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Human Cortical Motor Representation of the Larynx as Assessed by Transcranial Magnetic Stimulation (TMS)

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***Objectives:* To analyze characteristic features and details on motor-evoked potentials (MEPs) of the cricothyroid and vocalis muscles from single-pulse cortical transcranial magnetic stimulation (TMS) in normal subjects to characterize cortical motor representation of laryngeal muscles. *Study Design:* Prospective, experimental investigation on healthy volunteers. *Method:* MEPs of the cricothyroid and vocalis muscles elicited by cortical TMS with a figure–8-shaped coil were investigated in two groups of six healthy subjects each, with special regard to MEP amplitude as a function of the coil position on the head surface along the interaural line. *Results:* Bilateral reproducible responses of the cricothyroid and the vocalis muscles could be observed in all subjects. For the cricothyroid muscle, maximal responses were obtained at mean stimulus positions of 7.5 ± 1.4 cm (contralateral) and of 7.3 ± 1.3 cm (ipsilateral), respectively. For the vocalis muscle, we found maximal responses at mean stimulus positions of 10.3 ± 1.9 cm (contralateral) and of 9.6 ± 1.6 cm (ipsilateral), respectively. Despite a considerable overlap of these coil positions, from which reproducible MEPs could be elicited in both groups of the laryngeal muscles, statistically significant separation of the cricothyroid- and vocalis-associated cortical representation areas was possible. *Conclusions:* Our observations point to two different cortical motor representation areas, with the cricothyroid muscle-related area being located more medially. *Key Words:* Larynx, cricothyroid muscle, vocalis muscle, cortical representation, transcranial magnetic stimulation.**

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INTRODUCTION

Cortical representation of laryngeal muscles often is assumed to be localized in the most lateral part of the motorcortex. There are, however, only few reports on larynx-associated cortical motor representation areas.[1–3]

Transcranial magnetic stimulation (TMS), which was first introduced by Barker et al.,[4] offers a painless and noninvasive method of cortical stimulation. By use of focal stimulating coils, the somatotopical arrangement of the motorcortex according to the traditional homunculus could be confirmed.[5,6] On the basis of our own previous investigations on lingual and facial muscles,[7–10] we see that not only a characterization but also statistically significant separation of cortical motor representation areas of lingual, frontal, periocular, and the lower-lip mimetic muscles is possible by cortical TMS.

Motor-evoked potentials (MEPs) from laryngeal muscles can be elicited by cortical TMS, as has been reported by other investigators.[11,12] The aim of the present study was to investigate the electroneurographic features of the laryngeal representation at the cortical level in healthy volunteers to provide normative data with regard to future studies in patients with vocal-fold mobility disorders. Another question examined by our study was the possibility of separation between the representation areas of the cricothyroid muscle and those laryngeal muscles that are innervated by the recurrent laryngeal nerve, such as the vocalis muscle.

In contrast with facial and lingual muscles, recording of the laryngeal MEPs poses special difficulties to the investigators. The use of surface electrodes is not possible because the larynx is covered by thick layers of extralaryngeal muscles, such as the sternohyoid, sternothyroid, and the thyrohyoid muscles. Regardless of whether recording is performed transorally or transcutaneously, needle electrodes are required and may cause some inconvenience to the subjects because of pain and salivation. Furthermore, the correct position of the needle electrodes has to be monitored and adjusted during the investigation with regard to possible dislocation caused by accidental neck movements or swallowing. In conclusion, for laryn-

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geal studies with TMS, short examination procedures have to be achieved. The more commonly performed two-dimensional cortical mapping procedures provide detailed information on the cortical representation area investigated, but they require a large number of stimuli from various coil positions and may, therefore, be time consuming. Thus, the present study was focused on quantification of the larynx-associated cortical representation area along the interaural line as demonstrated successfully in previous investigations on other target muscles.[7–10,13]

SUBJECTS AND METHODS

Two groups of six healthy volunteers (group A, 6 males, mean age 32.8 years, median age 24.5 years, range 23–45 years; group B, 3 females and 3 males, mean age 30.2 years, median age 26 years, range 23–45 years) took part in our investigation. Two volunteers participated in both groups. The study was approved by the Ethics Committee of the University of Göttingen and complied with the declaration of Helsinki. All participants were informed in detail about the examination procedure and gave their written consent to participate in the study.

