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Suprahyoid Muscles Motor Evoked Potentials in Response to Transcranial Magnetic Stimulation

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Objective: The objective of this study was to reveal whether corticobulbar projection to the suprahyoid muscles (SHM) is contralateral or bilateral.
Methods: Thirty-nine healthy subjects between 27 and 77 years of age participated. All subjects underwent transcranial magnetic stimulation (TMS) in both cerebral hemispheres using surface EMG recording in bilateral SHM. One subject underwent TMS in cerebral hemisphere at the same time using needle and surface EMG recording in the contralateral and ipsilateral SHM. Eight subjects underwent TMS in both cerebral hemispheres using surface EMG recording in bilateral SHM, within 6 months of the first day.
Results: We obtained larger response in contralateral SHM than in ipsilateral SHM in the surface EMG recording. However, in the needle EMG recording, only contralateral SHM responses were evoked. TMS of either hemisphere evoked contralateral SHM motor-evoked potentials (MEPs) in all subjects [SHM latency: (left) 8.5 ± 0.9 ms, (right) 8.6 ± 1.1 ms]. There was no significant difference in latency between the first and second tests. In a case of right medullary infarction with left cortical stimulation, MEPs of right SMH were absent.
Conclusion: Corticobulbar projections to the SHM appear to be dominated by contralateral projections in healthy adults.

Key words: transcranial magnetic stimulation, suprahyoid muscles, corticobulbar projection, motor-evoked potentials, deglutition

1. INTRODUCTION

The majority of studies employing transcranial magnetic stimulation (TMS) in humans has focused on the responses elicited in hand and limb muscles. TMS generates motor-evoked potentials (MEPs) in contralateral hand and limb muscles at latencies consistent with conduction along corticomotoneuronal pathways. In recent years, there have been sporadic reports of TMS for studies related to swallowing, and the major target muscles are the pharyngeal [1] and esophageal [2] muscles, but there have been few reports on the suprahyoid muscles. The suprahyoid muscles (the digastric, mylohyoid, geniohyoid and stylohyoid muscles) depress the mandible during mastication and speech and raise the hyoid bone during swallowing. Thus, despite the importance of the suprahyoid muscles in swallowing, there have been few studies investigating this muscle group with TMS.

In 1989, Cruccu *et al.* observed bilateral responses in the anterior digastric muscles of 6 human subjects evoked by TMS with a circular coil centered over the vertex [3]. They suggested that this was evidence for bilateral descending corticobulber fibers to anterior digastric motoneurons. Although one hemisphere is preferentially activated with a circular coil, activation of both hemispheres cannot be excluded.

Hamdy *et al.* (1996) reported that both contralateral and ipsilateral mylohyoid muscle responses, of similar latency, were evoked in response to TMS in either the right or left hemisphere in 20 healthy subjects using a figure-8 coil [4]. This supports the assertion that cortical projections to the mylohyoid muscles are bilateral.

However, these experiments raise questions about, the possibility of cross-talk between surface recording electrodes, because bilateral suprahyoid muscles are close together. In addition, it is not clear how the motor thresholds (MT) could be determined for the ipsilateral suprahyoid muscles and the contralateral suprahyoid muscles. Furthermore, it is not clear how to elicit MEPs on both sides with focal TMS without direct ipsilateral activation of the trigeminal nerve in the cranial fossa.

On the other hand, Gooden *et al.* (1999) reported that corticobulbar projections to the digastric muscles in 12 subjects were bilateral, but stronger contralaterally than ipsilaterally, with the result from single motor-unit responses by focal TMS [5]. However there were few healthy subjects in that study. Therefore, the present study is designed to test whether corticobulbar projections to the suprahyoid muscles are contralateral or bilateral using focal TMS without direct ipsilateral activation of the trigeminal nerve in a large number of healthy adult subjects of varying ages.

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2. MATERIALS

2.1. Healthy subjects

Thirty-nine healthy subjects between 27 and 77 years [mean age 48.7 years: (S. D. 17.1 years), 19 female and 20 male] participated in this study. All subjects reported no current symptom of dysphagia or neurological impairment and no drug use that would potentially affect their swallowing or neurological function. For each task, subjects gave written informed consent to participate in the experiments in accordance with the Declaration of Helsinki. This study was conducted from 2004 to 2005 at Tokai University Oiso Hospital.

2.2 Experimental procedure

Transcranial magnetic stimulation

Single-pulse (monophasic) transcranial stimulation (TMS) of the cerebral cortex was achieved using a magnetic stimulator (Magstim 200, MAGSTIM; Whitland, Dyfield UK) connected to a 70-mm outer diameter figure-8 coil (maximal output of 2.2 Tesla). The coil was held tangentially to the skull with the long axis through two loops at an angle of 45° with the line between the nasion and inion, and with the handle facing posteriorly.

