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Research report

Efferent subcortical projections of the laryngeal motorcortex in the rhesus monkey

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Abstract

In order to better understand the descending voluntary vocal control pathway, the efferent subcortical projections of the laryngeal motorcortex were studied in the rhesus monkey (*Macaca mulatta*). For this purpose, the left motorcortex was exposed in three animals under narcosis. By electrical brain stimulation, sites were identified yielding vocal fold adduction. Effective sites were injected with the anterograde tracer biotin dextran amine. Subcortical projections could be traced within the forebrain to the putamen, caudate nucleus, claustrum, zona incerta, field H of Forel and a number of thalamic nuclei, with the heaviest projections to the nuclei ventralis lateralis, ventralis posteromedialis, including its parvocellular part, medialis dorsalis, centralis medialis, centrum medianum and reuniens. In the midbrain, labeling was found in the deep mesencephalic nucleus. In the lower brainstem, fibers terminated in the pontine and medullary reticular formation, locus coeruleus, nucleus subcoeruleus, medial parabrachial nucleus, nucleus of the spinal trigeminal tract, solitary tract nucleus and facial nucleus. No projections were found to the nucl. ambiguus. The fact that monkeys, in contrast to humans, lack a direct connection of the motorcortex with the laryngeal motoneurons suggests that this connection has evolved in the last few million years and might represent one of the factors that made speech evolution possible.

Theme: Motor systems and sensorimotor integration

Topic: Cortex

Keywords: Larynx area; Vocal fold control; Phonation; Neuroanatomy; Motor cortex; Rhesus monkey

Abbreviations: 1, Primary somatosensory cortex, Brodmann area 1; 2, Primary somatosensory cortex, Brodmann area 2; 3, Primary somatosensory cortex, Brodmann area 3; 3n, Oculomotor nerve; 3N, Oculomotor nucleus; 3V, third ventricle; 4, Primary motor cortex; 4n, Trochlear nerve; 4V, fourth ventricle; 5, Parietal cortex, Brodmann area 5; 6N, Abducens nucleus; 6DC, Caudal dorsolateral premotor cortex; 6DR, Rostral dorsolateral premotor cortex; 6VC, Caudal ventrolateral premotor cortex; 6VR, Rostral ventrolateral premotor cortex; 7, Parietal cortex, Brodmann area 7; 7n, Facial nerve; 7N, Facial nucleus; 8, Prefrontal cortex, Brodmann area 8; 9, Prefrontal cortex, Brodmann area 9; 10, Prefrontal cortex, Brodmann area 10; 11, Prefrontal cortex, Brodmann area 11; 11N, Accessory nerve nucleus; 12N, Hypoglossal nucleus; 21, Midtemporal cortex; 22, Superior temporal cortex; 25, Area 25 of cortex; 44, Lower postarcuate cortex; 45, Lower prearcuate cortex; 46, Prefrontal cortex, Brodmann area 46; 47L, Ventrolateral prefrontal cortex; AA, Anterior amygdaloid area; ac, Anterior commissure; Acb, Accumbens nucleus; AcbC, Accumbens nucleus, core; AcbSh, Accumbens nucleus, shell; acp, Anterior commissure, posterior part; AHA, Anterior hypothalamic area, anterior part; AHi, Amygdalohippocampal area; Am, Ambiguus nucleus; amt, Anterior middle temporal sulcus; APT, Anterior pretectal nucleus; APul, Anterior pulvinar; asd, Anterior subcentral dimple; AT, Anterior thalamic nucleus; Aq, Aqueduct; B, Basal nucleus (Meynert); BIC, Nucleus of the brachium of the inferior colliculus; BL, Basolateral amygdaloid nucleus; BM, Basomedial amygdaloid nucleus; bsc, Brachium of the superior colliculus; BST, Bed nucleus of the stria terminalis; Cb1, Cerebellar lobe 1; Cb2, Cerebellar lobe 2; Cb3, Cerebellar lobe 3; cc, Corpus callosum; Cd, Caudate nucleus; Ce, Central amygdaloid nucleus; CIC, Central nucleus of inferior colliculus; Cl, Claustrum; CL, Centrolateral thalamic nucleus; CM, Central medial thalamic nucleus; CMn, Centromedian thalamic nucleus; CnF, Cuneiform nucleus; Co, Cortical amygdaloid nucleus; cp, Cerebral peduncle; cr, Corona radiata; cs, Central sulcus; ctg, Central tegmental tract; Cu, Cuneate nucleus; DB, Diagonal band; DCIC, Dorsal cortex of the inferior colliculus; Dk, Nucleus of Darkschewitsch; DM, Dorsomedial hypothalamic nucleus; DTg, Dorsomedial

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1. Introduction

From neurological studies, it is known that the motorcortical larynx area plays a crucial role in voluntary control of vocal fold movements. Bilateral destruction of this area renders patients unable to speak and sing [4]. Electrical stimulation produces isolated vocal fold movements. Such movements cannot only be obtained by electrical stimulation of the human motorcortex [16], but also that of non-human primates, such as the chimpanzee [46], rhesus monkey [24,68,79] and squirrel monkey [23,30]. These species, therefore, may be considered as potential models in the neuroanatomical investigation of the human larynx area connections. In the rhesus monkey, the motorcortical larynx area is located between the inferior ramus of the arcuate sulcus anteriorly and the subcentral dimple posteriorly [24]. Cytoarchitectonically, it corresponds to area 6, according to Brodmann [10] and area 6 bα, FCBm and F5, according to Vogt and Vogt [76], von Bonin and Bailey [77] and Matelli et al. [50], respectively. Despite its importance in vocal control, very little is known about its neuroanatomical connections.

The present study is a part of a larger study on the efferent and afferent projections of the cortical larynx area in the rhesus monkey (*Macaca mulatta*) [67]. It will concentrate on the efferent projections to subcortical structures, using the anterograde tracing technique.

2. Materials and methods

The experiments were carried out in three rhesus monkeys, *M. mulatta*, weighing 4–7 kg. The same animals were used as in a previous study describing the cortico–cortical projections of the laryngeal motorcortex [67]. Under general anesthesia (mixture of 10 mg ketamine, 2 mg xylazine, 0.02 mg atropine sulfate in 0.2 ml sterile water/kg body weight given intramuscularly every 30 min for 2.5 h) the head was fixed in a stereotaxic apparatus (David Kopf Instruments, Tujunga, USA). The skin was incised in the temporal region and the bone removed above the inferior motor cortex in a diameter of 15–20 mm. In animal 1 the dura was dissected above the stimulation area for better visualization; in animals 2 and 3 stimulation was carried out transdurally. All animals were tested on the same (left) side for better comparability. By the aid of a monopolar stainless steel electrode (shaft diameter 250 μm), the cortex was explored for sites yielding vocal fold movement when electrically stimulated. Depending upon the stimulation effects, exploration was made at 6–12 probing sites. The stimulation parameters used were monophasic rectangular pulse trains of 1 ms pulse width, 70 Hz repetition rate and 3 s train duration. During exploration, a current intensity of 500 μA was used (impedance: 14 kOhm). If a site yielding vocal fold movement was found, threshold was determined. Thresholds ranged between 320

