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Low- and high-level coordination of orofacial motor actions

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Abstract

Orofacial motor actions are movements that, in rodents, involve whisking of the vibrissa, deflection of the nose, licking and lapping with the tongue, and consumption through chewing. These actions, along with bobbing and turning of the head, coordinate to subserve exploration while not conflicting with life-supporting actions such as breathing and swallowing. Orofacial and head movements are comprised of two additive components: a rhythm that can be entrained by the breathing oscillator and a broadband component that directs the actuator to the region of interest. We focus on coordinating the rhythmic component of actions into a behavior. We hypothesize that the precise timing of each constituent action is continually adjusted through the merging of low-level oscillator input with sensory-derived, high-level rhythmic feedback. Supporting evidence is discussed.

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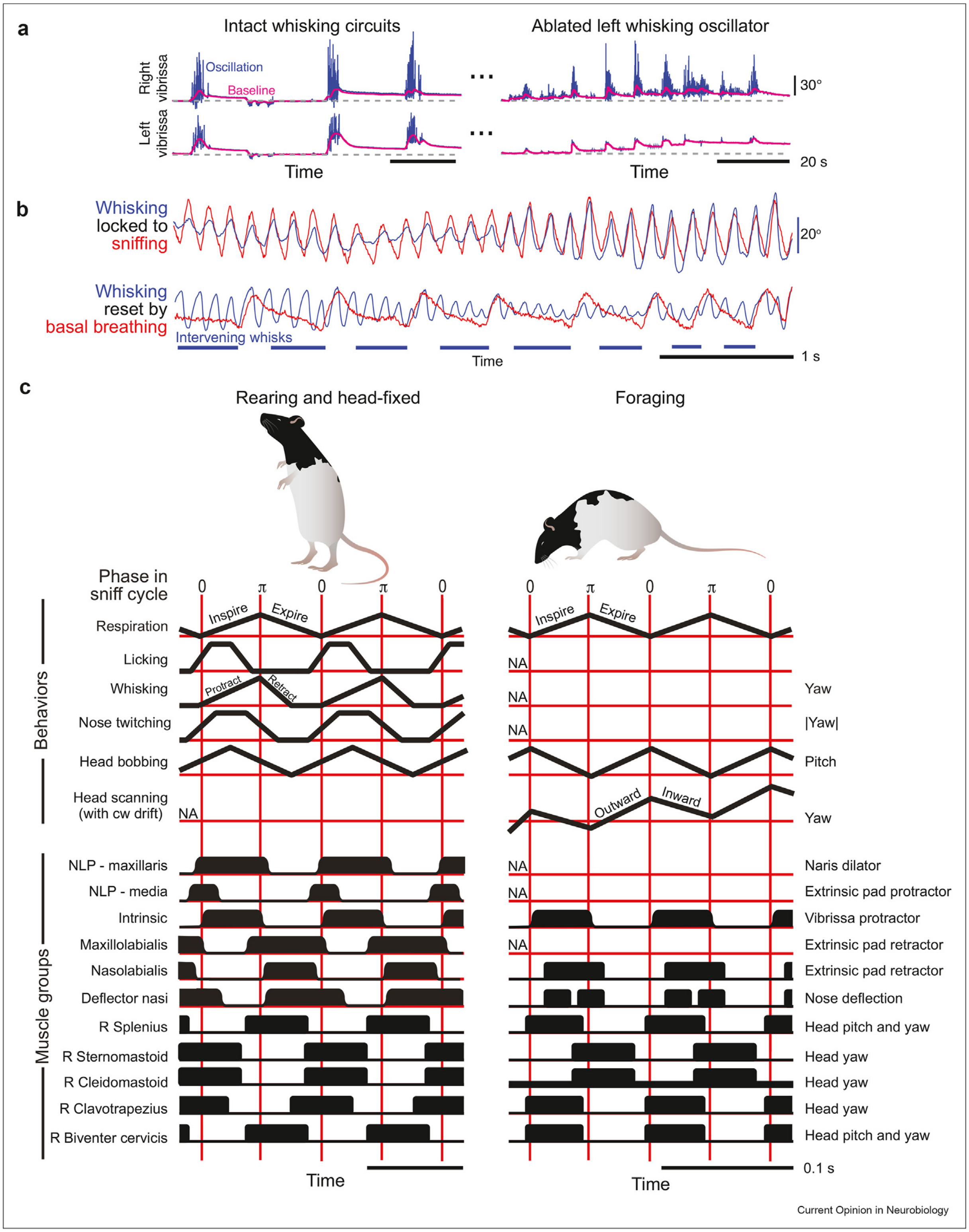
Animal behavior involves a seemingly complex arrangement of body movements. One way to understand behaviors is to decompose them into underlying primitives. This is the well-trodden path that was introduced by the neuroethologist Nikolaas Tinbergen [1]. The primitives are called motor actions. Actions refer to the movement of individual actuators by the underlying muscles and their control by neuronal motor circuitry. While this is an approximation that appeals to an engineering-like deconstruction of behavior in terms of modularity and hierarchical control, the analysis of a multitude of behaviors has supported the utility of this approach [2,3].

Many motor actions, and certainly those associated with orofacial and head movements, can be readily decomposed into a rhythmic component of the actuator movement and into a broad-band component that underlies a change in set-point or posture of the actuator. What is an example of experimental evidence for these two components? As illustrated by whisking, the rhythmic movement of the vibrissae consists of a rapid to-and-fro movement in a horizontal plane (blue, Figure 1a). The oscillations of the vibrissae typically persist for many cycles and support sampling of a large volume of space. To the extent that different orofacial senses, e.g., vibrissa touch and smell, are supported by rhythmic movement [4], the modulation of the phase of such movements can provide a reference signal to decode multi-sensory inputs [5,6].