Surface electromyographic (EMG) recording

Suprahyoid MEPs were recorded from the suprahyoid muscles using a pair of gel surface electrodes (NCS electrode; Nihon Kohden, Tokyo, Japan), having an interelectrode distance of 2 cm. Each pair of electrodes was positioned submentally, 1 cm lateral to the midline, one over the left suprahyoid muscles and the other over the right. Each electrode pair was connected to an EMG recording system (Neuropack MEB-2200; Nihon Kohden, Tokyo, Japan) with filter settings at 20 Hz to 5 kHz.

Each subject sat comfortably in a reclining chair. The cranial vertex (Cz) was identified according to the International 10–20 system, and was marked on the scalp. The figure-8 coil was discharged over both motor cortices, using an initial stimulation intensity of 1.1–1.3 Tesla (50–60% of stimulator output). Then the hot spot for stimulation anterior and lateral to the Cz was sought in 0.5 cm increments. The hot spot was defined as the stimulation point which elicited MEPs with the greatest amplitude.

Subsequently, the hot spot was stimulated using TMS starting at a sub-threshold intensity and increasing in 5% steps. The motor threshold (MT) for contralateral suprahyoid muscles was determined as the intensity that generated MEPs in the contralateral suprahyoid muscles greater than 30 μV [4] on at least 5 of 10 consecutive stimulations.

Five stimuli were then delivered to each scalp site at 120% MT, at 5-s intervals. To avoid inadvertent facilitation of cortically evoked responses, the subject was requested to keep as relaxed as possible and to minimize swallowing, coughing or speaking during the study [4].

2.3 Experimental protocols

2.3.1. Suprahyoid muscles MEPs after cortical stimulation

All of the 39 adult subjects participated in this protocol. Using both TMS and surface EMG recording, both right and left suprahyoid muscle MEPs were recorded.

For each subject, the mean latency of the 5 responses was used for analysis. Response latency refers to the interval (ms) between the stimulus and the onset of the MEPs.

2.3.2. MEPs in needle EMG and surface EMG recording

Two of the 39 subjects participated in this protocol. Using both TMS and surface EMG recording, the hot spot and MT for contralateral suprahyoid muscles was determined in both left and right hemispheres. Firstly, surface EMG responses were recorded from contralateral suprahyoid muscles and from ipsilateral suprahyoid muscles by TMS. After that, each concentric needle electrode (NM-030T; Nihon Kohden, Tokyo, Japan) was inserted into the target muscle on both sides between active and reference surface electrodes. Both surface and needle EMGs were recorded at the same time.

2.3.3. Reproducibility of suprahyoid muscle MEPs

Eight of 39 subjects (mean age, 40 y; range, 22–58 y; 7 men and 1 woman) participated. In order to provide an assessment of reproducibility, subjects were tested twice. The second study was conducted, in all cases, within 6 months of the first study. Using TMS and surface EMG recordings, contralateral suprahyoid muscle MEPs were recorded.

For each subject, the mean values of the MEPs were used for analysis. A paired t-test and Pearson's correlation coefficient were used to assess the reproducibility of the MEP latencies.

2.3.4. Patient

The patient was 43 year-old male with a right medullary infarction. The patient's consciousness was clear. The patient did not have hiccups, hoarseness, curtain signs or clear motor paralysis in the face or four extremities. In addition to ocular nystagmus, the patient had mild ataxic gait, swallowing difficulty and decreased pain and thermal sensation in the right face, trunk, and upper and lower extremities.

Head MRI conducted on day 6 of illness showed a high signal intensity area in the right caudal medulla on diffusion-weighted and FLAIR images. Videofluoroscopic (VF) examination of swallowing conducted on day 8 of the illness did not confirm reflection delay during the pharyngeal stage, but showed minor pharyngeal residue and laryngeal invasion infiltration with mildly decreased laryngeal raising.

TMS was administered on the ninth day after onset in a case of brainstem infarction with dysphagia. Using TMS and surface EMG recordings, both suprahyoid muscle MEPs were recorded. The patient gave informed consent to participate in these experiments in accordance with the Declaration of Helsinki.

3. RESULTS

3.1.1. Suprahyoid muscles MEPs after cortical stimulation

It was not easy to elicit suprahyoid muscles response with focal TMS without direct ipsilateral activation of the trigeminal nerve. However, without direct ipsilateral activation by a focal figure-8 coil, we obtained a larger response in the contralateral suprahyoid muscles than in the ipsilateral suprahyoid muscles (Fig. 2). Therefore we adopted only contralateral suprahyoid muscle re-

