

## Role of primary sensorimotor cortex and supplementary motor area in volitional swallowing: a movement-related cortical potential study

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**Satow, Takeshi, Akio Ikeda, Jun-ichi Yamamoto, Tahamina Begum, Dinh Ha Duy Thuy, Masao Matsuhashi, Tatsuya Mima, Takashi Nagamine, Koichi Baba, Tadahiro Mihara, Yushi Inoue, Susumu Miyamoto, Nobuo Hashimoto, and Hiroshi Shibasaki.** Role of primary sensorimotor cortex and supplementary motor area in volitional swallowing: a movement-related cortical potential study. *Am J Physiol Gastrointest Liver Physiol* 287: G459–G470, 2004. First published December 30, 2003; 10.1152/ajpgi.00323.2003.—We investigated the role of the cerebral cortex, particularly the face/tongue area of the primary sensorimotor (SMI) cortex (face/tongue) and supplementary motor area (SMA), in volitional swallowing by recording movement-related cortical potentials (MRCPPs). MRCPPs with swallowing and tongue protrusion were recorded from scalp electrodes in eight normal right-handed subjects and from implanted subdural electrodes in six epilepsy patients. The experiment by scalp EEG in normal subjects revealed that premovement Bereitschaftspotentials (BP) activity for swallowing was largest at the vertex and lateralized to either hemisphere in the central area. The experiment by epicortical EEG in patients confirmed that face/tongue SMI and SMA were commonly involved in swallowing and tongue protrusion with overlapping distribution and interindividual variability. BP amplitude showed no difference between swallowing and tongue movements, either at face/tongue SMI or at SMA, whereas postmovement potential (PMP) was significantly larger in tongue protrusion than in swallowing only at face/tongue SMI. BP occurred earlier in swallowing than in tongue protrusion. Comparison between face/tongue SMI and SMA did not show any difference with regard to BP and PMP amplitude or BP onset time in either task. The preparatory role of the cerebral cortex in swallowing was similar to that in tongue movement, except for earlier activation in swallowing. Postmovement processing of swallowing was lesser than that of tongue movement in face/tongue SMI; probably suggesting that the cerebral cortex does not play a significant role in postmovement processing of swallowing. SMA plays a supplementary role to face/tongue SMI both in swallowing and tongue movements.

deglutition; electrophysiology; human

SWALLOWING CONSISTS of well-coordinated sequential movements that make it possible to ingest fluid and food without aspiration. Swallowing requires a series of processes including voluntary and reflex motor control, intraoral sensory processing, salivation, and visceral regulation. Although swallowing is considered to be mediated principally by brain stem mechanisms, previous electrophysiological and clinical studies indi-

cate that the cerebral cortex also plays an important role in its regulation (25). The classical model of swallowing consists of three separate and yet interacting phases: oral (preparatory), pharyngeal, and esophageal phases (29), each with varying degrees of dependence on the central control mechanism. The preparatory phase can be initiated voluntarily, but once the fluid reaches the pharyngeal mucosa and exceeds the swallow threshold (6), the complicated sequential movements of swallowing occur automatically, and thus motor control of swallowing consists of two aspects, i.e., voluntary and automatic reflex movements. The previous studies investigating the cortical function in swallowing in humans have focused on two major issues: the cortical sites involved in swallowing and its hemispheric dominance.

Disturbance in swallowing (dysphagia) can occur in various central nervous system disorders, among others, strokes in cortical or subcortical areas whether unilateral or bilateral (21). As far as the supratentorial lesions are concerned, lesions in insula (4, 5), thalamus (1), the ventral periorlandic area, or the posterior part of the inferior frontal gyrus (27) are known to cause dysphagia. It has been reported that the resection of the face/mouth area of the primary sensorimotor (SMI) area results in transient dysphagia (19).

Previous neuroimaging studies (11, 12, 16, 17, 22, 30, 42) have demonstrated that swallowing recruits multiple cerebral regions including the face area of SMI, premotor cortex, insular cortex, frontal operculum, anterior cingulate cortex, and etc. However, those studies could not distinguish the activation by sensory feedback related to swallowing. Moreover, Kern et al. (17) suggested that the cortical areas activated by swallowing were similarly involved in swallowing-related movements such as jaw clenching, lip pursing, and tongue rolling. It might indicate, therefore, that the same cortical areas are commonly involved in those conditions accompanying swallowing.

The concept of hemispheric dominance in swallowing derives from the clinical observation of dysphagic patients (3, 5, 8, 25, 27, 34), and neuroimaging (11, 12, 16, 22, 30, 42) and transcranial magnetic stimulation studies (10) in healthy human subjects. Those studies demonstrated rather contradictory results, possibly because they focused on the asymmetrical activation of different cortical or subcortical areas.

Movement-related cortical potentials (MRCPPs) preceding self-paced, repetitive voluntary movements (9, 18, 35) are

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known to reflect a central motor control process with superior temporal resolution compared with other neuroimaging studies. In monkeys, Bereitschaftspotentials (BPs) were shown to reflect excitatory postsynaptic potentials generated at the superficial layer of the apical dendrites of cortical pyramidal neurons (2). Epicortical recording of MRCPs (13–15, 33, 41) is, due to its high signal-to-noise ratio of brain signals, useful for clarifying the functional organization of human motor cortices more distinctly than the scalp-recorded MRCPs. It has been reported that the SMI, supplementary motor area (SMA) proper and pre-SMA, are the main cortical generators of MRCPs (13, 14, 33, 41). By contrast, scalp-recorded MRCPs are appropriate for investigating the hemispheric dominance of those activities, because they are recorded from the whole scalp, whereas subdural electrodes cover only a restricted area around the epileptogenic zone in patients with intractable seizures.

Previous human studies of swallowing could not clearly distinguish between motor component and sensory feedback. In this regard, MRCPs in association with swallowing can clarify the sequential cerebral processing of swallowing more clearly than other studies. The premovement activity of MRCPs (BP) reflects motor components without sensory information time-locked to the movement onset, and the post-movement components such as motor potential or reafferent potential represent the cortical function related to motor execution and sensory feedback processing, respectively. Thus we employed this method to clarify the change of cortical activity in different phases of swallowing.

In the first experiment (MRCPs by scalp EEG recording), we aimed at clarifying whether the hemispheric dominance can be determined in the preparatory period of swallowing or not. The comparison was made between swallowing and tongue protrusion, because the initial part of swallowing was inevitably associated with tongue movements and MRCPs with tongue protrusion were previously studied (14). In the second experiment (MRCPs by epicortical EEG recording) aiming at delineating the cortical sites associated with swallowing, we analyzed the potentials generated by the face/tongue SMI and its adjacent areas defined by cortical stimulation mapping. We also evaluated MRCPs arising from SMA on the medial frontal cortex, because little has been studied about the functional significance of SMA in swallowing. On the basis of the notion that the brain stem is primarily involved in execution of swallowing, we also investigated epicortical MRCPs to ascertain whether the postmovement processing at the cortical level was less active in swallowing than in tongue protrusion.

## EXPERIMENTAL PROCEDURES

All subjects and patients gave written informed consent before the experiments. Procedures for *experiment 1* were approved by the Committee of Medical Ethics, Graduate School of Medicine, Kyoto University, and for *experiment 2* were approved by the National Epilepsy Center, Shizuoka Medical Institute of Neurological Disorders (No. 98–1).

### *Experiment 1: Scalp-Recorded MRCPs for Swallowing and Tongue Movements in Normal Subjects*

**Subjects.** Eight normal volunteers (7 men and 1 woman; ages 24–38 yr) participated in this study. All were right-handed, and none

had any history of neurological disorders, including swallowing disturbances.

**Movement tasks.** Subjects were seated in a reclining arm chair in a quiet room with their eyes kept open and fixating on the target placed 1.5 m in front of them during each recording session. Each subject performed two motor tasks: swallowing (Swallow) and tongue protrusion (Tongue).

For Swallow, the subjects were asked to keep 2–3 ml of water in their mouth for 5 to 10 s and then swallow it as briskly as possible with their jaw kept relaxed and slightly open. For Tongue, the jaw was kept relaxed in a slightly opened position, and the subject made brisk forward protrusion of the tongue with little articular movement immediately followed by a return to the resting position by relaxing the protruded tongue (14).