tegmental area; DPGi, Dorsal paragigantocellular nucleus; DpMe, Deep mesencephalic nucleus; DR, Dorsal raphe nucleus; DRt, Dorsal reticular nucleus; DV, Dorsal motor nucleus of vagus; EA, Extended amygdala; ec, External capsule; ecal, External calcarine sulcus; ECIC, External cortex of the inferior colliculus; ECu, External cuneate nucleus; eml, External medullary lamina; En, Endopiriform nucleus; ex, Extreme capsule; f, Fornix; fr, Fasciculus retroflexus; Gi, Gigantocellular reticular nucleus; Giα, Gigantocellular reticular nucleus, alpha part; GPe, External globus pallidus; GPi, Internal globus pallidus; Gu, Gustatory cortex; Gus, Gustatory thalamic nucleus (VPMpc); H1, Field of Forel; Hb, Habenula; Hip, Hippocampus; IAM, Interanteromedial thalamic nucleus; iar, Inferior arcuate sulcus; ic, Internal capsule; IC, Inferior colliculus; ICo, Intercollicular nucleus; icp, Inferior cerebellar peduncle; IMD, Intermediodorsal thalamic nucleus; IO, Inferior olive; ios, Inferior occipital sulcus; IP, Interpeduncular nucleus; ips, Intraparietal sulcus; IPul, Inferior pulvinar; IRt, Intermediate reticular nucleus; La, Lateral amygdaloid nucleus; LC, Locus coeruleus; LDS, Lateral dorsal thalamic nucleus; lf, Lateral fissure; LG, Lateral geniculate; LH, Lateral hypothalamic area; Li, Linear nucleus of the raphe; Lim, Limitans thalamic nucleus; ll, Lateral lemniscus; LLd, Dorsal nucleus of lateral lemniscus; LLv, Ventral nucleus of lateral lemniscus; LPB, Lateral parabrachial nucleus; LPGi, Lateral paragigantocellular nucleus; LPul, Lateral pulvinar; LS, Lateral septal nucleus; LSO, Lateral superior olive; lu, Lunate sulcus; LV, Lateral ventricle; mcp, Middle cerebellar peduncle; MDC, Mediodorsal thalamic nucleus, caudal part; MDD, Mediodorsal thalamic nucleus, dorsal part; MDL, Mediodorsal thalamic nucleus, lateral part; MDM, Mediodorsal thalamic nucleus, medial part; ME, Median eminence; Me, Medial amygdaloid nucleus; MG, Medial geniculate nucelus; ml, Medial lemniscus; mlf, Medial longitudinal fasciculus; MnR, Median raphe nucleus; Mo5, Motor trigeminal nucleus; MPB, Medial parabrachial nucleus; MPul, Medial pulvinar; MRt, Medial reticular nucleus; MS, Medial septal nucleus; MSO, Medial superior olive; oc, Olivocerebellar tract; OPro, Orbital proisocortex; opt, Optic tract; ox, Optic chiasm; PAG, Periaqueductal gray; PaS, Parasubiculum; PC, Paracentral thalamic nucleus; PCom, Nucleus of the posterior commissure; PCRt, Parvicellular reticular nucleus; PF, Parafascicular thalamic nucleus; PH, Posterior hypothalamic area; Pi, Pineal gland; pmt, Posterior middle temporal sulcus; Pn, Pontine gray; PN, Paranigral nucleus; PnC, Pontine reticular nucleus, caudal part; PnO, Pontine reticular nucleus, oral part; PnR, Pontine raphe nucleus; Po, Posterior thalamic nucleus; POA, Preoptic area; POI, Periolivary region; PP, Peripeduncular nucleus; PPTg, Pedunculopontine tegmental nucleus; Pr, Prepositus nucleus; Pr5, Principal sensory trigeminal nucleus; PRF, Prerubral field; ProM, Promotor cortex; ps, Principle sulcus; Pu, Putamen; PVG, Paraventricular gray; py, Pyramidal tract; RAm, Retroambiguus nucleus; RMC, Red nucleus, magnocellular part; RMg, Raphe magnus nucleus; RPC, Red nucleus, parvicellular part; Rt, Reticular thalamic nucleus; RtTg, Reticulotegmental nucleus of the pons; s5, Sensory root of the trigeminal nerve; sar, Superior arcuate sulcus; SC, Superior colliculus; scp, Superior cerebellar peduncle; SFi, Septofimbrial nucleus; SI, Substantia innominata; sm, Stria medullaris of the thalamus; SN, Substantia nigra; sol, Solitary tract; Sol, Solitary tract nucleus; SO, Supraoptic nucleus; sp5, Spinal trigeminal tract; Sp5, Spinal trigeminal nucleus; Sp5O, Spinal trigeminal nucleus, oral part; spcd, Superior precentral dimple; st, Stria terminalis; STh, Subthalamic nucleus; sts, Superior temporal sulcus; SubC, Subcoeruleus nucleus; ts, Tectospinal tract; Tz, Nucleus of the trapezoid body; tz, Trapezoid body; VAL, Ventral anterior thalamic nucleus, lateral part; VAM, Ventral anterior thalamic nucleus, medial part; VAMC, Ventral anterior thalamic nucleus, magnocellular part; Ve, Vestibular nucleus; VeI, Inferior vestibular nucleus; VeL, Lateral vestibular nucleus; VeM, Medial vestibular nucleus; VeS, Superior vestibular nucleus; VLL, Ventral lateral thalamic nucleus, lateral part; VLM, Ventral lateral thalamic nucleus, medial part; VMH, Ventromedial hypothalamic nucleus; VP, Ventral pallidum; VPL, Ventral posterolateral thalamic nucleus; VPM, Ventral posteromedial thalamic nucleus; VRt, Ventral reticular nucleus; VTA, Ventral tegmental area; xscp, Decussation of the superior cerebellar peduncle; ZI, Zona incerta

and 410 μA. A repetition rate of 70 Hz was chosen as, with the macroelectrodes used, this was the lowest rate with which a smooth (non-quavery) vocal fold movement was obtained; at the same time, the area yielding such a movement was smaller than when higher repetition rates were used. The exploration area was limited rostrally by the inferior branch of the arcuate sulcus, caudally by the subcentral dimple, ventrally by the Sylvian fissure and dorsally ca. 12 mm above the Sylvian fissure (Fig. 1). This area has been shown by Hast et al. [24] to contain the thyroarytenoid, cricothyroid and external laryngeal muscle representation in the rhesus monkey. Vocal fold movements were observed by indirect laryngoscopy. The type of vocal fold movement obtained in all subjects was an isolated bilateral symmetrical vocal fold adduction without laryngeal elevation. No changes in vocal fold length could be detected.

When a site producing vocal fold adduction was found,

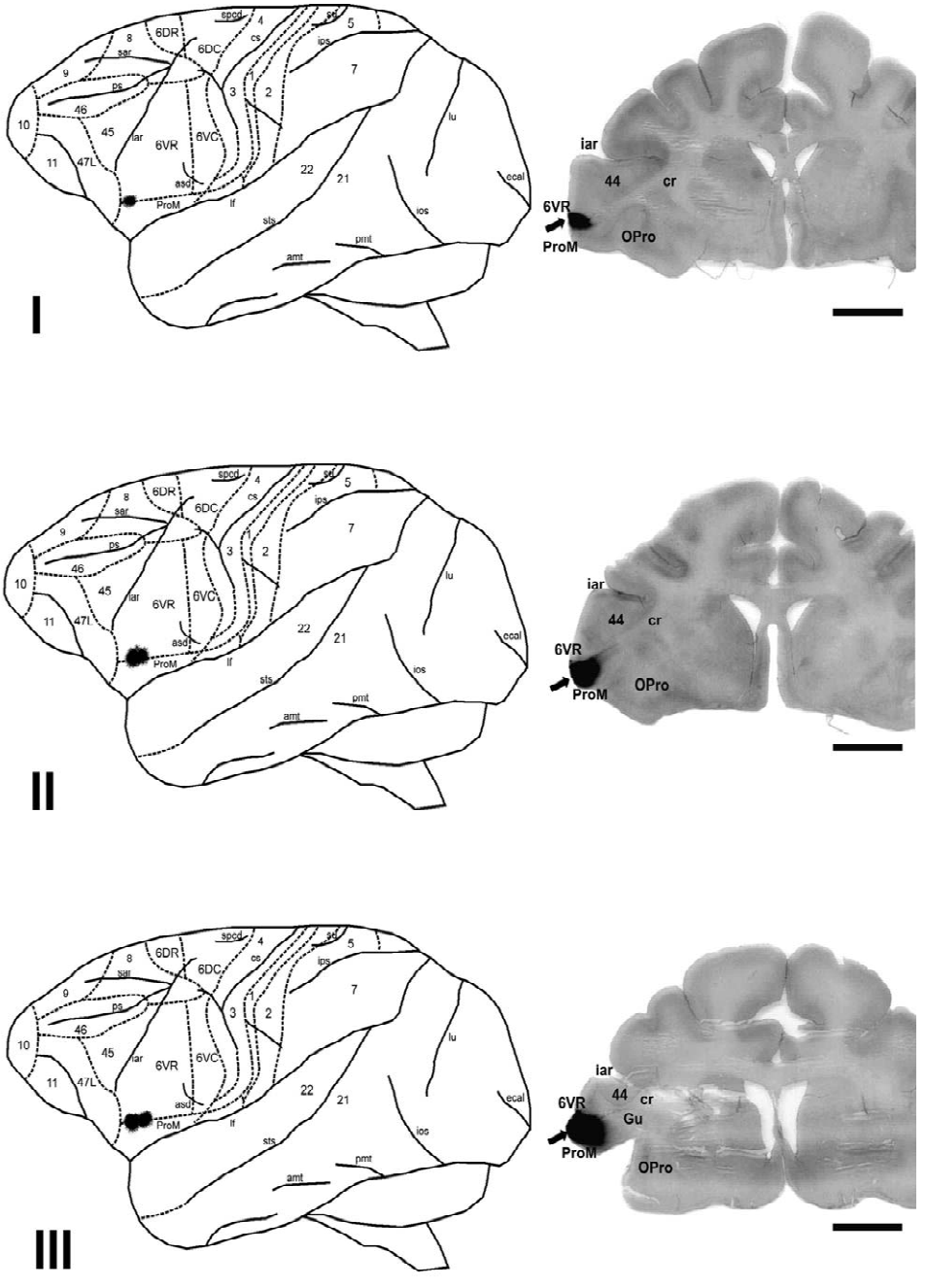


Fig. 1. Left: Lateral view of the brains of the experimental animals I–III, showing BDA injection sites (solid black areas). Right: Low-power photographs of the frontal sections of animals I–III at the level of the injection site (arrow). Cytoarchitectonic parcellation according to Paxinos et al. [55]. Scale: 7 mm. For structure identification, see the abbreviations list.

a drawing was made indicating the position of the stimulation site in relation to nearby blood vessels. In the animals with the intact dura, the site of electrode penetration was marked with ink. Then, the electrode was withdrawn, and the injection of an anterograde tracer was carried out into that site by the aid of a micromanipulator-driven Hamilton microsyringe with a cannula diameter of 0.47 mm. One microliter of 20% biotin dextranamine (BDA; Molecular Probes, Eugene, OR, USA) in 2% dimethyl sulfoxide was injected in animal 1. Animals 2 and 3 received two injections of 1.0 μl each. In the latter two animals, the injection sites were about 1.0 mm apart and both yielded vocal fold adduction when electrically stimulated. After the injection, the dura defect in animal 1 was covered with human dura (Lyodura, Braun, Melsungen, Germany) glued to the bone rim with Histoacryl (Braun, Melsungen, Germany). In the other two animals, the bone defect was closed with titanium-reinforced Gore-Tex Regenerative material (W.L. Gore & Associates, Inc., Arizona, USA). In all three animals, the wound was closed by sewing up muscle fascia and skin in two layers. After surgery, the animals were returned to their home cage and monitored for normal recovery. The monkeys received supplemental doses of an antibiotic (Baytril 0.1 ml/kg body weight) during the following 7 days after operation. Recovery was uneventful. After a survival period of 7 weeks, the animals were deeply anesthetized with an overdose of 16% pentobarbital sodium and were perfused with 2 l of physiological saline (37 °C), followed by 4 l of 4% paraformaldehyde in 0.1 M phosphate buffer (pH 7.2) at room temperature.