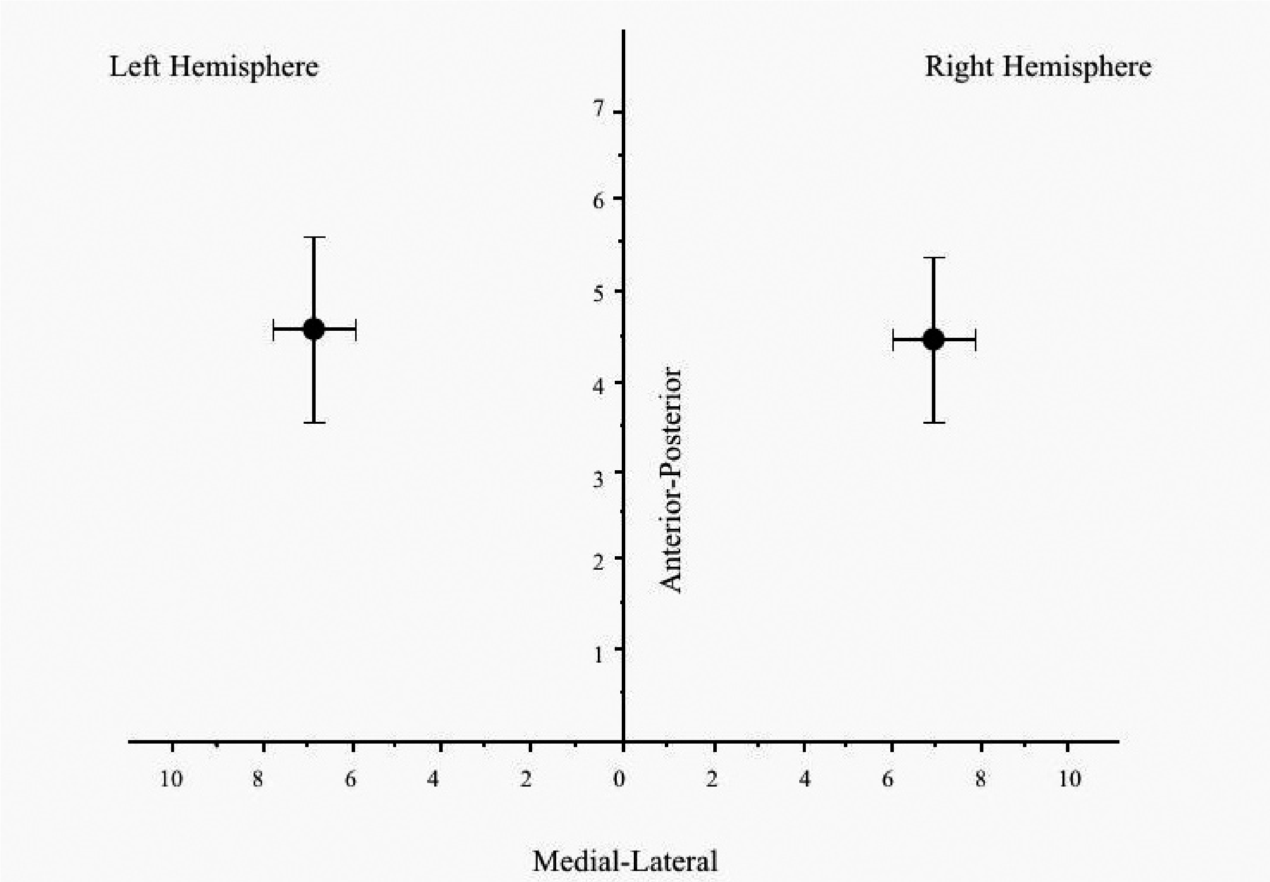

Fig. 1 A plot illustrating the medial-lateral and anterior-posterior positions (mean ± SD) in relation to the vertex for the site of maximum MEP size for the contralateral suprahyoid muscles.

sponses as MEPs, because the ipsilateral responses were not MEPs described in discussion, including the results of MEPs in needle EMG and surface EMG recording (3.1.2).

TMS of either hemisphere evoked MEPs in contralateral suprahyoid muscles in all healthy subjects. The MT and the hot spot for each subject are shown in Table 1. The average locations of the hot spots were anterior to Cz (left: 4.6 ± 1.0 cm, right: 4.5 ± 0.9 cm), and lateral to Cz (left: 6.8 ± 0.9 cm, right: 6.9 ± 0.9 cm). There was no significant left-to-right difference (Fig. 1). The average MT was not significantly different between left and right hemispheres (left 1.3 ± 0.1 tesla, right 1.3 ± 0.1 tesla).

Unpaired t-test showed no significant differences in latency between left suprahyoid muscles and right suprahyoid muscles (left: 8.5 ± 1.1 ms, right: 8.6 ± 0.9 ms). Furthermore, Pearson's correlation coefficients showed no significant correlations between MEPs latency and age.

3.1.2. MEPs in needle EMG and surface EMG recording

The data obtained using needle EMG and surface EMG recordings simultaneously could not be obtained from one subject. For the other subjects, larger responses in the contralateral suprahyoid muscles compared to the ipsilateral suprahyoid muscles appeared on the surface EMG, but only in the contralateral intramuscular EMG recording. With regard to the MEPs from the contralateral suprahyoid muscles, as indicated by the open triangles, the latency of MEPs confirmed by needle EMG matched the MEP latency observed on the surface EMG (Fig. 3).

