Voxel-based morphometry of auditory and speech-related cortex in stutterers

Deryk S. Beal[a], Vincent L. Gracco[c,d], Sophie J. Lafaille[a] and Luc F. De Nil[a,b]

[a]Department of Speech-Language Pathology, University of Toronto, [b]Toronto Western Research Institute, University Health Network, Toronto, Ontario, [c]School of Communication Sciences and Disorders, McGill University, Montreal, Quebec, Canada and [d]Haskins Laboratories, New Haven, Connecticut, USA

Correspondence to Deryk S. Beal, Department of Speech-Language Pathology, University of Toronto, 160 – 500 University Avenue, Toronto, ON M5G 1V7, Canada
E-mail: d.beal@utoronto.ca

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Stutterers demonstrate unique functional neural activation patterns during speech production, including reduced auditory activation, relative to nonstutterers. The extent to which these functional differences are accompanied by abnormal morphology of the brain in stutterers is unclear. This study examined the neuroanatomical differences in speech-related cortex between stutterers and nonstutterers using voxel-based morphometry. Results revealed significant differences in localized grey matter and white matter densities of left and right hemisphere regions involved in auditory processing and speech production. *NeuroReport* 18:1257–1260 © 2007 Lippincott Williams & Wilkins.

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Introduction

The aetiology of developmental stuttering is unknown but findings from previous neuroimaging studies have revealed differences in the neurophysiology of stutterers relative to nonstutterers. These studies have demonstrated that stutterers show (i) greater right hemisphere or bilateral activation in the sensorimotor and speech-related areas during a variety of speech perception and production tasks, (ii) reduced left hemisphere auditory activation during speech production, and (iii) a larger amount of activation in speech-related areas overall during speech production, including the cerebellum [1–6]. The exact interpretation of these observed differences remains in question but there is little doubt that stutterers activate brain regions in a functionally different manner from nonstutterers.

Structural brain differences may accompany the atypical functional activations in stutterers. Strub *et al.* [7] used computed tomography to study one pair of left-handed siblings who stuttered and reported atypical occipital asymmetry in both participants. They speculated that their findings suggested atypical asymmetry of the planum temporale, an area they argued was correlated with occipital lobe size. More recently, Foundas *et al.* [8,9] used volumetric magnetic resonance imaging (MRI) to compare the neuroanatomy of stutterers and nonstutterers and found atypical volume asymmetry in the planum temporale, prefrontal cortex and occipital lobe of stutterers. Sommer *et al.* [10], using diffusion tensor imaging, reported reduced fractional anisotropy in the white matter tracts in the left rolandic operculum adjacent to the face and mouth areas of the sensory motor cortex in stutterers.

Using voxel-based morphometry to assess cortical speech–language areas, Jancke *et al.* [11] analysed the brains of 10 nonstutterers and 10 stutterers. They found increased white matter volume in the right hemisphere of stutterers including the superior temporal gyrus, planum temporale, precentral gyrus and inferior frontal gyrus. It is somewhat surprising that, given the outcome of previous studies [8,9], no differences in grey matter were found between the two groups.

The reported neuroanatomical differences observed in stutterers may be related to behavioural distinctions outlined in the literature. Sasisekaran *et al.* [12] found that stutterers compared with nonstutterers were slower in phonological encoding, a task that is associated with Wernicke's area, including the planum temporale [13]. Stutterers also respond differently to altered auditory feedback during speech production compared with nonstutterers. Although delayed feedback often results in speech disruptions in nonstutterers, it has been shown to induce fluent speech in some stutterers [14]. Evidence linking structural and functional differences to the observable behaviour in stutterers comes from a volumetric MRI study that identified a subgroup of stutterers with an atypical rightward shift in planum temporale volume asymmetry and another with typical left asymmetry [14]. The atypical asymmetry subgroup presented with greater stuttering severity at baseline and responded more favourably to delayed auditory feedback compared with the typical asymmetry subgroup. Consequently, an increased understanding of differences in brain anatomy between stutterers and nonstutterers may help to explain interindividual behavioural differences.

