<table>
<thead>
<tr>
<th>Title</th>
<th>Contralateral dominance of corticomuscular coherence for both sides of the tongue during human tongue protrusion: An MEG study.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author(s)</td>
<td>Maezawa, Hitoshi; Mima, Tatsuya; Yazawa, Shogo; Matsuhashi, Masao; Shiraishi, Hideaki; Hirai, Yoshiyuki; Funahashi, Makoto</td>
</tr>
<tr>
<td>Citation</td>
<td>NeuroImage, 101: 245-255</td>
</tr>
<tr>
<td>Issue Date</td>
<td>2014-11-01</td>
</tr>
<tr>
<td>DOI</td>
<td></td>
</tr>
<tr>
<td>Doc URL</td>
<td><a href="http://hdl.handle.net/2115/57676">http://hdl.handle.net/2115/57676</a></td>
</tr>
<tr>
<td>Type</td>
<td>article (author version)</td>
</tr>
<tr>
<td>Additional Information</td>
<td></td>
</tr>
<tr>
<td>File Information</td>
<td>Manuscript.pdf</td>
</tr>
</tbody>
</table>

Hokkaido University Collection of Scholarly and Academic Papers: HUSCAP
Contralateral dominance of corticomuscular coherence for both sides of the tongue during human tongue protrusion: An MEG study

Hitoshi Maezawa a, Tatsuya Mima b, Shogo Yazawa c, Masao Matsuhashi b, Hideaki Shiraishi d, Yoshiyuki Hirai a, Makoto Funahashi a

a Department of Oral Physiology, Graduate School of Dental Medicine, Hokkaido University, Kita-ku, Sapporo 060-8586, Japan
b Human Brain Research Center, Graduate School of Medicine, Kyoto University, Sakyo-ku, Kyoto 606-8507, Japan
c Department of Systems Neuroscience, School of Medicine, Sapporo Medical University, Chuo-ku, Sapporo 060-8556, Japan
d Department of Pediatrics, Graduate School of Medicine, Hokkaido University, Kita-ku, Sapporo 060-8638, Japan

Tables: 3
Figures: 5

Corresponding author: Hitoshi Maezawa, DDS, PhD
Address: Department of Oral Physiology, Graduate School of Dental Medicine, Hokkaido University, Kita-ku, Sapporo, Hokkaido, 060-8586, Japan
TEL: 81-11-706-4229; FAX: 81-11-706-4229
E-mail: maezawa@den.hokudai.ac.jp

Abbreviations: ANOVA, Analyses of variance; APB, Abductor pollicis brevis; ECDs, Equivalent current dipoles; EMG, Electromyography; MEG, Magnetoencephalography; MEPs, Motor-evoked potentials; MRFs, Movement-related magnetic fields; MRI, Magnetic resonance images; MRPs, Movement-related potentials; SD, Standard deviation; SEM, Standard error of the mean; TMS, Transcranial magnetic stimulation.
Abstract

Sophisticated tongue movements contribute to speech and mastication. These movements are regulated by communication between the bilateral cortex and each tongue side. The functional connection between the cortex and tongue was investigated using oscillatory interactions between whole-head magnetoencephalographic (MEG) signals and electromyographic (EMG) signals from both tongue sides during human tongue protrusion compared to thumb data. MEG-EMG coherence was observed at 14–36 Hz and 2–10 Hz over both hemispheres for each tongue side. EMG-EMG coherence between tongue sides was also detected at the same frequency bands. Thumb coherence was detected at 15–33 Hz over the contralateral hemisphere. Tongue coherence at 14–36 Hz was larger over the contralateral vs. ipsilateral hemisphere for both tongue sides. Tongue cortical sources were located in the lower part of the central sulcus and were anterior and inferior to the thumb areas, agreeing with the classical homunculus. Cross-correlogram analysis showed the MEG signal preceded the EMG signal. The cortex-tongue time lag was shorter than the cortex-thumb time lag. The cortex-muscle time lag decreased systematically with distance. These results suggest that during tongue protrusions, descending motor commands are modulated by bilateral cortical oscillations, and each tongue side is dominated by the contralateral hemisphere.

Keywords: hypoglossal motor nucleus, isometric muscle contraction, magnetoencephalography, neural oscillation, primary motor cortex
1. Introduction

Fine tongue movements are important for speech articulation, mastication, swallowing, and airway patency. For example, the tongue’s role in speech articulation requires coordinated movement with the vocal cords, soft palate, lips, and teeth. These highly controlled movements are regulated by intricate communication between the sensorimotor cortex and muscles. This communication is partly oscillatory, which is reflected in the rhythmic interactions between the cortex and muscles (Mima and Hallett 1999).

Previous magnetoencephalographic (MEG) studies (Conway et al., 1995; Salenius et al., 1996, 1997; Brown et al., 1998), as well as electroencephalographic studies (Halliday et al., 1998; Mima et al., 2000), showed that oscillatory activity at 15–35 Hz in the primary motor cortex is coherence to electromyographic (EMG) activity in the contralateral hand and forearm muscles during isometric contractions. The maximum coherence activity recorded from the contralateral primary motor cortex revealed a somatotopic organization that was dependent on the body part in which EMG activity was recorded (Murayama et al., 2001). However, in spite of the fact that rhythmic interactions may contribute to sophisticated tongue movements, little is known about corticomuscular synchronization during isometric tongue protrusion in humans.

