Mechanisms and Neuronal Control of Vocalization in Vertebrates

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Abstract. Vocalization is a highly conserved innate behavior in vertebrates. It is mainly used in social encounters to communicate a variety of information for inter- and intra- specific interactions. In this review, we focus on the anatomical, biomechanics and neuronal circuits underlying vocalization across vertebrate species. In addition, we discuss our recent findings that assign to the nucleus of the solitary tract a critical role in innate vocalization. This brain center receives viscerosensory information, i.e. information from internal organs that includes the lungs and the larynx. Furthermore, subpopulations of neurons in the nucleus of the solitary tract directly connect to and entrain the activity of expiratory and laryngeal motor neurons. In mammals and amphibians, these motor neurons control essential biomechanical parameters used for vocalization, and similar motor neuron pools regulate vocal utterances in birds. Thus vocalization relies on a conserved neuronal circuit residing in the brainstem and spinal cord.

Introduction

Vocal communication is central in many social behaviors displayed by vertebrate species. Indeed, animals produce complex vocal sounds during encounters that include courtship, mating, territory disputes, mother-offspring interactions, and even to express emotional states (Garcia and Favaro, 2017; Heckman et al., 2017; Rohrmeier et al., 2015; Seyfarth and Cheney, 2003, 2010). It is perhaps not surprising that its relevance in inter- and intra- specific forms of animal interactions has been long recognized by etiologists, naturalists and evolutionary biologist, as the faithful elaboration of vocal sounds guarantees the proper integration of the individual into the group (Brudzynski, 2009; Darwin, 1872; Fisher and Marcus, 2006; Hernandez-Miranda et al., 2017). Human and dolphin vocal communication represents sophisticated examples of animal vocalization. In humans, verbal communication can be divided in speech (i.e. sound production) and language. Sound production depends on mechanical aspects, while language corresponds to a high-order brain function based on accepted rules to produce, combine and generate sounds that define specific words or ideas (Kang and Drayna, 2011). Whereas language is a characteristic of humans and requires learning, the ability to produce sounds is an innate feature that relies on breathing and on a neuronal circuit shared among mammals, birds and amphibians (Bass et al., 2008; Brudzynski, 2009; Elemans et al., 2015; Goodson and Bass, 2002; Margoliash and Hale, 2008).

In physics, sounds are defined as the vibration of an object in an elastic medium, which propagates as an audible wave of pressure through a transmission medium like a gas, a liquid or a solid material. For this reason, sound production cannot occur in vacuum or in outer space. Terrestrial, semiaquatic (amphibians) and some marine (i.e. cetaceans) vertebrates generate vocal sounds by modifying their breathing patterns (Gerhardt, 1994; Hernandez-Miranda et al., 2017; Newman, 1988; Riede, 2011; Riede and Goller, 2010; Schmidt and Martin Wild, 2014; Schmidt et al., 2012; Subramanian and Holstege, 2014). In mammals, forced exhalation of air during expiration energizes a set of specialized elastic muscular tissues -the vocal folds in the larynx- to produce sounds. In addition, mammalian vocalization also depends on several other anatomical structures that amplify vocal sounds. These structures are collectively known as resonant chambers and consist of the pharynx, the mouth and the nasal cavities (Brudzynski, 2009; Newman, 1988). Altogether, the lungs, the vocal folds and the resonant chambers form the so-called mammalian vocal apparatus, which is to a certain extend shared with amphibians (see below). The vocal apparatus of birds slightly differs to that of mammals, but avian vocalization is also tightly coupled to respiration. The avian vocal apparatus is composed of the syrinx, which lacks vocal folds but contains analogous membranes that serve as a vibrating tissue (Elemans et al., 2015). Marine vertebrates that do not breathe air, like most bony fishes, evolved other mechanisms to generate vocal sounds independently of an airflow and breathing (Ladich F., 2006). For instance, the majority of bony fishes use fast-contracting muscles, known as drumming muscles that locate in the swim bladder, as the main vocal apparatus (Bass et al., 1994).

In this review, we will discuss the anatomical structures, biomechanics and neuronal circuits that allow for vocal sound production in vertebrates, with a special emphasis on innate vocalization.

Sound production and the vocal apparatus of terrestrial and semiaquatic vertebrates

Terrestrial and semiaquatic vertebrates predominantly use the larynx (syrinx in birds; see below) to produce vocal sounds (Sasaki, 2006; Suthers, 2016). In mammals, there exists a great variability in the anatomy of the larynx. This heterogeneity is partially responsible for the enormous diversity of vocal sound types produced by distinct species, which range from ultrasounds (high-frequency sounds above 20 kHz) characteristics

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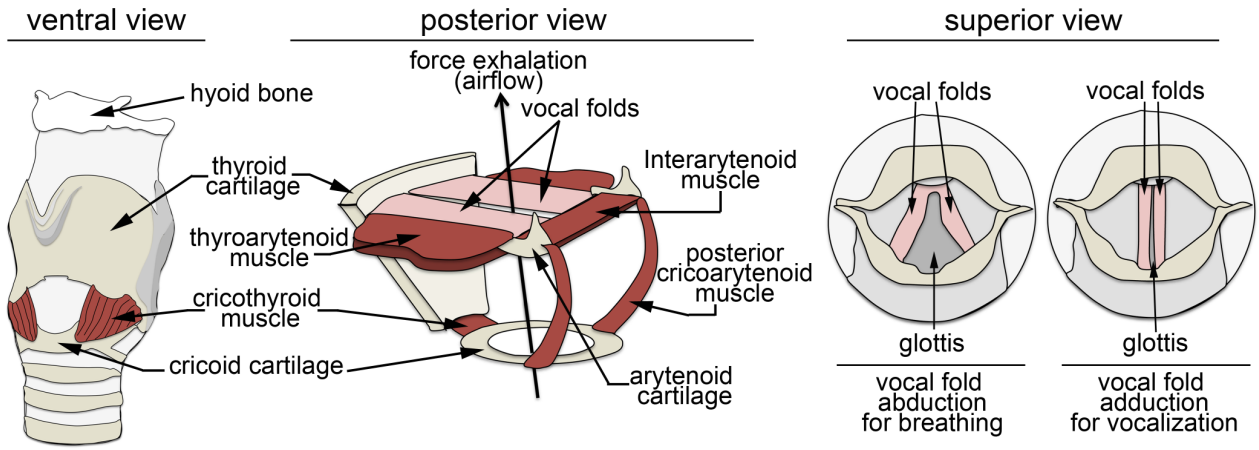

