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**Somatosensory evoked magnetic fields following tongue and hard palate
stimulation on the preferred chewing side**

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Abbreviations: aRMS, activated root-mean-square; BOLD, blood-oxygenation-level-dependent; ECDs, equivalent current dipoles; fMRI, functional magnetic resonance imaging; MEG, magnetoencephalography; PCS, preferred chewing side; SEFs, Somatosensory evoked fields; SEM, Standard error of the mean; SI, primary somatosensory cortex.

Abstract

Although oral sensory feedback is essential for mastication, whether the cortical activity elicited by oral stimulation is associated with the preferred chewing side (PCS) is unclear. Somatosensory evoked fields were measured in 12 healthy volunteers (6 with the right side as the PCS and 6 with the left side as the PCS) following tongue and hard palate stimulation. Three components were identified over the contralateral (P40m, P60m, and P80m) and ipsilateral [P40m(I), P60m(I), and P80m(I)] hemispheres. Since no component was consistently detected across subjects, we evaluated the cortical activity over each hemisphere using the activated root-mean-square (aRMS), which was the mean amplitude of the 18-channel RMS between 10 and 150 ms. For tongue stimulation, the aRMS for each hemisphere was 8.23 ± 1.55 (contralateral, mean $\pm$ SEM) and 4.67 ± 0.88 (ipsilateral) fT/cm for the PCS, and 5.11 ± 1.10 (contralateral) and 4.03 ± 0.82 (ipsilateral) fT/cm for the non-PCS. For palate stimulation, the aRMS was 5.35 ± 0.58 (contralateral) and 4.62 ± 0.67 (ipsilateral) fT/cm for the PCS, and 4.63 ± 0.56 (contralateral) and 4.14 ± 0.60 (ipsilateral) fT/cm for the non-PCS. For hard palate stimulation, the aRMS did not differ between the PCS and non-PCS, whereas for tongue stimulation, the contralateral hemisphere aRMS was significantly greater for the PCS than for the non-PCS. Thus, our results show that lateralized cortical activation was associated with the PCS for tongue, but not hard palate, stimulation; a potential

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1 reason for this may be the different sensory-inputs between these two areas, specifically
2 the presence or absence of fine motor function.

3

4 **Keywords:** magnetoencephalography; mastication; preferred chewing side; primary
5 somatosensory cortex; somatosensory evoked fields; somatosensory evoked potentials;
6 trigeminal nerve.

7

1. Introduction

The oral region is an important and sensitive anatomical structure that performs vital functions including mastication, vocalization, and breathing. Mastication is a sensorimotor activity that prepares food for swallowing. Although mastication can be bilateral, most people prefer one side of the mouth, known as the preferred chewing side (PCS) [1, 2]. Previous studies reported PCS effects on dental or facial parameters including occlusion, bite force, facial asymmetry, cusp form, or temporomandibular disorders [3–11]. However, little is known regarding whether the PCS is related to the central nervous system, especially cortical activity related to sensorimotor processing.

Using functional magnetic resonance imaging (fMRI), Shinagawa et al. [12] demonstrated that the intensity of the blood-oxygenation-level-dependent (BOLD) signal in the primary sensorimotor cortex was significantly greater in the hemisphere contralateral to the PCS during tongue movement. This finding suggests that chewing-related cortical activity is associated with the PCS. Although oral sensory feedback is essential for mastication [13, 14], limited information exists regarding whether cortical activity evoked with oral stimulation depends on the PCS.

A previous study reported that an asymmetric BOLD signal was observed in the primary somatosensory cortex (SI) between the PCS and non-PCS with mechanical

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1 tongue stimulation [15]. This is interesting given the unique characteristics of the
2 tongue. The tongue serves an investigatory motor function and receives “active touch”
3 sensory input during mastication. Active touch refers to the physical act of “touching”
4 [16]. This type of sensory input can be differentiated from “passive touch,” or the
5 passive act of being touched, which is associated with the hard palate in the oral region.

6 Sensory feedback from the hard palate plays an important role in mastication
7 along with the tongue, as the tongue and hard palate contact each other constantly
8 during mastication. However, the peripheral sensory input mechanism that provides the
9 sensory feedback is different for the tongue and hard palate. The principle difference in
10 sensory perception between these two areas is related to the presence or absence of fine
11 motor function. The hard palate has no motor function and receives “passive touch”
12 sensory input. However, it is unknown whether the hard palate is associated with a
13 lateralized cortical response specific for the PCS.

14 The objective of the present study was to investigate the effect of PCS on
15 evoked responses in the SI following tongue and hard palate stimulation using
16 magnetoencephalography (MEG). We used MEG to record evoked cortical activation
17 following trigeminal nerve stimulation since it offers adequate spatial accuracy while
18 maintaining excellent temporal resolution [17, 18].

2. Methods

2.1. Subjects

We studied 16 healthy volunteers (13 men and 3 women; age, 23–39 years; mean age, 28.8 years) with no history of neurological illness, orthodontic treatment, or either acute or chronic pain in the orofacial area. Participants were right-handed, as determined by the Edinburgh Handedness Inventory [19].

2.2. Ethics Statement

Written informed consent was obtained from all participants before the study; the study protocol was approved by the Hokkaido University Hospital Ethical Committee.

2.3. Determination of the PCS

The PCS was evaluated using 3 methods. First, we determined the first stroke of the chewing cycle. A piece of tasteless paraffin gum (GC, Tokyo, Japan) was placed on the center of the tongue, and the side to which the tongue moved the gum in the first chewing stroke was considered the PCS [10, 20]. Second, we determined the primary

chewing side during free mastication, by recording subjects on video (Canon, Tokyo, Japan) while they chewed paraffin gum freely for 2 min. The video was reviewed at a reduced speed, and after 1 min, the number of chewing strokes for each side was counted for 1 min. The side with the most strokes was considered the PCS. Lastly, we asked each subject which side they preferred [21].

