Cortical activation during human volitional swallowing: an event-related fMRI study

SHAHEEN HAMDY, DAVID J. MIKULIS, ADRIAN CRAWLEY, SHUWEN XUE, HELENA LAU, STANLEY HENRY, AND NICHOLAS E. DIAMANT
Departments of 1Gastroenterology and 3Medical Imaging, Playfair Institute of Neuroscience, Toronto Western Hospital, University of Toronto, Toronto, Ontario, Canada M5T 2S8; and 2Department of Gastroenterology, Hope Hospital, Salford M6 8HD, United Kingdom

Hamdy, Shaheen, David J. Mikulis, Adrian Crawley, Shuwen Xue, Helena Lau, Stanley Henry, and Nicholas E. Diamant. Cortical activation during human volitional swallowing: an event-related fMRI study. Am. J. Physiol. 277 (Gastrointest. Liver Physiol. 40): G219–G225, 1999.—Functional magnetic resonance imaging (fMRI) provides a safe, noninvasive method for studying task-related cortical neural activity. Because the cerebral cortex is strongly implicated in the control of human swallowing, we sought to identify its functional neuroanatomy using fMRI. In 10 healthy volunteers, a swallow event-related paradigm was performed by injecting 5 ml water bolus into the oral cavity every 30 s. Whole brain functional magnetic susceptibility (T2*)-weighted spiral imaging data were simultaneously acquired over 600 s on a 1.5-T magnetic resonance scanner, utilizing the blood oxygenation level-dependent technique, and correlation maps were generated using both >99% percentile rank and spatial extent thresholding. We observed areas of increased signal change consistently in caudal sensorimotor cortex, anterior insula, premotor cortex, frontal operculum, anterior cingulate and prefrontal cortex, caudal precentral and posterior parietal cortex, and precuneus and superiormedial temporal cortex. Less consistent activations were also seen in posterior cingulate cortex and putamen and caudate nuclei. Activations were bilateral, but almost every region, particularly the premotor, insular, and frontal opercular cortices, displayed lateralization to one or the other hemisphere. Swallow-related cortical activity is multidimensional, recruiting brain areas implicated in processing motor, sensory, and attention/affective aspects of the task.

cerebral cortex; deglutition; esophagus; functional magnetic resonance imaging; lateralization; motility; pharynx

THE CENTRAL REGULATION of swallowing involves “swallowing centers” in the brain stem, which receive sensory input from the oropharynx and esophagus and, together with peripheral peristaltic mechanisms, control much of the swallowing sequence (17, 25). However, the initiation of swallowing is a voluntary action that requires the integrity of sensorimotor areas of the cerebral cortex (27). If these higher centers, or their connections to the brain stem, are damaged, then patients have severe difficulty in starting a swallow (dysphagia) (5, 13). Pathophysiological evidence from stroke patients has implicated a number of cerebral regions important in the control of human swallowing, including frontal operculum and caudal precentral cortex (23, 29, 30), basal ganglia and thalamus (38), and insula (8). However, because of the heterogeneous nature of stroke in producing deficits of function, knowledge concerning the cortical neuroanatomy of swallowing based on such data remains unclear.

Recently, noninvasive techniques such as positron emission tomography (PET) (15) and transcranial magnetic stimulation (TMS) (14) have been employed to delineate more precisely the cortical representation of human swallowing. These studies have demonstrated that swallowing recruits multiple cerebral regions, most notably the caudolateral sensorimotor cortex, premotor cortex, insula, and temporopolar cortex, with differing degrees of hemispheric lateralization. One problem with PET studies, however, is the limited spatial resolution, which is at best around 6 mm (1). Furthermore, because block trial designs using interswell times of 10 s or less have to be applied, the resulting data may be distorted by the fact that esophageal peristalsis can be inhibited by swallowing occurring closer than 15 s apart (2, 36). TMS studies, by comparison, employ single cortical stimuli given several seconds apart. The consequence is that a full swallow is never evoked. Instead the response has to be monitored by recording the electromyogram of pharynx and esophagus from an intraluminal catheter inserted into the esophagus (4, 14). Thus information gathered using TMS refers only to the projections from motor regions of cortex to swallowing muscles and not necessarily the cortical activity associated with functional swallowing.

