Review

Laryngeal Motor Cortex and Control of Speech in Humans

Kristina Simonyan[1] and Barry Horwitz[2]

Abstract

Speech production is one of the most complex and rapid motor behaviors, and it involves a precise coordination of more than 100 laryngeal, orofacial, and respiratory muscles. Yet we lack a complete understanding of laryngeal motor cortical control during production of speech and other voluntary laryngeal behaviors. In recent years, a number of studies have confirmed the laryngeal motor cortical representation in humans and have provided some information about its interactions with other cortical and subcortical regions that are principally involved in vocal motor control of speech production. In this review, the authors discuss the organization of the peripheral and central laryngeal control based on neuroimaging and electrical stimulation studies in humans and neuroanatomical tracing studies in nonhuman primates. It is hypothesized that the location of the laryngeal motor cortex in the primary motor cortex and its direct connections with the brain stem laryngeal motoneurons in humans, as opposed to its location in the premotor cortex with only indirect connections to the laryngeal motoneurons in nonhuman primates, may represent one of the major evolutionary developments in humans toward the ability to speak and vocalize voluntarily.

Keywords

motor control, voice, speech, human, nonhuman primate

Voice is essential for human communication. Starting with the first cry at birth, the vocal repertoire develops throughout childhood into unique human speech. The development of the human ability to speak relies on the abilities to listen to speech, comprehend and process the meaning of the heard words, and coordinate laryngeal, respiratory, and orofacial muscles to communicate speech sounds. Together with body expressions, we use speech and other vocal gestures to define our needs and thoughts and to project our feelings and emotions.

Research on the mechanism of speech spans the centuries. Commonly, the topic of the brain basis of speech is discussed in relation to speech perception within the auditory cortex and speech production within the inferior frontal gyrus (i.e., Broca's area), whereas the involvement of the laryngeal motor cortex (LMC) is rarely addressed. Nevertheless, the LMC is imperative for the control of motor coordination of more than 100 muscles for voluntary production of voice, swallowing, and breathing, all of which represent vital functions for our existence and communication.

In this review, we will first briefly introduce the anatomy and peripheral nervous control of the larynx as an organ for voice production; we will then review the hierarchical organization of voice control from the brain stem

to the LMC, with a special focus on the role of the LMC in the control of voluntary learned voice production and on its interactions with other brain regions associated with speech control. We will present some hypotheses on the LMC evolutionary developments in humans and conclude with a summary and future directions.

Larynx and Its Peripheral Nervous Control

The larynx as a structure is phylogenetically much older than its role as a vocal organ. The first vertebrate larynx appeared in the lungfish more than 400 million years ago; however, the first vocalizations appeared much later, with the evolution of anurans about 250 million years ago.

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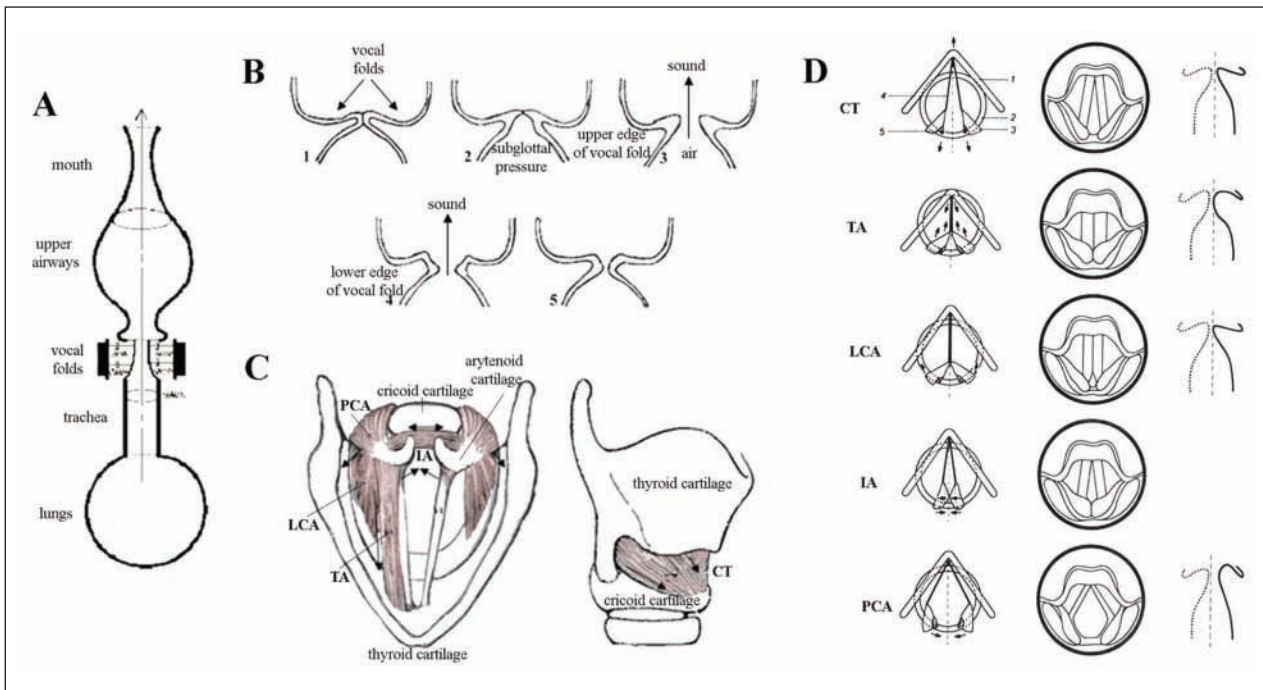Email: kristina.simonyan@mssm.edu