Brains were removed from the skull, cut into blocks, post-fixed in phosphate-buffered 4% paraformaldehyde for 2 days and then stored in 20% sucrose in 0.1 M phosphate buffer for cryoprotection at 4 °C for 4–5 days. The brains then were cut from the frontal pole to the caudal medulla in the stereotaxic frontal plane at 45 μm on a freezing microtome (Frigocut 2800, Reichert-Jung, Nussloch, Germany). Immunohistochemical tracer identification was carried out according to a modification of the procedures described by Veenman et al. [74] and Brandt and Apkarian [9]. A detailed description of the immunohistological procedure is found in the preceding paper [67].

Light microscopic evaluation was done in the bright and dark fields. Identification of brain areas followed the stereotaxic atlas of Paxinos et al. [55].

The experiments were approved by the animal ethics committee of the district government Braunschweig, Lower Saxony, Germany.

3. Results

Cytoarchitectonically, the injection sites corresponded to area 6VR and ProM, according to Paxinos et al. [55] (Fig. 1). The injection site of animal 1 had a diameter of about 2 mm. In animals 2 and 3, the two injection sites merged into each other and formed an injection area of about 2 by 3 mm.

The injection areas were characterized by an even distribution of dense, granular reaction product in the center and a less dense labeling with identifiable labeled perikarya in the periphery. Despite the fact that BDA is known to be transported anterogradely as well as retrogradely [19,63,80], only very few labeled perikarya were found outside of the injection area. This low number of retrogradely labeled cells prevented a proper analysis of reciprocal relationships between the injection area and other structures. In the following, we therefore will report only on the anterograde projections.

Terminal fields were distinguished from by-passing fibers by the irregular course, smaller diameter and rich ramification of the axons. At higher magnification, the axons showed numerous varicosities, partly in the form of boutons-en-passage, partly as terminal boutons of different size. Fig. 2 shows examples of both types of boutons. The Fig. also illustrates differences in the intensity of projections.

Efferent projection fibers could be traced to a large number of subcortical structures; 40 of them were found in all three animals. These structures are listed in Table 1. Fig. 3 shows the course of the projection fibers and their terminal fields in diagrammatic form. Only projection areas overlapping in at least two of the three animals have been introduced into the figure.

Within the telencephalon, projections could be followed bilaterally into the putamen, caudate nucleus and ipsilaterally into the claustrum, with the heaviest labeling in the putamen and the weakest in the claustrum. The putamen received its efferents via capsula interna, capsula externa and capsula extrema. The latter traversed the claustrum and external capsule before entering the putamen. The majority of fibers terminated in the ventralmost part of the putamen. Fibers to the caudate nucleus entered it via the corona radiata, internal capsule and from the external capsule by traversing the putamen and internal capsule. Terminals were mainly seen along the internal capsule. Occasionally, however, patches of terminals could also be seen some distance away from the internal capsule. All contralateral projections crossed the midline within the corpus callosum.

Diencephalic projections were widespread in the thalamus. They reached the thalamus from the internal capsule by crossing the reticular nucleus. The highest density of terminals within the ventral and lateral nuclear groups was found in the medial and lateral part of the nucl. ventralis lateralis (VLM, VLL) and in the nucl. ventralis posterior medialis (VPM), including its parvocellular part (VPMpc). The lateral and medial parts of the nucl. ventralis anterior (VAL, VAM), the nucl. ventralis posterior lateralis (VPL) and the reticular nucleus (Rt) showed labeling of moderate intensity. Within the intralaminar and medial nuclear groups, the nuclei centralis medialis (CM), medialis dorsalis, pars caudalis (MDC), centrum medianum (CMn) and reuniens (Re) received a strong

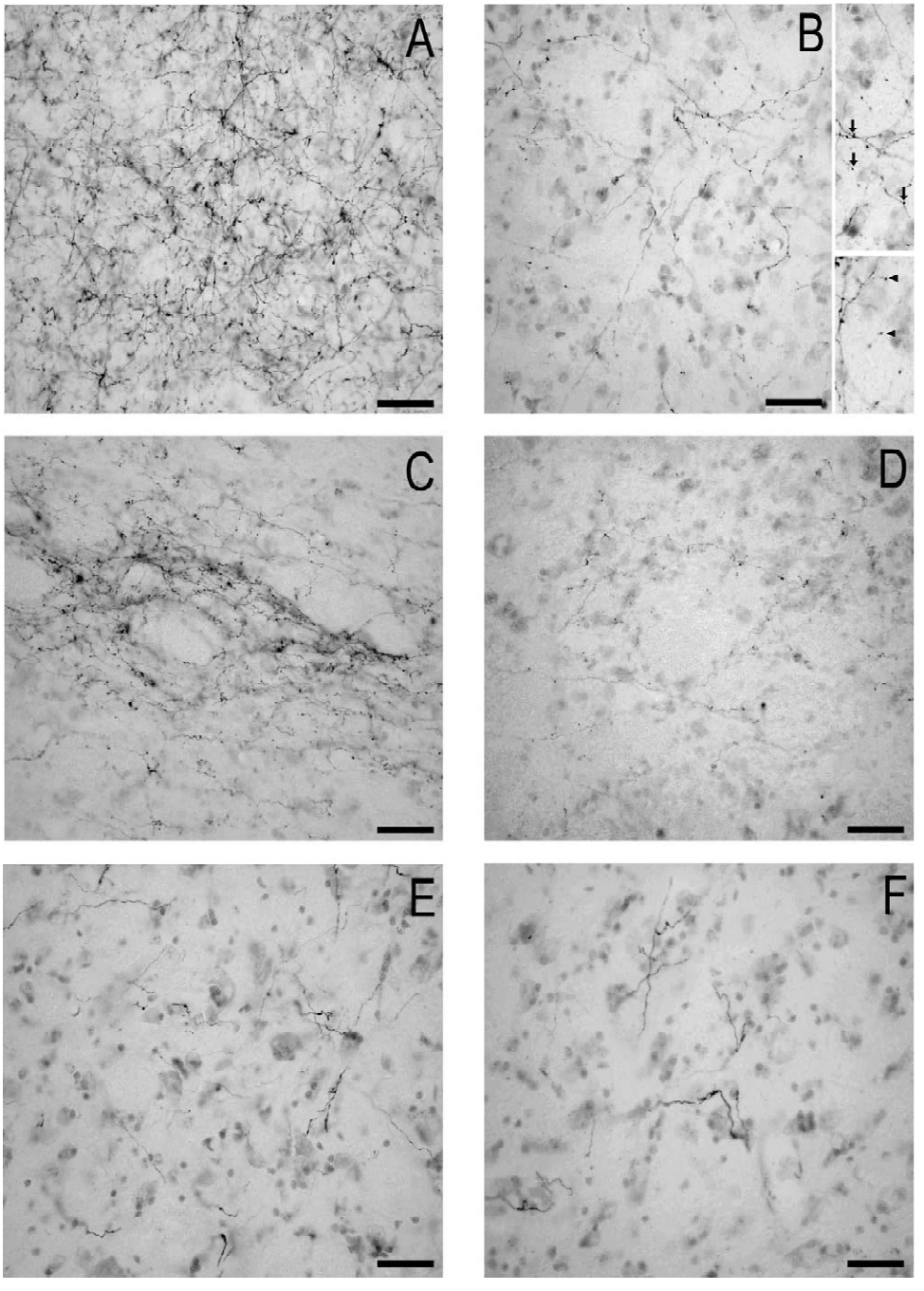


Fig. 2. Microphotographs of terminal labeling in the ipsilateral (A) and contralateral putamen (B), ipsilateral (C) and contralateral (D) ventral posteromedial thalamic nucleus, ipsilateral (E) and contralateral (F) solitary tract nucleus. Upper and lower insets in (B) show boutons-en-passage and boutons terminaux, respectively. All photographs were taken from animal II. Scale: 50 μm.

input, while the nuclei intermediodorsalis (IMD), medialis dorsalis, pars medialis and lateralis (MDM, MDL), paracentralis (PC) and centralis lateralis (CL) received only moderate projections. The majority of these projections were bilateral with an ipsilateral dominance. Projections were also traced into the pulvinar nuclei anterior (APul), lateralis (LPul) and medialis (MPul) as well as into field H (Forel) and the zona incerta (ZI). With the exception of the anterior pulvinar, these structures received only an ipsilateral input.

In the midbrain, terminal labeling was found in the ipsilateral deep mesencephalic nucleus (DpMe). None of the animals showed labeling in the red nucleus and periaqueductal gray.

