Opinion

How the brainstem controls orofacial behaviors comprised of rhythmic actions

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Mammals perform a multitude of well-coordinated orofacial behaviors such as breathing, sniffing, chewing, licking, swallowing, vocalizing, and in rodents, whisking. The coordination of these actions must occur without fault to prevent fatal blockages of the airway. Deciphering the neuronal circuitry that controls even a single action requires understanding the integration of sensory feedback and executive commands. A far greater challenge is to understand the coordination of multiple actions. Here, we focus on brainstem circuits that drive rhythmic orofacial actions. We discuss three neural computational mechanisms that may enable circuits for different actions to operate without interfering with each other. We conclude with proposed experimental programs for delineating the neural control principles that have evolved to coordinate orofacial behaviors.

Neural control of the mammalian face and mouth

It has long been postulated that there is a hierarchical control structure for motor acts in the nervous system [1,2]. Individual motor actions or primitives [3] can be executed singly or arranged in nested groups to form more complex behaviors. The nature of the interactions among the neural circuits that generate these actions and behaviors has been a topic of long-standing interest to neuroscientists. Interactions between different actions are unavoidable in the mammalian face and mouth, which contain sophisticated motor plants that serve a variety of basic physiological functions. These functions include breathing, nutrient ingestion, active sensation, and communication. Effective breathing, for example, requires orofacial movements that maintain upper airway patency [4], whereas nutrient ingestion requires chewing, licking, lapping, suckling, and swallowing. Sensory exploration also involves licking and chewing for taste, as well as fast breathing, or sniffing, for smell. In rodents, whisking of the mystacial vibrissae is used for touch [5,6]. In humans and some other mammalian species, specialized orofacial movements produce vocalizations or speech. These actions, which are central to mammalian life, must be coordinated with a high degree of precision to prevent blockages of the airway and other maladaptive interactions. For example, the feeding process (eating, drinking, and swallowing) involves spatiotemporally coordinated activities of more than 26 pairs of muscles and five cranial nerves to ensure proper breakdown of food, transfer of food or liquid bolus, and safe swallowing [7]. Consistent with the notion that such precise coordination represents a computationally demanding function of the nervous system, defects in orofacial coordination are prominent symptoms of many neurological and neurodegenerative diseases. In Parkinson's disease for example, impaired coordination of breathing and swallowing contributes to dysphagia (e.g., difficulty in swallowing) and respiratory impairment [8,9], which form the leading cause of aspiration pneumonia and death in these patients [10].

How does the nervous system coordinate the activities of different orofacial actions such as chewing, swallowing, and breathing? To answer this question it is first important to note that many mammalian orofacial behaviors involve periodic, or rhythmic movement. In fact rhythmicity characterizes some of the most basic, evolutionarily conserved types of movements, such as respiration, digestion, and many forms of locomotion. Considerable insight into the general problem of coordination among different rhythmic movements is addressed in the pioneering work of von Holst, which surveys the different types of coordinated fin movements in swimming teleost fish [11]. Like swimming, basic rhythmic orofacial movements are thought to depend on the presence of central pattern generators (CPGs), which could be implemented by small networks of neurons in the brainstem. In this review, we evaluate evidence for three possible mechanisms by which coordination both within and among orofacial actions can occur: (i) local interactions between potentially co-active circuits (CPGs) ensure their coordination; (ii) a central executive command system arbitrates the execution and amplitude of different actions; and (iii) peripheral feedback ensures the appropriate timing between different muscle groups (Figure 1). We believe studies of the brainstem may teach us general lessons about how nervous

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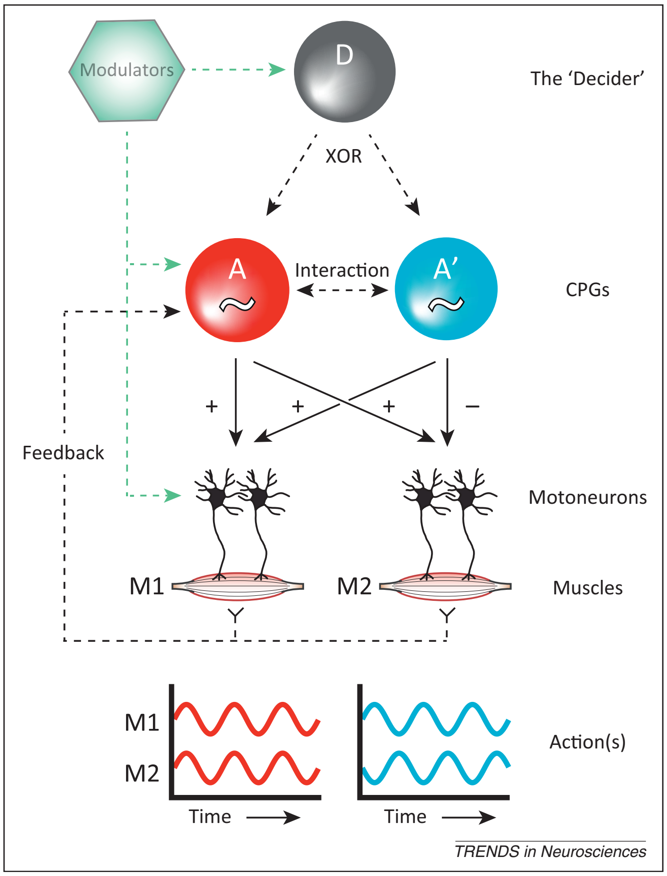


Figure 1. Schematic of the possible circuit arrangements for execution of different actions using a shared motor plant. Muscles M1 and M2 can both be used in different temporal patterns in two different actions, A and A′. Possible circuit interactions include: (1) CPGs interact and coordinate with each other; (2) higher-order centers (D) gate, or select separate CPGs; and (3) peripheral feedback into a CPG alters the phase relation between the muscles. Additionally, neuromodulators may act on either the CPGs themselves or their outputs to affect their frequency or amplitude. CPG, central pattern generator.

systems deal with computations that can be performed autonomously but then must interact at times.

Coordination of orofacial behaviors with breathing

Orofacial behaviors typically involve functions that affect the upper airway and therefore must be coordinated with breathing. The nature of this coordination constrains the organization of the neural circuits that control these behaviors. Rhythmic ingestive behaviors occur at frequencies that are faster than the 1–2 Hz frequency of basal respiration in rats. Chewing and mature suckling movements occur at ~4 Hz [12], and rhythmic licking at 5–7 Hz [13]. Rhythmic activities in the trigeminal (V), facial (VII), hypoglossal (XII), and respiratory (cervical) nerve rootlets can be elicited via bath application of NMDA in isolated brainstem preparations, suggesting that the brainstem alone is sufficient to generate rhythmic orofacial actions [14,15]. For such preparations, it has further been proposed that the slower breathing rhythm can reset the phase of the faster licking/suckling rhythm [15] (Figure 2A). Indeed, in behaving animals it appears that rhythmic licking and breathing are coordinated despite the difference in their frequencies [16] (Figure 2B).

With regards to rhythmic exploratory behaviors, whisking and sniffing have similar frequencies of 5–10 Hz and have been reported to occur in a phase-locked, one-to-one manner in rodents. Specifically, inspiration during sniffing is synchronous with vibrissa protraction, as first described by Welker in rats [5]. These behaviors involve the use of common muscles in the snout [4,17], and their robust one-to-one coordination suggests that they might depend on a common rhythm generator. Since Welker's initial qualitative observations, synchronous sniffing and whisking has been more completely described [18,19] and quantified [20,21] in several subsequent studies in rats. There is also evidence that high-frequency sniffing and whisking are phase locked in mice [20]; however, one study reported a lack of such coordination in this species [22]. Nonetheless, all of the recent studies of whisking behavior have found that whisking, like licking, can also occur during basal respiration [20–22]. The separable timing of the whisking and basal breathing motor outputs indicates that these actions are paced by separate rhythm generators (Figure 2C). During basal respiration, the slow breathing rhythm resets the faster vibrissa protraction rhythm, whereas vibrissa retraction is controlled by the breathing rhythm directly. These results suggest a hierarchical organization in which the breathing rhythm influences the whisking rhythm but not vice versa [20]. This organization is consistent with the aforementioned results from isolated brainstem preparations that elicit rhythmic hypoglossal outputs [14,15]. However, it remains to be determined whether this hierarchical organization extends to other orofacial behaviors in behaving animals.

