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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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 center-point 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 multi-sensory 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.

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