In the pons, projection fibers could be followed ipsilaterally into the medial parabrachial nucleus (MPB), nucleus subcoeruleus (SubC), locus coeruleus (LC), oral pontine reticular formation (PnO) and medial pontine gray (Pn).

In the medulla oblongata, fibers terminated bilaterally in the reticular formation, with the heaviest input into the

Table 1
Projections from the cortical larynx area

		Ipsi	Contra
Telencephalon	Putamen	+++	+
	Caudate nucleus	++	+
	Claustrum	+	+/−
Diencephalon	Reticular thalamic nucleus	+	−
	Ventral anterior thalamic nucleus, lateral part	++	+/−
	Ventral anterior thalamic nucleus, medial part	++	+
	Ventral lateral thalamic nucleus, lateral part	+++	+/−
	Ventral lateral thalamic nucleus, medial part	+++	+
	Ventral posteromedial thalamic nucleus	+++	+
	Ventral posterolateral thalamic nucleus	++	+
	Mediodorsal thalamic nucleus, lateral part	++	+/−
	Mediodorsal thalamic nucleus, caudal part	+++	++
	Mediodorsal thalamic nucleus, medial part	++	+
	Intermediodorsal thalamic nucleus	++	+
	Central medial thalamic nucleus	+++	++
	Reuniens thalamic nucleus	+++	++
	Paracentral thalamic nucleus	++	+
	Centromedian thalamic nucleus	+++	+
	Parafascicular thalamic nucleus	++	+
	Centrolateral thalamic nucleus	++	−
	Anterior pulvinar	+	+
	Medial pulvinar	+	−
	Lateral pulvinar	+	−
	Zona incerta	+	−
	Field H of Forel	++	−
Mesencephalon, pons, medulla	Deep mesencephalic nucleus	+	−
	Pontine gray	++	−
	Pontine reticular nucleus, oral part	++	−
	Medial parabrachial nucleus	+	−
	Locus coeruleus	+	−
	Subcoeruleus nucleus	++	−
	Spinal trigeminal nucleus	+++	++
	Solitary tract nucleus	+++	++
	Parvicellular reticular nucleus	+++	++
	Intermediate reticular nucleus	+++	++
	Gigantocellular reticular nucleus	++	+
	Gigantocellular reticular nucleus, alpha part	+	−
	Facial nucleus	++	−
	Dorsal reticular nucleus	++	+
	Medial reticular nucleus	++	+

+++ Heavy projection, ++ medium projection, + weak projection, +/− questionable projection, − no projection. Only those structures are listed that contained labeled terminals in all three animals on at least one side. Categorization of labeling is based on the average labeling across all animals.

intermediate (IRt) and parvicellular (PCRt) nuclei, and a moderate input into the gigantocellular (Gi), dorsal (DRt) and medial (MRt) nuclei. Heavy labeling was also found in the solitary tract nucleus (Sol) and spinal trigeminal nucleus (Sp5), and moderate labeling in the facial nucleus (7N). In none of the animals, there was labeling in the nucl. ambiguus and retroambiguus.

4. Discussion

Voluntary phonation requires the intactness of cortical as well as subcortical structures, as seen from numerous lesion studies in human patients and animal models (for a review, see Ref. [33]). In the past, most phonatory deficits due to subcortical lesions have been interpreted as the result of an interruption of the direct cortico-bulbar pathway. The present study makes clear that the cortical larynx area does not only project via the corticobulbar pathway to areas containing the motoneurons and premotor neurons involved in phonation. Instead, a large number of areas scattered throughout the subcortical forebrain and brainstem receive direct input from the cortical larynx area. There is, thus, no reason to assume that the cortico-bulbar pathway is the only pathway involved in vocal control.

The efferent projections of the laryngeal motorcortex largely correspond to the general scheme of motorcortical projections in mammals. Like other motorcortical areas,

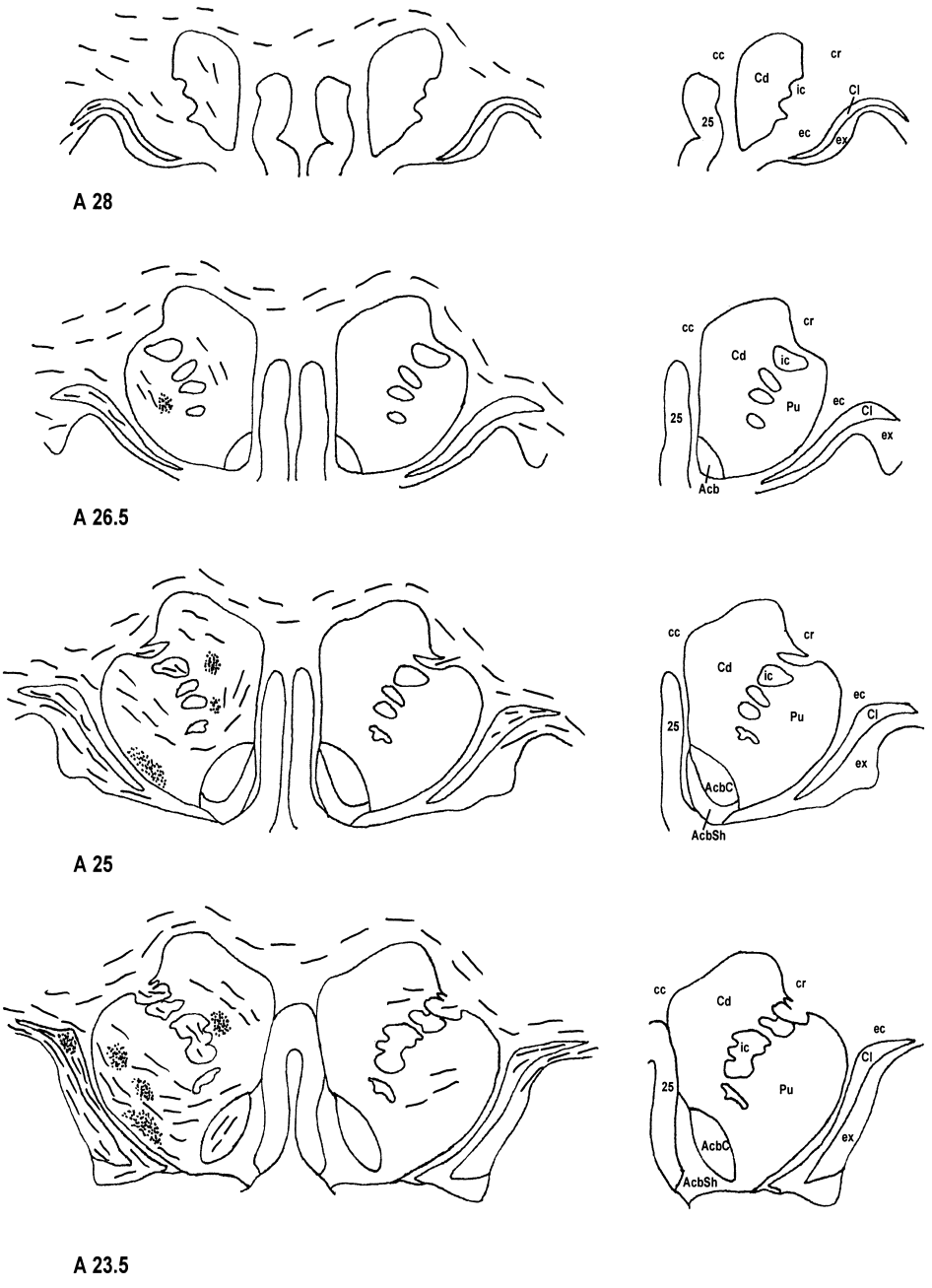


Fig. 3. Brain diagrams of the rhesus monkey in the frontal stereotaxic plane showing subcortical projection areas overlapping in at least two of the three experimental subjects. The diagrams were constructed by projecting the drawings of corresponding frontal planes of the three animals on each other. For brain structure identification, see the abbreviations list.

the larynx area projects to the basal ganglia putamen, caudate nucleus and claustrum. According to Künzle [40], the cortico-putaminal projection is somatotopically organized, with the cortical leg area projecting to the rostrodorsal putamen, the face area projecting to its caudoventral part, and the arm and trunk area in between. In the present study, terminals were found in the ventral putamen over a large anteroposterior distance. This means that there is an overlap of the projections coming from the face and the larynx area in the posterior putamen. The putamen rostral to the anterior commissure, in contrast, seems to receive input only from the larynx area.

