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Abbreviations: CT = cortical thickness; CWS = children who stutter; FAT = frontal aslant tract; FDR = false discovery rate; fNIRS = functional near infrared spectroscopy; fROI = functional region of interest; (GO)DIVA = (gradient order) directions into velocities of articulators; GMV = grey matter volume; ICC = intraclass correlation coefficient; IFG = inferior frontal gyrus; LGI = local gyrification index; PCA = principle components analysis; pSTG = posterior superior temporal gyrus; SA = surface area; SLD = stuttering-like disfluency; SMA = supplementary motor area; SSI-4 = Stuttering Severity Instrument-4; TAR = thickness-to-area ratio; vPMC = ventral premotor cortex.

Stuttering is a neurodevelopmental disorder that affects the smooth flow of speech production. Stuttering onset occurs during a dynamic period of development when children first start learning to formulate sentences. Although most children grow out of stuttering naturally, approximately 1% of all children develop persistent stuttering that can lead to significant psychosocial consequences throughout one's life. To date, few studies have examined neural bases of stuttering in children who stutter, and even fewer have examined the basis for natural recovery versus persistence of stuttering. Here we report the first study to conduct surface-based analysis of the brain morphometric measures in children who stutter. We used FreeSurfer to extract cortical size and shape measures from structural MRI scans collected from the initial year of a longitudinal study involving 70 children (36 stuttering, 34 controls) in the 3-10-year range. The stuttering group was further divided into two groups: persistent and recovered, based on their later longitudinal visits that allowed determination of their eventual clinical outcome. A region-of-interest analysis that focused on the left hemisphere speech network and a whole-brain exploratory analysis were conducted to examine group differences and group-by-age interaction effects. We found that the persistent group could be differentiated from the control and recovered groups by reduced cortical thickness in left motor and lateral premotor cortical regions. The recovered group showed an age-related decrease in local gyrification in the left medial premotor cortex (SMA and preSMA). These results provide strong evidence of a primary deficit in the left hemisphere speech network, specifically involving lateral premotor cortex and primary motor cortex, in persistent developmental stuttering. Results further point to a possible compensatory mechanism involving left medial premotor cortex in those who recover from childhood stuttering.

Introduction

Developmental stuttering is a childhood onset neurodevelopmental disorder that affects 1% of the general population. At its core, stuttering is a speech disorder characterized by frequently occurring involuntary disruptions such as sound/syllable and word repetitions, prolongations, and blocking of sounds that severely impede the fluent flow of speech production. Stuttering is linked to both structural and functional abnormalities in brain regions involved in motor control and timing of speech movements. One convergent finding from previous investigations points to anomalous function and anatomy in left hemisphere structures involved in speech production (referred to here as the speech network). For instance, left motor cortical regions that mediate speech planning and production, including the inferior frontal gyrus (IFG) and the adjacent ventral premotor cortex (vPMC), were found to exhibit abnormal developmental trajectories in gray matter volume (Beal *et al.*, 2015; Cykowski *et al.*, 2008; Kell *et al.*, 2009), increased cortical folding (Foundas *et al.*, 2001), decreased underlying white matter integrity (Chang *et al.*, 2009; Cykowski *et al.*, 2010; Fox *et al.*, 2000; Sommer *et al.*, 2002), and reduced cerebral blood flow (Desai *et al.*, 2016; Neef *et al.*, 2017) in stuttering speakers. In addition, relative to controls, stuttering speakers exhibit decreased structural (Beal *et al.*, 2013; Cai, Tourville, *et al.*, 2014; Chang and Zhu, 2013; Chang *et al.*, 2008; 2009; Cykowski *et al.*, 2010; Kronfeld-Duenias *et al.*, 2016; Watkins *et al.*, 2008) and functional connectivity (Chang *et al.*, 2011; Lu *et al.*, 2010; Qiao *et al.*, 2017) involving the left IFG/vPMC and other brain areas (e.g., the posterior superior temporal gyrus; pSTG) of the speech network that support fluent speech production.

In addition to anomalous anatomy and function of left hemisphere cortical structures, some right hemisphere homologues have been found to exhibit greater structural volume, greater number

of gyral banks/cortical folding (Cykowski *et al.*, 2008)[1], heightened functional activity (Chang *et al.*, 2009; Fox *et al.*, 2000), and greater structural connectivity (Neef *et al.*, 2017) in stuttering speakers.

The studies summarized above were all performed on adults who stutter. However, stuttering is a developmental disorder that starts in childhood (typically around 2-4 years of age), and it is well-known that those whose stuttering persists develop secondary behaviors that complicate interpretation of findings involving adults who stutter. To date there have been only a handful of neuroimaging studies of children who stutter (CWS), and like most of the adult studies mentioned above, many of these studies have relied on statistical tests that did not involve rigorous correction for the large number of voxel-based comparisons involved in a whole-brain analysis. Although the lack of statistical correction forces caution when considering the results of these studies due to the high potential for false positives, they provide an important foundation for generating hypotheses to "narrow the search area" for subsequent studies, which in turn allows for more definitive conclusions based on properly corrected statistics. The most common finding across morphometric studies of CWS (Beal *et al.*, 2013; Chang and Zhu, 2013; Chang *et al.*, 2008) is *anomalous structure within the left hemisphere speech network*. For example, an early study by Chang et al. (2008) used voxel-based morphometry to compare gray matter volume (GMV) in CWS and fluent children. The largest differences in GMV were found in left IFG and left precentral gyrus (which includes motor and premotor cortex); these areas are both crucial centers in the speech production network (Guenther, 2006). CWS had smaller GMV in these areas than controls. Beal et al. (2013) also found smaller inferior frontal gyrus GMV in CWS compared to fluent children, although in this study the differences were found bilaterally. Chang and Zhu (2013)

[1] (Foundas *et al.*, 2001) found greater cortical folding in both left and right sylvian opercula.

found structural differences between CWS and fluent children in white matter tracts primarily within the left hemisphere speech network, including connections between putamen, auditory cortex, SMA, and insula. Analyses of resting state functional connectivity in the same subjects largely corroborated the tractography results. Chow and Chang (2017), in the first longitudinal study of childhood stuttering, showed that CWS had significant decreases in white matter integrity along the left arcuate fasciculus-- a major white matter tract that interconnects the motor and auditory regions of the left hemisphere speech network. CWS also exhibited decreased white matter integrity in corpus callosum areas containing fibers that interconnect the bilateral motor and auditory cortices (Chow and Chang, 2017). This study further found that children who continue to stutter versus those who recover from stuttering could be differentiated by distinct developmental trajectories; compared to the recovered group, who showed normalized growth with age, the persistent children showed stagnant white matter integrity increases with age in the left arcuate fasciculus, anterior thalamic radiation, and cerebral peduncles. Related, although not a study of morphology, Walsh et al. (2017) used functional near infrared spectroscopy (fNIRS) to examine cortical activity focused on bilateral IFG and STG cortical areas during continuous speech production. The left IFG/ ventral premotor region was the only region showing significantly aberrant patterns of the hemodynamic response during the speech production task in CWS compared to controls. The group differences in the right hemisphere homologues (IFG, STG) were not significant (Walsh *et al.*, 2017).

Based on the prior studies of brain morphology in CWS cited above, we predicted that, compared to fluent children, children with persistent stuttering would display morphological anomalies in the network of left hemisphere cortical regions underlying speech production, and furthermore that children who recover from stuttering would show differences in morphology

compared to children whose stuttering persists. Since the exact anatomical locations of anomalies noted in prior studies of stuttering have varied within the speech network, we included core sensorimotor regions as well as higher-order cortical areas involved in speech production (Guenther, 2016). Within this context, the purpose of the current study was to identify differences in brain morphology between fluent children (the *control* group), children who stuttered initially but recovered (the *recovery* group), and children whose stuttering persists (the *persistent* group). We focus here on morphology of the cerebral cortex, including measures of the size and local gyrification of cortical regions of interest.