For both tasks, each movement was done in a self-paced manner without any external cue signal, at irregular intervals of 10–20 s or longer. During the interval for Swallow, subjects put water in their mouths for the next trial. Subjects were instructed to remain still and to avoid unnecessary movements of the face, tongue, and mouth as well as other limbs. They were also told to postpone the next task movement for several seconds if any accidental movements occurred before the task movements. A training period was given before the recording session until the examiner was satisfied with the subjects' performance.

Each recording session consisted of 10 min of the same task and several minutes of break between sessions to refresh the subjects. Each subject underwent 8–10 sessions each for Swallow and Tongue, which were carried out in a counterbalanced order across the subjects.

**Data acquisition.** All signals were recorded in digital format (model EEG2100; Nihon Kohden, Tokyo, Japan) with a sampling rate of 200 Hz, and were stored on magneto-optical disks for the subsequent off-line analysis. For recording EEGs, 19 Ag/AgCl shallow cup electrodes were fixed on the scalp with collodion, according to the International 10–20 System (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, O2), and all electrodes were referenced to linked earlobe electrodes. Electrooculograms (EOGs) were monitored by a pair of electrodes placed at the left and the right lateral canthus for horizontal eye movement, and by another pair of electrodes placed below and above the right eye for vertical eye movement. To identify the onset of tongue movement, a skin electrode placed at the upper edge of the right nasolabial fold and referenced to the linked earlobe electrodes, was used to record glossokinetic potential (GKP). The band-pass filter was set to 0.03–60 Hz for EEGs, EOGs, and GKP. To obtain a trigger pulse for swallowing, the surface electromyogram (EMG) with a band-pass filter of 5–60 Hz was recorded with a pair of cup electrodes placed 3 cm apart under the chin over the mylohyoid-geniohyoid-anterior digastric muscle complex [submental EMG (SM-EMG)] (7). The impedance of all electrodes was kept < 5 k $\Omega$  throughout the experiments.

**Data analysis.** After completing all sessions for each subject, the EEG, EOG, and GKP and/or SM-EMG were averaged with respect to the onset of swallowing or tongue protrusion. Onset of movement was determined visually on the continuously recorded data (Fig. 1A). The fiducial points for averaging were determined by off-line analysis on the basis of SM-EMG and GKP for Swallow and GKP for Tongue. Because the SM-EMG activity associated with Tongue was negligible in the preliminary experiment, it was not taken into account in the analysis of Tongue. Trials associated with artifacts, incomplete relaxation between tasks, or unnecessary tongue movements before the task identified by GKPs were excluded from further analysis. A total of >100 trials were selected for averaging. The averaged signals covered 5 s from 3 s before to 2 s after the onset of the movements. The baseline was corrected by subtracting the average value of the initial 100 points (500 ms) from the waveform for each channel. After confirming the reproducibility of waveforms in two ensembles of averaged EEGs, each consisting of >50 trials, a group average EEG was obtained.

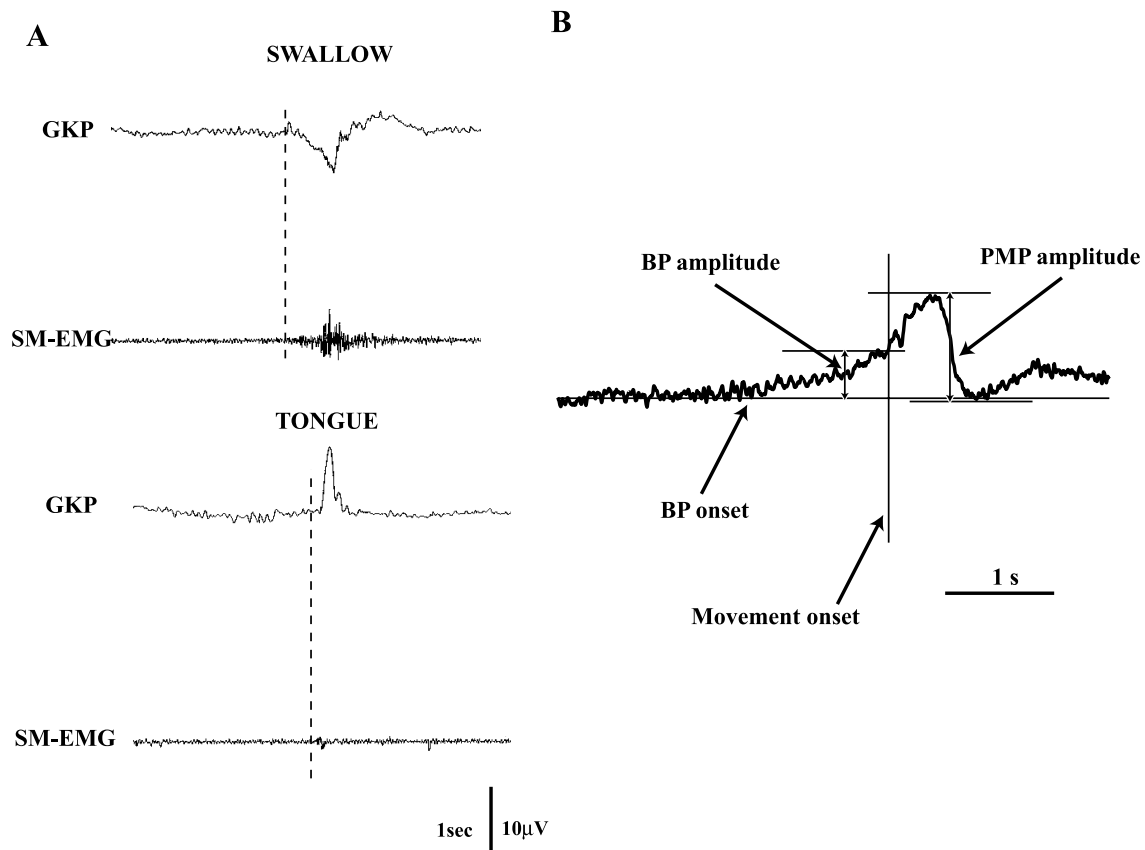


Fig. 1. A: examples of glossokinetic potential (GKP) and submental EMG (SM-EMG) associated with swallowing and tongue protrusion obtained in the preliminary experiment. Note that SM-EMG activity in tongue protrusion is negligible compared with tongue protrusion. In experiments 1 and 2, only GKP was recorded as the trigger for the tongue protrusion task. Broken lines indicate the fiducial point employed for averaging. B: components of movement-related cortical potential (MRCP) as studied by subdural grid electrodes and illustrations of their measurement. Bereitschaftspotential (BP) amplitude was measured from the baseline at movement onset. Postmovement potential (PMP) amplitude is the absolute value of the difference in amplitude between the initial negative peak and the peak in the opposite deflection after movement onset. For scalp-recorded EEG, analysis was restricted to BP amplitude and onset time.

Any surface-negative, premovement, slow-potential shift with no artifacts of similar waveform in EOG, GKP, or SM-EMG was accepted as BP. The BP onset time was determined visually at the time when the slow potential shift started to arise from the baseline (Fig. 1B). Because the waveforms after the movement onset were inevitably contaminated with the artifacts caused by the tongue or pharyngeal movements in both tasks (Fig. 2), the BP amplitude was measured at the time of SM-EMG and GKP onset from the baseline. Postmovement potentials (PMPs) were not analyzed for the same reason. Thus BP in this study represents an overall cortical activity in preparation for movements. BP onset was determined at an electrode showing the largest BP for each subject.

To compare the distribution of BP between the two tasks by canceling the effect of absolute amplitude difference, data were normalized by dividing values measured at all electrodes by maximal BP amplitude for each task for each individual subject (26). A repeated-measures ANOVA was then adopted with two factors [electrode position (Electrode) and task effect (Task)]. Comparison of BP onset between the two tasks was tested by Student's two-tailed paired *t*-test.

For determining the dominant side between the bilateral central motor areas in both tasks, two electrodes [C3 (left central) and C4 (right central)] were selected for further analysis, and the subtraction of its normalized BP amplitude ( $C3 - C4$ ) was calculated as the laterality index (LI); i.e.,  $LI > 0$  means the dominance on the left,  $LI < 0$  means the dominance on the right. Statistical analysis of LIs

was done for both tasks in each subject by nonparametric Wilcoxon's signed-rank test. Furthermore, we plotted the BP amplitude on the larger side against that on the smaller side for each task for each individual subject, and linear regression was calculated for each task. The difference between the two tasks was evaluated by discriminant analysis. All statistical analysis was done by commercially available software (SPSS version 11; SPSS, Chicago, IL). A *P* value  $< 0.05$  was accepted as statistically significant.

