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Original Article

Role of the anterior cingulate cortex in volitional swallowing: an electromyographic and functional magnetic resonance imaging study

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Anterior cingulate cortex (ACC) plays an important role in human volition, but its function in swallowing is not well known. We tested the hypothesis that visual inputs given before volitional swallowing modulate the ACC activity. We evaluated the relationship between visual effect on swallowing "behavior" and "brain activity" using EMG (electromyography) and fMRI (functional magnetic resonance imaging). Seven healthy volunteers participated in the EMG study, and 10 volunteers in the fMRI study. Visual images, i.e., photographs of food (DRINK) or general items (GENERAL), were used as the visual input and these were provided with (WS) or without (DS) water. Both behavioral and brain activity data were recorded during each trial in four (DRINK/WS, GENERAL/WS, DRINK/DS, GENERAL/DS) conditions. EMG study showed that the latency was significantly shorter with DRINK input than that with GENERAL input in the WS condition. Meanwhile, in the fMRI study, the maximum MR signal change was greater with GENERAL than that with DRINK in both WS and DS conditions. Thus, it appears that there was a relationship between swallowing behavior and the ACC activity in volitional swallowing.

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Introduction

Swallowing begins with a voluntary oral stage and progresses to involuntary pharyngeal and esophageal stages. During swallowing, descending impulses from the cerebral cortex and ascending impulses from the peripheral nervous system converge and are integrated in the medullary reticular formation, where the central pattern generator for swallowing is located[1-3]. Several electrophysiological studies have investigated the effect of water stimulation that activates peripheral receptors during the oral and pharyngeal stages of swallowing[4-7]. For instance, differences in the volume and properties of swallowed liquids can affect the pattern of swallowing[1,4]. On the other hands, swallowing movement is modulated not only by peripheral stimulus in the mouth but also by visual stimulus given prior to swallowing[8]. In the study, we speculated that appropriate visual stimulus modulated volitional aspects and facilitated swallowing movement, because visual input is thought to induce salivation for bolus preparation, transfer, and transport in the anticipatory stage of swallowing[9]. But this modulation occurred only when the water existed in the subject's mouth. It was assumed that the visual stimulus activated the cortical volition-related area irrespective of the presence of the peripheral stimulus, but its effect on swallowing movement was masked by the effect of peripheral stimulus. In recent neuroimaging studies, it has been reported that many cortical and subcortical foci are activated during swallowing[10-17]. These include the sensorimotor cortex, prefrontal cortex, anterior cingulate cortex (ACC), insula and the parieto-occipital region. Although the ACC is known to be active in volitional movement[18] and to be related to “human volition”, its role in human swallowing is yet to be elucidated. In a magnetoencephalographic (MEG) study, the activation of the ACC was reported to occur in the early stage [i.e., 2000ms before the electromyographic (EMG) onset of the suprahyoid muscle] of swallowing[19]. It was therefore suggested that the activation of the ACC was involved in cognitive process of swallowing.

In this study, we tested the hypothesis that visual inputs given prior to volitional swallowing modulate the ACC activity using event-related functional magnetic resonance imaging (fMRI). For this purpose, we carried out two experiments; EMG and fMRI experiments. First, we evaluated the visual effect on swallowing “behavior” using EMG, and then evaluated the visual effect on swallowing “brain activity” using fMRI.

Materials and Methods

Experiment 1 (EMG study)

Subjects: Seven healthy adult male volunteers, with a mean age of 28.1 years (range: 26.4-30.4 years), participated in Experiment 1. None showed clinical signs of gestational or gastrointestinal symptoms, and all were right-handed according to the Edinburgh Handedness Inventory[20]. Each subject gave his informed consent before the study, which was previously approved by the institutional ethics committee. The subjects were asked to refrain from drinking any beverage for at least 3 hours before the experimental session.

Stimulus: Three ml of water for water swallow (WS) or no (0 ml) water for dry swallow (DS) was provided on the dorsum of the subject’s tongue using a 5-ml syringe (SS-05SZ20, Termo, Japan) by the examiner as somatosensory inputs. Color photographs of drinkable items that would induce a desire to drink (e.g., a glass of beer; DRINK) and those of general items that would not induce a desire to drink (e.g., a pair of scissors; GENERAL) were presented randomly on a personal liquid crystal display (LCD) monitor (PLM-50, Sony, Japan) worn by the subject while lying supine in a dental chair as visual inputs. The subjects were asked to look at the object on the LCD screen without applying any special meaning to the object. The subjects were naïve to the categorization of visual stimuli as DRINK or GENERAL. By wearing the LCD monitor, the field of vision was completely blocked except for the monitor screen, so that the subject could not prepare for the placement of water on the tongue by the examiner.

