Corpus Callosum in Developmental Stuttering

Agenda

1) Background
   - Stuttering and role of the corpus callosum (CC)
   - Functional and structural brain findings
   - Behavioral findings relevant to hemispheric dominance

2) Method
   - Study 1: Adults who stutter (AWS)
   - Study 2: Children who stutter (CWS)

3) Implications
BACKGROUND

Functional abnormalities in Stuttering

• Different speech/language relevant regions show decreased and increased activation.

• Speech with stuttering episodes
  – ↑ activity in the motor system with prominent right hemisphere lateralization (Fox et al., 1996).
Functional abnormalities in Stuttering

• Speech in Fluency inducing condition
  – ↑ activity in the right frontal operculum (Giraud et al., 2008; Preibisch et al., 2003).

• Auditory processing
  – ↓ activity in left temporal regions (Braun et al., 1996; Chang et al., 2009; Fox et al., 1996).

Assessment: Atypical distribution of language related activity across hemispheres.
Structural abnormalities in Stuttering

Gray matter (VBM studies)

• Increase in the right and left superior temporal gyrus, and left inferior frontal gyrus extending into the precentral gyrus and insula in AWS (Beal et al., 2007).

• Reduced volume in the left inferior frontal gyrus and bilateral temporal regions in CWS (Chang et al., 2008).

Assessment: Atypical distribution of gray matter across hemispheres.
Structural abnormalities in stuttering

White matter (WM)

- **DTI Studies:** Reduced FA in speech-relevant areas in the left rolandic operculum near the oral sensorimotor areas, left superior longitudinal fasiculus, and CC (Cykowski et al., 2010; Sommer et al., 2002).

- **VBM Studies:** Increased volume in the right superior temporal gyrus (including planum temporale) and precentral gyrus (proximal to oral motor areas) (Jäncke et al., 2004).

**Assessment:** Decreased WM in LH with increases in RH.
Behavioral Studies in Stuttering

- Dichotic listening and Delayed Auditory Feedback (DAF)
  - Younger CWS presented fewer right ear advantage than controls (Blood, Blood & Hood, 1987).
  - RH male and female AWS featured smaller REA compared to controls (Blood & Blood, 1989).
  - Variable ear advantages in AWS, and atypical rightward PT asymmetry associated with atypical auditory processing (DAF) (Foundas et al., 2004a, 2004b).

Assessment: Weaker REA, more variable ear advantage and atypical auditory processing in CWS and AWS.
CC in typical development

- Studying CC is central to understanding inter-hemispheric coordination in complex human behaviors
  - Largest white matter tract in the brain.
  - One of the last structures to complete postnatal maturation that continues into early adulthood (Giedd et al., 1999; Keshavan et al., 2002).
  - Prominent size increases occur during early childhood and adolescence (Pujol et al., 1993).
Corpus Callosum in Typical Development

• CC maturation (size) proceeds in a rostral to caudal direction but rostrum is last to develop (Georgy et al., 1993; Giedd et al., 1999).

• CC myelination follows a caudal to rostral direction (Georgy et al., 1993; Giedd, 2004; Pujol et al., 1993).
CC in typical development

- Size increase is related to an increase in the degree of myelination, fiber density and fiber size (Aboitiz, 1992; Giedd et al., 1999).

- Size decrease is mainly associated with axonal pruning or cell death (Clarke et al., 1989).
DTI Illustration of Adult CC Connections

- Rostrum & genu: prefrontal lobe (green).
- Anterior body: premotor and supplementary motor areas (blue).
- Posterior midbody: primary motor cortex (dark blue), primary sensory cortex (red), parietal lobe (orange), temporal lobe (violet).
- Splenium: occipital lobe (yellow)

(Hofer & Frahm, 2006)
Current Perspectives on CC size and lateralization

- Smaller CC - more lateralization (Luders et al., 2010).
- Larger CC - less lateralization (Gootjes et al., 2006; O’Kusky et al., 1988; Witelson, 1989).
- Individuals with right hemisphere for speech have larger CC (O’Kusky et al., 1988).
CC IN STUTTERING

• Studies investigating bimanual coordination suggest unusual interhemispheric communication (Zelanik, Smith, Franz & Ho, 1997; Forster & Webster, 2001).

• Some evidence for atypical variability in ear advantage in AWS.

• Neuroimaging investigations point to
  – Atypical distribution of language/speech activity.
  – Increased brain tissue volumes in RH.

Assessment: These anomalies in stuttering may be mediated by differences in CC development.
Aim
• To investigate if developmental stuttering is associated atypical CC growth.

Hypotheses
• Developmental stuttering is associated with increased CC size and WM volume.
• Atypically large CC size and increased WM volume will be present in AWS and CWS.
STUDY 1: ADULTS

Participants
All right-handed males aged between 20-35 years old.

Adults who stutter (AWS) (n=11):
• Males with persistent stuttering.
• Severity ranged from mild to moderate stuttering.
• All AWS reported a history of speech therapy.

Controls (n=12):
• Normally fluent males without a history of stuttering.