The cricothyroid and vocalis muscles on each side were investigated as representatives of the superior laryngeal and recurrent laryngeal nerve system. MEPs were recorded bilaterally transcutaneously from left and right cricothyroid muscles (group A) by concentric needle electrodes (Erich Jaeger GmbH, Höchberg, Germany) and transorally from left and right vocalis muscles (group B) by hooked-wire electrodes (Inomed GmbH, Teningen, Germany), which were placed after surface spray anesthesia (Tetracaine 2%) into the true vocal cords under zoom endoscopic control in the awake subject. Application of the hooked-wire electrodes was performed by use of a special electrode-holding forceps (Inomed GmbH, Teningen, Germany). The correct position of the electrodes was controlled in both groups of subjects by additional spontaneous electromyogram recordings while the subjects were asked for a short voluntary phonation. The ground electrode was fixed at the proximal part of the arm. Single-pulse TMS was performed with a Novametrix Magstim 200 HP device discharging by way of a figure–8-shaped coil (double 70 mm coil; Magstim Co. Ltd, Whitland, UK) tangentially orientated over the scalp and aligned in the parasagittal plane with its handle pointing backward. Recordings were taken simultaneously ipsi- and contralateral to the stimulation side at rest without any voluntary background activity.

As a first step, the optimum coil position (OPS) on the interaural line was evaluated for each subject. At this coil position, the subject's individual threshold was determined. The recordings were then taken at 120% of the subjects' individual thresholds. The coil was moved stepwise along the interaural line at subsequent coil positions 1 cm apart between 1 and 13 cm lateral to the vertex. To minimize the inconvenience for the subjects resulting from needle electrodes, the number of consecutive MEP recordings taken from each coil position was limited to two to obtain short examination procedures. A dental suction device was used to minimize inconvenience caused by salivation. Positions where no MEPs could be produced were assigned a value of 0. Recordings were first analyzed and then averaged in amplitude and latency using a special amplifier (Micromed, Freiburg, Germany) with high and low pass filters set at 20 Hz and 3 kHz, respectively. We determined the mean (peak-to-peak) amplitude as well as the mean onset latency for each coil position. For further analysis, amplitudes were normalized with reference to the maximal evoked MEP (100%) in a mediolateral direction.

According to our previous studies,[7–10] the following variables were used to characterize MEPs as a function of the scalp positions stimulated by cortical TMS along the interaural line:

1. The optimum stimulus position on the interaural line from which maximal mean MEP amplitudes could be elicited (OPS);
2. The calculated mediolateral center defined as $CC = \Sigma A_i \times d_i / \Sigma A_i$, where CC = calculated center, A = relative amplitude, d = coil distance from the vertex, and i = coil position on the interaural line. This variable represents the amplitude-weighted center of the excitable cortical area (center of gravity) on the interaural line;
3. The number of scalp positions on the interaural line from which MEP amplitudes of at least one third could be elicited (A33);
4. The number of scalp positions on the interaural line from which MEP amplitudes of at least two thirds could be elicited (A67);
5. The mean MEP amplitudes at the optimum stimulus positions on the interaural line and in anterior-posterior direction (AOPS); and
6. The mean onset latency at the optimum stimulus position (LOPS).

Side-to-side comparisons within each group were performed with the paired t test. Despite the fact that there were two subjects participating in both groups, for comparisons between both groups, the unpaired t test was used because variability between individuals was assumed to be larger than within individuals. Results were regarded as significant when $P < .05$.

RESULTS

Bilateral MEPs could be elicited because of cortical TMS at various scalp positions, mostly between 2 and 13 cm lateral to the vertex on the interaural line in all subjects of both groups. The mean stimulus intensity was 69% of the maximum stimulator output (range 55–75%) for the cricothyroid and 75% (range 70–80%) for the vocalis muscle. The typical aspect of the cortical evoked bilateral MEPs is shown in Figure 1. The variables investigated are summarized in Table I. At coil positions more than 13 cm lateral to the vertex, no reproducible responses could be obtained. This was because the overlying concha did not permit close contact between the stimulating coil and the head surface.

