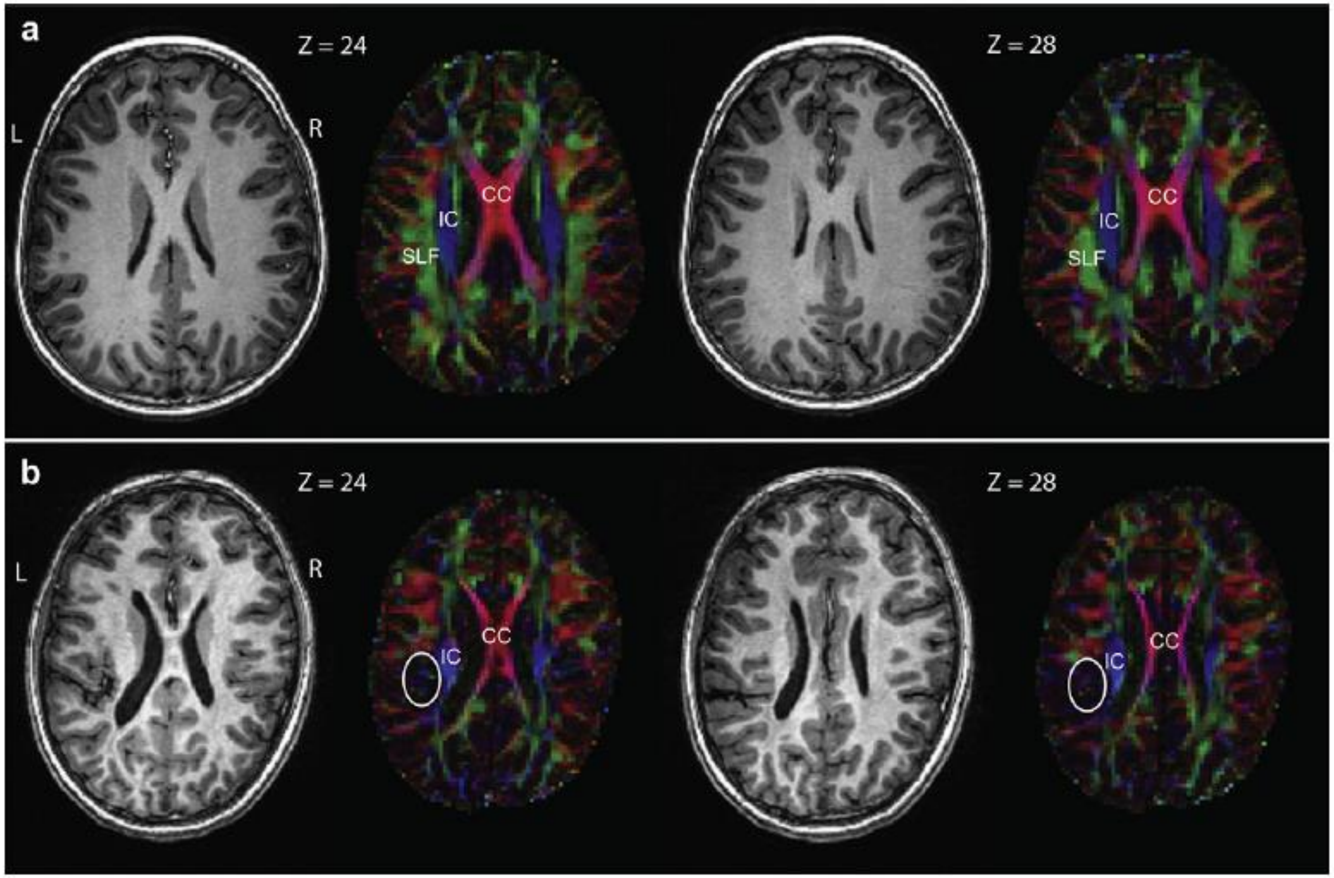


Fig. 1 – Axial slices from the control's (a) and patient's (b) T1-weighted images and corresponding RGB fiber orientation maps. The corpus callosum (CC), internal capsule (IC), and SLF/arcuate fasciculus are labeled on the control's RGB map. Absent on the patient's RGB map are the green voxels depicting regions with anterior/posterior fiber orientation, lateral to the blue voxels depicting superior/inferior fiber orientation of the IC. These missing longitudinally oriented voxels correspond to the superior longitudinal/arcuate fasciculus (open circle on patient's RGB map).

Yeatman and Feldman, Cortex 2011

Back to Klingberg: Poor readers have lower FA in temporo-parietal white matter

Neuron, Vol. 25, 493–500, February, 2000, Copyright ©2000 by Cell Press

Microstructure of Temporo-Parietal White Matter as a Basis for Reading Ability: Evidence from Diffusion Tensor Magnetic Resonance Imaging

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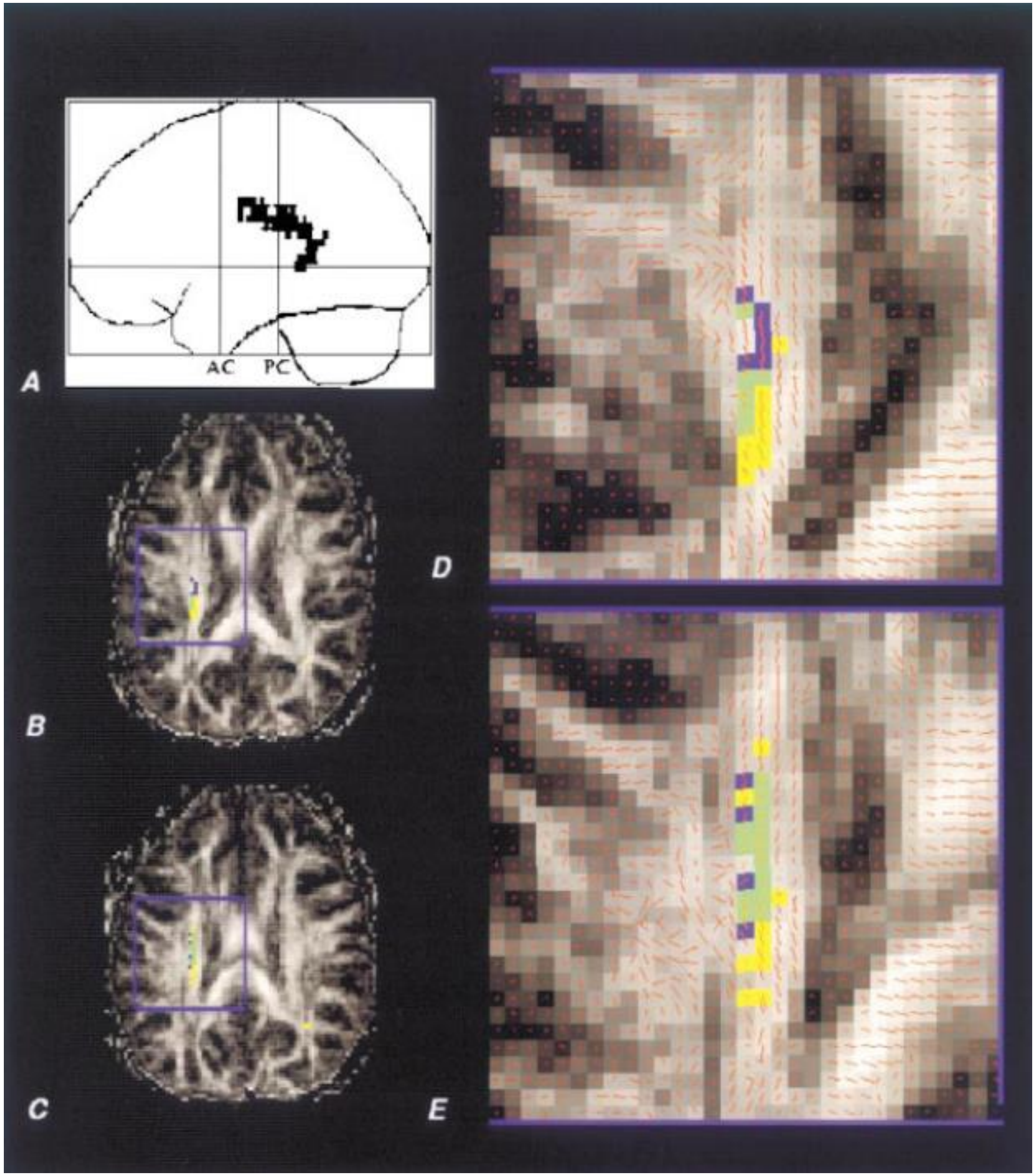
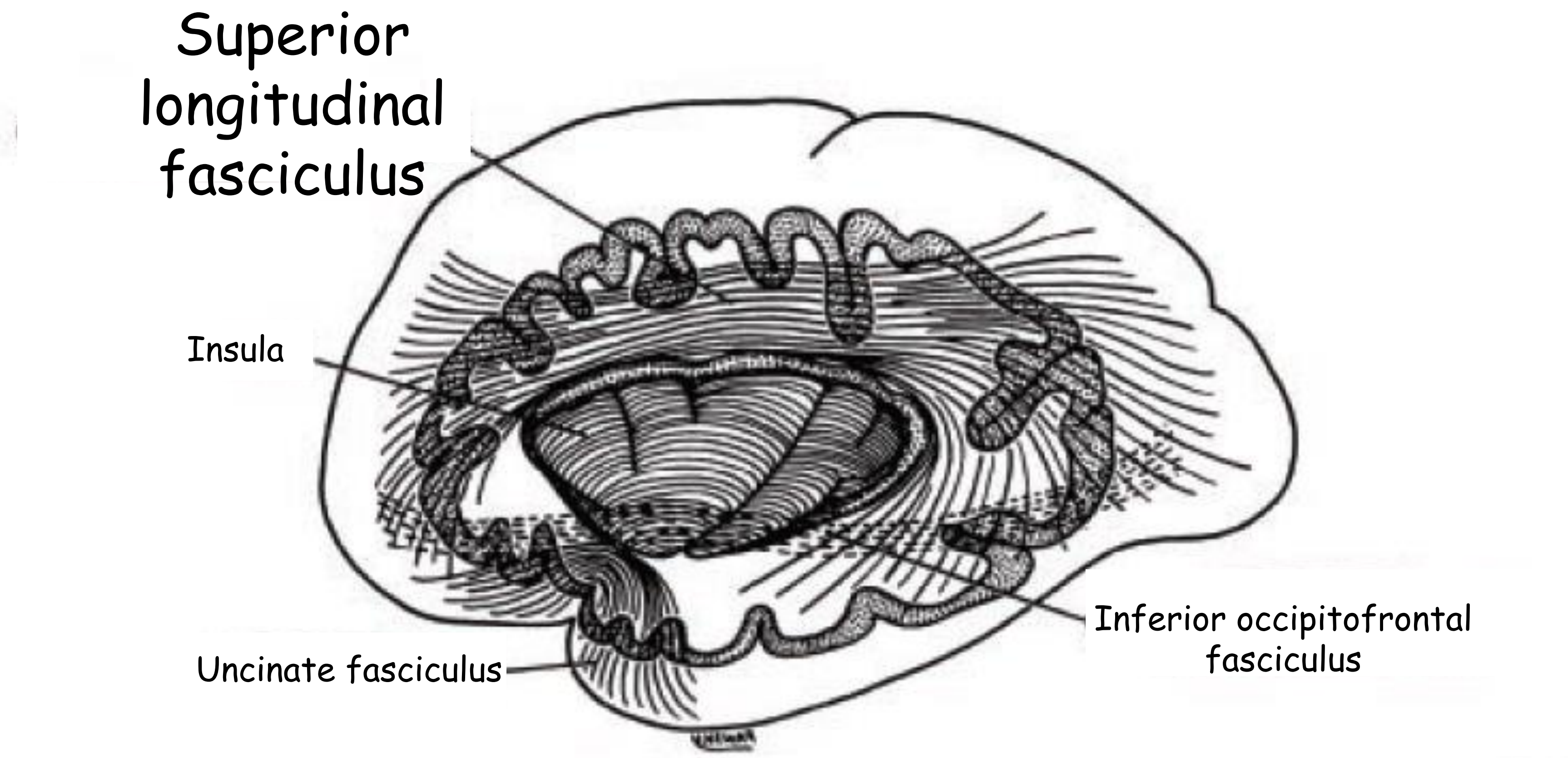