Task sequence: The experiment was carried out in the following fashion (Fig. 1). First, the subject was asked to view one of the visual images that were presented throughout the experimental session, then asked to perform a dry swallowing movement to empty the mouth (1st swallowing). Next, the subject was directed to either voluntarily perform the dry swallowing (DRY) movement again, or to swallow water (WATER) placed on the tongue (2nd swallowing). Thus, the experimental stimuli consisted of four conditions; DRINK/ WATER, GENERAL/ WATER, DRINK/ DRY, and GENERAL/ DRY. The instruction to swallow consisted of tapping the subject’s left knee lightly with an impulse force hammer (GK-3100, Ono Sokki, Japan). Each trial under the 4 experimental conditions was randomly repeated 7 times.

Data analysis: EMG activities were recorded with bipolar surface electrodes (NT-512G, Nihon Kohden, Japan) placed on the suprahyoid muscles. EMG signals were band-pass filtered (30Hz-1kHz), full-wave rectified and amplified by a bioelectric amplifier. EMG signals were stored in a DAT recorder (PC216, Sony, Japan), sampled, and measured using an A/D converter (Maclab ver.3.5: ADInstrument, Australia) on a personal computer (PowerbookG3, Macintosh, U.S.A). Each task was digitized at 400 Hz. The onset of the 2ndswallowing was determined by the peak negative displacement of the trace from an acceleration transducer that was fixed with surgical tape at the site of maximum projection of the thyroid cartilage. The latency between tapping the subject with the impulse hammer and the onset of the 2ndswallowing movement (i.e., transducer latency), and the maximum amplitudes of suprahyoid EMG activity were measured. (Fig. 2)

Wilcoxon’s signed rank test was used to compare the latency and the maximum EMG amplitudes among the 4 conditions. Statistical analysis was performed using Stat View 5.0 (Abacus Concepts, U.S.A.). Statistical significance was set at $p < 0.05$. The details of the methods used for the EMG study have been reported elsewhere[8].

Experiment 2 (fMRI study)

Subjects: Ten healthy adult male volunteers with a mean age of 27.8 years (range: 25.7-30.2 years) were

