Cerebral Cortical Representation of Automatic and Volitional Swallowing in Humans

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Martin, Ruth E., Bradley G. Goodyear, Joseph S. Gati, and Ravi S. Menon. Cerebral cortical representation of automatic and volitional swallowing in humans. *J Neurophysiol* 85: 938–950, 2001. Although the cerebral cortex has been implicated in the control of swallowing, the functional organization of the human cortical swallowing representation has not been fully documented. Therefore, the present study determined the cortical representation of swallowing in fourteen healthy right-handed female subjects using single-event-related functional magnetic resonance imaging (fMRI). Subjects were scanned during three swallowing activation tasks: a naïve saliva swallow, a voluntary saliva swallow, and a water bolus swallow. Swallow-related laryngeal movement was recorded simultaneously from the output of a bellows positioned over the thyroid cartilage. Statistical maps were generated by computing the difference between the magnitude of the voxel time course during *1*) a single swallowing trial and *2*) the corresponding control period. Automatic and volitional swallowing produced activation within several common cortical regions, the most prominent and consistent being located within the lateral precentral gyrus, lateral postcentral gyrus, and right insula. Activation foci within the superior temporal gyrus, middle and inferior frontal gyri, and frontal operculum also were identified for all swallowing tasks. In contrast, activation of the caudal anterior cingulate cortex was significantly more likely in association with the voluntary saliva swallow and water bolus swallow than the naïve swallow. These findings support the view that, in addition to known brain stem areas, human swallowing is represented within a number of spatially and functionally distinct cortical loci which may participate differentially in the regulation of swallowing. Activation of the insula was significantly lateralized to the right hemisphere for the voluntary saliva swallow, suggesting a functional hemispheric dominance of the insula for the processing of swallowing.

INTRODUCTION

Although the act of swallowing is thought to be mediated principally by brain stem mechanisms (for reviews, see Carpenter 1989; Jean 1990), converging evidence from electrophysiological and clinical studies indicates that the cerebral cortex also plays a fundamental role in swallowing regulation (for reviews, see Martin and Sessle 1993; Miller 1998). Studies employing cortical stimulation (Huang et al. 1989a; Martin et al. 1999; Miller and Bowman 1977; Sessle et al. 1995), cortical ablation or reversible inactivation (Larson et al. 1980; Narita et al. 1999; Sessle et al. 1995; Sumi 1972), and cortical neuronal recordings (Lund and Lamarre 1974; Luschei et al. 1971; Martin et al. 1997b) have begun to delineate the *detailed* functional organization of the cortical swallowing representation in animal models, particularly the nonhuman primate. In humans, reports of swallowing deficits following hemispheric stroke (Daniels and Foundas 1997; Meadows 1973; Robbins and Levine 1988), and cortical mapping studies employing electrical (Penfield and Rasmussen 1950) and transcranial magnetic stimulation (TMS) (Hamdy et al. 1996, 1997) have suggested that swallowing is represented within multiple cortical foci including the lateral pericentral and premotor cortices (Hamdy et al. 1996, 1997; Martin et al. 1997b, 1999; Narita et al. 1999), frontal operculum (Martin et al. 1999), and insula (Daniels and Foundas 1997). Given *1*) the possibility of differences between the human and nonhuman primate brain in terms of the cortical representation of swallowing, *2*) the interpretational limitations of surface cortical stimulation studies related to current spread and the inability to stimulate the sulcal depths and subcortical structures, and *3*) the inherent limitations of human lesion studies due to differences in lesion site, size, and acuteness across patients, in vivo studies of the intact human brain are pivotal to advancing our understanding of the neural control of swallowing. Recent advances in functional brain imaging offer the opportunity to examine the cortical representation of swallowing in healthy humans. A small number of studies have applied functional brain imaging to voluntary swallowing (Hamdy et al. 1999a,b; Mosier et al. 1999; Zald and Pardo 1999). However, automatic swallowing of saliva has not been investigated, even though this type of swallow accounts for a substantial proportion of the swallows produced by humans. Furthermore, while previous studies have identified several common regions of swallow-related activation, discrepancies between functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) were noted, underscoring the need for further studies.

The primary aim of the present study was to define the cerebral cortical representation of human swallowing using fMRI. Because human swallowing typically is executed with-

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TABLE 1. *Number of trials for each swallowing task per subject*

Subject	Naïve	Voluntary	Water
S1	5	8	9
S2	9	6	7
S3	5	12	12
S4	2	8	12
S5	4	10	na
S6	5	8	18
S7	5	9	8
S8	8	9	17
S9	5	12	7
S10	2	4	8
S11	0	9	7
S12	5	12	7
S13	0	6	5
S14	1	8	6

out conscious control, but can be produced voluntarily under certain conditions, for example, following a verbal instruction, and because these two types of swallows may have distinct cortical representations, the second aim of the study was to compare the patterns of cortical activation associated with "automatic" and "volitional" swallowing. Our third aim was to test the hypothesis that there is a functional lateralization for

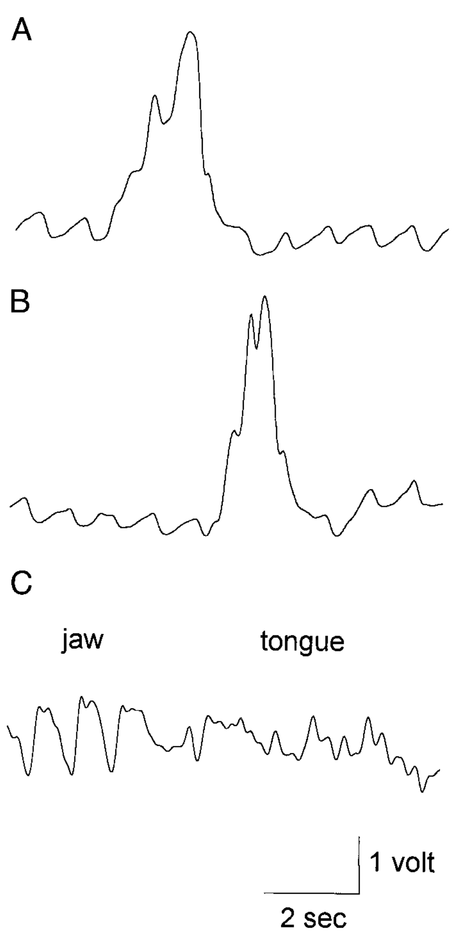

FIG. 1. Time course of the output of a respiratory bellows positioned around the neck over the thyroid cartilage showing laryngeal movements associated with a saliva swallow (*A*), a water bolus swallow (*B*), and jaw wagging and random tongue movements (*C*) for one subject. The low-amplitude, high-frequency oscillation corresponds to the carotid pulse.

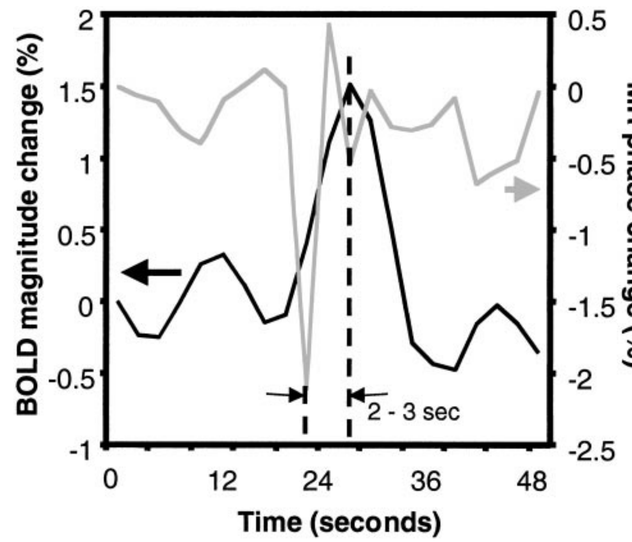

FIG. 2. Time courses of the blood-oxygenation-level–dependent (BOLD; black) and phase mode (gray) magnetic resonance (MR) signals during a single naïve saliva swallow for one subject. The BOLD signal time course was generated by defining a region of interest (ROI) that included all significantly activated voxels. The phase mode time course was generated using the same ROI.

swallowing within the human cerebral cortex (Hamdy et al. 1996, 1997).