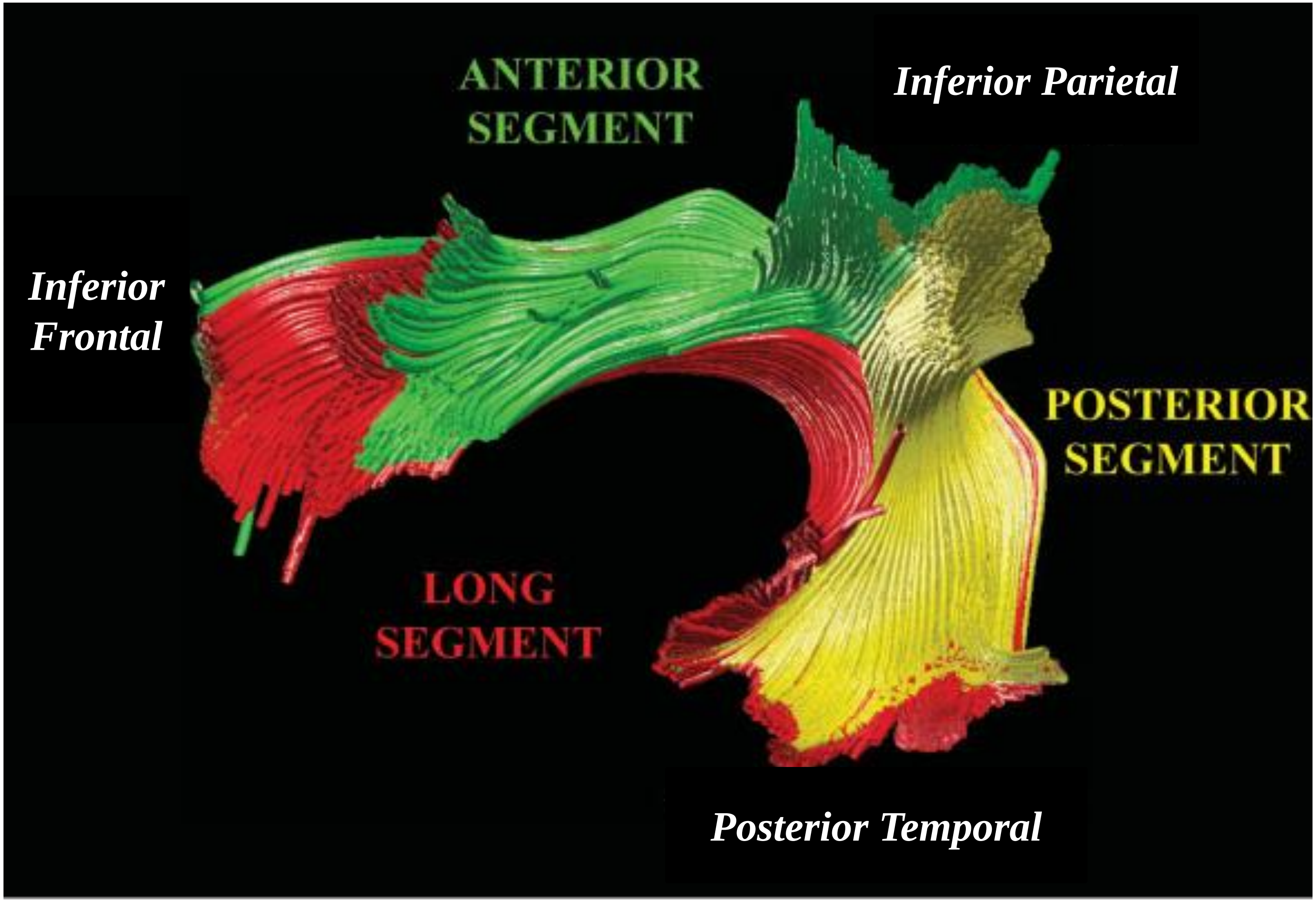
A popular interpretation: Impaired language connections (SLF)



Jellison, et al. AJNR 2004

But see Ben-Shachar, Dougherty and Wandell, Curr. Op. Neurobiol. 2007 for alternative interpretations

We now know that SLF is a mixture of several pathways

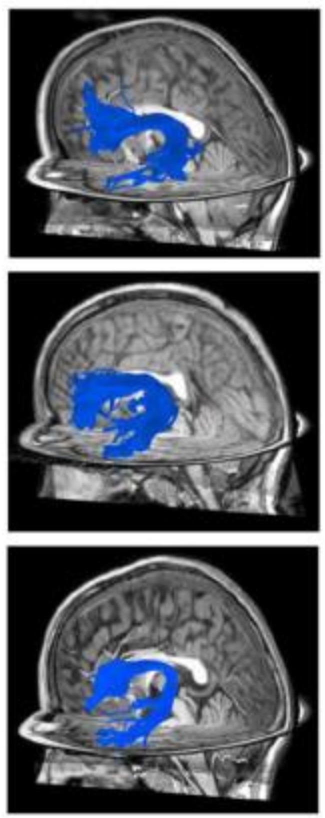


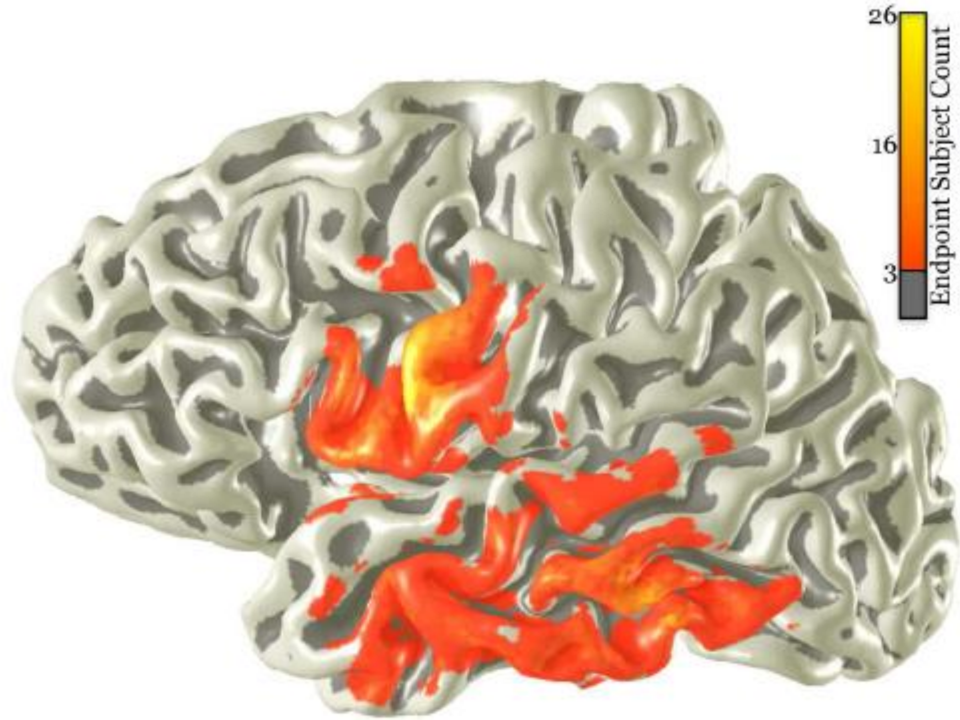
Catani, Jones and ffytche. Ann. Neurol. 2005

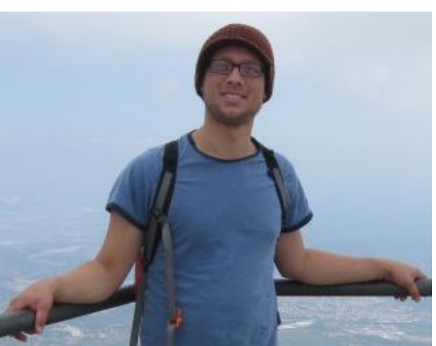
Is the arcuate fasciculus (fronto-temporal long segment of SLF) mediating reading signals?

SLF-long (arcuate) traced in 53 children 7-11y

Standard DTI protocol, 6 non-collinear directions, 8 repetitions, 2x2x2mm voxels

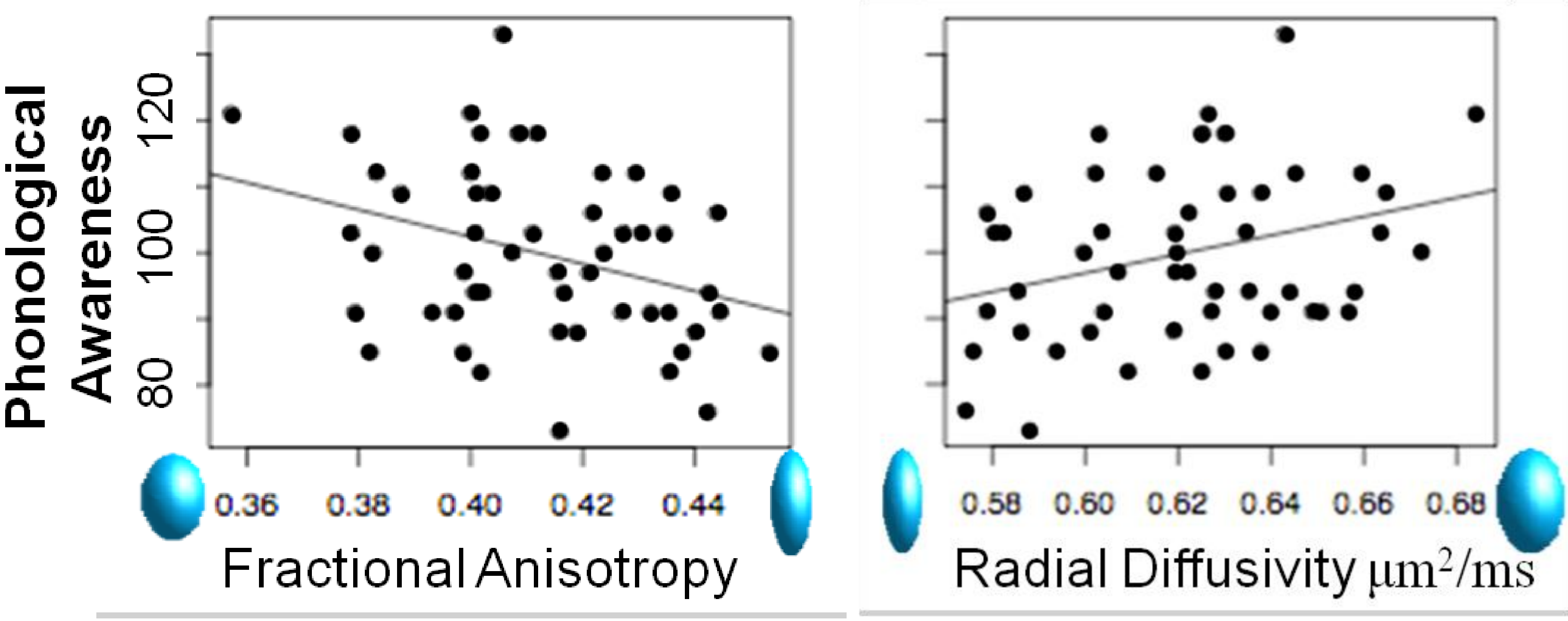






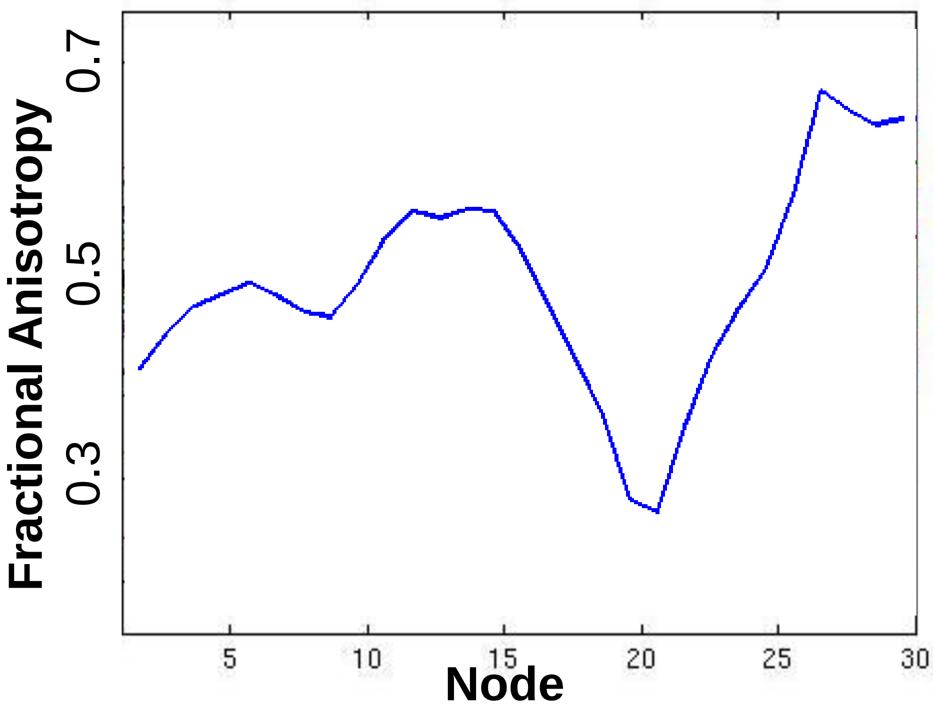
Yeatman, Dougherty, Rykhlevskaia, Sherbondy, Deutsch, Wandell and Ben-Shachar, JoCN (2011)