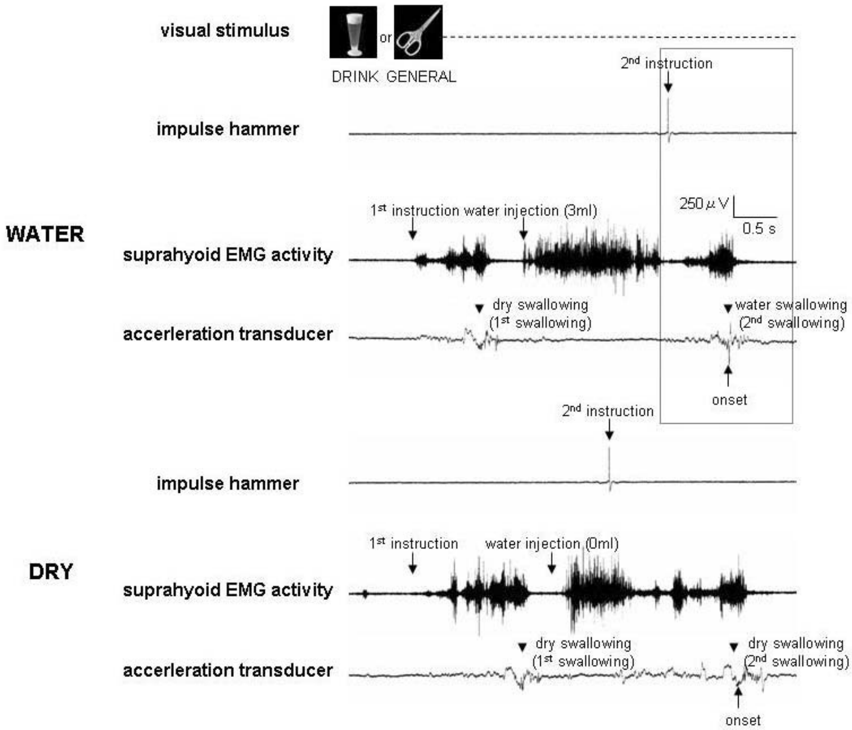

Fig. 1. A typical example of events during a single trial of the swallowing task in Experiment 1. Timings of visual stimulation and the output of the impulse hammer can be applied separately to water swallowing (WS) and dry swallowing (DS). Arrowheads depict swallowing movement detected by gross deflection of the acceleration transducer. The area indicated by the dotted line is shown for the analysis of electromyographic activity.

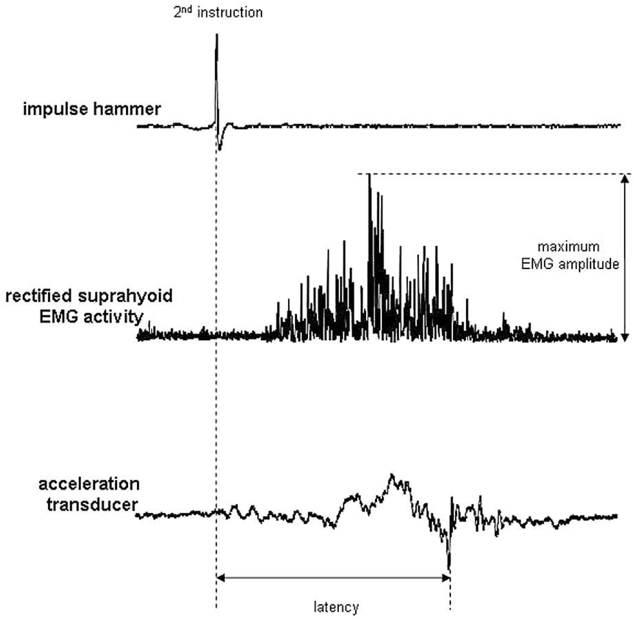

Fig. 2. A schematic illustration of the analysis of swallowing behavior in Experiment 1. Suprahyoid electromyographic (EMG) activity was full-wave rectified. See Experimental procedures for definitions of maximum EMG amplitude and latency to swallow.

studied. They were all consistent right-handers as measured by the Edinburgh Handedness Inventory. All of the experimental procedures complied with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the standards established by the institutional ethics committee. Written informed consent was obtained from all of the subjects before the study, after the nature of the experimental procedures had been fully explained.

Stimulus: Two ml of water for WS or no (0 ml) water for DS were provided subject's mouth via a plastic infusion catheter placed in the midline to place water on the dorsum of the subject's tongue as somatosensory inputs. Same color photographs used in Experiment 1 (i.e., DRINK and GENERAL), as visual inputs, were provided on a monitor screen inside the MRI scanner and projected by a projector placed outside the MRI scanner. In somatosensory task, subjects were provided only somatosensory inputs (i.e., WS, DS), and in visual/somatosensory task, subjects were provided a combination of the above inputs (i.e., DRINK/ WS, GENERAL/ WS, DRINK/ DS, GENERAL/ DS).

Task sequence: The experiment was carried out in the following fashion (Fig. 3). First, each subject was instructed to perform a dry swallowing movement (1st swallowing) by a visual command ("swallow") projected on the center of the screen inside the MRI scanner. This mandatory dry swallowing movement is to empty the mouth completely to avoid the effect of saliva in the subject's mouth. The visual command was immediately turned out and the subject was asked to watch the center of the black screen. After 10 seconds, visual input (DRINK or GENERAL) was presented on a monitor screen inside the MRI scanner, and then a room-temperature water bolus (2 ml or 0 ml; WS or DS) was provided into the subject's mouth via a plastic infusion catheter placed in the midline to place the water bolus on the dorsum of the tongue at a constant flow speed by the same trained examiner using a hand-held syringe. Within the next 4 seconds the same visual command "swallow" was projected again on the screen. Immediately after the visual command, subject was directed to perform either DS when 0 ml of water bolus had been provided or WS when 2 ml of water bolus had been provided (2nd swallowing). To determine the onset of each episode of swallowing, a plastic pneumographic belt was attached to the anterior neck of each subject at the level of the hyoid bone and connected to an MRI scanner. Each activity trial under the 6 experimental conditions (i.e., WS/DS in somatosensory task, DRINK/ WS, GENERAL/ WS, DRINK/ DS, GENERAL/ DS in visual/somatosensory task) was randomly repeated 6 times.

