

Published in final edited form as:

Trends Neurosci. 2014 July ; 37(7): 370–380. doi:10.1016/j.tins.2014.05.001.

How the brainstem controls orofacial behaviors comprised of rhythmic actions

Jeffrey D. Moore^{1,2,*}, David Kleinfeld^{1,3}, and Fan Wang^{4,*}

¹Graduate Program in Neurosciences, UC San Diego, La Jolla, CA 92093

²Department of Physics, UC San Diego, La Jolla, CA 92093

³Section on Neurobiology, UC San Diego, La Jolla, CA 92093

⁴Department of Neurobiology, Duke University Medical Center, Durham, NC 27710

Abstract

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 the 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 patency⁴, while 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,

© 2014 Elsevier Ltd. All rights reserved.

*Correspondence should be addressed to either Fan Wang (fan.wang@duke.edu) or Jeffrey D. Moore (j_moore@alum.mit.edu).

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

“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 swallowing⁷. 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 patients¹⁰.

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 fish¹¹. 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: (1) local interactions between potentially co-active circuits (CPGs) ensure their coordination, (2) a central “executive” command system arbitrates the execution and amplitude of different actions, and (3) peripheral feedback ensures the appropriate timing between different muscle groups (Fig 1). We believe studies of the brainstem may teach us general lessons about how nervous 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 which control these behaviors. Rhythmic ingestive behaviors occur at frequencies that are faster than the 1 to 2 Hz frequency of basal respiration in rats. Chewing and mature suckling movements occur at approximately 4 Hz¹², and rhythmic licking at 5 to 7 Hz¹³. 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 rhythm¹⁵ (Fig 2a). Indeed, in behaving animals it appears that rhythmic licking and breathing are coordinated despite the difference in their frequencies¹⁶ (Fig 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 rats⁵. These behaviors involve the use of common muscles in the snout^{4, 17}, and their robust one-to-one coordination suggested 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 a number of subsequent studies in rats. There is also evidence that high-frequency sniffing and whisking are phase locked in mice²⁰; however, one study reports a lack of such coordination in this species²². Nonetheless, all of the recent studies of whisking behavior 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 (Fig 2c). During basal respiration, the slow breathing rhythm resets the faster vibrissa protraction rhythm, while 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 versa²⁰. 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.

While breathing may exert influence over some orofacial rhythms, transient events may call for a temporary cessation of breathing that overrides 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 medulla²³. 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} (Fig 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.

Central pattern generators for breathing, chewing, licking, and swallowing in the brainstem

A central pattern generator (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 breathing³⁴ can occur without proprioceptive feedback, and without descending input from cortex³⁵. 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 of the brainstem. These regions contain both the primary sensory input nuclei (Fig 3a) and the final motor output nuclei (Fig 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.

(i) Locations of central pattern generators for breathing

The best characterized brainstem CPG in the mammalian nervous system is the circuitry in the ventral respiratory column that controls breathing^{42, 43}. 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^{44, 45} and necessary^{46, 47} 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^{48, 49} (Fig 3c). Since sniffing is part of the normal breathing behavior, it is presumed that pre-BötC also participates in the generation of sniffing²⁰, though the exact circuit mechanism by which the higher frequencies for sniffing are generated remains unknown¹⁹. 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^{50–52}. These different respiratory patterns are likely to involve different neuromodulatory influences⁵⁰ (Fig 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^{53–55}. 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 (Fig 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)⁵⁶. According to this proposal, the pre-BötC generates an internal time-keeping reference oscillation which can then be sub-divided 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^{57, 58}.

(ii) 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 “premotor” interneurons that project to motoneurons in different cranial motor nuclei. Early studies involved injecting classic retrograde neural tracers into cranial motor nuclei to directly label neurons projecting to those nuclei^{59, 60}. 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^{61, 62}. Most recently, the use of glycoprotein-deleted deficient rabies viruses (G-rabies) in combination with genetic complementation has enabled the selective identification of whisker, jaw, and tongue pre-motoneurons^{36, 38}. In contrast to earlier techniques, this use of G-rabies allows for transsynaptic retrograde labeling of only pre-motoneurons via intramuscular injection. These various tracing studies have identified locations of various orofacial pre-motoneurons in the brainstem (Fig 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 extent of the VII nucleus^{65, 66}. 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 closing⁶⁷. Other experiments demonstrate that neurons in the dorsal principal trigeminal nucleus (dPrV) burst rhythmically during fictive chewing in anesthetized and paralyzed rabbits⁶⁸ and raised the possibility that the chewing CPG is in the dPrV⁶⁹. In contrast to both these possibilities, a more recent study by Travers and colleagues demonstrates 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 have no effect⁷⁰. 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 (Fig 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, 71}. 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^{58, 72}. Extracellular recording found that the spiking activity of units in this region is phase-locked to rhythmic licking⁷³, and infusion of an inhibitory agonist into the IRt between the VII and XII nuclei blocks licking⁷⁴. Further, injection of a mu-opioid agonist in the same region alters the frequency of licking⁷⁵. Thus the CPG for licking, and possibly the CRG as well, is thought to be located in the IRt (Fig 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 exploratory movement. A recent study provides experimental evidence that the CPG for whisking is located in the ventral part of the IRt (vIRt) near nucleus ambiguus and dorsal-medial to the pre-BötC²⁰ (Fig 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), total of ten CPGs, located within or nearby 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 which 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 whisking²⁰ and licking rhythms^{14, 15} appear to be similarly reset by the breathing rhythm (Fig 2a–c); however the case of chewing remains equivocal in this respect²⁵. What is the neural circuit basis for such interactions between rhythmic actions? We note that breathing is robustly represented throughout the medulla⁴² near the sensory, motor, and premotor pattern generating nuclei for these other actions (Fig 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, 58}, and even directly to the VII³⁶ 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 promoter⁵⁷. These specific pre-BötC neurons, which are known to be part of the respiratory CPG network^{46, 76}, 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 (premotor neurons)^{58, 77, 78}, again suggesting that breathing paces other orofacial rhythms. In fact, in the *in vitro* isolated brainstem preparation, at resting stage, the rhythmic respiratory activities (1Hz) in the V, VII, XII nerve rootlets can be recorded^{15, 79}, whereas faster rhythmic activities appear only after the application of NMDA¹⁵.

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, 80, 81} (Fig 2d) and sighing⁵¹. Indeed, when the breathing CPG is inhibited following the occurrence of these activities, Motoneurons are gated off and breathing behavior is suppressed. However the occurrence of sighing and swallowing events are pegged to the preceding respiratory cycle^{25, 81, 82}, at least in the presence of normal inhibitory synaptic transmission⁵¹, and it is unknown whether rhythm-generating mechanisms internal to the pre-BötC continue under conditions in which respiratory output is suppressed⁵⁶. Thus, a much 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 non-respiratory 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 non-respiratory 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 midline⁶⁶,

suggesting that the equivalent CPGs on the two sides might interact through midline crossing axons in a manner similar to the breathing CPG⁴⁷.

