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Reduced fractional anisotropy in the anterior corpus callosum is associated with reduced speech fluency in persistent developmental stuttering

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ABSTRACT

Developmental stuttering is a speech disorder that severely limits one's ability to communicate. White matter anomalies were reported in stuttering, but their functional significance is unclear. We analyzed the relation between white matter properties and speech fluency in adults who stutter (AWS). We used diffusion tensor imaging with tract-based spatial statistics, and examined group differences as well as correlations with behavioral fluency measures. We detected a region in the anterior corpus callosum with significantly lower fractional anisotropy in AWS relative to controls. Within the AWS group, reduced anisotropy in that region is associated with reduced fluency. A statistically significant interaction was found between group and age in two additional regions: the left Rolandic operculum and the left posterior corpus callosum. Our findings suggest that anterior callosal anomaly in stuttering may represent a maladaptive reduction in interhemispheric inhibition, possibly leading to a disadvantageous recruitment of right frontal cortex in speech production.

1. Introduction

Developmental stuttering is a disorder of speech fluency, primarily characterized by prolongations, blocks and repetitions of sounds and/or syllables. The etiology of stuttering is not fully understood to date. One of the earliest theories on stuttering relates the disorder to atypical cerebral dominance (Moore, 1984; Travis, 1978; Travis & Johnson, 1934; Webster, 1997). Although initial attempts to provide evidence for this theory were mostly unsuccessful (see Kushner, 2012), modern functional brain imaging studies have established that adults-who-stutter (AWS) indeed exhibit different functional lateralization when compared to fluent speakers (Braun et al., 1997; De Nil, Kroll, & Houle, 2001; De Nil, Kroll, Kapur, & Houle, 2000; Kell et al., 2009; Neumann et al., 2005; Pool, Devous, Freeman, Watson, & Finitzo, 1991). These studies, as a whole, demonstrate that regions in the right hemisphere, particularly in the frontal cortex, are over-activated in AWS (see Brown, Ingham, Ingham, Laird, & Fox, 2005).

There is an ongoing debate on the functional significance of the right frontal over-activation observed in developmental stuttering. Some authors suggest that the greater recruitment of the right hemisphere is beneficial (Braun et al., 1997; Kell et al., 2009; Neef et al., 2011; Preibisch et al., 2003), whereas others suggest it is not (Brown et al., 2005; Chang, Synnestvedt, Ostuni, & Ludlow, 2010; Fox et al., 2000; Kronfeld-Duenias, Amir, Ezrati-Vinacour, Civier, & Ben-Shachar, 2014; Moore, 1984). There are also suggestions that the right hemisphere recruitment is maladaptive (Andrews, Quinn, & Sorby, 1972; Webster, 1997), that it is an outcome of negative emotions (Forster, 1995; Webster, 1993), or causally related to overt stuttering behavior (Boberg, Yeudall, Schopflocher, & Bo-Lassen, 1983; Fox et al., 1996; Wood, Stump, McKeehan, Sheldon, & Proctor, 1980). In fact, some combination of the above explanations could be true, given that over-activations were detected in several distinct right frontal regions. As the debate is still open after more than two decades of functional imaging studies on stuttering, alternative methodological approaches may be necessary.

The right frontal over-activation observed in AWS could be better understood in the context of the underlying structural

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properties of their brains. Several studies conducted over the last decade have detected structural anomalies in stuttering individuals, frequently in the form of reduced fractional anisotropy (FA) in white matter regions (see Cai et al., 2014; Cykowski, Fox, Ingham, Ingham, & Robin, 2010). The majority of FA reductions are in the left hemisphere, most notably in the left Rolandic Operculum (RO) (Chang, Erickson, Ambrose, Hasegawa-Johnson, & Ludlow, 2008; Connally, Ward, Howell, & Watkins, 2014; Kell et al., 2009; Sommer, Koch, Paulus, Weiller, & Buchel, 2002; Watkins, Smith, Davis, & Howell, 2008). This is commonly attributed to white matter tracts involved in speech motor control (Civier, Bullock, Max, & Guenther, 2013; Cykowski et al., 2010). Previous studies suggest that these left hemisphere anomalies are most likely related to the origin of the disorder (Chang et al., 2008; Kell et al., 2009), and that the right frontal cortex is recruited to cope with the deficiency (Chang, Horwitz, Ostuni, Reynolds, & Ludlow, 2011; Chang et al., 2008, 2010; Kell et al., 2009; Neef et al., 2011; Preibisch et al., 2003; Sowman, Crain, Harrison, & Johnson, 2014; Tourville & Guenther, 2011; Tourville, Reilly, & Guenther, 2008). Following such an interhemispheric reorganization, the right hemisphere may carry tasks usually carried out by the left hemisphere (e.g., Karbe et al., 1998).

We propose that interhemispheric reorganization in developmental stuttering may involve changes in the main highway connecting the hemispheres, namely, the corpus callosum. Indeed, several callosal anomalies were reported in stuttering individuals, with most studies pointing to the forceps minor (Beal, Gracco, Brettschneider, Kroll, & De Nil, 2013; Choo et al., 2011; Cykowski et al., 2010; Kell et al., 2009). This interhemispheric pathway connects the lateral and medial frontal cortices and crosses the midline via the genu of the corpus callosum (Abe et al., 2004). As the corpus callosum regulates the division of labor between the hemispheres (Geschwind & Galaburda, 1985), callosal differences observed in AWS might reflect subcortical plasticity that shifts control of speech production from the dysfunctional left hemisphere to the intact right hemisphere. But plasticity is not always beneficial: in acquired disorders, such as aphasia, interhemispheric reorganization is often deleterious (Hamilton, Chrysikou, & Coslett, 2011). Similarly, we hypothesize that reorganization-related callosal differences may intensify stuttering, possibly due to recruitment of brain regions not well adapted for speech production.

The goal of this study was to examine the relation between micro-structural properties of callosal connections and the level of speech fluency in adults who stutter. For the purpose of this paper, speech fluency is defined as the ability to speak without stuttering (note that fluency here does not concern articulatory rate, language proficiency, normal interruptions in speech flow, etc.). We first established reliable group difference in FA in the corpus callosum of AWS versus matched controls. We then conducted a focused correlation analysis within the AWS group, and examined the relation between speech fluency and FA in the implicated corpus callosum region. We were interested not only in the identification of a significant correlation, but more importantly, in the direction of the relation. We reasoned that if the least fluent individuals showed the most extreme anomaly in the callosal tracts, this would be considered evidence against beneficial plasticity. Finally, we also examined the contribution of age and its interaction with stuttering, in explaining white matter variability in the callosum and in other white matter regions.

