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A voxel-based morphometry (VBM) analysis of regional grey and white matter volume abnormalities within the speech production network of children who stutter

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Abstract

It is well documented that neuroanatomical differences exist between adults who stutter and their fluently speaking peers. Specifically, adults who stutter have been found to have more grey matter volume (GMV) in speech relevant regions including inferior frontal gyrus, insula and superior temporal gyrus (Beal et al., 2007; Song et al., 2007). Despite stuttering having its onset in childhood only one study has investigated the neuroanatomical differences between children who do and do not stutter. Chang et al. (2008) reported children who stutter had less GMV in the bilateral inferior frontal gyri and middle temporal gyrus relative to fluently speaking children. Thus it appears that children who stutter present with unique neuroanatomical abnormalities as compared to those of adults who stutter. In order to better understand the neuroanatomical correlates of stuttering earlier in its development, near the time of onset, we used voxel-based morphometry to examine volumetric differences between 11 children who stutter and 11 fluent children. Children who stutter had less GMV in the bilateral inferior frontal gyri and left putamen

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but more GMV in right Rolandic operculum and superior temporal gyrus relative to fluent children. Children who stutter also had less white matter volume bilaterally in the forceps minor of the corpus callosum. We discuss our findings of widespread anatomic abnormalities throughout the cortical network for speech motor control within the context of the speech motor skill limitations identified in people who stutter (Namasivayam and van Lieshout, 2008; Smits-Bandstra et al., 2006).

Keywords

speech motor control; persistent developmental stuttering; voxel-based; morphometry; magnetic resonance imaging (MRI)

Introduction

The aetiology of childhood stuttering remains unknown but because of its onset early in speech development and its genetic component it has been posited that predetermined neuroanatomical or neurophysiological distinctions increase an individual's susceptibility to the disorder (De Nil, 1999; De Nil, 2004). To this end, various studies have demonstrated that persistent developmental stuttering in adulthood is associated with neuroanatomical abnormalities throughout the neural network for speech production (Foundas et al., 2001; Foundas et al., 2003; Foundas et al., 2004; Jäncke et al., 2004; Sommer et al., 2002; Song et al., 2007; Watkins et al., 2008). Adults who stutter differ from fluent speakers in speech-relevant areas with regards to regional grey matter volume (GMV) as measured by voxel-based morphometry. However, the directionality of the results reported in the literature is inconsistent. Specifically, adults who stutter have been found to have more GMV in the left inferior frontal gyrus as well as the bilateral pre and post central gyri, superior temporal gyri, middle temporal gyri, basal ganglia and cerebellum (Beal et al., 2007; Lu et al., 2010; Song et al., 2007). Conversely, adults who stutter have also been found to have regional decreases in GMV in the left inferior frontal gyrus, left superior frontal gyrus as well as the bilateral middle frontal gyri, cerebellar posterior lobes, dorsal part of medulla and the cerebellar tonsil (Kell et al., 2009; Lu et al., 2010). Interestingly, not all studies have found differences in GMV in adults who stutter (Jäncke et al., 2004).

In addition to differences in GMV, adults who stutter have been found to have abnormalities in the white matter pathways that connect speech relevant cortical areas to one another. Using voxel-based morphometry, Jäncke et al. (2004) found that adults who stutter had more regional white matter volume (WMV) underlying a number of right hemisphere structures including the superior temporal gyrus, inferior frontal gyrus, precentral gyrus and the anterior middle frontal gyrus. More WMV in adults who stutter was also found in a previous voxel-based morphometry study completed in our laboratory, namely in pathways underlying the right inferior frontal gyrus, right insula and left middle temporal gyrus (Beal et al., 2007). Choo et al. (2011) reported more WMV in the rostrum and anterior midbody of the corpus callosum in adults who stutter relative to fluent speakers.

Sommer et al. (2002) used diffusion weighted imaging to measure differences in white matter connectivity in adults who stutter. They reported a focal decrease in fractional anisotropy of white matter underlying the left Rolandic operculum in adults who stutter relative to fluent controls. A similar finding was reported by Watkins et al. (Watkins et al., 2008) who found reduced fractional anisotropy values in the white matter underlying the left ventral premotor cortex in combination with reduced blood-oxygen level dependent (BOLD) signal in this grey matter region as measured by functional magnetic resonance imaging of a speech production task. Cykowski et al. (2010) also reported reduced FA in the white matter

underlying the inferior frontal gyrus, as well as the corpus callosum, in adults who stutter. Cykowski et al. concluded that all studies of FA in adults who stutter at that time had identified reduced FA in regions along the superior longitudinal fasciculus known to connect speech relevant motor and sensory grey matter regions.