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 co-activate 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 were found to be distributed rostrocaudally through IRT and PCRT where CPGs for different orofacial actions are thought to reside⁸³ (Fig 3c). Injecting different retrograde tracers into two different orofacial motor nuclei suggests the existence of IRT neurons projecting to both motor groups^{59, 84–86}. A recent monosynaptic rabies-mediated tracing study further shows that pre-motoneurons innervating tongue-protruding motoneurons simultaneously innervate jaw-opening and lip-lowing motoneurons³⁸, confirming the presence of interneurons with appropriate multi-motor targets. Chronic neuronal recording studies in the brainstem reticular formation also discovered “multifunctional” neurons, e.g. neurons showing responses during both swallowing and vocalization⁸⁷ or neurons responding during respiration, vocalization, and swallowing⁸⁸. Likewise, some neurons located laterally to the hypoglossal nucleus were found to be active during both masticatory movements and swallowing⁸⁹. A large proportion of neurons in the caudal IRT, as well as some within the XII motor nucleus, were responsive during both licking and swallowing, and subsets of them also show activities associated with gape responses^{73, 90}. Together, the anatomical and electrophysiological studies suggest chewing, licking, swallowing, 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 motoneurons³⁸.

Regulation of orofacial behaviors by higher-order brain regions

(i) Top-down activation of orofacial actions

While 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 frequency⁹¹. 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 whisking⁹² 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 reward⁹³. Cortical outputs from these regions project directly to the pons and medulla near where the rhythm and pattern-generating elements are located^{36, 72, 94–96}.

In addition to cortex, the cerebellum and basal ganglia were also found to activate and modulate some orofacial actions. For example, stimulation of the deep cerebellar nuclei in monkeys results in tongue movement⁹⁷. Removal of the cerebellum results in slightly slower licking rates in rodents but does not appear to affect the generation of either rhythmic licking⁹⁸ or coordinated whisking and sniffing¹⁸. Together with observations that the deep cerebellar nuclei project to orofacial-related regions of the medullary reticular formation and spike in phase with licking⁹⁹, these results may 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 both¹⁰⁰. Pharmacological manipulations of basal-ganglia circuitry¹⁰¹ or dopamine receptors¹⁰² 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 actions¹⁰³ (Fig 1). All told, there appear to be multiple independent pathways to activate brainstem CPGs.

(ii) 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 much slower time scales than the oscillatory rhythm, analogous to the separate control of frequency and amplitude in AM radio¹⁰⁴. Endocannabinoid agonists and antagonists affect the range of whisking without affecting the frequency¹⁰⁵, and spiking activity in primary motor cortex preferentially reports this slowly varying component^{104, 106, 107}. Serotonergic and other modulatory inputs may also serve to control the amplitude of whisking^{108–110} (Fig 1). Similarly the generation of the licking rhythm is independent of the amplitude of tongue muscle contractions^{71, 72}, and regulation of tonic jaw-force has been shown to depend on inputs from the cerebellum¹¹¹. 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 superior colliculus^{36, 63, 99, 112}.

Role of sensation in orofacial actions

Although basic rhythmic motor patterns are controlled by CPGs, they must be modulated or even initiated by external stimuli. Sensory inputs can mediate “reflex” motor outputs. More than 20 types of mono-synaptic and oligosynaptic orofacial reflexes have been identified and studied¹¹³. 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 mechanoreceptors³⁷. 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 object¹¹⁴. These vibrissa reflexes may serve to enhance the animal’s ability 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^{81, 115–117}. 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 feedback¹¹⁸, which reports the qualities of the food or liquid being ingested^{13, 119}. This modulation is thought to be mediated by primary sensory proprioceptors in Vmes which monitor resistance to the force applied by the jaw¹²⁰.

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 tracing³⁶. These neurons likely receive direct sensory inputs and thus are candidates to mediate various di-synaptic “sensory input-interneuron-motoneuron” circuits that may modulate whisking, *e.g.*, foveal whisking and whisking reflexes. It is important to note, however, that sensory modulation of rhythmic behaviors needs not necessarily be di-synaptic. For example, neurons located in Gi and LPGi (Fig 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^{36, 67, 96} 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 a number of 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 which 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 (Fig 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 is comprised of 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" interactions (Fig 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. 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 medulla¹²¹ can be targeted and manipulated *in vivo*. Such manipulations have already proven invaluable in parsing other motor circuits in the spinal cord¹²²⁻¹²⁴.

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 premotor nuclei that lie across the brainstem reticular formation (Fig 3d).

Acknowledgments

We thank Harvey J. Karten for the anatomical dataset used in the brainstem reconstruction (Fig 3), as well as Martin Deschênes and Winfred Denk for discussions. This work is supported by grants from National Institute of Health, (NS077986 and DE019440 to F.W. and NS058668 to D.K.) and the US/Israeli Binational Foundation (grant 2011432 to DK).