MRI scans: Whole brain imaging data was obtained by means of a 1.5T magnetic resonance system (Magnetom Vision, Siemens, Erlangen Germany) using a circularly polarized head coil. Head motion was minimized with a tightly-fitted foam pad. For functional imaging, gradient echo-type echo planar sequences with the following acquisition parameters were used: TR/TE: 1690 ms/60 ms; flip angle: 90 degrees; FOV: 192x192 mm; and pixel matrix: 64x64. Sixteen contiguous, 7-mm-thick slices were obtained on the axial plane for each subject. After image construction, functional images were analyzed using an SPM99 (Wellcome Department of Cognitive Neurology, London, UK). Five initial images were discarded from the analysis to eliminate the non-equilibrium effects of magnetization. All functional images were realigned to correct for head movement. A total of 256 (somatosensory task) and 470 (visual/somatosensory task) images were obtained in each of 16 sections.

Data analysis: Image processing and statistical analysis were carried out using SPM99[21,22]. All volumes were realigned to the first volume, spatially normalized[21] to a standard EPI template[23,24] and finally smoothed using a 7-mm full-width at half-maximum isotropic Gaussian kernel. Data analysis was performed by modeling the different trials ("WS" and "DS" for somatosensory task, "DRINK/ WS", "GENERAL/ WS", "DRINK/ DS" and "GENERAL/ DS" for visual/somatosensory task) as trains of delta functions convolved with a hemodynamic response function (HRF). Regions exhibiting significant responses during each task were identified. Activations were reported if they exceeded $p < 0.001$ (uncorrected) at a single-voxel level during 18-s period after water injection. The blood-oxygen-level-dependent (BOLD) signal was extracted from voxel in which a significant activation was observed during each task for 30 seconds starting from first visual command 'swallow'. Maximum BOLD signal changes were calculated by averaging the peak values of the temporal change in the BOLD signal among the 6 trials for each experimental condition in each of the 10 subjects. Wilcoxon's signed rank test was used to evaluate the statistical significance of the maximum BOLD signal change of both experimental conditions. All coordinates reported in this study are in accord with the system described by Talairach and Tournoux[24].

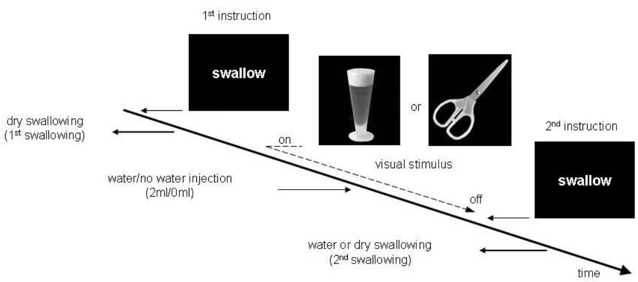

Fig. 3. Task sequence in Experiment 2. See Experimental procedures for details.

Results

Experiment 1:

The latency in the DRINK/WS condition [969.3± 178.1 ms; mean ± standard error of the mean (SE)] was significantly shorter ($p < 0.05$) than that in the GENERAL/ WS condition (1024.1±182.0 ms). On the other hand, there was no significant difference in the latency to swallow between the DRINK/ DS (1884.6± 283.2 ms) and GENERAL/ DS (2088.0±258.4 ms) conditions. The maximum EMG amplitude of the suprahyoid muscle in the DRINK/ WS condition (186.4±32.4 μV) was significantly less ($p < 0.05$) than that in the GENERAL/ WS condition (202.6±34.6 μV). In contrast, there was no significant difference in the maximum suprahyoid EMG amplitude during swallowing between the DRINK/ DS (208.2±33.3 μV) and GENERAL/ DS (207.0±37.5μV) conditions (Table1).

Experiment 2:

The activations of the ACC were shown in the both somatosensory task and visual/somatosensory task (Fig. 4). Areas of activation in the somatosensory task were localized rostrally, whereas those in the visual/somatosensory task were localized caudally. In the WS condition, the activation was widespread from rostral to caudal in the region of the ACC (Fig. 5).

