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ORIGINAL ARTICLE

Swallowing Preparation and Execution: Insights from a Delayed-Response Functional Magnetic Resonance Imaging (fMRI) Study

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Abstract The present study sought to elucidate the functional contributions of sub-regions of the swallowing neural network in swallowing preparation and swallowing motor execution. Seven healthy volunteers participated in a delayed-response, go, no-go functional magnetic resonance imaging study involving four semi-randomly ordered activation tasks: (i) "prepare to swallow," (ii) "voluntary saliva swallow," (iii) "do not prepare to swallow," and (iv) "do not swallow." Results indicated that brain activation was significantly greater during swallowing preparation, than during swallowing execution, within the rostral and intermediate anterior cingulate cortex bilaterally, premotor cortex (left > right hemisphere), pericentral cortex (left > right hemisphere), and within several subcortical nuclei including the bilateral thalamus, caudate, and putamen. In contrast, activation within the bilateral insula and the left dorsolateral pericentral cortex was significantly greater in relation to swallowing execution, compared with swallowing preparation. Still other regions, including a more inferior ventrolateral pericentral area, and adjoining Brodmann area 43 bilaterally, and the supplementary motor area, were activated in relation to both swallowing preparation and execution. These findings support the view that the preparation, and subsequent execution, of swallowing are mediated by a cascading pattern of activity within the sub-regions of the bilateral swallowing neural network.

Keywords Deglutition · Deglutition disorders · Human · Preparation · Execution · Neural control · Cerebral cortex · Brain imaging · fMRI

Introduction

Converging evidence from brain mapping studies in humans, and electrophysiological investigations in non-human primates, has suggested that swallowing is processed within a distributed supratentorial network comprising the primary sensorimotor cortex, premotor cortex,

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anterior cingulate cortex (ACC), frontoparietal operculum, and insula [1–19]. Activation within some, or all, of these brain areas has been reported in association with voluntary swallowing of a water bolus, voluntary saliva swallowing, or "autonomic" saliva swallowing in naïve subjects [3, 5, 6, 9, 10, 12, 14–16, 20, 21]. Swallow-related activation of the posterior cingulate cortex and basal ganglia also has been reported, though less consistently [6, 12, 21, 22].

Given the widely distributed nature of the neural representation of swallowing, different loci within the network have been postulated to mediate functionally distinct components of the swallowing act. For example, activation of the primary sensorimotor cortex has been attributed to swallowing motor initiation and execution processes [3, 6, 9, 10, 12, 14, 15], while involvement of non-primary motor regions, including the ACC, has been explained in terms of higher-order motor processing or attention [3, 6, 9, 10, 12, 14, 16]. Nevertheless, because few studies have directly addressed the possibility that specific regions within the swallowing representation are differentially engaged, their functional organization and significance for swallowing control remain poorly understood.

The present pilot study sought to elucidate the functional contributions of loci within the swallowing network in terms of swallowing preparation and swallowing motor execution. This study objective was based on three bodies of literature. First, electrophysiological studies have suggested that swallowing involves early preparation and subsequent execution phases, with these stages recruiting distinct brain regions. For example, in non-human primates, pre-swallow phase activity, but not the subsequent swallow execution phase, is impaired by reversible inactivation of the intracortical microstimulation (ICMS)-defined face primary motor cortex [17]; in contrast, swallowing execution is impaired by reversible inactivation of the ICMS-defined swallow primary motor cortex [23]. Second, three magnetoencephalography (MEG) studies [1, 2, 24] and three functional magnetic resonance imaging (fMRI) studies [9, 20, 25] have addressed cortical activity associated with the early and later phases of swallowing. While all three MEG studies reported preferential activation of different loci within the swallowing network in association with different phases of swallowing, the temporal activation patterns reported were inconsistent across studies. For example, Furlong et al. [2] found a shift from caudolateral to superior sensorimotor cortex in association with the pre-swallow and motor phases of water swallowing, respectively; Teismann et al. [24] reported a time-dependent activation shift from left- to right-hemisphere sensorimotor cortex activation in association with the early and later phases of volitional swallowing; and Dziewas et al. [1] showed that volitional swallowing activated the left mid-lateral pre- and postcentral gyri whereas swallowing preparation activated a more posterior area corresponding to the bilateral primary somatosensory cortex (SI). Because MEG is limited in its capacity to detect magnetic fields below the cortical surface [26], only the Dziewas group addressed swallow-related insular activation (i.e., reporting that the left insula was activated during both swallowing preparation and movement stages), and none of the studies examined activation of the basal ganglia. This relative lack of evidence on insular and basal ganglia activation represents a significant limitation in the existing literature on the neural control of swallowing planning and execution. Using fMRI, Malandraki et al. [9] reported activation of the premotor cortex [Brodmann area (BA) 6] and ACC during swallowing preparation, whereas volitional swallowing activated more widespread cortical and subcortical areas including the primary sensorimotor cortex, superior and inferior parietal cortices, cingulate gyrus, insula, thalamus, and basal ganglia. Activation of the sensorimotor cortex during both swallowing planning and execution was found to be greater among younger than older adults [20]. Mihai et al. [25] aimed to describe the temporal sequence of representation sites of swallowing and their functional connectivity using fMRI. The temporal analysis revealed a successive activation starting at the premotor cortex, supplementary motor area (SMA), and bilateral thalamus, followed by the primary sensorimotor cortex, the posterior insula, and cerebellum and culminating with activation in the pons shortly before subsiding. They found activation was lateralized initially to the left hemisphere and gradually moved to the right hemisphere over time.

The present study was also motivated by the limb motor control literature which has shown that several of the cortical loci implicated in swallowing are preferentially activated during the preparation and/or execution of voluntary limb movements; these include the primary motor cortex (MI), SMA, ACC, and premotor cortex [27–34]. Preparation of limb movements has been reported to activate the SMA, ACC, and premotor cortex [35–37], whereas MI activation has been associated with both limb movement preparation and execution [34].

Based on the foregoing evidence from swallowing and limb studies, it was hypothesized that swallowing preparation would preferentially activate the premotor cortex, SMA, and ACC, whereas the sensorimotor cortex and insula would be activated during both swallowing preparation and execution.

Some preliminary data from this study were reported in abstract form [38].

Methods

Subjects

Seven healthy volunteers, three female and four male (age 27.7 ± 1.3 years, mean ± SD), participated as subjects. One male and one female were left handed according to the Edinburgh Handedness Inventory [39]. All subjects had previous fMRI experience, and gave written informed consent prior to participating in the study. The study adhered to the MRI safety depositional guidelines established by the US Food and Drug Administration for clinical scanners, and was approved by the University of Western Ontario Review Board for Health Sciences Research involving human subjects.

Tasks

Prior to the experimental session, each subject was trained on the activation tasks and performed a supervised full-length practice run to ensure that he/she understood the experimental procedures. Each subject participated in six, 9-min functional imaging runs during a single experimental session. Each functional run consisted of four semi-randomly ordered activation tasks; two activation tasks were 'preparatory' in nature, and two were 'executory.' The four activation tasks were: (i) "prepare to swallow," (ii) "voluntary saliva swallow," (iii) "do not prepare to swallow," and (iv) "do not swallow." The following task instructions were provided prior to the imaging protocol: for the "prepare to swallow" task, the subject was instructed to prepare to swallow, and informed that a swallow cue would appear several seconds following the preparation cue. For the "voluntary saliva swallow" task, the subject was instructed to swallow his/her saliva once without producing exaggerated oral movements. For the "do not prepare to swallow" task and the "do not swallow" task, the subject was instructed to remain at rest without preparing to swallow, or swallowing, respectively.