When all 3 methods indicated the same PCS, that side was judged as the “evident PCS.” In 6 participants, it was the right side, and in 6 participants, it was the left side. The PCS in the remaining 4 participants could not be determined; therefore, they were excluded from the MEG recording session.

2.4. Stimulation of the tongue and hard palate

The stimulus was applied unilaterally on both sides of the tongue and hard palate using an electrical stimulator (SEN-3401, Nihon Kohden, Tokyo, Japan). We used a pair of pin electrodes (400- μ m diameter) with an inter-electrode distance of 3 mm for stimulation because they can safely deliver a low intensity stimulus to a small oral region [22–24]. The electrodes were affixed using adhesive tape. Tongue stimulation was applied 1 cm from the edge of the tongue, 3–4 cm from the tongue tip. For the hard palate, the stimulus was applied to the mucosa around the greater palatine

foramen [25]. We confirmed through self-reports that electrical stimulation occurred only at the stimulation site. During hard palate stimulation, subjects did not report sensations in the teeth or gums. The stimulus consisted of square, biphasic, constant current electric pulses (0.5 ms for 1 phase) applied at 1 Hz. The intensity at each stimulus site was set to 3 times the sensory threshold for that site. On average, stimulation was applied 600 times before stimulating the other side of the tongue or hard palate. The order in which stimulus sites and stimulus sides were selected was counterbalanced across subjects. To monitor subjects' alertness during the recording, the subjects were interviewed about their vigilance level before and after each recording session.

2.5. MEG recordings

Somatosensory evoked fields (SEFs) were recorded with a whole-head neuromagnetometer (VectorView, Elekta Neuromag, Helsinki, Finland) equipped with 204 planar gradiometers. The recording passband was 0.1–330 Hz and the sampling rate was 997 Hz. The analysis window for averaging was from 100 ms before to 500 ms after each trigger signal. The baseline was calculated from -50 to -5 ms before stimulus onset.

To visualize the locations of MEG sources, MRI scans of the head were obtained from all subjects with a Signa Echo-Speed 1.5-Tesla system (General Electric, Milwaukee, WI, USA).

2.6. Data analysis

We defined a response as the period when the signal exceeded 2 standard deviations (SD) of the baseline activity for at least 10 ms. The peak latency was measured from the channel showing the maximal signal over each hemisphere.

Isocontour maps were constructed at the selected time points. The digitized shape of each subject's head was fitted using a simple spherical head model. The sources of the magnetic fields were modeled as equivalent current dipoles (ECDs) whose location was estimated from the measured magnetic waveforms. We accepted only ECDs attaining 90% goodness-of-fit and a confidence volume smaller than 1000 mm³.

To estimate the cortical activation in each hemisphere, we used the activated root-mean-square (aRMS), as was used in our previous studies [22, 23]. First, we calculated the spatial summation of the RMS from the 18-channel waveforms, including the maximum amplitude channel over both hemispheres separately. Second, we

1 calculated the amplitude of the RMS between 10 and 150 ms (RMS[10,150]) and

2 subtracted the value of the baseline period (RMS[-50,-5]) to obtain the aRMS.

3 To judge the effect of head location on the laterality of the aRMS following tongue
4 and hard palate stimulation, distances between the head origin and ECD locations were
5 compared at the peak latency of the maximum magnitude component over the contralateral
6 hemisphere.

7 Data are expressed as the mean $\pm$ the standard error of the mean (SEM).

8 Differences in the sensory threshold between PCS and non-PCS stimulation were
9 examined for the tongue and hard palate data using the Wilcoxon signed-rank test.

10 Differences in the aRMS for each (contralateral and ipsilateral) hemisphere following
11 PCS and non-PCS stimulation were confirmed with the Friedman test and the Wilcoxon
12 signed-rank test with Bonferroni correction. The laterality between PCS and non-PCS
13 stimulation was checked using the Wilcoxon signed-rank test for the distance from the
14 head origin to the ECD location. The significance level was $p < 0.05$.

15

16 **3. Results**

17 *3.1. Sensory threshold*

We did not observe a significant difference in the sensory threshold between PCS (0.296 ± 0.037 mA) and non-PCS (0.300 ± 0.033 mA) tongue stimulation ($p = 0.914$), or between PCS (0.248 ± 0.022 mA) and non-PCS (0.229 ± 0.032 mA) hard palate stimulation ($p = 0.345$).

3.2. SEFs by tongue and hard palate stimulation

Clear responses were detected over the bilateral hemispheres in all participants. When the right side of the tongue was stimulated, a deflection was observed over the contralateral hemisphere (P80m) and over the ipsilateral hemisphere [P80m(I)] in a representative subject (subject 11; Fig. 1). In several other subjects, 4 additional components, P40m, P40m(I), P60m, and P60m(I) were identified; however, these components were not observed in subject 11 (Table 1).

The isofield contour maps of each component showed a dipolar pattern for the tongue and hard palate (Fig. 2a). Estimating the ECDs, the directions of ECDs were similarly posterior in all components. ECDs were all located around the lower part of the central sulcus for the tongue and hard palate (Fig. 2b).

The distance between the head origins and the dipole location following tongue stimulation of the PCS was 62.9 ± 1.8 mm, while the distance following stimulation of the

non-PCS was 61.3 ± 1.7 mm. The distance between the head origins and dipole for hard palate stimulation of the PCS was 63.8 ± 1.6 mm, while the distance for stimulation of the non-PCS was 64.1 ± 1.5 mm. No significant difference was observed between PCS and non-PCS stimulation for either the tongue ($p = 0.32$) or the hard palate ($p = 0.81$).