A somatotopically organized motorcortical projection has been reported also for the claustrum. According to Künzle [40], the input from the motorcortical face area ends in the rostrodorsal part of the claustrum, while the input from the arm and leg area ends in the intermediate and caudal part of the dorsal claustrum, respectively. In the present study, terminal labeling was not only found in the rostrodorsal part of the claustrum, but also at two separate

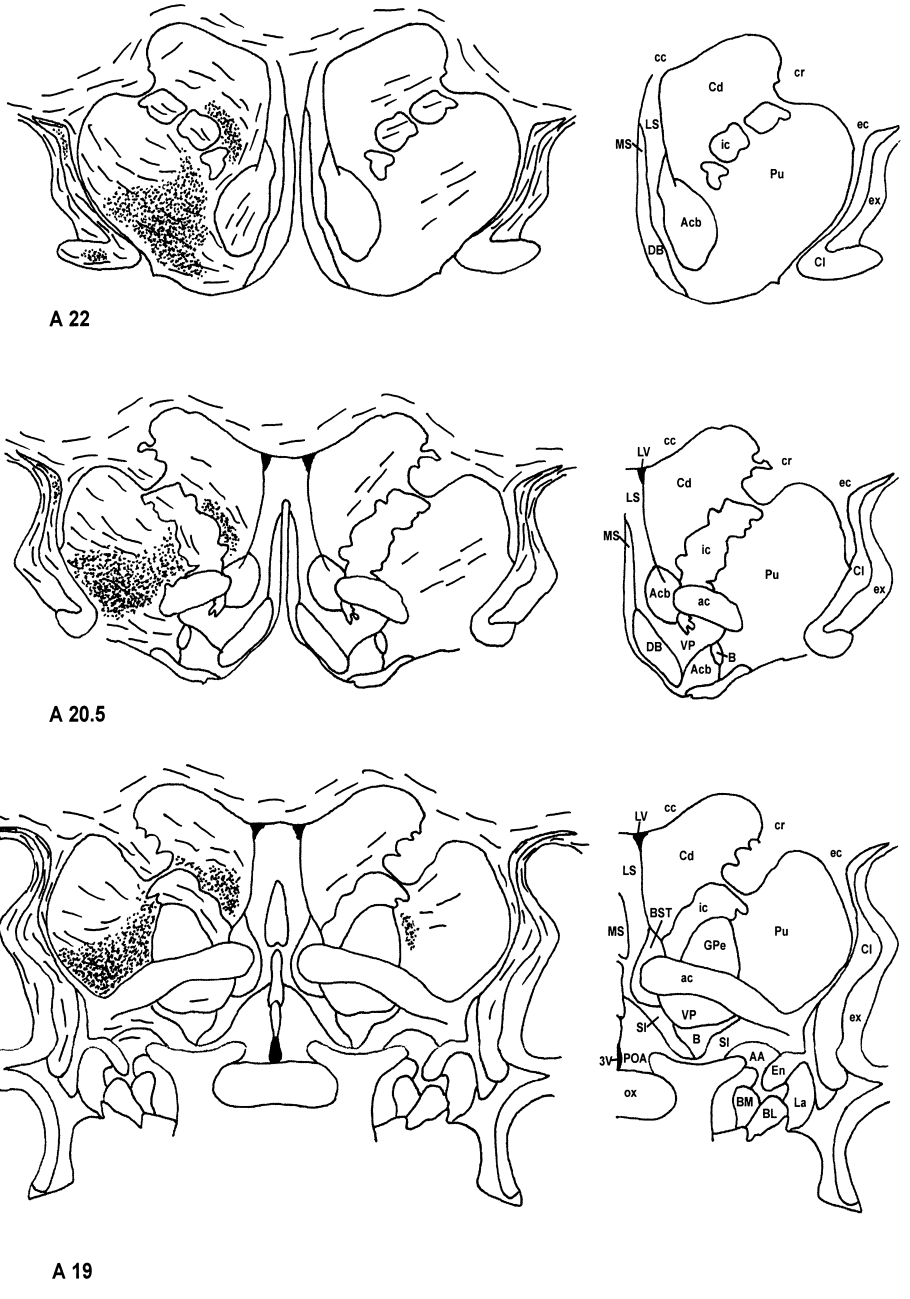


Fig. 3. (*continued*)

positions in the ventral part of the claustrum. This makes clear that the cortico-claustral projection is not a one-to-one projection; instead, single motorcortical sites project to several claustral regions. Similar holds for the cortico-caudate and, to some extent, also for the cortico-putaminal projection.

Projections to the putamen and caudate nucleus are unidirectional, that is, the motorcortical larynx area projects to these structures, but the latter do not project directly to the cortex [32]. The same holds for the connections of the face, leg and arm motorcortical representations [26]. In the study of Jürgens [32], however, some retrogradely labeled cells were found in the claustrum after horseradish peroxidase injections into the ipsilateral motorcortical larynx area. There is also known reciprocity between the claustrum and motorcortical hand representation as well as the premotor cortex and supplementary motor area [70].

The putamen receives by far the strongest projection of all telencephalic subcortical structures. It thus represents the main basal ganglia output structure of the motor cortex. Neurological studies in human patients have shown that lesions in the putamen can cause dysarthria and dysphonia [45,58]. Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies report speech-related activity in the putamen [7,39,54,59]. The

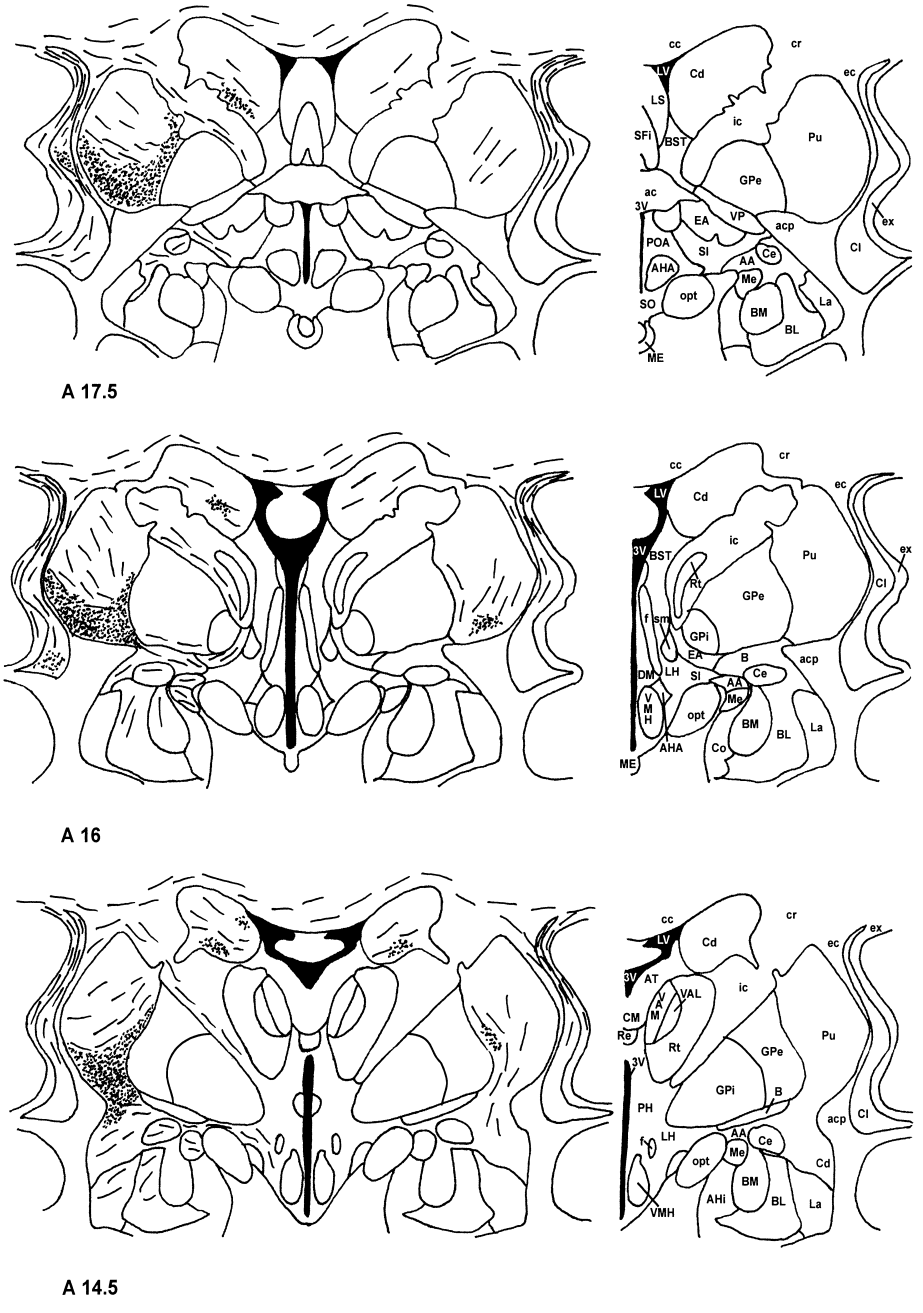


Fig. 3. (*continued*)

putamen thus is not only anatomically connected with the motorcortical mouth and larynx representation; it is also functionally involved in vocal control. The latter statement seems to hold for humans only, however. If the putamen is destroyed bilaterally in the squirrel monkey, no changes are found in vocal behavior [36]. As the squirrel monkey's vocalizations have been shown to be genetically determined in their acoustic structure [20], we conclude that the putamen is only involved in the production of learnt vocal patterns, such as speech and song, but not in the production of innate vocalizations, such as monkey calls and human laughing, moaning and crying.

It is still unclear via which pathway the putamen exerts its vocal control. One possible pathway has been described by Iwata et al. [28]. According to these authors, the ventral putamen projects into the dorsolateral substantia nigra, pars reticulata, which, in turn, projects to the parvicellular reticular formation, an area directly connected with phonatory motoneurons. Another alternative would be the well-known loop from the putamen via globus pallidus and ventrolateral thalamus back to the motorcortex, and from there down into the brainstem via the cortico-bulbar tract. Future studies will have to clarify the functional roles of these pathways in vocal control.