The broadband component of sensor movement tracks changes in the baseline position (magenta, Figure 1a). This component is typically slow compared to the period of rhythmic oscillations. Set-point or posture signals shift the region of interest sampled by orofacial sensors.

Figure 1



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Relationship of orofacial motor actions to breathing. (**a**) Vibrissa movement (blue) recorded with one-dimensional videography during whisking and nonwhisking intervals. Lesioning the vibrissa oscillator (vIRt) in one hemisphere quenches rhythmic whisking yet does not interfere with changes in baseline (set-point) protraction (red). The baseline protraction is seen to track between the two sides of the face before the lesions and after, even though rhythmic whisking is lost on the lesioned side. Adapted from Ref. [13]. (**b**) Whisking under two states in a head-fixed rat recorded with one-dimensional videography. The upper trace shows rapid, exploratory whisking (blue) that is phase-locked to sniffing (red), as recorded with a thermocouple implanted in

Examples include the forward thrust of vibrissae during exploration [7,8] and social contact [9]. Importantly, a change in set-point of an orofacial sensory may be tied to a change in heading; this occurs when a shift in vibrissa set-point compensates for head rotation [7,10].

Are rhythmic and postural broad-band components under independent control in behaving animals? A region of the medulla that contains the oscillator circuit for the rhythmic motions, the vibrissa intermediate reticular zone (vIRt), can be selectively disrupted on one side of the brain [11,12]. This causes the rhythmic whisking to disappear only on that side, while the baseline or set-point signal persists [13] (Figure 1a). Further, rats can be trained to manipulate their baseline signal independent of rhythmic whisking [14] and can dissociate whisking amplitude, an additional broadband signal, from timing [15]. These data point to the division and independent function of rhythmic and broadband signals into separate circuits. Ongoing studies of tongue movement suggest a similar division of function between such circuits (FW, unpublished).

A common source for modulation of rhythmic movements was suggested in the prescient work of Wallace I. Welker [16], who found that motor actions could be tied to the breathing cycle [4,11,17]. We again use the vibrissa system to illustrate these dynamics. When a rodent is foraging or rearing during exploration, breathing is fast and referred to as sniffing. In this case, whisking and sniffing are phase-locked at a one-to-one ratio [11,18] (Figure 1b). In contrast, there are epochs when animals breathe slowly but still whisk, with two or more whisks per breath. Here, breathing resets the whisking cycle, which otherwise runs freely between breaths [11] (Figure 1b). Phase-locking to the breathing cycle is not limited to whisking and occurs for all orofacial motor actions explored to date; examples include licking [19,20], nose twitching [4,17], shifts in the mystacial pad [11,17], which contains the follicles that move the vibrissae and sense touch, and sweeping of the head along all three Euler axes [4,17] (Figure 1c). Critically, coordination of movement with breathing is seen in the electromyogram of the muscles that drive these movements, implying that the breathing oscillator exerts influence through neuronal projections to the underlying circuits for the different motor actions [21,22]. Thus, the breathing oscillator, together with biophysical time delays for different actions, can provide the basic temporal pattern of orofacial behaviors.

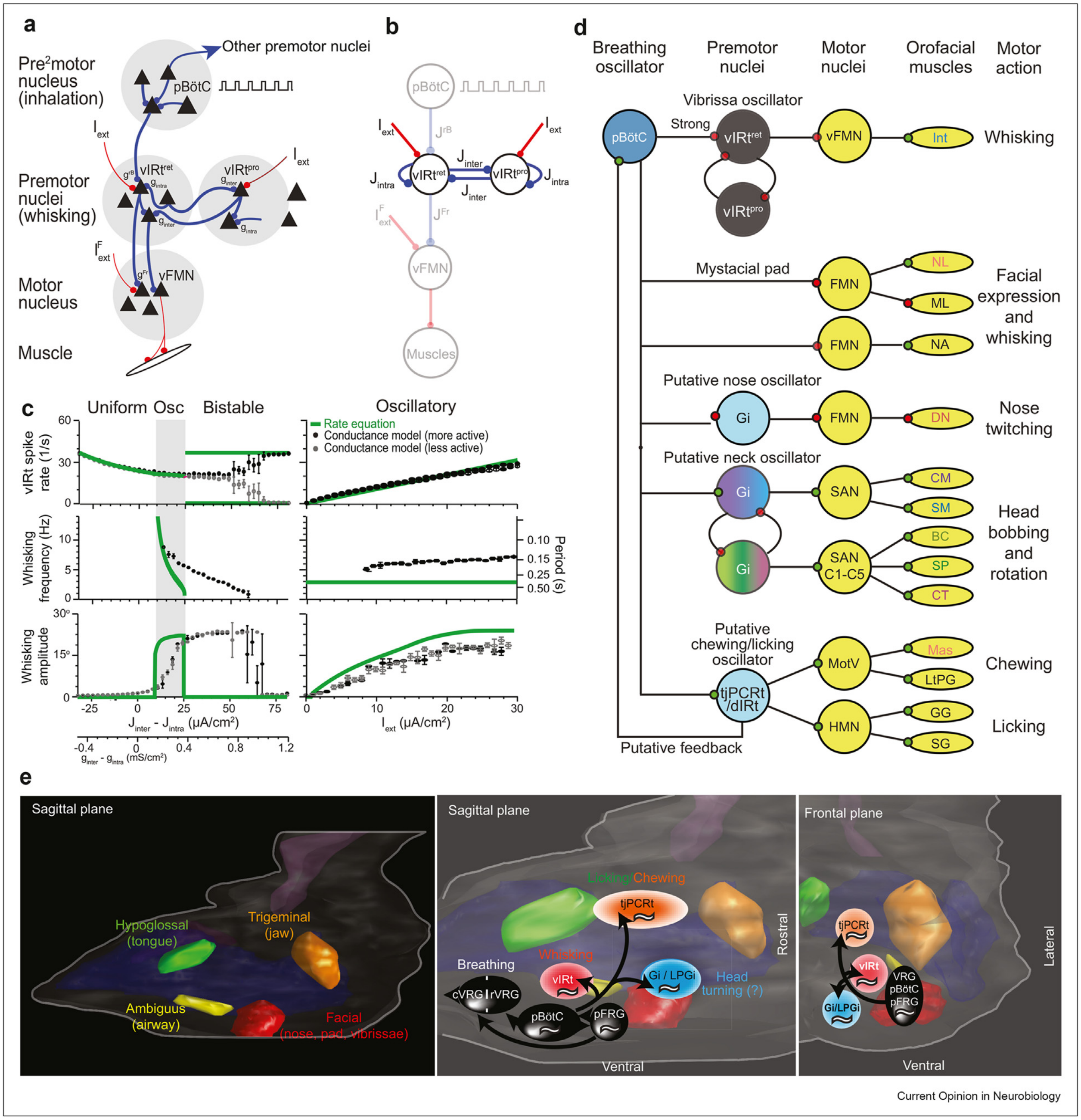
What are the ethological advantages of having orofacial behavior locked to a common oscillator? It appears that the onset of each breath initiates a “snapshot” of the orofacial sensory environment. Experimental data indicates that the phase relationship between breathing and motor actuators is altered by the behavioral context of the task [17]. In the case of a rat searching for food within an arena, the phase of head and nose movements relative to breathing, but not those of the vibrissae, concomitantly shifts by nearly π radians as the animal transitions from foraging with its head down and nose close to the floor to rearing up on its hindlimbs [17] (Figure 1c). During foraging, the nose moves into a new position before a breath is completed so that a fresh sample of odorant is obtained. These data highlight how the large-scale coordination of rhythmic motor actions may be optimized for behavioral context. Fine-scale coordination, as we will discuss, is an open issue.

