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CIRCUITS IN THE RODENT BRAINSTEM THAT CONTROL WHISKING IN CONCERT WITH OTHER OROFACIAL MOTOR ACTIONS

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Abstract—The world view of rodents is largely determined by sensation on two length scales. One is within the animal's peri-personal space; sensorimotor control on this scale involves active movements of the nose, tongue, head, and vibrissa, along with sniffing to determine olfactory clues. The second scale involves the detection of more distant space through vision and audition; these detection processes also impact repositioning of the head, eyes, and ears. Here we focus on orofacial motor actions, primarily vibrissa-based touch but including nose twitching, head bobbing, and licking, that control sensation at short, peri-personal distances. The orofacial nuclei for control of the motor plants, as well as primary and secondary sensory nuclei associated with these motor actions, lie within the hindbrain. The current data support three themes: First, the position of the sensors is determined by the summation of two drive signals, i.e., a fast rhythmic component and an evolving orienting component. Second, the rhythmic component is coordinated across all orofacial motor actions and is phase-locked to sniffing as the animal explores. Reverse engineering reveals that the preBötzinger inspiratory complex provides the reset to the relevant premotor oscillators. Third, direct feedback from somatosensory trigeminal nuclei can rapidly alter motion of the sensors. This feedback is disynaptic and can be tuned by high-level inputs. A holistic model for the coordination of orofacial motor actions into behaviors will encompass feedback pathways through the midbrain and forebrain, as well as hindbrain areas.

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Key words: coupled oscillators, facial nucleus, hypoglossal nucleus, licking, orienting, tongue, vibrissa.

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Abbreviations: ALM, anterior lateral motor; IRt, intermediate reticular; PrV, principal trigeminal nucleus; SpVC, spinal subnucleus caudalis; SpVIc, spinal subnucleus caudal interpolaris; SpVIr, spinal subnucleusrostral interpolaris; SpVM, spinal subnucleus muralis; SpVO, spinal trigeminal subnuclei pars oralis; vIRt, vibrissa IRt; VPMdm, ventral posterior medial nucleus of dorsal thalamus.

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INTRODUCTION

Coordination of neuronal circuits in the brainstem is essential for exploration, navigation, feeding, social interaction, and defense. A key advantage of studying such circuitry is the concurrent access that one has to sensory input, via sensory organs, and the muscular output of motor programs. This allows brainstem circuitry to be analyzed in terms of entire sensorimotor loops. In past years, this engineering-themed approach has made the analysis of brainstem circuitry a centerpoint of neuroscience, as highlighted by studies on the control of balance and visual stability in the vestibular and oculomotor system (Lisberger et al., 1987; Gittis and du Lac, 2006), the organization of respiratory centers (Feldman and Del Negro, 2006; Alheid and McCrimmon, 2008, Garcia et al., 2011), and the nature of nociceptive/tactile sensory pathways in the trigeminal system (Dubner et al., 1983).

A challenge in reverse engineering brainstem circuits concerns the identification of the circuit components that merge sets of motor actions into behaviors (Berntson and Micco, 1976). Ongoing efforts to delineate such circuits combine high-resolution behavioral quantification (Kurnikova et al., 2017), simultaneous recordings of brainstem circuits dynamics, and transsynaptic viral tracing (Kleinfeld et al., 2014; Stanek et al., 2014). Our particular focus is on closed sensorimotor loops, from sensor to the motor plant that controls the sensor, formed by orofacial circuits that are involved in active sensing of the nearby environment (Kleinfeld et al., 1999, 2006; Kleinfeld and Deschênes, 2011). This approach, interpreted with the analytical tools of control engineering, provides a means to reverse engineer the brainstem circuits that drive orofacial motor actions as well as coordinate these actions into holistic exploratory and orienting behaviors.

Here, we begin with a description of orofacial behavioral coordination and the underlying muscular control of relevant sensory organs (Fig. 1). These involve rhythmic motions that are tied to sniffing, as well as orienting movements, and include nose motion, head motion, and licking in addition to whisking. A high-level description of the overall organizing principles for the underlying brainstem control circuits is presented (Fig. 2), followed by a synopsis on the circuitry for the coordinated rhythmic aspect of orofacial motor actions (Fig. 3). We then focus on a brainstem-centric view of the known circuitry that drives orienting behaviors, with emphasis on the vibrissae (Fig. 4) and tongue (Fig. 5), organized in terms of a progression from sensory to motor areas. Lastly, our analysis provides an introduction to the notion of nested anatomical loops across multiple levels in the brain, which is illustrated for the vibrissa system by viewing the circuitry (Fig. 4) in terms of feedback loops (Fig. 6).

COORDINATION OF MULTIPLE OROFACIAL MOTOR ACTIONS

The head of a rodent is in constant motion, bobbing from side-to-side and up-and-down, as the animal explores its peri-personal space (Fig. 1A). Further, similar mobility extends to the face itself as the nose moves from side-to-side (Fig. 1B) and the vibrissa scan back and forth (Fig. 1C). One component of this motion is a rhythmic modulation in position that is phase-locked to sniffing, the rapid aspect of breathing. This occurs with a frequency that is centered near 7 Hz in rats and 11 Hz in mice. The rhythmic component is observed in the underlying muscular control (Fig. 1D), which shows that motion of a sensor is not secondary to nearby body movement; this is illustrated for the splenius capitus muscles that drive motion of the neck (Fig. 1A). In fact, the preBötzinger complex, which initiates inspiration, functions as a master oscillator that resets the premotor oscillator for whisking (Moore et al., 2013; Deschênes et al., 2016) and is conjectured to function in a similar fashion for other orofacial rhythmic motor actions (Kleinfeld et al., 2015), including nose motion, head motion, licking, and vocalization. Thus the inspiratory phase of each sniff corresponds to a ‘‘snapshot” of multisensory sampling of the peri-personal space (Fig. 1D).

A second aspect of motor actions for orofacial sensation concerns the slow, coordinated changes in the orientation of the sensors, such as the concerted motion of the head, nose, and vibrissae toward a source of odor (Esquivelzeta Rabell et al., 2017; Kurnikova et al., 2017). It is unknown whether the coordinated movement of each sensor maximizes sensory input, such as by sweeping odorants toward the nose. Actions that involve both vibrissa-touch and olfaction include elements of social interactions (Wolfe et al., 2011) as well as exploration (Yu et al., 2016), and lead to multimodal sensory inputs that are phase-locked to breathing. The coordination of these sensory inputs might lead to enhanced detection of external stimuli (Kleinfeld et al., 2014).

SENSORIMOTOR NETWORK TOPOLOGY

Sensorimotor systems are comprised of nested loops (Kleinfeld et al., 1999, 2006; Bosman et al., 2011). The overarching loop structure consists of central and peripheral parts (Fig. 2). Through the peripheral portion of the loop, sensor movements result in changing sensory signaling. Peripheral reafference, i.e., the sensation of self-motion through the deformation of the body, as well as feedback though contact with objects in the world can directly control subsequent movements.

The central portion of sensorimotor loops comprises pathways that link sensory feedback to motor control. The most direct pathway is a reflex arc in which projections from primary sensory afferents to the motor nucleus drive the motor plant. In parallel with reflex arcs, a multitude of other pathways mediate signal processing at many levels in the brain, including higher controllers, such as the cerebral cortex and cerebellum as we will discuss later. For muscles that participate in rhythmic motor actions, such as walking in the case of locomotion and whisking in the case of vibrissa-touch, an additional input consists of internal autonomous oscillators.