The current study extends beyond prior work in several ways. First, we analyzed data from a large pediatric sample spanning preschool- to school-age children (3-10-year olds at initial testing). This allowed us, for the first time, to examine cortical morphology differences encompassing children close to stuttering onset. Second, we compare cortical morphometry of children who start out stuttering but eventually recover to children whose stuttering persists. This is possible because the data are part of a longitudinal study that tracks fluency and brain morphometry of children who stutter over the course of several years. Third, we characterize changes in morphometry as a function of age in childhood stuttering and in typically developing children. Fourth, we utilize image processing and statistical analysis methods that provide increased sensitivity to group differences in morphology than those used in prior studies, including cortical surface reconstruction (Dale *et al.*, 1999) and a functional-anatomical parcellation of cerebral cortex designed specifically for studies of speech that accounts for individual differences in cortical anatomy, thereby providing increased statistical power (Nieto-Castanon *et al.*, 2003; Tourville and Guenther, 2012). Fifth, this is the first study to investigate local gyrification in

children. As noted above, this morphometric feature has been shown to differ in speech-related cortical areas of adults who stutter compared to fluent adults.

Materials and Methods

Participants

Participants included 70 children (36 CWS, 14 females; 34 controls, 17 females) between 37.1 and 129.2 months of age. Demographic information for the two groups can be found in Table 1. All participants were right-handed monolingual speakers of English. Children were scanned up to four times (one visit per year) as part of a longitudinal study of brain morphometry and function in CWS; here we report cross-sectional data using scans from each child's first session. Scans were obtained from 87 participants, with 17 of those participants being removed from the participant pool for the current study due to image quality issues (primarily motion-based) that prevented the extraction of cortical surfaces (16 participants) or morphometric measures (1 participant) using the FreeSurfer analysis software.

Participants completed a battery of standardized speech, language, and cognitive tests. They received audiometric hearing screening, oral-motor screening, and cognitive evaluations, details of which can be found in Chang et al. (2015). Children with scores below two standard deviations (SD) of the mean on any of the standardized assessments were excluded.

Stuttering severity was assessed using samples of spontaneous speech tasks with a parent and a certified speech-language pathologist. We calculated the percentage of disfluent syllables based on narrative samples and a monologue (storytelling) using a pictures-only book ['Frog, where are you?' (Mayer, 1969)]. In addition, the Stuttering Severity Instrument (SSI-4; (Riley, 2009)) was used to examine the frequency and duration of disfluencies occurring in the speech sample, as well as any physical concomitants associated with moments of stuttering; all of these

measures were incorporated into a composite stuttering severity rating. To determine measurement reliability of the Stuttering Severity Instrument score ratings, an intraclass correlation coefficient (ICC) was calculated based on two independent judges' ratings of SSI from a random subset (~44%) of the children's' speech samples. The ICC for the overall SSI measurement between two independent judges was 0.98.

All children were trained during a separate visit with a mock MRI scanner to familiarize them with the MRI environment and procedures, and to practice keeping still while lying down inside the bore for stretches of time. Recordings of MRI scanning noises were played during this session, so that children were aware that they would be hearing loud MRI sounds during scanning. This session was repeated in some children, as needed. All procedures used in this study were approved by the Michigan State University Institutional Review Board. Informed consent was obtained according to the Declaration of Helsinki. All children were paid a nominal remuneration, and were given small prizes (e.g., stickers) for their participation.

While all children who stuttered were diagnosed with stuttering during their initial visit, they were later categorized as recovered or persistent through a combination of measures acquired in subsequent visits. Specifically, a child was considered recovered if the composite SSI-4 score was below 10 at the second visit or thereafter. A child was categorized as persistent if the SSI-4 score was at or higher than 10 (corresponding to "very mild" in SSI-4 severity classification) at the second visit or thereafter, and the onset of stuttering had been at least 36 months prior to the most recent visit. Determination of recovery status also required the consideration of percent occurrence of stuttering-like disfluencies (%SLD) in the speech sample (>3 for persistent) as well as clinician and parental reports. Similar criteria were used to determine persistence versus recovery in stuttering children in previous studies (Yairi and Ambrose, 1999; Yairi *et al.*, 1996).

Using these criteria, we identified 11 children who recovered and 25 children with persistent stuttering in the final data set for the analyses. For controls, the inclusion criteria included: never diagnosed as stuttering, no family history of stuttering, lack of parental concern for their child's fluency, and a %SLD below 3. A total of 34 controls were included.

Table 1. Demographics and behavioral scores for all participant groups.

	Controls, *n*=34 (17 boys)		Persistent, *n*=25 (17 boys)		Recovered, *n*=11 (5 boys)	
	Mean (*SD*)	Range	Mean (*SD*)	Range	Mean (*SD*)	Range
Age at initial visit	6.6 (2.0)	3.3-10.8	6.4 (1.9)	3.1-9.6	5.8 (2.1)	3.8-9.4
SES[a]	6.2 (0.5)	5.0-7.0	6.1 (0.8)	4.0-7.0	6.3 (0.6)	5.0-7.0
IQ[a,b]	115.7 (12.6)	87-144	106.1 (16.4)	78-138	107.9 (12.5)	88-128
PPVT[b]	117.7 (12.9)	95-151	107.1 (9.9)	90-131	114.91 (17.3)	85-147
EVT[b]	115.5 (13.9)	90-149	105.5 (12.3)	85-134	109.7 (10.2)	94-127
GFTA[c]	104.2 (8.3)	76-123	102.2 (6.9)	87-118	108.1 (7.2)	99-121
SSI-4 at initial visit[d]	N/A	N/A	22.7 (7.4)	12-48	16.1 (4.1)	11-22
SSI-4 at final visit[d]	N/A	N/A	20.3 (9.2)	7-48	8.3 (2.1)	4-11
Months post-onset[a,]	N/A	N/A	38.2 (25.2)	6-90	24.1 (20.5)	7-70

[a]Tests measured only at each participant's initial visit
[b]Scores significantly lower in persistent than controls (two-sample t-test, p<.05)
[c]Scores significantly lower in persistent than recovered (two-sample t-test, p<.05)
[d]Scores significantly higher in persistent than recovered (two-sample t-test, p<.05)
SD, standard deviation; SES, socioeconomic status; IQ, intelligence quotient; PPVT, Peabody Picture Vocabulary Test; EVT, Expressive Vocabulary Test; GFTA-2, Goldman-Fristoe Test of Articulation; SSI-4, Stuttering Severity Instrument, Edition 4.

MRI acquisition

All MRI scans were acquired on a GE 3T Signa HDx MR scanner with an 8-channel head coil. During each session, whole brain T1-weighted inversion recovery fast spoiled gradient-recalled images (3D IRFSPGR) with CSF suppressed were obtained with the following parameters: time of echo = 3.8 ms, time of repetition of acquisition = 8.6 ms, time of inversion = 831 ms, repetition time of inversion = 2332 ms, flip angle = 8, field of view = 25.6 cm x 25.6 cm, matrix size = 256 x 256, slice thickness = 1 mm, and receiver bandwidth = +/-20.8 kHz. The T1-weighted images

were acquired as part of a longitudinal imaging study that also included acquisition of DTI and resting state fMRI data. Children viewed a movie, and a research staff member sat next to the child to ensure comfort and compliance throughout the scanning procedure (~40 minutes).

Image processing

FreeSurfer 5.3.0 (http://surfer.nmr.mgh.harvard.edu/) was used to automatically segment individual T1-weighted anatomical volumes and to generate three-dimensional reconstructions of each individual's cortical surface. The procedure included motion correction, intensity bias correction, skull stripping, and tissue classification. Triangular tessellation was then applied to create representations of white matter and pial surfaces. Image segmentation and surface reconstructions were visually inspected; when surface errors were present that were the result of poor image segmentation, manual edits were made in accordance with the FreeSurfer tutorial (https://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/TroubleshootingData) and surface reconstructions were regenerated.