Although breathing may exert an influence over some orofacial rhythms, transient events may call for a temporary cessation of breathing that over-rides the importance of supplying the body with oxygen. For example, noxious stimuli that may damage the airway can trigger a cessation of breathing and a corresponding pause of the respiratory patterning elements in the medulla [23]. Similarly, swallowing triggers a closure of the epiglottis to prevent clogging of the airway, and it appears to modify respiratory and chewing motor outputs [24,25] (Figure 2D). This hierarchical control between swallowing, breathing, sniffing, chewing, licking, and whisking must be reflected in the interactions among the neural circuits that generate these actions. Thus, we now turn our discussion to these putative brainstem neural circuits.

CPGs for breathing, chewing, licking, and swallowing in the brainstem

A CPG is operationally defined as a small network of neurons, or even a single neuron, whose activity can generate specific movements with correct timing and sequences in the absence of sensory feedback [26,27]. Various studies have suggested brainstem central origins for rhythmic whisking, chewing, and licking. Whisking, for example, can be generated in the absence of olfactory or trigeminal sensory input, and also after removal of the cortex [5,18,28,29]. Similarly, chewing [30,31], licking [32,33], and breathing [34] can occur without proprioceptive feedback, and without descending input from the cortex [35]. The major circuits that underlie the generation of rhythmic orofacial actions, including their putative CPGs, are thought to be located in the pons and medulla

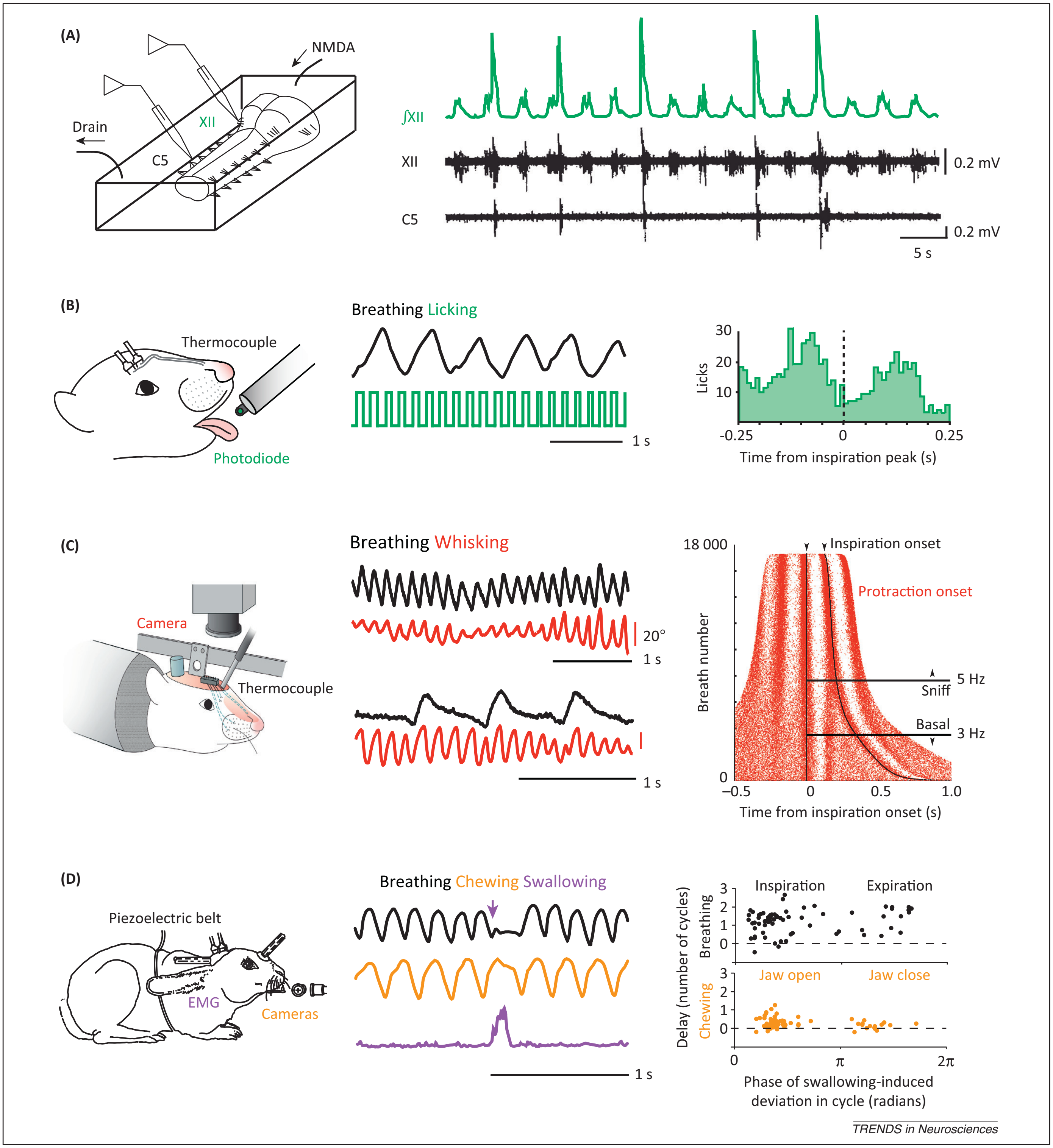


Figure 2. Coordination between breathing and other rhythmic orofacial actions. **(A)** An isolated brainstem preparation in which rhythmic bursts of fictive motor activity were induced via bath application of NMDA (left). Hypoglossal and phrenic motor outputs were monitored electrophysiologically via the XIIth cranial rootlet and the Vth cervical rootlet, respectively (black traces, right). The integrated activity of the XIIth rootlet is shown in green. Phrenic bursts are reported to reset the phase of the faster hypoglossal rhythm. Adapted from [15,121]. **(B)** Simultaneous monitoring of licking (green) and breathing (black) in an alert rat (left and middle) shows that the actions are coordinated (right). The occurrence of a lick is dependent on the phase of the respiratory cycle. Adapted from [16]. **(C)** Simultaneous monitoring of whisking (red) and breathing (black) in an alert rat (left and middle) show that the actions are coordinated (right). Protraction and inspiration are upward. Inspiration is synchronous with protraction on each cycle (top middle) during sniffing but only with a fraction of the cycles during basal respiration (bottom middle), as intervening whisks occur. Rasters of inspiration onset (black) and protraction onset (red) times relative to inspiration onset for individual breaths are ordered by the duration of the breath (right). At high respiratory rates, whisking and breathing show a 1:1 temporal relationship, while at lower breathing rates there are additional, intervening whisks between each breath. Adapted from [20]. **(D)** Simultaneous monitoring of chewing (orange), swallowing (purple), and breathing (black) in an alert rabbit (left and middle) reveal the nature of their coordination. Although breathing and chewing appear to be asynchronous, swallowing affects both rhythms. The occurrence of a swallowing movement delays subsequent breathing and chewing cycles. Adapted from [25].

of the brainstem. These regions contain both the primary sensory input nuclei (Figure 3A) and the final motor output nuclei (Figure 3B). Detailed descriptions of the main functions of the cranial motor nuclei (V, VII, IX, X, and XII) in driving each of the different orofacial behaviors are provided in Box 1.

Locations of CPGs for breathing

The best-characterized brainstem CPG in the mammalian nervous system is the circuitry in the ventral respiratory column that controls breathing [36,37]. The core neural circuitry that paces rhythmic breathing is located in the pre-Bötzinger complex (pre-BötC), a small region in the medulla ventral to the nucleus ambiguus. Specific populations of glutamatergic cells in the pre-BötC are both sufficient [38,39] and necessary [40,41] to generate the inspiratory rhythm. The pre-BötC is interconnected with the parafacial respiratory group (pFRG); a region that has been shown to control active expiration [42,43] (Figure 3C). Sniffing is part of the normal breathing behavior, therefore, it is presumed that pre-BötC also participates in the generation of sniffing [20], although the exact circuit mechanism by which the higher frequencies for sniffing are generated remains unknown [19]. Similarly, the pre-BötC is likely to be the key CPG for upper airway control during breathing, and is also involved in other breathing-related rhythms such as gasping and sighing [44–46]. These different respiratory patterns are likely to involve different neuromodulatory influences [44] (Figure 1).