Are there autonomous oscillators for motor actions, and if so, how does breathing entrain them? A concerted effort over the past decade revealed the circuitry for a hierarchical arrangement of oscillators that drives rhythmic whisking [11,12,23,24]. First, whisking can be autonomously generated by two subpopulations of neurons in the intermediate region of the medulla that constitute the vIRt oscillator. These neurons appear to be regularly spiking, i.e., there is no evidence for intrinsic oscillatory or bursting dynamics. The neurons in each subpopulation form solely inhibitory synaptic connections among themselves (g_{intra}, Figure 2a), as well as inhibitory connections between the two subpopulations (g_{inter}, Figure 2a). One subpopulation is active in phase with whisking, referred to as vIRt^{pro}, and the other is in antiphase with whisking, referred to as vIRt^{ret}. Neurons in the vIRt^{ret} subpopulation express parvalbumin and send inhibitory projections to the facial motoneurons that drive the vibrissae intrinsic muscles. Thus, the oscillatory component of whisking is driven by inhibition. The complete action involves the depolarization of the facial motoneurons that drive the intrinsic muscles to protract the vibrissae—this is a broadband signal—and oscillatory inhibitory input from the vIRt^{ret} to rhythmically hyperpolarize the facial motoneurons and retract the vibrissae. This circuit can be active in the absence of breathing, such as during the “intervening whisks” (Figure 1b), during which the retraction phase is passive [11].

Neurons in the vIRt^{ret} subpopulation receive strong inhibitory input from the preBötzinger complex

the nasal cavity. The lower trace shows whisking during slow, basal breathing; note the 3 to 5 whisks per breath that are referred to as intervening whisks and the reset of whisking by the onset of inhalation. Adopted from Ref. [11]. (**c**) Compilation of the timing of all rhythmic orofacial motor actions in rats with the behavior and underlying muscle activity plotted relative to phase in the breathing cycle. A phase of zero corresponds to the onset of inhalation. The data are segregated by behavioral state. Rearing corresponds to free-ranging animals that are elevated on their hind paws and breathe at a mean rate of 8 Hz; the timing of motor actions appears to be the same for head-fixed animals as for rearing animals. Foraging refers to animals with their noses close to the ground that locomote on all four limbs and breathe at a mean rate of 11 Hz. Abbreviation: NA, data not available. Adopted from Refs. [4,17].