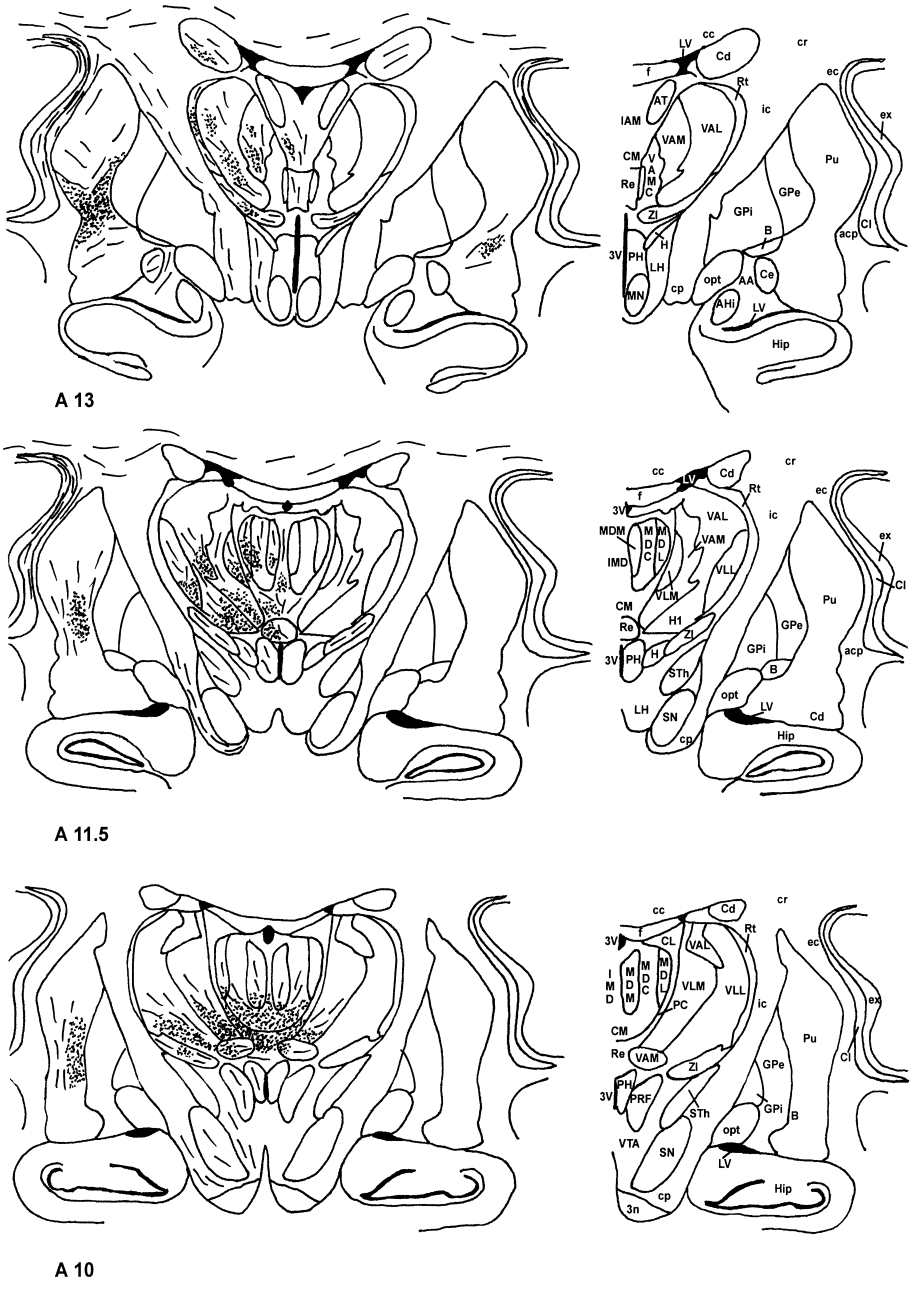


Fig. 3. (*continued*)

The rhesus monkey's projections of the cortical larynx area to the thalamus are essentially identical with those reported by Jürgens [31] for the squirrel monkey. They are also similar to the projections of the Java monkey's face motor cortex as described by Künzle [41], except that this author did not find projections to the nucl. ventralis anterior and the pulvinar complex. The latter two projections were found by Künzle in another study, however, when the tracer injections were made into the premotor cortex just rostral to the primary face motor cortex [42]. These findings suggest that only the intraoral representation of the facial motor cortex, which lies in area 6 instead of area 4, is directly connected with the nucl. ventralis anterior and pulvinar complex.

With respect to the type of terminals, Guillery [19] and Rouiller and Welker [63] report the existence of small as well as giant boutons in the terminal fields of cortico-thalamic projections. While giant boutons are assumed to characterize projections coming from layer VI, small boutons are found on layer V and VI neurons. In the present study, both giant and small boutons were found in the thalamus. This fits with the fact that the injection site in each animal invaded all six cortical layers.

Retrograde tracing studies in the macaque and squirrel

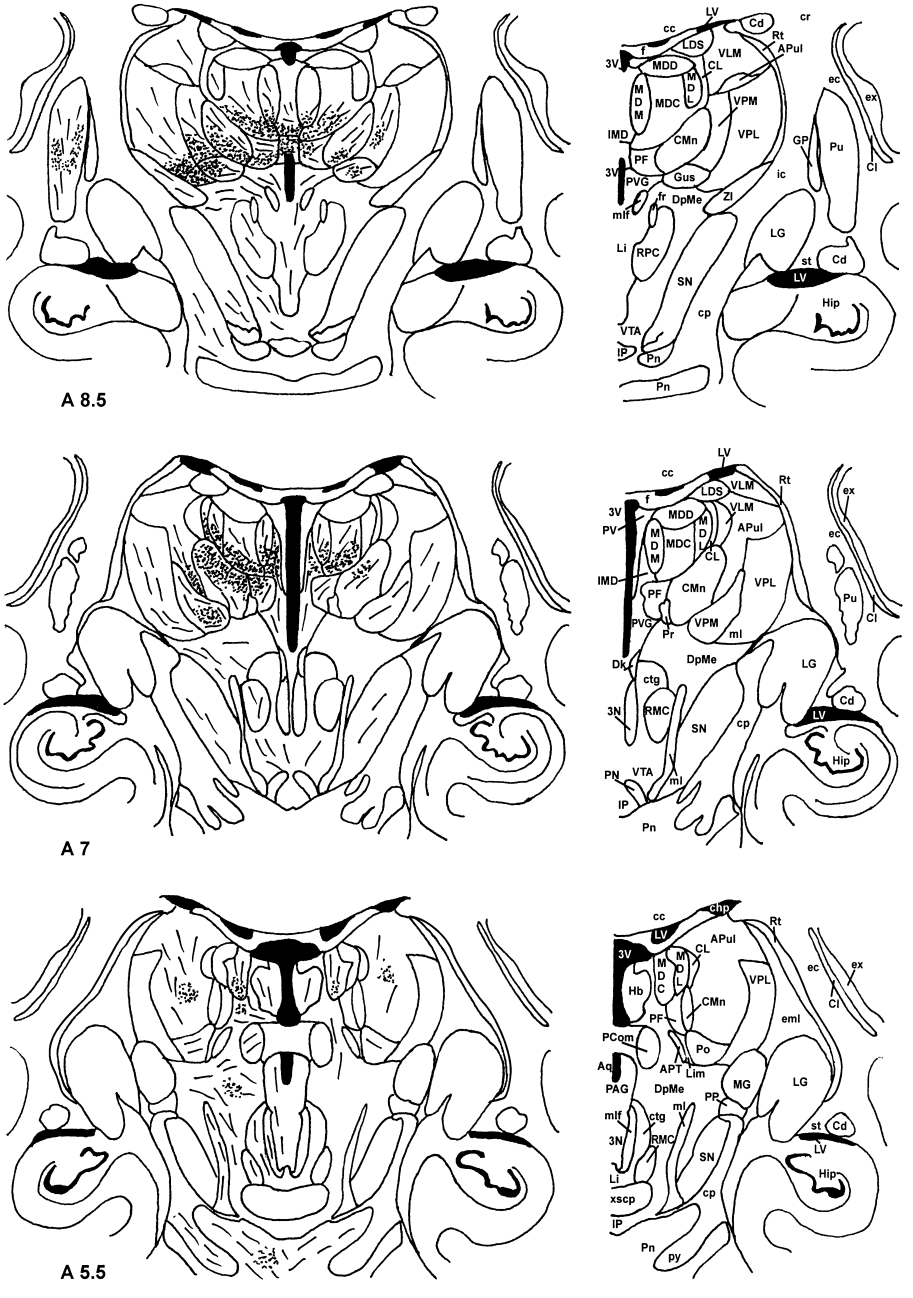


Fig. 3. (*continued*)

monkey show that a number of thalamic nuclei found in the present study to receive a direct input from the motorcortical larynx area are reciprocally connected with the laryngeal and facial motorcortex. Such nuclei are the nucl. ventralis lateralis, ventralis posterior medialis, reuniens, medialis dorsalis, centralis lateralis, centrum medianum, parafascicularis and pulvinaris [32,49,62].