Figure 1. *Anatomy of the larynx in mammals. Schemes depicting a ventral (on the left), a simplify dorsal (on the middle), and superior (on the right) view of the larynx in mammals. The basic anatomy of the larynx includes a pair of vocal folds, and four muscles: interarytenoid, thyroarytenoid, cricothyroid and posterior cricoarytenoid that are joint by cartilage. The gap between the vocal folds is known as the glottis. During basal breathing, the contraction of the posterior cricoarytenoid muscles pulls the arytenoid cartilages and vocal folds away from each other by abducting and externally rotating the arytenoid cartilages. Vocal fold abduction allows the passive movement of air through the larynx. During vocalization, the interarytenoid (also known as transverse and oblique arytenoid) muscles contract and bring together the vocal folds by adducting the arytenoid cartilages to close the glottis, thereby forming a partially barrier for airflow. Vocal sounds are produced when forced exhalation creates pressurized airflow that collides with the vocal folds, resulting in their vibration. Sound frequencies depend on the particular number of vocal fold vibrations, and the tension of the vocal folds, which is controlled by the cricothyroid and thyroarytenoid muscles. Schemes on left and right panels were adapted from https://en.wikipedia.org/wiki/Larynx. Scheme on the middle was adapted from Ladich and Winkler, 2017.*

of rodents to those infrasounds (low-frequency sounds under 20 Hz) elicited by elephants (Herbst et al., 2012; Hofer et al., 2002). As a reference, the human hearing range covers sound frequencies in the interval between 20 Hz and 20 kHz. The anatomical position of the larynx also varies in different mammals and even during postnatal development of certain species. For instance, adult humans have an unusual low larynx that rests near the bottom of the throat (about the level of C7), which results in an evolutionary long pharyngeal cavity thought to be responsible for the richness and wider range of vocal-tract shaped sounds distinctive of human speech (Fitch and Reby, 2001; Ghazanfar and Rendall, 2008). In contrast, baby humans and apes have a larynx in a much more upper position (about C5), which descends in humans during childhood and reaches its mature position during puberty, when changes in the pitch of the voice occur (Prakash and Johnny, 2015). The relative high position of the larynx in human babies and apes prevents them from producing all sounds characteristic of the mature human language, however it gives them the ability to breathe while eating (Goldfield et al., 2006). Conversely, the low position of the larynx in adult humans intersects the pathways between the stomach and the lungs, which increases the risk of choking while eating and speaking.

In general terms, the mammalian larynx consists of a pair of vocal folds and four muscles: interarytenoid, thyroarytenoid, cricothyroid and posterior cricoarytenoid muscles, which are interconnected by cartilages (Fig. 1) (Allen and Murcek, 2018). The aperture between the vocal folds is known as the glottis and its opening and closing is important for basal breathing and vocalization, respectively (Denk et al., 1998; Noordzij and Ossoff, 2006; Sasaki, 2006). During basal breathing, the contraction of the posterior cricoarytenoid muscles pulls the arytenoid cartilages and vocal folds away from each other allowing the passive movement of air through the larynx (Fig. 1). During vocalization, the interarytenoid muscles contract and bring together the vocal folds to close the glottis, thereby forming a partial barrier for airflow (Fig. 1). Vocal sounds are produced when forced exhalation of air creates a subglottal airflow pressure that collides with the vocal folds, causing their vibration. Notably, the length of the vocal folds and the specific number of vibrations produced by subglottal airflow pressure determine the frequency of vocal sounds. Sound frequencies also depend on the particular tension of the vocal folds, which is controlled by the cricothyroid and thyroarytenoid muscles (Fig. 1) (Riede, 2011; Titze, 2000).

Unlike other terrestrial vertebrates, birds do not posses a larynx or vocal cords but instead they evolved a sound producing apparatus known as the syrinx, which locates at the junction between the trachea and the bronchi (Fig. 2A). The syrinx is composed of a bilateral symmetric group of anatomic structures that include a paired set of strong muscles known as syringeal, several cartilages, vibrating membranes better known as labia, and a vocal tract (Suthers and Zollinger, 2004). The vocal apparatus of birds is very efficient when compared to that of mammals and amphibians, as it uses all forced expiratory airflow that passes through the syrinx in order to produce vocal sounds. Conversely, mammals vocalize

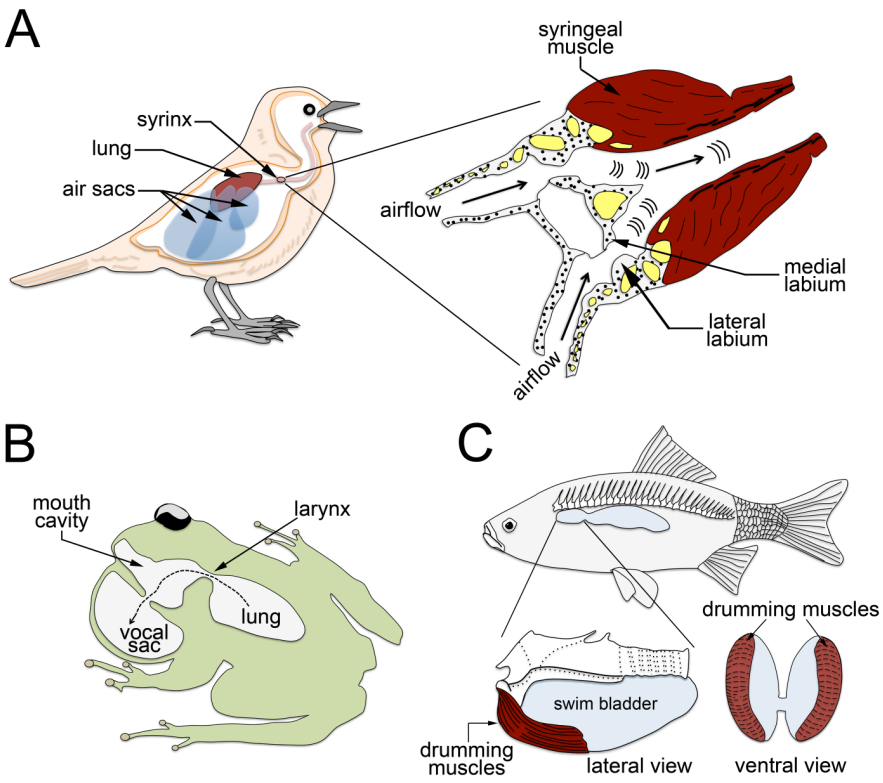

***Figure 2**. Anatomy of the vocal organ in non-mammalian vertebrates. (A) Schemes depicting the position (on the left) and structure (on the right) of the syrinx in birds. The basic anatomy of the larynx includes a paired set of strong muscles known as syringeal, several cartilages (in yellow), vibrating membranes known as labia, and a vocal tract. Air-containing appendages known as airs sacs receive and maintain inhaled air before passing it through the lungs, thereby functioning like a bellow device that continuously supplies pressurized expiratory airflow that forces vibration of the lateral and medial labia to produce vocalizations. Schemes adapted from https://academy.allaboutbirds.org/anatomy-of-bird-song-slides/ and Ladich and Winkler, 2017. (B) Scheme illustrating the vocal apparatus of amphibians, which shares anatomical structures with mammals, i.e. the larynx and vocal cords, and includes in addition vocal sacs. Like in mammals, amphibian vocal sounds are produced when forced exhalation sets off the vibration of the vocal folds. Scheme adapted from https://biologyboom.com/evolutionary-pressures-in-amphibians/ (C) Schemes illustrating the most common vocal apparatus of bony fishes. This sound-producing system depends on fast-contracting muscles know as drumming muscles that are associated with the swim bladder. Schemes adapted from https://u.osu.edu/biomuseum/category/biodiversity/local-fauna/page/2/ and Ladich and Winkler, 2017.*