Imaging

• T1-weighted MPRAGE (magnetization-prepared rapid acquisition gradient echo) sequence
  - (parameters: TR/TE=21 s/4.38 ms,
  - FOV 256 mm, matrix 256×160×128 mm3,
  - slice thickness 1.3 mm,
  - flip angle 8° bandwidth 130 Hz/pixel).

• Participants viewed a movie of their choice while being scanned.

• To minimize head movements, participants’ heads were padded with foam and lightly held in place with a strap across the forehead.
CC segmentation

- Segmentation of the CC was performed in a similar method as described in Sullivan et al. (2001).
CC area analysis

• Area was calculated using MIPAV (Medical Image Processing, Analysis, and Visualization) (McAuliffe et al., 2001).

• Investigators who were blinded to the sex, identity and diagnosis of each participant manually traced the area of the CC and each subsection.
CC area analysis

- Planned comparisons were performed for: (1) absolute area of the total CC, (2) absolute area of each subregion, and (3) relative area of each subregion.

  Relative CC area = CC subregion/the total CC area
  
  (Preis, Steinmetz, Knorr & Jäncke, 2000).

CC VBM analysis

- VBM performed with SPM 5.
- Between group comparisons were performed using voxel-wise two sample t-test with a statistical threshold of $p<0.01$ uncorrected.
RESULTS

Total CC area

- Larger overall CC in AWS ($p<.0001$).
Area of CC subsection

- Larger rostrum and anterior midbody in AWS \[\text{rostrum: } (p=0.014); \text{ anterior midbody: } (p=0.036).\]
- No difference in posterior midbody and splenium \[\text{posterior midbody: } (p=0.53); \text{ splenium: } (p=0.44).\]
• Anterior half of the CC > posterior half of the CC in AWS and controls.
Relative area

- The ratio of the posterior subsection over the entire CC was smaller in AWS than controls ($t(21)=3.00, p=0.003$).

- No differences were found in the ratio of the other subsections ($p=0.036$).
3) White matter volume

- Cluster of increased white matter predominantly encompassing the rostrum in AWS (1 cluster of 63 voxels, $p<0.01$ uncorrected).
Study 2: CHILDREN

Participants
• All right-handed boys between 9-13 years old.
• No other concomitant disorders besides stuttering.

Children with persistent stuttering (n=8):
• Began stuttering between 2 to 3 years old.
• Severity ranged from mild to moderate stuttering.
• All except one reported a history of speech therapy.

Children who recovered (n=6):
• Began stuttering between 2 to 3 years old.
• Recovered within 2-3 years of onset.
• Only one reported a history of therapy.

Control (n=7):
• Typically developing boys without a history of stuttering.

* Under review
METHOD

Imaging
• Identical to the adult study.

CC segmentation
• Identical to the adult study.

CC area analysis
• Identical to the adult study.
VBM analysis

• Identical to the adult study.
• Images registered on an adult template.
  — Several studies show that spatial normalization of scans from children older than 6 year can be successfully performed with adult template (Beal et al., 2011; Burgund et al., 2002; Kang et al., 2003; Muzik et al., 2000).
RESULTS

1) Reliability of CC area measurements

- Intra-class correlation (ICC) for intra-rater reliability was high (rostrum=0.98, anterior midbody=0.94, posterior midbody=0.93 and splenium=0.98).

- ICC for inter-rater reliability were also high (rostrum=0.92, anterior midbody=0.73, posterior midbody=0.89 and splenium=0.94).
2) Total area

- No difference in total CC size between groups ($p=0.60$).
3) Absolute area of subsections

- No difference in CC subregions between groups (rostrum: $p=0.49$; anterior midbody: $p=0.86$; posterior midbody: $p=0.65$; splenium: $p=0.19$).
4) Relative area of subsections

- No difference in relative area of CC subregions between groups (rostrum: \( p=0.387 \); anterior midbody: \( p=0.47 \); posterior midbody: \( p=0.30 \); splenium: \( p=0.45 \)).
5) White matter volume
• No differences were found between the 3 groups.
• No differences were found for “ever-stuttered” versus typically developing.
Summary of results - Children

• No differences between children with persistent stuttering, children who recovered from stuttering, and typically developing children in CC area, CC subregions, relative area of CC subsections and WM volume.

• Still working on formal direct comparisons between adult and child groups.
Results–Adults and Children

- Smaller total CC size in children compared to adults.
- AWS had a larger total CC area than adult controls.
- No difference between children who persisted in stuttering (CWSP), children who recovered from stuttering (CWSR) and control children in the total area of the CC.
• Smaller rostrum in children compared to adults.
• AWS had a larger rostrum than adult controls.
• No difference between children who persisted in stuttering (CWSP), children who recovered from stuttering (CWSR) and control children in the area of the rostrum.
• Smaller anterior midbody in children compared to adults.
• AWS had a larger anterior midbody than adult controls.
• No difference between children who persisted in stuttering (CWSP), children who recovered from stuttering (CWSR) and control children in the area of the anterior midbody.
• Smaller posterior midbody in children compared to adults.
• No difference between AWS and adult controls in the area of the posterior midbody.
• No difference between children who persisted in stuttering (CWSP), children who recovered from stuttering (CWSR) and control children in the area of the posterior midbody.
- Smaller splenium in children compared to adults.
- No difference between AWS and adult controls in the area of the splenium.
- No difference between children who persisted in stuttering (CWSP), children who recovered from stuttering (CWSR) and control children in the area of the splenium.
• Relative size of CC subsections similar between adults and children.
• Relative area of posterior CC subsection is smaller in AWS than adult controls. No differences were found in the relative area of the other subsections.
• No difference in the relative area of subsections between children who persisted in stuttering (CWSP), children who recovered from stuttering (CWSR) and control children.
## Discussion: Differences between adults and children