3.1.3. Reproducibility of suprahyoid MEPs

First and 2nd tests of the MT and hot spot data for each subject are shown in Table 2. To test the reproducibility of contralateral suprahyoid muscles MEPs latency in healthy subjects, MEPs were obtained for 8 subjects. There was no significant difference in latency between the first and second tests. There was a significant correlation between the first and second tests (left: r = 0.923, right: r = 0.942) (Fig. 4).

3.2 Patient

On right cortical stimulation, the optimal site for contralateral MEPs was 3 cm anterior and 9 cm lateral to the Cz. The MT for the contralateral suprahyoid muscles was 1.3 Tesla. MEPs with an average latency of 11.4 ± 0.6 ms were obtained from the left suprahyoid muscles. On left cortical stimulation, MEPs of the right suprahyoid muscles could not be obtained (Fig. 5).

4. DISCUSSION

Since the first report using TMS by Barker and coworkers [6], TMS has been used mainly for fundamental studies of motor system function, diagnosis, and assessment of motor disturbance, by reason of handiness and because it is a non-invasive procedure. TMS generates MEPs in contralateral hand and limb muscles at latencies consistent with conduction along corticomotoneuronal pathways. On the other hand,

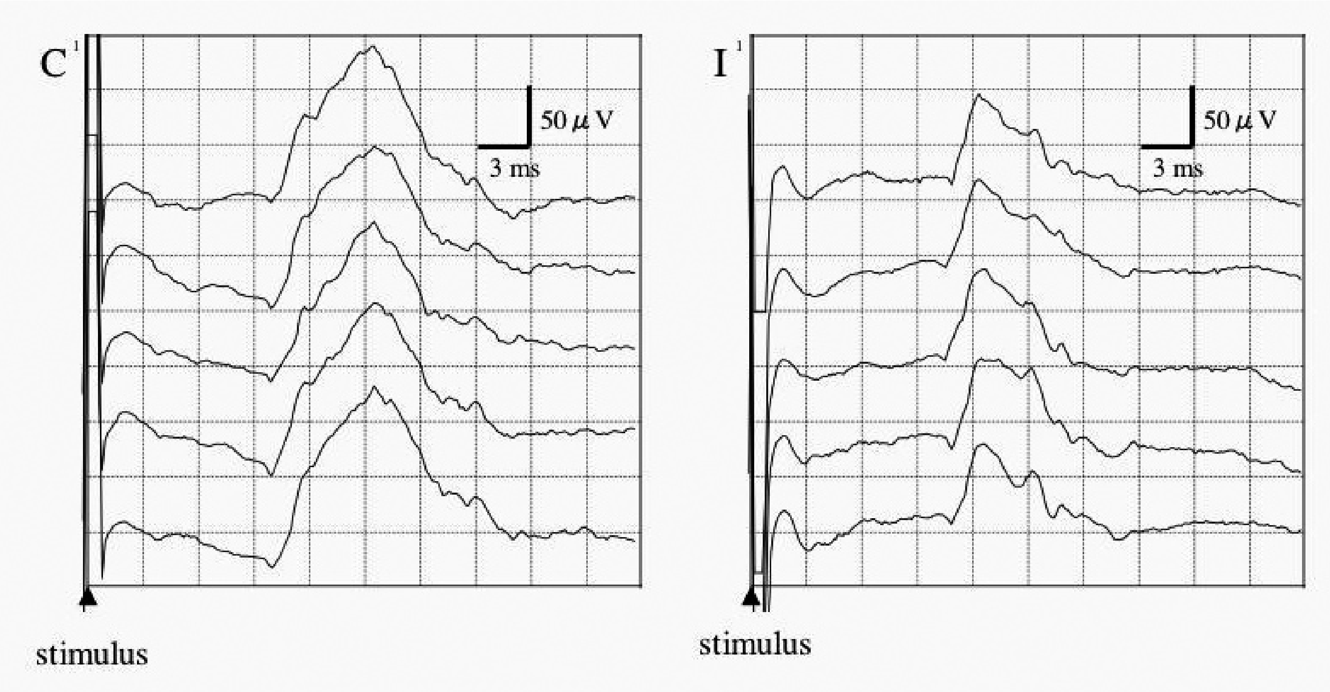

Fig. 2 Cortically evoked EMG responses recorded in one healthy subject (70 year-old, male) from contralateral & ipsilateral suprahyoid muscles.
Distance between the lines represents 3 ms on the horizontal axis, and 50 μV on the vertical axis.
I: ipsilateral suprahyoid muscles
C: contralateral suprahyoid muscles

there were few reports about corticobulbar projections to the suprahyoid muscles. Corticobulbar projections to the suprahyoid muscles were thought to be bilateral, but stronger contralaterally than ipsilaterally [5]. However, only less than twenty healthy subjects participated in these studies. Furthermore, the possibility remained that surface EMG responses may have resulted from cross-talk and / or direct stimulation of the trigeminal nerve giving rise to the measured responses in the ipsilateral suprahyoid muscles. Hence, alternative interpretations exist for previous studies of the innervation pattern of the suprahyoid muscles, and it has not been conclusively demonstrated that projections to the muscles are bilateral with contralateral dominance.

