The course of cortico-hypoglossal projections in the human brainstem
Functional testing using transcranial magnetic stimulation

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Summary
Cortico-hypoglossal projections were investigated in 11 patients with unifocal ischaemic lesions of different brainstem levels using transcranial magnetic stimulation. Lesion topography was documented by MRI studies. In seven patients the projections to the ipsi- and contralateral hypoglossal nuclei were separately affected. Pontine lesions at the ventral paramedian base close to the midline affect the contralateral projections while lateral lesions at the pontine base affect the ipsilateral projections. Lesions of the paramedian dorsal pontine base do not involve the cortico-hypoglossal projections. Our findings indicate that the cortico-hypoglossal fibres branch off the main ventral pyramidal tract. Lesions of the dorso- and mediolateral medulla impair only the ipsilateral projections. We conclude that ipsilateral projections enter the hypoglossal nucleus from its lateral aspect and that the contralateral projections cross the midline at the pontomedullary junction.

Keywords: cortico-hypoglossal projections; cortico-bulbar tract; brainstem; hypoglossal nerve; transcranial magnetic stimulation

Introduction
There is a relative paucity of information on the course of cortico-bulbar fibres in the human brainstem. Histological studies of human post-mortem material using the Marchi technique (Hoche, 1898; Barnes, 1901) resulted in the concept outlined by Dejerine (1914). More recent studies (Kuypers, 1958) have confirmed these results using the Nauta-Gygax technique.

With regard to the supranuclear hypoglossal fibres in the brainstem, it is still unclear (i) whether the fibres to the ipsi- and contralateral nuclei take separate courses in the cortico-bulbar tract; (ii) whether the ipsi- or contralateral fibres branch off the main ventral pyramidal tract (Sand, 1903) or, with other fibres, form an aberrant bundle running more dorsally near the medial lemniscus (Hoche, 1898; Dejerine, 1914); (iii) at which level these fibres branch off the main tract or aberrant bundle; and (iv) at which level they cross the midline to reach the contralateral nucleus.

Patients and methods
We report findings in 11 patients with unilocal ischaemic brainstem lesions. The localization was characterized by clinical findings and MRI studies. The cortico-bulbar projections from each hemisphere to either hypoglossal nucleus and the infranuclear pathways were investigated by transcranial magnetic activation (Muellbacher et al., 1994; Urban et al., 1994). Informed consent for this study was obtained from all participants and the study was approved by the local ethical committee.

Compound muscle action potentials were recorded in bipolar technique separately from either half of the tongue. Pairs of Ag/AgCl surface electrodes with an interelectrode distance of 18 mm were mounted on either side of a spoon-shaped metacrylate device adapted to the oral cavity. The position of the electrodes was over the lateral dorsum of the tongue. Preinnervation during cortical stimulation was achieved by pressing the tongue slightly against the mouthpiece.

Transcranial stimulation was performed using a Magstim 2005 (Novametrix) and a circular coil (mean diameter 9 cm) with a peak magnetic field of 2.0 T (according to the manufacturer’s specifications). The centre of the coil was positioned tangentially 4–6 cm lateral from Cz. For stimulation of the left (right) hemisphere, side ‘A’ (‘B’) was viewed from...
next day she showed moderate paresis and diminished sensation to touch and pinprick of her left upper and lower limbs while the cranial nerves were spared. Her speech was mildly dysarthric.

Magnetic stimulation of the left hemisphere evoked delayed responses of the right half of the tongue due to involvement of the contralateral projections. With stimulation of the right hemisphere responses were absent on the right half of the tongue and delayed on the left half, indicating impairment of the ipsi- and contralateral projections (Table 1). MRI documented a mid- to upper pontine lesion of the right basis pontis extending to the left side.

Patient 2
A 74-year-old man with a history of labile arterial hypertension suffered a sudden onset of mild dizziness, unsteady gait, slurred speech and weakness of the right side of the body. On examination speech was mildly dysarthric and he had a right supranuclear facial palsy, slight deviation of the tongue to the right side, and a right ataxic hemiparesis of the upper and lower limbs. Standing he showed ataxia with retropulsion and inability to walk.

Responses on both halves of the tongue were absent with magnetic stimulation of the left hemisphere. Stimulation of the right hemisphere showed delayed responses on the left half of the tongue. Follow-up examination after 18 days confirmed the absence of responses on both halves of the tongue to left cortical stimulation, while stimulation of the right hemisphere evoked normal responses (Table 1). MRI documented a left mid-pontine paramedian infarction of the basis pontis extending to the border of the tegmentum.