Figure 1. (A) Schematic view of the vocal and respiratory tracts. Voice originates in the larynx. First, the expiratory airflow from the lungs reaches the larynx through the trachea, where it sets the closed vocal fold tissue into self-excited oscillatations, due to which the larynx becomes the source of voice sound. Further, pressure from the vocal fold oscillations is resonated through the vocal tract and radiated from the mouth as voice. (B) Schematic sequence of events preceding voice production: 1) The vocal folds close immediately prior to voice production; 2) subglottal air pressure builds up below the vocal folds during exhalation; 3) the lower and upper edge of the vocal folds separate subsequently with the release of air and sound generation; 4) the vocal folds reapproximate, starting from their lower edge; and 5) the vocal folds close completely before the next sound production. (C) Superior and lateral views of the human larynx. Intrinsic laryngeal muscles and cartilages. TA = thyroarytenoid muscle; LCA = lateral cricoarytenoid muscle; PCA = posterior cricoarytenoid muscle; IA = interarytenoid muscle; CT = cricothyroid muscle. The arrows show the directions of the muscle contractions. (D) Schematic presentation of the laryngeal muscle function. The left column shows the location of the cartilages and the edge of the vocal folds when each of the laryngeal muscles is active. The arrows indicate the directions of the force exerted: 1) thyroid cartilage, 2) cricoid cartilage, 3) arytenoid cartilages, 4) vocal ligament, and 5) posterior cricoarytenoid ligament. The middle column shows the laryngeal view. The right column shows contours of the frontal section at the middle of the membranous portion of the vocal fold. The dotted line shows a state in which no muscle is activated. Reprinted from Hirano, copyright 1981, with kind permission of Springer Science+Business Media.

From a phonatory point of view, voice is produced when the expiratory airflow from the lungs sets the closed vocal folds of the larynx into vibration, converting aerodynamic power generated by the thoracic and abdominal muscles (subglottal component) into the basic sound wave (e.g., acoustic power). This sound wave is further filtered and amplified by oral articulators, such as the pharynx, tongue, palate, lips, and jaw (supraglottal component), and it is emitted from the mouth and nose as sound of voice (Fig. 1A, B).

Voice onset is required for production of vowels and voiced consonants (e.g., b, d), whereas voice offset is necessary for production of voiceless consonants (e.g., p, t). During speech production, voice onset is precisely timed, which allows linguistic distinctions between voiced and voiceless consonants, such as /d/ versus /t/. Changes in the subglottal pressure due to changes in lung volume, the elastic properties of the chest wall, and the active contraction of the intercostal and abdominal muscles lead to modulations of voice intensity, whereas the resonance characteristics of the supraglottal region (e.g., oral and pharyngeal cavities) influence the spectral properties of the sound.

Vocal fold movements are controlled by intrinsic and extrinsic laryngeal muscles. The intrinsic laryngeal muscles are confined to the larynx and participate in vocal fold closure (thyroarytenoid [TA], lateral cricoarytenoid [LCA], and interarytenoid muscles [IA]), opening (posterior cricoarytenoid [PCA] muscle), and lengthening (cricothyroid muscle [CT]; Fig. 1C, D). The extrinsic muscles connect the larynx with surrounding structures, such as the hyoid bone, sternum, and pharynx, and raise or lower the larynx within the neck relative to the spine to

modulate vocal fold length, fundamental frequency, oropharyngeal resonance frequencies, and formant structure.

All laryngeal muscles, with exception of the IA muscle, receive bilateral motor and sensory innervation from the superior laryngeal (SLN) and recurrent laryngeal (RLN) nerves branching from the vagal nerve. Although the internal branch of the SLN and the RLN provides laryngeal sensory innervation, the external motor branch of the SLN innervates the CT muscle; all other intrinsic laryngeal muscles receive their motor innervation from the RLN. The extrinsic muscles are primarily innervated from the ansa cervicalis. The motoneurons of the intrinsic laryngeal muscles are located in the nucleus ambiguus of the brain stem; the motoneurons of extrinsic muscles are situated near the hypoglossal nucleus. Motor and sensory nuclei of the subglottal (respiratory muscles) and supraglottal (orofacial muscles) components are located in the pons (trigeminal motor nucleus), brain stem (facial nucleus, hypoglossal nucleus, and nucleus ambiguus), and ventral horn of the spinal cord (cervical, thoracic, and lumbar regions). Bilateral innervation of almost all laryngeal muscles and, therefore, control of each half of the larynx by both left and right LMC is beneficial in preventing loss of voluntary voice control in patients with unilateral LMC damage, whereas bilateral LMC lesions render patients unable to speak and sing. On the other hand, damage to the branches of the vagal nerve results in the unilateral paralysis and paresis of the vocal fold (Jurgens 2002).

Two Pathways Controlling Voice Production

Central control of voice production is conducted by two parallel pathways: the limbic vocal control pathway, which is responsible for the control of innate nonverbal and emotional vocalizations, and the laryngeal motor cortical pathway, which regulates the fine motor control of voluntary voice production, such as speech and song, as well as voluntary production of innate vocalizations. These pathways are organized hierarchically, building from the basic levels in the lower brain stem and spinal cord to the most complex levels in the anterior cingulate cortex (ACC) and LMC, respectively (Fig. 2).

Voice control develops gradually throughout childhood for the control of speech production. As we mentioned earlier, the first vocalization occurs at birth as a shriek of the newborn. This and other types of nonverbal vocalizations in humans, such as an infant's cry and laughter, represent innate vocal reactions whose acoustic structure is genetically preprogrammed (Scheiner and others 2004). This means that infants do not need to hear the sounds of cry or laughter from others in order to produce them. These basic innate vocalizations are controlled by the sensory and motor nuclei of the lower brain stem (e.g., ambigual, trigeminal, facial, hypoglossal, solitary tract nuclei) and spinal cord (thoracic and lumbar ventral horn), which are responsible for the basic coordination of laryngeal, respiratory, and articulatory muscle activity (Fig. 2, subsystem I). The reticular formation of the pons and lower brain stem is another important structure for this type of vocal control. It plays a dual role in establishing connections between different phonatory nuclei and in coordinating basic vocal motor activities. Single-unit recording studies in the squirrel monkey have found that some vocalization-correlated neurons in the reticular formation are active only during specific vocalizations, whereas other neurons fire during various types of vocalizations or change their discharge rate based on the rhythmic frequency modulations of produced vocalizations (Kirzinger and Jurgens 1991; Luthe and others 2000). Furthermore, the reticular formation dorsal to the superior olive contains a vocalization pattern generator, the neuronal activity of which co-occurs with the neuronal firing of the phonatory ambigual, facial, and motor trigeminal nuclei (Hage and Jurgens 2006).