Some of these data have been briefly reported (Martin et al. 1997a, 1998).

METHODS

Subjects

Fourteen healthy female volunteers (age, 28 ± 6.2 yr; mean ± SD) who were right-handed, as measured by the Edinburgh Handedness Inventory (Oldfield 1971), served as subjects. None of the subjects had previous fMRI experience. All subjects gave written informed consent before participating in this study. The study protocol was approved by the University of Western Ontario Review Board for Health Sciences Research involving human subjects. The study adhered to the radio frequency power deposition guidelines established for clinical scanners by the Food and Drug Administration.

Tasks

Subjects performed a total of three swallowing tasks. Each task was performed during a separate imaging run (i.e., lasting 5 min for 1

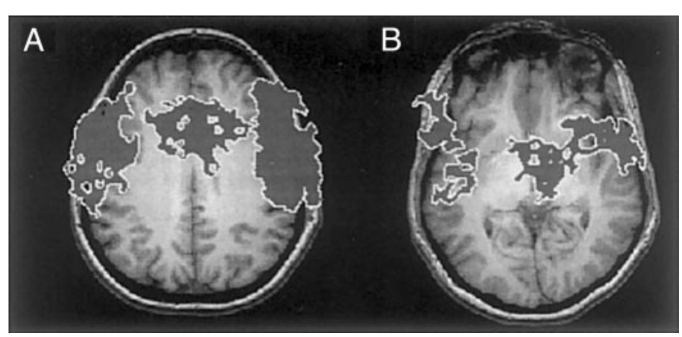

FIG. 3. Phase mode MR axial maps corresponding to the naïve saliva swallow for one subject. Swallow-related phase changes are apparent along the lateral surfaces of the hemispheres and the midline within slices encompassing the lateral pericentral cortex (*A*), and the insula (*B*).

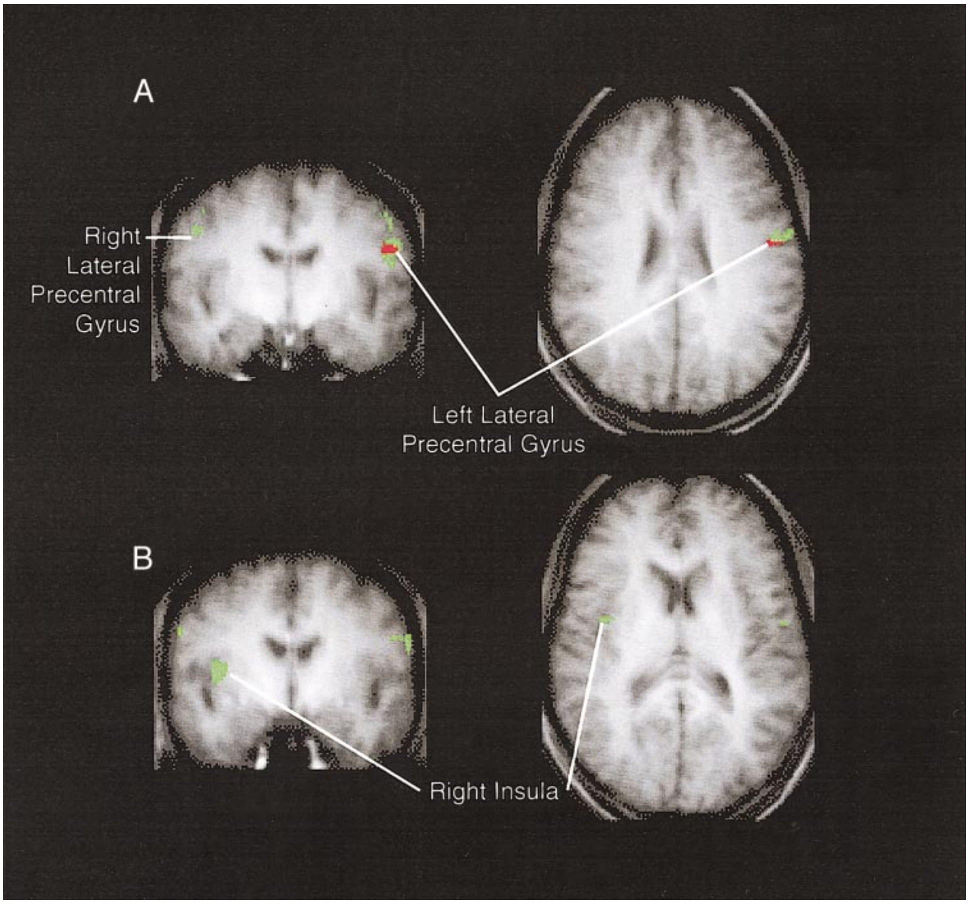

FIG. 4. Activation for a normalized brain volume using the Talairach-Tournoux coordinate system in the coronal (*left*) and axial (*right*) planes for all subjects during the naïve saliva swallow. Significantly activated voxels (red: voxel $P < 0.006$; green: voxel $P < 0.02$) within the lateral pericentral/premotor cortex (*A*) and the insula (*B*) are shown.

subject, 6 min for 2 subjects, and 8 min for the remaining 11 subjects) within the same experimental session. The imaging runs were increased from 5 to 8 min in attempts to obtain greater numbers of swallow trials. The number of swallow trials for each task and subject are given in Table 1.

NAIVE SALIVA SWALLOW. Subjects were informed that anatomic images were being collected and were instructed to relax and remain still without altering their vegetative functions such as breathing and swallowing. During this task, subjects were unaware that the experiment in which they were participating was aimed specifically at swallowing. This was confirmed during interviews conducted with the subjects immediately after the experimental session.

VOLUNTARY SALIVA SWALLOW. Subjects were instructed to swallow their accumulated saliva approximately once per minute in a self-paced fashion. They were directed not to produce exaggerated oral movements in attempts to increase or otherwise manipulate the accumulation of saliva, but rather to allow their saliva to accumulate passively prior to swallowing.

TABLE 2. *Stereotaxic coordinates of activation foci obtained during naïve saliva swallow*

Region	Brodmann's Area	*x*	*y*	*z*	*P* Value
Left lateral precentral gyrus	4, 6	−49	11	34	<0.006
	4, 6	−49	7	23	<0.006
Left lateral postcentral gyrus	43	−50	7	16	<0.006
Right lateral precentral gyrus	4, 6	46	8	34	<0.02
Right insula		37	3	12	<0.02
Right insula		37	3	6	<0.02

WATER BOLUS SWALLOW. Subjects were instructed to swallow a 3-ml bolus of room-temperature water that was delivered to the oral cavity through a length of 3-mm-diam flexible tubing attached to a 30-ml syringe controlled manually by the experimenter. The tubing was held between the subject's lips at midline and was stabilized at the level of the subject's chest by the subject's right hand. Rate of bolus delivery was once per minute. Subjects were instructed to swallow each volume of water as a single bolus.

IDENTIFICATION OF SWALLOWING. Single swallows were identified on the basis of a characteristic profile of laryngeal elevation (Logemann et al. 1992). An oscilloscope display screen was used to record laryngeal movements that were obtained from the output signal of a pressure transducer driven from expanding magnetic resonance (MR)-compatible bellows (Siemens, Erlangen, Germany) positioned comfortably over the subject's thyroid cartilage (see Fig. 1). The time at which the swallow-related laryngeal elevation began was recorded for all individual swallows throughout all fMRI scans. To ensure that they were naïve with respect to the aim of the naïve saliva swallow task, subjects were informed that the purpose of the bellows was to monitor their pulse.

