◆ **Human Brain Mapping 30:3209–3226 (2009)** ◆

Neural Activation of Swallowing and Swallowing-Related Tasks in Healthy Young Adults: An Attempt to Separate the Components of Deglutition

Georgia A. Malandraki,[1]* Bradley P. Sutton,[2] Adrienne L. Perlman,[1]
Dimitrios C. Karampinos,[3] and Charles Conway[2]

[1]*Department of Speech and Hearing Science, University of Illinois at Urbana-Champaign, Urbana, Illinois*
[2]*Department of Bioengineering, University of Illinois at Urbana-Champaign, Urbana, Illinois*
[3]*Department of Mechanical Engineering, University of Illinois at Urbana-Champaign, Urbana, Illinois*

◆

Abstract: Understanding the underlying neural pathways that govern the highly complex neuromuscular action of swallowing is considered crucial in the process of correctly identifying and treating swallowing disorders. The aim of the present investigation was to identify the neural activations of the different components of deglutition in healthy young adults using functional magnetic resonance imaging (fMRI). Ten right-handed young healthy individuals were scanned in a 3-Tesla Siemens Allegra MRI scanner. Participants were visually cued for both a "Swallow" task and for component/control tasks ("Prepare to swallow", "Tap your tongue", and "Clear your throat") in a randomized order (event-related design). Behavioral interleaved gradient (BIG) methodology was used to address movement-related artifacts. Areas activated during each of the three component tasks enabled a partial differentiation of the neural localization for various components of the swallow. Areas that were more activated during throat clearing than other components included the posterior insula and small portions of the post- and pre-central gyri bilaterally. Tongue tapping showed higher activation in portions of the primary sensorimotor and premotor cortices and the parietal lobules. Planning did not show any areas that were more activated than in the other component tasks. When swallowing was compared with all other tasks, there was significantly more activation in the cerebellum, thalamus, cingulate gyrus, and all areas of the primary sensorimotor cortex bilaterally. *Hum Brain Mapp 30:3209–3226, 2009.* © **2009 Wiley-Liss, Inc.**

Key words: neuroimaging; swallowing; fMRI; deglutition; neurophysiology

◆

INTRODUCTION

Deglutition is one of the primary functions that enable humans to sustain life. Because swallowing begins at the lips and ends at the stomach, a swallowing disorder (aka dysphagia) may become evident as a result of a disruption at any point along this route [Massey and Shaker, 1997]. When the ability to swallow is lost or impaired, the risk for disability or even death is greatly increased. Both neurological and mechanical deviations can result in dysphagia. A few examples of diseases or disorders that can result in dysphagia include stroke, dementia, Alzheimer's Disease, Parkinson's Disease, cerebral palsy, traumatic brain injury, and head and neck cancer [Massey and Shaker, 1997].

This work was performed at the Biomedical Imaging Center of the Beckman Institute at the University of Illinois at Urbana-Champaign.
Contract grant sponsors: Mary Jane Neer Research Fund Award of the College of Applied Health Sciences and the Campus Research Board of the University of Illinois at Urbana-Champaign

*Correspondence to: Georgia A. Malandraki, William S. Middleton Memorial Veterans Hospital, Madison 2500 Overlook Terrace, GRECC-11G, Madison, WI-53705.
E-mail: gmaland@medicine.wisc.edu

Received for publication 25 June 2008; Revised 12 November 2008; Accepted 5 January 2009
DOI: 10.1002/hbm.20743

Swallowing is a highly complex sensorimotor process [Jean, 2001; Miller, 1986; Miller, 1993]. Identification of the neural pathways that govern this complex sensorimotor action is essential to the process of correctly identifying and treating swallowing disorders. Advances in biomedical technology have allowed for a variety of new techniques to be used in the study of the neural control of human swallowing.

The most recent and advanced method of functionally imaging the brain, without the use of ionizing radiation, is with functional magnetic resonance imaging (fMRI). Functional MRI provides a safe, noninvasive method for investigating human brain processes and offers a spatial resolution of ~4 mm. It has been suggested to be a valuable adjunctive technique to conventional MR imaging in the investigation of dysphagia following cerebral damage [Ertekin and Aydogdu, 2003].

In the last decade, fMRI has been used in the investigation of the neural control of volitional swallowing [Hamdy et al., 1999a; Hartnick et al., 2001; Kern et al., 2001a,b; Martin et al., 2001, 2004, 2007; Mosier and Bereznaya, 2001; Mosier et al., 1999; Suzuki et al., 2003; Toogood et al., 2005]. These studies identified many supramedullary areas as having a significant role in deglutition, including the premotor cortex, the primary sensorimotor cortex, the insula, and certain limbic regions. However, these areas, as some authors note [Hamdy et al., 1999a; Mosier and Bereznaya, 2001], might not uniquely reflect swallowing-related regions of the brain, but rather regions responsible for tongue or jaw activation, or even for planning of sequential movements. Indeed, in most swallowing-related fMRI studies, researchers sought to identify cortical and subcortical areas that are active during the entire act of deglutition [Huckabee et al., 2003]. Physiologically, however, swallowing consists of three stages: the oral, pharyngeal, and esophageal stages. The oral stage of swallowing can be further divided into two phases, the oral preparatory and the oral transport phases [Perlman, 1994]. In the oral preparatory phase, the material, which is referred to as the bolus, is made ready to be swallowed. The oral transport phase of swallowing involves the transition of the bolus from the mouth to the oropharynx [Kahrilas et al., 1993]. After the bolus has been formed, the tip of the tongue is elevated toward the superior alveolar ridge while the soft palate elevates and the posterior tongue depresses [Dodds et al., 1990; Shaker et al., 1988]. The bolus is then propelled to the oropharynx as the tongue pushes the bolus superiorly and posteriorly [Blitzer, 1990; Dodds et al., 1990]. The pharyngeal stage involves the transportation of the bolus from the oropharynx and around a closed laryngeal cavity into the esophagus [Perlman and Christensen, 1997]. During the pharyngeal stage, laryngeal protection is really crucial and occurs through three major types of closure: closure of the true vocal folds, the false vocal folds, and tilting of the epiglottis.

To better understand the neural activation during swallowing, it is necessary to differentiate between neural activations that occur during planning of deglutition, and during each of these physiological stages, i.e., during the oral stage of swallowing, the pharyngeal stage, and during similar laryngeal closure tasks. To investigate the neural function of specific events associated with swallowing, it is essential to study the neural activation during each of these components of the swallowing process. To achieve this goal, three tasks representative of different swallowing stages were designed and examined in the present study. These were: a tongue-tapping task (defined as the upward movement of the tongue tip toward the alveolar ridge), which is similar to the upward movement of the tongue tip when bolus propulsion is initiated from the anterior portion of the oral cavity during the oral transport phase of swallowing [Logemann, 1998; Perlman, 1994]; a laryngeal (true vocal fold) closure task (throat clearing), which is also an essential component of laryngeal protection during the pharyngeal stage of swallowing; and a planning of swallowing task (cognitive preparation to swallow), which was investigated to examine potential neural areas of planning deglutition that have not been investigated extensively [Huckabee et al., 2003].

As previously reported, several studies have attempted to identify the neural correlates of swallowing using fMRI in healthy individuals [Hamdy et al., 1999a; Hartnick et al., 2001; Kern et al., 2001a,b; Martin et al., 2001, 2004, 2007; Mosier and Bereznaya, 2001; Mosier et al., 1999; Suzuki et al., 2003; Toogood et al., 2005]. One of the first published studies attempted to identify the cerebral regions involved in the motor control of voluntary swallowing of water and saliva swallows in eight healthy adults [Mosier et al., 1999]. Results suggested a bilateral activation in the precentral gyrus (primary motor cortex) and multiple activations in the: primary sensorimotor cortex, supplementary motor cortex (SMA), prefrontal cortex, Heschl's gyri, cingulate gurus, insula, Broca's areas, and superior temporal gyrus. These researchers also attempted to detect lateralization patterns in the cortical control of swallowing, but found variable results. Hamdy and his colleagues tried to determine the functional neuroanatomy of human volitional swallowing of water in 10 healthy adults using fMRI [Hamdy et al., 1999a]. Similarly, their findings showed activations of multiple brain areas, such as the: antero-rostral cingulate cortex, caudolateral sensorimotor cortex, anterior insula, frontal opercular cortex, superior premotor cortex, anteromedial temporal cortex, anterolateral somatosensory cortex, and precuneous. The researchers stated that these activations may not be specific to swallowing innervation, but rather may indicate innervations of the tongue and face as well [Hamdy et al., 1999a].

Several other studies published in the following years also aimed to elucidate the activations associated with volitional swallowing. Despite minor differences in methodology, these studies reported similar or identical results. Martin and colleagues studied 14 normal adult female subjects on three different swallowing tasks: naïve saliva swallow, voluntary saliva swallow, and voluntary water swallow. Results showed activations of the left lateral precentral gyrus, the left lateral post-central gyrus, the right lateral precentral gyrus, and the right insula during both automatic and voluntary swallows and in addition to those, activation of the right caudal anterior cingulate gyrus during the voluntary swallowing tasks [Martin et al., 2001]. Similar areas were also reported by others using fMRI to study swallow-related brain activation during water or dry swallows [Hartnick et al., 2001; Kern et al., 2001a,b; Martin et al., 2004; Mosier and Bereznaya, 2001; Suzuki et al., 2003; Toogood et al., 2005]. In a more recent study, Martin et al. (2007] investigated the neural activation of swallowing in nine healthy female subjects over 60 years of age (average age was 74.2 years). This study reported that deglutition in older women also activated multiple cerebral areas, such as the lateral pericentral, perisylvian, and anterior cingulate cortex (ACC) with post-central gyrus activation being more lateralized to the left for both dry and water swallows. Activation during the water swallows, however, was found to be increased in the prefrontal and premotor cortices compared with activation during dry swallows [Martin et al., 2007].

The behavioral role of the tongue during both the oral and pharyngeal stages of swallowing has been extensively studied [Dodds et al., 1990; Hori et al., 2006; Lazarus, 2006; Logemann, 1998; Shaker et al., 1988; Youmans and Stierwalt, 2006]. As already reported, the upward movement of the tongue tip to achieve the action of tongue tapping is similar to the upward movement of the tongue tip when bolus propulsion is initiated from the anterior portion of the oral cavity during the oral transport phase of swallowing [Logemann, 1998; Perlman, 1994]. It is, however, completely different from the lingual movement during the pharyngeal stage of swallowing. During the initiation of the pharyngeal stage and as the velum elevates and retracts, the base of the tongue moves posteriorly to achieve contact with the posterior and lateral pharyngeal walls [Corbin-Lewis et al., 2005].

The supramedullary neural control of lingual movements during swallowing has also been studied using fMRI. Corfield and colleagues reported brain activation related to tongue contraction in eight normal right-handed adults [Corfield et al., 1999]. Significant activations were found in the: bilateral primary sensorimotor cortex extending downward towards the operculum (OP), insula, supplementary motor area (SMA), cingulate gyrus, putamen, thalamus, and cerebellum. In the brainstem, activation was found to be significant in the rostrocaudal level of the medulla (at the location of the CN XII nuclei), but activations more ventral and lateral to this point were also noted. Activations in the medulla were observed in six out of the eight subjects.

Also, using fMRI, Watanabe and colleagues, aimed to determine brain activity associated with different visually cued tongue movements in 24 normal young adults [Watanabe et al., 2004]. The results were comparable to the ones reported by Corfield et al. (1999] and showed that during tongue movements the most active cerebral regions included the primary sensorimotor and the SMAs bilaterally, as well as the left inferior and superior parietal lobules (IPL and SPL).