Somatosensory task: The time course of activation had one peak during 30s-task sequence (Fig. 6a). The magnitude of the peak BOLD signal change in the WS condition (0.874±0.116%) was significantly greater than that in the DS condition (0.503±0.085%, Fig. 7a).

Visual/somatosensory task: The time course of activation had two peaks during 30s-task sequence (Fig. 6b). The magnitude of the peak BOLD signal change in the DRINK/ WS condition (0.731±0.200%) was significantly less than that in the GENERAL/ WS condition (0.954± 0.210%, Fig. 7b). Likewise, the magnitude of the peak BOLD signal change in the DRINK/ DS condition (0.583±0.099%) was significantly less than that in the GENERAL/ DS condition. (0.916±0.146%, Fig. 7b)

Number of voxels in each task: The number of voxels showed that motor area was activated unilaterally in somatosensory task and bilaterally in visual/somatosensory task, and same type of the activation was seen in the insula during the task with water (WS, DRINK/ WS, GENERAL/ WS, Table 2).

Discussion

Effect of visual inputs on the swallowing behavior

The results showed that in the WS condition, a DRINK (i.e., congruent) visual input caused an earlier onset of swallowing movement and induced a lower suprahyoid EMG amplitude than GENERAL (i.e., incongruent) visual inputs. However, this was not the case in the DS condition. This suggests that peripheral input from the oral cavity had a substantial effect on swallowing, while the appropriate visual input given during swallowing modulated the motor act cortically. The former study has been reported that stimulation of human cranial nerve afferents, trigeminal and vagal nerve fibers, facilitates cortical swallowing motor pathways[25].

Effect of visual inputs on the swallowing brain activity

In this study, we observed different areas in the ACC were activated depending on the type of stimulus. The activated area of the ACC in the visual/somatosensory task was localized caudally, whereas in the somatosensory task, that was widespread from the caudal to rostral ACC in the WS condition, and was localized rostrally in the DS condition. The ACC has two major subdivisions distinguished from its functions, and these include a dosal cognitive division and a rostral-ventral affective division[26,27]. We thought that the activation of the caudal part indicated that the existence of stimulus interplayed with cognitive function of the ACC, while the activation of the rostral part indicated that some kind of emotional factor was involved with or without water.

The rostral-ventral affective division

The present study revealed that the activity of the ACC was facilitated by the presence of water in the mouth during WS. Moreover, the time course of the

Table 1. Transducer latency and maximum amplitude of the suprahyoid electromyographic (EMG) activity are shown in 4 experimental conditions (mean±SE). Asterisks indicate where there are significant differences between DRINK and GENERAL in each of the two types of swallowing ($p < 0.05$).

peripheral input	WATER		DRY	
visual input	DRINK	GENERAL	DRINK	GENERAL
transducer latency (ms)	969.3±178.1*	1024.1±182.0	1884.6±283.2	2088.0±258.4
maximum suprahyoid EMG amplitude (μV)	186.4±32.4*	202.6±34.6	208.2±33.3	207.0±37.5

