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A Larynx Area in the Human Motor Cortex

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The map of the human motor cortex has lacked a representation for the intrinsic musculature of the larynx ever since the electrical stimulation studies of Penfield. In addition, there has been no attempt to localize this area using neuroimaging techniques. Because of the central importance of laryngeal function to vocalization, we sought to localize an area controlling the intrinsic muscles of the larynx by using functional magnetic resonance imaging and to place this area in a somatotopic context. We had subjects perform a series of oral tasks designed to isolate elementary components of phonation and articulation, including vocalization of a vowel, lip movement, and tongue movement. In addition, and for the first time in a neuroimaging study, we had subjects perform "glottal stops," in other words forced closure of the glottis in the absence of vocalizing. The results demonstrated a larynx-specific area in the motor cortex that is activated comparably by vocal and nonvocal laryngeal tasks. Converging evidence suggests that this area is the principal vocal center of the human motor cortex. Finally, the location of this larynx area is strikingly different from that reported in the monkey. We discuss the implications of this observation for the evolution of vocal communication in humans.

Keywords: fMRI, larynx, motor, phonation, speech, vocalization

Introduction

The motor homunculus of the human brain—seen in virtually every textbook of psychology and neuroscience—is based in large part on neurosurgical studies of electrical stimulation of the awake human brain carried out by Penfield et al. in the 1930s and 1940s (Penfield and Rasmussen 1950; Penfield and Roberts 1959). Neuroimaging studies during the last 2 decades have provided a general validation for the organization of the primary motor cortex of the human precentral gyrus (PcG) into 3 broad domains dorsoventrally: a leg area, a hand area, and a face area, respectively. In Penfield and Rasmussen's work on the control of speech, they described a sequential dorsoventral organization for the lips, jaw, tongue, and pharynx, respectively. However, they claimed to be unable to reliably localize the motor area for vocalization (i.e., the generation of a "vowel cry"), showing this function to overlap areas for articulation in an idiosyncratic manner across subjects: "... although vocalization may occur as an isolated response to stimulation, and consequently might be expected to have a constant sequential position in relation to the lips and tongue, we are forced to conclude that its representation really overlaps that of lips, jaw, and tongue movement" (Penfield and Rasmussen 1950, p. 91). In addition, Penfield's studies of vocalization never really established the link to laryngeal function per se. Thus, the motor homunculus, since its creation, has lacked a specific region for the control of the vocal folds of the larynx.

Such a region would have to regulate intrinsic vocal-fold muscles operating along 2 major dimensions. One dimension involves the opening (abduction) and closing (adduction) of the glottal space, whereas the other involves tensing and relaxing of the vocal folds for the purpose of pitch modulation. Adduction of the vocal folds—as produced by the lateral cricoarytenoid muscle under the influence of branchiomotor laryngeal neurons originating in the nucleus ambiguus of the medulla—is a required step in vocal production; phonation through vocal-fold vibration cannot occur unless the vocal folds are in an adducted position. But adduction also occurs during a host of nonvocal processes in which glottal closure is necessary, such as during childbirth, defecation, coughing, throat clearing, and the lifting of heavy objects (Seikel et al. 2005). One clinical use of vocal-fold adduction occurs during the Valsalva maneuver, in which forced expiratory movement against a closed glottis is used to assess autonomic control of cardiovascular function (Felker et al. 2006).

In the current study, we used functional magnetic resonance imaging (fMRI) to examine laryngeal function both in the absence and presence of vocalization, with a focus on the intrinsic musculature of the larynx. For the nonvocal task, we had subjects perform simple vocal-fold adduction (so-called "glottal stops"). This, then, was compared with a vocal counterpart in which subjects vocalized at the same rate using a central vowel. A major goal of the study was to define a somatotopic location for the larynx area, especially given the uncertainties presented in the work of Penfield. Hence, we included the conditions of lip movement and tongue movement because these effectors have well-established locations in the human homunculus, with the lip area being generally dorsal to the tongue (Penfield and Rasmussen 1950; Hesselmann et al. 2004).

Materials and Methods

Subjects

Sixteen subjects (8 males, 8 females), with a mean age of 28.4 years (ranging from 21 to 49 years), participated in the study after giving their informed consent (Clinical Research Ethics Board, University of British Columbia). Each individual was without neurological or psychiatric illness. Subjects were all fluent English speakers but were unselected with regard to either native language or handedness. Three of the subjects were left-handed, and all of them were native speakers of languages other than English (viz., Italian, Polish, or Urdu). One native Japanese speaker was right-handed.

Tasks

Subjects performed 6 oral tasks (1 task per fMRI scan), each one according to a simple blocked design of 16 s of a resting condition and

16 s of an oral task. The task order was randomized across scans. All tasks were performed with the eyes open. For the purposes of this article, 4 tasks of interest are described. 1) "Phonation" (vocalization) using the schwa vowel. Subjects were instructed to sing the first 5 notes of the major scale (in a register of their choice) using the schwa vowel, with the teeth together but with a very small lip opening to permit oral air flow and avoid humming. Hence, articulatory changes should have been minimal within the task blocks, as well as between the task and rest blocks; in fact, this is the most purely phonatory task of any vocalization task described in the literature. After each 5-note cycle, subjects were to take a gentle, controlled inspiration through the mouth. The recommended rate of vocalization was 1 Hz. 2) "Glottal stops". Subjects were instructed to perform glottal stops (i.e., forced adduction of the vocal folds) with the teeth together and the lips slightly cracked and to do so as breath phrases of 4–6 glottal stops followed by a gentle, controlled oral inspiration. The recommended rate of vocal-fold adduction was 1 Hz. Subjects were trained to the point that they could produce glottal stops comfortably in the absence of any voicing. 3) "Lip protrusion." Subjects were instructed to pucker their lips and then return them to a resting position and to do so at a rate of roughly 1 Hz. They were encouraged to make a small gesture and to avoid contracting other facial muscles. 4) "Vertical tongue movement" within the mouth. Subjects were instructed to move the tip of their tongue from the floor of the mouth to the hard palate with the lips together but with the teeth just slightly separated so as to create adequate space for tongue movement. The recommended rate was 1 Hz. Subjects underwent a 30-min training session on a day prior to the scanning session in order to learn how to perform the tasks in a highly controlled manner with a minimum of head or body movement. On the day of the scan, all the tasks were practiced again prior to entry into the scanner. We did not record behavioral performance in the scanner. During the debriefing after the scan, no subject reported having problems performing any of the tasks.