Patient 3
A 65-year-old woman with a history of arterial hypertension reported sudden weakness of her right limbs and slurred speech. On admission she showed marked dysarthria and mild ataxic hemiparesis on the right. The cranial nerves were not involved.

The only electrophysiological abnormality observed was the absence of responses on the right half of the tongue to magnetic stimulation of the left hemisphere (Table 1). MRI showed a small lower pontine lesion of the left paramedian basis pontis (Fig. 1).

Patient 4
A 60-year-old woman with a history of type II diabetes mellitus, hyperlipaemia and arterial hypertension suddenly developed weakness of the right side and slurred speech. The neurological examination showed marked dysarthria, saccadic horizontal pursuit movements, marked hemiparesis of the right upper limb and mild paresis of the lower limb. The cranial nerves were spared.

Magnetic stimulation of the left hemisphere showed no responses on the right half of the tongue and delayed responses on the left half of the tongue. Responses to right hemisphere

| Latencies (milliseconds) of the cortico-lingual conduction time following transcranial magnetic stimulation in 11 patients with ischaemic brainstem lesions. Stimulation was performed at either hemisphere and EMG registration separately from either half of the tongue. Control values (upper limit of normal findings: mean ± 2.5 SD) are based on the results in 35 volunteers. * Abnormal (delayed: more than the mean ± 2.5 SD) responses; –, responses absent. Absence of responses to right hemisphere was recorded. |
stimulation were normal (Table 1). MRI demonstrated a mid-to upper left pontine lesion of the paramedian basis pontis.

**Patient 5**

A 47-year-old woman with a history of heavy smoking was admitted following a sudden onset of slurred speech, weakness of the right arm and numbness of the right half of the body. On examination there was a mild dysarthria, mild weakness of lid closure on the right and mild right hemiparesis of the limbs. There was no tongue deviation or reduced tongue motility. Sensation to touch and pinprick was reduced on the entire right side of the body including the face.

Magnetic stimulation of the left hemisphere showed delayed responses on both halves of the tongue and normal responses to right hemisphere stimulation (Table 1). MRI revealed a left sided lesion in the upper two-thirds of the base of the pons (Fig. 2).

**Patient 6**

A 70-year-old man with long standing arterial hypertension suddenly developed slurred speech and weakness of the right side of the body. On examination, his speech was slightly dysarthric and he had a mild hemiparesis on the right side without cranial nerve involvement.
Fig. 2 MRI (T2-weighted): axial (A) and midsagittal (B) sections showing areas of increased signal intensity at the upper two thirds of the left base of the pons (Patient 5). (C) Transcranial magnetic evoked potentials of the same patient recorded at the right (upper trace) and left half (lower trace) of the tongue. Stimulation was applied to the left and right hemisphere (left and right side of the figure, respectively). Abnormal responses (greater than the mean+2.5 SD) are marked by an asterix.

Responses on both halves of the tongue were absent with magnetic stimulation of the left hemisphere (Table 1). MRI showed a left pontine infarction in the middle third of the base of the pons.

**Patient 7**

A 51-year-old man with a history of heavy smoking suddenly experienced unsteady gait. Slight dysarthria and a mild cerebellar type gait ataxia were observed on examination.

Magnetic stimulation revealed entirely normal responses (Table 1). MRI demonstrated a bilateral paramedian mid-pontine lesion at the dorsal part of the basis pontis.

**Patient 8**

A 55-year-old man with a history of labile arterial hypertension suddenly developed slurred speech and clumsiness of the right hand. On admission to hospital, he was shown to have a slight dysarthria and impaired finger motility on the right side.

Magnetic stimulation showed normal results (Table 1). MRI
Fig. 3 MRI: axial (T2-weighted) (A) and coronar (T1-weighted) (B) sections showing right-sided dorso- and mediolateral medullary lesion (Patient 11). (C) Transcranial magnetic evoked potentials of the same patient recorded at the right (upper trace) and left half (lower trace) of the tongue. Stimulation was applied to the left and right hemisphere (left and right side of the figure, respectively).

demonstrated left midpontine paramedian ischaemia of the dorsal part of the base of the pons.

Patient 9
A 67-year-old man with a 5-year history of type II diabetes mellitus and arterial hypertension reported the sudden onset of slurred speech and heaviness of his right arm with difficulty in writing. Examination revealed markedly dysarthric speech. He showed Horner’s syndrome on the left, but no further cranial nerve involvement. The tendon reflexes were increased on the right and Babinski’s sign was positive. The right upper limb showed a slight pronator drift and slowing of rapid alternating and finger movements.