The involvement of the forebrain is not essential for production of innate vocalizations. It has been reported that even anencephalic infants, who lack the entire forebrain but have an intact brain stem, are still able to vocally react to painful stimuli (Monnier and Willi 1953). However, in older children, innate vocalizations come under voluntary control, sometimes involving mimicking of vocal utterances. For example, cry can be produced in the absence of pain or suppressed in the presence of pain. For this higher level of vocal control, that is, voluntary initiation of innate vocalizations and control of their emotional status, the brain stem phonatory nuclei and the vocal pattern generator require an input from the higher brain regions, such as the periaqueductal gray (PAG) and ACC (Fig. 2, subsystem II). The PAG receives direct projections from the ACC as well as from other cortical and subcortical regions controlling limbic, sensory, motor, cognitive, and arousal systems (Dujardin and Jurgens 2005). The PAG projects to the reticular formation of the lower brain stem, thus representing a neuroanatomical and functional relay station within the ACC–PAG–brain stem pathway. The PAG plays primarily a gating role in triggering a vocal response and modulating its intensity, whereas the ACC is involved in voluntary control of voice initiation and its emotional intonation. Destruction of the ACC results in a loss of voluntary control of emotional intonations during speaking, whereas lesions in the PAG lead to mutism. Interestingly, destruction of the ACC does not interfere with the production of vocalizations elicited at the level of the PAG and brain stem reticular formation; however, destruction of the PAG abolishes vocalizations from the
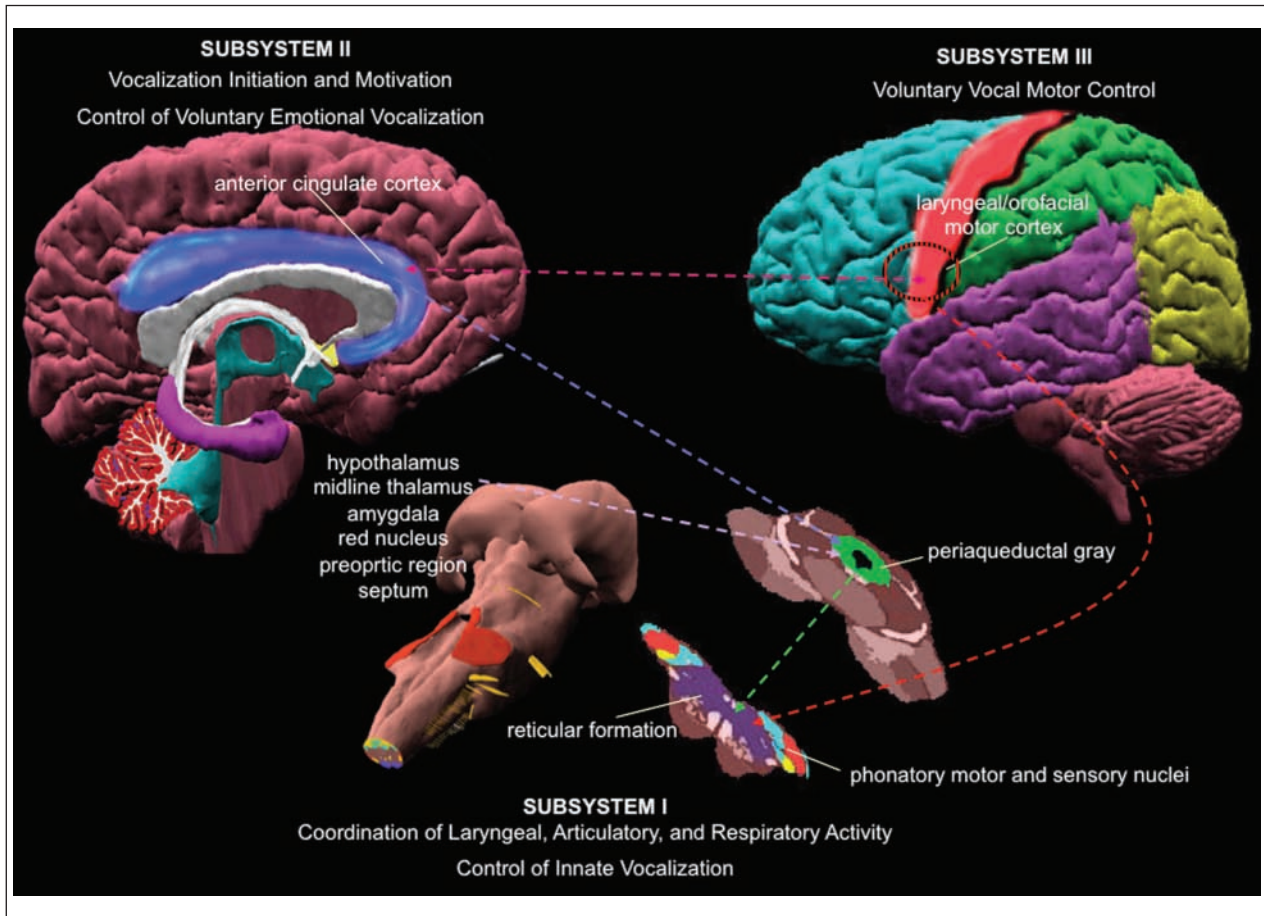
Figure 2. Hierarchical organization of central voice control in humans and nonhuman primates. The figure depicts different levels of the voice control system. The lowest level (subsystem I) is represented by the brain stem and spinal cord sensorimotor phonatory nuclei. This subsystem is responsible for the coordination of laryngeal, articulatory, and respiratory control during production of innate vocalizations. The higher level within this system (subsystem II) is represented by the periaqueductal gray (PAG), ACC, and limbic input structures, such as the hypothalamus, midline thalamus, amygdala, red nucleus, preoptic region, and septum. This subsystem is responsible for initiation of vocalizations and control of voluntary emotional vocalizations. The highest level is represented by the laryngeal/orofacial motor cortex with its input and output regions (subsystem III). This subsystem is responsible for voluntary vocal motor control of speech and song production. The dotted lines show simplified connections between different regions within the voice-controlling system.