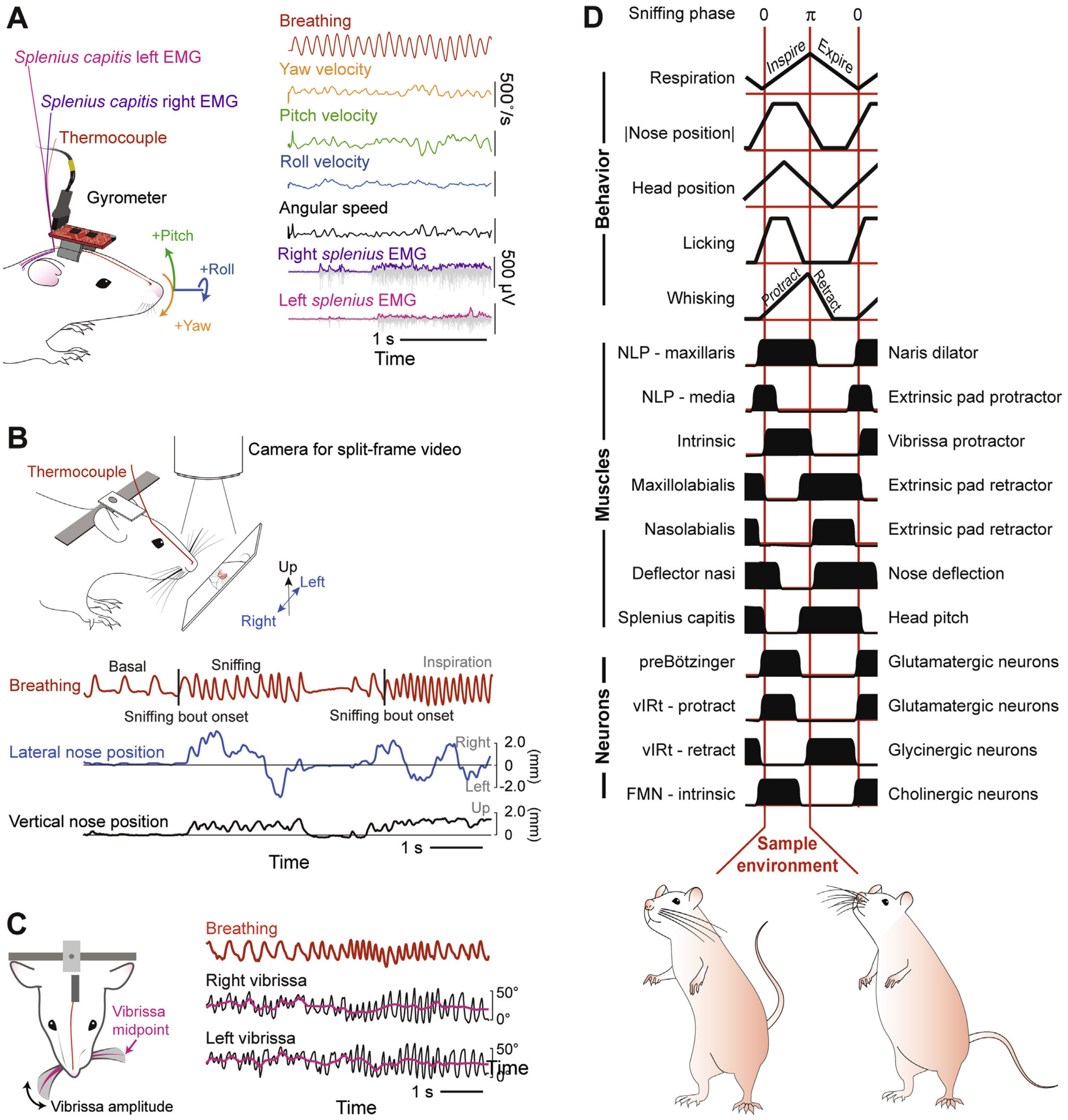


Fig. 1. Orofacial motor actions and their relation to the sniff cycle (A) Example of measurement of head position versus time. Angular velocity of the head and activation of the neck muscles is recorded in the free-ranging animal, along with breathing. Note rhythmic component of motion locked to breathing along with slow deflections. Adapted from Kurnikova et al. (2017). (B) Example of motion of the nose in head-fixed rats captured with videography; the thermocouple records respiration. Basal breathing occurs during rest and sniffing during exploration. Adapted from Kurnikova et al. (2017). (C) Schematic of the view of a camera for tracking the vibrissae. Breathing was measured with a thermocouple. The time-series shows breathing (red) and the position of the left (green) and right (black) C2 vibrissa; the midpoint of whisking (magenta overlay) was computed as the average between the upper and lower envelope of the cycle-by-cycle angle of the vibrissa. Adapted from Kurnikova et al. (2017). (D) Idealized time-ordered patterns of behavioral, neuronal and muscular activities associated with different phases of the respiratory rhythms. Note that the extrinsic pad retractor and protractor muscles may activate during basal respiration when the amplitude of respiration increases. Adapted from Deschênes et al. (2016), Liao and Kleinfeld (2016), Kurnikova et al. (2017).

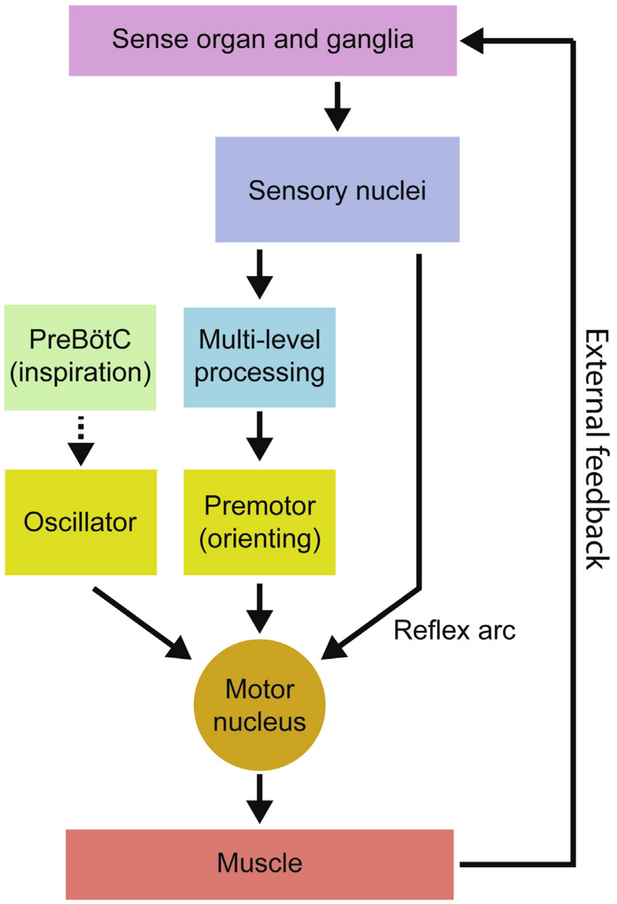


Fig. 2. Schema for the organization of sensorimotor systems. Each orofacial muscle in innervated by motor neurons that receive inputs from diverse sets of premotor neurons located throughout the brainstem. Direct projections from primary sensory nuclei to motor neurons mediate reflexive actions (right), whereas the rhythmic component of muscle activation is controlled by central pattern generator oscillators (left). Additional premotor populations predominantly mediate the effects of broad upstream motor and limbic controllers (central, schematized as a single projection).

HINDBRAIN OSCILLATORS AND COORDINATION OF OROFACIAL MOTOR ACTIONS

The premotor circuitry that drives rhythmic orofacial motor actions depends on several underlying oscillators. The predominant oscillator is the preBötzinger complex for inspiration (Smith et al., 1991; Feldman et al., 2013) (Fig. 3). This initiates the breathing cycle. The subsequent activation of a post-inspiratory complex, thought to be the Bötzinger complex but under re-evaluation (Anderson et al., 2016), leads to expiration. Forced expiration, as occurs during physical exertion, additionally involves the parafacial respiratory group (Molkov et al., 2017). The output from the preBötzinger includes a band of collaterals within the intermediate reticular (IRt) formation that rise toward the ventral edge of the hindbrain (Tan et al., 2010) and span multiple premotor populations of neurons (Moore et al., 2014). The preBötzinger output is now known to modulate the premotor-whisking oscillator, denoted the vibrissa IRt (vIRt) formation (Moore et al., 2013). The vIRt provides rhythmic inhibition of the facial motoneurons that drive the intrinsic muscles of the vibrissa mystacial pad (Deschênes et al., 2016). The motoneurons for intrinsic muscles summate this rhythmic inhibitory input with sustained excitation from diverse premotor inputs for the combined control of vibrissa orientation and rhythmic whisking (Fig. 1C).

Additional pathways from the respiratory complex can control active orofacial exploration (Berg and Kleinfeld, 2003) (Fig. 3). When animals sniff, output from the preBötzinger complex appears to directly drive motoneurons of the extrinsic muscles (Deschênes et al., 2016). This results in retraction and early protraction of the mystacial pad (Hill et al., 2008; Simony et al., 2010), although the detailed relation of this phasing remains unsettled. Beyond whisking, it is conjectured that the respiratory complex entrains yet-to-be confirmed oscillators for rhythmic movements of the nose, tongue, and probably head (Kleinfeld et al., 2014) (Fig. 3). The temporal regularity of phase-locked signals, in principle, can improve the fidelity of decoding the stimuli during motor planning (Kleinfeld et al., 2014) and/or play a role in the saliency of the sensory input through further phase-locking with the hippocampal theta rhythm (Grion et al., 2016; Kleinfeld et al., 2016).

Other brainstem structures have a direct impact on respiration and thus rhythmic orofacial motor actions. Of note, the Kölliker–Fuse nucleus is reciprocally connected to the preBötzinger complex (Feil and Herbert, 1995; Tan et al., 2010) and plays an essential role in the control of breathing, e.g., glutamatergic stimulation of the Kölliker–Fuse nucleus elicits apnea (Chamberlin and Saper, 1994). Ongoing work suggests that the Kölliker–Fuse nucleus also has a direct impact on whisking through a projection to the vibrissa region facial motor nucleus (Takatoh et al., 2013).

In addition to the preBötzinger complex, a second fundamental oscillator in the hindbrain regulates chewing (Fig. 3). Crucially, chewing is not phase locked with breathing (McFarland and Lund, 1993; Liao and Kleinfeld, 2016). The rhythmic motion of the tongue will coordinate with breathing during licking (Welzl and Bures, 1977), but the coordination shifts so that motion of the tongue is coherent with jaw motion during chewing (Travers et al., 2010; Liao and Kleinfeld, 2016). The strongest evidence to date appears to place the chewing oscillator in the dorsal principal trigeminal nucleus (PrV) or the proximal reticular formation (Kolta et al., 2007) (Fig. 3). Chewing does not play a direct role in exploratory orofacial behaviors.