The recent advance of functional magnetic resonance imaging (fMRI) now provides a safe, noninvasive method for exploring how the human cerebral cortex processes information during a task. In particular, fMRI allows a detailed investigation of the functional neuroanatomy of the human brain with a spatial resolution of ~2 mm or less (1). The underlying principles behind fMRI relate to the sensitivity of MRI in detecting slight physiological alterations in neuronal activation via a complex function of changes in blood flow, blood volume, and blood oxygenation (37). The magnetic resonance signal changes predominantly depend on the concentration of blood deoxyhemoglobin, which acts as an intravascular contrast agent for MRI. The higher the concentration of deoxyhemoglobin the lower the detected signal. Contrary to expectation, the blood oxygenation level-dependent (or BOLD) effect induces increased signals in areas of increased neural activity because regional cerebral blood flow delivery of oxyhemoglobin greatly outstrips oxygen demand (or tissue
METHODS

Subjects. Ten healthy adult volunteers (7 male, 3 female, mean age 32 yr, age range 22–61 yr) were studied. None reported any swallowing problems before the study, and all were right-handed according to the Edinburgh Handedness Inventory (26). Each subject gave informed consent before the study, which was previously approved by the Executive of the Toronto Hospital Committee for Research on Human Subjects.

Monitoring the swallow. To determine the onset of each swallow event, a specially built plastic pneumographic belt (Dept. of Medical Engineering, Toronto Western Hospital, Toronto, ON) was attached to the anterior neck of each subject at the level of the hyoid bone and connected to a high-sensitivity multichannel chart recorder (R612 dynograph, Beckman Instruments, Schiller Park, IL). The recorder incorporated input signal-conditioning couplers (type 9853B, Beckman Instruments) for amplification, direct current filtering, data recording, and display during acquisition of the functional data. A time marker incorporated into the chart recorder allowed precise off-line event timing of each swallow to be measured in conjunction with the functional data.

Peroral water injection. With the use of a hand-held syringe, 5-ml water boluses were injected into the oral cavity every 30 s via a plastic infusion catheter placed in the midline, ~4 cm from the incisors, to facilitate swallowing. Each bolus was infused over 1 s, following which the subject would initiate a volitional swallow within ~4 s.

MRI scanning. The scanner used was a 1.5 T magnetic resonance system (GE Signa Echospeed, General Electric Medical Systems, Milwaukee, WI). Functional data were acquired as magnetic susceptibility (T2*)-weighted images with four shot gradient-echo spiral sequence imaging utilizing the BOLD contrast effect and using the following parameters: repetition time = 800 ms, echo time = 40 ms, flip angle (α) = 67°, field of view = 300 × 300 mm. Ten contiguous pure axial slices, 7 mm apart, were acquired for each subject, with the most caudal slice commencing ~5 mm inferior to the anterior commissure. Total functional imaging time was 600 s. In addition, to serve as background for the functional data, high-resolution anatomic spin lattice relaxation time (T1)-weighted spoiled gradient-echo images were also acquired for all the slices in each subject. Finally, so as to allow later transformation of the data into standard stereotactic space, a high-resolution T1-weighted three-dimensional volumetric scan of the whole brain was acquired in each subject to aid anatomic localization.

Experimental protocol. Before the study, each subject was asked to refrain from taking any stimulants (e.g., caffeine, alcohol) for at least 12 h before the scan. Each experiment was performed in the supine position, with the subject lying comfortably in a darkened room and with their head firmly secured by a tightly fitting foam pad within the head coil to reduce motion artifact. The pneumographic belt was then applied to the anterior neck, after which the water infusion catheter was inserted perorally. The subject’s head was then correctly aligned within the scanner, using crosshair projection lights located in the gantry of the MRI magnet. The high-resolution scan was then conducted.