ACC but not from the brain stem reticular formation (Jurgens 2002). Thus, although the ACC and PAG are important in shaping voluntary control of voice initiation and emotional modulation, the reticular formation represents the basic executing level of this pathway.

The highest level within the hierarchy of the voice-controlling system is represented by the LMC and its input and output structures (Fig. 2, subsystem III). The ability to learn new vocalizations is very limited, perhaps impossible, in nonhuman primates and other mammals (except whales and dolphins). Their vocalizations are exclusively emotional, with each type of vocalization conveying only one meaning. In humans, in contrast, the development of the ability to produce innumerable learned vocal utterances for

speech and song depends on the fine motor control by the LMC. Although lesions in this region have almost no effects on monkey vocalizations, they abolish speech production in human patients (Jurgens 2002). Such patients are occasionally able to initiate phonation, such as grunts, wails, and laughs, but they do not succeed in voluntary modulations of pitch, intensity, and the harmonious quality of their vocalizations. The preservation of nonverbal vocalizations in patients with bilateral damage to the LMC may be due to parallel organization of the LMC and ACC-PAG pathways, one controlling voluntary voice production and the other controlling the initiation of basic vocal reactions.

For proper coordination of learned vocal patterning and voice initiation, the LMC and ACC-PAG pathways
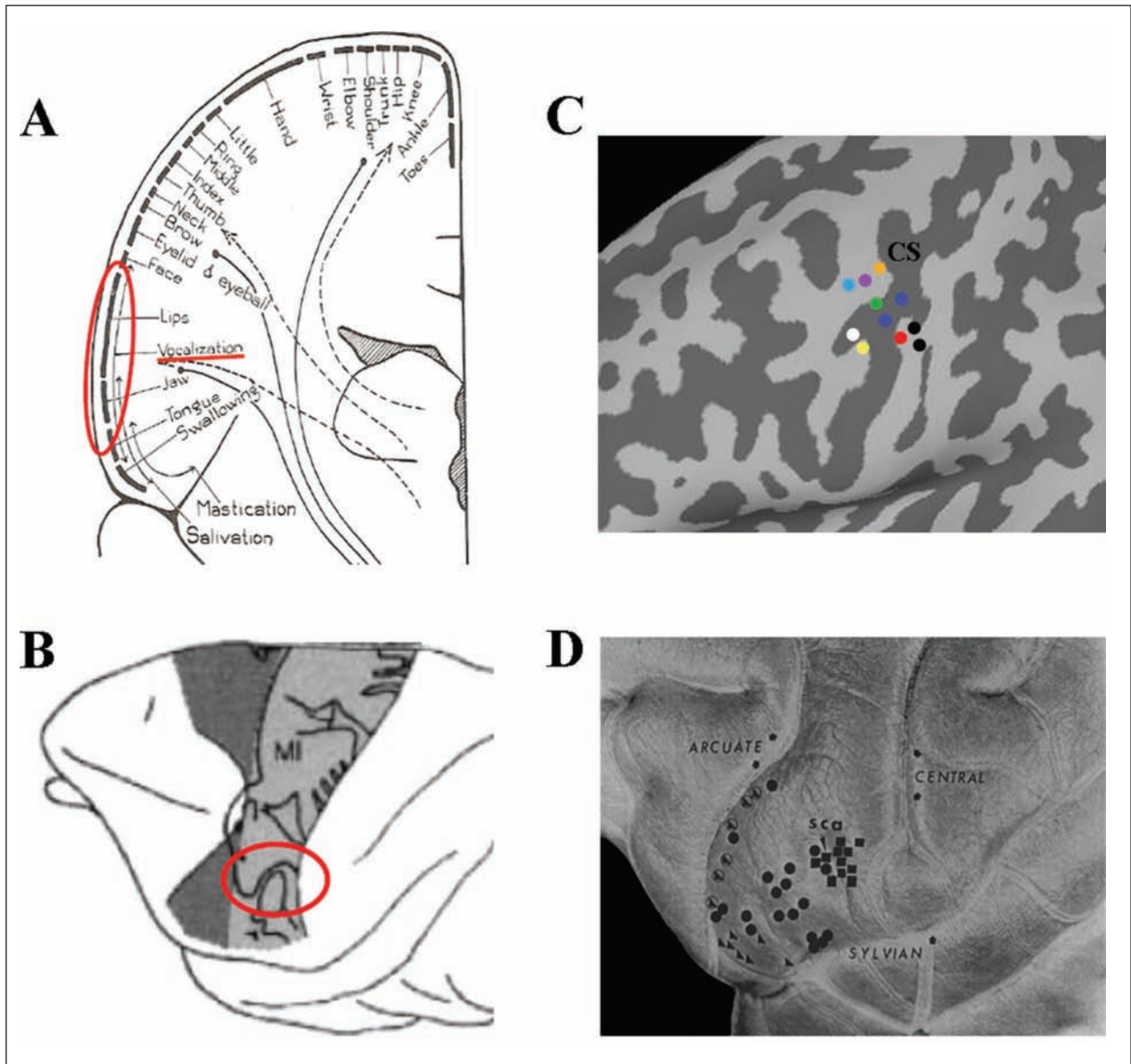
Figure 3. Laryngeal motor cortical representation. Schematic views of body representation within the motor cortex (A) in humans ("motor homunculus" according to Penfield and Bordley 1937) and (B) in the rhesus monkey ("motor simiculus" according to Woolsey and others 1952. Reprinted from Fadiga and others, copyright 2000, with permission from Elsevier. (C) The laryngeal motor cortical region in humans as defined in neuroimaging studies. The colored circles represent the reported peaks of activation in the following studies of syllable production: orange, Bohland and Guenther (2006); purple, Olthoff and others (2008); light blue, Terumitsu and others (2006); green, Loucks and others (2007); blue, Brown and others (2008); red, Wilson and others (2004); black, Simonyan and others (2009); white, Riecker and others (2008); and yellow, Peeva and others (2010). CS = central sulcus. (D) The laryngeal motor cortical region in the rhesus monkey. Topographical representation of the laryngeal muscles: cricothyroid = right-angled triangle; thyroarytenoid = circle; combination of the cricothyroid and thyroarytenoid = encircled right-angled triangle; extrinsic laryngeal muscles = square. sca = sulcus subcentralis anterior (subcentral dimple). Reprinted from Hast and others, copyright 1974, with permission from Elsevier.