MRI experiments

All imaging experiments were performed on a Varian/Siemens UNITY *INOVA* 4 Tesla (T) whole-body imaging system (Varian, Palo Alto, CA; Siemens, Erlangen, Germany) equipped with 25 mT/m actively shielded whole-body gradients. A whole-head quadrature birdcage radio frequency (RF) coil was used to transmit and receive the MR signal. The subject's head was immobilized with foam padding that was fit snugly between the head and a Plexiglas head holder within the head coil.

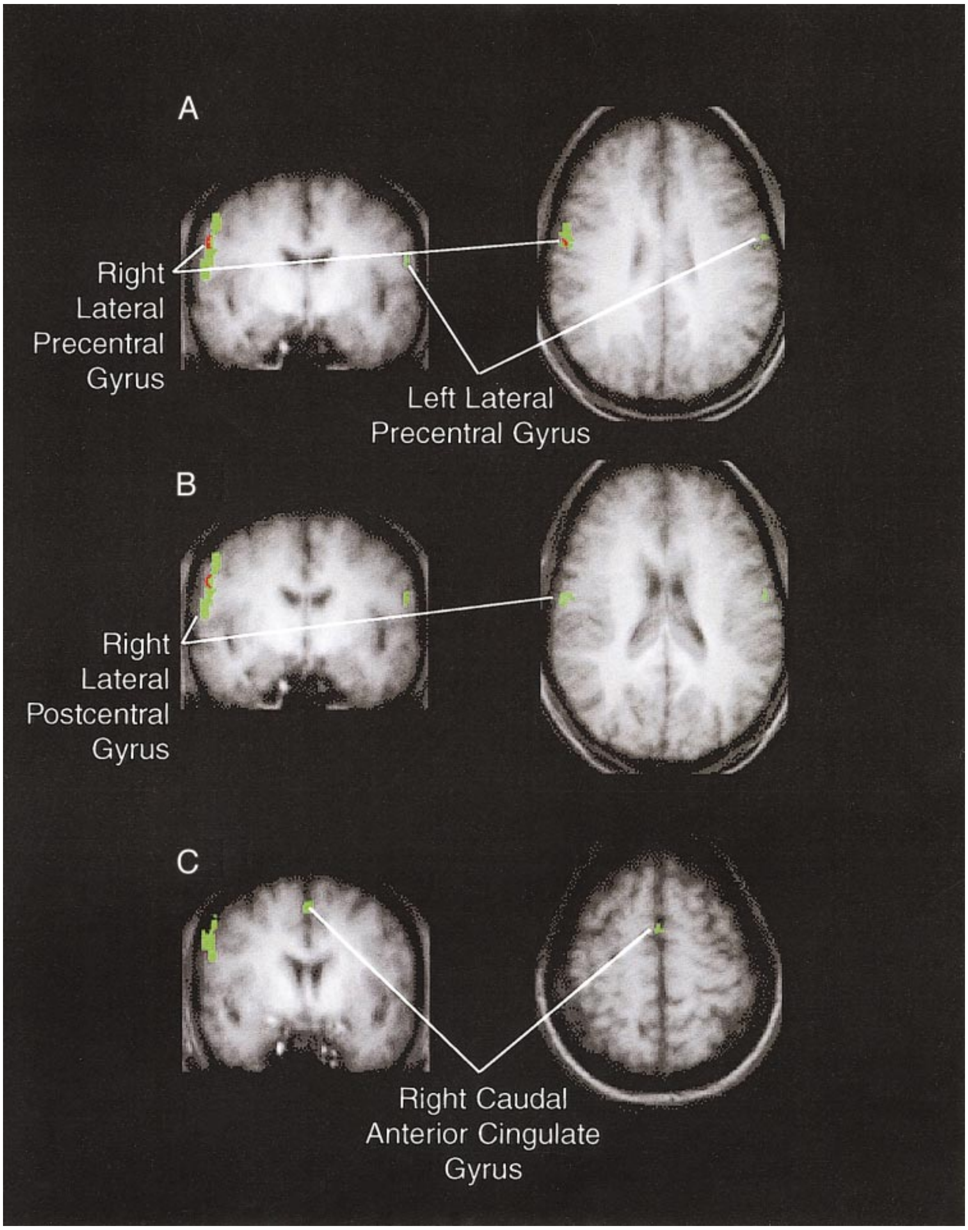

FIG. 5. Activation for a normalized brain volume using the Talairach-Tournoux coordinate system in the coronal (*left*) and axial (*right*) planes for all subjects during the voluntary saliva swallow. Significantly activated voxels (red: voxel $P < 0.006$; green: voxel $P < 0.02$) within the lateral precentral gyrus (*A* and *B*), the lateral postcentral gyrus (*B*), and the anterior cingulate cortex (*C*) are shown.

Imaging planes for the functional scans were prescribed with the aid of a high resolution [256 × 256, 22 cm field of view (FOV)] sagittal anatomic image with gray/white matter contrast (i.e., T1-weighted) acquired using a magnetization-prepared fast low-angle shot (FLASH) imaging sequence [inversion time (TI) = 500 ms, echo time (TE) = 6 ms, repetition time (TR) = 12 ms, flip angle =11°, 8-mm slice thickness]. The prescribed image planes consisted of nine equally spaced, contiguous slices (8 mm thick, no gap) oriented in a plane approximately parallel to the anterior commisure (AC)-posterior commisure (PC) plane and extending from the superior extent of the paracentral lobule to the inferior extent of the insula. During each

TABLE 3. *Stereotaxic coordinates of activation foci obtained during voluntary saliva swallow*

Region	Brodmann's Area	*x*	*y*	*z*	*P* Value
Right lateral precentral gyrus	4, 6	50	0	33	<0.006
	4, 6	53	6	24	<0.006
Left lateral precentral gyrus	4, 6	−55	9	27	<0.02
Right lateral postcentral gyrus	43	55	6	16	<0.02
Left lateral postcentral gyrus	43	−54	7	17	<0.02
Right caudal anterior cingulate	24/32	1	−2	47	<0.02

TABLE 4. *Stereotaxic coordinates of activation foci obtained during water swallow*

Region	Brodmann's Area	*x*	*y*	*z*	*P* Value
Left lateral precentral gyrus	4, 6	−48	7	25	<0.006
Left lateral postcentral gyrus	43	−54	9	18	<0.006
Right lateral precentral gyrus	4, 6	53	2	21	<0.006
Right depth of central sulcus	43/4	53	6	15	<0.006
Right postcentral gyrus	3/1/2	55	19	24	<0.02
	43	58	7	15	<0.02
Right insula		39	4	11	<0.02
		40	4	6	<0.02
Right caudal anterior cingulate	24/32	4	−7	44	<0.02