3.3. *aRMS for the tongue and hard palate*

RMS waveforms for tongue stimulation in a representative subject (subject 11) are shown in Figure 3a. The RMS waveforms were variable across subjects (Fig. 4). The aRMS calculated from the contralateral and ipsilateral hemispheres were 8.23 ± 1.55 and 4.67 ± 0.88 fT/cm for the PCS, and 5.11 ± 1.10 and 4.03 ± 0.82 fT/cm for the non-PCS, respectively (Fig. 5). RMS waveforms for hard palate stimulation in a representative subject (subject 11) are shown in Figure 3b. For palate stimulation, the aRMS for the contralateral and ipsilateral hemispheres were 5.35 ± 0.58 and 4.62 ± 0.67 fT/cm for the PCS, and 4.63 ± 0.56 and 4.14 ± 0.60 fT/cm for the non-PCS, respectively (Fig. 5). The Friedman test revealed a significant main effect for aRMS of the tongue ($p = 0.001$). The Wilcoxon signed-rank test with Bonferroni correction on the responses to tongue stimulation revealed a significant difference in the aRMS between the PCS and non-PCS in the contralateral hemisphere ($p = 0.005$), and between the aRMS for the

PCS in the contralateral hemisphere and the aRMS for the non-PCS in the ipsilateral hemisphere ($p = 0.003$). The Friedman test on the responses to hard palate stimulation revealed no significant differences in aRMS ($p = 0.368$).

4. Discussion

We demonstrated that PCS stimulation produced different SEFs in response to tongue and hard palate stimulation. Specifically, hemispheric cortical activation was associated with the PCS for tongue stimulation, but not for hard palate stimulation.

Previous trigeminal SEF studies have not shown lateralized responses to stimulation of the right and left sides of the lip [17, 24, 26] and tongue [22, 27]. However, there are no reports regarding the difference in trigeminal SEFs relative to PCS and non-PCS stimulation. In our study, tongue stimulation of the PCS resulted in SEFs that were larger in amplitude than those elicited by non-PCS stimulation. This result is consistent with a previous fMRI study [15] in which the BOLD signal derived from the contralateral SI evoked with PCS stimulation was significantly greater than that evoked with non-PCS stimulation. However, only right-side PCS stimulation was examined in that study. Here, PCS stimulation was divided evenly between the right and

left sides; we observed that cortical activation evoked by tongue stimulation was dependent on the PCS.

Cortical representations can be altered in association with changes in peripheral sensory input. For example, subjects who play string instruments reportedly have a larger representation in the SI of the left digits than of the right digits, and the strength of the cortical representation of the fingering left digits was correlated with how long the subject had been playing the string instrument [28]. This result suggests that reorganization in the SI occurs in accordance with the use of each peripheral region. Thus, increased tongue SEFs for the PCS may be due to the use-dependent enlargement of the cortical reorganization in the SI of the tongue region.

However, in the present study, the laterality of SEFs was not associated with the PCS for hard palate stimulation. The data obtained in this study do not provide a clear explanation for this finding. However, one explanation may be related to the different mechanisms of sensory input between the tongue and hard palate, specifically the presence or absence of motor function. The tongue receives “active touch” sensory input during mastication, whereas the hard palate receives “passive touch” sensory input. It has been previously reported by Gibson [16] that there are differences in how active touch and passive touch are perceived. In active touch, a person touching someone or

1 something produces an objective and environmentally external impression of the person
2 or object that is being touched. This is in contrast to passive touch, in which items
3 touching an individual evoke a distinctly different subjective percept that is more of an
4 internal sensation confined to oneself rather than to the environment. This internal
5 sensation is riveting and has a sense of immediacy not found in active touch [29]. A
6 recent fMRI study on texture perception revealed greater activation in the contralateral
7 SI during active touch than during passive touch [30]. This result suggests that active
8 and passive touch have different effects on the processing of sensory information in the
9 SI. Since the peripheral sensory inputs for active touch have a stronger influence on
10 cortical activation in the SI than passive touch, changes in the cortical representations of
11 the tongue region may be more remarkable than the changes in the representations of
12 the hard palate region. Thus, the effect of side differences between the PCS and
13 non-PCS may be significant for tongue SEFs, but not for hard palate SEFs.

14 Some previous studies reported that the asymmetry in handedness is reflected
15 in the SI [31–33], but other studies reported symmetrical cortical representations related
16 to handedness [34, 35]. The main reason for this discrepancy may be due to the
17 specificity of the handedness. Handedness is more often an effect of social learning and
18 peripheral factors than other peripheral side preferences such as footedness, eyedness,

and earedness [36]. For example, left-handed people were often encouraged to switch to being right-handed. In fact, it has been suggested that the PCS is positively correlated with footedness, eyedness, and earedness, but is less related to handedness [10]. The effect of social factors on handedness may make it difficult to evaluate the cortical representations related to handedness. On the other hand, given the lack of social influences on the PCS, this may allow for easier detection of changes in the cortical representations related to the PCS.

