Cerebral cortical representation of reflexive and volitional swallowing in humans

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Kern, Mark K., Safwan Jaradeh, Ronald C. Arndorfer, and Reza Shaker. Cerebral cortical representation of reflexive and volitional swallowing in humans. Am J Physiol Gastrointest Liver Physiol 280: G354–G360, 2001.—The purpose of this study was to compare cerebral cortical representation of experimentally induced reflexive swallow with that of volitional swallow. Eight asymptomatic adults (24–27 yr) were studied by a single-trial functional magnetic resonance imaging technique. Reflexive swallowing showed bilateral activity concentrated to the primary sensory/motor regions. Volitional swallowing was represented bilaterally in the insula, prefrontal, cingulate, and parietooccipital regions in addition to the primary sensory/motor cortex. Intrasubject comparison showed that the total volume of activity during volitional swallowing was significantly larger than that activated during reflexive swallows in either hemisphere (P < 0.001). For volitional swallowing, the primary sensory/motor region contained the largest and the insular region the smallest volumes of activation in both hemispheres, and the total activated volume in the right hemisphere was significantly larger compared with the left (P < 0.05). Intersubject comparison showed significant variability in the volume of activity in each of the four volitional swallowing cortical regions. We conclude that reflexive swallow is represented in the primary sensory/motor cortex and that volitional swallow is represented in multiple regions, including the primary sensory/motor cortex, insular, prefrontal/cingulate gyrus, and cuneus and precuneus region. Non-sensory/motor regions activated during volitional swallow may represent swallowing-related intent and planning and possibly urge.

voluntary swallowing; deglutition; control of deglutition

THE CENTRAL NEURAL CONTROL mechanism of swallowing is not completely understood; however, a large body of evidence indicates the existence of two levels of control at the brain stem (9, 16, 23, 30) and the cerebral cortex (13, 14, 21, 24, 25, 33, 34, 39). Current understanding of the cerebral cortical involvement in swallowing is still developing, but clinical evidence derived from patients with cerebrovascular accident (CVA) (2, 12, 15, 22, 27, 38) and, more recently, functional studies of the human brain (13, 14, 25, 39) indicate cortical involvement in swallowing to be multifocal and bilaterally represented. Most commonly cited of these foci include those corresponding to areas in the sensory/motor cortex, prefrontal cortex, anterior cingulate, and insular (13, 14, 25, 39) and parietooccipital regions (14, 39). The nature of involvement of these foci in various aspects of volitional swallowing such as intent, urge, planning, previous experience, and sensory/motor control has not been systematically investigated.

In addition to volition, swallowing can be initiated reflexively by direct injection of minute amounts of water into the pharynx. These swallows are irrepressible and occur despite the intention to avoid swallowing (31). Since there is no volitional input for initiation of a reflexive swallow, comparison of its cortical representation with that of volitional swallow can provide a study model that can potentially increase our understanding of the non-sensory/motor cortical control of swallowing.

The aim of the present study, therefore, was to compare the cerebral cortical representation of experimentally induced pharyngeal reflexive swallow with that of volitional swallow using blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI) technique.

METHODS

Eight asymptomatic right-handed adult subjects (age 24–27 yr, 5 male, 3 female) were studied. Study protocols were approved by the Human Research Review Committee of the Medical College of Wisconsin, and subjects gave written informed consent before the studies. All subjects completed a detailed health-related questionnaire before each study and did not have any present or previous history of dysphagia or other gastrointestinal-related diseases. Cerebral cortical activity was monitored in all subjects using a BOLD technique.