Following reconstruction, each subject's cortical surface was divided into 62 distinct anatomical regions (***parcels***) per hemisphere based on individual anatomical landmarks according to the SLaparc parcellation system (Tourville and Guenther, 2012). A representative cortical surface template was constructed from the surface reconstructions of 28 participants, including 14 CWS (7 female; mean age 82 months) and 14 control (7 female; 88 months). The SLaparc parcellation system was mapped from the FreeSurfer adult *fsaverage* template to the representative pediatric surface template and an expert rater (J.T.) manually inspected and corrected the resulting labeled surface to ensure accurate adherence to the SLaparc parcellation system. Each individual surface reconstruction was co-registered to the representative template and the SLaparc labels were

mapped from the template to the individual surface. Template generation, surface co-registration, and surface-to-surface label mapping were all completed with tools in the FreeSurfer 5.3.0 software distribution.

Five morphometric measures were extracted from FreeSurfer for each anatomical parcel: average cortical thickness (CT), surface area (SA), volume, thickness-to-area ratio (TAR), and local gyrification index (LGI).

Two types of analyses were run to detect group morphometry differences: a ***hypothesis-based analysis*** focused on finding expected morphometry differences between groups in the left hemisphere speech network with statistical corrections for the number of regions and morphometric measures (as described in *Analyses of group differences* below), and an ***exploratory analysis*** involving all 62 parcels per hemisphere with no statistical correction for the number of regions. The hypothesis-based analysis was limited to 26 of the 62 left hemisphere parcels that have been identified as part of the speech production network based on prior functional neuroimaging studies (see Guenther, 2016 for review). These regions were grouped into 14 ***functional regions of interest (fROIs)***, each containing 1-3 anatomically defined parcels from the SLaparc parcellation. Table 2 lists the set of fROIs and corresponding anatomical parcels, and Figure 1 illustrates the fROIs and parcels on an inflated cortical surface. This "nested" approach, which is an example of a hierarchical fixed-sequence testing procedure for multiple hypothesis testing (Bretz *et al.*, 2008), was used to maximize statistical power in subsequent analyses of group differences by utilizing subject-specific regions of interest based on expected function-anatomy associations (Nieto-Castanon *et al.*, 2003) while providing more precise localization of group differences within larger fROIs that contain multiple anatomical sub-regions. The fROIs used here include core sensorimotor areas (primary motor cortex, medial premotor cortex, lateral premotor

cortex, primary somatosensory cortex, higher order somatosensory cortex, primary auditory cortex, anterior higher order auditory cortex, posterior higher order auditory cortex) as well as association and paralimbic regions that have been implicated in speech production (inferior frontal gyrus *pars opercularis*, inferior frontal gyrus *pars triangularis*, inferior frontal sulcus, frontal orbital cortex, posterior supramarginal gyrus, and anterior insula); see Guenther (2016) for hypothesized functions of these regions in speech.

Table 2. Functional regions of interest (fROIs) and corresponding anatomical parcels. See caption of Figure 1 for anatomical parcel abbreviations and Tourville & Guenther (2012) for details regarding anatomical landmarks delineating anatomical parcels.

fROIs (n=14)	**Anatomical parcels (n=26)**
Lateral premotor cortex	vPMC, midPMC
Medial premotor cortex	SMA, preSMA
Primary motor cortex	midMC, aCO, vMC
Primary somatosensory cortex	pCO, vSC
Higher order somatosensory cortex	PO, aSMg
Primary auditory cortex	Hg
Anterior higher order auditory cortex	PP, aSTg, adSTs
Posterior higher order auditory cortex	pSTg, pdSTs, PT
Inferior frontal gyrus *pars opercularis*	IFo, pFO
Inferior frontal gyrus *pars triangularis*	IFt, aFO
Inferior frontal sulcus	pIFs
Frontal orbital cortex	FOC
Posterior supramarginal gyrus	pSMg
Anterior insula	aINS

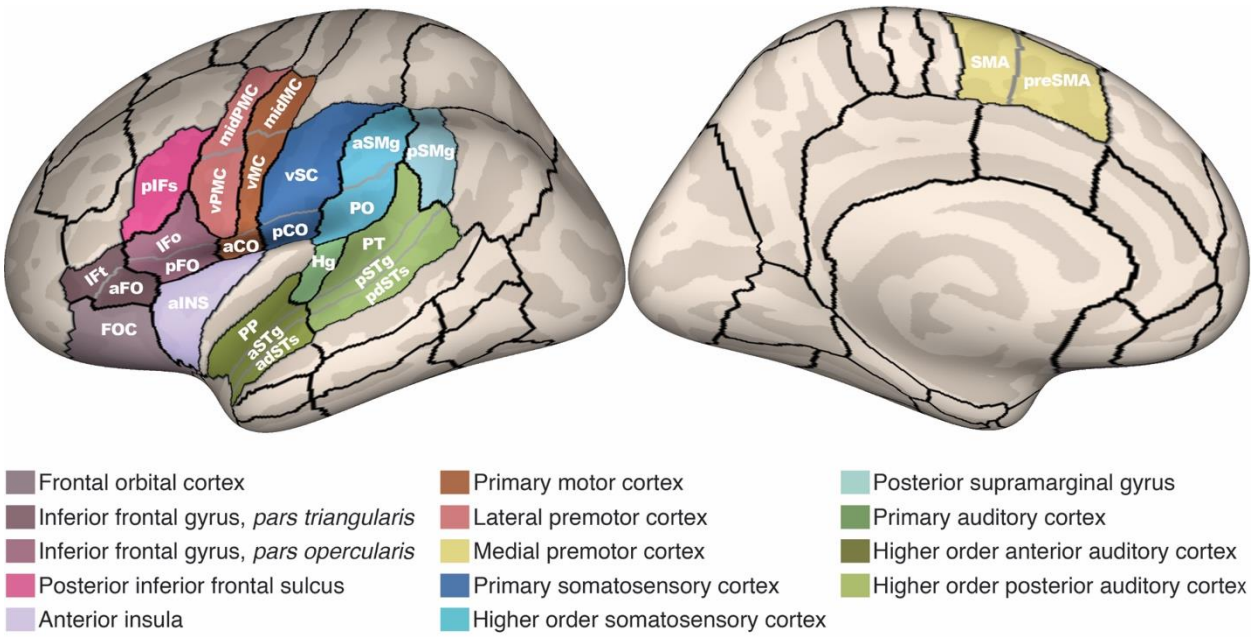

Figure 1. Functional regions of interest (fROIs; color-coded shading). The fROIs and associated anatomical parcels are shown on an inflated reconstruction of a representative left hemisphere cortical surface. Abbreviations: aCO=anterior central operculum; adSTs=anterior dorsal superior temporal sulcus; aINS=anterior insula; aFO=anterior frontal operculum; aSMg=anterior supramarginal gyrus; aSTg=anterior superior temporal gyrus convexity; FOC=frontal orbital cortex; Hg=Heschl's gyrus; IFo=inferior frontal gyrus *pars opercularis* convexity; IFt=inferior frontal gyrus *pars triangularis* convexity; midMC=middle motor cortex; midPMC=middle premotor cortex; pCO=posterior central operculum; pdSTs=posterior dorsal superior temporal sulcus; pFO=posterior frontal operculum; pIFs=posterior inferior frontal sulcus; PO=parietal operculum; PP=planum polare; preSMA= pre-supplementary motor area; pSMg=posterior supramarginal gyrus; pSTg=posterior superior temporal gyrus convexity; PT=planum temporale; SMA=supplementary motor area; vMC=ventral motor cortex; vPMC=ventral premotor cortex; vSC=ventral somatosensory cortex.

Morphometric measure selection

We investigated two aspects of cortical morphology in separate analyses: ROI *size* and *gyrification*. For the gyrification analysis, the FreeSurfer measure LGI, which characterizes the amount of cortex within sulcal folds compared to the outer cortex, was the dependent variable. For the ROI size analysis, we first performed a dimensionality reduction analysis using all four

FreeSurfer measures of ROI size (CT, SA, volume, and TAR). This analysis was motivated by redundancies in the ROI size measures, which significantly reduce statistical power if all measures are included in an analysis involving statistical correction for multiple comparisons. To ameliorate this potential problem, the four FreeSurfer size measures were submitted to a principal component analysis after being converted to z-scores separately for each of the 62 anatomical parcels per hemisphere, and then concatenated across all subjects and parcels. We found that the first two principal components explained 98% of the variance. We then determined how much of the variance of the original four measures could be captured by each possible combination of two measures. Among all possible pairs, SA and CT together explained the most variance (96%) across the original four variables, compared to 98% for the first two PCA components. Based on these analyses, we chose to use SA and CT as our two dependent variables for subsequent ROI size analysis since (i) they account for the vast majority of the variance in the original four measures in a non-redundant fashion, and (ii) they are more straightforward to interpret than the first two PCA components.