Magnetic Resonance Imaging

Magnetic resonance images were acquired with a Philips Achieva 3-Tesla Magnetic Resonance Imaging (MRI) at the MRI Research Centre of the University of British Columbia in Vancouver. The subject's head was firmly secured using a custom head holder and "memory" pillow. Earplugs were used to help block out scanner noise. Subjects performed each task as 16-s epochs of an oral task alternating with 16-s epochs of rest. During each task epoch, the name of the task ("Lips," "Glottal Stops," etc.) positioned above a crosshair was projected from an LCD projector onto a screen mounted at the head of the MRI table, with an angled mirror on the head coil reflecting text from the screen into the participant's field of view. During the rest periods, the word "Rest," positioned above a crosshair, was projected onto the screen. Subjects were to keep their eyes on the crosshair at all times. All stimuli were created and presented using Presentation software (Neurobehavioral Systems, Albany, CA).

Functional images sensitive to the "blood oxygen level–dependent" (BOLD) signal were collected with a gradient echo sequence (repetition time = 2000 ms, echo time = 30 ms, flip angle 90 degrees, 36 slices, 3 mm slice thickness, 1 mm gap, matrix = 80 × 80, field of view = 240 mm, voxel size 3 mm isotropic), effectively covering the whole brain (145 mm of axial extent). A total of 192 brain volumes were acquired over 6 min and 24 s of scan time, corresponding with 12 alternations between 16-s epochs of rest and 16-s epochs of task.

Image Analysis

Functional images were reconstructed offline, and the scan series were realigned and motion corrected using the methods in SPM2 (Wellcome Department of Cognitive Neurology, University College London, UK), as implemented in Matlab (Mathworks, Natick, MA). Although subject motion was a concern for this study, analysis of the realignment parameters indicated that translation and rotation corrections did not exceed an acceptable level of 1.5 mm and 1.5 degrees, respectively, for any of the participants. Following realignment, a mean functional image was computed for each run. The mean image was normalized to the Montreal Neurological Institute (MNI) template (Friston, Ashburner, et al. 1995; Friston, Holmes, et al. 1995), and this transformation was then applied to the corresponding functional series. The normalized functional images (4 mm isotropic voxels) were smoothed with an 8-mm (full-width-at-half-maximum) isotropic Gaussian filter. The BOLD response for each task block was modeled as the convolution of a 16-s boxcar with a synthetic hemodynamic response function composed of 2 gamma functions. Beta weights associated with the modeled hemodynamic responses were computed to fit the observed BOLD-signal time course in each voxel for each subject using the General Linear Model, as implemented in SPM2. Each subject's data were processed using a fixed-effects analysis, corrected for multiple comparisons using family-wise error, with a threshold of $P < 0.05$ ($t > 4.99$) and no extent threshold. Contrast images for each task-versus-rest analysis for each subject were brought forward into a random-effects analysis, where a significance level of $P < 0.025$ was employed ("false-discovery rate" correction for multiple comparisons for the whole brain; Genovese et al. 2002) and no extent threshold. The critical t value varied across contrasts: $t > 3.96$ for glottal stops and phonation, $t > 4.36$ for tongue movement, and $t > 4.47$ for lip movement). MNI coordinates were converted into the coordinates of Talairach and Tournoux (1988) using a nonlinear transformation, as implemented in the WFU PickAtlas (Maldjian et al. 2003) and based on the method of Brett (http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach), except for the case of the cerebellum, where MNI coordinates are retained. This was because of errors incurred by coordinate conversion.

The peak locations were determined using SPM's Volume command. Several of the larger clusters had multiple significant voxels, anywhere between 2 and 10. Voxels that were directly adjacent to the peak voxel and were in the same functional domain (same gyrus and Brodmann area) were generally not reported separately, whereas those that were in distinct functional areas (either different gyri or Brodmann areas or both) were reported as additional coordinates.

Results

Two principal findings are reported here. First, the peak activations in the motor cortex for glottal stops and those for phonation were virtually identical in each of the 16 subjects, thus arguing that there is a common motor region underlying adduction/abduction and tensing/relaxing of the vocal folds, the major functions of the intrinsic musculature of the larynx. We refer to this general region as the larynx/phonation area (LPA) of the motor cortex. There were 2 sets of activation peaks bilaterally (see Fig. 1 and Table 1): a ventromedial peak located deep in the central sulcus that corresponds with Brodmann area 4p and a dorsolateral peak located in area 6 which is more superficial. These 2 LPA peaks outline a kind of wedge, extending from a sulcal position ventrally to a gyral position dorsally and anteriorly. These data replicate a similar 2-peak organization for the M1 activations reported by Wilson et al. (2004) for monosyllable production but extend it to a nonvocal laryngeal task. Supplementary Figure 1 shows data for the glottal stops task for 2 single subjects registered onto their own anatomical MRI's, demonstrating that the ventromedial peak is deep in the central sulcus and that the dorsolateral peak is more anterior and gyral. Subject 11 shows a clear distinction between the 2 peaks (see the slice at $y = -8$), whereas subject 10 does not.

Table 1 and Figure 2 show the overwhelming similarity in the activation patterns for glottal stops and phonation even outside the motor cortex, the principal exception being temporal-lobe auditory areas, which were active during phonation but not glottal stops (although individual subjects did show activation here, as can be seen in Supplementary Fig. 1). These included regions of the right superior temporal sulcus that have been implicated in voice perception (Belin et al. 2000, 2002). The one superior temporal region that did show activity in the group analysis during glottal stops was the area known as "cortex of