The tongue has three unique characteristics compared to limb muscles; first, the tongue receives innervation from both hypoglossal nerves. Penfield and Rasmussen (1950) first investigated the somatotopic representation of the tongue in the human primary motor cortex by directly stimulating the cortex during epilepsy surgery. In their study, the tongue representation was located bilaterally and was inferior to the hand and foot representations. Thus, oscillatory activity may also be recorded in both

Maezawa et al.
hemispheres during tongue protrusion at cortical regions that are more inferior than the regions showing oscillatory activity during finger contraction. Second, skilled tongue movements may be accurately regulated by descending motor commands from the bilateral primary motor cortex to both sides of the tongue. However, it is not known whether hemispheric dominance and tongue-side differences exist for the functional connection between the cortex and tongue during human tongue protrusion. It is important to investigate the hemispheric dominance of the tongue region in the human motor cortex, since sophisticated tongue movements may be controlled by higher human brain functions, such as by Broca’s region for speech production. Third, the tongue is located on the midline of the body. Marsden et al. (1999) reported that the low-frequency band played an important role in axial muscles, allowing them to act as a functional whole during postural control. Thus, such oscillatory synchronization at a low frequency may also play a role in tongue maintenance. Furthermore, the time lag between the cortex and tongue may decrease systematically with a decrease in corticomuscular distance compared to the time lag between the cortex and limbs.

The objective of this study was to investigate the functional connection between both cortical hemispheres and each side of the tongue during human tongue protrusion, using a whole-head MEG machine. This study aimed to identify hemispheric and tongue-side differences in coherence, time lags between the cortex and tongue, and cortical representations of the tongue muscles during tongue protrusion by comparing these data with data recorded during bilateral thumb contractions.

2. Materials and Methods

2.1. Subjects

Maezawa et al.
Fifteen right-handed healthy volunteers (11 men, 4 women; aged 21–35 years; mean age, 27.4 years) were studied. None of the subjects had a history of neurological or psychiatric disorders. Written informed consent was obtained from all subjects before they were included in the study, in accordance with the study protocol approved by the Ethical Committee of Dental Medicine of Hokkaido University.

### 2.2. Tasks for EMG Recording

The subjects performed a task requiring weak and sustained protrusions (20%–30% of maximal strength of a subjective scale) of their tongue. These tongue movements were performed with their mouth slightly open and without the tongue touching the lips. Subjects performed the tongue protrusion task for approximately 10–15 min, with a 30-s rest period interleaved between 2-min recording periods. For the dorsum of the tongue muscles, bipolar surface EMG activity was recorded bilaterally and simultaneously using pairs of disposable EMG electrodes (Vitrode V, Nihon Kohden, Tokyo, Japan). To confirm that the temporal and/or masseter muscles were inactive during tongue protrusion, EMG activity was recorded bilaterally and simultaneously from the temporal and masseter muscles during the tongue protrusion task in the first 5 subjects. We did not detect EMG contamination from the temporal or masseter muscles during tongue protrusion in these subjects; therefore, EMG activity from these muscles (temporal and masseter muscles) was not recorded in the remaining subjects.

For comparison, the coherence was calculated with the bipolar surface EMG activity recorded during isometric thumb contractions of the bilateral abductor pollicis brevis (APB) muscles that were performed in a separate session. In this task, subjects achieved weak, tonic contractions (20%–30% of maximal strength of a subjective scale) of the
right and left sides of the APB for approximately 10–15 min, with a 30-s rest period interleaved between 2-min recording periods. The testing order between the tongue and thumb was counterbalanced among subjects.

2.3. MEG and EMG Recordings

Neuromagnetic signals were measured with a helmet-shaped 306-channel apparatus (VectorView, Elekta Neuromag, Helsinki, Finland) in a magnetically shielded room and were recorded simultaneously with surface EMG recordings. This device had 102 trios that were composed of a magnetometer and a pair of planar gradiometers oriented orthogonally. Only 204 planar gradiometers were used for analysis, detecting the largest signal above the corresponding generator source (Hämäläinen et al., 1993). MEG and EMG signals were recorded with a bandpass filter of 0.1–300 Hz and digitized at 997 Hz. The exact position of the head with respect to the sensor array was determined by measuring the magnetic signals from 4 indicator coils placed on the scalp. The coil locations, as well as 3 predetermined landmarks on the skull, were identified with a three-dimensional (3D) digitizer (Isotrack 3S1002; Polhemus Navigator Sciences, Colchester, VT, USA). This information was used for co-registration of the MEG signal and the individual magnetic resonance images (MRI) obtained with a Signa Echo-Speed 1.5-Tesla system (General Electric, Milwaukee, WI, USA).

2.4. Data Analysis

The EMG signals were high-pass filtered at 1 Hz and rectified to extract the timing information of motor unit potentials, regardless of their shape (Rosenberg et al., 1989). The coherence spectra between the MEG and rectified EMG signals were calculated.
using Welch’s method (Welch, 1967) of spectral density estimation with a Hanning window, 1-Hz frequency resolution, and non-overlapping samples. MEG-EMG coherence values (Coh\textsubscript{xy}) were calculated according to the following equation:

\[ \text{Coh}_{xy}(\lambda) = |R_{xy}(\lambda)|^2 = \frac{|f_{xy}(\lambda)|^2}{f_{xx}(\lambda) \cdot f_{yy}(\lambda)} \]

In this equation, \( f_{xx}(\lambda) \) and \( f_{yy}(\lambda) \) are MEG auto-spectra values and rectified EMG signals for a given frequency \( \lambda \), and \( f_{xy}(\lambda) \) is the cross spectrum between them. The EMG-EMG coherence spectra between the right and left sides were also calculated for the tongue and thumb in the same manner as the MEG-EMG coherence spectra analysis. Coherence is expressed as a real number between 0 and 1, where 1 indicates a perfect linear association between two signals, and 0 indicates a complete absence of linear association.