**Results.** As for the task performance, six subjects reported that Tongue was more difficult to carry out than Swallow. Figure 2 shows the representative waveforms for each task. In both tasks, postmovement EEG and EOG activities were contaminated with prominent artifacts arising from oropharyngeal movements.

The BP was maximal at the midline vertex in all for both tasks. The normalized amplitude values at each electrode between the two tasks did not disclose any significant effect of Task on Electrode [ $F(18,252) = 0.406$ ,  $P > 0.05$ ], indicating that the common areas were activated in association with Swallow and Tongue (Table. 1). The BP onset time (mean  $\pm$  SD) for Swallow and Tongue was  $-2.08 \pm 0.21$  and  $-1.74 \pm 0.23$  s, respectively. The BP onset in Swallow was significantly earlier with respect to the movement onset than in Tongue [ $t(7) = 3.315$ ,  $P = 0.012$ ].

Figure 3 shows the LI in each task for each subject. LI was  $0.12 \pm 0.20$  (median  $\pm$  SD) for swallowing and  $0.07 \pm 0.06$  for tongue movement. Wilcoxon's signed-rank test disclosed no significant difference between the two tasks ( $P > 0.05$ ). The absence of a significant

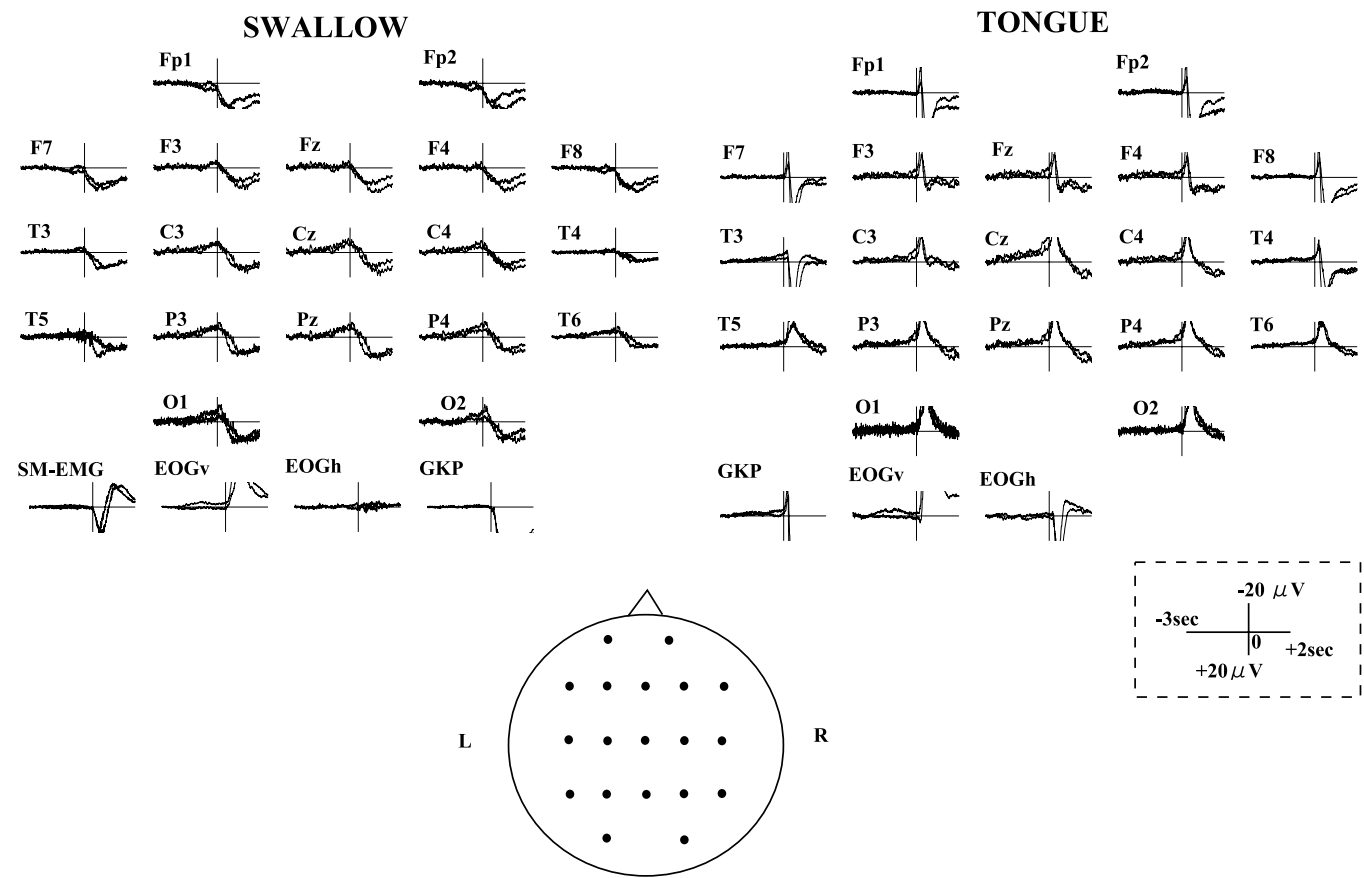


Fig. 2. Averaged scalp-recorded MRCP, electrooculograms (EOGs), GKP, and surface electromyogram (EMG) activities associated with swallowing (Swallow) and tongue protrusion (Tongue) tasks in a representative normal subject. They are arranged in accordance with the electrode location. Surface EMG and GKP show the satisfactory performance for Swallow and Tongue, without any tongue movement before movement onset. Note that the significant artifact caused by tongue and pharyngeal muscle activities is seen in EEG and EOGs after the movement onset. L and R, left and right.

Table 1. Normalized amplitude of BP in experiment 1

| Electrode | Swallow     | Tongue      |
|-----------|-------------|-------------|
| Fp1       | 0.17 (0.61) | 0.22 (0.26) |
| Fp2       | 0.21 (0.70) | 0.33 (0.19) |
| F3        | 0.58 (0.30) | 0.45 (0.25) |
| F4        | 0.49 (0.37) | 0.46 (0.20) |
| C3        | 0.78 (0.39) | 0.67 (0.26) |
| C4        | 0.65 (0.23) | 0.60 (0.23) |
| P3        | 0.60 (0.40) | 0.66 (0.27) |
| P4        | 0.65 (0.35) | 0.69 (0.28) |
| O1        | 0.46 (0.35) | 0.40 (0.17) |
| O2        | 0.33 (0.31) | 0.40 (0.21) |
| F7        | 0.43 (0.47) | 0.35 (0.23) |
| F8        | 0.32 (0.40) | 0.31 (0.21) |
| T3        | 0.51 (0.33) | 0.42 (0.23) |
| T4        | 0.30 (0.27) | 0.27 (0.29) |
| T5        | 0.47 (0.23) | 0.40 (0.16) |
| T6        | 0.50 (0.33) | 0.41 (0.18) |
| Fz        | 0.59 (0.37) | 0.48 (0.26) |
| Cz        | 1.00 (0.37) | 1.00 (0.37) |
| Pz        | 0.64 (0.40) | 0.66 (0.28) |

Values are mean (SD) microvolts of 8 subjects. Repeated-measures ANOVA did not show any significant difference between patients who performed 2 motor tasks; swallowing (Swallow) and tongue protrusion (Tongue) ( $P > 0.05$ ).

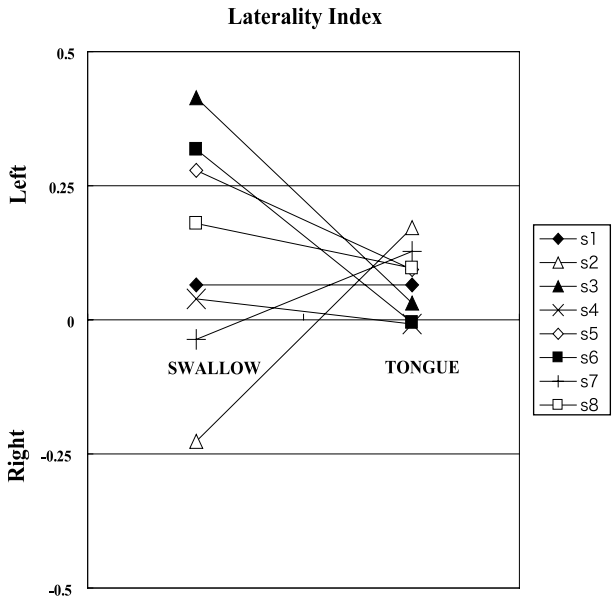


Fig. 3. Laterality index (LI) of Swallow and Tongue for each individual subject (s1-s8). LI is expressed as the subtraction of the normalized BP amplitude of C4 from that of C3, indicating that the plus value reflects the left side dominance and vice versa. Note that the LI for Tongue tends to converge on zero, whereas that for Swallow is variable.