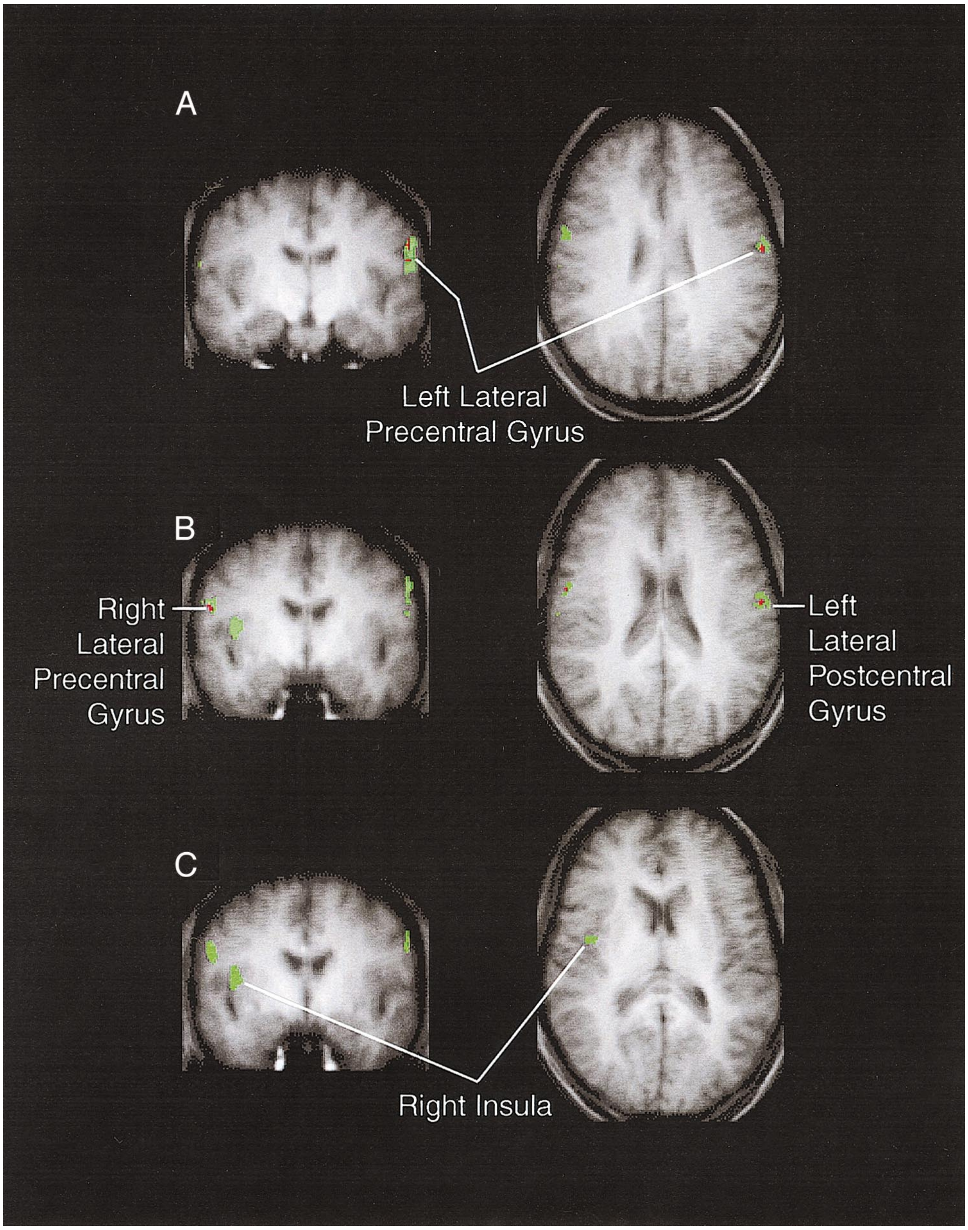

FIG. 6. Activation for a normalized brain volume using the Talairach-Tournoux coordinate system in the coronal (*left*) and axial (*right*) planes for all subjects during the water bolus swallow. Significantly activated voxels (red: voxel $P < 0.006$; green: voxel $P < 0.02$) within the lateral precentral gyrus (*A*), the lateral postcentral gyrus (*B*), and the insula (*C*) are shown.

functional task described above, blood-oxygenation-level–dependent (BOLD) images (i.e., T2*-weighted) were acquired continuously using an interleaved, four-segment, echo planar imaging (EPI) sequence (64×64 matrix size, TE = 15 ms, flip angle = 45°, 22 cm FOV, volume collection time = 2.34 s). Each image was corrected for physiologic fluctuations using a navigator echo that was collected at the beginning of every image segment (Hu and Kim 1994). At the end of the experimental session, anatomic reference images were acquired along the same orientation as the functional images using a three-dimensional version of the FLASH sequence described above ($256 \times 256 \times 64$ matrix, reconstructed slice thickness = 2 mm).

fMRI data analysis

Image analyses were performed using Stimulate v5.7 (Strupp 1996). All analyses were performed within individual subjects, as well as performed separately for each swallowing task. The magnitude of the MR signal within each image voxel as a function of image number or time (i.e., the MR time course) was examined initially for evidence of baseline drift that was subsequently removed by applying a high-pass frequency filter to the MR time course data. Images also were reconstructed using the MR signal phase (Wood 1992) to deterime whether swallow-related movements of the tongue and mandible occurring outside the imaging FOV contributed to large changes in MR signal phase at times corresponding to the recorded laryngeal movements. Such phase changes are not always detectable as motion artifact in the magnitude of the MR signal since the motion actually occurs outside the imaging FOV. However, the resulting phase modulaton can alter the magnitude of the magnetic field in nearby imaging slices and thus contribute to false-positives in the magnitude data (Birn et al. 1999). To identify image voxels whose signal intensity was modulated by this mechanism, we performed a correlation of the MR signal phase time course about each time point corresponding to a swallow-related laryngeal movement with a delta function at the time of swallow and zero at time points about the swallow. Any voxels exhibiting a positive or negative correlation with the delta function ($r > 0.65$, cluster size >6) were considered to be related to artifact and were disregarded in further analyses.

A single swallowing trial in the image data time course was defined

TABLE 5. *Regions of swallow-related activation in individual subjects*

	Subject													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
A. Naïve saliva swallow														
Lateral precentral gyrus	B	B	B	B	B	L	B	B	B	R	na	B	na	L
Lateral postcentral gyrus	L	B	L	B	R		L	L	B		na	R	na	L
Insula	B	R	B	B	R	R	B	L	B	L	na	B	na	
Superior temporal gyrus	L	R			L	L	L	B	L	L	na		na	R
Middle frontal gyrus	R	L					R				na		na	B
Inferior frontal gyrus	R				R	L			B	R	na	R	na	R
Anterior cingulate cortex		B^{I}						R^{R,C}	L^{R}	L^{R}	na		na	R^{I,C}
Posterior cingulate cortex											na	B	na	
Frontal operculum, inner face			L	L					L		na		na	
Medial frontal gyrus								R		R	na	B	na	
Cuneus											na	L	na	B
B. Voluntary saliva swallow														
Lateral precentral gyrus	B	B	B	B	B	B	B	B	R	B	B	B	B	R
Lateral postcentral gyrus	B	R	B	B	L		B	L	B	L				R
Insula	R	B	R	B	B	R	R		B	B	B	R	B	R
Superior temporal gyrus			B		B		B		L	B	R		B	R
Middle frontal gyrus	R	L		R	R		R				R		B	R
Inferior frontal gyrus	R			R					R	R		R		
Anterior cingulate cortex	L^{I,C}	L^{R,I}	R^{C}	R^{C}			R^{C}	B^{I,C}	B^{I,C}	B^{I,C}	R^{C}	B^{R,C}	B^{I,C}	B^{I,C}
Posterior cingulate cortex												B		
Frontal operculum, inner face		L		L		R				L	R			
Medial frontal gyrus									R	L	R	R	L	
Cuneus										R	L	R	L	
C. Water bolus swallow														
Lateral precentral gyrus	B	B	B	B	na	R	B	B	R	B	R	B	B	L
Lateral postcentral gyrus	B	B		B	na	L	R	B	L	B	R	B	B	B
Insula	R	L	R	R	na		R	R	R	B	L	R	B	
Superior temporal gyrus		R	R	B	na	R		B	L	R	R			
Middle frontal gyrus	L	R		R	na			R	L		R	B	L	L
Inferior frontal gyrus	L	L			na			B	L			R	R	
Anterior cingulate cortex		B^{I,C}	R^{I,C}	B^{I,C}	na		R^{C}	B^{I,C}	R^{C}	R^{I,C}	R^{C}	R^{R}	R^{C}	B^{I,C}
Posterior cingulate cortex	L				na									B
Frontal operculum, inner face				L	na	R				R	R		L	
Medial frontal gyrus					na							R	L	
Cuneus					na						B		B	B