Transcranial stimulation of the left hemisphere revealed absent responses on the right half of the tongue and delayed responses on the left half (Table 1). MRI documented infarction of the medial two-thirds of the left cerebral peduncle, extending as a small stripe into the left tegmental region.

Patient 10
A 73-year-old woman with a history of diabetes mellitus and arterial hypertension complained of a sudden tendency to fall
to the right side, difficulty in swallowing and hoarseness. On admission to hospital, she was found to have an impaired corneal reflex on the right, slight weakness of the right corner of the mouth, recurrent nerve paresis on the right, dysphagia, weakness of the right soft palate and slight tongue deviation to the right. Romberg’s test showed a tendency to fall to the right.

Magnetic stimulation of the right hemisphere demonstrated delayed responses on the right half of the tongue (Table 1). Electric stimulation of either peripheral hypoglossal nerve showed identical amplitudes. The patient refused electromyographic examination of the tongue. MRI demonstrated a lesion of the right upper dorso-lateral medulla oblongata near the ponto-medullary junction.

**Patient 11**

A 61-year-old man with a history of arterial hypertension noticed the sudden onset of rotational vertigo, nausea, vomiting, a tendency to fall to the right, numbness of the right face and diminished temperature sensation of the left hand. After 3 days he also developed difficulty in swallowing, hoarseness and horizontal diplopia on right lateral gaze. On admission he showed cranial nerve signs on the right such as Horner’s syndrome, mild abducens paresis, a diminished corneal reflex, weakness of the soft palate, recurrent nerve paresis and dysphagia. Tongue movements were normal. Sensation to touch was diminished on the right side of the face and sensation to pinprick and temperature was reduced over the left side of the body sparing the face. He showed severe dysmetria on the right on the finger-to-nose and heel-to-knee test and was unable to stand or to walk.

Magnetic stimulation of the right hemisphere showed absent responses on the right half of the tongue (Table 1). EMG examination of the right half of the tongue was normal. Electrical stimulation of either peripheral hypoglossal nerve showed identical amplitudes. MRI demonstrated a right-sided dorso- and mediolateral medullary lesion (Fig. 3).

**Discussion**

Cortico-bulbar fibres project bilaterally from either hemisphere to the hypoglossal nuclei (Brodal, 1981). Degeneration studies had demonstrated monosynaptic connections between the cortico-bulbar fibres and the hypoglossal nucleus neurons (Iwatsubo et al., 1990). The functional approach to the cortico-hypoglossal projections is achieved by transcranial magnetic stimulation. Muscle activity is recorded from either half of the tongue. This technique has been proven to be considerably more sensitive than the clinical examination of tongue motility (Urban et al., 1994). The present patient series has confirmed these findings. Only two out of nine patients (Patients 2 and 11) show electro-physiological impairment of the cortico-hypoglossal projections which had clinical signs of tongue movement disorder. With ischaemic cerebral lesions, the degree of limb muscle paresis correlates to increasing latency and decreasing amplitude of the muscle response following transcranial stimulation. The degree of limb paresis is considerably more sensitive than the clinical examination of tongue motility (Urban et al., 1990). The functional approach to the cortico-bulbar fibres and the hypoglossal nucleus neurons (Iwatsubo et al., 1990) has been proven to be considerably more sensitive than clinical examination of tongue motility (Urban et al., 1994). The present patient series has confirmed these findings. Only two out of nine patients (Patients 2 and 11) showed identical amplitudes. EMG examination of the right half of the tongue was normal. Electrical stimulation of either peripheral hypoglossal nerve showed identical amplitudes. MRI demonstrated a lesion of the right upper dorso-lateral medulla oblongata near the ponto-medullary junction.

**Fig. 4 Schematic drawing of pontine infarction areas affecting the contralateral cortico-hypoglossal projections only (Patients 1, 2 and 3). For didactic reasons all lesions are shown at one half of the pons. In Patient 1, the infarction was on the right side and in Patients 2 and 3 on the left side.**

Abbruzzese et al., 1991; Ferbert et al., 1992). These parameters allow estimation of the degree of functional impairment of the fast conducting and large diameter pyramidal fibres (Eisen and Shtybel, 1990). It may, therefore, be concluded that absent responses indicate a more severe affection of the projections than delayed responses. The amplitudes of the transcranial evoked potentials show a wide intra-individual variation (Amassian et al., 1989; Eisen et al., 1991). This also applies to tongue muscle responses (Urban et al., 1994). In consequence, only absent or delayed (mean + 2.5 SD) responses were considered abnormal in the present study. Control values for cortical stimulation were obtained from 35 healthy subjects (Urban et al., 1994) which were in the same range as those reported by Muellbacher et al. (1994) who investigated nine subjects with a comparable recording technique.

