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Brain anatomy differences in childhood stuttering

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Stuttering is a developmental speech disorder that occurs in 5% of children with spontaneous remission in approximately 70% of cases. Previous imaging studies in adults with persistent stuttering found left white matter deficiencies and reversed right–left asymmetries compared to fluent controls. We hypothesized that similar differences might be present indicating brain development differences in children at risk of stuttering. Optimized voxel-based morphometry compared gray matter volume (GMV) and diffusion tensor imaging measured fractional anisotropy (FA) in white matter tracts in 3 groups: children with persistent stuttering, children recovered from stuttering, and fluent peers. Both the persistent stuttering and recovered groups had reduced GMV from normal in speech-relevant regions: the left inferior frontal gyrus and bilateral temporal regions. Reduced FA was found in the left white matter tracts underlying the motor regions for face and larynx in the persistent stuttering group. Contrary to previous findings in adults who stutter, no increases were found in the right hemisphere speech regions in stuttering or recovered children and no differences in right–left asymmetries. Instead, a risk for childhood stuttering was associated with deficiencies in left gray matter volume while reduced white matter integrity in the left hemisphere speech system was associated with persistent stuttering. Anatomical increases in right hemisphere structures previously found in adults who stutter may have resulted from a lifetime of stuttering. These findings point to the importance of considering the role of neuroplasticity during development when studying persistent forms of developmental disorders in adults.

Keywords: Stuttering; Gray matter; White matter fiber tracts; Diffusion tensor imaging; Voxel-based morphometry; Speech disorders; Fractional anisotropy

Introduction

Developmental stuttering is a speech disorder that typically begins prior to age 6, occurring in approximately 5% of all preschool-age children (Bloodstein, 1995). Although 70–80% recover spontaneously without formal treatment (Yairi and Ambrose, 1999), approximately 1% of adults continue to have persistent stuttering beyond school age (Bloodstein, 1995). When stuttering persists into adulthood, persons face a lifetime of coping with a chronic speech disorder with only short-term treatment benefits, often followed by relapse (Finn, 2003).

Several brain function differences have been found during speech in stuttering adults: (1) reduced or abnormal activity in the auditory association areas (Braun et al., 1997; Fox et al., 2000; Salmelin et al., 1998); (2) increased activity in the right frontal and left cerebellar regions relating to stuttering (Braun et al., 1997; De Nil et al., 2001; Fox et al., 2000); (3) abnormal timing relationships between premotor and primary motor regions in the left hemisphere (Salmelin et al., 2000); and (4) increased activity in the left putamen, ventral thalamus and inferior anterior cingulate related to stuttering (Braun et al., 1997). Whether increases in activity in the right hemisphere speech regions represent compensatory brain activation for stuttering or brain function differences underlying stuttering has been debated (Braun et al., 1997; Fox et al., 2000; Ludlow, 2000). Some have found right-sided increases both during speech production and other tasks, suggesting that greater right

Abbreviations: PWS, people who stutter; VBM, voxel-based morphometry; GMV, gray matter volume; DTI, diffusion tensor imaging; FA, fractional anisotropy; ROI, region of interest; PT, planum temporale; STG, superior temporal gyrus; SMG, supramarginal gyrus; RO, rolandic operculum; BA, Brodmann's area.

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hemisphere activation may be inherent in adults who stutter (Preibisch et al., 2003).

Anatomical differences in stuttering adults include anomalous gyri in the perisylvian frontotemporal regions and bilateral increases and atypical right–left asymmetry in the planum temporale (Foundas et al., 2001, 2004). Increased white matter volumes were found in the right hemisphere, including the superior temporal gyrus, using voxel-based morphometry (VBM) (Jancke et al., 2004), while reduced white matter integrity on fractional anisotropy was found in the left inferior arcuate fasciculus linking the temporal and frontal areas in adults who stutter (FA) (Sommer et al., 2002).

Previous brain imaging studies have only examined adults who stutter. Because asymmetries in brain structure in adults could have resulted from functional differences during development as has been shown for handedness (Buchel et al., 2004), language laterality (Nucifora et al., 2005), reversed laterality (Dorsaint-Pierre et al., 2006), bilingualism (Mechelli et al., 2004), and instrument practice (Gaser and Schlaug, 2003a), some of the brain structure differences in adults may have occurred as a result of stuttering. This study examined brain structure differences between children who developed stuttering during preschool-age and their age matched peers. We hypothesized that differences would be present in the left hemisphere brain regions involved in speech production in children who stuttered during the preschool years. Further, we expected that the differences would be less pronounced in children who had spontaneously recovered from stuttering in comparison with those who continued to stutter.

Materials and methods

Subjects

Right-handed boys between 9 and 12 years were recruited for study. Inclusion criteria required that no other speech or language deficits were present on standardized speech and language testing including: the Peabody Picture Vocabulary test (PPVT) (Dunn, 1959), the Expressive Vocabulary test (EVT) (Williams, 1999), and three subtests of the Test of Oral Language Development (TOLD-I:3) (Newcomer and Hammill, 1992). Three groups of children were included: those who had recovered from preschool-age stuttering, those who had persistent stuttering, and fluent controls.

Recovered children had stuttered between 2 and 3 years of age and participated in a longitudinal study of early preschool childhood stuttering at the University of Illinois (Yairi and Ambrose, 1999). Within 6 months post-onset of stuttering, they were examined by speech language pathologists and diagnosed as having had mild to moderate developmental stuttering on a measure of stuttering severity in childhood.[1] They were followed every 6 months until the time of recovery, usually 2–3 years post-onset (Ambrose and Yairi, 1999). Children with persistent stuttering between 9 and 12 years who were without co-occurring developmental speech, language, behavioral, cognitive or neurological disorders were recruited as well as children who served as a control group and were matched with the other groups on age and language skills. All subjects had normal hearing and were right-handed on the Edinburgh Handedness Battery (Oldfield, 1971) (Table 1). Separate consent forms were signed by each parent(s) and child and the University of Illinois Campus IRB approved the study.

Three groups met the criteria for study: eight with persistent stuttering, seven who had documented recovery from stuttering, and seven controls. More than 40 children with persistent stuttering were screened but did not meet the rigorous subject selection criteria due to co-occurring developmental speech, language, behavioral, cognitive, or neurological disorders (i.e., attention deficit and hyperactivity disorder, learning disability, dyslexia, etc.). Others were excluded from all three groups due to uneasiness in the MRI setting and/or excessive head movement. The three groups did not differ on any of the measures of speech and language or other characteristics ($p > 0.05$) except speech fluency (Table 1).

MRI

High-resolution T1-weighted MPRAGE scans (sequence parameters: TR/TE = 21 s/4.38 ms, FOV 256 mm, matrix 256 × 160 × 128 mm^3, slice thickness 1.3 mm, flip angle 8°, bandwidth 130 Hz/pixel) and a high-resolution DTI scan (TR/TE = 42 s/92 ms, slice thickness 5 mm, FOV 224 mm, acquisition matrix 256 × 256 × 20 mm^3, 6 non-collinear directions with b value = 1000 s/mm^2 and low b value = 0 s/mm^2, bandwidth 1860 Hz/pixel) were acquired on a 3T Siemens Allegra scanner.

