Neural Control of Tongue Movement With Respect To Respiration and Swallowing

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Neural Control of Tongue Movement with Respect to Respiration and Swallowing

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ABSTRACT: The tongue must move with remarkable speed and precision between multiple orofacial motor behaviors that are executed virtually simultaneously. Our present understanding of these highly integrated relationships has been limited by their complexity. Recent research indicates that the tongue's contribution to complex orofacial movements is much greater than previously thought. The purpose of this paper is to review the neural control of tongue movement and relate it to complex orofacial behaviors. Particular attention will be given to the interaction of tongue movement with respiration and swallowing, because the morbidity and mortality associated with these relationships make this a primary focus of many current investigations. This review will begin with a discussion of peripheral tongue muscle and nerve physiology that will include new data on tongue contractile properties. Other relevant peripheral oral cavity and oropharyngeal neurophysiology will also be discussed. Much of the review will focus on brainstem control of tongue movement and modulation by neurons that control swallowing and respiration, because it is in the brainstem that orofacial motor behaviors sort themselves out from their common peripheral structures. There is abundant evidence indicating that the neural control of protrusive tongue movement by motoneurons in the ventral hypoglossal nucleus is modulated by respiratory neurons that control inspiratory drive. Yet, little is known of hypoglossal motoneuron modulation by neurons controlling swallowing or other complex movements. There is evidence, however, suggesting that functional segregation of respiration and swallowing within the brainstem is reflected in somatotopy within the hypoglossal nucleus. Also, subtle changes in the neural control of tongue movement may signal the transition between respiration and swallowing. The final section of this review will focus on the cortical integration of tongue movement with complex orofacial movements. This section will conclude with a discussion of the functional and clinical significance of cortical control with respect to recent advances in our understanding of the peripheral and brainstem physiology of tongue movement.

Key words. Hypoglossal, complex movement, brainstem, motor cortex, muscle properties.

(I) *Introduction*

The tongue is a mass of uncompartmentalized interdigitating muscles that rapidly and accurately changes the direction of its movement in response to the demands of multiple complex orofacial behaviors. These behaviors include respiration, swallowing, mastication, speech, licking, gaping, coughing, gagging, and vomiting. Five of these processes (respiration, swallowing, mastication, licking, and gaping) are controlled by central pattern generators that are located in the medulla and pons of the brainstem and that transform ascending and descending signals into rhythmic and patterned behaviors (Dellow and Lund, 1971; Wiesenfeld *et al.*, 1977; Jean, 1984a,b; Dinardo and Travers, 1994; Nakamura and Katakura, 1995; Westberg *et al.*, 1998; Travers *et al.*, 2000). The speed and precision with which the tongue must move between these essentially concurrent behaviors are governed by its contractile properties, the intrinsic properties of hypoglossal motoneurons, generator-produced rhythmic modulation of hypoglossal motoneuron activity, and descending influences from cortical and subcortical nuclei. Investigations of the neural control of tongue movement have contributed significantly to our present limited understanding of the neural control of complex orofacial behaviors. Future studies may offer insight into the neural substrate underlying the rapid switching that occurs among complex behaviors such as respiration, swallowing, and tongue movement.

Knowledge of tongue neurophysiology and its modulation by neurons that control complex movements has been retarded by obstacles such as investigators' inability to measure tongue contractile properties and by the lack of substantive information about neural circuitry at the brainstem and cortical levels of the neuraxis. Some of these problems have been overcome by recent innovations in study techniques that have enabled us to investigate the relationships between tongue movement and other complex orofacial behaviors more completely. In this review, we will discuss the results of studies published during the past decade that have shaped our current knowledge of the neural control and contractile properties of the tongue. Additionally, control of the oropharynx and larynx will be reviewed as it relates either directly or indirectly to the modulation of tongue movement. At the brainstem level, somatotopy within the hypoglossal nucleus (NXII), selected aspects of hypoglossal motoneuron membrane properties, and hypoglossal afferents relevant to respiration and swallowing will be examined. Neural networks controlling complex orofacial movements such as respiration and swallowing will also be reviewed as they relate to modulation of hypoglossal motoneurons. We will conclude our review process with a discussion of the cortical control of tongue movement and the potential for plasticity within this system, particularly with regard to dysfunction and clinical relevance.