Throat clearing (also referred to as soft coughing) is a very important protective mechanism for the airway and lungs, and in normal individuals occurs as a result of penetration or aspiration of particulate matter, pathogens, secretions, postnasal drip, or mediators associated with inflammation [Canning, 2006]. For the present study throat clearing (soft coughing) was defined as the production of "two pairs of throat clearings through the mouth as a brief inspiration followed by forced expiration for each pair with the glottis closed at the beginning of expiration similar to a spontaneous cough" but with less force [Simonyan et al., 2007; Widdicombe and Fontana, 2006]. Patients with neurological disorders, pulmonary difficulties, or anatomical alterations involving the laryngeal area may have a compromised cough reflex, and as a result exhibit different degrees of dysphagia, and are at a higher risk for developing aspiration pneumonia [Mosconi et al., 1991].

Regarding the neural control of coughing, it is known that vagal afferent nerves are responsible for initiating the cough reflex [Canning, 2006; Widdicombe, 1996], as well as that areas in the medulla and pons of the brainstem are the most likely regulators of the reflexive cough [Widdicombe, 1996]. Supramedullary regions, however, that may modulate these brainstem centers for coughing are not well known [Canning, 2006; Simonyan et al., 2007; Widdicombe et al., 2006]. Clinical studies have reported that voluntary cough can be diminished in patients with cerebrovascular accidents (CVAs) in the frontoparietal area and in the basal ganglia [Addington et al., 1999]; however, little is known about the supramedullary control of coughing in the normal healthy population [Widdicombe et al., 2006].

Recently, Simonyan and colleagues [Simonyan et al., 2007] employed fMRI to study the supramedullary control of coughing and sniffing in 15 healthy adults. Their analysis showed multiple areas activated during both of these respiratory actions including the precentral gyrus, the post-central gyrus extending to the inferior frontal gyrus (area 44) rostrally, to the OP (1–4), and to the insula ventrally, and to the superior temporal and supramarginal gyri caudally, as well as the SMA extending to the anterior and middle cingulate cortex. Significant subcortical activation was noted to involve the ventral and dorsomedial thalamus, the caudate nucleus, the putamen and lateral globus pallidus. In the cerebellum, activation was observed bilaterally at the declive and culmen and at the right fastigial nucleus. Areas that were found to be significantly activated during both voluntary coughing and normal breathing included the substantia nigra and the dentate nucleus of the cerebellum bilaterally. The left precuneus, the lingual and inferior temporal gyri bilaterally, the amygdala, the lateral thalamus, and subthalamic nucleus bilaterally extending caudally to the pontomesencephalic region were all areas that were activated during voluntary coughing. Interestingly, the sole area exclusively active during voluntary coughing, but not during sniffing or breathing, was the area at the pontomesencephalic junction, extending to the brainstem.

Areas involved in the planning and cognitive preparation of the act of swallowing have not been extensively studied [Huckabee et al., 2003]. Understanding the neural control of planning deglutition will provide greater insight as to how the entire swallowing sequence is implemented. It will further enable better identification and treatment of patients diagnosed with swallowing apraxia, i.e., a disorder in motor planning and preparation of swallowing characterized by a delay in initiation of bolus transfer with no lingual movement or by lingual searching movements before the oral transport phase is initiated [Daniels, 2000; Logemann, 1998]. Swallowing apraxia has been associated with periventricular white matter and anterior cortical left hemispheric lesions [Robbins and Levine, 1988].

During planning of voluntary single hand and finger movements, the supplementary motor area (SMA) of the cortex is bilaterally activated [Orgogozo and Larsen, 1979; Roland et al., 1980]. Furthermore, it has been shown that planning of an internally guided (i.e., guided from one's own memory) movement results in a larger activation in the SMA while planning of externally guided movements (i.e., movements as response to external sensory cues) results in greater activation of the lateral premotor cortex [Gerloff et al., 1997; Jenkins et al., 2000; Tanji, 1996]. Recent research reported the involvement of the basal ganglia in the planning of motor actions, suggesting possible interactive frontal–basal circuits playing a significant role in motor planning [Elsinger et al., 2006].

The neural control of planning deglutition has received limited attention. One study used electroencephalography (EEG) to investigate planning of swallowing with execution [Huckabee et al., 2003]. The investigators recorded EEG data from 20 healthy young adults during voluntary swallowing and a control finger movement task. Their goal was to examine the potential presence of a premotor potential, known as the Bereitschaftspotential (BP), during the premotor planning of voluntary deglutition. They reported that the pharyngeal swallowing task elicited EEG activity in the supplementary motor cortex with a rapid declination ~500 ms before the initiation of movement, suggesting that the SMA plays a role in the planning of this motor action.

The aim of the present study was to identify the anatomical locations of the functional sites in the human cortex, subcortical areas, and cerebellum that are activated during swallowing and three related events: tongue tapping, throat clearing, and planning of deglutition without execution in healthy young adults. In an effort to separate the neural activation of different components of deglutition, it was hypothesized that areas activated during voluntary swallowing would be the same as those activated during the execution of three control tasks reflective of motor and cognitive functions associated with deglutition.

In many of the previously reported studies, a 1.5-Tesla MRI scanner was used to find the specific activations reported [Hamdy et al., 1999a; Mosier and Bereznaya, 2001; Mosier et al., 1999; Suzuki et al., 2003]. Monitoring of the swallowing compliance during the experiments was not always reported and a similar inconsistency was observed in addressing movement-related artifacts. The present investigation was able to take advantage of the increased sensitivity of a 3-Tesla MRI scanner and to use recent advancements in fMRI technology to provide more accurate information on the neural control of the different components of normal swallowing in healthy young adults.

MATERIALS AND METHODS

Subjects

Ten right-handed healthy individuals (five males and five females) with a mean age of 21.7 years (21.7 ± 2 years, mean ± SD), and no history of speech or swallowing difficulties or any neurological involvement, were recruited for this study. All potential participants were screened through an oral motor examination to ensure the existence of healthy normal oral sensorimotor function. Also, all subjects were right-handed as measured by the Edinburgh Handedness Inventory [Oldfield, 1971] and gave written informed consent before participating in the study. None of the subjects had previous fMRI experience. The study protocol was approved by the University of Illinois at Urbana-Champaign Institutional Review Board.

Tasks

The experimental design was an event-related design with jittered Interstimulus Intervals (ISIs) ranging in duration from 7 to 32 s. Jittering refers to the randomization of the intervals between stimulus events [Huettel et al., 2004]. Thus, tasks were presented intermixed in randomized intervals in six different 6-min functional scanning runs. The randomization of the tasks' order and intervals in each of the runs was completed with the optseq2 software program [Dale, 1999; Dale et al., 1999]. Each run contained five repetitions of each task, therefore each task was completed a total of 30 times during the experiment.

Tasks included: voluntary swallowing of 3 ml of water at room temperature, planning of a swallow without execution, tapping of the tip of the tongue against the alveolar ridge, and throat clearing. Tongue tapping was used to enable differentiation between tongue motion during an oral transport phase action and tongue movement during swallowing. Throat clearing, a laryngeal closure task, was utilized to help in the identification of neural areas involved in laryngeal closure. Planning was investigated to identify neural areas involved in the cognitive preparation of deglutition.

An LCD projection screen was used to visually cue the participants with instructions to "Swallow", "Prepare to swallow", "Tap your tongue", and "Clear your throat" at randomized time intervals. A specially designed system for controlled liquid release was utilized for the delivery of the 3-ml water boluses. The system consisted of a clear plastic infusion tube (4-feet long), a hand-held syringe (60-ml capacity), and a one-way flow valve. The administration of liquid bolus was controlled by the experimenter and consisted of controlled volumes (3 ml) of water, at room temperature, injected into the oral cavity of the participants.

For the voluntary swallow task, participants were instructed to swallow 3 ml of water every time the visual cue "Swallow" (and a bolus thereafter) was presented. Immediately preceding the "Swallow" command, participants saw the visual command "Prepare to swallow." For the planning (anticipatory) task, participants were trained to anticipate the swallowing process every time the visual cue "Prepare to swallow" was presented; however, they did not receive a bolus nor did they see the visual command "Swallow"; thus, they did not perform the motor task. Participants did not know if the command to swallow would follow the preparatory command. At the instances where the command "Swallow" was following the "Prepare to swallow" command, the experimenter injected the water as soon as the subjects saw the command "Prepare to swallow," i.e., ~4 s before the command "Swallow" was shown. That allowed for the water to be injected before the command "Swallow" would appear on the subjects' screen. In the third task, participants were instructed to tap their tongue twice every time the visual cue "Tap your tongue" appeared. In the fourth task, participants were instructed to produce a gentle throat-clearing task every time the visual cue "Clear your throat" appeared.

Behavioral Interleaved Gradient (BIG) methodology was used to address movement-related artifacts [Gracco et al., 2005]. Using this method, a 3-s gap during which images were not acquired followed 2 s of image acquisition. During the 3-s gap period, the subjects performed the swallow, tongue tapping, planning of the swallow, or the throat clearing as instructed.

All subjects were pre-trained to the tasks during a 45-min training session that generally occurred the day preceding the actual experiment, but had occurred as many as 3 days before. During this session, participants were trained to perform all tasks while lying down and to practice remaining as still as possible while tasks were completed inside a mock magnet.

Monitoring of Swallowing and Throat Clearing Trials

The swallowing and throat clearing trials were verified from their laryngeal movement patterns. Laryngeal movements were monitored by attaching an MR-compatible infant respiratory belt (Lafayette Instruments) around the neck of the subject. The MR physiologic unit recorded two waveforms to monitor both swallowing and throat clearing and to keep track of the scanning periods versus quiet periods in the run, the respiratory waveform and a sequence-timing pulse trigger. Laryngeal movements associated with swallowing and throat clearing trials were easily distinguished by their distinct patterns (Figs. 1 and 2).

Scanning Protocol

The MRI experiments were performed on the 3-Tesla Siemens Allegra MRI scanner located at the Biomedical Imaging Center (BIC) of the University of Illinois at Urbana-Champaign (UIUC). Two high-resolution anatomical scans were acquired for the registration of the functional images using FEAT (FMRI Expert Analysis Tool) Version 5.4, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). A T1-weighted MPRAGE 3D image (with 160 slices per slab, on a 256 × 256 matrix, 1.1-mm slice thickness and TR = 2250 ms, TE = 2.62 ms, and flip angle 9°, TI = 900 ms) was acquired. Also, a T2-weighted turbo-spin echo (TSE) scan was acquired to get anatomical information from the functional slice prescription. The TSE acquisition had the following parameters: field of view (FOV) of 240 mm, TR of 3 s, 34 slices, with 4-mm slice thickness. Registration to high-resolution structural and/or standard space images was carried out using FLIRT (FMRIB's Linear Image Registration Tool) [Jenkinson et al., 2002].

For the functional images, multislice EPI acquisition was acquired with the following EPI parameters: TE of 30 ms, TR of 5 s (including 3-s quiescent period), on a 64 × 64 matrix with an FOV of 240 mm. Seventy-four volumes of 34 axial interleaved slices of 4-mm thickness were collected during each run/session.

fMRI Data Analysis

fMRI data processing was carried out using FEAT (FMRI Expert Analysis Tool) Version 5.91, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl) [Smith et al., 2004]. The following prestatistics processing was applied; motion correction using MCFLIRT [Jenkinson et al., 2002]; slice-timing correction using Fourier-space time-series phase-shifting; nonbrain removal using BET [Smith, 2002]; spatial smoothing using a Gaussian kernel of FWHM 9.0 mm; grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor; highpass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma = 50.0 s).