The children lay still in the bore of the magnet while viewing a movie of their choice through MRI compatible goggles. Head motion was minimized with tightly padded cushions placed in the head coil and around the shoulders. The children wore earplugs to mask scanner noise and headphones to hear the sounds of the movie. The procedure required less than 30 minutes to complete. Of the 22 children tested, one MPRAGE scan from one child with persistent stuttering was excluded due to movement artefacts while his DTI scan was acceptable and retained for FA analysis. Hence, 21 subjects' data were entered for VBM/gray matter analyses and 22 for DTI analyses.

Table 1
Means and standard deviations (in parentheses) for stuttering severity, age, language tests, and handedness

	Persistent stuttering ($n=8$)	Fluent controls ($n=7$)	Recovered from stuttering ($n=7$)
Stuttering severity	2.38 (0.78)	0 (0)	0.1 (0.25)
Age in months	132 (20.2)	128 (13.2)	130 (19)
PPVT-III	104 (15.7)	110 (18.4)	113 (16.6)
EVT	99 (16)	101 (17.5)	104 (11.6)
TOLD-SC (sentence combining)	8.71 (2.93)	9.14 (2.67)	9.86 (1.95)
TOLD-PV (picture vocabulary)	10.9 (2.67)	12 (3.37)	12.6 (2.37)
TOLD-WO (word ordering)	8.57 (1.17)	10.3 (4.35)	9 (2.31)
Handedness index	92.5 (8.36)	91.0 (12.8)	94.2 (12)

[1] Stuttering severity was determined by taking the average of ratings from three 8-point scales: frequency of stuttering-related disfluencies (part-word repetitions, single syllable word repetitions, and blocks or prolongations); duration of stuttering moments; and tension. An additional point was added for associated secondary behaviors. Ratings between 1 and 7 indicated severity from very mild to very severe stuttering (Yairi and Ambrose, 1999).

Voxel-based morphometry (VBM)

Whole-brain group comparisons of regional gray matter volume (GMV) used an optimized VBM technique (Good et al., 2001), with additional steps compared to standard VBM. For spatial normalization and segmentation, we used a customized study-specific template. This was created by registering all subjects' raw skull stripped images, via a 12-parameter affine transformation, to a previously published pediatric template based on 67 children in the 9–12 age range (Wilke et al., 2003) in Montreal Neurological Institute (MNI) space (ICBM152). The resulting images were averaged and smoothed with a 12-mm full width half maximum (FWHM) kernel to produce the study-specific template for subsequent image registrations. Individual skull-stripped images were segmented into gray matter, white matter, and cerebrospinal fluid using FSL's automated segmentation algorithm (Zhang et al., 2001) and normalized into the pediatric template space using parameters derived from the initial registration of raw images to the pediatric template. The segmented tissue volumes were averaged and smoothed creating probability maps in a second segmentation step, and the raw images were again registered to the study-specific template. The transformation matrix from this registration was applied to the partial volumetric maps of the three tissue types derived from the second segmentation, while standardizing the three tissue volumetric maps to the study-specific template. To correct for any change in absolute volume in individual images following spatial normalization, we multiplied the segmented volumetric maps by the Jacobian determinants derived in the registration. This allowed group comparisons in GMV rather than gray matter density (Ashburner and Friston, 2000). The 3D tissue maps were then smoothed with an 8 mm FWHM Gaussian kernel before statistical analysis.

The effect of stuttering status on GMV was examined on a voxel by voxel basis throughout the brain using a general linear model with age as a covariate. Total brain volume and total GMV, based on each individual's segmented tissue maps in native space, were comparable in the three groups, eliminating the need for covariates. All analyses used tools provided by FSL (functional and structural brain image analysis tools, by Image Analysis Group, FMRIB, Oxford, UK; http://www.fmrib.ox.ac.uk/fsl/). Several contrasts were conducted; the combined persistent and recovered stuttering groups were compared with normally fluent controls, and the persistent and recovered groups were each contrasted with the fluent controls and the recovered and persistent groups were compared. In the statistical parametric maps, only regions exceeding an uncorrected voxel-wise threshold of $p<0.001$ were considered significant.

Region of interest (ROI) analyses of gray matter volume

In addition to whole-brain VBM analyses, GMV data were further analyzed in bilateral pre-defined ROIs previously associated with speech production in the literature: frontal Brodmann areas 44 and 45 (BA44, 45), superior temporal gyrus (STG), supramarginal gyrus (SMG), and planum temporale (PT). The frontal ROIs were defined using probabilistic cytoarchitectonic maps available for BA44 and 45 (Amunts et al., 2004) and implemented in AFNI (Cox, 1996) (http://afni.nimh.nih.gov/afni/) based on postmortem cytoarchitectonic studies with stereotaxic information in MNI space (Eickhoff et al., 2005). The maximum probability maps for bilateral BA44 and 45 were registered into the same space as each subjects' standardized gray matter maps. Because no probabilistic cytoarchitectonic maps were available for STG, SMG, and PT, Talairach daemon (Lancaster et al., 2000) was used to define STG and SMG on a standardized brain. The bilateral PTs were drawn manually on a single standardized brain map similar to methods used in previous studies (Dorsaint-Pierre et al., 2006; Rojas et al., 2005). The PT was defined by the horizontal bank of the STG from the first Heschl's sulcus anteriorly to the vertical bank or the end of the horizontal portion of the sylvian fissure. The posterior ascending and descending rami were excluded, consistent with conventional PT measurements (Rojas et al., 2005) (intra-rater reliability was measured, alpha = 0.98). All ROIs were registered into the same space as each individual's GMV. Mean GMV was computed from voxel values within each ROI and extracted from each subject's smoothed GMV map. Pearson correlation coefficients (r) were computed between GMV for each ROI and age, handedness, and language test scores within each group (fluent, persistent, and recovered). Variables with an $r\geq 0.80$ ($p\leq 0.05$) were used as covariates in the analyses of variance (ANOVA).

The three groups (persistent and recovered stuttering groups and the fluent controls) were compared on an ANOVA with repeated factors of ROIs and right and left sides examining group by ROI and group by side interactions. If the main group effects or interactions were statistically significant ($p<0.05$), then post hoc analyses of group effects were conducted for each structure or side. The persistent and the recovered stuttering groups were also compared each with the controls as well as with each other using ANOVAs to examine group effects and ROI and side interactions with group. If the main effects of either group, or group interactions were statistically significant ($p<0.05$), then post hoc analyses of group effects were conducted for each structure.