Each task was performed in response to a visual cue that was back-projected onto a mirror positioned above the subject's eyes. The two preparation cues were colored ovals: a green filled oval instructed the subject to "prepare to swallow," while a red filled oval cued the subject to "do not prepare to swallow" (Fig. 1). The two execution cues involved a line drawing of a man drinking a glass of liquid: this drawing, framed in a green border, served as the "voluntary saliva swallow" task cue, while the same line drawing, framed and crossed with a red line, was the cue for the "do not swallow" task. Each trial began with the presentation of one of the two preparation cues, followed 10 or 12 s later by the presentation of one of the two execution cues. The execution cue was followed by a 15–20 s rest period. There were 16 trials in each functional run.

Each subject participated in two *matched* runs in which the "prepare to swallow" cue was always followed by the "voluntary saliva swallow" cue, and the "do not prepare to swallow" cue was always followed by the "do not swallow" cue. Each of these *matched* runs contained eight "prepare to swallow–voluntary saliva swallow" matched trials and eight "do not prepare to swallow–do not swallow" matched trials. The other four functional runs, which were designated *mismatched* runs, consisted of equal numbers of matched trials and mismatched trials. Matched trials paired the "prepare to swallow" with the "voluntary saliva swallow" cue, or the "do not prepare to swallow" cue with the "do not swallow" cue. Mismatched trials involved the pairing of the "prepare to swallow" cue with the "do not swallow" cue, and the "do not prepare to swallow" cue with the "voluntary saliva swallow" cue. During the experimental session, all subjects performed the matched runs before the mismatched runs, and subjects were not informed that they would be participating in mismatched runs until after they had completed the matched runs. Prior to commencing the first mismatched run, a scripted instruction informed the subject that subsequent runs would contain both matched and mismatched trials, but no indication was given as to which trial would be matched and which would be mismatched. The subject was also instructed to treat the preparation cues in the same manner during the mismatched runs as during the matched runs. The matched runs were conducted prior to the mismatched runs to avoid any weakening in the salience of the preparation cues within the matched runs by the uncertainty of mismatched trials.

Identification of Swallowing and Swallow Response Latency

Single swallowing trials were verified on the basis of their distinct profiles of laryngeal movement [10, 40]. The output signal of a pressure transducer driven from expanding MR-compatible bellows (Siemens, Erlangen, Germany) placed over the subject's thyroid cartilage recorded laryngeal movements (PowerLab, 5.2.2). In addition to identifying swallowing trials, this signal detected the subject's carotid pulse.

The swallow response latency was defined as the time from the computer-generated trigger for the "voluntary saliva swallow" cue to the peak amplitude of the swallow-related laryngeal movement signal. Swallow latencies were calculated separately for the (a) matched runs, (b) matched trials of the mismatched runs, and (c) mismatched trials of the mismatched runs.

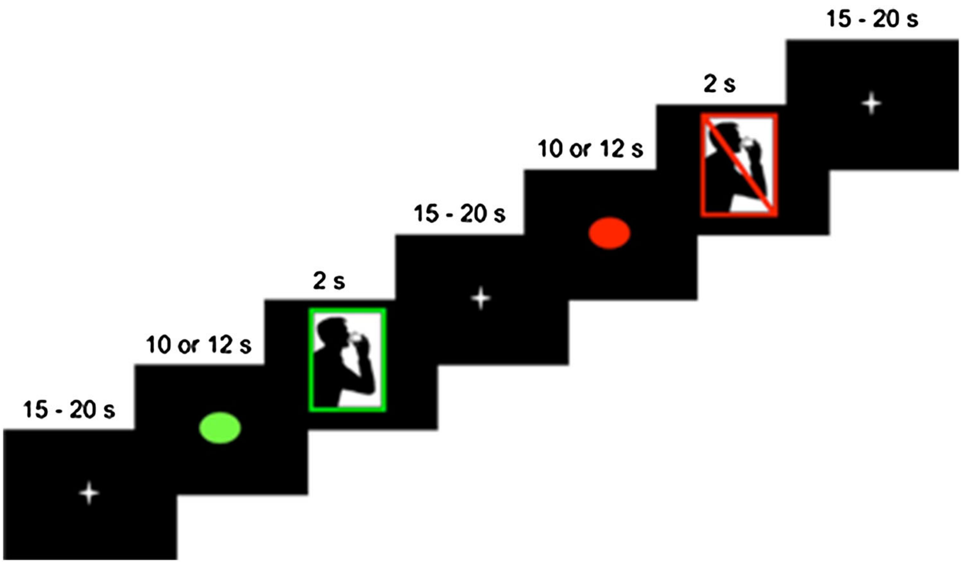

Fig. 1 Visual cues presented to the subject during a matched "swallow" trial and a matched "do not swallow" trial. The duration of the presentation of each cue (in seconds) is indicated

MRI Experiments

All subjects were imaged using a Varian UNITY INOVA 4 Tesla (T) whole-body imaging system (Varian, Palo Alto, CA) equipped with 40 mT/m Siemens Sonata actively shielded whole-body gradients and amplifiers (Siemens, Erlangen, Germany). A whole-head quadrature birdcage radio frequency coil transmitted and received the MR signal [41]. The subject's head was immobilized using foam padding fit snugly between the subject's head and a Plexiglas head cradle within the head coil.

Imaging planes for the functional scans were prescribed with the aid of a high-resolution [256 × 256, 28.0 cm field of view (FOV)] sagittal anatomic image with gray/white matter contrast (i.e., T_1-weighted) acquired using a 3-dimensional (3-D) gradient echo (GE) sequence with spiraled waveforms [inversion time (T_I) = 750 ms, echo time (T_E) = 3.5 ms, repetition time (T_R) = 8 ms, flip angle = 11°, 5-mm slice thickness]. Functional data were collected from eight contiguous, 10-mm-thick axial slices oriented in a plane approximately parallel to the anterior commissure (AC)–posterior commissure (PC) line and extending from the superior extent of the paracentral lobule to the approximate level of the AC–PC plane. Blood oxygenation level-dependent (BOLD) images (i.e., T_2^*-weighted) were acquired continuously using an interleaved, two-segment, GE sequence with spiraled waveforms (64 × 64 matrix size, $T_R = 500$ ms, $T_E = 15$ ms, flip angle = 22°, 22.0 cm FOV, volume collection time = 1 s) during each functional task described above. Each image was corrected for physiologic fluctuations using a navigator echo that was collected at the beginning of every image segment [42]. Anatomic reference images were acquired at the end of the experimental session, along the same orientation as the functional images using a 3-D GE sequence with spiraled waveforms (256 × 256 × 128 matrix size, 2.0 mm reconstructed slice thickness, $T_I = 130$ ms, $T_R = 50$ ms, $T_E = 3.0$ ms).

fMRI Data Analysis

Preprocessing

Previous fMRI studies have shown that swallow-related movements of the tongue and jaw occurring immediately outside the imaging FOV can produce false-positive BOLD signal changes by disturbing the magnetic field in nearby imaging slices [43], producing both magnitude and phase changes in the complex-valued MRI signal [10]. Hemodynamic changes within the microvasculature (i.e., the vasculature smaller than intracortical veins), in contrast, are expected to produce only magnitude changes in the MR signal [44]. Based on these findings, we applied a motion suppression algorithm that estimates and removes the fraction of the BOLD signal arising from motion by measuring its influence on the phase angle of the complex-valued MRI time series [44]. The effectiveness of this algorithm has been previously verified by our laboratory [12].