using only a fraction of the forced expiratory airflow (e.g. only 2% in humans) that moves across the larynx. This efficiency is a consequence of the uniqueness of avian respiratory system (Schmidt and Martin Wild, 2014). In contrast to mammals that possess big and very elastic lungs, birds have small rigid lungs and a limited lung capacity. To compensate this deficiency, bird evolved accessory anatomic air-containing structures known as the air sacs (Fig. 2A) (Duncker, 2004). Airs sacs are not directly involved in the exchange of gases, but instead they receive and maintain inhaled air before passing it through the lungs, thereby functioning like a bellow device that continuously supplies pressurized expiratory airflow (Riede and Goller, 2010). In addition to this, air sacs also function as resonant chambers and are thus important players in shaping the spectral composition of the emitted vocal sounds.

Amphibians and some marine (e.g. cetaceans) vertebrates also use expiratory airflow on vibrating tissue to produce vocal sounds (Suthers, 2016). The vocal apparatus of amphibians shares anatomical structures with mammals, i.e. the larynx and vocal cords, but encompasses additional structures known as the vocal sacs (Fig. 2B) (Ryan and Guerra, 2014). Similar to avian air sacs, the amphibian vocal sacs function like a resonant chamber to amplify and efficiently radiate vocal sounds. Because amphibians can live both underwater and on land, they have developed a sophisticated air-recycling system used underwater to avoid frequent trips to the surface. This air-recycling system is independent of air breathing, as the nostrils and the mouth remain closed underwater (Kime et al., 2013; Suthers, 2016). This system moves air from the lungs into the vocal sac across the larynx, which is used on land to produce vocalizations (Fig. 2B) (Gerhardt, 1994; Gridi-Papp, 2008). Like semiaquatic amphibians, cetaceans possess an air recycling system and their vocal apparatus includes a larynx, a nasal passage with associated nasal air sacs that locate between the larynx and the blowhole (Ladich and Winkler, 2017). Although the precise sound-producing mechanism used by cetaceans is not completely understood, it is believe that vocal sounds are produced when pressurized air from the nasal air sacs is forced through the nasal passage and into the larynx (Suthers, 2016) .

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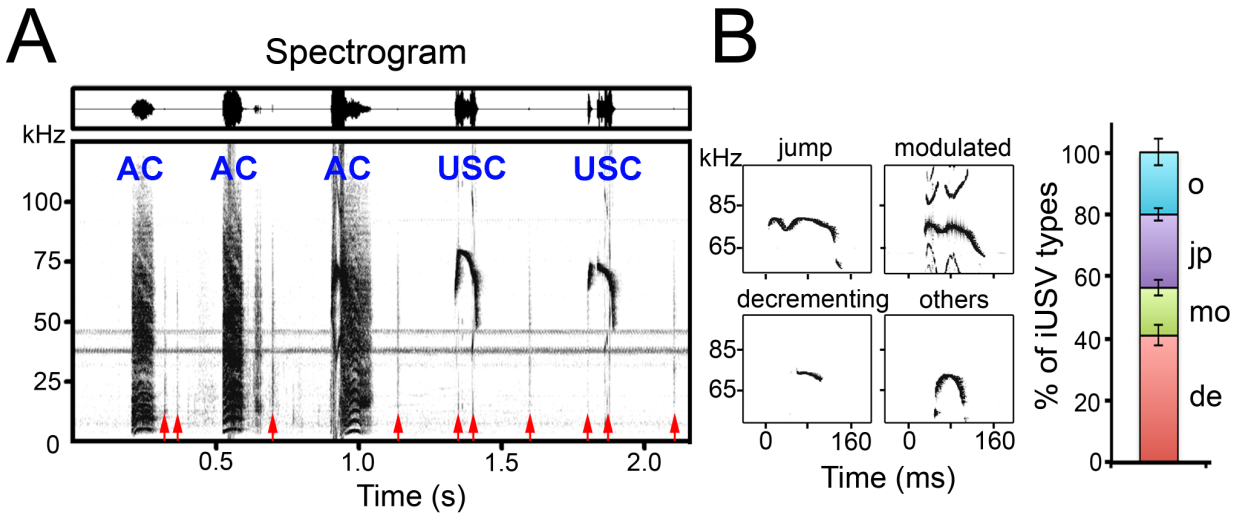

Figure 3. *Vocal repertoire of neonatal mice. (A) Spectrogram (bottom) and waveform (top) traces illustrating audible (AC) and ultrasonic (USC) calls elicit by a newborn mice upon mechanical (touch) stimulation. In addition to audible and ultrasonic calls, newborn mice produce short non-vocal sounds called clicks (red arrows). (B) On the left, representative spectrograms of single ultrasonic calls produced during isolation. Note that ultrasonic calls are complex and can be classified according to their shapes and frequency in jump (jp), modulated (mo), decrementing (de) and other (o) calls. On the right, percentage of jump, modulated, decrementing and other ultrasonic calls in newborn mice isolated from the litter.*

Sound production and the vocal apparatus of marine vertebrates

Bony fishes, with the notable exception of lungfishes and labyrinth fishes, do not breathe air and as a consequence have evolved several mechanisms to produce vocalizations independently of breathing and airflow (Parmentier, 2015). These sound-producing mechanisms are divided in three main groups according to the anatomic structures involved to produce vocalizations: the swim bladder, pectoral muscles or head structures. The swim bladder, a gas filled organ that is primarily used for buoyancy control, is typically used by bony fishes to generate sounds (Fig. 2C) (Blaxter and Tytler, 1978; Fine et al., 2016). It contains fast-contracting muscles, called drumming (also known as sonic or vocal) muscles, which actively vibrate to produce sounds. Drumming muscles are the fastest contracting muscles characterized in vertebrates, and their activity causes the swim bladder to contract and expand at a rapid rate, thereby creating drumming sounds (Boyle et al., 2015; Ladich, 1997; Ladich and Winkler, 2017; Ladich F., 2006). The majority of sounds produced in this way are short pulses with frequencies ranging from 45 – 60 Hz up to 250 – 300 Hz. When using pectoral muscles or head structures, bony fishes produce vocalizations by stridulation, i.e. production of sounds by rubbing together body parts (Ladich, 1997).