P40m, the first recognizable component in this study, was detected over both hemispheres. A previous study demonstrated that the initial component of the tongue SEFs by electric stimulation had an anteriorly directed current with a peak latency of around 19 ms [37]. Thus, P40m, which has a posteriorly directed current, does not represent the initial component of tongue SEFs. Since none of the components was detected consistently across subjects, we could not adopt them as reliable parameters for assessing cortical activity. Instead, we employed the aRMS parameter following previous studies [22, 23], which is calculated by a 2-step analysis using spatial and temporal summation. The RMS analysis is advantageous because it allows us to use multi-generator sources. In fact, we failed to identify a single reliable dipole for the activity around the tongue region within the SI [22]. However, RMS analyses also have

disadvantages since the RMS is affected by the distance between the head's location and MEG sensors, which might differ between hemispheres. Since we did not find any hemispheric differences in the distance between the head origins and dipole locations, we could ignore the significant effect from the relative ECD location between hemispheres assuming that the head surface of the subjects was fitted adequately and closely to the MEG helmet.

In conclusion, the effect of PCS on cortical activation was different between the tongue and hard palate. Asymmetrical cortical activation was observed with regard to the PCS in the tongue, but not in the hard palate.

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Conflicts of interest

None of the authors has any conflicts of interest in relation to this work.

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11

1 Table 1. Somatosensory evoked field latencies for the tongue and hard palate

Tongue						
Contra.	P40m		P60m		P80m	
	n	Latency (ms)	n	Latency (ms)	n	Latency (ms)
PCS stim.	6	42.6 ± 1.9	6	62.7 ± 2.4	6	84.0 ± 1.4
Non-PCS stim.	4	46.3 ± 1.4	4	67.0 ± 2.3	6	82.8 ± 4.2
Ipsi.	P40m(I)		P60m(I)		P80m(I)	
	n	Latency (ms)	n	Latency (ms)	n	Latency (ms)
PCS stim.	3	47.0 ± 1.5	6	63.0 ± 1.2	6	90.7 ± 4.0
Non-PCS stim.	3	40.7 ± 3.7	7	61.4 ± 2.3	4	84.4 ± 5.5
Hard palate						
Contra.	P40m		P60m		P80m	
	n	Latency (ms)	n	Latency (ms)	n	Latency (ms)
PCS stim.	6	38.2 ± 0.9	7	60.4 ± 2.3	4	87.3 ± 2.7
Non-PCS stim.	6	40.5 ± 2.0	7	62.6 ± 2.1	4	88.3 ± 6.0
Ipsi.	P40m(I)		P60m(I)		P80m(I)	
	n	Latency (ms)	n	Latency (ms)	n	Latency (ms)
PCS stim.	7	42.1 ± 2.3	5	58.8 ± 2.1	5	84.0 ± 5.9
Non-PCS stim.	3	42.0 ± 3.8	7	60.0 ± 1.3	4	83.8 ± 5.5

- 2 Contra., Contralateral hemisphere; Ipsi., Ipsilateral hemisphere; PCS stim., Preferred
- 3 chewing side stimulation; Non-PCS stim., Non-preferred chewing side stimulation
- 4

Figure legends

Figure 1. Whole-head magnetic waveforms of somatosensory evoked fields (SEFs) elicited by tongue stimulation of the preferred chewing side (PCS; right side) in a representative subject (subject 11). **(a)** The top view of the SEFs recorded by the planar 204-channel recording shows clear responses over the parietotemporal areas bilaterally. Root-mean-square waveforms (shown in Fig. 3.) were calculated from the 18-channel waveforms (traces within dashed outlines), including the maximum amplitude channel over both hemispheres separately. Each trace started 50 ms before and ended 300 ms after stimulus onset. **(b, c)** Traces in circles from (a) have been enlarged to highlight the component that was identified in the maximum amplitude channels over the contralateral (b) and ipsilateral (c) hemispheres.

Figure 2. Isocontour map and dipole location following right-side tongue stimulation in a representative subject (subject 11). **(a)** The contour map was obtained from P80m component. The contour steps are 20 fT. Red and blue lines indicate outgoing and incoming magnetic fluxes, respectively. Green arrows show the location and direction of equivalent current dipole (ECD) projected on the skull surface producing the somatosensory evoked field distribution. Arrowheads indicate the negative pole of the ECD. The direction of ECD is posterior. **(b)** ECD was superimposed on the slices of magnetic resonance images (first 2 panels) and surface rendering image (last panel) of the subject. ECD was located in the lateral part of the central sulcus.

