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The laryngeal motor cortex: its organization and connectivity

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Our ability to learn and control the motor aspects of complex laryngeal behaviors, such as speech and song, is modulated by the laryngeal motor cortex (LMC), which is situated in the area 4 of the primary motor cortex and establishes both direct and indirect connections with laryngeal motoneurons. In contrast, the LMC in monkeys is located in the area 6 of the premotor cortex, projects only indirectly to laryngeal motoneurons and its destruction has essentially no effect on production of species-specific calls. These differences in cytoarchitectonic location and connectivity may be a result of hominid evolution that led to the LMC shift from the phylogenetically 'old' to 'new' motor cortex in order to fulfill its paramount function, that is, voluntary motor control of human speech and song production.

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Introduction

The larynx participates in a wide range of vital behaviors, such as breathing, swallowing and voice production, all of which are indispensable for our existence and communication. While breathing and swallowing are innate behaviors, the ability to produce voice for speaking and singing involves intensive learning and requires a proper integration between several brain networks for the motor output of an uttered word. The ability to control laryngeal muscles voluntarily is most remarkable in actors and singers, who are able, on demand, to raise and lower the larynx, regulate the amount of airflow through the vocal folds, tense and relax the vocal folds, and even move each vocal fold separately in order to modulate their speaking or singing voice.

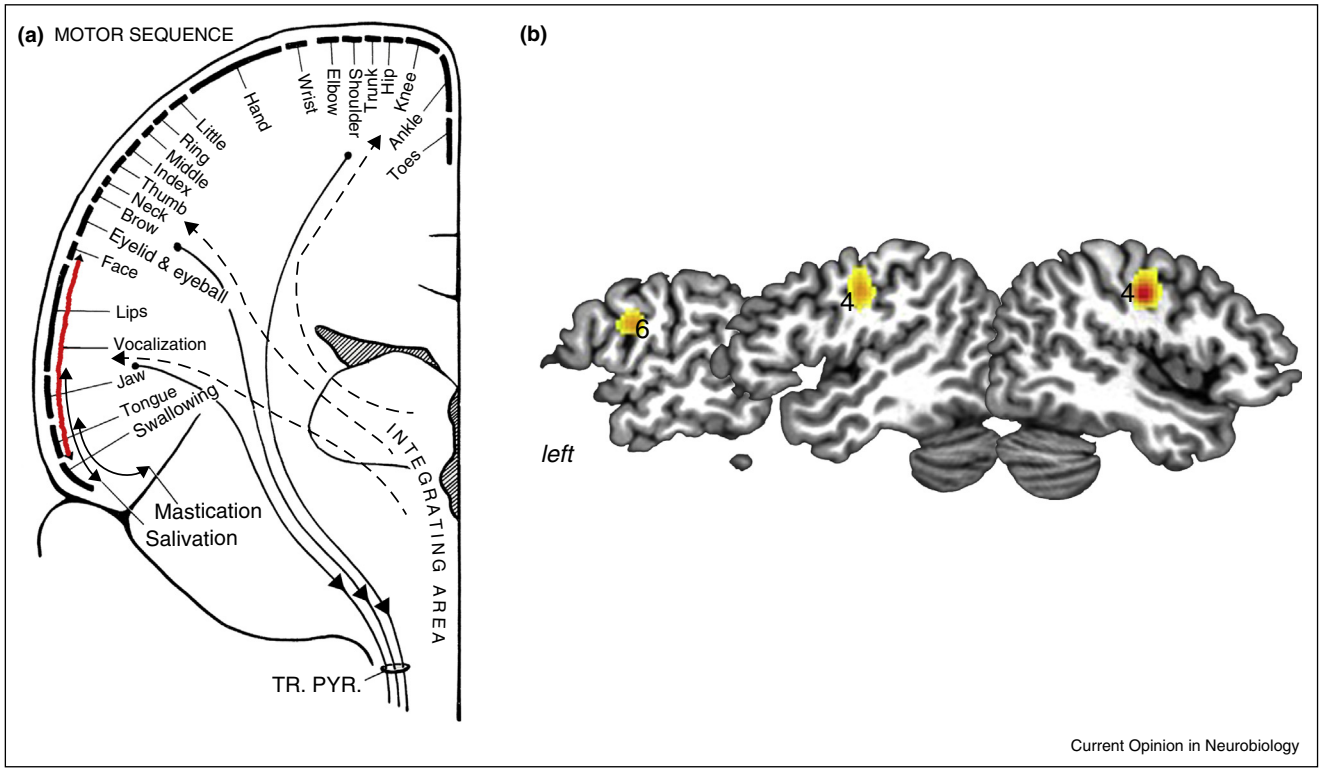
Voluntary voice production in humans is under the direct control of the laryngeal motor cortex (LMC), which gives rise to a final common cortical motor pathway descending via the corticobulbar tract and communicating with laryngeal motoneurons in the brainstem to innervate the laryngeal muscles. In regard to the central motor control, the open question is what (neurologically) makes us humans unique in our ability to learn and produce voice for speech and song as oppose to other primate species, which have limited, if any, capacity for vocal learning and voluntary voice production [1,2••]. A possible candidate brain region that appears to have grossly similar but importantly distinct topology and connectivity in humans compared to other mammals is the LMC itself.