converge in at least two regions, as found in neuroanatomical studies in nonhuman primates. One such region is the ACC itself, which has direct reciprocal connections with the LMC (Simonyan and Jurgens 2002, 2005a). The other region is the reticular formation of the brain stem, which projects directly to the phonatory motoneurons

(Hannig and Jurgens 2006). Thus, the vocal motor control system appears to be separated into two parallel pathways for learned and innate vocalizations, coordination and interactions of which are indispensible for proper voice control.

Localization of the Laryngeal Motor Cortex

As we stated earlier, the role of the LMC is essential in the control of voluntary laryngeal behaviors, both learned, such as speech and song, and innate, such as production on demand of laughter, coughing, breathing, and so forth. The ability to control various laryngeal behaviors voluntarily is most prominent in humans, whereas other species, including nonhuman primates, have limited ability to produce their vocalizations voluntarily.

First observations of the larynx representation within the motor cortex were made in the 1930s. Shortly after the report by Oscar Foester (1936) that bilateral vocal fold movements in humans can be produced with electrical stimulation of the motor strip of one hemisphere, Wilder Penfield and colleagues described the representation of vocalization in the inferior portion of the motor cortex above the jaw and below the lip muscles representations (Penfield and Bordley 1937; Fig. 3A). Nearly the same somatotopy was observed in the monkey brain with the representation of the larynx region above the Sylvian fissure (Woolsey and others 1952; Fig. 3B). On the other hand, electrical stimulation studies failed to identify the larynx representation in the motor cortex of lower mammals, such as the dog and cat (Milojevic and Hast 1964).

Although the implications of the LMC in the control of voice production is significantly different between humans and nonhuman primates, much of our understanding about the organization of the LMC comes from research in nonhuman primates, primarily in the rhesus and squirrel monkeys. The LMC in these species is situated between the inferior branch of the arcuate sulcus anteriorly and the subcentral dimple posteriorly (Hast and others 1974; Fig. 3D). This region contains small populations of neurons that are selectively active during either conditioned or spontaneous vocalizations (Coude and others 2009). Among these, the majority of neurons specific for conditioned vocalization discharge before voice onset, whereas a smaller number of neurons are time locked with voice onset.

The larynx area is surrounded by the representations of the tongue, lip, and masticatory muscles and is considered to be part of the primary motor cortex, although cytoarchitectonically, it corresponds to the premotor cortex, area 6, in nonhuman primates (Jurgens 1974; Simonyan and Jurgens 2002). Electrical stimulation of this region with simultaneous laryngeal electromyographic recordings in the rhesus monkey revealed that the intrinsic and extrinsic laryngeal muscles have separate representations within the LMC (i.e., topographical organization; Hast and others 1974; Fig. 3D).

More than half a century after Foester's and Penfield's seminal observations, studies of the LMC in humans have been recently revived with the advent of noninvasive neuroimaging techniques. Recent investigations in humans have shown that the LMC is located more dorsally from the Sylvian fissure (Khedr and Aref 2002; Rodel and others 2004) than originally proposed (Penfield and Bordley 1937). Similar to nonhuman primates, the human LMC is organized topographically, although compared with the monkey's brain, the representation of the laryngeal muscles is reversed, with the CT muscle located more medially than the TA muscle (Rodel and others 2004). However, in contrast to the monkey, recent studies have substantially revised the location of the LMC in humans. From the earlier works of Penfield and colleagues, it is notable that the motor homunculus identifies a representation of a behavior (vocalization) rather than an organ (larynx) in the inferior portion of the motor cortex (Fig. 3A). As behavior, vocalization requires not only laryngeal muscle activity but also orchestrated activity of the respiratory and orofacial movements. Hence, it is not surprising that, on the map of the motor homunculus, vocalization as behavior, in contrast to the single-organ representation, encompasses quite a large region within the motor cortex, overlapping with the lip, jaw, and tongue representations, without, however, a specific reference to the larynx. Thus, the location of the human LMC remained largely unknown until recently. Neuroimaging studies using different vocal tasks were finally able to separate and localize the laryngeal region within the primary motor cortex (Brown and others 2008; Loucks and others 2007; Rodel and others 2004; Simonyan and others 2009; Wilson and others 2004), predominantly in the area 4p (Fig. 3C).