Figure 2



The circuit for the whisking oscillator and its proposed extension for other orofacial motor actions. (**a**) Cartoon of the basic circuit derived from the experimental evidence [11,12,23]. The preBötzinger complex (pBötC) provides a rhythmic inhibitory input to entrain or reset the whisking oscillator (Figure 1b), formed by inhibitory neurons in the vIRt^{pro} and vIRt^{ret} clusters. The neurons in each cluster interact through synaptic connections with conductance g_{intra}, while those in different clusters interact with conductance g_{inter}. All neurons receive an external excitatory input I_{ext}. Neurons in the vIRt^{ret} cluster project to motoneurons in the vibrissa region of the facial motor nucleus (vFMN). These cells receive an excitatory external input I^{F}_{ext} that protracts the vibrissae. Adopted from Ref. [24]. (**b**) Schematic of the reduced vIRt oscillator for mean-field analysis. The individual synapses have been replaced by net currents, with J_{intra} as the current within each of the vIRt^{pro} and vIRt^{ret} clusters and J_{inter} as the current between the vIRt^{pro} and vIRt^{ret} clusters. Adopted from Ref. [24]. (**c**) Results from the mean-field analysis, which yields equations for the average rate of spiking, whisking amplitude, and whisking frequency (green). We also show the results from the numerical simulation of the conductance-based equations using detailed parameters for the network (light and dark gray). The left column highlights the three regions of operation as a function of the differential synaptic current J_{inter} - J_{intra}. The right column highlights the change in performance as a function of the input current. The simulations yield the same three regions of operation, but with a broader range for the oscillatory state that now permeates the bistable region of operation. Adopted from Ref. [24]. (**d**) Compilation of the known and hypothesized circuitry for entrainment of all rhythmic orofacial motor actions and head movement to breathing during epochs of exploration and, for the case of the tongue and jaw, to a putative feeding oscillator during chewing. Whisking involves oscillatory drive from the vibrissa intermediate reticular zone (vIRt) to the vibrissa facial motoneurons (vFMN) that project to the intrinsic (Int) muscles in the mystacial pad that protract the follicles. During sniffing, (pBötC) that drives inspiration [25–27]. Thus, the onset of inspiration will reset the output of $vIRt^{ret}$ neurons. The apparent synchronization of whisking with sniffing is a consequence of inhibition-of-inhibition (Figure 1b) on each whisking cycle. Such synchronization is also accompanied by active movement of the mystacial pad that boosts protraction and provides active retraction [28]. While the connection from the pBötC to the vIRt is strong, the feedforward nature of the hierarchy allows the rhythmicity to be conceptualized as two modules (Figure 2a): one formed from the $vIRt^{pro}$ and $vIRt^{ret}$ subpopulations that can autonomously oscillate, and the other formed from the pBötC and the $vIRt^{ret}$ subpopulation, with $vIRt^{ret}$ neurons functioning as an inhibitory relay of the pBötC oscillatory output.

The sum of the experiment work is sufficiently complete to permit a detailed conductance-based model of the vIRt as well as the reduction of this model to mean-field equations [29]. This approach yields formulas and thus insight into the control of ethologically relevant parameters such as the amplitude and frequency of whisking. Yet it involves the assumptions that the number of cells is arbitrarily large, the rate of spiking is sufficiently high so that individual spikes are not informative per se, and that the adaptation current that underlies the rhythm is arbitrarily slow compared to the time of synaptic transmission. With these assumptions in mind, what have we learned from a mean-field approach to understanding the vIRt [24] (Figure 2b)? First, the circuit has three regions of operation as a function of the difference in connection strengths between neurons in the $vIRt^{pro}$ and $vIRt^{ret}$ subpopulations (Figure 2c). When the total synaptic input from neurons in the same subpopulation exceeds that from the neighboring subpopulation ($J_{intra} > J_{inter}$, Figure 2c), all $vIRt^{pro}$ and $vIRt^{ret}$ neurons are uniformly active. This can lead to constant protraction of the vibrissae. Oscillations emerge when the synaptic input from the neighboring subpopulation dominates (gray band for $J_{inter} > J_{intra}$, Figure 2c), yet only for a range of differences where the cellular adapting current is sufficient to quench spiking. As the relative strength of the synaptic input between subpopulations increases, the adapting current cannot be overcome, and the circuit ceases to oscillate. The dynamics transition to a bistable output, much like networks with crossed inhibition that are proposed to explain perceptual rivalry [30]. Thus, the architecture of the brainstem oscillator for whisking may serve a variety of computational roles.

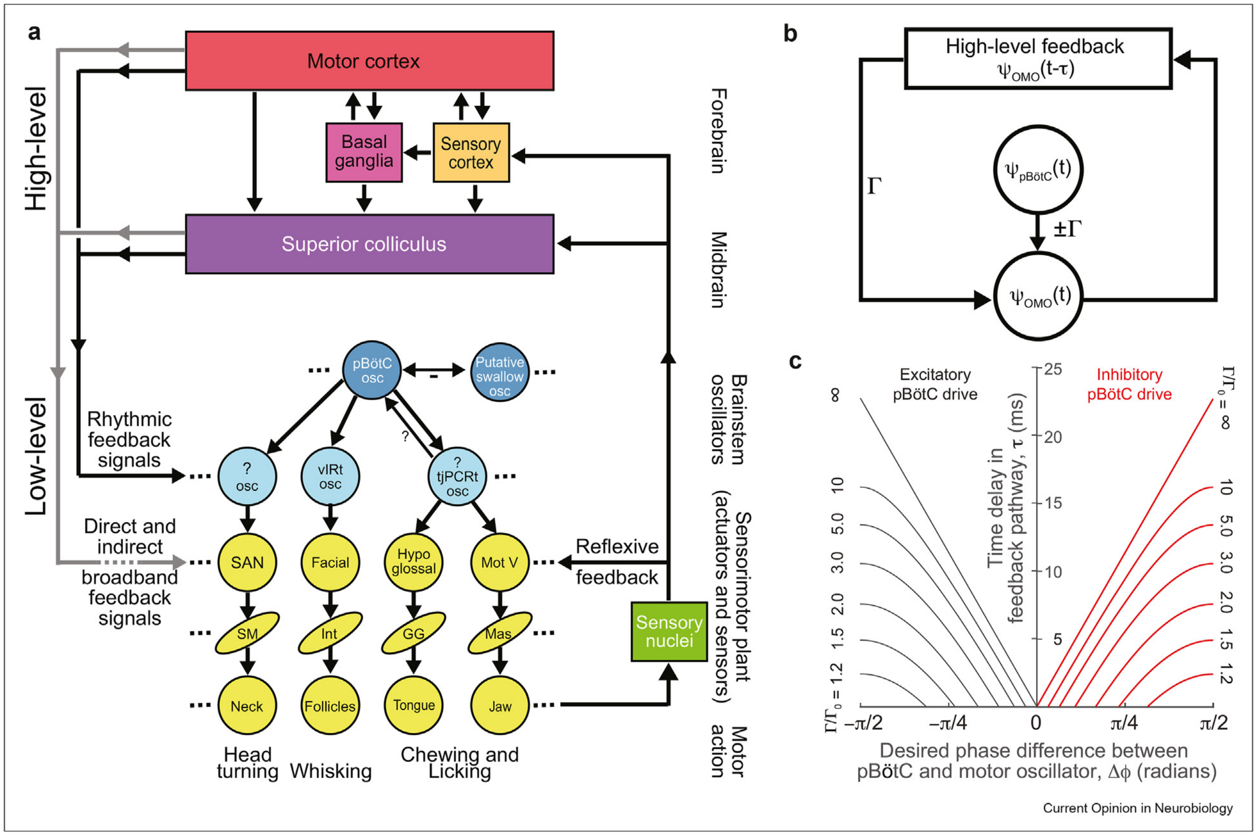
The model for the vIRt exhibits strong modularity of function within the oscillatory phase (green curves, Figure 2c). The frequency of oscillation depends only on the relative strength of the synaptic inputs (J_{inter} - J_{intra}, Figure 2c) and not on the strength of the external drive (I_{ext}, Figure 2c). On the other hand, the amplitude of whisking depends only on the strength of an external drive. Numerical simulations of the conductance equations for this network, which contains a realistic number of neurons and does not involve simplifying assumptions, confirm these conclusions. Further, the simulations show that spike-to-spike variability that emerges from the small size of the network will increase the extent of the oscillatory region but not alter our conclusions on modularity (gray and black dots, Figure 2c). Thus, “Deus sive Natura” has generated a circuit that functionally isolates the different control parameters.