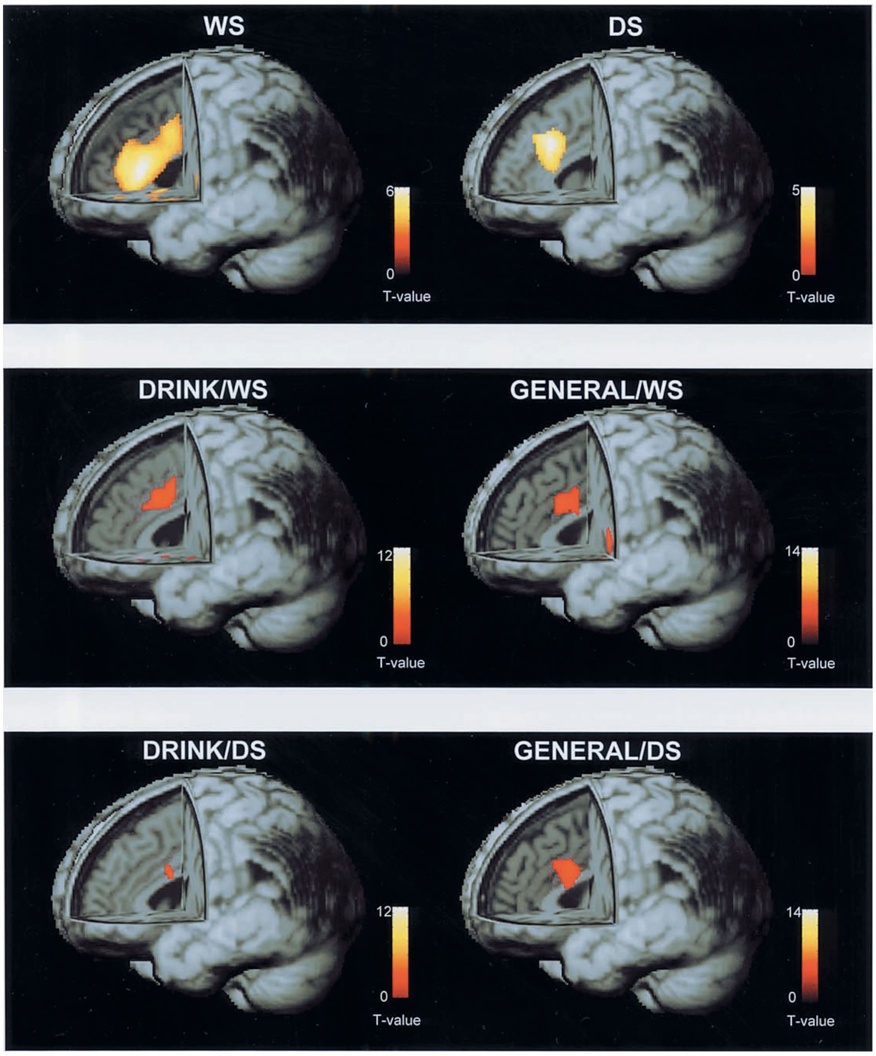

Fig. 4. Statistical parametric maps of brain regions constructed by a group analysis (n=10), showing significant increases in blood oxygenation level-dependent (BOLD) contrast associated with each of the 6 swallowing tasks (WS, DS, DRINK/ WS, GENERAL/ WS, DRINK/ DS, GENERAL/ DS), at a statistical threshold of $p < 0.001$ (uncorrected) at a single-voxel level and $p < 0.05$ (corrected) at the cluster level. Clusters of activation were overlaid onto a T1-weighted anatomical magnetic resonance image. The color calibration bar shows the magnitude of the T value.

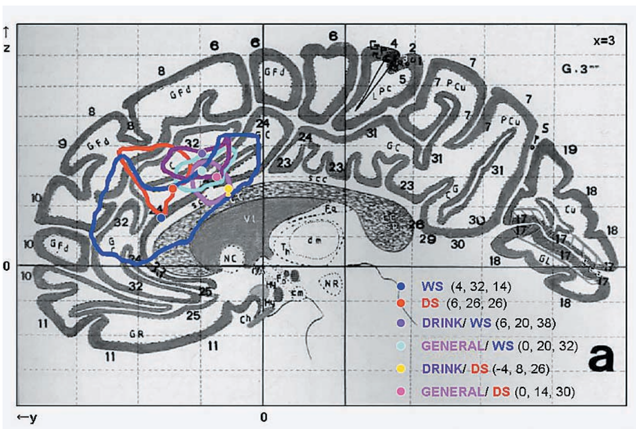

Fig. 5. Superimposition of the activation area and the voxel of highest significance in the ACC with each task on Talairach atlas sections by using the SPM extension program. Talairach coordinates were also shown. The activations in the somatosensory task were localized rostrally, whereas those in the visual/somatosensory task were localized caudally in the area of ACC.