References

1. Weiss, P. Self-differentiation of the basic patterns of coordination. Williams & Wilkins; 1941.
2. Tinbergen N. The Study of Instinct. 1951
3. Mussa-Ivaldi FA, Bizzi E. Motor learning through the combination of primitives. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences.* 2000; 355:1755–1769.
4. Sherrey JH, Megirian D. State dependence of upper airway respiratory motoneurons: Functions of the cricothyroid and nasolabial muscles of the unanesthetized rat. *Electroencephalography and Clinical Neurophysiology.* 1977; 43:218–228. [PubMed: 69532]
5. Welker WI. Analysis of sniffing of the albino rat. *Behaviour.* 1964; 12:223–244. (1964).
6. Vincent SB. The function of the vibrissae in the behavior of the white rat. *Behavior Monographs.* 1912; 1:7–81.
7. Lund J. Mastication and its control by the brain stem. *Critical Reviews in Oral Biology & Medicine.* 1991; 2:33–64. [PubMed: 1912143]
8. Gross RD, et al. The coordination of breathing and swallowing in Parkinson's disease. *Dysphagia.* 2008; 23:136–145. [PubMed: 18027027]
9. Troche MS, Huebner I, Rosenbek JC, Okun MS, Sapienza CM. Respiratory-swallowing coordination and swallowing safety in patients with Parkinson's disease. *Dysphagia.* 2011; 26:218–224. [PubMed: 20623304]
10. Monteiro L, et al. Swallowing impairment and pulmonary dysfunction in Parkinson's disease: The silent threats. *Journal of the neurological sciences.* 2014; 339:149–152. [PubMed: 24572726]
11. von Holst E. Die relative Koordination als Phänomen und als Methode zentralnervöser Funktionsanalyse. *Ergebnisse der Physiologie.* 42:228–306. (193).
12. Westneat MW, Hal WG. Ontogeny of feeding motor patterns in infant rats: an electromyographic analysis of suckling and chewing. *Behavioral Neuroscience.* 1992; 106:539. [PubMed: 1616619]
13. Travers JB, Norgren R. Electromyographic analysis of the ingestion and rejection of sapid stimuli in the rat. *Behavioral neuroscience.* 1986; 100:544. [PubMed: 3741605]
14. Katakura N, Jia L, Nakamura Y. NMDA-induced rhythmical activity in XII nerve of isolated CNS from newborn rats. *Neuroreport.* 1995; 6:601–604. [PubMed: 7605909]
15. Nakamura Y, Katakura N, Nakajima M. Generation of rhythmical ingestive activities of the trigeminal, facial, and hypoglossal motoneurons in in vitro CNS preparations isolated from rats and mice. *Journal of Medical and Dental Sciences.* 1999; 46:63–73. [PubMed: 10805320]
16. Welzl H, Bures J. Lick-synchronized breathing in rats. *Physiological Behavior.* 1977; 18:751–753.
17. Hill DN, Bermejo R, Zeigler HP, Kleinfeld D. Biomechanics of the vibrissa motor plant in rat: Rhythmic whisking consists of triphasic neuromuscular activity. *Journal of Neuroscience.* 2008; 28:3438–3455. [PubMed: 18367610]
18. Semba K, Komisaruk BR. Neural substrates of two different rhythmical vibrissal movements in the rat. *Neuroscience.* 1984; 12:761–774. [PubMed: 6472619]
19. Deschênes M, Moore JD, Kleinfeld D. Sniffing and whisking in rodents. *Current Opinion in Neurobiology.* 2012; 22:243–250. [PubMed: 22177596]
20. Moore JD, et al. Hierarchy of orofacial rhythms revealed through whisking and breathing. *Nature.* 2013; 497:205–210. [PubMed: 23624373]
21. Ranade S, Hangya B, Kepecs A. Multiple Modes of Phase Locking between Sniffing and Whisking during Active Exploration. *The Journal of Neuroscience.* 2013; 33:8250–8256. [PubMed: 23658164]

22. Cao Y, Roy S, Sachdev RN, Heck DH. Dynamic correlation between whisking and breathing rhythms in mice. *Journal of Neuroscience*. 2012; 32:1653–1659. [PubMed: 22302807]
23. Lawson EE, Richter DW, Czyzyk-Krzeska MF, Bischoff A, Rudesill RC. Respiratory neuronal activity during apnea and other breathing patterns induced by laryngeal stimulation. *Journal of Applied Physiology*. 1991; 70:2742–2749.
24. Miller F, Sherrington C. Some observations on the bucco-pharyngeal stage of reflex deglutition in the cat. *Experimental Physiology*. 1915; 9:147–186.
25. McFarland DH, Lund JP. An investigation of the coupling between respiration, mastication, and swallowing in the awake rabbit. *Journal of Neurophysiology*. 1993; 69:95–108. [PubMed: 8433136]
26. Rossignol S, Dubuc R. Spinal pattern generation. *Current Opinion in Neurobiology*. 1994; 4:894–902. [PubMed: 7888774]
27. Kleinfeld D, Sompolinsky H. Associative neural network model for the generation of temporal patterns: Theory and application to central pattern generators. *Biophysical Journal*. 1988; 54:1039–1051. [PubMed: 3233265]
28. Gao P, Bermejo R, Zeigler HP. Vibrissa deafferentation and rodent whisking patterns: Behavioral evidence for a central pattern generator. *Journal of Neuroscience*. 2001; 21:5374–5380. [PubMed: 11438614]
29. Berg RW, Kleinfeld D. Rhythmic whisking by rat: Retraction as well as protraction of the vibrissae is under active muscular control. *Journal of Neurophysiology*. 2003; 89:104–117. [PubMed: 12522163]
30. Goodwin GM, Luschei ES. Effects of destroying spindle afferents from jaw muscles on mastication in monkeys. *Journal of Neurophysiology*. 1974
31. Enomoto S, Schwartz G, Lund J. The effects of cortical ablation on mastication in the rabbit. *Neuroscience Letters*. 1987; 82:162–166. [PubMed: 3696490]
32. Jüch P, Van Willigen J, Broekhuijsen M, Ballintijn C. Peripheral influences on the central pattern-rhythm generator for tongue movements in the rat. *Archives of Oral Biology*. 1985; 30:415–421. [PubMed: 3861147]
33. Grill HJ, Norgren R. The taste reactivity test. II. Mimetic responses to gustatory stimuli in chronic thalamic and chronic decerebrate rats. *Brain Research*. 1978; 143:281–297. [PubMed: 630410]
34. von Euler C. The contribution of sensory inputs to the pattern generation of breathing. *Canadian Journal of Physiology and Pharmacology*. 1981; 59:700–706. [PubMed: 6274493]
35. Lovick TA. The behavioural repertoire of precollicular decerebrate rats. *Journal of Physiology*. 1972; 226:4P–6P.
36. Takatoh J, et al. New modules are added to vibrissal premotor circuitry with the emergence of exploratory whisking. *Neuron*. 2013; 77:346–360. [PubMed: 23352170]
37. Nguyen Q-T, Kleinfeld D. Positive feedback in a brainstem tactile sensorimotor loop. *Neuron*. 2005; 45:447–457. [PubMed: 15694330]
38. Stanek E IV, C S, Takatoh J, Han B, Wang F. Monosynaptic premotor circuit tracing reveals neural substrates for oro-motor coordination. *eLife*. 2014 **In Press**.
39. Halsell C, Travers S, Travers J. Ascending and descending projections from the rostral nucleus of the solitary tract originate from separate neuronal populations. *Neuroscience*. 1996; 72:185–197. [PubMed: 8730716]
40. Norgren R. Projections from the nucleus of the solitary tract in the rat. *Neuroscience*. 1978; 3:207–218. [PubMed: 733004]
41. Haidarliu S, Golomb D, Kleinfeld D, Ahissar E. Dorsorostral snout muscles in the rat subserve coordinated movement for whisking and sniffing. *Anat Rec (Hoboken)*. 2012; 295:1181–1191. [PubMed: 22641389]
42. Smith JC, Abdala APL, Rybak IA, Paton JFR. Structural and functional architecture of respiratory networks in the mammalian brainstem. *Philosophical Transactions of the Royal Society of London B*. 2009; 364:2577–2587.
43. Feldman JL, Del Negro CA. Looking for inspiration: new perspectives on respiratory rhythm. *Nature Reviews Neuroscience*. 2006; 7:232–241.