2. Methods

2.1. Participants

We recruited fourteen adults who stutter (M:F = 11:3; mean age 32.14, standard deviation (SD) 10.17, range 19–52) and fourteen fluent controls (M:F = 11:3; mean age of 31.36, SD 8.95, range 19–47). The participants were right handed according to the Edinburgh inventory (Oldfield, 1971), and all were native Hebrew speakers, with no prior history of neurological or psychiatric disorders. All participants in the AWS group had a history of stuttering since childhood. In addition, two independent speech-language pathologist (SLP) experts confirmed the diagnoses of stuttering based on audiovisual recordings of each individual's experimental session (for details, see Section 2.2). The two SLP experts also assessed stuttering severity using the Stuttering Severity Instrument (SSI-3, Riley, 1994). An average SSI-3 score of 24.36 (SD: 7.62; range [9.5–41.5]) was measured in the AWS participants, ranging from very mild to very severe stuttering. We were able to collect therapy history from 12 out of 14 AWS. All twelve underwent treatments of various kinds and durations at one or more points in their life. However, no participant was receiving speech therapy at the time of the study, or had received treatment within the two preceding years. Fluent participants were assigned to the control group based on their self-report of having no history of stuttering, and were pair-matched with the AWS on the basis of age and gender (see Table 1). The two groups did not differ significantly on handedness, age or education. The study was approved by the institutional ethics committee of Bar Ilan University and by the Helsinki committee at Tel Aviv Sourasky Medical Center. Written informed consent was obtained from each participant prior to the study.

2.2. Data acquisition: Behavioral

Each participant went through an unstructured interview. The participant was seated in a quiet room together with the experimenter, and was asked to talk for 10 min about a neutral topic, such as a recent travel experience, a movie or a book. The experimenter was instructed to refrain from interrupting the speaker, and to ask questions only when the participant was having difficulties finding a topic to talk about. In addition to the interview, participants performed other behavioral tasks not reported in this study. The sessions were recorded with a digital video camera (Sony DCR-DVD 106E, Sony Corporation of America, New York, NY) and with a high-quality microphone (Sennheiser PC21, Sennheiser Electronic Corporation, Berlin, Germany).

2.3. Data acquisition: MRI

Magnetic Resonance Imaging (MRI) data were collected using a 3T scanner (Signa Excite, General Electric Medical Systems, Milwaukee, WI, USA) located at the Tel Aviv Sourasky Medical Center. Scanning was conducted with an eight-channel head coil for parallel imaging. Head motion was minimized by padding the head with cushions, and participants were asked to lie still during the scan.

A standard diffusion tensor imaging (DTI) protocol was applied by means of a single-shot spin-echo diffusion-weighted echo-planar imaging sequence (FOV = 240 mm; 128×128 matrix; 68 ± 5 2-mm thick axial slices covering the entire cerebrum; voxel size: $\sim 2 \times 2 \times 2$ mm). 19 diffusion-weighted volumes ($b = 1000$ s/mm^2) and one reference volume ($b = 0$ s/mm^2) were acquired using a standard direction matrix (Sasson, Doniger, Pasternak, Tarrasch, & Assaf, 2012). This protocol was repeated twice without averaging, such that tensors were fit to the entire dataset from both scans (see Section 2.5). Scanning 19 directions twice was motivated by the fact that all our participants (study and control groups) are inexperienced and are likely to move as the scan gets longer. Short scan time (350 s per scan) reduces the chances of within-scan motion which is hard to correct, while maintaining robust anisotropy measurements (Jones, 2004). An added benefit of the

Table 1
Individual participant details for age, sex, handedness and education.

#	Age (years)		Sex		Handedness score[a]		Education (years)	
	CON	AWS	CON	AWS	CON	AWS	CON	AWS
1	19	19	F	F	100	100	12	12
2	23	23	M	M	100	100	12	12
3	24	24	M	M	40	80	15	15
4	25	24	M	M	60	100	12	12
5	26	26	M	M	100	100	15	15
6	27	26	M	M	80	100	18	12
7	28	27	F	F	100	100	13	15
8	31	31	F	F	100	100	20	18
9	29	32	M	M	100	80	19	18
10	31	33	M	M	80	100	12	15
11	41	42	M	M	80	100	18	14
12	43	44	M	M	100	80	12	18
13	45	47	M	M	100	100	18	n.a
14	47	52	M	M	100	100	17	n.a
Mean (SD)	31.36 (8.95)	32.14 (10.17)	11M/3F	11M/3F	88.57 (18.75)	95.71 (8.52)	15.21 (3.04)	14.67 (2.39)

CON = controls; AWS = adults who stutter; n.a = not available.
[a] According to the Edinburgh inventory (Oldfield, 1971). Scores range between −100 for complete left handedness, and 100 for complete right handedness.

repeated acquisition is improved signal-to-noise ratio (SNR), which reduces measurement noise (see Yeatman et al., 2011).

High resolution T1 anatomical images were acquired using a 3D fast spoiled gradient-recalled echo sequence (FSPGR; 149 ± 12 1-mm thick axial slices, covering the entire cerebrum; voxel size: $1 \times 1 \times 1$ mm).

2.4. Behavioral data analysis

To allow quantitative assessment of speech fluency, the audio recording of each interview was transcribed until obtaining at least 600 consecutive syllables produced by the participant (the exact number slightly varied between participants because we avoided cutting the last transcribed sentence in the middle, and instead included all of it). Transcriptions were extracted from audio recordings, based on reports that visual information does not improve the reliability of measuring stuttering frequency (Macdonald Coyle & Mallard, 1979; Williams, Wark, & Minifie, 1963), and in order to simplify methodology. Disfluencies were annotated on the transcription separately by each of two trained research assistants (RAs), and then both transcriptions and disfluency annotations were re-evaluated by an experienced SLP. Disagreements between the SLP and the RAs, or between the RAs themselves, were discussed until a consensus was reached. For each participant, we calculated the number of syllables where stuttering-like disfluencies (SLDs, see Ambrose & Yairi, 1999) occurred. In essence, SLDs include part-word repetitions, monosyllabic-word repetitions and disrhythmic phonations. All other disfluency types, which are typically not regarded as stuttering per se (i.e., interjections, revisions or phrase repetitions), were not included. Based on the above measurements, we then calculated the percentage of stuttered syllables (%st.sy) for each participant (Yairi & Ambrose, 2005). We chose to analyze the percentage of stuttered syllables on speech production collected in a single task (spontaneous speech in an unstructured interview), rather than collapsing across several tasks (as in the SSI-3). This choice was guided by the assumption that averaging across different speech tasks might discard important variability in the amount of stuttering that accompanies different tasks. We decided to run this analysis specifically on data collected from an unstructured interview, and not on data collected during overt reading, because the former is a more natural speech scenario.

Individual fluency scores were defined as 1/[%st.sy]. This transformation was applied to normalize the distribution of the behavioral measure. The transformation also facilitated the presentation of the main result in terms of a positive correlation between speech fluency and FA, which is more intuitive compared to the alternative presentation – a negative correlation between stuttering frequency and FA.