ARCHITECTONICS OF THE VIBRISSA SENSORIMOTOR SYSTEM

In active exploration, whisking is coordinated with other rhythmic orofacial behaviors and phase locked with sniffing (Fig. 1D). What is the underlying circuit that governs the over-all control of the motor plant for whisking and the processing of vibrissa-based touch signals? Here we focus on a “brainstem” centric map of

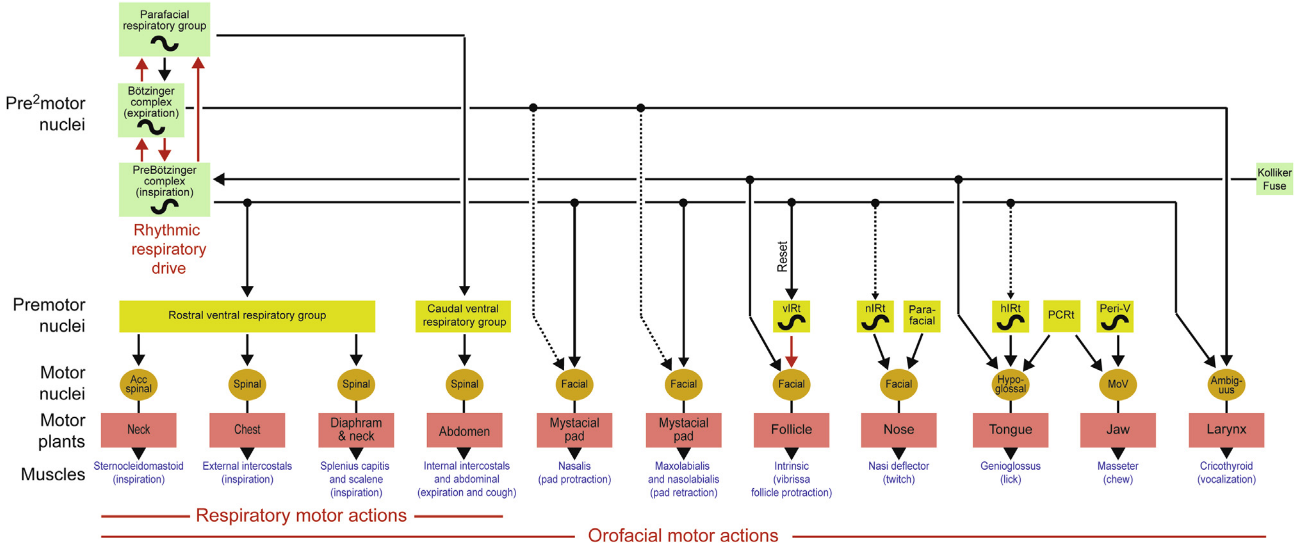


Fig. 3. Schematic circuit of coupled neuronal oscillators in the brainstem. Muscles, motoneurons that control breathing, vibrissa, face, jaw, tongue, and airway along with known premotor nuclei to each of the motoneuron pools. The putative neuronal oscillators are marked with a "∼". Summarized from (Nakamura and Katakura, 1995; Travers et al., 1997, 2010; Feldman and Del Negro, 2006; Tan et al., 2010; Moore et al., 2013; Takatoh et al., 2013; Molkov et al., 2017). Breathing control centers (green) project to putative premotor controllers of diverse orofacial musculature (yellow). Dashed lines are connections based on functional rather than anatomical data. Abbreviations: Acc. spinal (accessory spinal nucleus); MoV (motor trigeminal nucleus); nIRt, hIRt, and vIRt (nasal, hypoglossal, and vibrissa intermediate reticular formation, respectively); PCRt (parvocellular reticular formation); Peri-V (peri-trigeminal area).

connections that begin with the trigeminal input and project directly and indirectly to the facial motoneurons for control of the intrinsic muscles (Fig. 4). Our presentation is driven by the available data and thus overemphasizes cortical loops while minimizing cerebellar loops and ignoring hippocampal loops as well as other forebrain areas such as lateral hypothalamus and the central nucleus of the amygdala. While each of the latter areas can influence vibrissa sensory and/or motor processing (Dietrich et al., 2015; Tovote et al., 2016; Han et al., 2017), the underlying circuitry is largely uncharted. We further address only the circuitry for the intrinsic muscles as the extrinsic muscles of the mystacial pad receive direct input from the respiratory complex (Deschênes et al., 2016) (Fig. 3).

Sensory plant

The vibrissa follicle–sinus complex provides the first stage for transduction of vibrissa touch as well as the motor drive for whisking through ensheathing muscle slings (Rice et al., 1986). In particular, mechanosensory transduction depends on bending of the vibrissae (Quist and Hartmann, 2012; Hires et al., 2013) and deformation of the encapsulating follicle blood sinus and epithelial specializations (Whiteley et al., 2015), i.e., the Merkel disks (Ikeda et al., 2014; Maksimovic et al., 2014), as well as specialized club endings of axons that capture the highest frequency deformations (Tonomura et al., 2015). Primary sensory axons travel via superficial or deep infraorbital branches of the trigeminal nerve (Dorfl, 1985; Rice et al., 1986). Each vibrissa follicle–sinus complex is innervated by a unique set of ∼100 ganglion cells, which each express one type of mechanoreceptor and projects to the periphery via one unbranched axon (Welker and Van der Loos, 1986; Li et al., 2011; Sakurai et al., 2013; Tonomura et al., 2015). Thus this first step in sensory transduction provides a high-fidelity spatial and temporal representation of vibrissa movement from individual follicles to non-overlapping subsets of parent trigeminal ganglion neurons (Jones et al., 2004), with resultant single-vibrissa receptive fields for individual ganglion cells. Vibrissa afferents are broadly classified as rapidly adapting or slowly adapting, but their relationship to the six types of axon terminal specializations is incompletely understood (Ebara et al., 2017; Takatoh et al., 2018).

A central question is how the trigeminal system encodes both vibrissa touch and also position in the whisk cycle. For many muscles, spindle afferents carry proprioceptive signals, yet such afferents were not identified in the mystacial pad muscles or nerve fibers (Semba and Egger, 1986; Moore et al., 2015). Rather, ganglion cell responses to both artificial or awake whisking imply that trigeminal ganglion cells report self-motion in addition to touch (Szwed et al., 2003; Leiser and Moxon, 2007; Severson et al., 2017). This phenomenon is referred to as peripheral reafference. Physiological blockade of activity of either Merkel disks in the follicle–sinus complex or their primary sensory afferents is sufficient to reduce performance of a behavioral tactile task (Ikeda et al., 2014; Maksimovic et al., 2014; Woo et al., 2014; Severson et al., 2017). These studies demonstrated that parent ganglion cells are selectively activated by "active touch", i.e., the conjunction of vibrissa receptive within the protraction–retraction cycle and touch (Severson et al., 2017). This suggests that the activation