L, left hemisphere activation; R, right hemisphere activation; B, bilateral activation. Superscript letters: R, rostral anterior cingulate cortex; I, intermediate anterior cingulate cortex; C, caudal anterior cingulate cortex.

as commencing when a laryngeal elevation onset was recorded and terminating several seconds before the subsequent laryngeal elevation onset indicating the beginning of the next swallowing trial. A boxcar correlation function incorporating a variable temporal delay to allow for the intrinsic delay of the hemodynamic response was used to correlate with each single swallowing trial at a liberal correlation value ($r > 0.40$) and to identify the temporal location of the maximum change in MR signal magnitude in response to a single swallow. A more conservative analysis was then performed using a Student's *t*-test to create a map of image voxels exhibiting a significant increase in MR signal ($P < 0.01$) above baseline during the time points as identified in the boxcar correlation analysis. The baseline MR signal within a single swallowing trial was defined as the average MR signal magnitude during a period of several seconds prior to the subsequent swallowing trial. Finally, one map representing the average percent change in MR signal across all swallowing trials in one task was generated by the "logical AND" combination of all of the single swallowing trial maps.

As a means of determining whether patterns of cortical activation associated with swallowing were characterized by hemispheric asymmetry, activation in the left and right hemispheres was compared for each swallowing task. Because preliminary examination of our maps indicated that the activation foci occurred primarily within the lateral pericentral cortex and the insula, analyses of hemispheric asymmetry were conducted separately for these two cortical regions. For each swallowing task, regions of interest were defined, which included *1*) all activated pixels in the lateral pericentral area, including Brodmann's areas (BA) 4, 6, 44, 47, 3, 2, 1, and 43, or *2*) all activated pixels corresponding to the insula. For these two regions of interest, activation was defined as the product of the number of significantly activated voxels and their average percent change in signal intensity (i.e., total activity). Hemispheric activation was expressed as the ratio of the activation within one hemisphere to the total bilateral activation within the region of interest. Mean differences between right- and left-hemisphere activations across subjects were tested for statistical significance for each swallowing task with paired *t*-tests ($P < 0.05$).

Although a major goal of this study was to identify cortical sites involved in the regulation of swallowing in single trials in single subjects, group analysis was performed to identify group trends in the data. For each subject, the activation map for each task, as well as the anatomic reference images, were transformed to stereotaxic space using the coordinate system of Talairach and Tournoux (1988). One

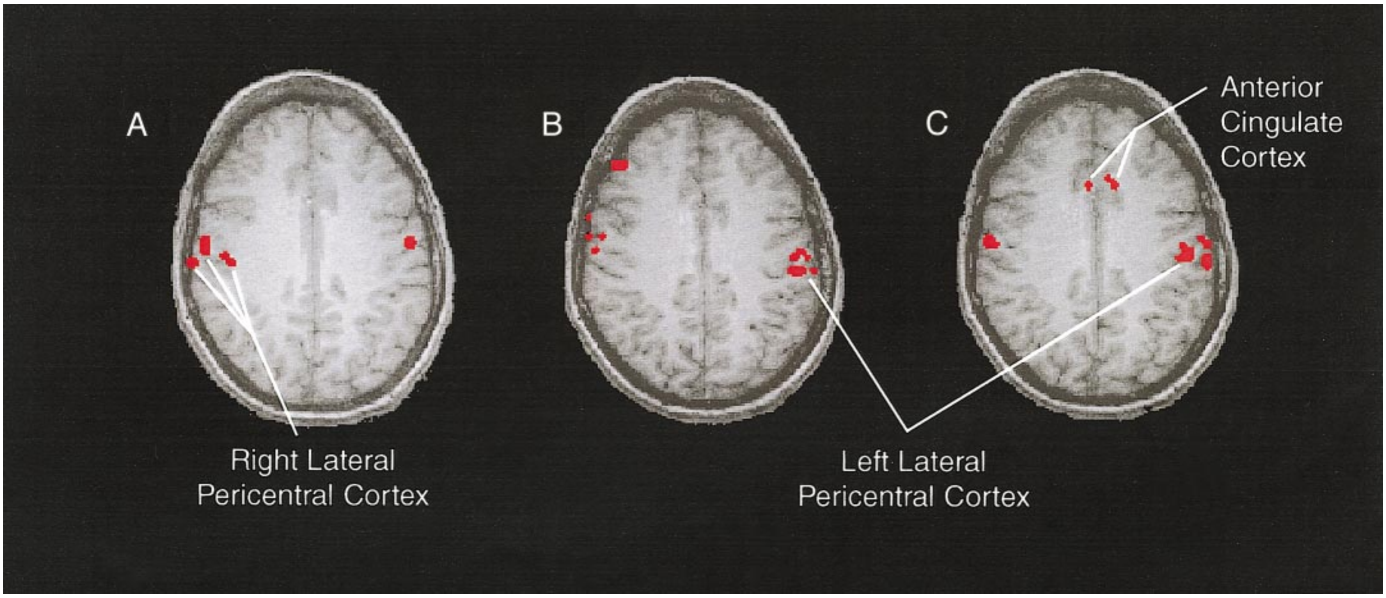

FIG. 7. BOLD activation maps for one subject corresponding to the naïve saliva swallow (*A*), voluntary saliva swallow (*B*), and water bolus swallow (*C*). The axial slices encompass the lateral pericentral/premotor cortex.

group map representing all subjects was created by generating the logical AND of all subjects' stereotaxic maps for each swallowing task. The percent change in signal intensity for each subject then was determined for voxels corresponding to the group maps for each task and examined statistically across subjects using a Student's *t*-test ($P < 0.05$). Thus the resulting voxel *P* values were not corrected for the transformation to stereotaxic space.

RESULTS

MR signal changes associated with single swallowing trials

Single swallows consistently were associated with *1*) BOLD signal increases within multiple cortical regions and *2*) large focal changes in MR phase. Across the three swallowing tasks, the mean swallow-related BOLD signal change ranged from 1.2 to 1.3% for a prominent activation focus within the lateral pericentral/premotor cortex, and from 0.8 to 0.9% for activation within the insula. For the same activation foci, the mean duration of the BOLD signal change ranged from 7.6 to 9.2 s, across swallowing conditions. Statistically significant swallow-related MR phase changes were brief (≤2 s) in comparison to the BOLD signal increases, occurred at or immediately following the onset of the BOLD magnitude signal increase, and preceded the BOLD signal peak intensity for single swallows (see Fig. 2). These phase changes were found primarily along the lateral surfaces of the hemispheres and the mid-line, particularly within the inferior-most slices examined in the present study (see Fig. 3).

Activation foci associated with naïve saliva swallow

Multiple regions of significant activation were obtained with the naïve saliva swallow (see Table 2 and Fig. 4). Across subjects, the most prominent and consistent activation foci were located within the left lateral precentral gyrus, including BA 4 and 6, and the left lateral postcentral gyrus corresponding to BA 43. Other prominent regions of activation across subjects were located within the right lateral precentral gyrus (i.e., including BA 4 and 6) and the right insula, immediately posterior to the verticofrontal (VCA) plane of Talairach and Tournoux (1988) (i.e., the vertical plane traversing the posterior margin of the AC).

The activation maps of individual subjects revealed additional regions of activation (see Table 5). These corresponded to the right lateral postcentral gyrus (i.e., BA 43), left postcentral gyrus (i.e., BA 3/1/2), left insula, superior temporal gyrus, middle frontal gyrus, inferior frontal gyrus, and the anterior cingulate cortex (ACC) (Paus et al. 1993, 1996). Activation of the primary motor cortex (i.e., BA 4) within the lateral precentral gyrus occurred in 10 of the 12 subjects.