The task-related responses were analyzed using multiple linear regression with a single regressor for each task convolved with a canonical hemodynamic response function and motion parameter estimates were used as additional regressors of no interest in the multiple regression analysis. For each subject, data were analyzed using FILM (FMRIB's Improved Linear Model) with local autocorrelation correction and a time-series analysis for each voxel was performed [Woolrich et al., 2001]. A higher-level

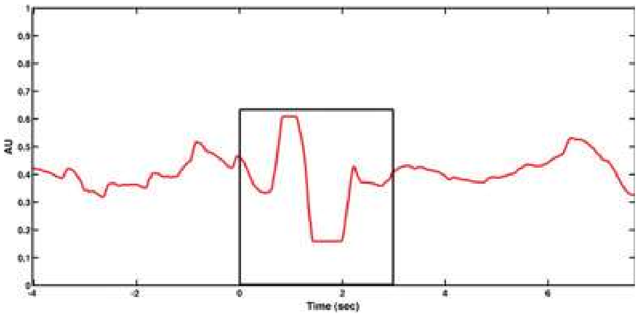

Figure 1.
Time course of the output of a bellows positioned around the subject's neck over the thyroid cartilage for a water-swallowing trial (red), for a single subject. Time = 0 indicates the time at which the subject was visually cued to complete the task. AU on the *y*-axis stands for Arbitrary Units. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

group analysis was then employed using the FMRIB Local Analysis of Mixed Effects (FLAME) [Beckmann et al., 2003] module in FSL and a one-sample *t*-test was performed for each task to determine significant group activations in each and every task. The group Z (Gaussianized T/F) statistic images were thresholded using clusters determined by $Z > 3.09$ at a corrected cluster significance threshold of $P = 0.05$ using the theory of Gaussian Random Fields (GRF). To compare neural activation between tasks, another mixed effects analysis was performed with subjects treated as random effects and tasks as fixed factors. For each control/component task, paired *t*-tests were performed between it and the other component tasks. A conjunction analysis was performed on the *t*-test results between a component task and other tasks. The minimum z-score image for each voxel was used to determine if a certain control task was significantly more activated than any other task. This procedure was also performed for the swallowing task versus the component tasks. In addition to this procedure, region-of-interest (ROI) analyses were also employed to further elucidate the differentiation between tasks.

The primary motor and somatosensory cortices, the premotor area, and the insula have been most consistently reported as activated areas during swallowing tasks [Hamdy et al., 1999a; Kern et al., 2001a,b; Martin et al., 2001, 2004, 2007; Mosier and Bereznaya, 2001; Mosier et al., 1999; Suzuki et al., 2003; Toogood et al., 2005]. Thus, the ROI analyses performed used these areas of interest to enable comparison of activation between tasks. Anatomical sections to define the primary motor cortex (Areas 4a and 4p) [Geyer et al., 1996], the primary sensory cortex (Areas 3a, 3b, 1, and 2) [Geyer et al., 1999; Geyer et al., 2000; Grefkes et al., 2001], and the premotor cortex (Area 6) [Geyer, 2004] were based on the maximum probability maps (MPM) and macrolabel maps [Eickhoff et al., 2005] of the Statistical Parametric Mapping Anatomy Tool box. The insula ROI was defined by hand and based on the MNI atlas. Mean percent BOLD signal change was extracted per ROI in each subject and was used as the dependent variable in the two-way within subjects Analysis of Variance (ANOVA), examining effects of tasks and ROIs.

RESULTS

Response Latency of the Swallows and the Throat-Clearing Events

The mean latency from the visual command for each task to the completion of the laryngeal movement signal associated with the water swallows was 2.255 s (±0.42 SD). The mean latency for the throat-clearing events was 2.559 s (±0.35 SD). These latency data indicate that participants responded promptly to the visual cues in both the water-swallowing and the throat-clearing tasks, with the response latency difference between the two tasks being minimal.

Group Activations in Each of the Four Tasks

The 3-ml water swallowing evoked significant activation in several brain regions (Fig. 3a–d). The most prominent group activations were observed bilaterally in the insular cortex (Brodmann Area 13), the middle and superior frontal gyrus (Brodmann Areas 6, 8, and 9), the precentral gyrus (BA 4), and the post-central gyrus (BA 3). A number of regions in the temporal lobe were activated, as well as the superior and inferior parietal lobules and the cingulate gyrus (BAs 24, 30, 31) bilaterally. Subcortical activations were observed in portions of the thalamus and the basal ganglia. Several cerebellar regions in both the anterior and posterior lobes were found to be significantly activated.

Throat clearing resulted in significant bilateral activation of the cingulate area (BAs 32, 31, 24), multiple regions in the frontal cortex including BAs 6, 9, 45, the insular cortex (BA 13), the pericentral area including the primary motor

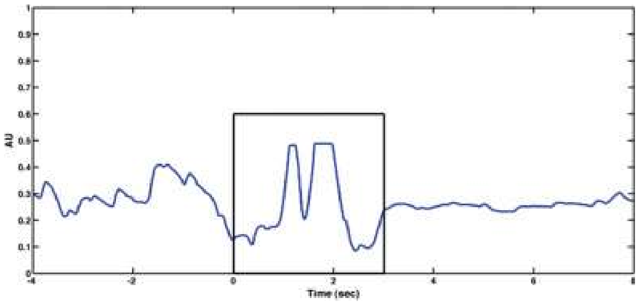

Figure 2.
Time course of the output of a bellows positioned around the subject's neck over the thyroid cartilage for one throat-clearing event (blue) for a single subject. Time = 0 indicates the time at which the subject was visually cued to complete the task. AU stands for on the *y*-axis Arbitrary Units. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

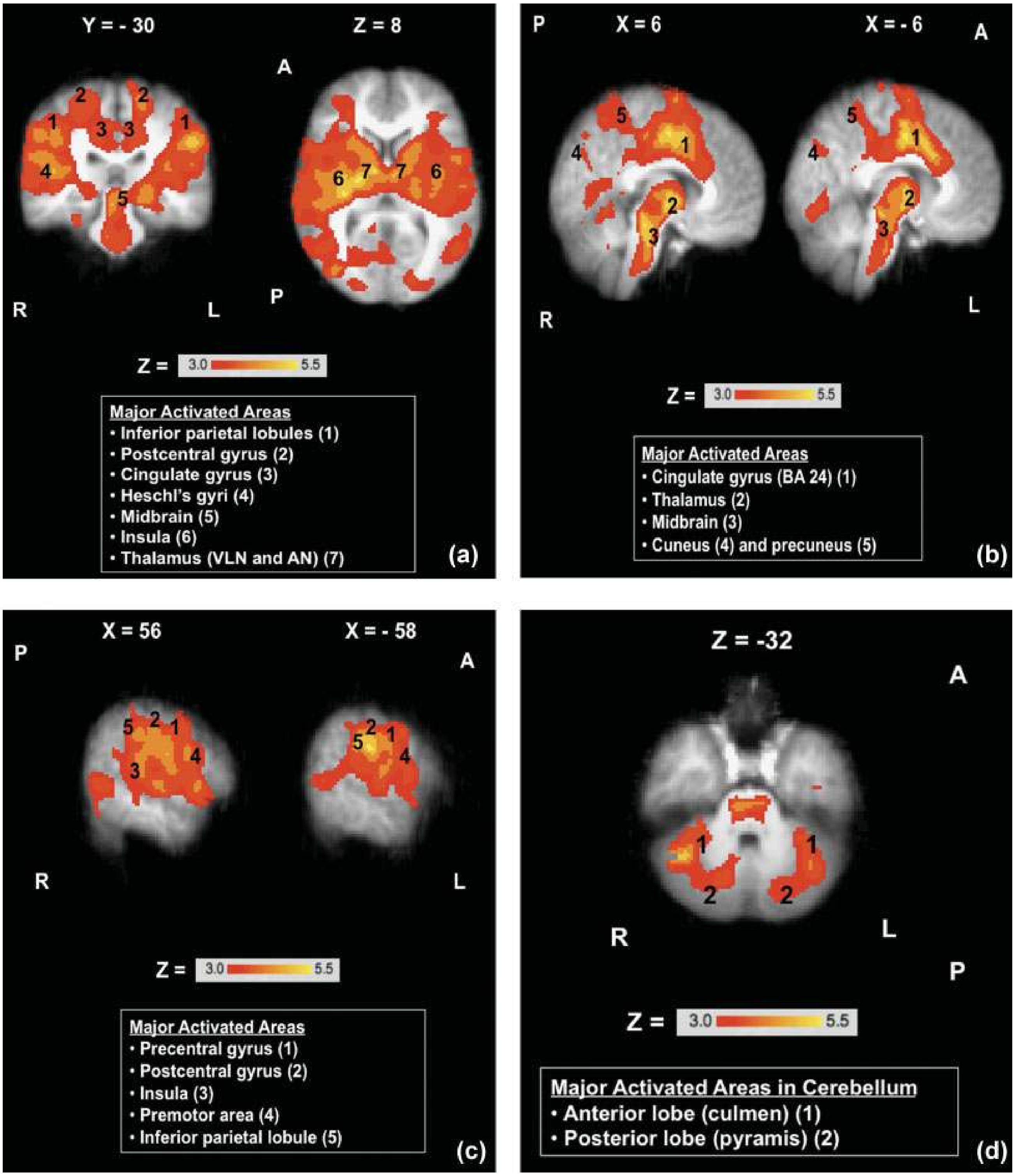

Figure 3.

a–d: Areas of significant activation (*Z* score = 3–5.5) during swallowing (*N* = 10). Boxes report the major activated areas. Images are shown in radiological convention (the right hemisphere is shown on the left). Coordinates are given in MNI space in mm. A = Anterior, P = Posterior, L = Left Hemisphere, R = Right Hemisphere.

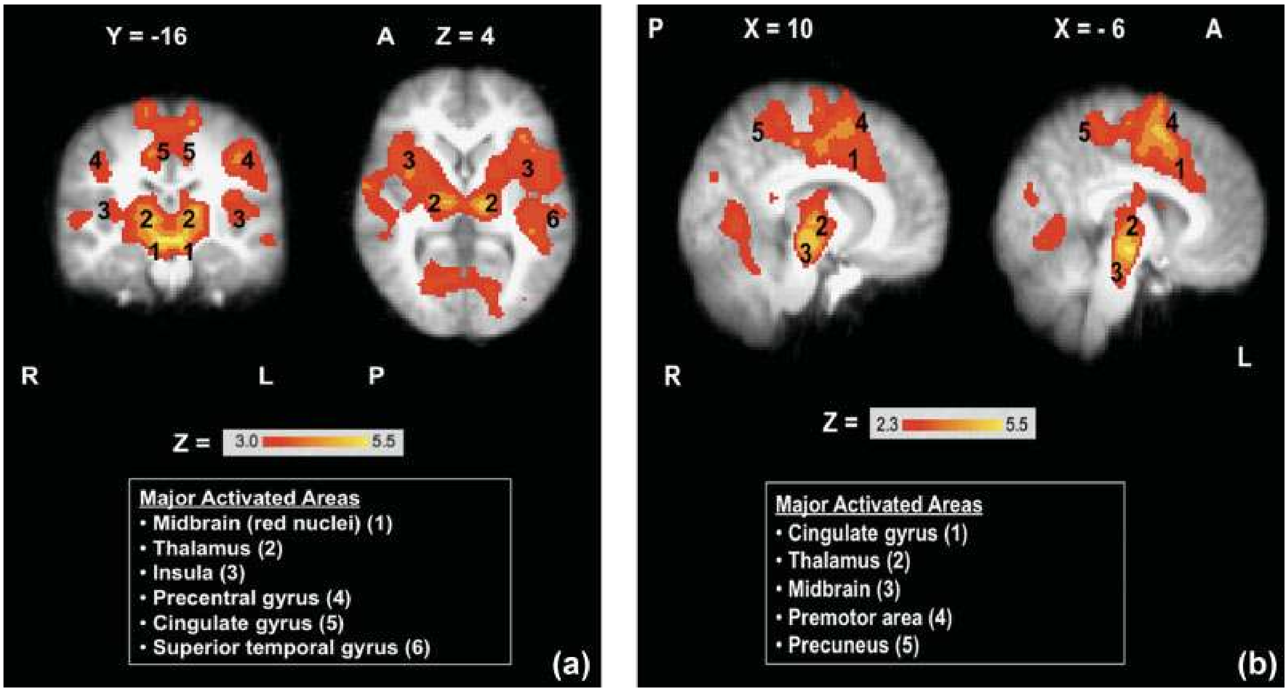

Figure 4.

a and **b**: Areas of significant activation (Z score = 3–5.5) during throat clearing (N = 10). The boxes report the major activated areas. Images are shown in radiological convention (the right hemisphere is shown on the left). Coordinates are given in MNI space. A = Anterior, P = Posterior, L = Left Hemisphere, R = Right Hemisphere.

and sensory cortices, and portions of the superior and middle temporal gyrus. Subcortically, throat clearing activated areas of the thalamus, the putamen and areas of the midbrain (red and subthalamic nuclei) in both hemispheres (Fig. 4a,b). Bilateral activation of the posterior lobe of the cerebellum was also seen during this task.