During functional data acquisition, each subject performed a total of 20 wet swallows, following which a three-dimensional volumetric scan was performed. Data analysis. All calculations and image transformations were performed on a Sun Ultrasparc workstation (Sun Computers Europe, Surrey, UK) using both in-house software and Stimulate version 5.0 fMRI analysis software package (University of Minnesota, Minneapolis, MN) (34) and using a modification of the methodology used for event-related fMRI of tasks involving brief motion (6). After reconstruction of the functional and anatomic data, each subject’s images were realigned using Stimulate’s automated image reregistration algorithm, so as to correct for motion-related artifact, and transformed for functional analysis. An event-related Gaussian-derived reference function, with appropriate hemodynamic shift that best fit the hypothesis response function, was then used to analyze the acquired data on a voxel by voxel (voxel size = 2.4 × 2.4 × 7 mm) basis using a correlation coefficient value thresholding of >99% percentile rank. A series of three differing shifts of the reference function curve at 3 s apart were applied, and the resulting activations were assessed. The shift giving the best activations was then selected and applied to all the individual data sets. A separate spatial extent thresholding was also applied, with voxel clusters only being accepted if they were greater than two voxels in size. To aid neuroanatomic localization, activation maps generated in Stimulate were then displayed in three-dimensional volumetric mode using Analyze of Functional Neuroimaging software (MCWAFNI, Medical College of Wisconsin, Milwaukee, WI), which allowed transformation into standard stereotactic space (35).

RESULTS

Swallowing was well tolerated by all subjects during the scans. In two subjects, a minor proportion of the swallows were double swallows. In these circumstances, analysis was performed using the first swallow per 30-s epoch.

Signal changes. The percent increases in cortical signal activity for each subject, averaged across all swallows (in 30-s epochs) for all regions of interest with significant activations, are shown in Fig. 1. The results show that there was a highly consistent signal change waveform [mean increase = 1.5 ± 0.6% (SD)], which had a peak occurring 19 ± 3 s after the onset of the swallow (onset = 2.6 ± 0.8 s) relative to the bolus, this being well after the time period when movement-related artifact is greatest. A region by region analysis showed that there was no temporal difference in the sequence of activations associated with swallowing except in the case of the cingulate and premotor activations. In relation to these cortical sites, both the
Areas of increased cerebral activation. The regions, which demonstrated strongest activations across all subjects, are shown in detail in Table 1, and representative examples of these activations are displayed for two individuals as high-resolution three-dimensional volume brain images in Figs. 2 and 3. Consistent activations were observed in anterorostral cingulate cortex, caudolateral sensorimotor cortex, anterior insula, frontal opercular cortex, superior premotor cortex, anteromedial temporal cortex, anterolateral somatosensory cortex, and precuneus. Less consistent activations were seen in posterior cingulate cortex, left putamen, left caudate nucleus, and posterior parietal cortex in less than half of the subjects. Of interest, it was evident that, whereas activations were bilateral in most regions, insular, opercular, and premotor cortices were strongly lateralized in most subjects to either hemisphere, with the insula predominantly to the right hemisphere. Strongest activations (largest voxel clusters) were generally observed to be in the anterior cingulate cortex, premotor cortex, opercular cortex, and sensorimotor cortex.

**DISCUSSION**

Our study has demonstrated that single-event-related fMRI can be used to effectively identify the cortical processing associated with human volitional swallowing. In particular, we observed that multiple cerebral regions were recruited during swallowing, most notably the anterior cingulate cortex, the pericentral cortex, insula, and premotor cortex, with differing degrees of symmetry between hemispheres. These findings are consistent with those of previous PET activation data for swallowing, which showed a similar recruitment pattern (15), and with TMS data (4, 14), which demonstrated strong and relatively direct connections from regions of motor and premotor cortex to the muscles of the pharynx and esophagus.

It is noteworthy, however, that there were distinct differences between our fMRI findings and the previous findings described with PET. fMRI demonstrated a clear activation of the superior premotor cortex (Brodmann's areas 6, 8) that was not seen in the PET study, and, in contrast to the PET study, in which the individual sensorimotor activation displayed strong degree of lateralization, the motor cortex activations seen in our study were usually more bilateral. Such differences most likely relate to the nature of the two different imaging modalities and to the contrasting paradigm designs between the two studies.