For each subject, data obtained from the left and right hemisphere were averaged because there was no evidence of any difference in side (left vs. right hemi-

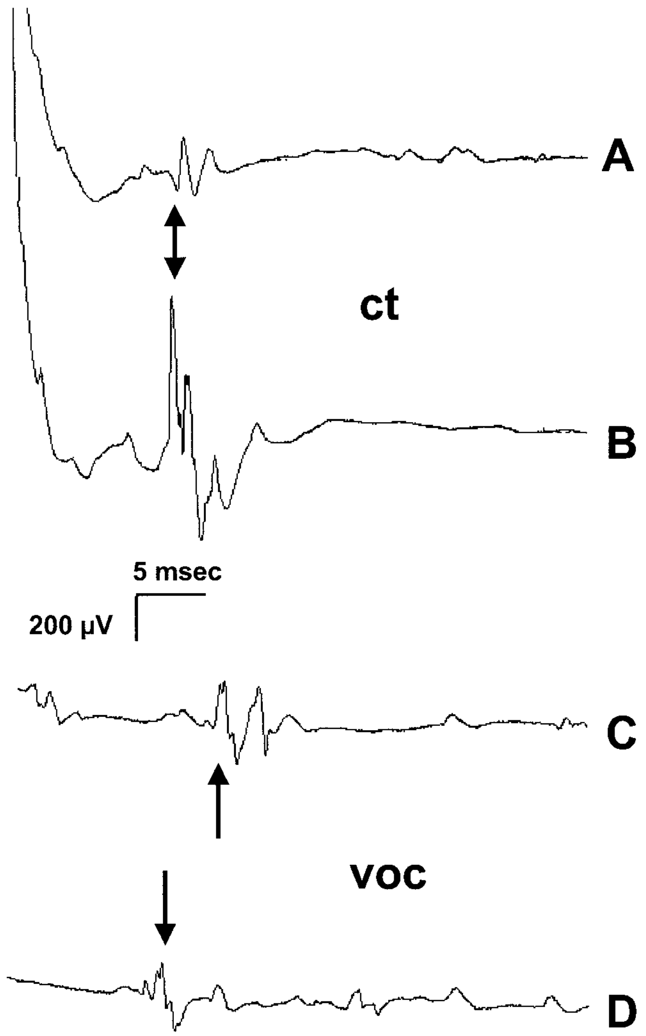

Fig. 1. Typical aspect of bilateral motor-evoked potentials (MEPs) (arrows) of cricothyroid (ct) and vocalis (voc) muscles resulting from cortical transcranial magnetic stimulation (TMS). Trace A/B = cricothyroid muscle, ipsilateral/contralateral response; trace C/D = vocalis muscle, ipsilateral/contralateral response.

sphere) or in dominance (dominant vs. nondominant hemisphere) for all variables investigated ($P > .05$) within each group.

Comparing ipsi- and contralateral mean amplitudes between both groups, we saw there was a wide overlap of those scalp positions from which cricothyroid and vocalis muscle could be stimulated but with a clear tendency of the cortical representation area of the cricothyroid muscle to lie more medial than the vocalis muscle (Fig. 2). This observation is supported by significant differences between the calculated centers (CC) and the OPS.

For the cricothyroid muscle, mean onset latency was 10.8 ± 1.7 milliseconds and 10.1 ± 1.5 milliseconds for ipsi- and contralateral responses, respectively. For the right vocalis muscle, we observed mean onset latencies of 10.7 ± 1.7 milliseconds (ipsilateral stimulation) and 10.8 ± 1.8 milliseconds (contralateral stimulation). For the left vocalis muscle, mean onset latency was prolonged up to 11.7 ± 2.4 milliseconds (ipsilateral stimulation) and up to 11.1 ± 1.8 milliseconds (contralateral stimulation).

DISCUSSION

The bilateral responses of the laryngeal muscles that we could elicit by cortical TMS confirm the bilateral cortical motor representation of the larynx. Mean onset latencies of approximately 10 milliseconds were of similar size as those reported in previous studies on the mimetic and lingual muscles,[5,7–10,14–16] pointing to the primary motorcortex as the site of excitation. In contrast with facial and lingual muscles, however, data obtained on the laryngeal muscles caused by cortical TMS are rare. Thumfart et al.[11] reported on muscle responses in 52 healthy subjects with onset-latencies between 9.5 and 12 milliseconds. The investigators used bipolar hooked-wire electrodes, which were placed transorally into the vocalis and the posterior cricoarytenoid muscle. Khedr and Aref[12] investigated MEPs of the thyroarytenoid and cricothyroid muscles in 26 normal subjects. Recordings on both target muscles were taken with concentric-needle electrodes. Cortical stimulation elicited bilateral responses in both muscles in a similar manner to our observations. Onset latencies reported varied between 8.3 and 11.3 milliseconds, with statistically significant prolongation for the left thyroarytenoid muscle caused by the elongated course of the left recurrent laryngeal nerve. In our study, there was a tendency toward longer latencies for the left vocalis muscle, but a statistically significant side-difference could not be evaluated, which may be because of the small number of volunteers.

