Sensory stimulation activates both motor and sensory components of the swallowing system

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Volitional swallowing in humans involves the coordination of both brainstem and cerebral swallowing control regions. Peripheral sensory inputs are necessary for safe and efficient swallowing, and their importance to the patterned components of swallowing has been demonstrated. However, the role of sensory inputs to the cerebral system during volitional swallowing is less clear. We used four conditions applied during functional magnetic resonance imaging to differentiate between sensory, motor planning, and motor execution components for cerebral control of swallowing. Oral air pulse stimulation was used to examine the effect of sensory input, covert swallowing was used to engage motor planning for swallowing, and overt swallowing was used to activate the volitional swallowing system. Breath-holding was also included to determine whether its effects could account for the activation seen during overt swallowing. Oral air pulse stimulation, covert swallowing and overt swallowing all produced activation in the primary motor cortex, cingulate cortex, putamen and insula. Additional regions of the swallowing cerebral system that were activated by the oral air pulse stimulation condition included the primary and secondary somatosensory cortex and thalamus. Although air pulse stimulation was on the right side only, bilateral cerebral activation occurred. On the other hand, covert swallowing minimally activated sensory regions, but did activate the supplementary motor area and other motor regions. Breath-holding did not account for the activation during overt swallowing. The effectiveness of oral–sensory stimulation for engaging both sensory and motor components of the cerebral swallowing system demonstrates the importance of sensory input in cerebral swallowing control.
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Introduction

Swallowing is a life sustaining function that is essential for food ingestion and controls secretions both while awake and asleep. A diffuse, bilateral cerebral system is involved in human swallowing, and is critical for volitional swallowing control (Ertekin and Aydogdu, 2003). Functional neuroimaging of volitional swallowing has demonstrated that several regions are involved, including the primary motor cortex, supplementary motor area, primary sensory cortex, cingulate cortex, insula, operculum, prefrontal cortex (Hamdy et al., 1999; Kern et al., 2001a,b; Martin et al., 2007; Martin et al., 2001; Martin et al., 2004) basal ganglia, thalamus, and cerebellum (Martin et al., 2007; Martin et al., 2004; Suzuki et al., 2003). Swallowing relies on sensory inputs from food or secretions in the oropharynx, which trigger afferents in the trigeminal, glossopharyngeal and superior laryngeal nerves (Jean, 1984, 2001; Shaker and Hogan, 2000). These inputs reach the brainstem regions (Contreras et al., 1982; Kalia and Sullivan, 1982) and are important to the patterned response components of swallowing. However, it is unknown to what degree sensory stimulation is involved in the activation of this broad cerebral system during volitional swallowing.

Several attributes of volitional swallowing may underlie the extensive pattern of brain activation for this behavior, including sensory input from saliva or food being swallowed, motor planning, motor execution, and proprioceptive feedback during swallowing execution. A few studies have contrasted swallowing with related oral–motor tasks involving tongue, jaw and lip movements and found a similar pattern of cerebral activation to that elicited by volitional swallowing (Kern et al., 2001a; Martin et al., 2004). This similarity may be due, in part, to sensory stimulation in the oral region. Because sensory input is critical to safe and efficient swallowing in humans (Jafari et al., 2003), it is important to determine to what degree the cerebral system involved in volitional swallowing can be activated by isolated sensory input.

Swallowing is typically elicited by food or secretions passing through the oropharynx and engaging afferent branches of the

cranial nerves innervating that region. These cranial nerve inputs reach the dorsal brain stem pattern generator for swallowing, as established from animal studies (Ertekin and Aydogdu, 2003; Jean, 1990, 2001). In humans, the behavioral effects of these sensory inputs on swallowing have been studied using oro-pharyngeal stimulation and sensory block. Air pressure or mechanical stimulation of glossopharyngeal nerve (GPN) afferents from the oropharynx elicits swallowing (Theurer et al., 2005) and cortical responses (Fujiu et al., 1994). Stimulation of the superior laryngeal nerve (SLN) using either water presented to the hypopharynx or air pressure to the mucosa overlying the arytenoid cartilages will elicit laryngeal closure reflexes, an airway protective component of swallowing (Bhabu et al., 2003; Shaker and Hogan, 2000; Shaker et al., 2003). On the other hand, disrupting this sensory input via temporary anesthesia of the SLN bilaterally (Jafari et al., 2003) can significantly impair swallowing in healthy adults, although anesthesia to oro-pharyngeal mucosa only prolonged the duration of pharyngeal contraction (Ali et al., 1994). Sectioning of the GPN reduced swallowing frequency in the cat to 67% of control levels (Ootani et al., 1995).

Although sensory input is known to be important for swallowing, little is known about the degree to which the cerebral system involved in volitional swallowing can be activated by sensory stimulation in the oral cavity or pharynx. Neuroimaging can be used to determine which particular brain regions are activated by peripheral sensory stimulation related to swallowing. One study used mechanical stimulation of the anterior faucial pillar and elicited bilateral cortical evoked responses in healthy adults (Fujiu et al., 1994), although localization of the responses was not possible because imaging was not included. Magnetoencephalography (MEG) can provide information regarding cortical (but not subcortical) substrates, and was used in two studies related to sensory activation and swallowing. Gow et al. (2004) showed activation of caudolateral, primary sensorimotor cortex in three subjects in response to pharyngeal electrical stimulation. The temporal coordination of stimulation due to water infusion and oral retention of a water bolus just prior to swallow initiation was studied by Furlong et al. (2004) using MEG. Water infusion preferentially activated the caudolateral sensorimotor cortex while swallowing and tongue movement activated more superior regions in the sensorimotor cortex. These studies suggest that peripheral sensory stimulation may elicit activation of some of the swallowing-related regions. Using functional MRI to study the cortical and subcortical patterns of activation during sensory stimulation in contrast with volitional swallowing can map the full extent of activation similarity between the two states.

Motor planning for volitional swallowing may also activate the swallowing system. Covert tasks are when the subject imagines a behavior without executing it. These can induce similar regions of activation to motor execution, including the supplementary motor area (SMA), premotor cortex, cerebellum, and basal ganglia (Lacourse et al., 2005; Lotze et al., 1999; Stephan et al., 1995). Although motor planning regions are frequently elicited, activation of primary motor cortex is generally less for a covert versus an overt task (Lotze et al., 1999; Roth et al., 1996). Another difference between covert and overt execution is the absence of proprioceptive feedback as a result of movement. This may explain why there is minimal activation of primary sensory regions by covert tasks, although activation of multisensory integration areas does occur (Gerardin et al., 2000; Stephan et al., 1995; Szameitat et al., 2007). Finally, overt tasks such as swallowing should produce brain activation in motor planning and execution regions, as well as sensory regions due to proprioceptive feedback. Overt swallowing also includes an apneic period that occurs in the middle of swallowing when the airway is closed. Whether this apneic period accounts in part for the cerebral activation seen in volitional swallowing has not been determined.