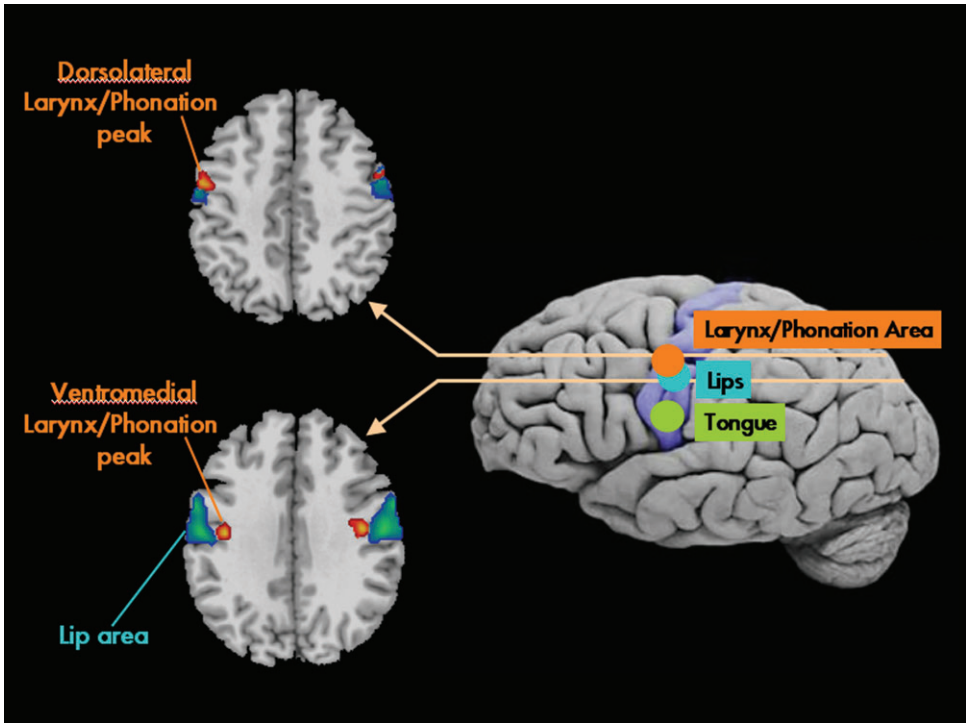

Figure 1. The right side shows a human brain with the approximate locations of the somatotopic representations for the lips and tongue situated along the violet-shaded PcG (brain image courtesy of S. Mark Williams). Listed in addition is the LPA identified in the current study. The left panel contains 2 axial sections (MNI template brain) showing brain activations for phonation (orange color) and lip protrusion (blue color). The 2 horizontal lines on the brain on the right side show the approximate slice levels. The top slice (MNI *z* coordinate of 46) shows the location of the dorsolateral larynx/phonation peak, and the bottom slice (MNI *z* coordinate of 34) shows the ventromedial peak. See Table 1 for the Talairach coordinates. These images (*t* maps) are thresholded to $P < 0.025$, corrected for multiple comparisons using the false-discovery rate ($t > 3.96$).

the dorsal Sylvian fissure at the parietal-temporal junction" (Spt), at the temporoparietal junction. This area has been implicated in audiomotor integration for vocal production, as shown by its activation during vocal imagery (Hickok et al. 2003) as well as musical discrimination tasks (Brown and Martinez 2007). Our results show for the first time that this area can be activated in the absence of vocalization, vocal imagery, or strong auditory stimulation. As shown in Table 1 and Figure 2, Spt activity was significantly stronger during vocalization than during vocal-fold adduction alone. It is unclear if this effect was due to auditory stimulation, increased laryngeal activity (e.g., recruitment of the cricothyroid muscle), or some sensorimotor interaction between the two.

The second principal finding is that the human LPA, instead of being located ventral to the tongue area—as is suggested in several sources (Jürgens et al. 1982; Fong et al. 2004; Duffy 2005; Ludlow 2005; Guenther et al. 2006)—is instead located in a dorsal position directly adjacent to the lip area in all 16 subjects (see Fig. 1). The M1 activations for lip movement gave 2 bilateral regions of activation (Table 2): a unique anterior peak in area 6 at –57, 4, 35 and 61, 6, 33 and a posterior peak in area 4 at –51, –12, 34 and 57, –10, 32 which was quite proximate to one of the foci for tongue movement at –63, –10, 28 and 57, –12, 32 (see Hesselmann et al. 2004, for a discussion of lip/tongue overlap in this general region). Looking at a comparison to the larynx data, the ventromedial LPA peak was situated medial to the common lip/tongue peak, whereas the dorsolateral LPA peak was dorsal to the unique anterior lip area (see Fig. 1). Hence, the human larynx area appears to have a novel localization next to the articulators, being much further away from the pharynx area than might be expected based on somatotopic considerations alone.

Looking to the presumed human homologue of the monkey larynx area—the so-called Rolandic operculum, at the confluence of Brodmann areas 6, 4, and 43—we saw a minor left-hemisphere activation for the glottal stops task at –57, –11, 14 (see Table 1 and Fig. 2). However, we did not see any activity here for phonation. By contrast, we saw large, highly significant bilateral activations in this region for tongue movement at –63, –10, 16 and 66, –8, 21, with much weaker, though bilateral, activity for lip movement at –60, –13, 19 and 57, –15, 19. Hence, the Rolandic operculum contains, at least in part, the ventral portion of the somatotopic tongue and lip representations and therefore functions more related to articulation than phonation. In addition, there is neuroimaging evidence for activity in this general region during pharynx-based swallowing tasks (Suzuki et al. 2003; Martin et al. 2004; Harris et al. 2005), as predicted by the Penfield homunculus. Hence, one can hypothesize that the Rolandic operculum has a stronger association with the "extrinsic" laryngeal musculature than the intrinsic muscles (Vilkman et al. 1996), muscles that also serve more general roles in tongue and pharyngeal functioning. In the Rhesus monkey, this part of the frontoparietal operculum is reciprocally connected with the larynx area, which itself is located more rostrally in the ventral premotor cortex (Simonyan and Jürgens 2002, 2005). Further work is needed to clarify the role of this area in vocal production. However, in terms of the principal goal of this study, it is quite clear that it is the LPA, not the Rolandic operculum, that is the major motor region for voluntary control of the intrinsic musculature of the larynx. Activity here was

Table 1
Glottal stops and phonation contrasted with rest

Region	*x*	*y*	*z*	*t*	*x*	*y*	*z*	*t*
	Glottal stops				Phonation			
Frontal								
Right								
PcG (ventromedial LPA) (4)	44	−10	34	5.28	44	−8	34	5.83
Supplementary motor area (6)					8	7	55	5.50
Frontal operculum (44)	59	8	11	5.95	61	8	9	5.46
PcG (dorsolateral LPA) (6)	53	4	42	5.91	50	−2	37	4.77
Left								
Supplementary motor area (6)	−4	5	57	8.06	−4	7	57	6.61
PcG (ventromedial LPA) (4)	−38	−14	32	5.28	−40	−10	30	5.78
PcG (dorsolateral LPA) (6)	−53	0	42	6.05	−51	0	44	5.55
Frontal operculum (44)	−55	7	18	6.49	−59	6	11	5.32
Rolandic operculum (43)	−57	−11	13	5.48				
Temporal								
Right								
Superior temporal sulcus					51	−10	2	7.31
Middle temporal gyrus (21)					50	−29	1	6.63
Superior temporal sulcus					55	−10	0	6.23
STS/Anterior STG					53	−2	−5	5.05
Left								
Posterior STG/Area Spt (22)	−46	−34	15	5.87	−42	−38	17	11.09
Posterior STG (22)					−50	−19	3	10.30
Posterior STG (22)					−55	−32	13	8.01
Auditory Assoc. Cortex (42)					−63	−24	16	6.18
STS/Anterior STG					−55	−4	−5	4.13
Cerebellum (MNI coordinates)								
Right								
Lobule VIIIA					24	−66	−50	9.16
Lobule VI	24	−62	−22	5.67	26	−62	−26	7.39
Lobule VI	36	−56	−32	4.45	34	−60	−28	7.29
Vermis, lobule VI					12	−70	−18	4.71
Left								
Lobule VI	−24	−62	−30	7.91	−26	−60	−28	5.16
Vermis, lobule VI					−8	−68	−16	6.93
Lobule VI/Crus I	−40	−58	−34	5.49	−36	−66	−26	6.73
Lobule VIIIA	−22	−74	−50	5.29	−22	−72	−50	6.46
Lobule VIIIA					−34	−54	−50	5.14
Subcortical								
Subthalamic nucleus					22	−12	−3	4.31
Subthalamic nucleus					−18	−6	−5	3.98