Together the above studies provide mounting evidence that the speech relevant neuroanatomic structures, and the associated underlying white matter pathways, of adults who stutter differ from fluently speaking control participants. However, it remains unclear if these differences exist closer to the time of stuttering onset or if they are the result of the lifetime experiences of the adults who stutter. It is known, for example, that extensive intellectual and motor training can lead to increases in GMV in associated brain regions and that individuals with an accumulated experience of a certain expertise (e.g., musicianship or navigational skills) present with more GMV in related cortex (Bermudez and Zatorre, 2005; Bermudez et al., 2009; Han et al., 2009; Maguire et al., 2003). Therefore, it is clear that experience impacts GMV. As such it is important to extend the current body of knowledge regarding GMV composition of adults who stutter, who are distant in time from the onset of the disorder, to children who stutter, who are closer to the onset of the disorder.

At the time of writing, only one study had examined the neuroanatomical correlates of stuttering in children despite the fact that stuttering is typically manifested in speech prior to the age of 6 years (Yairi and Ambrose, 1999). Chang et al. (2008) investigated GMV differences using voxel-based morphometry and fractional anisotropy differences in white matter using diffusion tensor imaging in children aged 9 to 12 years old who were stutterers, recovered stutterers or fluent speakers. The children who stutter demonstrated distinct GMV differences relative to the children who were recovered stutterers and the fluent children. Relative to fluent children, children who stutter had less GMV in bilateral inferior frontal gyrus and middle temporal gyrus. Conversely, adults who stutter have been found to have more GMV in left inferior frontal gyrus and right middle temporal gyrus relative to fluent adults (Beal et al., 2007). Relative to children who were recovered stutterers, the children who stutter had more GMV in bilateral precentral gyrus and superior temporal gyrus in addition to other brain regions (Chang et al., 2008). These findings are consistent with findings of more GMV in bilateral precentral gyrus (Beal et al., 2007) and superior temporal gyrus in adults who stutter relative to fluent adults (Song et al., 2007) and may be an indicator of individuals who are at risk for chronic stuttering.

With regards to results of the whole-brain white matter analysis, Chang et al. (2008) reported that children who stutter showed higher FA than fluent controls in the right inferior longitudinal fasciculus and uncinate fasciculus. Chang et al. (2008) did not discuss the implications of these findings but it is worth noting that the uncinate fasciculus connects the inferior frontal gyrus with the anterior portions of the temporal lobe and as such has been speculated to play a role in auditory-motor processing (Wan and Schlaug, 2010). However, differences between a combined group of children who stutter and children who had recovered from stuttering relative to fluent children were comparable to previous findings in adults who stutter. Similar to adults who stutter, the combined group had lower fractional anisotropy in the left arcuate fasciculus underlying the left ventral motor cortex. Chang et al. (2008) concluded that this white matter deficiency may exist in people who stutter regardless of age. However, the combined group also differed from fluent children in three other white matter pathways not previously implicated in adults who stutter. Specifically, the combined group had lower fractional anisotropy in the bilateral corticospinal tract and in a novel region identified as the posterior branch of the superior longitudinal fasciculus underlying the left supramarginal gyrus relative to the fluent children. The combined group also had a small area of higher fractional anisotropy along the right inferior longitudinal fasciculus.

Given the unique neuroanatomical differences identified in children who stutter, it is important that continued investigation of this population be completed to further our understanding of the neural correlates of stuttering closer to its onset in childhood. The intent of the current study is not to reveal brain structures related to the aetiology of stuttering, but rather to describe how neuroanatomical differences in children who stutter may be associated with the disorder in its early stages. Based on the prior findings of Chang et al. (2008) in children who stutter, we predicted that less GMV would be found in bilateral inferior frontal gyrus and middle temporal regions in children who stutter relative to fluent children. Based on prior findings of more GMV in bilateral superior temporal gyrus in adults who stutter (Beal et al., 2007) versus fluent adults and similar findings in children who stutter versus children who had recovered from stuttering (Chang et al., 2008), we predicted that children who stutter would differ from fluent children in this manner. Lastly, we investigated if the previous finding of more WMV in the rostrum and anterior midbody of the corpus callosum in adults who stutter relative to their same-aged peers (Choo et al., 2011) would extend to children who stutter.