In this study, our attention focused on MEPs of contralateral suprahyoid muscles. We demonstrated that MEPs from contralateral suprahyoid muscles, recorded by surface EMG, were highly reproducible without laterality. We also obtained only MEPs of the contralateral suprahyoid muscles in needle EMG recordings, though surface EMG responses were obtained from bilateral suprahyoid muscles by TMS in healthy subjects. In addition, we confirmed that there was a medullary infarction in one case in which we did not obtain MEPs of the contralateral suprahyoid muscles by TMS using surface EMG recording.

4.1. Suprahyoid muscles MEPs after cortical stimulation

As would be expected from Penfield's homunculus, the hot spot for eliciting MEPs in masticatory muscles with focal TMS was anterolateral to that of the contralateral hand area [5]. The mylohyoid responses were more anterolateral than the pharyngeal responses, which, in turn, were more anterolateral than the esophageal responses [9]. When compared to the four extremities, the amplitudes of MEPs reported previously for the pharynx and mylohyoid muscles were small and required relatively high TMS intensities [9].

We considered that an angle of stimulating coil for nasion-inion line was one of the important factors to decide the location of the hot spot. The location of the hot spot in report of Plowman-Prine EK *et al.*was different from our results [10]. However, the direction of coil was different from this study. In this study, location of the hot spot was analogous with Hamdy *et al* using the same direction of coil [4].

We confirmed that cortical motor projections to the left and right suprahyoid muscles could be stimulated in all healthy adults under conditions in which the stimulus site and stimulus intensity avoided direct ipsilateral activation of the trigeminal nerve. Our results demonstrated that MEPs from contralateral suprahyoid muscles were obtained from the suprahyoid muscles in all subjects at the hot spot, which lends further support for results from previous studies [4, 9]. We conclude that corticobulbar projections to the suprahyoid muscles involve contralateral projections, without exception. In addition, there was no left-right asymmetry in the latencies of MEPs in any of our subjects, representing a wide range of ages.

During our experimental procedures, all subjects were instructed to remain as relaxed as possible because a relaxed state of the suprahyoid muscles was required to minimize fluctuations in response latencies [8]. In a previous study, voluntary contraction of the anterior digastric muscle (approximately 10% maxi-

Table 1 Motor threshold and hot spot data for each healthy subject

Subjects	Hemisphere	Motor threshold (tesla)	Hot spot (cm) lateral from Cz	Hot spot (cm) anterior from Cz
1	Right	1.1	6.5	3.5
	Left	1.2	6.5	5.0
2	Right	1.3	7.5	3.0
	Left	1.3	7.0	3.5
3	Right	1.3	6.0	5.5
	Left	1.4	7.0	4.5
4	Right	1.4	8.0	5.0
	Left	1.4	6.5	3.5
5	Right	1.3	7.0	4.5
	Left	1.3	8.5	5.5
6	Right	1.1	6.5	3.5
	Left	1.2	7.5	4.0
7	Right	1.1	5.5	6.0
	Left	1.2	5.5	5.0
8	Right	1.3	8.5	5.0
	Left	1.3	6.0	4.0
9	Right	1.4	7.5	4.5
	Left	1.4	7.5	6.0
10	Right	1.3	8.5	5.0
	Left	1.3	6.0	4.0
11	Right	1.3	5.5	5.0
	Left	1.3	6.0	3.0
12	Right	1.2	7.5	4.0
	Left	1.1	8.0	4.0
13	Right	1.3	7.5	4.5
	Left	1.3	7.0	7.0
14	Right	1.3	6.5	4.0
	Left	1.2	6.0	4.0
15	Right	1.2	5.5	4.0
	Left	1.2	6.0	5.0
16	Right	1.2	6.0	4.0
	Left	1.1	6.0	4.0
17	Right	1.4	6.0	3.5
	Left	1.4	6.0	3.5
18	Right	1.3	6.5	4.5
	Left	1.4	7.0	3.0
19	Right	1.3	7.5	5.5
	Left	1.4	8.0	5.5
20	Right	1.3	7.5	4.5
	Left	1.3	7.0	4.0
21	Right	1.4	6.0	4.5
	Left	1.4	6.5	5.5
22	Right	1.1	6.0	3.0
	Left	1.2	5.5	3.5
23	Right	1.3	6.0	4.0
	Left	1.3	6.0	4.0
24	Right	1.4	6.5	4.5
	Left	1.3	6.0	4.0
25	Right	1.4	8.5	5.5
	Left	1.4	8.0	7.0
26	Right	1.3	6.0	4.5
	Left	1.3	6.0	4.5
27	Right	1.2	6.0	3.5
	Left	1.1	6.5	3.0
28	Right	1.4	8.0	6.5
	Left	1.4	8.0	5.5
29	Right	1.4	7.5	5.5
	Left	1.3	8.0	5.5
30	Right	1.3	8.0	5.0
	Left	1.3	8.5	6.0
31	Right	1.3	7.5	5.0
	Left	1.3	7.5	5.0
32	Right	1.3	7.0	4.0
	Left	1.4	7.0	4.5
33	Right	1.1	6.5	3.0
	Left	1.1	6.0	3.5
34	Right	1.4	8.0	7.0
	Left	1.3	8.0	6.0
35	Right	1.4	7.5	5.0
	Left	1.4	7.5	5.5
36	Right	1.3	8.0	4.0
	Left	1.4	7.5	5.5
37	Right	1.3	6.5	4.0
	Left	1.3	6.5	4.0
38	Right	1.2	6.0	3.0
	Left	1.1	6.0	3.0
39	Right	1.2	7.5	4.0
	Left	1.2	7.0	4.0
average	Right	1.3	6.9	4.5
	Left	1.3	6.8	4.6