MRI echo planar and spoiled gradient recalled acquisition at steady state (GRASS) anatomic images (32) were acquired in the sagittal plane for 13 contiguous slices, 10 mm in thickness, spanning the whole brain volume. MRI scanning was performed on either a 1.5 Tesla General Electric Signa scanner (GE Medical Systems, Wauwatosa, WI) in two subjects or on a 3 Tesla Bruker scanner (Bruker Medical, Karlsruhe, Germany) in six subjects. Each scanner was equipped with a custom three-axes head coil designed for rapid gradient field switching and a shielded, transmit/

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receive “birdcage” radio frequency coil to acquire a time course of echo planar images across the entire brain volume with the desired slice specifications. Echo planar images resolved to 64 × 64 pixels/slice at repetition time of 1 s and echo time of 40 ms were obtained during six scanning sequences with a 1-min interval between scans.

**Eliciting volitional and reflexive swallow.** Both volitional and reflexive swallowing were performed during single-trial “event-related” fMRI scanning sequences (6). The single-trial technique has been shown to be a reliable method for detecting deglutitive fMRI swallowing activity with little of the noise-related artifact associated with repetitive swallowing (6–8). Subjects were cued to swallow volitionally once every 30 s by a single, gentle tap on the right leg. Reflexive swallowing was provoked by rapid injection of a predetermined threshold volume of room temperature water into the pharynx, directed posteriorly, once every 30 s. Before placing each subject into the MRI scanner, a two-lumen ribbon-like catheter (2 × 4 mm) was inserted transnasally within the pharynx. The catheter injection port was manometrically positioned 2 cm above the pharyngoesophageal high-pressure zone, such that the injection port faced the posterior pharyngeal wall. A threshold water-injection volume was established for each subject that would ensure the triggering of reflexive swallowing. For the eight tested subjects, the threshold volume for eliciting a pharyngeal swallow was 0.59 ± 0.07 ml (mean ± SE), with a range of 0.5–1.0 ml. Before reflexive-swallow MRI sequences, subjects were instructed that there would be intermittent injections of water in their throats making them swallow, similar to the prescan period, but that they should make a concerted effort not to volitionally swallow during these scans.

Six paradigm-driven, 3-min fMRI scanning sequences were performed on each subject. Three scanning sequences of single-trial volitional swallows were followed by three scans of reflexive swallows. During volitional swallowing, no bolus was introduced and the subjects swallowed their ambient saliva. In either case, subjects swallowed once every 30 s for a total of 5 swallows for each 3-min sequence. A single baseline scan was performed, during which the swallow-signal tap on the leg was administered without volitional swallowing to determine the effect of this cue on the cerebral fMRI signal.

**Data analysis.** A nonbiased method of detecting cerebral cortical regions of stimulus-related changes in oxy/deoxyhemoglobin concentration was used to correlate an idealized wave representative of the stimulus paradigm to the actual MRI-generated magnetic signals. With the use of the single-trial technique, magnetic signal data from each 30-s epoch, starting with the image after a single swallow and ending with the image before the subsequent swallow, were averaged over the entire scanning sequence. As illustrated in Fig. 1, for each pixel of every echo planar slice image set, a graph of time vs. magnetic field intensity could be made. A schematic example of such a time series is shown, wherein gradual signal intensity changes follow the abrupt, artifactual signal change associated with the motion of swallowing. The five swallow epochs from this time series were averaged by using the motion artifact spike as a temporal reference to create an average time series of magnetic signals and images. All averaged data were then correlated to an idealized response waveform to differentiate regions of swallow-induced cortical activity from regions of quiescence. This correlation technique for detecting cortical signals has been used for many different forms of stimuli, including gastrointestinal stimulation (6, 7, 18).