The main input structure within the thalamus is the nucl. ventralis lateralis. This nucleus is part of two important motor control loops. One is the cortico-ponto-cerebello-thalamo-cortical pathway; the other is the cortico-striato-pallido-thalamo-cortical pathway [26]. The nucl. ventralis lateralis has a somatotopical organization with the representation of the face muscles medially and the trunk and upper and lower extremities more laterally [22,75]. Fibers from the laryngeal motorcortex terminate in the ventromedial part of both the lateral and medial subnuclei of the ventrolateral nucleus. Lesions in the ventrolateral nucleus of man have been reported to cause monotonous and breathy voice, raised fundamental frequency and an increase in jitter [2]. Electrical stimulation produces vocalization [64]. PET and fMRI studies report speech- and song-related bilateral activity in this region [7,8,54]. Single-unit recordings in the cat have revealed voc-

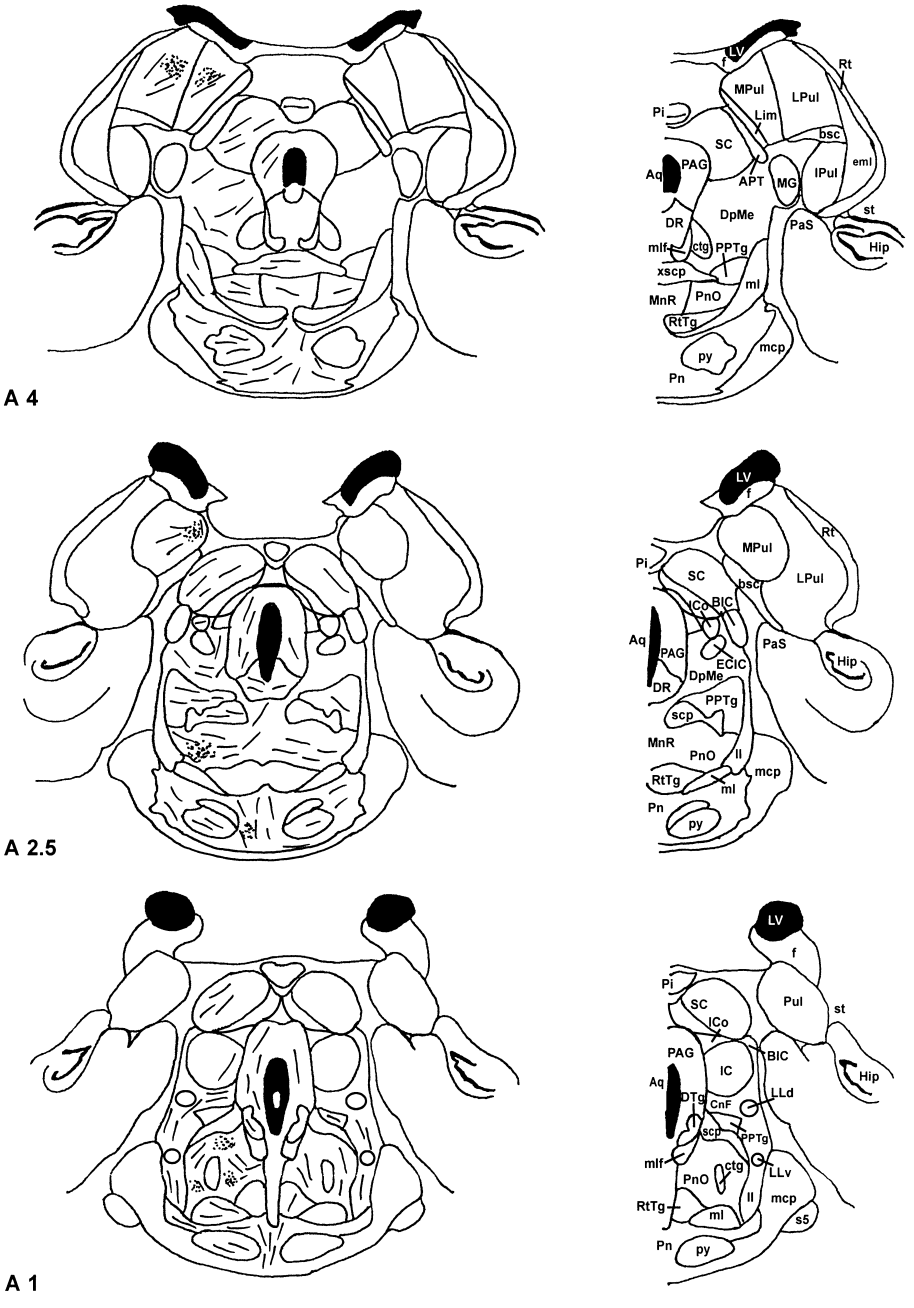
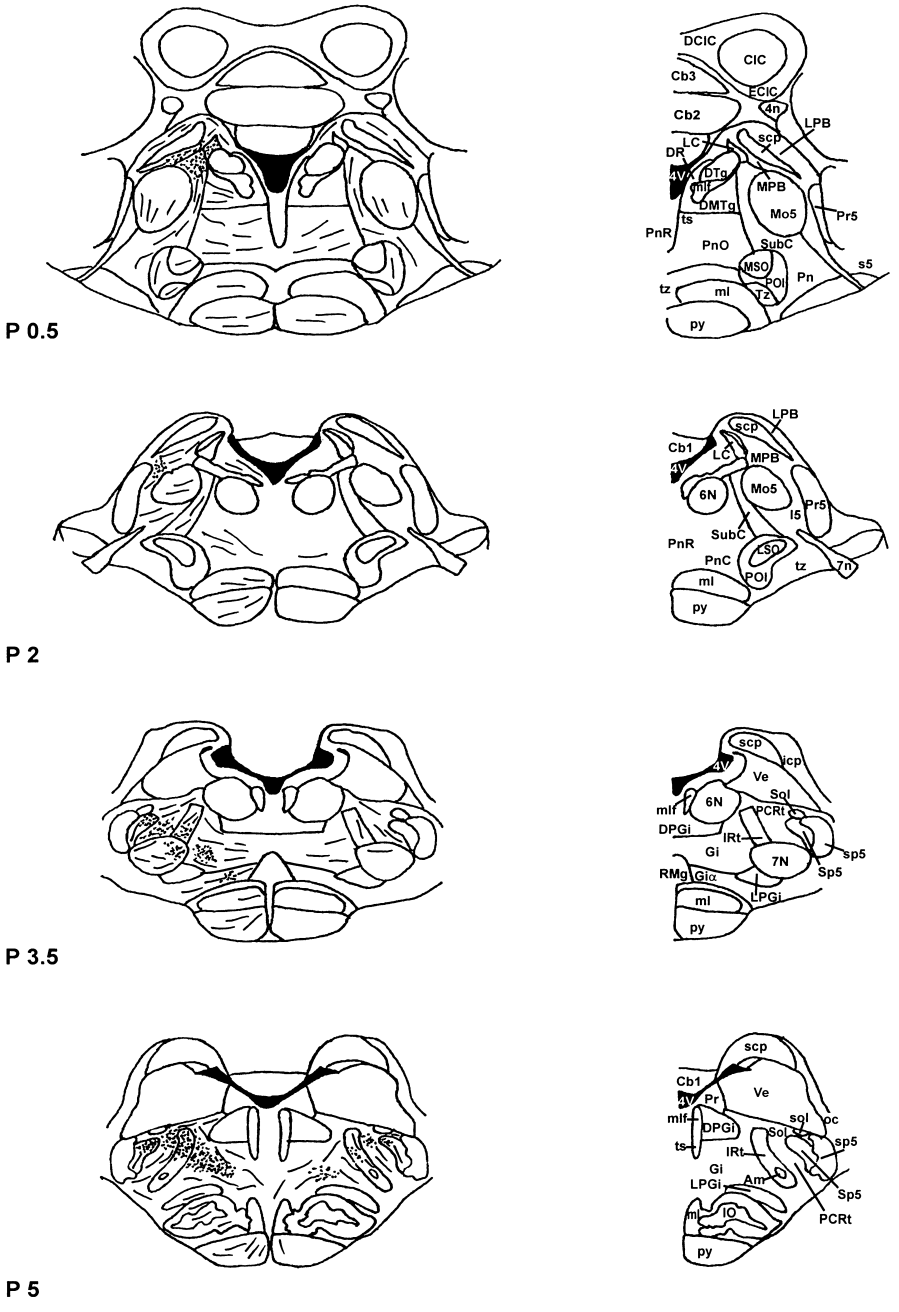


Fig. 3. (*continued*)

alization-related neuronal activity in the medial part of the ventrolateral nucleus [14]. The ventrolateral nucleus forms reciprocal connections with the primary motor cortex, premotor cortex, Broca's area and supplementary motor area [52,62], all of which are known to produce vocalization when electrically stimulated in man [56,57].

Another heavily labeled thalamic nucleus is the nucl. ventralis posteromedialis, especially its ventromedial and parvocellular part. According to Künzle [41], the extraoral motorcortical face area projects to the dorsolateral part of the nucl. ventralis posteromedialis, but not to the parvocellular part. The latter seems to be devoted to the processing of intraoral stimuli, gustatory as well as somatosensory [60]. Single-unit recordings in the nucl. ventralis posteromedialis of humans have revealed speech-related activity [51]. Electrical stimulation of this nucleus during vocalization in the squirrel monkey has led to a deterioration of vocal structure [12]. Lesions of this nucleus and its main cortical projection area, the sensory face cortex, have been made responsible for the syndrome of afferent motor aphasia, a syndrome characterized by dysarthric speech due to an interruption of the kinaesthetic and proprioceptive feedback from the phonatory organs [47].