In principle, for rhythmic movements, there could be a separate central rhythm generator (CRG) that works as a clock, and downstream pattern generators that orchestrate the periodic motor sequences based on input from the clock. Such CPG architectures have been proposed for both breathing and locomotion [47–49]. For breathing, it is thought that neurons in the pre-BötC generate the rhythm and neurons in the ventral respiratory group drive the appropriate pools of spinal motoneurons (Figure 3C). However, it has recently been proposed that the pre-BötC itself contains both rhythm- and pattern-generating elements (i.e., a separate CRG and CPG) [50]. According to this proposal, the pre-BötC generates an internal time-keeping reference oscillation that can then be subdivided to generate the fundamental respiratory drive signal. There is anatomical and physiological evidence to suggest that the respiratory drive signal is then 'broadcast' to multiple CPG elements further downstream [51,52].

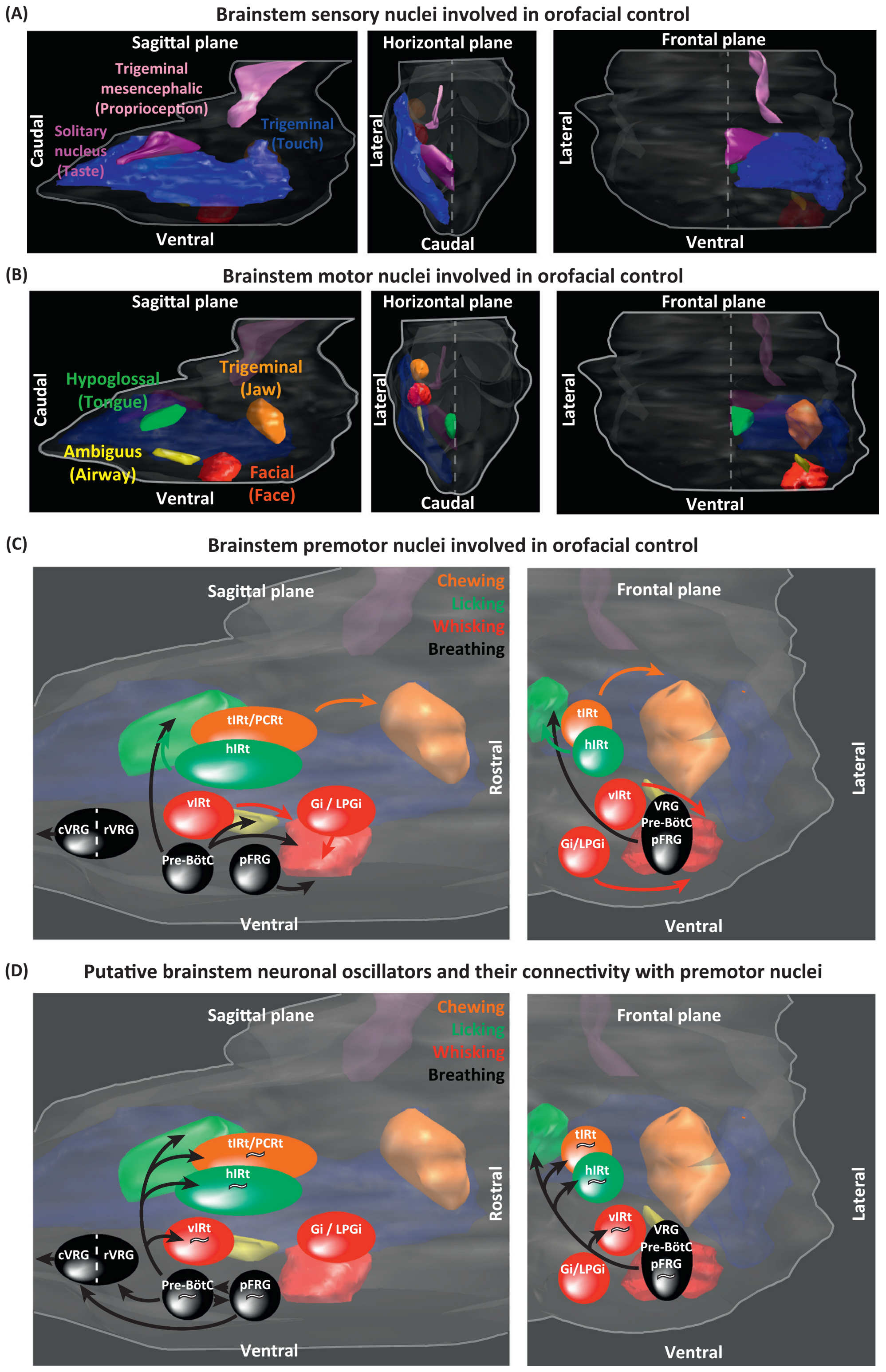
Putative locations of the CPGs for ingestive and exploratory orofacial behaviors

As a starting point to identify the specific neuronal components of orofacial CPGs, there have been many efforts to survey 'pre-motor' interneurons that project to motoneurons in different cranial motor nuclei. Early studies involved injecting classic retrograde neural tracers into cranial motor nuclei to label neurons projecting directly to those nuclei [53,54]. Later, replication-competent pseudorabies or rabies viruses were injected into muscles of interest, and as the viruses spread retrogradely across synapses, they labeled both pre-motoneurons and neurons oligosynaptically connected with motoneurons [55,56]. Most recently, the use of glycoprotein-deleted deficient rabies viruses (ΔG-rabies) in combination with genetic complementation has enabled the selective identification of vibrissa, jaw, and tongue pre-motoneurons [57,58]. In contrast to earlier techniques, this use of ΔG-rabies allows for trans-synaptic retrograde labeling of only pre-motoneurons via intramuscular injection. These tracing studies have identified locations of various orofacial pre-motoneurons in the brainstem (Figure 3C). Details of the anatomical locations of key groups of putative pre-motoneurons are summarized in Box 2.

The locations of pre-motoneurons arising from these tracing studies have been used to guide functional observational and manipulation studies to identify orofacial CPGs. Using fictive rhythmic chewing preparations in guinea pigs, it was suspected that the minimal pattern-generating circuitry for mastication included the reticular formation between the rostral extent of the V nucleus and the caudal extend of the VII nucleus [59,60]. This work led to the hypothesis that chewing involves a CRG in the oral division of the medial gigantocellular reticular formation (Gi/GcO) that provides input to a more caudal CPG region in the parvocellular reticular formation (PCRt) to coordinate the timing between jaw opening and jaw closing [61]. Other experiments demonstrate that neurons in the dorsal principal trigeminal nucleus (dPrV) burst rhythmically during fictive chewing in anesthetized and paralyzed rabbits [62] and raised the possibility that the chewing CPG is in the dPrV [63]. In contrast to both these possibilities, a more recent study by Travers and colleagues demonstrated that inactivation of the PCRt and the intermediate reticular formation (IRt) between the VII and XII nuclei diminishes chewing activity and food intake in alert rats, whereas injections into Gi/GcO had no effect [64]. This study suggests the alternative possibility that the chewing CPG may be located more caudally in the medulla, and that the role of Gi/GcO may be to relay cortical commands to this medullary CPG rather than to generate the chewing rhythm itself (Figure 3D). Nonetheless, differentiating between these hypotheses will require manipulations that demonstrate sufficiency and necessity of these various regions in alert, behaving animals.

Like chewing, rhythmic licking involves centrally generated, coordinated actions of the jaw opener, tongue protruder, and tongue retractor muscles [13,65]. Interneurons that are presynaptic to XII motoneurons are concentrated in the IRt. This region is dorsomedial to the pre-BötC and ventrolateral to the XII motor nucleus [52,66]. Extracellular recording found that the spiking activity of units in this region is phase-locked to rhythmic licking [67], and infusion of an inhibitory agonist into the IRt between the VII and XII nuclei blocks licking [68]. Furthermore, injection of a μ-opioid agonist in the same region alters the frequency of licking [69]. Thus the CPG for licking, and possibly the CRG as well, is thought to be located in the IRt (Figure 3D). This region overlaps with the IRt region necessary for chewing, consistent with the fact that both behaviors require coordinated jaw and tongue movements.