44. Smith JC, Ellenberger HH, Ballanyi K, Richter DW, Feldman JL. Pre-Bötzinger complex: A brainstem region that may generate respiratory rhythm in mammals. *Science*. 1991; 254:726–729. [PubMed: 1683005]
45. Janczewski WA, Tashima A, Hsu P, Cui Y, Feldman JL. Role of inhibition in respiratory pattern generation. *The Journal of Neuroscience*. 2013; 33:5454–5465. [PubMed: 23536061]
46. Tan W, et al. Silencing preBötzinger Complex somatostatin-expressing neurons induces persistent apnea in awake rat. *Nature Neuroscience*. 2008; 11:538–540.
47. Bouvier J, et al. Hindbrain interneurons and axon guidance signaling critical for breathing. *Nature neuroscience*. 2010; 13:1066–1074.
48. Janczewski WA, Feldman JL. Distinct rhythm generators for inspiration and expiration in the juvenile rat. *The Journal of Physiology*. 2006; 570:407–420. [PubMed: 16293645]
49. Pagliardini S, et al. Active expiration induced by excitation of ventral medulla in adult anesthetized rats. *The Journal of Neuroscience*. 2011; 31:2895–2905. [PubMed: 21414911]
50. Doi A, Ramirez JM. Neuromodulation and the orchestration of the respiratory rhythm. *Respiratory Physiology & Neurobiology*. 2008; 164:96–104. [PubMed: 18602029]
51. Lieske S, Thoby-Brisson M, Telgkamp P, Ramirez J. Reconfiguration of the neural network controlling multiple breathing patterns: eupnea, sighs and gasps. *Nature Neuroscience*. 2000; 3:600–607.
52. John WMS. Medullary regions for neurogenesis of gasping: noeud vital or noeuds vitals? *Journal of Applied Physiology*. 1996; 81:1865–1877. [PubMed: 8941503]
53. Feldman JL. Neurophysiology of breathing in mammals. *Comprehensive Physiology*. 1986
54. Kiehn O. Locomotor circuits in the mammalian spinal cord. *Annu. Rev. Neurosci*. 2006; 29:279–306. [PubMed: 16776587]
55. Grillner S. The motor infrastructure: from ion channels to neuronal networks. *Nature Reviews Neuroscience*. 2003; 4:573–586.
56. Kam K, Worrell JW, Janczewski WA, Cui Y, Feldman JL. Distinct Inspiratory Rhythm and Pattern Generating Mechanisms in the preBötzinger Complex. *The Journal of Neuroscience*. 2013; 33:9235–9245. [PubMed: 23719793]
57. Tan W, Pagliardini S, Yang P, Janczewski WA, Feldman JL. Projections of preBötzinger complex neurons in adult rats. *Journal of Comparative Neurology*. 2010; 518:1862–1878. [PubMed: 20235095]
58. Koizumi H, et al. Functional imaging, spatial reconstruction, and biophysical analysis of a respiratory motor circuit isolated *in vitro*. *Journal of Neuroscience*. 2008; 28:2353–2365. [PubMed: 18322082]
59. Travers JB, Yoo JE, Chandran R, Herman K, Travers SP. Neurotransmitter phenotypes of intermediate zone reticular formation projections to the motor trigeminal and hypoglossal nuclei in the rat. *Journal of Comparative Neurology*. 2005; 488:28–47. [PubMed: 15912497]
60. Isokawa-Akesson M, Komisaruk BR. Difference in projections to the lateral and medial facial nucleus: Anatomically separate pathways for rhythmical vibrissa movement in rats. *Experimental Brain Research*. 1987; 65:385–398. [PubMed: 3556466]
61. Dobbins EG, Feldman JL. Differential innervation of protruder and retractor muscles of the tongue in rat. *Journal of Comparative Neurology*. 1995; 357:376–394. [PubMed: 7673474]
62. Fay RA, Norgren R. Identification of rat brainstem multisynaptic connections to the oral motor nuclei in the rat using pseudorabies virus. II. Facial muscle motor systems. *Brain Research Reviews*. 1997; 25:276–290. [PubMed: 9495559]
63. Grinevich V, Brecht M, Osten P. Monosynaptic pathway from rat vibrissa motor cortex to facial motor neurons revealed by lentivirus-based axonal tracing. *Journal of Neuroscience*. 2005; 25:8250–8258. [PubMed: 16148232]
64. Arriaga G, Zhou EP, Jarvis ED. Of mice, birds, and men: the mouse ultrasonic song system has some features similar to humans and song-learning birds. *PloS One*. 2012; 7:e46610. [PubMed: 23071596]
65. Nozaki S, Iriki A, Nakamura Y. Location of central rhythm generator involved in cortically induced rhythmical masticatory jaw-opening movement in the guinea pig. *Journal of Neurophysiology*. 1986; 55:806–825. [PubMed: 3517246]