Activation foci associated with voluntary saliva swallow

The voluntary saliva swallow was associated with several regions of significant activation (see Table 3 and Fig. 5). The most prominent focus across subjects corresponded to the right lateral precentral gyrus, including BA 4 and 6, and particularly along the caudal bank of the precentral sulcus (i.e., BA 6). Other prominent regions of activation across subjects were located within the *1*) left lateral precentral gyrus, including BA 4 and 6, *2*) left and right lateral postcentral gyri (i.e., BA 43 bilaterally), and *3*) the right caudal ACC, as described by Paus et al. (1996) (i.e., $Z = 4.25$ to $Z = 5.0$ in the axial plane; BA 6/32).

Individual subject activation maps indicated additional regions of activation (see Table 5). These were located within the insula, particularly on the right, the superior temporal gyrus, middle frontal gyrus (see Fig. 7*B*), inferior frontal gyrus corresponding to BA 44 or 47, inner face of the frontal operculum, and the intermediate ACC corresponding to BA 32/24 (i.e., $Z = 2.8$ to $Z = 3.9$ in the axial plane).

Activation foci associated with water bolus swallow

The water bolus swallow was associated with significant activations within several cortical regions (see Table 4 and Fig.

6). Across subjects, the most prominent and consistent activation foci were located within the *1*) left lateral precentral gyrus, including BA 4 and 6, *2*) left lateral postcentral gyrus (i.e., BA 43), *3*) right lateral precentral gyrus (i.e., BA 4 and 6), and *4*) the depth of the right central sulcus. Other prominent regions of activation across subjects were located within the right lateral postcentral gyrus at two loci corresponding to BA 3/1/2 and BA 43, the right insula, immediately posterior to the VCA plane, and the right caudal ACC (i.e., BA 32/24).

Individual subject activation maps indicated the following additional areas of activation: the left insula, superior temporal gyrus, middle frontal gyrus, inferior frontal gyrus corresponding to BA 44 or 47, the inner face of the frontal operculum, and the intermediate ACC (see Fig. 7*C*).

Comparison of activations across swallowing tasks

The three swallowing tasks produced similar regions of activation. However, activation of the caudal ACC was significantly more likely in association with the voluntary saliva swallow (Fisher's exact test, $P < 0.05$) and the water bolus swallow (Fisher's exact test, $P < 0.05$) than with the naïve saliva swallow. Activation of the intermediate ACC also was more common in association with the voluntary swallowing tasks compared with the naïve swallowing task.

Hemispheric asymmetry of cortical activation

The numbers of subjects showing a left- over right-hemisphere activation asymmetry for the pericentral cortex were 9/12 for the naïve swallow, 6/14 for the voluntary saliva swallow, and 7/13 for the water swallow; the remaining subjects showed a right over left hemisphere asymmetry. Across subjects, the mean activations within the left and right pericentral cortex were not statistically significantly different for any of the swallowing tasks (see Fig. 8*A*), although the left over right hemisphere difference for the naïve swallow approached significance (i.e., $P = 0.06$). Only one subject showed a clear left hemisphere lateralization of activation for the pericentral cortex for all three swallowing tasks. For the remaining subjects, the hemisphere with the greater activation varied across tasks. *Subject 4*, for example, showed a right-hemisphere lateralization during the naïve saliva swallow compared with a left hemisphere asymmetry during both the voluntary saliva and water bolus swallows (see Fig. 7).

Activation of the insula was lateralized to the right hemisphere for 6 of 11 subjects for the naive swallow, 9 of 13 subjects for the voluntary saliva swallow, and 9 of 12 for the water swallow. Across subjects, the difference between the right and left hemisphere insular activation was statistically significant for the voluntary saliva swallow ($T = 2.26$, df $= 12$, $P = 0.044$; see Fig. 8*B*).

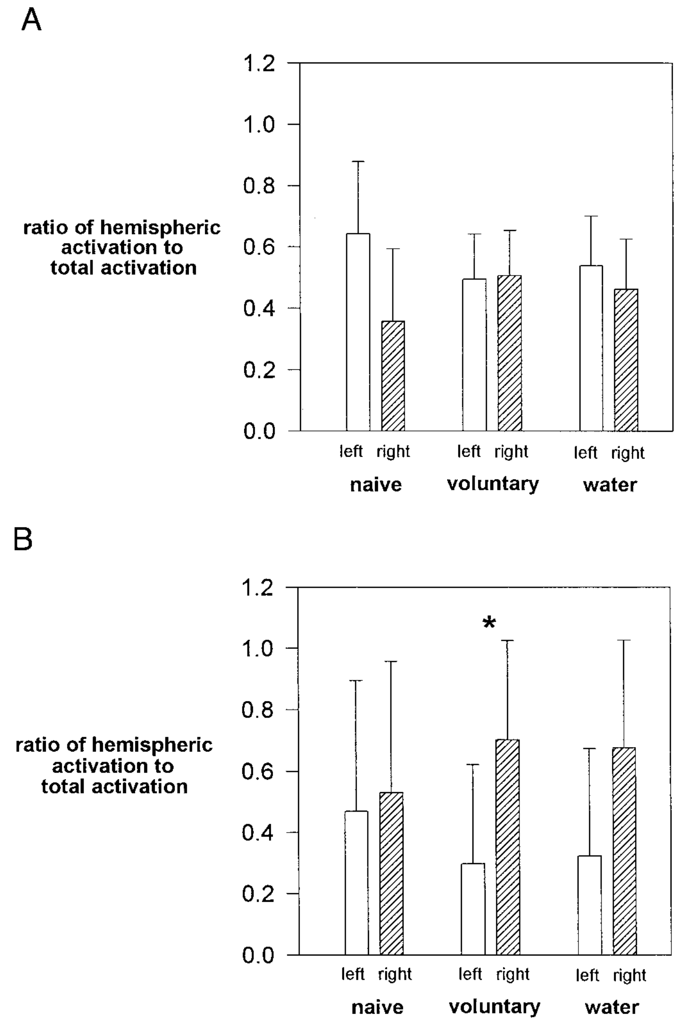

FIG. 8. Ratio of mean right-hemisphere activation and mean left-hemisphere activation to total activation for the lateral pericentral cortex (*A*) and insula (*B*) for the naïve saliva, voluntary saliva, and water bolus swallowing tasks for all subjects. Right hemisphere insular activation was significantly greater than left hemisphere insular activation for the voluntary saliva swallow ($P = 0.044$).

DISCUSSION

This study has provided the first documentation that voluntary *and* automatic swallowing are processed within the human cerebral cortex. Both types of swallowing were associated with activation of a number of spatially and functionally distinct cortical regions. The most prominent and consistent activation foci were located within the lateral precentral gyrus, including BA 4 and 6, the lateral postcentral gyrus, and the right insula. Activation foci within the superior temporal gyrus, middle and inferior frontal gyri, frontal operculum, and anterior cingulate gyrus also were identified, although these were less consistent across subjects and tasks, and less prominent than the pericentral and insular activation foci. Whereas water bolus and voluntary and automatic swallows of saliva produced similar spatial patterns of cortical activation, activation of the caudal anterior cingulate gyrus was more likely in association with the voluntary saliva and water bolus swallowing tasks than with the naïve saliva swallow. These findings are consistent with the view that voluntary and automatic swallowing are represented within distributed networks of functionally distinct cortical foci that participate fundamentally, and perhaps differentially, in the control of human swallowing.

Magnetic resonance signal changes associated with swallowing

Our finding that the magnitude of the BOLD response associated with single swallowing trials was approximately 1.2%

for the pericentral/premotor cortex and 0.8% for the insula is in keeping with previous reports that have documented BOLD signal changes ranging from approximately 0.5 to 5% (Buckner et al. 1996; DeYoe et al. 1994; Hamdy et al. 1999a; Hinke et al. 1993; Menon and Goodyear 1999; Toma et al. 1999). The present finding that the swallow-related BOLD response ranged in duration from approximately 8 to 9 s, across brain regions, subjects, and tasks, also is consistent with previous findings indicating that the BOLD response duration is 8–11 s (Buckner et al. 1996; Dale and Buckner 1997; Hinke et al. 1993; Konishi et al. 1996; Toma et al. 1999).