Covariate analysis of demographic factors

The potential confounding influence of demographic factors was addressed by performing a multivariate regression to identify significant covariation between four demographic variables (age, sex, IQ, and socioeconomic status) and three morphometric outcome measures (CT, SA, LGI) and three morphometric outcome measures (CT, SA, LGI) aggregated across all anatomical parcels. This analysis was limited to the set of 34 control participants. In addition, ANOVA was used to identify potential differences in demographic factors between the three subject groups. Demographic variables that showed statistically significant covariation with the outcome measures

or significant group differences were used as control covariates in subsequent analyses. Because language test scores are highly correlated with IQ, scores for PPVT and EVT were not included in these analyses to avoid multicollinearity issues. GFTA was also excluded since it may reflect greater articulatory variability that is associated with stuttering (e.g., Blood *et al.*, 2003; Louko *et al.*, 1990; Melnick *et al.*, 2003; St. Louis and Hinzman, 1988; Wolk *et al.*, 1993), particularly in persistent relative to recovered children who stutter (Paden *et al.*, 1999; Usler *et al.*, 2017).

Analyses of group differences

The chosen morphometric measures for ROI size and gyrification were submitted to analyses of covariance (ANCOVA). Main effects of group and age-by-group interactions were examined. Age, sex, and IQ were also included as control covariates in the analyses. The outcome measures for the cortical size analysis were SA and CT. LGI was the outcome measure for the cortical gyrification analysis. The contrasts of interest focusing on group differences included main group effects and group-by-age interactions. In other words, the analyses used F-tests to evaluate the presence of differences between groups in the cross-sectional developmental profiles of the outcome measures of interest, irrespective of whether these differences were linked to differences in the average levels of the outcome measure within each group (main group effects) or whether they were linked to differences in the strength of age-related changes in the outcome measure within each group (group-by-age interactions).

The hypothesis-based ANCOVA analysis involved the 14 left hemisphere speech network fROIs (containing a total of 26 anatomical parcels). For cortical size analyses, we first performed an omnibus test across all 26 anatomical parcels in the 14 fROIs to identify which individual measure(s) (SA, CT) showed significant group differences (two separate ANCOVAs, one per

measure), using False Discovery Rate (FDR) to correct for multiple comparisons across these two measures. For each significant measure found in this analysis, we then performed an ANCOVA analysis to identify significant group differences within each of the 14 fROIs (14 separate ANCOVAs, one per fROI), using FDR to correct for multiple comparisons across these 14 ROIs. Finally, for each significant measure and fROI combination, we identified significant group differences within the anatomical parcels that comprise the fROI (a variable number of ANCOVAs, one per anatomical parcel within each fROI), using FDR to correct for multiple comparisons across these parcels. For the gyrification analysis, we performed an ANCOVA analysis to identify significant group differences in LGI within each of the 14 fROIs (14 separate ANCOVAs, one per fROI), using FDR to correct for multiple-comparisons across these fROIs, then identified significant group differences within the anatomical parcels that comprise the fROI (a variable number of ANCOVAs, one per anatomical parcel within each fROI), using FDR to correct for multiple comparisons across these parcels.

The exploratory analysis involved all 62 anatomical parcels in each hemisphere and followed the above steps except that (i) no statistical corrections were applied for multiple comparisons across regions, and (ii) a single multivariate test (MANCOVA) involving all three morphometric measures (SA, CT, LGI) was used to identify significant group differences within each fROI. A second exploratory MANCOVA was performed to identify group differences in left-right asymmetry, in the form of a laterality index computed as (Left – Right) / (Left + Right), for each of the three morphometric measures.

Results

Demographic factors

A multiple regression aimed at identifying covariation between demographic factors (age, sex, IQ, and SES) and morphometric outcome measures (CT, SA, and LGI) in the control group found significant effects of age ($F(3,27) = 10.34$, $P = 0.0001$) and sex ($F(3,27) = 4.02$, $P = 0.017$). These demographic measures were thus included as control covariates in subsequent between-group analyses. Older subjects exhibited greater SA and lower CT when compared to younger subjects. Females exhibited greater SA and LGI compared to males. Group differences in demographic measures were identified by entering these variables as dependent measures in an ANOVA with group as independent factor. This revealed significant differences between groups in IQ ($F(2,68) = 3.66$, $P = 0.0309$), with controls exhibiting a higher mean IQ (115.7) than the persistent (106.0) and recovered (107.9) groups. IQ was thus included as an additional control covariate in subsequent analyses.

Hypothesis-based group analyses

Group effect analyses were performed on the 14 left hemisphere speech network fROIs and corresponding anatomical parcels as described in *Methods*. Separate analyses were performed for ROI size (with outcome measures CT and SA) and gyrification (with outcome measure LGI).

Omnibus tests across individual ROI size measures within all left hemisphere fROIs lumped into a single region revealed significant group effects for CT ($F(4,62) = 3.02$, $P = 0.024$, $P\text{-}FDR = 0.048$) but not for SA ($F(4,62) = 0.89$, $P = 0.474$), thereby supporting our primary hypothesis of group differences in morphometry within the left hemisphere speech network, in particular for CT. Subsequent analysis steps for ROI size were thus performed only on CT in left hemisphere speech fROIs. ANCOVA analysis of group differences within individual fROIs

revealed significant group effects for CT in two of the fROIs in the left hemisphere: lateral premotor cortex ($\chi^2(8) = 22.13$, $P = 0.005$, *P-FDR* = 0.035), and primary motor cortex ($\chi^2(12) = 28.27$, $P = 0.005$, *P-FDR* = 0.035). Post hoc analysis of these fROIs identified significant group CT differences in four anatomical parcels within these fROIs: midPMC ($F(4,62) = 3.55$, $P = 0.011$, *P-FDR* = 0.026), vMC ($F(4,62) = 3.20$, $P = 0.019$, *P-FDR* = 0.026), vPMC ($F(4,62) = 3.17$, $P = 0.020$, *P-FDR* = 0.026), and aCO ($F(4,62) = 3.13$, $P = 0.021$, *P-FDR* = 0.026). Finally, post hoc analyses discriminating between main group effects and age-by-group interactions for CT within these four anatomical parcels allowed us to characterize the effects within those regions as follows:

(i) midPMC group effects were dominated by main between-group differences ($F(2,62) = 6.57$, $P = 0.003$, *P-FDR* = 0.005), with the persistent group having lower CT compared to the recovery and control groups ($t(62)=3.26$, $P = 0.002$, *P-FDR* = 0.007; see Figure 2A),

(ii) vMC group effects (Figure 2B) were dominated by main between-group differences ($F(2,62) = 5.64$, $P = 0.006$, *P-FDR* = 0.011), with lower CT in the persistent compared to the recovery group ($t(62) = 3.36$, $P = 0.001$, *P-FDR* = 0.005),

(iii) vPMC group effects (Figure 2C) were dominated by group-by-age interactions ($F(2,62) = 4.29$, $P = 0.018$, *P-FDR* = 0.036), with CT decreasing with age in the persistent group but not the control group ($t(62) = -2.881$, $P = 0.005$, *P-FDR* = 0.022), and

(iv) aCO group effects (Figure 2D) were driven by a combination of both main between-group differences ($F(2,62) = 3.16$, $P = 0.049$, = 0.098) and group-by-age interactions ($F(2,62) = 2.37$, $P = 0.102$, *P-FDR* = 0.102), but no significant individual effects.

