Journal of Oral Science, Vol. 60, No. 3, 329-335, 2018

Original

Prefrontal cortex activity during swallowing in dysphagia patients

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(Received June 24, 2017; Accepted October 3, 2017)

Abstract: Prefrontal cortex activity is modulated by flavor and taste stimuli and changes during swallowing. We hypothesized that changes in the modulation of prefrontal cortex activity by flavor and taste were associated with swallowing movement and evaluated brain activity during swallowing in patients with dysphagia. To evaluate prefrontal cortex activity in dysphagia patients during swallowing, change in oxidized hemoglobin (z-score) was measured with near-infrared spectroscopy while dysphagia patients and healthy controls swallowed sweetened/unsweetened and flavored/unflavored jelly. Total z-scores were positive during swallowing of flavored/unsweetened jelly and negative during swallowing of unflavored/sweetened jelly in controls but negative during swallowing of sweetened/unsweetened and flavored/unflavored jelly in dysphagia patients. These findings suggest that taste and flavor during food swallowing are associated with positive and negative z-scores, respectively. Change in negative and positive z-scores may be useful in evaluating brain activity of dysphagia patients during swallowing of sweetened and unsweetened food.

Keywords: z-score; dysphagia; deglutition; prefrontal cortex; flavored and sweetened jelly.

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J-STAGE Advance Publication: May 24, 2018
Color figures can be viewed in the online issue at J-STAGE.
doi.org/10.2334/josnusd.17-0238
DN/JST.JSTAGE/josnusd/17-0238

Introduction

Substantial evidence indicates that taste and flavor stimuli during swallowing modulate cortical motor pathways and motor output (1,2). Thus, flavor and taste stimuli may be involved in modulating swallowing movement. Clinical studies reported that food flavors alter the ability to chew or swallow in healthy persons and dysphagia patients (3-6). Thus, cortical activity is altered by flavor and taste stimuli in dysphagia patients, and modulates swallowing movement.

The prefrontal cortex is involved in attention, and in sensation of flavor and taste (7,8). Furthermore, swallowing movement is thought to modulate prefrontal cortex activity in healthy persons (9). However, it is unclear how sensory inputs are involved in motor outputs related to mastication and swallowing in persons with dysphagia or masticatory dysfunction. Near-infrared spectroscopy (NIRS) studies have shown that food-related stimuli,

Table 1 Clinical characteristics of controls and dysphagia patients

Age(y)/sex	Dementia	Stroke	Schizo-phrenia	Dysphagia training	Food	Denture wearing	Other symptoms
Healthy subjects							
85/M	–	–	–	–	normal food	(upper PD / lower PD)	
79/F	–	–	–	–	normal food	(upper CD / lower CD)	
71/M	–	–	–	–	normal food	(upper PD / lower PD)	
72/F	–	–	–	–	normal food	(upper CD / lower CD)	
66/M	–	–	–	–	normal food	(upper PD / lower PD)	
81/F	–	–	–	–	normal food	(upper PD / lower PD)	
73/F	–	–	–	–	normal food	(upper CD / lower PD)	
Dysphagia patients							
85/M	+	+	–	+	chopped food FOIS: Level. 6	(upper CD / lower CD)	depression motor deficit in the left side
94/F	+	–	–	+	soft food FOIS: Level. 4	(upper CD / lower CD)	depression motor deficit in the lower half body
90/F	–	+	–	+	soft food FOIS: Level. 5	(upper CD / lower PD)	
79/F	+	+	–	+	soft food FOIS: Level. 5	(upper CD / lower CD)	
81/F	+	+	–	+	soft food FOIS: Level. 5	(upper PD / lower PD)	depression motor deficit in the right side

CD: complete denture, PD: partial denture, FOIS: Functional Oral Intake Scale (Level. 1-7)

Table 2 Flavored items assessed in controls and dysphagia patients

Point	Point
Cooked rice	Green tea
Miso (soybean paste)	Coffee
Laver	Chocolate
Soy sauce	Domestic gas
A bakery	Garbage
Butter	Timber
Curry	Sweat
Roasted garlic	Feces
A tangerine	Flowers
Strawberry	Perfume

including flavor and taste, cause consistent activation of the prefrontal cortex (10). Existing evidence strongly suggests that the prefrontal cortex is involved in swallowing movements and that flavor and taste sensations modulate that activity.