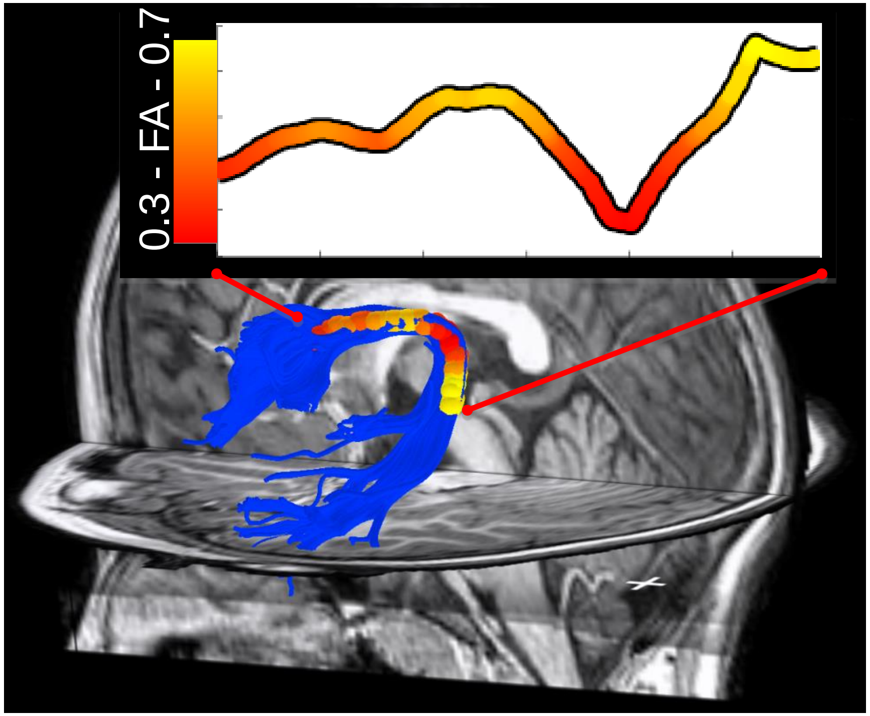
Modest correlation with phonological awareness in left SLF-long



1. **Higher** FA predicts **lower** age-standardized phonological awareness score
2. **No correlation** between PA and FA in **left aSLF** (!), right SLF-long, left CST

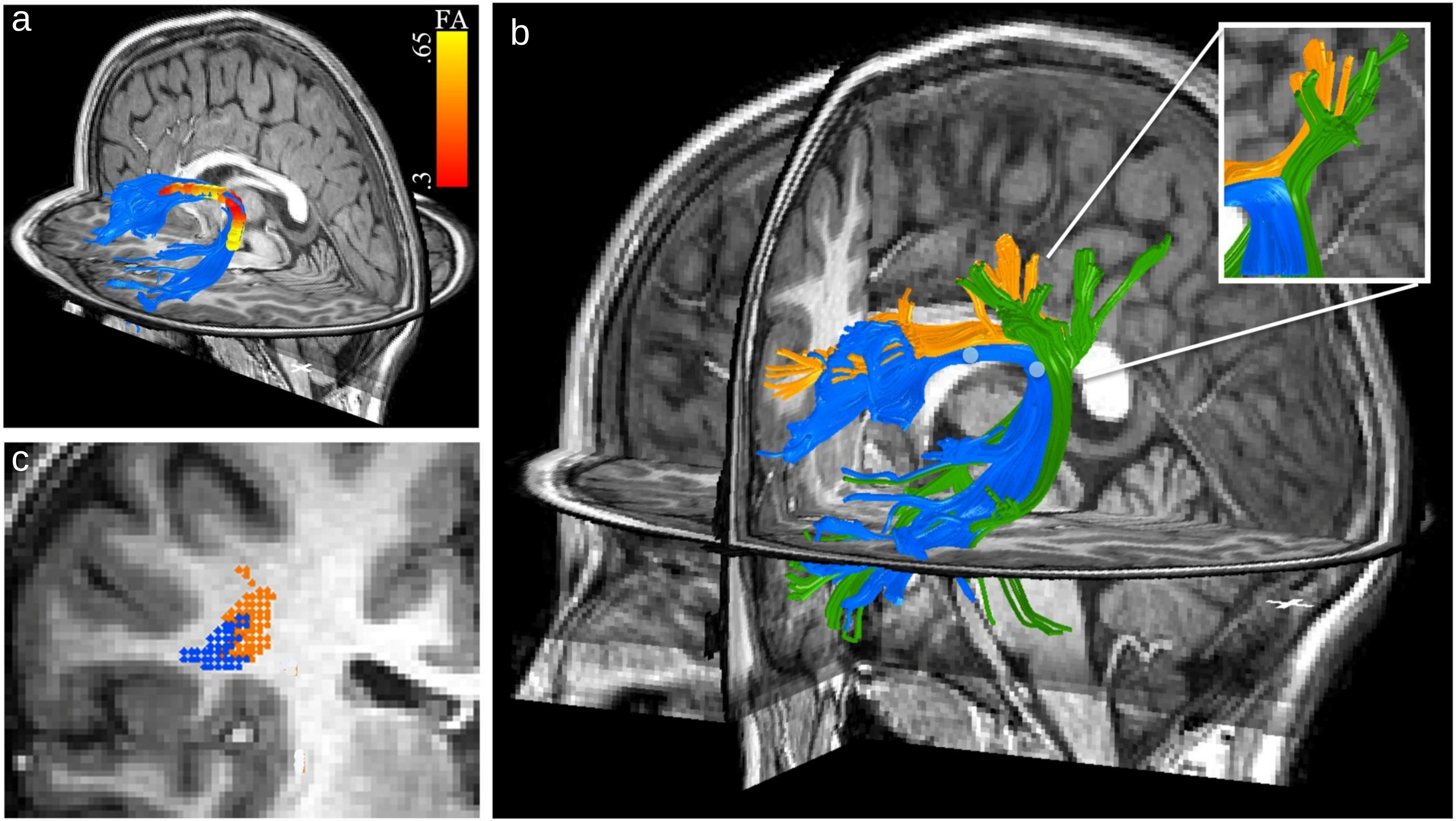
Significant FA Variation Along Arcuate Trajectory



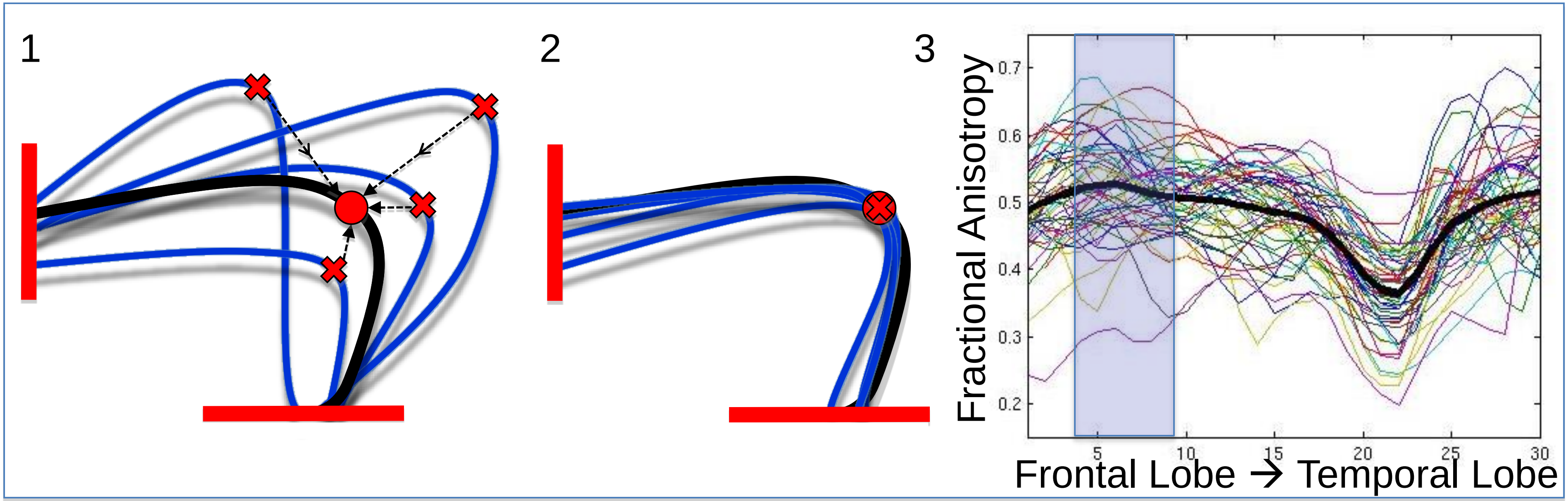


- Each subject showed an FA “dip” where the segments diverge
- However: dip location varies between subjects

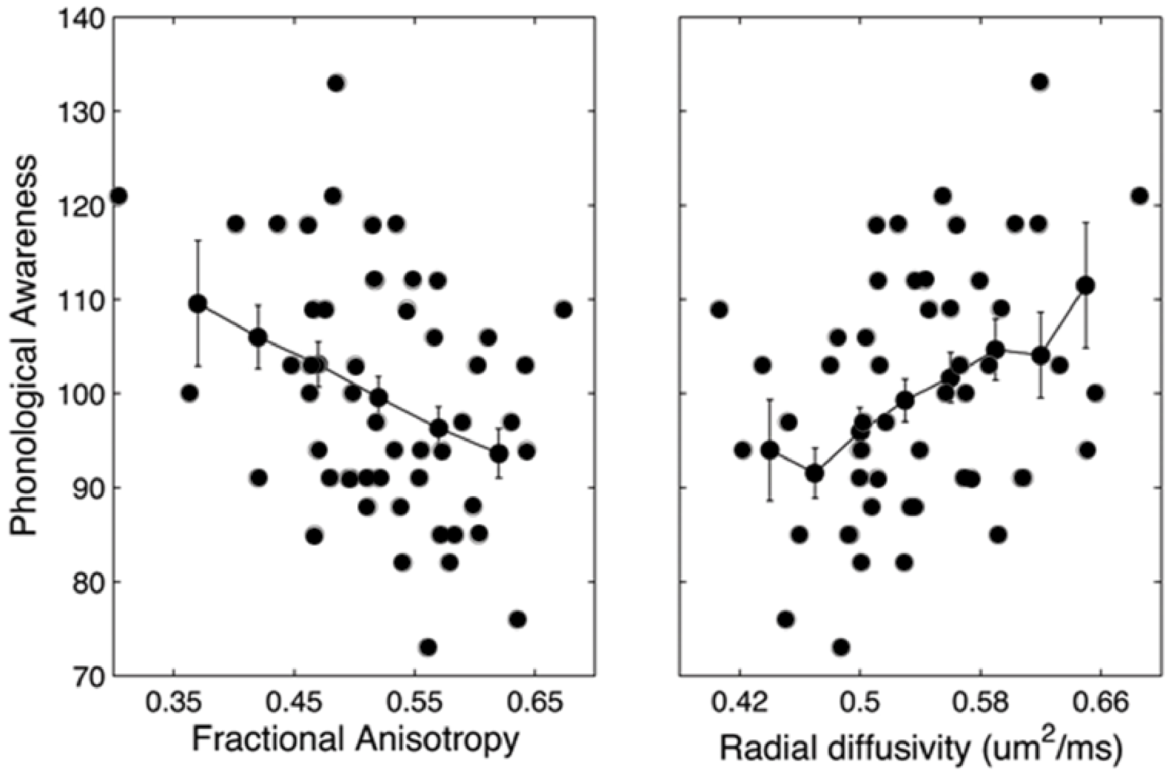
FA dip reflects pathway junction



FA trajectory alignment

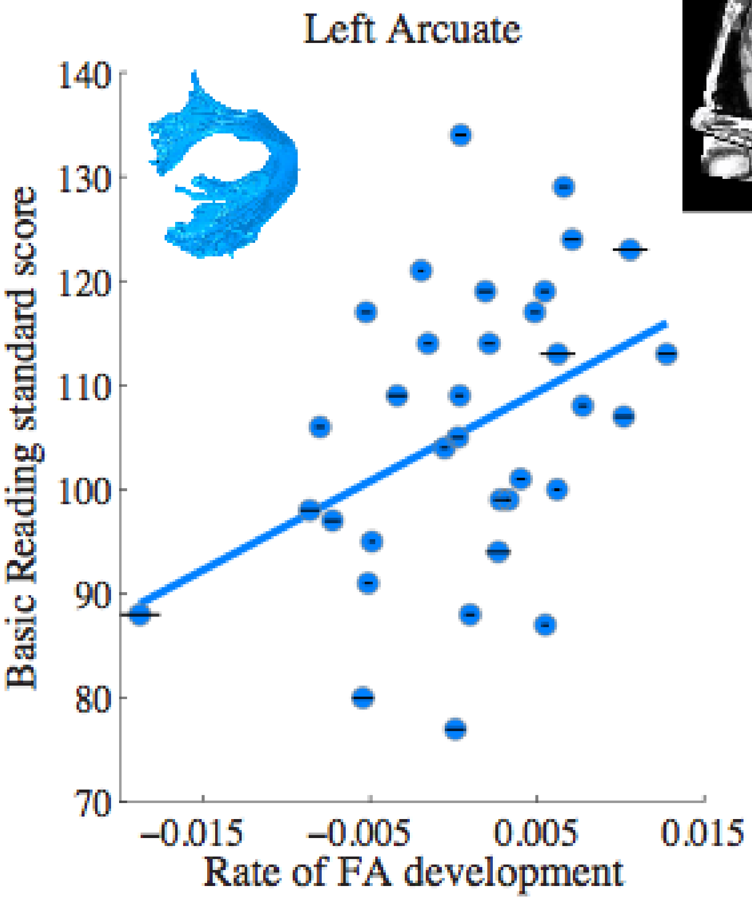


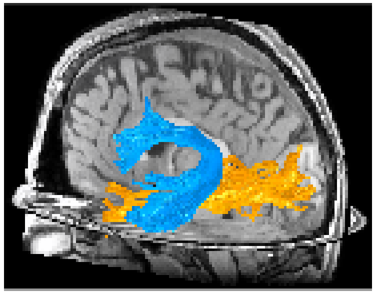
Behavioral Correlation is Stronger after FA profile alignment

