Central Pattern Generators

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Y. Hisa (ed.), *Neuroanatomy and Neurophysiology of the Larynx*, DOI 10.1007/978-4-431-55750-0_14

14.1 Brainstem Mechanisms Underlying Laryngeal Movements

Brainstem functions as not only a relay station of descending inputs from higher center but also pattern-generating system which can provide suitable reactions to protect ourselves from risks and to maintain homeostasis.

Laryngeal movements, such as breathing, phonation, and airway protective reflexes including swallowing and coughing, can be generated and controlled by the specific neuronal networks in the brainstem, which can be influenced by descending signals from higher center. These specific neuronal networks are called as "the central pattern generators (CPGs)."

The brainstem, where the CPG networks involved in the laryngeal movements exist, is anatomically classified as three subdivisions: (1) medulla oblongata, (2) pons, and (3) midbrain. Each area includes the specific neuronal groups that could participate in the generation of these behaviors.

For example, the cranial motoneurons including the laryngeal, pharyngeal, esophageal, and hypoglossal motoneurons, which can contribute to the generation of the laryngeal motor activities including breathing, vocalization, and airway protective reflexes, are located in the medulla. In particular, the laryngeal motoneurons are located in the loose formation of the nucleus ambiguus (NA), whereas the pharyngeal motoneurons are distributed in the semicompact formation of the NA. On the other hand, the neurons that project to the lumbar spinal cord or the NA are located in the nucleus retroambiguus (NRA), presumably acting as the premotor neurons of the abdominal or laryngeal motoneurons, respectively [1, 2]. The afferent of the upper airway and alimentary tract terminates in the nucleus tractus solitarius (NTS) and spinal trigeminal nucleus [3]. The midbrain periaqueductal gray (PAG) contributes significantly to the generation of vocalization [4].

The neuronal networks of the central respiratory pattern generator mainly exist in the medulla and pons. The respiratory neurons located in the ventrolateral NTS and adjacent reticular formation are known as the dorsal respiratory group (DRG) [5, 6]. On the other hand, the respiratory neurons in the ventrolateral medulla and pons constitute a longitudinal column extending from the facial nucleus to the rostralmost part of the cervical spinal cord in the lateral tegmental field. This column is subdivided into the following regions: (1) the retrotrapezoid/parafacial respiratory group (RTN/pFRG) anatomically corresponding to the ventrolateral to the facial nucleus, (2) the Bötzinger complex (BötC) located in the retrofacial nucleus and surrounding reticular formation (RF), (3) the pre-Bötzinger complex (pre-BötC) located just caudal to the retrofacial nucleus, (4) the rostral ventral respiratory group (rVRG) localized at the level of the NA, and (5) the caudal ventral respiratory group (cVRG) corresponding to the level of the NRA [7]. In addition, the pontine respiratory group (PRG) is located in the dorsolateral pons (Fig. 14.1) [8].

The physiological and anatomical organization of the CPGs regarding various laryngeal movements is still not fully understood. In the following sections, we addressed the issue how brainstem neuronal networks contribute to the generation of the laryngeal movements including respiration, vocalization, swallowing, and coughing.

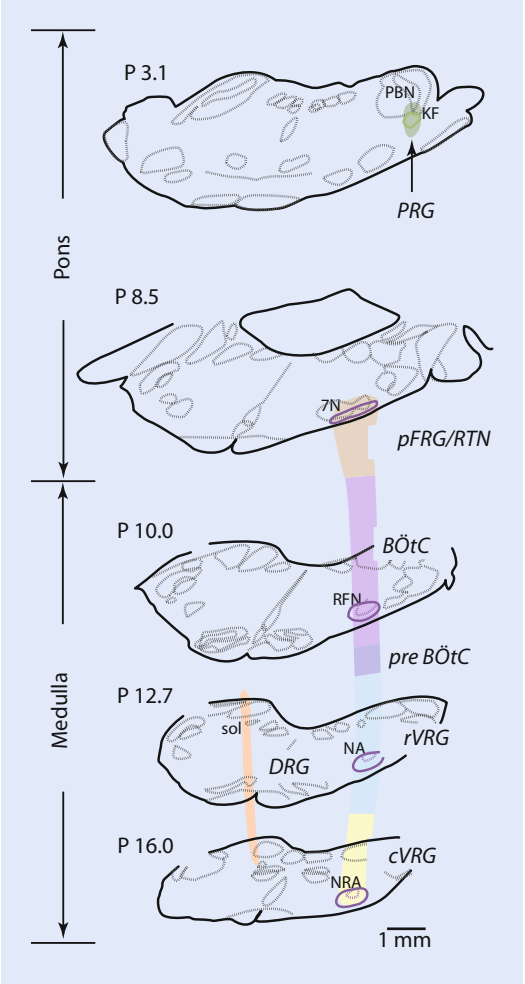


Fig. 14.1 Schematic drawing of the respiratory centers in the brainstem. *Colors* indicated in the transverse sections with reference to Berman's atlas [56] represent rostrocaudal extent of the respiratory groups including pontine respiratory group (PRG), parafacial respiratory group/retrotrapezoid nucleus (pFRG/RTN), the Bötzinger complex (BötC), the pre-Bötzinger complex (pre-BötC), the rostral ventral respiratory group (rVRG), the caudal ventral respiratory group (cVRG), and the dorsal respiratory group (DRG). In addition, numbers at the top of each transverse section indicate the level posterior (P) to stereotaxic zero. *KF* Kölliker-Fuse nucleus, *NA* nucleus ambiguus, *NRA* nucleus retroambiguus, *RFN* retrofacial nucleus, *sol* solitary tract, *7N* facial nucleus

14.2 Brainstem Vocalization Area

Human vocalization is produced by forced expiration accompanied by glottal closure being enhanced by resonance effect of nasal and pharyngeal cavity. In the animal model, vocalization is also consisted of the patterned movements of the vocal fold adduction and tension with abdominal constriction subsequent to inhalation. The PAG plays an important role in the generation of this patterned motion,

since mutism can be attributed to lesion of the PAG [9–12]. As such, many investigators have focused on the physiological and anatomical role in the PAG in terms of how vocal movements can be generated. Electrical or chemical stimulation of the PAG evokes vocalization in monkeys and felines [13–15]. Tract-tracing studies have also revealed the direct connections from the PAG to the NRA, which can act as the final common pathway of PAG-induced vocalization [16]. Furthermore, as reported by Shiba et al. [17], dysfunction of the NRA abolished vocalization evoked by stimulation of the PAG, suggesting that this common pathway could be critical to produce PAG-induced vocalization.

We have also studied the brainstem vocal area and established fictive vocalization model in guinea pigs, in order to compare the mechanisms of brainstem vocalization with in other animals and to elucidate whether guinea pigs can be substitute for those animals to investigate brainstem mechanism underlying vocalization [18].

We first employed electrical stimulation from the midbrain to the lower brainstem systematically, such that we identified auditory vocalization during stimulation at the specific sites (Fig. 14.2). Although guinea pigs can produce four typical vocalization calls, purr, chatter, chirp, and whistle, PAG-induced vocalization can represent two types of call: purr and whistle [19–22]. In this study, the call site stimulation could only produce the low whistle sound, probably because of the experimental setting. These call sites were distributed continuously from the lateral PAG to the ventromedial medulla at the level of the NA via the lateral part of the pontine reticular formation (Fig. 14.2). Although this "PAG-medulla call area" did not continue to the caudal medulla, this area corresponded to the vocal pathway in other animals, which suggests that the vocal animals could possess the similar neuronal pathway involved in vocalization. On the other hand, our study showed chemical stimulation could evoke vocalization not only to the PAG but also to the pontine reticular formation and parabrachial region. There appear to be slight differences between the call sites that evoked by chemical stimuli in guinea pigs and those in other animals. For example, on the basis of our results, application of the excitatory amino acid did not evoke vocal reaction in guinea pigs in the area including the midbrain tegmentum and the pontine paralemniscus area where chemical stimuli can evoke vocalization in monkeys and bats, respectively [14, 23]. These differences may be attributed to the discrete extension of vocal center or sparsely distributed vocal-related cells in guinea pigs. As described above, the NRA is thought to be a critical area underlying vocalization especially adductor activity during the expiratory phase of vocalization [17]. Our data support this hypothesis, since we found that chemical stimuli in the vicinity of the NRA exhibited rhythmic activity of the vocal adductor muscle (Fig. 14.3).

Again, in order to get to the bottom of the vocal CPG, it is necessary to study the cellular and network properties of the vocal-related neurons in the brainstem. Therefore, we then established fictive vocalization model using paralyzed guinea pigs, which represented the specific features of bursting activity of the superior laryngeal nerve (SLN), the abdominal nerve (ABD), followed by the phrenic nerve (PHR) activation (Fig. 14.4). Consequently, we have established the animal model for investigating brainstem vocal mechanism in guinea pigs.

14.3 Brainstem Circuitry Involved in Swallowing

Swallowing is generated by spatially and temporally coordinated muscle contraction of oral cavity, pharynx, larynx, and esophagus, resulting in successful transition of the bolus without aspiration. These stereotyped movements are controlled by a consequence of the network activity of the swallowing CPG (Sw-CPG). The neurons of the Sw-CPG are mainly distributed in the medulla oblongata, since the supramedullary components are not essential for the generation of swallowing reflex. Previous studies have indicated that these neurons are predominantly located in the nucleus tractus solitarius (NTS) and in the medullary reticular formation (RF) [24–26].

The functional role of neurons in the Sw-CPG has been proposed by Jean [26]: the neurons in and around the NTS are involved in the swallowing rhythm generation, and the neurons in the ventral part of the RF convey signals representing the swallowing movements to the cranial motoneurons. On the other hand, Broussard et al. [27] have advocated the predictive theory regarding the Sw-CPG that the neurons in the interstitial (NTS is) and intermediate subnuclei of the NTS (NTS int) that can receive inputs from upper airway tract have direct projections to the semicompact formation of the NA, which includes pharyngeal and laryngeal motoneurons, contributing to the pharyngeal stage of swallowing, whereas the cells in the central subnucleus of the NTS, to which the NTS int and NTS is neurons can project, send axons to the compact formation of the NA, which includes esophageal motoneurons, contributing to the esophageal stage.