We hypothesized that prefrontal cortex activity would change during swallowing of sweet and flavored jellies and that these changes could be used to evaluate brain activity in persons with dysphagia. NIRS is portable and noninvasive and is therefore a convenient method to measure brain activity in hospitalized patients. Using NIRS, we investigated prefrontal cortex activity in healthy volunteers and dysphagia patients during swallowing of sweetened/unsweetened and flavored/unflavored jelly, to determine if taste and flavor stimuli modulate prefrontal cortex function in dysphagia patients.

Materials and Methods

The study protocol was approved by the Ethical Committee of Nihon University School of Dentistry (EP2009-13). The study purpose and procedures were explained to all participants before they took part in the study.

Participants

Seven healthy adults (controls; 3 men and 4 women; age, 75.3 ± 6.6 years; range, 66-85 years) and 5 patients with dysphagia and brain lesions (1 man and 4 women; age, 85.8 ± 6.2 years; range, 79-94 years) were enrolled. The prefrontal cortex was intact in all participants. The controls had no functional deficits in mastication, swallowing, flavor perception, or tasting abilities. The patients with dysphagia had been diagnosed as having swallowing disorders related to mastication and swallowing, as indicated by a history of rehabilitation therapy. The clinical characteristics of the participants are shown in Table 1.

To evaluate ability to discriminate flavors, the controls and dysphagia patients were interviewed to determine if they could distinguish 20 different flavors. The following numbers were assigned for flavor detectability: 2 points for highly detectable, 1 point for moderately detectable, and 0 point for undetectable (Table 2). The total score was calculated for all participants (maximum score: 40), and percentages of total discrimination scores were calculated for each participant.

Sweet orange-flavored jelly was used because all participants were able to discriminate it in our preliminary

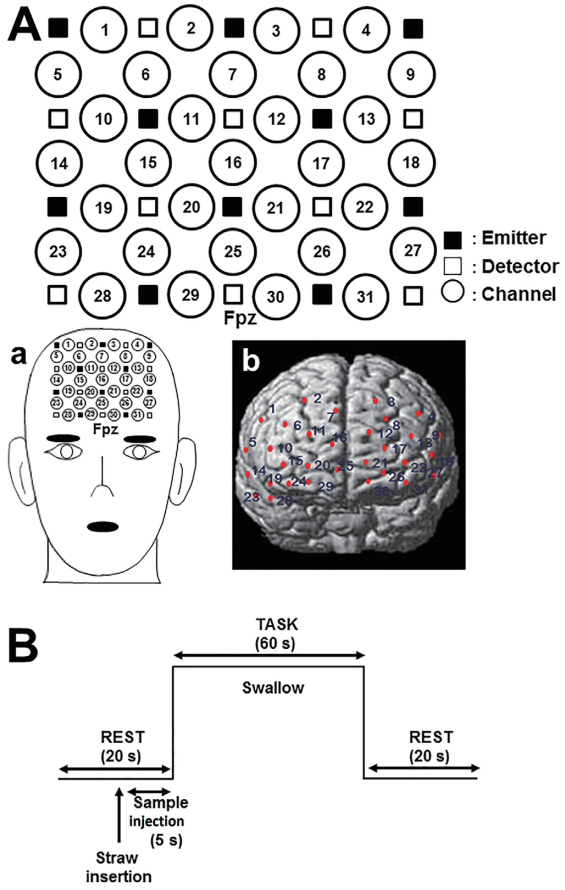

Fig. 1 Location of electrodes and task timing. A: Location of the 31 electrodes placed on the prefrontal cortex, B: Illustration of the swallowing task for participants. (a) Inset diagrams show the electrodes on the face and (b) the averaged frontal brain.

study. We first investigated the capacity to distinguish sweetness by using four solutions with different sucrose concentrations (10, 30, 50, and 100 mM). Five mL of sucrose solution (concentration, 10 to 100 mM) was placed in the mouth, to measure the discrimination threshold for sweetness, i.e., the detection value for sucrose concentration.

To evaluate swallowing ability, the number of times a participant swallowed saliva in 30 s was counted. Movement of laryngeal cartilage was defined as a swallow.