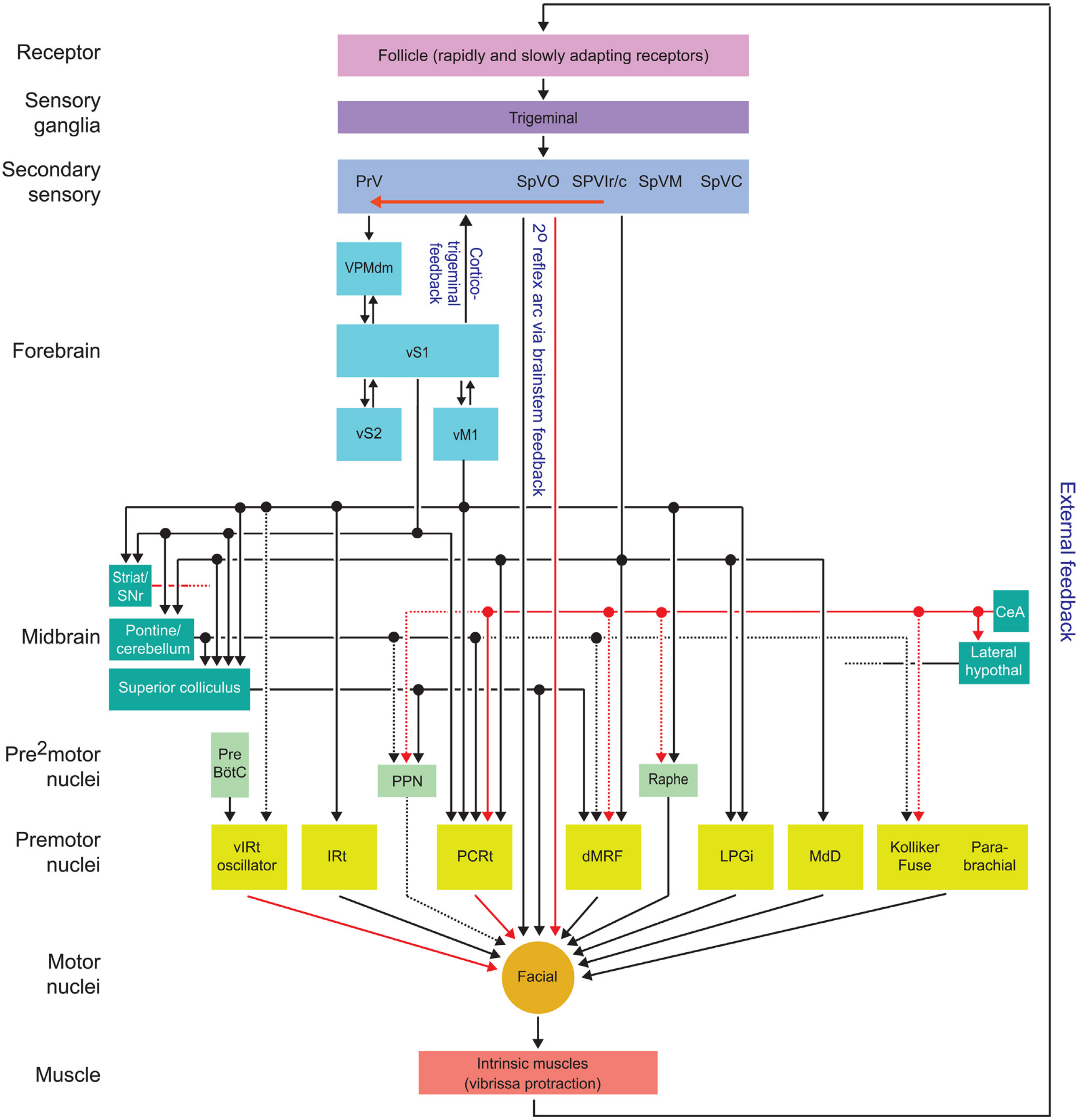


Fig. 4. ''Feedforward'' circuit diagram for the circuit for the intrinsic muscles that drive protraction of the vibrissae. Arrow signifies the direction of signal flow; red signifies inhibitory and black signifies excitatory connections. Compiled data as described in the text. Many feedback connections and interconnections among premotor structures have been excluded for simplicity. Dashed lines are connections based on functional rather than anatomical data. Abbreviations: PrV (principal trigeminal nucleus); SpVO (spinal subnucleus oralis); SpVIr and SpVIc (rostral and caudal divisions of spinal subnucleus interpolaris, respectively); SpVM (spinal subnucleus muralis); SpVC (spinal subnucleus caudalis); VPMdm (dorsomedial aspect of the ventral posterior medial nucleus of dorsal thalamus); vS1 (vibrissa primary sensory cortex); vS2 (vibrissa secondary sensory cortex); vM1 (vibrissa motor cortex); Stria/SNr (striatum/substantia nigra pars reticulata); CeA (central amygdala); Pontine/cerebellum (circuit from pontine nuclei through cerebellar deep nuclei); lateral hypothal (lateral hypothalamus); PPN (pedunculopontine nucleus); Raphe (Raphe nuclei); PreBötC (preBötzinger respiratory complex); vIRt (vibrissa intermediate reticular zone); IRt (intermediate reticular formation); PCRt (parvocellular reticular formation); dMRF (dorsal midbrain reticular formation); LPGi (lateral paragigantocellular reticular formation); and MdD (dorsal medullary reticular formation).

of Merkel cells in the follicle–sinus complex is a likely origin of peripheral reafference.

In addition to myelinated low-threshold mechanoreceptor input to the trigeminal ganglia, the follicles are innervated by numerous unmyelinated axons or ''free nerve endings''. These axons course via the superficial sensory nerve to concentrate at the upper regions of the follicle; these unmyelinated fibers

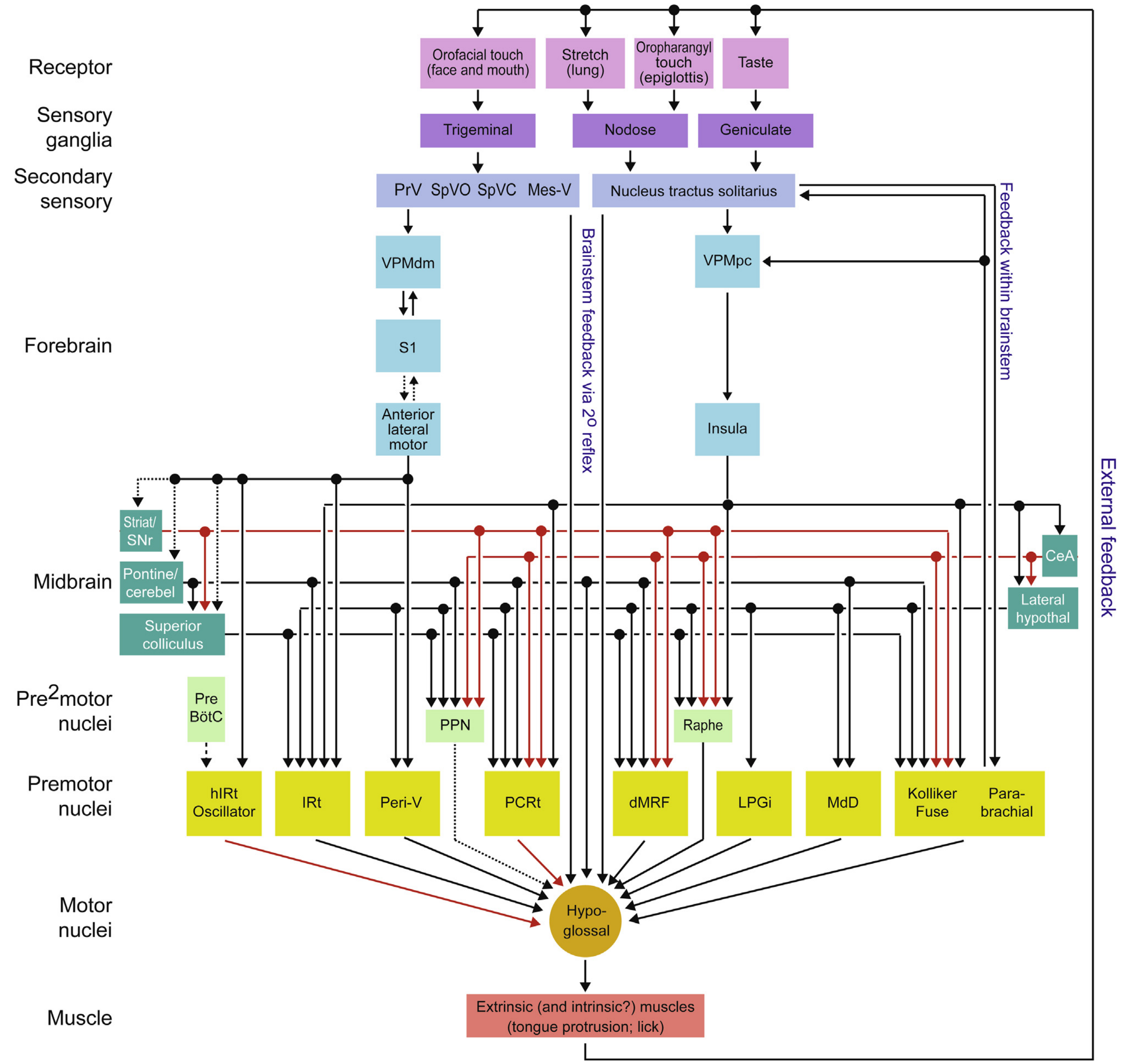
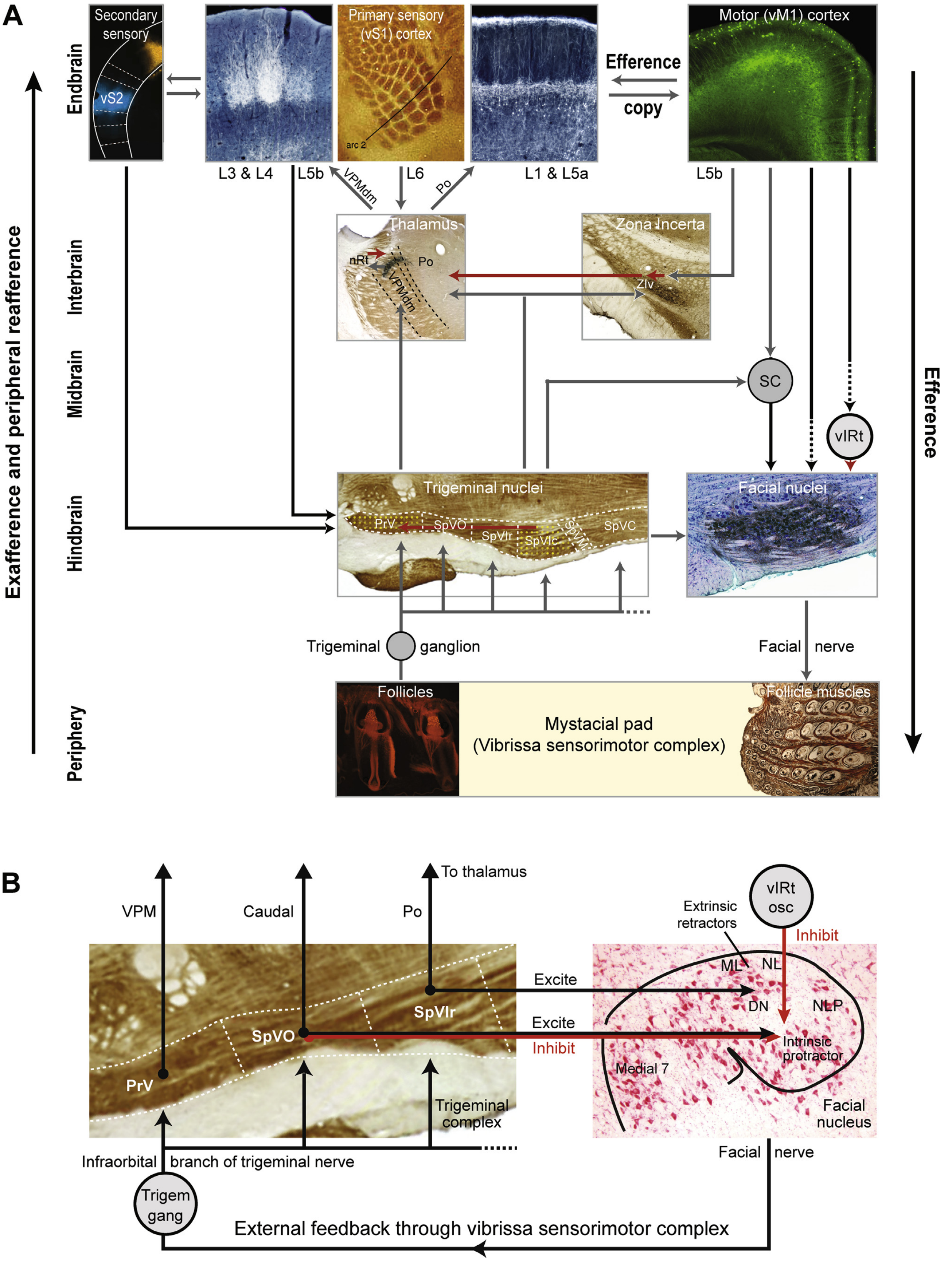