To reveal the neuronal activity and morphology of the Sw-CPG, we recorded and labeled the swallowing-related neurons (SRNs), whose activity changed during fictive swallowing evoked by electrical stimulation of the SLN, in the medulla oblongata in anesthetized paralyzed guinea pigs [28]. Fictive swallowing was identified by bursting activity of the recurrent laryngeal nerve (RLN), the thyrohyoid branch of the hypoglossal nerve (Th-XII), or the pharyngeal branch of the vagal nerve (Ph-X), which corresponds to the pharyngeal stage of swallowing (Fig. 14.5a). The activity of SRNs was classified by three types: (1) early neurons, which fired during the RLN burst corresponding to the pharyngeal stage of swallowing, (2) late neurons that were activated after the RLN burst presumably corresponding to the esophageal stage, and (3) inhibited neurons, whose activity ceased during swallowing (Fig. 14.5b). Our results also indicated that these SRNs were broadly distributed in the NTS and RF, and

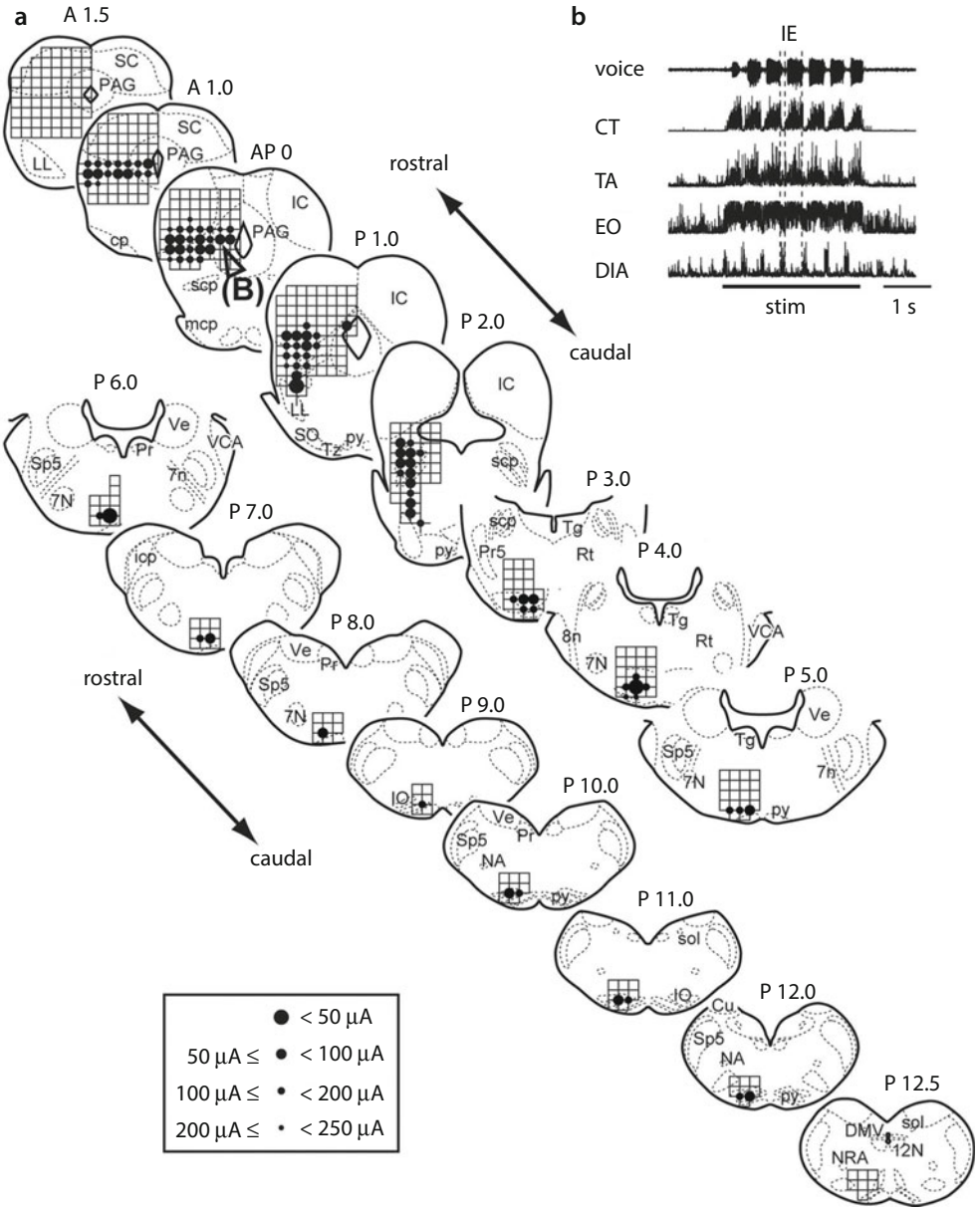


Fig. 14.2 (**a**) Locations of brainstem sites where electrical stimulation evoked vocalization in a guinea pig are shown in transverse sections. The vocal sites are indicated by *closed circles* on the intersections of grid lattices (in 0.5 mm) where electrical stimuli were delivered. The threshold current for evoking vocalization is depicted as *circle* diameter. *Cp* cerebral peduncle, *Cu* cuneate nucleus, *IC* inferior colliculus, *icp* inferior cerebellar peduncle, *IO* inferior olive, *LL* lateral lemniscus, *mcp* middle cerebellar peduncle, *PAG* periaqueductal gray, *Pr* prepositus nucleus, *Pr5* principal sensory trigeminal nucleus, *py* pyramidal tract, *Rt* reticular nucleus, *SC* superior colliculus, *scp* superior cerebellar peduncle, *SO* superior olive, *Sp5* spinal trigeminal tract, *Tg* tegmental nucleus, *Tz* trapezoid body, *VCA* ventral cochlear nucleus, *Ve* vestibular nucleus, *7n* facial nerve, *8n* vestibulocochlear nerve, *DMV* dorsal motor nucleus of the vagus, *12N* hypoglossal nucleus. (**b**) Representative activities of the laryngeal and respiratory muscles during electrical stimulation to the call sites. This vocal-related muscle activity was recorded at the site designated by *open arrowhead* in the "PAG-medulla call area." Vocalization is characterized by the activation of the diaphragm (DIA) [inspiratory phase (I)] followed by the bursting activity of the thyroarytenoid (TA), cricothyroid (CT), and external oblique (EO) muscles [expiratory phase (E)]. Periods of stimulation are indicated by thick lines at the bottom of electromyographic records. stim: duration of electrical stimulation to the call site (From Ref. [18])

their axonal projections represented part of complex neuronal circuitry (Fig. 14.6). As shown in this study, almost all of the SRNs in the NTS had axonal collaterals to the NTS, which suggests that there is the neuronal circuit within the NTS such as the dorsal swallowing group proposed by Jean [26]. Otherwise, the SRNs in the NTS and RF often projected to each other's area, whereas some neurons in the NTS and RF sent axon to the cranial motor nuclei including the NA and hypoglossal nuclei. In addition, some neurons in the RF projected to the other side of the brainstem. In conclusion, we proposed the probable neuronal circuitry involved in swallowing: the SRNs could constitute the local neuronal

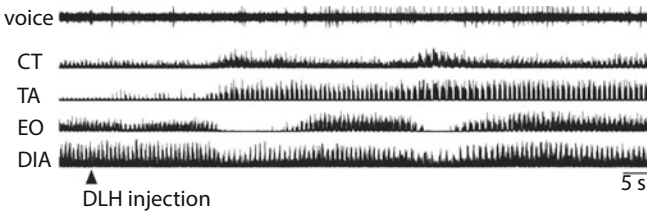


Fig. 14.3 Changes in laryngeal and respiratory muscle activities after excitatory amino acid [D,L-homocysteic acid (DLH)] injection in the vicinity of the nucleus retroambiguus (NRA). DLH injection increased TA and CT muscle activity but did not produce vocalization. The initiation of DLH injection is indicated by an *arrowhead* (From Ref. [18])

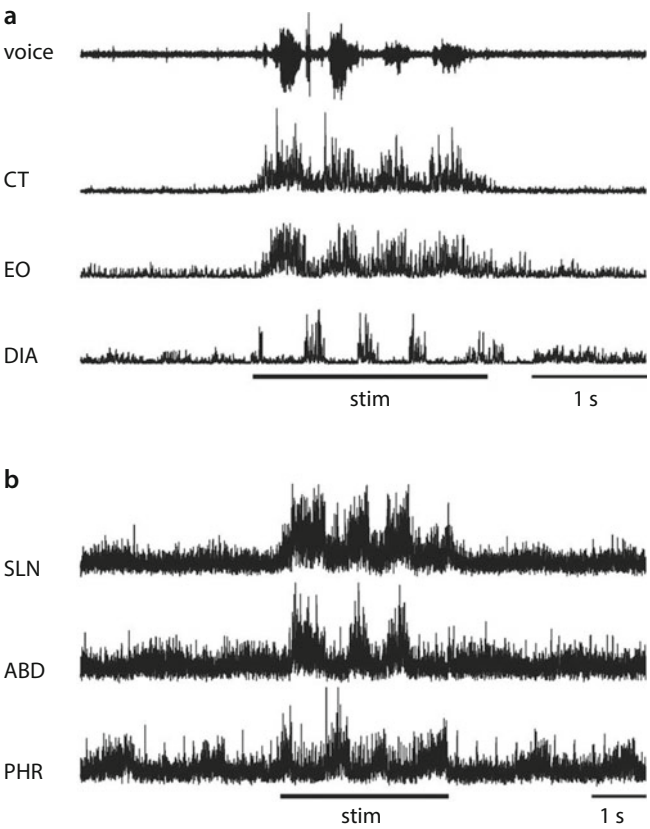


Fig. 14.4 The motor pattern of the laryngeal and respiratory muscle (**a**) and nerve (**b**) activities during PAG-induced vocalization before (**a**) and after (**b**) paralyzation, respectively. The data in **a** and **b** were obtained in the same animal. Period of call site stimulation (stim) is indicated by *thick line* at the bottom of each panel. *SLN* the external branch of the superior laryngeal nerve, *ABD* the L1 abdominal muscle nerve, *PHR* the C5 phrenic nerve (From Ref. [18])

circuits within the NTS that may contribute to the swallowing rhythm generation, the reciprocal connections between the NTS and RF that may shape the motor outputs, the bilateral interconnections in the RF that may synchronize the swallowing outputs, the connections from the NTS and RF to the cranial motor nuclei involved in swallowing that may act as the premotor neurons, and the motoneurons that may integrate the swallowing motor outputs (Fig. 14.7). Further studies will be necessary to understand the network mechanisms involved in swallowing. For example, if the intrinsic properties of the SRNs could be investigated, the more detailed network properties responsible for the generation of this well-coordinated motor sequence would be revealed.