Method

Participants

Eleven children who stutter and 11 fluently speaking children participated in this study. The participants were boys who ranged in age from 6 to 12 years old and who spoke English as their primary language.^{1, 2} Participation required that no speech or language deficits be revealed upon standardized testing with the Goldman Fristoe Test of Articulation – Second Edition (Goldman and Fristoe, 2000) and the Peabody Picture Vocabulary Test – Third Edition (Dunn and Dunn, 1997). Children who scored more than 1 standard deviation below the mean of these standardized measures were excluded from participation.

All participants were right handed as tested with the Edinburgh handedness inventory (Oldfield, 1971) and had a negative history of developmental or neurological impairment via parent report. The children who stutter all had their onset prior to age 5 years old and had been stuttering persistently for a minimum of 2 years. They ranged in severity from very mild (7) to severe (34) on the Stuttering Severity Instrument – Third Edition (Riley, 1994). The two groups did not differ in age, articulation ability or language ability ($p > .05$) (Table 1). The children gave informed assent and their parents gave informed written consent. The Research Ethics Board at the Hospital for Sick Children in Toronto approved this study.

Data Acquisition

Testing involved a pre-neuroimaging 1.5-hour session for articulation, language and hearing screening as well as tasks unrelated to the current analysis. The initial session was followed by a scanning session at the neuroimaging facilities at the Hospital for Sick Children in Toronto. As part of a larger neuroimaging protocol, anatomic magnetic resonance images were obtained for voxel-based morphometry analysis. A 1.5-T Signa Excite HD 12.0 MRI system (GE Medical Systems, Milwaukee, WI) with an 8 channel head coil was used to obtain neuroanatomical images. A T1-weighted 3D fast spoiled gradient echo sequence (flip

¹The impact of handedness and sex on brain structure development is poorly understood. The sex ratio of boys to girls who stutter for this age group is 3:1 (Bloodstein & Ratner, 2008) and thus renders difficult the recruitment of the critical number of left handed children and girls who stutter required for a formal investigation of these variables. Therefore the current study sample was limited to right-handed boys who stutter as a control for the potential confounds of sex and handedness.

²This age group was selected relative to the usual length of recovery that ranges 2 to 3 years (Yairi & Ambrose, 1999) and the age of onset 2 to 5 years old (Bloodstein, 2006) with the rationale that children identified as stuttering at age 7 are likely to show predictive signs of recovering or persisting in the future. It is more difficult to predict recovery in children who are of preschool age as at least 70% as these children are likely to recover. Only children who did not show signs of recovery were eligible for the study.

angle = 9°, TE = 4.2ms, TR = 9ms) was used to generate 114 locs/slab 1.5-mm-thick axial slices (256 × 192 matrix, 24 cm field of view). Pixels were squared post processing ultimately resulting in a 256×256 viewing matrix.

Data Analysis

Preprocessing—Voxel-based morphometric analysis of the data was done with SPM8 (Wellcome Trust Centre for Neuroimaging, London; <http://www.fil.ion.ucl.ac.uk/spm/software/spm8/>) using the voxel-based morphometry toolbox version 8 (VBM8; <http://dbm.neuro.uni-jena.de/vbm/>). Customized paediatric tissue probability maps were created with the template-o-matic (TOM8) toolbox (Wilke et al., 2008) for SPM8. Paediatric tissue probability maps were used to minimize the potential confounds introduced by the differences in cortical thickness, cortical surface area and cortical folding between children and adults inherent in using an adult template (Yoon et al., 2009). Via the TOM toolbox, we used the general linear model to statistically isolate the influence of age (6 to 12 years old), gender (male) and handedness (right) on brain structure to create custom paediatric tissue probability maps based on reference data from the NIH study of normal brain development (<http://www.bic.mni.mcgill.ca/niHPD/info/>). We used a matched pairs approach to create the priors such that only the age, gender and handedness matched reference maps relative to each study participant were averaged (Wilke et al., 2008). The average custom paediatric tissue probability maps, along with the T1 image, are shown in Figure 1.