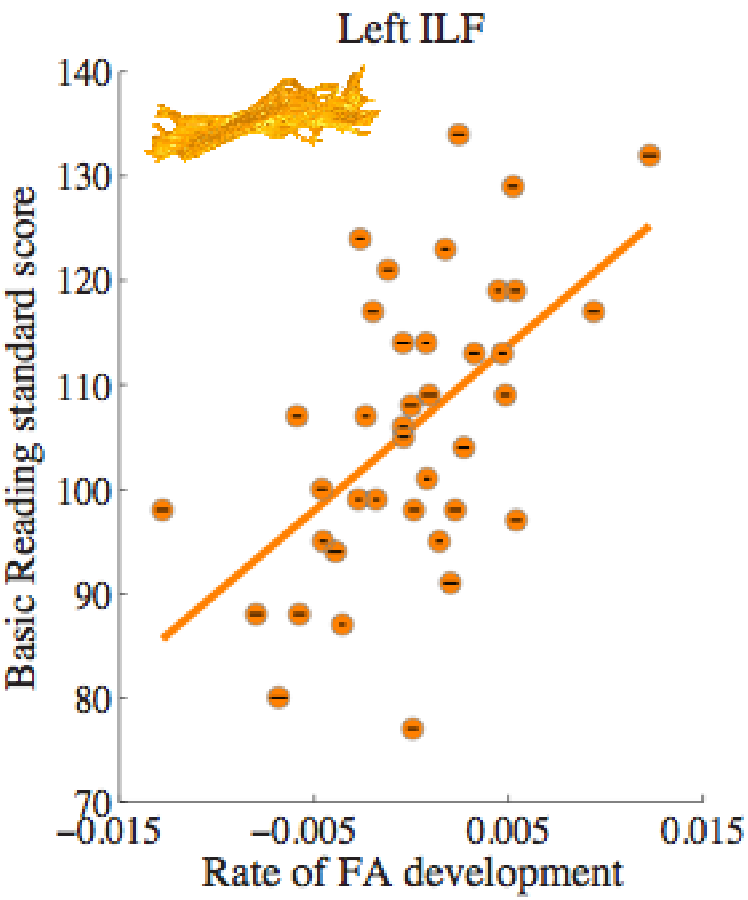


Yeatman, Ben-Shachar and colleagues, JoCN (2011)

Longitudinal analysis: Rate of pathway development correlates with reading skill

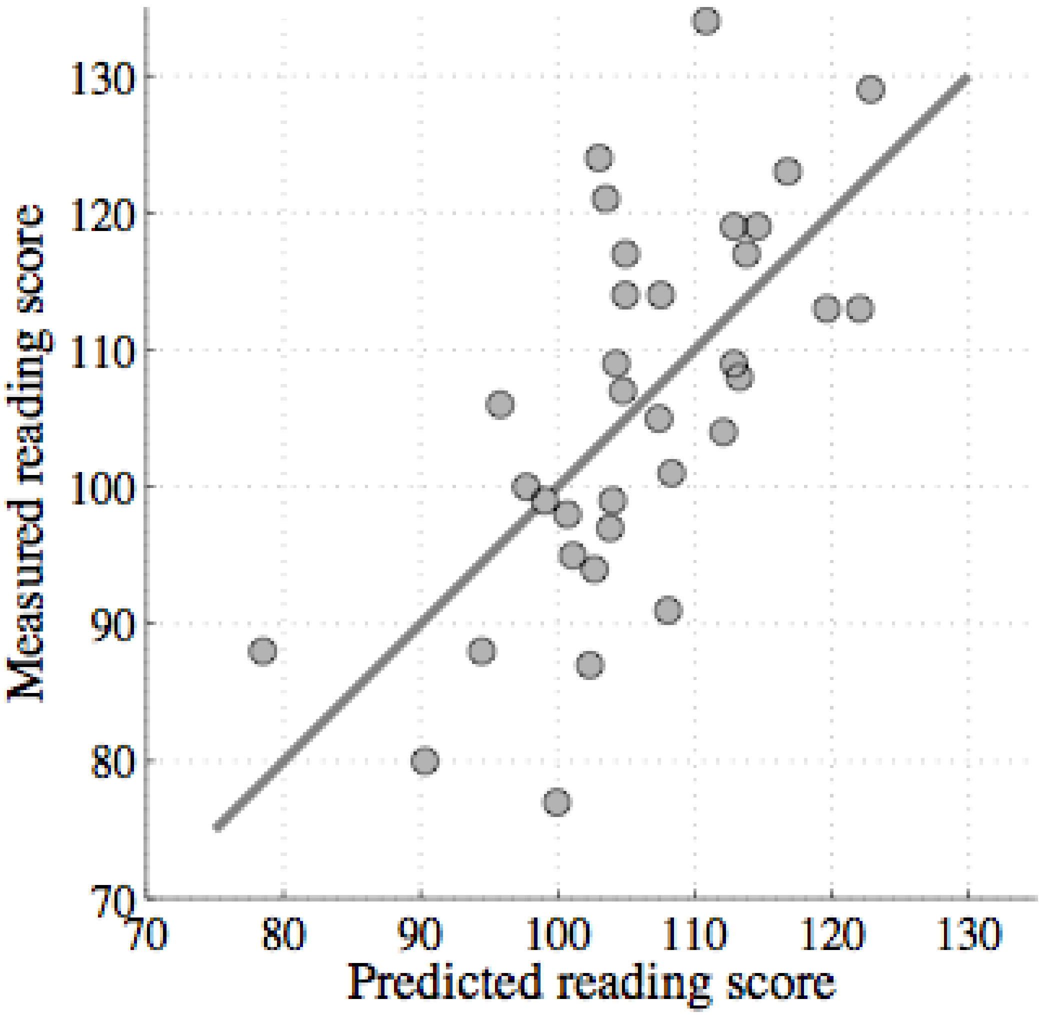




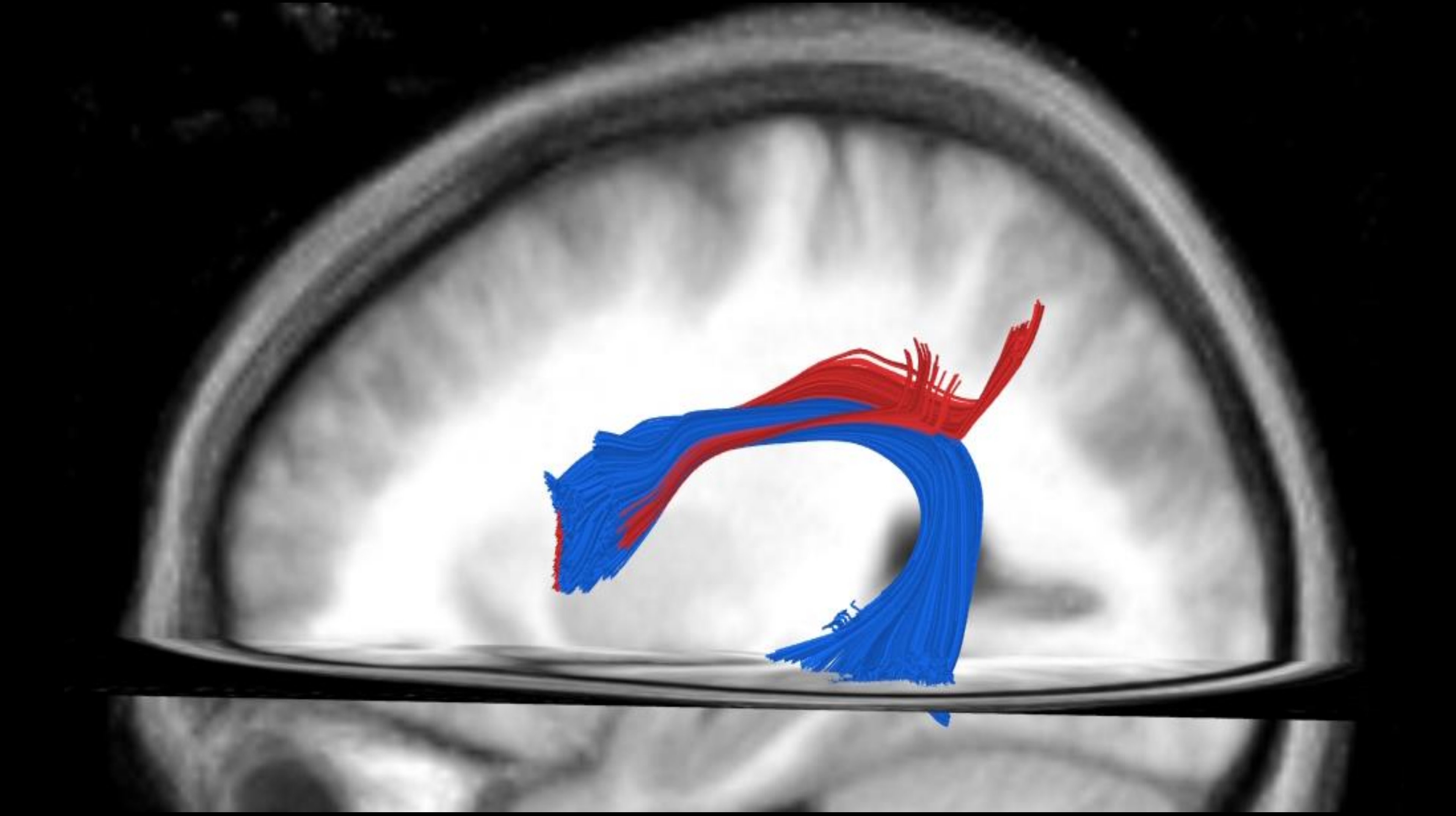


Yeatman et al., PNAS 2012

Reading is predicted as a weighted sum of AF and ILF growth estimates

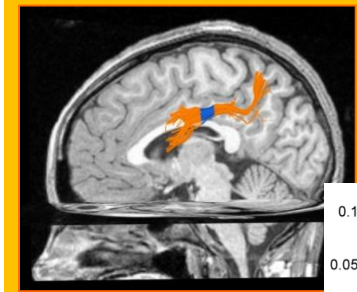


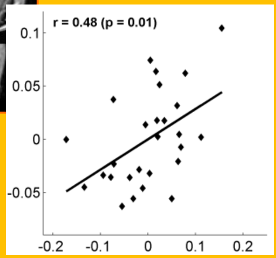
Yeatman et al., PNAS 2012

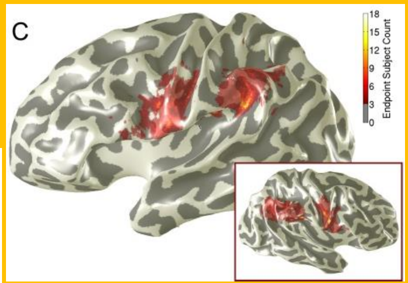


Is there a functional dissociation between the anterior and long segments of the SLF?

Maybe.
Left aSLF correlates with mental math





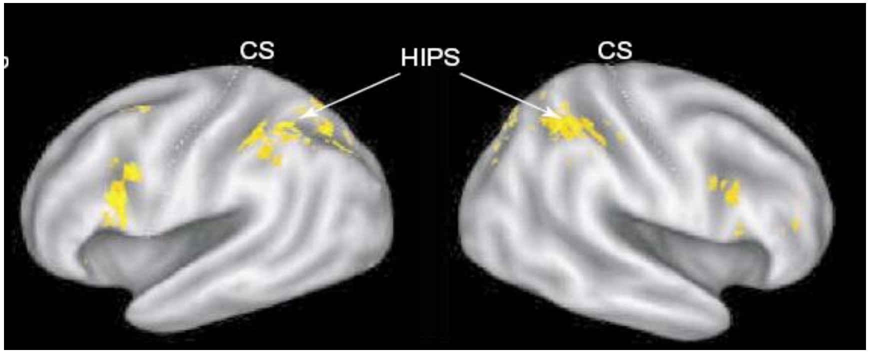


Tsang, Dougherty, Deutsch, Wandell and Ben-Shachar, PNAS 2009

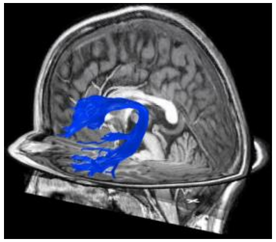
Current Opinion in Neurobiology 2004, 14:218–224

Arithmetic and the brain

Stanislas Dehaene*, Nicolas Molko, Laurent Cohen and Anna J Wilson



Interim summary



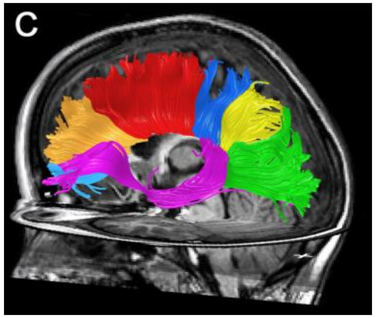
- Phonological awareness is related to diffusivity properties in temporal callosal fibers and in the long segment of the SLF (“arcuate”).