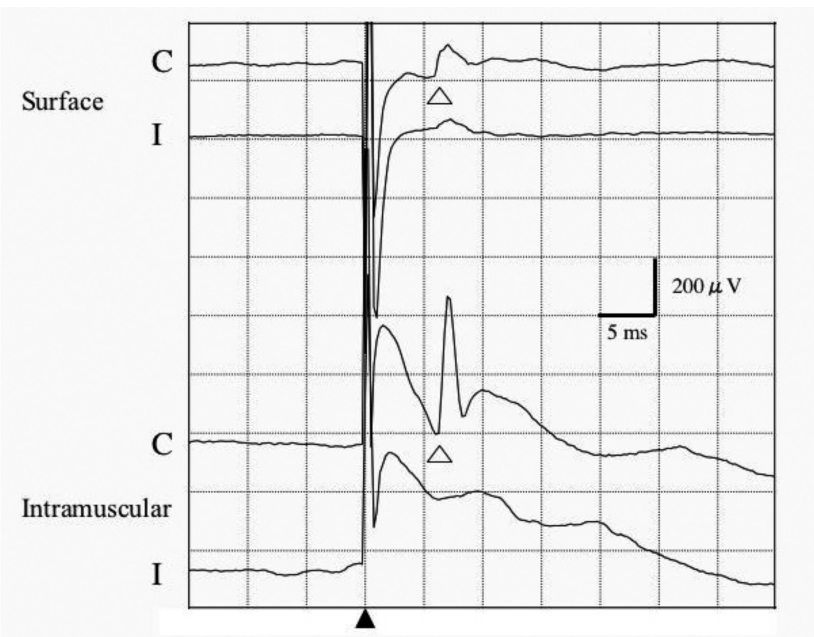

Fig.3 Cortically evoked EMG responses recorded in one healthy subject (45 year-old, male) from contralateral & ipsilateral suprahyoid muscles.
Distance between lines represents 5 ms on the horizontal axis, and 200 μV on the vertical axis.
I: ipsilateral suprahyoid muscles
C: contralateral suprahyoid muscles

Table 2 First and 2nd test of motor threshold and hot spot data for each healthy subject

		Motor threshold (tesla)		Hot spot (cm) lateral from Cz		anterior from Cz	
Subjects	Hemisphere	1st	2nd	1st	2nd	1st	2nd
1	Right	1.1	1.1	6.5	6.0	3.5	4.0
	Left	1.2	1.2	6.5	6.5	5.0	5.0
2	Right	1.3	1.3	7.5	7.0	3.0	4.0
	Left	1.3	1.3	7.0	7.0	3.5	3.5
3	Right	1.3	1.3	6.0	6.5	5.5	5.0
	Left	1.4	1.4	7.0	7.0	4.5	5.0
4	Right	1.4	1.4	8.0	8.0	5.0	5.0
	Left	1.4	1.4	6.5	7.0	3.5	4.0
5	Right	1.3	1.3	7.0	7.0	4.5	4.5
	Left	1.3	1.3	8.5	8.0	5.5	6.0
6	Right	1.1	1.1	6.5	6.5	3.5	3.5
	Left	1.2	1.2	7.5	7.0	4.0	5.0
7	Right	1.1	1.1	5.5	5.5	6.0	5.5
	Left	1.2	1.2	5.5	6.0	5.0	5.0
8	Right	1.3	1.3	8.5	8.5	5.0	4.5
	Left	1.3	1.3	6.0	6.5	4.0	4.0

mum) facilitated the amplitude of contralateral MEPs [5], which was more strongly affected than latency [8]. Therefore, a subject's level of relaxation may require electromyographic monitoring in future studies.

4.2. MEPs in needle EMG and surface EMG recordings

For cortical projections to the neck muscles, sternomastoid innervation appears to be midway between that of distal muscles and axial muscles that are synergic and always coactivatied bilaterally, such as the diaphragm [11]. Similar results were found for the splenius, but innervation of the trapezius seems exclusively contralateral. [7, 8].