In the PET study, a block trial of increasing frequencies of swallowing was performed using an interevent interval of 10 s or less between swallows. By comparison, our study used a single-event approach with swallows occurring every 30 s. Because repeated swallows that occur in close temporal proximity (every 15 s or less) to each other can induce a centrally mediated inhibition of esophageal peristalsis both in the striated and smooth muscle segments (36), it is possible that block trial studies using high-frequency repeated swallows may result in a masking or suppression of the premotor activity. If so, then our fMRI finding suggests that the premotor activity is in some way related to activation of the esophagus. Indeed, it has previously been demonstrated using TMS that the pathways projecting from the cortex to the striated muscle esophagus may be primarily located in these premotor areas (4). It is also possible that the longer interstimulus interval within our paradigm of swallowing every 30 s in a conscious and volitional manner may have favored the premotor activations identified.

Our present study confirms that the caudolateral sensorimotor cortex is important in the initiation of swallowing (27). This region of cortex is closely linked to control of tongue and face, and so the presence of swallowing activity in this region is not surprising. Its relationship with the premotor regions, also seen in our study, is somewhat less clear. However, it does appear that, in terms of the cortical motor control of human swallowing, there may be two distinct patterns of activity: the caudolateral motor cortex, which may be associated with initiation of the full swallowing sequence at the highest level, and the premotor regions,
Table 1. Individual details of the cerebral loci with increased activation during volitional swallowing

<table>
<thead>
<tr>
<th>Localization</th>
<th>Brodmann’s Areas</th>
<th>Mean Spatial Coordinates (x, y, z), mm</th>
<th>Individual Activation Distributions for Each Subject</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right anterior cingulate cortex</td>
<td>32, 33</td>
<td>2, 52, 4</td>
<td>+ + + + + + + + +</td>
</tr>
<tr>
<td>Left anterior cingulate cortex</td>
<td>32, 33</td>
<td>−2, 53, 8</td>
<td>+ + + + + + + + +</td>
</tr>
<tr>
<td>Right sensorimotor cortex</td>
<td>4, 6</td>
<td>43, −3, 24</td>
<td>+ + + + + + + + +</td>
</tr>
<tr>
<td>Left sensorimotor cortex</td>
<td>4, 6</td>
<td>−35, −21, 16</td>
<td>+ + + + + + + + +</td>
</tr>
<tr>
<td>Right insula</td>
<td>16</td>
<td>29, 23, −5</td>
<td>+ + + + + + + + +</td>
</tr>
<tr>
<td>Left insula</td>
<td>16</td>
<td>−30, −24, −8</td>
<td>+ + + + + + + + +</td>
</tr>
<tr>
<td>Right frontal operculum</td>
<td>44</td>
<td>52, 27, 9</td>
<td>+ + + + + + + + +</td>
</tr>
<tr>
<td>Left frontal operculum</td>
<td>44</td>
<td>−39, 41, 10</td>
<td>+ + + + + + + + +</td>
</tr>
<tr>
<td>Right premotor cortex</td>
<td>6, 8</td>
<td>50, 19, 29</td>
<td>+ + + + + + + + +</td>
</tr>
<tr>
<td>Left premotor cortex</td>
<td>6, 8</td>
<td>−48, 19, 26</td>
<td>+ + + + + + + + +</td>
</tr>
<tr>
<td>Right temporal cortex</td>
<td>21, 22</td>
<td>53, −20, −6</td>
<td>+ + + + + + + + +</td>
</tr>
<tr>
<td>Left temporal cortex</td>
<td>21, 22</td>
<td>−51, −17, −4</td>
<td>+ + + + + + + + +</td>
</tr>
<tr>
<td>Right parietal cortex</td>
<td>5</td>
<td>41, −48, 48</td>
<td>+ + + + + + + + +</td>
</tr>
<tr>
<td>Left parietal cortex</td>
<td>5</td>
<td>−39, −46, 51</td>
<td>+ + + + + + + + +</td>
</tr>
<tr>
<td>Left caudate nucleus</td>
<td>−26, 2, 4</td>
<td>+ + + + + + + + + + +</td>
<td></td>
</tr>
<tr>
<td>Left putamen</td>
<td>−22, 5, −1</td>
<td>+ + + + + + + + + + +</td>
<td></td>
</tr>
<tr>
<td>Right posterior cingulate cortex</td>
<td>23, 31</td>
<td>9, −41, 31</td>
<td>+ + + + + + + + +</td>
</tr>
<tr>
<td>Left posterior cingulate cortex</td>
<td>23, 31</td>
<td>−9, −48, 30</td>
<td>+ + + + + + + + +</td>
</tr>
<tr>
<td>Right prefrontal cortex</td>
<td>10</td>
<td>29, 48, 10</td>
<td>+ + + + + + + + +</td>
</tr>
<tr>
<td>Left prefrontal cortex</td>
<td>10</td>
<td>−24, 60, 8</td>
<td>+ + + + + + + + +</td>
</tr>
<tr>
<td>Right occipital cortex</td>
<td>18</td>
<td>−20, −77, 20</td>
<td>+ + + + + + + + +</td>
</tr>
<tr>
<td>Left occipital cortex</td>
<td>18</td>
<td>33, −67, 20</td>
<td>+ + + + + + + + +</td>
</tr>
<tr>
<td>Right precuneus</td>
<td>7, 31</td>
<td>24, −65, 36</td>
<td>+ + + + + + + + +</td>
</tr>
<tr>
<td>Left precuneus</td>
<td>7, 31</td>
<td>−48, −63, 33</td>
<td>+ + + + + + + + +</td>
</tr>
</tbody>
</table>