It remains to be determined if the hierarchical circuit for whisking generalizes across other orofacial motor actions that, at least partially, are phase-locked to breathing (Figure 1c). It is likely that the circuit for the rhythmic components of head bobbing (pitch) and rotation (yaw and roll) follows a similar scheme [17] (Figure 2d). The oscillator for rhythmic nose movement remains unknown [31]. The extrinsic facial muscles in the mystacial pad are driven directly by input from the pBötC [11], as opposed to the intrinsic vibrissa muscles that act on the follicles and are driven through the vIRt (Figure 2d). Rhythmic motion of the tongue and jaw appears to depend on a premotor oscillator [32–34] (Figure 2d); interestingly, the rhythm of tongue and jaw movement will shift from locking to breathing during licking and exploration to free-running during chewing (DK and S-ML unpublished). The nominal positions of the pBötC and the different premotor oscillators are presented in Figure 2e.

facial muscles also drive the nasalis (NA), the extrinsic protractor muscle, and the maxillolabialis (ML) and nasolabialis (NL), the extrinsic retractor muscles, that move the pad in coordination with whisking. Nose twitching involves a yet undescribed oscillator, likely in the gigantocellular (Gi) region of the reticular formation, that projects to motoneurons in the facial motor nucleus that innervate the deflector nasi (DN). Head turning involves a yet undescribed oscillator, also likely in the Gi region of the reticular formation, that projects to motoneurons that form part of the spinal accessory nucleus (SAN) and drive the sternomastoid (SM) and cleidomastoid (CM) muscles in the neck and projects to motoneurons in the spinal level C1 to C5 ganglia that drive the clavotrapezius (CT), the splenius (SP), and the biventer cervicis (BC) muscles in the neck. Licking and chewing involve an oscillator under study in the tongue-jaw region of the parvocellular reticular formation (tjPCRt), with a potential accessory nucleus in the dorsal aspect of the intermediate reticular zone (dIRt) that presumably drives the hypoglossal motonucleus (hMN) and the trigeminal motonucleus (MotV). Trigeminal MotV drives the masseter (Mas), temporalis, and medial pterygoid jaw closing muscles and the lateral pterygoid (LtPG) jaw opening muscle. The hypoglossal nucleus drives the genioglossus (GG), the protractor muscle, the hyoglossus and styloglossus (SG), the retractor muscles, and the palatoglossus, the elevation muscle. Extension of the summary in Ref. [17]. (**e**) Anatomy of neural circuits involved in generating orofacial actions. The left panel is the three-dimensional reconstruction of the pons and medulla, showing the pools of cranial motoneurons that control the jaws (orange), face (red), airway (yellow), and tongue (green). The middle and right panels are brainstem oscillators (marked as “~”) and their connections. Breathing-related regions are shown in black. Additional abbreviations: caudal/rostral ventral respiratory groups (cVRG and rVRG, respectively), parafacial respiratory group (pFRG), and lateral paragigantocellular reticular formation (LPGi).

Is the timing of different orofacial motor actions fine-tuned during a behavior? Recent experiments on corrective actions of the tongue alone suggest the likelihood of this strategy [35,36]. How might this occur? We address the feasibility of corrective measures from a computational perspective. Our hypothesis is that the pBötC sets the initial phase differences among the motor actions in a behavior and that adjustments occur on a cycle-by-cycle basis to best complete a task. In its simplest form, the pBötC entrains the oscillators for each motor action through connections at the level of the brainstem, i.e., low-level control (Figure 3a). The sensation of movement then provides the basis for a feedback input to each oscillator. The relative timing between the different orofacial motor actions is presumed to be computed in the sensory and motor cortices and/or the superior colliculus (SC), both of whose outputs project to the proper premotor nuclei in the