Although recent investigations have made substantial contributions to our understanding of the complexities surrounding tongue movement, much remains to be done, especially with regard to clin-

ical application. Disruption of the neural control of tongue movement can seriously impede the function of rhythmic behaviors. Of those physiological processes involving the tongue, respiration and swallowing are associated with the highest morbidity and mortality. In fact, hypoglossal motoneuron dysfunction has been proposed to be a primary contributor to respiratory disorders such as sleep apnea and Sudden Infant Death Syndrome (SIDS) (Mitra *et al.*, 1986; Haddad and Donnelly, 1990; O'Kusky and Norman, 1992; Kubin *et al.*, 1996; Urban *et al.*, 1996). Furthermore, swallowing disorders (*i.e.*, dysphagia) associated with hypoglossal motoneuron dysfunction can lead to aspiration pneumonia and its consequences. The contribution of tongue movement disruption to the dysfunction of other complex behaviors has not yet been appreciated, because so little is known about their interactions. For this reason, our review of the relationship of tongue movement to complex orofacial behaviors will focus on respiration and swallowing.

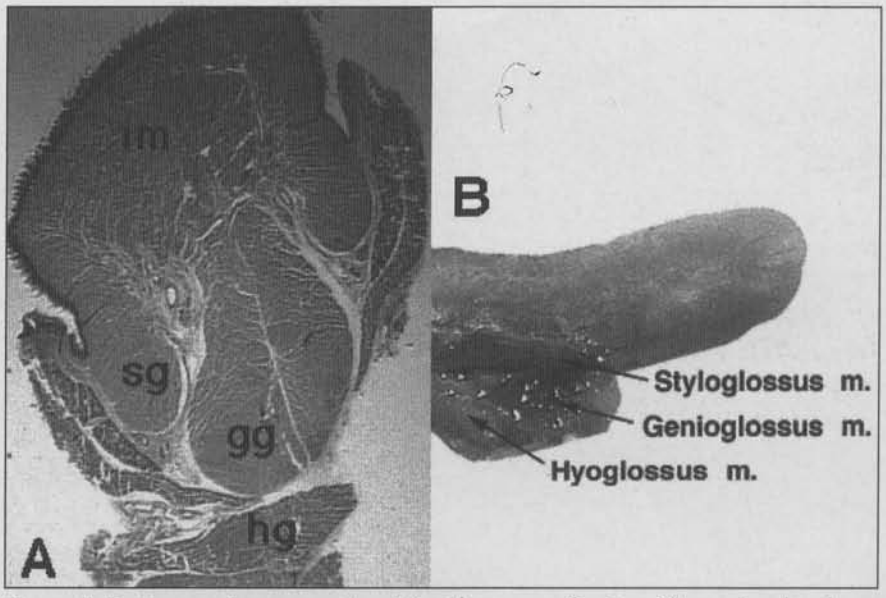

Figure 1. Rat tongue in cross-section (A) at low magnification. This section has been taken from the mid-tongue area (B) to illustrate the lack of muscle compartmentalization and the interdigitation of muscle fibers. Extrinsic muscles released from their proximal bony attachments are labeled in Panel B. The remainder of the tongue is comprised of unattached intrinsic muscles. im, intrinsic muscle; sg, styloglossus muscle; gg, genioglossus muscle; hg, hyoglossus (modified from Sawczuk and Tepper, 1997).

