Research article

White matter tractography of the neural network for speech-motor control in children who stutter

Ehsan Misaghia,b, Zhaoran Zhangc, Vincent L. Gracco d,e, Luc F. De Niif, Deryk S. Bealg,h⁎

a Neuroscience and Mental Health Institute, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, AB, Canada
b Institute for Stuttering Treatment and Research, Department of Communication Sciences and Disorders, Faculty of Rehabilitation Medicine, University of Alberta, Edmonton, AB, Canada
c College of Life Sciences, Sichuan University, Chengdu, Sichuan, China
d School of Communication Sciences and Disorders, McGill University, Montreal, QC, Canada
e Haskins Laboratories, New Haven, CN, USA
f Institute for Stuttering Treatment and Research, Department of Communication Sciences and Disorders, Faculty of Rehabilitation Medicine, University of Alberta, Edmonton, AB, Canada
g Bloordview Research Institute, Holland Bloordview Kids Rehabilitation Hospital, Toronto, ON, Canada

ABSTRACT

Stuttering is a neurodevelopmental speech disorder with a phenotype characterized by speech sound repetitions, prolongations and silent blocks during speech production. Developmental stuttering affects 1% of the population and 5% of children. Neuroanatomical abnormalities in the major white matter tracts, including the arcuate fasciculus, corpus callosum, corticospinal, and frontal aslant tracts (FAT), are associated with the disorder in adults who stutter but are less well studied in children who stutter (CWS). We used deterministic tractography to assess the structural connectivity of the neural network for speech production in CWS and controls. CWS had higher fractional anisotropy and axial diffusivity in the right FAT than controls. Our findings support the involvement of the cortico-striatal network early in persistent developmental stuttering.

1. Introduction

Stuttering is a neurodevelopmental disorder characterized by sound repetitions, prolongations and silent blocks that impair speech production. The disorder affects 1% of the general population and 5% of children [1]. Stuttering first presents in children aged 18–60 months and progresses along one of two developmental courses: 75% of children experience complete recovery within 2 years of onset, while the disorder persists into adulthood in the opposing 25% of children [2]. Genetic and neural mechanisms have been implicated in the disorder but remain poorly understood [3].

Structural connectivity deficits have been identified throughout the neural network for speech and language function in both children who stutter (CWS) and adults who stutter (AWS). White matter volume of the frontal radiation of the corpus callosum has been found to be lower in CWS than controls in at least one study [4], but findings in the literature are inconsistent with a second study failing to find such a difference [5]. Fractional anisotropy (FA) of the arcuate fasciculus, corpus callosum and corticospinal tract has also been found to be lower in CWS than controls [6,7]. A recent longitudinal study replicated these FA findings and further showed that CWS have reduced FA growth rates in the left arcuate fasciculus and corpus callosum relative to controls that were not apparent in children who had recovered from stuttering [8]. Relatedly, people who stutter also have reduced grey matter volume growth rates in the left posterior inferior frontal gyrus (pIFG) relative to controls [9]. The reduced grey matter volume growth rates of the left pIFG documented in people who stutter may be the result of structural connectivity deficits in the corpus callosum and arcuate fasciculus that ultimately limit the region’s ability to communicate the critical articulatory coding information to the remainder of the speech neural network in the timely and sequential nature necessary for fluent speech production.

AWS have been shown to have increased white matter volume in the left middle temporal gyrus, right pIFG and right insula [10]. AWS also have lower FA in the white matter underlying the left pIFG, ventral premotor cortex and middle primary motor cortex [11–13], along with a lower cortico-cortical structural connection strength in the left hemisphere relative to controls [12]. As the previously identified...
deficits are clustered around the left pIFG and its white matter tract connections to the ventral premotor and motor cortices, supplementary motor area (SMA) and posterior superior temporal gyrus in people who stutter, we were interested in studying the major tracts that network these nodes. Namely, the major white matter tracts connecting the left pIFG to the neural network for speech production are the arcuate fasciculus, corticospinal tract, corpus callosum and the lesser studied frontal aslant tract (FAT).

The FAT is an obliquely oriented, white matter pathway that connects the pIFG, ventral premotor and motor cortices and SMA and is known to be strongly left lateralized in typical right-handed individuals [14,15]. There is mounting evidence that the structural integrity of the FAT is critical for speech and language function. Structural abnormalities in the FAT are associated with nonfluent primary progressive aphasia (PPA) and are correlated with measures of mean length of utterance and words per minute in patients with PPA [16]. The FAT was recently implicated in persistent developmental stuttering. A study found higher mean diffusivity (MD) in the FAT bilaterally in AWS than controls [17]. To date, the FAT has not been a targeted neuroanatomic structure of interest in structural connectivity studies of CWS, likely due to the lack of sensitivity to this tract by the white matter analysis methods previously employed with the population. Deterministic tractography analysis of diffusion tensor data is a method known to accurately identify FAT.