The native structural T1 volumes were segmented into grey matter, white matter and cerebrospinal fluid tissue classifications using the adaptive Maximum A Posterior technique employed in the VBM8 toolbox (Rajapakse et al., 1997). The tissue segments were then used for a partial volume estimation of the mixed segment classes grey matter – white matter and grey matter – cerebral spinal to facilitate accurate segmentation (Tohka et al., 2004). A spatially adaptive non-local means denoising filter was applied to the data followed by a Markov Random Field denoising filter (Manjon et al., 2010). The segmented data were affine registered to the previously created paediatric tissue probability maps. The affine registered segmented images were then modulated by dividing by the Jacobian determinants of the warp field to correct for local differences in shape. The modulated affine registered tissue segments were used to calculate the non-linear deformation parameters via low dimensional standard SPM8 normalization to the study-specific paediatric template. The normalized modulated non-linear images were checked for sample homogeneity and no outlier images were detected. The grey matter images were smoothed with an 8mm full-width-half-maximum filter (FWHM) to facilitate inferences about regionally specific group differences and to minimize smoothing across sulci. The white matter images were smoothed with a 12mm FWHM filter to facilitate inferences about group differences along major white matter pathways.

Statistical Analysis—Native space global volumes of grey matter, white matter and cerebral spinal fluid classifications were calculated for each participant. Independent t-tests were used to test for group differences in total intracranial volume and each of total grey matter volume, total white matter volume and cerebral spinal fluid volume.

The smoothed, normalized modulated non-linear grey and white matter images were used for between group comparisons via separate independent t-tests. Absolute threshold masks of 0.3 and 0.7 were applied to the grey and white matter images respectively. Total intracranial volume was not used as a covariate as the non-linear images represent volume of grey matter corrected for individual brain sizes (<http://dbm.neuro.uni-jena.de/vbm8/VBM8-Manual.pdf>). Age, demeaned within group, was included in the statistical model as a nuisance variable. The study-specific paediatric template was used to superimpose and

localize significant clusters. An uncorrected voxel-wise threshold of $p < .001$ and an expected voxels per cluster threshold (>37), to eliminate spurious small clusters, were applied to the resultant statistical parametric maps. Pearson bivariate correlation analyses were completed between each of the surviving clusters and the composite score of the Stuttering Severity Index – 3rd Edition within the group of children who stutter.

Results

No significant group differences were observed in native total intracranial volume ($t(20) = 1.18$, $p = .25$), total GMV ($t(20) = 1.33$, $p = .20$), total WMV ($t(20) = 1.72$, $p = .87$) or total cerebral spinal fluid volume ($t(20) = 1.01$, $p = .33$; Table 2). As shown in Figure 2, the children who stutter were found to have significantly less GMV in 5 different regions relative to control participants. Region labels, sizes and z-statistics are reported in Table 3. The largest clusters of less GMV were found in the left and right inferior frontal gyri. Specifically, in the left inferior frontal gyrus clusters of less GMV were found in the pars opercularis, pars triangularis and pars orbitalis. In the right inferior frontal gyrus one cluster of less GMV was found in the pars triangularis and extended posterior to the pars opercularis. GMV in this cluster correlated negatively with stuttering severity ($r = -.84$, $p = .001$). Another cluster of less GMV was found in the right pars opercularis, dorsal to the previous cluster. Less GMV was also found in the left putamen of children who stutter relative to the control participants. Also shown in Figure 2 are the 5 clusters of more regional GMV found in the children who stutter relative to the control group. Interestingly, all of the clusters of higher GMV were in right hemisphere regions. More GMV was found in the right Rolandic operculum extending into the medial aspect of the pars opercularis, right superior temporal gyrus, right inferior parietal lobule and post central gyrus. Children who stutter were also found to have less WMV bilaterally in the forceps minor of the corpus callosum. No regions were found to have more WMV in the children who stutter relative to the control group.