In this protocol, MEPs from contralateral suprahyoid muscles were recorded using needle EMG and surface EMG at the same time. As a result, it was confirmed that contralateral MEPs were a consequence of stimulation in the contralateral suprahyoid muscles by TMS. This result lends further support to the validity of MEPs latencies obtained from contralateral surface recordings. On the other hand, we obtained larger responses in the contralateral suprahyoid muscles than in ipsilateral suprahyoid muscles from the surface EMG recordings, but only on the contralateral needle EMG recordings. Therefore, ipsilateral responses seemed to be due to cross-talk. These results support our conclusion that corticobulbar projections to the suprahyoid muscles are mainly contralateral.

However, the possibility remains that needle electrodes were not properly placed in the ipsilateral suprahyoid muscle, so that ipsilateral MEPs might have been missed by the needle recording. Further study might be necessary to determine whether corticobulbar projections to the suprahyoid muscles are bilaterally or contralaterally dominant.

4.3. Reproducibility of Suprahyoid MEPs

Even when the second test was conducted without disclosing the hot spot from the first test, high reproducibility was observed for the latencies of MEPs. It was confirmed that the cortical motor projection to the contralateral suprahyoid muscles could be stimulated repeatedly in a stable manner by TMS.

Therefore, failure to obtain MEPs from the suprahyoid muscles by TMS, according to the measurement methods in the present study, may indicate a pathological finding.

4.4. Patient

In the patient with a right medullary infarction, the MEPs of the contralateral suprahyoid muscles could not be stimulated using TMS, thus it indicated the possibility of an abnormality. With regard to the patient's VF findings during the pharyngeal stage, impaired hyoid bone and laryngeal raising was mild. By as-

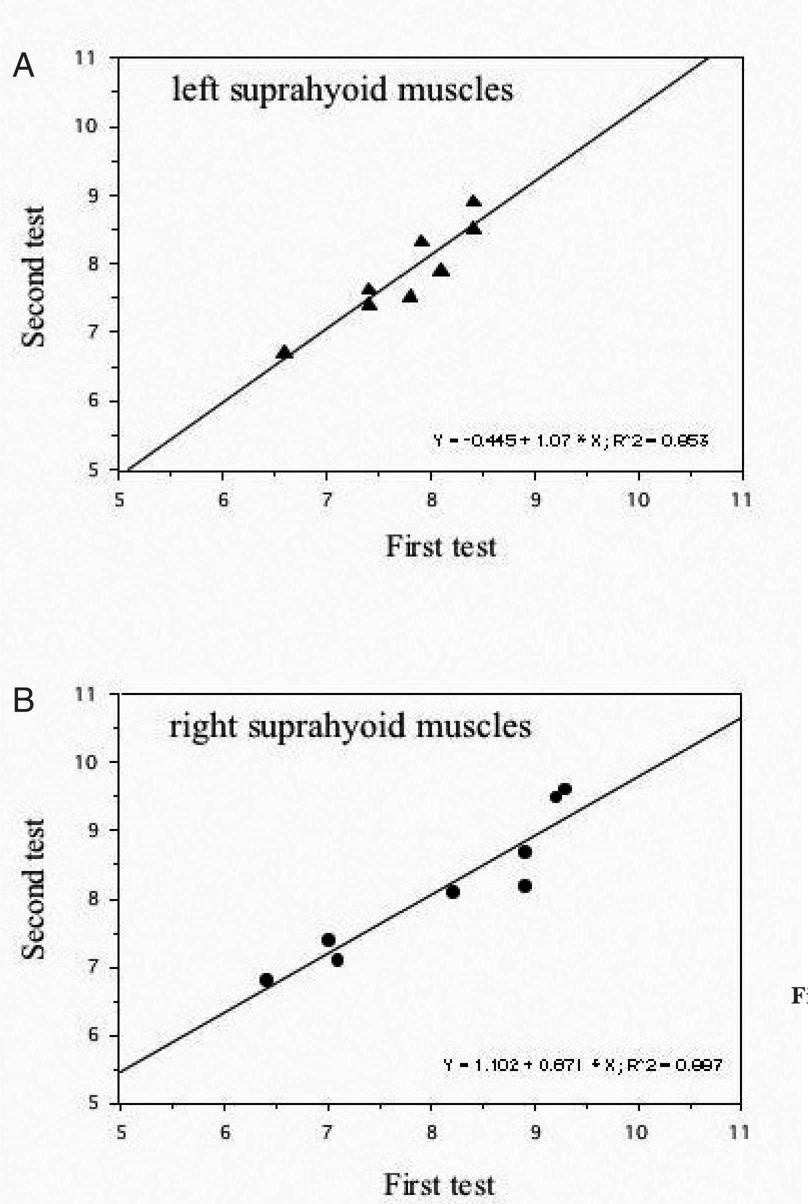

Fig.4 Reproducibility of suprahyoid MEPs latency
A: Left suprahyoid muscles MEPs latency by TMS of the right hemisphere.
B: Right suprahyoid muscles MEPs latency by TMS of the left hemisphere.

suming that there is left and right dominance in the cortical motor projection to the suprahyoid muscles, the possibility that the non-dominant side controlling swallowing function was impaired could not be denied. It is possible that swallowing function was maintained, even when the cortical motor projection to the suprahyoid muscles was impaired, irrespective of dominance.