Data Analysis

Subsequent image analyses were performed using BrainVoyager v4.9 [45]. Volume time courses were created by co-registering the two-dimensional (2-D) functional slices with the 3-D anatomic images. Anatomic images were aligned with the AC–PC plane and transformed to standard stereotaxic space [46]. The data were then spatially smoothed with a Gaussian filter (full width at half maximum = 4 mm) for subsequent analyses.

Both single-subject and group data analyses were performed. Brain activation associated with preparing to swallow, swallowing, not preparing to swallow, and not swallowing was identified using multiple regression analyses. A square-wave function representing the time course of the activation task was convolved with a γ function ($\delta = 1.25$; $\tau = 2.5$) representing the hemodynamic impulse response [47, 48] to generate predictors. Experimental time courses were derived from the task triggers. Both preparation and execution predictors were assigned a duration of 2 s. Incorrect trials were identified using the laryngeal movement signal and excluded from the analysis (9 trials out of 656 were excluded).

The statistical analysis was based on the general linear model in which the MR signal was modeled in terms of a number of predictors representing the various experimental tasks. These tasks included "prepare to swallow," "voluntary saliva swallow," "do not prepare to swallow," and "do not swallow" in the matched and mismatched runs. Multiple regression analyses were tested, on a voxel-by-voxel basis, for significant activation associated with the activation tasks.

Contrasts

Four voxel-wise *t*-statistic contrast analyses were performed to differentiate brain activation associated with swallowing planning and swallowing execution. Each of the four contrasts tested whether the mean MR signals associated with two task predictors were significantly different. *Contrast 1* tested for voxels in which activation associated with the "prepare to swallow" task was significantly different from that associated with the "voluntary saliva swallow" task within the matched runs. *Contrast 2* identified voxels in which there was a significant difference between activation associated with the "prepare to swallow" and "do not prepare to swallow" tasks within the matched runs. *Contrast 3* tested for voxels in which activation associated with the "voluntary saliva swallow" task was significantly different from that associated with the "do not swallow" task within the matched runs. *Contrast 4* examined swallowing execution when it was, or was not, preceded by a preparation period by comparing the matched swallow trials (i.e., "prepare to swallow–voluntary saliva swallow") of the mismatched runs with the mismatched swallow trials (i.e., "do not prepare to swallow–voluntary saliva swallow") of the mismatched runs. The results of these four contrasts were interpreted in relation to each other in attempt to achieve greater insights into both preparation-related, and execution-related, brain activation than would be anticipated based on a single contrast or a smaller corpus of contrasts.

Region-of-Interest Analysis

A region-of-interest (ROI) analysis was performed to examine activation within the cortical regions that have been consistently implicated in swallowing by previous studies [3–6, 10, 12, 14–16, 21]. Nine anatomically defined ROIs were examined. These corresponded to the: (1) ventrolateral precentral gyrus corresponding to BA 4, (2) ventrolateral postcentral gyrus corresponding to BAs 1–3, (3) precentral gyrus corresponding to BA 4 excluding the lateral precentral gyrus, (4) postcentral gyrus corresponding to BAs 1–3 excluding the lateral postcentral gyrus, (5) BA 43, (6) insula, (7) premotor cortex corresponding to lateral BA 6, (8) SMA corresponding to mesial BA 6, and pre-SMA (i.e., BA 6/8), and (9) ACC corresponding to BAs 24 and 32.

The precentral and postcentral gyri were divided into lateral ($Z \leq 37$) and non-lateral ($Z \geq 38$) regions based on preliminary data analyses indicating that these ROIs contained distinct activation foci. The insular ROI was defined with respect to two Talairach volumes: between $Y = -26$ to 4, $X = -20$ to -44; $Z = -6$ to 20, and between $Y = 5$ to 26, $X = -32$ to -44; $Z = -6$ to 20. BA 6 was divided into the premotor cortex laterally and the SMA medially using the Talairach coordinate $X = 17$.

Prominent areas of activation that were located outside of these nine prescribed ROIs were also documented in terms of their Talairach coordinates.

Time Course Analyses

Average MR time courses corresponding to prominent activation volumes for each contrast analysis were obtained by averaging the MR signals associated with all trials within each experimental condition. The matched and mismatched runs contained trials in which either a 10 s, or a 12 s, preparation period preceded the execution cue. Averaging across both the 10- and 12-s trials would have resulted in time courses in which the signal was unreliable after 10 s. To avoid this problem, the 10- and 12-s trials were averaged separately.

Results

Swallowing Response Latencies

The laryngeal movement data indicated that subjects swallowed once in response to the "voluntary saliva swallow" cue. There were no instances of swallowing in response to the "do not swallow" cue, and changes in the laryngeal signal were not observed in response to either of the preparation cues. The mean swallow latencies (±standard error) for the (1) matched runs (comprised of matched trials only), (2) matched trials within the mismatched runs, and (3) mismatched trials within the mismatched runs were 1.07 ± 0.03, 1.19 ± 0.04, and 1.33 ± 0.04 s, respectively, for the group of seven subjects. A one-way ANOVA with post hoc comparisons indicated that the mean swallow latencies for (a) the matched runs, and (b) the matched trials of the mismatched runs were both significantly shorter than the swallow latency for the mismatched trials of the mismatched runs ($p < 0.025$). While the swallow latencies for the matched runs were greater than the latencies for the matched trials of the mismatched runs, the difference was not significant ($p > 0.05$).

Group Analyses

The results of the group analyses, and Talairach coordinates corresponding to activation volumes identified in each statistical contrast, are given in Appendices 1 and 2.

Matched Runs

Contrast 1: "Prepare to swallow" Versus "Voluntary saliva swallow" *Prepare to Swallow*

Activation associated with the "prepare to swallow" task was significantly (p_{cor} <0.0001) greater than activation associated with the "voluntary saliva swallow" task within four of the nine ROIs: the bilateral ACC, bilateral (Left > Right) premotor cortex, postcentral gyrus, particularly in the left hemisphere, and a small area of the left precentral gyrus. The ACC activation comprised two large non-contiguous foci: the rostral ACC along the rostral (i.e., BA 32) and caudal (i.e., BA 24) banks of the cingulate sulcus [49]; ($X = \pm 3 \leftrightarrow 8$, $Y = 29 \leftrightarrow 35$, $Z = 13 \leftrightarrow 16$; see Appendix 1); and the intermediate ACC (i.e., $Z = 31$–34) along both the rostral ($Y = 14$–24) and caudal ($Y = 6$–8) banks of the cingulate sulcus. The premotor cortex activation was located on the caudal bank of the precentral sulcus. The postcentral gyrus activation involved (1) the lateral BA 3 bilaterally, (2) the left central sulcus (i.e., extending superiorly to inferiorly $Z = 62$–53), and (3) the rostral bank of the left postcentral sulcus (i.e., BA 2; Fig. 2).