Figure 3



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Hypothetical scheme for concurrent low-level and high-level control of the timing of orofacial motor actions. (**a**) Schematic. "Low-level" neuronal computation corresponds to orofacial motor oscillators, shown here as premotor nuclei, that are entrained by output from the pBötC and drive a particular group of muscles. Peripheral reference and/or proprioception lead/s to inputs to the midbrain and forebrain and "high-level" computations that feedback to the premotor oscillators and potentially the motor nuclei. The high-level computations adjust the detailed timing, or equivalently, the phase, of the individual motor actions that comprise a behavior. Head turning involves a yet undescribed oscillator, likely in the gigantocellular (Gi) region of the reticular formation, that projects to motoneurons that form part of the spinal accessory nucleus (SAN) and drive the sternomastoid (SM) and cleidomastoid muscles in the neck and projects to motoneurons in the spinal level C1 to C5 ganglia that drive the clavotrapezius, the splenius, and the biventer cervicis muscles in the neck. Whisking involves oscillatory drive from the vibrissa intermediate reticular zone (vIRt) to the facial motoneurons that project to the intrinsic (Int) muscles in the mystacial pad that protract the follicles. During sniffing, facial muscles also drive the nasalis, the extrinsic protractor muscle, and the maxillolabialis and nasolabialis, the extrinsic retractor muscles, that move the pad in coordination with whisking. Licking and chewing involve an oscillator under study in the parvocellular reticular formation (tjPCRt) that presumably drives the hypoglossal motonucleus and the trigeminal motonucleus (MotV). The hypoglossal nucleus drives the genioglossus (GG), the protractor muscle, the hyoglossus and styloglossus, the retractor muscles, and the palatoglossus, the elevation muscle. Trigeminal MotV drives the masseter (Mas), temporalis, and medial pterygoid jaw closing muscles and the lateral pterygoid jaw opening muscle. (**b**) Schematic of a minimal phase-coupled oscillator model to demonstrate how combined low- and high-level inputs can tune the phase of a motor action. $\Psi_{\text{pBötC}}(t)$ and $\Psi_{\text{OMO}}(t)$ are the phases of the pBötC output and the orofacial motor oscillator, respectively, Γ is a coupling constant, and the high-level feedback is presumed to alter a delay-time, τ, that is separately optimized for each action. The experimental observation of both inhibitory as well as excitatory projections from the pBötC [22] accounts for the choice of sign of the pBötC to orofacial oscillator connection. (**c**) Plot of the calculated phase difference, $\Delta\phi$, between the output of the pBötC and that of the orofacial oscillator as a function of delay-time, coupling constant, and sign of the pBötC to orofacial oscillator connection. We used $f_{\text{pBötC}}$ = 11 Hz, and f_{OMO} = 8 Hz, and note that $\Gamma_0 \equiv 2\pi(f_{\text{pBötC}} - f_{\text{OMO}})$.

medulla [37] (Figure 3a). A related idea has been suggested for fine control of locomotion [38].

A toy model based on coupled phase oscillators [39] highlights how, in principle, the confluence of low- and high-level pathways can reliably control the relative timing between motor actions (Figure 3b). In these models, only the timing of the actions and not the magnitude of their motion is varied. Our interest is in small changes in timing, or, equivalently, phase, within one period of a rhythmic cycle. We consider the control for a single motor action and take the feedback pathway to impose a time delay τ relative to the brainstem pathway. We write:

$$\frac{d\psi_{pB\ddot{o}tC}(t)}{dt} = 2\pi f_{pB\ddot{o}tC}$$

and

$$\frac{d\psi_{OMO}(t)}{dt} = 2\pi f_{OMO} \pm \Gamma \sin\left[\psi_{pB\ddot{o}tC}(t) - \psi_{OMO}(t)\right] + \Gamma \sin[\psi_{OMO}(t-\tau) - \psi_{OMO}(t)]$$

where $\psi_{pB\ddot{o}tC}(t)$ is the phase and $f_{pB\ddot{o}tC}$ is the frequency of the pBötC oscillator, $\psi_{OMO}(t)$ is the phase and f_{OMO} is the free-running frequency of the orofacial motor oscillator, and the coupling constants, Γ, are taken as positive and equal with a sign that accounts for the nature of the pBötC to motor nucleus connection [40], i.e., inhibitory for the vibrissa (Figure 2a). Under entrainment, $\psi_{OMO}(t) = \psi_{pB\ddot{o}tC}(t) + \Delta\phi$ where $\Delta\phi$ is the desired phase delay between ψ_{OMO} and $\psi_{pB\ddot{o}tC}$. The required delay τ is (Figure 3c):

$$\tau = \frac{1}{2\pi f_{pB\ddot{o}tC}} \sin^{-1}\left(\mp \sin\Delta\phi - 2\pi \frac{f_{pB\ddot{o}tC} - f_{OMO}}{\Gamma}\right).$$