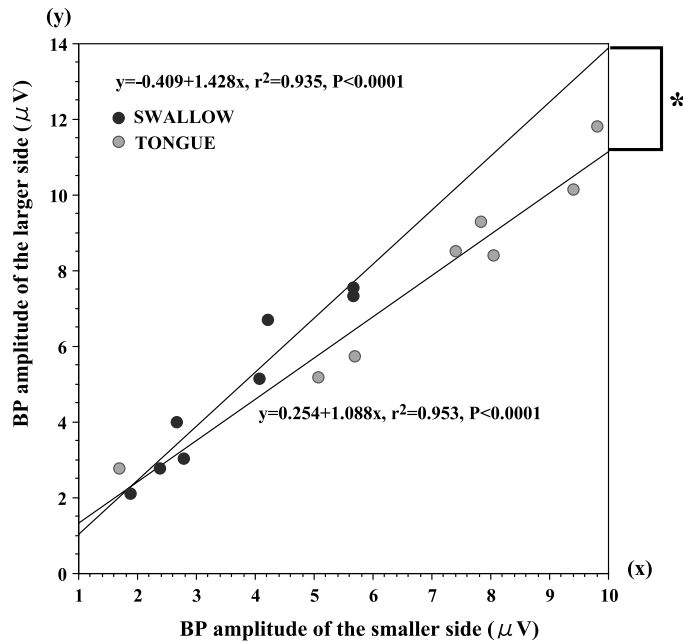


Fig. 4. Relationship of BP amplitude between the two homologous central areas, Swallow and Tongue. Discriminant analysis disclosed significant difference between Swallow and Tongue. Solid lines are linear regressions (Swallow:  $r^2 = 0.935$ ,  $P < 0.0001$ ; Tongue:  $r^2 = 0.953$ ,  $P < 0.0001$ ).

difference of LI between Swallow and Tongue was due to relatively large interindividual variability of LI in Swallow, despite the fact that LI for Tongue tended to be small (no laterality). Moreover, we could not determine any consistent dominant side specific for either task. Therefore, we tried to determine the dominant side on the basis of BP amplitude. When the BP amplitude of the larger side was plotted against that of the smaller side for both tasks, a simple linear regression revealed a significant correlation for each task (Swallow:  $r^2 = 0.935$ ,  $P < 0.0001$ ; Tongue:  $r^2 = 0.953$ ,  $P < 0.0001$ ) (Fig. 4). Furthermore, the regression coefficients were 1.428 ( $P < 0.001$ ) for Swallow and 1.088 ( $P < 0.001$ ) for Tongue. Discriminant analysis revealed the significant difference between Swallow and Tongue (Wilks'  $\lambda = 0.479$ ,  $\chi^2 = 9.559$ ,  $P = 0.008$ ). Comparatively, BP is more asymmetric for Swallow than for Tongue, although the larger side is not consistent across the subjects even in Swallow.

#### Experiment 2: Epicortically Recorded MRCPS for Swallowing and Tongue Movements

**Subjects.** We studied six patients (two men and four women, ages 15–34 yr) with medically intractable partial epilepsy. All patients underwent chronic implantation of subdural electrodes (the number of electrodes implanted were 76–99) as a part of the presurgical evalu-

ation. All were right handed, and the intracarotid amyntal test revealed that the left hemisphere was speech dominant in all patients. The clinical profiles of investigated patients are listed in Table 2.

**Electrode placement.** Electrocorticograms (ECoGs) were recorded from subdural electrodes made of platinum (Ad-Tech, Racine, WI). Each electrode was 4 mm in diameter with 2.3 mm of exposure diameter to the cortical surface, and the center-to-center interelectrode distance was 1 cm. The electrodes were placed on the medial (Medial) and lateral surface (Lateral) of the frontoparietal lobes on the right hemisphere in five patients (patients 1 and 3–6) and on the left hemisphere in one (patient 2). Patient 4 had subdural electrodes placed on the Medial of the parietal lobe, and thus electrodes did not cover the SMA. Because MRCPS with upper and lower limb movements as well as Swallow and Tongue did not elicit any identifiable potentials in this case, the analysis was done only for the electrodes on Lateral.

**Functional mapping of cortical areas.** High frequency electric cortical stimulation was done for each individual electrode for clinical purposes, and somatosensory-evoked potentials were also recorded when necessary. Details of the methodology for stimulation and the subsequent cortical mapping have been described elsewhere (13, 20). Cortical regions in which the stimulation elicited muscle contraction were defined as “positive motor areas,” and areas in which the stimulation caused interference with tonic motor activity or rapid alternating movements were defined as “negative motor areas.”

As for identification of SMI on the perirolandic area, when muscle twitch was observed in the contralateral face and/or tongue by electrical stimulation, that area was named face/tongue primary motor area (MI). Face/tongue primary somatosensory area (SI) was identified if the stimulation elicited only the somatic sensation without any movements. In this study, face/tongue MI and SI are called face/tongue SMI. Face/tongue SMI could not be identified by electrical stimulation only in patient 3.

In Medial, SMA can be divided into two areas, caudal SMA (SMA proper) and rostral SMA (pre-SMA). Electrical stimulation elicited positive or negative motor responses (20) on Medial. The vertical anterior commissural (VAC) line was regarded as the anatomical border between the rostral and caudal SMA (38, 43). In the present experiment, negative motor area on Medial was identified caudal to the VAC line in two patients (patients 2 and 5). Thus the electrodes located caudal to the VAC line, regardless of whether electrical stimulation elicited positive or negative motor responses, were grouped into caudal SMA. To determine the anatomical location of the VAC line in patients 2 and 5, we used the plain lateral view of skull X-ray film and the sagittal view of T1-weighted MRIs (15). For this purpose, in patients 1, 3, and 6, the sagittal view of T1-weighted MRIs and/or three-dimensional CT scan obtained after implantation of subdural electrodes were used.

**Movement paradigm.** The movement paradigms investigated were exactly the same as those employed in experiment 1.

**Data acquisition.** Continuous ECoGs were recorded simultaneously from 76–99 subdural electrodes. For recording ECoGs, all

Table 2. Clinical profiles of six patients investigated with subdural electrodes in experiment 2

|                              | Patient No.      |                  |                  |                    |                  |                  |
|------------------------------|------------------|------------------|------------------|--------------------|------------------|------------------|
|                              | 1                | 2                | 3                | 4                  | 5                | 6                |
| Age (yr)/sex                 | 15/W             | 20/M             | 33/M             | 32/W               | 34/W             | 28/W             |
| Diagnosis                    | R FLE            | L FLE            | R FLE            | R FLE              | R FLE            | R FLE            |
| Subdural electrode placement | R frontal        | L frontal        | R frontal        | R frontal          | R frontal        | R frontal        |
|                              | Lateral + Medial | Lateral + Medial | Lateral + Medial | Lateral (+ Medial) | Lateral + Medial | Lateral + Medial |
| No. of electrodes            | 82               | 77               | 80               | 76                 | 86               | 99               |

M, man; W, woman; R, right; L, left; FLE, frontal lobe epilepsy; Lateral + Medial, subdural electrodes were placed both on lateral and medial surface of the frontal lobe.

subdural electrodes were referenced to a scalp electrode placed on the skin over the mastoid process contralateral to the side of electrode implantation, and for the data analysis, they were referenced to one subdural electrode judged to be silent in terms of epileptogenicity and cortical function. GKP referenced to a scalp electrode placed on the skin contralateral to the side of implantation, and SM-EMG were used to identify the movement onset. All input signals were digitized at the sampling rate of 500 Hz and stored on magneto-optical disks with a digital EEG equipment (model EEG1100, Nihon Kohden, Tokyo, Japan). Data were digitally band-pass filtered at 0.03–120 Hz for ECoG and GKP and 5–120 Hz for SM-EMG for further analysis. EOGs were not monitored in *experiment 2*.