Fig. 5. ''Feedforward'' circuit diagram for muscles of the tongue, i.e., geni- hyo-, chondro-, stylo- and patato-glossus. Arrow signifies the direction of signal flow; red signifies inhibitory and black signifies excitatory connections. Compiled data as described in the text. Many feedback connections and interconnections among premotor structures have been excluded for simplicity. Dashed lines are connections based on functional rather than anatomical data. Abbreviations: PrV (principal trigeminal nucleus); SpVO (spinal subnucleus oralis); SpVC (spinal subnucleus caudalis); Mes-V (mesencephalic sensory nucleus); VPMdm (ventral posterior medial nucleus, dorsomedial); VPMpc (ventral posterior medial nucleus, parvicellular division); S1 (primary sensory) cortex; ALM (anterior lateral motor) cortex; SNr (substantia nigra pars reticulata); CeA (central amygdala); Pontine/ cerebellum (circuit from pontine nuclei through cerebellar deep nuclei); lateral hypothal (lateral hypothalamus); PPN (pedunculopontine nucleus); Raphe (Raphe nuclei); PreBötC (preBötzinger respiratory complex) hIRt (hypoglossal intermediate reticular zone); IRt (intermediate reticular formation); Peri-V (peri-trigeminal area); PCRt (parvocellular reticular formation); dMRF (dorsal midbrain reticular formation); LPGi (lateral paragigantocellular reticular formation); and MdD (dorsal medullary reticular formation).

are not of sympathetic origin (Ebara et al., 2017). Unlike the mechanoreceptor afferents, little is known about the distribution or physiological properties of the parent neuron somata in the trigeminal ganglia for these afferents.

Multiple somatotopic maps in the trigeminal nucleus complex

The trigeminal ganglia project into the brainstem trigeminal complex via ascending and descending central axonal branches. The trigeminal complex is comprised of six main subdivisions (Torvik, 1956; Clarke and Bowsher, 1962; Furuta et al., 2006; Matthews et al., 2015): the PrV, spinal trigeminal subnuclei pars oralis (SpVO), rostral interpolaris (SpVIr), caudal interpolaris (SpVIc), muralis (SpVM), and caudalis (SpVC). In nucleus PrV and subnuclei SpVIc and SpVC (Belford and Killackey, 1979a,b; Tonomura et al., 2015), the central axons of the trigeminal ganglion cells map to structures


A
Exafference and peripheral reafference
Endbrain
Interbrain
Midbrain
Hindbrain
Periphery
Secondary sensory
vS2
Primary sensory (vS1) cortex
arc 2
L3 & L4
L5b
VPMdm
L6
Po
L1 & L5a
Efference
copy
Motor (vM1) cortex
L5b
Thalamus
nRt
Po
VPMdm
Zona Incerta
ZIv
SC
vIRt
Trigeminal nuclei
PrV
SpVO
SpVIr
SpVIc
SpVM
SpVC
Facial nuclei
Trigeminal ganglion
Facial nerve
Follicles
Mystacial pad (Vibrissa sensorimotor complex)
Follicle muscles
Efference
B
VPM
Caudal
Po
To thalamus
PrV
SpVO
SpVIr
Trigeminal complex
Infraorbital branch of trigeminal nerve
Trigem gang
Excite
Excite
Inhibit
vIRt osc
Inhibit
Extrinsic retractors
ML
NL
DN
NLP
Intrinsic protractor
Medial 7
Facial nucleus
Facial nerve
External feedback through vibrissa sensorimotor complex

that are well defined by cytological and histological borders, denoted “barrelettes” (Ma and Woolsey, 1984). These form topographic maps of the relative position of the vibrissae on the mystacial pad. Further, at the level of a functionally defined trigeminal nerve afferent types, such as those with terminal club endings for light touch, the central processes of individual ganglion cells are distributed across trigeminal nuclei with dense input to the nucleus PrV barrelettes and collateral projections to all other subnuclei (Tonomura et al., 2015).

Feedback among trigeminal subnuclei

A class of neurons in nucleus PrV responds to activation of multiple vibrissae, which is a departure of the single-vibrissa activation patterns found for primary sensory neurons of the trigeminal ganglia (Minnery and Simons, 2003). One mechanism for generation of multi-vibrissa receptive fields is the extension of neighboring nerve afferents across barrelettes and the widespread dendritic arborization across barrelettes (Jacquin et al., 2015). This mechanism might complement a substrate of interneuron outputs that originate in subnucleus SpVIc and terminate with inhibitory connections in nucleus PrV (Jacquin et al., 1989; Furuta et al., 2008), as well as an excitatory projection from subnucleus SpVC to nucleus PrV (Furuta et al., 2008). The computational necessity of multi-vibrissa responses in nucleus PrV and their role in sensorimotor processing remain unclear.

Corticotrigeminal feedback

In addition to connections between trigeminal subnuclei, the trigeminal complex also relays to cortex and receives feedback via corticotrigeminal projections (Smith et al., 2015). Projections from nucleus PrV ascend to the dorsal medial aspect of the ventral posterior medial nucleus of dorsal thalamus (VPMdm), where they make three sets of representations (Urbain and Deschênes, 2007b); reviewed in (Deschênes et al., 2005). One of these representations, the dorsal medial aspect of the VPMdm, constitutes the primary afferent pathway. Neurons in VPMdm thalamus project to the middle and deep layers of vibrissa primary sensory (vS1) cortex (Shepherd et al., 2005). Crucially, this pathway carries the most salient information of vibrissa position and touch (Chiaia et al., 1991a,b; Moore et al., 2015) (Fig. 4). This information is relayed to the vibrissa primary sensory (vS1) and secondary sensory (vS2) cortices.

Direct feedback connections to the caudal trigeminal spinal subnuclei arise from both vS1 (Matyas et al., 2010; Sreenivasan et al., 2015) and vS2 (Knutsen et al., 2015) cortices. The projection from vS1 cortex to spinal subnucleus SpVIc can gate the activity of PrV neurons via inhibition from subnucleus SpVIc to nucleus PrV (Furuta et al., 2010). This architecture is in the form of a classic inhibitory feedback circuit (Black, 1953) that in principle can lower the noise and increase the temporal sensitivity of the cortical response.

Premotor nuclei

We already noted that a region in the IRt zone, the vIRt, functions as the premotor oscillatory nucleus for the rhythmic component of whisking (Moore et al., 2013; Deschênes et al., 2016). In contrast, the non-rhythmic aspects of whisking are mediated by the plethora of premotor centers in the reticular formation, spinal trigeminal subnuclei, and other brainstem premotor nuclei (Isokawa-Akesson and Komisaruk, 1987; Hattox et al., 2002). We emphasize the dual role of spinal trigeminal subnuclei as both primary sensory and premotor regions (Fig. 4). Anterograde tracing revealed trigeminal complex inputs to premotor centers that project to the facial motor nucleus (Zerari-Mailly et al., 2001). In particular, spinal trigeminal subnuclei project extensively to the dorsal medullary reticular formation, the parvocellular reticular and IRt formations, as well as others (Fig. 4). Subsequent viral tracing from muscles in the mystacial pad allowed selective identification of vibrissa-specific trigeminal outputs from subnuclei SpVO and SpVIr (Takatoh et al., 2013). These form a brainstem-level, di-synaptic reflex arc (Fig. 4). Projections from subnucleus SpVO lead to rapid, contact-induced inhibition followed by excitation to the intrinsic muscles while those from subnucleus SpVIr lead to contact-induced retraction of the mystacial pad (Bellavance et al., 2017).