The differences in the cytoarchitectonic location of the LMC between humans and nonhuman primates deserve special attention. The representation of the LMC in the primary motor cortex (area 4) in humans, as opposed to its location in the premotor cortex (area 6) in nonhuman primates, may represent one of the major evolutionary developments in humans toward the ability to speak and vocalize voluntarily. The LMC representation in area 4 of the motor cortex may have enabled the establishment of a unique direct connection between the LMC and laryngeal motoneurons of the brain stem for faster neuronal transmission and direct control over the coordinated activity of complex laryngeal, orofacial, and respiratory movements for speech production. In monkeys, this connection is indirect, and hence the control of the brain stem laryngeal motoneurons is limited. We hypothesize that this neuroanatomical difference may underlie the very limited ability of nonhuman primates to learn and control their vocalizations voluntarily.
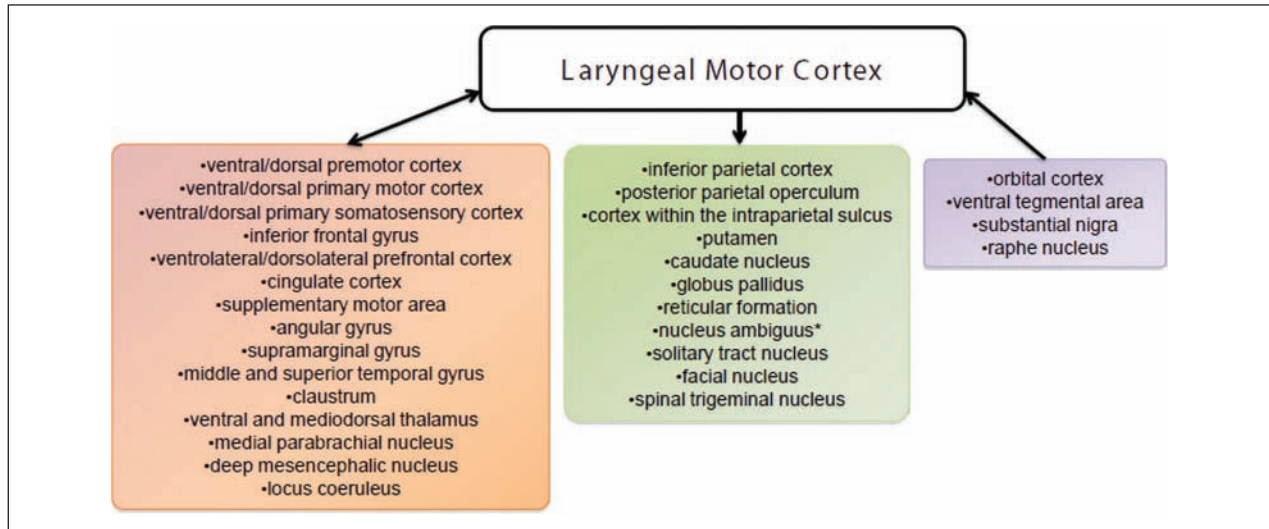
Figure 4. Cortical and subcortical networks of the laryngeal motor cortex. Block diagrams illustrate the reciprocal (pink box), outgoing (green box), and incoming (purple box) connections of the laryngeal motor cortex as defined using neuroanatomical tracing studies in nonhuman primates and diffusion tensor tractography in humans. Asterisk (*) indicates that the projection from the laryngeal motor cortex to the nucleus ambiguus exists only in humans but not in nonhuman primates.

Laryngeal Motor Cortical Networks

Despite the differences in the representation of the larynx area in the motor cortex and in its anatomical and functional distinctions between humans and nonhuman primates, the latter species still remains a valuable model for studying the neuroanatomical projections of the LMC using invasive tract-tracing techniques. Such investigations in nonhuman primates can be considered complementary to diffusion tensor tractography (DTT) studies in humans for categorization of directionality of the LMC connections (efferent v. afferent), which is otherwise impossible to define using only the DTT approach. Hence, in the following, we will review the LMC networks based on studies using both DTT in humans (Simonyan and others 2009) and neuroanatomical tract tracing in the rhesus and squirrel monkeys (Jurgens 1976; Simonyan and Jurgens 2002, 2003, 2005a, 2005b). We will further review the interaction of the LMC with the main cortical and subcortical regions indispensible for voluntary voice production based on neuroimaging studies of voice and speech in humans.

A series of recent investigations has shown that both humans and nonhuman primates share a common network of extensive cortical and subcortical connections with the LMC (Fig. 4). Nearly all cortical connections of the LMC are reciprocal, that is, the LMC both receives and sends information to these regions. The regions reciprocally connected with the LMC are the surrounding ventral and dorsal premotor, primary motor, and somatosensory cortices at their orofacial and trunkal representations, inferior frontal gyrus (IFG), ventrolateral and dorsolateral

prefrontal cortex, insula, cingulate cortex, supplementary motor area (SMA), angular (AG), supramarginal (SMG), middle, and superior temporal gyri, claustrum, ventral and mediodorsal thalamus, medial parabrachial nucleus, deep mesencephalic nucleus, and locus coeruleus. The only cortical region projecting to the LMC without receiving an input from it is the orbital cortex, which is assumed to have only a very indirect involvement in vocal control (Price 1996), as well as subcortically the ventral tegmental area, substantia nigra, and raphe nucleus. On the other hand, the cortical regions that receive projections from the LMC but do not send connections back are the inferior parietal cortex, posterior parietal operculum, and cortex within the intraparietal sulcus, as well as subcortically the putamen, caudate nucleus, globus pallidus, and brain stem nuclei (i.e., reticular formation and spinal trigeminal, solitary tract, and facial nuclei).