(II) *Peripheral Physiology Relevant to Tongue Movement*

(A) Contractile properties of the tongue

(1) Tongue muscle morphology

The tongue is a muscular hydrostat composed of 8 muscles that provide its skeletal support and generate its movement (Kier and Smith, 1985; Napadow *et al.*, 1999). The primary constraint on the direction of movement is the shape of the oral cavity and the proximal attachments. Four muscles are extrinsic and four are intrinsic to the tongue. The extrinsic muscles include the styloglossus and hyoglossus, which are tongue retruders, and the genioglossus and geniohyoid, which are tongue protruders. They have bony attachments at their proximal extents and insert into the base of the tongue distally. The 4 intrinsic muscles include the vertical, transverse, superior longitudinal, and inferior longitudinal. They have no bony attachment and are thought to perform movements of the tongue requiring more precision. Because muscles of the tongue are not compartmentalized and interdigitate in a variety of planes (Fig. 1), they have been, historically, very difficult to study as distinct entities. New creative techniques have enabled some investigators to overcome these limitations (Prigozy *et al.*, 1997; Sutlive *et al.*, 1999, 2000).

Immunohistochemical and molecular genetic techniques have been utilized by Prigozy *et al.* (1997) to type mouse tongue muscle fiber and troponin-C isoforms. They determined that the adult mouse tongue muscle is exclusively composed of fast muscle fibers as defined by the expression of fast Type II myosin heavy-chain proteins (MHC) in the absence of slow Type I isoforms. Their work confirms the results of Parker-Thornburg *et al.* (1992), indicating that tongue muscle matures during fetal development prior to embryonic day 18, which is in contrast to other rodent skeletal muscle, that matures during the post-natal period. It also is in contrast to other orofacial muscles such as the masseter muscle, that has immature α-cardiac MHC isoforms in the adult (Sciote *et al.*, 1994). Early maturation of the mouse tongue is also evident by predominance of the adult isoforms of troponin C (TnC) by embryonic day 18. TnC proteins bind Ca^{++} and transduce the excitation signals for muscle contraction. The presence of these TnC isoforms suggests that adult tongue contractile properties are operative *in utero*, a property necessary for feeding immediately at birth.

(2) Hypoglossal nerve anatomy

The hypoglossal nerve (XIIn) provides the only motor innervation to the muscles of the tongue. The main nerve trunk divides into medial and lateral branches in the anterior neck lateral and superior to the larynx. The medial branch innervates the extrinsic protruders (genioglossus and geniohyoid muscles) and their homologous intrinsic muscles, whereas the lateral branch innervates the extrinsic retruders (styloglossus and hyoglossus) and their homologous intrinsic muscles. Unfortunately, detailed anatomic maps of intrinsic muscle innervation have been prohibited by the lack of muscle compartmentalization and the extensive muscle interdigitation (Lee *et al.*, 1996).

Controversy has existed for many years regarding the composition of XIIn, which was thought to carry only efferent axons from the hypoglossal nucleus to the tongue muscles (Sumi, 1969). However, recent studies in the rat (O'Reilly and Fitzgerald, 1990) and cat (Takeuchi *et al.*, 1990; Fukui *et al.*, 1992) confirm the previous suggestion that there is also a small contribution (< 25%) from non-hypoglossal afferent and efferent axons. The major proportion of the afferent cell bodies is in the superior cervical ganglion, whereas a scant group is in the jugulo-nodose ganglion, and a minor number of efferent axons have their cell bodies in the facial and salivatory nuclei (O'Reilly and Fitzgerald, 1990). O'Reilly and Fitzgerald (1990) described salivatory nucleus efferents to the small autonomic ganglia found along the inferior aspect of the tongue. They also suggested that the facial contribution may be a developmental anomaly that has no apparent functional value. They determined that some efferent hypoglossal axons and proprioceptive afferents from cervical ganglia exit the upper spinal cord with the ansa cervicalis but join the XIIn trunk just prior to its division into the medial and lateral branches. Although the contributions from donated non-XII afferents and efferents make up less than 25% of XIIn (O'Reilly and Fitzgerald, 1990), their presence may partly explain the bundling pattern described in the human XIIn (Mackinnon and Dellon, 1995), which appears to be monofascicular to its most