Neuronal control of mammalian vocalization

The neurological bases of human and mammalian vocalization have been intensively studied for decades. Vocal sound production is tightly coupled to the respiratory system and relies on the tension of the vocal folds as well as on the precise coordination of laryngeal and expiratory muscles, which together create the biomechanical force necessary for sound production, i.e. the subglottal air pressure (see above) (Riede, 2011). Motor neurons controlling these muscular groups are widely distributed along the brainstem (i.e. the midbrain, pons and medulla oblongata) and the spinal cord (Jurgens, 2009). Specifically, laryngeal motor neurons residing in the ventral medullary nucleus ambiguus control vocal fold tension and laryngeal muscles (Shiba et al., 2007a; Shiba et al., 2007b), whereas motor neurons located in the ventral horn of lower thoracic (T7-T12) and upper lumbar (L1) spinal cord segments govern the activity of expiratory intercostal and abdominal (internal and external oblique) wall muscles, respectively (Abdala et al., 2009; Barrett et al., 1994; Iscoe, 1998; Saji and Miura, 1990). In addition, motor neurons located in the trigeminal motor nucleus (in the pons) as well as the facial, ambiguus and hypoglossal motor nuclei (all in the medulla oblongata) are important players in shaping up the articulation of vocal sounds by regulating movement of several orofacial structures that include the tongue and the mouth (Kirzinger and Jurgens, 1985; Magoun et al., 1937). How these widely distributed motor neurons synchronize their activity to produce vocal sounds is not completely understood, but several studies show that voluntary and involuntary neuronal circuits can coordinate their activity during vocalization.

Voluntary control of vocal utterances in humans, primates and other mammals largely depends on high order brain areas located in the laryngeal motor cortex, the inferior frontal gyrus (Broca's area) and the anterior cingulate cortex, which directly and indirectly project onto motor neurons modulating laryngeal, expiratory and orofacial musculature (Simonyan, 2014; Simonyan and Horwitz, 2011). The intactness of such decending pathways is essential for generating the remarkable richness and complexity that characterized learned language and human verbal comunication (Kumar et al., 2016). Nevertheless, several lines of research indicate that forebrain-descending pathways are dispensable