Taken together, the results of previous behavioural and neuroimaging studies provide converging evidence for a deficit in central auditory and associated cortical areas in stutterers. The extent to which these functional differences are accompanied by abnormal morphology in auditory related areas of the brain in stutterers, however, is unclear. The main purpose of this study was to examine the neuroanatomical differences in auditory cortex between stutterers and nonstutterers. In addition, this study aimed to partially replicate and extend the findings of the only other voxel-based morphometry study of stutterers [11] by using an increased sample size and novel, state-of-the-art voxel-based morphometry techniques [15].

Methods

This research study was approved by the University Health Network Research Ethics Board and all participants provided written informed consent. Twenty-six male stutterers, mean age 30.29 years (SD=7.12) participated in the study. All were diagnosed with developmental stuttering as assessed by a speech-language pathologist. The Stuttering Severity Index scores ranged from 5 to 49 with eight participants classified as very mild, nine as mild, six as moderate, one as severe and two as very severe. Their data were compared with 28 male nonstutterers, mean age 30.53 years (SD=6.44), with no previous history of neurological, speech, language or hearing deficits. All participants were right-handed as defined by a minimum score of 8 on the Edinburgh Handedness Inventory [16] and had English as their primary language.

Imaging

A 1.5-T Echospeed MRI system (GE Medical Systems, Milwaukee, Wisconsin, USA) and a standard quadrature head coil were used to obtain all images. A T1-weighted three-dimensional inversion recovery-prepared fast spoiled gradient echo (FSPGR) sequence [flip angle=20°, echo time (TE)=5.2 ms, repetition time (TR)=12 ms, preparation time-300 ms] was used to generate 124 1.5-mm-thick sagittal slices (256 × 256 matrix). The field of view was 24 × 24 cm for 34 participants and 30 × 30 cm for 22 participants. Before morphometric processing, images with larger voxel size were resliced to match the smaller voxel size of the other images. The larger voxel sized images were evenly distributed between the two groups (12/28 nonstutterers, 10/26 stutterers).

Voxel-based morphometry

Voxel-based morphometric analysis of the data was performed with SPM5 (Wellcome Trust Centre for Neuroimaging, London, UK) using all default options. A detailed description of the steps involved in processing data for voxel-based morphometry is available in the SPM5 manual (http://www.fil.ion.ucl.ac.uk/spm/) [17]. In SPM5 spatial normalization, segmentation and modulation are processed simultaneously using a unified segmentation algorithm [15]. In contrast to optimized voxel-based morphometry, which was used in SPM2 and in which these steps were completed sequentially, this study used the unified segmentation algorithm in SPM5 to simultaneously calculate image registration, tissue classification and bias correction using our participants' structural MR images combined with the tissue probability maps provided in this version of SPM. Structural MR images were segmented into grey matter, white matter and cerebrospinal fluid tissue classifications. The segmented and modulated normalized images were smoothed with a 10 mm full-width-half-maximum filter.

Analysis

Group comparisons were conducted using a two sample *t*-test with an absolute threshold mask of 0.05 and total intercranial volume and original voxel sizes as covariates. Whole brain data were analysed using a height threshold of T=3.26 ($P<0.001$ uncorrected) and an extent threshold of 50 voxels [11]. An average template based on the segmented anatomical scans of the participants was used to superimpose and localize significant clusters. For the analysis of the auditory cortex, a small volume correction was applied for using the region of interest mask available in the SPM Anatomy Toolbox [18].

Results

Volume measures

No significant group differences were observed in total intercranial volume (P=0.95), total grey matter volume (P=0.56), total white matter volume (P=0.33) or total cerebral spinal fluid volume (P=0.42).