Note: Stereotaxic coordinates and peak *t*-score values for activations in the glottal stop and phonation tasks as contrasted with rest. MNI coordinates generated using SPM2 were converted to Talairach coordinates using the WFU Pickatlas, except for the case of the cerebellum, in which case MNI coordinates have been retained due to location errors that occur with conversion. Brain atlas coordinates in Tables 1 and 2 are in millimeters along the left–right (*x*), anterior–posterior (*y*), and superior–inferior (*z*) axes. In parentheses after each brain region is the Brodmann area, except for the cerebellum, in which case the anatomical labels of Schmahmann et al. (2000) are used. STG, superior temporal gyrus; STS, superior temporal sulcus.

unequivocally present in all the subjects during both vocal-fold adduction alone and vocalization. The Rolandic operculum instead seems to represent tongue and pharyngeal muscles that double as extrinsic muscles of the larynx, which aid in pitch control through elevation and depression of the larynx as a whole (Vilkman et al. 1996).

Discussion

By comparing nonvocal and vocal laryngeal tasks side by side, we have demonstrated for the first time the colocalization of these 2 types of activities in a larynx-specific region of the human motor cortex. We discuss here the function and somatotopic localization of this area in the context of vocal communication in humans.

The Principal Vocal Area

In this study, we have identified a putative larynx area of the human motor cortex and shown it to be the region of peak activity for vocalization as well. The common activation of this region for nonvocal and vocal laryngeal tasks suggests that the neural representation for adduction/abduction of the vocal folds is close to or the same as that for tensing/relaxing of the vocal folds. Although we observed 2 peaks of activation for the laryngeal tasks, our experiment did not permit us to ascribe functional differences to the two. Rödel et al. (2004), using transcranial magnetic stimulation (TMS), were able to selectively stimulate the principal tenser or relaxer muscles of the vocal folds, a finding consistent with work in the monkey (Hast et al. 1974; see below). Although some overlap in representation was found for the 2 muscles, the tenser (cricothyroid) showed a more medial scalp localization than the relaxer (thyroarytenoid). Further work will be needed to determine if the 2 areas of activation found in our study have different functional roles, perhaps in representing different muscles of the larynx. The TMS results of Rödel et al. suggest that this should indeed be the case, as does the fact that the cricothyroid muscle is innervated by a different branch of the vagus nerve than the other intrinsic laryngeal muscles.

Two voxel-based meta-analyses of neuroimaging studies of overt speech production have been published. Both of them showed peak activations for the motor cortex in the region of the LPA. Turkeltaub et al. (2002) published a meta-analysis of 11 studies of oral reading, and found the M1 activations to be at –48, –10, 34 and 44, –8, 32 (our conversion to Talairach), close to our ventromedial peak. Likewise, Brown et al. (2005) performed 2 parallel meta-analyses of 8 studies of oral reading in stutterers and fluent controls, respectively. The peak M1 activations for the control subjects were at –49, –9, 32 and 54, –10, 34, and those for the stutterers were at –45, –16, 31 and 48, –12, 32. The peaks from all these meta-analyses match our ventromedial LPA peak quite well. Interestingly, this region of the motor cortex was shown to be overactive bilaterally in stutterers compared with fluent controls, hence qualifying as a candidate region at which a functional anomaly may be present in stutterers. Fox et al. (2001) performed an analysis of the "mouth" region of the motor cortex that combined meta-analysis of 5 published studies of speech production along with a within-laboratory compilation of data from 3 previously performed studies. The consensus coordinates for the combination of all these data were at –46, –11, 35 and 48, –9, 35, again quite close to our ventromedial peak. Finally, a meta-analysis of 11 studies of overt singing (Brown S, Laird AR, Pfordresher PQ, Turketaub P, Liotti M., in preparation) found peak M1 activations in a similar location to these speech coordinates, though slightly dorsal at –50, –10, 40 and 54, –4, 38. This is closer to our dorsolateral region, but posterior to it.

It should be pointed out that although the standard Penfield homunculus reprinted in books shows vocalization "smeared out" across the orofacial region of the homunculus, there are indications that Penfield thought of vocalization as having a more discrete localization, such as in the image seen on p. 200 of Penfield and Roberts (1959). In this image, vocalization is situated in the exact location that we have identified as the LPA, adjacent to the lip representation. Penfield and Rasmussen reported observing involuntary lip movements in half of the instances in which they elicited vocalization (p. 89). In addition, the region of the LPA is the location where Penfield and Roberts reported producing speech arrest in their patients (p. 123). Hence, whereas Penfield's work is only rarely cited in neuroimaging studies of speech and song (e.g., Guenther et al. 2006), the current fMRI study is in many ways nothing more than