Right–left asymmetries in GMV between groups

To examine right–left asymmetries, we computed a similar asymmetry quotient (AQ) to that previously used in adults who stutter (Foundas et al., 2003), by subtracting the right GMV from the left and dividing the result by half of the total of the left and right GMV for each region. ANOVAs examined group effects and structure by group interactions between the controls with the combined persistent and recovered stuttering group. Similar analyses were also conducted between the persistent and recovered groups.

Relationships between ROI GMV within groups

The bases for examining relationships between ROI GMV within each group came from the extensive longitudinal studies done by others (Sowell et al., 2004). These authors examined cortical thickness changes in brains of normal children between ages 5 and 11, a similar age range as was studied in our study. Sowell et al. (2004) found two brain regions increased in cortical thickness in this age range while all other regions decreased in thickness during this age range. Regions increasing in thickness included the left inferior frontal (left BA44) and left perisylvian temporal regions (left STG), both thought to be involved in speech processing (Hickok and Poeppel, 2004, 2007). Therefore, we predicted that in normal children if left BA44 and the left STG regions both have different developmental trajectories from other regions then the correlation between these and other cortical

regions not found to increase by Sowell et al. (2004) would be low. On the other hand, if children who are at risk for stuttering show different brain development patterns from normally fluent children then they might have different relationships between these two speech regions and other brain regions over this age range. We hypothesized that developmental trajectories of the left inferior frontal, and the left temporal regions would be attenuated in children who stutter, and might therefore show greater correlations with other cortical region not shown by Sowell et al. (2004) to increase with development in this age range. The supramarginal gyrus (SMG) was included because this region is adjacent to the STG and based on a recent DTI tractography study was found to have dense connections to the classic frontotemporal language areas (Catani et al., 2005) but was not found to increase with development between 5 and 11 years (Sowell et al., 2004).

To test whether stuttering and control groups differed in their relationships between the classic frontotemporal speech/language regions and surrounding areas across the age range (9–12 years), we computed correlation coefficients between GMV in the left BA44 and other cortical regions including the right BA44, right BA45, left BA45, right SMG, left SMG, and the right STG and the left STG. Similarly, we computed the correlation coefficients within groups between the left STG and other frontal and temporoparietal structures. The resulting r values were converted to Fisher's Z scores to conduct comparisons using a normally distributed measure. Four group comparisons were conducted: ANOVAs compared the Z values obtained for the combined stuttering and fluent groups for the BA44 with other structures and for the STG with other structures. Similarly, Z scores were compared between the persistent and recovered groups for the BA44 relationships and for the STG relationships.

Tract-based spatial statistics on fractional anisotropy maps

Fractional anisotropy (FA) measures directionality of water diffusivity and is an index of white matter organization in the brain (Basser and Pierpaoli, 1996), with 1 representing perfectly anisotropic diffusion and 0 representing perfectly isotropic diffusion. Here whole-brain FA maps were computed for each individual using FMRIB's diffusion toolbox (Smith et al., 2004). The diffusion and non-diffusion weighted images from each individual were merged into a 3-dimensional (3D) file, and then merged into a 4-dimensional file, with subject as the 4th dimension. The 4D file was corrected for eddy currents and then fit to a diffusion tensor model at each voxel.

The FA data were analyzed on a whole-brain basis using voxel-wise statistical analysis (with no pre-defined voxels or tracts of interest) using tract-based spatial statistics (TBSS) (Smith et al., 2006). This method addresses alignment issues with VBM-style analyses of FA data by using a non-linear registration of all subjects' FA data onto a common registration target (standardized into MNI152 space), and creating a "skeletonized" mean FA image of tracts common to all subjects. TBSS projects all subjects' FA data onto this mean FA skeleton before applying voxel-wise across-subject statistics to produce a more Gaussian distribution with less across-subject FA variability, resulting in a more robust and sensitive analysis of multiple subject diffusion imaging data (Smith et al., 2006). The FA values were thresholded at 0.2 to exclude gray matter voxels. A general linear model examined the effect of stuttering status on FA values, with age and handedness as covariates. Statistical parametric maps were thresholded at a voxel-wise $p<0.001$ (uncorrected).

ROI analyses of fractional anisotropy

The ROI analysis focused on the arcuate fasciculus underlying the rolandic operculum (RO) on each side and the corticospinal tracts, thought to play a role in speech motor control. All ROIs were created using the avwmaths utility available through FSL. The RO was examined because of a previous DTI finding of less FA in white matter underlying the left RO in stuttering adults (Sommer et al., 2002). The left RO ROI comprised of $5\times5\times5$ voxels drawn on an unsmoothed mean FA skeleton map, surrounding the coordinate −42, −9, 25 in the left RO region. The right RO was drawn in a similar manner at the coordinate 40, −9, 29. These ROIs were visually inspected to ensure correct placement within homotopic regions in the arcuate fasciculus underlying the RO region in each subject, comparable to the previous study in stuttering adults (Sommer et al., 2002). Additional regions adjacent to the RO are also considered critical in the interface between speech production and speech perception (Hickok and Poeppel, 2004, 2007) and may play a role in stuttering. In the frontal region white matter underlying BA44 was of theoretical importance to speech production (Broca's area) (coordinates: −38, 24, 10 (left) and 37, 27, 9 (right)). In the posterior temporoparietal region, white matter underlying the SMG (BA40) (coordinates: −36, −37, 29 (left), 36, −34, 30 (right)) was identifying as being closely connected based on a recent DTI tractography study that found dense connections to the classic frontotemporal language areas (Catani et al., 2005). Both ROIs were $5\times5\times5$ mm^3 drawn on a standardized mean FA map and visually inspected for correct placement for each subject.

The corticospinal tract ROI comprised of $10\times10\times10$ voxels placed on focus coordinates −21, −19, −2 (left) and 25, −23, −1 (right). Mean FA values (based on FA values exceeding 0.2) were extracted from the bilateral ROIs for each subject using the avwstats utility of FSL. The corticospinal tracts were also examined given previous findings of motor control difficulties in adults who stutter (Borden, 1983).

Statistical comparisons of ROIs between groups

Pearson r values were computed between subjects' RO FA values on each side and age, handedness, and language test scores to identify covariates required for the group comparisons ($r>0.80$). The three groups were compared on a group ANOVA also testing for group interactions with ROIs on the right and left sides. If the main effects were statistically significant ($p<0.05$), then post hoc analyses of group effects were conducted for each structure. The persistent and the recovered stuttering groups were also compared using a group ANOVA while testing for ROI and side interactions. If the main effects were statistically significant ($p<0.05$), then post hoc analyses of group effects were conducted for each ROI.