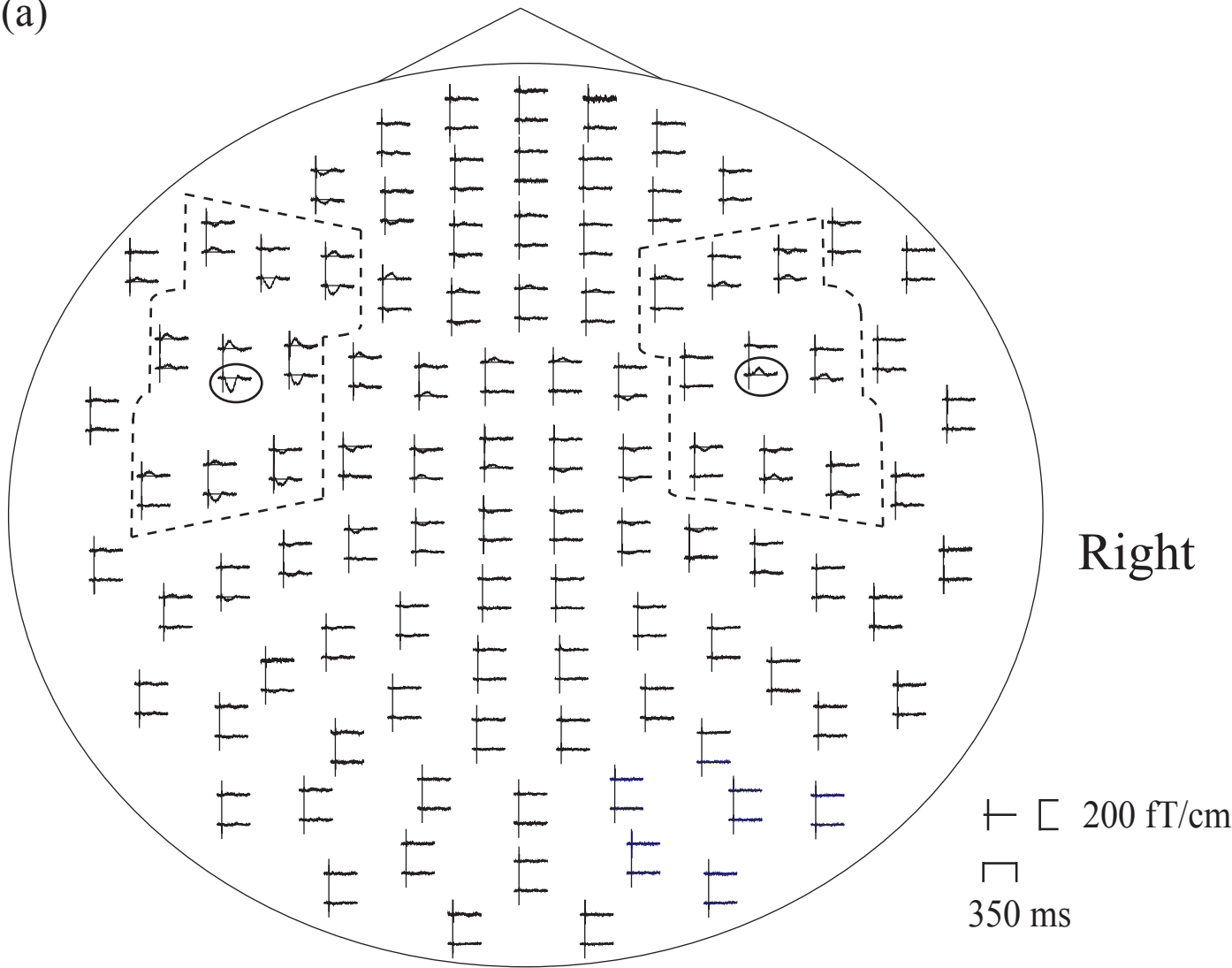
Figure 3. The root-mean-square (RMS) waveforms for tongue and hard palate stimulation in a representative subject (subject 11). The vertical scale was 50 fT/cm.

The 2 dashed lines in each figure show the time points of 10 and 150 ms. **(a)** With tongue stimulation, the amplitude of the RMS waveform in the contralateral hemisphere with preferred chewing side (PCS) stimulation was larger than that for non-PCS stimulation. **(b)** No clear differences in RMS amplitude were observed between PCS and non-PCS hard palate stimulation. stim., stimulation; contra., contralateral; ipsi., ipsilateral.

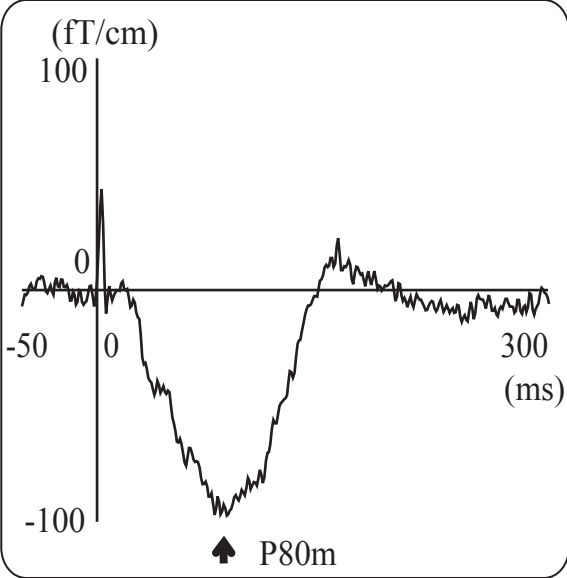
Figure 4. The root-mean-square (RMS) waveforms with tongue stimulation in 4 subjects (subjects 2, 4, 5, and 10). The vertical scale is 40 fT/cm. The two dashed lines in each figure show the time points of 10 and 150 ms. RMS waveforms were variable across subjects. PCS, preferred chewing side; stim., stimulation; contra., contralateral; ipsi., ipsilateral.

Figure 5. The activated root-mean-square (aRMS) value for both hemispheres with tongue and hard palate stimulation. Although no significant differences in aRMS were observed between preferred chewing side (PCS) and non-PCS stimulation of the hard palate, the aRMS of the contralateral hemisphere with PCS stimulation was significantly larger than that for non-PCS stimulation of the tongue. stim., stimulation; contra., contralateral; ipsi., ipsilateral; NS, not significant; $*p < 0.05$; error bars indicate standard deviation.