Discussion

The current study aimed to further characterize the neuroanatomic abnormalities in grey and white matter previously identified in children who stutter relative to fluent controls. We identified various regional GMV abnormalities throughout the network for speech production, and less WMV within the forceps minor of the corpus callosum, in children who stutter relative to fluent controls. Children who stuttered more severely were found to have less GMV in a region encompassing the right inferior frontal gyrus and Rolandic operculum than children who stuttered less severely. Our findings indicate a key role for the structural development of the bilateral inferior frontal gyri in persistent developmental stuttering and the underlying corpus callosum that communicates between hemispheres. The current findings have broad implications for our understanding of grey and white matter development in people who stutter across the lifespan as well as for accounts of stuttering put forward within models of speech motor control.

Grey matter volume abnormalities in persistent developmental stuttering

As predicted, we found less GMV in the left and right inferior frontal gyri of children who stutter relative to the fluent controls. This finding was consistent with that of the only other voxel-based morphometry study of children who stutter (Chang et al., 2008), despite some variations in methodology between the two studies. We employed an adaptive Maximum A Posteriori segmentation approach with partial volume estimation and denoising as implemented in the VBM8 toolbox for SPM8, an improvement over the optimized voxel-based morphometry routine used in the aforementioned study (Ashburner and Friston, 2000; Ashburner and Friston, 2005; Rajapakse et al., 1997). Thus it appears that less GMV in the

inferior frontal gyri of children who stutter relative to fluent controls is a robust and replicable finding.

The inferior frontal gyri are key regions within the neural network that underlies speech motor control. Evidence of their influence over articulation comes from a broad range of sources. Invasive electrical stimulation of the inferior frontal gyri in human participants demonstrated a functional link to primary motor cortex (Greenlee et al., 2004; Greenlee et al., 2007). Furthermore, transcranial magnetic stimulation of the inferior frontal gyri have demonstrated interference with articulatory control in fluent controls (Devlin and Watkins, 2007). A wealth of functional brain imaging studies has shown that the inferior frontal gyri are more active during articulation relative to baseline states (Chang et al., 2009; Ghosh et al., 2008; Horwitz et al., 2003; Levelt, 2004; Papoutsis et al., 2009; Poldrack et al., 1999; Sörös et al., 2006). Thus, our identification of less GMV in these regions at an early stage of stuttering development indicates the importance of cortical speech motor control in the disorder.

Some researchers have proposed that stuttering is associated with defective inverse models of the speech motor system (Hickok, 2012; Max et al., 2004). Inverse models are hypothesized functional units of the speech motor system that are responsible for the transformation of sensory information, such as that related to somatosensory or auditory targets, to speech motor programs (Guenther, 1994; Guenther, 1995; Houde et al., 2002; Perkell et al., 1997; Ventura et al., 2009). The inverse models serve to update and maintain the neural representations of speech sounds and are proposed to be critical for speech sound acquisition and motor learning (Bailly, 1997; Guenther, 1994; Perkell et al., 1997). Interestingly, the neural representations of speech motor programs are hypothesized to be associated with neuronal populations in the posterior part of the left inferior frontal gyrus (Golfopoulos et al., 2010; Guenther, 2006; Tourville and Guenther, 2011). Our current finding of less GMV in the inferior frontal gyri of children who stutter relative to fluent controls is consistent with the hypothesis that stuttering is related to faulty inverse models (Hickok, 2012; Max et al., 2004). Specifically, the lesser GMV observed in the inferior frontal gyri of children who stutter may reflect neuronal underdevelopment as a result of the faulty inverse model's inability to sufficiently establish the speech motor plans thought to be represented in this population of neurons. This type of neural underdevelopment is thought to result in unstable speech motor programs as demonstrated by the highly variable speech movements displayed by people who stutter relative to fluent controls (Kleinow and Smith, 2000; Smith and Kleinow, 2000; Smith et al., 2010). There is also some preliminary evidence to suggest that people who stutter are more frequently dysfluent on words that are higher in phonological complexity further implicating the process of articulatory coding in the disorder (LaSalle and Wolk, 2011).