- Changes in diffusivity of the arcuate and ILF predict reading skills (better than a single snapshot).

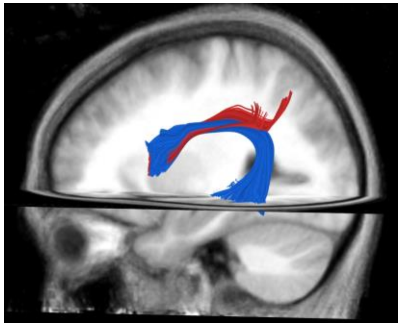
- The anterior segment (frontal-parietal) can be functionally dissociated from the long segment of the SLF.
- There may well be other cognitive skills associated with the SLF (e.g., Lebel and Beaulieu 2009, Catani et al. 2007; Wilson et al., 2011, Rolheiser et al., 2011).

Methodological take home messages

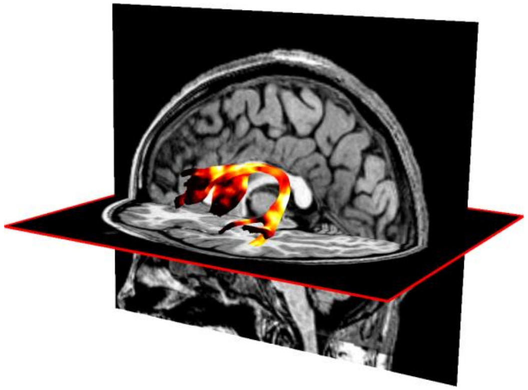
- Individualized tractography can pick up functional correlations that may be missed by voxel based methods



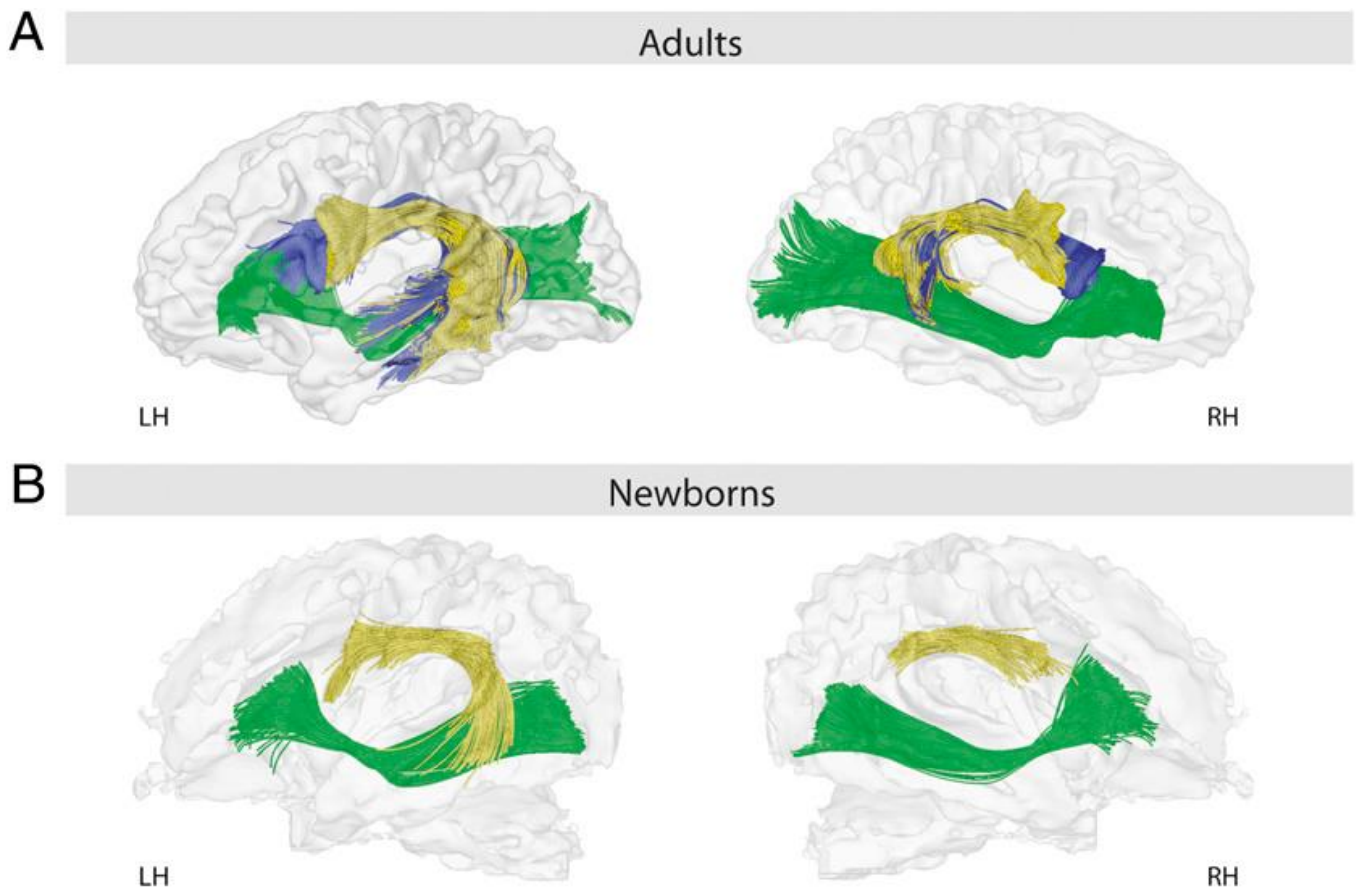
- Analyze each SLF segment separately



- Examine the whole profile of diffusion parameters along the tract



Know your limits: Missing tracts, endpoint reliability



Perani, Friederici et al., PNAS 2011

Extending the language pathways: DTI allows the discovery of new tracts in the (living) human brain

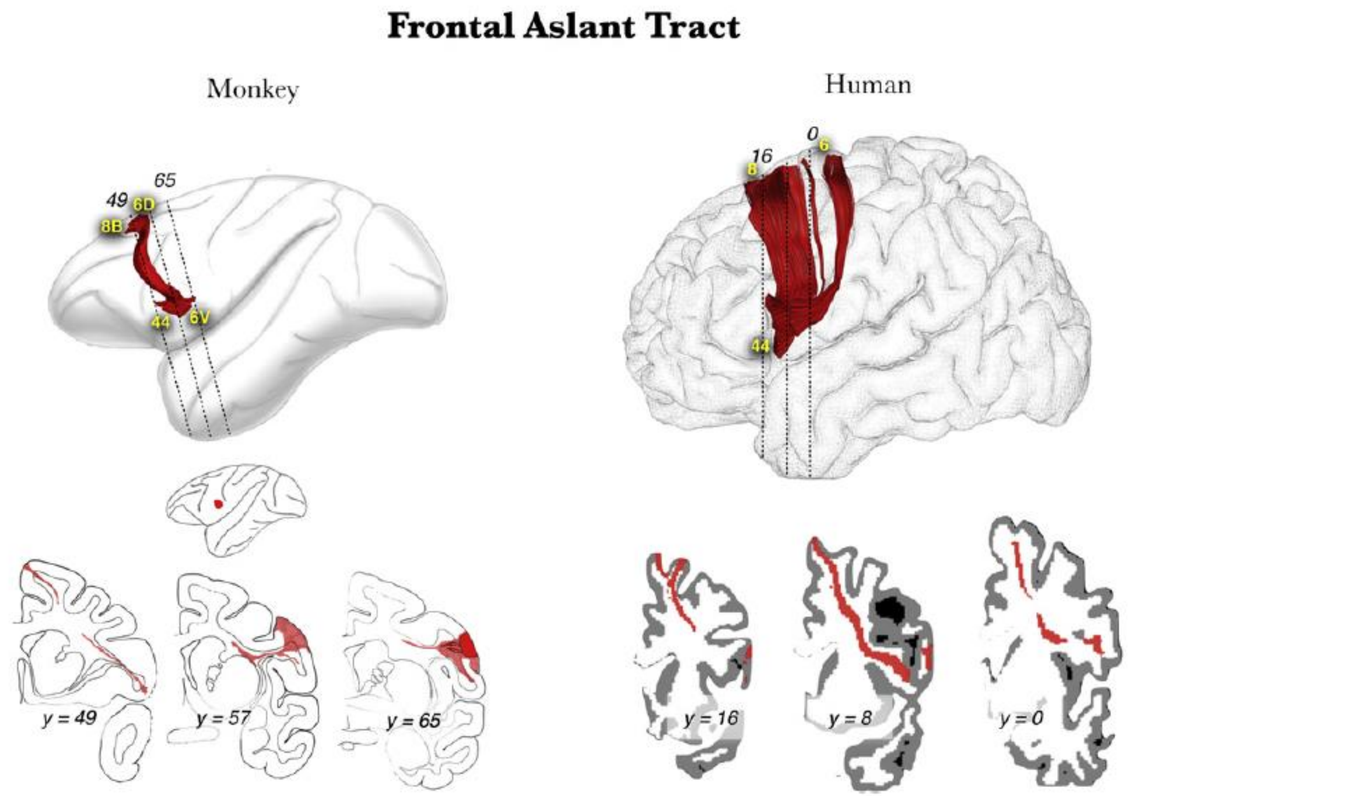
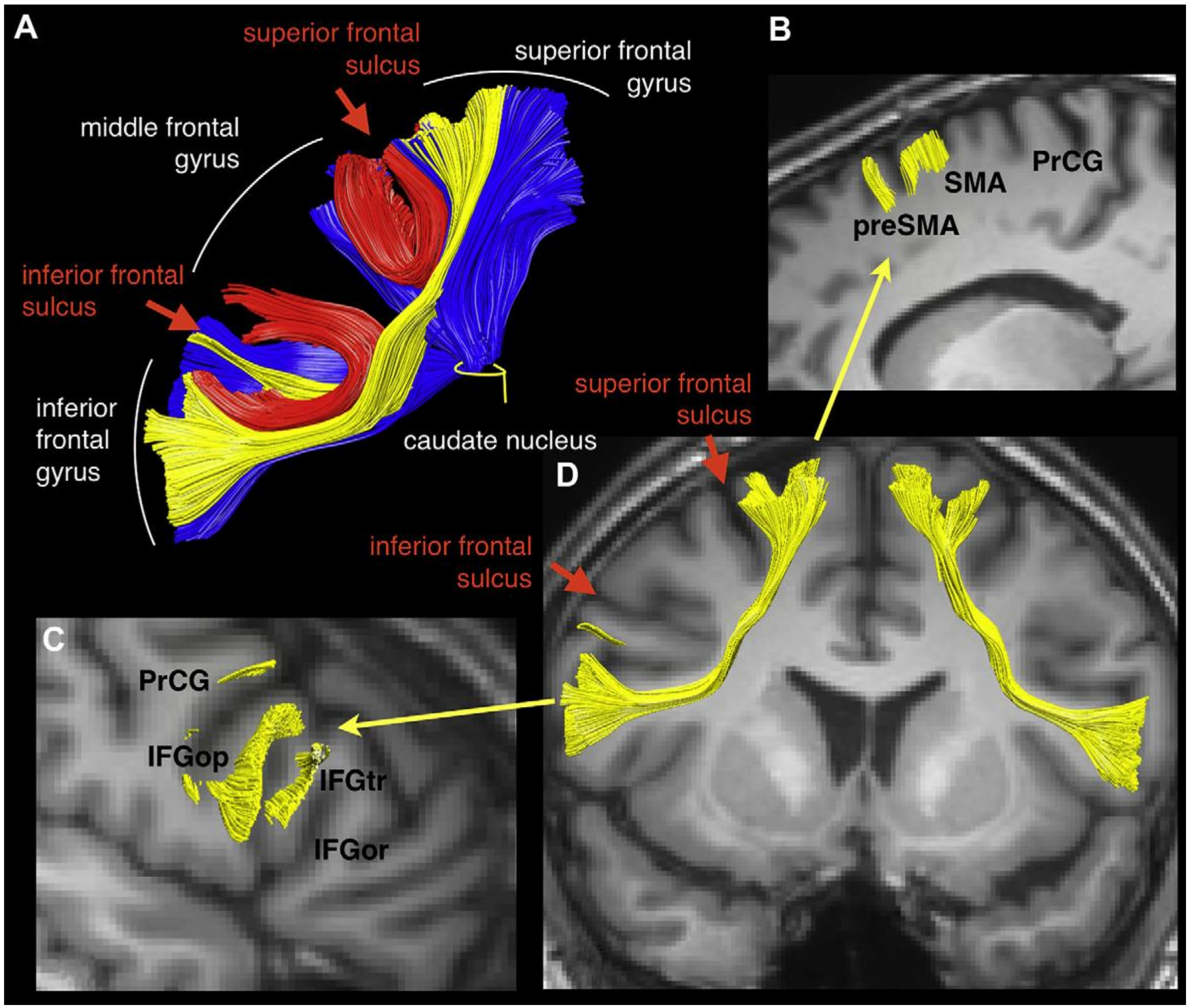


Fig. 6 – Reconstructions of the frontal aslant tract: comparison between post-mortem axonal tracing in monkey (case 25 modified from Schmahmann and Pandya, 2006) and human in vivo SD tractography shows simian-human similarities.