Tongue tapping activated multiple cortical and subcortical regions (Fig. 5a–c). These included the primary motor cortex (BA 4), the primary sensory cortex (BA 3, 1, 2), the premotor area (BA 6), and the frontal Brodmann Areas 8 and 45. Activations were also found in the cingulate gyrus (BA 32, 24, 31), the thalamus, the insula, and the superior and inferior parietal lobules bilaterally (BA 7). Planning of deglutition without execution bilaterally activated the premotor cortex (BA 6), and the dorsal, and ventral anterior cingulate areas (BAs 32 and 24) (see Fig. 6).

Comparison Between Tasks

Comparisons between the three component/control tasks (see Fig. 7) showed that areas more activated during throat clearing, included the posterior insula (BA 13), parts of the pericentral area including BAs 3, 4, and 5, and the midbrain bilaterally. Tongue tapping showed higher activations than the other two control tasks in portions of the premotor and precentral cortex (BAs 4, 6, 9) and the postcentral gyrus and the parietal lobules (BAs 2 and 40). Planning did not show any areas that were more activated than the motor tasks.

Additionally, when swallowing was compared to all other tasks, several areas had more significant activation during swallowing than any of the control tasks. These areas included the thalamus, the anterior cingulate gyrus (BA 24), the anterior insula and portions of the post- and pre-central cortices, and the cerebellum bilaterally. Figure 7 shows the areas that were mostly activated by each of the three motor tasks (swallowing, throat clearing, and tongue tapping).

The two-way within-subjects ANOVA identified a significant main task effect ($F_{3,27}$ = 35.639, P = 0.000) and a significant ROI effect ($F_{7,63}$ = 5.756, P = 0.005). The task by ROI interaction was also significant ($F_{21,\ 189}$ = 6.227, P = 0.000). Since the main effect for task was significant, individual ROIs were evaluated for the task effect, to examine whether tasks activated significantly differently in each ROI. For this purpose eight one-way ANOVAs were performed, one for each ROI. The independent variable was the task and included four levels: swallow, throat clear, tongue tap, and plan, and the dependent variable was the percent signal change in each ROI.

For the primary motor cortex areas, the ANOVA tests were significant (BA4a $F_{3,36}$ = 12.603, P = 0.000; BA4p

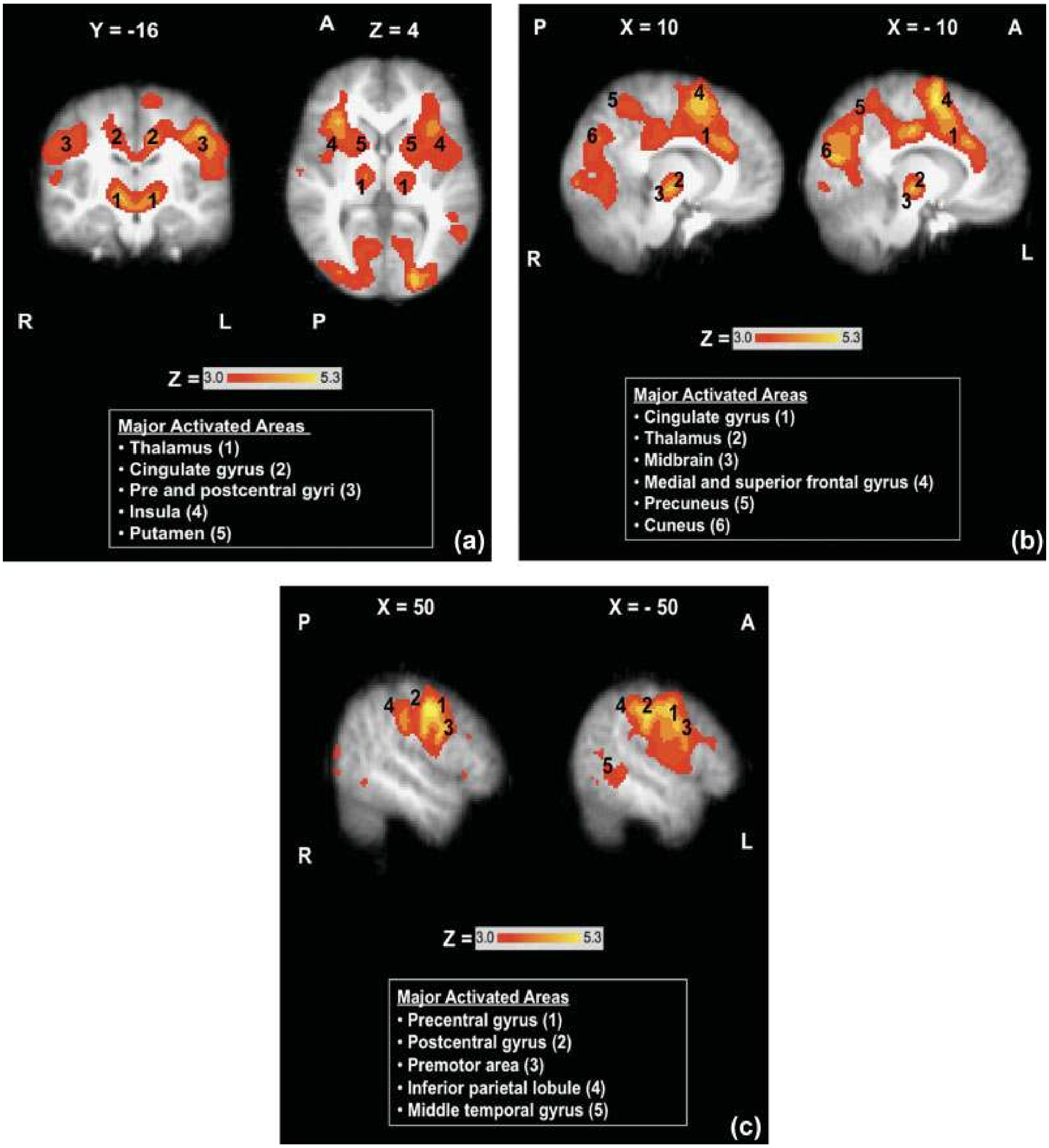

Figure 5.

a–**c**: Areas of significant activation (*Z* score = 3–5.3) during tongue tapping (*N* = 10). The boxes report the major activated areas. Images are shown in radiological convention (the right hemisphere is shown on the left). Coordinates are given in MNI space. A = Anterior, P = Posterior, L = Left Hemisphere, R = Right Hemisphere.

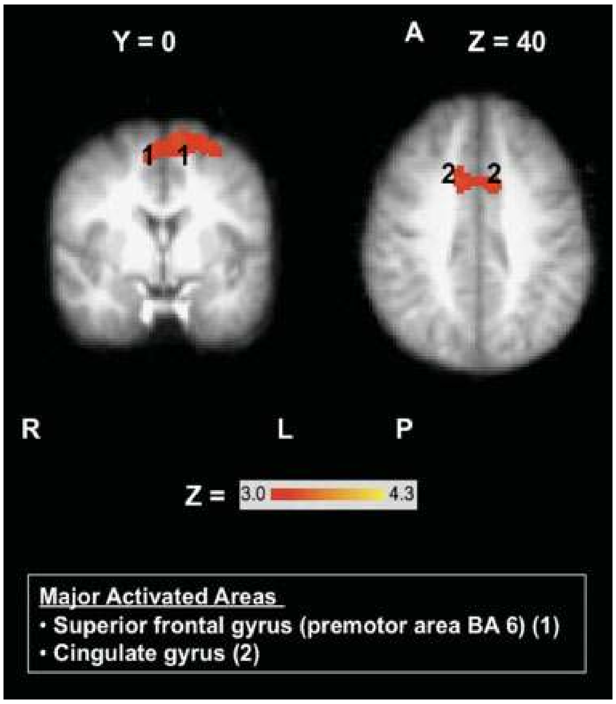

Figure 6.
Areas of significant activation (Z score = 3–4.3) during planning of deglutition without execution. The boxes report the major activated areas. Images are shown in radiological convention (the right hemisphere is shown on the left). Coordinates are given in MNI space. A = Anterior, P = Posterior, L = Left Hemisphere, R = Right Hemisphere.

$F_{3,36}$ = 21.444, P = 0.000) and follow-up *post hoc* comparisons were conducted using the Tukey HSD test. Results revealed that swallowing elicited significantly higher activation in BA4a than tongue tapping (P = 0.000) and planning (P = 0.000); and throat clearing elicited higher activation than planning (P = 0.004). In BA4p swallowing showed significantly higher activation than all other tasks ($P < 0.04$), and tongue tapping and throat clearing higher activation than planning ($P < 0.034$).

For the primary sensory cortex the ANOVA tests were also significant (BA1 $F_{3,36}$ = 14.823, P = 0.000; BA2 $F_{3,36}$ 19.513, P = 0.000; BA3a $F_{3,36}$ = 25.285, P = 0.000; BA3b $F_{3,36}$ = 23.505, P = 0.000) and *post hoc* pairwise comparisons were conducted using the Tukey HSD test as well. Results revealed that swallowing elicited significantly higher activation in all sections of the primary somatosensory cortex than any of the other tasks ($P < 0.001$); throat clearing and tongue tapping both elicited higher activation than planning in BAs 3a and 3b ($P < 0.014$). Significantly higher activation in BA2 during throat clearing was also observed compared to planning (P = 0.041). No significant differences in all areas of PSC activation were observed between throat clearing and tongue tapping.

For the premotor cortex (BA 6) the ANOVA test was significant ($F_{3,36}$ = 11.394, P = 0.000) as well, and *post hoc* pairwise comparisons were also conducted using the Tukey HSD test. Once more, results revealed that swallowing elicited significantly higher activation in BA6 than any of the other tasks ($P < 0.031$); throat clearing and tongue tapping both elicited higher activation in the premotor area than planning ($P < 0.031$).