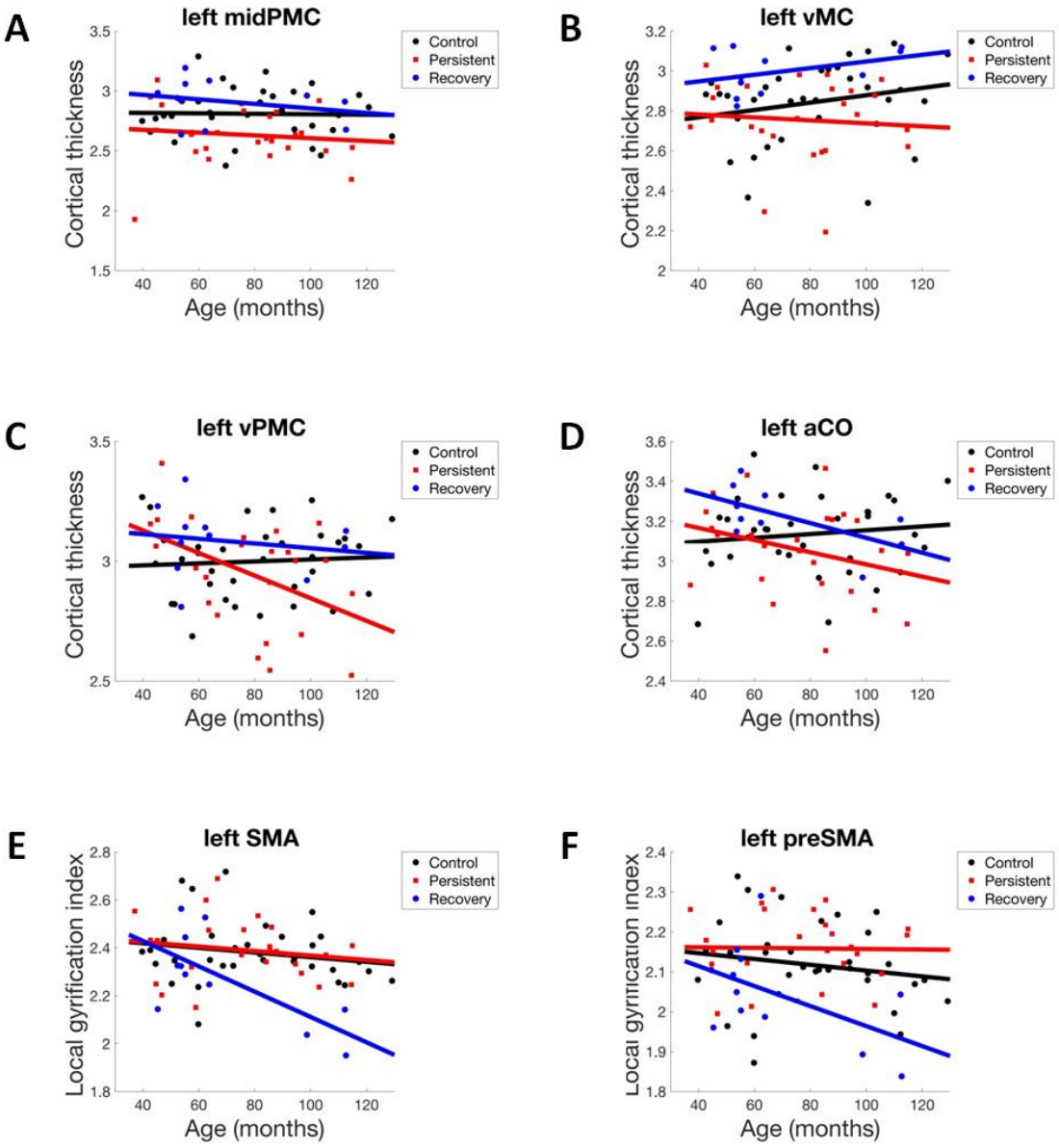

Figure 2. Premotor, motor, and medial motor cortical areas showing significant group differences in morphometry. Significant morphometric group differences (*P-FDR* < 0.05) were identified in ANCOVA analyses of group differences in left hemisphere speech network morphology, plotted as a function of age. See caption of Figure 1 for anatomical parcel abbreviations.

The fROI analysis for gyrification revealed significant group effects in one left hemisphere fROI only: medial premotor cortex ($\chi^2(8)=24.36$, p=0.002, p-FDR=0.028). Post hoc analysis identified significant group LGI differences in both anatomical parcels within this fROI: SMA

(F(4,62)=3.80, p=0.008, p-FDR=0.016); and preSMA (F(4,62)=3.09, p=0.022, p-FDR=0.022). Finally, post hoc analyses discriminating main group effects and age-by-group interactions for LGI within these parcels identified both significant main and interaction effects in SMA (main effect F(2,62)=6.027, p=0.004, p-FDR=0.008; interaction effect F(2,62)=3.55, p=0.035, p-FDR=0.035) consistent with a decrease in LGI with age in the recovery group but not in the persistent or control groups (T(62)=-2.43, p=0.018, p-FDR=0.036; Figure 2E), as well as a significant main effect in preSMA (F(2,62)= 5.794, p=0.005, p-FDR=0.010) consistent with reduced LGI in the recovery group compared to the persistent or control groups (T(62)=-3.25, p=0.002; Figure 2F).

A summary of the significant group differences from the hypothesis-based analyses plotted on an inflated cortical surface is provided in Figure 3.

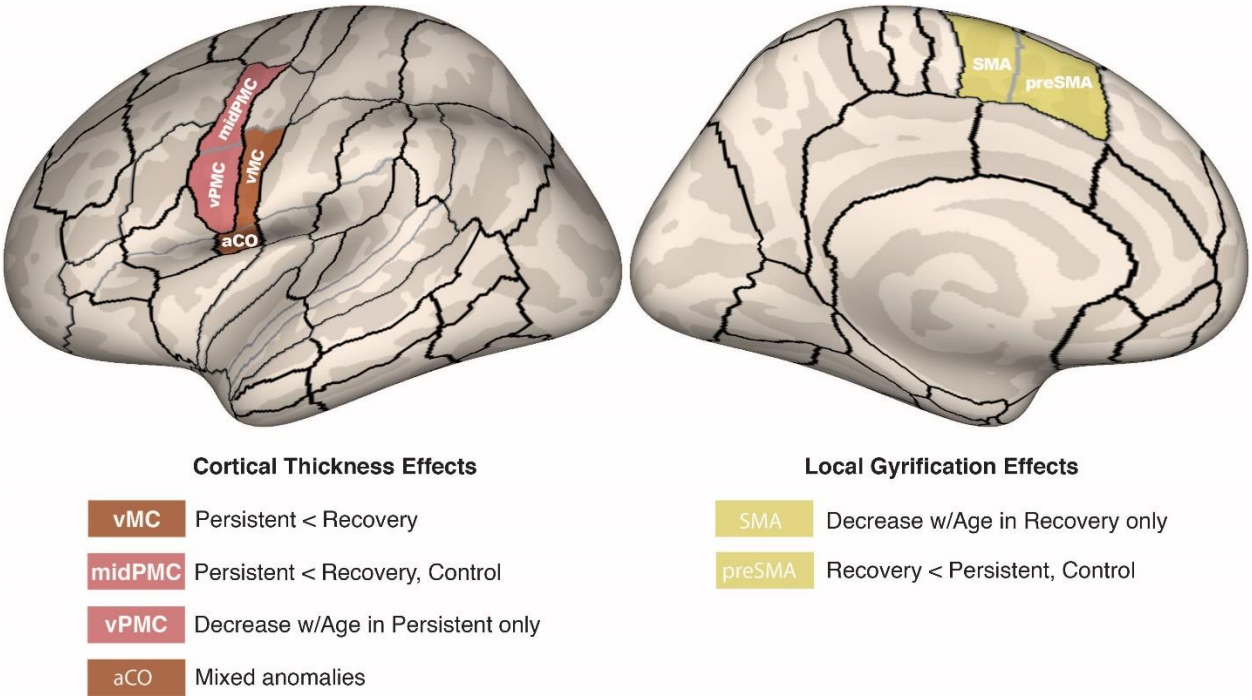

Figure 3. Summary of significant group differences in left hemisphere cortical morphology. Areas showing significant group differences are plotted on an inflated cortical surface template. Abbreviations: CT=cortical thickness; LGI=local gyrification index. See caption of Figure 1 for anatomical parcel abbreviations.