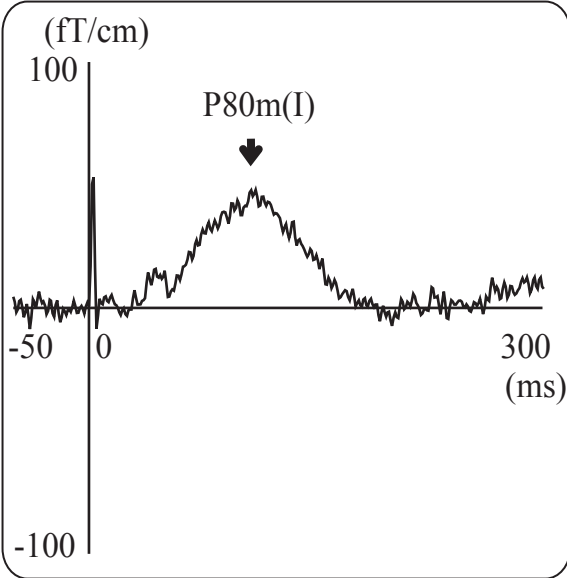
(a)



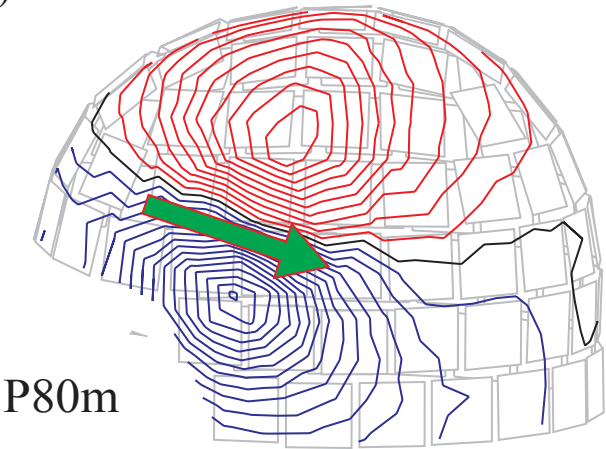
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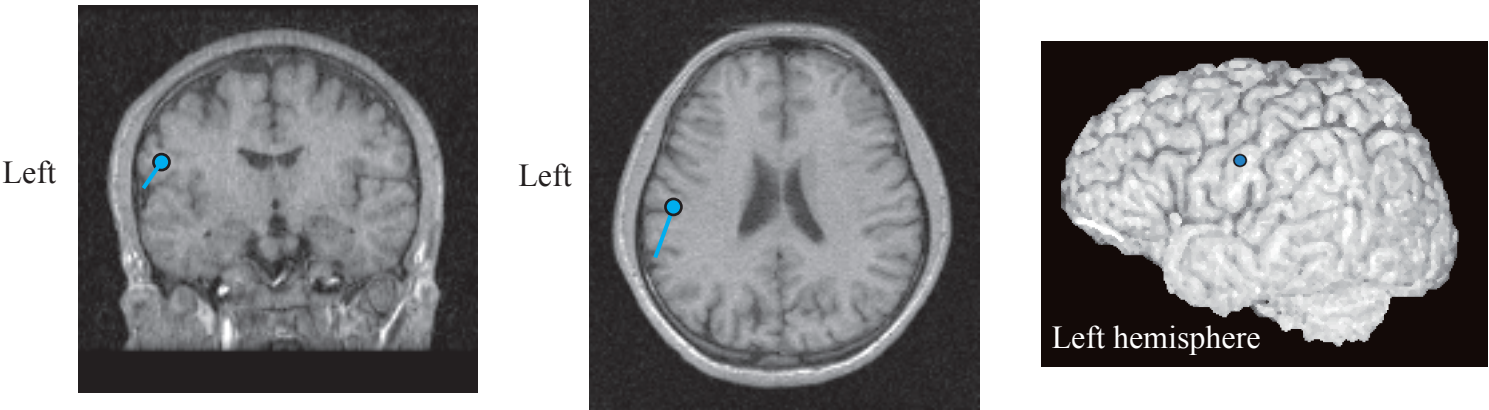
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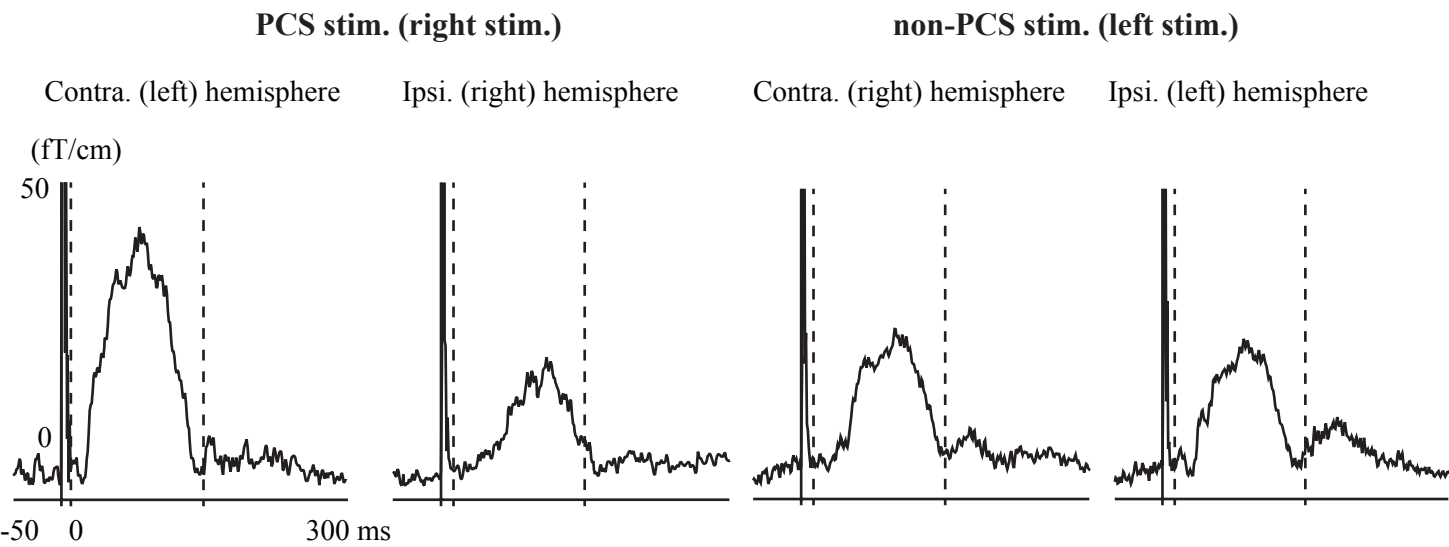
(a)