The initial 5 s of each EMG signal recorded during the task was excluded from analysis. Epochs with artifacts identified by visual inspection were rejected from the analysis, thus yielding 556 ± 103 (mean ± standard deviation [SD]) (ranging from 404 to 701) samples for the tongue and 544 ± 111 (ranging from 400 to 703) samples for the thumb. Based on the method by Rosenberg et al. (1989), coherence above \( Z \) was considered to be significant at \( p < 0.01 \), where \( Z = 1 - 0.01^{(1/L-1)} \). \( L \) was the total number of samples used in the estimation of auto and cross spectra.

To evaluate the stability of the EMG signals, rectified EMG signals were averaged with a 50-point moving average filter. The stability of the EMG signals was calculated for each muscle that showed statistically significant coherence according to the following equation, as described in the previous study (Lim et al., 2011):

\[ \text{Maezawa et al.} \]
Stability of EMG = 1 − \frac{\text{SD of rectified and averaged EMG}}{\text{Mean of rectified and averaged EMG}}

The cross-correlogram in the time domain was investigated by applying an inverse Fourier transformation to the averaged cross spectra of the right side of the tongue and thumb. Isocontour maps were constructed at the time points showing cross-correlogram peaks. The sources of the oscillatory MEG signals were modeled as equivalent current dipoles (ECDs) for the right side of the tongue and thumb. To estimate the location of the ECDs, a spherical head model, whose center best fit the local curvature of the surface of an individual’s brain as determined by the MR images, was adopted (Sarvas 1987). Only ECDs attaining an 85% goodness-of-fit were accepted.

2.5. Statistics

Data are expressed as the mean ± standard error of the mean (SEM). The coherence value was normalized with an arc hyperbolic tangent transformation to stabilize the variance (Halliday et al., 1995). The frequency and coherence values of the tongue were compared using repeated measures analyses of variance (ANOVA) with the within-subjects factor of the side of the tongue (right vs. left) and hemisphere (contralateral vs. ipsilateral). Post hoc comparisons were performed using paired t-tests with the Bonferroni corrections. The frequency and coherence values of the thumb were analyzed between the right and left sides using paired t-tests.

The coherence of the contralateral hemisphere was statistically compared between the tongue and thumb with a paired t-test. In addition, the EMG stability was compared between the tongue and thumb with a paired t-test after logarithmic transformation.
Correlations of peak frequency of coherence spectra were computed across subjects using the Pearson product-moment correlation coefficient.

The contralateral ECD locations in each axis (x-axis, y-axis, and z-axis) were analyzed between the right side of the tongue and thumb using paired t-tests. The x-axis passes through the preauricular points from left to right, while the y-axis passes through the nasion, and the z-axis points upward from the plane determined by the x- and y-axes. The cortex-muscle time lag was compared between the contralateral hemispheres for the right side of the tongue and thumb using paired t-tests. The statistical significance level was set to p < 0.05.

3. Results

3.1. Coherence

Figure 1A provides the power spectra of MEG [1] and EMG [2] during tongue protrusion in subject 10. Distinct peaks were detected at 11 and 21 Hz of MEG [1] from the left sensorimotor cortex, and 3, 7, and 24 Hz of EMG [2] for the right side of the tongue. Figure 1A [3] shows the EMG-EMG coherence spectra between tongue sides. Clear peaks of EMG-EMG coherence were observed at 3, 7, and 24 Hz between tongue sides.

Figure 1B shows the spatial distribution of the coherence spectra between MEG and EMG activity recorded from the right side of the tongue in Subject 10. Coherence signals were detected at 23 Hz (amplitude, 0.0266) over the contralateral hemisphere (Fig 1B[2]) and at 25 Hz (0.0119) over the ipsilateral hemisphere (Fig 1B [4]). Coherence MEG signals also were observed at lower frequencies over the contralateral
hemisphere at 10 Hz (amplitude, 0.0110) (Fig 1B [3]) and at 3 Hz (0.0115) over the ipsilateral hemisphere (Fig 1B [4]).

3.1.1. EMG stability and EMG-EMG coherence between sides

The value of log-transformed stability of EMG for the tongue and thumb were -0.22 ± 0.01 and -0.30 ± 0.02, respectively. The EMG stability for the tongue was higher than that for the thumb (p= 0.005).

For the tongue, significant coherence signals between the right EMG and left EMG were detected at 14–32 Hz and 3–10 Hz in all subjects (Table 1). The mean peak of these frequency bands was 21.2 ± 1.6 Hz and 6.7 ± 0.6 Hz, respectively. For the thumb, the EMG-EMG coherence signal was not above the statistical significance level in any of the subjects.

3.1.2. MEG-EMG coherence at 15–35 Hz

Table 2 shows the peak frequencies of MEG-EMG coherence for the tongue and thumb across subjects. Coherence signals were observed at 16–35 Hz for the right side of the tongue over the contralateral hemisphere in 13 subjects and over the ipsilateral hemisphere in 10 subjects. Coherence signals for the left side of the tongue were detected at 14–36 Hz over the contralateral and ipsilateral hemispheres in 13 and 12 subjects, respectively. The mean frequency for each hemisphere was 23.6 ± 1.4 Hz (contralateral, mean ± SEM) and 23.3 ± 1.7 Hz (ipsilateral) for the right side of the tongue, and 24.8 ± 1.8 Hz (contralateral) and 23.0 ± 1.4 Hz (ipsilateral) for the left side of the tongue.

Maezawa et al.
For the thumb, coherence signals were observed at 15–30 Hz in 13 subjects for the right side and at 15–33 Hz in 13 subjects for the left side. The mean frequencies (± SEM) for the thumb were 21.8 ± 1.4 Hz and 20.5 ± 1.7 Hz for the right and left sides, respectively.