14.4 Multifunctional Respiratory Neurons in Relation to the Laryngeal Movements

The larynx plays a crucial role in voice production, the airway defensive reflexes including swallowing and coughing, as well as respiration [29–33]. In addition, vocalization and these airway defensive reflexes are generated by contractions of the respiratory and upper airway muscles, whose motor actions can take in oxygen and release carbon dioxide in the lung during breathing. These non-respiratory behaviors are thus required by modification of normal respiratory rhythm. The phenomenon that respiratory rhythm is altered in synchrony with these behaviors suggests that the neuronal networks responsible for respiration and those non-respiratory behaviors are overlapped and therefore the respiratory CPG can be shared among the CPGs of those non-respiratory behaviors.

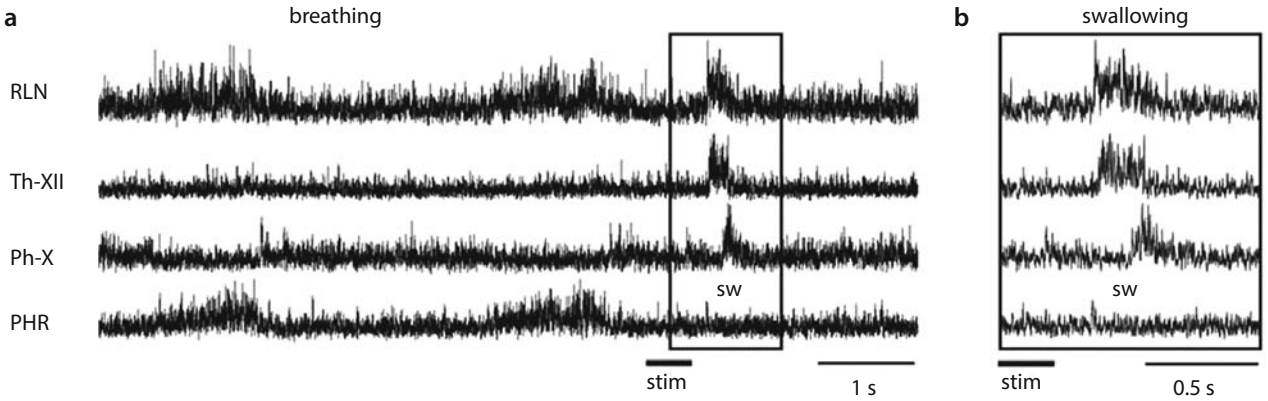
To determine whether the respiratory neurons are included among the CPGs of those behaviors, we compared the activity of the respiratory neurons during breathing with that during those non-respiratory behaviors such as vocalization, swallowing, and coughing in anesthetized paralyzed guinea pigs [34].

Respiratory rhythmogenesis is thought to be regulated by the brainstem neural network, consisting of the DRG, the longitudinal column from pFRG/RTN to cVRG, and PRG, as described above (Fig. 14.1) [7]. We focused on the respiratory neurons located between the BötC and rVRG.

To elucidate the neuronal activity during respiratory and non-respiratory behaviors, we recorded the extracellular activity of the respiratory neurons during fictive respiration, vocalization, swallowing, and coughing. To evoke fictive vocalization, we delivered electrical stimulation to the PAG or the pontine call site in the dorsal pontine tegmentum (Fig. 14.8a) [18, 35]. Fictive swallowing was elicited by electrical stimulation of the SLN (Fig. 14.8b) [28, 36]. Fictive coughing was evoked by mechanical irritation of tracheal mucosa or by electrical stimulation of the RLN and identified by bursting activity of the RLN and ABD preceded by PHR activity (Fig. 14.8c) [37, 38].

We recorded three types of respiratory neurons in the rostral ventrolateral medulla: expiratory, inspiratory, and phase-spanning neurons (Fig. 14.9). The expiratory and inspiratory neurons were additionally characterized regarding their firing rate trajectories: augmenting (AUG), decrementing (DEC), and constant (CON) firing patterns. The phase-spanning neurons were subdivided into the inspiratory-expiratory (IE) and expiratory-inspiratory (EI) neurons.

The specific tendency of firing pattern was observed for each type of the respiratory neurons during the non-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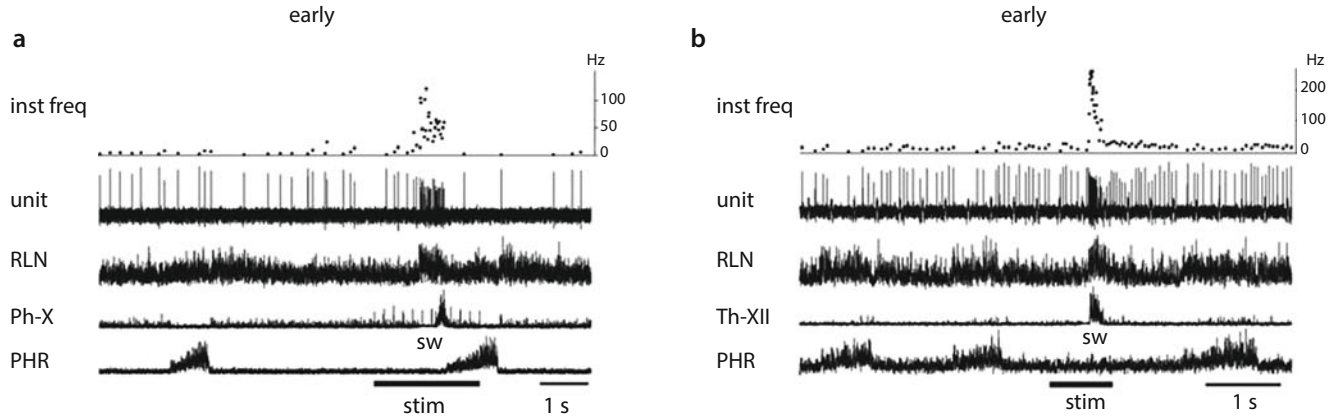
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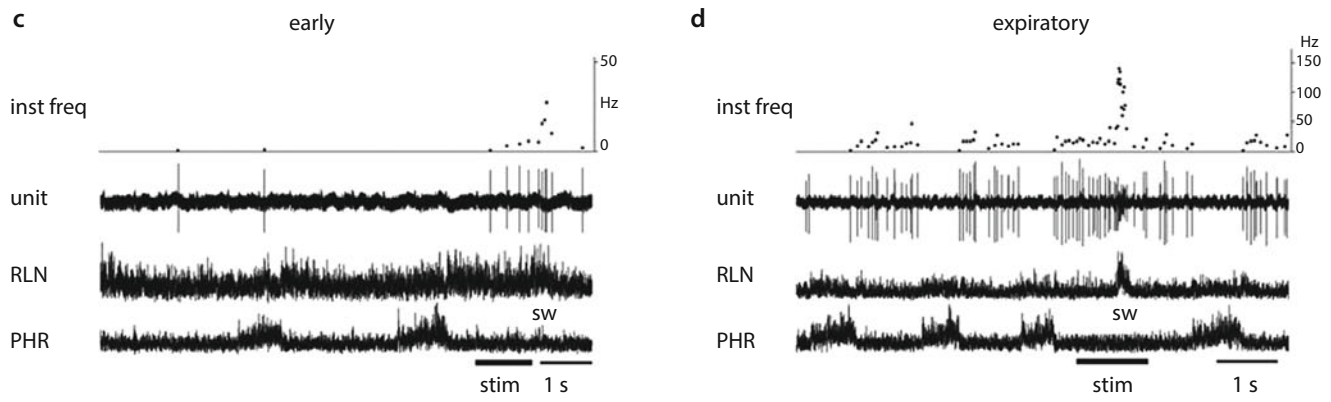
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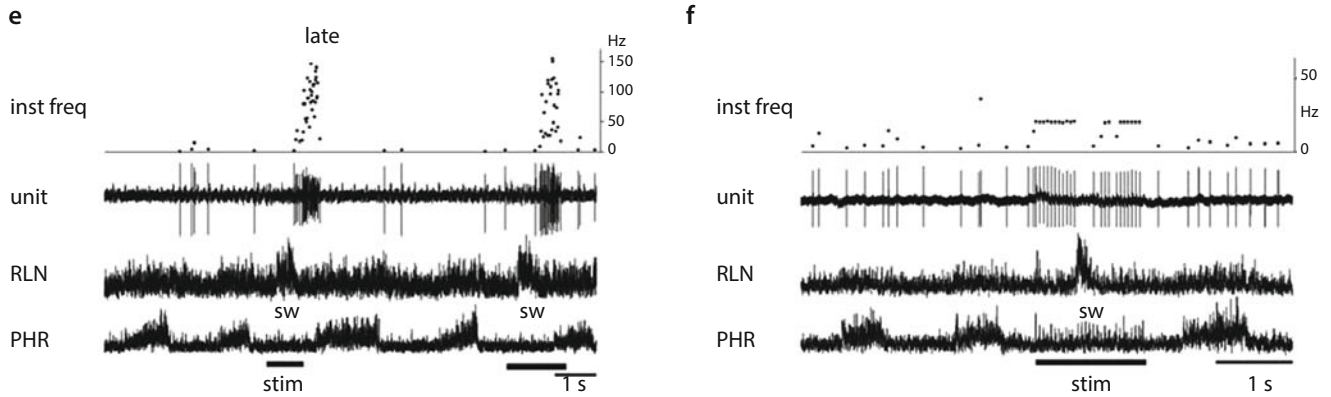
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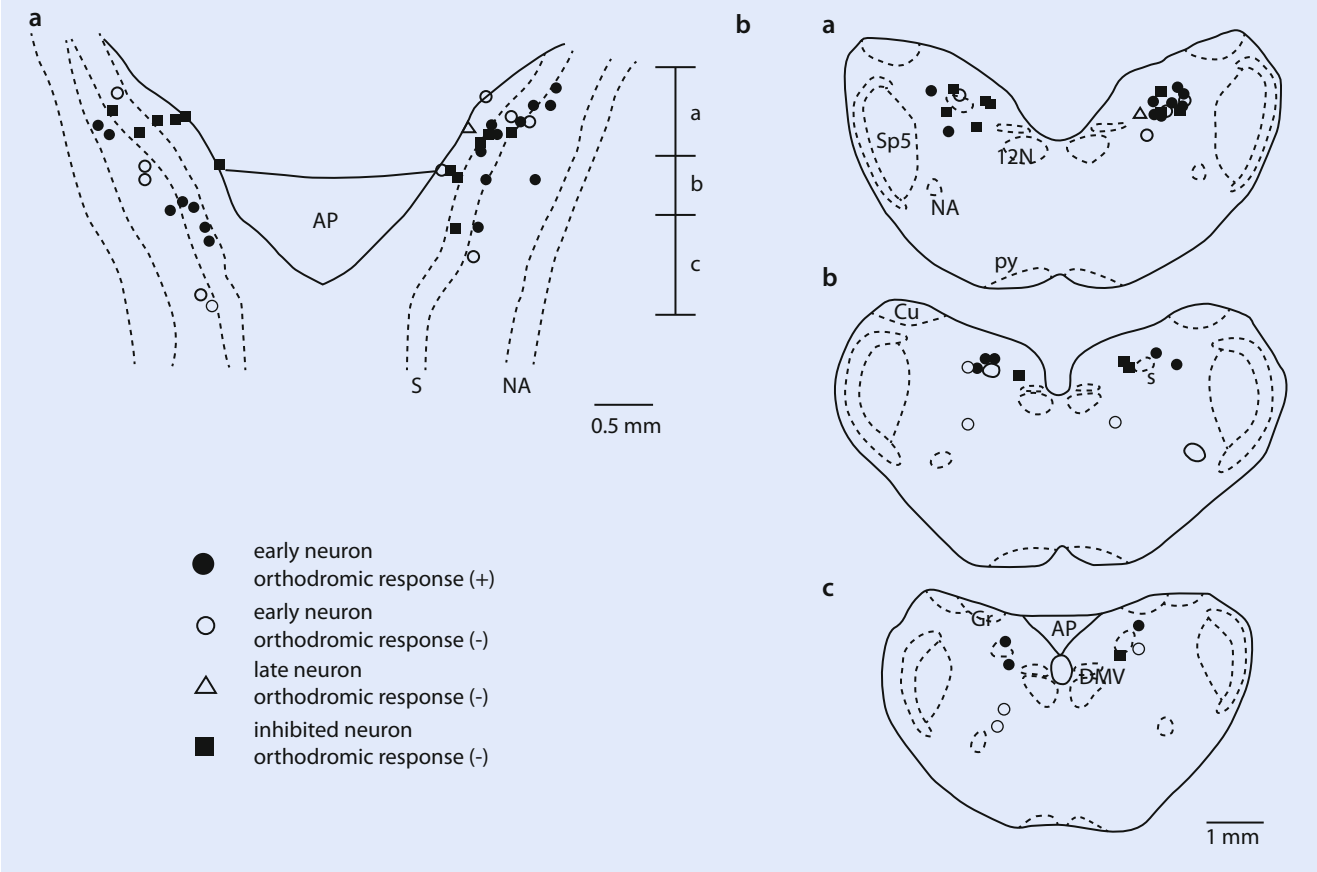