Although the human swallowing center is supposed to be located in the medulla oblongata, its entire picture including left and right dominance has not been clarified. According to Vuilleumier *et al.* (1995) and Kim *et al.* (1994), when dividing the medulla oblongata into rostral and caudal portions, bulbar symptoms such as swallowing difficulty are marked with rostral damage [12, 13]. In the present patient, the infarct lesion was caudal, thus agreeing with the finding that swallowing difficulty was mild. However, swallowing difficulty may not become marked even if damage is rostral [14]. In this study, we considered that the patient had some damage on the right side of the nucleus of the spinal tract of the trigeminal nerve, and that this may be the reason why MEPs of the contralateral suprahyoid muscles could not be recorded. Using MRI imaging, we located the lesion in the right medulla oblongata. However, it was possible that the latencies of the left suprahyoid muscles were affected by edema in the acute stage. It is assumed that chronologic assessment from the acute stage to the chronic stage may be necessary in future studies.

In this study, we obtained larger responses in the contralateral suprahyoid muscles than in the ipsilateral suprahyoid muscles using surface EMG recordings, but only on the contralateral intramuscular EMG recording. These results support the conclusion that the corticobulbar projections to the suprahyoid muscles are contralaterally dominant. We concluded that the corticobulbar projections to the suprahyoid muscles involve contralateral terminations without exception in healthy subjects. In future studies, it may be necessary to clarify the right-left dominance at the level of the brainstem and cerebral hemispheres to further clarify the details of the corticobulbar projections to the suprahyoid muscles.

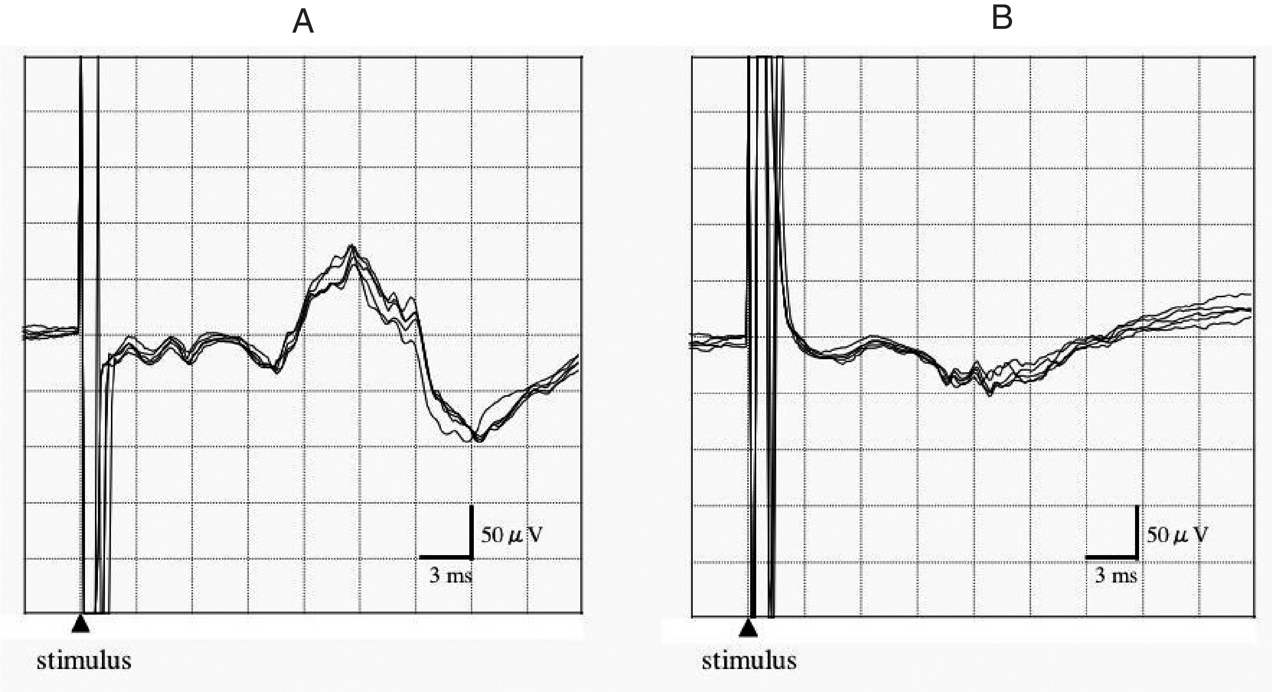

Fig.5 Cortically evoked EMG responses recorded in one patient from the contralateral suprahyoid muscles. Distance between lines represents 3 ms on the horizontal axis, and 50 μV on the vertical axis. A = left suprahyoid muscles. B = right suprahyoid muscles.

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