Results

Group whole-brain comparisons on gray matter volume

Statistical parametric maps show the results of contrasts in GMV between the combined stuttering and control groups (Fig. 1A), between the persistent and controls (Fig. 1B) and between the recovered and the controls (Fig. 1C). The combined stuttering

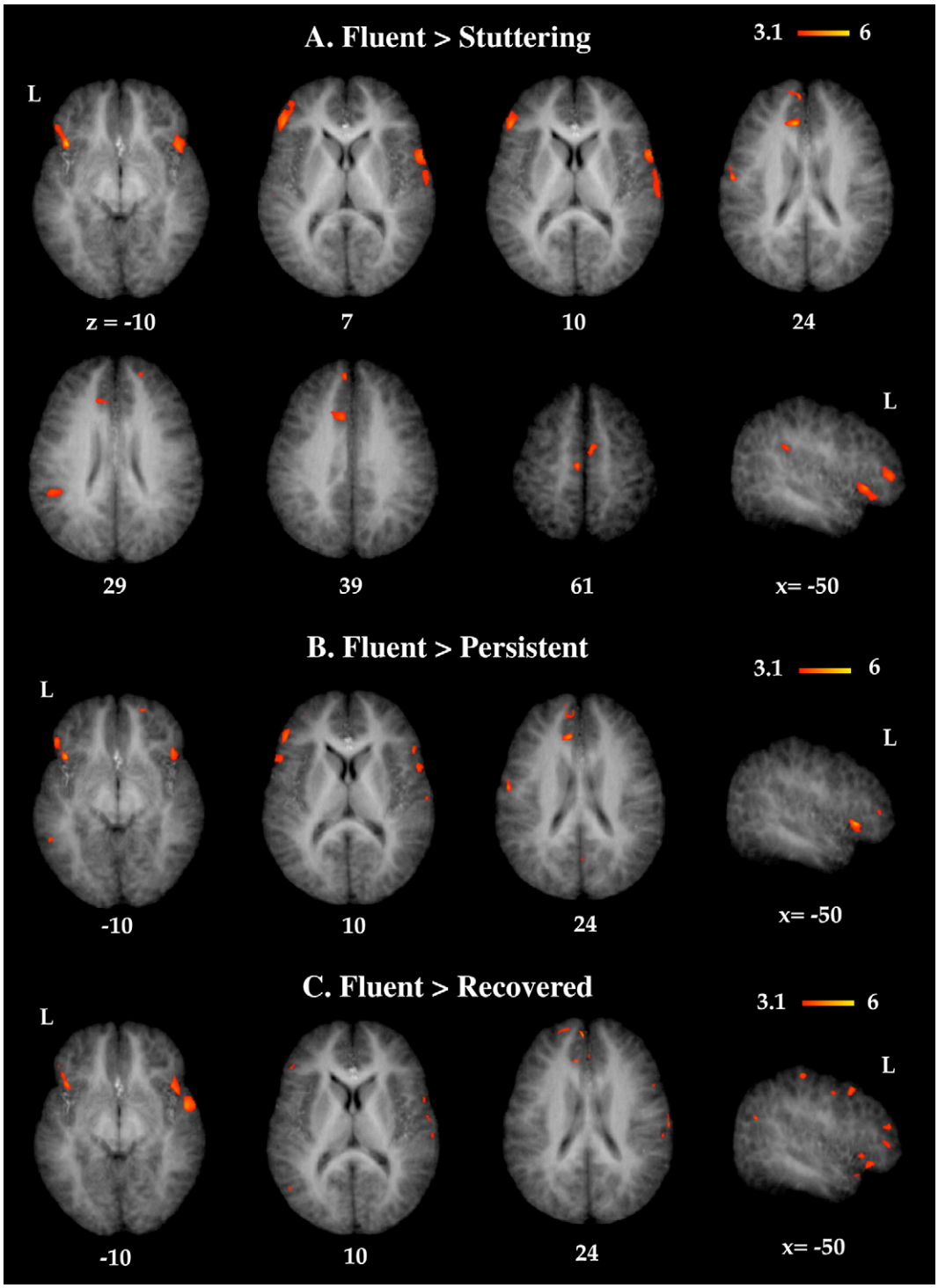


Fig. 1. Statistical parametric maps of the *Z* statistic overlaid on an averaged brain based on all subjects (statistical maps thresholded at $p<0.001$, uncorrected). Images are displayed in neurological convention. (A) Areas where the control group exhibited significantly more GMV compared to the stuttering group. (B) Areas where the persistent group exhibited significantly less GMV compared to control group. (C) Areas where the recovered group exhibited significantly less GMV compared to the control group.

group had significantly less GMV than the controls in the bilateral inferior frontal gyrus (BA44, 45, 47), left anterior cingulate gyrus (BA32), bilateral supplementary motor area (SMA) (BA6), left SMG (BA40), right motor/postcentral gyri (BA4, 43), and right temporal regions (BA21, 37) (Fig. 1A). The coordinates of significant clusters and voxels within clusters that exhibited maximal differences in contrasts between the fluent controls and the combined stuttering group are listed at the top of Table 2. The control group did not have significantly less volume than the combined stuttering group in any region.

Table 2
Regions, coordinates, and peak *Z* scores of significantly different gray matter voxels in whole-brain VBM analysis

Region	BA	*x*	*y*	*z*	Voxel extent	Max *Z*
Fluent controls>stuttering						
Inferior frontal gyrus (L)	47	−44	19	−9	715	5.66
Precentral gyrus (L)	4	−61	−10	26	141	4.94
Anterior cingulate (L)	32	−10	35	24	366	4.87
Inferior frontal gyrus (L)	45	−54	34	10	1159	4.42
Inferior frontal gyrus (R)	47	43	26	−12	759	4.12
Precentral gyrus (R)	44	60	11	13	1000	4.07
Superior frontal gyrus (L)	6	−9	4	69	281	3.96
Postcentral gyrus (R)	43	69	−19	16	688	3.92
Medial frontal gyrus (L)	6	−7	−22	61	159	3.86
Middle temporal gyrus (L)	37	−38	−66	13	194	3.77
Supramarginal gyrus (L)	40	−54	−43	30	273	3.71
Medial frontal gyrus (R)	6	6	−6	61	153	3.65
Middle temporal gyrus (R)	21	63	0	−7	109	3.52
Precentral gyrus (R)	6	22	−23	77	175	3.46
Recovered>persistent						
Cingulate gyrus (R)	32	14	5	44	278	4.86
Cingulate gyrus (R)	32	10	22	34	240	4.52
Cerebellar culmen (L) (III)	N/A	−6	−41	−27	154	3.5
Inferior temporal gyrus (R)	37	42	−65	−12	129	3.83
Recovered<persistent						
Cerebellar declive (R)	N/A	7	−84	−17	935	4.88
Precentral gyrus (R)	6	35	−16	65	740	4.66
Inferior parietal lobe (R)	40	52	−31	55	2913	4.61
Superior temporal gyrus (L)	22	−63	−62	12	2098	4.54
Superior temporal gyrus (R)	38	54	3	−6	213	4.09
Precentral gyrus (L)	6	−40	−18	70	837	4.03
Middle frontal gyrus (L)	10	−30	60	20	555	3.87
Cerebellar declive (L)	N/A	−48	−50	−28	368	3.73

As shown in Figs. 1B and C, the regions where the persistent group had less GMV than the controls and where the recovered group had less GMV than the controls were similar. Fig. 2A and Table 2 show the persistent group had significantly less GMV than the recovered group in the cingulate gyrus in the right hemisphere (BA24, 32), while Fig. 2B and Table 2 show that the recovered group exhibited significantly less GMV than the persistent group in the bilateral medial temporal gyrus/STG (MTG/STG) (BA22, 39), bilateral precentral gyri (BA6), and bilateral cerebellar regions.