66. Chandler SH, Tal M. The effects of brain stem transections on the neuronal networks responsible for rhythmical jaw muscle activity in the guinea pig. *The Journal of Neuroscience*. 1986; 6:1831–1842. [PubMed: 3712013]
67. Nakamura Y, Katakura N. Generation of masticatory rhythm in the brainstem. *Neuroscience Research*. 1995; 23:1–19. [PubMed: 7501294]
68. Tsuboi A, Kolta A, Chen C, Lund J. Neurons of the trigeminal main sensory nucleus participate in the generation of rhythmic motor patterns. *European Journal of Neuroscience*. 2003; 17:229–238. [PubMed: 12542659]
69. Kolta A, Brocard F, Verdier D, Lund JP. A review of burst generation by trigeminal main sensory neurons. *Archives of Oral Biology*. 2007; 52:325–328. [PubMed: 17178100]
70. Travers JB, Herman K, Travers SP. Suppression of third ventricular NPY-elicited feeding following medullary reticular formation infusions of muscimol. *Behavioral neuroscience*. 2010; 124:225. [PubMed: 20364882]
71. Wiesenfeld Z, Halpern BP, Tapper DN. Licking behavior: Evidence of hypoglossal oscillator. *Science*. 1977
72. Travers JB, Dinardo LA, Karimnamazi H. Motor and premotor mechanisms of licking. *Neuroscience and Biobehavioral Reviews*. 1997; 21:631–647. [PubMed: 9353796]
73. Travers JB, DiNardo LA, H K. Medullary reticular formation activity during ingestion and rejection in the awake rat. *Experimental Brain Research*. 2000; 130:78–92. [PubMed: 10638444]
74. Chen Z, Travers SP, Travers JB. Muscimol infusions in the brain stem reticular formation reversibly block ingestion in the awake rat. *American Journal of Physiology: Regulatory, Integrative, and Comparative Physiology*. 2001; 280:R1085–R1094.
75. Kinzeler NR, Travers SP. μ -Opioid modulation in the rostral solitary nucleus and reticular formation alters taste reactivity: evidence for a suppressive effect on consummatory behavior. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*. 2011; 301:R690.
76. Stornetta RL, et al. A group of glutamatergic interneurons expressing high levels of both neurokinin-1 receptors and somatostatin identifies the region of the pre-Bötzing complex. *Journal of Comparative Neurology*. 2003; 455:499–512. [PubMed: 12508323]
77. Ono T, Ishiwata Y, Inaba N, Kuroda T, Nakamura Y. Modulation of the inspiratory-related activity of hypoglossal premotor neurons during ingestion and rejection in the decerebrate cat. *Journal of Neurophysiology*. 1998; 80:48–58. [PubMed: 9658027]
78. Fukuda Y, Honda Y. Differences in respiratory neural activities between vagal (superior laryngeal), hypoglossal, and phrenic nerves in the anesthetized rat. *Japanese Journal of Physiology*. 1982; 32:387–398. [PubMed: 6813545]
79. Koizumi H, et al. Differential discharge patterns of rhythmical activity in trigeminal motoneurons during fictive mastication and respiration *in vitro*. *Brain research bulletin*. 2002; 58:129–133. [PubMed: 12121822]
80. Yamanishi T, T K, Koizumi H, Ishihama K, Nohara K, Komaki M, Enomoto A, Yokota Y, Kogo M. Alpha-2 adrenoceptors coordinate swallowing and respiration. *Journal of Dental Research*. 2010; 89:258–263. [PubMed: 20139342]
81. Doty RW, Bosma JF. An electromyographic analysis of reflex deglutition. *Journal of Neurophysiology*. 1956
82. Cherniack N, Euler Cv, Glogowska M, Homma I. Characteristics and rate of occurrence of spontaneous and provoked augmented breaths. *Acta Physiologica Scandinavica*. 1981; 111:349–360. [PubMed: 6797251]
83. Travers JB, Norgren R. Afferent projections to the oral motor nuclei in the rat. *Journal of Comparative Neurology*. 1983; 220:280–298. [PubMed: 6315785]
84. Amri M, Car A, Roman C. Axonal branching of medullary swallowing neurons projecting on the trigeminal and hypoglossal motor nuclei: demonstration by electrophysiological and fluorescent double labeling techniques. *Experimental Brain Research*. 1990; 81:384–390. [PubMed: 1697811]
85. Li Y-Q, Takada M, Mizuno N. 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 Research*. 1993; 611:160–164. [PubMed: 8518944]

86. Popratiloff AS, et al. Hypoglossal and reticular interneurons involved in oro-facial coordination in the rat. *Journal of Comparative Neurology*. 2001; 433:364–379. [PubMed: 11298361]
87. Chiao G, Larson C, Yajima Y, Ko P, Kahrilas P. Neuronal activity in nucleus ambiguus during deglutition and vocalization in conscious monkeys. *Experimental brain research*. 1994; 100:29–38. [PubMed: 7813650]
88. Larson CR, Yajima Y, Ko P. Modification in activity of medullary respiratory-related neurons for vocalization and swallowing. *Journal of Neurophysiology*. 1994; 71:2294–2304. [PubMed: 7931518]
89. Amri M, Lamkadem M, Car A. Effects of lingual nerve and chewing cortex stimulation upon activity of the swallowing neurons located in the region of the hypoglossal motor nucleus. *Brain research*. 1991; 548:149–155. [PubMed: 1868328]
90. Dinardo LA, Travers JB. Hypoglossal neural activity during ingestion and rejection in the awake rat. *Journal of neurophysiology*. 1994; 72:1181–1191. [PubMed: 7807203]
91. Dellow P, Lund J. Evidence for central timing of rhythmical mastication. *The Journal of Physiology*. 1971; 215:1. [PubMed: 5579653]
92. Haiss F, Schwarz C. Spatial segregation of different modes of movement control in the whisker representation of rat primary motor cortex. *Journal of Neuroscience*. 2005; 25:1579–1587. [PubMed: 15703412]
93. Komiyama T, et al. Learning-related fine-scale specificity imaged in motor cortex circuits of behaving mice. *Nature*. 2010; 464:1182–1186. [PubMed: 20376005]
94. Zhang G, Sasamoto K. Projections of two separate cortical areas for rhythmical jaw movements in the rat. *Brain Research Bulletin*. 1990; 24:221–230. [PubMed: 2322856]
95. Valverde F. Reticular formation of the albino rat's brain stem cytoarchitecture and corticofugal connections. *Journal of Comparative Neurology*. 1962; 119:25–53. [PubMed: 13924447]
96. Hattox AM, Priest CA, Keller A. Functional circuitry involved in the regulation of whisker movements. *Journal of Comparative Neurology*. 2002; 442:266–276. [PubMed: 11774341]
97. Bowman J, Aldes L. Organization of the cerebellar tongue representation in the monkey. *Experimental Brain Research*. 1980; 39:249–259. [PubMed: 6772461]
98. Bryant JL, Boughter JD, Gong S, LeDoux MS, Heck DH. Cerebellar cortical output encodes temporal aspects of rhythmic licking movements and is necessary for normal licking frequency. *European Journal of Neuroscience*. 2010; 32:41–52. [PubMed: 20597972]
99. Lu L, Cao Y, Tokita K, Heck DH, Boughter JD Jr. Medial cerebellar nuclear projections and activity patterns link cerebellar output to orofacial and respiratory behavior. *Frontiers in neural circuits*. 2013; 7
100. Yasui Y, Tsumori T, Ando A, Domoto T. Demonstration of axon collateral projections from the substantia nigra pars reticulata to the superior colliculus and the parvicellular reticular formation in the rat. *Brain Research*. 1995; 674:122–126. [PubMed: 7539705]
101. Nakamura S, Muramatsu S, Yoshida M. Role of the basal ganglia in manifestation of rhythmical jaw movement in rats. *Brain Research*. 1990; 535:335–338. [PubMed: 2073612]
102. Chandler SH, Goldberg LJ. 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 Research*. 1984; 323:297–301. [PubMed: 6525515]
103. Hikosaka O. GABAergic output of the basal ganglia. *Progress in Brain Research*. 2007; 160:209–226. [PubMed: 17499116]
104. Hill DN, Curtis JC, Moore JD, Kleinfeld D. Primary motor cortex reports efferent control of vibrissa position on multiple time scales. *Neuron*. 2011; 72:344–356. [PubMed: 22017992]
105. Pietr MD, Knutsen PM, Shore DI, Ahissar E, Vogel Z. Cannabinoids reveal separate controls for whisking amplitude and timing in rats. *Journal of Neurophysiology*. 2010; 104:2532–2542. [PubMed: 20844105]
106. Friedman WA, Zeigler HP, Keller A. Vibrissae motor cortex unit activity during whisking. *Journal of Neurophysiology*. 2012; 107:551–563. [PubMed: 21994257]