The laryngeal motor cortex: location

In contrast to other body part representations within the primary motor cortex, the exact LMC location in humans remained largely unknown until recently. Based on the seminal work by Penfield and colleagues in 1930s–1950s [3••], the LMC was assumed to be located somewhere within the vocalization area in the inferior portion of the precentral gyrus, just above the swallowing and below the face representations (Figure 1a). Using direct electrical stimulation, the LMC was also identified in the chimpanzee, rhesus monkey, and squirrel monkey but its location was far rostrally within the precentral gyrus [4•,5] compared to Penfiled's vocalization area in humans [3••]. The existence of a motor cortical region specialized for isolated vocal fold movements was questioned in other mammals, such as the dog and cat [6]. A recent study reported that the laryngeal motor cortical representation might exist in mice and is possibly involved in the modulations of pitch of ultrasound vocalizations [7], although these findings and their homology with the human and non-human primate LMC require further investigation.

The LMC regions in humans and non-human primates are considered to be homologues [2••,8] because, while stimulated, both yield an approximation (or adduction) of vocal folds to the midline of the larynx, which is independent from the movement of the other facial or upper body muscles [4•,9–13]. Physiologically, vocal fold adduction is necessary for the majority of laryngeal behaviors, such as voice production, coughing, sneezing, stabilizing thorax for lifting heavy weights, etc. A recent series of neuroimaging studies suggested that the LMC in humans is located more caudally within the precentral gyrus compared to the LMC of non-human primates [4•,5]

Figure 1



(a) The 'Motor sequence' within the primary motor cortex with the extensive vocalization region in the inferior portion of the precentral gyrus [62]. **(b)** Meta-analysis of 19 fMRI studies between 2000 and 2013 using activation likelihood estimation (ALE) of brain function during voice production (GingerALE software). Bilateral peaks of LMC activation were found in the area 4p with an additional peak of activation in the left area 6 [15]. Data are presented on a series of sagittal slices in the standard Talairach-Tournoux space.

and more dorsally from the Sylvian fissure than originally thought based on the vocalization mapping studies by Penfield and colleagues [3••]. We conducted a meta-analysis of 19 functional MRI (fMRI) studies between 2000 and 2013 in healthy humans during production of meaningful and meaningless syllables, vowels, glottal stops, and phonation with and without articulatory movements and identified that the bilateral peaks of activation corresponding to the LMC are located in the primary motor cortex (area 4 of Brodmann [14]) [15] (Figure 1b). This finding is in line with high-resolution multi-electrode cortical recording study during syllable production [16] and transcranial magnetic stimulation (TMS) study of the motor cortex during resting and voice production [17,18,19], which reported the laryngeal muscle representation in the dorsal portion of the ventral primary motor cortex. Furthermore, the location of this region corresponds to the motor cortical area where left hemisphere lateralized brain activity during reading is associated with *FOXP2* polymorphism [20]. The peak of activity within the LMC, as identified in our meta-analysis study, was located in the posterior part of area 4 (i.e. area 4p of Geyer *et al.* [21,22]). It has been shown that the area 4p is involved in initiation and execution of motor commands as well as modulation of movement-related attention as oppose to the area 4a (the anterior part of area 4), which functionally resembles the secondary motor cortex by requiring higher-order sensory feedback for motor execution [23–25].

The meta-analysis of neuroimaging literature has also showed an additional peak of activation in the left premotor cortex (area 6 of Brodmann) [15] (Figure 1b), which is similar to the location of monkey LMC, as described below. Studies using direct electrical stimulation of the motor strip in the macaque have identified the laryngeal muscle representation only between the inferior branch of the arcuate sulcus rostrally and the subcentral dimple caudally [4,11,26] (Figure 2b). A similar location of LMC was also described in the squirrel monkey [12,27,28]. The LMC region in the rhesus monkey was shown to contain vocalization-related neurons [26]. Cytoarchitectonically, this region falls within the premotor cortex (area 6 of Brodmann [14], area 6bα of Vogt and Vogt [29], area FCBm of von Bonin and Bailey [30], area F5 of Matelli *et al.* [31], area 6VR(F5)/ProM of Paxinos *et al.* [32], or area F5(6Va/Vb) of Saleem and Logothetis [33]). However, extensive explorations of the precentral gyrus with direct