Anatomical and physiological data suggest some premotor structures receive inputs from primary vibrissa motor (vM1) cortex. Classical studies based on dye transport have identified vM1 cortical fibers in premotor structures including the IRt formation, parvocellular reticular, and gigantocellular reticular formations (Zerari-Mailly et al., 2001; Alloway et al., 2010). Virus tracing confirmed projections from vM1 cortex to the IRt formation (Sreenivasan et al., 2016). It will be of interest to determine whether these descending projections specifically

Fig. 6. Schematic circuit of the vibrissa somatosensorimotor system in terms of nested loops. (A) Nested loops in the somatosensorimotor system. Only the pathways from the vibrissae to the brainstem and up through neocortex are shown. Black arrows indicate excitatory projections while red arrows are inhibitory projections. Adapted from Kleinfeld and Deschênes (2011). (B) Expanded diagram of first-order feedback loops involved in reflex motion of the vibrissae. Intrinsic protractor motoneurons receive both excitatory and inhibitory inputs from subnucleus SpVO, whereas nasolabialis and maxillolabialis retractor motoneurons receive excitatory input from subnucleus SpVIr neurons that also project to Po thalamus. Adapted from Bellavance et al. (2017). The plane of the trigeminus has been tilted by ~30° from that in part A. Abbreviations: vS1 (vibrissa primary sensory cortex); vS2 (vibrissa secondary sensory cortex); vM1 (vibrissa motor cortex); PrV (principal trigeminal nucleus); SpVO (spinal subnucleus oralis); SpVIr and SpVIc (rostral and caudal divisions of spinal subnucleus interpolaris, respectively); SpVM (spinal subnucleus muralis); SpVC (spinal subnucleus caudalis); VPMdm (ventral posterior medial nucleus, dorsomedial); Po (medial division of the posterior group nucleus); nRt (nucleus reticularis); ZIv (ventral aspect of the zona incerta); SC (superior colliculus); vIRt (vibrissa intermediate reticular formation); NLP (nasolabialis profundus extrinsic protractor muscle); ML (maxolabialis extrinsic retractor muscle); NL (nasolabialis extrinsic retractor muscle); and DL (deflector nasi).

include synapses onto premotor vIRt neurons, the site of the vibrissa oscillator.

From a functional perspective, intracellular stimulation of single layer 5 pyramidal cells in vM1 cortex evokes rhythmic whisker movements (Brecht et al., 2004b). This motor activation could arise from projections to premotor regions within the reticular formation or from a direct, albeit sparse projection to ventrolateral facial motor neurons (Grinevich et al., 2005; Sreenivasan et al., 2015). Alternatively, while projections from vM1 cortex to the trigeminal nuclear complex have been reported as absent (Smith et al., 2015) or limited to SpVO (Sreenivasan et al., 2015), this claim is under re-evaluation (Mercer Lindsay et al., 2016) and might provide yet another pathway from vM1 cortex to vibrissa motoneurons. Several additional structures, including the deep cerebellar nuclei and central amygdala (Hopkins and Holstege, 1978; Asanuma et al., 1983), project to brainstem regions. However, it is presently unclear whether these projections specifically target vibrissa premotor neurons.

The projections to the parvocellular reticular formation are of particular interest. While the specific relation of this region to vibrissa function has not been charted, a range of brain areas that relate to orofacial motor actions target the parvocellular reticular formation. Retrograde dye tracing identified afferents from motor cortex, as discussed above, as well as sensory cortex, deep cerebellar nuclei, substantia nigra pars reticulata, superior colliculus, the contralateral parvocellular reticular, IRt, and gigantocellular reticular formations, orofacial spinal trigeminal nuclei, and the parabrachial nucleus (Shammah-Lagnado et al., 1992). The parvocellular reticular formation is thus strategically positioned to integrate/arbitrate broad sensory and motor signals.

Midbrain motor control

The superior colliculus receives input from neurons with multi-vibrissa fields originating from trigeminal nucleus PrV and subnuclei SpVO and SpVIr, with terminals that end in the sensory intermediate layer of the colliculus. Corticocollicular innervation to the intermediate layer originates from vS1 cortex (Zakiewicz et al., 2014; Castro-Alamancos and Favero, 2016) and vM1 cortex (Miyashita et al., 1994). The intermediate layers respond vigorously to active and passive whisker deflection when multiple vibrissae move together, but these responses rapidly depress. The responses driven by corticocollicular stimulation are weaker, but more persistent, than trigeminocollicular responses. These data suggest that trigeminocollicular inputs code for novelty in the periphery while corticocollicular inputs subserve changes in sensitivity by neocortex behavioral state (Castro-Alamancos and Favero, 2016).

Electrical microstimulation of the superior colliculus produces short latency vibrissa protractions that are sustained for the duration of the stimulus (Castro-Alamancos and Keller, 2011; Stanek et al., 2014). These likely reflect the direct projections from deep layers of the superior colliculus to the facial motor nucleus (Travers and Norgen, 1983; Vidal et al., 1988). However, it is unknown how the extensive local circuitry within the superior colliculus transforms vibrissa signals as they pass from intermediate sensory layers to deep motor output layers. Such circuitry might serve to coordinate vibrissa movements with broader aspects of orientation. For example, microstimulation of vibrissa units also produces coordinate movements of eyes and pinna along with vibrissae (Castro-Alamancos and Keller, 2011).

Cerebellum

As in the case of cortex and the superior colliculus, neurons in many regions of the cerebellum respond vigorously to tactile stimuli. The cerebellum receives extensive somatosensory information from cortical and brainstem sources (Torvik, 1956; Jacquin et al., 1982; Mihailoff et al., 1985; Hartmann and Bower, 1998; Leergaard et al., 2000; O'Connor et al., 2002). Vibrissa stimulation is a strong driver of Purkinje cells (Shambes et al., 1978; Loewenstein et al., 2005; Bosman et al., 2010), and vibrissa somatosensory signaling has been implicated in motor planning via corticocerebellar loops (Proville et al., 2014). It remains unknown whether the cerebellum has an additional role in the control of vibrissa movements per se (Bower, 1997). Consistent with a potential motor control function, vibrissa movements are correlated with activity in deep nucleus output neurons (Lu et al., 2013), where local microstimulation has been shown to evoke vibrissa movement in decerebrate rats (Cicirata et al., 1989). Projections from the cerebellum target broad areas of the reticular formation that contain orofacial premotor neurons (Cohen et al., 1958; Asanuma et al., 1983; Takatoh et al., 2013). Future efforts are needed to clarify the set of muscles and motor actions that are specifically controlled by cerebellar outputs.

Basal ganglia

The striatum receives topographically organized afferents from vM1 and vS1 cortices as well as posterior medial thalamus (Leergaard et al., 2000; Hoffer and Alloway, 2001; Smith et al., 2012). Striatal medium spiny neurons respond to vibrissa stimulation (Mowery et al., 2011), with unimodal responses in dorsal lateral regions but multisensory responses in dorsal medial regions (Reig and Silberberg, 2014). The importance of vibrissa signaling in the basal ganglia in guiding behavior has not been determined. The requirement of dopamine for normal vibrissa sensory signaling in striatum (Ketzef et al., 2017), plus the central role of the basal ganglia in reward-based sensor orientation (Hikosaka, 2007), suggests a plausible role of the substantia nigra pars reticulata, an output nucleus of the basal ganglia, in slow changes in vibrissa position. An intriguing possibility is that adjustments in set-point are influenced via nigral projections to the superior colliculus.

Modulation

Cholinergic neurons in the pedunculopontine nucleus comprise a key component of the reticular activating system and innervate several brain regions implicated in vibrissa motor control (Fig. 4), including the superior colliculus, where cholinergic agonists increase the response of units to passive and active touch of whiskers (Bezdudnaya and Castro-Alamancos, 2014). The superior colliculus also projects back to the pedunculopontine nucleus (Martinez-Gonzalez et al., 2011) to form a potential feedback loop.

Of interest, the ascending output fibers of pedunculopontine nucleus project to the basal forebrain, whose activity has been previously shown to augment the responsiveness of cortical units to vibrissa (Berg et al., 2005). Selective optogenetic stimulation of pedunculopontine nucleus terminals in the basal forebrain was sufficient to elicit behavioral effects of whisking and sniffing (Lee et al., 2014). Thus cholinergic modulation by the pedunculopontine nucleus, along with serotonergic modulation by the Raphe nucleus (Hattox et al., 2003), may profoundly change the nature of whisking based on the brain state of the animal (Ganguly and Kleinfeld, 2004).

ARCHITECTONICS OF THE LINGUAL SENSORIMOTOR SYSTEM

A broad set of orofacial behaviors depends critically on movement of the tongue. As for the case of whisking, one component of the lingual movement is phase-locked to the respiratory rhythm under licking and some behavioral contexts (Lowe and Sessle, 1973; Welzl and Bures, 1977) (Fig. 1D). Tongue movements are well integrated with facial, oral, and pharyngeal musculature. They are critical for communication, feeding, and breathing. Similar to the vibrissa movements, mammalian tongue movements arise from coordinated activation of extrinsic and intrinsic muscles groups (Sonntag, 1925; Abd-El-Malek, 1938; Lowe, 1980). The hypoglossal motor nucleus in the caudal aspect of the medulla contains the motor neurons that control both muscle groups (Lewis et al., 1971).