In addition to its role in the control of ingestive orofacial movements, the IRt has been implicated in exploratory movement. A recent study provides experimental evidence



TRENDS in Neurosciences

Figure 3. Anatomy of neural circuits involved in generating and coordinating orofacial actions. **(A)** 3D reconstruction of the pons and medulla, which contain regions that receive primary somatosensory inputs. Cutaneous inputs from the face innervate the trigeminal sensory nuclei (blue). Proprioceptive innervation of the jaw muscles arises from cells in the trigeminal mesencephalic nucleus (pink). Gustatory inputs from the tongue innervate the solitary nucleus (NTS). The structure is shown in the sagittal (left), horizontal (middle) and frontal (right) planes. Light transparent structures correspond to the motor nuclei in B. **(B)** The same reconstruction as in A, showing the pools of cranial motoneurons that control the jaws (orange), face (red), airway (yellow), and tongue (green). Conventions are as in A. Light transparent structures correspond to the sensory nuclei in A. **(C)** The same reconstruction as in A and B, showing the approximate locations of known pre-motor nuclei to each of the motoneuron pools in A. Pre-motor nuclei are color coded according to the primary motor nucleus that they innervate. The brainstem is shown in the sagittal (left) and frontal (right) planes. Breathing-related regions are shown in black. **(D)** The same reconstruction as A–C, highlighting the locations of the putative neuronal oscillators (marked as ~) that generate breathing (black), whisking (red), licking (green), and chewing (orange). Conventions are as in A–C. The location of the chewing oscillator remains unresolved. Abbreviations: cVRG, caudal ventral respiratory group; dPrV, dorsal principal trigeminal nucleus; Gi, gigantocellular reticular formation; hIRt, hypoglossal intermediate reticular formation; LPGi, lateral paragigantocellular reticular formation; PCRt, parvocellular reticular formation; pFRG, parafacial respiratory group; Pre-BötC, pre-Bötzinger complex; rVRG, rostral ventral respiratory group; tIRt, trigeminal intermediate reticular formation; vIRt, vibrissa intermediate reticular formation.

Box 1. Anatomy of the brainstem sensory neurons, motoneurons, and general sensory feedback circuits

Vth ganglion (VG): contains trigeminal sensory neurons that detect and transmit somatosensory stimuli from the face and mouth to the brainstem. Neurons in the VG have extensive collateral projections to the brainstem trigeminal complex that span the entire rostral–caudal axis of the hindbrain (Figure 3A).

Trigeminal mesencephalic nucleus (Vmes): contains proprioceptive sensory neurons that innervate muscle spindles of the jaw muscles as well as periodontal ligaments (Figure 3A). Vmes neurons project directly to cranial motoneurons (mainly trigeminal) to provide monosynaptic proprioceptive feedback to these motoneurons.

Brainstem trigeminal complex: receives VG sensory inputs (blue-shaded area in Figure 3A in main text). This complex has traditionally been divided into four subnuclei: caudalis (SpC), interpolaris (SpI), oralis (SpO), and principalis (PrV). Subpopulations of neurons within each of the four subnuclei are believed to relay the sensory feedback information onto motoneurons [57,58,109].

Nucleus tractus solitarii (**NTS**, or solitary nucleus): receives inputs from taste-related sensory afferents (Figure 3A). Interneurons in NTS relay taste information to the hypoglossal (XII) nucleus, as well as to the medullary reticular formation, to regulate reflexive oromotor behaviors [122,123].

Motoneurons that control orofacial behaviors are located in four main nuclei: the trigeminal (V), facial (VII), ambiguus (NA, which give rise to IXth and Xth cranial nerves), and hypoglossal (XII) motor nuclei that span the pons and medulla (Figure 3B).

V motoneurons innervate jaw muscles, such as the masseter, that break down food during chewing.

VII motoneurons control multiple groups of muscles on the face, including muscles that drive whisking and sniffing actions [124].

XII motoneurons innervate tongue muscles such as those used for licking.

NA motoneurons supply muscles involved in swallowing and vocalization (through the IXth and Xth cranial nerve).

Box 2. Summary of the locations of brainstem pre-motoneurons and their target motoneurons

Intermediate reticular formation (IRt) contains large numbers of putative pre-motoneurons for different cranial motoneuron pools, with neurons at different dorsal–ventral and rostral–caudal positions in the IRt providing inputs to different motoneurons [53,54,57,58] (Figure 3C).

Pre-Bötzinger (pre-BötC), Bötzinger complex, parafacial respiratory group (pFRG) contain a small number of neurons presynaptic to VII and XII motoneurons [20,52,57] (Figure 3C).

Parvocellular reticular formation (PCRt), as well as the caudally located medullary reticular formation, contains pre-motoneurons for different cranial motoneuron pools. In particular, a large number of neurons in the rostral PCRt were found to be presynaptic to V motoneurons [56] (Figure 3C).

Gigantocellular (Gi) and lateral paragigantocellular (LPGi) reticular formation was reported to contain sparsely labeled pre-motoneurons for V, VII, and XII motoneurons in various tracing studies (Figure 3C).

Other sources of pre-motor inputs not shown in Figure 3C: Pre-motoneurons were observed in nuclei receiving the corresponding sensory afferent inputs, that is, in Vmes, NTS, the brainstem trigeminal complex. All motoneurons receive varying extents of inputs from the superior colliculus, the Kolliker–Fuse and/or parabrachial area, and the midbrain reticular formation near the red nucleus. The motor cortex provides limited and sparse direct presynaptic inputs onto cranial motoneurons [57,106], with the exception of the vocal motoneurons, located in the ambiguus nucleus, which may receive more extensive direct cortical inputs [125].

that the CPG for whisking is located in the ventral part of the IRt (vIRt) near the nucleus ambiguus and dorsal–medial to the pre-BötC [20] (Figure 3D). Units in this region phase-lock to rhythmic whisking, are necessary for its production, and project to the VII motoneurons that control vibrissa protraction. Local application of a glutamatergic agonist near this region produces sustained rhythmic bursts of spikes in the vIRt and corresponding phase-locked rhythmic vibrissa movements. All told, it appears that the brainstem contains CPGs for breathing, chewing, suckling, licking, swallowing, and whisking, with one on each side (left and right sides), a total of ten CPGs, located within or near regions of the medullary IRt. How these CPGs interact to coordinate various orofacial behaviors is considered below.

The ‘breathing primacy’ hypothesis for coordinating multiple orofacial actions

It is likely, as noted above, that there is a hierarchical control structure that ensures that orofacial behaviors do not interfere with each other. One possibility is that many of these actions are paced by the breathing CPG. Indeed, the whisking [20] and licking rhythms [14,15] appear to be similarly reset by the breathing rhythm (Figure 2A–C); however, the case of chewing remains equivocal in this respect [25]. What is the neural circuit basis for such interactions between rhythmic actions? We note that breathing is robustly represented throughout the medulla [36] near the sensory, motor, and pre-motor pattern generating nuclei for these other actions (Figure 3C,D). The pre-BötC has widespread projections throughout the medulla – these include extensive projections through the IRt where the putative CPGs for other orofacial rhythmic movements are located [20,52], and even directly to the VII [57] and XII motor nuclei themselves. In particular, the projections of somatostatin (sst) expressing neurons in the pre-BötC have been mapped using AAV viral vectors that express GFP under the control of the sst promoter [51]. These specific pre-BötC neurons, which are known to be part of the respiratory CPG network [40,70], also have extensive collateral arborizations in the IRt as they extend dorsomedially towards the XII nucleus. Other work shows that pre-BötC-generated rhythmic inspiratory drive directly modulates the activities of XII motoneurons and interneurons directly presynaptic to XII motoneurons (pre-motoneurons) [52,71,72], again suggesting that breathing paces other orofacial rhythms. In fact, in the *in vitro* isolated brainstem preparation, at resting stage, the rhythmic respiratory activities (1 Hz) in the V, VII, and XII nerve rootlets can be recorded [15,73], whereas faster rhythmic activities appear only after the application of NMDA [15].

Is breathing at the top of the hierarchy of control? The argument against this idea notices those instances in which normal breathing may be interrupted by more immediately critical influences, such as swallowing [25,74,75] (Figure 2D) and sighing [45]. Indeed, when the breathing CPG is inhibited following the occurrence of these activities, motoneurons are gated off and breathing movements are suppressed. However, sighing and swallowing events are pegged to the preceding respiratory cycle [25,75,76]; at least in the presence of normal inhibitory synaptic transmission [45], and it is unknown whether rhythm-generating mechanisms internal to the pre-BötC continue under conditions in which respiratory output is suppressed [50]. Thus, a more detailed and accurate understanding of breathing rhythm and pattern generators is needed to determine the nature of these apparent interdependencies. It will be exciting to examine the connectivity and functional interactions between pre-BötC and other orofacial CPGs.