The ANOVA did not reveal a significant main effect for the frequency of coherence between tongue sides (p = 0.713) and hemispheres (p = 0.458). The mean frequency was not significantly different between sides for the thumb (p = 0.492). No significant correlation of peak frequency existed between the right hemisphere and right side of the tongue and the right hemisphere and left side of the tongue (p = 0.966), or between the left hemisphere and right side of the tongue and the left hemisphere and left side of the tongue (p = 0.054). No significant correlation of peak frequency existed between the contralateral hemisphere and right side of the tongue and the ipsilateral hemisphere and right side of the tongue (p = 0.116), or between the contralateral hemisphere and left side of the tongue and the ipsilateral hemisphere and left side of the tongue (p = 0.538).

No significant correlation of peak frequency existed between the left hemisphere and right side of the tongue and the left hemisphere and right side of the thumb (p = 0.430), or between the right hemisphere and left side of the tongue and the right hemisphere and left side of the thumb (p = 0.887).

The mean MEG-EMG coherence value for each hemisphere was 0.0176 ± 0.0019 (contralateral, mean ± SEM) and 0.0133 ± 0.0021 (ipsilateral) for the right side of the tongue, and 0.0150 ± 0.0016 (contralateral) and 0.0118 ± 0.0011 (ipsilateral) for the left side of the tongue (Fig 2A[1]). The mean values (±SEM) for the thumb were 0.0226 ± 0.0015 and 0.0258 ± 0.0044 for the right and left sides, respectively (Fig 2A[2]). The ANOVA revealed a significant main effect for the magnitude of coherence between
hemispheres ($p < 0.001$), but no significant main effect of side of the tongue ($p = 0.538$) or interaction ($p = 0.165$). The paired $t$-test with Bonferroni correction revealed a significant difference in the coherence value between the contralateral and ipsilateral hemispheres for the right side of the tongue ($p = 0.002$) and between the contralateral and ipsilateral hemispheres for the left side of the tongue ($p = 0.008$). No significant difference was observed for the contralateral coherence between tongue sides ($p = 0.016$), or for the ipsilateral coherence between tongue sides ($p = 0.803$). No significant difference was detected for thumb coherence between sides ($p = 0.557$).

The value of contralateral coherence for the tongue and thumb were $0.0163 \pm 0.0014$ and $0.0242 \pm 0.0010$, respectively. The coherence for the tongue was smaller than that for the thumb ($p= 0.003$).

3.1.3. MEG-EMG coherence at 2–10 Hz

A distinct coherence peak was discerned for the tongue at low frequencies (2–10 Hz). This peak was observed over the contralateral hemisphere in 9 subjects and over the ipsilateral hemisphere in 9 subjects for the right side of the tongue, and detected over the contralateral hemisphere in 9 subjects and over the ipsilateral hemisphere in 12 subjects for the left side of the tongue, respectively (Table 3). The mean frequency for each hemisphere was $5.9 \pm 1.0$ Hz (contralateral, mean $\pm$ SEM) and $4.7 \pm 0.8$ Hz (ipsilateral) for the right side of the tongue, and $5.0 \pm 0.9$ Hz (contralateral) and $5.3 \pm 0.5$ Hz (ipsilateral) for the left side of the tongue. The ANOVA did not reveal a significant main effect for the frequency of coherence between tongue sides ($p = 0.108$) and hemispheres ($p = 0.647$).

Maezawa et al.
No significant peak frequency correlation existed between the right hemisphere and right side of the tongue and the right hemisphere and left side of the tongue \((p = 0.282)\), or between the left hemisphere and right side of the tongue and the left hemisphere and left side of the tongue \((p = 0.074)\). No significant correlation of peak frequency existed between the contralateral hemisphere and right side of the tongue and the ipsilateral hemisphere and right side of the tongue \((p = 0.339)\), or between the contralateral hemisphere and left side of the tongue and the ipsilateral hemisphere and left side of the tongue \((p = 0.461)\).

The mean value of MEG-EMG coherence for each hemisphere was \(0.0180 \pm 0.0041\) (contralateral, mean ± SEM) and \(0.0149 \pm 0.0016\) (ipsilateral) for the right side of the tongue, and \(0.0168 \pm 0.0014\) (contralateral) and \(0.0160 \pm 0.0026\) (ipsilateral) for the left side of the tongue. The ANOVA did not reveal a significant main effect for the magnitude of coherence between hemispheres \((p = 0.617)\) and tongue sides \((p = 0.374;\ Fig\ 2B)\).

### 3.2. Cortical Sources of MEG-EMG Coherence

The isofield contour maps showed a clear dipolar pattern for the tongue (Fig 3A [1]) and the thumb (Fig 3B [1]). The orientations directed anteriorly for the tongue and directed anteromedially for the thumb in one subject (subject 10). The ECDs were located at the inferior part of the central sulcus for the tongue (Fig 3A [2]). The sources corresponding to the thumb were located over the contralateral primary motor cortex (Fig 3B [2]), with the thumb source located superior, posterior, and medial to the tongue area.
The sources for tongue muscle contractions were estimated to be in the contralateral primary motor cortex in 10 subjects and in the ipsilateral primary motor cortex in 4 subjects. The sources for the thumb were located in the contralateral primary motor cortex in 11 subjects. The paired t-test indicated that the ECD locations for the tongue were located significantly anterior (mean, 15.0 mm; \( p = 0.002 \)) and inferior (mean, 14.5 mm; \( p = 0.008 \)) to those for the thumb (Fig 4A). The ECD locations for the tongue were not significantly lateral (mean, 8.6 mm; \( p = 0.066 \)) to those for the thumb. The source current orientations for oscillatory activity corresponding to tongue contractions differed among subjects (Fig 4B). The source current orientations for thumb contractions were directed medially, anteriorly, and superiorly in all subjects (Fig 4B).