Areas of activation outside of the prescribed ROIs corresponded to the superior, middle, and medial frontal gyri, bilateral thalamus, caudate, globus pallidus, putamen, PCC, superior temporal gyrus, inferior parietal lobule, precuneus, and cuneus.

Voluntary Saliva Swallow

Activation associated with the "voluntary saliva swallow" task was significantly greater than activation associated with the "prepare to swallow" task within six of the nine ROIs. There was prominent activation of the insula bilaterally, extending to its anterior and posterior aspects. The remaining five ROIs corresponded to sensorimotor cortical regions: the left ventrolateral precentral and postcentral gyri (i.e., BA 4/6 at $Z = 30$–40; BA 3 at $Z = 30$) and, more inferiorly, a smaller right ventrolateral precentral gyrus activation along the central sulcus (i.e., BA 4, $Z = 16$); left precentral gyrus (BA 4/6), right precentral gyrus within the central sulcus ($Z = 50$), the right postcentral gyrus (i.e., BA 3, 1, $Z = 56$–61), and a small area of the left premotor cortex.

Areas of activation found outside the ROIs corresponded to the superior, middle, and inferior frontal gyri, inferior parietal lobule, cuneus, and precuneus.

Contrast 2: "Prepare to swallow" Versus "Prepare to not swallow" *Prepare to Swallow*

Preparation-related activity was significantly (p_{cor} <0.0001) greater than activity associated with not preparing to swallow within five of the nine ROIs including the ventrolateral precentral and postcentral gyri bilaterally, and the contiguous BA 43 bilaterally. This activation focus was inferior to the ventrolateral activation focus observed in association with swallowing execution in *Contrast 1*. Activation was also found within the left premotor cortex in a region inferior to the premotor focus found in relation to swallowing preparation in *Contrast 1* (i.e., $Z = 15 \leftrightarrow 23$). Activation was found within contiguous regions of the SMA and pre-SMA bilaterally, and within the adjacent caudal ACC bilaterally (Fig. 3).

Areas of activation outside of the prescribed ROIs corresponded to the middle frontal gyrus, inferior parietal lobule, bilateral thalamus and putamen, and right caudate.

Prepare to Not Swallow

No voxels within the defined ROIs were identified in which activation associated with not preparing to swallow was significantly (p_{cor} >0.0001) greater than activation associated with swallowing preparation. The bilateral medial frontal gyrus was the only area of activation outside the prescribed ROIs.

Contrast 3: "Voluntary saliva swallow" Versus "Do not swallow" *Voluntary Saliva Swallow*

Swallow-related activity was significantly (p_{cor} <0.0001) greater than activation associated with not swallowing within all nine ROIs (Fig. 4). Two activation foci were found within the ventrolateral precentral and postcentral gyri: a superior region of the left precentral

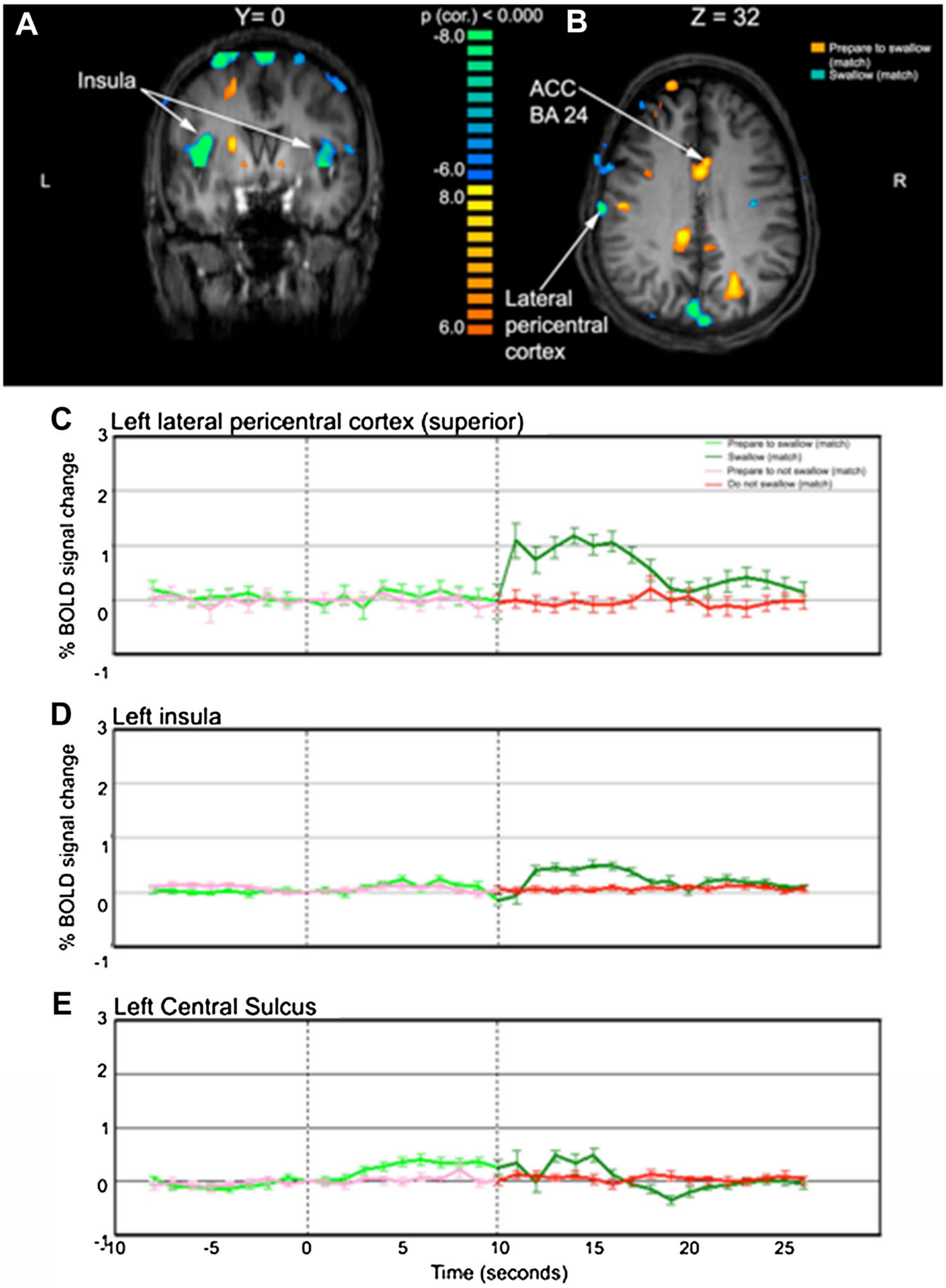

Fig. 2 Contrast of brain activation, identified in terms of the BOLD responses, associated with swallowing preparation and swallowing execution (Contrast 1). Data are shown for the group of seven subjects. Regions of significant (p_{cor} <0.0001) activation are displayed on normalized coronal (**a**) and axial (**b**) brain slices from one subject. Talairach–Tournoux plane coordinate is displayed above each brain image. The MR percent signal change within the superior left ventrolateral pericentral cortex, the left insula, and the left central sulcus following the presentation at Time = 0 of 'prepare to swallow' (*light green*) and 'do not prepare to swallow' (*pink*) and the presentation at Time = 10 of 'swallow' (*dark green*) and 'do not swallow' (*red*) are shown in **c**, **d**, and **e**, respectively

gyrus ($Z = 31$–37) which corresponded to the focus identified as being related to swallowing execution in Contrast 1; and an inferior, bilateral pericentral region, extending to the adjacent BA 43 bilaterally ($Z = 14$–22) and corresponding to the region associated with swallowing preparation in Contrast 2. There was also a prominent activation focus of the postcentral gyrus strongly lateralized to the right hemisphere, and a small focus within the left precentral gyrus. There was a large focus within the insula bilaterally. Activation was also found bilaterally in the SMA and premotor cortex, and in left BA 24 of the ACC.