Spatial coordinates refer to the stereotactic space of Talairach and Tournoux (Ref. 35). Subjects 1–7 are male and 8–10 are female.

Fig. 2. Cortical activation patterns in 1 subject, shown as a series of magnetic resonance imaging (MRI) orthogonal planes (A–F). Activations shown include right caudolateral pericentral gyri (somatosensory cortex, Brodmann’s areas 2, 3; A and B), bilateral (right > left) middle and superior frontal gyri (premotor cortex, Brodmann’s areas 6, 8; C and D), right anterior insula cortex (E), and right caudolateral posterior parietal cortex/precuneus (Brodmann’s areas 7, 39; F).
which may be more modulatory and concerned with “priming” the pharyngoesophageal components of swallowing. It is interesting to note that our study did demonstrate more bilateral activation of the sensorimotor areas, but clear asymmetries were shown in cerebral activation within premotor cortex and insula for swallowing. The insula, also observed with PET to lateralize, activated mainly in the right hemisphere in right-handed males. The premotor asymmetries described correlate well with the findings from TMS studies (14), showing that pharyngeal and esophageal motor projections from areas anterior to the primary motor strip are asymmetrically represented in most subjects, without a clear handedness relationship but with a tendency to be greater in the right hemisphere. This further suggests that the premotor activity seen in our study reflects cortical control mechanisms important in pharyngoesophageal motility, especially esophageal rather than more oral stage functions associated with swallowing. Moreover, our finding from analyses with differing temporal shifts that the premotor region activates early in the swallow sequence does implicate a role for it in the preparation or priming the esophagus for the on-coming bolus. Future studies using techniques with better temporal resolution, for example, magnetoencephalography, should help determine the specific role of the premotor cortex in the central regulation of swallowing.

The anterior cingulate cortex activation seen in our study is relatively rostral, being close to those areas of anterior cingulate cortex typically described for emotional responses to noxious stimuli and even angina pain (11, 31, 37, 39). This more rostral region (surrounding the perigenual aspects of the cingulate gyrus) has also been shown in animals to have a visceromotor role: stimulation evoking alterations in respiration and non-verbal vocalizations and, in its more inferior aspects, visceromotor changes including nausea, vomiting, epigastric sensation, and salivation (8). Furthermore, the anterior cingulate cortex is recognized to be important in other more heterogeneous functions, including attention and as an emotional affect (9, 10, 11, 39). Thus its activation with swallowing may reflect a role for this region in the mediation of visceromotor activity such as digestive functions or may indicate an affective/attentive response to the challenge of swallowing safely and on command within the restricted environment of an MRI scanner.