To address the gap in knowledge regarding the structural integrity of the FAT in CWS and its potential importance for fluent speech production early in stuttering onset, we used deterministic tractography to virtually dissect the FAT and assess its diffusion metrics, as well as the other major white matter tracts that connect the pIFG to the speech neural network, in CWS and matched controls.

2. Materials and methods

2.1. Participants

A total of twenty-two children (11 CWS, 11 controls) ranging from 6 to 12 years of age participated in the study. All of the children were male, right handed as determined by the Edinburgh handedness inventory [18], spoke English as their first language and had a reported negative history for neurological impairments. The CWS ranged in severity from very mild to severe on the Stuttering Severity Instrument – Third Edition (SSI-3) [19]. Inter-rater reliability for the SSI-3 scores was high (ICC = 0.964). All of the children had normal hearing, articulation and receptive vocabulary abilities as screened with a pure-tone hearing test, the Goldman-Fristoe Test of Articulation – Second Edition [20] and the Peabody Picture Vocabulary Test (PPVT) – Third Edition [21]. The two groups did not differ in age and articulation nor receptive vocabulary ability (p > 0.05). Table 1 below lists the age, and PPVT and SSI scores of the participants. All participants were able to complete the research protocol. The parents gave informed written consent and the children gave informed assent. The research study was approved by the Toronto Hospital for Sick Children’s Research Ethics Board.

Table 1
Summary statistics for participants’ age, PPVT-3 and SSI-3 scores.

<table>
<thead>
<tr>
<th>Group</th>
<th>Parameter</th>
<th>Age (months)</th>
<th>PPVT Score</th>
<th>SSI Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>Mean</td>
<td>119.18</td>
<td>121.45</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>22.46</td>
<td>11.94</td>
<td>N/A</td>
</tr>
<tr>
<td>CWS</td>
<td>Mean</td>
<td>114.18</td>
<td>118.73</td>
<td>22.09</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>18.07</td>
<td>17.26</td>
<td>8.39</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>92–148</td>
<td>88–139</td>
<td>7–34</td>
</tr>
</tbody>
</table>

SD: Standard Deviation.

2.2. Data acquisition

The data were collected as part of a larger research protocol that included other experiments for which results are reported elsewhere [4,22]. Pertinent to the current study, neuroanatomical images were acquired from all participants using a 1.5-T Signa Excite III HD 12.0 MRI system (GE Medical Systems, Milwaukee, WI) and an eight-channel head coil. We collected diffusion-weighted data via two runs of a single-shot echo planar imaging (EPI) sequence, each with the same 15 noncollinear directions (TE = 82.3 ms, TR = 17s, matrix size: 128 × 128, FOV: 25 cm, b = 1000 s/mm²) and 2 b = 0 images. We also collected T1-weighted images using a 3D fast spoiled gradient echo (FSPGR) sequence (flip angle = 15°, TE = 4.2 ms, TR = 9 ms) with 100 1.5-mm-thick axial slices (matrix size: 256 × 192, FOV: 24 cm).

2.3. Tractography and virtual dissection

All of the images were visually inspected, and images corrupted by acquisition errors (e.g., ghosting, missing slices) or extraneous movement [23], were excluded from further analysis. For each participant, we merged the two runs of diffusion images to create datasets with 4 b = 0 and 30 b = 1000 images. Eddy current and motion distortion correction was done using ExploreDTI [24]. To ensure accurate tract dissection, we differed the angle, length and FA values for tractography according to the characteristics of the specific tract under analysis. Tract specific parameters used for tractography are shown in Table 2 [17,25].

2.3.1. Frontal aslant tract (FAT)

The FAT was identified using the method proposed by Catani and colleagues [14]. One of the two regions of interest (ROIs) was placed in the sagittal view encompassing the pIFG and the other one was placed in the superior frontal gyrus encompassing the SMA and pre-SMA (Fig. 1).