Exploratory group analyses

Exploratory analyses used MANCOVA to identify potential main group effects or group-by-age interactions across the three subject groups (control, persistent, and recovery) within any of the three outcome measures (SA, CT, and LGI). These analyses were performed separately within each parcel across a total of 124 parcels covering both hemispheres. Three parcels survived a threshold of $p<0.01$ (uncorrected), suggesting potential effects pending replication: left SMA, right posterior parahippocampal gyrus (pPH), and left posterior ventral superior temporal sulcus (pvSTs). In left SMA, group effects ($\chi^2(12) = 30.43$, $P = 0.002$) were driven mainly by LGI differences ($F(4,62) = 3.80$, $P = 0.008$), consistent with the results observed in our main confirmatory analyses (namely, a decrease in LGI with age for the recovered group but not the other two groups; see Figure 2F). (Note that the lack of any significant left hemisphere speech network differences beyond those identified in the nested hypothesis-based analyses indicates that the use of larger fROIs in the hypothesis-based analyses did not mask group differences that may have been apparent in only one of the anatomical parcels within the fROI.) Right pPH effects were also driven by differences in LGI ($F(4,62) = 4.11$, $P = 0.005$), with LGI trending upward with age in the control group but downward in the other two groups (Figure 4A). Left pvSTs effects appeared to be driven by differences in CT ($F(4,62) = 4.67$, $P = 0.002$), with CT trending more strongly downward with age in the persistent group than the other two groups (Figure 4B).

It is possible that the uncorrected p-value threshold of $p<0.01$ used for the exploratory analysis was less sensitive than the FDR-corrected threshold of 0.05 used in the hypothesis-based analysis stream, which in turn might explain why we found several left hemisphere anomalies but no right hemisphere anomalies in the speech network. To eliminate this possibility, we applied the

hypothesis-based analysis stream to the right hemisphere speech network and still found no right hemisphere group differences.

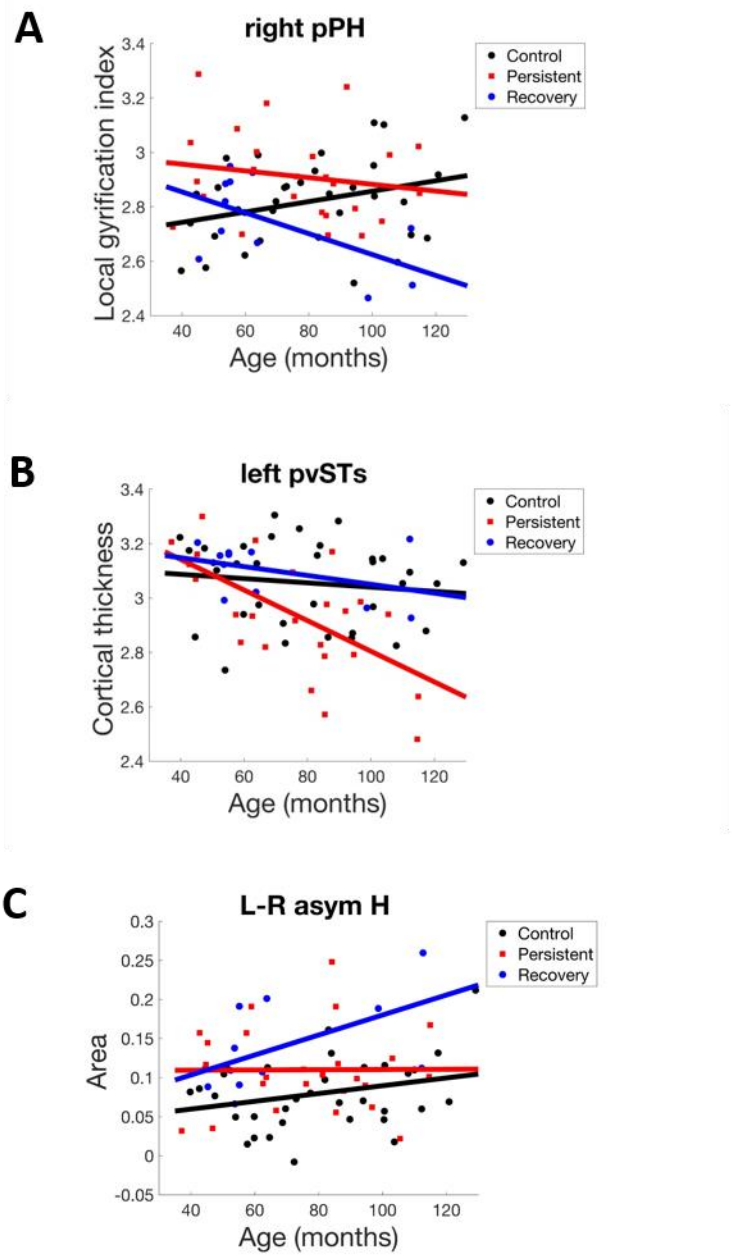

Figure 4. Areas with morphometric differences identified in the exploratory analyses (p<0.01, uncorrected), plotted as a function of age. Abbreviations: H= Heschl's gyrus; L-R asym= left/right asymmetry (laterality index); pPH= posterior parahippocampal gyrus; pvSTS= posterior ventral superior temporal sulcus.

A second exploratory analysis was performed to look for possible group differences in left/right asymmetry by calculating laterality indices for the three morphometric measures (SA, CT, and LGI) and submitting them to a MANCOVA analysis as described above. Only one region, Heschl's gyrus, exhibited a significant group difference at the $p<0.01$ uncorrected threshold ($\chi^2(12) = 30.01$, $P = 0.003$), driven primarily by differences in SA asymmetry. As illustrated in Figure 4C, the persistent and recovery groups had higher left-right SA asymmetry in Heschl's gyrus compared to the control group. Furthermore, the recovery and control groups show a tendency for this asymmetry to increase with age, whereas asymmetry for the persistent group remains flat across age.

Discussion

In this study, we sought to determine if gray matter morphology in speech-related brain regions, as well as its developmental trajectory (determined cross-sectionally), would distinguish between three groups of young children: those who recovered from stuttering, those with persistent stuttering, and controls with no history of stuttering. To this end, we utilized a statistically sensitive fROI-based analysis of the cortical ribbon to derive and compare morphometric measures including CT, SA, volume, TAR, and LGI across groups. Preliminary analyses indicated that the vast majority of the variability in the data could be captured with three of these measures: the size measures CT and SA, and the gyrification measure LGI. Subsequent analyses identified several group differences in CT and LGI in left hemisphere motor and premotor areas that are involved in speech production.

Based on previous findings reporting reduced gray matter volume in CWS in structures in the left hemisphere speech network, we expected to find focal CT decreases in these regions for CWS relative to controls. The current results showed this to be the case for children with persistent

stuttering specifically: there was significantly decreased CT in left premotor and primary motor areas in the persistent stuttering group compared to the other groups. In the lateral premotor cortex, the persistent stuttering group had lower CT in the ventral premotor cortex (vPMC) compared to the control group and in the middle premotor cortex (midPMC) compared to both recovery and control groups. The persistent group also showed decreased CT with age in vPMC that was not evident in the other groups. In primary motor cortex, we found lower CT in vMC for persistent compared to recovered stuttering group. An effect of group was also found for anterior central operculum (aCO), which is adjacent to vMC and forms part of the Rolandic operculum, an area where previous studies of adults (Sommer *et al.*, 2002), and children who stutter (Chang *et al.*, 2008) reported decreased integrity of underlying white matter tracts. Although no significant pairwise group differences were found in aCO, the data were consistent with the vMC finding of lower CT in persistent compared to recovered children (Figure 2D).

The results further showed significant group differences with LGI in left medial premotor cortical areas. This included a decrease in LGI with age in supplementary motor area (SMA) of the recovery group but not the control or persistent groups (Figure 2E), and lower LGI in preSMA in the recovery group compared to the control and persistent groups (Figure 2F). No significant group effects or interactions between group and age were found for SA.