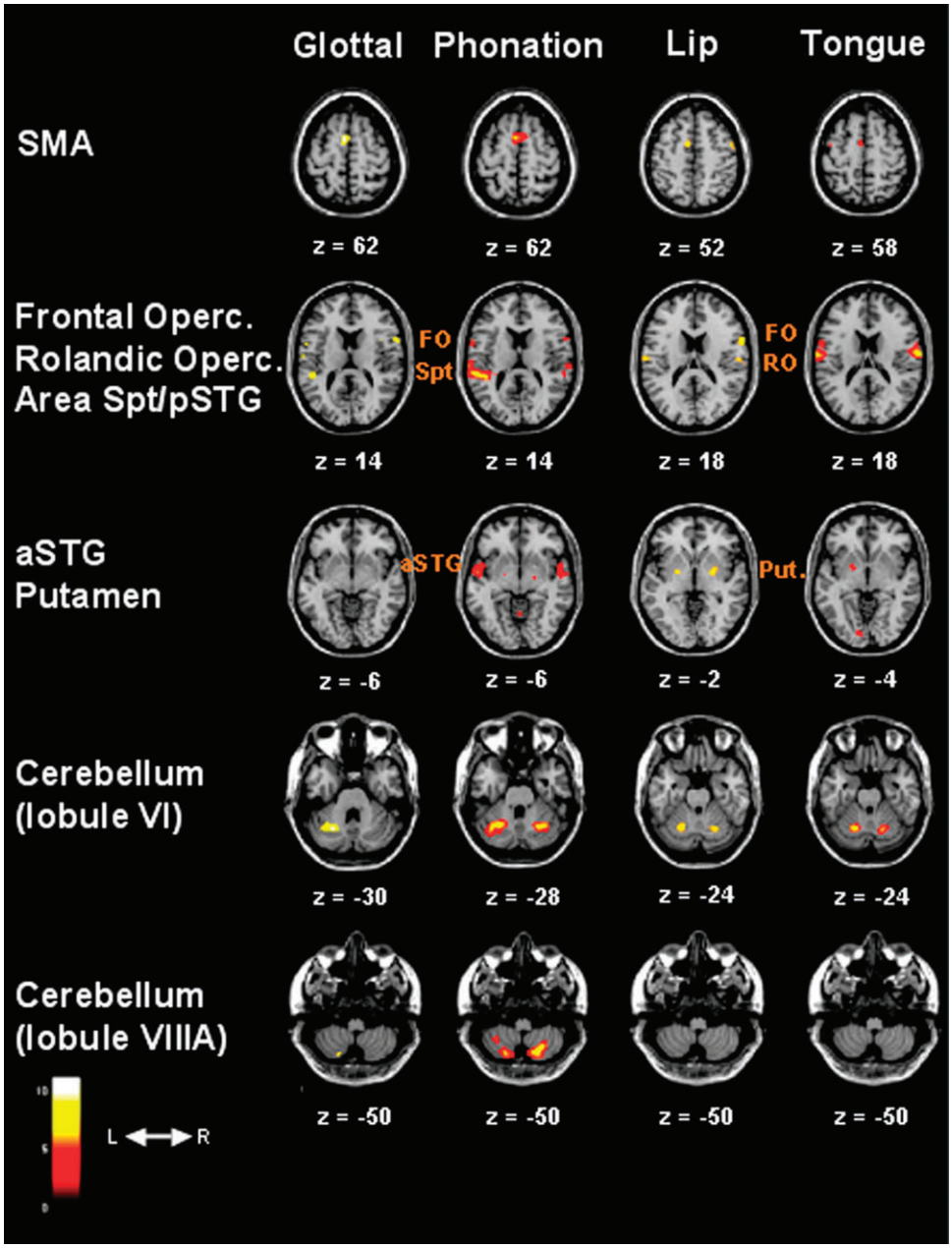

Figure 2. Group activations for the 4 oral tasks outside the motor cortex registered onto the MNI template brain; MNI *z* coordinates are given below each slice. These images are thresholded to $P < 0.025$, corrected for multiple comparisons using the false discovery rate ($t > 3.96$ for glottal stops and phonation, $t > 4.47$ for lip movement, and $t > 4.36$ for tongue movement). Notable is the activity in the SMA for all 4 tasks; the frontal operculum for all 4 tasks; the Rolandic operculum mainly in the tongue task but also more weakly for the lip and glottal tasks; area Spt in both the glottal and phonation tasks; the anterior STG (temporal pole; planum polare) in the phonation task only; the basal ganglia mainly with tongue and lip movement; cerebellar lobule VI in all 4 tasks; and cerebellar lobule VIII principally in the phonation task. SMA, supplementary motor area; Frontal operc. and FO, frontal operculum; Rolandic operc. and RO, Rolandic operculum; Spt, cortex of the dorsal Sylvian fissure at the parietal-temporal junction; aSTG, anterior part of the superior temporal gyrus; Put., putamen.

a validation of what Penfield et al. observed during brain stimulation.

In sum, neuroimaging data on overt vocalization, both spoken and sung, as well as Penfield's findings on both speech elicitation and speech arrest, suggest that the area that we have identified as the LPA is the major region for vocal control in the human motor cortex. Our data provide the first evidence that this region of the motor cortex is a larynx area and not some poorly specified "mouth" or "face" area. Such a finding should have strong implications for speech motor disorders, including Parkinsonian dysphonia (Liotti et al. 2003), spastic dysarthria (Kent 2000), spasmodic dysphonia (Grillone and Chan 2006), anterior opercular syndrome (Bakar et al. 1998, also known as Foix–Chavany–Marie syndrome), and aprosodia (Ross 1981) among others (Duffy 2005). As mentioned above, the LPA region has been shown to be overactive in stutterers compared with fluent control subjects performing the same vocalization tasks (Brown et al. 2005).

Perception as well as Production

Having characterized the role of the LPA in overt vocalization, we would like to examine its potential role in perception as

Table 2
Lip and tongue movement contrasted with rest

Region	*x*	*y*	*z*	*t*	*x*	*y*	*z*	*t*
	Lips				Tongue			
Frontal								
Right								
Rolandic operculum (43)	57	−15	19	5.12	65	−7	21	13.30
PcG: common peak (4)	57	−10	32	8.54	57	−12	32	6.63
Frontal operculum (44)	63	10	12	8.22	61	10	11	5.70
PcG: lip, anterior peak (6)	61	6	33	7.72				
Left								
PcG: common peak (4)	−51	−12	34	8.18	−63	−10	28	9.07
PcG: lip, anterior peak (6)	−57	4	35	8.11				
PcG: tongue peak (6)					−53	3	24	8.71
Rolandic operculum (43)	−60	−13	19	5.59	−63	−9	15	8.49
Supplementary motor area (6)	−6	2	48	6.12	−4	−1	53	5.15
Frontal operculum (44)	−44	4	7	5.58				
Basal ganglia								
Right								
Putamen	22	−4	−5	6.43				
Putamen	24	2	7	4.99				
Left								
Putamen	−22	−4	6	5.92	−22	0	6	6.15
Putamen	−20	−4	−1	5.25	−20	2	−3	6.18
Cerebellum (MNI coordinates)								
Right								
Lobule VI	24	−60	−24	5.48	18	−66	−24	7.42
Left								
Lobule VI	−22	−60	−24	5.48	−20	−64	−24	10.38

Note: Stereotaxic coordinates and peak *t*-score values for activations in the lip movement and tongue movement tasks as contrasted with rest. As with Table 1, all MNI coordinates except for those in the cerebellum have been converted to Talairach coordinates. PcG, precentral gyrus.

well. We will examine a convergence of auditory findings dealing with the overlap of passive perception, mental imagery, and perceptual discrimination in the larynx motor cortex.

Studies showing activation of the motor cortex during passive perception of acoustic stimuli are few in number. Wilson et al. (2004) demonstrated activation of the motor cortex during passive perception of meaningless monosyllables. The motor cortex coordinates reported for speech perception were at –50, –4, 43 and 54, –1, 41 (our conversion to Talairach), nearly identical to one of the 2 peaks shown for overt syllable production in the same study. As mentioned above, these 2 peaks match our LPA coordinates quite well. Next, Pulvermüller et al. (2006) showed that passive perception of monosyllables beginning with either the labial consonant /p/ or the alveolar consonant /t/ stimulated the corresponding part of the PcG activated by lip or tongue movement, respectively. In a similar vein, Hauk et al. (2004) showed that the motor cortex could be activated in a somatotopic fashion when subjects passively read words that signified actions mediated by effectors controlled by those regions. Hence, words related to the mouth (e.g., lick) led to activity near the region activated during oral movement. Finally, studies using TMS have shown that listening to speech, as compared with listening to nonspeech sounds, increases motor-evoked potentials in the lip muscles (Watkins et al. 2003; Watkins and Paus 2004) and tongue muscles (Fadiga et al. 2002) produced by magnetic stimulation of the motor cortex. Similar perceptual enhancements of motor excitability have been obtained for the hand area of the motor cortex (reviewed in Fadiga et al. 2005). Altogether, these observations support the emerging "cognitive" view of the motor cortex (Georgopoulos 2000).