The aim of this study was to differentiate sensory, motor planning, and motor execution components of the cerebral control of swallowing. Covert swallowing could identify those components of the cerebral system that are involved in motor planning but are not dependent on sensory stimulation or swallowing execution. Oral–sensory stimulation could preferentially engage sensory regions, with minimal activation in motor planning and execution regions. On the other hand, overt swallowing should engage sensory, motor planning and execution components of the swallowing network. We hypothesized that 1) oral air pulse stimulation would predominantly activate sensory components of the cerebral swallowing system, whereas 2) covert swallowing would predominantly activate the motor planning components of the swallowing system. To determine whether cerebral activation that occurred during overt swallowing was associated with breath-holding as one of the components of swallowing, we also included a breath-holding condition.

Materials and methods

Subjects

Fourteen healthy adults (7 males) between the ages of 21 and 52 years participated in the study (mean=36 years, SD=10.4). Thirteen were right-handed on the Edinburgh Handedness Inventory (Oldfield, 1971). Subjects had no history of neurological, swallowing, or psychiatric disorders and were healthy at the time of testing. All subjects provided written informed consent prior to participating in the study, which was approved by the Institutional Review Board of the National Institute of Neurological Disorders and Stroke, National Institutes of Health.

Tasks and equipment

Four conditions were employed during functional imaging: oral–sensory (air pulse) stimulation, covert swallowing, overt swallowing, and breath-holding. Before the scanning session, subjects were trained to assure correct task performance. While in the scanner, subjects were cued for all tasks using a visual symbol (black and white drawings). Symbols were the same size, with similar lightness/darkness levels, and depicted 1) a tube with flow of air for the oral–sensory stimulation, 2) a light bulb for covert swallowing, 3) a glass for overt swallowing, and 4) lungs with an X over them for breath-holding.

During oral–sensory stimulation, subjects received a series of air pulses to the back of the mouth via a dental impression fitted from the right lower molars to the front incisors. A foam dental tray was filled with fast acting dental putty (Express STD, 3M ESPE), and an impression was made of the lower right dentition. Once hardened, this flexible rubber impression provided a stable base over the teeth. The impression was thinned and a ~4 in. piece of silicone tubing (outer diameter, O.D.=1/8 in., inner diameter, I.D.=1/16 in.) was added medially with additional putty to secure the tubing. The impression and tubing were fit so that the posterior tube opening targeted the peritonsillar region, and the anterior tube extended from

the mouth. The impression was then shaved to a final thickness of ~4 mm and was placed in the subject's mouth 30 min prior to scanning to allow the subject to acclimate to any sensory changes. The impression remained in place for the entire scanning session.

Compressed medical grade air was delivered through a pressure valve via polyurethane tubing (O.D. 1/4 in., I.D. 1/8 in., ~36 ft) to a two-way on/off valve in the control room driven by a stimulus control box. When the two-way solenoid valve was opened, the air pulse stimulus was routed into the scanner room through polyurethane tubing (O.D. 1/8 in., I.D. 1/16 in., ~36 ft) to the silicone tubing extending from the subject's mouth. Air pressure at the air source was 50 psi, but was attenuated by the tubing length and transitions to an output pressure of 2–3 psi at the subject's mouth. During each air pulse stimulation trial, a series of six discrete 110 ms duration air pulses were presented at a rate of two pulses per second (s). All stimuli were controlled using Eprime stimulus presentation software (Psychology Software Tools, Inc., Pittsburgh, PA).

During overt swallowing, subjects were instructed to swallow their own saliva while minimizing any head motion. During covert swallowing, subjects were instructed to imagine what they feel and do when swallowing their own saliva. After the scanning session, subjects rated on a visual analog scale their attention during covert swallowing to: (a) how swallowing feels (sensory aspects), (b) what they do when swallowing (motor aspects), and (c) what swallowing looks like (visual aspects).

Swallowing was continuously monitored using an MRI compatible pneumatic belt placed on the neck at the thyro-hyoid level and adjusted to provide a maximum change during a swallow (Fig. 1). An additional pneumatic belt was placed over the abdomen to record abdominal movement during respiration. The resulting signals were displayed and recorded using a PowerLab 16/30 data acquisition system (ADInstruments, Inc., Colorado Springs, CO).