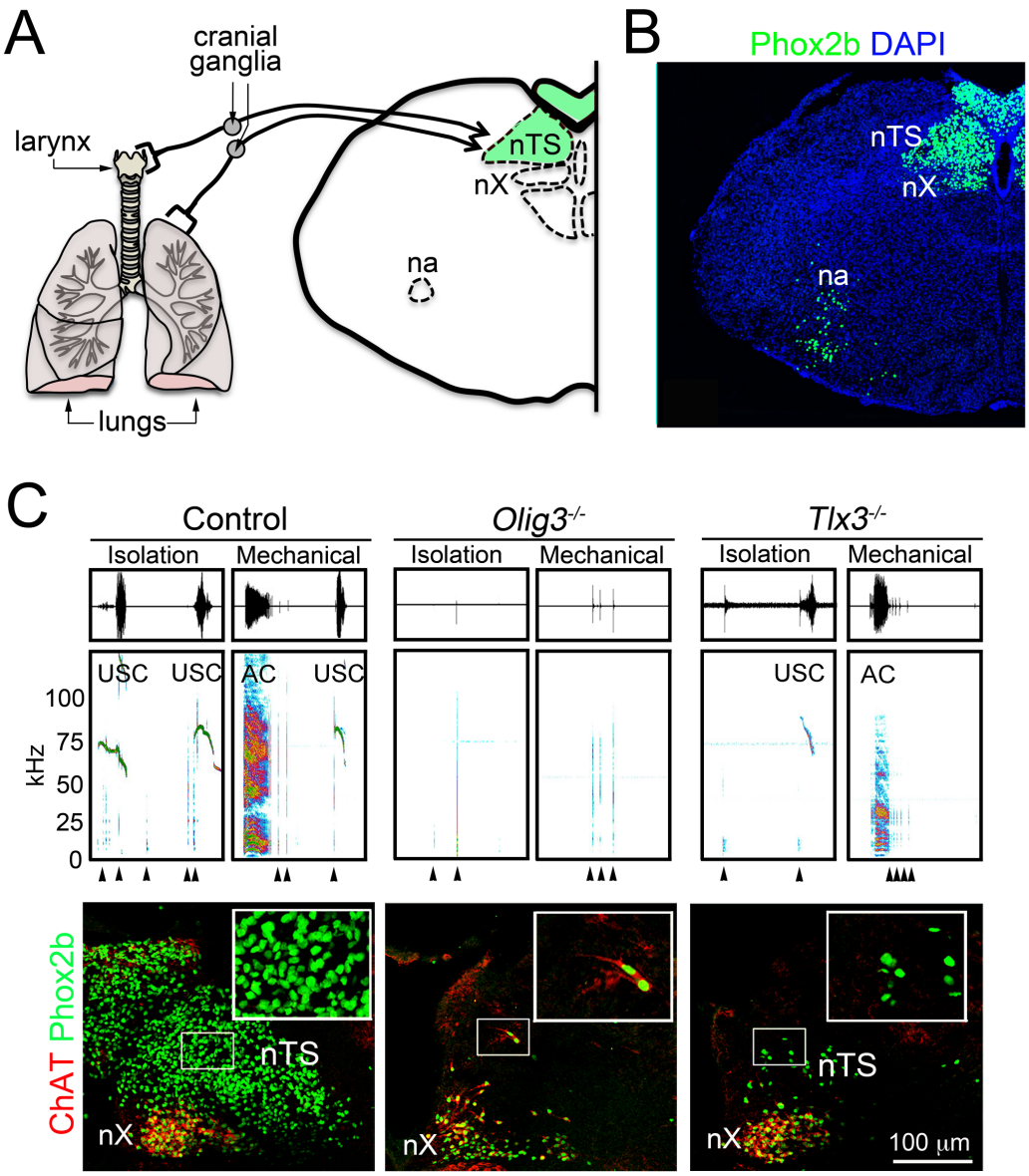

Figure 4. *The nucleus of the solitary tract is essential for innate vocalization. (A) Schematic illustration of laryngeal (innervating the larynx) and pulmonary (innervating the lungs) cranial ganglia afferents that convey sensory information from the larynx and lung to the nucleus of the solitary tract (nTS), which locates in the caudal-dorsal medulla oblongata. The nucleus ambiguus (na) contains motor neurons that innervate laryngeal muscles. (B) Transverse section of the caudal medulla oblongata in mice stained with antibodies against Phox2b (in green). Note that the nucleus of the solitary tract as well as the vagal (nX) and ambiguus (na) motor nuclei is immunoreactive for Phox2b. DAPI (in blue) was used as a counterstain. (C) Top, representative spectrograms and waveform traces illustrating vocalization behavior of Control, Olig3 (Olig3$^{-/-}$) and Tlx3 (Tlx3$^{-/-}$) mutant newborn mice in isolation or after mechanical (touch) stimulation. Bottom, histological analysis of Phox2b+ (green) neurons in the nucleus of the solitary tract of Control, Olig3 and Tlx3 mutant pups. Choline acetyl-transferase (ChAT, red) antibodies were used to distinguished Phox2b+/ChAT- neurons of the solitary tract nucleus from neighboring Phox2b+/ChAT+ motor cells of the vagal nucleus. Insets are magnifications of the boxed areas. Note that the total elimination of Phox2b+/ChAT- cells in the nucleus of solitary tract of Olig3 mutant pups correlates with complete mutism, i.e. absence of audible (AC) and ultrasonic (USC) calls. The pronounced reduction in the number of these cells in Tlx3 mutant mice results in weak an infrequent vocal call activity. Panel C was adapted from Hernandez-Miranda et al., 2017*

for innate mammalian vocalization. For instance, early studies in cows, cats or dogs documented that surgical ablation of forebrain structures, anterior to the inferior colliculus of the midbrain, did not impair their capacity to moo, meow or bark, respectively (Blessing, 1997; Onodi, 1902; Penfield, 1922). More recently, Hammerschmidt and colleagues demonstrated that transgenic mice lacking the cerebral cortex and hippocampus are fully capable of producing ultrasonic calls in different behavioral contexts (Hammerschmidt et al., 2015). Similarly, humans born with little or no cerebral hemispheres had been reported to be able to produce rudimentary vocal sounds, such as cries, laughs and sighs, albeit not achieving any degree of learned language (Celesia, 1993). Lastly, human speech

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seems to be also independent of cerebellar function, as patients born without this brain structure can develop normal speech and language (Yu et al., 2015). These studies had indicated that the rudimentary form of human vocal utterances and animal vocalization are innate behaviors, which neuronal circuits serving for it most likely exist in the brainstem and/or in the spinal cord.

In a quest to identify brainstem neurons responsible for vocalization, Graham Brown at the University of Manchester was the first to experimentally suggest the periaqueductal gray, located in the caudal midbrain, as a place containing neurons important for regulating call production (Brown, 1915). In particular, Brown showed that stimulation of the rostral periaqueductal gray in decerebrated chimpanzees could elicit a great variety of vocal sounds, some of which even resembling natural laughing. Ever since, several other neurophysiologists have subsequently confirmed and extended Brown's observations in other primates - including gibbons, squirrel and rhesus monkeys - as well as in cats, rats, guinea pigs and bats (Apfelbach, 1972; Jurgens and Ploog, 1970; Magoun et al., 1937; Martin, 1976; Suga et al., 1973; Yajima et al., 1976). Furthermore, lesion studies aimed to fully transect the periaqueductal gray are effective in abolishing calls in primates as well as in cats, dogs and rats (Adametz and O'Leary, 1959; Jurgens and Pratt, 1979; Kelly et al., 1946; Skultety, 1958, 1962).

The periaqueductal gray is a complex neuroanatomical structure, which strategic position in the midbrain allows it to receive and relay ascending and descending sensory-motor commands capable of triggering vocalization (Beitz, 1982; Cameron et al., 1995; Koutsikou et al., 2015; Marchand and Hagino, 1983; Meller and Dennis, 1991). In addition to vocalization, the periaqueductal gray has been reported to be important in modulating many other animal behaviors that depend on precise adjustments of respiratory patterns, such as the fight-or-flight response, pain, anxiety, panic and fear/freezing response (Behbehani, 1995; Bondarenko et al., 2016; Graeff et al., 1993; Kincheski et al., 2012; Koutsikou et al., 2015; Loyd and Murphy, 2009; Subramanian and Holstege, 2014; Zhang et al., 1990). Hence, changes in basal (eupneic) breathing are mediated by the periaqueductal gray in a context-specific manner. Indeed, direct electrophysiological stimulation on different compartments of the periaqueductal gray can transform basal breathing into different respiratory patterns that correspond to particular behaviors associated with the stimulated region (Subramanian et al., 2008). For instance, stimulation of the dorso-medial periaqueductal gray slows down breathing and produces a dyspnea-like deficit in cats, which in humans we experience as the feeling that one cannot breathe. This respiratory change is in accordance with the function of this area in mediating fear, anxiety and defensive responses in which breathing can get halted (Bandler and Carrive, 1988; Subramanian et al., 2008). In the case of vocalization, stimulation on margins of the lateral and ventrolateral periaqueductal gray produces pronounced changes in inspiratory and expiratory activity associated with meow and hiss vocalizations in cats (Davis et al., 1993; Subramanian et al., 2008). Despite the fundamental role of the periaqueductal gray in modulating breathing patterns to cope with particular animal behaviors, it does not innervate any motor neuron group, neither in the brainstem nor in the spinal cord. To execute its motor influence on breathing regulation, the periaqueductal gray instead uses several neuronal groups located in the pons (such as the parabrachial and Kolliker-Fuse nuclei) or the medulla oblongata (i.e. the nucleus of the solitary tract and retroambiguus nucleus) (Bandler and Tork, 1987; Farkas et al., 1998; Holstege, 1989; Krout et al., 1998; Subramanian et al., 2008).

The nucleus of the solitary tract an essential novel element in the neuronal circuit serving for vocalization

Newborn mice are a good model to explore neuronal circuits serving for innate vocalization, as they actively produce complex calls that encompass broadband audible (100 ms, 20 Hz - 80 kHz) and ultrasonic (50-100 ms, 50-80 kHz) calls immediately after birth (Fig. 3). In addition, pups can produce short audible (1-2 ms, 20 Hz -80 kHz) non-vocal sounds known as clicks (red arrows in Fig. 3A). Newborn calls are context-specific, as pups produce complex ultrasounds and short clicks when isolated, and a combination of audible calls, ultrasounds and short clicks in response to mechanical stimulation.