2.5. Imaging data preprocessing

We visually inspected the raw T1 and diffusion-weighted images for corrupt volumes and visible artifacts. The diffusion-weighted images were then corrected automatically for eddy current distortions and head motion, using code from SPM5 (Friston & Ashburner, 2004; Rohde, Barnett, Basser, Marenco, & Pierpaoli, 2004). We verified successful motion correction by picking a subset of slices randomly for each participant and visually comparing between the original and motion-corrected slices. The two reference images ($b = 0$) were registered to the AC-PC aligned T1 image using a rigid body mutual-information maximization algorithm, and averaged into a single image. Each of the 38 diffusion-weighted volumes ($b = 1000$) was then registered to the mean b0 reference image. We combined the eddy current correction, motion correction, and anatomical alignment transformations into one omnibus transformation, and applied it to the raw diffusion images. The transformed images were resampled to $2 \times 2 \times 2$ mm voxels. By applying the transformation only once, we minimize unnecessary smoothing caused by interpolation. Following this procedure, the table of gradient directions was appropriately adjusted to fit the resampled diffusion data (Leemans & Jones, 2009).

Tensors were fit to each voxel of the raw diffusion-weighted data using a least-squares algorithm (Chang, Jones, & Pierpaoli, 2005). We extracted the three eigenvalues of the tensor in order to calculate FA, which is the normalized standard deviation of the eigenvalues (Basser & Pierpaoli, 1996). FA indicates the degree to which the iso-diffusion ellipsoid is anisotropic, and in regions of white matter, it relates to micro-structural properties of the fiber tracts (Jones, Knosche, & Turner, 2013). For each voxel, we also calculated AD (axial diffusivity), which is equal to the first eigenvalue of the diffusion tensor, and RD (radial diffusivity), the average of the second and third eigenvalues. Data preprocessing was performed using the open-source 'mrDiffusion' package (http://white.stanford.edu/newlm/index.php/Software).

2.6. DTI data analysis with Tract-Based Spatial Statistics

Statistical analysis was performed using Tract-Based Spatial Statistics (TBSS, Smith et al., 2006, 2007), which is implemented

in the FSL software package (http://www.fmrib.ox.ac.uk/fsl/). Individual FA volumes were registered to the FMRIB58 template, a high-resolution ($1 \times 1 \times 1$ mm voxel size) standard-space FA image supplied by FSL, and a mean-FA image was generated by averaging the aligned FA volumes of all participants (AWS and controls). The TBSS algorithm then searched for the local maxima voxels of the mean-FA image to create a mean-FA skeleton – a voxel-thick skeleton of the centers of major tracts. Voxels with mean FA < 0.3 were removed from the skeleton, to ensure that the skeleton includes only white matter voxels (virtually identical results were found using a lower threshold that only excluded voxels with FA < 0.2; see Supplementary Text 1 for the subtle differences found between the thresholds). For each participant, TBSS generated a subject-specific FA skeleton image by projecting nearby maximum FA values (in the participant's individual FA volume) onto the common mean-FA skeleton. Lastly, the same nonlinear warps and projections used to register the FA volumes to the template and to project FA to the mean-FA skeleton, were applied to the AD and RD images, generating subject-specific AD and RD skeleton images.

2.6.1. FA group differences

We first performed a voxel-wise analysis to detect FA reductions in developmental stuttering: the individual FA skeleton images of the AWS and controls were compared with a *t*-test, at each voxel of the skeleton. The resulting statistical parametric maps were thresholded at $t(26) > 3.435$ ($p < 0.001$, one-tailed, uncorrected). We limited the analysis of group difference to FA reductions based on previous findings of lower FA in stuttering individuals versus fluent speakers (see Cai et al., 2014; Cykowski et al., 2010). To correct for multiple comparisons, we used a cluster-based thresholding method (Nichols & Holmes, 2002). Clusters were formed with the same threshold used for the voxel-wise thresholding ($t > 3.435$), and assigned *p*-values corrected for multiple comparisons using permutation-based non-parametric tests with 5000 random permutations (a standard method used in previous TBSS studies, e.g., Govindan, Makki, Wilson, Behen, & Chugani, 2010; Kell et al., 2009). The permutation testing was performed with the "Randomise" algorithm provided by FSL (Nichols & Holmes, 2002). Results were considered significant at $p < 0.05$ (one-tailed, corrected). For each cluster where AWS had lower FA values than controls, we calculated the mean AD and RD for the cluster, for each participant. We also performed *t*-tests on both AD and RD to evaluate the source of significant FA differences.

2.6.2. Correlation between fluency measures and FA values

For each cluster where AWS had significantly lower FA values than controls, we calculated the mean FA of the cluster, for each participant. Using a Pearson correlation analysis, we then computed a correlation coefficient between cluster FA and fluency score within the group of AWS. To evaluate the robustness of correlations, we used a bootstrap analysis with 10,000 iterations. Next, to evaluate whether it is the variability in AD or RD that drives the correlation between FA and fluency, we tested the significance of the correlations between either AD or RD and the fluency scores.

To detect correlations which are not necessarily accompanied by a significant group effect, we repeated the correlation analysis across the whole-brain, i.e., for each voxel of the skeleton. Clusters reported here are those which survived correction for multiple comparisons using cluster-based thresholding with a cluster-forming threshold of $p < 0.001$ (two-tailed) (Nichols & Holmes, 2002), or those with 5 voxels or more.

2.6.3. Interactions with age

Our sample spans a large age range, which allowed us to examine correlations and interactions with age. We performed a post-hoc analysis of age effects in regions where FA covaried with fluency. First, we examined the interaction between Group (AWS, control) and Age, in predicting regional mean FA. For this and subsequent analyses, age was log-transformed to normalize its distribution. We also examined the categorical interaction between Group and Age-group (below-median age versus above-median age). Next, these effects were examined across the entire FA skeleton. Significant results are reported at $p < 0.05$ (two-tailed), corrected for multiple comparisons (cluster forming threshold $p < 0.001$, two-tailed).

For each cluster with significant interaction, we calculated the mean FA of the significant cluster and compared AWS versus controls within each of the age groups, using simple *t*-tests. Last, to test for age effects within each group separately, we calculated correlation coefficients between log(Age) and FA within each of the two experimental groups. For all significant effects, we repeated the analysis also using AD and RD.

2.6.4. Partialling out age

In a post-hoc analysis, we re-examined FA group differences, with log(Age) included as a covariate in the general linear model used for the whole-brain analyses. The statistical analysis was identical to the main analysis except for the reduced degree of freedom due to the inclusion of the covariate. In another post-hoc analysis, we calculated partial Pearson correlations between fluency score and FA in clusters where AWS had significantly lower FA values than controls, while controlling for log(Age).

3. Results

3.1. Behavioral results

Our samples are well matched for age, gender, handedness and education (see Table 1 for individual demographic information). Importantly, our AWS group had a wide range of stuttering frequencies (%st.sy ranging from 2.79 to 14.01; Mean %st.sy = 7.42, SD = 3.68). This allowed us to examine the correlations between speech fluency and white matter properties.