<table>
<thead>
<tr>
<th>Groups</th>
<th>Overall CC area</th>
<th>Area of CC subsection</th>
<th>Relative area of CC subsection</th>
<th>WM volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>AWS</td>
<td>Larger than control</td>
<td>Larger rostrum and anterior midbody</td>
<td>Smaller relative posterior CC</td>
<td>One cluster of increased WM in the rostrum</td>
</tr>
<tr>
<td>Adults vs. Children</td>
<td>Smaller CC in children</td>
<td>Similar relative CC size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CWS</td>
<td>Not different from control</td>
<td>Not different from control</td>
<td>Not different from control</td>
<td>Not different from control</td>
</tr>
</tbody>
</table>
Discussion

• Neural reorganization across the midline may not be established in school age children.

• Taken together, the adult and children studies suggest that deviations from normal CC development may not be present in children.

• Atypical CC development could develop in later childhood or adolescence in the adolescent phase of CC growth.

• Chronic stuttering may alter the mechanism(s) that directs callosal development.
Discussion

• Changes in the CC may reflect adaptations or compensations that function to increase the ability to mediate symptoms of stuttering.

• Changes in the CC may also be the result of a maladaptive response to stuttering.

• These results are correlational but suggest that remediation in pre-school and school-age CWS is needed before pathological anomalies become established as a consequence of long-term adaptations to stuttering.
Future directions

• Direct comparisons of AWS & CWS in terms of:
  — CC relationship to forebrain volume.
  — Influence of sex on CC size and myelination.
  — CC size and stuttering severity.
  — CC fiber direction and integrity.
Acknowledgments

I would like to thank Dr. N. Ambrose and Dr. T. Loucks for their invaluable help and guidance throughout this study.
The authors would like to thank the individuals who participated in the study.
The study was partially supported by an NIH RO1 DC 05210 - Subtypes and Associated Risk Factors in Stuttering (P.I. Nicoline Ambrose, former P.I. Ehud Yairi), American Speech Language Hearing Foundation New Investigators Research Grant (P.I. Torrey Loucks) and an Internal Research Board Grant from the University of Illinois (P.I. Torrey Loucks).

“My stuttering has helped me view many things in many different perspectives. It has gifted me to deal with different things - to look at other people and be accepting of them. I don’t see it as a fault. I see it as a gift”. (Ryan, age 14).

Drawing from the Stuttering Gallery
"Getting stuck on words hurt."
CC in disorders and TBI

- Children with developmental language delay have smaller CC relative to their brain volume although the absolute size is similar to typically developing children (Herbert et al., 2003; 2005).
- Individuals with Tourette’s syndrome have larger CC (Baumgardner et al., 1996).
- Children with Attention Deficit/Hyperactivity Disorder have larger anterior CC (Gilliam et al., 2011).
## Study in Children

### Method

#### Participants

<table>
<thead>
<tr>
<th>Test</th>
<th>Persistent (SD)</th>
<th>Recovered (SD)</th>
<th>Control (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peabody Picture Vocabulary Test (PPVT)</td>
<td>104.13 (15.69)</td>
<td>123.00 (19.01)</td>
<td>109.86 (18.41)</td>
</tr>
<tr>
<td>Test of Language Development-3 (TOLD-I:3)</td>
<td>8.57 (1.90)</td>
<td>9.50 (2.07)</td>
<td>10.29 (4.35)</td>
</tr>
</tbody>
</table>
CC topography

Fibers
(1) Thin, largely unmyelinated fibers, densely packed:
   - Highest density in the genu and splenium
(2) Large, highly myelinated fibers, less densely packed:
   - Highest density in the posterior midbody of the CC

(Wahl & Ziemann, 2008)

Tracked representations of the lip (red), hand (green) and foot (yellow) passing through the CC (from Wahl et al., 2007).
Reconciling reduced integrity of CC (Cykowski et al., 2010) and increased CC size and WM volume in AWS

- Anisotropy influenced by a number of factors including packing of fibers, fiber orientation and fiber crossings (Chepuri et al., 2001; Leow et al., 2009).

- Higher FA are typically associated with tighter fiber packing and fewer obliquely oriented axons (Wahl et al., 2007).

- Regions with complex multi-directional fiber crossings tend to have lower FA values.

- Higher number of obliquely oriented fibers in the body of the CC and less densely packed fibers in the posterior midbody may result in lower FA values that may not be due to decreased WM volume or CC size (Chepuri et al., 2001; Moody et al., 1988; Wahl et al., 2007).