Next, at least 2 studies of musical (phonatory) imagery have shown activation in or near the LPA. Halpern and Zatorre (1999) found activity in this region during tasks in which subjects heard the first part of a familiar tune and had to mentally image a continuation. The foci for this were at –48, –6, 41 and 51, –1, 47, the left-hemisphere focus being close to our dorsolateral site. A similar region, but in the left hemisphere only, was active when subjects listened to short melodies and had to imagine repetitions of those same melodies in their head. Next, Callan et al. (2006) examined the covert singing of familiar melodies (vs. rest) and found activity near the LPA at 53, –4, 37 (our conversion to Talairach; the coordinate for this analysis was obtained from the authors and is not reported in their paper).

Finally, studies of musical discrimination, which in principle have no explicit subvocalization component (as does imagery), have shown that when subjects perform same/different discriminations of pairs of melodies, the LPA is again activated at –43, –5, 40 and 43, 4, 38, (Gaab et al. 2003, our conversion to Talairach) and at –48, –8, 38 and 50, 0, 34 (Brown and Martinez 2007). For the latter study, the coordinates for discrimination matched very closely those for overt vocalization in the same subjects at –48, –8, 40 and 54, –6, 40 (Brown et al. 2004). Hence, the common activation of the LPA during passive perception, perceptual discrimination, vocal imagery, and vocal production suggests that this area mediates audition in addition to vocalization and hence audiomotor integration. Although further work will be needed to assess the validity of this hypothesis, similar arguments have been made regarding other somatotopic regions of the motor cortex (Fadiga et al. 2005; Pulvermüller 2005). It is worth pointing out that published work dealing with auditory mirror neurons (Kohler et al. 2002; Rizzolatti and Craighero 2004) has focused on the connection between audition and manually generated sounds. In our opinion, the most evolutionarily significant sensorimotor link for the human auditory system is without question the vocal system (Brown et al. 2004) and not the manual system. This is especially so given the unique capacity of humans among primates for vocal imitation and vocal learning (Brown 2007).

One observation that emerges from this analysis is that covert tasks that do not have a direct vocal-motor component to them (such as perception, imagery, and discrimination) show a tendency for more dorsolateral activation peaks in the motor cortex, which might suggest that the dorsolateral LPA peak is more of a "premotor" area compared with a "primary motor" function of the ventromedial peak. However, about a third of the single subjects showed activations exclusively in the dorsolateral region during both glottal stops and phonation. Therefore, the premotor/motor distinction for the 2 LPA peaks cannot be the whole story.

Respiration

Perhaps the biggest potential confound in this study relates to our inability to control for the contribution of expiration to the activations in the laryngeal tasks (which were matched between themselves for expiration). In this regard, it is interesting to note that the single imaging study that has analyzed expiration (as compared with inspiration) found 2 distinct foci of activation in the motor cortex (Ramsay et al. 1993). One was in the trunk region, in the same location to where inspiration was reported in that study. The second focus was, surprisingly, in the face area. Its coordinates were quite proximate to the LPA peaks reported in this study, namely –44, –4, 40 and 46, –2, 36. These results raise the possibility that there is an expiratory area very close to the larynx area, which might support

respiratory/phonatory coordination during vocalization. Vocal-respiratory coupling is known to occur in the parabrachial nucleus of the pons in most mammals (e.g., Smotherman et al. 2006). It is not unreasonable, therefore, to think that such a process could occur at the cortical level in humans. The fact that Penfield was able to elicit vocalization in his patients by stimulation of the "face" area of the PcG (i.e., independent of the trunk area) suggests that stimulation of this region must have been sufficient to generate the expiratory drive and subglottic pressure necessary for vocalization to occur.

So although our study cannot adequately rule out the contribution of expiration to our activations (nor can any of the published studies of overt speech or singing for that matter), it is possible that there are both larynx and expiratory representations in this same region of the motor cortex. In support of this, Petrides et al. (2005), in characterizing the homologue of Broca's area (area 44) in the Rhesus monkey, found that electrical stimulation of this region not only led to movement of oral effectors such as the lips and jaw but also elicited expiratory movements. One can speculate that the potential convergence of expiration, phonation, and articulation in regions such as the motor cortex and Broca's area would facilitate the coordination of effectors during vocal production, perhaps supporting coarticulation in humans.

Evolutionary Implications

A critical question is how our human data compare with what is known about the larynx representation in nonhuman primates. Just as with humans, knowledge about the cortical control of laryngeal function in nonhuman primates is quite sparse. Cortical representations for the intrinsic and extrinsic musculature of the larynx have been examined in only 2 monkey species and, to date, there is no evidence that such areas play any role at all in vocalization. Not only does stimulation of the cortical larynx area fail to elicit vocalization (Jürgens 1974) but also lesions encompassing not only this area (Kirzinger and Jürgens 1982) but also the entire orofacial region of the motor cortex (Jürgens et al. 1982) have no major effect on spontaneous calling in squirrel monkeys. Likewise, lesioning of the cortical larynx area in Rhesus monkeys has no effect on conditioned calling (Sutton et al. 1974). Hence, it has been suggested that the larynx area serves principally nonvocal laryngeal functions in monkeys (Simonyan and Jürgens 2005). In addition, important connectivity differences exist between humans and nonhuman primates such that humans are thought to have a direct connection between the cortical larynx area and the nucleus ambiguus (Kuypers 1958), compared with an indirect connection in monkeys, where the primary projection is to the reticular formation (Jürgens 1976). This direct connectivity in humans is reflected in the very short latencies seen for stimulation of the laryngeal muscles (on the order of 10 ms) by TMS (Rödel et al. 2004).