Regions of cortical signal changes associated with swallowing are shown graphically as color-overlaid images stereotaxically mapped on the anatomic images in the Talairach-Tournoux coordinate system (35). Correlation statistics, image registration, and three-dimensional display were facilitated by the Analysis of Functional Neuroimages (AFNI) software package written by Robert Cox of the Medical College of Wisconsin Biophysics Research Institute (10). The AFNI software runs on a Pentium III–based Linux workstation (Southwest Computers, Houston, TX). AFNI allows the user to display a three-dimensional “brick” of MRI data transformed from images captured as a sequence of two-dimensional images. The software also was used to detect regions of cortical activity using the correlation technique described above as well as to display cortical volumetric regions of correlated fMRI signal change as color maps overlaid on the three-dimensional anatomic images. Our criteria for including a volume element, or voxel, as a region of correlated activity required the calculated correlation between the actual MRI time series magnetic signal and the idealized response waveform to be £0.70. Furthermore, we applied the additional clustering (5) requirement that a displayed region of correlated activity must be represented by a cluster of three or more contiguous correlated voxels. In the present

![Fig. 1. Schematic diagram of the single-trial analysis technique.](http://example.com/image.png)
study, we used a 64 × 64-pixel matrix for each sagittal image covering a 240 × 240-mm field of view and a slice thickness of 10 mm to be able to include the whole cerebral cortex. Thus one echo planar image voxel was \( \frac{240}{64} \times \frac{240}{64} \times 10 = 141 \) mm\(^3\). According to our criteria, an activated cluster must be \( > 422 \) mm\(^3\).

Using these techniques, we 1) determined the areas of the cerebral cortex that became activated during volitional and reflexive swallows, 2) measured the volume of activated voxels during each task, and 3) compared the swallow-related signal intensity change during swallowing to that of preswallow baseline fMRI signal intensity. All values are expressed as means ± SE unless stated otherwise.

**RESULTS**

All tested subjects showed a discernable fMRI BOLD response to both reflexive and volitional swallowing. However, there were substantial differences between cortical representation of reflexive and volitional swallowing (Fig. 2). Reflexive swallowing showed bilateral activity concentrated to the primary sensory/motor regions. Volitional swallowing, on the other hand, was represented bilaterally in the insula and the prefrontal, anterior cingulate, and parietooccipital regions in addition to the primary sensory/motor cortex.

Table 1 shows the Brodemann areas of cortical activation regions for each tested subject. The regions common to both reflexive and volitional swallows were the primary sensory/motor cortex at or near the central gyrus and including regions both in the lateral and medial aspects of the cortical hemispheres. Intrasubject comparison showed that the total volume of activated voxels during volitional swallowing (2,050 ± 164

![](G356.png)

**Table 1. Regions of activation during reflexive and volitional swallowing**

<table>
<thead>
<tr>
<th>Subject Number</th>
<th>Reflexive Swallowing</th>
<th>Volitional Swallowing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>2</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>3</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>4</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>5</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>6</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>7</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>8</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

% Subjects with activity  50  13  38  100  100  13  38  13  25  100  100  38  13  13  50  100  38  13  13  50  25  88  50

Numbers indicate Brodemann’s Areas. I, insula; AC, anterior cingulate (Brodemann’s Areas 24, 32, and 33). X indicates activation. For both reflexive and volitional swallows, there were areas that became activated in all subjects and also areas that were activated in an overwhelming majority of subjects. These areas include Brodemann’s Areas 4 and 6 for reflexive swallowing and 4, 6, 19, and 1 for volitional swallowing.
and 2,674 ± 149 μl for left and right hemispheres, respectively) was significantly larger than that activated during reflexive swallows (1,430 ± 309 and 704 ± 160 μl for left and right hemispheres, respectively) in either hemisphere (Table 2) (P < 0.001). One-way ANOVA showed significant intrahemispheric variability among the four regions of interest for the volume of fMRI activation during volitional swallowing. Multiple comparison using the Tukey correction showed that, for volitional swallowing, the primary sensorimotor region contains the largest and the insular region the smallest volumes of activation in both hemispheres (Table 2). On average, the total area of activated voxels in the right hemisphere was significantly larger compared with the left (Table 2) (P < 0.05).