One type of brainstem circuit that controls tongue movements involves neuronal oscillators that transform descending and local signals into rhythmic and coordinated behaviors, i.e., licking, chewing, and swallowing (Dellow and Lund, 1971; Lowe, 1980; Nakamura and Katakura, 1995; Jean, 2001; Miller, 2002) (Fig. 5). A second type of circuit makes use of sensory feedback. Dense afferent innervation of the face, tongue, mouth, and airway provide fine somatosensory and chemosensory feedback to brainstem circuitry. Tactile signals from the oral cavity, including the tongue and teeth, are carried by trigeminal ganglia to all divisions of the trigeminal sensory complex, particularly in dorsal regions of the subnuclei (Sessle and Greenwood, 1976; Shigenaga et al., 1986a,b). In complement to trigeminal complex signaling, visceral afferent and taste signals are topographically organized in the nucleus of the tractus solitarius (Sessle, 1973; King, 2007). Taste and sensory signals from the mucous membranes of the pharynx, the posterior third of the tongue, and the tonsils are carried via the facial, glossopharyngeal, and vagus nerves (Torvik, 1956; Carleton et al., 2010). These visceral afferents are integrated in the nucleus of the tractus solitarius with secondary sensory signals from trigeminal subnuclei (Burton et al., 1979; Contreras et al., 1982; Aldes and Boone, 1985; Pinganaud et al., 1999; Zhang et al., 2001).

Feedback in lingual sensorimotor control

A large component of tongue movements arise from elementary and complex reflexes (Miller, 2002). These reflexes rely on di- and tri-synaptic pathways that link trigeminal, hypoglossal, and vagal afferents to hypoglossal motor control. In their simplest form, brainstem reflexes are controlled by a disynaptic arc in which neurons from sensory nuclei synapse onto motoneurons (Fig. 2). In particular, the trigeminal nuclei form extensive brainstem projections that include synapses directly onto hypoglossal motor neurons (Burton et al., 1979; Aldes and Boone, 1985; Pinganaud et al., 1999; Zhang et al., 2001). Neurons that lie in the dorsal part of nucleus PrV project to the hypoglossal motor nucleus (Pinganaud et al., 1999). In contrast, subnuclei SpVI and SpVC contain intermingled premotor neurons, including some that collateralize to both the facial and hypoglossal nuclei. This is suggestive of a locus for interaction of different orofacial motor actions within the trigeminal spinal nuclei. Lastly, a projection from the mesencephalic trigeminal neurons to the hypoglossal motor nucleus is likely to underlie the jaw-to-tongue reflex, in which jaw opening results in tongue protrusion (Zhang et al., 2001; Luo et al., 2006), which plays a critical role in maintaining airway patency (Miller, 2002).

The nucleus of the tractus solitarius sends sparse direct and numerous indirect projections to the hypoglossal motor nucleus. Direct projections arise from a caudal region in the nucleus of the tractus solitarius that receives afferents via the glossopharyngeal and vagus nerves (Torvik, 1956; Contreras et al., 1982; Borke et al., 1983; Travers and Norgen, 1983). The function of this direct projection remains unknown, whereas indirect projections from the nucleus of the tractus solitarius to the hypoglossal motor nucleus via the parabrachial sensory nucleus and medullary reticular formation play a central role in swallowing and food rejection reflexes (DiNardo and Travers, 1997; Jean, 2001; Lang, 2009).

Oscillators for rhythmic licking

As in the case of whisking, motion of the tongue is modulated in phase with respiration during breathing (Doty and Bosma, 1956; Sauerland and Mitchell, 1970; Harvold et al., 1973; Lowe and Sessle, 1973; Welzl and Bures, 1977; Wiesenfeld et al., 1977; Sawczuk and Mosier, 2001). Rhythmic licking is commonly faster than basal breathing but the onset of licking is reset by breathing (Welzl and Bures, 1977). This parallels the case of whisking and basal breathing (Moore et al., 2013). The occurrence of licking and breathing at different rates indicates the existence of an independent licking oscillator (Travers et al., 1997; Koizumi et al., 2008; Stanek et al., 2014). The one-to-one relation of licking to the sniff cycle (Liao and Kleinfeld, 2016) and the absence of licking during pharmacological block of spiking by neurons throughout the IRt formation lend support to the hypothesis that a subregion of the IRt formation, denoted the hypoglossal

IRt (hIRt) formation, comprises an essential component of the licking oscillator (Travers et al., 1997; Ono et al., 1998; Chen et al., 2001) (Figs. 3 and 5).

Ingestive behaviors require precise coordination of the musculature of the jaw, face, tongue, and airway. The central role of the tongue in each aspect of feeding suggests that several oscillators and/or premotor nuclei can recruit hypoglossal motor neurons. Several populations of neurons in the IRt and parvocellular reticular formations project to multiple orofacial nuclei (Li et al., 1993; Travers et al., 2005; Stanek et al., 2014) and likely underlie distinct aspects of feeding, including chewing (Nakamura and Katakura, 1995; Lund et al., 1998; Morquette et al., 2012). While tongue movements during chewing are largely in phase with jaw opening (Dellow and Lund, 1971; Morimoto and Kawamura, 1973; Lund, 1991; Liao and Kleinfeld, 2016), tongue movements also display a prominent non-rhythmic component that positions food in the mouth (Abd-El-Malek, 1955). Further, as noted earlier, the rhythmic motion of the tongue will dramatically shift from phase-locking with breathing during licking (Welzl and Bures, 1977) to locking with chewing during ingestion (Travers et al., 2010; Liao and Kleinfeld, 2016). The nature of these dynamics, as well as the control of multiple lingual muscles during licking, chewing, and swallowing, depends on unknown brainstem circuit mechanisms that enable action sequencing across different premotor nuclei.

Control of the posture of the tongue is analogous to the set-point of the vibrissa, albeit a more complicated motor act given the much greater degrees of freedom for the tongue. Tongue posture is a primary factor of pharynx patency. Synchronous tongue protrusion and inspiration improve upper airway flow by dilating the oropharynx (Blom, 1960; Lei, 1961; Lowe and Sessle, 1973; Miller and Bowman, 1974; Bartlett, 1986). The pontine respiratory group, including the parabrachial nucleus and the Kölliker–Fuse, is involved in respiratory control (Molkov et al., 2017). Stimulation of the Kölliker–Fuse activates tongue protrusion muscles (Kuna and Remmers, 1999; Yokota et al., 2011) and thus may underlie some component of respiration–lingual synchrony.

Premotor networks and descending controllers

Descending projections to brainstem circuits arise from diverse regions of the motor and limbic systems (Fig. 5) and provide a plausible circuit basis for goal-directed orofacial actions.

Cerebral cortex

The most extensively studied high-level controller of tongue movements is the motor cortex, which can evoke licking, chewing, and swallowing (Sessle, 2011). Recent work highlights the importance of the anterior lateral motor (ALM) cortex in driving movement of the tongue (Komiyama et al., 2010) and, further, supplies anatomical evidence for a direct connection from ALM cortex to the region that contains a candidate licking oscillator, the hIRt (Ono et al., 1998; Li et al., 2015). ALM cortex appears to be a hub that plans and executes voluntary licking under sensorimotor learning tasks (Guo et al., 2014a,b; Li et al., 2015, 2016), however it is notable that licking related to food and water consumption is retained in decerebrate animals (Woods, 1964). Pyramidal tract neurons in layer 5 project to the hIRt region and have activity patterns consistent with a directional motor command (Li et al., 2015). In addition to direct projections from ALM cortex to the region that contains the hIRt, ALM cortex projects to the motor related, lateral sector of superior colliculus, that in turn projects to premotor neurons in the region that contains the hIRt (Yasui et al., 1994). This projection might coordinate tongue movements and the general orientation or the head and face muscles, although the relative roles of the direct and indirect connections between ALM cortex and the hIRt in the control of the direction of licking remain unknown. All told, the current experimental evidence implies that ALM cortex is a major source of a motor command that initiates learned directional licking.

Basal ganglia

The ventral–lateral portion of the striatum receives orofacial cortical afferents (McGeorge and Faull, 1987) and contains neurons that modulate their firing in relation to licking (Mittler et al., 1994). Basal ganglia output neurons in the substantia nigra pars reticulata project to diverse premotor tongue regions (Hopkins and Niessen, 1976; Schneider, 1986; von Krosigk et al., 1992; Yasui et al., 1992; Tsumori and Yasui, 1997) (Fig. 5). Further, orofacial actions can be readily evoked by perturbations to the striatum or substantia nigra pars reticulata (Delfs and Kelley, 1990; Inchul et al., 2005), although orofacial actions evoked from the basal ganglia are abnormal in form. Thus, additional approaches are needed to delineate the normal function of nigral afferents to brainstem. The substantia nigra pars reticulata strongly inhibits the lateral superior colliculus, which has been proposed to mediate the effects of the basal ganglia on orofacial actions (Redgrave et al., 1980). It remains undetermined whether the orofacial deficits that follow collicular perturbations reflect specific motor effects or are a consequence of broad sensory neglect and orienting deficits (Wang and Redgrave, 1997).