Interactions among nonrespiratory CPGs and multifunctional neurons

Taking a page from the vertebrate and invertebrate locomotion CPGs, in which the left and right CPGs of the same segment, as well as the CPGs between different segments, have reciprocal connections and thus interact to coordinate different muscles during locomotion, it is conceivable that the different nonrespiratory orofacial CPGs also interact to coordinate oromotor activities. The simplest form of interaction is bilateral synchrony as seen in chewing, which is known to be dependent on commissural axons crossing the midline [60], suggesting that the equivalent CPGs on the two sides might interact through midline crossing axons in a manner similar to the interaction of the breathing CPGs [41].

Is there evidence supporting the interactions of CPGs for the more intricate coordination of multiple groups of muscles such as those observed for feeding behaviors? For example, during rhythmic chewing of food, the tongue positions food between the surfaces of the teeth, while the jaw moves the teeth to break down the food; hence the jaw and tongue move at the same frequency. The tongue-protruding muscle and the jaw-opening muscle are generally active at the same phase in the chewing cycle, but the activities of the tongue-retracting and the jaw-closing muscles are active at the opposing phase (so one does not bite one's own tongue). It is thought that the CPGs controlling tongue motoneurons (XII) and the CPGs controlling jaw motoneurons (V) interact with each other in a sophisticated manner to coactivate the synergistic muscle groups while reciprocally inhibiting the antagonistic muscle groups. However, this remains an untested hypothesis, because the precise neuronal populations comprising the different CPGs remain largely unknown.

Nonetheless, there is anatomical and physiological evidence to support the existence of neurons that take part in multiple orofacial CPGs. As described above, many labeled pre-motoneurons are distributed rostrocaudally through the IRt and PCRt where CPGs for different orofacial actions are thought to reside [77] (Figure 3C). Injecting different retrograde tracers into two different orofacial motor nuclei suggests the existence of IRt neurons projecting to both motor groups [53,78–80]. A recent monosynaptic rabies-mediated tracing study further shows that pre-motoneurons innervating tongue-protruding motoneurons simultaneously innervate jaw-opening and lip-lowing motoneurons [58], confirming the presence of interneurons with appropriate multi-motor targets. Chronic neuronal recording studies in the brainstem reticular formation also discovered multifunctional neurons, for example, neurons showing responses during both swallowing and vocalization [81] or neurons responding during respiration, vocalization, and swallowing [82]. Likewise, some neurons located laterally to the XII motor nucleus were found to be active during both masticatory movements and swallowing [83]. A large proportion of neurons in the caudal IRt, as well as some within the XII motor nucleus, are responsive during both licking and swallowing, and subsets of them also show activities associated with gape responses [67,84]. Together, the anatomical and electrophysiological studies suggest chewing, licking, swallowing, and gaping may share neural substrates in brainstem. These studies raise the possibility that multifunctional CPGs control multiple orofacial actions; or alternatively, that different CPGs may recruit different populations of multi-target pre-motoneurons to coordinate the activities of different motoneurons [58].

Regulation of orofacial behaviors by higher-order brain regions

Top-down activation of orofacial actions

Although the pattern-generating circuits for chewing, licking, sniffing, and whisking are located in the brainstem, their activity is most likely gated by higher-order brain regions, including the cortex, cerebellum, basal ganglia, and superior colliculus. In support of this idea, stimulation of a region now called the cortical masticatory area produces rhythmic, coordinated jaw–tongue movements that occur at a fixed frequency of 4 Hz irrespective of the stimulation frequency [85]. These fictive chewing movements appear to be similar to the temporal sequences of jaw and tongue muscle activation during natural chewing and do not depend on sensory feedback. Likewise, rhythmic whisking [86] can be activated by electrical stimulation of the motor cortex, and tongue protrusions during rhythmic licking are dependent on frontal cortical areas in a sensory detection task in which mice were trained to lick for a reward [87]. Cortical outputs from these regions project directly to the pons and medulla near where the rhythm and pattern-generating elements are located [57,66,88–90].

In addition to the cortex, the cerebellum and basal ganglia also activate and modulate some orofacial actions. For example, stimulation of the deep cerebellar nuclei in monkeys results in tongue movement [91]. Removal of the cerebellum results in slightly slower licking rates in rodents but does not appear to affect the generation of either rhythmic licking [92] or coordinated whisking and sniffing [18]. Together with observations that the deep cerebellar nuclei project to orofacial-related regions of the medullary reticular formation and spike in phase with licking [93], these results suggest that the cerebellum plays a role in modulating rather than patterning orofacial behaviors. Similarly, inputs from the basal ganglia have been shown to influence chewing and licking either directly or through the superior colliculus, or through both [94]. Pharmacological manipulations of basal-ganglia circuitry [95] or dopamine receptors [96] can induce rhythmic jaw movements in anesthetized rodents. Dopaminergic activation of jaw movements depends on the superior colliculus, whereas electrical stimulation of cortex does not, and it has been proposed that the basal ganglia may play a specific role in arbitrating between different orofacial actions [97] (Figure 1). All told, there appear to be multiple independent pathways to activate brainstem CPGs.

Top-down control of movement amplitude

There is evidence from multiple behaviors to suggest that in addition to activating brainstem CPGs for orofacial behaviors, the central nervous system has control over the amplitude of the movements that is independent of the rhythm-generating circuitry. Behavioral evidence suggests that rats modulate the range of whisking on slower time scales than the oscillatory rhythm, analogous to the separate control of frequency and amplitude in AM radio [98]. Endocannabinoid agonists and antagonists affect the range of whisking without affecting the frequency [99], and spiking activity in primary motor cortex preferentially reports this slowly varying component [98,100,101]. Serotonergic and other modulatory inputs may also serve to control the amplitude of whisking [102–104] (Figure 1). Similarly, the generation of the licking rhythm is independent of the amplitude of tongue-muscle contractions [65,66], and regulation of tonic jaw-force has been shown to depend on inputs from the cerebellum [105]. Together, the results suggest that control of rhythmic orofacial behaviors may involve the combination of a fast oscillatory drive signal controlled by a brainstem CRG, and slower amplitude and set-point modulation controlled by one or more independent mechanisms. These inputs may converge on brainstem motoneurons or on specific pre-motoneurons, such as those located outside the CPG, and those in the superior colliculus [57,93,106,107].

Role of sensation in orofacial actions

Although basic rhythmic motor patterns are controlled by CPGs, they can be modulated or even initiated by external stimuli. Sensory inputs can mediate reflexive motor outputs. More than 20 types of monosynaptic and oligosynaptic orofacial reflexes have been identified and studied [108]. These hard-wired circuits allow sensory inputs to coordinate the actions of multiple muscles to produce stereotyped behaviors, and thus constitute the lowest level of orofacial control.

Let us first consider whisking. At a reflex level, vibrissa contact with an object activates a brainstem-mediated positive feedback circuit, causing the vibrissa to follow through with the whisk and apply pressure to activate mechanoreceptors [109]. On longer time scales, contact can cause a decrease in vibrissa velocity to increase the time in which the vibrissa remains in contact with the object [110]. These vibrissa reflexes may serve to enhance the ability of the animal to identify and characterize external tactile stimuli in the environment.

Let us next consider the swallowing process. Through the movements of jaw and tongue muscles, a food or liquid bolus is formed and then transferred to the back of the mouth to reach the pharynx. The pharyngeal muscles transport the bolus further down to the esophagus, and at the same time laryngeal muscles close the airway. Finally, laryngeal muscles carry out peristaltic transport of the bolus through the esophagus. During these processes, different muscles are activated in a sequential manner [75,111–113]. Sequential activation of different sensory afferents by the moving food bolus can trigger sequential sensorimotor reflexes, which are thought to play an important role in the transitions between the different ingestive motor patterns. In addition to sensory-triggered reflexes, the rates and patterns of jaw and tongue movement depend on trigeminal sensory feedback [114], which reports the qualities of the food or liquid being ingested [13,115]. This modulation is thought to be mediated by primary sensory proprioceptors in Vmes, which monitor resistance to the force applied by the jaw [116].

In contrast to primary sensory neurons, we have only begun to discover which interneurons in the brainstem mediate sensory modulation of orofacial motor activities. Recently, several groups of vibrissa pre-motoneurons in the brainstem trigeminal complex were identified using deficient rabies-mediated monosynaptic tracing [57]. These neurons likely receive direct sensory inputs and thus are candidates to mediate various disynaptic sensory input–interneuron–motoneuron circuits that may modulate whisking, for example, foveal whisking and whisking reflexes. It is important to note, however, that sensory modulation of rhythmic behaviors need not necessarily be disynaptic. For example, neurons located in Gi and LPGi (Figure 3C) are known to respond to sensory stimuli even though sensory afferents do not directly project to these regions. Furthermore, many motor cortical neurons were found to project to these regions in various tracing experiments [57,61,90] and therefore these neurons are candidates for integrating both top-down and sensory inputs.