The average percentage of maximum magnetic signal change in the primary sensorimotor cortex associated with volitional swallowing in both hemispheres was significantly higher compared with that of reflexive swallow (P < 0.05) (Table 3). The percent maximum magnetic signal intensity change was calculated for each significantly correlated voxel as the maximum increase in signal intensity from baseline divided by the baseline signal intensity. For volitional swallow, one-way ANOVA showed significant intrahemispheric variability among the four regions of interest with respect to the fMRI signal intensity in the left hemisphere during volitional swallowing. Multiple comparison using the Tukey correction showed the insular region to exhibit the smallest (P < 0.05) percent signal increase. Similar differences were not detected in the right hemisphere.

Intersubject comparison showed that, for volitional swallowing, there was significant variability in the volume of activated voxels in each of the four cortical regions of interest (P < 0.05). Similar intersubject variability was also found for reflexive swallow (Table 2). An analysis of the cortical activity volume for reflexive and volitional swallowing with respect to hemispheric dominance is shown in Fig. 3. As seen for the common area of activity for both swallows, the average volume of activation is larger on the left primary sen-

Table 2. Comparison of the volume of activated voxels (μl) during volitional and reflexive swallows

<table>
<thead>
<tr>
<th>Subject</th>
<th>Left Hemisphere</th>
<th>Right Hemisphere</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reflexive Swallow</td>
<td>Volitional Swallow</td>
</tr>
<tr>
<td></td>
<td>SM</td>
<td>ACFF</td>
</tr>
<tr>
<td>1</td>
<td>2,606 ± 510</td>
<td>782 ± 104</td>
</tr>
<tr>
<td>2</td>
<td>1,560 ± 300</td>
<td>1,211 ± 279</td>
</tr>
<tr>
<td>3</td>
<td>300 ± 103</td>
<td>1,715 ± 318</td>
</tr>
<tr>
<td>4</td>
<td>882 ± 160</td>
<td>255 ± 51</td>
</tr>
<tr>
<td>5</td>
<td>599 ± 179</td>
<td>497 ± 120</td>
</tr>
<tr>
<td>6</td>
<td>1,766 ± 387</td>
<td>848 ± 181</td>
</tr>
<tr>
<td>7</td>
<td>2,640 ± 445</td>
<td>970 ± 208</td>
</tr>
<tr>
<td>8</td>
<td>1,095 ± 210</td>
<td>2,491 ± 589</td>
</tr>
</tbody>
</table>

Mean ± SE of 1–8: 1,430 ± 309* | 1,096 ± 253* | 483 ± 163 | 250 ± 45* | 421 ± 123 | 704 ± 160 | 1,253 ± 225 | 583 ± 165 | 392 ± 33 | 446 ± 97

Values are means ± SE. SM, the primary sensory/motor region including Brodmann Areas 1, 2, 3, 4, and 6; ACFF, the anterior cingulate gyrus and pre-frontal cortex including Brodmann Areas 24, 32, and 33; I, insular cortex, paralimbic gyri deep within the lateral fissure, extending caudally parallel to the lateral fissure with a smaller portion located more rostrally; PO, parieto-occipital regions including Brodmann Areas 17, 18, 19, 26, 30, and 31. *P < 0.05 for right vs. left hemisphere.

Table 3. Average percentage of maximum magnetic signal change in cerebral cortical regions representing volitional and reflexive swallowing

<table>
<thead>
<tr>
<th>Subject</th>
<th>Left Hemisphere</th>
<th>Right Hemisphere</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reflexive Swallow</td>
<td>Volitional Swallow</td>
</tr>
<tr>
<td></td>
<td>SM</td>
<td>ACFF</td>
</tr>
<tr>
<td>1</td>
<td>3.0 ± 0.3</td>
<td>3.0 ± 0.1</td>
</tr>
<tr>
<td>2</td>
<td>2.8 ± 0.1</td>
<td>3.1 ± 0.1</td>
</tr>
<tr>
<td>3</td>
<td>2.8 ± 0.2</td>
<td>3.3 ± 0.1</td>
</tr>
<tr>
<td>4</td>
<td>2.7 ± 0.1</td>
<td>3.4 ± 0.2</td>
</tr>
<tr>
<td>5</td>
<td>2.9 ± 0.2</td>
<td>3.3 ± 0.3</td>
</tr>
<tr>
<td>6</td>
<td>3.3 ± 0.3</td>
<td>3.3 ± 0.1</td>
</tr>
<tr>
<td>7</td>
<td>2.9 ± 0.2</td>
<td>3.1 ± 0.1</td>
</tr>
<tr>
<td>8</td>
<td>3.0 ± 0.2</td>
<td>3.2 ± 0.1</td>
</tr>
</tbody>
</table>