The location of the larynx-controlling regions in both the Rhesus monkey and the squirrel monkey is quite different from that which we are reporting here for the human area. In both monkey species, the larynx area is located anterior to the PcG, in the opercular part of the premotor cortex, corresponding to the rostral part of area 6; this is considered to be a nontypical primary motor location even for the monkey (Simonyan and Jürgens 2002, 2005). Hast et al. (1974) found distinct representations for the cricothyroid and thyroarytenoid muscles here, as well as regions of combined responses to both muscles. The cricothyroid responses were mainly in the region of the arcuate sulcus, with the thyroarytenoid responses being posterior to that. These types of studies have served as the basis for the assumption that the human larynx area is located in the most ventral part of the motor strip, perhaps near the Rolandic operculum (Jürgens et al. 1982; Fong et al. 2004; Duffy 2005; Ludlow 2005; Guenther et al. 2006). Our work has not led to a support of this assumption. Although we found activations in the vicinity of the Rolandic operculum in the current study, they seemed to be more strongly associated with tongue movement than the laryngeal tasks analyzed here. In addition, imaging studies of pharyngeal function during voluntary swallowing reliably show activity in this part of the homunculus, as predicted from the Penfield map. Hence, the Rolandic operculum might in fact represent the extrinsic, rather than intrinsic, muscles of the larynx. In support of this, Hast et al. (1974) localized the extrinsic muscles of the Rhesus monkey as being posterior to the intrinsic muscles, in the ventral part of the PcG, essentially the same location where they are found in humans.

The possibility exists, therefore, that the dorsal-posterior representation of the intrinsic muscles of the larynx—in the vicinity of the lip area of the PcG—is an evolutionary novelty and especially one related to the emergence of important human-specific features of communication, including 1) voluntary control of vocalization, 2) vocal learning based on vocal imitation, 3) coarticulation, and 4) the rapid oscillatory cycling between voiced and unvoiced sounds that is so characteristic of speech. Furthermore, and as mentioned above, the potential existence of an expiratory area in this same region of the motor cortex might be an additional novel feature supporting the coordination of respiration and phonation during human vocalization. This putative conjunction of respiration, phonation, and articulation in humans would be consistent with proposals of "small world architectures," in which brain areas that are functionally linked tend to have short path lengths (Sporns and Zwi 2004). Clearly, much work is needed to identify cortical larynx representations in nonhuman primate species in order to know whether the human area has undergone some kind of evolutionary migration to its current precentral location, along with associated connectivity changes to its branchiomotor targets. The existence of the rostral location of the larynx area in both an Old World monkey (Rheusus monkey) and a New World monkey (squirrel monkey)—despite 35 million years of evolutionary separation—might suggest that this is indeed the ancestral state for primates and that the human location is derived and novel. If so, this would be an important addition to the list of unique, evolved features of the human brain (Preuss 2004). In this scenario, the representation for the extrinsic muscles has retained its ventral, precentral position, whereas that for the intrinsic muscles has migrated dorsally toward the lips.

Conclusions

We have searched for a representation of the intrinsic muscles of the larynx in the human motor cortex by comparing nonvocal and vocal laryngeal tasks, as well as articulatory tasks to provide a somatotopic context. We identified a part of the motor cortex adjacent to the lip area as being important for both nonvocal and vocal laryngeal tasks. An analysis of the neuroimaging literature strongly suggests that this is the principal region of

the motor cortex controlling vocalization, both spoken and sung. It also appears to be a point of convergence between perception and production for audiovocal processing. Finally, the location of this area, compared with that of the larynx-controlling region of the 2 monkey species in which it has been investigated, suggests that the human location is evolutionarily novel, perhaps related to the emergence of voluntary control of vocalization as well as vocal learning in humans.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

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Notes

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References

Bakar M, Kirschner HS, Niaz F. 1998. The opercular-subopercular syndrome: four cases with review of the literature. Behav Neurol. 11:97–103.

Belin P, Zatorre RJ, Ahad P. 2002. Human temporal-lobe response to vocal sounds. Cogn Brain Res. 13:17–26.

Belin P, Zatorre RJ, Lafaille P, Ahad P, Pike B. 2000. Voice-selective areas in human auditory cortex. Nature. 403:309–312.

Brown S. 2007. Contagious heterophony: a new theory about the origins of music. Musicae Scientiae. 11:3–26.

Brown S, Ingham RJ, Ingham JC, Laird AR, Fox PT. 2005. Stuttered and fluent speech production: an ALE meta-analysis of functional neuroimaging studies. Hum Brain Mapp. 25:105–117.

Brown S, Martinez MJ. 2007. Activation of premotor vocal areas during musical discrimination. Brain Cogn. 63:59–69.

Brown S, Martinez MJ, Hodges DA, Fox PT, Parsons LM. 2004. The song system of the human brain. Cogn Brain Res. 20:363–375.

Callan DE, Tsytsarev V, Hanakawa T, Callan AM, Katsuharab M, Fukuyama H, Turner R. 2006. Song and speech: brain regions involved with perception and covert production. Neuroimage. 31:1327–1342.

Duffy JR. 2005. Motor speech disorders: substrates, differential diagnosis, and management. 2nd ed. St. Louis (MO): Elsevier.

Fadiga L, Criaghero L, Buccino G, Rizzolatti G. 2002. Speech listening modulates the excitability of tongue muscles: a TMS study. Eur J Neurosci. 15:399–402.

Fadiga L, Criaghero L, Olivier E. 2005. Human motor cortex excitability during the perception of others' action. Curr Opin Neurobiol. 15:213–218.

Felker GM, Cuculich PS, Gheorghiade M. 2006. The Valsalva maneuver: a bedside "biomarker" for heart failure. Am J Med. 119:117–122.

Fong J, Sandhu G, Ellaway P, Davey N, Strutton P, Murphy K, Guz A. 2004. What do we know about human cough? Pulm Pharmacol Ther. 17:431–434.

Fox PT, Huang A, Parsons LM, Xiong J-H, Zamarippa F, Rainey L, Lancaster JL. 2001. Location-probability profiles for the mouth region of the human primary motor-sensory cortex: model and validation. Neuroimage. 13:196–209.

Friston KJ, Ashburner J, Frith CD, Poline J-B, Heather JD, Frackowiak RSJ. 1995. Spatial registration and normalization of images. Hum Brain Mapp. 3:165–189.

Friston KJ, Holmes AP, Worsley KJ, Poline J-B, Frith CD, Frackowiak RSJ. 1995. Statistical parametric maps in functional imaging: a general linear approach. Hum Brain Mapp. 2:189–210.

Gaab N, Gaser C, Zaehle T, Jancke L, Schlaug G. 2003. Functional anatomy of pitch memory: an fMRI study with sparse temporal sampling. Neuroimage. 19:1417–1426.

Genovese CR, Lazar NA, Nichols T. 2002. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. Neuroimage. 15:870–878.

Georgopoulos AP. 2000. Neural aspects of cognitive motor control. Curr Opin Neurobiol. 10:238–241.

Grillone GA, Chan T. 2006. Laryngeal dystonia. Otolaryngol Clin North Am. 39:87–100.

Guenther FH, Ghosh SS, Tourville JA. 2006. Neural modeling and imaging of the cortical interactions underlying production. Brain Lang. 96:280–301.

Halpern AR, Zatorre RJ. 1999. When that tune runs through your head: a PET investigation of auditory imagery for familiar melodies. Cereb Cortex. 9:697–704.