Thiebaut de-Schotten et al., Cortex 2012

The Frontal Aslant Tract



CORTEX 48 (2012) 273–291

Short frontal lobe connections of the human brain

Marco Catani[a,1,*], Flavio Dell'Acqua[a,b,c,1], Francesco Vergani[d], Farah Malik[a], Harry Hodge[a], Prasun Roy[a], Romain Valabregue[e] and Michel Thiebaut de Schotten[a,f]

doi:10.1093/brain/awt163

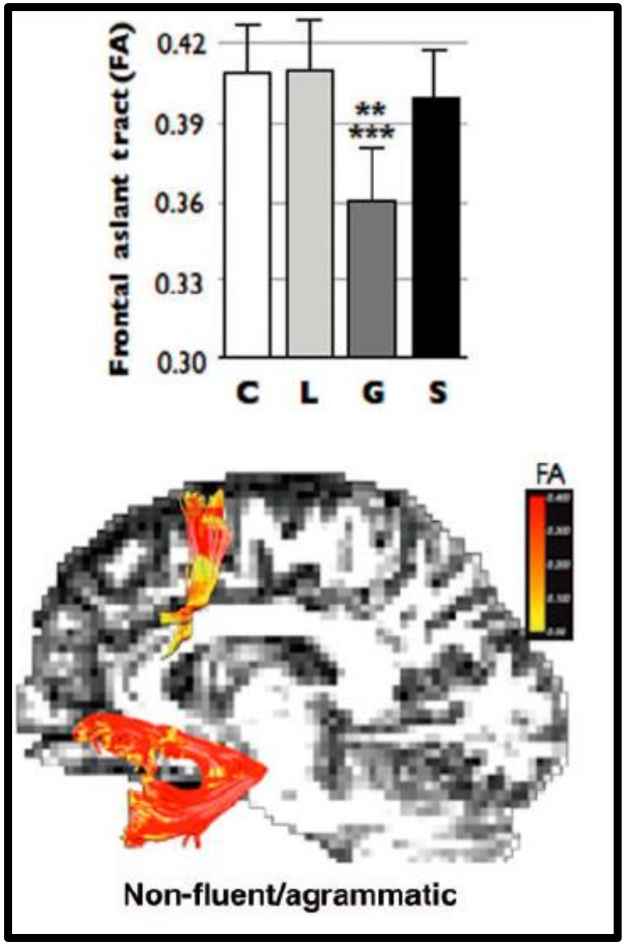
Brain 2013: 136; 2619–2628 | 2619

BRAIN
A JOURNAL OF NEUROLOGY

A novel frontal pathway underlies verbal fluency in primary progressive aphasia

Marco Catani,[1] Marsel M. Mesulam,[2,3] Estrid Jakobsen,[1] Farah Malik,[1] Adam Martersteck,[2] Christina Wieneke,[2] Cynthia K. Thompson,[2] Michel Thiebaut de Schotten,[1,4] Flavio Dell'Acqua,[1,5,6] Sandra Weintraub[7] and Emily Rogalski[2]

The frontal aslant tract is impaired in non-fluent PPA



Is the frontal aslant tract involved in stuttering?

Vered Kronfeld-Duenias · Ofer Amir ·
Ruth Ezrati-Vinacour · Oren Civier ·
Michal Ben-Shachar

Brain Structure and Function 2014

Methods

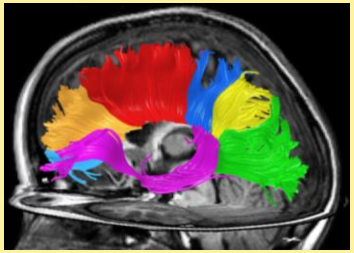
Table 1 Subject demographics and fluency measures

	AWS (N = 15)	Controls (N = 19)	Significance level
Age (years)	31.733 (9.93)	33.26 (9.91)	n.s
Gender	12M/3F	16M/3F	n.s
Handedness[a]	96 (8.28)	89.63 (17.84)	n.s
Education[b] (years)	14.7 (2.86)	15.31 (2.8)	n.s
Speech rate (#SPS)	4.7 (1.18)	5.96 (0.78)	$p < 10^{-3}$
SLD (%)	12.36 (16.73)	2.17 (1.03)	$p < 0.05$
St. Syll. (%)	7.86 (3.95)	2.1 (0.99)	$p < 10^{-6}$

Each participant goes through:

Session 1

Session 2



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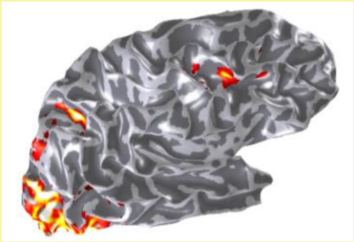
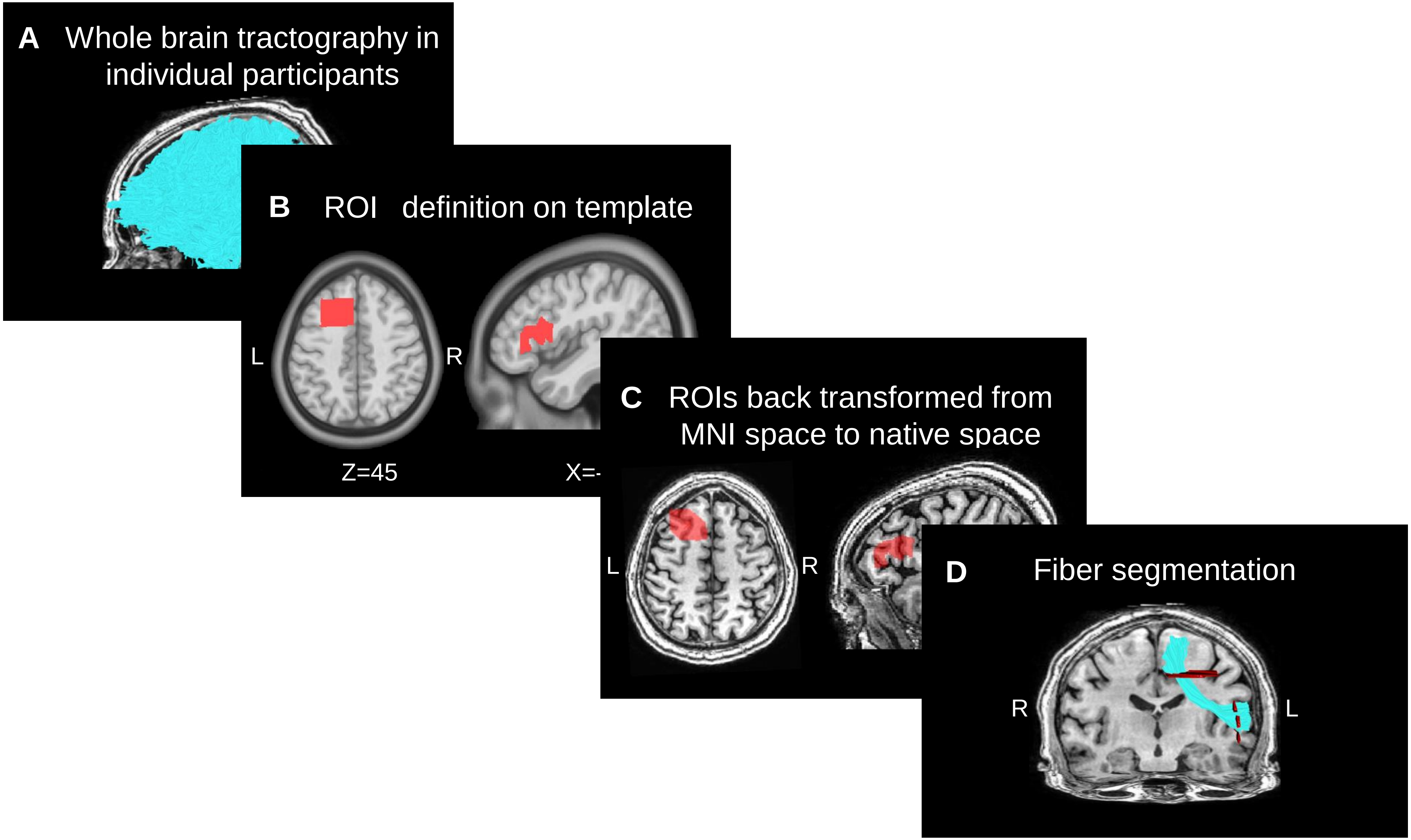


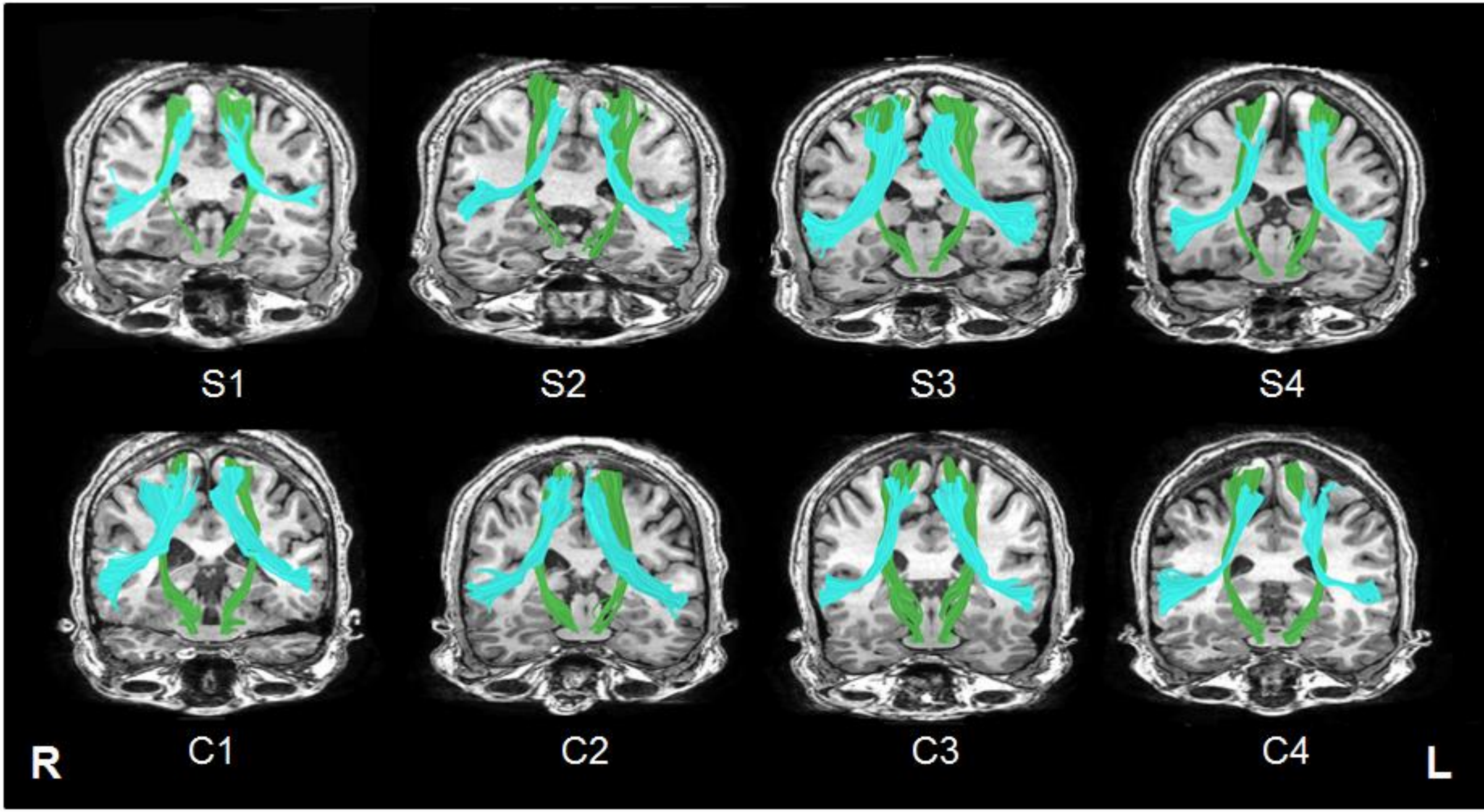
Stuttering severity assessment

- Participants are asked to speak about an experience they had such as a trip abroad
- 10min of spontaneous speech is recorded
- Stuttering events are classified and counted by two research assistants guided by Prof. Ofer Amir (dept. of Communication disorders, TAU).
- Calculate: % stuttered syllables, syllables per second, …