3.3. Time Lags between MEG and EMG Signals

Figure 5A shows the cross-correlograms for the tongue [1] and thumb [2] in subject 10. The peaks of the cross-correlograms were observed at 7 ms and 17 ms before EMG onset over the contralateral rolandic sensors for the tongue and thumb, respectively.

Figure 5B presents the mean time lags between the cortex and tongue muscle and the mean time lags between the cortex and thumb muscle for all subjects who met the criteria for the contralateral source localization analysis. The mean time lag for the tongue was 9.1 ± 1.2 ms (mean ± SEM) (range, 3–16 ms) in 10 subjects. The time lag for the thumb was 18.0 ± 0.5 ms (range, 16–21 ms) in 11 subjects. The time lag between the cortex and muscle was shorter for the tongue than for the thumb according to the paired \( t \)-test (\( p = 0.001 \)). The ipsilateral hemisphere data for the tongue was excluded from statistical analysis because of small sample sizes (\( n = 4 \)).
4. Discussion

The present study demonstrates an oscillatory interaction between the bilateral cortex and hypoglossal motoneuron pools innervating both sides of the tongue muscle during a maintained tongue protrusion task. Two coherence peaks were observed over both hemispheres at 15–35 Hz and 2–10 Hz for each side of the tongue.

4.1. Coherence between MEG and EMG

4.1.1. Coherence at 15–35 Hz

Corticomuscular coherence occurring at 15–35 Hz may be associated with the coordination of voluntary movements and may result from periodicities in common synaptic inputs to motoneurons (Farmer et al., 1993a, 1993b; Mills and Schubert, 1995). Such rhythmic activity in the primary motor cortex drives spinal motoneurons through the corticospinal tract and plays a role in synchronizing motor unit activity (Salenius et al., 1997; Kilner et al., 1999). During tongue protrusion, the primary motor cortex controls tongue movements through outputs to hypoglossal motoneuron pools. Laine et al. (2012) reported in an electroencephalographic study that single motor units recorded from the tongue muscles with needle electrodes showed cortical entrainment at frequencies between 15–40 Hz during tongue protrusion. However, they failed to record reliable coherence with multiunit EMG activity. In the present study, we successfully demonstrated cortical entrainment of tongue multiunit EMG activity at 15–35 Hz for both sides of the tongue.

The coherence signal was observed over both hemispheres for both tongue sides, but only over the contralateral hemisphere for the thumb. Previous transcranial magnetic stimulation (TMS) studies reported that unilateral focal cortical TMS could elicit lingual

Maezawa et al.
motor-evoked potentials (MEPs) bilaterally (Meyer et al., 1997; Ghezzi et al., 1998; Rödel et al., 2003). Because the tongue is innervated bilaterally by corticobulbar fibers through the hypoglossal nucleus, it is likely that cortical oscillation occurs in both hemispheres during tongue protrusion. Moreover, these studies of lingual MEPs reported that higher mean amplitudes were detected contralateral to the stimulated side. This result is consistent with our result in which the tongue coherence value was greater for the contralateral hemisphere than for the ipsilateral hemisphere in both tongue sides. These results may reflect a predominance of descending contralateral corticonuclear projections from the primary motor cortex to the tongue muscle during human tongue protrusion.

Hemispheric dominance was not detected for the contralateral coherence value between the right and left hemispheres in our study. This result was consistent with that of a previous human study regarding task-related modulation in the 20 Hz range during non-verbal mouth movements using MEG (Salmelin and Sams, 2002). The post-movement rebound of the motor cortical 20-Hz activity was significantly larger over the left hemispheric during the verbal task, but it was not different between hemispheres during the non-verbal task. Moreover, a previous functional MRI study suggested that left hemispheric dominance was detected during self-initiated silent speech production, while no hemispheric dominance was observed during non-verbal tongue protrusion (Wildgruber et al., 1996). Thus, given these results during non-verbal tongue protrusion in humans, the oscillatory motor commands from the bilateral motor cortex were contralateral dominant for each tongue side, but contralateral neural oscillation may not have a hemispheric lateralization for each side of the tongue. Further
study is needed to determine whether hemispheric lateralization of the functional coupling between the cortex and tongue exists during verbal tongue movements.

The finding of smaller coherence for the tongue compared to the thumb might indicate a weaker functional connection between the tongue and cortex compared to the thumb and cortex. This finding is in agreement with previous studies in which proximally located muscles showed less coherence during isometric contractions compared to distally located muscles (Marsden et al., 1999; Farmer et al., 1993a). However, because neuromuscular interaction of the tongue was detected in both hemispheres, while interaction of the thumb was observed only in the contralateral hemisphere, it might be difficult to simply compare the coherence of the contralateral hemisphere between the tongue and thumb while evaluating the functional connections.

Lim et al. (2011) have reported that greater levels of coherence are associated with high levels of EMG stability when analyzing the coherence of the thumb and little finger. However, in our study, the EMG stability of the tongue was higher than that of the thumb despite the finding of lower coherence for the tongue. The reason for this might be that the bilateral innervation of the hypoglossal nerves enables stable tongue movement with less neuromuscular interaction, unlike in the case of the thumb, which is innervated by one side of the recurrent branch of the median nerve. In addition, it is also possible that the cortical control of skeletal and visceral muscles might differ. Further study is needed on the association of EMG stability and coherence of the tongue, which is located on the body midline.