A mixed design was used, with three discrete trials of a behavior/ condition occurring every 10 s within a 30 s block. The slow epochs
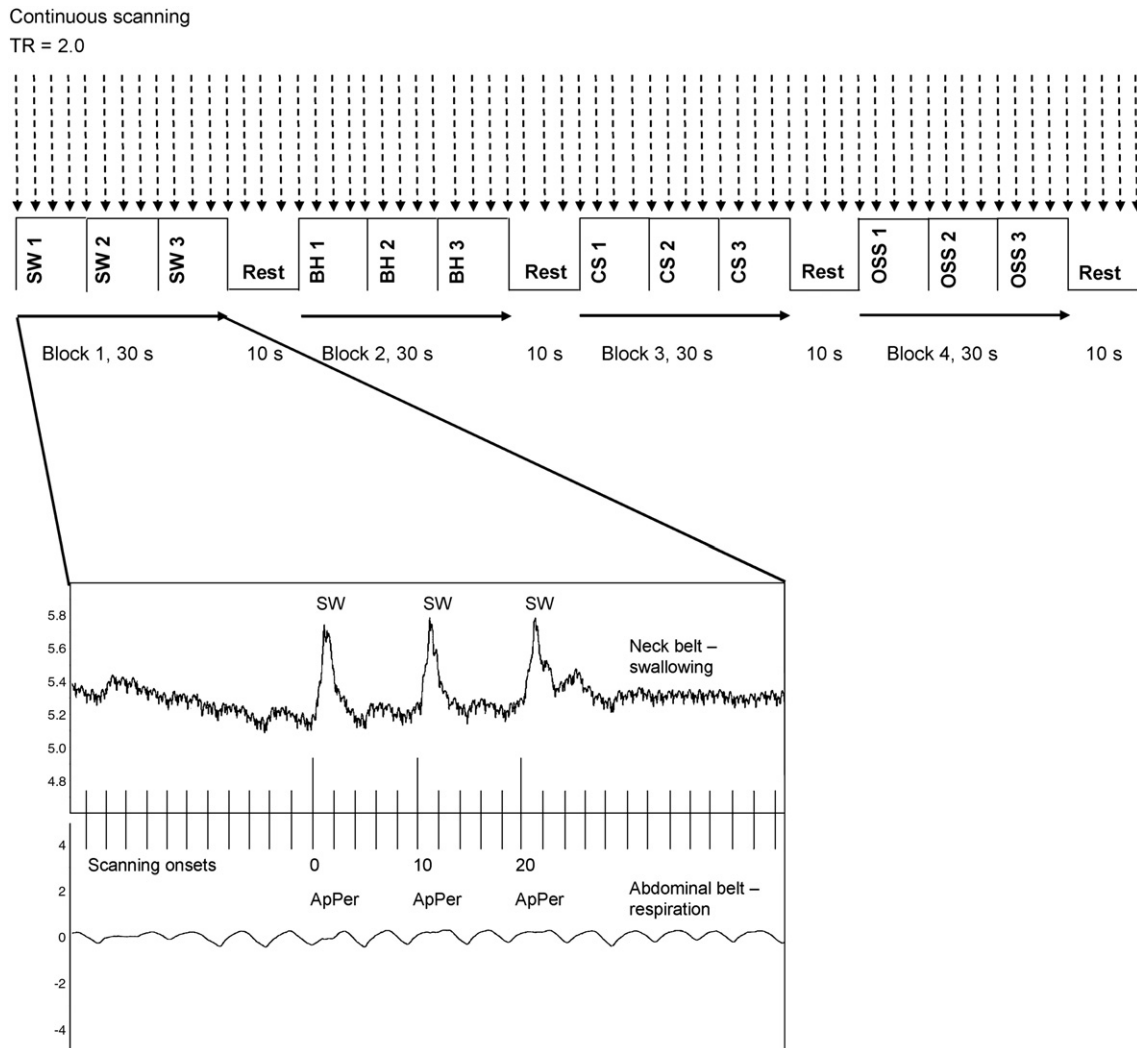

Fig. 1. Schematic of the fMRI design. Each block contained three trials of a given condition. Trials were elicited every 10 s, with each trial lasting 3 s, followed by 7 s of rest prior to the next trial. After the 3rd trial of each set, an additional 10 s of rest/fixation was imposed (Rest). SW = overt swallowing, CS = covert swallowing, OSS = oral–sensory stimulation, and BH = breath-holding. Scanning was continuous with initiation of a full brain scan every 2 s beginning at 0 when a trial began and continuing throughout a run. An example of the swallowing and respiratory movement signals from the pneumatic belts for one subject is shown in an expanded 30 s block. Amplitude displacements in the swallow signal can be seen for each of the three swallow trials. Brief apneic periods (ApPer) can be seen in the respiratory signal during each swallow (SW).

of one trial every 10 s were synchronized with continuous scanning and full brain coverage every 2 s. Three discrete stimulus trials for the same condition (e.g. air pulse stimulation) were presented separately at time points 0, 10, and 20 s within a 30 s block (Fig. 1). Each trial lasted for 3 s followed by 7 s of rest/fixation. Scanning onsets were synchronized to occur at 0 s, 2, 4, 6, and 8 s after trial onset. With a TR of 2.0 s, we sufficiently sampled the data to capture the form of the hemodynamic response for each of the three trials within a block.

For the swallowing condition, we avoided the problematic aspects of repetitive dry swallows by using a similar approach to that of Suzuki et al. (2003) of requiring swallows only once every 10 s. This interval allowed sufficient recovery time (7 s or greater) between swallows (Kleinjan and Logemann, 2002) (Fig. 1). For each trial, subjects were told to initiate the behavior when the visual cue appeared and to terminate the behavior when the visual cue disappeared 3 s later. After producing a behavior, subjects were told to rest quietly for 7 s and attend to the fixation cross presented at the center of the screen. Following the 3rd trial in each set, an additional rest period of 10 s was introduced while subjects continued to fixate/rest (for 17 s total) prior to the next 30 s block. Scanning during this additional 10 s period allowed for accurate sampling of the baseline. The blocks for each condition were randomly presented, with all four conditions (overt swallowing, covert swallowing, oral–sensory stimulation, and breath-holding) included in each run. Three blocks per condition were collected during each scanning run, yielding 9 trials for each of the four conditions per run. Five runs were conducted over a scanning session, yielding a total of 45 trials per condition.

Functional image acquisition

An 8 channel head coil was used in a 3.0 T scanner (Signa, General Electric Medical Systems, Milwaukee, WI). To minimize head movements, the head was stabilized with a strap across the forehead and cushions on both sides within the head coil. Four initial scans at the beginning of each run allowed for stabilization of the magnetization gradients and were not included in the data analysis. Continuous scanning acquisition was used to collect echo-planar images during each scanning run using: TR=2.0 s, TE=30 ms, flip angle=90°, FOV=240 mm, 35 sagittal slices, and slice thickness= 4 mm (no gap), with 240 volumes acquired per run.

A high resolution, T1-weighted structural scan for anatomic localization and co-registration was also collected using the following parameters: MPRAGE, TE=3.0 ms, TI=450 ms, flip angle=10°, bandwidth=31.25, FOV=240 mm, slices=128, and slice thickness=1.3 mm (no gap).

Functional image analysis

All image processing and analysis was performed using AFNI (Cox, 1996) software. False-positive activation was minimized by including multiple motion parameters in the regression model and using a cluster threshold (Soltysik and Hyde, 2006). Preprocessing steps included a motion correction algorithm for three translation and three rotation parameters. The motion estimates indicated that most subjects had head motion of less than 2 mm during scanning. To further reduce movement artifacts, all 6 motion parameters were entered in the multiple regression analysis. Functional volumes were spatially blurred with a 4 mm full-width at half max Gaussian filter. For each voxel within each run, the hemodynamic response

(HDR) signal time course was normalized. The amplitude co-efficients for the four conditions were then estimated using multiple linear regression, in which a gamma variate waveform was convolved with a 3 s boxcar function to match the stimulus presentation time. This produced an elongated gamma variate function; thus the possible swallowing motion artifacts (usually in the first few seconds of the response) were predominantly included in the noise versus signal response. Uncued swallows throughout each functional run were entered as a separate regressor of no interest to control for their effects during other conditions. Hemo-dynamic response effects due to uncued swallows were therefore minimized from the results for each of the conditions of interest. Each subject's data sets were transformed to the Talairach and Tournoux coordinate system (Talairach and Tournoux, 1988).