**Data analysis.** The onset of movement was determined off-line as in *experiment 1*, and a total of >100 trials were averaged. The analysis epochs are the same as in *experiment 1*. The baseline was corrected by subtracting the average value of the initial 250 points (500 ms) from the waveform for each channel.

Analysis of BP as a premovement component was done similarly to that in *experiment 1*. The difference of BP amplitude and BP onset between Swallow and Tongue was compared by using Student's two-tailed paired *t*-test at the local maximum of BP.

To investigate the postmovement cerebral processing in each movement, the largest amplitude difference during the initial 2 s of the postmovement segment (PMP amplitude) was measured at each electrode (Fig. 1A). This value seems to reflect both motor potential and refferent potential, each related to motor execution and sensory feedback, respectively (9, 35). Because the time course of neural processing after movement onset differs between tongue protrusion and swallowing (37) leading to variable peak time and morphology of PMPs across subjects or between tasks, we employed PMP amplitude to represent an overall activity of the postmovement cortical processing. Statistical analysis used for BP was similarly applied to the analysis of PMP.

For investigating the amplitude distribution of each activity (BP and PMP), the distribution map was constructed for Lateral and Medial, respectively. Active area was defined by the electrodes showing the activities of >75% of the local maximum. Hence, the distribution maps show the location of electrodes with the local maximum and adjacent areas showing activities of >75% of the maximum. The areas of the distribution maps were compared between Swallow and Tongue, and then between Lateral and Medial by Wilcoxon's signed-rank test.

In five patients in whom subdural electrodes were placed both Lateral and Medial (*patient 1–3, 5, and 6*), all parameters mentioned above were compared between those of Lateral and Medial by Wilcoxon's signed-rank test.

**Results.** Both Swallow and Tongue tasks were well performed by all patients without any problems. All patients reported that Swallow was easier to execute than Tongue. Fig. 5 shows the waveforms at selected channels from Lateral and Medial for Swallow and Tongue in *patient 2*. Distribution maps of BP and PMP on Lateral and Medial are shown in Figs. 6 and 7, respectively. Amplitude of BP and PMP and BP-onset time of each individual patient are presented in Tables 3 and 4, respectively.

**PREMOVEMENT ACTIVITY: BP.** 1) Lateral convexity of the frontal lobe. Because we explicitly intended to study the involvement of perirolandic area including face/tongue SMI in swallowing vs. tongue movements, we investigated the area showing the local maximum of BP relative to the face/tongue SMI as determined by electrical stimulation (Fig. 6). Of five patients (*patients 1, 2, and 4–6*) in whom electrical stimulation identified the face/tongue SMI, the local maximum of BP for Swallow and Tongue was located within the face/tongue SMI in four (*patients 1, 2, 4, and 5*) and three (*patients 2, 4, and 5*) patients, respectively. As for *patient 3*, in whom electrical stimulation could not identify face/tongue SMI, its local maximum for Swallow and Tongue was located at the ventral part of implanted grid, suggesting that the activity could

reflect the potentials from the face/tongue SMI. Regarding areas showing the local maximum of BP for Swallow and Tongue, three patients (*patients 2, 5, and 6*) showed concordant results. In two of them (*patients 2 and 5*), it was situated at the face/tongue SMI and in the remaining case (*patient 6*) just adjacent to the face/tongue SMI. In three patients (*patients 1, 3, and 4*) in whom the local maximum of BP was different in place between the two tasks, the two areas were apart by ~4.1 cm in one (*patient 1*) and just next to each other in two (*patients 3 and 4*).

BP onset time measured at the electrode of the local maximum was significantly earlier in Swallow than in Tongue [mean onset  $\pm$  SD; Swallow:  $-2.00 \pm 0.38$  s, Tongue:  $-1.23 \pm 0.56$  s;  $P = 0.009$ ,  $t(5) = 4.133$ ] (Table 4). BP amplitude (mean  $\pm$  SD) at the local maximum was  $-54.6 \mu V \pm 20.1$  for Swallow and  $-52.8 \pm 20.1 \mu V$  for Tongue [ $P > 0.05$ ,  $t(5) = -0.215$ ] (Fig. 8). The number of active electrodes was not significantly different between Swallow and Tongue (Wilcoxon's signed-rank test;  $P > 0.05$ ).

2) Medial wall of the frontal lobe. Among five patients in whom the medial frontal lobe was investigated, only the caudal SMA was investigated in *patient 1* and both rostral and caudal SMA in the others. BPs for Swallow and Tongue were mainly located caudal to VAC line (Fig. 7).

The local maximum of BP for Swallow was seen in the caudal SMA in four patients (*patients 1, 2, 5, and 6*) and in the rostral SMA in one (*patient 3*). That for Tongue was located in the caudal SMA in all cases. Its local maximum for Swallow and Tongue was concordant in two patients (*patients 1 and 2*) but not in the others. In patients in whom the local maximum was different between Swallow and Tongue, the two areas were next to each other in two patients (*patients 5 and 6*). In *patient 3*, the active areas for Swallow were adjacent to those for Tongue, although the local maximum was ~3.1 cm apart.

Nonparametric comparison revealed that the BP onset time for Swallow was earlier than that for Tongue (Wilcoxon's signed-rank test;  $P = 0.043$ ), but BP amplitude between Swallow and Tongue did not show any difference ( $P > 0.05$ ). The distribution of BP showed that the local maximum of BP in Swallow was located rostral in two patients, caudal in one, and the same in two, compared with that of Tongue. The number of active electrodes was not significantly different between Swallow and Tongue (Wilcoxon's signed-rank test;  $P > 0.05$ ).

3) Lateral vs. Medial. For Swallow, comparison between Lateral and Medial in five patients (*patients 1–3, 5, and 6*) in whom both Lateral and Medial were studied, did not show any significant difference between the two regions in either BP amplitude or onset time (Wilcoxon's signed-rank test;  $P > 0.05$ ). This was the case also for Tongue (Wilcoxon's signed-rank test;  $P > 0.05$ ).

**POSTMOVEMENT ACTIVITY: PMP.** 1) Lateral convexity of the frontal lobe. The local maximum of PMP for Swallow and Tongue was located mainly within or adjacent to the face/tongue SMI (Fig. 6). With regard to Swallow, the local maximum of PMP was seen at the same electrode as that of BP in one patient (*patient 1*) and at different electrodes in the others. The local maximum of PMP for Tongue was located at the same electrode as that of BP in two patients (*patients 2 and 6*) and at different electrodes in the others. The local maximum of PMP for Swallow and Tongue was concordant only in one patient (*patient 5*). In the others, its local maximum for Swallow was apart from that for Tongue by the distance of 1–4.5 cm. The former adjoined the latter in four patients (*patients 2, 3, 4, and 6*).

PMP amplitude (mean  $\pm$  SD) was significantly smaller in Swallow ( $73.8 \pm 22.1 \mu V$ ) than in Tongue ( $105.7 \pm 43.4 \mu V$ ) [ $P = 0.023$ ,  $t(5) = -3.023$ ] (Fig. 8). The number of active electrodes was not significantly different between Swallow and Tongue (Wilcoxon's signed-rank test;  $P > 0.05$ ).