Concluding remarks and future directions

Orofacial actions and behaviors are mediated by several specific circuits in the brainstem. The common features of these circuits suggest some tantalizing organizational principles of the brainstem jungle of neural networks. Specifically, the brainstem reticular formation, and in particular the IRt, appears to contain CPGs and multifunctional neurons for various orofacial movements. Nonetheless, conclusive evidence for the exact locations and cell types comprising CPGs and CRGs and for most of the orofacial movements is still lacking. Future studies that can identify such cell populations will provide a window into some of the most robust and fundamental computations performed in the nervous system.

We began by proposing three candidate computational mechanisms that could underlie the coordination among different orofacial actions (Figure 1), and presented evidence that the brainstem neural circuits mediating these actions use each of these mechanisms in some form or another. However, much work is needed to clarify the specific populations of cells that carry out these functions. The respiratory CPG that comprises neurons in the pre-BötC makes extensive projections throughout the IRt and could mediate resetting of rhythmic orofacial movements; however, direct anatomical and functional evidence for inputs from pre-BötC neurons to each group of CPG neurons for orofacial actions remains to be acquired. Another unsolved question is to identify key groups of neurons that mediate the gating and amplitude control of different orofacial actions. Specifically, how much of this regulation is mediated by such top-down versus lateral interations (Figure 1)? In the cases of whisking and chewing, neurons located in LPGi are good candidates to link motor cortical inputs to motoneurons and perhaps to pre-motor CPG neurons [57]. Precise functional manipulations of different pre-motoneuron and interneuron populations, such as LPGi, and examination of their synaptic inputs and outputs will help determine whether they are the 'gate keepers' for episodic orofacial movements. Finally, the details of sensory inputs that mediate feedback, feedforward, or reflex control of motoneuron activities, including the coordination of multiple groups of motoneurons in complex orofacial behaviors, are currently lacking. Modern genetic and circuit analysis tools will be crucial to the above studies. Evidence of particular groups of neurons with specific circuit functions is likely to come from studies in which molecularly defined cell populations in the medulla [117] can be targeted and manipulated *in vivo*. Such manipulations have already proven invaluable in parsing other motor circuits in the spinal cord [118–120].

The rich physiology of orofacial movements affords us the opportunity to delineate the various brainstem neural circuits that generate the diverse motor programs and coordinate motor sequences. Ultimately, such studies will lead to the identification of a set of generalizable neural modules for building motor control programs. Different basic motor actions can be created by assembling the defined basic modules using different configurations. We suggest that coordinated and complex behaviors can be generated by linking these basic actions into a hierarchy with a bus-like architecture in which signals from the breathing CPG in the pre-BötC are projected to different modules, including pre-motor nuclei that lie across the brainstem reticular formation (Figure 3D).

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References

1 Weiss, P. (1941) *Self-differentiation of the Basic Patterns of Coordination*, Williams & Wilkins
2 Tinbergen, N. (1951) *The Study of Instinct*, Clarendon Press, (Oxford)
3 Mussa–Ivaldi, F.A. and Bizzi, E. (2000) Motor learning through the combination of primitives. *Philos. Trans. R. Soc. Lond. B: Biol. Sci.* 355, 1755–1769
4 Sherrey, J.H. and Megirian, D. (1977) State dependence of upper airway respiratory motoneurons: functions of the cricothyroid and nasolabial muscles of the unanesthetized rat. *Electroencephalogr. Clin. Neurophysiol.* 43, 218–228
5 Welker, W.I. (1964) Analysis of sniffing of the albino rat. *Behaviour* 12, 223–244
6 Vincent, S.B. (1912) The function of the vibrissae in the behavior of the white rat. *Behav. Monogr.* 1, 7–81
7 Barlow, S.M. (2009) Central pattern generation involved in oral and respiratory control for feeding in the term infant. *Curr. Opin. Otolaryngol. Head Neck Surg.* 17, 187–193
8 Gross, R.D. *et al.* (2008) The coordination of breathing and swallowing in Parkinson's disease. *Dysphagia* 23, 136–145
9 Troche, M.S. *et al.* (2011) Respiratory-swallowing coordination and swallowing safety in patients with Parkinson's disease. *Dysphagia* 26, 218–224
10 Monteiro, L. *et al.* (2014) Swallowing impairment and pulmonary dysfunction in Parkinson's disease: the silent threats. *J. Neurol. Sci.* 339, 149–152
11 von Holst, E. (1939) Die relative koordination als phänomen und als methode zentralnervöser funktionsanalyse. *Erg. Physiol.* 42, 228–306
12 Westneat, M.W. and Hal, W.G. (1992) Ontogeny of feeding motor patterns in infant rats: an electromyographic analysis of suckling and chewing. *Behav. Neurosci.* 106, 539
13 Travers, J.B. and Norgren, R. (1986) Electromyographic analysis of the ingestion and rejection of sapid stimuli in the rat. *Behav. Neurosci.* 100, 544
14 Katakura, N. *et al.* (1995) NMDA-induced rhythmical activity in XII nerve of isolated CNS from newborn rats. *Neuroreport* 6, 601–604
15 Nakamura, Y. *et al.* (1999) Generation of rhythmical ingestive activities of the trigeminal, facial, and hypoglossal motoneurons in in vitro CNS preparations isolated from rats and mice. *J. Med. Dent. Sci.* 46, 63–73
16 Welzl, H. and Bures, J. (1977) Lick-synchronized breathing in rats. *Physiol. Behav.* 18, 751–753
17 Hill, D.N. *et al.* (2008) Biomechanics of the vibrissa motor plant in rat: rhythmic whisking consists of triphasic neuromuscular activity. *J. Neurosci.* 28, 3438–3455
18 Semba, K. and Komisaruk, B.R. (1984) Neural substrates of two different rhythmical vibrissal movements in the rat. *Neuroscience* 12, 761–774
19 Deschênes, M. *et al.* (2012) Sniffing and whisking in rodents. *Curr. Opin. Neurobiol.* 22, 243–250
20 Moore, J.D. *et al.* (2013) Hierarchy of orofacial rhythms revealed through whisking and breathing. *Nature* 497, 205–210
21 Ranade, S. *et al.* (2013) Multiple modes of phase locking between sniffing and whisking during active exploration. *J. Neurosci.* 33, 8250–8256
22 Cao, Y. *et al.* (2012) Dynamic correlation between whisking and breathing rhythms in mice. *J. Neurosci.* 32, 1653–1659
23 Lawson, E.E. *et al.* (1991) Respiratory neuronal activity during apnea and other breathing patterns induced by laryngeal stimulation. *J. Appl. Physiol. (1985)* 70, 2742–2749
24 Miller, F. and Sherrington, C. (1915) Some observations on the bucco-pharyngeal stage of reflex deglutition in the cat. *Exp. Physiol.* 9, 147–186
25 McFarland, D.H. and Lund, J.P. (1993) An investigation of the coupling between respiration, mastication, and swallowing in the awake rabbit. *J. Neurophysiol.* 69, 95–108
26 Rossignol, S. and Dubuc, R. (1994) Spinal pattern generation. *Curr. Opin. Neurobiol.* 4, 894–902
27 Kleinfeld, D. and Sompolinsky, H. (1988) Associative neural network model for the generation of temporal patterns: theory and application to central pattern generators. *Biophys. J.* 54, 1039–1051
28 Gao, P. *et al.* (2001) Vibrissa deaffentation and rodent whisking patterns: behavioral evidence for a central pattern generator. *J. Neurosci.* 21, 5374–5380
29 Berg, R.W. and Kleinfeld, D. (2003) Rhythmic whisking by rat: retraction as well as protraction of the vibrissae is under active muscular control. *J. Neurophysiol.* 89, 104–117
30 Goodwin, G.M. and Luschei, E.S. (1974) Effects of destroying spindle afferents from jaw muscles on mastication in monkeys. *J. Neurophysiol.* 37, 967–981
31 Enomoto, S. *et al.* (1987) The effects of cortical ablation on mastication in the rabbit. *Neurosci. Lett.* 82, 162–166
32 Jüch, P. *et al.* (1985) Peripheral influences on the central pattern-rhythm generator for tongue movements in the rat. *Arch. Oral Biol.* 30, 415–421
33 Grill, H.J. and Norgren, R. (1978) The taste reactivity test. II. Mimetic responses to gustatory stimuli in chronic thalamic and chronic decerebrate rats. *Brain Res.* 143, 281–297
34 von Euler, C. (1981) The contribution of sensory inputs to the pattern generation of breathing. *Can. J. Physiol. Pharmacol.* 59, 700–706
35 Lovick, T.A. (1972) The behavioural repertoire of precollicular decerebrate rats. *J. Physiol.* 226, 4P–6P
36 Smith, J.C. *et al.* (2009) Structural and functional architecture of respiratory networks in the mammalian brainstem. *Philos. Trans. R. Soc. Lond. B: Biol. Sci.* 364, 2577–2587
37 Feldman, J.L. and Del Negro, C.A. (2006) Looking for inspiration: new perspectives on respiratory rhythm. *Nat. Rev. Neurosci.* 7, 232–241
38 Smith, J.C. *et al.* (1991) Pre-Botzinger complex: a brainstem region that may generate respiratory rhythm in mammals. *Science* 254, 726–729