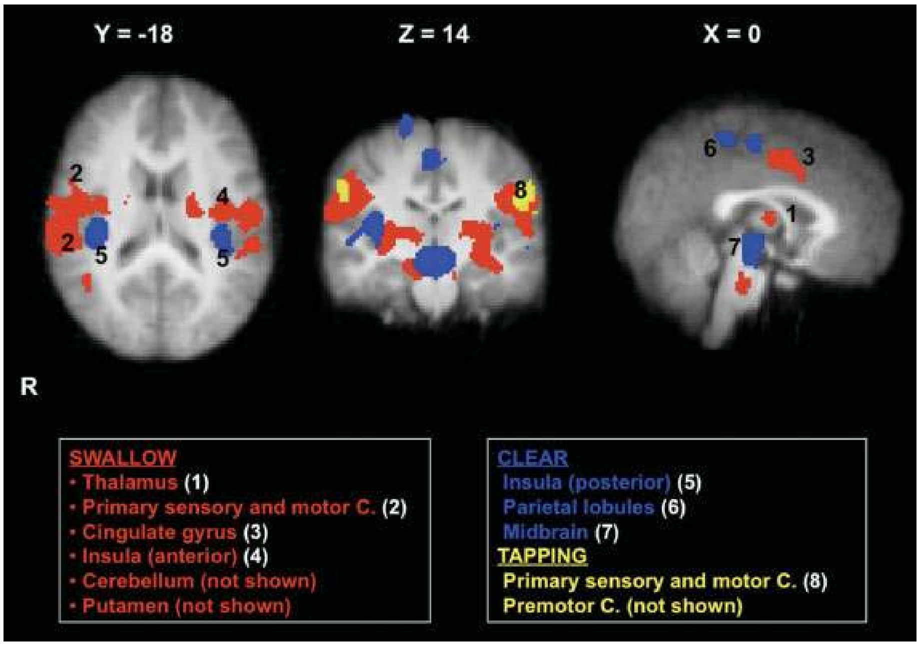

Figure 7.
Areas of most significant activation during swallowing (shown in red), during throat clearing (shown in blue), and during tongue tapping (shown in yellow). Boxes report the areas. Images are shown in radiological convention (the right hemisphere is shown on the left). Coordinates are given in MNI space.

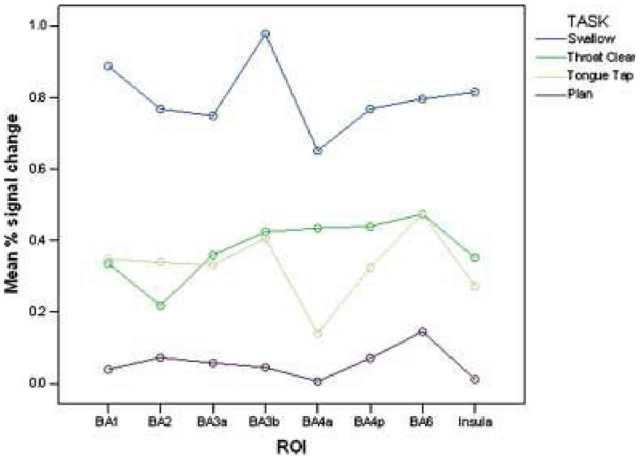

Figure 8.
Mean percent signal change in all ROIs for all four tasks. BA = Brodmann Area. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Lastly, for the insula the ANOVA test was significant ($F_{3,36} = 25.305$, $P = 0.000$) too. *Post hoc* pairwise comparisons were conducted using the Tukey test. A similar pattern was observed in the results. Swallowing elicited significantly higher activation in the insula than any of the other tasks ($P = 0.000$); throat clearing and tongue tapping both elicited higher insular activation than planning ($P = 0.005$ and $P = 0.04$, respectively).

Figure 8 shows the mean percent signal change for all four tasks and ROIs. As can be observed in the graph, swallowing indeed shows higher activations than all other tasks in all areas. It is also obvious that planning elicited the least amount of activation in all areas across subjects. Tongue tapping overall elicited higher activations than throat clearing only in BA2, whereas throat clearing elicited higher activations than tongue tapping in BA 4a and 4p and in the insular cortex. Despite these trends, the differences in activation noted between tongue tapping and throat clearing did not reach statistical significance. The fact that the ROI analysis did not verify the significant differences between these two tasks that were observed with the voxelwise conjunction analysis is probably because of the fact that the ROI analysis included larger regions that were anatomically defined, likely diluting the signal differences.

DISCUSSION AND SIGNIFICANCE

In healthy young adults multifocal regions were found to be activated during swallowing of 3-ml water. These findings are in agreement with many previously reported findings of studies on the neural control of swallowing in healthy adults, [Hamdy et al., 1999a; Hartnick et al., 2001; Kern et al., 2001a,b; Martin et al., 2001, 2004, 2007; Mosier and Bereznaya, 2001; Mosier et al., 1999; Suzuki et al., 2003; Toogood et al., 2005; Zald and Pardo, 1999]. Specifically, water swallowing significantly activated pericentral and perisylvian areas, the cingulate gyrus, the insula, the thalamus, premotor and prefrontal regions, parieto-occipital areas, and the cerebellum.

Our intention was a separation of the neural control of different components associated with deglutition in order to have a better understanding of the neural control of these components. To achieve this goal we hypothesized that areas activated during voluntary water swallowing would be the same as those activated during the execution of three component/control tasks reflective of motor and cognitive functions associated with deglutition. The section that follows discusses the major sites of activation that were observed during each of the examined tasks and their known or suspected role in deglutition in healthy young adults.

Primary Sensorimotor Cortex and Frontal Operculum

Activations in the primary motor cortex (BA 4), the primary somatosensory cortex (BAs 1, 2, 3), and the inferior frontal gyrus including the frontal OP (BAs 44, 45) during water swallowing were among the most prominent findings of the present study. Activation of these areas has also been one of the most common findings of previous neuroimaging [Hamdy et al., 1999a; Hartnick et al., 2001; Kern et al., 2001a,b; Martin et al., 2001, 2004, 2007; Mosier and Bereznaya, 2001; Mosier et al., 1999; Suzuki et al., 2003; Toogood et al., 2005] and electrophysiological studies of deglutition in humans and nonhuman primates [Hamdy et al., 1999a; Huang et al., 1989; Martin et al., 1999; Miller and Bowman, 1977]. Activation of this area has been reported for both saliva and water swallows [Kern et al., 2001a; Martin et al., 2001].

It has been suggested that the primary motor cortex constitutes a controlling region for muscle activity in the oropharynx and the esophagus during swallowing [Hamdy et al., 1996; Kern et al., 2001a]. Both saliva and water swallowing have been found to evoke activation of the primary sensorimotor cortex [Kern et al., 2001a; Martin et al., 2001], indicating that this area is involved in both voluntary and automatic aspects of the swallowing sequence.

Electrical stimulation of the area ventral to the precentral cortex (Brodmann's Areas 44, 1, 3, and 6) and stimulation of the face and masticatory motor and somatosensory cortex have been shown to elicit both swallowing and mastication in primates [Huang et al., 1989; Martin et al., 1999; Miller and Bowman, 1977]. TMS studies in humans have also shown that stimulation anterolaterally to the motor cortex can elicit electromyographic activity in oral and pharyngeal muscles known to be active during swallowing [Hamdy et al., 1999b].

Also, lesions in the most lateral portion of the precentral gyrus and the posterior portion of the inferior frontal gyrus have been frequently associated with dysphagia [Alberts et al., 1992; Celifarco et al., 1990; Robbins and Levine, 1988]. Such lesions may result in difficulties with the oral transport phase, the initiation of the pharyngeal stage, or in apraxia of swallowing [Robbins and Levine, 1988]. Others have also linked activation of the sensorimotor cortex with the initiation of the pharyngeal stage of swallowing [Hamdy et al., 1999a].

The involvement of this area in tongue movements has been previously described by several fMRI studies [Corfield et al., 1999; Kern et al., 2001a; Martin et al., 2004; Watanabe et al., 2004]. The lateral pericentral cortex activation during tongue movements may reflect motor activation of the tongue primary motor area or the sensory stimulation of the oral structures caused by the tongue movements or both [Martin et al., 2004]. Coughing has also been found to activate the primary sensorimotor cortex in healthy young adults [Simonyan et al., 2007].

In the present study, sensorimotor cortex and frontal OP activation was also seen during tongue tapping and throat clearing. When paired *t*-test comparisons were employed to compare activations between the three component/control tasks, tongue tapping showed more significant activations in this area than throat clearing and planning. This possibly reveals a more active role of the primary sensorimotor cortex in tongue movement (i.e., an oral component of deglutition) than in throat clearing and planning. The oral components of swallowing are the most voluntary elements of deglutition [Ertekin and Aydogdu, 2003] and thus, are expected to be represented more cortically.

Premotor Cortex

In the present investigation the premotor cortex (BA 6) was significantly activated during swallowing and during all control tasks. This finding is in agreement with results of many previous neuroimaging studies implicating the premotor cortex in the control of swallowing, [Hamdy et al., 1999a; Kern et al., 2001a,b; Martin et al., 2001, 2004, 2007; Mosier and Bereznaya, 2001; Mosier et al., 1999; Suzuki et al., 2003; Toogood et al., 2005], tongue movements [Corfield et al., 1999; Kern et al., 2001a; Martin et al., 2004; Watanabe et al., 2004] and coughing [Simonyan et al., 2007].

The premotor area (BA 6) is known for its role in motor planning and execution [Deiber et al., 1996; Tanji and Mushiake, 1996]. Relative to swallowing, however, the role of the premotor cortex is not completely understood [Hamdy et al., 1999a]. EEG data have indicated that a premotor potential is present in this area ~500 ms before the initiation of swallowing movements [Huckabee et al., 2003]. Mosier and Bereznaya (2001] also support the view that BA 6 is involved in the control of planning of sequential swallowing movements. Others, however, postulate that this region is more likely to modulate pharyngoesophageal components of the swallowing act [Hamdy et al., 1999a], rather than premotor planning. The fact that activation of the premotor cortex was observed during all the examined tasks in the present study contradicts the latter assumption, because tongue tapping, throat clearing, and planning of deglutition do not have pharyngoesophageal components. On the contrary, it possibly indicates the motor planning component present during swallowing, as well as during all the examined tasks. Further investigation of this activation is needed to identify the exact role of the premotor cortex in swallowing and related tasks.

Cingulate Cortex

Several areas of the cingulate gyrus were found to be activated during the swallowing task, including the ventral anterior cingulate area 24, the dorsal anterior cingulate area 32, and the dorsal posterior cingulate area 31, the intermediate and the posterior cingulate gyrus. The ACC has been frequently implicated in swallowing [Hamdy et al., 1999a; Kern et al., 2001a,b; Martin et al., 2001, 2004, 2007; Mosier and Bereznaya, 2001; Mosier et al., 1999]. ACC activation has been suggested to mediate attention, and emotional affect [Davis et al., 1997; Derbyshire et al., 1998], as well as emotional response to pain and noxious stimuli and sensorimotor planning [Devinsky et al., 1995]. In swallowing, researchers have suggested that ACC activation might reflect regulation of digestive functions [Hamdy et al., 1999a], or affective/attentive reactions to the swallowing task [Hamdy et al., 1999a; Kern et al., 2001a].

The exact role of the ACC in swallowing, however, is still not completely understood [Martin et al., 2001; Toogood et al., 2005]. Studies relating to swallowing have reported inconsistent results regarding the exact site of the cingulate cortex that is active during swallowing. One study has reported activation of the rostral ACC during water swallowing [Hamdy et al., 1999a], whereas the results of another study from the same research laboratory show the caudal part of the ACC to be active during water swallowing [Hamdy et al., 1999b]. Other investigators have observed more prominent activation of the rostral ACC during saliva (spontaneous) swallows and more prominent activation of the caudal and intermediate ACC during water (volitional) swallows [Martin et al., 2001; Toogood et al., 2005], indicating a somatotopic organization of the ACC relating to voluntary versus involuntary aspects of the swallowing act.

Activation of the ACC has been previously observed during tongue movements [Corfield et al., 1999; Kern et al., 2001a; Martin et al., 2004; Watanabe et al., 2004] and during coughing in healthy adults as well [Simonyan et al., 2007]. In the present study, activation of the anterior and/or the intermediate cingulate gyrus was observed during all four tasks, making the interpretation of this activation even more challenging. The present results may indicate two possible explanations; first, ACC activation during these tasks could indicate that ACC controls affective/attentive reactions to a task in general [Hamdy et al., 1999a; Kern et al., 2001a]; second, it may indicate that it has a role in sensorimotor planning, preparation, and processing of oropharyngeal tasks [Martin et al., 2004; Simonyan et al., 2007] that was a component of all the examined tasks.