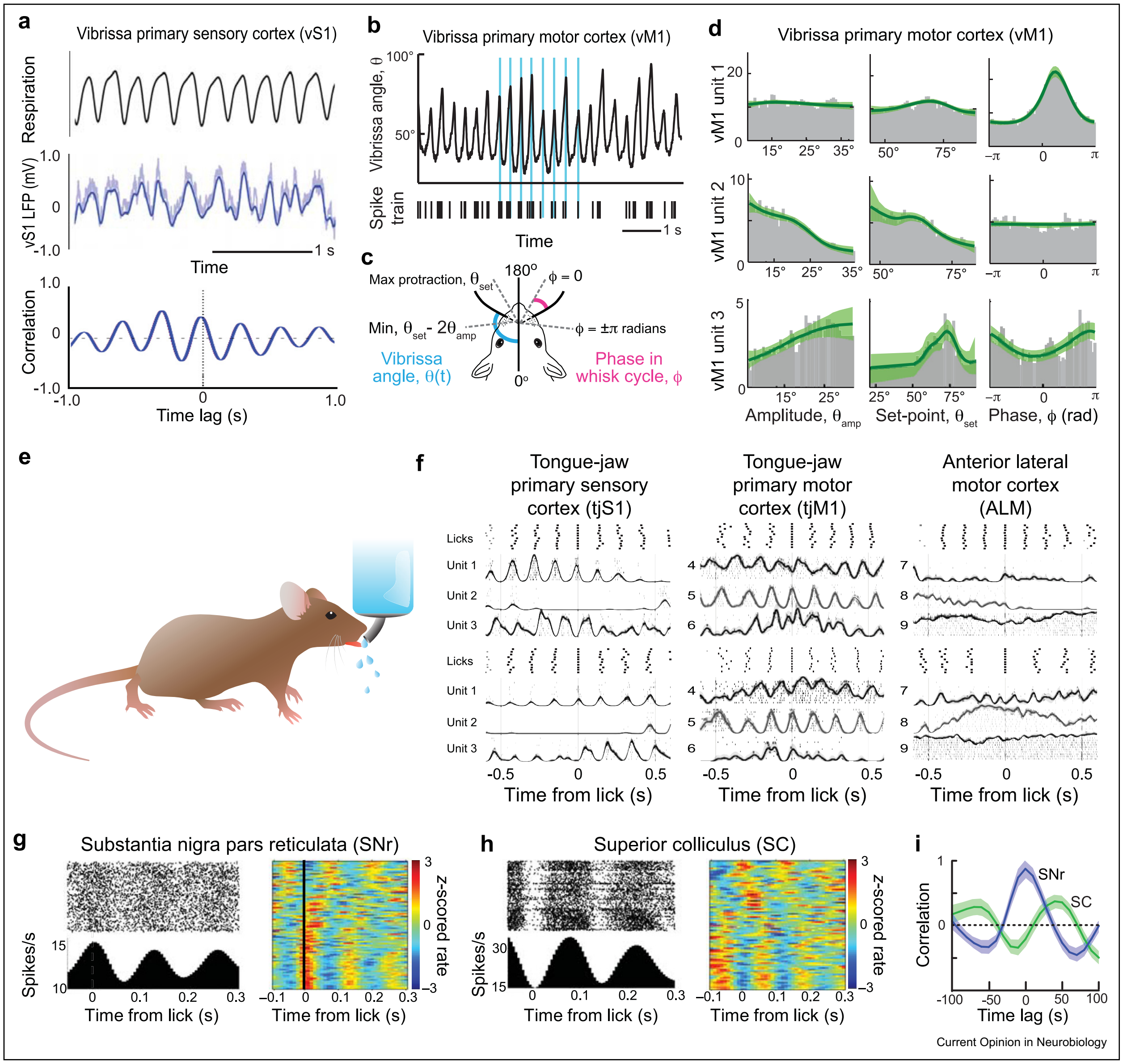
This analysis, using experimental values for $f_{pB\ddot{o}tC}$ and f_{OMO} [17] (Figure 3c), shows that near linear modulation of the relative phase between a motor action and breathing is achieved for physiological values of τ and a value of Γ chosen to comply with the range of the phase shift. This scheme can be readily generalized to multiple actions, where the contribution of each motor action to a behavior is tuned by high-level control. Lastly, rhythmic feedback can also be directed to the motor nuclei (Figure 3a) for an additional phase shift through linear summation that is enabled by the high firing rate of motoneurons [41].

Our model requires the involvement of "high-level" areas in the midbrain and forebrain to receive phase information about breathing cycles and to compute feedback signals to premotor and possibly motor nuclei for each motor action. The breathing signal may be derived from olfactory pathways and/or peripheral reference. Behaviors that combine head movement and whisking [7,10], or head movement and licking [42], provide a natural approach to test our hypothesis. What is the current evidence to support this approach? For the vibrissa system, self-motion during exploration leads to rhythmic modulation of the spike rate of neurons in the vibrissa primary sensory (vS1) cortex that are phase-locked to breathing [43] (Figure 4a). Projections from the vS1 cortex to targets in the spinal trigeminal nuclei provide feedback to alter whisking [44,45]. At the level of vibrissa primary motor (vM1) cortex, the spike rate of individual units is modulated by phase in the whisk cycle during exploration [46] (Figure 4b–d), which we interpret as modulation by breathing in these experiments. Like the case for vS1 cortex, projections from vM1 cortex influence orofacial output through projections to the spinal trigeminal nuclei [47], as well as through the SC.

Evidence in support of our hypothesis within the lingual system is encouraging (Figure 4e–i). Rhythmic modulation of spike rates is observed in tongue-jaw primary sensory (tjS1) and primary motor (tjM1) cortices in mice during tasks that report rhythmic licking of a spout [36] (Figure 4f). Rhythmic licking signals are further observed in the anterior lateral motor (ALM) cortex [35,36] (Figure 4f); related work in macaques indicates similar coordination during feeding [48]. Of particular importance, transient inactivation of ALM cortex leads to a loss of fine control of tongue extension [35], thus implicating motor cortex in the fine control of orofacial motor actions. Projections from the motor cortex act directly on brainstem premotor nuclei and indirectly through the SC, which projects to a plethora of brainstem targets [37] and can modulate exploration in phase with breathing [49]. Finally, robust rhythmic signals concurrent with tongue extrusion are found in the output from the basal ganglia, i.e., the lateral part of the substantia nigra pars reticularis (SNr), to the SC as well as within the lateral part of the SC [50] (Figure 4g–i). In total, these studies support the feasibility of mapping the high-level circuitry that adjusts the timing of the rhythmic actions that form an orofacial behavior.