Functionally, the LMC is connected with most of these structures to fulfill its main task: the voluntary control of voice production. Interconnections of the LMC with the surrounding somatosensory cortex and inferior parietal cortex are important for integration of proprioceptive and tactile feedback from the orofacial, respiratory, and laryngeal regions during voice production. Neuroimaging studies of overt and covert voice and speech production have consistently reported activation of the primary sensorimotor cortex (e.g., Bohland and Guenther 2006; Horwitz and others 2003; Loucks and others 2007; Riecker and others 2000). Activation in this region is organized somatotopically, with the orofacial and laryngeal activation occupying the ventral portion of the sensorimotor cortex and the

respiratory activation represented as two discrete loci in the dorsal region of the trunk representation and in the ventral region overlapping with the laryngeal and orofacial activation (Brown and others 2009; Loucks and others 2007; Simonyan and others 2007). Interestingly, only voluntary exhalation, which is required for voice production, but not inhalation elicits activation of both the dorsal and ventral sensorimotor cortex (Ramsay and others 1993). The orchestration of simultaneous laryngeal, orofacial, and respiratory muscle activity at the cortical sensorimotor level becomes apparent when one of its components is voluntarily modulated or altered. A recent study of functional LMC networks during syllable production showed that when subjects were asked to produce voice with minimal orofacial movements and at similar breathing depth, that is, the modulation of two of three components of the voice production system, the LMC displayed reduced functional connectivity with both orofacial and respiratory sensorimotor cortices to maintain the specific level of task production (Simonyan and others 2009). The influences of the somatosensory cortex on the motor cortex become even more apparent when the auditory feedback, another online monitoring system of correct voice and speech production, is altered, and the encoding of auditory input is challenged, for example, in the presence of very loud noise (Guenther 2006; Peschke and others 2009). These observations suggest not only that the ventral sensorimotor region contains a simple ensemble of motor and sensory components of the voice-controlling system (e.g., laryngeal, orofacial, and respiratory) but also that it acts as a higher-level centralized region, coordinating exhalatory airflow necessary for setting the vocal folds into vibration and modulating the orofacial articulators for voluntary production of different types of vocal behaviors.

With respect to the inferior parietal cortex, including the SMG and AG, this region represents one of a few higher-order sensorimotor centers for coordination of both speech production and comprehension. The inferior parietal cortex is known to be involved in complex phonological and semantic processing and monitoring of the verbal response to suppress phonemic errors (e.g., Fiebach and others 2007; Hocking and others 2009; Zheng and others 2010).

The LMC requires an input from the IFG for motor planning of voice and speech production. The IFG is another brain region in which the control of speech production and comprehension converge. Its pars orbitalis is involved in the retrieval of semantic information (de Zubicaray and McMahon 2009; Tyler and others 2010), and its pars opercularis is responsible for hierarchical sequencing of linguistic and nonlinguistic sequences (Tettamanti and others 2009; Willems and others 2009) and articulatory preparation to speech production (Papoutsi and others 2009; Zheng and others 2010). Because the IFG is prominent in the processing of information necessary for long-term preparation of learned oromotor sequences, it is not surprising that the IFG is usually active during the production of long sequences of syllables and words (e.g., Horwitz and others 2003; Ozdemir and others 2006; Wise and others 1999) and only rarely during production of single syllables (Brown and others 2008; Ghosh and others 2008; Loucks and others 2007). Despite the fact that the IFG activation is not always observed in studies of differential complexity of voice and speech production, the strong functional and structural connectivity between the IFG and LMC appears to be responsible for motor preparation and processing of all components of speech production (e.g., laryngeal, orofacial, or respiratory; Greenlee and others 2004; Simonyan and others 2009).

The reciprocal connections of the LMC with the SMA are needed for preparation for vocal motor command execution. Accordingly, it has been shown that the offset of the late vocal-related cortical potentials in the SMA precedes those in the LMC, pointing to the involvement of the LMC only after the motor preparatory phase in the SMA (Galgano and Froud 2008). The SMA is active during various voluntary laryngeal tasks (e.g., Ghosh and others 2008; Loucks and others 2007; Ozdemir and others 2006; Simonyan and others 2007). More specifically, it has been shown that activation in the anterior pre-SMA was related to effortful word selection, activation in the posterior pre-SMA was related to the control of syllable sequencing, and activation in the SMA proper was related to overt articulation (Alario and others 2006). Recently, the SMA has also been identified as a motor component of the speech monitoring network (van de Ven and others 2009). Furthermore, electrical stimulation of this region has been reported to elicit vocalizations in humans (Penfield and Welch 1951) but not in monkeys (Jurgens 2002). Similarly, bilateral lesions in the SMA have no effect on monkey vocalizations. In contrast, in humans, such lesions severely reduce the motivation to employ propositional speech, whereas nonpropositional (automatic) speech remains almost intact (so-called transcortical motor aphasia). Functional connections between the LMC and SMA are left lateralized and are particularly stronger with the pre-SMA during learned voice production compared with innate laryngeal behavior, such as breathing (Simonyan and others 2009). It thus appears that the connectivity between the LMC and the pre-SMA, a region responsible for processing of higher-order motor plans for subsequently ordered movement execution (Matsuzaka and others 1992; Shima and Tanji 1998; Tanji and Shima 1996), plays a central role in sequencing and initiation of complex learned vocal movements during speech production.

It is important to note that the LMC has a reciprocal structural connection with the ACC but not with the PAG, as identified based on neuroanatomical tract-tracing

studies in nonhuman primates. The lack of connections between the LMC and PAG fits well with the separation between the two descending pathways controlling voice production, limbic and motor cortical. Similarly, in the monkey, the PAG blockade has no effect on vocal fold movements elicited from the LMC, as opposed to the drastic effects on vocalization elicited by limbic structures (Jurgens 2002). The LMC thus appears to control voluntary voice production via a pathway bypassing the PAG, although it establishes connections with the ACC for shaping emotional intonations during speech production. As noted earlier, the connection between the LMC and ACC serves as one of the two links at which two pathways controlling innate emotional and learned vocalizations converge.