Although the neural deficits underlying stuttering are still an active topic of debate, many researchers have posited that the core deficit in stuttering is in the left hemisphere basal ganglia-thalamo-cortical motor circuit (Alm, 2004; Chang and Zhu, 2013; Civier *et al.*, 2013; Maguire *et al.*, 2000; 2004; 2002) which we will refer to here as the ***BG motor loop***. It should be noted that we did not directly assess potential structural differences in the BG region itself, given our focus on cortical measures, but rather discuss the cortical findings relevant to the BG motor loop

network. The brain areas in which we found structural anomalies in CWS are all key components of this circuit (Middleton & Strick, 2000), which has been implicated in the selection and initiation of motor acts within behavioral sequences (e.g., (Brotchie *et al.*, 1991; Marsden and Obeso, 1994; Mink, 1996) including the sequence of gestures for a word or syllable (Bohland *et al.*, 2010; Bohland and Guenther, 2006).

According to the DIVA neurocomputational model of speech motor control (Guenther, 2006; Guenther *et al.*, 2006), neurons in left hemisphere vPMC represent well-learned speech sequences such as frequently produced syllables in a *speech sound map*, and activation of a syllable's representation in this map leads to the readout of a finely tuned motor program for the syllable via projections to vMC, cerebellum (via the pons), and the BG motor loop. The GODIVA model (Bohland *et al.*, 2010; Civier *et al.*, 2013) is an extension of DIVA that describes the neural circuitry underlying speech sound sequencing and motor program initiation. The DIVA/GODIVA framework accounts for a wide range of behavioral and neural findings concerning speech sequencing, and stuttering can be induced in computer simulations of the GODIVA model by impairing the BG motor loop (Civier *et al.*, 2013). In GODIVA, the BG motor loop is responsible for initiating the articulatory gestures within a syllabic motor program at the right instants in time by activating neurons in an *initiation map* in SMA. Projections from sensory, motor, and premotor cortical areas to the putamen provide a detailed "sensorimotor context" that the BG monitors to determine exactly when to initiate the next gesture in the sequence. For example, left vPMC provides information about the syllable currently being produced, SMA and vMC provide information about the ongoing articulatory gesture, ventral somatosensory cortex (vSC) provides information about the current somatosensory state, and posterior auditory cortex (pAC) provides information about the current acoustic signal being produced. When the BG recognize that the

current gesture is nearly complete, a "completion signal" is sent to SMA that extinguishes activity in the initiation map neurons coding the current gesture and activates the neurons coding the next gesture.

Consideration of our morphometry results within the DIVA/GODIVA theoretical framework leads to the following interpretations. Lower CT in vMC and vPMC in CWS may be indicative of impaired neural processing in these areas, which in turn makes it relatively difficult for the BG motor loop to identify the proper sensorimotor context for initiating the next gesture in a speech sequence, leading to moments of stuttering. Alternatively, reduced CT in vMC and vPMC may be a secondary consequence of impaired neural processing within the basal ganglia or SMA that leads to less effective activation of motor programs in vPMC/vMC, and this reduced activity in turn leads to thinner cortex through some currently unknown neurodevelopmental process. The fact that significant differences found in persistent stuttering children were primarily in early developing cortical morphology (CT) provides some support for the former possibility. Future research that incorporates longitudinal modeling, as well as combined analysis of functional and structural MRI data may further elucidate this issue.

Our findings of group differences in SMA/preSMA LGI are more difficult to interpret. Cortical gyrification during the postnatal period shows peak growth between 2-6 years of age (Raznahan *et al.*, 2011) with generally protracted decreases in 6-year-olds and older. Cortical gyrification supports expansion of surface area, and it has been shown that increased LGI links to better cortical function such as higher intelligence (Luders *et al.*, 2005). On the other hand, higher mean levels of gyrification was found in children with autism relative to controls across the 4-12-year range, with abnormal age-related gyrification increases in the autism group (Yang *et al.*, 2016); see also (Chow and Chang, 2017; Hardan *et al.*, 2004; Jou *et al.*, 2010). Greater gyrification

is also linked to local short-range hyper-connectivity in children with autism (Schaer *et al.*, 2013; Walsh *et al.*, 2017). In addition, LGI was negatively correlated with more years of training (e.g., expert versus untrained divers: (Guenther, 2016; Zhang *et al.*, 2016), indicating that decreasing LGI might represent synaptic pruning to support efficient neural circuitry supporting optimal function behaviors (Li *et al.*, 2014; White *et al.*, 2010).

Given that the persistent stuttering group did not show any LGI difference in SMA/preSMA compared to controls (anomalies were found only in the recovery group), it seems unlikely that this finding represents a root cause of stuttering. Instead, a decrease in LGI with age in the recovery group suggests that changes in left SMA/preSMA function and/or structure may somehow offset the neural processing impairments that caused these children to stutter when they were younger. Left SMA/preSMA is interconnected with the left posterior IFG via the frontal aslant tract ([FAT]; (Dick *et al.*, 2014)), which was shown in recent studies to support language production (Catani *et al.*, 2013). More specific to stuttering, Kronfeld-Duenias et al. (2016) reported that the left FAT exhibited greater mean diffusivity (MD) in stuttering speakers relative to controls, and that left FAT MD values were negatively correlated with speech rate in stuttering speakers. The authors argued that increased MD could have stemmed from "… a noisy communication (reduced synchrony) between IFG and SMA…" and that lower MD values "…predict faster transmission between inferior frontal language regions and the preSMA/SMA involved in speech planning and production." (p. 378). In another study, Kemerdere and colleagues (2015) showed with axonal stimulation of FAT, which provides a transient virtual lesion to the stimulated area, that disruption of left FAT led to transitory stuttering (Kemerdere *et al.*, 2015). These studies suggest the critical role of the left FAT in fluent speech production. If increased gyral folding is linked to increased connectivity of short tracts interconnecting local areas (Ecker

et al., 2016), lessening of the LGI in the SMA/preSMA may indicate synaptic pruning and fine-tuning of neural circuits involving this region. Namely, we speculate that decreased LGI with age in the left SMA/preSMA in the recovery group may underlie better long-range connectivity between left SMA/preSMA and left IFG that helps achieve more fluent speech. Future studies that combine examination of LGI and DTI tractography in stuttering children (persistent, recovered), would help confirm these ideas.

Although our exploratory finding of CT anomalies in left pvSTs (a higher order auditory cortical area) must be interpreted with caution due to the use of uncorrected statistics, it is possible that impaired auditory input to the putamen from pvSTs may contribute to difficulties in recognizing the proper sensorimotor context for initiating upcoming gestures. An intriguing alternative possibility is motivated by the observation that the persistent group starts out with similar pvSTs CT to the control and recovery groups at around 40 months of age but the persistent group shows a decline in CT with age not seen in the other groups (Figure 4B). It is well-established that a number of auditory feedback manipulations (e.g., masking noise, frequency-shifted feedback, or delayed auditory feedback (Adams and Ramig, 1980; Andrews *et al.*, 1980; Foundas *et al.*, 2013; Ingham *et al.*, 2009; 2012; Saltuklaroglu *et al.*, 2009; Stuart *et al.*, 2008) can induce fluency in people who stutter, at least temporarily. These manipulations may work because they reduce the likelihood that the basal ganglia will detect a mismatch in the sensorimotor context (in the form of a mismatch between expected and actual auditory feedback) for initiating the next gesture in the sequence. Over time, the brains of people with persistent stuttering may (subconsciously) learn to inhibit auditory processing of their own speech, thereby reducing (but not eliminating) the likelihood of a moment of stuttering (Guenther, 2016). Support for this idea comes from studies investigating sensorimotor adaptation to auditory perturbations, which indicate

that adults who stutter show reduced adaptation compared to controls (Cai *et al.*, 2012; Cai, Beal, *et al.*, 2014; Loucks *et al.*, 2012; Nudelman *et al.*, 1992) whereas CWS show the same amount of adaptation as fluent children (Daliri *et al.*, 2017).