In addition to children who stutter having less GMV in bilateral inferior frontal gyri relative to fluent controls, we also found that children who stuttered more severely had less GMV in a cluster of voxels spanning the right inferior frontal gyrus and Rolandic operculum than those children who stutter who were mildly affected (Figure 2B). Functional activity is known to decrease in the left inferior frontal gyrus and putamen with learning to articulate a novel pseudoword in adult fluent controls thus implicating these left hemisphere regions in the acquisition of speech motor programs (Rauschecker et al., 2008). The putamen is known to demonstrate activity changes with motor sequence learning in fluent controls (Doyon et al., 2003; Lehericy et al., 2005; Orban et al., 2011). Recall that we found less GMV in the left putamen of children who stutter. Our findings are especially interesting in the context of the emerging behavioral evidence for speech motor sequence learning difficulties experienced by people who stutter. People who stutter are known to have lesser improvement in reaction time and longer sequence durations during the early phases of

motor sequence learning (Bauerly and De Nil, 2011; Smits-Bandstra et al., 2006). Unfortunately, extremely little is known about long term behavioral motor sequence learning deficits in people who stutter and to date no publication has detailed the neural differences.

In the current study, the less severe children who stutter may have benefited from cortical reorganization such that the representations of speech motor programs are now being developed primarily in the right inferior frontal gyrus in compensation for the faulty internal model. This conceptualization of persistent developmental stuttering is further supported by the fact that adults who stutter have less robust white matter pathways connecting the left pars opercularis and the posterior superior temporal gyrus and inferior parietal cortex (Chang et al., 2011). These pathways are thought to facilitate the functioning of the inverse model (Golfinopoulos et al., 2010). Additionally, both children and adults who stutter have less fractional anisotropy in the white matter pathways underlying this region (Chang et al., 2008; Cykowski et al., 2010; Sommer et al., 2002; Watkins et al., 2008).

The putamen, and the basal ganglia as a whole, play an important role in speech motor sequencing and control (Bohland and Guenther, 2006; Grabski et al., 2011; Riecker et al., 2005) and in general motor sequence learning (Lehéricy et al., 2005; Toni et al., 1998). The basal ganglia have been implicated in stuttering (for a review, see Alm, 2004). Lesions in the basal ganglia, and their associated frontal cortical connections, were recently found to differentiate patients who developed neurogenic stuttering post stroke from patients who did not develop the disorder post stroke (Theys et al., 2012). Contrary to our current finding, adults with persistent developmental stuttering have been found to have more GMV in the left putamen compared to fluently speaking adults (Lu et al., 2010). The shift in directionality of volumetric abnormality with age, in people who stutter, may be indicative of an abnormal trajectory of neuroanatomical development in the left putamen. A recent fMRI study of speech production in adults who stutter found a negative correlation between stuttering severity and the degree of blood oxygen level dependent signal change from rest to speech in the left putamen as well as other basal ganglia structures (Toyomura et al., 2011). Furthermore, lesions of the putamen have been associated with acquired stuttering and speech characterized by inappropriate sequencing of articulatory gestures and slow transitions between sounds (Ciabarra et al. 2000; Pickett et al., 1998). Our finding of less GMV of the left putamen in children who stutter is interesting in light of the behavioural data that has demonstrated speech sequence learning and performance limitations in adults who stutter relative to control participants (Namasivayam and van Lieshout, 2008; Smits-Bandstra et al., 2006; Smits-Bandstra and De Nil, 2007).

We also found reduced GMV in the left hemisphere pars orbitalis of the inferior frontal gyrus in children who stutter. This finding is consistent with the only other study of GMV in children who stutter (Chang et al., 2008). Anatomically, this region is located just anterior and inferior to the pars triangularis and is cytoarchitecturally defined as BA47. The pars orbitalis is known to have a preferential response for processing the human voice over other auditory stimuli (Fecteau et al., 2005; Leff et al., 2008) and has been observed to be active during vocalization production (Schulz et al., 2005). Although the exact function of this region remains poorly defined in the literature, it appears that it plays a role in both speech processing and speech production (Fecteau et al., 2005; Leff et al., 2008; Schulz et al., 2005) and in unassisted recovery from stuttering (Kell et al., 2009). As such it is interesting that this area should be implicated in children who stutter. As our cohort consisted of school-aged children who persisted to stutter for more than 2 years post onset it is possible that the reduced GMV that we observed in the left pars orbitalis is related to the low likelihood of recovery in such a population. Other brain regions, such as the pars opercularis, that are known to be active during both speech perception and production have been proposed to

play a key role in speech acquisition (Guenther and Vladusich, In press; Hickok, 2009; Lotto et al., 2009). The rationale being that these regions are integrating perceptual information from the speech signal into the cortical representations of speech sounds with the goal of updating and maintaining their stability. Reduced GMV in the pars orbitalis may reflect decreased neural resources available for this type of updating in children who persist to stutter.