Only few experimental studies exist on the cortical motor representation of the larynx. Penfield and Boldrey[1] described "vocalization" caused by direct cortical electrical stimulation (DCES) in a localized area in the human precentral gyrus, which was between the area for eyelid movements above and mouth below. In another study,[2] this area of vocalization was reported to have no fixed relation to the somatotopical sequence of elements of the face area. Because laryngeal and extralaryngeal muscles both contribute to the process of vocalization, this cortical motor area described cannot be considered as specific for laryngeal muscles. Thus, in our opinion, the primary cortical motor origin of the motor responses elicited could not be fully confirmed. In the rhesus monkey, contractions of the laryngeal muscles could be observed that were caused by DCES in an area between the subcentral dimple caudally and the inferior branch of the arcuate sulcus rostrally occupying the lateral-most position of the motorcortex.[3] This region, however, is normally considered to be premotor rather than motor.[17] Because laryngeal activation was not detected by use of MEP recordings, no data on onset latencies of laryngeal responses caused by DCES were described in those studies. In contrast with humans, however, there is no evidence of direct connections between the motorcortex and the laryngeal motoneurons in monkeys, suggesting that this connection has evolved in the last few million years, representing one of the factors that made speech evolution possible.[18]

Despite various reports on cortical mapping of various target muscles by use of focal cortical TMS, no data

TABLE I.
Summary of Variables Characterizing the Cortical Representation of the Cricothyroid and the Vocalis Muscle Along the Interaural Line as Assessed by Cortical Transcranial Magnetic Stimulation.

Variable	Cricothyroid Muscle (Group A)	Vocalis Muscle (Group B)	Significance (Student's Unpaired *t* test)
$\mathrm{CC}_{\mathrm{contra}}$/cm	7.3 ± 0.4 (6.4–8.2)	9.0 ± 0.5 (7.5–10.4)	<.0001
$\mathrm{CC}_{\mathrm{ipsi}}$/cm	7.1 ± 0.6 (5.8–8.0)	9.1 ± 0.9 (6.8–12.8)	<.002
$\mathrm{OPS}_{\mathrm{contra}}$/cm	7.5 ± 1.4 (5–11)	10.3 ± 1.9 (6–13)	<.02
$\mathrm{OPS}_{\mathrm{ipsi}}$/cm	7.3 ± 1.3 (4–11)	9.6 ± 1.6 (8–13)	<.02
$\mathrm{A33}_{\mathrm{contra}}$	7.4 ± 1.2 (6.0–9.5)	8.3 ± 2.2 (4–10.0)	NS
$\mathrm{A33}_{\mathrm{ipsi}}$	7.7 ± 2.2 (5.5–11.0)	8.1 ± 1.7 (7.0–10.5)	NS
$\mathrm{A67}_{\mathrm{contra}}$	4.0 ± 1.6 (2.0–6.0)	4.3 ± 3.0 (1.0–7.5)	NS
$\mathrm{A67}_{\mathrm{ipsi}}$	3.9 ± 1.7 (1.5–6.0)	4.7 ± 1.5 (2.5–6.5)	NS
$\mathrm{A}_{\mathrm{OPS\ contra}}$/mV	0.44 ± 0.42 (0.06–1.24)	0.23 ± 0.20 (0.02–0.61)	–*
$\mathrm{A}_{\mathrm{OPS\ ipsi}}$/mV	0.57 ± 0.43 (0.06–1.15)	0.27 ± 0.27 (0.03–0.88)	–*

CC = mediolateral calculated center; OPS = optimum stimulation position on the interaural line; AOPS = mean amplitude at OPS; A33 (A67) = number of those coil positions from which MEP amplitudes of at least one third (two thirds) of the maximum mean amplitude could be elicited; ipsi (contra) = ipsilateral (contralateral) to the stimulation side; NS = not significant.