2.3.2. Corpus callosum

As shown in Fig. 2, we divided the corpus callosum into three parts based on the proposed scheme of [26]. The genu of the corpus callosum was defined as the anterior ¼ of the corpus callosum length in the midline, the splenium as the posterior ¼ and the body as the middle portion between the genu and splenium. To delineate the genu of the corpus callosum, an inclusive region of interest (i.e., AND ROI) was placed in the midline encompassing the anterior ¼ of the corpus callosum width and two origin regions of interest (SEED ROIs) were placed two slices (4 mm) parasagittal to the midline encompassing the same area. In order to prune extraneous fibers, we placed two parasagittal exclusive regions of interest (i.e., NOT ROIs) just lateral to the corticospinal tract. Another NOT ROI was placed in the middle of the corpus callosum width in the coronal view to remove potential backward projections of the fibers that may not be related to the genu. For the splenium, we used the posterior ¼ of the callosum width for the AND ROI in the midline and placed two SEED ROIs two slices parasagittal to the midline. Two NOT ROIs were drawn in the sagittal plane, just lateral to the optic radiations and a NOT ROI was placed in the cerebellum at the level of the pons to prune extraneous fibers that potentially go to the cerebellum. The area in between the AND ROIs placed for the genu

Table 2
Tractography parameters used for different tracts.

<table>
<thead>
<tr>
<th>Tract</th>
<th>FA Threshold</th>
<th>Angle Limitation</th>
<th>Fiber Length (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal Aslant Tract</td>
<td>0.15</td>
<td>30°</td>
<td>20–500</td>
</tr>
<tr>
<td>Corpus Callosum</td>
<td>0.2</td>
<td>30°</td>
<td>50–500</td>
</tr>
<tr>
<td>Arcuate Fasciculus</td>
<td>0.2</td>
<td>70°</td>
<td>10–500</td>
</tr>
<tr>
<td>Corticospinal Tract</td>
<td>0.2</td>
<td>30°</td>
<td>50–500</td>
</tr>
</tbody>
</table>
and splenium was considered the body and we placed an AND ROI there. Two SEED ROIs were placed two slices parasagittal just as the ones placed for the splenium and genu and two NOT ROIs were placed parasagittal to the corticospinal tract just as the ones placed for the genu. Another NOT ROI was drawn encompassing the whole brain directly under the AND ROI of the midline for the body to remove potential extraneous fibers going in the inferior direction.

2.3.3. Arcuate fasciculus

The arcuate fasciculus was defined in the sagittal plane using the method described by Forkel and colleagues [27]. As shown in Fig. 3, two ROIs were used to delineate the anterior segment of the arcuate fasciculus. We placed one of the two ROIs over the inferior frontal gyrus (ROI 1) and the other one over the supramarginal and angular gyri (ROI 2). The long segment was defined by two ROIs that included the same anterior ROI as the one used to virtually dissect the anterior segment (ROI 1) and a new ROI on Wernicke’s area at the level of the posterior superior and middle temporal gyri (ROI 3). The posterior segment was defined using ROI 2 (the posterior ROI of the anterior segment) and ROI 3 (Wernicke’s area ROI used in the long segment). The right arcuate fasciculus ROIs were drawn using the same method as its left counterpart.

2.3.4. Corticospinal tract (CST)

The CST was virtually dissected using two AND ROIs, one in the level of the pons encompassing one of the two blue circular areas and the other in the level of the cortex encompassing the dorsal pre- and post-central gyri, known to be the cortical origins of this tract [28]. The left blue circle in the pons in combination with the left cortical ROI was used to delineate the left CST (Fig. 4) and the right counterparts of those areas were used for the right CST.

2.3.5. Inter-rater reliability

Two authors (EM and ZZ) completed the virtual dissection process.
for each tract. Raters were blind to the group membership of the participant for the purpose of virtual dissection. Inter-rater reliability ranged from acceptable to excellent (Table 3). The dissections done by the first author (EM) were considered for this study.