In a recent study, our group demonstrated that the viscerosensory nucleus of the solitary tract, in the dorsal medulla, is an essential component in the circuit that transforms breaths into calls in neonatal mice (Hernandez-Miranda et al., 2017). This nucleus receives information from peripheral viscerosensory neurons, i.e. information from internal organs like among others, the lungs and the larynx (Fig. 4A,B). We identified this brain center by screening vocal sound production in newborn mice of various mutant strains that specifically disrupt development of distinct neuronal subtypes in the brainstem. In particular, our screen revealed that two strains display severe vocalization deficits: Olig3 and Tlx3 mutant mice (Fig. 4C). More specifically, we observed that Olig3 mutant pups are unable to vocalize in any context and feature the complete absence of Phox2b+ neurons in the nucleus of the solitary tract, whereas Tlx3 mutant pups rarely vocalize and display a severe reduction of Phox2b+ cells (Hernandez-Miranda et al., 2017). We validated this correlation by engineering mice that selectively lack all Phox2b+ neurons in the nucleus of the solitary tract (which we called TxPh1 mice), or that severely reduce the number of Phox2b+ cells in this brain center (called TxPh2 mice). Anatomical and physiological analyses on these animals demonstrated that the complete ablation of such Phox2b+ neurons results in muteness, while the partial elimination of Phox2b+ neurons severely impaired vocalization but does not eradicate this behavior (Hernandez-Miranda et al., 2017). Thus, the nucleus of the solitary tract contains essential neurons for innate vocalization

The nucleus of the solitary tract has long be known to regulate several breathing reflexes, such as the Hering-

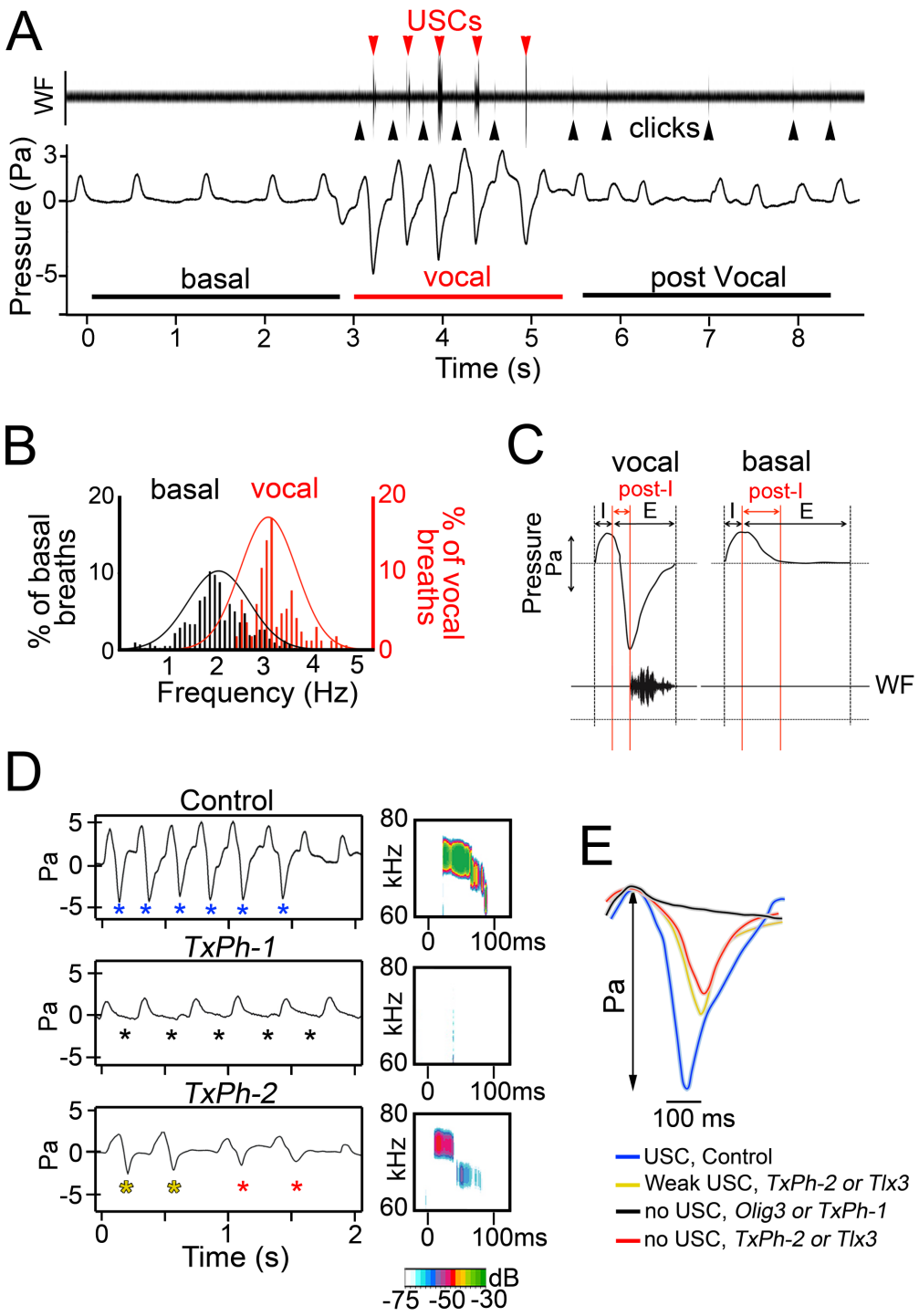

Figure 5. *Vocal breathing behavior in mice that lack the nucleus of the solitary tract. (A) Waveform and plethysmographic traces illustrating basal and vocal breathing episodes in control mice. Red and black arrowheads point to USCs and clicks, respectively. (B) During vocalization, breathing frequencies change from about 2 Hz to more than 3 Hz. (C) Plethysmographic recording and waveforms (WF) during a representative vocal and a basal expiration. Inspiratory (I), expiratory (E), and post-inspiration phases (post-I, red lines) are indicated. Note that ultrasonic calls occur at the peak of post-inspiratory pressure activity during a vocal expiration (D) Left, plethysmographic recordings of control, TxPh-1, and TxPh-2 mice. Blue asterisks indicate expirations of control mice that produced USCs. Black asterisks indicate expirations of TxPh-1 mice that produce no USCs. Red and yellow asterisks indicate expirations of TxPh-2 mice that produced no calls or weak calls, respectively. Right, spectrograms from control, TxPh-1 and TxPh-2 mice. Note that only clicks are observed in TxPh-1 mice. Sound intensity (in dB) is color-coded. (E) Representative plethysmographic traces of individual post-inspiratory phases in control (blue), Olig3−/−, and TxPh-1 mice (indistinguishable, shown together in black), as well as TxPh-2 or Tlx3−/− mice that were associated with weak or no calls are shown in yellow and red, respectively. Panels A-E were adapted from Hernandez-Miranda et al., 2017.*