3.2. Reduced FA in AWS in the anterior corpus callosum

In a voxel-wise group comparison across the entire FA skeleton, we detected a single significant cluster showing lower FA in AWS compared with controls (Fig. 1A; $p < 0.05$, one-tailed, corrected for multiple comparisons). This FA difference is located in the left anterior corpus callosum (forceps minor). Mean FA values in the forceps minor are 0.783 for AWS (SD = 0.025) and 0.844 for controls (SD = 0.031). Further analysis revealed that, compared with controls, AWS have significantly higher RD in the forceps minor ($p < 0.0005$, two-tailed), with only a trend toward lower AD ($p = 0.093$). Table 2 lists all regions showing group differences in FA. To compare with previous findings, we also report clusters larger or equal in size to 5 voxels, that did not survive correction for multiple comparisons ($p < 0.001$, one-tailed, uncorrected). These include other regions of the corpus callosum, bilateral corticospinal tract, bilateral thalamic radiations, and left superior longitudinal fasciculus (SLF). Because age effects were detected in our data (see below), we repeated the above analysis with log(Age) as a covariate. In this post-hoc analysis, AWS still exhibited lower FA in the forceps minor compared with controls ($p < 0.001$, one-tailed, uncorrected; 38 voxels, MNI coordinate [−7,31,6]), but this effect did not survive the correction for multiple comparisons ($p = 0.054$).

3.3. FA in the anterior corpus callosum correlates with fluency scores

To clarify the behavioral implications of reduced FA in the forceps minor, we examined the correlation between FA values and fluency scores in the AWS group. We found a significant positive

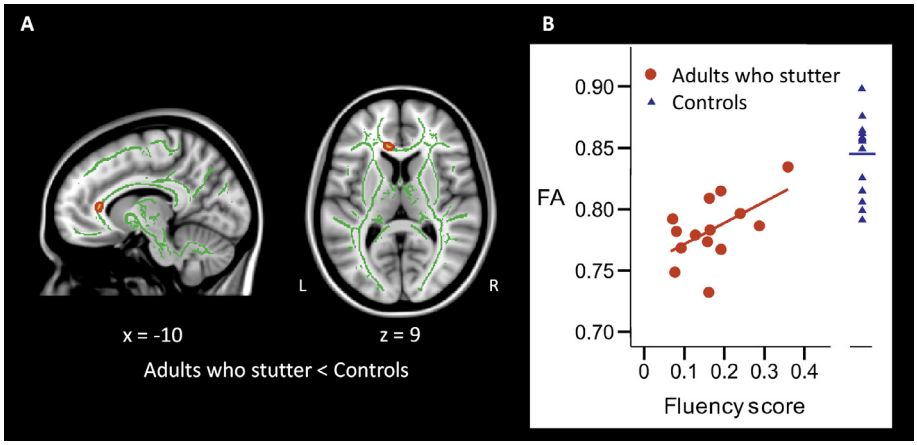

Fig. 1. Fluency in stuttering adults correlates with fractional anisotropy (FA) in the forceps minor. (A) Lower FA in adults who stutter versus fluent speakers. Significant results are shown with a red-to-yellow overlay ($p < 0.05$, one-tailed, corrected for cluster size using permutation testing). Adults who stutter have lower FA in the forceps minor of the corpus callosum (see Table 2 for cluster size and MNI coordinate). For visualization, the thresholded statistical image is dilated using FSL tools, which fill the image out into the local tracts. Results are overlaid on the mean-FA skeleton (green) laid over the MNI T1 template. (B) A scatter plot showing a significant correlation between fluency score and FA in the forceps minor in adults who stutter ($r(12) = 0.548$, $p < 0.05$, two-tailed). For each participant, FA was calculated as the average FA of the region of significant group difference shown in panel A. Fluency score was defined as 1/[%st.sy] (see Section 2.4). For comparison, FA values in the forceps minor in controls are shown as well. The mean FA of the control group is indicated by a short horizontal line.

Table 2
Regions, peak MNI coordinates, cluster sizes, peak *t* scores for difference in FA, and mean FA, AD and RD values, of clusters of voxels in the FA skeleton with reduced FA in adults who stutter compared with controls.

White matter region	*X*	*Y*	*Z*	Voxels[a]	Max *t*	FA CON	FA AWS	AD CON[b]	AD AWS[b]	RD CON[b]	RD AWS[b]
p < 0.05, one-tailed, corrected for cluster size											
Forceps minor	−10	31	9	40	4.6	0.84	0.78	1.78	1.72	0.25	0.33
p < 0.001, one-tailed, uncorrected, voxel extent ⩾ 5											
Body of corpus callosum	1	20	16	34	5.53	0.76	0.69	1.70	1.69	0.35	0.45
Body of corpus callosum	1	26	11	20	4.75	0.80	0.74	1.73	1.70	0.30	0.38
Forceps major/Right optic radiation	27	−72	17	18	5.28	0.73	0.64	1.60	1.45	0.37	0.44
Anterior limb of left internal capsule	−14	10	4	15	4.33	0.71	0.62	1.46	1.46	0.38	0.48
Left anterior thalamic radiation	−26	38	17	10	5.88	0.46	0.36	1.19	1.12	0.57	0.66
Left corticospinal tract	−6	−24	−31	10	4.57	0.64	0.57	1.14	1.11	0.37	0.43
Right anterior thalamic radiation	27	38	14	8	4.52	0.51	0.43	1.11	1.07	0.47	0.54
Left corticospinal tract/SLF	−29	−20	31	8	4.23	0.44	0.34	1.15	1.09	0.58	0.66
Right corticospinal tract	12	−25	66	7	4.45	0.56	0.47	1.12	1.13	0.43	0.52
Forceps minor	10	31	−1	7	4.27	0.87	0.82	1.88	1.78	0.21	0.28
Forceps minor	13	27	15	5	4.32	0.79	0.72	1.70	1.65	0.32	0.39
Left anterior thalamic radiation/Left IFOF	−35	31	11	5	4.07	0.49	0.44	1.14	1.09	0.54	0.59

CON = controls; AWS = adults who stutter; SLF = superior longitudinal fasciculus; IFOF = inferior fronto-occipital fasciculus.
[a] Voxel size: 1 x 1 x 1 mm.
[b] μ^2/ms.

correlation between fluency scores (1/[%st.sy]) and FA values in the forceps minor (Fig. 1B; $r(12) = 0.548$, $p < 0.05$, two-tailed). The 95% confidence interval for the correlation coefficient (based on a bootstrap analysis) was [0.018,0.849], indicating that this correlation is different from 0 at $p < 0.05$, two-tailed. Neither AD nor RD in the forceps minor were significantly correlated with fluency score, though RD could explain 18.4% of the variability in fluency scores, while AD could only explain 1% of variability. Lastly, a post-hoc analysis repeated the correlation between fluency score and FA, this time partialling out log(Age). The result was a stronger correlation ($r(11) = 0.608$, $p < 0.05$, two-tailed) compared to the original analysis.