Fig. 14.6 Locations of SRNs recorded in our study. Letters beside the horizontal section (**a**) show the anterior-posterior region represented by each of the transverse sections (**b**). *Circles*, *triangles*, and *squares* represent locations of early-, late-, and inhibited-type neurons, respectively. *Closed* and *open symbols* represent neurons that did and did not respond orthodromically to single-shock stimulation of the SLN, respectively. *AP* area postrema, *Gr* gracile nucleus (From Ref. [28])

Fig. 14.5 Motor patterns of fictive breathing (**a**-(*a*)) and swallowing (**a**-(*b*)). Fictive swallowing was identified by bursting activities of the recurrent laryngeal nerve (RLN), pharyngeal branch of the vagus nerve (Ph-X), and the thyrohyoid muscle branch of the hypoglossal nerve (Th-XII) evoked by stimulation of the superior laryngeal nerve (SLN). High-speed recordings in the period indicated by the *rectangular box* in (**a**-(*a*)) are shown in (**a**-(*b*)). The pharyngeal stage of swallowing began with the bursts of the RLN and Th-XII, whereas the Ph-X burst lagged behind in time of onset. Duration of SLN stimulation (stim) is indicated by the *horizontal bars* at the bottom. Firing patterns of swallowing-related neurons (SRNs) (**b**), including early (**b**-(*a*) to **b**-(*d*)), late (**b**-(*e*)), and inhibited (**b**-(*f*)) neurons. Early neurons fired during the whole pharyngeal stage (**b**-(*a*)), during its early part (**b**-(*b*)), and during its latter part (**b**-(*c*)), respectively. The expiratory-related neuron in panel **b**-(*d*) was activated during the RLN burst. Meanwhile, the late neuron in panel **b**-(*e*) was activated after the swallowing-related RLN burst corresponding to the esophageal stage. The inhibited neuron in panel **b**-(*f*) stopped firing during the pharyngeal stage. *Inst freq.* instantaneous frequency (From Ref. [28])

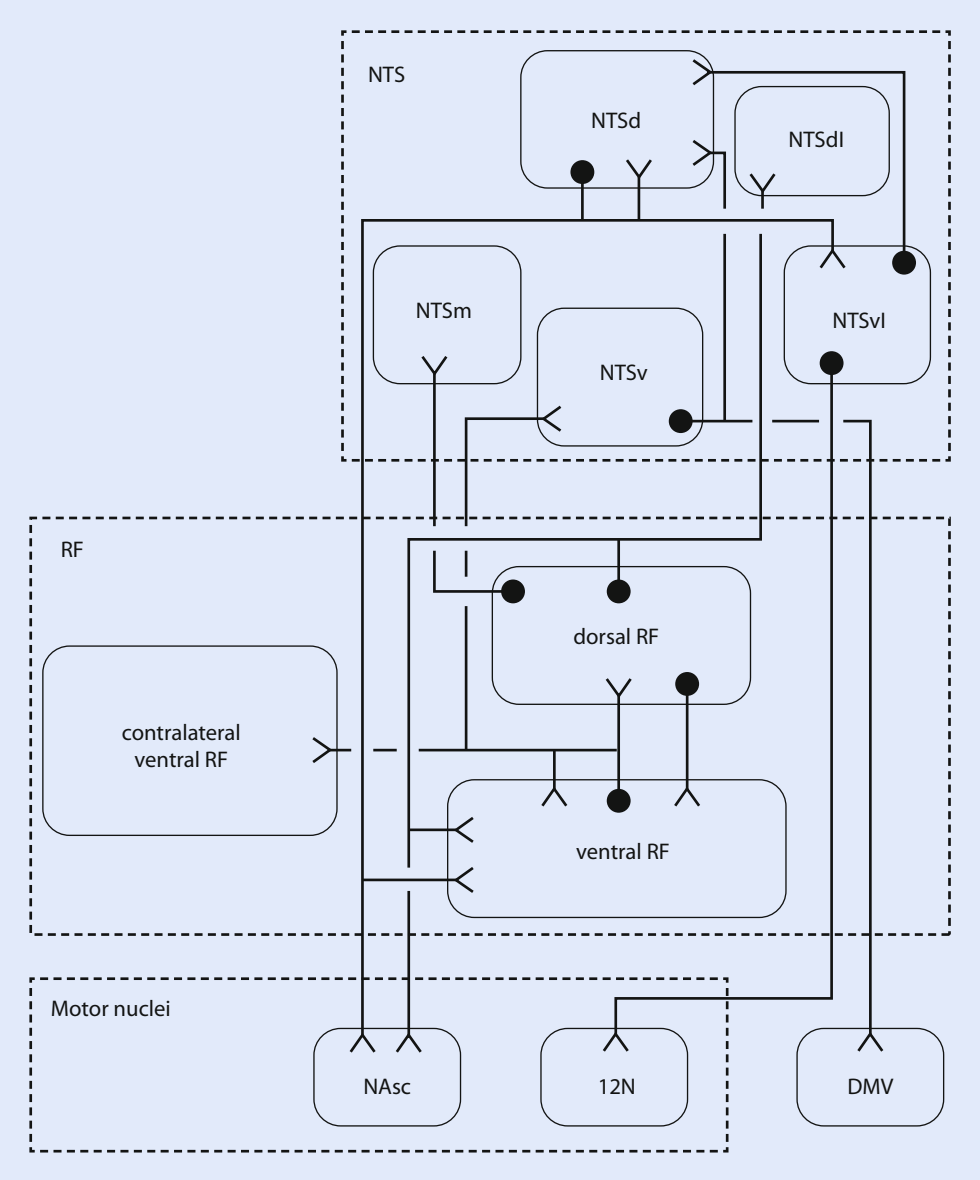

Fig. 14.7 Schematic drawing of the possible neuronal networks of the SRNs. The neuronal connections within the NTS, the interconnections between the NTS and RF, the bilateral connections in the RF, and connections from the NTS or RF to the cranial motor nucleus were identified in our study (From Ref. [28])