Food samples

Four different sample jellies were used in this study: unflavored/unsweetened jelly, unflavored/sweetened jelly, flavored/unsweetened jelly, and flavored/sweetened jelly. Flavored jelly was prepared by mixing orange-flavored liquid with jelly, and sweetened jelly was prepared by mixing sugar with jelly.

Commercially available jellies with orange, apple, grape, and banana flavors (Takasago International Co., Tokyo, Japan) were used as samples. The sample jelly was prepared by mixing jelly powder (6 g, Jelly Takumi Neo, SARAYA Co. Tokyo, Japan) with hot distilled water (80°C, 600 mL), after which the mixture was cooled to room temperature. Sugar (27 g) was added to the 150-mL mixture for sweetened jelly, and 0.5 mL of orange-flavored liquid was added to the 150-mL mixture for flavored jelly, thereby yielding flavored/sweetened jelly (orange flavor + sweetened), flavored/unsweetened jelly (orange flavor), unflavored/sweetened jelly (sweetened), and unflavored/unsweetened jelly. The participants tasted these four jellies, and all were able to discriminate the orange-flavored jelly, which was therefore used in this study.

Experimental procedures

A light topography device (NIRS) with 31 channels (FOIRE-3000, Shimazu, Kyoto, Japan) was used to record brain blood flow by measuring oxidized hemoglobin (oxyHb). The 31 channels were placed on the forehead of participants, with 3-cm interchannel intervals, in accordance with the international 10/20 system used for electroencephalography (Fig. 1). The lower channels were positioned along the Fp1-Fp2 line (Fig. 1Aa). The participants wore an eye mask and sat in a dental chair in a quiet, dark room. Their heads were fixed in a chair head-holder. The experimental tasks were started after stable brain blood flow was recorded for a continuous period of 5 to 10 min.

Participants tasted the four different jelly samples (2.0 mL each), in random order. The experimental protocol, illustrated in Fig. 1B, was as follows: 20 s for resting, 5 s for sample ingestion, and swallowing within 60 s. During the task, participants were asked to consume the samples in one swallow, without chewing. This trial was repeated three times. Movement of laryngeal cartilage was visually observed, to detect swallowing.

Data analysis

NIRS data were obtained through a low-pass filter and were analyzed after being smoothed three times to eliminate motion artifacts with the Savitzky-Golay method. All data were stored on the hard disk of a personal computer system and analyzed offline. Baseline blood flow with oxyHb was calculated during the 20-s rest period before and after swallowing. Raw data from each channel were converted into a z-score, which was calculated by using the mean and standard deviation of oxyHb change during the 10-s rest periods before and after the task. The mean and standard deviation were then respectively transformed into z-scores of 0 and 1 in every

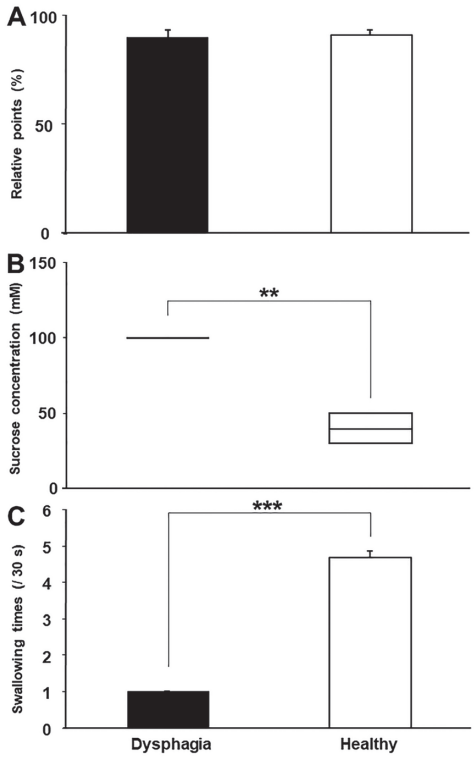

Fig. 2 Discrimination of flavor (A) and taste (B) and swallowing ability (C) in controls and dysphagia patients. A: Mean total discrimination score. Vertical bars indicate S.E.M. (n = 5 or 7); P = 0.831, t-test. B: Median sucrose discrimination threshold. P < 0.01 Mann-Whitney U test. C: Mean number of laryngeal cartilage movements during 30 s. Vertical bars indicate S.E.M. (n = 5 or 7). P < 0.001, t-test ***P < 0.001.

