Cerebral cortical representation of reflexive and volitional swallowing in humans

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Received 15 May 2000; accepted in final form 25 September 2000. —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.

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/
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 swallowing to determine the effect of this cue on the cerebral signal.

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

![Swallow epochs](image)

**Fig. 1.** Schematic diagram of the single-trial analysis technique. For each set of acquired image data, every voxel contains a time series of magnetic intensity signals, some of which show a high-frequency signal increase (motion “spike”) associated with swallow-related movement followed by a slowly changing signal associated with swallow-related cerebral cortical blood oxygen level-dependent (BOLD) changes. The signal “spike” is used to identify swallow epochs, which combine to generate an average functional magnetic resonance imaging (fMRI) signal waveform.
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 \( \frac{240}{64} \times \frac{240}{64} \times 10 = 141 \text{ mm}^3 \). According to our criteria, an activated cluster must be \( >422 \text{ mm}^3 \).

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 parieto occipital 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. Intrsubject comparison showed that the total volume of activated voxels during volitional swallowing (2,050 ± 164

Table 1. Regions of activation during reflexive and volitional swallowing

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

% Subjects
with activity 50 13 38 100 100 13 38 13 25 100 100 38 13 13 50 100 38 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 I 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 sensory/motor 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 sensory/motor 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-
areas are also involved in deglutition. The functional
37). It is clear, on the basis of the findings of the
eemanating from more than one sensory modality (26,
association area of the brain. It integrates information
response to various stimuli, particularly painful ones
about the internal state of the body homeostasis. Insu-
lar lesions affect the ability to exhibit emotion in re-
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 swallow-
ing.
Contrary to the multifocal cortical representation of
the volitional swallow, cerebral cortical representation
of reflexive pharyngeal swallowing was found to be fo-
cused on the primary sensory/motor cortex. Reflexive/
pharyngeal swallow occurs in response to direct pha-
ryngeal stimulation either by inadvertent premature
spill of oral bolus or reflux of gastric content into the
pharynx (31). Pharyngeal reflexive swallowing is irre-
pressible and can be induced experimentally by injec-
tion of minute amounts of water into the pharynx
directed posteriorially. 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 ob-
erved in volitional swallowing probably represents
the volitional aspects of the swallow such as intent,
urge, decisionmaking, and memory, as well as informa-
tion 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 swallowing there was a signifi-
cantly larger left hemispheric volume of activated vox-
dels 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 aspira-
tion (2, 11, 20), diminished deglutitive hyolaryngeal
mechanics (20), poor timing and coordination of de-
glutitive 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 reflec-
tive pharyngeal swallow in the primary sensory/motor
region, documented in this study, offers an explanation
for this clinical finding.

Fig. 3. Average volume of cortical activation in the primary sensory/motor region for volitional and reflexive swallowing in all tested subjects. Reflexive swallowing is characterized by greater activated cortical volume in the left hemisphere, whereas volitional swallowing shows greater volume in the right hemisphere. *P < 0.05 by paired t-test corrected for multiple comparison.

DISCUSSION
In this study, we compared the topography of the
cerebral cortical regions that are associated with reflec-
tive 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 re-
gions 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 hypothala-
mus 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. Insu-
lar lesions affect the ability to exhibit emotion in re-
sponse 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 swallow-
ing.

The activation of non-sensory/motor cortical regions
involved with swallowing is clinically evidenced by
development of swallowing disorders following CVA
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22, 27, 38) not directly related to the sensory/motor aspect of swallowing.

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During the volitional swallows in our study, subjects swallowed their oropharyngeal salivary contents of undetermined volume present at the time of deglutition. 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