107. Gerdjikov TV, Haiss F, Rodriguez-Sierra OE, Schwarz C. Rhythmic Whisking Area (RW) in Rat Primary Motor Cortex: An Internal Monitor of Movement-Related Signals? *Journal of Neuroscience*. 2013; 33:14193–14204. [PubMed: 23986253]
108. Hattox AM, Li Y, Keller A. Serotonin regulates rhythmic whisking. *Neuron*. 2003; 39:343–352. [PubMed: 12873389]
109. VanderMaelen C, Aghajanian G. Intracellular studies showing modulation of facial motoneurone excitability by serotonin. 1980
110. Harish O, Golomb D. Control of the firing patterns of vibrissa motoneurons by modulatory and phasic synaptic inputs: A modeling study. *Journal of Neurophysiology*. 2010; 103:2684–2699. [PubMed: 20200122]
111. Larson CR, Sutton D. Effects of cerebellar lesions on monkey jaw-force control: implications for understanding ataxic dysarthria. *Journal of speech and hearing research*. 1978; 21:309. [PubMed: 100657]
112. Miyashita E, Shigemitsu M. The superior colliculus relays signals descending from the vibrissal motor cortex to the facial nerve nucleus in the rat. *Neuroscience Letters*. 1995; 195:69–71. [PubMed: 7478258]
113. Miller A. Oral and pharyngeal reflexes in the mammalian nervous system: their diverse range in complexity and the pivotal role of the tongue. *Critical Reviews in Oral Biology & Medicine*. 2002; 13:409–425. [PubMed: 12393760]
114. Grant RA, Mitchinson B, Fox CW, Prescott TJ. Active touch sensing in the rat: anticipatory and regulatory control of whisker movements during surface exploration. *Journal of Neurophysiology*. 2009; 101:862–874. [PubMed: 19036871]
115. Thexton AJ, Crompton A, German RZ. Electromyographic activity during the reflex pharyngeal swallow in the pig: Doty and Bosma (1956) revisited. *Journal of Applied Physiology*. 2007; 102:587–600. [PubMed: 17082375]
116. German RZ, Crompton A, Thexton AJ. Integration of the reflex pharyngeal swallow into rhythmic oral activity in a neurologically intact pig model. *Journal of Neurophysiology*. 2009; 102:1017–1025. [PubMed: 19515957]
117. Yamada Y, Yamamura K, Inoue M. Coordination of cranial motoneurons during mastication. *Respiratory Physiology & Neurobiology*. 2005; 147:177–189. [PubMed: 16087147]
118. Inoue T, et al. Modifications of masticatory behavior after trigeminal deafferentation in the rabbit. *Experimental Brain Research*. 1989; 74:579–591. [PubMed: 2707333]
119. Thexton A, Hiiemae KM, Crompton A. Food consistency and bite size as regulators of jaw movement during feeding in the cat. *Journal of Neurophysiology*. 1980; 44:456–474. [PubMed: 7441310]
120. Morimoto T, Inoue T, Masuda Y, Nagashima T. Sensory components facilitating jaw-closing muscle activities in the rabbit. *Experimental Brain Research*. 1989; 76:424–440. [PubMed: 2767194]
121. Gray PA. Transcription factors define the neuroanatomical organization of the medullary reticular formation. *Frontiers in Neuroanatomy*. 2013; 7
122. Bui TV, et al. Circuits for Grasping: Spinal dI3 Interneurons Mediate Cutaneous Control of Motor Behavior. *Neuron*. 2013; 78:191–204. [PubMed: 23583114]
123. Hägglund M, et al. Optogenetic dissection reveals multiple rhythmogenic modules underlying locomotion. *Proceedings of the National Academy of Sciences*. 2013; 110:11589–11594.
124. Goulding M. Circuits controlling vertebrate locomotion: Moving in a new direction. *Nature Reviews of Neuroscience*. 2009; 10:507–518.
125. Nakamura Y, Katakura N, Nakajima M, Liu J. Rhythm generation for food-ingestive movements. *Progress in Brain Research*. 2004; 143:97–103. [PubMed: 14653154]

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 VG have extensive collateral projections to the brainstem trigeminal complex that span the entire rostral-caudal axis of the hindbrain (Fig 3a).

Trigeminal mesencephalic nucleus (Vmes): contains proprioceptive sensory neurons that innervate muscle spindles of the jaw muscles as well as periodontal ligaments (Fig 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 (the blue-shaded area in Fig 3a). This complex has traditionally been divided into four subnuclei: caudalis (SpC), interpolaris (SpI), oralis (SpO), and principalis (PrV). Sub-populations of neurons within each of the four subnuclei are believed to relay the sensory feedback information onto motoneurons^{36–38}.

Nucleus tractus solitarii (NTS, or solitary nucleus): receives inputs from taste-related sensory afferents (Fig 3a). Interneurons in NTS relay taste information to hypoglossal nucleus, as well as to the medullary reticular formation, to regulate reflexive oromotor behaviors^{39,40}.

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 (Fig 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 actions⁴¹.

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^{36, 59, 6038} (Fig 3c).

Pre-Bötzinger (pre-BötC), Bötzing complex, parafacial respiratory group (pFRG) contains small number of neurons pre-synaptic to VII and XII motoneurons^{36,20, 58} (Fig 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 motoneurons⁶² (Fig 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 (Fig 3c).

Other sources of pre-motor inputs not shown in Fig 3c: Pre-motoneurons were observed in nuclei receiving the corresponding sensory afferent inputs, *i.e.*, 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. Motor cortex provides limited and very sparse direct presynaptic inputs onto cranial motoneurons^{36, 63}, with the exception of the vocal motoneurons, located in the ambiguous nucleus, which may receive more extensive direct cortical inputs⁶⁴.

Highlights

1. Mammalian face and mouth contain sophisticated motor plants that produce diverse orofacial behaviors.
2. Brainstem contains key neural circuits that drive and coordinate different cranial motoneurons to produce various orofacial actions.
3. All orofacial actions are coordinated with breathing.
4. Three major neural computational mechanisms coordinating orofacial actions are discussed.