2) Medial wall of the frontal lobe. Significant PMP for Swallow and Tongue was mainly observed at the caudal SMA, but in two patients (*patients 3 and 6*) the rostral SMA was also involved in

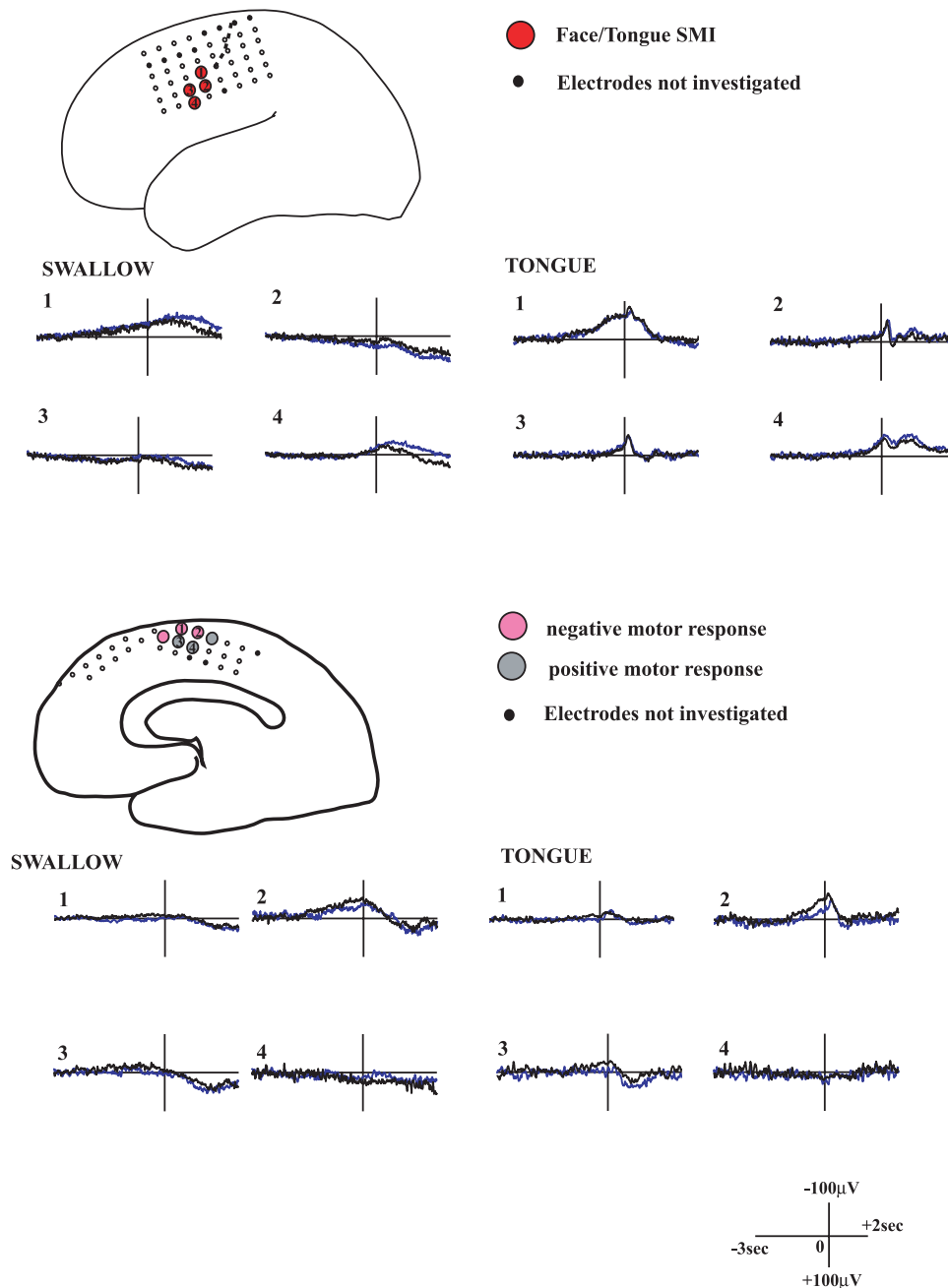


Fig. 5. Waveforms of MRCP from selected channels on the vertical surface of the frontoparietal lobes on the right hemisphere (Lateral) and medial surface of the frontoparietal lobes on the right hemisphere (Medial) for Swallow and Tongue in *patient 2*. Note that the BP onset time for Swallow is earlier than that for Tongue both on Lateral and Medial. BP amplitude for Swallow is comparable to that for Tongue both on Lateral and Medial, but PMP amplitude for Tongue is larger than that for Swallow on Lateral.

generation of PMP for Swallow (Fig. 7). The local maximum of PMP for Swallow and Tongue was located within the caudal SMA in four patients (*patients 2, 3, 5, and 6*) and adjacent to it in the remaining case (*patient 1*). Its local maximum for Swallow and Tongue was concordant in three patients (*patients 1–3*). Even in the remaining two patients (*patients 5 and 6*), the local maximum for Swallow was adjacent to that for Tongue.

PMP amplitude (mean  $\pm$  SD) did not show any difference between Swallow ( $78.2 \pm 27.7 \mu V$ ) and Tongue ( $86.1 \pm 25.5 \mu V$ ) ( $P > 0.05$ , Wilcoxon's signed-rank test) (Fig. 8). The number of active electrodes with significant PMP did not show any significant difference between Swallow and Tongue (Wilcoxon's signed-rank test;  $P > 0.05$ ).

3) Lateral vs. Medial. For each task, comparison of PMP amplitude between Lateral and Medial did not show any significant difference (Wilcoxon's signed-rank test;  $P > 0.05$ ).

## DISCUSSION

In the present study, we obtained the following findings. First, in the scalp recording, BP for Swallow was maximal at the midline vertex and widely distributed. Comparison between bilateral central regions showed asymmetrical distribution, but its dominant side was not consistent across subjects. However, BP for Tongue was also maximal at the midline vertex, and the asymmetrical distribution between bilateral central regions was observed to a lesser degree. Second, in the epicortical recording, the face/tongue SMI or its adjacent area was involved in the generation of BP not only for Tongue but also for Swallow. Third, between-task comparison revealed that the PMP amplitude on Lateral was significantly larger for

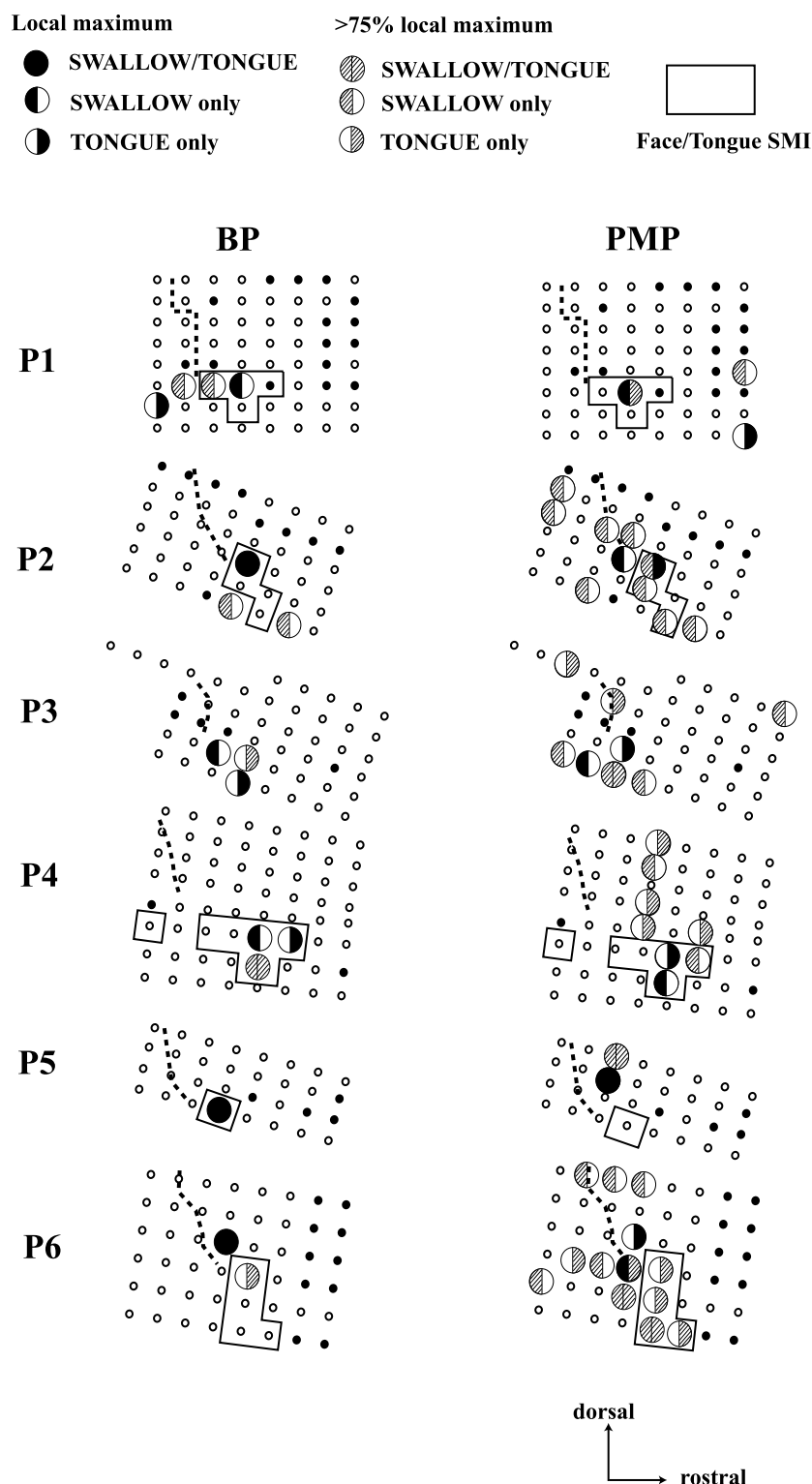


Fig. 6. Distribution of BP and PMP for Swallow and Tongue on Lateral. This map demonstrates the electrodes with significant BP and PMP activity and their local maximum for each patient. Small open circle, electrodes without significant BP or PMP. Small filled circle, electrodes not investigated due to high impedance or epileptogenicity (ictal onset or frequent interictal spikes). Broken lines indicate the central sulcus identified by intraoperative inspection and somatosensory-evoked potential recording. Area enclosed by lines indicates the face/tongue SMI determined by electrical stimulation. BP and PMP for Swallow and Tongue are seen within or around the face/tongue SMI with overlapping distribution except for *patient 1* (BP and PMP for Tongue in this patient are seen relatively apart from the face/tongue SMI).