No peak frequency correlations existed between the hemispheres and tongue sides during tongue protrusion. This result may suggest that the neural circuit works independently of each hemisphere and each tongue side for human tongue protrusion.

Maezawa et al.
Moreover, no peak frequency correlations existed between the contralateral hemispheres for the tongue and thumb. This result may suggest that during isometric contraction of different body parts, the neural circuits operate independently of each other.

**4.1.2. Coherence at 2–10 Hz**

In the present study, the peak frequency of the corticomuscular coherence extended into a low band at 2–10 Hz. The physiological interpretation of corticomuscular coherence varies depending on the frequency band. For example, 15–35 Hz synchronization reflects cortical entrainment of motoneuron pools. Although the coupling mechanism within the low frequency range is still unclear, there are some potential explanations for this coupling during tongue protrusion.

The lower frequency oscillation acts on a large number of motor units, both within a single muscle and between multiple muscles (De Luca et al., 1982, 1993). Marsden et al. (1999) suggested that axial muscles are influenced by lower frequency oscillations, thus allowing the axial muscles to act as a functional whole during postural control. This is in contrast to the coherence that occurs at frequencies around 15–35 Hz, which likely reflect the activity of corticomotoneuronal inputs to the motoneurons of a given muscle. Thus, the low oscillatory frequency may play an essential role in the postural maintenance of the tongue. A previous corticomuscular coherence study (Murayama et al., 2001) of the paraspinal and abdominal muscles in the body trunk reported coherence at 7–11 Hz in some subjects as well as coherence at 15–35 Hz. The difference in the number of subjects with coherence at the low frequency between the tongue and trunk is possibly due to a difference in the strength of functional connections formed by corticomotoneuronal projections to each muscle in the tongue or trunk. In fact, the
coherence at 15–35 Hz for the tongue, which was about two-thirds of that for the thumb, was relatively larger than that for the trunk, which was about one-fifth of that for the thumb (Murayama et al., 2001).

The presence of tremor may be another possible explanation. Jerbi et al. (2007) reported that during a continuous hand visuomotor task, significant and slow oscillatory activity (2–5 Hz) was observed over the contralateral primary somatosensory cortex with time-varying hand speeds. During maintained tongue protrusion in our study, it was sometimes difficult for subjects to keep the tongue at a steady position because the tongue is characteristically a free-moving muscle. As the power spectra of the tongue EMG showed low frequency peaks, the oscillation may be due to the unintended slight movement of the tongue.

It is also possible that the low frequency oscillation is related to the role that the tongue plays in speech production. Ruspantini et al. (2012) reported that coherence oscillatory coupling between the cortex and mouth muscles is strongest at 2–3 Hz, which are also the frequencies of spontaneous speech and the typical rate of word production. The low oscillatory frequency may play an important role in smooth tongue performance during word production.

4.2. Source Localization of Coherence Cortical Activity

Coherence MEG activity was located in the tongue motor area during tongue contraction over the contralateral hemisphere in 10 subjects and over the ipsilateral hemisphere in 4 subjects, but only over the contralateral hemisphere during thumb contraction in 11 subjects.
As the source areas of coherence cortical activity showed global somatotopy, the cortical representations for the tongue muscles were inferior and anterior to those for the thumb. This result is consistent with the movement-related magnetic fields (MRFs) observed with forward movement of the tongue in a previous study (Nakasato et al. 2001). In that study, the ECDs for the MRFs were localized in the central sulcus, which was inferior (mean, 14.4 mm) and anterior (mean, 7.6 mm) to the ECDs for the N20 response observed in the somatosensory evoked fields following median nerve stimulation, similar to our finding of the different ECD locations between the tongue and thumb.

In the present study, the source current orientations for oscillatory activity corresponding to tongue contractions differed among subjects, which was in contrast to the constant current orientation during thumb contraction. The results for the variable orientations of the tongue dipoles among the subjects were consistent with the findings of a previous study that recorded movement-related potentials (MRPs) from subdural electrodes during tongue-forward movements in patients with epilepsy (Ikeda et al., 1995). They reported that the polarities were different among the subjects at the same tongue motor area. We have suggested two possibilities to explain the variability of the dipole orientation in the tongue primary motor cortex.

The first reason is a functional one. Previous subdural electrode (Urasaki et al., 1994) and functional MRI (Martin et al., 1997; Meier et al., 2008) studies have reported that the primary motor cortex of the tongue region overlaps with the regions for some other oral muscles, such as the lips and mandible, which generate basic tongue movements. Thus, the brain representation of the tongue might differ inter-individually within the brain region controlling several oral muscles. This variability in neural

Maezawa et al.
population within the primary motor cortex may cause the variable orientations of the dipoles during a tongue-protrusion task. Such modulation of cortical activation in the tongue region would facilitate the highly coordinated movements required for tasks, such as swallowing, speech, and mastication.

The second reason is an anatomical one. Every body part is represented in the primary motor cortex, and these representations are arranged somatotopically. The tongue region is represented in the lowest portion of the gyrus adjacent to the Sylvian fissure (Penfield, 1950; Meier et al., 2008). Anatomically, the crown of this region involves complex geometry and varies across individuals. Thus, such complex anatomical configuration of the tongue primary motor cortex may cause the variable orientations of the dipoles.