Do Not Swallow

Activation associated with the do not swallow task was significantly (p_{cor} <0.0001) greater than activation associated with swallowing within the precentral and postcentral gyri (i.e., within the central sulcus and on the rostral bank of the postcentral sulcus), bilateral pre-SMA, left SMA, premotor cortex, and rostral and intermediate ACC.

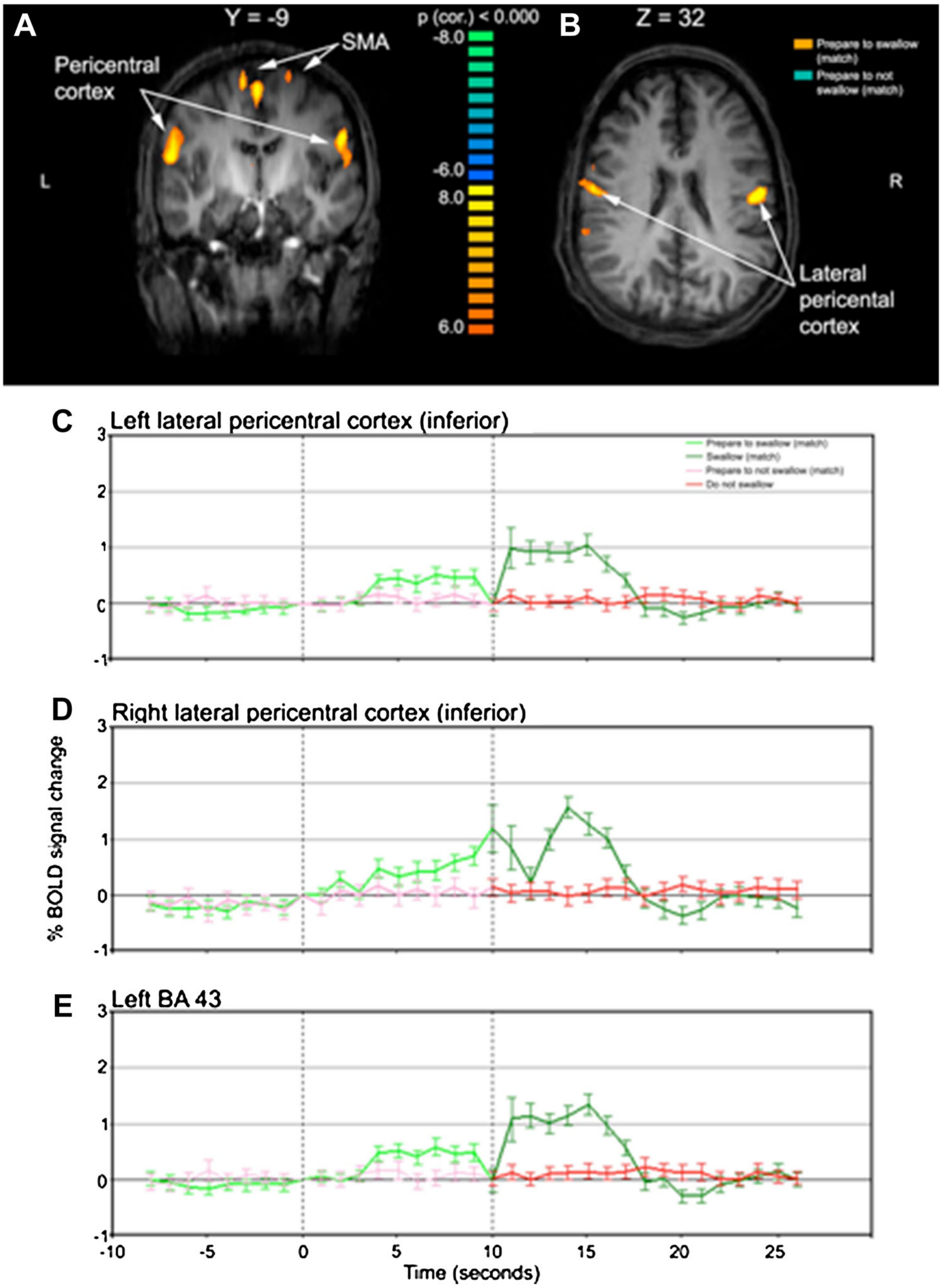

Fig. 3 Contrast of brain activation, identified in terms of the BOLD responses, associated with preparing to swallow and not preparing to swallow (Contrast 2). Data are shown for the group of seven subjects. Regions of significant (p_{cor} <0.0001) activation are displayed on normalized coronal (**a**) and axial (**b**) brain slices from one subject. Talairach–Tournoux plane coordinate is displayed above each brain image. The MR percent signal change within the inferior left lateral pericentral cortex, the inferior right lateral pericentral cortex, and left BA 43 following the presentation at Time = 0 of ‘prepare to swallow’ (*light green*) and ‘do not prepare to swallow’ (*pink*) and the presentation at Time = 10 of ‘swallow’ (*dark green*) and ‘do not swallow’ (*red*) are shown in **c**, **d**, and **e**, respectively

Activation foci outside of the prescribed ROIs corresponded to the superior and middle frontal gyri, superior temporal gyrus, caudate, and globus pallidus.

Mismatched Runs

Contrast 4: Matched Swallowing Versus Mismatched Swallowing *Contrast 4* identified voxels in which activation associated with the matched swallow trials (i.e., when the “voluntary saliva swallow” cue was preceded by the “prepare to swallow” cue) was significantly (p_{cor} <0.0001) different from activity associated with the mismatched swallow trials (i.e., when the “voluntary saliva swallow” cue was preceded by the “do not prepare to swallow” cue). Therefore, this contrast compared swallowing that occurred following a preparation cue with swallowing that occurred following a cue to not prepare to swallow.