Grey matter analysis

No areas of increased grey matter density were found in the nonstutterers relative to the stutterers. In contrast, results revealed five significant clusters of increased grey matter density in stutterers versus nonstutterers. The results are superimposed onto the segmented anatomical template in Fig. 1a and b and summarized in Table 1. The largest cluster of increased grey matter density was found in the right superior temporal gyrus. More specifically, increased density was observed in the primary auditory cortex extending posteriorly into BA 22 and inferiorly into the middle temporal gyrus (BA 21) (small volume correction, P=0.005). Two clusters of increased grey matter density were also identified in the left superior temporal gyrus. One had its peak in the left primary auditory cortex extending back into BA 22 (small volume correction, P=0.011). The other cluster peaked anteriorly in the left temporal pole in BA 38. A significant cluster was also

Table 1 Increased density differences for stuttering participants relative to nonstuttering participants at $P<0.001$ uncorrected

Anatomical region	Laterality	x	y	z	Z score	Cluster size
Grey matter						
Superior temporal gyrus	R	56	−12	−4	4.42	271
Superior temporal gyrus	L	−28	10	−28	3.78	95
Inferior frontal gyrus	L	−48	10	18	3.75	83
Cerebellum	R	16	−42	−46	3.63	73
Superior temporal gyrus	L	−54	−12	6	3.61	72
White matter						
Insula	R	48	2	6	3.95	95
Inferior frontal gyrus	R	38	20	14	3.76	108
Middle temporal gyrus	L	−50	−22	−14	3.65	66

found in the left inferior frontal gyrus (BA 44) extending into the precentral gyrus and insula. Lastly, increased grey matter density was found at the level of the right cerebellar tonsil.

White matter analysis

No areas of increased white matter density were found in the nonstutterers versus the stutterers. In contrast, three significant clusters of increased white matter density were identified in the stutterers relative to the nonstutterers. The stutterers within BA 20.

Discussion

The primary aim of our study was to examine the presence of morphological differences in auditory cortex in stutterers while considering the possibility that other anatomical sites may also be implicated. The secondary aim of our study was to partially replicate and extend the findings of the only other voxel-based morphometry study of stutterers [11] by using an increased sample size and the most recent advances in voxel-based morphometry analysis employed in SPM5 [15]. The results differ from those of the previous voxel-based morphometry study of stutterers by Jancke *et al.* [11] in that the current study found significant differences in both grey matter and white matter densities of stutterers in various neuroanatomical regions. Overall, bilateral grey matter density differences were found in the superior temporal gyrus with a larger increase on the right compared with the left hemisphere. Inferior frontal lobe differences included BA 44 bilaterally with increased grey matter density on the left hemisphere and increased white matter density on the right hemisphere extending into the insula. Two additional temporal regions with increased grey matter density were found on the left hemisphere, on the middle temporal gyrus (BA 20) and on the rostral portion of the superior temporal gyrus (BA 38). Finally, a region of increased grey matter density was noted on the [illegible]

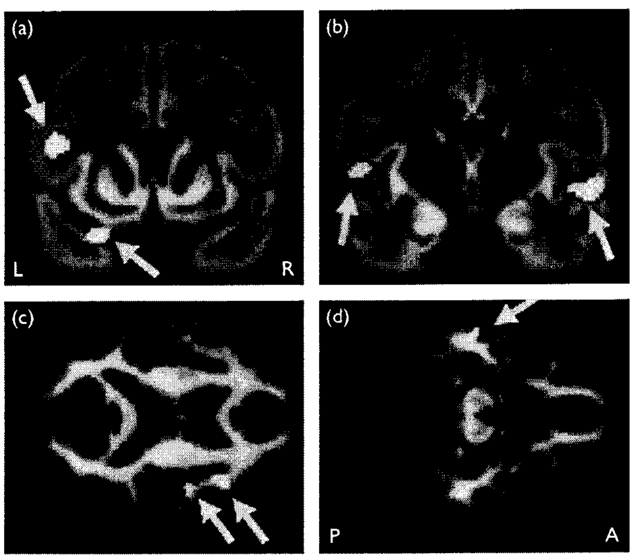

Fig. 1 Anatomical areas with greater density in stuttering relative to nonstuttering participants. All results are presented in neurological convention. (a) Coronal view of increased grey matter density in left inferior frontal gyrus and left temporal pole at coordinate $y=10$. (b) Coronal view of increased grey matter density in left and right superior temporal gyrus at coordinate $y=-12$. (c) Axial view of increased white matter density in two areas of the right insula at coordinate $z=14$. (d) Axial view of increased white matter density in left middle temporal gyrus at $z=-14$.