Beyond sensorimotor regions, research over the past decade has underscored the presence of neural oscillations that couple with the respiratory rhythm across the "highest order" brain regions including those not specifically implicated in olfactory processing. In rodents, this includes the parietal cortex [51], the medial prefrontal cortex [52–54], the dorsomedial prefrontal cortex [55], the hippocampus [52,53,56,57], and the amygdala [53,58]. Moreover, the phase of the respiration rhythm can entrain other brain rhythms; for instance, the amplitude of gamma oscillations in the prefrontal cortex [43,59] is modulated by the breathing rhythm, as

Figure 4



Oscillations in neuronal activity in forebrain and midbrain structures that are linked to breathing. (**a**) The top two traces show an example of a concurrent measurement of breathing with a thermistor embedded in the nasal cavity and the local field potential in the vibrissa primary sensory (vS1) cortex. The bottom trace shows the cross-correlation, which has essentially no time lag. Adopted from Ref. [43]. (**b**) Recording of vibrissa position using one-dimensional videography concurrent with single-unit recording in vibrissa primary motor (vM1) cortex. The blue lines indicate an epoch of spikes that are tightly timed for whisking. Note that breathing was not recorded in these animals, but the animal whisked in a manner that was subsequently associated with breathing [11,18]. Adopted from Ref. [46]. (**c**) Schematic that illustrates the transformation of the measured vibrissa motion, in terms of angle relative to the midline, into phase coordinates. A Hilbert transform converts the angle, denoted θ(t), into set-point (θ_{set}), amplitude (θ_{amp}), and phase (ϕ) components defined by $\theta(t) = \theta_{set}(t) - \theta_{amp}(t)[1+\cos\phi(t)]$. Adopted and modified from Ref. [46]. (**d**) The result of a Hilbert decomposition for the coding of vibrissa position by three different units in the vM1 cortex. Units 1 and 3 show a dependence on phase in the whisk cycle in addition to the more slowly varying setpoint and amplitude. Adopted from Ref. [46]. (**e**) Sketch of a rodent licking. Original art by Julia Kuhl. (**f**) Recordings from three different cortical areas related to movement of the tongue including the primary sensory (tjS1), primary motor (tjM1), and anterior lateral motor (ALM) cortices. The animal performed a sequential licking task across an array of spouts. Note that breathing was not recorded in these animals, but the animal licked in a manner that is associated with breathing [11,18]. Shown are raster plots for three units per area with time-zero aligned to a lick in the middle of a sequence. The top three traces show responses for right-to-left licking across the array of spouts, and the bottom three traces show responses for left-to-right licking. Adopted from Ref. [36]. (**g**) Activity in the major output nucleus of the basal ganglia, the substantia nigra pars reticularis (SNr), is time-locked to the lick cycle in mice. The left trace is the rate histogram of spikes that occurred within a bout of licking. The oscillations in the neuronal activity are tightly coupled and positively correlated with the oscillations of the lick cycle; while breathing was not recorded in these animals, the animal licked in a manner that is associated with breathing [11,18]. The dashed line indicates the time of spout contact. The right trace is the spike density for a population of neurons. Each row corresponds to the activity of one cell. Adopted from Ref. [50]. (**h**) Activity in the superior colliculus (SC) is time-locked to the lick cycle in mice. All conditions are the same as in panel G, except that here the oscillations in the neuronal activity are negatively correlated with the oscillations of the lick cycle. Adopted from Ref. [50]. (**i**) The spike-triggered average, i.e., the correlation and standard error of the mean, of neural activity in the SNr and SC at the start of each lick show that neurons in the SNr and SC exhibit antiphase oscillations during licking. Adopted from Ref. [50].

are the timing of cortical “on and off” states [53] and hippocampal sharp-wave ripples [53,56]. Thus, breathing rhythm plays a role in the integration of sensory input with memory and emotional state.

Is there a role for respiration as a timing mechanism in cognition? Recent studies in humans highlight the potential broad behavioral effects of respiration on nonolfactory cognition. For instance, nasal but not oral respiration is reported to improve performance accuracy in a visual-spatial task [60], fear discrimination [61], and memory retrieval [61]. Further, the phase in the breathing cycle is coupled with the onset of voluntary self-timed tasks as diverse as motor execution [62,63], motor imagery [63], and visual imagery [63]. These results motivate the need to devise cognitive assays for rodents that permit the assessment of potential mechanistic pathways for respiration-dependent decisions.

To summarize, orofacial motor actions in rodents are coordinated to form orofacial behaviors, in significant part, by the pBötC oscillator for inhalation (Figure 1c). For the case of whisking, the underlying circuit has been delineated as a hierarchy in which a free-running whisking oscillator is reset and, during periods of sniffing, is entrained by breathing (Figure 2a,b). By extension, a similar architecture permits the pBötC oscillator to set the relative timing of all constituent motor actions through low-level control (Figure 2d). We hypothesize that feedback from high-level brain processing can modulate the precise timing of individual actions to optimize the placement of actuators and sensors and thus raise the effectiveness of a behavior. We present a theoretical argument (Figure 3) and experimental evidence (Figure 4) in support of this idea. Going forward, studies to deconstruct the circuits that underlie orofacial behaviors will be aided by advances in fast, automated processing of orofacial movements and facial expression [64,65].

Contributions

The NIH BRAIN circuit team of MD, MNE, DG, DK, DHO and FW set the focus and conceived the organization of this review, ME, DK and S-ML curated the literature, and DK wrote the manuscript with assistance from ME and S-ML.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

Data availability

No data was used for the research described in the article.

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