Matched Swallow

None of the prescribed ROIs contained voxels in which activation associated with the matched swallow trials was significantly (p_{cor} <0.0001) greater than the activation

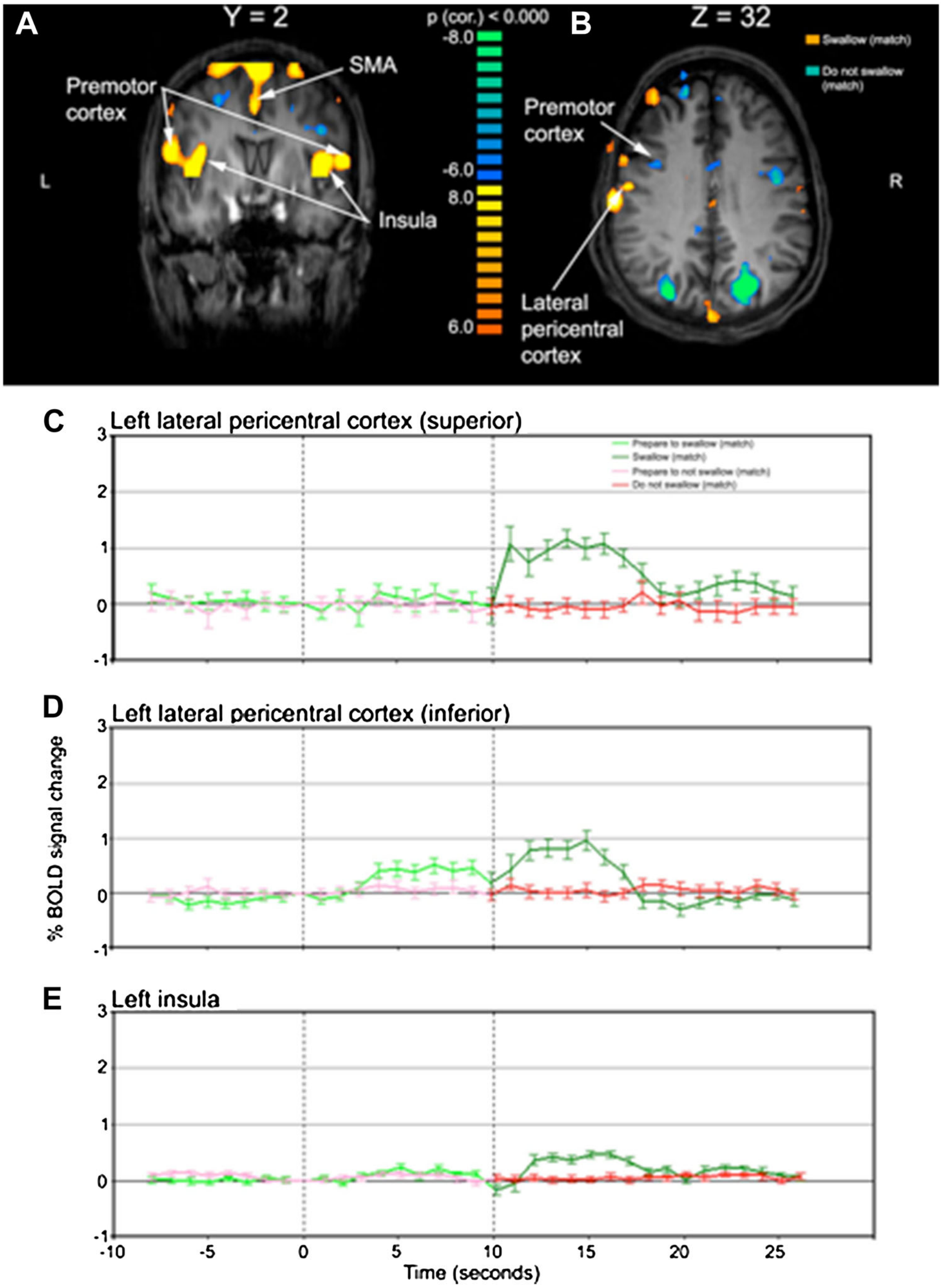

Fig. 4 Contrast of brain activation, identified in terms of the blood oxygenation level-dependent (BOLD) responses, associated with swallowing and not swallowing (Contrast 3). Data are shown for the group of seven subjects. Regions of significant (p_{cor} <0.0001) activation are displayed on normalized coronal (**a**) and axial (**b**) brain slices from one subject. Talairach–Tournoux plane coordinate is displayed above each brain image. The MR percent signal change within the superior left lateral pericentral cortex, the inferior left lateral pericentral cortex, and left insula following the presentation at Time = 0 of 'prepare to swallow' (*light green*) and 'do not prepare to swallow' (*pink*) and the presentation at Time = 10 of 'swallow' (*dark green*) and 'do not swallow' (*red*) are shown in **c**, **d**, and **e**, respectively

associated with the mismatched swallow trials. Areas of activation outside of the ROIs were the cuneus and precuneus.

Mismatched Swallow

Activation associated with the mismatched swallow trials was significantly (p_{cor} <0.0001) greater than activation associated with the matched swallow trials in all ROIs except the insula. The most prominent activation foci corresponded to the bilateral precentral gyrus, right postcentral gyrus, and bilateral premotor cortex (Fig. 5). Areas of activation outside of the ROIs were found within the superior, middle, inferior, and medial frontal gyri, superior and middle temporal gyri, superior and inferior parietal gyri, PCC, paracentral lobule, occipital gyrus, cuneus and precuneus, thalamus, and caudate.

Discussion

The present pilot study tested the hypothesis that subregions within the swallowing neural network make differential contributions to swallowing preparation and swallowing execution. In support of the hypothesis, brain activation was significantly greater during swallowing preparation, than during swallowing execution, within the rostral and intermediate ACC bilaterally, premotor cortex (left > right hemisphere), pericentral cortex (left > right hemisphere), and within several subcortical nuclei including the bilateral thalamus, caudate, and putamen. In contrast, activation within the bilateral insula and the left dorsolateral pericentral cortex was significantly greater in relation to swallowing execution, compared with swallowing preparation. Still other regions, including a more inferior ventrolateral pericentral area, and adjoining BA 43 bilaterally, and the SMA, were activated in relation to both swallowing preparation and execution. These preliminary findings support the view that the preparation, and subsequent execution, of swallowing are mediated by a cascading pattern of activity within sub-regions of the bilateral swallowing neural network.

Experimental Approach

This fMRI study identified the hemodynamic correlates of subjects' responses to visual instructions regarding