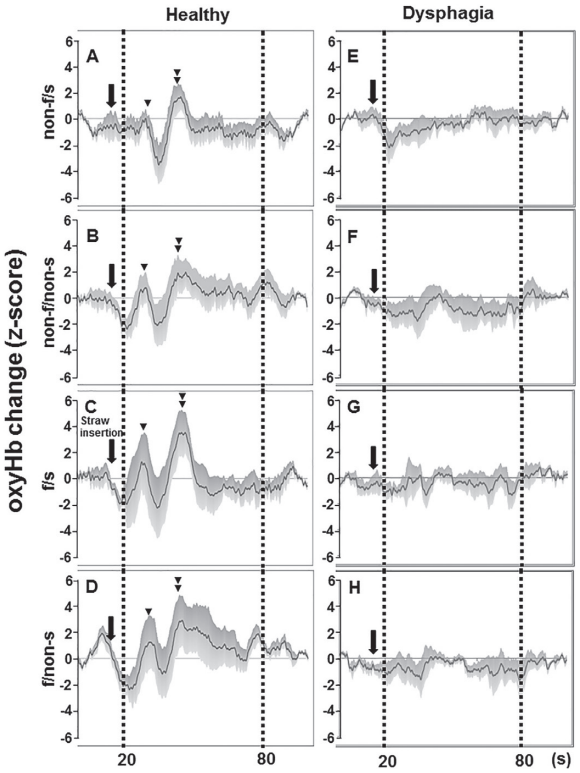

Fig. 3 Total change in oxyHb (z-score). A-D: Z-scores in healthy participants; E-H: Z-scores in dysphagia patients during swallowing of unflavored/sweetened jelly (A, E), unflavored/unsweetened jelly (B, F), flavored/sweetened jelly (C, G), and flavored/unsweetened jelly (D, H). Non-f/s: unflavored/sweetened jelly; non-f/non-s: unflavored/unsweetened jelly; f/s: flavored/sweetened jelly; and f/non-s: flavored/unsweetened jelly in this and the following Figures. Single and double arrowheads indicate early and late positive z-scores, respectively.

channel, by using the formula

$Z_i = \frac{x_i - \bar{x}}{s}$ (x_i: raw data, $\bar{x}$: average, S: standard deviation)

All z-scores across channels were averaged, and mean z-scores were compared between trials and between controls and dysphagia patients.

Statistical analysis

Data were analyzed with SPSS software (IBM, Tokyo, Japan). Statistical analyses were performed by Student's t-test for discrimination of flavor and swallowing frequency, and by Mann-Whitney U test for median sucrose discrimination threshold. Two-way ANOVA followed by the Tukey test was used to compare z-scores for swallowing of flavored/sweetened, unflavored/sweetened, flavored/unsweetened, and unflavored/unsweetened jelly samples in controls and dysphagia patients. A P value of less than 0.001 was considered to indicate statistical significance.

Results

Flavor, taste, and swallowing abilities in dysphagia patients

We studied flavor and taste perception and swallowing movement in controls and dysphagia patients. Ability to discriminate flavors did not differ between the controls and dysphagia patients (Fig. 2A); however, the sucrose detection threshold was significantly lower in the controls than in the dysphagia patients (Fig. 2B). In addition, swallowing frequency was significantly lower in dysphagia patients (Fig. 2C).

Total z-scores for tasks

Total z-score was calculated as the mean of z-scores recorded from each channel during each swallowing task. Next, large positive-negative-positive z-scores were recorded in controls during the swallowing tasks (Fig. 3A-D). Mean peak latencies for the two positive z-scores initiated at the start of the swallowing task were 10.2 ± 0.83 s and 26.0 ± 1.22 s (Fig. 3A-D) in healthy