respiratory behaviors in this study. The E-AUG neurons in the BötC whose activity can suppress the upper airway motoneuronal activity were generally silent during vocalization, swallowing, and the compressive phase of coughing (Fig. 14.10) [39–42]. This inactivation may facilitate the activity of laryngeal motoneurons during these behaviors. Many E-DEC neurons in the rVRG were activated during all behaviors tested, some of which are possibly upper airway respiratory motoneurons including laryngeal motoneurons (Fig. 14.11) [8, 43–47]. Many E-CON neurons were activated during vocalization and coughing, but did not discharge during swallowing. Some vocal-inactive E-AUG and E-CON neurons resumed firing when the vocal activity was attenuated at the last part of the stimulus-induced expiration (Figs. 14.10a and 14.12). Although their functional role has not been declared, the cells may play a role in the termination of vocalization. The I-AUG neurons, broadly distributed in the rVRG, were typically activated in synchrony with the phrenic discharge during vocalization and coughing [47]. On the contrary, some "late-inspiratory neurons" discharged during the expiratory phase of coughing, probably contributing to the inspiratory-expiratory phase transition or acting as the pharyngeal motoneurons during coughing (Fig. 14.13) [48, 49]. Some I-AUG neurons fired during the period of "swallow-breath," suggesting that these neurons, which could be the phrenic premotor neurons, participate in the generation of "swallow-breath" [47]. The discharge patterns of I-DEC neurons remained unchanged during the inspiratory phase of vocalization and coughing, while these neurons were silent during swallowing. The

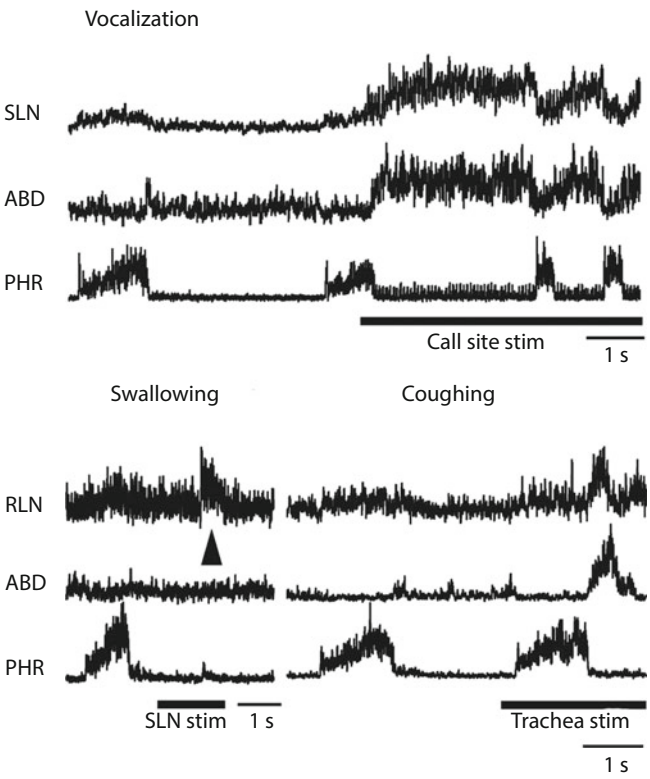

Fig. 14.8 Activities of the efferent nerves innervating the upper airway muscles involved in vocalization (**a**), swallowing (**b**), and coughing (**c**). Fictive vocalization was evoked by electrical stimulation of the periaqueductal gray or pontine call site. The vocal phase was identified by bursting activity of the SLN and the ABD followed by activation of the PHR (**a**). Electrical stimulation of the SLN elicited fictive swallowing identified by bursting activity of the RLN (*arrowhead*) (**b**). Fictive coughing, which was evoked by mechanical stimulation of the trachea, consisted of an abrupt burst of the abdominal nerve accompanied by bursting activity of the RLN following phrenic nerve activation (**c**) (From Ref. [34])

I-CON neurons were activated during the inspiratory phase of vocalization and coughing. Many phase-spanning neurons, which may play a role in the phase transition during respiration, fired during vocalization, swallowing, and coughing (Figs. 14.14 and 14.15) [50–52]. The strong activation of these neurons during the vocal phase may play a key role in the preservation of vocal emission as well as the phase transition, whereas the activation during swallowing may inhibit respiration. On the other hand, the EI neurons, some of which could be the pharyngeal motoneurons, may help to keep the pressure of forceful coughing [49]. However, the connectivity between the phase-spanning neurons and the other brainstem respiratory neurons, including laryngeal motoneurons, remains unknown. Further studies are needed to explore this possibility.

Based on our data, we propose that the respiratory neuronal networks possess the ability to reconfigurate their own networks and that the individual respiratory neuron alters its activity in a specific manner, which is adjustable to provide each non-respiratory behavior. Our data thus support the view that the medullary respiratory neurons are multifunctional and can be shared in the CPGs involved in the non-respiratory laryngeal behaviors.

14.5 Perspectives

While the principal function of the larynx is phylogenetically the airway protection including feeding and expelling the foreign body to prevent airway from aspiration, various laryngeal functions including phonation have been acquired during the course of evolution. Simultaneously, the network organization responsible for these behaviors should have been constructed. Despite the complexity of the CPG networks, it is reasonable that the brainstem neuronal networks serve the efficient and effective processing during these behaviors. To realize this concept, multifunctional neuronal activity may be indispensable. Previous studies have emphasized the importance of the premotor neurons including respiratory neurons that can directly control laryngeal movements, which may have multifunctional properties [27, 41, 53–55]. On the contrary, the behavior-specific neurons, such as the SRNs reported in our study, are likely to play an essential role in the generation of these behaviors. Although these CPG networks are not fully understood, the declaration of both the physiological and anatomical properties of the CPG neurons will improve understanding of the network mechanisms responsible for the laryngeal movements.

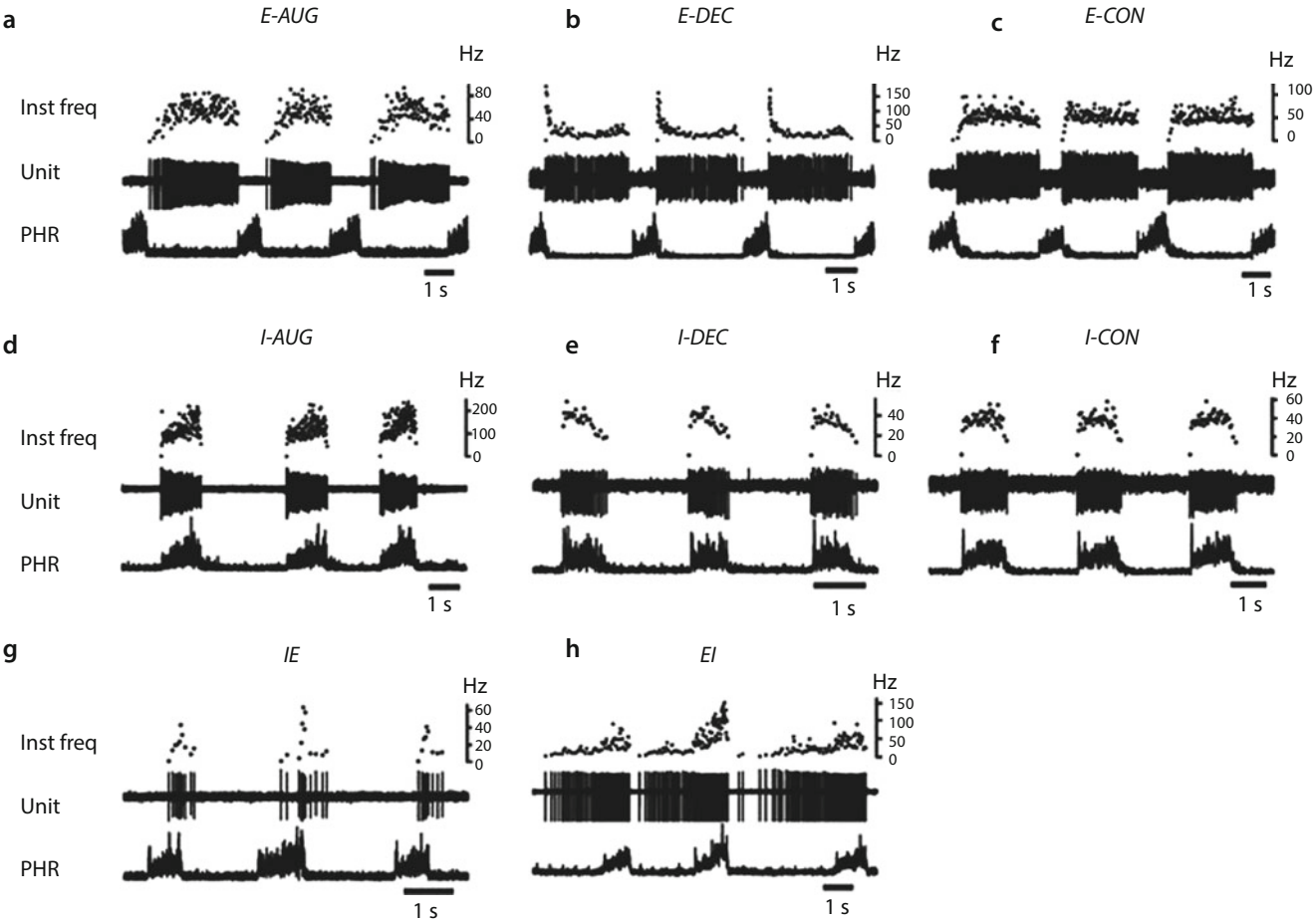

Fig. 14.9 Subtypes of respiratory neurons in the rostral ventrolateral medulla. Expiratory neurons with an augmenting (E-AUG) (**a**), decrementing (E-DEC) (**b**), and constant (E-CON) (**c**) firing patterns, exhibiting a gradual increase, decrease, and no change in firing rates during the expiratory phase, respectively. Inspiratory neurons with augmenting (I-AUG) (**d**), decrementing (I-DEC) (**e**), and constant (I-CON) (**f**) firing patterns. Panels (**g**) and (**h**) show cell firings with phase-spanning activity which began during inspiration and continued into expiration (inspiration to expiration phase spanning, IE) and began during expiration and continued into inspiration (expiration to inspiration phase spanning, EI), respectively (From Ref. [34])