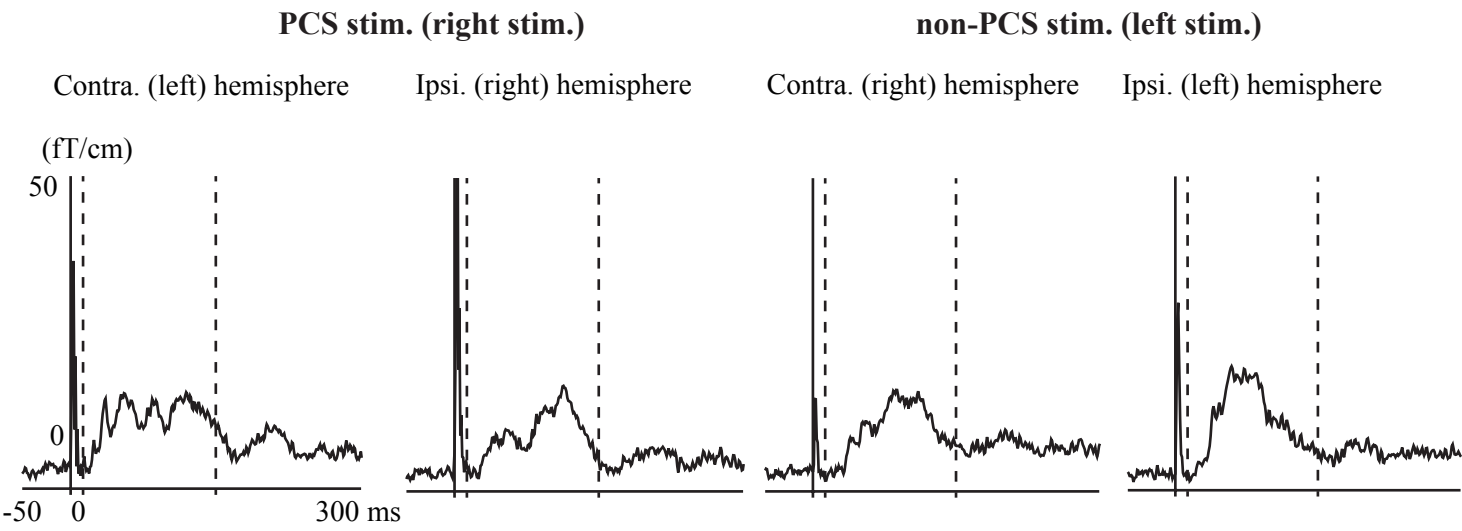
(b)



(a) Tongue

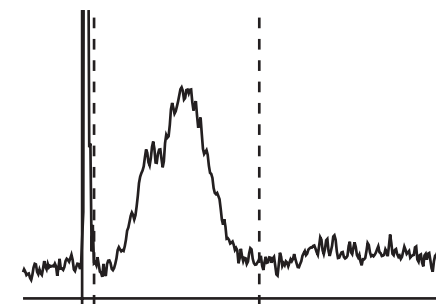
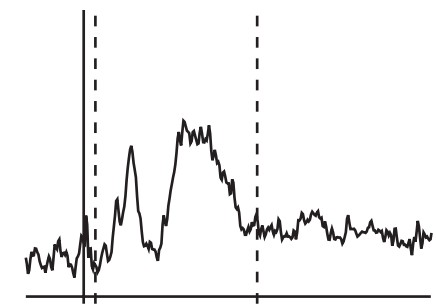
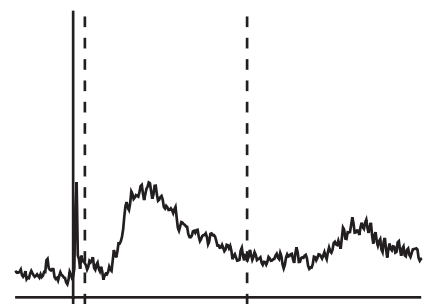
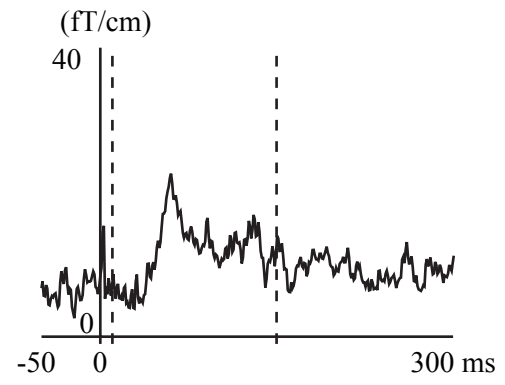


