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

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Why study white matter?

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

• 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

Articulatory network
- pIFG, PM, anterior insula (left dominant)

Sensorimotor interface
- Parietal–temporal Spt (left dominant)

Spectrotemporal analysis
- Dorsal STG (bilateral)

Phonological network
- Mid-post STS (bilateral)

Combinatorial network
- aMTG, aITS (left dominant?)

Lexical interface
- pMTG, pITS (weak left-hemisphere bias)

Conceptual network
- Widely distributed

Input from other sensory modalities

Via higher-order frontal networks

Dorsal stream

Ventral stream
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

Image courtesy of Dr. Ugur Ture
We can now estimate fascicles in living humans.
Water diffusion probes white matter structure

Water diffusion is faster along the fascicle

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

Water diffusion is slower perpendicular to the fascicle

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

Image courtesy of George Bartzokis
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)
- Summarize tensor shape: FA
- Follow principal diffusion direction to reconstruct fiber bundles

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

\[0 \leq FA \leq 1\]
DTI reveals White Matter Structure

Mean Diffusivity

Anisotropy

Principal Direction

**MD (μm²/msec)**

FA: Dimensionless
DTI of reading pathways
Pre-DTI literature: Corpus callosum is different in dyslexia

Hynd et al., 1995

Von Plessen et al., 2002

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.
First DTI-dyslexia study:
Poor readers have lower FA in a temporo-parietal white matter region (Klingberg et al. 2000)
Why is there no group difference reported in the callosum using voxel based DTI methods?

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.

Dougherty, Ben-Shachar et al., PNAS 2007
Segmentation of the callosum

Find the location where these fibers pass through the callosum

Anterior commissure

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.

Diffusion perpendicular to the fibers

\[ r = 0.52 \ (27\%) \]

\[ p < 0.0002 \]

Dougherty et al., PNAS 2007
Clinical application: premature birth

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?

Anterior Third  | Midbody  | Posterior Third
---|---|---
Front | Back

- Superior parietal
- Posterior parietal
- Superior Frontal
- Anterior Frontal
- Orbital Frontal
- Indeterminate
Quantitative comparison

FA

Callosal segment

- Occ
- p.Par
- s.Par
- Temp
- s.Fron
- a.Front
- Orb

patient
control
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 fasciculus

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).
Poor readers have lower FA in temporo-parietal white matter
A popular interpretation: Impaired language connections (SLF)

We now know that SLF is a mixture of several pathways.
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**
Each subject showed an FA “dip” where the segments diverge

However: dip location varies between subjects
FA dip reflects pathway junction
FA trajectory alignment

1.

2.

3.

Frontal Lobe → Temporal Lobe

Fractional Anisotropy
Behavioral Correlation is Stronger after FA profile alignment

$r = -0.36, p < 0.01$ (yep, still negative..)

$r = 0.35, p < 0.01$

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

A  
Adults

B  
Newborns

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.
The Frontal Aslant Tract
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

<table>
<thead>
<tr>
<th></th>
<th>AWS (N = 15)</th>
<th>Controls (N = 19)</th>
<th>Significance level</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>31.733 (9.93)</td>
<td>33.26 (9.91)</td>
<td>n.s</td>
</tr>
<tr>
<td>Gender</td>
<td>12M/3F</td>
<td>16M/3F</td>
<td>n.s</td>
</tr>
<tr>
<td>Handedness(a)</td>
<td>96 (8.28)</td>
<td>89.63 (17.84)</td>
<td>n.s</td>
</tr>
<tr>
<td>Education(b) (years)</td>
<td>14.7 (2.86)</td>
<td>15.31 (2.8)</td>
<td>n.s</td>
</tr>
<tr>
<td>Speech rate (#SPS)</td>
<td>4.7 (1.18)</td>
<td>5.96 (0.78)</td>
<td>(p &lt; 10^{-3})</td>
</tr>
<tr>
<td>SLD (%)</td>
<td>12.36 (16.73)</td>
<td>2.17 (1.03)</td>
<td>(p &lt; 0.05)</td>
</tr>
<tr>
<td>St. Syll. (%)</td>
<td>7.86 (3.95)</td>
<td>2.1 (0.99)</td>
<td>(p &lt; 10^{-6})</td>
</tr>
</tbody>
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Each participant goes through:

Session 1

Session 2

+
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

A. Whole brain tractography in individual participants

B. ROI definition on template

C. ROIs back transformed from MNI space to native space

D. Fiber segmentation
Define the frontal aslant and CST in each individual bilaterally.
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

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

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 listening to speech.

Halag-Milo et al., In prep
Enhanced right frontal activation in adults who stutter when listening to speech

**Δ BOLD signal (Speech - SCN)**

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<thead>
<tr>
<th></th>
<th>Stutter CON</th>
<th>Stutter CON</th>
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<tbody>
<tr>
<td>LIFG</td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
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<tr>
<td>RIFG</td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
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</tbody>
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**Lateralization Index**

- **Stutter**
- **Control**

**Threshold (-log(p))**

- **p < 10^-3**
- **p < 10^-8**

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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