4.3. Time Lags between MEG and EMG Signals

In all cases, the cortical signal preceded the muscle signal in time, and the time lag between the two signals depended on the pathway length between the cortex and muscle. We observed that the time lag was shorter for the tongue than for the thumb. Gross et al. (2000) reported that the time lag between the cortex and a given muscle, which was determined from the coherence MEG and EMG signals observed during the strongest corticomuscular synchrony, agreed well with the conduction times measured with TMS. The mean latencies of the lingual MEPs were 7.8 (Ghezzi et al., 1998), 8.5 (Meyer et al., 1997), and 9.5 ms (Rödel et al., 2003) for the contralateral hemisphere, which were similar to the corticomuscular mean latency of 9.1 ms in the present study. The short corticomuscular latency for the contralateral tongue muscles suggests the activation of a fast-conducting corticonuclear connection through the hypoglossal motor nucleus.
compared to the contralateral thumb muscles, which pass through spinal motoneuron pools.

We found a difference in the mean time lag at 8.9 ms between the cortex and tongue (mean, 9.1 ms) and the cortex and thumb (mean, 18.0 ms). Assuming that the conduction time from cortex to brainstem and synaptic delay were almost equal between the cortex and tongue and the cortex and thumb, the difference in the mean time lag at 8.9 ms was attributed to the spinal and peripheral conduction time.

The tongue motor pathway runs through the hypoglossal nerve nucleus, and the thumb motor pathway runs through the spinal cord. Because the efferent nerves for the tongue and thumb pass through different motor pathway, it is difficult to correctly determine the difference in the tract lengths. However, assuming that the length difference in the motor pathways between the tongue and thumb is 50 cm and that the conduction velocity is 50 m/s (Kakuda et al., 1992), the difference in the time lag between the cortex and tongue and the cortex and thumb can be calculated to be 10 ms, which is almost equal to our observed value at 8.9 ms.

In conclusion, our results show that oscillatory interaction between the cortex and muscles occurs not only for the thumb muscles, but also for the tongue muscles. Furthermore, this interaction occurs over both hemispheres within 2 peak frequency bands at 15–35 Hz and 2–10 Hz. The corticomuscular interaction at 15–35 Hz for the tongue muscle was contralaterally dominant for both sides of the tongue. The cortical sources agree with a global somatotopy in the primary motor cortex. The time lags associated with this interaction are consistent with previous results showing an overall time decrease as the distance between the cortex and muscle decreases. These results suggest that during human tongue protrusion, oscillatory motor commands are
modulated by the bilateral motor cortex, with a contralateral hemispheric dominance for each tongue side.

Acknowledgements

This work was supported by Grants-in-Aid for Scientific Research (B)24300192 (TM), (C)23591488 (HS), and (C)25462883 (MF), Grant-in-Aid for Exploratory Research (24650226) (TM), and Grants-in-Aid for Young Scientists (B)25862071 (HM) from the Japan Society for the Promotion of Science.
References


Maezawa et al.


Maezawa et al.
### Table 1. Peak frequencies of EMG-EMG coherence between tongue sides

<table>
<thead>
<tr>
<th>Sub</th>
<th>2–10 Hz</th>
<th>15–35 Hz</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>18</td>
</tr>
<tr>
<td>5</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>6</td>
<td>7</td>
<td>21</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>9</td>
<td>6</td>
<td>29</td>
</tr>
<tr>
<td>10</td>
<td>3</td>
<td>24</td>
</tr>
<tr>
<td>11</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>12</td>
<td>6</td>
<td>17</td>
</tr>
<tr>
<td>13</td>
<td>8</td>
<td>25</td>
</tr>
<tr>
<td>14</td>
<td>9</td>
<td>21</td>
</tr>
<tr>
<td>15</td>
<td>6</td>
<td>32</td>
</tr>
<tr>
<td>Range</td>
<td>3–10</td>
<td>14–32</td>
</tr>
<tr>
<td>-------</td>
<td>------</td>
<td>-------</td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td>6.7 ± 0.6</td>
<td>21.2 ± 1.6</td>
</tr>
</tbody>
</table>

EMG, Electromyography; Sub, Subject number; SEM, Standard error of the mean.
Table 2. Peak frequencies of MEG-EMG coherence for the tongue and thumb at 15–35 Hz

<table>
<thead>
<tr>
<th>Sub</th>
<th>Tongue (Hz)</th>
<th>Thumb (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right (Hz)</td>
<td>Left (Hz)</td>
</tr>
<tr>
<td></td>
<td>Con</td>
<td>Ipsi</td>
</tr>
<tr>
<td>1</td>
<td>21</td>
<td>N</td>
</tr>
<tr>
<td>2</td>
<td>28</td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td>32</td>
<td>N</td>
</tr>
<tr>
<td>4</td>
<td>26</td>
<td>18</td>
</tr>
<tr>
<td>5</td>
<td>21</td>
<td>19</td>
</tr>
<tr>
<td>6</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>7</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>8</td>
<td>21</td>
<td>19</td>
</tr>
<tr>
<td>9</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>10</td>
<td>23</td>
<td>25</td>
</tr>
<tr>
<td>11</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>12</td>
<td>31</td>
<td>N</td>
</tr>
<tr>
<td>13</td>
<td>22</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>15</td>
<td>21</td>
<td>22</td>
</tr>
</tbody>
</table>


Mean ±: 23.6 ±  23.3 ±  24.8 ±  23.0 ±  21.8 ±  20.5 ±

SEM: 1.4  1.7  1.8  1.4  1.4  1.7

MEG, Magnetoencephalography; EMG, Electromyography; Sub, Subject number; Con, Contralateral hemisphere; Ipsi, Ipsilateral hemisphere; N, Not detected, SEM, Standard error of the mean.
**Table 3.** Peak frequencies of MEG-EMG coherence for the tongue at 2–10 Hz