3.4. Fluency and age effects in the left Rolandic operculum

In a whole-brain correlation analysis, we found that the largest cluster where FA correlated with fluency scores in AWS was in the left anterior RO (positive correlation; Fig. 2A; $p < 0.001$, two-tailed, uncorrected; 9 voxels, MNI coordinate [−49,1,20]). Although the effect did not survive correction for multiple comparisons, it was the only cluster that exceeded our cluster-size threshold of 5 voxels. Unlike previous reports, however, there was no group difference between AWS and controls in that region. One possible explanation for the discrepancy with previous findings is the large age range of our participants, which may have masked group differences. We ran several post-hoc analyses to investigate this possibility, using FA in the left anterior RO as the predicted variable. We detected a significant interaction between Group (AWS, control) and Age-group (below and above the median age of 28.5) ($F(1,24) = 12.71$, $p < 0.005$, two-tailed). As shown in Fig. 2B and C, AWS in the below-median age group have significantly lower FA compared with controls ($t(12) = -2.630$, $p < 0.05$, two-tailed), whereas in the above-median age group, the opposite effect is found ($t(12) = 2.471$, $p < 0.05$, two-tailed). When examining AD and RD in left anterior RO, only AD differed between the groups: in the below-median age group there was a trend toward lower AD in AWS ($p = 0.054$), and in the above-median age group AWS had higher AD than controls ($t(12) = 2.804$, $p < 0.05$, two-tailed). Additional analyses showed a significant negative correlation in the control group between log(Age) and FA of the left anterior

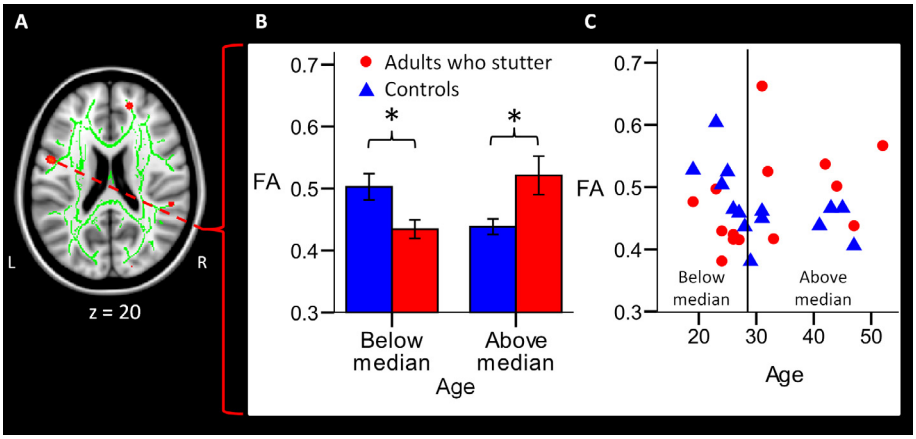

Fig. 2. Inverse group differences in FA of the left Rolandic Operculum (RO) depending on age. (A) Whole brain analysis of the correlation between fluency score and FA in adults who stutter. Results for $p < 0.001$, two-tailed, uncorrected, are shown with a red-to-yellow overlay (clusters are dilated for the sake of visualization, as in Fig. 1). The only cluster that exceeded our cluster-size threshold is a region of positive correlation in the left RO (9 voxels, MNI coordinate [−49,1,20]). (B) Significant interaction between Group and Age-group in the left RO ($F(1,24) = 12.71$, $p < 0.005$, two-tailed). For each participant, FA was calculated as the average FA in the RO region of significant correlation shown in panel A. Error bars represent ± 1 SEM. (C) Shown is a scatter plot of FA against age in both groups. FA is calculated as in panel B. The median age of the entire cohort (28.5) is marked by a vertical line. *$p < 0.05$, two-tailed.

RO ($r(12) = -0.573$, $p < 0.05$, two-tailed, uncorrected), but only AD showed a trend toward decrease with age ($p = 0.06$). No such correlation between log(Age) and FA was found in the AWS group ($p > 0.1$). This could also explain why we did not find a significant interaction between Group and log(Age) in that region ($p > 0.1$).

To establish that the interaction between Group and Age-group generalizes beyond the specific method used here for identifying the left anterior RO, we conducted a separate analysis in which we defined that region independently, using a coordinate from a previous study (Watkins et al., 2008), and covering a larger portion of white matter. That study reported a group difference in the anterior RO in a sample of participants who were all between the ages 14–27, which encompass our young age range. Thus our findings are in agreement in the young age range, and we can now test the effect of age looking at the FA pattern in the older age range in our sample, within the same region. The analysis based on the Watkins et al. coordinate again detected a significant interaction between Group and Age-group in FA values extracted from the left anterior RO ($F(1,24) = 9.45$, $p < 0.01$, two-tailed; see Supplementary Text 2 and Supplementary Fig. 1). This finding generalizes the Group-by-Age interaction we detected in the anterior RO (Fig. 2) beyond the specific contrast used for defining the region and its exact size.

3.5. Group by age interaction in the posterior corpus callosum

Following the significant age-related effects detected in the left anterior RO, we examined the interaction between Group (AWS, control) and log(Age) across the whole brain. A single region in the left posterior corpus callosum showed significant interaction between Group and log(Age) (Fig. 3A; $p < 0.005$, two-tailed; 62 voxels, MNI coordinate [−25,−55,18]). In AWS, log(Age) and FA were positively correlated in this region (Fig. 3B; $r(12) = 0.542$, $p < 0.05$, two-tailed), but correlations were not detected with neither AD nor RD ($p > 0.1$). In controls, a negative correlation was observed between log(Age) and FA (Fig. 3C; $r(12) = -0.870$, $p < 0.0001$, two-tailed), similarly to previous findings (e.g., Lebel, Caverhill-Godkewitsch, & Beaulieu, 2010). The correlation stemmed from changes in both AD and RD, as each of them was significantly correlated with log(Age) ($r(12) = -0.697$ and $r(12) = 0.844$, respectively, $p < 0.05$, two-tailed). In the younger (below-median) age group, reduced FA was found in AWS compared to controls ($t(12) = -4.735$, $p < 0.001$, two-tailed), and this difference was due to both decreased AD and elevated RD in AWS ($t(12) = -4.09$ and $t(12) = 3.86$, respectively, $p < 0.05$, two-tailed). In the older (above-median) age group the difference in FA was not significant ($p > 0.1$).

3.6. Effects in a male-only cohort

Previous brain imaging studies detected important differences between males and females who stutter (Chang & Zhu, 2013; Connally et al., 2014; Ingham et al., 2004). We therefore repeated the analyses in a male-only subsample of our cohort ($N = 11$ AWS and 11 controls). In a whole-brain group analysis, we detected a significant cluster showing lower FA in male AWS compared with male controls (see Supplementary Fig. 2; $p < 0.05$, one-tailed, corrected; 36 voxels, MNI coordinate [−29,−20,31]). This FA difference is located in a white matter region that may belong to either left corticospinal tract or left SLF (57% and 9%, respectively, according to the Juelich Histological Atlas). The forceps minor cluster, detected in the main mix-sex analysis, was reduced to 33 voxels in the male-only group comparison, and thus failed to pass correction for multiple-comparisons. In the whole-brain correlation analysis within the male AWS, we detected several clusters that passed our uncorrected statistical criteria ($p < 0.001$, two-tailed, uncorrected, 5 voxels or more). The largest was a cluster of negative correlation between fluency score and FA at the left intra-parietal sulcus (see Supplementary Fig. 3; 10 voxels, [−20,−65,36]). However, no correlation passed a corrected significance threshold in the male-only sample.