39 Janczewski, W.A. *et al.* (2013) Role of inhibition in respiratory pattern generation. *J. Neurosci.* 33, 5454–5465
40 Tan, W. *et al.* (2008) Silencing preBötzinger complex somatostatin-expressing neurons induces persistent apnea in awake rat. *Nat. Neurosci.* 11, 538–540
41 Bouvier, J. *et al.* (2010) Hindbrain interneurons and axon guidance signaling critical for breathing. *Nat. Neurosci.* 13, 1066–1074
42 Janczewski, W.A. and Feldman, J.L. (2006) Distinct rhythm generators for inspiration and expiration in the juvenile rat. *J. Physiol.* 570, 407–420
43 Pagliardini, S. *et al.* (2011) Active expiration induced by excitation of ventral medulla in adult anesthetized rats. *J. Neurosci.* 31, 2895–2905
44 Doi, A. and Ramirez, J.M. (2008) Neuromodulation and the orchestration of the respiratory rhythm. *Respir. Physiol. Neurobiol.* 164, 96–104
45 Lieske, S. *et al.* (2000) Reconfiguration of the neural network controlling multiple breathing patterns: eupnea, sighs and gasps. *Nat. Neurosci.* 3, 600–607
46 John, W.M.S. (1996) Medullary regions for neurogenesis of gasping: noeud vital or noeuds vitals? *J. Appl. Physiol.* 81, 1865–1877
47 Feldman, J. (1986) Neurophysiology of breathing in mammals. In *Handbook of Physiology, The Nervous System IV, Intrinsic Regulatory Systems of the Brain* (Bloom, F.E., ed.), pp. 463–524, Bethesda, American Physiological Society
48 Kiehn, O. (2006) Locomotor circuits in the mammalian spinal cord. *Annu. Rev. Neurosci.* 29, 279–306
49 Grillner, S. (2003) The motor infrastructure: from ion channels to neuronal networks. *Nat. Rev. Neurosci.* 4, 573–586
50 Kam, K. *et al.* (2013) Distinct inspiratory rhythm and pattern generating mechanisms in the preBötzinger complex. *J. Neurosci.* 33, 9235–9245
51 Tan, W. *et al.* (2010) Projections of preBötzinger complex neurons in adult rats. *J. Comp. Neurol.* 518, 1862–1878
52 Koizumi, H. *et al.* (2008) Functional imaging, spatial reconstruction, and biophysical analysis of a respiratory motor circuit isolated *in vitro*. *J. Neurosci.* 28, 2353–2365
53 Travers, J.B. *et al.* (2005) Neurotransmitter phenotypes of intermediate zone reticular formation projections to the motor trigeminal and hypoglossal nuclei in the rat. *J. Comp. Neurol.* 488, 28–47
54 Isokawa-Akesson, M. and Komisaruk, B.R. (1987) Difference in projections to the lateral and medial facial nucleus: anatomically separate pathways for rhythmical vibrissa movement in rats. *Exp. Brain Res.* 65, 385–398
55 Dobbins, E.G. and Feldman, J.L. (1995) Differential innervation of protruder and retractor muscles of the tongue in rat. *J. Comp. Neurol.* 357, 376–394
56 Fay, R.A. and Norgren, R. (1997) Identification of rat brainstem multisynaptic connections to the oral motor nuclei in the rat using pseudorabies virus. II. Facial muscle motor systems. *Brain Res. Rev.* 25, 276–290
57 Takatoh, J. *et al.* (2013) New modules are added to vibrissal premotor circuitry with the emergence of exploratory whisking. *Neuron* 77, 346–360
58 Stanek, E. *et al.* (2014) Monosynaptic premotor circuit tracing reveals neural substrates for oro-motor coordination. *ELife* http://dx.doi.org/10.7554/eLife.02511
59 Nozaki, S. *et al.* (1986) Location of central rhythm generator involved in cortically induced rhythmical masticatory jaw-opening movement in the guinea pig. *J. Neurophysiol.* 55, 806–825
60 Chandler, S.H. and Tal, M. (1986) The effects of brain stem transections on the neuronal networks responsible for rhythmical jaw muscle activity in the guinea pig. *J. Neurosci.* 6, 1831–1842
61 Nakamura, Y. and Katakura, N. (1995) Generation of masticatory rhythm in the brainstem. *Neurosci. Res.* 23, 1–19
62 Tsuboi, A. *et al.* (2003) Neurons of the trigeminal main sensory nucleus participate in the generation of rhythmic motor patterns. *Eur. J. Neurosci.* 17, 229–238
63 Kolta, A. *et al.* (2007) A review of burst generation by trigeminal main sensory neurons. *Arch. Oral Biol.* 52, 325–328
64 Travers, J.B. *et al.* (2010) Suppression of third ventricular NPY-elicited feeding following medullary reticular formation infusions of muscimol. *Behav. Neurosci.* 124, 225
65 Wiesenfeld, Z. *et al.* (1977) Licking behavior: evidence of hypoglossal oscillator. *Science* 196, 1122–1124
66 Travers, J.B. *et al.* (1997) Motor and premotor mechanisms of licking. *Neurosci. Biobehav. Rev.* 21, 631–647
67 Travers, J.B. *et al.* (2000) Medullary reticular formation activity during ingestion and rejection in the awake rat. *Exp. Brain Res.* 130, 78–92
68 Chen, Z. *et al.* (2001) Muscimol infusions in the brain stem reticular formation reversibly block ingestion in the awake rat. *Am. J. Physiol. Regul. Intergr. Comp. Physiol.* 280, R1085–R1094
69 Kinzeler, N.R. and Travers, S.P. (2011) μ-Opioid modulation in the rostral solitary nucleus and reticular formation alters taste reactivity: evidence for a suppressive effect on consummatory behavior. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 301, R690–R700
70 Stornetta, R.L. *et al.* (2003) A group of glutamatergic interneurons expressing high levels of both neurokinin-1 receptors and somatostatin identifies the region of the pre-Bötzinger complex. *J. Comp. Neurol.* 455, 499–512
71 Ono, T. *et al.* (1998) Modulation of the inspiratory-related activity of hypoglossal premotor neurons during ingestion and rejection in the decerebrate cat. *J. Neurophysiol.* 80, 48–58
72 Fukuda, Y. and Honda, Y. (1982) Differences in respiratory neural activities between vagal (superior laryngeal), hypoglossal, and phrenic nerves in the anesthetized rat. *Jpn. J. Physiol.* 32, 387–398
73 Koizumi, H. *et al.* (2002) Differential discharge patterns of rhythmical activity in trigeminal motoneurons during fictive mastication and respiration *in vitro*. *Brain Res. Bull.* 58, 129–133
74 Yamanishi, T. *et al.* (2010) Alpha-2 adrenoceptors coordinate swallowing and respiration. *J. Dent. Res.* 89, 258–263
75 Doty, R.W. and Bosma, J.F. (1956) An electromyographic analysis of reflex deglutition. *J. Neurophysiol.* 19, 44–60
76 Cherniack, N. *et al.* (1981) Characteristics and rate of occurrence of spontaneous and provoked augmented breaths. *Acta Physiol. Scand.* 111, 349–360
77 Travers, J.B. and Norgren, R. (1983) Afferent projections to the oral motor nuclei in the rat. *J. Comp. Neurol.* 220, 280–298
78 Amri, M. *et al.* (1990) Axonal branching of medullary swallowing neurons projecting on the trigeminal and hypoglossal motor nuclei: demonstration by electrophysiological and fluorescent double labeling techniques. *Exp. Brain Res.* 81, 384–390
79 Li, Y-Q. *et al.* (1993) Identification of premotor interneurons which project bilaterally to the trigeminal motor, facial or hypoglossal nuclei: a fluorescent retrograde double-labeling study in the rat. *Brain Res.* 611, 160–164
80 Popratiloff, A.S. *et al.* (2001) Hypoglossal and reticular interneurons involved in oro-facial coordination in the rat. *J. Comp. Neurol.* 433, 364–379
81 Chiao, G. *et al.* (1994) Neuronal activity in nucleus ambiguus during deglutition and vocalization in conscious monkeys. *Exp. Brain Res.* 100, 29–38
82 Larson, C.R. *et al.* (1994) Modification in activity of medullary respiratory-related neurons for vocalization and swallowing. *J. Neurophysiol.* 71, 2294–2304
83 Amri, M. *et al.* (1991) Effects of lingual nerve and chewing cortex stimulation upon activity of the swallowing neurons located in the region of the hypoglossal motor nucleus. *Brain Res.* 548, 149–155
84 Dinardo, L.A. and Travers, J.B. (1994) Hypoglossal neural activity during ingestion and rejection in the awake rat. *J. Neurophysiol.* 72, 1181–1191
85 Dellow, P. and Lund, J. (1971) Evidence for central timing of rhythmical mastication. *J. Physiol.* 215, 1–13
86 Haiss, F. and Schwarz, C. (2005) Spatial segregation of different modes of movement control in the whisker representation of rat primary motor cortex. *J. Neurosci.* 25, 1579–1587
87 Komiyama, T. *et al.* (2010) Learning-related fine-scale specificity imaged in motor cortex circuits of behaving mice. *Nature* 464, 1182–1186
88 Zhang, G. and Sasamoto, K. (1990) Projections of two separate cortical areas for rhythmical jaw movements in the rat. *Brain Res. Bull.* 24, 221–230
89 Valverde, F. (1962) Reticular formation of the albino rat's brain stem cytoarchitecture and corticofugal connections. *J. Comp. Neurol.* 119, 25–53