2.4. Statistical analysis

We were able to identify all the tracts in all participants, except the left FAT in one control, and the long segment of the right arcuate fasciculus in another control and two CWS participants. All identified tracts were used in the analysis. We used ExploreDTI to calculate the scalar measurements of the diffusion tensor including FA, mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) for all the identified tracts. Briefly, FA and RD are positively associated with fiber density and myelination of the white matter tract and therefore structural integrity whereas MD and AD are negatively associated with these white matter properties. The measurements associated with the virtually dissected tracts were exported from ExploreDTI and imported into the IBM SPSS Statistics 22 (IBM Corp. Released 2013. IBM SPSS Statistics for Macintosh, Version 22.0. Armonk, NY) for statistical analyses. Multiple mixed analyses of variance (ANOVA) were performed on FA, MD, AD, RD, and volume of each tract with the hemisphere (left vs. right) as the within-subjects factor and the group (CWS vs. control) the between-subjects factor. Results were accepted as statistically significant if the p-value was below the Bonferroni corrected threshold of \( p = 0.01 \) (\( p = 0.05/5 \)) to account for the 5 variables tested. Post-hoc t-tests were used to identify the precise differences when the ANOVA was significant. Bivariate correlations between age, PPVT scores, and SSI scores and the diffusion measures were explored using Pearson’s correlation coefficient for the white matter tracts extracted. Due to the exploratory nature of the correlation analyses, results were accepted as statistically significant if the p-value was below 0.05 uncorrected for multiple comparisons.

Table 3

<table>
<thead>
<tr>
<th>Tract</th>
<th>ICC</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAT</td>
<td>0.844</td>
</tr>
<tr>
<td>CST</td>
<td>0.950</td>
</tr>
<tr>
<td>Corpus Callosum</td>
<td></td>
</tr>
<tr>
<td>Genu</td>
<td>0.733</td>
</tr>
<tr>
<td>Body</td>
<td>0.616</td>
</tr>
<tr>
<td>Splenium</td>
<td>0.874</td>
</tr>
<tr>
<td>Arcuate Fasciculus</td>
<td></td>
</tr>
<tr>
<td>Anterior Segment</td>
<td>0.830</td>
</tr>
<tr>
<td>Long Segment</td>
<td>0.998</td>
</tr>
<tr>
<td>Posterior Segment</td>
<td>0.803</td>
</tr>
</tbody>
</table>

All the ICCs were calculated based on the tract volume.

Fig. 3. (A) The sagittal view of the ROIs used to delineate various parts of the arcuate fasciculus on a representative subject’s diffusion image. (B) The arcuate fasciculus fibers shown in a representative subject. The long segment is shown in blue, anterior segment in pink and posterior segment in yellow. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Fig. 4. (A) The ROIs used to extract the corticospinal tract shown on a coronal slice from a representative participant’s diffusion image. (B) The bilateral corticospinal tract in a representative participant.
That studies [29,32]. The individual variability of white matter micro-
control, a theory supported by previous behavioral and neuroimaging
subtle abnormalities within the left hemisphere network for motor
may be related to the beginnings of right hemisphere compensation for
right FAT white matter microstructure most like that of controls’ may
be poised to shift towards pre-pubescent recovery versus those with
more abnormal profiles, but future research will be required to fully
explore such an association. Increased white matter density in the right
inferior frontal gyrus, a region connected by the FAT to the SMA has
been previously reported in AWS [10]. In CWS, the greater the grey
matter density of the right inferior frontal gyrus, the greater their
speech fluency, or the less severe their stuttering [4]. Furthermore, the
left inferior frontal gyrus has been found to develop abnormally over
the lifespan of people who stutter spanning in age from 6 to 49 years old
[9], while the right inferior frontal gyrus develops along a relatively
normal trajectory. Taken together, these findings indicate the im-
portance of the right inferior frontal gyrus and its possible relation to
the corticostriatal network to compensate for speech dysfluencies ob-
erved in AWS.

Abnormalities of the FAT have been previously reported in AWS. Kronfeld-Duenias and colleagues [17] found that AWS had greater MD in the FAT bilaterally relative to controls. MD is the average diffusivity in all directions of a neural filament. As such, greater MD values indicate compromised structural integrity of the white matter tract. Interestingly, the same authors found that the lower the MD values in the left FAT, the more the speech rate of the AWS approached that of the controls. Our results lend further support to the important role that FAT may have in the generation of fluent speech. Although the characterization of speech dysfluency is different in nonfluent primary progressive aphasia, evidence has shown that diffusion metrics in the left FAT are associated with speech fluency measures in this population. Catani and colleagues [16] reported a negative correlation between RD values and speech fluency, as well as a positive correlation between FA and speech fluency (lexical access) in this patient population. As higher RD typically represents decreased structural integrity of the white matter, and higher FA is associated with greater structural integrity, it is reasonable to conclude that speech fluency is dependent to an extent on the structural integrity of the left FAT. We did not observe any group differences in the left FAT between children and AWS may represent an abnormal trajectory of white matter de-
velopment in this tract. Future research should follow CWS longitudi-