Group activation maps for each condition were generated using a mixed effects analysis of variance (ANOVA) of the amplitude coefficients. The AlphaSim module of AFNI (Cox, 1996) using 1000 Monte Carlo simulations and a voxel-wise p-threshold of 0.0001 indicated that a cluster size of less than 17 contiguous voxels should be rejected at a corrected family-wise p value of <0.01. A stringent thresholding level was used to localize clusters

Table 1
Brain activation for overt swallowing, given in Talairach and Tournoux coordinate system

Brain region	Volume (mm³)	Maximum Z score	Coordinates		
			x	y	z
Overt swallowing					
R Postcentral gyrus	13936	6.01	57	−7	22
R Precentral gyrus		5.21	57	1	26
R Insula		5.37	43	3	6
R Rolandic operculum		5.29	55	3	12
R Supramarginal gyrus		4.60	57	−19	22
R Substantia nigra	7384	5.38	13	−19	−6
R Thalamus		4.65	13	−17	5
R Pallidum		5.09	14	−2	5
R Putamen		4.80	29	−10	−3
L Thalamus		4.55	−11	−18	2
L Pallidum		4.65	−20	−6	0
L Putamen		5.01	−23	−1	−3
L Postcentral gyrus	6120	5.70	−55	−9	38
L Precentral gyrus		5.23	−51	−11	32
L Rolandic operculum		5.16	−51	−7	12
R Cerebellum	5656	5.31	9	−49	−30
Cerebellar vermis		5.01	7	−51	−27
L Cerebellum		4.99	−14	−54	−20
R/L Supplementary motor area	1640	5.05	1	−5	50
L Supplementary motor area		4.81	−6	−4	47
L Middle cingulate cortex		4.18	−3	7	39
R Middle cingulate cortex		4.05	5	4	43
L Cerebellum	632	4.99	−23	−45	−18
~R Pallidum	552	5.09	13	−3	6
R Lingual gyrus	480	4.62	23	−81	−4
R Fusiform gyrus	328	4.37	37	−47	−10
L Insula	312	4.35	−31	9	12
L Middle occipital gyrus	232	5.09	−25	−91	−2
R Cerebellum	224	4.81	9	−61	−38
R Lingual gyrus	192	4.51	1	−63	2
R Superior temporal gyrus	168	4.28	51	−37	16
R Supplementary motor area	160	4.54	13	−7	62
R Cerebellum	144	4.47	41	−53	−22
~L Cerebellum	144	4.71	−4	−33	−3
Total volume for task	38304				

more specifically to regions and hemispheres. This cluster threshold was used for whole brain analysis of each condition against baseline rest.

Region of interest (ROI) analyses

An apriori ROI analysis was included to quantitatively differentiate the activation associated with sensory, motor planning, and motor execution regions. The ROIs were defined anatomically and extracted from neuroanatomical atlas plug-ins available in AFNI. Primary motor cortex (M1) areas 4a and 4p (Geyer et al., 1996), primary sensory cortex (S1) areas 3a, 3b, 1, 2 (Geyer et al., 1999; Geyer et al., 2000; Grefkes et al., 2001) and secondary somatosensory cortex area OP4 (Eickhoff et al., 2006a,b) were extracted using maximum probability maps whereas the insula, middle cingulate cortex, supplementary motor area (SMA), thalamus, putamen and pallidum were extracted from macrolabel maps (Eickhoff et al., 2005). ROIs were extracted for the right and left hemispheres and then applied to the functional datasets for each subject to isolate activation associated with each of these regions.

Within each ROI, the total volume of voxels that were active was determined by implementing the AlphaSim module using a

Table 2
Brain activation for oral–sensory stimulation, given in Talairach and Tournoux coordinate system

Brain region	Volume (mm^3)	Maximum Z score	Coordinates		
			x	y	z
Oral–sensory stimulation					
L Insula	9096	5.47	−35	−3	0
L Superior temporal gyrus		5.07	−57	−15	14
L Heschl's gyrus		5.00	−45	−17	12
L Supramarginal gyrus		5.03	−55	−29	24
L Postcentral gyrus		5.13	−49	−11	44
L Precentral gyrus		5.10	−49	−3	36
L Rolandic operculum		4.95	−41	−17	18
R Superior temporal gyrus	8424	5.51	57	−29	22
R Rolandic operculum		5.41	59	−15	14
R Insula		5.07	39	−9	14
R Supramarginal gyrus		5.06	59	−21	22
R Postcentral gyrus		4.61	56	−16	29
R Cerebellum	808	4.67	23	−61	−18
R Insula	664	4.89	39	−9	−4
L Cerebellum	608	5.34	−21	−59	−20
L Fusiform gyrus	472	4.62	−31	−47	−14
L Superior temporal gyrus	360	4.78	−41	−33	16
R Inferior temporal gyrus	336	4.35	43	−51	−14
L Supramarginal gyrus	320	4.63	−55	−39	24
L Middle occipital gyrus	312	4.79	−31	−89	6
R Fusiform gyrus	296	4.39	37	−45	−20
R Thalamus	264	4.93	19	−29	2
R Middle occipital gyrus	264	4.54	31	−79	4
~L Thalamus	216	5.14	−19	−19	−2
L Middle cingulate cortex	200	4.86	−11	−23	38
R Fusiform gyrus	192	4.43	39	−63	−18
R Precentral gyrus	184	4.68	53	−3	32
R Putamen	168	4.25	27	−17	4
L Inferior parietal lobule	168	4.78	−31	−47	40
L Inferior temporal gyrus	152	4.42	−43	−43	−12
R Inferior occipital gyrus	144	4.43	39	−79	−8
~L Thalamus	144	4.63	−11	−25	0
L Middle temporal gyrus	144	4.39	−53	−59	8
Total volume for task	23936				

Table 3
Brain activation for covert swallowing, given in Talairach and Tournoux coordinate system