It has been mentioned already that the projections to the



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pulvinar are not typical for the primary motor cortex in general, but only for its intraoral part. It is of interest in this context that brain stimulation and lesion studies point to a possible role of the pulvinar in speech processing. According to Ojemann et al. [53], electrical stimulation of the left pulvinar in human patients induces nominal aphasia. Left-sided lesions of the pulvinar have been reported to cause anomia, verbal perseveration, neologism and reduced speech activity [61,73].

At the level of the midbrain, the periaqueductal gray represents a crucial relay station of the limbic vocalization pathway. Its destruction leads to mutism in the squirrel monkey [34]. Vocalizations electrically elicitable from the anterior cingulate cortex and hypothalamus can be blocked by blocking the excitatory neurotransmission in the periaqueductal gray [35]. In contrast to the drastic effects of periaqueductal gray blockade on vocalization elicited from limbic structures, there is no effect at all of periaqueductal blockade on vocal fold movements elicited from the cortical larynx area [35]. This lack of effect fits with the finding of the present study that there is a lack of direct connection of the cortical larynx area with the

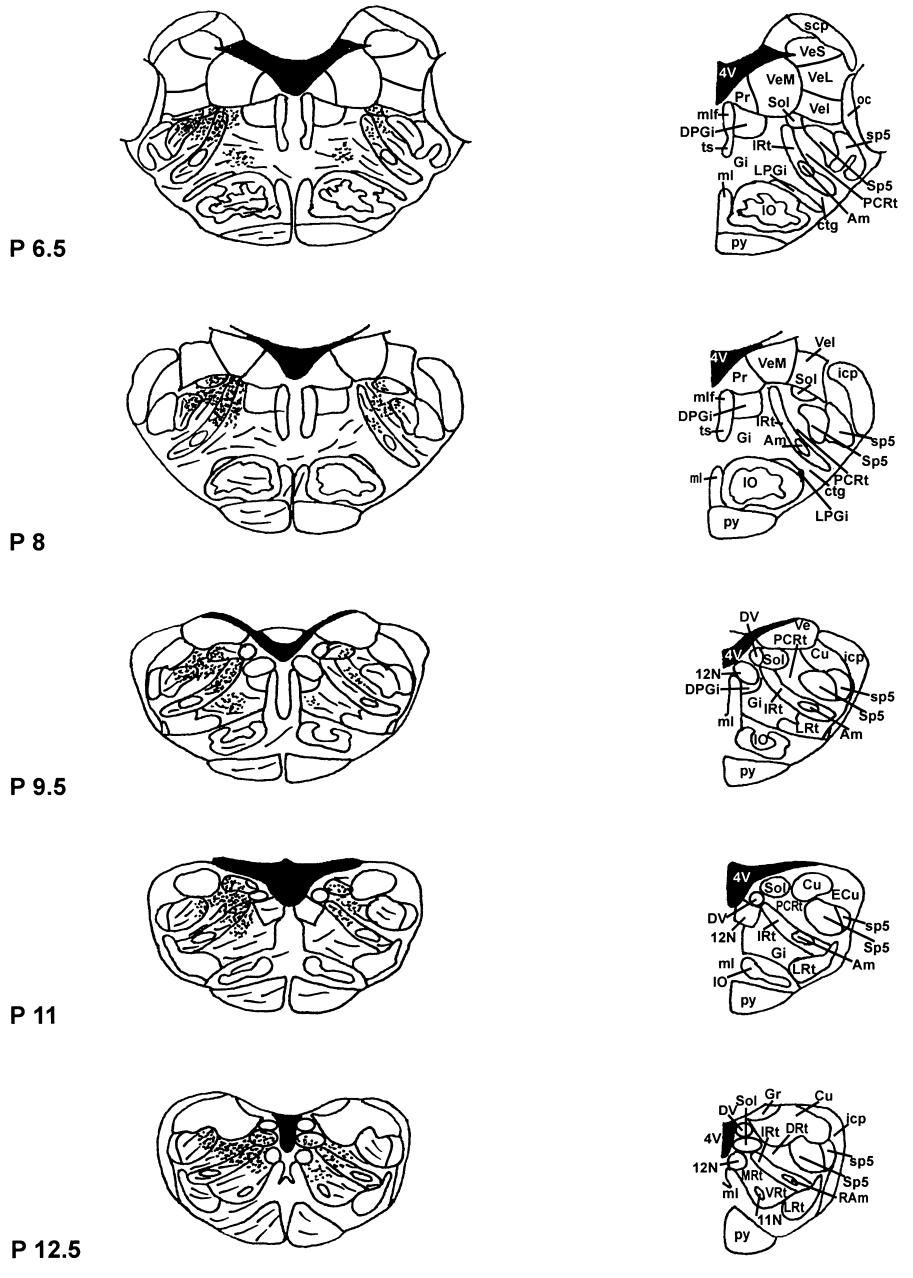

Fig. 3. (*continued*)

periaqueductal gray. The cortical larynx area thus seems to control the vocal folds via a pathway bypassing the periaqueductal gray.

Another midbrain structure that was free of terminals in the present study, but usually considered to be a typical output structure of the motor cortex, is the red nucleus. An explanation for this discrepancy is given by a study of Humphrey et al. [27]. These authors injected a retrograde tracer into the nucleus ruber of macaques and found retrogradely labeled cells in the upper, but not the lower face cortex. As the upper face cortex contains the representations of external face muscles, whereas the lower face cortex contains the representations of intraoral muscles, the findings of Humphrey et al. fit well with the lack of cortico-rubral connections in the present study.

At the midbrain-pons transition, a weak projection area was found in the medial parabrachial nucleus. Such a cortico-parabrachial projection from the motorcortical face area has been reported also for the rat [82], guinea pig [13], cat [81], tree shrew [3], squirrel monkey [31] and Java monkey [21]. Single-unit recording studies in the cat [15] and squirrel monkey [38] have revealed vocalization-correlated activity in this region. Most of the vocalization-correlated cells, however, changed their activity also in relation to quiet respiration. The majority increased its activity during expiration or in the late inspiratory phase

[15]. Electrical stimulation with short pulse trains induces phase switching from inspiration to expiration and from expiration to inspiration [11]. Prolonged stimulation elicits abdominal straining movements [17]. Destruction is followed by apneustic breathing [78]. The parabrachial region, especially its lateralmost part, projects massively into the nucl. retroambiguus, a structure containing expiratory premotor neurons [18]. These findings suggest that the parabrachial region participates in the respiratory component of vocalization control. More specifically, it seems to be involved in the gating of vocal onset on the basis of the momentary respiratory status.

Another pontine region receiving direct input from the larynx area is the pontine gray. The pontine gray represents one of the classical input structures of the cerebellum. The direct connection of the cortical larynx area with the pontine gray thus means that the cerebellum receives oligosynaptic information from the motor cortex on its vocal fold-controlling activity. It is in line with these anatomical connections that cerebellar lesions have a deteriorating effect on speech production. The deteriorating effect is characterized by irregular changes in fundamental frequency and intensity, explosive voice onset, scanning speech rhythm and slowed speech tempo [1,44]. Still more dramatic effects on speech are found when the lesions invade the pontine gray itself. In this case, a complete loss of voluntary motor control, including speech, is observed (locked-in syndrome) [5]. Only a few non-verbal emotional vocal utterances, such as moaning, crying and laughing, survive. The much more severe effect of pontine lesions than cerebellar lesions make clear that the complete loss of speech in the locked-in syndrome is not due to an isolated pontine gray lesion, but to a combined destruction of pontine gray and traversing cortico-bulbar and cortico-spinal fibers.

In the present study, no terminals were found in the nucl. ambiguus, that is, the site of the laryngeal motoneurons. A lack of cortico-ambigual projections was also reported for the squirrel monkey [31], tree shrew [66], cat [69] and rat [72]. In humans, in contrast, direct connections of the motor cortex with the nucl. ambiguus do exist [29,43]. This direct cortico-ambigual connection seems to be a very recent acquisition in hominid evolution and possibly represents one of the prerequisites for speech development. In non-human primates and other mammals, with their very limited voluntary control on phonation, the cortical larynx area has only an indirect access to the laryngeal motoneurons. Structures that have been shown in the present study to receive direct input from the cortical larynx area and which are known from the literature to project to the nucl. ambiguus are the parvicellular, intermediate and dorsal reticular nuclei as well as the solitary tract nucleus [6,71]. All these structures have been shown in a single-unit recording study in the squirrel monkey to contain neurons with vocalization-correlated activity [48]. A major part of these neurons changed their activity with changes in the fundamental frequency. Many of these neurons started to fire already some time before vocalization onset. That is, both the solitary tract nucleus as well as the reticular nuclei are potential candidates for cortico-ambigual relay stations. The importance of these structures in vocal control is underlined by the observation that their electrical stimulation during ongoing vocalization causes a deterioration of vocal structure [12]. Lesions in the reticular formation and solitary tract nucleus also have been reported to affect vocalization [37]. It is of interest that another structure known to be directly connected with the nucl. ambiguus and being essential for vocal production, the nucl. retroambiguus, does not receive direct input from the cortical larynx area in the rhesus monkey [25,65,83]. The nucl. retroambiguus, due to its connections with the expiratory motoneurons in the thoracic and lumbar spinal cord, is assumed to coordinate laryngeal and respiratory activity during phonation. The lack of a direct input from the cortical larynx area to the nucl. retroambiguus makes clear that the nucl. retroambiguus is not a primary relay station of the cortico-ambigual pathway.

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