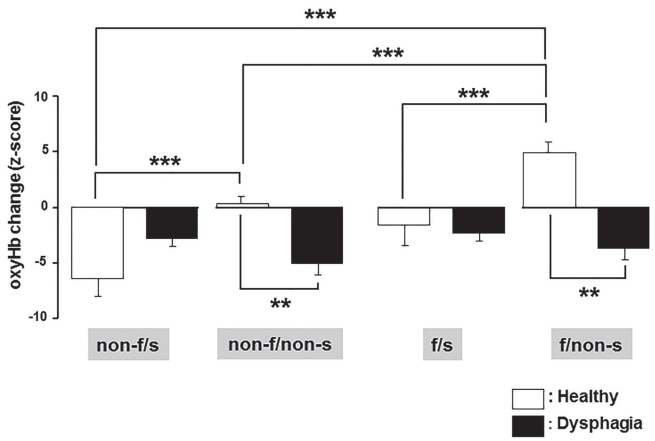

Fig. 4 Total change in oxyHb (z-score) during swallowing tasks in controls and dysphagia patients. $^{**}P < 0.01$, $^{***}P < 0.001$. Comparison of z-scores between trials. Vertical bars indicate S.E.M. Overall: $F(3,90) = 41.449$, $P < 0.0001$, two-way ANOVA; *post-hoc* Tukey test: $P < 0.001$: non-f/s jelly vs non-f/non-s jelly, $P < 0.001$: non-f/s jelly vs f/non-s jelly, $P < 0.001$: non-f/non-s jelly vs f/non-s jelly, $P < 0.001$: f/s jelly vs f/non-s jelly. Comparison of z-scores between dysphagia patients and controls. Vertical bars indicate S.E.M. Overall: $F(3,240) = 7.877$, $P < 0.0001$, two-way ANOVA; *post-hoc* Tukey test: $P < 0.01$ healthy vs dysphagia in non-f/non-s jelly, $P < 0.01$; healthy vs dysphagia in f/non-s jelly; $P < 0.01$.

participants. Conversely, small, irregular waves were recorded in patients with dysphagia during swallowing, Exact peak latencies could not be measured in dysphagia patients (Fig. 3E-H).

Comparison of z-scores

Z-scores for the controls differed after swallowing unflavored/unsweetened and flavored/sweetened jelly (Fig. 3B, C), but no such difference was seen in dysphagia patients. Moreover, total mean z-scores significantly differed for the controls during jelly swallowing (Fig. 4). Interestingly, total z-score showed a negative change during swallowing of sweetened jelly and a positive change during swallowing of unsweetened jelly (Fig. 4, unflavored/sweetened vs unflavored/unsweetened: −6.05 ± 1.47 vs 0.36 ± 0.10, $P < 0.001$; flavored/sweetened vs flavored/unsweetened: −1.67 ± 1.45 vs 4.76 ± 1.22, $P < 0.001$). Furthermore, total z-scores became positive during swallowing of flavored/unsweetened and unflavored/unsweetened jelly. These findings indicate that swallowing of flavored/sweetened jelly is associated with negative z-scores, whereas swallowing of unflavored/unsweetened jelly is associated with positive z-scores. In dysphagia patients, z-scores were negative during swallowing tasks, and mean z-scores did not significantly differ between tasks (Fig. 4, unflavored/sweetened: −2.66 ± 0.83; unflavored/unsweetened: −4.86 ± 1.17; flavored/sweetened: −2.29 ± 0.63; flavored/unsweetened: −3.54 ± 1.13). Moreover, total z-scores for swallowing of unflavored/unsweetened and flavored/unsweetened jelly were significantly lower in dysphagia patients than in the controls (Fig. 4).

Discussion

Flavor and taste perception and swallowing ability

Several of the present patients had dementia and complications of stroke, which are associated with hyposmia (11-13) and hypogeusia (14,15). To determine if participants had functional deficits in smell and taste, controls and dysphagia patients were asked to participate in a questionnaire flavor test and a test of the capacity to distinguish sweetness. The ability to discriminate flavors did not differ between these groups (Fig. 2A); however, the sucrose detection threshold was significantly lower in the controls (Fig. 2B). Further, the frequency of saliva swallowing within 30 s was significantly lower in dysphagia patients than in the controls (Fig. 2C).