ROI comparisons on GMV

Pearson *r* values greater than 0.8 between age and GMV were positive in the left STG in the controls and negative in the left BA44 and right BA45 in the stuttering group. Similarly, values greater than 0.80 were positive between handedness and GMV in the right SMG and the right and left PT in the controls; and the left BA44 and the right and left BA45 in the persistent stuttering group. When all three groups were combined, age was related to GMV in the right BA45 and handedness was related to mean GMV in the right SMG and the right and left PT. Therefore, both age and handedness were included as covariates for the two group comparisons.

An overall ANOVA comparing all three groups (fluent controls, persist stuttering, and recovered from stuttering) with repeated comparisons across structures and side demonstrated significant group differences between the three groups ($F=7.692$, $p=0.005$). The post hoc tests demonstrated significant group effects on the left BA44 ($F=5.373$, $p=0.017$), the left BA45 ($F=4.429$, $p=0.031$), the left STG ($F=12.315$, $p=0.001$), and the right STG ($F=9.046$, $p=0.003$). Post hoc testing revealed that the fluent controls only differed significantly from the recovered group on each of these structures (L44 $F=29.97$, $p\leq0.0005$; L45 $F=9.63$, $p=013$; LSTG $F=19.07$, $p=0.002$; RSTG $F=11.845$, $p=0.007$) and that the recovered and persist group differed on the LSTG ($F=11.89$, $p=0.007$) and the RSTG ($F=11.29$, $p=0.008$) as shown in Fig. 3.

Right–left asymmetries in GMV between groups

The ANOVA comparing the left–right asymmetry quotients (AQ) between the combined persistent and recovered stuttering groups and the controls showed no group effect ($F=0.417$, $p=0.526$) or the group by structure interaction ($F=0.615$, $p=0.658$). Similarly, the persistent and recovered stuttering groups did not differ ($F=0.051$, $p=0.825$), with no group by structure interaction ($F=0.192$, $p=0.937$). The AQs were close to zero for all of the structures except the PT where all three groups had similar mean AQs of 0.100 ± 0.40.

Relationships between ROI GMV within groups

Because gray matter density and thickness change with age in the left hemisphere during childhood (Sowell et al., 2003, 2004; Toga et al., 2006), we examined relationships in GMV between brain regions involved in speech production within each group by computing Pearson *r* correlation coefficients between ROI GMVs. In the controls, positive *r* values greater than 0.8 occurred between the right and left SMG (Fig. 4). The persistent and recovered groups had *r* values similar to the controls between the right and left SMG but had *r* values greater than the controls between the left BA44 and the left BA45, and between the left STG and the left BA44, whereas all three groups had similar relationships between the left and right STGs (Fig. 4).

The degree of relationship between GMV in the left BA44 and left STG with other regions (right BA44, right BA45, left BA45, right SMG, left SMG, and the right STG and the left STG) were compared between groups using *r* values converted to Fisher's *Z* scores. The combined stuttering group had higher *Z* values (mean=0.807) than the fluent controls (mean=0.134) for the left BA44 with other structures ($F=8.191$, $p=0.021$). Similarly, the combined stuttering groups had higher *Z* values (mean=0.896) for the left STG with other structures than the fluent group (mean=0.269). This difference was statistically significant ($F=14.16$, $p=0.006$).

When the persistent and the recovered groups were contrasted, they had similar left BA44 relationships; the recovered group had similar *Z* values (mean=0.842) to the persistent group (mean=0.959) with no group difference ($F=0.304$, $p=0.593$). Further, for STG relationships with other structures, the mean *Z* scores for the recovered (mean=0.898) and the persistent group (mean=1.090) were similar and did not differ ($F=1.615$, $p=0.239$).

Group whole-brain comparisons on fractional anisotropy

Compared to the combined stuttering group (persistent and recovered), the normally fluent children exhibited significantly

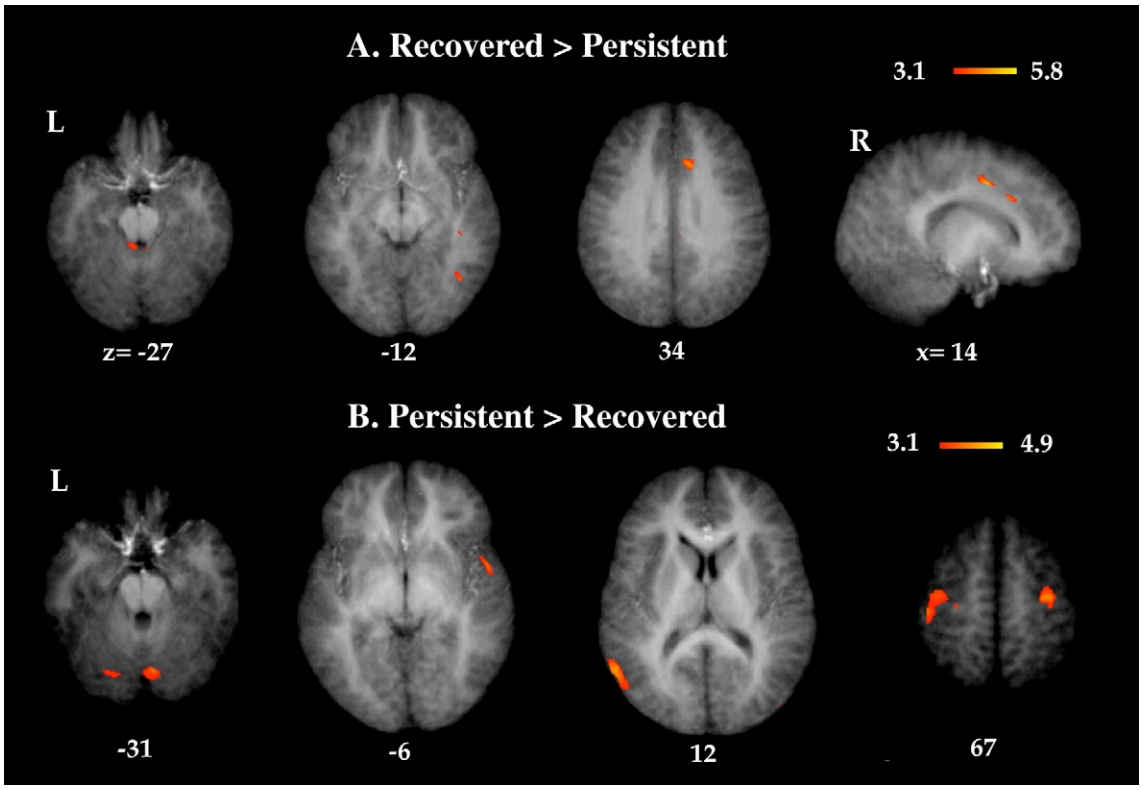


Fig. 2. Statistical parametric maps of the *Z* statistic overlaid on an averaged brain based on all subjects (statistical maps thresholded at $p<0.001$, uncorrected). Images are displayed in neurological convention. (A) Areas where the recovered group exhibited significantly more GMV compared to the persistent stuttering group. (B) Areas where the persistent group exhibited significantly more GMV compared to recovered group.