Mean ± SE of 1–8: 2.9 ± 0.2* | 3.2 ± 0.1 | 3.1 ± 0.3 | 2.8 ± 0.07* | 3.1 ± 0.2 | 2.7 ± 0.1* | 3.2 ± 0.2 | 3.1 ± 0.3 | 3.0 ± 0.04 | 3.2 ± 0.2

Values are means ± SE. *P < 0.05 for reflexive vs. volitional swallowing.
areas are also involved in deglutition. The functional present study and previous reports (13, 14), that these 37). It is clear, on the basis of the findings of the emanating from more than one sensory modality (26, 36). The precuneus region is part of the posterior association area of the brain. It integrates information about the internal state of the body homeostasis. Insu-

sory/motor cortex for reflexive swallowing, but the con-
verse is true for volitional swallowing (P < 0.05).

DISCUSSION

In this study, we compared the topography of the cerebral cortical regions that are associated with reflexive and volitional swallows. Study findings indicate significant differences between cortical representation of volitional and reflexive swallows in humans. In concordance with previous studies (13, 14, 25, 39), findings of the present study show that multiple regions of the human cerebral cortex are involved with volitional swallow. These not only include the primary sensory/motor cortex but also involve areas such as the prefrontal cortex, anterior cingulate gyrus, and insular cortex as well as areas corresponding to cuneus and precuneus regions. These latter areas are believed to be involved in a number of functions not necessarily directly related to swallowing. The anterior cingulate gyrus, for example, is important in conscious feeling and in the processing of stimuli linked to emotion. The activation of pharyngoesophageal sensory pathways could conceivably be conveyed to the anterior cingulate gyrus either directly or after a relay in the hypothalamus and amygdala. Similarly, the prefrontal cortex is involved in the generalized arousal associated with emotional experiences (1, 19).

Recent studies have shown that the insular cortex receives projections from the thalamic nuclei and that its neurons are important for processing information about the internal state of the body homeostasis. Insular lesions affect the ability to exhibit emotion in response to various stimuli, particularly painful ones (36). The precuneus region is part of the posterior association area of the brain. It integrates information emanating from more than one sensory modality (26, 37). It is clear, on the basis of the findings of the present study and previous reports (13, 14), that these areas are also involved in deglutition. The functional importance of this multifocal cortical involvement in swallowing is clinically evidenced by development of swallowing disorders following CVA involving a wide range of cortical regions (2, 12, 15, 22, 27, 38) not directly related to the sensory/motor aspect of swallowing.

Contrary to the multifocal cortical representation of the volitional swallow, cerebral cortical representation of reflexive pharyngeal swallow was found to be focused on the primary sensory/motor cortex. Reflexive/ pharyngeal swallow occurs in response to direct pharyngeal stimulation either by inadvertent premature spill of oral bolus or reflux of gastric content into the pharynx (31). Pharyngeal reflexive swallow is ir-

Pressible and can be induced experimentally by injec-

tion of minute amounts of water into the pharynx directed posteriorly. Earlier studies comparing the biomechanical events during volitional and pharyngeal reflexive swallows have shown that, except for the absence of lingual peristalsis and transfer of oral bolus into the pharynx, all other biomechanical deglutitive events during reflexive pharyngeal swallow are similar to those of volitional swallows (31). For this reason, the activation of non-sensory/motor cortical regions observed in volitional swallowing probably represents the volitional aspects of the swallow such as intent, urge, decisionmaking, and memory, as well as information processing related to deglutition. This notion is partially supported by recent reports of activation of cingulate gyrus, parietooccipital regions, and insular cortex in healthy volunteers experiencing a swallowing urge (17).