4. Discussion

Our results demonstrate that in adults who stutter, reduced FA in the forceps minor (anterior corpus callosum) is associated with reduced speech fluency. Moreover, this relationship exists in a region where AWS have significantly lower FA compared with controls. Taken together, these results show that AWS have atypical brain structure, and suggest that the extent of anomaly is related to an individual's level of stuttering. We conclude that reduced FA in the forceps minor does not arise from beneficial neuroplastic changes. If that was the case, then AWS with more deviant FA values should have been more fluent. Our data show, however, that they are actually less fluent. These results corroborate a previous

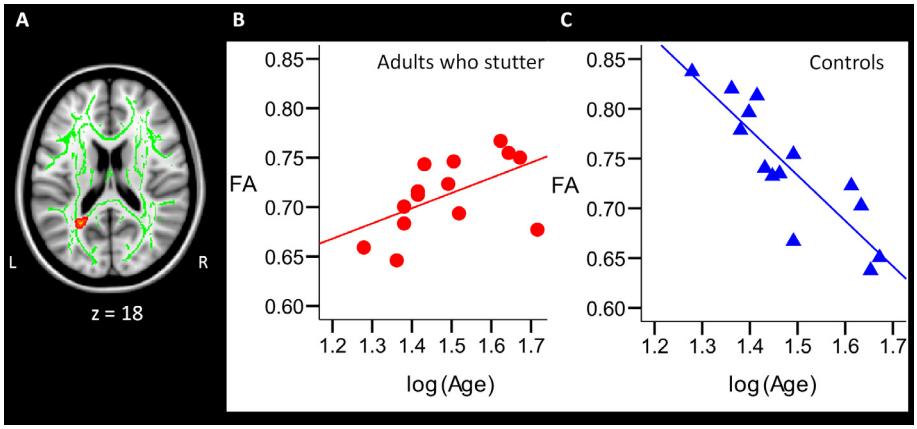

Fig. 3. Stuttering adults and controls show inverse correlations between FA and age in posterior corpus callosum. (A) Significant results are shown with a red-to-yellow overlay ($p < 0.05$, two-tailed, corrected for cluster size by permutation testing). There is an interaction between Group and log(Age) in the left posterior corpus callosum ($p < 0.005$, two-tailed; 62 voxels, MNI coordinate [−25, −55, 18]; dilated for the sake of visualization, as in Fig. 1). (B) Scatter plot shows a significant positive correlation between log(Age) and FA in the left posterior corpus callosum in adults who stutter ($r(12) = 0.542$, $p < 0.05$, two-tailed). For each participant, FA was calculated as the average FA of the region of significant interaction shown in panel A. (C) Log(Age) and FA in the left posterior corpus callosum are negatively correlated in fluent speakers ($r(12) = -0.870$, $p < 0.0001$, two-tailed). FA was calculated as before.

study, where a significant group difference in FA was detected in a similar but more diffuse region (Cykowski et al., 2010). The current study localizes the effect to the forceps minor, but more importantly, provides new information regarding the behavioral correlates of the anomaly. If the FA reductions in the forceps minor are not attributed to beneficial plasticity, they might result from maladaptive or epiphenomenal plasticity (cf. Hamilton et al., 2011); either as a reaction to the continuous experience of stuttering, or as a response to a core deficit somewhere else in the brain. Alternatively, it is possible that the forceps minor anomaly is closely related to the origin of the disorder, as we discuss briefly toward the end of the discussion.

4.1. The relation between structural callosal and functional differences

Atypical interhemispheric signaling in developmental stuttering has been previously suggested (Choo et al., 2011; Forster & Webster, 2001; Greiner, Fitzgerald, & Cooke, 1986; Webster, 1986, 1988, 1990, 1997; Yeudall, 1985; Zelaznik, Smith, Franz, & Ho, 1997). But what is the functional significance of the specific anomaly detected in this study? The forceps minor is known to connect several regions in the lateral and medial frontal cortices (Abe et al., 2004; Chao et al., 2009; Pannek et al., 2010). We suggest that the forceps minor fibers affected in stuttering connect the left inferior frontal gyrus (IFG) with its right homologue. Similarly to the forceps minor, structural properties in the left IFG correlate with fluency measures (Kell et al., 2009). As callosal fibers may be inhibitory (Bloom & Hynd, 2005; Ni et al., 2009; van der Knaap & van der Ham, 2011), reduced FA in fibers interconnecting the IFGs could indicate release from inhibition of the right IFG, therefore causing over-activation (cf. Putnam, Wig, Grafton, Kelley, & Gazzaniga, 2008). Such interhemispheric reorganization in stuttering can account for the multiple reports that AWS have elevated neural activity in the right frontal cortex, including the right IFG (Braun et al., 1997; Brown et al., 2005; De Nil et al., 2000, 2001; Kell et al., 2009; Neumann et al., 2005; Pool et al., 1991). It might also account for findings that stuttering individuals have abnormal gyrification patterns in the right hemisphere (Cykowski et al., 2008; Foundas, Bollich, Corey, Hurley, & Heilman, 2001), as well as abnormal cerebral asymmetry (Foundas et al., 2003; Mock et al., 2012; Strub, Black, & Naeser, 1987).

4.2. Is the recruitment of right frontal regions beneficial?

Assuming that FA reductions in anterior callosum reflect interhemispheric reorganization (not core deficit), the results of our correlation analysis suggest that this form of plastic changes is not beneficial to AWS. Specifically, the correlation analysis suggests that AWS would not benefit from a resulting recruitment of the right frontal cortex (for a similar argument in Aphasia, see Hamilton et al., 2011). There are mixed results regarding the functional contribution of right frontal over-activation in developmental stuttering. Some studies found positive correlations between right frontal over-activation and stuttering frequency (Fox et al., 2000; Ingham, Grafton, Bothe, & Ingham, 2012), while others found negative correlations (Braun et al., 1997; Kell et al., 2009; Preibisch et al., 2003). It should be noted that some of the latter results are complicated by potential confounding effects of speech rate (see Ingham et al., 2012). Moreover, in the studies that used functional MRI (fMRI), stuttering frequency was measured off-line (outside the scanner), separately from neural activations (a common practice in fMRI studies, where scanning noise induces fluency in most participants, due to the auditory masking effect, see Kell et al., 2009). Lastly, it is also possible that whether the over-activation is beneficial or not is location-specific. Previous studies of stuttering detected significant correlations in distinct right frontal regions (M1, ventral premotor, IFG, operculum, insula, orbitofrontal cortex). Based on our results, we predict that over-activation in right frontal regions innervated by the forceps minor will be positively related to on-line stuttering frequency when speech rate is properly controlled.

A powerful approach for studying the causal relations between fluency and right frontal over-activation is measuring changes in brain activation associated with short-term or long-term fluency enhancement. Two previous studies indicated that the choral speech fluency-enhancer reduces hyperactivity in the right premotor cortex (Fox et al., 1996, 2000). Similarly, right frontal hyperactivity diminished after AWS were treated with haloperidol (Wood et al., 1980), a drug known to alleviate stuttering symptoms (Brady, 1991), but that effect failed to be replicated when using other fluency-enhancing methods (Braun et al., 1997; De Nil et al., 2008; Toyomura, Fujii, & Kuriki, 2011). Lastly, several longitudinal studies showed that right hemispheric hyperactivity was attenuated following intensive therapy programs (Boberg et al., 1983; De

Nil, Kroll, Lafaille, & Houle, 2003; Neumann et al., 2003, 2005). Therefore, we suggest that results of some of the functional studies can be interpreted as providing support for the view that right frontal recruitment is non-beneficial. Further replications are required to verify that this effect is not specific to a given sample or experimental design.