It is noteworthy that a previous fMRI study of water bolus swallowing reported that the peak signal change occurred 19 $\pm$ 3 s following the onset of the swallow-related laryngeal movement (Hamdy et al. 1999a). This value is markedly greater than the findings of the present study and falls well outside the range of BOLD peak latency values reported for other brain regions and activation tasks (see previous paragraph). This substantial discrepancy suggests the possibility that the BOLD signal increase reported by Hamdy et al. (1999a) was related not only to swallowing but also to other events occurring after the swallow.

Cortical involvement in volitional and automatic swallowing

The present finding that the cerebral cortex was activated during voluntary swallowing of saliva and swallowing of a water bolus is not unexpected perhaps, given that both tasks required the subject to swallow "at will" and, in so doing, execute voluntary movements. It is well established that deficits of volitional swallowing can occur following hemispheric stroke (Robbins and Levine 1988). Indeed, patients with infarcts involving the left lateral frontal cortex have been reported to exhibit so-called "apraxia of swallowing" characterized by impaired volitional swallowing but relatively preserved automatic swallowing (Robbins and Levine 1988). Our demonstration that the cortex was activated not only in association with volitional swallowing but also in relation to the *automatic* (naïve) swallowing of saliva is more surprising and deserves special note. Previous studies showing that swallowing can be evoked in the decerebrate or anesthetized preparation by stimulation of the pharyngeal or laryngeal mucosa and by electrical stimulation of the superior laryngeal nerve (for reviews, see Dubner et al. 1978; Miller 1982) have indicated that the brain stem circuitry alone can mediate reflexive swallowing under experimental conditions in animals. In contrast, the present finding of cortical activation in association with the naïve saliva swallow suggests that the cerebral cortex plays a role even in this highly automatic type of swallowing in humans.

Activation foci associated with swallowing

Swallowing was associated with activation of a number of spatially discrete cortical regions in the present study. These cortical regions are both cytoarchitectonically and functionally distinct (Talairach and Tournoux 1988), suggesting the possibility that they may be differentially involved in the regulation of swallowing. Future studies that determine the temporal patterns of activation across cortical foci in relation to the execution of swallow-related movements will offer important insights into the specific roles of each cortical focus in swallowing regulation. This approach has been employed in studies of cortical activation associated with voluntary finger movements (Gerloff et al. 1998).

Lateral precentral gyrus: primary motor cortex and premotor cortex

The most consistent and prominent region of activation, across subjects and swallowing tasks, corresponded to the lateral precentral gyrus and included the primary motor cortex (MI; i.e., BA 4) and the premotor cortex (i.e., BA 6). This finding confirms and extends previous human brain mapping studies showing that the oral, pharyngeal, and esophageal musculature (Hamdy et al. 1996) and voluntary swallowing (Hamdy et al. 1999a,b; Mosier et al. 1999; Zald and Pardo 1999) are represented on the precentral cortex. Our finding is consistent with the recent report that swallowing, either in isolation or in association with other oral movements, can be evoked by intracortical microstimulation (ICMS) applied to the most lateral aspect of face MI, and to the more lateral premotor cortex corresponding to BA 6 in awake monkeys (Martin et al. 1999).

The present finding that MI was activated in over 80% of the subjects in association with the automatic (naïve) saliva swallow is of particular interest, given that this cortical region is classically considered to be involved in *voluntary* movement execution. The primary motor cortex previously has been implicated in the control of swallowing in that the firing rates of single neurons in face MI are modulated in relation to swallowing of a juice reward and/or naturally occurring swallowing in the awake monkey (Martin et al. 1997b). Our finding of a prominent activation focus corresponding to MI during the naïve saliva swallow supports the conclusion of Martin et al. (1997) that the classical view of MI playing a primary role in operantly conditioned movements, but a relatively minor role in the control of semi-automatic movements involving the same muscles, may need to be re-examined.

In the present study, the activation focus within the lateral premotor area (i.e., BA 6) frequently was located within the caudal bank of the precentral sulcus, suggesting the possibility that this area plays a fundamental role in swallowing control. This region lies rostral to the ICMS-defined primate cortical swallowing representation reported by Martin et al. (1999). Future studies in both humans and nonhuman primates are required to determine the functional organization of this region of premotor cortex in relation to swallowing, as well as other orofacial motor behaviors.

Lateral postcentral gyrus

In the present study, all three swallowing tasks yielded activation of the lateral postcentral gyrus localized to BA 3/2/1 and/or BA 43. The lateral aspect of the postcentral gyrus, corresponding to the face primary somatosensory cortex, has been implicated in swallowing previously in that ICMS applied to this region evokes swallowing and/or rhythmic jaw movements in the awake monkey (Huang et al. 1989b; Martin et al. 1999). While the more lateral BA 43 has not been implicated in swallowing per se, this region appears to be involved in a variety of related functions including the processing of sensory stimuli applied to the human face (Hodge et al. 1998), and taste sensation in monkeys and humans (Burton and Benjamin 1971; Cerf et al. 1998; Faurion et al. 1998). The three swallowing tasks employed in the present study would be expected to involve the processing of oropharyngeal sensory inputs in *1*) monitoring salivary accumulation or water bolus delivery and transport, and *2*) stimulation of the oropharynx by the movements of the jaw, tongue, palate, and pharyngeal musculature involved in swallowing. Thus our finding of swallow-related activation of the postcentral gyrus may reflect various types of oropharyngeal sensory processing and underscores the importance of afferent information in the regulation of both voluntary and automatic swallowing.

Insula

The present finding that the insula was activated in association with both the automatic and voluntary swallow is consistent with recent studies suggesting a role for the insula in swallowing (Daniels and Foundas 1997; Hamdy et al. 1999a). Anatomic studies have shown that the insula receives afferent inputs from, and/or projects to, several brain regions implicated in swallowing including the lateral and mesial premotor cortices, the primary and secondary somatosensory cortex, the frontal, parietal, and temporal opercula, the orbitofrontal cortex, and the anterior cingulate gyrus (for review, see Augustine 1996). Moreover, physiologic studies in a number of species including nonhuman primates and humans indicate that the insula plays a role in mediating both sensory and motor aspects of alimentary tract function involving the oropharynx, esophagus, and possibly other areas of the gastrointestinal tract (Binkofski et al. 1998; Kern et al. 1998; Penfield and Faulk 1955). The transition area between the inner face of the frontal operculum and the insula is believed to represent a primary gustatory cortex (Kobayakawa 1996), with additional gustatory fields possibly located within the insula, temporal operculum, and the foot of the pre- and postcentral gyri (Cerf et al. 1998; Faurion et al. 1998). The insula also has been implicated in visceral (autonomic) motor function (Penfield and Faulk 1955), somatic sensation of the orofacial region in primates (Schneider et al. 1993), voluntary oral movement control (Raichle 1991), and speech motor control (Dronkers 1996). Taken together, these findings suggest that the swallow-related insular activation documented in the present study could represent a number of sensory and/or motor processes involved in the regulation of swallowing.