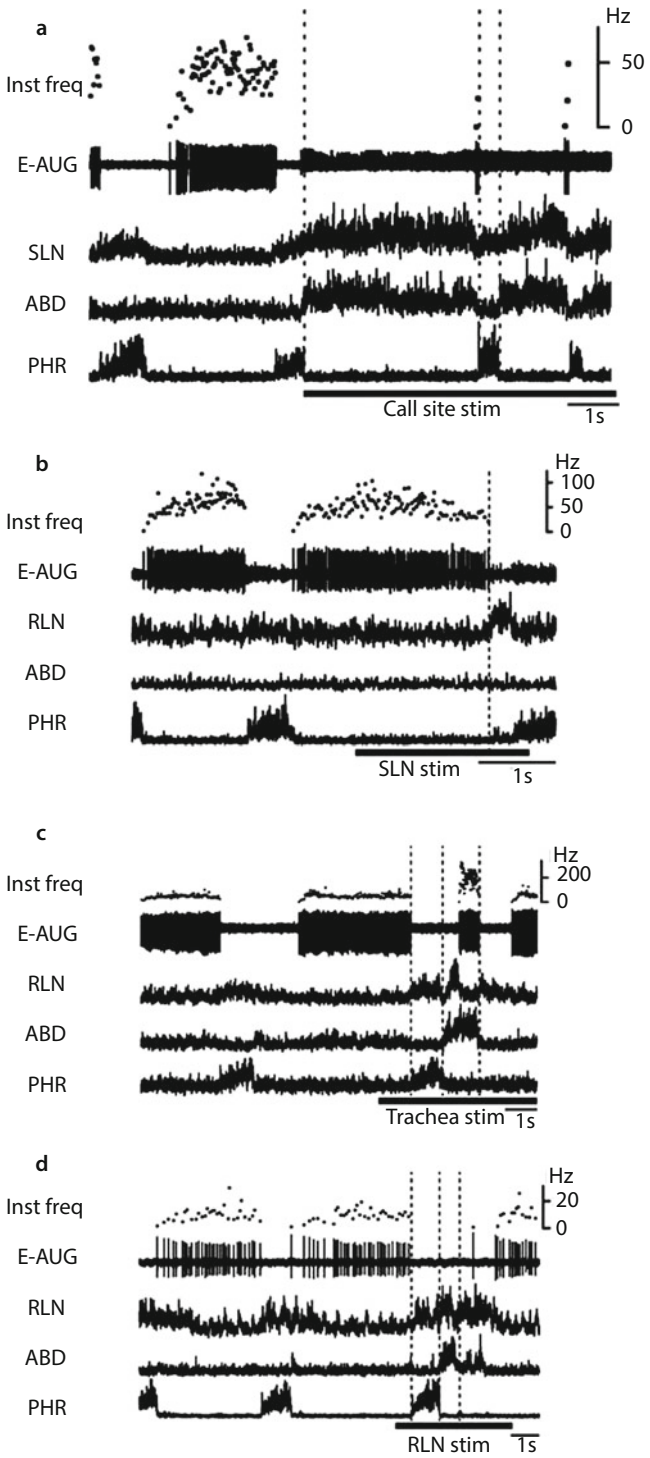

Figure 14.10 Representative firing patterns of the E-AUG neurons during vocalization (**a**), swallowing (**b**), and coughing (**c, d**). The vocalization-inactive E-AUG neuron in panel **a** was silent during the period of SLN and ABD bursts corresponding to the vocal phase. The E-AUG neuron in panel **b** was silent during swallowing identified by the swallow-related RLN burst induced by SLN stimulation. The E-AUG neuron in panel **c** fired just after the bursting activity of the RLN during the expiratory phase of coughing presumably corresponding to the expulsive phase of coughing. The E-AUG neuron in panel **d** was silent during fictive coughing. *Thick line* at the bottom of each panel represents the stimulus duration of the call site, SLN, RLN, or tracheal mucosa (call site stim, SLN stim, RLN stim, or trachea stim). *Dashed lines* indicate the respiratory phase transitions of vocalization (**a**), coughing (**c**), and the initiation of swallowing (**b**) (Reproduced, with permission, from Ref. [34] (2014))

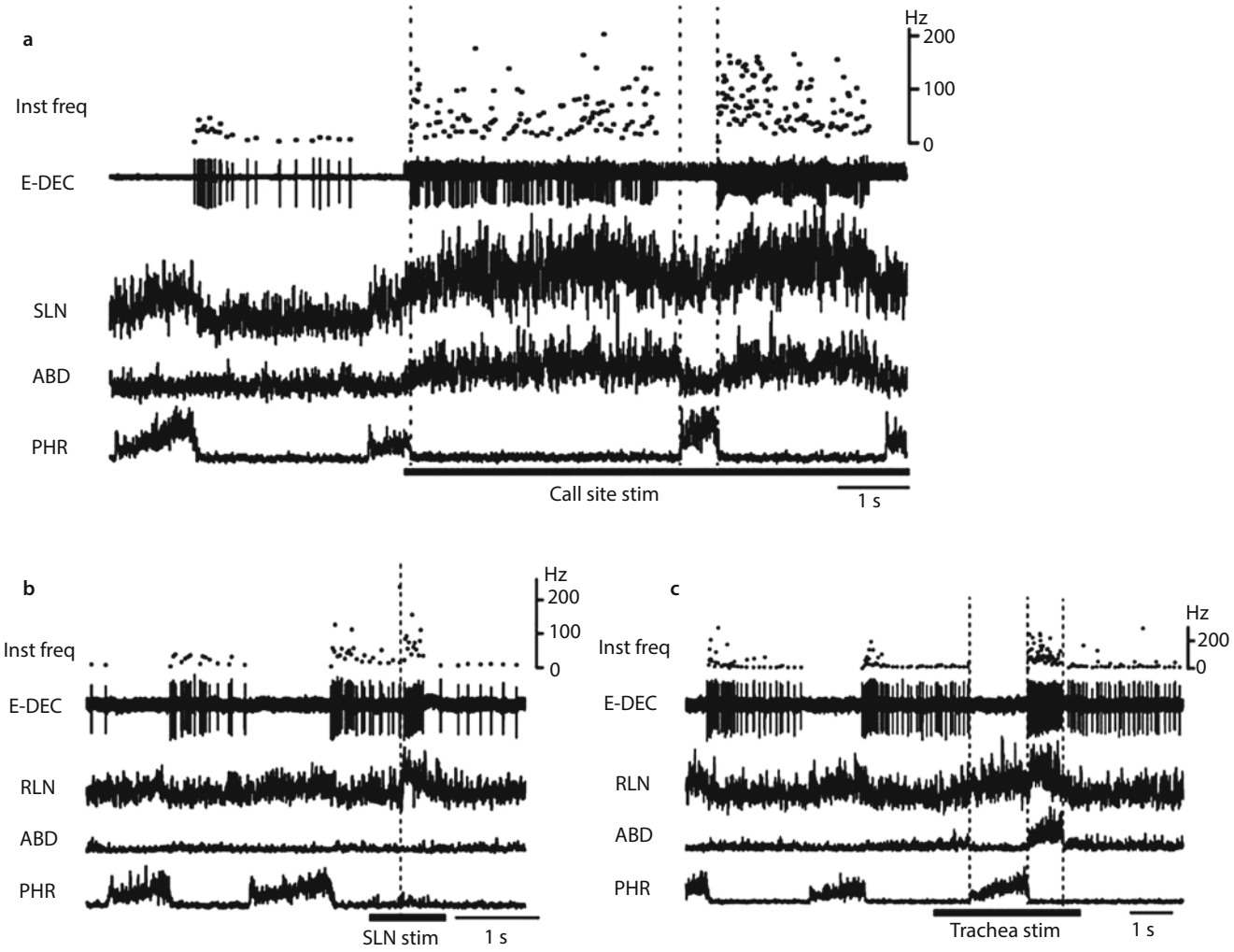

Fig. 14.11 Activity of the E-DEC neurons during vocalization (**a**), swallowing (**b**), and coughing (**c**). The E-DEC neuron in panel **a** showed increased firing rates during vocalization compared to before stimulation. The E-DEC neuron in panel **b** was activated during swallowing. The E-DEC neuron in panel **c** was activated with a decrementing discharge pattern during the expiratory phase of coughing (Reproduced, with permission, from Ref. [34] (2014))

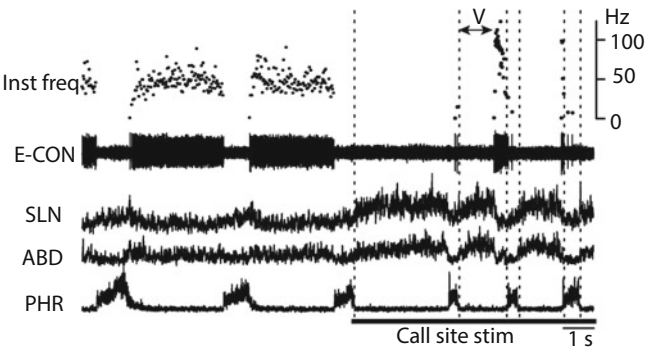

Fig. 14.12 The E-CON neuron was silent during the period of SLN and ABD bursts corresponding to the vocal phase (V), but fired at the end of the stimulus-induced expiration during which the bursts were attenuated (Reproduced, with permission, from Ref. [34] (2014))