Additionally, the posterior cingulate gyrus was found to be activated during swallowing and throat clearing. The posterior cingulate cortex is believed to be an association area that has reciprocal connections with the thalamus and an active role in integrating sensory information [Yukie, 1995]. Activation of this area along with activation of other sensory areas (primary somatosensory cortex, precuneus, parietal lobules, thalamus) in swallowing could indicate a role in receiving and processing sensory information from the oropharyngeal areas and in modulating motor actions through connections with the primary motor cortex and the insula [Hamdy at al. 1999a].

Parieto-Occipital Regions

During the swallowing task, activation of multiple areas in the parietal and occipital lobes was also observed. Apart from the primary somatosensory cortex, activations were seen in the superior parietal lobule (SPL) and inferior parietal lobule (IPL), as well as in the cuneus and precuneus. SPL and IPL have been implicated in information processing of spatially specific movements [Watanabe et al., 2004], and spatial feedback of motor actions [Desmurget et al., 2001]. The IPL in particular has been suggested to play a role in self-monitoring of spatial movements and integration of visual and proprioceptive information with ongoing motor control [Inoue et al., 1998]. Activation of the SPL and the IPL was also observed during tongue tapping in the present study, but not during throat clearing or planning. This indicates that the parietal lobules are more likely involved in the oral components of deglutition (i.e., tongue movement) and could play a role in the spatial processing of tongue movements or could be involved in processing proprioceptive feedback in the oral cavity [Inoue et al., 1998; Watanabe et al., 2004]. Activation of the IPL and the SPL has also been reported by other fMRI studies that studied the neural control of tongue movements [Corfield et al., 1999; Watanabe et al., 2004].

The cuneus and precuneus have been identified as activated areas during swallowing tasks in several fMRI studies [Hamdy et al., 1999a; Kern et al., 2001a,b; Martin et al., 2001; Mosier et al., 1999; Toogood et al., 2005]. In general, the posterior parietal cortex is thought to play a role in integrating sensory input with motor output, remembering somesthetic information [Andersen and Buneo, 2002] and associating visual and auditory cues to sensory/motor responses [Donner et al., 2002]. In swallowing, it has been proposed that these areas might play a role in reception and higher processing of sensation from the oropharyngeal and esophageal areas [Hamdy et al., 1999a].

Interestingly, however, in the “Go-No Go” paradigm that Toogood and colleagues employed to study neural activation during swallowing, they found that activation of the precuneus and the cuneus was not statistically different in the swallow versus the no-swallow condition, suggesting that the cuneus and precuneus activation may not be directly related to the motor act of swallowing [Toogood et al., 2005]. These areas have been implicated in multiple cognitive and perceptual tasks, including sequence processing [Catalan et al., 1998], integration of visuomotor information and visual perceptual tasks [Donner et al., 2002]. Toogood and colleagues [2005] suggest that activation of these areas is more likely due to visual, tactile, or auditory cueing for the task execution, rather than associated with the swallowing task per se.

Occipito-parietal activations during tongue movements have not been consistently reported by other fMRI studies. Many studies have found such activations during different tongue movement paradigms [Kern et al., 2001a; Martin et al., 2004; Watanabe et al., 2004]; however, in the study of Corfield et al. [1999], the only parietal area observed to be active during isometric tongue contraction was the primary somatosensory cortex. During coughing, Simonyan et al. [2007] reported activations in the left precuneus and the supramarginal gyri caudally.

Activation in the precuneus and the cuneus was also observed during most tasks. The fact that activation in the cuneus and precuneus was so frequently observed probably supports the conclusion of Toogood et al. (2005] that activation of these parieto-occipital regions is associated with visual, tactile, or auditory cueing for the task execution and not necessarily with the motor act of swallowing. Additionally, a Go-No Go paradigm was not followed in the present research, thus the role of the cuneus and precuneus in deglutition and related tasks cannot be fully specified by the results of this investigation.

Insular Cortex

Additionally, the insular cortex was activated during water swallowing in the present study. Clinical studies have revealed that insular lesions can result in dysphagia [Alberts et al., 1992; Daniels and Foundas, 1997; Hamdy et al., 1997; Stickler et al., 2003], with some authors specifically associating lesions in the right anterior insula with swallowing difficulties [Daniels and Foundas, 1997; Hamdy et al., 1997]. Functional MRI studies have also shown that the insular cortex is activated during swallowing tasks [Hamdy et al., 1999a; Kern et al., 2001a; Martin et al., 2004; Mosier and Bereznaya, 2001; Mosier et al., 1999; Toogood et al., 2005]. Insular activation has been found to be either bilateral, [Kern et al., 2001a; Mosier et al., 1999; Mosier and Bereznaya, 2001; Suzuki et al., 2003], or more significant in the right hemisphere [Martin et al., 2001; Martin et al., 2004].

In general, there is great inconsistency in the exact insular location reported as active during swallowing and related tasks. Some research describes the anterior insula as active during swallowing and the posterior during tongue movement [Martin et al., 2001; Zald and Pardo, 1999], whereas others report the posterior insula activated during swallowing [Martin et al., 2004]. The specific location of this activation remains questionable [Martin et al., 2004]. The insula, however, is thought to regulate sensory-motor integration between primary cortical and subcortical sites, gustatory sensation, and visceral motor rhythm, [Augustine, 1996; Mosier et al., 1999]. Furthermore, insular involvement has been implicated in voluntary oral motor control [Raichle, 1991] and speech motor control [Dronkers, 1996]. Regarding swallowing, insular activation may regulate the kinematics of movement and the temporal sequence of events during swallowing [Mosier et al., 1999], or could reflect the integration between multiple sensory and/or motor processes involved in deglutition [Martin et al., 2001].

Activation of the insular cortex has also been seen during different tongue movement tasks [Corfield et al., 1999; Kern et al., 2001a; Martin et al., 2004] and during coughing [Simonyan et al., 2007]. This possibly supports the sensory-motor integration role of the insula [Simonyan et al., 2007] or its involvement in oral motor control [Raichle, 1991].

In our study insular activation was also seen during throat clearing and tongue tapping. After the paired *t*-test comparisons, however, it was shown that bilateral activations in the anterior insula are more significant during swallowing compared to all other tasks. Interestingly, activation in the right posterior insula was more significant during throat clearing compared to tongue tapping and planning. These results suggest that the entire insular cortex plays a role in swallowing, with the posterior insula possibly being more implicated in less voluntary and more automatic portions of the swallow, such as laryngeal closure (i.e., throat clearing).

Thalamus

The thalamus was activated bilaterally during the swallowing task in the present experiment. The thalamus is a structure known as a relay station for sensory information traveling into higher cortical areas [Connors et al., 1998], with some nuclei also acting as association areas [Connors et al., 1998; Mosier et al., 1999]. Thalamic infarcts have been associated with dysphagia [Paciaroni et al., 2004; Tan et al., 2004]. During fMRI studies the localization of specific thalamic nuclei involved in swallowing and related tasks can be challenging. The thalamus has been reported to be activated in other neuroimaging studies of deglutition [Mosier et al., 1999; Mosier and Bereznaya, 2001; Suzuki et al., 2003]; however, the specifics of this activation remain unclear.

Activation in the thalamus during tongue movements [Corfield et al., 1999; Martin et al., 2004; Watanabe et al., 2004] and during coughing [Simonyan et al., 2007] has been previously reported. Although most studies have difficulty identifying and reporting activations in specific thalamic nuclei, Simonyan et al. (2007] reported ventral and dorsomedial thalamic nuclei activations during coughing.

Thalamic activations were also observed during tongue tapping and throat clearing in this study. It has been proposed that thalamic activation during swallowing and related tasks suggests the sensory and motor input processing through thalamocortical and thalamostriatal connections [Mosier et al., 1999] and transferring of this information to higher cortical structures [Simonyan et al., 2007]. Such processing and transferring of sensorimotor information is also present during both tongue tapping and throat clearing and could explain the thalamic activations seen during these tasks as well.

Cerebellum

In the present study participants exhibited bilateral cerebellar activation during swallowing. Cerebellar activation during deglutition has been reported only by few fMRI studies [Suzuki et al., 2003; Mosier et al., 1999, 2001]. It should be noted, however, that many of these investigations focused on identifying cortical and subcortical activations and did not examine the cerebellum [Hamdy et al., 1999a; Kern et al., 2001a,b; Martin et al., 2001].

Cerebellum has been implicated in the control of adaptive coordination, the organization of sensory input with motor output and the learning of sequential movements [Hikosaka et al., 1999; Thach et al., 1992]. Additionally, it is thought to operate in a feed-forward pattern that enables efficient control of movements [Nowak et al., 2007]. In swallowing, the cerebellum may offer an adaptive modulation of the lingual and pharyngeal musculature, enabling the accurate internal representation needed for a functional swallow to occur [Mosier and Bereznaya, 2001].

Activation of the cerebellum during tongue movements has been reported by several functional neuroimaging studies [Corfield et al., 1999; Watanabe et al., 2004; Zald and Pardo, 1999]. Rhythmic isometric tongue contractions [Corfield et al., 1999], as well as lateral tongue movements [Zald and Pardo, 1999], and intraoral sensory stimulation of the tongue with water [Zald and Pardo, 2000] are known to evoke activations of multiple cerebellar foci. Bilateral activation of the dentate nucleus, the declive and culmen, and right cerebellar activation at the fastigial nucleus has also been identified during coughing in healthy adults [Simonyan et al., 2007].

Regarding the control tasks examined in the present study, limited cerebellar activation was observed only during throat clearing. Tongue tapping and planning did not significantly activate the cerebellum. This finding could indicate that the cerebellum is more actively involved in the modulation of the pharyngolaryngeal muscles and the coordination of sensory input with motor output during the pharyngeal rather than the oral components of the swallow.

According to Suzuki et al. (2003] studies that found cerebellar activation used a self-paced swallowing task and had a pre-scanning training component. Thus, the cerebellar activation seen on these swallowing studies can reflect a learning of the task component or can be related to the coordination and organization of sensory input and motor outputs during deglutition. In the present investigation, the swallowing task was not self-paced; however, there was a prescanning training session for all subjects. The fact that cerebellar activation was not seen during all tasks contradicts the argument that cerebellar activation reflects a learning of the tasks component. If this was the case, cerebellar activation should be seen during all three motor tasks examined (i.e., swallowing, tongue tapping, and throat clearing).

Considerations

There are considerations that may have influenced some of the results of the present investigation. First, all tasks examined were volitionally initiated by the visual commands. Thus, it is possible that some of the activations seen have greater weighting on those networks that are involved in voluntary motor and cognitive tasks, and less weighting on networks that are associated with more automatic components of these tasks. Future investigations should also attempt to examine the specified tasks in a spontaneous paradigm that would allow for identification of areas purely involved in the automatic execution of these tasks. It has to be mentioned, however, that for the swallowing task, a water bolus was given to the subjects and since a bolus elicits swallowing, this may partially remedy this problem.