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Breuer reflex that prevents over-inflation of the lungs by curtailing inspiration and allowing expiration to occur (Zoccal et al., 2014). In our recent work, we showed that mouse ultrasonic vocalizations occur exclusively during events of fast breathing and active expiration that we called "vocal breathing" (Fig. 5A-C). During basal breathing, inspiration depends on the contraction of the diaphragm, whereas expiration is passive and relies on the recoiling of the elastic lungs. When newborn mice produce ultrasonic calls, they abruptly change their respiratory frequencies from approximately 2 Hz (basal breathing) to more than 3 Hz (Fig. 5B). This change in breathing frequencies is accompanied by the appearance of active expirations that produce pronounced changes in pressures during the early expiratory phase (also known as post-inspiratory) of the breathing cycle (Fig. 5C). In mice that lack Phox2b+ neurons in the nucleus of the solitary tract (such as Olig3 and TxPh1) no pressure was observed in the expiratory phases of fast breathing cycles, whereas mice with reduced numbers of Phox2b+ neurons (Tlx3 and TxPh2 animals) produced blunted pressure during expiration (Fig. 5D,E). Interestingly, the quantification of the pressure changes in Tlx3 and TxPH2 animals indicates that a minimal change of 35Pa/sec is required in order to elicit a successful call. Thus, the nucleus of the solitary tract specifically operates during the expiratory phase of the breathing cycle to produce vocalizations. Expiratory activity of the nucleus of the solitary tract might arise from its bidirectional connection with the Kölliker-Fuse nucleus, a brain center known to be a major source of expiratory drive in breathing (Alheid et al., 2011; Dutschmann and Dick, 2012; Dutschmann and Herbert, 2006; Hernandez-Miranda et al., 2017).

Vocalization is a highly energetic behavior that demands abundant air in the lungs and the correct tension of the vocal folds to produce the expiratory pressures necessary for vocal sound production. Pulmonary stretch receptor and laryngeal afferents convey sensory information, concerning lung expansion and laryngeal muscle activity, respectively, directly onto the nucleus of the solitary tract (Fig. 4A) (Davis et al., 1993; Nakazawa et al., 1997). Surgical de-afferentation of pulmonary and laryngeal sensory information has been shown to severely disrupt vocalization in mammals (Davis et al., 1993; Nakazawa et al., 1997; Shiba et al., 1995; Thoms and Jurgens, 1981). In addition, the nucleus of the solitary tract also receives somatosensory information from the body and the face via spinal cord projection neurons and primary somatosensory neurons of the facial and trigeminal nerve (King, 2007). Thus, it directly receives and integrates a variety of sensory information important for vocalization, and can relay it to other brainstem centers to execute vocalization. In particular, we and others have shown that the nucleus of the solitary tract forms bidirectional connections with all brainstem nuclei displaying vocalization-relate activity, such as the periaqueductal gray, the parabrachial complex and the nucleus retroambiguus (Alheid et al., 2011; Bandler and Tork, 1987; Hernandez-Miranda et al., 2017)

The coordination of laryngeal and expiratory motor neuron activity had been thought to exclusively depend on premotor neurons of the nucleus retroambiguus, a loose neuronal population located posterior to the nucleus ambiguus, which receive descending commands from the periaqueductal gray (Subramanian and Holstege, 2009). However, the presence of periaqueductal gray and retroambiguus premotor neurons does not suffice to produce vocalizations in mice that lack the nucleus of the solitary tract (Hernandez-Miranda et al., 2017). Interestingly, we observed that the nucleus of the solitary tract directly connects and functionally entrains laryngeal and expiratory motor neurons (Fig. 6), which indicates that it can coordinate laryngeal and expiratory motor activity (Hernandez-Miranda et al., 2017). It is important to note that the function of the nucleus of the solitary tract in vocalization appears to be conserved across mammalian species; as numerous neurons in this nucleus were reported to be active during vocal utterances of monkeys (Luthe et al., 2000).

Neuronal control of avian vocalization

Avian vocalizations include innate calls and learned songs, which complexity and development very much resemble that of acquired human language (Brainard and Doupe, 2002). Indeed, human babies seem to learn to babble in a similar fashion as birds learn new songs (Lipkind et al., 2013). Similar to mammals, song production in birds involves the coordination of three major groups of muscles: in the syrinx, controlling respiration, and regulating the upper vocal tract and jaw. Motor neurons innervating the syrinx locate in the tracheosyringeal (hypoglossal) nucleus, which also supplies motor innervation to the tongue (Faunes et al., 2017; Wild, 2004). The main source of descending commands onto the tracheosyringeal nucleus is the nucleus robustus of the arcopallium, a region homologous to the mammalian amygdala (Wild, 1993b). Like in mammalian species, expiratory motor neurons innervating intercostal and abdominal muscles locate in the lower thoracic and upper lumbar spinal cord (Suthers, 1997; Suthers, 2016). Motor neurons innervating the upper vocal tract and jaw are widely distributed in the pons and medulla oblongata, but like in mammals, these neurons locate in the trigeminal, hypoglossal and facial motor nuclei (Wild and Krutzfeldt, 2012). Syringeal and expiratory motor coordination in birds has also been reported to be regulated by the nucleus retroambiguus, which receives descending commands from the nucleus robustus of the arcopallium (Wild, 1993a). Thus the overall basic neuronal circuitry underlying vocalization in birds and mammals is largely conserved. In birds, the stimulation of a midbrain area homologous to the mammalian periaqueductal gray can also elicit a variety of vocal utterances (Brown, 1971; Delius, 1971; Peek and Phillips, 1971; Potash, 1970). Presently, it is not known whether the nucleus of the solitary tract is also essential for avian vocalization and the regulation of expiratory and syringeal motor neuron activity. Nevertheless, numerous lines of research indicate that the respiratory function of the nucleus of the solitary tract in mediating breathing