Cerebellum

Oral and perioral sensory responses are prominent in cerebellum Crus I and II (Shambes et al., 1978; Apps and Hawkes, 2009), which receive a broad spectrum of orofacial sensory inputs from the trigeminal complex (Jacquin et al., 1982; Jacquin and Zeigler, 1983; Van Ham and Yeo, 1992), and potentially orofacial-based sensory reward signals from an unknown mossy fiber source (Wagner et al., 2017). Several classes of cerebellar neurons display firing patterns related to tongue movements, which suggests that the cerebellum might play an active role in tongue motor control. Purkinje cells in Crus I and II modulate activity during licking (Bryant et al., 2010) and, importantly, complex-spike-lick-responses in Purkinje cells are maintained following deafferentation of oral and perioral trigeminal sensory feedback (Welsh et al., 1995). Interneurons in the cerebellum molecular layer in Crus II specifically exhibit firing patterns that correlate with licking kinematics, but not tongue position, and chemogenetic suppression of activity in this interneuron class alters tongue movements and decreases licking rates (Gaffield and Christie, 2017). In addition, output neurons in the medial deep cerebellar nucleus, i.e., the fastigial nucleus, exhibit spiking that is locked with licking (Lu et al., 2013). Stimulation of the fastigial nucleus can evoke tongue movements and complex orofacial actions (Bowman and Aldes, 1980; Berntson and Torello, 1982), and application of muscimol to the cerebellar nuclei decreases licking rate and efficiency (Bryant et al., 2010). Moreover, neurons in the fastigial nucleus projects to diverse premotor tongue areas and directly to the hypoglossal nuclei (Cohen et al., 1958; Asanuma et al., 1983; Teune et al., 2000; Stanek et al., 2014). These projections, together with the representation of both sensory and motor signals, are highly suggestive of an integrative role of cerebellar circuits in sensory-guided tongue control.

Additional putative tongue control regions

Afferents to brainstem tongue premotor areas additionally arise from regions outside of the traditional somatomotor system (Hopkins and Holstege, 1978; Holstege, 1987; Van Bockstaele et al., 1989; Grofova and Keane, 1991; Shammah-Lagnado et al., 1992; Ugolini, 1995; Karimnamazi and Travers, 1998; Almeida et al., 2002). Among these are projections from the lateral hypothalamus and central amygdala (Hopkins and Holstege, 1978; Holstege, 1987), both of which have been implicated as key regulators of feeding behaviors (Kaku, 1984; Kapp et al., 1985; Schwartzbaum, 1988; Petrovich, 2011). As in the case of control of the set-point of the vibrissa, the plethora of pre- and pre^{2}motor nuclei suggests that there are several tongue controllers, consistent with the broad diversity of tongue behaviors and evidence that many high-level areas are capable of evoking or perturbing tongue movements (Bowman and Aldes, 1980; Berntson and Torello, 1982; Kaku, 1984; Schwartzbaum, 1988; Inchul et al., 2005; Li et al., 2015).

REDRAWING THE ANATOMY TO EMPHASIZE NESTED CORTICAL LOOPS AND SENSORY FEEDBACK PATHWAYS

The anatomy of sensorimotor systems may be reworked from a sensory-to-motor flow diagrams (Figs. 4 and 5) to ones that follow the anatomy more explicitly to emphasize the nested loop structure and feedback at various circuit stages (Kleinfeld et al., 1999, 2006; Bosman et al., 2011) We do this for the vibrissa sensorimotor system (Fig. 6A), noting that similar nested loop architectures appear common in motor control circuits.

Brainstem sensory feedback loops

The most direct feedback loops in motor control are direct sensory nucleus to motor neuron loops. Such connections likely mediate automatic or innate aspects of sensorimotor behaviors. In the vibrissa system, projections from trigeminal subnuclei mediate many aspects of motor control. In particular, projections from the spinal trigeminal subnuclei to intrinsic muscle motor neurons (Nguyen and Kleinfeld, 2005; Sherman et al., 2013; Sreenivasan et al., 2015; Bellavance et al., 2017) drive vibrissa movements (Klein and Rhoades, 1985; Hill et al., 2008; Simony et al., 2010). Neurons in subnucleus SpVO project to intrinsic muscle motor neurons and supply a touch-induced biphasic response, with fast inhibition followed by excitation (Bellavance et al., 2017) (Fig. 6B). This leads to transient decrement in the electromyogram of the mystacial pad (Kleinfeld et al., 2002) and a dip in the touch response (Deutsch et al., 2012). A class of neurons in rostral subnucleus SpVIr drives retraction of the mystacial pad (Bellavance et al., 2017) (Fig. 6B) and modulates the period of contact. These feedback signals lead to a ‘‘caressing'' of an object by the vibrissa and appear to operate as a proportional–differential controller (Best, 1984), although the computations role of such feedback in improving recognition of the environment is a matter of speculation. Local trigeminal circuitry also shapes ascending sensory processing: cells in subnucleus SpVIc inhibit neurons in nucleus PrV (leftward red arrow in brainstem row; Fig. 6A) and provide sensory feedback to spatially and temporally sharpen sensory responses (Furuta et al., 2008; Bellavance et al., 2010).

Thalamocortical projections

The monosynaptic projections within the medulla are paralleled by multiple polysynaptic pathways at the level of the hindbrain and midbrain, *e.g.*, the superior colliculus and reticular formation, and by pathways that extend through the forebrain (Kleinfeld et al., 1999) (Fig. 6A). Projections from nucleus PrV ascend to VPMdm thalamus, which forms a closed loop with inhibitory cells in nucleus reticularis (nRt, red arrow in middle row; Fig. 6A), and then further project to the middle and deep layers of vS1 (Shepherd et al., 2005). They cluster into columns that maintain a one-to-one relation with the spatial distribution of the vibrissae; reviewed in (Lefort et al., 2009) (top row, Fig.6A).

The second set of ascending projections emanates from trigeminal subnucleus SpVIr to the part of the posterior medial (Po) thalamus complex that borders the VPMdm thalamus. These include both direct excitatory input from subnucleus SpVIr as well as inhibitory input that comes indirectly via projections to the ventral aspect of the zona incerta (Bartho et al., 2002). The latter input is part of a forebrain loop in which activity in Po thalamus is modulated by projection neurons from vM1 cortex to zona incerta, which inactivates an inhibitory input to Po thalamus (Urbain and Deschênes, 2007a) (back-to-back red arrows in middle row; Fig. 6A). Neurons in Po thalamus project to the septa between columns and primarily form connections with dendrites on the surface and middle layers of vS1, *i.e.*, layers 1 and 5a, in a pattern that appears complementary to that formed by input from VMPdm thalamus (top row; Fig. 6A).

Corticofugal pathways

The classically described sensory and motor regions of cortex are highly interconnected at the level of the cortex itself as well as through subcortical interactions and feedback from cortex to thalamus. The highest level feedback loop in the vibrissa system is completed by descending projections from cortex to the vibrissa motoneurons in the facial motor nucleus (Fig. 6A). The dominant pathway of cortical-induced movement of the vibrissae is from vM1 cortex (Brecht, 2004; Brecht et al., 2004a; Berg et al., 2005; Auffret et al., 2017). This involves indirect connections through the superior colliculus and other midbrain and hindbrain structures (Miyashita et al., 1994; Hattox et al., 2002), as well as a direct, albeit sparse projection (Grinevich et al., 2005) (right column, Fig. 6A). A second pathway for activation of the vibrissae involves a projection from vS1 cortex (Matyas et al., 2010) that drives cells in spinal trigeminal subnuclei that further project to the facial nucleus (Bellavance et al., 2017) (Fig. 6A). The vS1 cortical projections lead to protraction of the vibrissa, while a second, recently described projection from vS2 cortex leads to retraction of the vibrissa (Knutsen et al., 2015) so that, together, vS1 and vS2 cortices can shift the position of the vibrissa in a push–pull fashion. How vibrissa motor neurons combine parallel premotor inputs remains poorly understood. More generally, the anatomical data suggest that motor neurons themselves might serve as arbitrators of the control of motor output from different levels in the brain, a role consistent with their electrotonically long dendrites and active currents (Nguyen and Kleinfeld, 2005).

OPEN ISSUES ON THE COORDINATION OF MOTOR ACTIONS IN BEHAVIORS

The exploratory motor actions that have been quantified so far exhibit rhythmic components as well as directed movements. Our past work demonstrated that coordination of the rhythmic components by inspiratory breathing is a key element of exploratory behavior. Yet such stringent synchrony would appear to limit the behavioral repertoire of the animal, suggesting that the control structure for undiscovered stereotypic behaviors may have a more fluid strategy. In particular, are orofacial behaviors organized by brainstem circuits and gated and/or modulated under different contexts by descending controllers? Studies in which inhibitory output from the amygdala is interpreted as “releasing” different behaviors support this view (Fadok et al., 2017; Han et al., 2017; Sanford et al., 2017). Alternatively, are stereotypic behaviors coordinated and directed from outside the brainstem per se, such as in motor cortex or cerebellum? While long-duration electrical stimuli in motor cortex can lead to holistic behaviors (Graziano et al., 2002), the interpretation of such experiments remains controversial (Schwartz, 2007). Under either scenario, a key circuit-level question is how the brainstem arbitrates high-level inputs, such as from the motor cortex, the cerebellum, the amygdala, and so forth, to produce well-controlled behavior. We hope to resolve the hierarchical control structure of the vibrissa system, as a canonical sensorimotor system, in the coming years.

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