Tongue than that for Swallow despite smaller activity of EMG in Tongue (Fig. 1). However, the amplitude of BP did not show any difference between Swallow and Tongue. Fourth, caudal SMA and/or rostral SMA was active in both Swallow and Tongue, without any significant difference between Swallow and Tongue in terms of BP and PMP amplitude. Fifth, these parameters of MRCPS did not show any significant difference

between the lateral convexity (Lateral) and the medial wall (Medial) of the frontal lobe. Sixth, the distribution of BP and PMP did not show any consistent difference between Swallow and Tongue either on Lateral or Medial, and the active areas for Swallow and Tongue overlapped to various degrees. Finally, BP onset time for Swallow was earlier than that for Tongue.



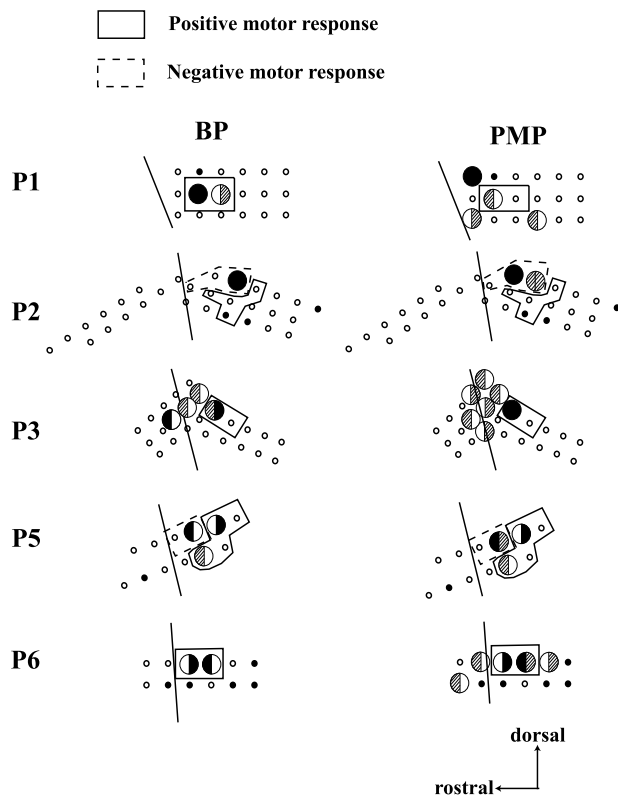


Fig. 7. Distribution of BP and PMP for Swallow and Tongue on Medial. Straight lines indicate the vertical anterior commissural (VAC) line (border between the rostral and caudal SMA). Area enclosed by solid lines shows positive motor response to electrical stimulation; area enclosed by broken lines shows negative motor response to electrical stimulation. Other symbols are the same as those for Fig. 6. BP and PMP are seen within or around the caudal SMA. Patient 3 shows BP and PMP also in the rostral SMA. In patient 6, the rostral SMA is involved in the generation only of PMP.

These observations could demonstrate the role of the cerebral cortex in volitional swallowing as follows. Face/tongue SMI is engaged in preparation for volitional swallowing, as is for tongue movement. Postmovement processing of volitional swallowing takes place in the face/tongue SMI to a lesser degree than that of tongue movement. Medial frontal cortex (caudal/rostral SMA) is commonly involved in volitional swallowing and tongue movement, suggesting that SMA is involved in motor performance itself without task specificity. In either task, comparison between face/tongue SMI and SMA did not show any difference in amplitude of either BP or PMP, and in BP onset, indicating the parallel processing of swallow-

Table 4. BP onset time for Swallow and Tongue in experiment 2 for each individual patient

| Patients No. | Lateral |        | Medial  |        |
|--------------|---------|--------|---------|--------|
|              | Swallow | Tongue | Swallow | Tongue |
| 1            | -1.91   | -1.06  | -1.16   | -0.27  |
| 2            | -2.10   | -1.76  | -1.74   | -0.83  |
| 3            | -2.08   | -0.75  | -2.16   | -1.73  |
| 4            | -2.17   | -2.00  | —       | —      |
| 5            | -1.31   | -0.56  | -1.53   | -0.72  |
| 6            | -2.45   | -1.25  | -1.97   | -1.14  |
| Mean         | -2.00   | -1.23* | -1.71   | -0.94† |
| SD           | 0.38    | 0.56   | 0.39    | 0.54   |

Values are in seconds, Paired *t*-test revealed significant difference between Swallow and Tongue (\*†*P* < 0.05). A separate comparison between Lateral and Medial in each task showed no significant difference.

ing and tongue movements in the two areas. Earlier onset of preparatory activity of volitional swallowing than tongue movement might reflect the complexity of the motor sequences associated with swallowing, and it is lateralized to either hemisphere.

#### Face/Tongue SMI and Volitional Swallowing

Previous neuroimaging studies in humans investigating the central control mechanism of the swallowing revealed involvement of bilateral SMIs corresponding to the face/tongue SMI (11, 12, 16, 22, 42). Kern et al. (17) pointed out by using a functional MRI that the cortical areas involved in swallowing were also activated by swallow-related motor tasks such as jaw clenching, lip pursing, and tongue rolling. These human studies suggest that the lateral perirolandic area is active in association with swallowing. However, these studies could not exclude the possibility that the activation in those areas reflects the sensory input associated with swallowing. The present study demonstrated that the face/tongue SMI or its adjacent areas are actively involved in the preparation stage of volitional swallowing. The face/tongue SMI was also involved in tongue protrusion with overlapped generator to that of swallowing. In primate studies, it has been more specifically postulated that the face SMI and tongue MI are involved in swallowing (24, 40). Reversible cooling of bilateral face-MI at least partially disrupted swallowing or masticatory movements in primates (31, 39). Although the swallowing task employed in the present study was different from theirs; i.e., self paced, voluntary swallowing in this study vs. swallowing of a juice reward in theirs, our result is consistent with theirs.

Table 3. BP and PMP amplitude at the local maximum on Lateral and Medial for each individual patient in experiment 2

| Patient No. | BP      |        |         |        | PMP     |        |         |        |
|-------------|---------|--------|---------|--------|---------|--------|---------|--------|
|             | Lateral |        | Medial  |        | Lateral |        | Medial  |        |
|             | Swallow | Tongue | Swallow | Tongue | Swallow | Tongue | Swallow | Tongue |
| 1           | -44.0   | -27.1  | -30.7   | -21.3  | 66.1    | 77.2   | 49.3    | 81.7   |
| 2           | -30.9   | -60.8  | -34.3   | -35.3  | 54.4    | 93.3   | 74.3    | 72.4   |
| 3           | -80.0   | -60.0  | -53.6   | -108.5 | 93.6    | 124.9  | 81.4    | 123.4  |
| 4           | -69.5   | -82.7  |         |        | 61.1    | 81.2   |         |        |
| 5           | -66.6   | -52.4  | -116.0  | -43.7  | 109.0   | 185.6  | 122.9   | 96.8   |
| 6           | -36.3   | -33.9  | -93.9   | -58.9  | 58.8    | 72.0   | 63.3    | 56.2   |

Values are microvolts.