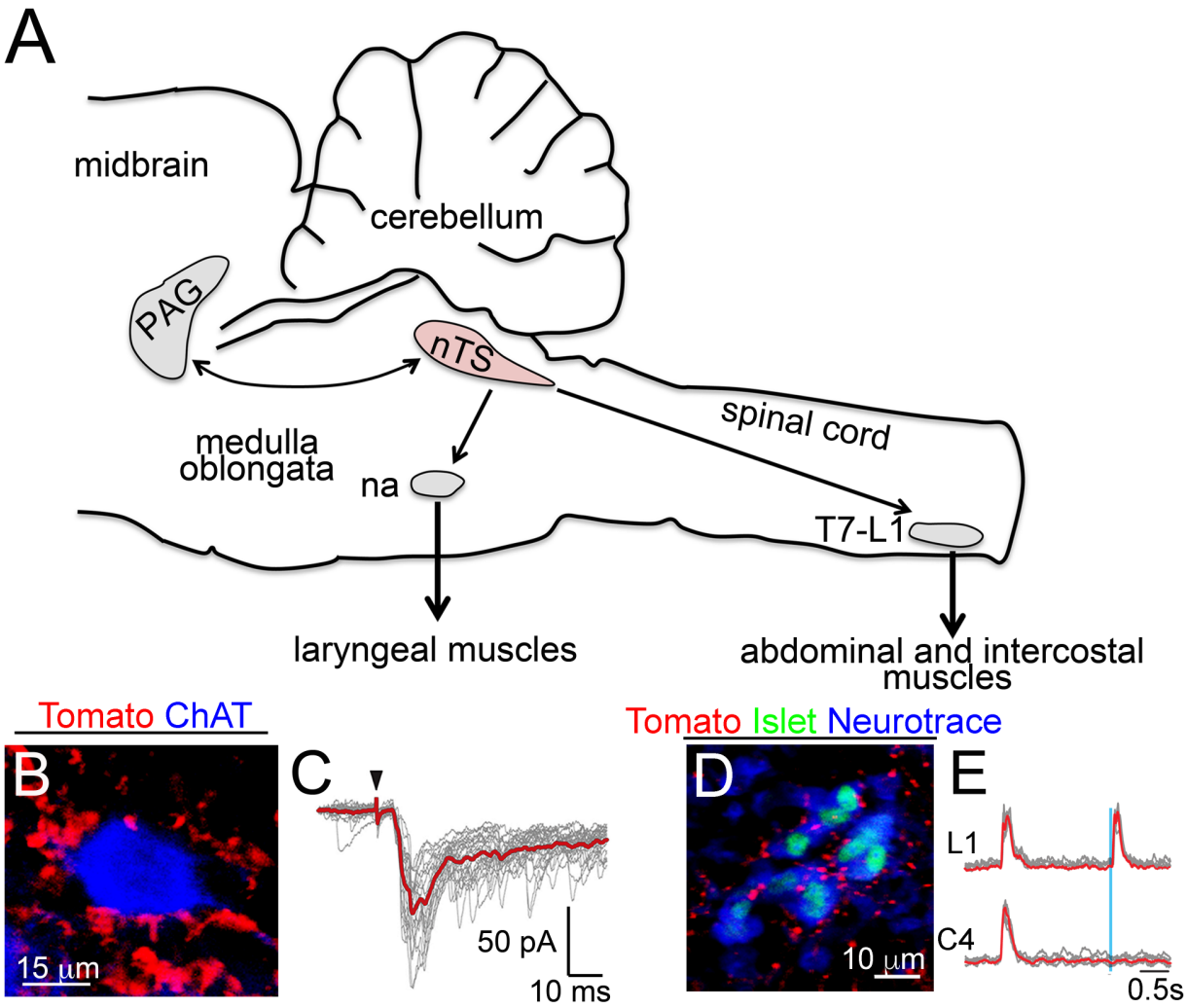

Figure 6. *Neurons of the nucleus of the solitary tract directly connect and entrain expiratory and laryngeal motor neurons. (A) Schematic sagittal view of the mouse brainstem (i.e. midbrain and medulla oblongata) and spinal cord illustrating the anatomical distribution of laryngeal (na) and expiratory (T7-L1) motor neurons. By combining anterograde and retrograde axonal tracing with intersectional genetic strategies to selectively label neurons of nucleus of the solitary tract (nTS), we observed that the nTS tract forms bilateral connections with the periaqueductal gray (PAG) and directly connects with laryngeal and expiratory motor neurons (see Hernandez-Miranda et al., 2017). (B) Representative ChAT+ (blue) laryngeal motor neuron of the nucleus ambiguus receiving dense innervation from neurons of the solitary tract nucleus that were labeled with Tomato (red) fluorescent protein. (C) Patch-clamp recordings of laryngeal motor neurons after solitary tract electrical stimulation in slice preparations. The red trace shows an average of 25 individual excitatory postsynaptic currents, and individual traces are shown in gray. Black arrowhead indicates the onset of stimulation. (D) Representative expiratory motor neurons positive for Islet (green) and neurotrace (blue) that locate in the ventral horn of the spinal cord at lumbar 1 level, which receive dense innervation from neurons of the solitary tract nucleus that were labeled with Tomato (red) fluorescent protein. (E) Superimposition of individual (gray) and average (red) traces of L1 (expiratory) and C4 (inspiratory) motor root activity after light stimulation (blue line) on channelrhodopsin+ nTS neurons in hindbrain-spinal cord preparations taken from control mice at birth. Light stimulation triggers only L1, but not C4, motor roots responses. Note that inspiratory (C4) and expiratory motor roots (L1) are rhythmically active in the absence of light and fire synchronously in hindbrain-spinal cord preparations; in vivo, they are not firing in a synchronous manner. Panels B-E were adapted from Hernandez-Miranda et al., 2017.*

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reflexes and the general input-output connectivity of this brain center is largely conserved in birds and mammals (Katz and Karten, 1983; Schmidt and Martin Wild, 2014; Wild, 2004; Wild and Arends, 1987; Wild et al., 1990; Wild et al., 2009).

Neuronal control of amphibian and bony fish vocalization

In most amphibians, like in mammals and birds, vocalization results from the contraction of the laryngeal muscles and the expiratory oblique muscles in the abdominal wall (Emerson and Boyd, 1999). Laryngeal muscles are controlled by motor neurons located in the nucleus ambiguus, while expiratory muscles are innervated by lower thoracic and upper lumbar motor neurons (Butler, 1996). Anatomical evidence on premotor neurons controlling laryngeal and expiratory activity is scarce in amphibians. Nevertheless, it is known that laryngeal motor neurons receive primarily premotor input from the pre-trigeminal nucleus, which in turn receives descending forebrain commands from the region of the ventral striatum, the amygdala, the thalamus and the preoptic area (Walkowiak, 1992; Wetzel et al., 1985). Like in birds, it is presently unknown whether the nucleus of the solitary tract regulates amphibian vocalization, but its connectivity and role in mediating breathing reflexes suggest a conserved function of this brainstem center from amphibians to mammals (Gargaglioni et al., 2007; Gargaglioni and Milsom, 2007).

The neuronal circuit serving for fish vocalization is relatively simple when compared with other high order vertebrates. In fishes that utilize the swim bladder as a vocal apparatus, there exists only one neuronal motor pool controlling drumming muscles, which has been mapped to locate in a caudal region of the medulla oblongata close or even perhaps analogous to where laryngeal and syringeal motor neurons exist in mammals and birds, respectively (Bass et al., 2008; Bass et al., 1994).

Conclusion

Vocalization is an innate behavior largely conserved across vertebrate species. An ancestral neuronal brain circuit serves for innate vocalization and resides in the rudimentary brainstem. In mammals, birds and amphibians, vocalization depends on expiratory airflow and the tension of the larynx (in mammals and amphibians) and the syrinx (in birds).

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