Because prior morphometry studies involving CWS consistently found anomalies in the left hemisphere speech areas (with right hemisphere findings in CWS being less consistent, though not absent; e.g., (Beal *et al.*, 2013)) we focused our hypothesis-based analysis on the left hemisphere speech network, allowing us to use statistical tests that were rigorously corrected for multiple comparisons. Nonetheless, it is noteworthy that our exploratory analysis did not find any significant right hemisphere speech network anomalies, even with a p-value threshold that was not corrected for multiple comparisons. The exploratory analysis did find a significant group difference in right pPH, but this difference is difficult to interpret given that pPH is not generally considered to be a speech area. The pPH is part of the limbic system and has been linked to contextual associations (Aminoff *et al.*, 2013), including contextual cues in speech such as sarcasm (Rankin et al., 2009). While this was an unexpected finding, the significance of social context for stuttering severity is well established (Craig *et al.*, 2014; Yaruss & Quesal, 2006). Thus, hypothesis-driven future studies of stuttering focused on the limbic system including the right pPH might be warranted. According to the DIVA/GODIVA framework, feedforward motor programs for speech sequences are essentially stored in left vPMC (as discussed above), whereas right hemisphere vPMC is more heavily involved in sensory feedback-based adjustments of the motor commands. This is consistent with our finding of only left hemisphere anomalies in CWS since stuttering is an impairment of the readout of stored motor programs.

In contrast to our finding of only left hemisphere morphology differences in CWS, morphometry studies of adults who stutter consistently find right hemisphere anomalies in the

speech network, mostly in the form of larger ROI sizes/thicknesses and stronger white matter tracts (Jancke *et al.*, 2004; Neef *et al.*, 2017), which contrasts sharply with the smaller ROI sizes/thicknesses and weaker tracts found in the left hemisphere of CWS (Beal *et al.*, 2013; Chang *et al.*, 2008; 2015; Chow and Chang, 2017). The natural interpretation of this pattern of results within the DIVA/GODIVA framework is that the core deficit in stuttering is an impairment of the left hemisphere feedforward control system (and thus left hemisphere anomalies are found in both adults and children who stutter), and this deficit forces over-reliance on right hemisphere feedback control mechanisms, eventually leading to right hemisphere morphological changes seen in adults who stutter.

One additional finding from our exploratory analyses was a group difference in left-right asymmetry in Heschl's gyrus, which is the location of the primary auditory cortex. A prior study involving adults found reduced asymmetry in the planum temporale (PT), an auditory cortical region immediately caudal to Heschl's gyrus, of adults who stutter compared to age-matched controls (*Foundas et al.*, 2001). However, a more recent study that included younger participants failed to replicate this PT asymmetry difference (Gough *et al.*, 2017), and the current study's results do not support reduced asymmetry in CWS for either Heschl's gyrus (where we found increased asymmetry in CWS) or PT (where we found no significant group differences). One possible reason for these apparently conflicting findings may be that asymmetry in PT and/or Heschl's gyrus changes with age in different ways for CWS compared to controls. Tentative support for this view is found in Figure 4C, which indicates that laterality of Heschl's gyrus SA increased with age in control participants and recovered stutterers, while asymmetry in persistent stutterers remained constant across age. A similar pattern was found for gray matter density in PT by Gough et al. (2018). Extrapolating into adulthood, this could lead to a situation where adults

who stutter have decreased laterality compared to those who do not. At present this interpretation should be considered speculative given the exploratory nature of our asymmetry analysis; however, our results provide a strong rationale for a future study of auditory cortical asymmetries in stuttering using longitudinal data and/or a large cohort covering a larger age range.

While we have thus far applied the DIVA/GODIVA theoretical framework to guide interpretation of our current findings, other theoretical accounts could provide alternative explanations. The significant group differences in CT found in the medial premotor cortex, for example, might be explained in the context of this region being involved in generating movements that result from internal as opposed to external cues. This is interesting in light of hypotheses proposing that stuttering may result from an internal timing deficit related to impairment of basal ganglia thalamocortical connections that leads to the inability to generate or maintain internally-paced movements such as fluent speech production (Alm, 2004; Etchell *et al.*, 2014; Wieland *et al.*, 2015).

A so-called rhythm perception and timing network (Grahn and Rowe, 2009) includes putamen, SMA, and PMC, regions which continue to be reported in neuroimaging and neurophysiological studies of stuttering (Chang and Zhu, 2013; Chang *et al.*, 2016; Civier *et al.*, 2013; De Nil *et al.*, 2003; Giraud *et al.*, 2008; Kell *et al.*, 2009; Lu *et al.*, 2009; 2010; Neumann *et al.*, 2005; Toyomura *et al.*, 2011). The present study focuses examination of surface-based cortical morphometric measures and thus we cannot comment on subcortical regions that form critical components of this network. The cortical regions that are heavily interconnected with the putamen, however, including vMC, vPMC, medial PMC, differentiated the persistent stuttering children from the other groups. Further, age related decreases in the gyrification measure LGI in the SMA/preSMA were found in the recovered group. The SMA and putamen form the "main core

timing network" (Merchant *et al.*, 2013), and significantly decreased functional connectivity between these areas has been found in stuttering children relative to controls (Chang and Zhu, 2013). The present finding of age related LGI decreases in left SMA/preSMA in the recovery group thus leads to an intriguing question: could recovery be supported not only through a better long-range connectivity between SMA/preSMA and the left IFG, but also with the putamen, a major node of the rhythm/timing network? Current research underway that combines morphometric measures with DTI in a longitudinal design will help us answer this question.

In sum, we report the first morphometric study of childhood stuttering focused on surface based cortical measures. The children who would eventually persist in stuttering showed early differentiation from the control and the eventually recovered groups in cortical thickness in left motor and lateral premotor areas. These results corroborate findings of aberrant articulatory coordination and movement indices in children who stutter, particularly in boys who are more likely to persist in stuttering symptoms (Walsh *et al.*, 2015). The children who would eventually recover showed decreased gyrification in left SMA/preSMA, which we tentatively interpret as a possible indicator of improved long-range connectivity with other cortical and subcortical areas that may help achieve fluent speech production. These results provide novel information that contributes to our expanding knowledge base on the neural bases of stuttering and the possible basis for chronicity versus natural recovery from stuttering.

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Figure captions

Figure 1. Functional regions of interest (fROIs; color-coded shading). The fROIs and associated anatomical parcels are shown on an inflated reconstruction of a representative left hemisphere cortical surface. Abbreviations: aCO=anterior central operculum; adSTs=anterior dorsal superior temporal sulcus; aINS=anterior insula; aFO=anterior frontal operculum; aSMg=anterior supramarginal gyrus; aSTg=anterior superior temporal gyrus convexity; FOC=frontal orbital cortex; Hg=Heschl's gyrus; IFo=inferior frontal gyrus *pars opercularis* convexity; IFt=inferior frontal gyrus *pars triangularis* convexity; midMC=middle motor cortex; midPMC=middle premotor cortex; pCO=posterior central operculum; pdSTs=posterior dorsal superior temporal sulcus; pFO=posterior frontal operculum; pIFs=posterior inferior frontal sulcus; PO=parietal operculum; PP=planum polare; preSMA= pre-supplementary motor area; pSMg=posterior supramarginal gyrus; pSTg=posterior superior temporal gyrus convexity; PT=planum temporale; SMA=supplementary motor area; vMC=ventral motor cortex; vPMC=ventral premotor cortex; vSC=ventral somatosensory cortex.

Figure 2. Premotor, motor, and medial motor cortical areas showing significant group differences in morphometry. Significant morphometric group differences (*P-FDR* < 0.05) were identified in ANCOVA analyses of group differences in left hemisphere speech network morphology, plotted as a function of age. See caption of Figure 1 for anatomical parcel abbreviations.

Figure 3. Summary of significant group differences in left hemisphere cortical morphology. Areas showing significant group differences are plotted on an inflated cortical surface template. Abbreviations: CT=cortical thickness; LGI=local gyrification index. See caption of Figure 1 for anatomical parcel abbreviations.

Figure 4. Areas with morphometric differences identified in the exploratory analyses (p<0.01, uncorrected), plotted as a function of age. Abbreviations: H= Heschl's gyrus; L-R asym= left/right asymmetry (laterality index); pPH= posterior parahippocampal gyrus; pvSTS= posterior ventral superior temporal sulcus.

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