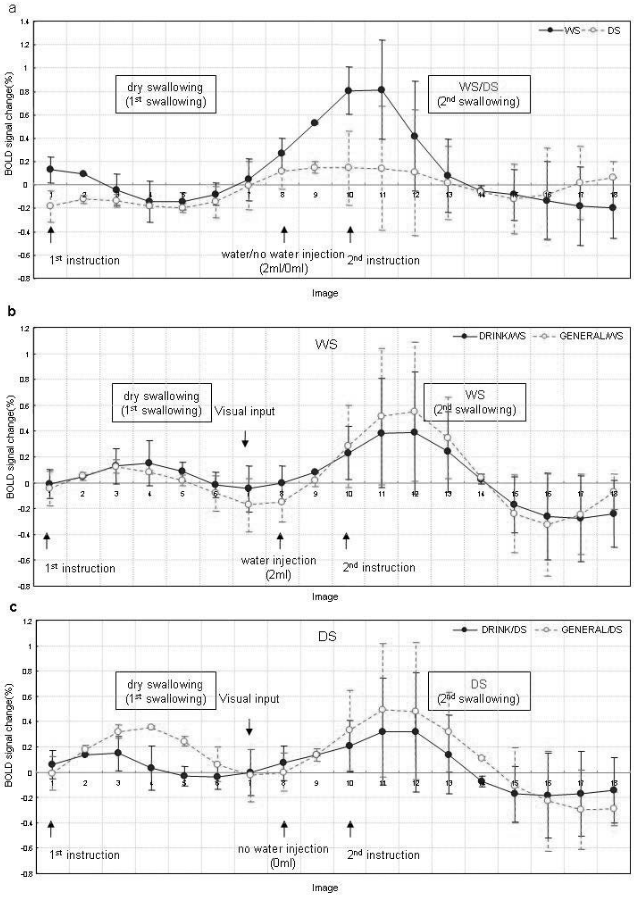

Fig. 6. Time profiles of the average percentage change in blood oxygenation level-dependent (BOLD) signal in the area of the anterior cingulate gyrus (ACC) associated with the swallowing task (n=10). The BOLD signal was extracted from voxel of highest significance which was shown in Fig.5. a, Signal response in the ACC [Talairach coordinates: (4, 32, 14) for the WS condition (filled circles) and (6, 26, 26) for the DS condition (open circles)]. b, Signal response in the ACC in the WS condition [Talairach coordinates: (6, 20, 38) for the DRINK condition (filled circles) and (0, 20, 32) for the GENERAL condition (open circles)]. c, Signal response in the ACC in the DS condition [Talairach coordinates: (-4, 8, 26) for the DRINK condition (filled circles) and (0, 14, 30) for the GENERAL condition (open circles)].

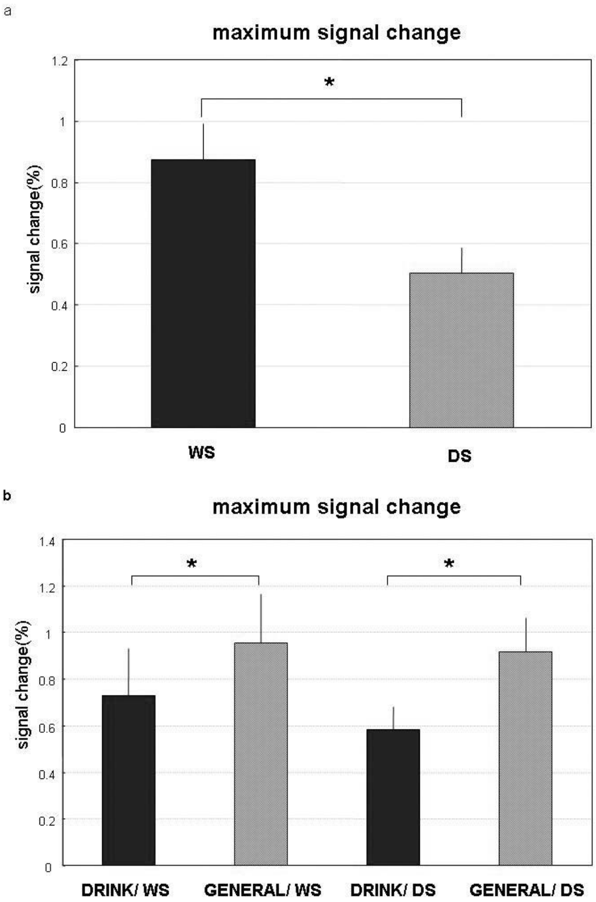

Fig. 7. Maximum percentage BOLD signal change associated with the swallowing task in the ACC. a, *: $p < 0.05$ between WS and DS conditions. b, *: $p < 0.05$ between DRINK and GENERAL conditions. Error bars indicate the standard error of the mean (SE).