Interestingly, the regions of more GMV that we identified in children who stutter, relative to their fluently speaking peers, were located only in the right hemisphere. Children who stutter were found to have more GMV in the right Rolandic operculum, middle frontal gyrus, superior temporal gyrus and inferior parietal lobule. The right middle frontal gyrus, frontal operculum (anterior to the Rolandic operculum) and inferior parietal lobule are all areas known to over-activate in adults who stutter in positron emission tomography and fMRI studies of speech production (Brown et al., 2005). The right superior temporal gyrus is connected with the respective inferior frontal gyrus directly via the arcuate fasciculus and indirectly via a lateral pathway through the inferior parietal cortex (Catani et al., 2005; Gharabaghi et al., 2009). The current finding of more GMV in the right superior temporal gyrus in children who stutter is consistent with that of a previous study from our laboratory of adults who stutter (Beal et al., 2007). This region, along with the left superior temporal gyrus, has been shown to activate more strongly during fluency enhancing speech conditions, such as speaking paced with a metronome or choral speech, in adults who stutter relative to fluently speaking control participants (Toyomura et al., 2011). The right superior temporal gyrus has also been found to be more active during prolonged speech and voluntary stuttering, two additional fluency enhancing speaking conditions, relative to simple word repetition in adults who stutter (De Nil et al., 2008).

White matter volume abnormalities in persistent developmental stuttering

In addition to GMV abnormalities, we found less WMV bilaterally in the forceps minor of the corpus callosum of children who stutter relative to fluent controls. The forceps minor connect the lateral surfaces of the left and right hemispheres of the brain and, as such, construct a white matter pathway known to be important for the transmission of neural signals between hemispheres. In general, the interhemispheric communication facilitated by the corpus callosum is known to be important for both oral and written language development (Paul, 2011). Our current finding of less WMV may be indicative of constrained neural resources for interhemispheric communication in children who stutter. Structural deficits in the corpus callosum have been previously implicated in stuttering. Cykowski et al. (2008) used diffusion imaging and found reduced anisotropy in the region of the forceps minor in adults who stutter relative to fluent controls indicative of poor interhemispheric connectivity. However, Choo et al. (2011) used voxel-based morphometry to specifically examine the corpus callosum and found that adults who stutter had more WMV throughout the midportion of the rostrum. The directionality of the results across studies and between adults and children who stutter and their fluently speaking peers are conflicting and the reason for these differences is unclear. Interestingly, the corpus callosum is larger in patients with epilepsy who have confirmed right lateralization of language function as identified via sodium amytal injection (O'Kusky et al., 1988).

In addition to more WMV in the corpus callosum, adults who stutter have been found to have more WMV in pathways underlying the right inferior frontal gyrus, insula, superior temporal gyrus and precentral gyrus relative to fluent controls (Beal et al., 2007; Jäncke et al., 2004). The current study did not identify WMV abnormalities in children who stutter outside of the corpus callosum. Further research is required to understand the developmental trajectory of the white matter pathways underlying the speech production network in

children who stutter. It may be the case that WMV in these pathways increases as people who stutter age and the brain reorganizes with experience.

Study Limitations

As reported above, reduced GMV was found in bilateral pars opercularis and pars triangularis, as well as the left pars orbitalis, in children who stutter relative to their fluently speaking peers. These anatomical regions are located close to each other and our findings in these areas may be susceptible to the requirement to spatially smooth the data in VBM (Davatzikos, 2004). We used a smoothing filter of 8mm, enough to blur results across the anatomic boundaries of the pars orbitalis, pars triangularis and pars opercularis. Thus it is difficult to distinguish with a high degree of accuracy if one of these areas is less while another is not. However, our finding of GMV differences across these areas is consistent with previous voxel-based morphometry studies in children and adults who stutter (Beal et al., 2007; Chang et al., 2008; Song et al., 2007). As morphometry measurements are influenced by a number of grey matter properties including cortical thickness and folding it is difficult to tell what the specific underlying contributory factor to the reduced volume may be. For example, adults who stutter have been found to have subtle differences in cortical folding, characterised by a larger number of sulci connecting with the origin of the Sylvian fissure relative to fluent controls (Cykowski et al., 2008). As such, future studies should apply cortical thickness and cortical folding analyses to people who stutter to further characterize the specific contributing factors to the volume differences and the potential changes in these attributes over the course of development.