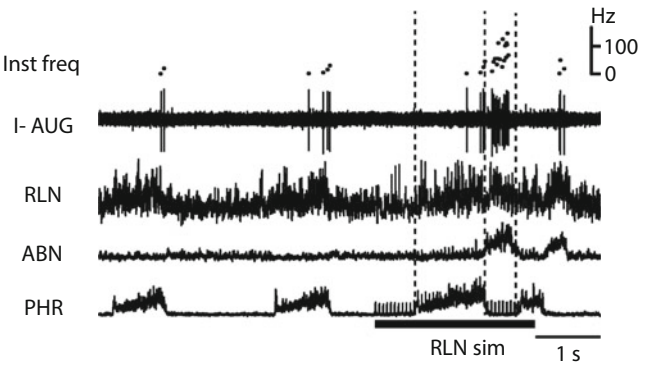

Fig. 14.13 Firing of the inspiratory neurons during coughing. This late-onset I-AUG neuron was activated during the expiratory phase of coughing (Reproduced, with permission, from Ref. [34] (2014))

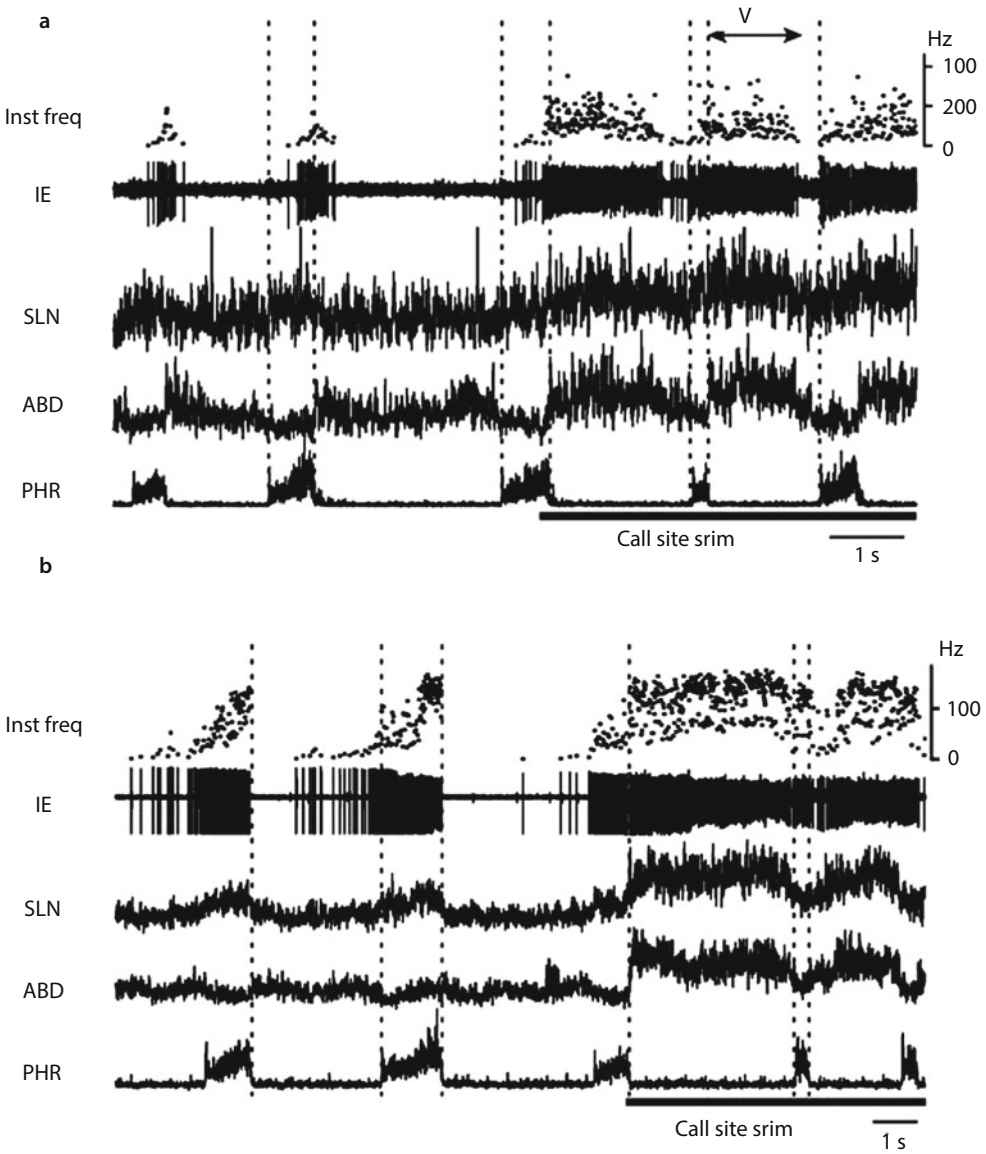

Fig. 14.14 Activity of phase-spanning neurons during vocalization. The IE neuron in panel (**a**) strongly fired during the vocal phase. This neuron sometimes ceased its firing when the vocal-related SLN and ABD bursts were attenuated at the end of the expiratory phase during the call site stimulation. The EI neuron in panel (**b**) weakly fired during the late expiration of control respiration, but strongly fired throughout the vocal phase (From Ref. [34])

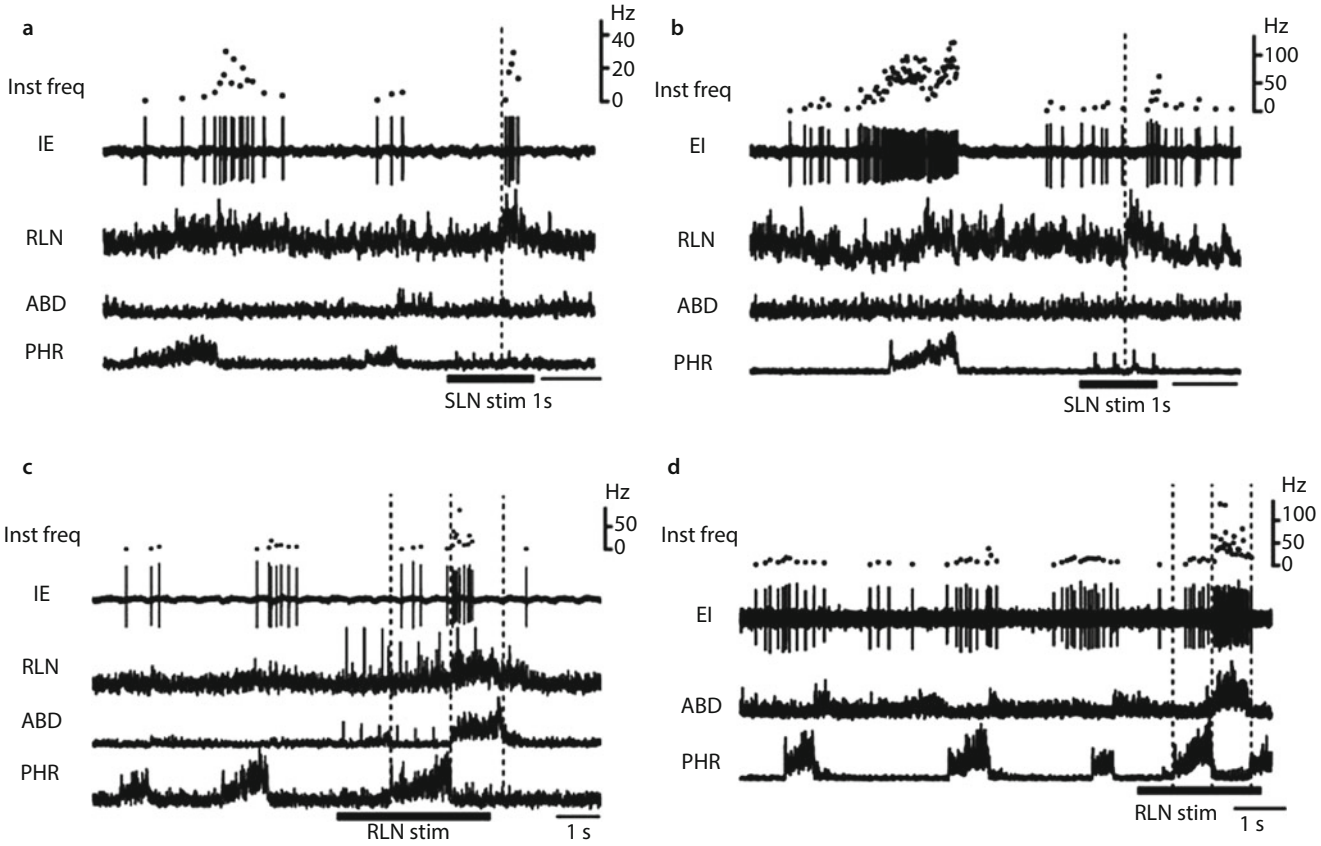

Fig. 14.15 Firing patterns of phase-spanning neurons during swallowing (**a, b**) and coughing (**c, d**). The IE neuron in panel **a** discharged during swallowing. The EI neuron in panel **b** began to fire approximately 0.3 s after the onset of the RLN burst. The IE neuron in panel **c** fired at the onset of the expiratory phase of coughing. The EI neuron in panel **d** strongly discharged during the expiratory phase of coughing (Reproduced, with permission, from Ref. [34] (2014))