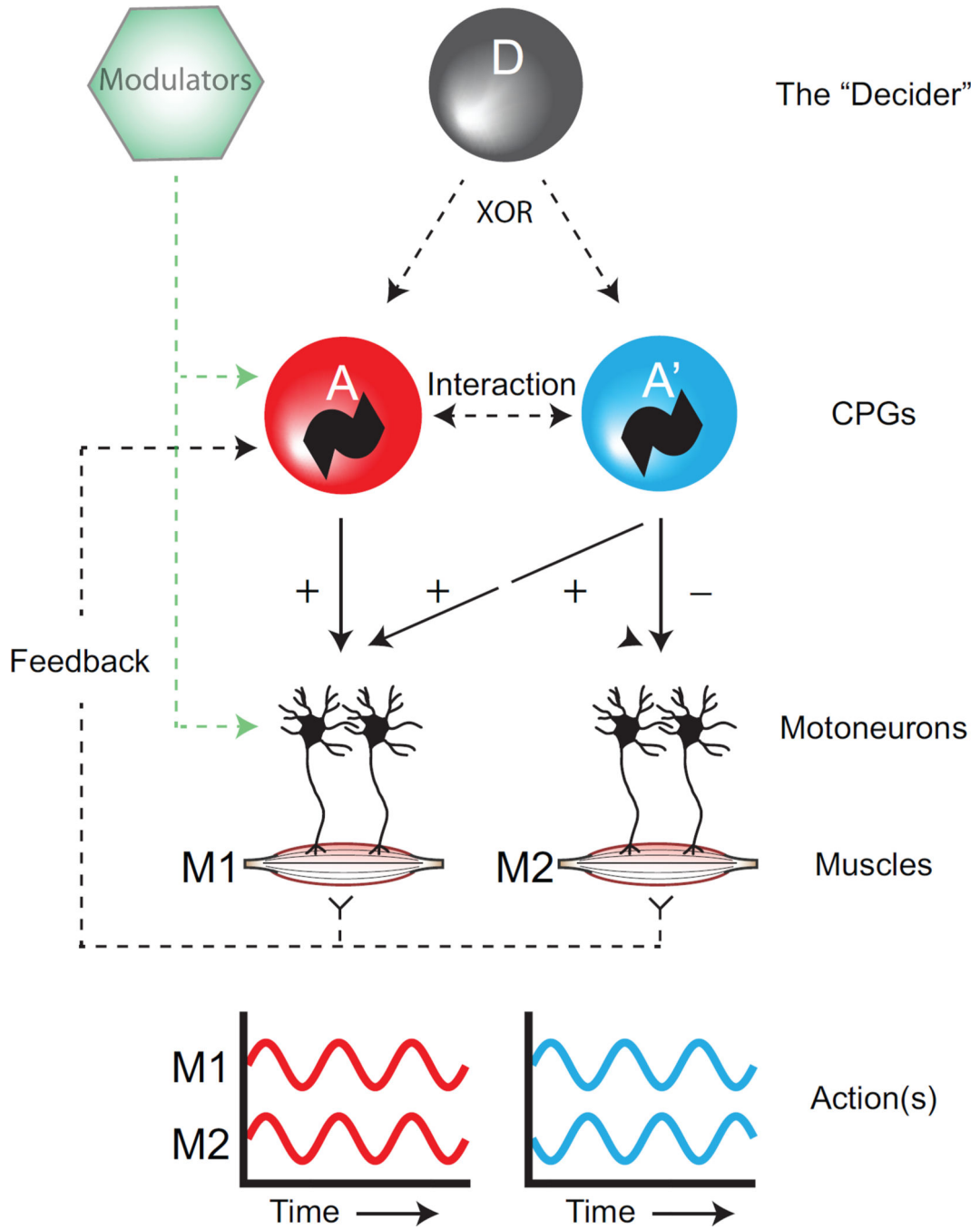


Figure 1. Schematic of the possible circuit arrangements for execution of different actions using a shared motor plant
 Muscles M1 and M2 can both be used in different temporal patterns in two different actions, A and A'. Possible circuit interactions include: (1) CPGs interact and coordinate each other,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