Conclusion

The widespread anatomic abnormalities that we identified throughout the neural network supporting speech production in children who stutter may result in the breakdown of transmission of sensory and motor information necessary for efficient and accurate speech motor learning and control. Our findings of reduced GMV in the bilateral inferior frontal gyri as well as the left putamen distinguish children who stutter from adults who stutter, who have been previously found to have more GMV in these regions (Beal et al., 2007; Lu et al., 2010; Song et al., 2007). It appears that the trajectory of cortical grey matter development in these key speech motor control regions, and the white matter pathways that underlie them, may be abnormal in people with persistent developmental stuttering and that this problem exists at as early as school age. Future investigations that utilize a large cohort of people who stutter, spanning in age from childhood to adulthood, are needed to clarify the developmental nature of these neuroanatomical abnormalities and the potential deficits in motor learning that may be associated with them and the disorder of persistent developmental stuttering itself.

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Figure 1. Sample axial slices ($z = 0$) of the custom paediatric templates used for spatial normalization in the current study. Shown above in (A) is the T1 template, (B) the segmented grey matter tissue prior and (C) the segmented white matter tissue prior.

Figure 2.

Statistical parametric maps of the regionalized grey and white matter volume differences (threshold at $p < .001$, uncorrected) found between children who do and do not stutter overlaid on axial slices of the custom paediatric T1 template. Images are displayed in neurological convention (left is left). The regions where the children who stutter demonstrated significantly less grey and white matter volume than controls are shown in red and green respectively. The regions where the children who stutter demonstrated significantly more grey matter volume than controls are shown in yellow. No regions of increased white matter volume were found in the children who stutter relative to the controls. The z-level of the axial slice on display from the custom paediatric template is reported beneath each image.

Table 1

Means and standard deviations of participant characteristics

	Control participants (n = 11) Mean (SD) Range	Children who stutter (n = 11) Mean (SD) Range
Age in months	119.18 (22.46) 74 – 144	114.18 (18.07) 92 – 148
Handedness	95.18 (9.01) 73 – 100	97.73 (5.06) 87 – 100
GFTA-II	104.36 (2.98) 97 – 109	102.45 (6.15) 87 – 108
PPVT-III	121.45 (11.94) 105 – 138	118.72 (17.26) 88 – 139
SSI-III	-	22.09 (8.40) 7 – 34

Table 2

Means and standard deviations of grey matter, white matter, cerebral spinal fluid (CSF) and total intra-cranial volume measurements.

	Control participants (n = 11) Mean (SD)	Children who stutter (n = 11) Mean (SD)
Grey matter volume	816.98 (47.21)	850.35 (68.79)
White matter volume	535.47 (37.45)	538.37 (41.76)
CSF volume	145.31 (19.63)	157.27 (34.23)
Total intra-cranial volume	1497.76 (75.41)	1546.00 (111.59)

Table 3

Regions of significantly different grey and white matter volume for children who stutter relative to controls from the whole-brain voxel-based morphometry analysis at $p < .001$ uncorrected.

Region	Laterality	MNI Coordinate			Z-score	Cluster size
		x	y	z		
Grey matter: Children who stutter < fluent controls						
Ventral pars triangularis extending to pars orbitalis	Left	-46	50	-6	4.28	167
Dorsal pars triangularis	Right	42	29	27	4.27	73
Ventral pars opercularis	Left	-42	26	3	3.83	89
Ventral pars opercularis	Right	46	21	4	3.63	395
Putamen	Left	-15	14	0	3.38	47
Grey Matter: Children who stutter > fluent controls						
Middle frontal gyrus	Right	30	47	33	4.13	55
Rolandic operculum	Right	51	0	9	4.04	68
Post central gyrus	Right	32	-45	62	3.62	67
Superior temporal gyrus	Right	62	0	0	3.55	58
Interior parietal lobule	Right	40	-48	57	3.34	55
White matter: Children who stutter < fluent controls						
Forceps minor	Left	-20	30	1	3.08	40
Forceps minor	Right	18	38	9	3.04	38