higher FA values in three white matter tracts: the corticospinal/corticobulbar tract bilaterally, the left arcuate fasciculus in the RO region, and a posterior-lateral region underlying the SMG area (Fig. 5). The SMG region appeared to be outside the superior longitudinal fasciculus proper, on a posterior branch, possibly an indirect frontotemporal pathway, recently identified in a DTI tractography study (Catani et al., 2005). Only a small cluster in the right inferior longitudinal fasciculus/uncinate fasciculus had higher FA in the stuttering children compared to the fluent controls (not shown) (Table 3).

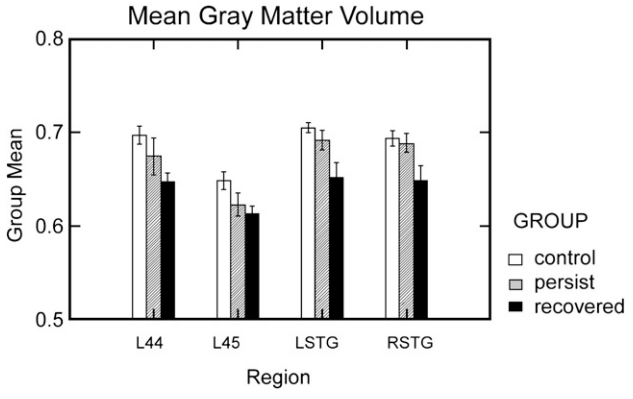
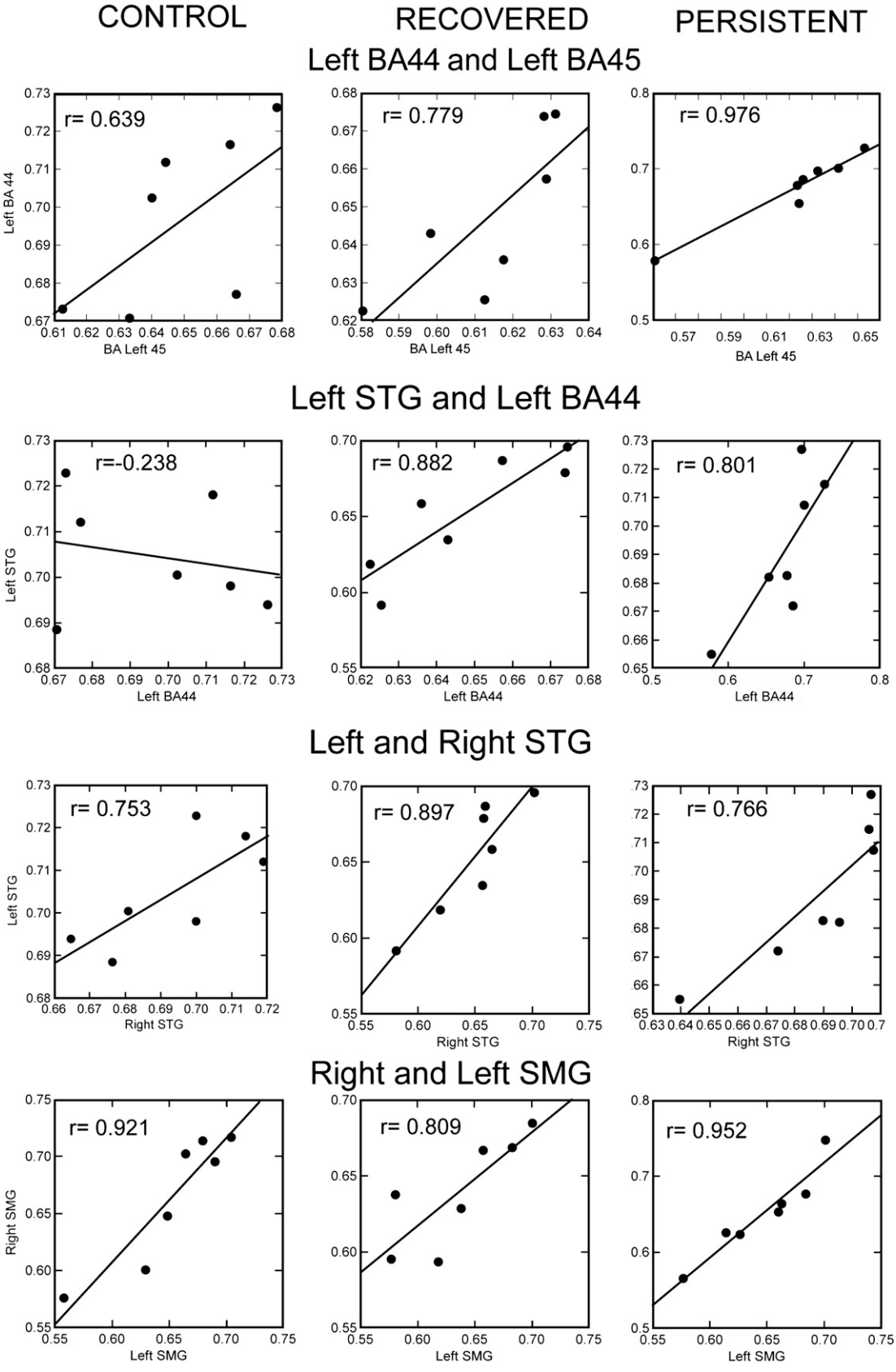


Fig. 3. Bar graphs of the mean gray matter volumes (GMV) and standard errors for left Brodmann's area 44 (LBA44) and left Brodmann's area 45 (LB45), the left superior temporal gyrus (LSTG), and the right STG sides in all three groups, the fluent controls (white bars), the persistent stuttering children (hatched bars), and the recovered children (solid black bars).

ROI results for FA

To determine if covariates needed to be included in the ROI analyses for mean FA, we examined relationships of mean FA with age and handedness. No relationships ($r>0.80$) were found in the fluent controls or the persistent stuttering groups between age or handedness and mean FA values in any of the four regions (frontal operculum, corticospinal, rolandic operculum, and supramarginal gyrus) on either the right or left sides. Although the recovered group had significant positive relationships of age with mean FA in the right and left corticospinal tract and the right frontal operculum and with handedness in the right corticospinal tract and the right SMG, there were no relationships when all three groups were combined and therefore no covariates were included in the analysis.