Harris ML, Julyan P, Kulkarni B, Gow D, Hobson A, Hastings D, Zweit J, Hamdy S. 2005. Mapping metabolic brain activation during human volitional swallowing: a positron emission tomography study using [18F]fluorodeoxyglucose. J Cereb Blood Flow Metab. 25:520–526.

Hast MH, Fischer JM, Wetzel AB, Thompson VE. 1974. Cortical motor representation of the laryngeal muscles in Macaca mulatta. Brain Res. 73:229–240.

Hauk O, Johnsrude I, Pulvermüller F. 2004. Somatopic representation of action words in human motor and premotor cortex. Neuron. 41:301–307.

Hesselmann V, Sorger B, Lasek K, Guntina-Luchius O, Krug B, Sturm V, Goebel R, Lackner K. 2004. Discriminating the cortical representation sites of tongue and lip movement by functional MRI. Brain Topogr. 16:159–167.

Hickok G, Buchsbaum B, Humphries C, Muftuler T. 2003. Auditory-motor interaction revealed by fMRI: speech, music, and working memory in area Spt. J Cogn Neurosci. 15:673–682.

Jürgens U. 1974. On the elicitability of vocalization from the cortical larynx area. Brain Res. 81:564–566.

Jürgens U. 1976. Projections from the cortical larynx area in the squirrel monkey. Exp Brain Res. 25:401–411.

Jürgens U, Kirzinger A, von Cramon D. 1982. The effects of deep-reaching lesions in the cortical face area on phonation: a combined case report and experimental monkey study. Cortex. 18:125–139.

Kent RD. 2000. Research on speech motor control and its disorders: a review and prospective. J Commun Disord. 33:391–428.

Kirzinger A, Jürgens U. 1982. Cortical lesion effects and vocalization in the squirrel monkey. Brain Res. 233:299–315.

Kohler E, Keysers C, Umilta MA, Fogassi L, Gallese V, Rizzolatti G. 2002. Hearing sounds, understanding actions: action representation in mirror neurons. Science. 297:846–848.

Kuypers HGJM. 1958. Corticobulbar connections to the pons and lower brainstem in man: an anatomical study. Brain. 81:364–388.

Liotti M, Ramig LO, Vogel D, New P, Cook CI, Ingham RJ, Ingham JC, Fox PT. 2003. Hypophonia in Parkinson's disease: neural correlates of voice treatment revealed by PET. Neurology. 11:432–440.

Ludlow CL. 2005. Central nervous system control of the laryngeal muscles in humans. Respir Physiol Neurobiol. 147:205–222.

Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH. 2003. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. Neuroimage. 19:1233–1239.

Martin RE, MacIntosh BJ, Smith RC, Barr AM, Stevens TK, Gati JS, Menon RS. 2004. Cerebral areas processing swallowing and tongue movement are overlapping but distinct: a functional magnetic resonance imaging study. J Neurophysiol. 92:2428–2443.

Penfield W, Rasmussen T. 1950. The cerebral cortex of man: a clinical study of localization of function. New York: The Macmillan Company.

Penfield W, Roberts L. 1959. Speech and brain mechanisms. Princeton (NJ): Princeton University Press.

Petrides M, Cadoret G, Mackey S. 2005. Orofacial somatomotor responses in the macaque monkey homologue of Broca's area. Nature. 435:1235–1238.
Preuss TM. 2004. What is it like to be human? In: Gazzaniga MS, editor. The cognitive neurosciences III. Cambridge (MA): MIT Press. p. 5–22.
Pulvermüller F. 2005. Brain mechanisms linking language and action. Nat Rev Neurosci. 6:576–582.
Pulvermüller F, Huss M, Kherif F, Martin FMP, Hauk O, Shtyrov Y. 2006. Motor cortex maps articulatory features of speech sounds. Proc Natl Acad Sci USA. 103:7865–7870.
Ramsay SC, Adams L, Murphy K, Corfield DR, Grootoonk S, Bailey DL, Frackowiak RS, Guz A. 1993. Regional cerebral blood flow during volitional expiration in man: a comparison with volitional inspiration. J Physiol. 461:85–101.
Rizzolatti G, Craighero L. 2004. The mirror-neuron system. Annu Rev Neurosci. 27:169–192.
Rödel RMW, Olthoff A, Tergau F, Simonyan K, Kraemer D, Markus H, Kruse E. 2004. Human cortical motor representation of the larynx as assessed by transcranial magnetic stimulation TMS. Laryngoscope. 114:918–922.
Ross ED. 1981. The aprosodias: functional-anatomic organization of the affective components of language in the right hemisphere. Arch Neurol. 38:561–569.
Schmahmann JD, Doyon J, Toga AW, Petrides M, Evans AC. 2000. MRI atlas of the human cerebellum. San Diego (CA): Academic Press.
Seikel JA, King DW, Drumright DG. 2005. Anatomy and physiology for speech, language, and hearing. 3rd ed. Clifton Park (CA): Thomson.
Simonyan K, Jürgens U. 2002. Cortico-cortical projections of the motorcortical larynx area in the rhesus monkey. Brain Res. 949:23–31.
Simonyan K, Jürgens U. 2005. Afferent cortical connections of the motor cortical larynx area in the rhesus monkey. Neuroscience. 130:133–149.
Smotherman M, Kobayasi K, Ma J, Zhang S, Metzner W. 2006. A mechanism for vocal-respiratory coupling in the mammalian parabrachial nucleus. J Neurosci. 26:4860–4869.
Sporns O, Zwi JD. 2004. The small world of the cerebral cortex. Neuroinformatics. 2:145–162.
Sutton D, Larson C, Lindeman RC. 1974. Neocortical and limbic lesion effects on primate phonation. Brain Res. 71:61–75.
Suzuki M, Asada Y, Ito J, Hayashi K, Inoue H, Kitano H. 2003. Activation of cerebellum and basal ganglia on volitional swallowing detected by functional magnetic resonance imaging. Dysphagia. 18:71–77.
Talairach J, Tournoux P. 1988. Co-planar stereotaxic atlas of the human brain. New York: Thieme Medical Publishers.
Turkeltaub PE, Eden GF, Jones KM, Zeffiro TA. 2002. Meta-analysis of the functional neuroanatomy of single-word reading: method and validation. Neuroimage. 16:765–780.
Vilkman E, Sonninen A, Hurme P, Körkkö P. 1996. External laryngeal frame function in voice production revisited: a review. J Voice. 10:78–92.
Watkins K, Paus T. 2004. Modulation of motor excitability during speech perception: the role of Broca's area. J Cogn Neurosci. 16: 978–987.
Watkins KE, Strafella AP, Paus T. 2003. Seeing and hearing speech excites the motor system involved in speech. Neuropsychologia. 48:989–994.
Wilson SM, Saygin AP, Sereno MI, Iacobini M. 2004. Listening to speech activates motor areas involved in speech production. Nat Neurosci. 7: 701–702.