Another link between the limbic and motor cortical vocal pathways is present at the level of the brain stem reticular formation, specifically in its dorsal and parvocellular reticular nuclei, which are further directly connected with laryngeal motoneurons in the nucleus ambiguus; the articulatory motoneurons in the trigeminal motor, facial, and hypoglossal nuclei; and the expiratory motoneurons in the thoracic and upper lumbar spinal cord (Bernard and others 1990; Thoms and Jurgens 1987; VanderHorst and others 2001). Combined electrical stimulation and lesioning studies have shown that bilateral lesions in this region block vocalizations elicited from the PAG and vocal fold movements elicited from the LMC (Jurgens and Ehrenreich 2007; Shiba and others 1997). Because both limbic and motor cortical pathways come together in the reticular formation of the brain stem, it has been suggested that this region is involved in vocal motor coordination of both innate and learned voice production (Jurgens and Ehrenreich 2007). Its functional properties are more important in vocal motor control in nonhuman primates than in humans due to the lack of direct projections from the LMC to the nucleus ambiguus in the former species and, therefore, their reduced ability to directly modulate activity of brain stem laryngeal motoneurons (Jurgens 1976; Simonyan and Jurgens 2003). In humans, in contrast, direct connections do exist between the LMC and the nucleus ambiguus (Iwatsubo and others 1990; Kuypers 1958). This direct LMC-ambigual connection together with the LMC representation in the primary motor cortex appear to be very recent acquisitions in hominid evolution and may be regarded as crucial prerequisites for speech control.

In addition to direct LMC–brain stem laryngeal motoneuron connections, the LMC establishes a widespread network of subcortical connections, most of which project further down to the brain stem phonatory motoneurons. The putamen receives the strongest of all telencephalic subcortical projections from the LMC, thus representing the main basal ganglia output structure of the LMC. Putaminal lesions cause dysarthria and dysphonia in humans but have no effect on monkey vocalizations (Jurgens 2002), suggesting the involvement of the putamen only in learned voluntary voice and speech production but not in the production of innate vocalizations. Motor cortical connections to the putamen are somatotopically organized with the leg area projecting to the rostrodorsal putamen, the arm and trunk occupying its central part, the face area projections to the caudoventral putamen, and the larynx area connecting with the ventral putamen over a large anterioposterior extent (Kunzle 1975; Simonyan and Jurgens 2003). It appears that there is an overlap of projections from the face and larynx areas in the posterior (postcommissural) putamen (i.e., part of the sensorimotor functional striatal loop), whereas the putamen rostral to the anterior commissure (i.e., part of the associative and limbic striatal loops) receives input only from the LMC. Direct connections of the LMC with all striatal functional subdivisions, including the sensorimotor, associative, and limbic loops, may represent important factors in the integrative control of different aspects of speech production, ranging from motor control to motivation and cognitive processing of speech.

Another subcortical region that is directly connected with the LMC is the thalamus, specifically its ventral lateral, ventral posterior, medial, and centromedian groups of nuclei. Single-unit recordings in the ventral thalamus have shown voice- and speech-related neuronal activity (Farley 1997; McClean and others 1990). Furthermore, the ventral thalamus has reciprocal connections with the LMC, IFG, and SMA, the electrical stimulation of which also produces vocalization in humans (Penfield and Roberts 1959). Besides the direct role of the ventral thalamus in vocal sensorimotor coordination of learned voice production, it represents an important relay station of the cortico-striato-pallido-thalamo-cortical and cortico-ponto-cerebello-thalamo-cortical loops for integration of sensorimotor information from the basal ganglia and cerebellum. Both pathways, finally, connect the LMC with the laryngeal motoneurons after synapsing in the reticular formation of the brain stem.

In conclusion, the central control of human voice production is organized hierarchically. As the highest level of this control system, the human LMC is indispensible for the control of learned but not innate vocalizations. To fulfill its function, the human LMC has direct connections with the brain stem laryngeal motoneurons, as well as participation in a widespread network of cortical and subcortical connections, which further indirectly connect the LMC with laryngeal motoneurons. Thus, voluntary voice production is controlled by the LMC and is executed through the multiple pathways both directly and indirectly descending to the brain stem laryngeal motoneurons. This is supported also by the fact that a combined interruption of the direct and indirect LMC-motoneuronal pathways

abolishes the ability to produce voice and speech voluntarily, similar to bilateral lesions in the LMC alone (Bauer and others 1980; Urban and others 1996).

Future Directions

Although over the past few years we have seen advances in understanding of the LMC's role in human voice and speech production, there are still a number of unanswered questions about its structural and functional organization and interactions with other brain regions in both healthy humans and patients with neurological voice and speech disorders. In particular, further research is needed both in humans and nonhuman primates for characterization of subcomponents of the LMC networks. To date, the LMC projections have been identified using trans-synaptic tracers, such as ^{3}H-leucine, biotin dextran amine, and wheat germ agglutinin conjugated with horseradish peroxidase, in nonhuman primates and using unconstrained probabilistic DTT in healthy humans. Both techniques provide information about the projecting regions to and from the LMC but lack information about whether the given connection between the LMC and the target region is direct or indirect via other relay stations. To derive a more complete characterization of the LMC structural networks, neuroanatomical studies using tracers that are transported in a time-dependent manner to label synaptically connected neuronal chains (Kelly and Strick 2000) should be conducted in nonhuman primates and further verified in healthy humans using multimodal neuroimaging techniques.

Future research should also focus on the organization of functional LMC networks during different components of laryngeal behaviors and on interactions between limbic and motor cortical parallel pathways. Similarly, given that speech production, as one of the most rapid human motor actions, has a strong temporal dimension, the temporal characteristics of the LMC activity remain to be explored. The significance of these studies is paramount for future investigations of altered structural and functional links within the central voice control system in patients with neurological voice and speech disorders.

Another unknown aspect is the laryngeal representation in the primary somatosensory cortex and its interactions with the LMC. The earlier studies by Penfield and colleagues lacked the mapping of the larynx representation in the primary somatosensory cortex. Since then, no attempts have been reported to identify the laryngeal somatosensory region, although it is known that lesions in the inferior postcentral gyrus cause dysarthria due to the interruptions of kinesthetic and proprioceptive feedback from the phonatory organs (Luria 1964).

Finally, it is unknown, to date, how different neurotransmitters (e.g., dopamine, GABA) influence and modulate the human LMC networks during voice and speech production. This information will be crucial in identifying the target brain regions for the development of new neuropharmacological options to modulate the LMC activity in patients with neurological voice problems.

Declaration of Conflicting Interests

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