Superior/middle temporal gyrus

The largest increases in grey matter density in stutterers were found in the right superior temporal gyrus, in particular the primary auditory cortex (BA 41) extending posteriorly into BA 22 and inferiorly into BA 21. A cluster of increased grey matter density was also identified in the left superior temporal gyrus including BA 41 and BA 22. The primary auditory cortex is responsible for the initial processing of all sound, including speech [19]. The posterior part of BA 22 in the left hemisphere encompasses Wernicke's area, including the planum temporale, which has been implicated in accessing a word's phonological code [13]. Evidence, however, exists to suggest that the planum temporale is not specialized for phonetic analysis *per se* but rather involved in any acoustic analysis requiring segregation of quickly changing acoustic cues [20,21]. Previous studies have identified abnormal right greater than left asymmetry of the planum temporale, a part of Wernicke's area, in stutterers [8,14]. The structural differences identified in the planum temporale of stutterers in this study taken together with the potential role of the planum temporale in analysis of temporal acoustic cues and the behaviourial observations of some stutterers', increased fluency with temporally shifted auditory feedback point to the importance of this finding for differentiating stutterers from nonstutterers.

These results confirm Foundas *et al.*'s [8,9,14] earlier observations but differ from the findings of Jancke *et al.* [11]. These data show that the increased grey matter density extends beyond the planum temporale to include more anterior areas of the superior temporal gyrus. Our structural results, taken together with previous reports of functional activation differences in stutterers at the level of the auditory cortex during speech production, demonstrate that atypical processes in this cortical region critically differentiate between stutterers and nonstutterers. Differences were found not only in the right hemisphere but also included left BA 21, demonstrating that differences between stutterers and nonstutterers involve various regions of the brain bilaterally and are not limited to the right hemisphere [2]. These observed differences may point to an innate, possibly genetically determined, atypical development of brain regions important for speech development. Indeed, there is strong evidence of a genetic factor in developmental stuttering [22]. At present it cannot, however, be excluded that the structural differences, at least in part, are practice-induced and result from increased reliance on auditory feedback in stutterers during speech production. Indeed, it has been well established that increased skill practice often results in structural changes in cortex [23].

Inferior frontal gyrus/insula/cerebellum

In addition to the differences in the temporal cortices, increased grey matter density in areas related to speech motor control including the left inferior frontal gyrus extending posteriorly to the precentral sulcus and medially into the insula of stutterers was found. Interestingly, these areas are part of a group of areas previously identified in neuroimaging studies as overactive during speech production [1–6]. In addition, differences in grey matter were located at the level of the right cerebellar tonsil. The role of this cerebellar structure in speech production is not clear, but a number of reports have suggested that lesions of this site may result in deficiencies in speech perception and production [24] and deserves further exploration.

Increased density was also observed for the stuttering participants in the white matter underlying the insula and extending ventrally to the pars triangularis, pars opercularis, precentral gyrus and superior temporal gyrus. In addition, increased white matter density was found in the left middle temporal gyrus, consistent with the findings reported by Jancke and colleagues [11]. This increase in white matter volume in the right homologues of speech motor control areas is of interest considered together with Sommer *et al.*'s [10] finding of decreased white matter fiber tracts identified in the left rolandic operculum in stutterers. The findings of this study suggest an abnormal rightward asymmetry in white matter volume connecting areas crucial for motor speech movement. It is possible that the increased white matter underlying the right homologues of Broca's area is compensatory for the breakdown of white matter connections underlying this area in the left hemisphere which may lead to stuttering [25].

Conclusion

This study has demonstrated anomalous morphology in the superior temporal gyri of stutterers, extending beyond the planum temporale to include the primary auditory cortices, and other speech-related anatomical sites. These findings, taken together with similar findings in previous studies, now establish the presence of acquired and/or innate structural brain differences in grey and white matter between stuttering and nonstuttering individuals.

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