An overall ANOVA comparing all three groups was not significant for overall group effects ($F=0.592$, $p=0.563$); however, because there were significant region by side effects ($F=6.51$, $p=0.002$), the individual regions were tested for group effects. Only the left arcuate fasciculus differed between the three groups ($F=3.68$, $p=0.045$) with no significant difference between the three groups on the right side (Fig. 6). A comparison between the persistent and the controls on the left side was significant ($F=8.593$, $p=0.012$) while the recovered and the controls did not differ ($F=2.446$, $p=0.144$). When the two stuttering groups


CONTROL
RECOVERED
PERSISTENT
Left BA44 and Left BA45
r= 0.639
r= 0.779
r= 0.976
Left BA 44
BA Left 45
Left STG and Left BA44
r=-0.238
r= 0.882
r= 0.801
Left STG
Left BA44
Left and Right STG
r= 0.753
r= 0.897
r= 0.766
Left STG
Right STG
Right and Left SMG
r= 0.921
r= 0.809
r= 0.952
Right SMG
Left SMG

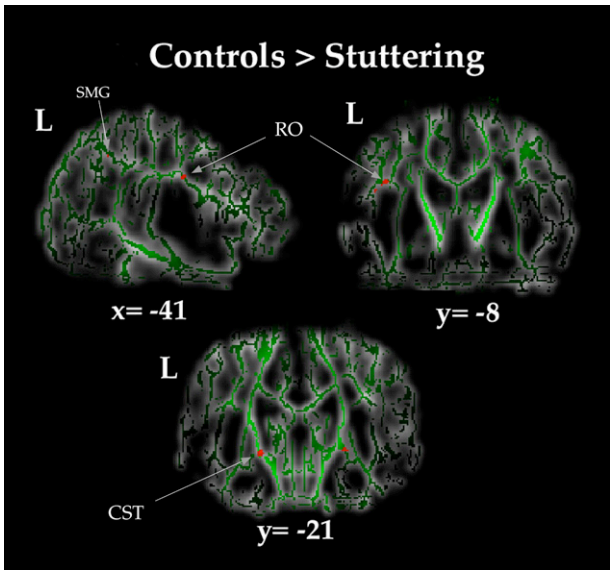


Fig. 5. Areas where normally fluent children exhibited significantly higher FA values compared to stuttering children (persistent and recovered) are shown in red overlaid on the mean FA skeleton (green) and the mean FA map. *Z* values were thresholded at an uncorrected $p<0.001$.

were compared on this region on the right and left sides, no significant differences were found on either side.

Discussion

Gray and white matter anatomical differences were found between children who had stuttered during preschool regardless of recovery and their fluent peers. White matter integrity, as measured by FA, was reduced underlying the left RO on both the TBSS and the FA ROI analysis. This area overlaps the oral–facial motor regions in the left hemisphere and tended to be reduced in the children with persistent stuttering. This decrease was in the same location as previously found in adults who stutter (Sommer et al., 2002) when compared to fluent controls. The similarities of our findings to those of Sommer et al. (2002) suggest that regardless of age, a decrease in FA underlying the left motor areas for the oral articulators tends to be a significant attribute of brain anatomy in persons who stutter.

Previously VBM measures of both white and GMV in adults who stutter (Jancke et al., 2004) found right-hemispheric increases in white matter volume in the STG, the PT, the inferior frontal gyrus (BA44), the white matter underlying face and mouth representation, and the anterior middle frontal gyrus. Stuttering adults also lacked the normal left–right asymmetry in white matter volume in the auditory cortex (Jancke et al., 2004). Because of reports of inconsistencies using VBM to assess white matter (Buchel et al., 2004; Gaser and Schlaug, 2003b), we used FA rather than white matter volume. Therefore, our FA results cannot be directly compared to those of the adult VBM study. FA measures of the white matter tracts in children who stuttered did not show any increases on the right in those who stuttered, although a non-significant trend of greater right-sided FA was seen in the group that had recovered from stuttering (Fig. 6). Studies are needed in adults to determine if FA measures show right–left differences in adults similar to the VBM results (Jancke et al., 2004). If so, right-sided increases in white matter volume may develop in persons who stutter after 12 years of age.

The gray matter differences found between children who stuttered and their fluent controls demonstrated *reduced* volume on the left side in BA44, BA45, and STG and bilaterally in the PT. We did not find any left to right asymmetry differences between groups, particularly in the PT, the only region with left to right asymmetry at this age. These GMV results in childhood differ from previous findings in adults who stutter that showed bilateral increases in the PT and atypical right to left asymmetry (Foundas et al., 2001). An important caveat is that GMV as measured by VBM may be influenced by cortical folding and gray matter thickness. Hence, caution is needed because of increased variability/folding in the left frontal and temporal gyri has been reported in adults who stutter (Foundas et al., 2001). Possibly increased cortical folding in the left hemisphere (consistent with adult morphometric observations) was obscured when measuring GMV, although this is unlikely given the reduced GMV found in the groups who stuttered. Comparison with previous adult studies is not straightforward; the adults included left handers and women in the stuttering group (Foundas et al., 2001), which may have influenced the degree of asymmetry found between the two hemispheres. Future studies examining cortical complexity (Eckert et al., 2006) as well as cortical thickness (Sowell et al., 2004) in equivalent samples are needed to compare studies in adults and children.

Only a few differences were found between the recovered and persistent stuttering groups. Although the combined stuttering groups had reduced GMV in the left STG compared to their fluent peers, the persistently stuttering children had greater GMV than the recovered group in the left and right STG. The GMV differences in the persistent group are in agreement with the findings of increased volume in the right and left PT in adults who stutter (Foundas et al., 2001). A longitudinal study is needed to determine if these increases in GMV in the STG in the persistent group developed as a result of continuing to struggle with stuttering or were present at the onset of stuttering.

Although reduced left- to right-sided asymmetries in the PT were found in adults who stutter (Foundas et al., 2001), we found no asymmetry differences between the controls and the stuttering children. A long-held premise in stuttering is that right hemisphere brain mechanisms are involved to a greater degree during speech in persons who stutter than in fluent speakers (Travis, 1978). Some have postulated that greater right hemisphere involvement may interfere with speech fluency in persons who stutter (Andrews et al., 1972; Webster, 1986). Functional brain imaging studies have shown increased right hemisphere activation in the motor speech areas during stuttering that becomes reduced when speech becomes more fluent (Braun et al., 1997; Fox et al., 2000), indicating that increased activation in the right hemisphere during stuttering may

Fig. 4. Scatterplots of the relationships within each group (fluent controls (CONTROL), recovered (RECOVERED), persistent (PERSISTENT) stuttering children) of their gray matter volume (GMV) for four structure combinations (the left Brodmann's area 44 (LBA44) and left Brodmann's area 45 (LB45), the left Brodmann's area 45 (LB45), the left superior temporal gyrus (LSTG), the right and left STG, and the right and left supramarginal gyrus (SMG)). The *r* values are Pearson correlation coefficients relating each subjects' GMV values in each of the two structure pairs.