Tract segmentation

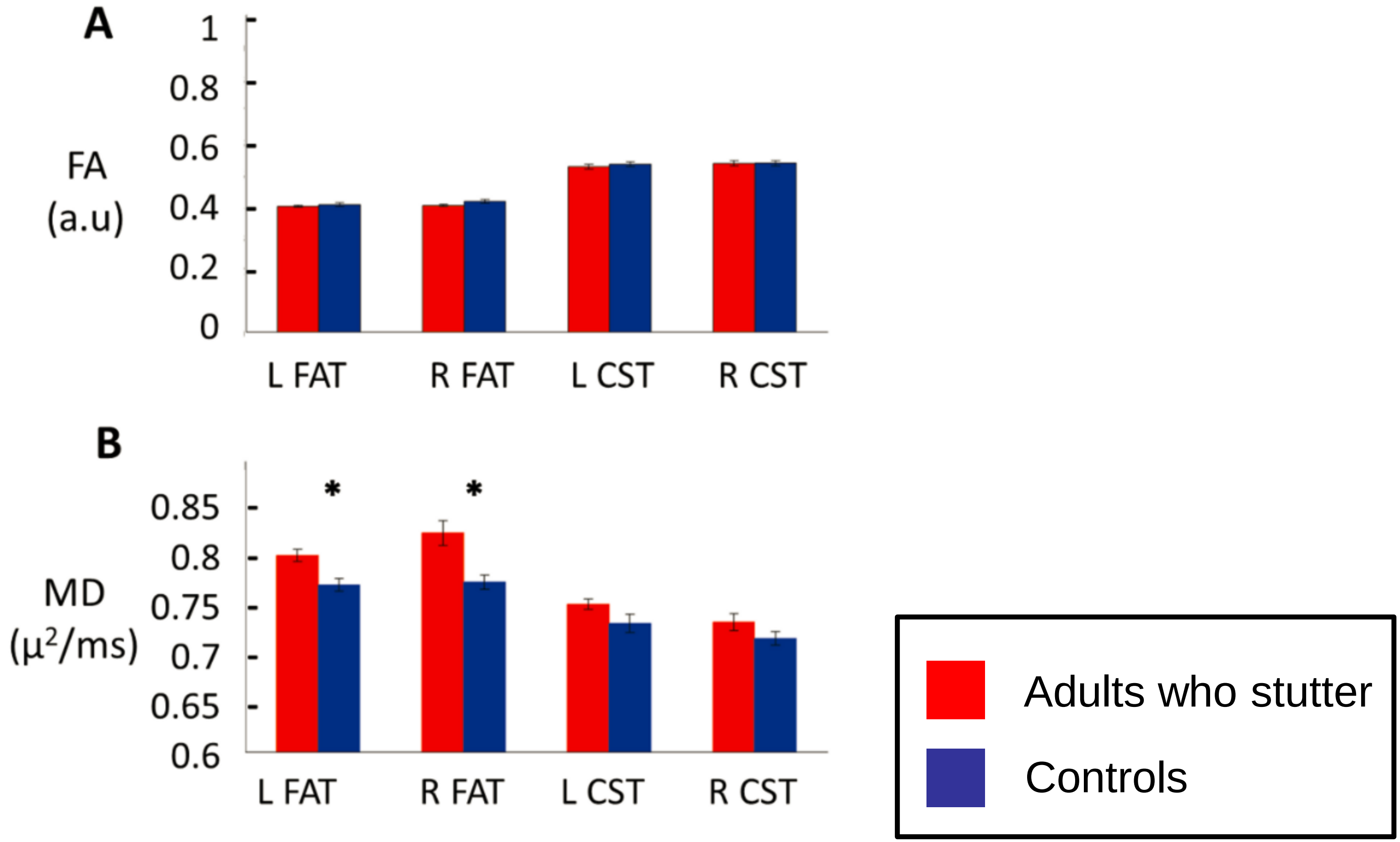


Define the frontal aslant and CST in each individual bilaterally



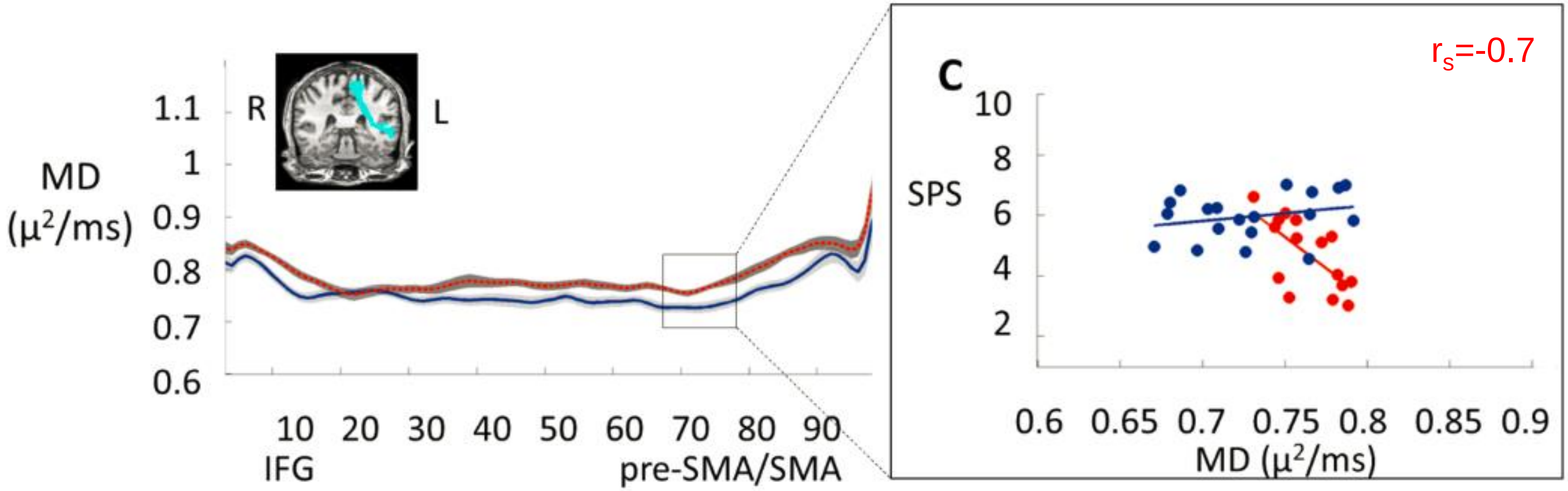
Kronfeld-Duenias et al., Brain Structure and Function (2014)

1st finding: Elevated MD in bilateral Aslant in stuttering



Kronfeld-Duenias et al., Brain Structure and Function (2014)

2nd finding: MD in L-aslant correlates with speech rate in stuttering



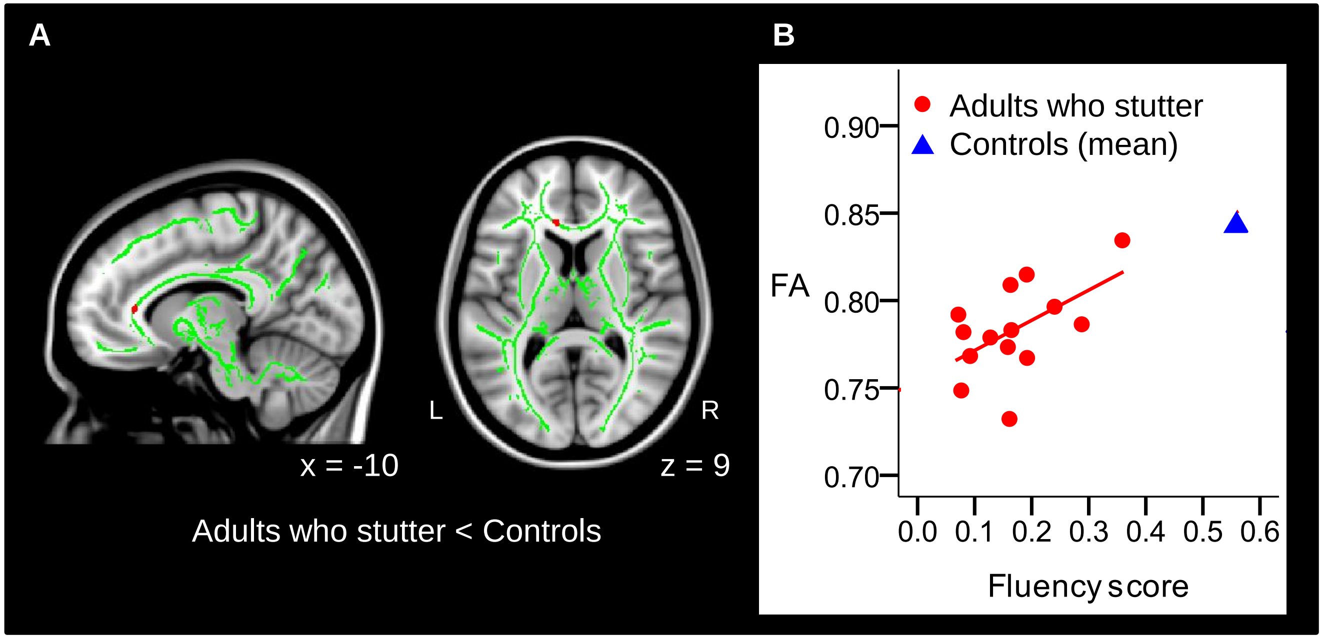
Adults who stutter

Controls

Kronfeld-Duenias et al., Brain Structure and Function (2014)

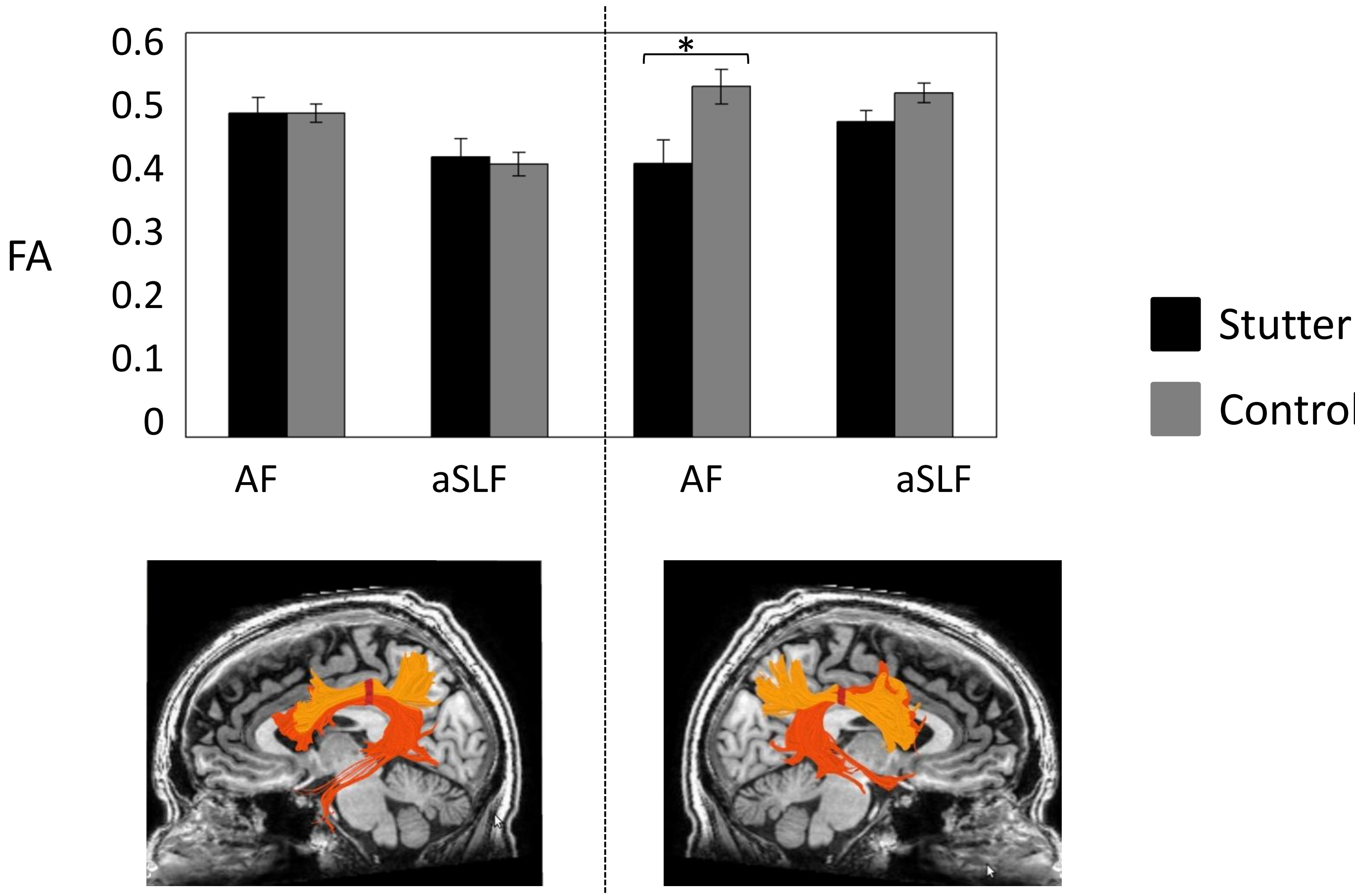
A few other interesting facts we discovered about the neural basis of stuttering

Whole brain analysis in registered brains: Callosal properties correlate with stuttering severity