Within the primary sensory/motor cortex, activated volumes during volitional swallow were significantly larger on the right hemisphere compared with the left. This finding corroborates previous reports (13, 14). On the contrary, for reflexive swallow there was a significantly larger left hemispheric volume of activated vox-

els compared with the right hemisphere. The func-

tional significance of this finding is not currently known.

Studies of the relationship between brain injury and associated deglutitive deficits report both anterior and posterior cortical insult, as well as brain stem stroke in isolation or combination with cortical lesions, to be associated with dysphagic symptoms such as aspiration (2, 11, 20), diminished deglutitive hyolaryngeal mechanics (20), poor timing and coordination of deglutitive events (11, 28, 29), and sensory discrimina-
tion. These findings suggest the involvement of multi-
ple cortical regions in volitional swallowing. The findings of a multifocal representation of volitional swallowing, documented in the present study, may offer some explanation for these diverse clinical find-
ings.

Some CVA patients without detectable brain stem involvement exhibit a deficit in pharyngeal reflexive swallow. The cerebral cortical representation of reflexive pharyngeal swallow in the primary sensory/motor region, documented in this study, offers an explanation for this clinical finding.
During the volitional swallows in our study, subjects swallowed their oropharyngeal salivary contents of undetermined volume present at the time of deglution. The reflexive swallows in our study were elicited by rapid injection of a water bolus into the pharynx, albeit a small volume (0.56 ± 0.06 ml). Thus there is a possible difference in the amount of swallowed liquid in the two types of swallows in our study. Published reports of unstimulated salivary flow range between 0 and 2.07 ml/min. (4). Although it is impossible to know with certainty the differences in swallowed volumes during the volitional and reflexive swallows in our studies, it seems unlikely that such small differences in swallowed volumes would result in the significant differences in the observed cortical activity. In the present study, we did not independently assess compliance with the instruction to “not volitionally swallow” during reflexive swallow scans. These volitional swallows potentially could affect the results for reflexive swallow. However, a volitional swallow would have been associated with a high-frequency “noise” spike on the recordings of fMRI at a time when no swallow stimulus was given. Such occurrences were not recorded during our studies.

Our use of a light tap on the leg as a signaling cue for volitional swallowing could potentially have resulted in a cortical response that was integrative of a sensory stimulus and a motor response. Although this is a possibility, we note that similar regions of activation for volitional swallowing have been reported using other signaling methods, such as visual cues (6, 7, 14). It seems unlikely that integrative effects from these different kinds of cues would yield similar regions of cortical activity. Furthermore, pilot studies in our lab and by others (13) of ad lib swallowing show similar regions of activation in the absence of any cueing stimuli.

In conclusion, reflexive pharyngeal swallow is represented in the primary sensory/motor cerebral cortex. This finding may explain some of the pharyngeal phase dysphagia in patients with hemispheric CVA. Also, cerebral cortical representation of volitional swallow is different from that of reflexive pharyngeal swallow. The former is represented in multiple cortical regions, including the primary sensory/motor cortex, insular, prefrontal/cingulate gyrus, and cuneus and precuneus regions, whereas the latter is represented in the primary sensory/motor cortex. These findings may explain the frequent occurrence of oral pharyngeal dysphagia in post-CVA patients with involvement of diverse regions of the brain. Areas of the cerebral cortex activated during volitional swallowing, in addition to the primary sensory/motor cortex, may represent the volitional aspect of the swallowing such as intent, planning, and possibly urge.

REFERENCES