Table 3
Regions, coordinates, and peak *Z* scores of significantly different white matter voxels in whole-brain FA analysis (TBSS)

Region	*x*	*y*	*z*	Voxel extent	*Z*
Fluent controls>stuttering					
Corticospinal/posterior thalamic radiation (L)	−23	−20	−1	28	4.14
Corticospinal/cortiopontine tract (L)	−19	−18	−6	17	3.41
Arcuate fasciculus (L)	−41	−9	25	21	3.51
Superior longitudinal tract (SLF) (L)	−48	−27	35	20	3.72
SLF (posterior, lateral near BA40) (L)	−40	−51	40	16	3.32
Corticospinal/posterior thalamic radiation (R)	26	−25	−1	16	3.86
Stuttering>fluent controls					
Uncinate fasciculus (R)	25	15	−24	15	3.33
Inferior longitudinal fasciculus (R)	31	20	−17	13	3.38
Recovered>persistent					
External capsule (R)	33	−21	−5	61	4.03
Superior longitudinal fasciculus (R)	48	−54	3	38	4
Corpus callosum (R)	17	−31	32	17	3.36
Internal capsule (retrolenticular part) (R)	36	−33	3	13	3.68

be compensatory (Braun et al., 1997; Fox et al., 2000; Preibisch et al., 2003). Perhaps both the anatomical and functional increases in right hemisphere speech related areas in adults are the result of compensatory mechanisms used over a lifetime of stuttering.

Recent research has shown that alterations in behavior and brain function can produce changes in brain anatomy. Gray and white matter volume differences emerge in the left hemisphere speech areas relative to the right in relation to hemispheric dominance for language during development (Dorsaint-Pierre et al., 2006). Gray matter increases follow motor training in adults (Draganski et al., 2004) and after a lifetime of practice in musicians (Gaser and Schlaug, 2003b). Increased left inferior parietal lobe gray matter density relates to the age of acquisition and second language proficiency (Mechelli et al., 2004). Similarly, regional increases in white matter tracts relate to the extent of piano practicing (Bengtsson et al., 2005), language laterality in adults relates to asymmetries in the arcuate fasciculus (Nucifora et al., 2005), and FA underneath the precentral gyrus is increased contralateral to the dominant hand relative to the non-dominant hand (Buchel et al., 2004). Therefore, a life-long enhanced use of right hemisphere brain mechanisms for speech in persons who stutter could result in right hemisphere white and gray matter increases and a reduction in left–right asymmetries. The lack of finding similar increases in right hemisphere speech areas in the children who stutter in this study suggests that right hemisphere enhancement develops with continued stuttering into adulthood. This might explain why right hemisphere speech regions are increased in adults who have stuttered for a lifetime and were not found in children who stutter. Perhaps the STG increases found in children with persistent stuttering over those who recovered from stuttering are the result of continuing to stutter for 6 to 9 years after onset. Increases in the white matter volume of the right STG have also been found in stuttering adults (Jancke et al., 2004).

During childhood, structural changes occur in brain development with growth differences between brain regions. Between 5 and 11 years, the greatest increases in cortical thickness occur in the perisylvian regions bilaterally and in the left inferior frontal area in particular (Sowell et al., 2004). Given the disparities in growth that occur between regions in this age range, GMV in the left BA44 would not be expected to relate to GMV in the left BA45 and the left STG as was found in the controls (Fig. 4). However, the GMV of the left BA44 was closely related with the left BA45 and the left STG in both stuttering groups and particularly in the persistent group to a greater degree than in the controls. This suggests a growth pattern difference in the children who stuttered for the left BA44 and left STG regions. Because other regions such as the right and left SMG were similar in all three groups, the gray matter development in the left inferior frontal area (Broca's area), and the STG may be specific regions of differences in children who stutter. Normally gray matter thickness increases in this area between 5 and 11 years of age (Sowell et al., 2004) and growth in BA44 region was shown to relate to phonological development (Lu et al., 2007). We eliminated all children with phonological deficits from participating in our study in order to examine children who were without other deficits besides stuttering. However, a high proportion of children who stutter also have phonological deficits in speech during the early period of speech development (Wolk et al., 1993). Perhaps delays in growth of the left BA44 may be related to a risk for both types of speech disorders.

This study had several limitations. Children were studied between 9 and 12 years of age, past the age when stuttering first begins, but studying younger children was challenging without sedation. To study children without other speech or behavioral deficits besides stuttering, almost 50% of the subjects contacted did not qualify, reducing the power of our statistical comparisons, particularly for the VBM study. Through DTI, however, we replicated the reduced FA findings in the arcuate fasciculus underlying the left rolandic opercular region previously found in adults (Sommer et al., 2002). Although adult studies have had similar group sizes, larger sample sizes are needed for studies involving children, given the increased group variance due to ongoing gray and white matter development in children (Toga et al., 2006). Our VBM results should be considered preliminary for this reason and need to be replicated with a larger sample. Further, by restricting the sample to right-handed boys who stuttered, our

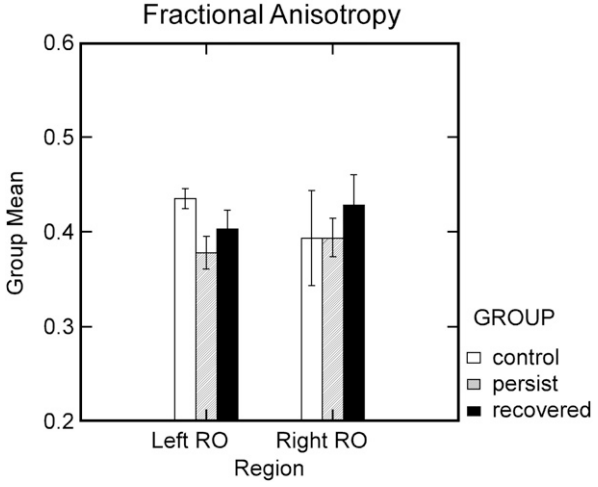


Fig. 6. Bar graph of group mean FA values and standard errors for the white matter tract underlying the rolandic operculum on the left and right sides in all three groups, the fluent controls (white bars), the persistent stuttering children (hatched bars), and the recovered children (solid black bars).

sample was not representative of all children who stutter, many of whom have other developmental disorders. The relationship between brain development in stuttering and other speech and language disorders such as dyslexia, Williams syndrome, and specific language impairment needs to be examined as similar regions may be involved in these other disorders (Eckert et al., 2006, 2005; Watkins et al., 2002).

In conclusion, our results suggest that stuttering is related to deficits in the development of white matter tracts underlying the oral facial motor regions on the left and reduced gray matter growth in the inferior frontal region (Broca's area) also in the left hemisphere. These two regions are part of the anterior portion of the perisylvian language center (Catani et al., 2005) and are functionally related during speech production (Greenlee et al., 2004). Developmental deficits in this network for speech production may represent risk factors for the onset of childhood stuttering during childhood.

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