Frontal operculum

In some subjects, swallowing was associated with activation of the inferior frontal gyrus corresponding to *1*) the inner face of the frontal operculum, or *2*) BA 44 on the cortical convexity adjacent to the Sylvian fissure. Both electrophysiologic and clinical studies have implicated the frontal operculum in swallowing. Swallowing and rhythmic jaw movements can be evoked by ICMS applied to the inner face of the frontal operculum in the awake monkey (Huang et al. 1989b; Martin et al. 1999). Sensation of the human mouth and pharynx have been localized to the operculum (Penfield and Fauk 1955), and, as discussed above, the transition zone between frontal operculum and insula appears to be a primary gustatory representation. In contrast, BA 44 is part of Broca's area and is classically considered to subserve motor speech production. However, our finding of swallow-related activation of this region, even during the automatic swallow, and similar findings using PET (Hamdy et al. 1999b) and fMRI (Hamdy et al. 1999a) suggest that this area of cortex also may play a role in the control of nonspeech orofacial sensorimotor behaviors. This view is supported by the finding that BA 44 is activated in association with a voluntary tongue-motor task in humans (Erhard et al. 1996).

Anterior cingulate cortex

The ACC is thought to be a multifunctional region processing sensory, motor, and cognitive information (Devinsky et al. 1995). The rostral part of the ACC, encompassing BA 25, 24, 32, and 33, is believed to be involved in affect, autonomic regulation and visceromotor control, and vocalization. It is notewothy however, that West and Larson (1995) found that single neurons in this region fire in relation to other orofacial motor behaviors performed by monkeys, such as tongue protrusion, suggesting the possibility of a more basic role in orofacial functon. The more dorsal and caudal ACC is believed to be involved in skeletomotor control, including movement regulation and premotor function, response selection and attention to willed action, and nociception (Devinsky et al. 1995). Single neurons in this region are modulated preceding self-paced movements in monkeys (Shima et al. 1991).

The activation foci identified in the present study corresponded to the rostral, intermediate, and caudal aspects of the ACC (Pauss et al. 1993, 1996). However, activation of the rostral ACC was seen almost exclusively during the naïve saliva swallow, whereas activation of the caudal and intermediate ACC was associated with the voluntary saliva and water bolus swallowing tasks. We interpret these activation foci within the intermediate and caudal ACC as possibly reflecting premotor and/or attentional processing involved in voluntary swallowing. This interpretation is plausible given that, in the voluntary saliva swallow, subjects swallowed in a self-paced fashion approximately once per minute, requiring them to maintain temporal vigilence and decide when a swallow was required. In the water bolus condition, athough swallowing was not self-paced, the subjects were required to monitor when the water bolus had been fully delivered, make a deliberate choice to swallow at a particular time following bolus delivery, and swallow in a controlled fashion. The present results differ from those of Hamdy et al. (1999a), who reported activation within the rostral ACC, corresponding to BA 32/33 during water bolus swallowing.

Temporal lobe

Our finding of swallow-related activation of the superior temporal gyrus, corresponding to Brodmann's areas 42/41 and 22, is similar to that of Hamdy et al. (1999a), who found activation of Brodmann's areas 22 and 21 during a water bolus swallow. The temporal lobe has been implicated in a number of functions that are related to swallowing. For example, PET findings suggest that the anteromedial temporal lobe is involved in human taste quality recognition (Small et al. 1997), while fMRI and magnetoencephalographic studies have shown activation of the opercular aspect of the superior temporal lobe during taste perception tasks (Faurion et al. 1998; Kinomura 1994; Kobayakawa 1996). While the temporal lobe activation documented in the present study could reflect a function related to swallowing, such as taste, the activation foci we identified corresponded to the primary auditory and association auditory cortices and were remote from the region identified by Small et al. (1997) in relation to taste. Further, in both our study and that of Hamdy et al. (1999a), subjects swallowed saliva and/or water rather than tastants, calling into question the possible contribution of taste in the resulting patterns of activation.

We propose that the temporal lobe activations found in the present study reflect the processing of the acoustic correlates of swallowing by the auditory cortex. Swallow-related sounds that are audible to the swallower, via bone conduction of the acoustic energy, could include those related to eustacian tube function, as well as those associated with the rapidly modulating oropharyngeal cavity and moving bolus. All subjects wore ear plugs during the present experiments, and we have confirmed that one can clearly hear the sounds of swallowing over the noise produced by the MR scanner. Moreover, given the behavioral context within which the subjects swallowed in our study, it is likely that they were attending to many aspects of their swallowing, including, perhaps, not only oropharyngeal sensorimotor events but also their acoustic correlates. Faurion et al. (1998) have reported activation of the opercular region of the superior temporal gyrus (i.e., auditory cortex) during a taste task in which subjects swallowed the tastants. Given our present findings, it is conceivable that the temporal lobe activations reported by Faurion et al. (1998) reflected processing of the sounds of swallowing of the tastants.

Hemispheric lateralization of swallowing representation

Our finding of statistically greater activation of the right, compared with the left, insula during the voluntary swallowing of saliva suggests a functional lateralization of insular processing for swallowing. Lateralization of insular function also has been reported in studies of taste (Cerf et al. 1998; Fukuda et al. 1991), cardiovascular function (Oppenheimer et al. 1992), and auditory processing (Kushner et al. 1987). Interestingly, Cerf et al. (1998) reported that lateralization of insular activation for taste was related to handedness, with the dominant hemisphere showing greater activation. While all of the subjects in the present study were strongly right-handed, our findings, together with those of Cerf et al. (1998) point toward the potential importance of future swallowing studies in which insular activation is examined as a function of handedness.

In contrast, we found no evidence of a clear functional asymmetry of the swallowing representation within the pericentral/premotor cortex, neither across subjects nor within individual subjects across swallowing conditions. This finding is consistent with previous reports on water bolus (Hamdy et al. 1999b) and volitional saliva (Mosier et al. 1999) swallowing, and extends earlier findings by showing that the lack of asymmetry applies also to the naïve saliva swallow. Our finding that the hemisphere with the larger swallowing activation varied as a function of swallowing task within individual subjects challenges the view that there is a hemispheric dominance for swallowing (Hamdy et al. 1996, 1999a,b) and suggests instead that the mechanisms underlying the functional lateralization of the processing of swallowing are complex and related to the behavioral context within which the swallow occurs.

Limitations of the present investigation

Because the present study was aimed at examining all swallow-related activation within the cerebral hemispheres, the spatial resolution employed did not allow us to differentiate specific gyri or regions therein in some cases. Future high resolution fMRI investigations of particular activation sites, such as the pericentral or insular cortex, are needed to determine the detailed swallow-related functional anatomy of these regions. In the present study, swallows were identified from a laryngeal movement signal recorded from the output of a pressure transducer positioned over the thyroid cartilage. The transducer produced a highly specific swallow-related signal that was readily distinguishable from other movements such as those related to jaw wagging and random tongue movements. Nevertheless, because of the possibility of some ambiguity between recorded laryngeal movements associated with swallowing and other pharyngolaryngeal gestures, future studies should incorporate additional methods of identifying swallows such as submental electromyography. Finally, given our novel findings on automatic swallowing, it is crucial that the "naïve" swallows were indeed automatic and did not involve any volitional component. As mentioned in METHODS, interviews conducted immediately following the experimental sessions indicated that none of the subjects were aware that the first functional scan was a study of swallowing. Indeed, all subjects were surprised at this information. Given that subjects were instructed to relax and remain still during this experiment, we find no reason to believe that the subjects were concentrating specifically on swallowing or swallowing volitionally.

Implications

The present demonstration that the hemodynamic correlate of averaged, single swallowing trials can be detected with fMRI at 4 Tesla indicates that swallowing is amenable to single-event fMRI paradigms. This finding has important implications for future fMRI studies of swallowing, as well as studies of other orofacial motor behaviors such as speech production, in which task-coupled motion of the mouth and/or pharynx can produce large fluctuations in the MR signal (Birn et al. 1999). Given the likelihood of motion artifact in such studies, the application of single-event paradigms, in which the contribution of motion is minimized by modifications to the acquisition and/or analysis protocols, is crucial. In addition, because single-event paradigms allow for random intermixing of different trial types (Buckner et al. 1996), future investigations into the effects of sensory manipulation of swallowing, for example, by varying bolus temperature, consistency, or taste, appear feasible.

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