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References

1. Miller AD, Tan LK, Lakos SF. Brainstem projections to cats' upper lumbar spinal cord: implications for abdominal muscle control. Brain Res. 1989;493(2):348–56.
2. VanderHorst VG, Terasawa E, Ralston 3rd HJ. Monosynaptic projections from the nucleus retroambiguus region to laryngeal motoneurons in the rhesus monkey. Neuroscience. 2001;107(1):117–25.
3. Altschuler SM, Bao X, Bieger D, Hopkins DA, Miselis RR. Viscerotopic representation of the upper alimentary tract in the rat: sensory ganglia and nuclei of the solitary and spinal trigeminal tracts. J Comp Neurol. 1989;283(2):248–68. 1989/05/08 ed.
4. Jürgens U. Neural pathways underlying vocal control. Neurosci Biobehav Rev. 2002;26(2):235–58.
5. Berger AJ, Averill DB, Cameron WE. Morphology of inspiratory neurons located in the ventrolateral nucleus of the tractus solitarius of the cat. J Comp Neurol. 1984;224(1):60–70.
6. Iscoe S, Grélot L, Bianchi AL. Responses of inspiratory neurons of the dorsal respiratory group to stimulation of expiratory muscle and vagal afferents. Brain Res. 1990;507(2):281–8.
7. Feldman JL, Del Negro CA. Looking for inspiration: new perspectives on respiratory rhythm. Nat Rev Neurosci. 2006;7(3):232–42.
8. Bianchi AL, Denavit-Saubié M, Champagnat J. Central control of breathing in mammals: neuronal circuitry, membrane properties, and neurotransmitters. Physiol Rev. 1995;75(1):1–45.
9. Adametz J, O'Leary JL. Experimental mutism resulting from periaqueductal lesions in cats. Neurology. 1959;9:636–42.
10. Botez MI, Barbeau A. Role of subcortical structures, and particulary of the thalamus, in the mechanisms of speech and language. Int J Neurol. 1971;8:300–20.
11. Esposito A, Demeurisse G, Alberti B, Fabbro F. Complete mutism after midbrain periaqueductal gray lesion. Neuroreport. 1999;10:681–5.
12. Kelly AH, Beaton LE, Magoun HW. A midbrain mechanism for facio-vocal activity. J Neurophysiol. 1946;9:181–9.
13. Jürgens U, Pratt R. Role of the periaqueductal grey in vocal expression of emotion. Brain Res. 1979;167(2):367–78.
14. Jürgens U, Richter K. Glutamate-induced vocalization in the squirrel monkey. Brain Res. 1986;373(1–2):349–58.
15. Zhang SP, Davis PJ, Bandler R, Carrive P. Brain stem integration of vocalization: role of the midbrain periaqueductal gray. J Neurophysiol. 1994;72(3):1337–56.
16. Holstege G. Anatomical study of the final common pathway for vocalization in the cat. J Comp Neurol. 1989;284(2):242–52.
17. Shiba K, Umezaki T, Zheng Y, Miller AD. The nucleus retroambigualis controls laryngeal muscle activity during vocalization in the cat. Exp Brain Res. 1997;115:513–9.
18. Sugiyama Y, Shiba K, Nakazawa K, Suzuki T, Hisa Y. Brainstem vocalization area in guinea pigs. Neurosci Res. 2010;66(4):359–65.
19. Syka J, Suta D, Popelar J. Responses to species-specific vocalizations in the auditory cortex of awake and anesthetized guinea pigs. Hear Res. 2005;206(1–2):177–84.
20. Suta D, Kvasnak E, Popelar J, Syka J, Kvaˇ E, Kva E, et al. Representation of species-specific vocalizations in the inferior colliculus of the guinea pig. J Neurophysiol. 2003;90(6):3794–808.

21. Suta D, Popelar J, Kvasnak E, Syka J. Representation of species-specific vocalizations in the medial geniculate body of the guinea pig. Exp Brain Res. 2007;183(3):377–88.
22. Kyuhou S, Gemba H. Two vocalization-related subregions in the midbrain periaqueductal gray of the guinea pig. Neuroreport. 1998;9(7):1607–10.
23. Behrend O, Schuller G. The central acoustic tract and audio-vocal coupling in the horseshoe bat. Rhinolophus rouxi. Eur J Neurosci. 2000;12(12):4268–80.
24. Kessler JP, Jean A. Identification of the medullary swallowing regions in the rat. Exp Brain Res. 1985;57(2):256–63. 1985/01/01 ed.
25. Umezaki T, Matsuse T, Shin T. Medullary swallowing-related neurons in the anesthetized cat. Neuroreport. 1998;9:1793–8.
26. Jean A. Brain stem control of swallowing: neuronal network and cellular mechanisms. Physiol Rev. 2001;81:929–69.
27. Broussard DL, Lynn RB, Wiedner EB, Altschuler SM. Solitarial premotor neuron projections to the rat esophagus and pharynx: implications for control of swallowing. Gastroenterology. 1998;114(6):1268–75.
28. Sugiyama Y, Shiba K, Nakazawa K, Suzuki T, Umezaki T, Ezure K, et al. Axonal projections of medullary swallowing neurons in guinea pigs. J Comp Neurol. 2011;519(11):2193–211.
29. Ludlow CL. Central nervous system control of the laryngeal muscles in humans. Respir Physiol Neurobiol. 2005;147:205–22.
30. Jürgens U. The neural control of vocalization in mammals: a review. J Voice. 2009;23(1):1–10. 2008/01/22 ed.
31. Paydarfar D, Gilbert RJ, Poppel CS, Nassab PF. Respiratory phase resetting and airflow changes induced by swallowing in humans. J Physiol. 1995;483(1):273–88.
32. Miller AJ. The neurobiology of swallowing and dysphagia. Dev Disabil Res Rev. 2008;14(2):77–86.
33. Karlsson JA, Sant'Ambrogio G, Widdicombe J. Afferent neural pathways in cough and reflex bronchoconstriction. J Appl Physiol. 1988;65(3):1007–23.
34. Sugiyama Y, Shiba K, Mukudai S, Umezaki T, Hisa Y. Activity of respiratory neurons in the rostral medulla during vocalization, swallowing, and coughing in guinea pigs. Neurosci Res. 2014;80:17–31.
35. De Lanerolle NC. A pontine call site in the domestic cat: behavior and neural pathways. Neuroscience. 1990;37(1):201–14.
36. Nishino T, Honda Y, Kohchi T, Shirahata M, Yonezawa T. Effects of increasing depth of anaesthesia on phrenic nerve and hypoglossal nerve activity during the swallowing reflex in cats. Br J Anaesth. 1985;57(2):208–13.
37. Bolser D. Fictive cough in the cat. J Appl Physiol. 1991;71:2325–31.
38. Grélot L, Milano S. Diaphragmatic and abdominal muscle activity during coughing in the decerebrate cat. Neuroreport. 1991;2(4):165–8.
39. Jiang C, Lipski J. Extensive monosynaptic inhibition of ventral respiratory group neurons by augmenting neurons in the Bötzinger complex in the cat. Exp Brain Res. 1990;81(3):639–48.
40. Ono K, Shiba K, Nakazawa K, Shimoyama I. Synaptic origin of the respiratory-modulated activity of laryngeal motoneurons. Neuroscience. 2006;140(3):1079–88.
41. Shiba K, Nakazawa K, Ono K, Umezaki T. Multifunctional laryngeal premotor neurons: their activities during breathing, coughing, sneezing, and swallowing. J Neurosci. 2007;27(19):5156–62.
42. Sakamoto T, Katada A, Nonaka S, Takakusaki K. Activities of expiratory neurones of the Bötzinger complex during vocalization in decerebrate cats. Neuroreport. 1996;7:2353–6.
43. Ezure K. Synaptic connections between medullary respiratory neurons and considerations on the genesis of respiratory rhythm. Prog Neurobiol. 1990;35(6):429–50.
44. Zheng Y, Barillot JC, Bianchi AL. Are the post-inspiratory neurons in the decerebrate rat cranial motoneurons or interneurons? Brain Res. 1991;551(1–2):256–66.
45. Nonaka S, Katada A, Sakamoto T, Unno T. Brain stem neural mechanisms for vocalization in decerebrate cats. Ann Otol Rhinol Laryngol Suppl. 1999;108:15–24.
46. Sakamoto T, Nonaka S, Katada A. Control of respiratory muscles during speech and vocalization. In: Miller AD, Bianchi AL, Bishop BP, editors. Neural control of the respiratory muscles. Florida: CRC Press; 1996. p. 249–58.
47. Oku Y, Tanaka I, Ezure K. Activity of bulbar respiratory neurons during fictive coughing and swallowing in the decerebrate cat. J Physiol. 1994;480(Pt 2):309–24.
48. Bianchi AL, Gestreau C. The brainstem respiratory network: an overview of a half century of research. Respir Physiol Neurobiol. 2009;168(1–2):4–12. 2009/05/02 ed.
49. Grélot L, Barillot JC, Bianchi AL. Pharyngeal motoneurones: respiratory-related activity and responses to laryngeal afferents in the decerebrate cat. Exp Brain Res. 1989;78(2):336–44.
50. Cohen MI. Discharge patterns of brain-stem respiratory neurons during Hering-Breuer reflex evoked by lung inflation. J Neurophysiol. 1969;32(3):356–74.
51. Von Euler C. Brain stem mechanisms for generation and control of breathing pattern. In: Cherniack NS, Widdicombe JG, editors. Handbook of physiology: section 3, the respiratory system. Bethesda: Americal Physiological Society; 1986. p. 1–67.
52. Schwarzacher SW, Smith JC, Richter DW. Pre-Bötzinger complex in the cat. J Neurophysiol. 1995;73(4):1452–61.
53. Kuna ST, Remmers JE. Premotor input to hypoglossal motoneurons from Kolliker-Fuse neurons in decerebrate cats. Respir Physiol. 1999;117(2–3):85–95.
54. Ono T, Ishiwata Y, Inaba N, Kuroda T, Nakamura Y. Modulation of the inspiratory-related activity of hypoglossal premotor neurons during ingestion and rejection in the decerebrate cat. J Neurophysiol. 1998;80:48–58.
55. Gestreau C, Dutschmann M, Obled S, Bianchi AL. Activation of XII motoneurons and premotor neurons during various oropharyngeal behaviors. Respir Physiol Neurobiol. 2005;147(2–3):159–76.
56. Berman ALI. The brain stem of the cat. Madison: University of Wsconsin Press; 1968.