Civier et al., Under review

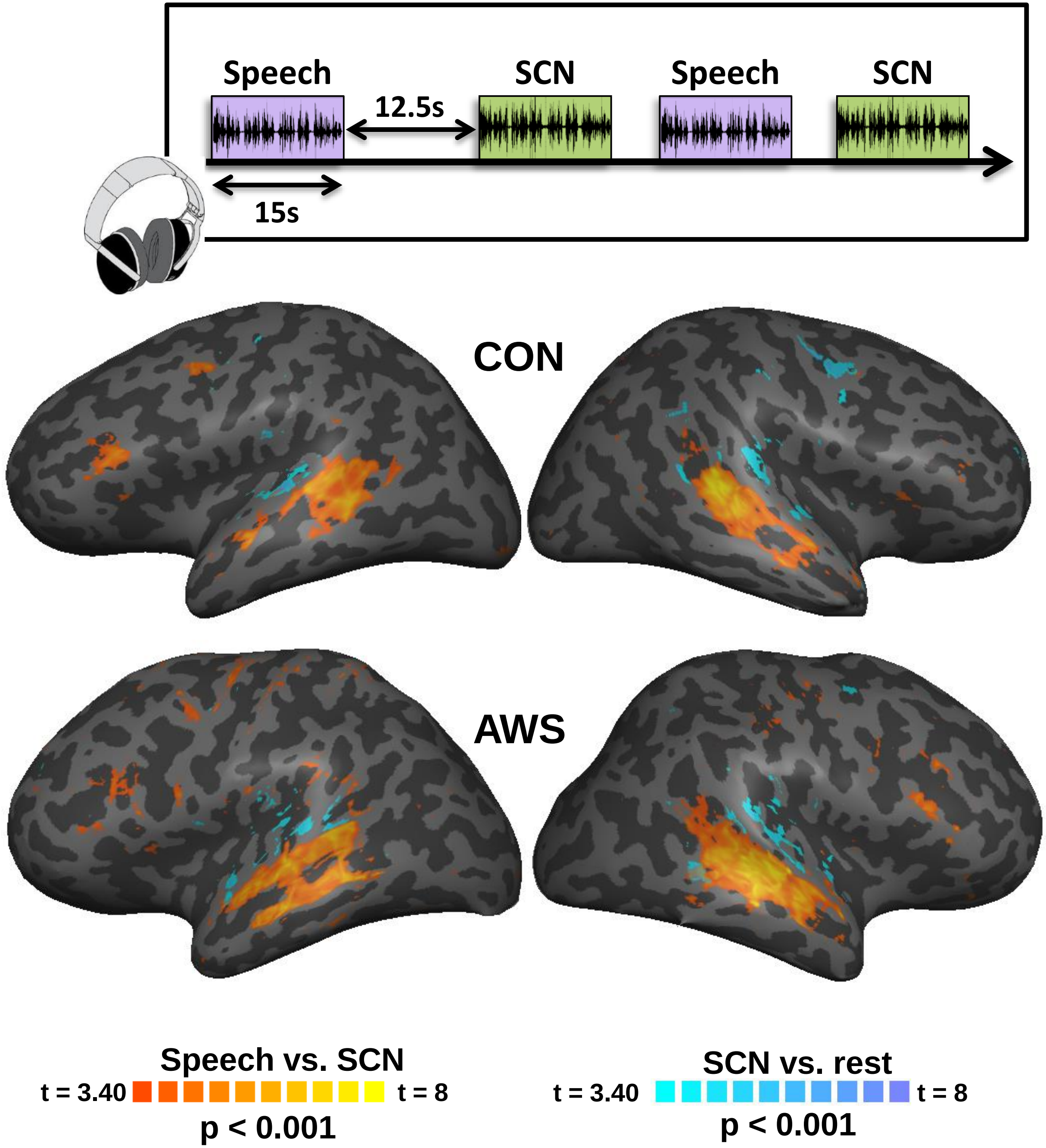
FA reduction in a compact region within the right arcuate fasciculus



Left ***Right***

Kronfeld-Duenias et al., under revision

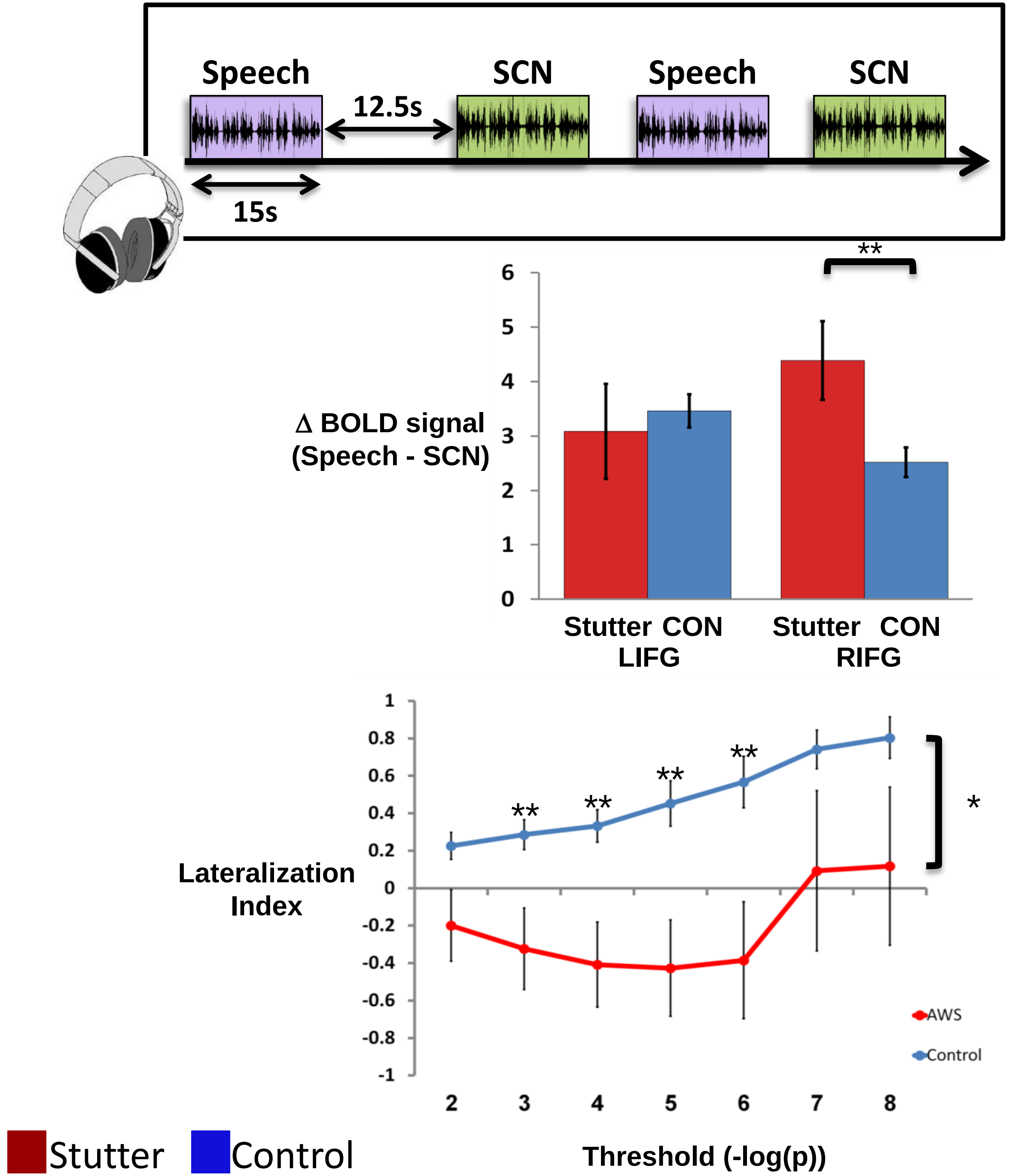
In fMRI: Adults who stutter show increased right frontal activation when listening to speech



Halag-Milo et al., In prep

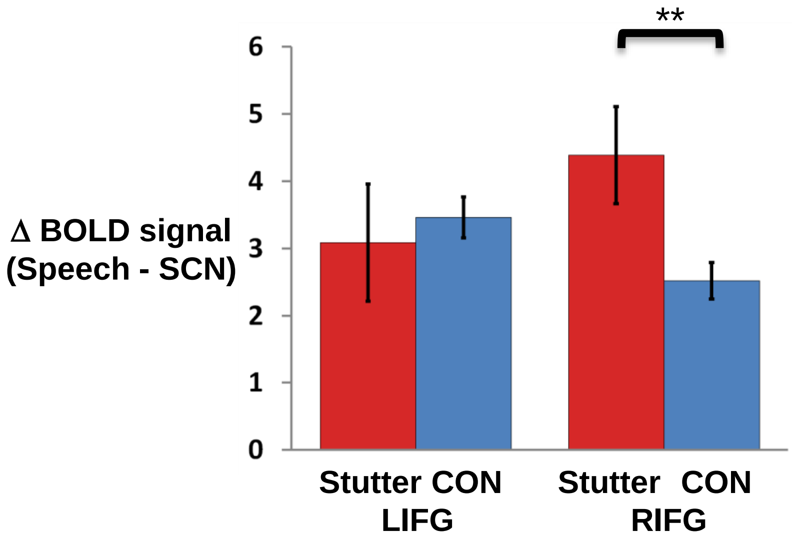
In fMRI:

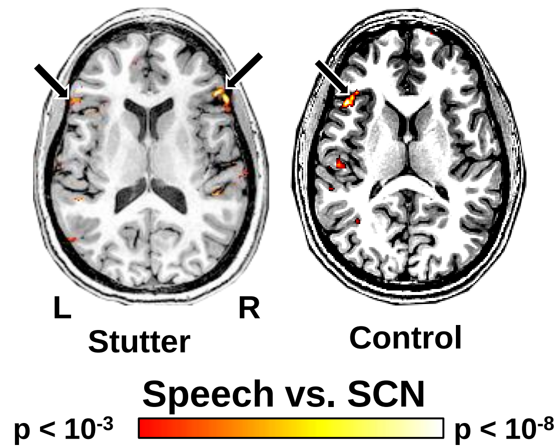
Adults who stutter show increased right frontal activation when <u>listening</u> to speech

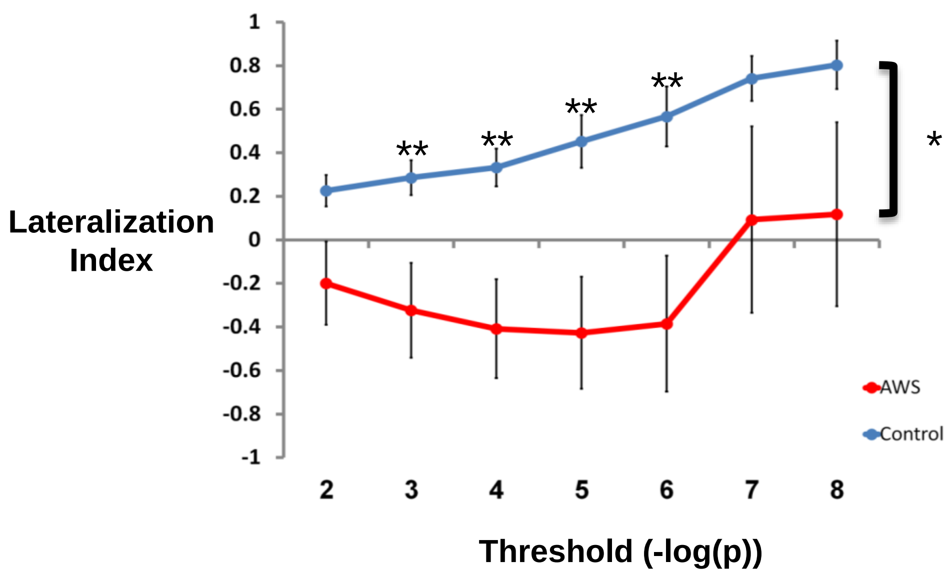


Halag-Milo et al., In prep

Enhanced right frontal activation in adults who stutter when listening to speech







Stutter Control

Halag-Milo, In prep

Summary

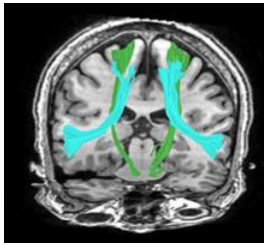
Adults who stutter show:

- Elevated MD in bilateral Frontal Aslant Tract
- Correlation between MD and speech rate in left Aslant and left CST
- Reduced FA in the anterior callosum and a correlation with stuttering severity
- Reduced volume of the left arcuate fasciculus
- Reduced anisotropy in the right arcuate fasciculus
- Enhanced involvement of right inferior frontal cortex in processing speech

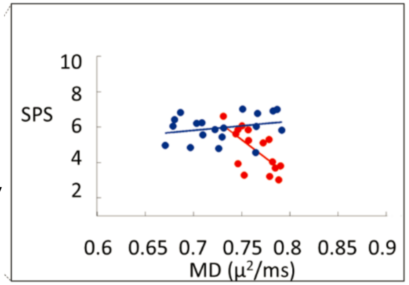
Interpretation

- What we have seen so far suggests that stuttering, at least in adults, is a bi-hemispheric phenomenon.
- It has been suggested that the left hemisphere is damaged and the right hemisphere is compensating for it. Our findings do not support this idea - the difference in the Aslant is bilateral, and its direction is identical in both hemispheres.
- Changes in frontal callosal connectivity may lead to reduced inhibitory control from the left IFG to its right homologue. As we know from aphasia studies, the right IFG is limited in its ability to produce fluent language.
- Our findings support the theory that the frontal aslant tract is essential for producing fluent speech.

General take home message: dMRI



- Diffusion tractography can serve to identify known tracts as well as to extend the familiar territory of the language pathways into uncharted new frontiers
- Once sufficient groundwork has been done to validate a new pathway, its functional contributions can be studied via correlations with specific behavioral components



- Convergence with other methods is extremely important
- Better interpretation of diffusion parameters (FA, MD, RD, ..) should be sought using Q-MR methods

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