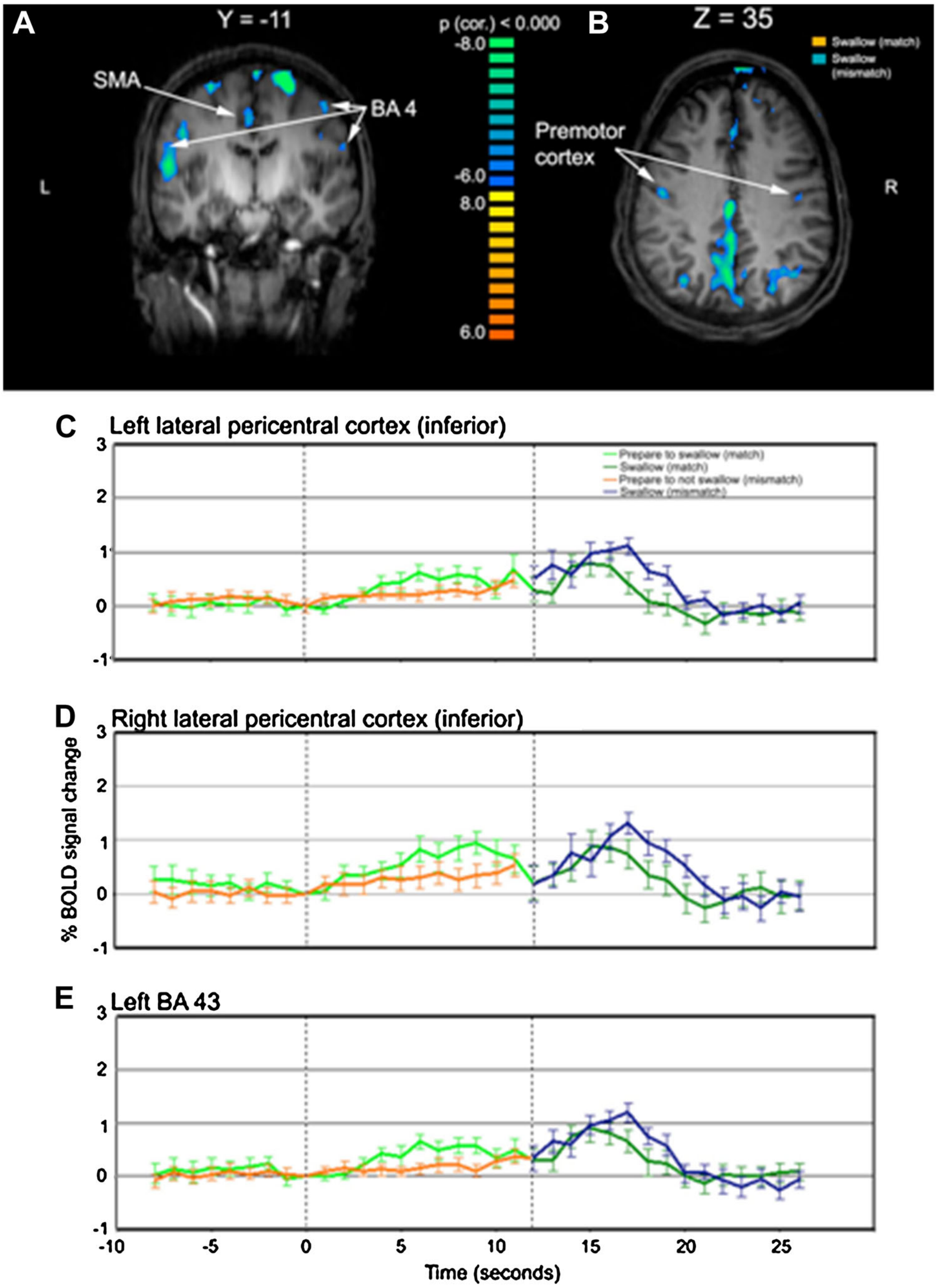

Fig. 5 Contrast of brain activation, identified in terms of the blood oxygenation level-dependent (BOLD) responses, associated with matched and mismatched swallowing (Contrast 4). Data are shown for the group of seven subjects. Regions of significant (p_{cor} <0.0001) activation are displayed on normalized coronal (**a**) and axial (**b**) brain slices from one subject. Talairach–Tournoux plane coordinate is displayed above each brain image. The MR percent signal change within the superior left lateral pericentral cortex, the inferior right lateral pericentral cortex, and left BA 43 following the presentation at Time = 0 of 'prepare to swallow' (*light green*) and 'do not prepare to swallow' (*pink*) and the presentation at Time = 12 of 'swallow' (*dark green*) and 'do not swallow' (*red*) are shown in **c**, **d**, and **e**, respectively

swallowing preparation and swallowing execution. While previous fMRI research examined the preparation and execution of water bolus swallowing [9, 20], the present study investigated voluntary saliva swallowing in order to examine swallowing in the absence of the oral delivery and subsequent manipulation of an externally provided liquid or solid [5, 10].

A delayed-response task paradigm was employed in which a visual cue instructing the subject on task preparation was followed, 10 or 12 s later, by another visual cue instructing task execution. This delayed-response task was employed as a means of extending the period of preparation so that brain activation associated with swallowing preparation, or swallowing execution, could be differentiated with fMRI, notwithstanding its relatively coarse temporal resolution [47]. While delayed-response tasks have been reported extensively in the cognitive neuroscience literature [50, 51], their appropriateness in studies of swallowing has not been established previously. Nevertheless, in support of the validity of this experimental approach, swallowing preparation may span several seconds as afferent information regarding the evolving oral environment is processed. This afferent input could relate to the gradual accumulation of saliva and increasing wetness of the oral mucosa prior to saliva swallowing [52], or the progressive modification of the texture of an ingested solid as it is masticated and mixed with saliva prior to bolus swallowing [53]. Evidence indicating that this afferent information regulates swallowing initiation and execution [54] supports the need for studies that examine the neural mechanisms that are engaged during the period of several seconds prior to swallowing elicitation.

Within the context of the delayed-response task, the present study further employed a go, no-go paradigm in which the subject was instructed to prepare to swallow, or not, and to swallow, or not, across trials. This experimental paradigm provided an opportunity to dissociate swallowing preparation and swallowing execution through the statistical comparison of various task conditions, for example, swallowing preceded by a “preparation cue” and swallowing preceded by a “do-not-prepare” cue.

Behavioral Findings: Swallowing Latency

The swallowing latency data indicated that swallowing was executed immediately following the visual swallow cue (i.e., mean latency = 1.07 ± 0.03 s). Further, the mean swallow latency during the matched trials was significantly less than that associated with the mismatched trials. This finding supports the view that the “prepare to swallow,” and “do not prepare to swallow,” cues did engage different readiness states prior to swallowing execution.

Regions Activated Preferentially During Swallowing Preparation

The present finding that activation within the (i) rostral and intermediate regions of the bilateral ACC, and (ii) premotor cortex, and precentral gyrus, of the left > right hemisphere, were significantly greater during the swallowing preparation period, compared with the swallowing execution phase, of the delayed-response swallowing task suggests that these brain regions contribute principally to swallowing preparation or planning. Previous studies of limb movement in humans and non-human primates have implicated the ACC and premotor cortex, and the interconnected MI, in movement planning [35, 55–60], implicating MI in mental imagery and processing of upstream preparation signals leading to seamless execution at the “go” signal [61, 62]. With respect to swallowing, Malandraki et al. [9] also reported ACC and premotor activation during swallowing preparation. The present findings extend this report by suggesting that swallowing preparation may be mediated specifically by the rostral and intermediate regions of the ACC. Rostral ACC activation has been reported in association with naïve saliva swallowing [10], and both rostral ACC and premotor cortex were activated by swallowing of a 5 ml water bolus that was injected into the oral cavity over a 1 s period and followed by swallowing within the subsequent 4 s [6]. The present study, and the earlier study by Hamdy et al. [6], both imposed delays on the initiation of swallowing, the former through a delayed-task paradigm, and the latter by virtue of a peroral water-injection technique. In addition to its role in the processing of emotion and pain, the rostral ACC has been implicated in cognitive control processes, including sustained attention to response [63], response inhibition [64, 65], and action selection [66]. The left premotor cortex also has been implicated in response inhibition [67]. The present findings suggest that the rostral ACC and left premotor cortex may contribute to the cognitive control processes involved in preparing to swallow following an imposed delay. This delayed-swallow-response scenario bears similarity to the clinical practice of instructing patients to hold an ingested bolus in the mouth before initiating swallowing during an instrumental swallowing assessment.