A number of other regions observed in our study that become active during swallowing, including the somato-
sensory cortex, posterior parietal cortex, precuneus, and posterior cingulate cortex, are likely to have a sensory role in the control of swallowing. For example, the somatosensory cortex has been linked (along with the secondary somatosensory cortex and insula) to a receptive field for afferent input from the esophagus (3) and in primates has been shown to influence swallowing-related movements when cooled (20, 22). The posterior parietal cortex is recognized to play a heteromodal role in sensory perception, including body surface localization, memory of somesthetic environment, and integration of sensory input with motor output (19). The posterior cingulate cortex and precuneus are considered association areas, which have rich reciprocal connections with the thalamus and consequently are thought to play a role in integrating sensory information (19). It might therefore be speculated that these regions are utilized in the reception and higher processing of sensation arising from the oropharynx and esophagus, which may be then linked to modulation of the motor activity via connectivity with precentral cortex and insula.

The insula and frontal opercular activations seen in our study are in regions of cortex previously linked to human and animal swallowing, masticatory, and visceral behavior (24, 28, 32). In primates, stimulation of the insula will evoke swallowing, whereas stimulation of the frontal operculum preferentially induces mastication but at higher stimulation levels will also evoke the swallow sequence (21, 22). In humans, damage to both the insula and the operculum (e.g., bilateral opercular syndrome) will often result in dysphagia (8). Moreover, there is evidence suggesting that the right insula may have a greater role in swallowing control than the left insula (9).

The temporal and prefrontal cortex activations seen in our study are particularly intriguing. The anterior temporal cortex has been linked to sensory processing of taste and recognition of gustatory stimuli (33). However, the region activated in our study appears more posterior and lateral to this secondary taste area, being just medial to the secondary association area of temporal cortex. This latter region functions mainly in the perception or the mental imagery of auditory and visual stimuli (19). The medial temporoparietal area observed during our study might be a more heteromodal association area involved with cognitive processing of sensory input with motor output. Of relevance, anecdotal evidence using single-photon emission computerized tomography has linked hypometabolism of this region with swallowing difficulties and associated primary progressive aphasia (12). Furthermore, this region has extensive connections with paralimbic and limbic structures, including the prefrontal cortex, which was also active in our study (18). The prefrontal cortex has been associated with both preparation and planning of cognitive tasks and more inferiorly with vegetative and autonomic functions such as pressor responses, respiration, and olfaction (18). Thus these regions could play a supplementary role in the regulation of swallowing, either as higher centers involved with the integration of the sensorimotor aspects of swallowing and feeding or linked to swallowing because of its relationship with taste, and the imagery of food.

The duration and peak levels of the oxygenation-dependent brain fMRI signal changes measured in our study in response to swallowing were considerably longer and later than have been described for other sensory and motor systems like the visual cortex and somatic motor cortex. The signal changes peaked some 9–12 s after the swallow event, indicating that they were unlikely to be related to motion-induced artifact. Furthermore, the consistent nature of the waveform between subjects strongly implies that at least for swallowing the time course of associated neuronal activity is prolonged. The physiological origin of this phenomenon is obscure, but it may relate to the fact that the process of swallowing, from mouth to stomach, can take as long as 6–12 s (36). This long-lasting event incorporates secondary motor activity in the esophagus and continual modulatory ascending sensory input with descending motor output. Therefore, a more sustained cerebral response, perhaps through associated feedback loops from cortex to periphery, may maintain the BOLD-type effect.

In conclusion, single-event-related fMRI identifies multiple regions of cerebral activation associated with the voluntarily triggered swallow, most pronounced in the anterior cingulate cortex, caudal sensorimotor cortex, premotor cortex, insular and frontal opercular cortex, and temporal cortex, with differing levels of cerebral lateralization. These findings help in the understanding of how the cerebral cortex operates in controlling this complex but essential visceromotor function.

We thank Dr. Louis Ying for assistance during the conduct of the study and Dr. J. C. Rothwell and Professor D. G. Thompson for support and advice.

S. Henry is funded by the Medical Research Council of Great Britain and via a British Digestive Foundation/Hunt Memorial Fund and Hurst Centenary Fund Travel Fellowship.

Address for reprint requests and other correspondence: N. E. Diamant, Gl Molitgy Laboratory, Rm. 12-419, Mc.Aughlan Pavillion, Toronto Western Hospital, 399 Bathurst St., Toronto, ON, Canada M5T 2S8 (E-mail: ndiamant@playfair.utoronto.ca).

Received 28 December 1998; accepted in final form 29 March 1999.

REFERENCES