(b) Palate

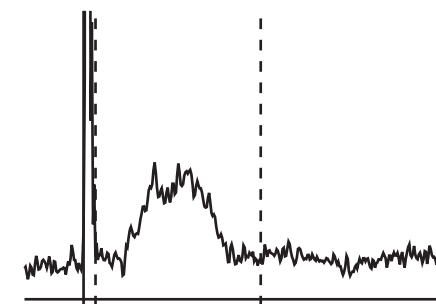
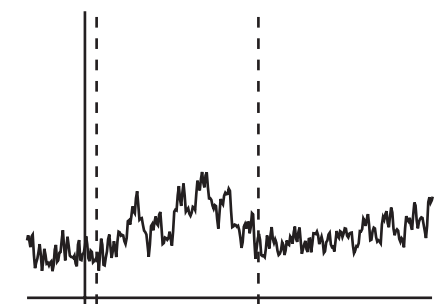
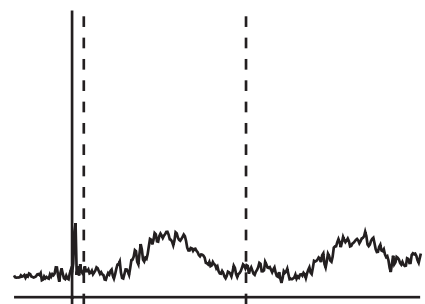
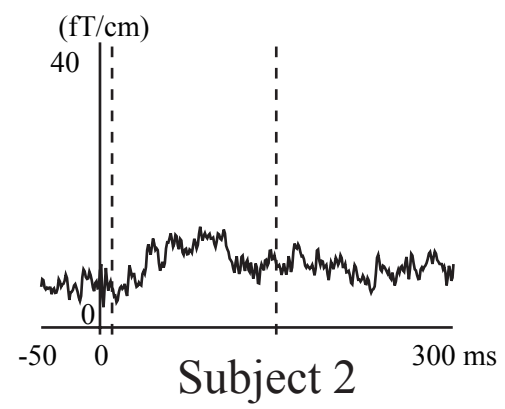


PCS stim.

Contra.



Ipsi.



Subject 2

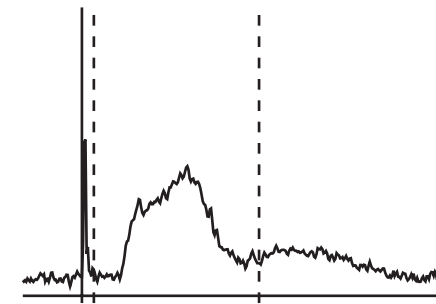
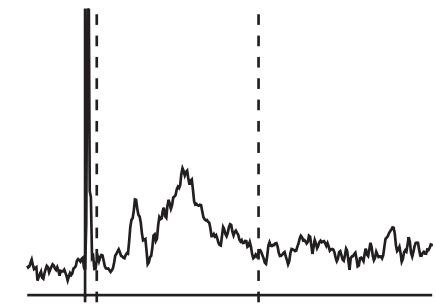
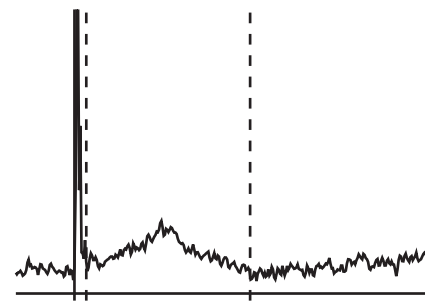
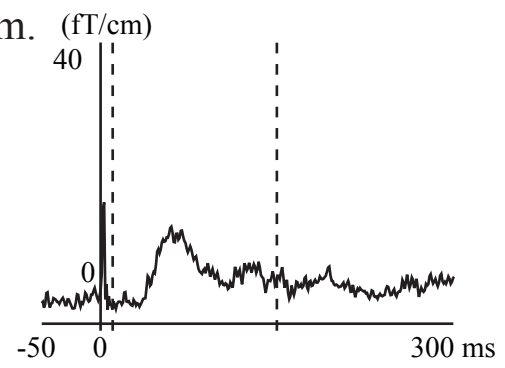
Subject 4

Subject 5

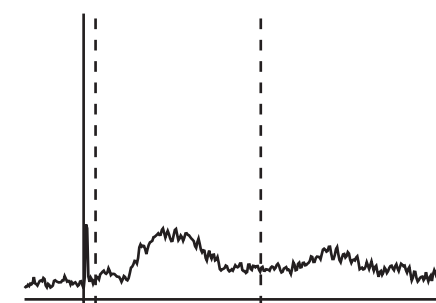
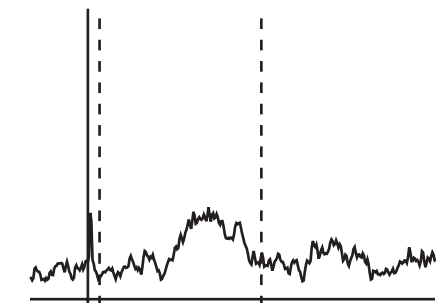
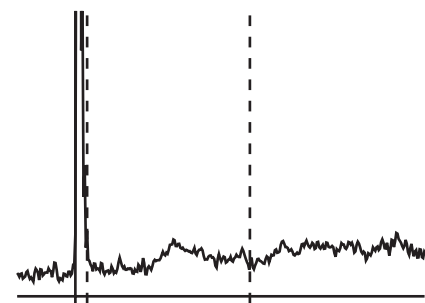
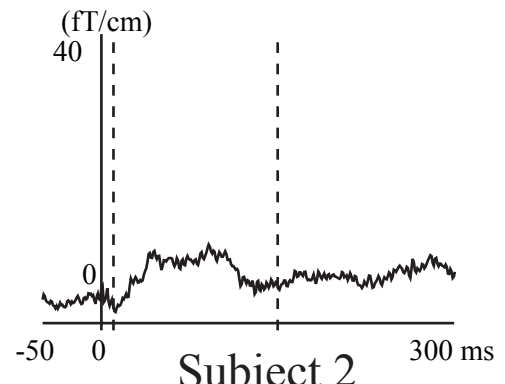
Subject 10

Non-PCS stim.

Contra.



Ipsi.



Subject 2

Subject 4

Subject 5

Subject 10

aRMS of the tongue and hard palate