Another consideration is that the present study did not address the role of the brainstem in the neural control of the tasks examined. Although activation in some midbrain nuclei, the pons, and the medulla was seen during swallowing and throat clearing, these activations cannot be specifically and accurately attributed to these tasks. Brainstem activation is expected during most components of deglutition, because of the fact that highly complex brainstem circuitry is required to produce a completely functional swallow [Jean, 2001; Miller, 1993]. BOLD fMRI is thought to have sufficient sensitivity and resolution to identify activation in the brainstem [Corfield et al., 1999]. Despite this, respiratory and cardiac cycles cause tissue movements that are prominent in the brainstem [Poncelet et al., 1992]. Thus, to accurately correlate brainstem activation with a specific task under examination, careful physiological monitoring of the respiratory and the cardiac cycles is required. These physiological data should then be regressed out of the statistical model to show which brainstem activation is truly associated with the actual examined task. In the present study the respiratory input located at the magnet table was used for the monitoring of the swallowing and the throat-clearing events, and thus respiratory cycle information could not be collected. Cardiac cycle data were acquired but were not analyzed at this time. Analysis of those data may provide more accurate information on brainstem activation during the examined tasks. Correlation of the physiological data with the fMRI data has not been attempted at this point. Future studies should also include such a correlation.

Furthermore, fMRI testing requires the subjects to lie supine during scanning. Although dry swallowing in the supine position occurs when people lie down or when they are asleep, swallowing of liquid in the supine position is not a common practice. Behavioral changes in the swallowing physiology in the supine position have been reported [Barkmeier et al., 2002; Castell et al., 1990; Inagaki et al., 2007; Ingervall and Lantz, 1973; Johnsson et al., 1995], but are not thought to significantly alter a swallow. Additionally, it is doubtful that the neural activation of swallowing would change between the upright and supine positions. Indeed, studies using TMS [Hamdy et al., 1998] that examine subjects in the upright position have found many of the same cortical areas implicated in swallowing as these reported by most fMRI studies.

In the present experiment the participants were visually cued to all tasks. As previously discussed, this mode of cueing may explain some of the parieto-occipital activations. Whether some of these activations are actually associated with the tasks examined remains unclear. Specifically activation in the cuneus and precuneus was found in a “Go-No Go” paradigm study to be associated with visual, tactile, or auditory cueing for task execution and not necessarily with the motor act of swallowing [Toogood et al., 2005]. Such a paradigm was not followed in the present investigation, thus the role of the cuneus and precuneus in deglutition and related tasks cannot be fully specified by these results. Future research using different cued presentations to elicit swallowing could elucidate the functional role of these areas in cued voluntary swallowing [Toogood et al., 2005].

Another limitation was that sensory components of the swallowing sequence were not presently examined. Neural areas responsible for sensory processing and integration of sensory and motor information were found to be active during many of the examined tasks in both age groups. Since a sensory task was not included in the current experimental design, the exact activation and role of these areas can only be implied. Recently, two fMRI studies attempted to identify supramedullary areas involved in oropharyngeal sensation [Sörös et al., 2008; Lowell et al., 2008]. Both studies found that the neural network responsible for sensory innervation of the oropharyngeal areas is very similar to the one activated during the motor task of swallowing, including the primary sensorimotor cortex, the thalamus, insula, frontal regions, the premotor area, and the anterior cingulate [Lowell et al., 2008; Sörös et al., 2008]. Nevertheless, it should be noted that the air-pulse stimulation that was used in both studies as the sensory stimulation technique, frequently evoked swallowing or other pharyngolaryngeal movements ~6–7 s following the stimulation. Thus, some of the activation seen in those studies might also reflect areas of swallowing activation, and cannot be exclusively attributed to the sensory stimulation. Future investigations using sensory stimulation components that will not elicit the motor act could clarify the areas that are solely associated with sensation in the oropharyngeal area.

CONCLUSION

In conclusion, the present study verified previously reported findings of the neural control of swallowing in healthy adults, [Hamdy et al., 1999a; Hartnick et al., 2001; Kern et al., 2001a,b; Martin et al., 2001, 2004, 2007; Mosier and Bereznaya, 2001; Mosier et al., 1999; Suzuki et al., 2003; Toogood et al., 2005; Zald and Pardo, 1999]. As in most other studies, swallowing significantly activated pericentral and perisylvian areas [Hamdy et al., 1999a; Hartnick et al., 2001; Kern et al., 2001a,b; Martin et al., 2001, 2004, 2007; Mosier and Bereznaya, 2001; Mosier et al., 1999; Suzuki et al., 2003; Toogood et al., 2005; Zald and Pardo, 1999].

Examination of the different tasks, however, provided a greater insight in the neural control of the different components of deglutition. Specifically, results indicated that oral components of the swallow (such as tongue tapping) more significantly activate cortical areas and specifically the primary motor and sensory cortices bilaterally, as well as the parietal lobules. The oral components of swallowing are the more voluntary elements of deglutition [Ertekin and Aydogdu, 2003] and thus, are expected to be represented more cortically.

On the contrary, pharyngeal components (such as throat clearing, i.e., a laryngeal closure task) tended to show higher activation in subcortical areas, i.e., the posterior insula. These findings suggest that the most automatic components of deglutition (such as laryngeal closure) may rely more heavily on subcortical networks. No areas were found to be more activated during planning. This finding suggested that some motor planning is present as a preliminary action in all motor tasks examined and deserves further examination.

Finally, the areas more activated during swallowing included thalamic areas, the cingulate gyrus, and the anterior insula, suggesting that some aspects of the swallow were not captured by the three component/control tasks. This is not surprising if one considers that the two motor tasks (tongue tapping and throat clearing) are reflective but not the same oral and pharyngeal tasks performed during the swallow. Additionally, sensory components of the swallow, including taste, were not investigated in the present study; this could help to explain some of these activations [Zald and Pardo, 1999]. Future research in the same direction should include examination of the neural activation of the sensory components of the swallow.

ACKNOWLEDGMENTS

The authors thank the staff and management of the Biomedical Imaging Center of the Beckman Institute at UIUC.

REFERENCES

Addington WR, Stephens RE, Gilliland KA (1999): Assessing the laryngeal cough reflex and the risk of developing pneumonia after stroke: An interhospital comparison. Stroke 30:1203–1207.

Alberts MJ, Horner J, Gray L, Brazer SR (1992): Aspiration after stroke: Lesion analysis by brain MRI. Dysphagia 7:170–173.

Andersen RA, Buneo CA (2002): Intentional maps in posterior parietal cortex. Annu Rev Neurosci 25:189–220.

Augustine JR (1996): Circuitry and functional aspects of the insular lobe in primates including humans. Brain Res Rev 22:229–244.

Barkmeier JM, Bielamowicz S, Takeda N, Ludlow CL (2002): Laryngeal muscle activation patterns during upright and supine swallowing. J Appl Physiol 93:740–745.

Beckmann C, Jenkinson M, Smith SM (2003): General multi-level linear modelling for group analysis in FMRI. NeuroImage 20:1052–1063.

Blitzer A (1990): Approaches to the patient with aspiration and swallowing disabilities. Dysphagia 5:129–137.

Canning BJ (2006): Anatomy and neurophysiology of the cough reflex: ACCP evidence-based clinical practice guidelines. Chest 129 (S1):33S–47S.

Castell JA, Dalton CB, Castell DO (1990): 3haryngeal and upper esophageal sphincter manometry in humans. Am J Physiol Gastrointest Liver Physiol 258:G173–G178.

Catalan MJ, Honda M, Weeks RA, Cohen LG, Hallett M (1998): The functional neuroanatomy of simple and complex sequential finger movements: A PET study. Brain 121:253–264.

Celifarco A, Gerard G, Faegenburg D, Burakoff R (1990): Dysphagia as the sole manifestation of bilateral strokes. Am J Gastroenterol 85:610–613.

Connors BW, Landisman CE, Reid RC (1998): Thalamus: Organization and function (Vol. 1), Experimental and Clinical Aspects (Vol 2). Trends Neurosci 21:539–540.

Corbin-Lewis K, Liss JM, Sciortino KL (2005): Clinical Anatomy and Physiology of the Swallow Mechanism. Clifton Park, NY: Thomson Delmar Learning.

Corfield DR, Murphy K, Josephs O, Fink GR, Frackowiak RSJ, Guz A, Adams L, Turner R (1999): Cortical and subcortical control of tongue movement in humans: A functional neuoroimaging study using fMRI. J Appl Physiol 86:1468–1477.

Dale AM (1999): Optimal experimental design for event-related fMRI. Hum Brain Mapp 8:109–114.

Dale AM, Greve DN, Burock MA (1999):Optimal Stimulus Sequences for Event-Related fMRI. Fifth International Conference on Functional Mapping of the Human Brain. Duesseldorf, Germany.

Daniels SK (2000): Swallowing apraxia: A disorder of the praxis system? Dysphagia 15:159–166.

Daniels SK, Foundas AL (1997): The role of the insular cortex in dysphagia. Dysphagia 12:146–156.

Davis KD, Taylor SJ, Crawley AP, Wood ML, Mikulis DJ (1997): Functional MRI of pain- and attention-related activations in the human cingulate cortex. J Neurophysiol 77:3370–3380.

Deiber MP, Ibanez V, Sadato N, Hallett M (1996): Cerebral structures participating in motor preparation in humans: A positron emission tomography study. J Neurophysiol 75:233–247.

Derbyshire SWG, Vogt BA, Jones AKP (1998): Pain and stroop interference tasks activate separate processing modules in anterior cingulate cortex. Exp Brain Res 118:52–60.

Desmurget M, Grea H, Grethe JS, Prabalnc C, Alexander GE, Grafton ST (2001): Functional anatomy of nonvisual feedback loops during reaching: A positron emission tomography study. J Neurosci 21:2919–2928.

Devinsky O, Morrell MJ, Vogt BA (1995): Contributions of anterior cingulated cortex to behavior. Brain 118:279–306.

Dodds WJ, Stewart ET, Logemann JA (1990): Physiology and radiology of the normal oral and pharyngeal phases of swallowing. Am J Roentgenol 154:953–963.

Donner TH, Ketterman A, Diesch E, Ostendorf F, Villringer A, Brandt SA (2002): Visual feature and conjunction searches of equal difficulty engage only partially overlapping frontoparietal networks. NeuroImage 15:16–25.

Dronkers NF (1996): A new brain region for coordinating speech articulation. Nature 384:159–161.

Eickhoff SB, Stephan KE, Mohlberg H, Grefkes C, Fink GR, Amunts K, Zilles K (2005): A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. Neuroimage 25:1325–1335.

Elsinger CL, Harrington DL, Rao ,SM (2006): From preparation to online control: Reappraisal of neural circuitry mediating internally generated and externally guided actions. Neuroimage 31:1177–1187.

Ertekin C, Aydogdu I (2003): Neurophysiology of swallowing. Clin Neurophysiol 114:2226–2244.

Gerloff C, Corwell B, Chen R, Hallett M, Cohen LG (1997): Stimulation over the human supplementary motor area interferes with the organization of future elements in complex motor sequences. Brain 120:1587–1602.

Geyer S (2004): The microstructural border between the motor and the cognitive domain in the human cerebral cortex. Adv Anat Embryol Cell Biol 174(I–VIII):1–89.

Geyer S, Ledberg A, Schleicher A, Kinomura S, Schormann T, Burgel U, Klingberg T, Larsson J, Zilles K, Roland PE (1996): Two different areas within the primary motor cortex of man. Nature 382:805–807.

Geyer S, Schleicher A, Zilles K (1999): Areas 3a, 3b, and 1 of human primary somatosensory cortex. Neuroimage 10:63–83.

Geyer S, Schormann T, Mohlberg H, Zilles K (2000): Areas 3a, 3b, and 1 of human primary somatosensory cortex. Part 2: Spatial normalization to standard anatomical space. NeuroImage 11:684–696.

Gracco VL, Tremblay P, Pike B (2005): Imaging speech production using fMRI. Neuroimage 26:294–301.

Grefkes C, Geyer S, Schormann T, Roland P, Zilles K (2001): Human somatosensory area 2: Observer-independent cytoarchitectonic mapping, interindividual variability, and population map. Neuroimage 14:617–631.