Brain region	Volume (mm^3)	Maximum Z score	Coordinates		
			x	y	z
Covert swallowing					
R Inferior temporal gyrus	6928	5.27	47	−69	−4
R Inferior occipital gyrus		5.06	35	−77	−2
R Fusiform gyrus		5.06	29	−59	−14
R Cerebellum		4.93	33	−67	−20
R Middle occipital gyrus		4.86	33	−79	4
L Fusiform gyrus	4624	5.45	−27	−43	−16
L Cerebellum		5.39	−37	−65	−20
L Inferior occipital gyrus		5.22	−43	−65	−6
L Supplementary motor area	1288	4.87	−1	−9	62
R Supplementary motor area		4.51	4	−11	61
R Middle cingulate cortex		4.18	7	7	40
R Putamen	1176	4.75	27	1	8
R Insula		4.52	39	7	6
R Inferior frontal gyrus	1016	5.3	53	13	10
R Superior temporal gyrus		4.53	54	1	1
L Insula lobe	776	4.56	−33	−1	12
L Inferior frontal gyrus	664	4.65	−49	9	10
L Middle occipital gyrus	568	4.82	−29	−85	6
R Superior temporal gyrus	416	4.43	57	−39	16
L Middle cingulate cortex	368	4.74	−7	7	42
L Cerebellum	320	5.14	−23	−79	−18
R Superior occipital gyrus	304	4.62	23	−79	34
R Middle cingulate cortex	160	4.49	5	−19	44
L Supramarginal gyrus	152	4.68	−51	−37	24
R Precentral gyrus	152	4.94	41	−15	44
R Postcentral gyrus	136	4.24	25	−35	56
Total volume for task	19048				

small volume correction that included all ROIs. Voxels that fell within a cluster of 18 or more contiguous voxels (voxel-wise p-threshold of 0.001) at a corrected family-wise p value of <0.05 were defined as active. The volume of active voxels was converted to a percentage of the ROI volume. To reduce the number of comparisons, mean

Table 4
Brain activation for breath-holding, given in Talairach and Tournoux coordinate system

Brain region	Volume (mm^3)	Maximum Z score	Coordinates		
			x	y	z
Breath-holding					
L Middle occipital gyrus	1216	5.06	−27	−85	−2
L Inferior occipital gyrus		4.62	−27	−83	−5
R Superior Temporal gyrus	808	4.79	59	−33	22
R Supplementary motor area	712	4.67	3	−1	56
L Supplementary motor area		4.00	−5	−9	55
R Insula lobe	600	4.88	43	3	2
R Inferior frontal gyrus		4.16	56	8	10
R Rolandic operculum		4.21	50	4	9
R Lingual gyrus	592	4.77	25	−81	−4
R Inferior occipital gyrus		4.66	33	−77	−5
L Fusiform gyrus	496	4.60	−35	−65	−14
R Supramarginal gyrus	408	4.84	53	−37	40
R Fusiform gyrus	176	4.80	37	−43	−18
R Cerebellum		4.48	33	−43	−21
R Precentral gyrus	136	4.67	45	−7	36
Total volume for task	5144				

values of percent volume for some regions were combined, resulting in a composite for the M1 (4a and 4p) and S1 (1, 2, 3a, 3b) regions. Two-way repeated ANOVAs examined differences in the voxel-wise corrected, percent volume across condition and ROI ($p < 0.05$), one comparing oral–sensory stimulation to overt swallowing and the other comparing covert to overt swallowing. Significant interaction effects of condition and hemisphere were evaluated with follow-up paired t-tests for each ROI with a correction for multiple comparisons ($p < 0.01$).

Results

Uncued, automatic swallows were recorded and counted for the time occurring during scanning for each condition, which equaled 603 trials totaling 6030 s (i.e. 100.5 min) per each condition. The frequency of uncued swallows per minute for each condition was low: 0.75 uncued swallows/min during oral–sensory (air pulse) stimulation, 0.45 uncued swallows/min during covert swallowing

and 0.55 uncued swallows/min during breath-holding. Uncued swallow events were entered as a regressor of no interest into the multiple regression step of the AFNI analysis to minimize any effect on the conditions of interest, and the results reported here are after uncued swallow effects were removed.

Multiple brain regions that were activated during overt swallowing were also activated during oral–sensory stimulation and to a lesser extent during covert swallowing (Tables 1–4). These regions included the insula, M1, S1, putamen, occipital lobe, superior temporal gyrus, supramarginal gyrus, fusiform gyrus, and multiple sub regions of the cerebellum. During overt swallowing (Fig. 2a), additional clusters of activation included a) the frontal operculum (BA 44) and parietal operculum (OP 1, 3, 4), b) the SMA and middle cingulate cortex, c) the thalamus (ventral posterior lateral nucleus, ventral posterior medial nucleus, ventral lateral nucleus, medial dorsal nucleus), and d) the globus pallidus bilaterally.

During oral–sensory stimulation (Fig. 2b), additional clusters of activation included: a) the left and right parietal operculum (OP 1–4),
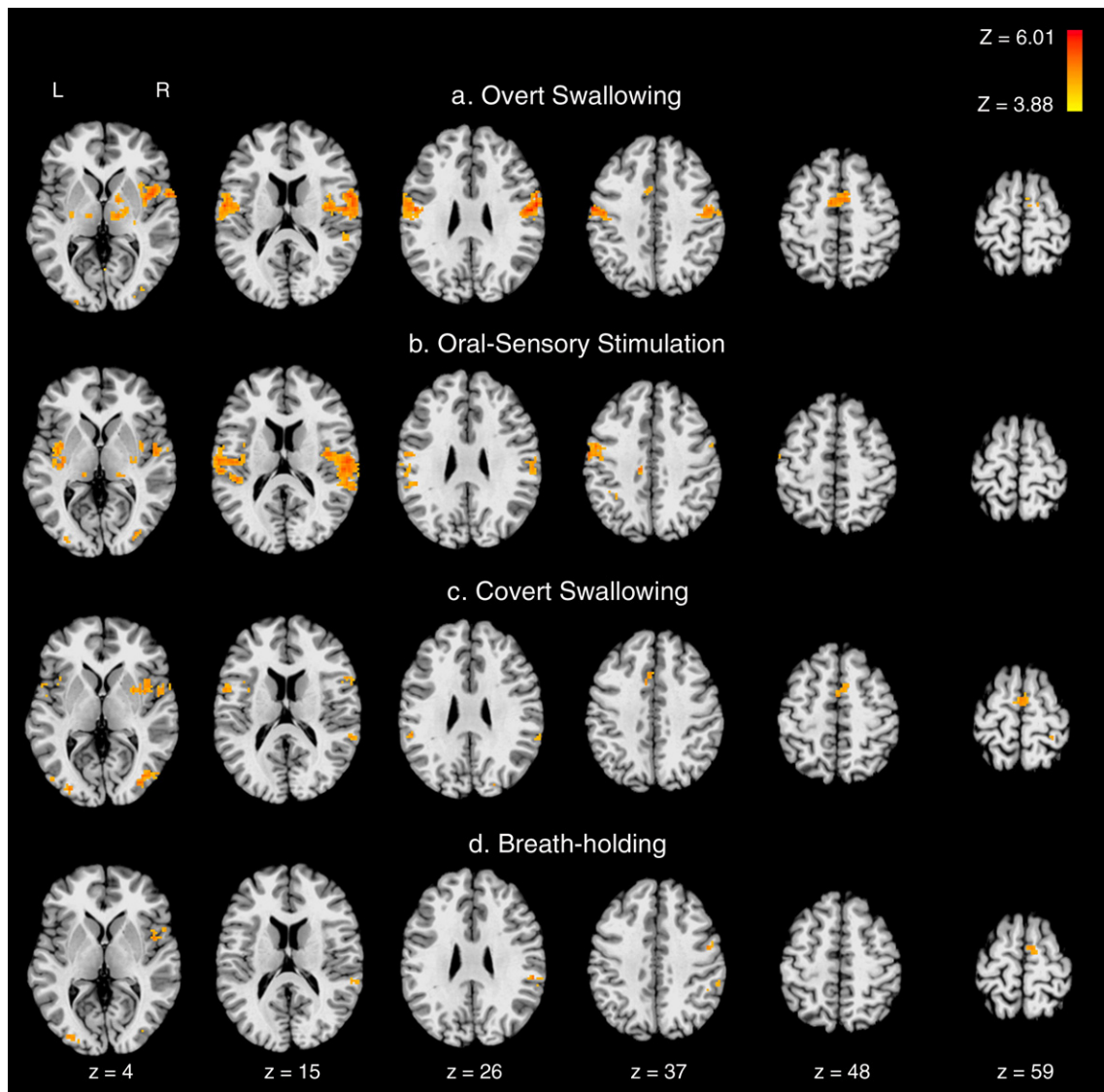

