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How the brainstem controls orofacial behaviors comprised of rhythmic actions

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

Neural control of the mammalian face and mouth

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

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

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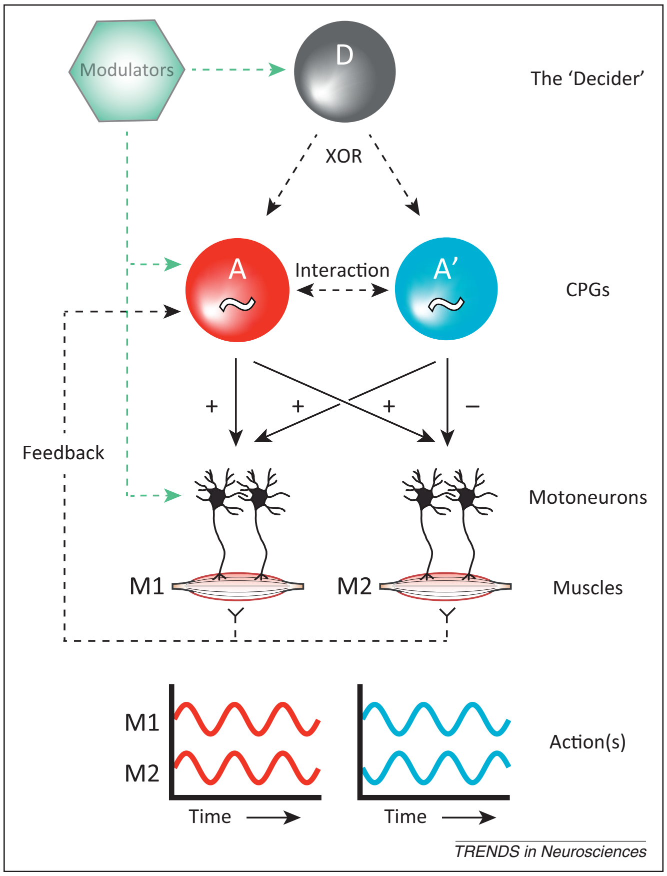

Figure 1. Schematic of the possible circuit arrangements for execution of different actions using a shared motor plant. Muscles M1 and M2 can both be used in different temporal patterns in two different actions, A and A′. Possible circuit interactions include: (1) CPGs interact and coordinate with each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

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

Coordination of orofacial behaviors with breathing

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

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

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

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

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