*Comparison not useful because of different recording techniques.

have been published on the MEP amplitude of the laryngeal muscles as a function of the coil position on the head surface reflecting cortical representation patterns of the laryngeal muscles in humans. For the activation of the contralateral laryngeal muscles, the point of optimum excitability, which may coincide with the center of the larynx-associated representation area, was described to be approximately 8 cm lateral and 1 cm anterior to the vertex by use of a figure-8 coil.[12] In the study of Thumfart et al.,[11] the coil was centered 4 cm below the vertex for cortical stimulation. Because they used a circular coil with a diameter of 8.5 cm, this OPS described appears to be similar. Both groups of investigators did not further separate between the laryngeal muscles innervated by the superior laryngeal and the recurrent laryngeal nerves, respectively. In our study, the localization of the OPS lateral to the vertex was approximately 7.5 cm for the cricothyroid and approximately 10 cm for the vocalis muscles. Cortical stimulation performed only from OPSs, however, provides no information about the amplitude of the MEPs in relation to the stimulating-coil position and bears the risk of errors. Thus, with regard to a comparison of different target muscles, the mediolateral CC is a more sensitive parameter to characterize a cortical motor representation area. This variable reflects its mediolateral extension as well as the mean amplitudes at each coil position.[7–10,19] With regard to OPS and CC, we observed statistically significant differences between the cricothyroid and vocalis muscles despite a considerable overlap of coil positions from which reproducible MEPs could be elicited in target muscles both ipsi- and contralaterally to the stimulation side. These findings seem to be consistent with two separate representation areas on the human primary motor-cortex for the laryngeal muscles innervated by the superior laryngeal and the recurrent laryngeal nerves. Similar data on A33 and A67 for both laryngeal muscles may point to a similar mediolateral extension of both cortical representation areas. It has to be pointed out that the area from which cortical MEPs can be elicited by TMS does not represent the size of the cortical motor representation field obtained by DCES.[20] Because the site of stimulation even in so-called focal coils is up to 4 cm long, a similar area within the brain may be activated. Thus, stimulation of a circumscript cortical area may be possible, at least partially from distant coil positions.[21] Nevertheless, CC, A33, and A67 are useful variables for in vivo investigations on the somatotopical arrangement of the cortical motor representation areas and for monitoring changes in the cortical representation patterns caused by nerve lesions in humans.

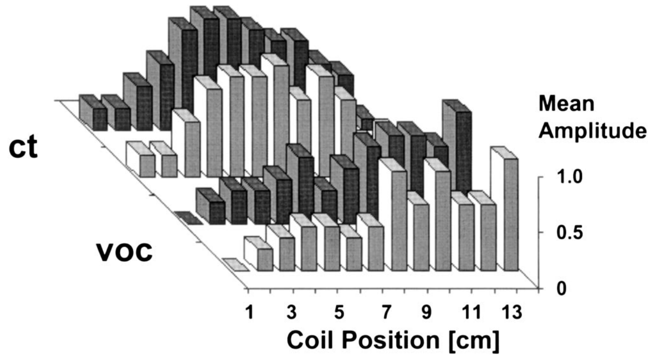

Fig. 2. Mean relative amplitudes of cricothyroid (ct) and vocalis (voc) muscles obtained by focal cortical transcranial magnetic stimulation (TMS) along the interaural line. Ipsilateral responses (white columns); contralateral responses (dark columns).

Comparing the results of the present study with those obtained in our previous investigations on distal hand, facial, and lingual muscles,[7–10] values on CC and OPS are similar to those of the lower-lip muscles for the cricothyroid muscle and to those of forehead muscles for the vocalis muscle. Because the area of speech arrest was found to be congruous with the region of facial motor responses,[22] this fact has to be taken into account in TMS studies on facilitation or inhibition of speech with regard to an accidental simultaneous stimulation of the laryngeal motor area.

The traditional view of a lateral-most localization of the laryngeal muscles cannot be confirmed by our data. For more detailed information on localization and extension of the laryngeal cortical representation areas, two-dimensional cortical mapping procedures would be useful, which, however, may be time consuming and therefore inconvenient to the subjects investigated.

For a complete evaluation of the efferent pathway of the intrinsic laryngeal muscles, data on cortical representation patterns of other target muscles are needed, including the posterior cricoarytenoid muscle. This will be the subject of future investigations, which are in preparation by our group. The results may then serve as a reference for experiments in patients with vocal-fold motion restriction of various etiologies to study possible changes in cortical motor representation caused by cortical plasticity. Another interesting question will be the possibility of a selective stimulation of different intrinsic laryngeal muscles by use of special ultra focal stimulating coils, which perhaps may offer new therapeutic options in patients with vocal-fold motion disorders.

CONCLUSION

As our study indicates, a characterization of the cortical representation areas of the cricothyroid and the vocalis muscles is possible by use of one-dimensional cortical TMS along the interaural line in humans. Furthermore, a statistically significant separation of the two cortical motor representation areas is possible. These findings point to two different cortical motor representation areas for the laryngeal muscles innervated by the superior and recurrent laryngeal nerves.

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