Results obtained in seven out of the 11 patients (Patients 1, 2, 3, 4, 9, 10 and 11) illustrate that the cortico-bulbar fibres to the ipsi- and contralateral hypoglossal nuclei may be affected separately even in the presence of monophasic brainstem lesions. Both ipsi- and contralateral projections are involved with predominantly large pontine lesions located in the paramedian base ipsilateral to the stimulated hemisphere (Patients 1, 2, 4, 5 and 6). Lesions of the ventral pontine base located close to the midline, only impair the contralateral projections (Patient 1 on stimulation of the left hemisphere; Patient 2 on first examination on stimulation of the right hemisphere; Patient 3) and the main lesions involving the ipsi- and contralateral projections extend considerably (Patient 1) or slightly (Patient 2) beyond the midline, respectively. In both patients only the contralateral fibres were disturbed. In Patient 3 the very small lesion was located in the most medial part of the pontine base and only the contralateral projections were damaged in this patient. Lesions extending to the lateral part of the basis pontis affected the ipsilateral cortico-hypoglossal projections and due to the substantial extension of these lesions...
Fig. 5 Schematic drawing of pontine infarction areas affecting ipsi- and contralateral cortico-hypoglossal projections (Patients 1, 2, 4, 5 and 6). For didactic reasons all lesions are shown at one half of the pons. In Patient 1 the infarction was on the right side and in Patients 2, 4, 5 and 6 on the left side.

Fig. 6 Schematic drawing of pontine infarction areas sparing cortico-hypoglossal projections (Patients 7 and 8). For didactic reasons all lesions are shown at one half of the pons. In Patient 7 the infarction was on the right side and in Patient 8 on the left side.

in all patients, were accompanied by contralateral projection involvement (Patients 1, 2, 4, 5 and 6). At the pontine level the cortico-hypoglossal projections were affected when the lesion reached the ventral aspect of the base of the pons (Patients 1, 2, 3, 4, 5 and 6) (Fig. 5). Lesions of the dorsal paramedian pontine base at the midpontine level did not affect the cortico-hypoglossal projections (Patients 7 and 8) (Fig. 6). Lesions of the dorso- and mediolateral medulla oblongata (Patients 10 and 11) only affected ipsilateral cortico-hypoglossal projections. This suggests that the ipsilateral supranuclear fibres enter the hypoglossal nucleus from the lateral aspect. In Patients 10 and 11, a lesion of the infranuclear hypoglossal pathway can be ruled out, due to the absence of an abnormal response of the right side of the tongue with stimulation of the left hemisphere (Urban et al., 1994). The following pattern of cortico-hypoglossal projections emerged on the basis of our findings: the fibres to the contralateral nucleus pass through the medial part of the ventral pontine base near the midline, while fibres to the ipsilateral nucleus run through the lateral part. This corresponds to the histological findings in human autopsy material (Hoche, 1898; Sand, 1903) and to results reported on degeneration and tracer studies in cats (Holstege and Kuypers, 1977; Holstege et al., 1977b).

The lesions along the cranio-caudal axis were located in the medial part of the cerebral peduncle (Patient 9), and in the upper (Patients 1, 4 and 5), mid- (Patients 2 and 6) and lower (Patient 3) base of the pons. At all of these locations the projections to the contralateral hypoglossal nucleus were affected. The more lateral location of the upper pontine level in Patient 5 was also observed by Töpper et al. (1995). Two patients (Patients 10 and 11) showed dorsolateral lesions of the upper medulla near the pontine border. In both patients only the ipsilateral cortico-hypoglossal projections were affected. The main decussation of these fibres is therefore located close to the pontomedullary junction. This corresponds to findings obtained by anterograde degeneration studies in the cat (Holstege and Kuypers, 1977).

We have thus far not found any evidence in support of cortico-hypoglossal fibres running along with an aberrant bundle described by Hoche (1898), Barnes (1901), Dejerine (1914) and Kuypers (1958). In contrast, our results are in agreement with the findings of Sand (1903) who described branching of the main ventral pyramidal tract and denied the existence of an aberrant bundle.

References


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