Hamdy S, Aziz Q, Rothwell JC, Crone R, Hughes D, Tallis RC, Thompson DG (1997): Explaining oropharyngeal dysphagia after unilateral hemispheric stroke. Lancet 350:686–692.

Hamdy S, Aziz Q, Rothwell JC, Hobson A, Thompson DG (1998): Sensorimotor modulation of human cortical swallowing pathways. J Physiol 506:857–866.

Hamdy S, Aziz Q, Rothwell JC, Singh KD, Barlow J, Hughes DG, Tallis RC, Thompson DG (1996): The cortical topography of human swallowing musculature in health and disease. Nature Med 2:1217–1224.

Hamdy S, Mikulis DJ, Crawley A, Xue S, Lau H, Henry S, Diamant NE (1999a): Cortical activation during human volitional swallowing: An event-related fMRI study. Am J Physiol 277:G219–G225.

Hamdy S, Rothwell JC, Brooks DJ, Bailey D, Aziz Q, Thompson DG (1999b) Identification of the cerebral loci processing human swallowing with H2 15O PET activation. J Neurphysiol 81:1917–1926.

Hartnick CJ, Rudolph C, Willging JP, Holland SK (2001): Functional magnetic resonance imaging of the pediatric swallow: Imaging the cortex and the brainstem. Laryngoscope 111:1183–1191.

Hikosaka O, Nakahara H, Rand MK, Katsuyuki S, Lu X, Nakamura K, Miyachi S, Doya K (1999): Parallel neural networks for learning sequential procedures. Trends Neurosci 22:464–471.

Hori K, Ono T, Nokubi T (2006): Coordination of tongue pressure and jaw movement in mastication. J Dent Res 85:187–191.

Huang CS, Hiraba H, Sessle BJ (1989): Input-output relationships of the primary face motor cortex in the monkey (Macaca fascicularis). J Neurophysiol 61:350–362.

Huckabee ML, Deecke L, Cannito MP, Gould HJ, Mayr W (2003): Cortical control mechanisms in volitional swallowing: The Bereitschaftspotential. Brain Topogr 16:3–17.

Huettel SA, Song AW, McCarthy G (2004): Functional Magnetic Resonance Imaging. Sunderland, MA: Sinauer Associates, Inc.

Inagaki D, Miyaoka Y, Ashida I, Ueda K, Yamada Y (2007): Influences of body posture on duration of oral swallowing in normal young adults. J Oral Rehabil 34:414–421.

Ingervall B, Lantz B (1973): Significance of gravity on the passage of bolus through the human pharynx. Arch Oral Biol 18:351–356.

Inoue K, Kawashima R, Satoh K, Kinomura S, Goto R, Koyama M, Sugiura M, Ito M, Fukuda H (1998): PET study of pointing with visual feedback of moving hands. J Neurophysiol 79:117–125.

Jean A (2001): Brain stem control of swallowing: Neuronal network and cellular mechanisms. Physiol Rev 81:929–960.

Jenkins IH, Jahanshahi M, Jueptner M, Passingham RE, Brooks DJ (2000): Self-initiated versus externally triggered movements: Part II. The effect of movement predictability on regional cerebral blood flow. Brain 123 (Part 6):1216–1228.

Jenkinson M, Bannister P, Brady M, Smith S (2002): Improved optimisation for the robust and accurate linear registration and motion correction of brain images. Neuroimage 17:825–841.

Johnsson F, Shaw D, Gabb M, Dent J, Cook I (1995): Influence of gravity and body position on normal oropharyngeal swallowing. Am J Physiol Gastrointest Liver Physiol 269:G653–G658.

Kahrilas PJ, Lin S, Logemann JA, Ergun GA, Facchini F (1993): Deglutitive tongue action: Volume accommodation and bolus propulsion. Gastroenterology 104:152–162.

Kern M, Birn R, Jaradeh S, Jesmanowicz A, Cox R, Hyde J, Shaker R (2001a): Swallow-related cerebral cortical activity maps are not specific to deglutition. Am J Physiol Gastrointest Liver Physiol 280:G531–G538.

Kern MK, Jaradeh S, Arndorfer RC, Shaker R (2001b): Cerebral cortical representation of reflexive and volitional swallowing in humans. Am J Physiol Gastrointest Liver Physiol 280:G354–G360.

Lazarus C (2006): Tongue strength and exercise in healthy individuals and in head and neck cancer patients. Semin Speech Lang 27:260–267.

Logemann JA (1998): Evaluation and Treatment of Swallowing Disorders, 2nd ed. Austin, TX: Pro-Ed.

Lowell SY, Poletto CJ, Knorr-Chung BR, Reynolds RC, Simonyan K, Ludlow CL (2008): Sensory stimulation activates both motor and sensory components of the swallowing system. Neuroimage 42:285–295.

Martin R, Barr A, MacIntosh B, Smith R, Stevens T, Taves D, Gati J, Menon R, Hachinski V (2007): Cerebral cortical processing of swallowing in older adults. Exp Brain Res 176:12–22.

Martin RE, Goodyear BG, Gati JS, Menon RS (2001): Cerebral cortical representation of automatic and volitional swallowing in humans. J Neurophysiol 85:938–950.

Martin RE, Kemppainen P, Masuda Y, Yao D, Murray GM, Sessle BJ (1999): Features of cortically evoked swallowing in the awake primate (Macaca fascicularis). J Neurophysiol 82:1529–1541.

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

Massey BT, Shaker R (1997):Introduction to the field of deglutition and deglutition disorders. In:Perlman AL, Schulze-Delrieu KS, editors. Deglutition and Its Disorders. San Diego, CA/London: Singular Publication Group, pp 1–13.

Miller AJ (1986): Neurophysiological basis of swallowing. Dysphagia 1:91–100.

Miller AJ (1993): The search for the central swallowing pathway: The quest for clarity. Dysphagia 8:185–194.

Miller AJ, Bowman JP (1977): Precentral cortical modulation of mastication and swallowing. J Dent Res 56:1154.

Mosconi P, Langer M, Cigada M, I.C.U.G.I.C(1991): Epidemiology and risk factors of pneumonia in critically ill patients: Intensive care unit group for infection control. Eur J Epidemiol 7:320–327.

Mosier KM, Bereznaya I (2001): Parallel cortical networks for volitional control of swallowing in humans. Exp Brain Res 140: 280–289.

Mosier KM, Liu WC, Maldjian JA, Shah R, Modi B (1999): Lateralization of cortical function in swallowing: A functional MR imaging study. Am J Neuroradiol 20:1520–1526; Neurobiol 6:782–787.

Nowak DA, Topka H, Timmann D, Boecker H, Hermsdörfer J (2007): The role of the cerebellum for predictive control of grasping. Cerebellum 6:7–17.

Oldfield RC (1971): The assessment and analysis of handedness: The edinburgh inventory. Neuropsychologia 9:97–113.

Orgogozo JM, Larsen B (1979): Activation of the SMA during voluntary movements in man suggests it works as a supramotor area. Science 206:847–850.

Paciaroni M, Mazzotta G, Corea F, Caso V, Venti M, Milia P, Silvestrelli G, Palmerini F, Parnetti L, Gallai V (2004): Dysphagia following stroke. Eur Neurol 51:162–167.

Perlman AL (1994): Normal swallowing physiology and evaluation. Curr Opin Otolaryngol Head Neck Surg 2:226–232.

Perlman AL, Christensen J (1997):Topography and functional anatomy of the swallowing structures. In:Perlman AL, Schulze-Delrieu KS, editors. Deglutition and Its Disorders. San Diego, CA/London: Singular Publication Group. pp15–42.

Poncelet BP, Wedeen VJ, Weisskoff RM, Cohen MS (1992): Brain parenchyma motion: Measurement with cine echo-planar MR imaging. Radiology 185:645–651.

Raichle ME (1991): Memory mechanisms in the processing of words and word-like symbols. Exploring brain functional anatomy with positron tomography. Ciba Found Symp 163:198–204.

Robbins J, Levine RL (1988): Swallowing after unilateral stroke of the cerebral cortex: Preliminary experience. Dysphagia 3:11–17.

Roland PE, Larsen B, Lassen NA, Skinhoj E (1980): SMA and other cortical areas in organization of voluntary movement in man. J Neurophysiol 43:118–136.

Shaker R, Cook IJS, Dodds WJ, Hogan WJ (1988): Pressure-flow dynamics of the oral phase of swallowing. Dysphagia 3:79–84.

Simonyan K, Saad ZS, Loucks TM, Poletto CJ, Ludlow CL (2007): Functional neuroanatomy of human voluntary cough and sniff production. Neuroimage 37:401–409.

Smith S (2002): Fast robust automated brain extraction. Hum Brain Mapp 17:143–155.

Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TEJ, Johansen-Berg H, Bannister PR, De Luca M, Drobnjak I, Flitney DE, Niazy R, Saunders J, Vickers J, Zhang Y, De Stefano N, Brady JM, Matthews PM (2004): Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 23 (S1):208–219.

Sörös P, Lalone E, Smith R, Stevens T, Theurer J, Menon RS, Martin RE (2008): Functional MRI of oropharyngeal air-pulse stimulation. Neuroscience 153:1300–1308.

Stickler D, Gilmore R, Rosenbek JC, Donovan NJ (2003): Dysphagia with bilateral lesions of the insular cortex. Dysphagia 18:179–181.

Suzuki M, Asada Y, Ito J, Hayashi K, Inoue H, Kitano H (2003): Activation of the cerebellum and basal ganglia on volitional swallowing detected by functional magnetic resonance imaging. Dysphagia 18:71–77.

Tan EK, Chan LL, Chang HM (2004): Severe bruxism following basal ganglia infarcts: Insights into pathophysiology. J Neurol Sci 217:229–232.

Tanji T (1996): New concepts of the supplementary motor area. Curr Opin Neurobiol 6:782–787.

Tanji J, Mushiake H (1996): Comparison of neuronal activity in the supplementary motor area and primary motor cortex. Brain Res Cogn Brain Res 3:143–150.

Thach WT, Goodkin HP, Keating JG (1992): The cerebellum and the adaptive coordination of movement. Annu Rev Neurosci 15:403–442.

Toogood JA, Barr AM, Stevens TK, Gati JS, Menon RS, Martin RE (2005): Discrete functional contributions of cerebral cortical foci in voluntary swallowing: A functional magnetic resonance imaging (fMRI) "Go, No-Go" study. Exp Brain Res 161:81–90.

Watanabe J, Suguira M, Miura N, Watanabe Y, Maeda Y, Matsue Y, Kawashima R (2004): The human parietal cortex is involved in spatial processing of tongue movement-an fMRI study. Neuroimage 21:1289–1299.

Widdicombe J (1996): Sensory neurophysiology of the cough reflex. J Allergy Clin Immunol 98 (Part 2):S84–S91.

Widdicombe J, Eccles R, Fontana G (2006): Supramedullary influences on cough. Resp Physiol Neurobiol 152:320–328.

Widdicombe J, Fontana G (2006): Cough: What's in a name? Eur Respir J 28:10–15.

Woolrich MW, Ripley BD, Brady JM, Smith SM (2001): Temporal autocorrelation in univariate linear modelling of FMRI data. Neuroimage 14:1370–1386.

Youmans SR, Stierwalt JA (2006): Measures of tongue function related to normal swallowing. Dysphagia 21:102–111.

Yukie M (1995): Neural connections of auditory association cortex with the posterior cingulate cortex in the monkey. Neurosci Res 22:179–187.

Zald DH, Pardo JV (1999): The functional neuroanatomy of voluntary swallowing. Ann Neurol 46:281–286.

Zald DH, Pardo JV (2000): Cortical activation induced by intraoral stimulation with water in humans. Chem Senses 25:267–275.