If the right frontal cortex indeed substitutes for a dysfunctional speech motor control system in the left hemisphere (see Section 1), why is fluency not improved with greater right frontal cortex engagement? Based on the DIVA model of speech production (Golfinopoulos, Tourville, & Guenther, 2010), we propose that the pars triangularis of the right IFG, which receives forceps minor projections, may have a role in an alternative speech production network consisting of right frontal and bilateral temporal regions (Tourville et al., 2008). Rather than using memorized motor programs, which AWS might not be able to select/initiate properly (Civier et al., 2013), this brain network relies on the relatively slow auditory and somatosensory feedback channels to generate motor programs on-the-fly (Golfinopoulos et al., 2011; Tourville et al., 2008). As this mode of speech control has severe limitations on processing speed, that network is likely to fail when producing rapid speech segments (Civier, Tasko, & Guenther, 2010; Max, Guenther, Gracco, Ghosh, & Wallace, 2004). Thus, although this alternative feedback-based speech production network is initially recruited to alleviate stuttering (Tourville & Guenther, 2011; Tourville et al., 2008), it turns out to be inadequate, and ends up worsening symptoms (Civier et al., 2010). According to this proposal, greater activation of the right IFG pars triangularis may indicate a more extensive utilization of the network and thus is associated with deterioration rather than improvement in fluency. That said, recruitment of right hemispheric motor regions (e.g., right PMd) could benefit other, non-speech, motor functions of AWS (Neef et al., 2011). We tentatively suggest that the deciding factor for right hemisphere utility is the rate and nature of the task performed.

4.3. Age- and group-dependent FA differences

Previous studies found reduced FA in stuttering individuals in the left anterior RO (for review, see Cai et al., 2014), but this was not the case in our data. We hypothesized that in our cohort, group differences are masked by age effects. Indeed, we found an interaction between Group and Age-group in the left anterior RO, with the younger AWS (below-median age) having reduced FA compared with controls. These results suggest that age is an important factor in analysis of FA differences in AWS. Reduced FA in AWS in the anterior RO could be specific to young cohorts. For example, reduced FA in AWS in this region was reported in a previous study that recruited only young participants, ages 14–27 (Watkins et al., 2008), and in a more recent study, where 80% of the participants were 28 years old or younger (Connally et al., 2014). Such FA reductions in young AWS may be due to aberrant development or under-utilization of pathways passing through the left anterior RO, such as the arcuate fasciculus connecting frontal and temporal regions (see Connally et al., 2014). These pathways could be involved in some aspects of phonological processing (e.g., phonological awareness), which are presumably atypical in children who stutter (e.g., Weber-Fox, Spruill, Spencer, & Smith, 2008), and, to a lesser degree, in adults who stutter (Weber-Fox, Spencer, Spruill, & Smith, 2004). Indeed, previous studies demonstrated a relation between FA in the arcuate fasciculus and phonological awareness (Vandermosten et al., 2012; Yeatman et al., 2011).

Our findings further suggest that the FA group difference in the left anterior RO flips its sign in older AWS (Fig. 2). Unfortunately, a comparison with previous studies is not possible because none has analyzed FA specifically in older AWS. The discrepancy between the RO effects in younger and older participants could be explained by the age-related reduction in FA which occurs in the left anterior RO in the control group (also see Burzynska et al., 2010; Inano, Takao, Hayashi, Abe, & Ohtomo, 2011), but not in the AWS group. People who stutter may experience late maturation of the previously mentioned phonology-related pathways via the left anterior RO. Indeed, it has been shown that some phonological deficits recorded in children who stutter partially resolve as they mature (Weber-Fox et al., 2004, 2008). Accordingly, FA within these pathways may increase slowly during childhood and adolescence (which accounts for the reduced FA in young AWS), but will 'catch-up' or even surpass controls later on in life (accounting for the inverse effect in older AWS). Given the large individual variability in stuttering phenomenology and in age effects on white matter structure, further interpretation of the age modulations we report should wait for replication in larger cohorts.

When we looked across the brain for similar Group-by-Age interactions, we found it in only one additional location. In the left posterior callosal tracts FA declined with age in fluent speakers, whereas in AWS it increased with age. It is well documented that FA in this region declines with age in fluent speakers (Burzynska et al., 2010; Inano et al., 2011; Lebel et al., 2010). However, the opposite trend, which we detected in AWS, is reported here for the first time. Importantly, several fibers interdigitate in the posterior callosal region that showed the inverse age effect in AWS. These include the tapetum and the forceps major (Abe et al., 2004; Jarbo, Verstynen, & Schneider, 2012; Oishi, Faria, van Zijl, & Mori, 2011), which interconnect the temporal lobes and the occipital lobes, respectively (Chao et al., 2009; Dougherty, Ben-Shachar, Bammer, Brewer, & Wandell, 2005; Dougherty et al., 2007; Hofer & Frahm, 2006; Park et al., 2008). Posterior parietal callosal tracts pass through that region as well, but those do not show the age-related reduction in FA observed in our control group (Lebel et al., 2010). Given their similarity to the age effects in the left anterior RO, the age-related changes in the left posterior corpus callosum are easier to reconcile with atypical development of the connections between the temporal lobes. Temporal callosal tracts have been previously related to phonological processing (Dougherty et al., 2007), and thus may follow a developmental path similar to that of the left RO white matter.

4.4. Sex-bias of effects

Our sample was dominated by male participants, in a way that reflects the over-representation of males in AWS broadly (Yairi & Ambrose, 2013). It is possible that some of the effects we detected stem from the male participants only, or that subtle male-specific effects were disguised by the inclusion of female AWS. When we limit the analysis to males only, AWS show significant FA reduction in a white matter region that may belong to either left corticospinal tract or left SLF (this effect only appeared in the uncorrected results of the original mix-sex analysis; see Table 2). A similar group difference was reported about 10 mm laterally in a study of male-only AWS (Kell et al., 2009). Interestingly, both the left corticospinal tract and the left SLF showed up in previous male-only stuttering studies (Chang et al., 2008; Cykowski et al., 2010; Kell et al., 2009) (but see also Connally et al., 2014, for a mixed-sex sample that detected a similar difference). Hopefully, future DTI studies with much larger Ns would be powered to examine potential sex-differences in the neural correlates of stuttering, beyond the immense individual variability characteristic of sex related differences (e.g., Ingalhalikar et al., 2014) .