activity had one peak that corresponded to 2nd swallowing in the 30s-task sequence, and the brain activity that related to 1st swallowing was not seen (Fig. 6). This suggests that the activity was not related to swallowing but to specific condition of 2nd swallowing. We supposed two possibilities about activity of this area. First, we supposed about thirst because of the dryness of the subject's mouth by 1st swallowing. This may reflect the thirst level that is motivational state of the subject, since there was a positive correlation between the ACC activation level and the subjective rating of the pleasantness of the water[28,29]. On the other hands, pregenual cingulate was activated by aversive gustatory stimulus, and this region was thought to be related to unpleasant emotional states[30]. In the WS condition, the water was injected into subject's mouth without expectation, while there was no water injection in 1st swallowing and was visual input prior to water injection in visual/somatosensory task. Moreover, they had to swallow the water bolus in an unnatural supine position. These experimental conditions might make them unpleasant in our study. However, the activity was seen in DS condition, we considered that first possibility, thirst, was related to the activity of this area in our study.

The dorsal cognitive division

Activation of the ACC has been reported in many previous neuroimaging studies on swallowing[10-17], and the ACC is thought to process attention to volitional actions and sensory stimuli. Results of a visual choice reaction task suggested that the ACC activation reflected the intentional amount of effort that a subject uses in a task, since the degree of such activation is negatively correlated with the reaction time[31,32]. In the present study, the maximum percentage BOLD signal change in the ACC elicited by a DRINK stimulus was significantly smaller than that with a GENERAL stimulus in both the WS and DS conditions. This area of activity had two peaks that corresponded to 1st and 2nd swallowing; therefore, it appears to be swallow-related activity. Thus, presentation of a DRINK stimulus during volitional swallowing may support and facilitate the subject's volition to swallow more than a GENERAL stimulus. In other words, the subject uses more effort to swallow without a contextual visual cue. Indeed, it has been reported that there is a proportionate increase in the ACC activation with an increase in task difficulty[32,33].

Cooperation with other brain areas

The ACC is an interface of motor control and cognitive aspects, so that it has many connections with other brain areas. In the swallow-related brain area, the insula and motor area also have connection with the ACC. Insula which is thought as taste area and projects on the ACC and motor area is projected by the ACC. In this study, these areas showed the left hemispheric activation in the somatosensory task and bilateral hemispheric activation in the visual/somatosensory task in the WS condition (Table 2). The hemispheric dominance of the swallow-related brain activity is under debate in a lot of studies. In a study[39] using MEG, which is superior to other neuroimaging methods in the temporal resolution, the motor area showed a different type of activation between the preparation and the execution phases of swallowing, though the insula was activated only left side in the both phases; the left hemisphere dominance in the execution phase, and the bilateral activation in the preparation phase. The activation of the motor area seen in our study may suggest that the presentation of visual input, both DRINK and GENERAL, facilitate the preparation phase of swallowing. The visual input such as food pictures also activated the right insula[40]. Taking these data into account, it is suggested that visual input during DRINK condition modulates initiation of swallowing behavior through the right insula and the dorsal part of the ACC.

Our results imply that there was relationship between swallowing behavior and brain activity. Our behavioral data suggested appropriate visual input reduced latency and muscle activity in WS condition. In other words, swallowing movement carried out smoothly by appropriate visual input and water stimulus. On the other hand, neuronal data showed the activity of the area of volitional effort and thirst by visual input. Thus, it appears that visual input reduced effort for swallow and water stimulus increased pleasantness of the water, which results in smooth swallowing movement. However, further study is needed to prove this assumption.

Table 2. The number of activated voxels in 6 tasks in the swallow-related area from 10 subjects data. Data was given by exploring the swallow-related area from each cluster which activated at the level of p<0.001 and calculating its population in the clusters using SPM99 extension program.

Task		Anterior cingulate		Motor/premotor		Occipital		Insular	
		L	R	L	R	L	R	L	R
Somatosensory task	WS	396	522	71	1			15	
	DS	90	1	34		10			
Visual/somatosensory task	DRINK/ WS		36	85	19	182	448	139	54
	GENERAL/ WS	19	12	209	82	240	610	64	12
	DRINK/ DS	16				276	631		
	GENERAL/ DS	21	33		1	406	895		

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