Fig. 2. Brain imaging results for voxel-wise comparisons of all conditions were based on average group data. Significant clusters of activation ($p < 0.01$ corrected) are displayed for a. overt swallowing>baseline, b. oral–sensory stimulation>baseline, c. covert swallowing>baseline, and d. breath-holding>baseline.
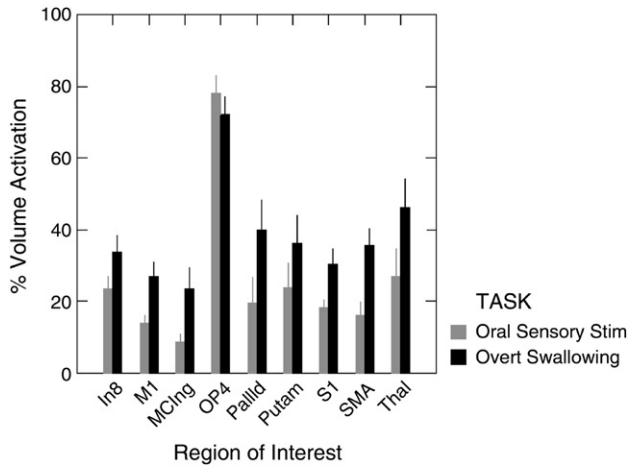
Fig. 3. Oral–sensory stimulation versus overt swallowing *t*-test results for region of interest (ROI) analysis showing combined left and right hemisphere mean percent volume activation (error bar = standard error of measurement) for each region based on individual subject analysis. Ins—insula, M1—primary motor cortex, MCing—middle cingulate cortex, OP4—operculum 4, Pallid—globus pallidus, Putam—putamen, S1—primary sensory cortex, SMA—supplementary motor area, and Thal—thalamus.

b) the left and right thalamus (pulvinar, ventral posterior lateral nucleus), and c) the left Heschl's gyrus. When overt swallowing was contrasted with oral–sensory stimulation, greater activation occurred during swallowing in only two regions: the right precuneus and the lateral portion of the caudate nucleus, bilaterally. No regions showed greater activation during oral–sensory stimulation than during overt swallowing. Volume of activation for oral–sensory stimulation (23,936 mm^3) was less than that for overt swallowing (38,304 mm^3).

During covert swallowing (Fig. 2c), additional clusters of activation included the right and left SMA and the middle cingulate cortex. Overt swallowing produced greater activation than covert swallowing in a) the left and right S1 and parietal operculum, b) the right M1, c) the right insula and thalamus, and d) the left and right cerebellum. Conversely, no regions showed greater activation during covert swallowing than during overt swallowing. Volume of activation for covert swallowing (19,048 mm^3) was less than that for overt swallowing (38,304 mm^3).

Breath-holding activated several regions of the overt swallowing cerebral system (Fig. 2d), but with substantially less volume of activation than overt swallowing (5144 mm^3 versus 38,304 mm^3 for overt swallowing). The majority of regions that were active during overt swallowing remained significantly active when contrasted with breath-holding, including the M1, S1, parietal operculum, thalamus, putamen, pallidum, insula, middle cingulate gyrus and cerebellum. No regions showed greater activation during breath-holding than during overt swallowing.

Comparison of conditions across ROIs

An initial three-way ANOVA (condition, ROI, hemisphere) showed no significant main effects for hemisphere ($F(1,12)=3.65$, $p=0.080$). To explore the possibility of gender differences, gender was entered into this ANOVA as a between-group factor. However, no significant male to female differences were found ($F(1,12)=0.18$, $p=0.680$). Due to the non-significant effects for hemisphere, left and right hemispheres were combined within each ROI and two-way ANOVAs were performed.

Oral–sensory stimulation and overt swallowing

The two-way repeated measures ANOVA for oral–sensory stimulation and overt swallowing showed no significant main effect for condition ($F(1,13)=4.31$, $p=0.058$), with a significant main effect for ROI ($F(8,104)=34.24$, $p<0.001$). Significant interaction effects were found for condition by ROI ($F(8,104)=3.01$, $p=0.004$). Due to the significant interactions, follow-up individual *t*-tests were performed for each ROI at $p<0.01$ (Fig. 3).

In multiple sensory-related regions, percent volume was equivalent during oral–sensory stimulation and overt swallowing. In the S1 ($t(13)=2.32$, $p=0.038$), OP4 ($t(13)=-1.06$, $p=0.309$), insula ($t(13)=1.67$, $p=0.119$) and thalamus ($t(13)=1.80$, $p=0.096$), comparisons of percent volume for oral–sensory stimulation and overt swallowing were non-significant.

In motor-related regions, several similarities across conditions were also seen. In the SMA ($t(13)=2.78$, $p=0.016$) and M1 ($t(13)=2.59$, $p=0.022$), only a non-significant trend toward greater activation occurred for overt swallowing versus oral–sensory stimulation. Similarly, in the middle cingulate cortex ($t(13)=2.15$, $p=0.051$), putamen ($t(13)=1.28$, $p=0.223$), and globus pallidus ($t(13)=2.22$, $p=0.045$) the percent volume was equivalent between oral–sensory stimulation and overt swallowing.