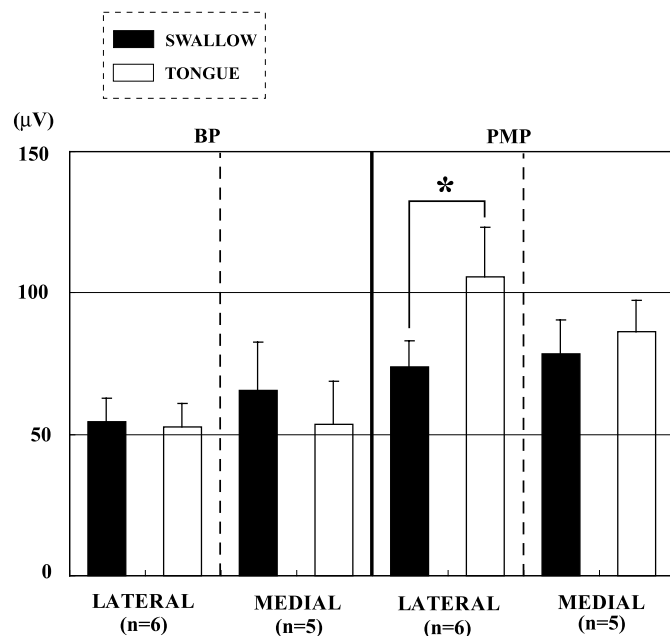


Fig. 8. BP and PMP amplitude (means  $\pm$  SE) at the local maximum on Lateral and Medial for each task. BP amplitude did not show any significant difference between Swallow and Tongue either on Lateral or Medial. On Lateral, PMP amplitude for Tongue was significantly larger than Swallow (\* $P < 0.05$ , paired  $t$ -test). In a separate comparison between Lateral and Medial ( $n = 5$ ), neither BP nor PMP showed any difference in amplitude.

The BP amplitude associated with swallowing and tongue protrusion in those areas did not show any difference, suggesting that the face/tongue SMI plays an important role equally in preparation for voluntary swallowing and tongue protrusion at least for the initial stage, the finding that has not been pointed out in earlier studies.

For studying the postmovement processing in volitional swallowing, we analyzed the largest amplitude difference during the 2-s epoch after the movement onset as an indicator of its overall activity. Because the motor and sensory processing associated with swallowing is essentially different from that with the tongue protrusion task, the simple comparison of waveforms between swallowing and tongue protrusion is not justified. Additionally, the period of 2 s can represent at least the oropharyngeal phase of swallowing, despite the fact that swallowing comprises a sequence of motor and sensory processing lasting  $> 2$  s. In this analysis, we found that PMP amplitude was larger in the tongue protrusion task than in swallowing, although the peripheral EMG activity (Fig. 1) and sensory input were apparently larger in swallowing. This finding would indicate that once the initial steps of volitional swallowing started in the cortex the brain stem reflex mechanism is a main driving force for swallowing, as described in the traditional concept of the brain stem mechanism of swallowing. It remains inconclusive in this study, however, which component of postmovement processing, motor execution or sensory feedback, is different between the two tasks.

#### SMA and Volitional Swallowing

As for the medial frontal lobe, the local maximum of BP for volitional swallowing was located rostral to that for tongue protrusion in two patients, caudal in one and at the same area

in two. This variability in the representation of volitional swallowing and tongue protrusion in SMA may be consistent with the finding of *experiment 1* that showed no difference in the distribution of scalp-recorded BP between swallowing and tongue protrusion. To our knowledge, there have been only a few studies explicitly pointing out the involvement of medial frontal, nonprimary motor cortices in swallowing. Some studies (12, 16, 22) found that the nonprimary motor areas in the medial frontal lobe were activated by swallowing, and SMA activation was correlated to its role in preparation and execution of sequences of movements. In the present study, there was no significant difference in BP and PMP amplitude between volitional swallowing and tongue protrusion, suggesting that SMA might not play a specific role in volitional swallowing. Comparison between the lateral convexity and the medial wall of the frontal lobe did not demonstrate any difference in BP amplitude, distribution or onset latency, suggesting a parallel processing not only for tongue movement but also for swallowing. This concept of the supplementary rather than supramotor role of SMA is consistent with the previous MRCP study for SMA proper (13). However, because of the small number of the patients investigated in this study, the conclusion as to the functional significance of SMA in swallowing remains to be confirmed in further studies. Furthermore, we could not clearly distinguish the role of the caudal SMA from that of the rostral one. It is important to focus on SMA in the future study on cortical processing of swallowing.

#### Hemispheric Laterality in Cortical Representation of Volitional Swallowing

In *experiment 1*, we showed that BP associated with volitional swallowing was maximal at the midline vertex, but it was lateralized to either hemisphere depending on the subject, whereas BP with tongue protrusion was relatively more symmetrically distributed. There have been a number of studies demonstrating dominant hemisphere in human swallowing. Clinically, it has been known that an approximately one-third of patients with unilateral hemispheric stroke show dysphagia or aspiration. Some studies demonstrated that the swallowing is represented mainly on the right side (5), but others did not (3, 8, 25, 27, 34). Most studies with PET or functional MRI (11, 12, 16, 22, 42) often focused on asymmetric activation of the insular cortex in swallowing. Hamdy et al. (12) showed that the SMI showed variable dominancy for swallowing across subjects, and Martin et al. (22) demonstrated a variability in dominant hemispheres in voluntary water swallow, the task that was also employed in the present study. It is uncertain whether *experiment 1* in the present study can reflect the activity arising from the insular cortex or not, because it is impossible to identify the insular activity, if any, by the current technique of MRCP recording. Therefore, we cannot directly compare our results with those of neuroimaging studies. Hamdy et al. (10) in their transcranial magnetic stimulation study showed that the corticobulbar projection to the swallowing-related musculatures has a lateralized representation to either hemisphere, independent of the subjects' handedness. Although they concluded that the asymmetrical representation of swallowing might reflect laterality of the premotor activity, our results showing that the face/tongue SMI generates BPs with laterality might be consistent with their result, possibly in

view of the fact that the crown part of face/tongue SMI might mainly include Brodmann's area 6 (32, 43). Our results can add a novel finding that volitional swallowing can be represented to a greater degree by one hemisphere than the other even in its early preparatory period.

### *Role of Cerebral Cortex in Volitional Swallowing*

Bilateral inactivation by cooling of face MI in monkeys did not affect swallowing (39). It is possible to hypothesize that the cerebral cortex alone does not play an essential role in swallowing. This brain stem reflex mechanism of swallowing could be consistent with our finding that PMP was less pronounced in volitional swallowing than in tongue protrusion. Because BP with volitional swallowing was not significantly different from that with tongue protrusion, it can be postulated that the cerebral cortex is involved at least in preparation for voluntary swallowing to a greater degree compared with execution or sensory feedback processing. The earlier onset of BP associated with volitional swallowing than tongue protrusion was observed both at the face/tongue SMI and its adjacent area (Lateral) and also at the SMA (Medial). It suggests that the cerebral cortex can prepare earlier for swallowing than for the other, probably because it involves multiple muscles in a complex way or a sequence of movements (36).

In the present experiments, we recorded MRCPs with volitional swallowing both in normal subjects with scalp electrodes and in epilepsy patients with subdural electrodes. Thus this study enabled accurate location of active cortical areas on one hand and the lateralized representation of preparatory activities in association with volitional swallowing on the other. In addition, epicortically recorded MRCPs could demonstrate the differential role of SMI in volitional swallowing and tongue movements. When the potentials are recorded from subdural electrodes, however, it always carries a possibility that they do not cover the whole functional cortical areas and the pathological cortices are also covered. Hence, we investigated chiefly the face/tongue SMI or the caudal and rostral SMA defined by electrical stimulation or by anatomical landmark and excluded the epileptogenic areas from further analysis. Because of the interindividual variability of epicortically recorded potentials, we applied within-subject comparison in *experiment 2*. Furthermore, the distribution analysis of BP or PMP in this study could not elucidate the accurate number of their generator sources. It is possible that multiple generators could exist in various cortical or subcortical areas related to motor control (33). Even on the lateral convexity investigated in the present study, BP and PMP seemed to be present in multiple areas. It is impossible to elucidate all the cortical areas actually involved in the MRCP generation, because we could not determine the precise location by 3D-MRI anatomically. The possibility that some inhibitory mechanisms like pharyngeal closure might have an influence on the BP for voluntary swallowing cannot be excluded.

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