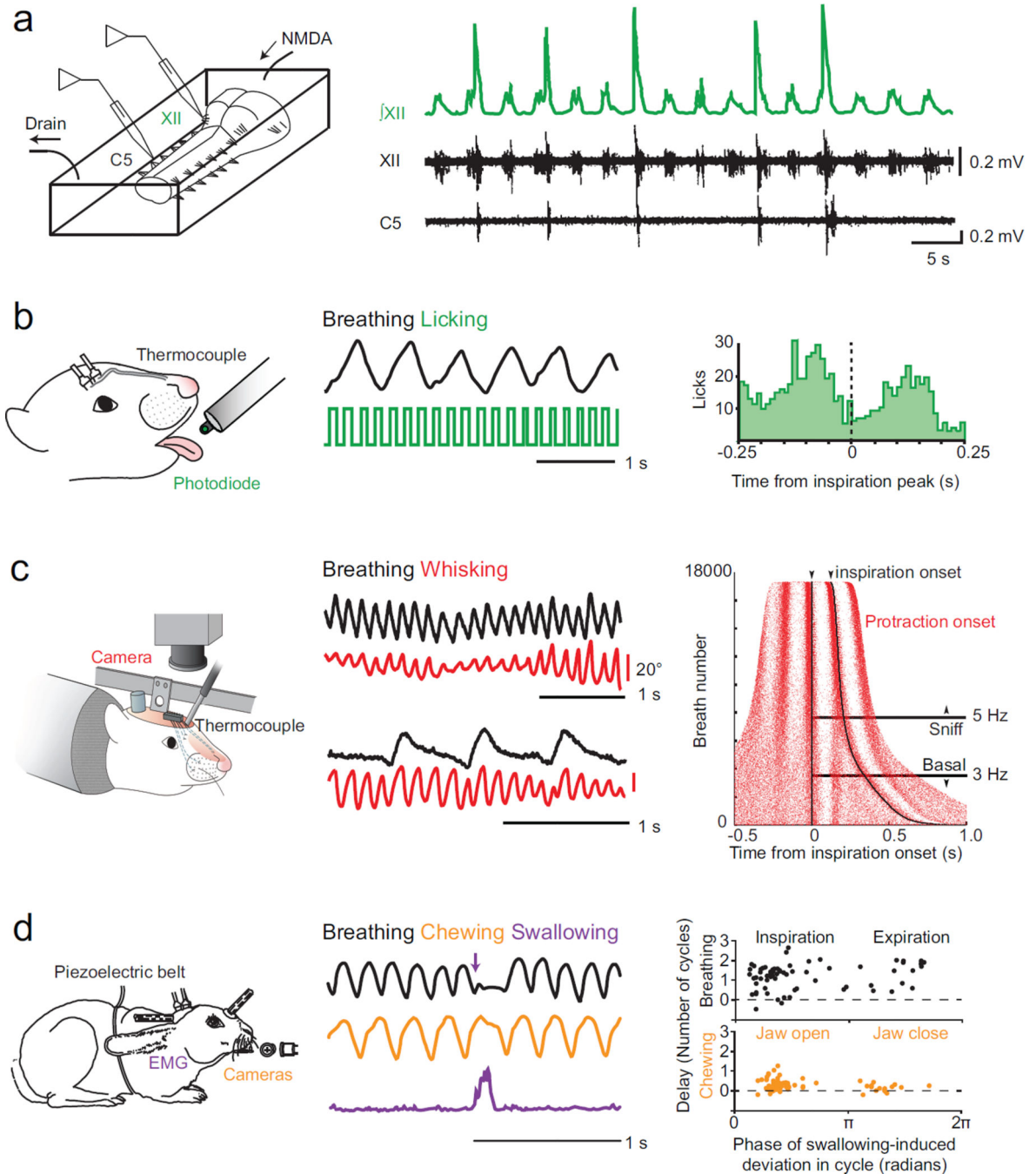


Figure 2. Coordination between breathing and other rhythmic orofacial actions

(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 5th 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, 125}.

(b) Simultaneous monitoring of licking (green) and breathing (black) in an alert rat (left and middle) show that the actions are coordinated (right). The occurrence of a lick is dependent on the phase of the respiratory cycle. Adapted from¹⁶.

(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 the onset of inspiration for individual breath 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 from²⁰.

(d) Simultaneous monitoring of chewing (orange), swallowing (purple), and breathing (black) in an alert rabbit (left and middle) reveal the nature of their coordination. While breathing and chewing appear to be asynchronous, swallowing affects both rhythms. The occurrence of a swallowing movement delays subsequent breathing and chewing cycles. Adapted from²⁵.

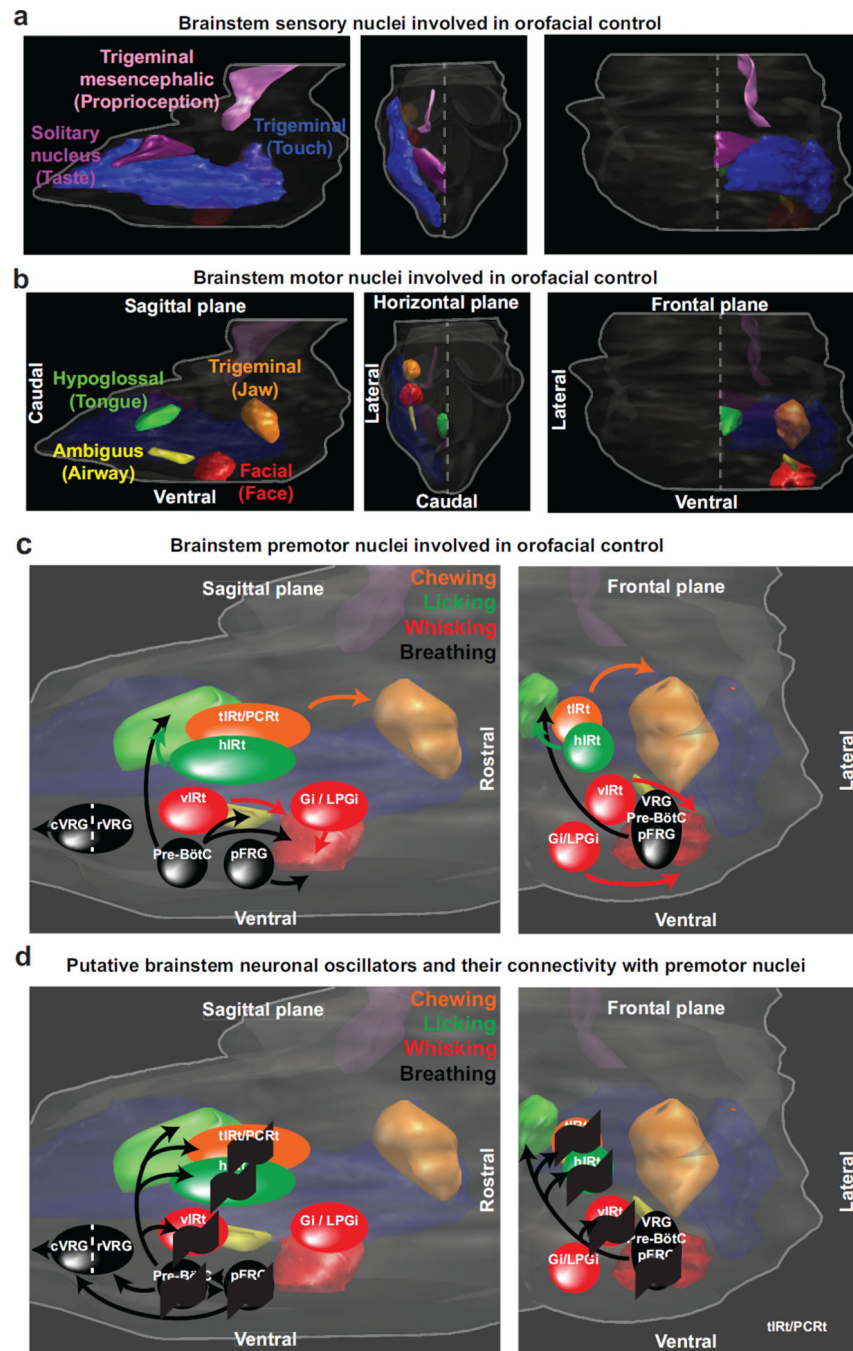


Figure 3. Anatomy of neural circuits involved in generating and coordinating orofacial actions
(a) Three-dimensional reconstruction of the pons and medulla, which contain regions that receive primary somatosensory inputs. Cutaneous inputs from the face innervate the trigeminal sensory nuclei (blue). 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 **panel b**.

(b) The same reconstruction as in **panel a**, showing the pools of cranial motoneurons that control the jaws (orange), face (red), airway (yellow), and tongue (green). Conventions are as in **panel a**. Light transparent structures correspond to the sensory nuclei in **panel a**.

(c) The same reconstruction as in **panels a and b**, showing the approximate locations of known premotor nuclei to each of the motoneuron pools in **panel a**. Premotor 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. Abbreviations are as follows: parvocellular reticular formation (PCRt), caudal/rostral ventral respiratory groups (cVRG and rVRG, respectively), hypoglossal/vibrissa/trigeminal intermediate reticular formation (hIRt, vIRt, tIRt, respectively), preBotzinger complex (Pre-BotC), parafacial respiratory group (pFRG), gigantocellular reticular formation (Gi), lateral paragigantocellular reticular formation (LPGi), and dorsal principal trigeminal nucleus (dPrV).

(d) The same reconstruction as in **panels 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 **panels a–c**. The location of the chewing oscillator remains unresolved.