Fig. 5. (A) Fractional anisotropy differences of the frontal aslant tract between and within groups. a.u.: arbitrary units (B) Axial diffusivity differences in the frontal aslant tract between and within groups. *, ** and *** denote significance at the p < 0.05, p < 0.01 and p < 0.001 levels, respectively. The blue lines indicate the 95% confidence interval. CON: Control, CWS: Children Who Stutter. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3. Results

We observed significant hemisphere by group interactions for FA (F (1, 19) = 11.179, p = 0.003) and AD (F (1, 19) = 21.352, p < 0.0005) in the FAT. As shown in Fig. 5, the post hoc t-tests revealed that FA (t (20) = −2.93, p = 0.008) and AD (t (20) = −2.6, p = 0.017) of the right FAT were higher in the CWS group relative to that of the control group. Within the CWS group, FA and AD in the right FAT were signi-
ificantly greater than in the left FAT (t (10) = −4.718, p < 0.001 for FA and t (10) = 2.848, p = 0.017 for AD) while within the control group, the left FAT had greater AD values than the right FAT (t (9) = 5.073, p < 0.001); the opposite direction of that observed in the CWS group. We also observed significant hemisphere main effects for RD (F (1, 19) = 15.27, p = 0.001) and tract volume (F (1, 19) = 10.25, p = 0.005) in FAT. We did not observe significant group differences in the corpus callosum, arcuate fasciculus and the corticospinal tract. We also found main effects for hemisphere in the CST and AF. For details see supplementary material Table S1. There were no other significant
findings.

4. Discussion

We used diffusion tensor imaging, deterministic tractography and
virtual dissection to identify and measure the structural integrity of the
FAT, for the first time, in CWS. We aimed also to replicate previous
findings of white matter abnormalities across the other major tracts
underlying the neural network for speech production; namely, the
arcuate fasciculus, CST and the corpus callosum. Only diffusion metrics
of the FAT differed between the CWS and controls.

As shown in Fig. 5, CWS had greater FA and AD in the right FAT
compared to the right FAT in controls thus indicating a high integrity
and myelination of these tracts in CWS. Our metrics indicated that the
structural integrity and myelination of the right FAT was greater in
CWS than controls. The FAT is a major white matter tract connecting the
pre-SMA, SMA, pIFG and ventral premotor and motor cortices. Functionally, these regions are known to be a part of the corticostriatal
network and are implicated in motor sequencing tasks. Our current
results document microstructural abnormalities within this network
that have long been implicated in developmental stuttering [29–31].
That CWS had a more highly developed right FAT relative to controls
may be related to the beginnings of right hemisphere compensation for
subtle abnormalities within the left hemisphere network for motor
control, a theory supported by previous behavioral and neuroimaging
studies [29,32]. The individual variability of white matter micro-
structure observed within the CWS in our study may be indicative of the
differing states of the structural network relative to the progression of
the speech disorder across participants and their varied treatment ex-
periences. One possible interpretation may be that individual CWS with
right FAT white matter microstructure most like that of controls’ may
be poised to shift towards pre-pubescent recovery versus those with

E. Misaghi et al.
Neuroscience Letters 668 (2018) 37–42
sample of school-aged boys with persistent developmental stuttering, across a relatively large age-range for this stage of development, whereas the other studies included a larger sample of children across wider age range and a mixed group of children with recovered and persistent stuttering. Our current results are representative of whole wider age range and a mixed group of children with recovered and across a relatively large age-range for this stage of development, sample of school-aged boys with persistent developmental stuttering, studies. As such, we strived to identify robust di analysis relative to the voxel-based approaches employed in other studies. We speculated that the abnormal hemispheric dominance of FAT development in our group of CWS may be the beginnings of early compensation for deficits within speech neural network, such as the abnormal trajectory of gray matter development in left inferior frontal gyrus [4,9].

Conflicts of interest

The authors declare that they do not have any conflicting interests.

Disclosures

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent/assent was obtained from all individual participants included in the study.

Acknowledgements

Our research was supported by the Canadian Institutes of Health Research (MOP-68969) to LFJ and by the National Institute on Deafness and Other Communication Disorders (R01-DC-007603) to VLG. DSB received funding from the Canadian Institutes of Health Research and Other Communication Disorders (R01-DC-007603) to VLG. DSB, V.L. Gracco, L.F. De Nil, Speech-induction suppression of evoked auditory fields in children who stutter, Neuroimage 54 (2011) 2994–3003.

References


Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version, at https://doi.org/10.1016/j.neulet.2018.01.009.