4.5. Atypical anterior callosal properties in AWS

Two previous studies have reported reduced FA in the anterior callosum of AWS, similar to our findings (Cai et al., 2014; Cykowski

et al., 2010). However, two other studies report on group differences that go in the opposite direction. A study by Kell et al. (2009) found increased FA in the forceps minor of adults who stutter. This finding might represent a different segment of the forceps minor that connects different cortical regions, as the cluster of voxels with increased FA reported by Kell et al. is located about 20 mm ventrally ($z = -10$) compared with the cluster of decreased FA reported here ($z = 9$). Another study, by Choo et al. (2011), showed that the anterior callosum of AWS has increased midsagittal area and white matter volume, which at first sight seem contradictory to our finding as well. However, some structural white matter anomalies, such as those involving increased number of obliquely oriented axons, may result in reduced FA values which are not necessarily coupled with decreased white matter volume, and might even be associated with increased one (see discussion in Choo, Chang, Zengin-Bolatkale, Ambrose, & Loucks, 2012).

Regardless of the direction of the group effect, the above studies failed to find a correlation in the AWS group between structural measures of the anterior callosum and behavioral measures of stuttering (Cai et al., 2014; Choo et al., 2011; Cykowski et al., 2010; Kell et al., 2009). This mismatch could be explained by differences in several factors, including the specific sample of participants, the specific part of the corpus callosum investigated, the type of the structural measurement, and the procedure for behavioral assessment. In particular, our behavioral measure was stuttering frequency in an unstructured interview (see Section 2.2), whereas previous studies used self-assessed stuttering severity (Choo et al., 2011), or measures where stuttering frequency is averaged across several speech tasks (Cai et al., 2014; Cykowski et al., 2010; Kell et al., 2009). Stuttering frequencies in different speech tasks are not well correlated (e.g., Wymbs, Ingham, Ingham, Paolini, & Grafton, 2013), and thus, averaging might discard important variability and make the results harder to interpret (also see Section 2.4).

4.6. Interpretation of FA differences

FA is affected by many structural properties of white matter, including directional coherence, myelination, and axonal density and diameter (Jones et al., 2013). In the medial regions of the corpus callosum, directional coherence is an unlikely factor in explaining FA differences, since the fibers are mostly oriented along the left-right axis. In this region, therefore, FA is mostly affected by other factors: the intracellular milieu of axons (axoplasm), which mainly contributes to the AD measure (Beaulieu, 2002), and the diameter and density of axons, as well as the permeability of cell membranes and myelin sheaths, which mainly contribute to RD (Sen & Basser, 2005). The pattern we detected, in which group differences in the forceps minor stem mostly from RD, goes against an anomaly in the intracellular "gel" in AWS, but still allows for an anomaly in one or more of the micro-structural properties that affect RD. One possibility is that myelin sheaths in the forceps minor are more permeable to diffusing water in AWS (see Cykowski et al., 2010), with the level of permeability affecting fluency level (hence, the ability of RD to explain large percentage of the variability in fluency scores). The greater permeability leads to higher RD values (Song et al., 2005), and accordingly, to lower FA values in AWS compared with controls. Unfortunately, in less coherent tissue as can be found in the anterior RO and the lateral posterior corpus callosum, it is much more difficult to interpret diffusivity measures in terms of the properties of underlying tissue (Wheeler-Kingshott & Cercignani, 2009). Such interpretations could benefit from future studies utilizing quantitative MR methods that allow more direct measurement of tissue properties (e.g., Assaf, Blumenfeld-Katzir, Yovel, & Basser, 2008; Mezer et al., 2013).

4.7. Study limitations

The principal limitation of this study lies in the small sample size combined with the heterogeneous group of participants. However, even with this limited statistical power, we were able to detect effects in both the anterior and posterior corpus callosum, which remained significant after correction over the whole-brain. While we took great care to match AWS with controls on age and gender, we did not limit our samples in terms of age range, and ended up with a wide range of ages (19–52 years). This unintended large range revealed unexpected novel interactions with age, as reported above. Admittedly, a sample size of 14 participants per group is rather small for testing age effects, beyond the existing individual differences in fluency and other measures. This could be improved in future studies on larger cohorts and using longitudinal designs (cf. Yeatman, Dougherty, Ben-Shachar, & Wandell, 2012). Another limitation is in the scope of the study, due to the fact that our fluency score does not capture all aspects of stuttering. Future correlation studies should also consider, for example, emotional reactions, avoidance behaviors, and speech motor control anomalies associated with the disorder (Bloodstein & Ratner, 2008).

While DTI cannot differentiate between opposite directions of signal transmission or between excitatory and inhibitory connections, we hypothesized here that the impaired callosal fibers are left-to-right inhibitory projections. However, callosal fibers likely project in both directions, and many are excitatory rather than inhibitory (Bloom & Hynd, 2005). If the anterior callosal fibers with reduced FA are excitatory, our results can still fit with right frontal over-activation in stuttering, if one considers the negative correlation recently reported between FA and BOLD (Blood-oxygen-level dependent) responses (e.g., Burzynska et al., 2013). According to this hypothesis, reduced FA may indicate deterioration in the quality of structural connections, and such deterioration may not allow for efficient use of gray matter resources in target brain regions. Inefficient use of gray matter, in turn, would require more energy resources, reflected in stronger BOLD response, as AWS indeed exhibit in the right frontal cortex. In this scenario, stuttering would not result from over-reliance on sensory-based control (as suggested in Section 4.2), but rather, from less efficient utilization of such a control scheme (see Cai et al., 2012). A more direct interpretation of our results would be attainable once the direction and type of the callosal fibers affected in stuttering is better characterized. One promising direction involves brain stimulation methods that elicit/suppress responses, and can selectively excite either left-to-right or right-to-left fibers (e.g., Sommer et al., 2009).

The results of the current study are consistent with the theory that left hemisphere impairment is closely related to the origin of the disorder, and that neuroplastic changes in the corpus callosum are later outcomes. However, since the cohort in this study only consisted of adults, our results cannot exclude the possibility that the order of events in childhood is reversed, i.e., anomalies in the corpus callosum lead to plasticity in left hemisphere structures. This latter scenario is consistent with several reports of acquired stuttering due to callosal damage, while there are hardly any reports of acquired stuttering due to damage in the vicinity of the left RO (Ludlow & Loucks, 2003). Unfortunately, studies involving younger participants do not clarify the order of events either, as school-age children who stutter are reported to have anomalies in both the corpus callosum and the left RO (Beal et al., 2013; Chang et al., 2008; but see also Choo et al., 2012). Hopefully, longitudinal white matter studies involving preschool-age children who stutter would clarify which of the two anomalies precedes the other. Furthermore, at present we cannot rule out the possibility that none of the anomalies is a core deficit, and both are outcomes of some other deficiency, such as elevated dopamine levels (Civier et al., 2013).

5. Conclusions

The primary conclusion of this study is that forceps minor anomalies in developmental stuttering do not represent beneficial neuroplastic changes. Following our assumption that the recruitment of right frontal regions in stuttering is driven by structural changes in the corpus callosum, we also made a derived suggestion: that the right frontal recruitment may be non-beneficial as well. This is consistent with recent modeling studies illustrating that right frontal recruitment in developmental stuttering may be a deleterious response to a structural impairment in the left hemisphere (Civier et al., 2010, 2013).

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bandl.2015.01.012.

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