Effects of flavor and taste on z-score

Change in oxyHb concentration is very sensitive to regional cerebral blood flow and strongly correlated with blood oxygenation level-dependent (BOLD) signals (16,17). Thus, we analyzed change in oxyHb, as it appears to be the best indicator of brain activity. This relationship suggests that the frontal cortical area, where positive z-scores were observed, is strongly activated during swallowing of unsweetened jelly. The prefrontal cortex is involved in emotional and psychological stress and in multiple cognitive functions (18-20). It is thought to be activated during initiation of a variety of motor actions, and prefrontal cortex activity is modified in association with these measures. We observed significant changes in total z-score during swallowing of flavored and/or sweetened jelly in healthy controls. Positive total z-scores were obtained during swallowing of flavored or unflavored/unsweetened jelly, which suggests that the prefrontal cortex is strongly activated during swallowing of unsweetened jelly. Furthermore, we noted early small and late large total z-score waves during swallowing in healthy participants but not in patients with dysphagia, which appears to be a unique feature of total z-score waves (Fig. 3). These two waves were observed within 30 s of the start of the swallowing task. This observation suggests that initiation of swallowing is associated with the onset of these waves. However, more-precise analysis is required in order to determine the exact function of these waves.

We used NIRS to measure hemodynamic responses in

the prefrontal cortex. Functional brain imaging is thought to reveal task-specific increases in human brain activity associated with various mental activities (21). Although traditional neuroimaging has focused on task-related signal increases related to neural activation, task-related signal decreases have not yet been thoroughly investigated (22). The origin of signal decreases has never been fully explained, and reasons other than neural inhibition have been suggested (21,23). Nevertheless, the exact meaning of increases and decreases in task-related signals is unclear.

We considered the importance of z-score differences in each group. Unfortunately, the present results do not reveal the mechanisms underlying z-score differences associated with flavor and taste differences in healthy participants. We hope to address these questions in future studies.

Clinical implications

We observed obvious changes in z-score amplitude patterns in healthy controls during swallowing of sweetened and unsweetened, and flavored and unflavored, jelly. These changes in z-score amplitude pattern differed between the controls and dysphagia patients. In all dysphagia patients, z-score patterns during jelly swallowing were irregular during swallowing of flavored and/or sweetened jelly.

Selection of an appropriate rehabilitation plan is important for improving swallowing movement in dysphagia patients. To select the optimal rehabilitation plan for dysphagia patients, rehabilitation effectiveness must be objectively evaluated for each patient. Total z-score and its distribution pattern might be useful in objectively evaluating whether flavored and/or sweetened food is appropriate for individual dysphagia patients.

Technical considerations

In this study, recording channels were placed on each participant's forehead, and oxyHb concentration was measured indirectly during jelly swallowing by using NIRS. Because the recording area was limited to the prefrontal cortex, it is difficult to collect direct evidence of functional interaction between swallowing and brain activity. In addition, the present data may include changes originating from several factors, including swallowing movement, flavor discrimination, and tasting. Therefore, change in z-score may reflect overall flavor- and taste-related modulation, as well as swallowing movement.

Furthermore, the ability to discriminate sweetness was lower in dysphagia patients than in the controls, and dysphagia patients were slightly older. These differences might explain discrepancies in prefrontal cortex activity. Future studies should investigate if these differences affect swallowing movement in dysphagia patients.

Functional MRI (fMRI) is frequently used to analyze human brain activity during mastication and swallowing (24-26) but is not always possible for persons with brain damage (27-29), as they may have difficulty communicating and participating in fMRI analysis (30,31). However, NIRS is a convenient method for evaluating brain activity in such patients (32-34). Furthermore, by detecting changes in blood hemoglobin concentrations associated with alterations in neural activity, NIRS can be used for noninvasive assessment of human brain function through the intact skull. NIRS instrumentation is also more portable than fMRI devices, thereby facilitating measurement of brain activity. However, NIRS cannot entirely replace fMRI because it can only be used to scan cortical tissues, whereas fMRI can be used to measure activity throughout the brain. NIRS can be used to map or image a particular area and can yield absolute quantitative data for a few specific points.

Acknowledgments

This study was supported in part by research grants from the Sato and Uemura Funds of Nihon University School of Dentistry and by JSPS KAKENHI (Grant-in-Aid for Young Scientists (B) #25861869). We thank O. Nakayama for preparing samples, and the Shiofune-en Nursing Home for the Aged for allowing us to analyze hospital patients.

Conflict of interest

The authors have no conflict of interest regarding the authorship or publication of this article.

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