Covert and overt swallowing

The two-way repeated measures ANOVA for covert and overt swallowing showed a significant main effect for condition ($F(1,13)=13.40$, $p=0.003$) and ROI ($F(8,104)=11.06$, $p<0.001$). Significant interaction effects were found for condition by ROI ($F(8,104)=11.73$, $p<0.001$). Due to the significant interactions, follow-up individual *t*-tests were performed for each ROI at $p<0.01$ (Fig. 4).

In multiple sensory-related regions, percent volume was significantly greater during overt swallowing than during covert swallowing. In the S1 ($t(13)=3.04$, $p=0.009$), OP4 ($t(13)=7.88$, $p<0.001$) and thalamus ($t(13)=5.39$, $p<0.001$), significantly greater activation occurred during overt swallowing than during covert
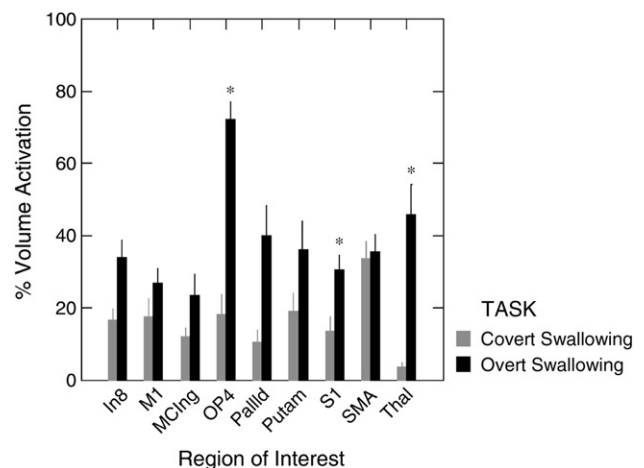

Fig. 4. Covert versus overt swallowing *t*-test results for region of interest (ROI) analysis showing combined left and right hemisphere mean percent volume activation (error bar = standard error of measurement) for each region based on individual subject analysis. Ins—insula, M1—primary motor cortex, MCing—middle cingulate cortex, OP4—operculum 4, Pallid—globus pallidus, Putam—putamen, S1—primary sensory cortex, SMA—supplementary motor area, Thal—thalamus.

swallowing. However, the comparison of insula percent volume was non-significant between the two conditions ($t(13)=2.64$, $p=0.021$), with a trend toward greater activation during overt swallowing.

Activation of motor-related regions was similar for covert and overt swallowing. In the SMA ($t(13)=0.27$, $p=0.793$), M1 ($t(13)=1.36$, $p=0.196$), middle cingulate cortex ($t(13)=1.70$, $p=0.112$), and putamen ($t(13)=1.81$, $p=0.094$), comparisons of percent volume for covert and overt swallowing were non-significant, with a non-significant trend toward greater percent volume for overt swallowing in the globus pallidus ($t(13)=2.88$, $p=0.013$).

The visual analog scale results indicated that during covert swallowing subjects attended more to the motor aspects (mean=81.1 mm, SD=17.6) than the sensory aspects of swallowing (mean=65.1 mm, SD=27.3), and least to the visual aspects of swallowing (mean=37.5 mm, SD=30.2).

Discussion

The regions activated by overt swallowing were consistent with previous fMRI studies and included the M1, S1, operculum, SMA and cingulate cortex, insula, portions of the parietal cortex, basal ganglia regions, and cerebellum. The contrast between overt swallowing and breath-holding examined whether the brief breath-holding period during the swallow (about 1 s) could account for the central activation pattern associated with overt swallowing. Volitional brief breath-holding tasks can induce a hemodynamic response (HDR) (Abbott et al., 2005); therefore, any brain activation associated with the breath-holding task in this study could relate to the task and its executive function requirements, as well as blood oxygenation level changes resulting from a brief decrease in oxygen. Although there were several brain regions activated by breath-holding in this study, the neural substrates that were activated for overt swallowing remained significantly activated even when breath-holding was subtracted out. Previous studies that have investigated neural correlates for swallowing have not considered whether activation associated with swallowing might be primarily accounted for by the breath-holding component that swallowing involves. Our results indicate that the majority of brain activation associated with swallowing is resulting from swallowing itself and not the brief breath-holding that occurs within each swallow. Subsequent discussion focuses on the other two conditions of interest, oral–sensory stimulation and covert swallowing, which both activated multiple components of the cerebral system for volitional swallowing.

Oral–sensory stimulation activated very similar neural correlates as overt swallowing; only the right precuneus and a small portion of the lateral caudate nucleus were activated to a significantly greater extent by overt swallowing than by oral–sensory stimulation in the whole brain analysis. Previous researchers found that that a sensory stimulus related to swallowing can activate sensorimotor cortex or caudolateral opercular cortex using MEG (Furlong et al., 2004; Gow et al., 2004). Our results support these previous findings and further show that extensive cortical and subcortical swallowing regions were engaged by oral air pulse stimulation. Covert swallowing activated many of the same regions as overt swallowing but to a lesser extent. M1 and S1 activation was significantly greater for overt swallowing. This is consistent with previous studies that have shown limited or reduced primary sensorimotor activation during covert conditions compared to hand movement execution (Lacourse et al., 2005; Stephan et al., 1995). Although subjects reported attending to motor and somewhat less to sensory components of swallowing during covert swallowing, this did not result in as high sensorimotor

activation as during overt swallowing. The greater activation in the right insula and bilateral parietal operculum during overt swallowing may reflect greater sensory feedback and sensorimotor integration during overt versus covert swallowing. No regions showed greater activity during covert swallowing compared to overt swallowing, indicating that covert swallowing did not significantly engage other brain regions than those involved in swallowing.

Overall, the overt swallowing task elicited a greater volume of activation than either of the other two conditions. This was expected based on the greater representation of constituent functions in overt swallowing as compared to the two related conditions. For covert swallowing, neither the sensory feedback nor motor execution aspects of overt swallowing were present, whereas during oral stimulation neither the planning nor the motor execution aspects of overt swallowing were present. However, oral–sensory stimulation elicited activation to a greater extent than covert swallowing in both the motor and sensory regions involved in swallowing.