<table>
<thead>
<tr>
<th>Tongue (Hz)</th>
<th>Right</th>
<th>Left</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub</td>
<td>Con</td>
<td>Ipsi</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>3</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>N</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>N</td>
<td>5</td>
</tr>
<tr>
<td>9</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>11</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>12</td>
<td>N</td>
<td>2</td>
</tr>
<tr>
<td>13</td>
<td>7</td>
<td>N</td>
</tr>
<tr>
<td>14</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Range</td>
<td>2–10</td>
<td>2–9</td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td>5.9 ± 1.0</td>
<td>4.7 ± 0.8</td>
</tr>
</tbody>
</table>

MEG, Magnetoencephalography; EMG, Electromyography; Sub, Subject number; Con, Contralateral hemisphere; Ipsi, Ipsilateral hemisphere; N, Not detected; SEM, Standard error of the mean.
Figure legends

Figure 1. Single subject (Subject 10) data for tongue protrusion. A. Power spectra for the MEG signal [1] recorded from a sensor from the left sensorimotor cortex and the EMG signal [2] recorded from the right tongue muscle. MEG and EMG spectra are plotted on a logarithmic scale. Each trace goes from 0 to 45 Hz. Distinct peaks in these spectra were detected at 11 and 21 Hz for MEG and 3, 7, and 24 Hz for EMG. [3] EMG-EMG coherence spectra show clear peaks at 3, 7, and 24 Hz between sides of the tongue. B. MEG-EMG coherence for the right side of the tongue. [1] The whole-head waveforms of MEG-EMG coherence spectra. Coherence spectra show clear peaks over the parietotemporal areas bilaterally with contralateral (left) hemispheric dominance. Each trace goes from 0 to 45 Hz. The horizontal gray line in each column indicates the 99% significance level. [2–4] The gray traces in ovals from [1] have been enlarged to highlight the two peaks that were identified in the maximum amplitude channels over the contralateral [2, 3] and ipsilateral [4] hemispheres. Coherence peaks were observed at 23 Hz [2] and 10 Hz [3] over the contralateral hemisphere, and at 25 Hz and 3 Hz [4] over the ipsilateral hemisphere.

Figure 2. The amplitude of corticomuscular coherence for the tongue and thumb across subjects (mean ± SEM). The mean values were significantly different from zero (dashed lines indicate the level of statistical significance with the confidence limit). A [1]. The tongue coherence value at 15–35 Hz was significantly different between the contralateral and ipsilateral hemispheres for both sides of the tongue. The coherence value of the contralateral hemisphere was not significantly different between the right and left sides of the tongue. [2]. The thumb coherence value was not significantly
different between the right and left sides. B. The tongue coherence value was not significantly different among hemispheres and tongue sides at 2–10 Hz. NS, Not significant; Con, Contralateral hemisphere, Ipsi, Ipsilateral hemisphere.

Figure 3. Isocontour maps and dipole locations for the tongue and thumb in subject 10. The contour map was obtained from the time points showing cross-correlation peaks for the tongue (A[1]) and thumb (B[1]). Red and blue lines indicate outgoing and incoming magnetic fluxes, respectively. Green arrows show the location and direction of equivalent current dipoles (ECDs) projected on the skull surface. Arrowheads indicate the negative pole of the ECDs. ECDs (blue dots) for the tongue (A[2]) and thumb (B[2]) were superimposed on the slices of magnetic resonance images of the subject. The direction of the blue line indicates the negative pole of the ECDs. Both of the ECDs were located at the central sulcus, but the ECD locations for the tongue were estimated more inferiorly, anteriorly, and laterally than the locations for the thumb. Rt, Right.

Figure 4. Dipole locations (A) and dipole orientations (B) across subjects. A. Averaged ECD locations on the x-, y-, and z-axes for the tongue and thumb across subjects. Data points represent the mean ± SEM. The ECD locations for the tongue were located significantly inferior and anterior to those for the thumb. The ECD locations for the tongue were not significantly lateral to those for the thumb. The x-axis passes through the preauricular points from left to right, while the y-axis passes through the nasion, and the z-axis points upward from the plane determined by the x- and y-axes. B. Dipole orientations for the tongue and thumb in the x-y plane [1] and in the x-z plane [2] across subjects. The current orientations of tongue ECDs differed significantly among subjects,
which contrasted with the stable direction of thumb ECDs with a mesial, anterior, and superior direction. NS, Not significant; Rt, Right.

**Figure 5.** A. The 200-ms long cross-correlograms between the MEG and EMG activity from the tongue [1] and thumb [2] muscles in subject 10. Each trace started 100 ms before and ended 100 ms after EMG onset. The vertical line indicates the time of zero lag. [1] The largest peak in MEG occurs 7 ms before the onset of tongue EMGs over the contralateral rolandic sensors. [2] The largest peak in MEG occurs 17 ms before the onset of thumb EMGs over the contralateral rolandic sensors. B. Time lag between the cortex and tongue and between the cortex and thumb across subjects (mean ± SEM). The time lag between the cortex and tongue was significantly shorter than that between the cortex and thumb.
A. Power spectra of MEG [1] and EMG [2], and EMG-EMG coherence between sides [3]

B. MEG-EMG coherence for right side of the tongue
A. Coherence value at 15–35 Hz

[1] Tongue

B. Coherence value at 2–10 Hz for the tongue
A. Tongue
[1] Isocontour map
[2] Dipole location and orientation

B. Thumb
[1] Isocontour map
[2] Dipole location and orientation
A. Averaged dipole locations across subjects

B. [1]. Dipole orientations in the x-y plane across subjects

[2]. Dipole orientations in the x-z plane across subjects
A. Cross-correlograms

[1] Tongue

-100 ms                  0                 100 ms

-7 ms

[2] Thumb

-100 ms                  0                 100 ms

-17 ms

B. Time lag between the MEG and EMG signal

Tongue

Thumb

0  5  10  15  20 ms

*