90 Hattox, A.M. *et al.* (2002) Functional circuitry involved in the regulation of whisker movements. *J. Comp. Neurol.* 442, 266–276
91 Bowman, J. and Aldes, L. (1980) Organization of the cerebellar tongue representation in the monkey. *Exp. Brain Res.* 39, 249–259
92 Bryant, J.L. *et al.* (2010) Cerebellar cortical output encodes temporal aspects of rhythmic licking movements and is necessary for normal licking frequency. *Eur. J. Neurosci.* 32, 41–52
93 Lu, L. *et al.* (2013) Medial cerebellar nuclear projections and activity patterns link cerebellar output to orofacial and respiratory behavior. *Front. Neural Circuits* 7, 56
94 Yasui, Y. *et al.* (1995) Demonstration of axon collateral projections from the substantia nigra pars reticulata to the superior colliculus and the parvicellular reticular formation in the rat. *Brain Res.* 674, 122–126
95 Nakamura, S. *et al.* (1990) Role of the basal ganglia in manifestation of rhythmical jaw movement in rats. *Brain Res.* 535, 335–338
96 Chandler, S.H. and Goldberg, L.J. (1984) Differentiation of the neural pathways mediating cortically induced and dopaminergic activation of the central pattern generator (CPG) for rhythmical jaw movements in the anesthetized guinea pig. *Brain Res.* 323, 297–301
97 Hikosaka, O. (2007) GABAergic output of the basal ganglia. *Prog. Brain Res.* 160, 209–226
98 Hill, D.N. *et al.* (2011) Primary motor cortex reports efferent control of vibrissa position on multiple time scales. *Neuron* 72, 344–356
99 Pietr, M.D. *et al.* (2010) Cannabinoids reveal separate controls for whisking amplitude and timing in rats. *J. Neurophysiol.* 104, 2532–2542
100 Friedman, W.A. *et al.* (2012) Vibrissae motor cortex unit activity during whisking. *J. Neurophysiol.* 107, 551–563
101 Gerdjikov, T.V. *et al.* (2013) Rhythmic whisking area (rw) in rat primary motor cortex: an internal monitor of movement-related signals? *J. Neurosci.* 33, 14193–14204
102 Hattox, A.M. *et al.* (2003) Serotonin regulates rhythmic whisking. *Neuron* 39, 343–352
103 VanderMaelen, C. and Aghajanian, G. (1980) Intracellular studies showing modulation of facial motoneurone excitability by serotonin. *Nature* 287, 346–347
104 Harish, O. and Golomb, D. (2010) Control of the firing patterns of vibrissa motoneurons by modulatory and phasic synaptic inputs: a modeling study. *J. Neurophysiol.* 103, 2684–2699
105 Larson, C.R. and Sutton, D. (1978) Effects of cerebellar lesions on monkey jaw-force control: implications for understanding ataxic dysarthria. *J. Speech Hear. Res.* 21, 309–323
106 Grinevich, V. *et al.* (2005) Monosynaptic pathway from rat vibrissa motor cortex to facial motor neurons revealed by lentivirus-based axonal tracing. *J. Neurosci.* 25, 8250–8258
107 Miyashita, E. and Shigemi, M. (1995) The superior colliculus relays signals descending from the vibrissal motor cortex to the facial nerve nucleus in the rat. *Neurosci. Lett.* 195, 69–71
108 Miller, A. (2002) Oral and pharyngeal reflexes in the mammalian nervous system: their diverse range in complexity and the pivotal role of the tongue. *Crit. Rev. Oral Biol. Med.* 13, 409–425
109 Nguyen, Q-T. and Kleinfeld, D. (2005) Positive feedback in a brainstem tactile sensorimotor loop. *Neuron* 45, 447–457
110 Grant, R.A. *et al.* (2009) Active touch sensing in the rat: anticipatory and regulatory control of whisker movements during surface exploration. *J. Neurophysiol.* 101, 862–874
111 Thexton, A.J. *et al.* (2007) Electromyographic activity during the reflex pharyngeal swallow in the pig: Doty and Bosma (1956) revisited. *J. Appl. Physiol.* 102, 587–600
112 German, R.Z. *et al.* (2009) Integration of the reflex pharyngeal swallow into rhythmic oral activity in a neurologically intact pig model. *J. Neurophysiol.* 102, 1017–1025
113 Yamada, Y. *et al.* (2005) Coordination of cranial motoneurons during mastication. *Respir. Physiol. Neurobiol.* 147, 177–189
114 Inoue, T. *et al.* (1989) Modifications of masticatory behavior after trigeminal deafferentation in the rabbit. *Exp. Brain Res.* 74, 579–591
115 Thexton, A. *et al.* (1980) Food consistency and bite size as regulators of jaw movement during feeding in the cat. *J. Neurophysiol.* 44, 456–474
116 Morimoto, T. *et al.* (1989) Sensory components facilitating jaw-closing muscle activities in the rabbit. *Exp. Brain Res.* 76, 424–440
117 Gray, P.A. (2013) Transcription factors define the neuroanatomical organization of the medullary reticular formation. *Front. Neuroanat.* 7, 7
118 Bui, T.V. *et al.* (2013) Circuits for grasping: spinal dI3 interneurons mediate cutaneous control of motor behavior. *Neuron* 78, 191–204
119 Hägglund, M. *et al.* (2013) Optogenetic dissection reveals multiple rhythmogenic modules underlying locomotion. *Proc. Natl. Acad. Sci. U.S.A.* 110, 11589–11594
120 Goulding, M. (2009) Circuits controlling vertebrate locomotion: moving in a new direction. *Nat. Rev. Neurosci.* 10, 507–518
121 Nakamura, Y. *et al.* (2004) Rhythm generation for food-ingestive movements. *Prog. Brain Res.* 143, 97–103
122 Halsell, C. *et al.* (1996) Ascending and descending projections from the rostral nucleus of the solitary tract originate from separate neuronal populations. *Neuroscience* 72, 185–197
123 Norgren, R. (1978) Projections from the nucleus of the solitary tract in the rat. *Neuroscience* 3, 207–218
124 Haidarliu, S. *et al.* (2012) Dorsorostral snout muscles in the rat subserve coordinated movement for whisking and sniffing. *Anat. Rec. (Hoboken)* 295, 1181–1191
125 Arriaga, G. *et al.* (2012) Of mice, birds, and men: the mouse ultrasonic song system has some features similar to humans and song-learning birds. *PLoS ONE* 7, e46610