Differentiation of the sensory aspects of swallowing

The ROI analysis showed that oral stimulation activated sensory regions to a similar degree as overt swallowing, consistent with our hypothesis. Both primary and secondary somatosensory cortices were activated during oral–sensory stimulation to equivalent levels as overt swallowing. OP4, as part of the secondary somatosensory cortex, is considered a sensory integration area (Young et al., 2004). Similar somatosensory activation was elicited in a previous study with air pulse stimulation to the soft palate (Yoshida et al., 2006). In our study, activation in S1 and OP4 during unilateral air pulse stimulation occurred at nearly identical levels in both the right and left hemispheres, consistent with the finding that secondary somatosensory cortex generally shows bilateral activation, even when the peripheral stimulus is unilateral (Bingel et al., 2003; Young et al., 2004). Covert swallowing minimally engaged primary or secondary somatosensory cortices, indicating that direct sensory input is needed to elicit sensory swallowing regions.

Several other regions assessed in the ROI analysis were involved in both sensory and motor functions. The sensory regions of the thalamus (specifically the ventral posterior lateral nucleus) may have contributed to its equivalent activation by oral–sensory stimulation and overt swallowing. The lack of those sensory inputs during covert swallowing could explain the significantly lower thalamic activation as compared to overt swallowing.

Activation of the insula was also equivalent for overt swallowing and oral–sensory stimulation. The insula is involved in multiple sensorimotor functions, including taste and smell (Francis et al., 1999), pain, temperature and visceral sensation processing (Brooks et al., 2005), physiologic sense of the body (Craig, 2003) sense of volitional movement (Hallett, 2007) and pleasant or aversive aspects of stimuli (Anders et al., 2005; Francis et al., 1999). Insula activation has been consistent across studies of swallowing (Hamdy et al., 1999; Kern et al., 2001b; Martin et al., 2001; Martin et al., 2004; Toogood et al., 2005). Because insula activation showed a trend to be greater during overt swallowing than covert swallowing, the sensory processing components of swallowing may have contributed to its activation.

Differentiation of motor planning and execution regions across conditions

Motor correlates of the swallowing cerebral system were differentiated by the covert and overt swallowing conditions. Covert

swallowing elicited activation in the SMA as was expected, but also engaged regions associated with motor execution, contrary to our hypothesis. Both the cingulate cortex and the supplementary motor area are important to movement planning and movement initiation (Deiber et al., 1996; Deiber et al., 1999; Donohue et al., 2008). The equivalent activation of the SMA by both covert and overt swallowing, and a trend towards greater activation by overt swallowing versus oral–sensory stimulation indicates that motor planning aspects of swallowing were differentiated by covert swallowing. However, other areas related to motor initiation and execution were activated equivalently by both covert swallowing and oral–sensory stimulation relative to overt swallowing, demonstrating that both swallowing-related conditions evoked activation of the cerebral motor swallowing system.

There are several possible reasons for the motor activation evidenced during the oral–sensory stimulation and covert swallowing. In normal swallowing, when food or secretions pass the anterior faucial pillar region, the motor pattern associated with the pharyngeal phase of swallowing is typically initiated. Therefore, stimulating this region with the oral air pulse stimulus may have activated the entire cortical system for swallowing, including motor regions. The frequency of uncued swallows during the study was low, and their effects on the other conditions were minimized by including these events as a regressor of no interest. However, although the pressure sensing pneumatic belt allowed us to factor out any effects from a complete swallow, more subtle oral, laryngeal, or pharyngeal movement could have occurred during oral–sensory stimulation or covert swallowing and produced some motor activation. Previous studies involving tactile stimulation to the hand or foot have also shown activation of motor areas such as the M1, pre SMA and SMA in addition to the expected somatosensory activation (Bodegard et al., 2001; Young et al., 2004). Possible links between sensory afferents and motor regions such as the SMA may explain motor activation following sensory tasks (Oishi et al., 2003). Covert swallowing also engaged multiple motor-related regions. These results are consistent with previous fMRI studies which have demonstrated that motor execution regions such as the M1, putamen, caudate nucleus and cingulate cortex can all be engaged by covert tasks involving preparatory or imaginary movement (Gerardin et al., 2000; Lotze et al., 1999; Szameitat et al., 2007).

Limitations of the study

Percent volume activation for the regions of interest showed a great deal of inter-subject variability, with large standard errors. The range in subject age (21–52 years) may have contributed to this variability. Gender differences did not appear to contribute to variance. Previous studies have shown high inter- or intra-subject variability in the regions of activation, laterality of activation, and activation across swallow-related tasks (Martin et al., 2001; Mosier et al., 1999). Additional studies are needed to determine whether separate age groups would show similar patterns of neural activation while performing oral–sensory stimulation or covert swallowing tasks.

Clinical implications

The ability to engage a similar cerebral system to real swallowing during covert swallowing and oral–sensory stimulation has important implications for treatment of persons with dysphagia. For treatment purposes, swallowing-related tasks may engage multiple components of the swallowing network, and air pulse stimulation could provide a means for augmenting sensory input to both the brainstem and cortical swallowing control centers. Stimulation of the faucial pillar region of the oral cavity in patients with dysphagia has showed mixed results for improving swallowing (Power et al., 2006; Rosenbek et al., 1991; Rosenbek et al., 1996), but these researchers did not employ air pulse stimulation. Future studies are needed to determine whether air pulse stimulation or covert swallowing can engage cerebral swallowing regions in patients with neurological impairment, and the rehabilitative potential of these tasks for persons with swallowing disorders.

Furthermore, imaging individuals with swallowing disorders presents many technical and safety challenges. Using tasks that effectively engage similar cerebral regions as real swallowing but do not require actual swallowing can provide a critical alternative for studying swallow-related cerebral activation in patients and for assessing cortical plasticity changes in these individuals.

Conclusions

Oral–sensory stimulation and covert swallowing were found to activate many neural correlates of volitional swallowing. Both motor and sensory regions of the volitional swallowing system were engaged by oral air pulse stimulation. This cortical activation indicates that sensory inputs from oro-pharyngeal regions innervated by the glossopharyngeal nerve can engage much of the cerebral swallowing system. Covert swallowing minimally engaged the sensory regions, but elicited activation in multiple motor-related regions of the swallowing system.

The ability to elicit similar neural correlates to overt swallowing through oral–sensory stimulation and covert swallowing has important implications for intervention in swallowing disorders secondary to neurological disease. Oral air pulse stimulation may augment sensory input and engage both brainstem and cerebral control centers, potentially impacting the volitional components of swallowing. Furthermore, in patients with unilateral sensory deficits, oral–sensory stimulation applied to the intact side may bilaterally engage the cerebral swallowing control regions.

Acknowledgments

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