Activation within several subcortical nuclei, including the thalamus, caudate, and putamen, also was significantly greater during swallowing preparation than during swallowing execution, implicating these subcortical nuclei in swallowing preparation in particular. This is in contrast to Malandraki et al. [9] who reported thalamus and basal ganglia activation preferentially during swallowing execution compared with swallowing planning. The thalamus is characterized by oral and pharyngeal receptive fields and is activated during upper airway sensory processing [68]. As such, early activation of the thalamus during the swallow preparation period may reflect processing of the oropharyngeal environment in preparation for timely swallowing execution. The striatum that comprises the caudate and putamen, has been implicated in cognitive motor control, including response inhibition, controlled execution of movement, and decision-based actions toward a reward [66, 69]. This type of cognitive activity would appear relevant to the present experimental paradigm in which subjects made go, or no-go, sequential decisions based on visual cues.

Regions Activated Preferentially During Swallowing Execution

In the present study, activation within the dorsolateral pericentral cortex (Left > Right hemisphere) and the bilateral insula were associated predominantly with swallowing execution. The present finding of dorsolateral pericentral cortical activation preferentially during swallowing execution is consistent with Malandraki et al. [9] who reported primary sensorimotor cortex activation during swallowing execution compared with swallowing preparation. Swallowing execution-related activity within the lateral pericentral cortex has been identified by numerous other studies [3, 6, 10, 12, 14–16]. In non-human primates, neurons in face MI fire in relation to swallowing; reversible inactivation of MI impairs swallowing; and ICMS of MI can evoke swallowing. In humans, TMS studies have suggested that the oral and pharyngeal muscles involved in swallowing are represented within the anterolateral motor cortex [70, 71].

The present finding of insular activation preferentially during swallowing execution is consistent with Malandraki et al. [9] but distinct from Dziewas et al. [1] who reported left insular activation during both swallowing preparation and movement stages. The insula is a functionally diverse structure, integrating information from distinct regions of the brain. Both the anterior and posterior insula have been implicated in swallowing control [6, 12, 72, 73]. The anterior insula is known to process visceral sensation from the pharynx [74], vibrotactile stimulation [75], gustation [76], and emotions including disgust [77]. Sensory input is originally processed in SI, which sends projections to MI and the anterior insula [78, 79]. Neurons within both MI and the anterior insula have orofacial receptive fields [78, 80]. In contrast, the posterior insula is involved in autonomic regulation [81, 82], including heart rate and respiration. A meta-analysis of brain-imaging studies of swallowing implicated the right anterior insular cortex in water swallowing and the right posterior insula in voluntary saliva swallowing [83]. Electrical stimulation of the right posterior inferior insula in a patient with an insular tumor resulted in the disruption of sequential water swallowing and self-reported "stuttered swallowing" [84]. Insular mapping in patients with epilepsy elicited viscerosensory effects, including unpleasant laryngopharyngeal constriction [85] or sensations of a pharyngeal constriction and a sensation of swallowing associated with mastication [86].

Regions Activated During Both Swallowing Preparation and Swallowing Execution

In the present study, bilateral activation of BA 43, and the ventrolateral precentral ($Z = 20 \leftrightarrow 28$) and lateral postcentral ($Z = 22 \leftrightarrow 30$) gyri, were identified in association with swallowing preparation in Contrast 2, and swallowing execution in Contrast 3. Consistent with these findings, activation in these foci was not identified in Contrast 1, suggesting that these regions were active in association with both swallowing preparation and execution, with the result that no net activation was seen when the contrast between the two conditions was obtained in Contrast 1.

Preparation-related activity within the sensorimotor cortex during the delay period may represent the translation of the preparation cue into a specific movement sequence, involving a form of motor imagery. Previous studies have reported activation within primary somatosensory cortex in association with imagined hand, foot, and tongue movements [87–89]. Such motor imagery is believed to play a role in driving motor neurons and initiating movement [69]. Somatosensory processing during movement preparation may contribute to shaping subsequent movements. Previous studies have shown that the volume of the bolus to be swallowed influences swallow-related tongue movement, hyoid bone movement magnitude, and the opening of the upper esophageal sphincter [90, 91]. Preparation-related activity within MI also could result from response preparation occurring within upstream areas of the motor system that is conveyed to MI [34].

BA 43, a somatosensory association and integration area, receives inputs from SI [92], which could account for the similar activation patterns across these two regions observed in the present study. BA 43 has been implicated in human facial sensation [93], taste sensation in both humans and monkeys [94–96], and swallowing and tongue elevation [12]. These findings, along with the findings of the current study, suggest that activation within this region is associated with swallow-related sensory processing. Swallowing execution-related activity within the primary somatosensory cortex and BA 43 has been identified by several studies in association with oral motor behaviors such as swallowing and tongue elevation [12, 93]. Activation within these regions may reflect sensory stimulation of the oropharynx and tongue during the early stages of swallowing.

Temporal Sequence of Swallowing Activation

The present study identified successive activation across multiple brain areas during swallowing preparation and execution, beginning with the rostral and intermediate ACC, premotor cortex (Left > Right), pericentral cortex (Left > Right), the bilateral thalamus, caudate, and putamen during the swallowing preparation stage, and followed by activation within the bilateral insula and the left dorsolateral pericentral cortex during swallowing execution. Activation of the ventrolateral pericentral area, and adjoining BA 43 bilaterally, and the SMA, spanned both swallowing preparation and execution. Mihai et al. [25] reported a generally similar temporal sequence, starting at the premotor cortex, SMA, and bilateral thalamus, followed by the primary sensorimotor cortex, the posterior insula, and cerebellum and culminating with activation in the pons.

The present study found evidence of a shift from ventrolateral pericentral to dorsolateral pericentral activation across swallowing preparation and execution. Similarly, Furlong et al. [2] found a shift from caudolateral to superior sensorimotor cortex in association with the pre-swallow and motor phases of water swallowing, respectively. Electrophysiological studies in non-human primates have found that activity within MI following a cue indicating the direction of a forthcoming movement is located inferior to that associated with movement execution [97]. An fMRI study mapping preparation- and execution-related activity within human MI in association with finger movement also identified distinct inferior and superior activation foci [34]. Activation within the more inferior focus was associated with both preparation and execution, but exhibited stronger activation in association with movement execution.

The present study did not find evidence of a clear shift in lateralization of activity across the preparation and execution phases of the swallowing task. This is in contrast to previous studies that have generally reported various patterns of shifting lateralization across swallowing preparation and execution [1, 24, 25].

Study Limitations

The present findings are considered preliminary in that they are based on a small sample that was heterogeneous in terms of gender and handedness. Another limitation of the study is that the delayed swallowing execution imposed by the task paradigm may have resulted in atypical saliva swallowing and associated brain activation. This caution could be said to apply generally to swallowing studies in which subjects are cued to swallow, and particularly those involving bolus swallowing within the context of the fMRI scanner.

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