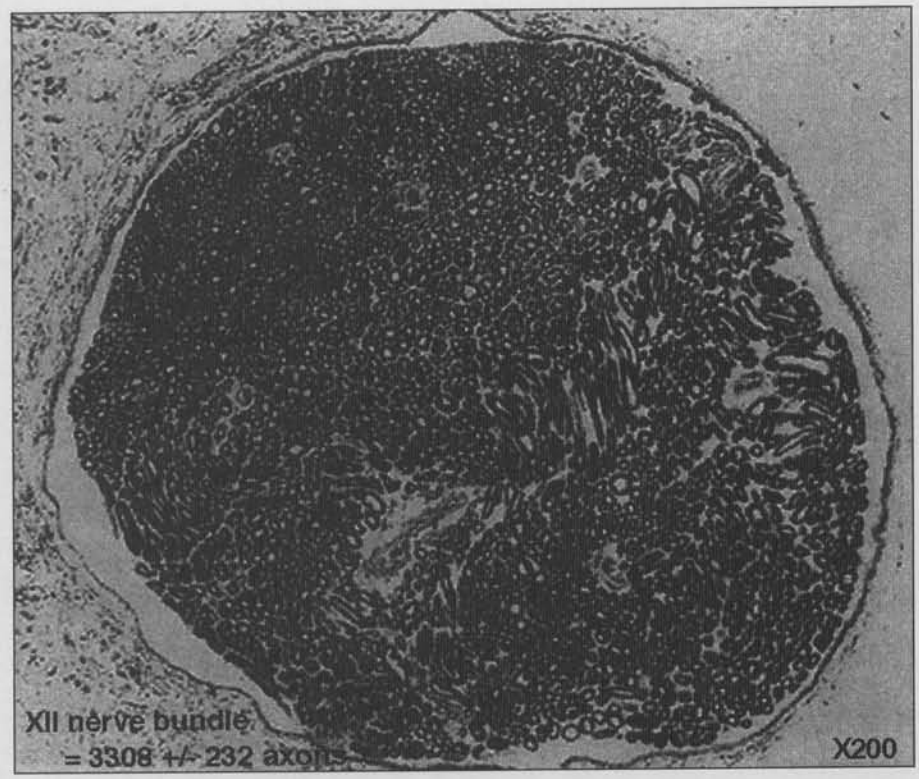

Figure 2. The rat hypoglossal nerve bundle contains between 3000 and 3500 axons that are primarily (> 2250 to 2625) hypoglossal efferents. These nerves direct tongue movement by responding to signals from neurons that control orofacial behaviors in the brainstem. (Modified from Kalantarian *et al.*, 1998)

distal aspect, where it branches into 5 fascicules. The remainder of this discussion will focus on hypoglossal efferents which are the major contributors to XIIn (> 75%).

The remarkably large mean number of myelinated axons (9200 ± 2182) reported by Mackinnon and Dellon (1995) suggests that, even after adjustment for donated afferents and efferents, more than 7000 axons comprise the efferent portion of the human XIIn that is devoted to motor control of the human tongue. The estimated number of axons in the rat XIIn is between 3300 and 3700 (Lewis *et al.*, 1971; Lodge *et al.*, 1973; Kalantarian *et al.*, 1998; Fig. 2). Results of electron microscopic imaging suggest that < 1% of these axons are unmyelinated (Lodge *et al.*, 1973). If corrected for donated axons, the number of axons in the peripheral nerve is a reasonable match with the estimated number of motoneurons in the rat hypoglossal nucleus (NXII), which is between 2500 and 3500 depending on the technique used to stain and count the neurons (Lewis *et al.*, 1971; McClung and Goldberg, 1999).

Regardless of the exact number of neurons innervating tongue muscles, it is much higher than the number of motoneurons devoted to groups of limb muscles (*e.g.*, about 1000 motoneurons innervate the posterior compartment of the cat limb, which includes soleus, plantaris, and medial and lateral gastrocnemius) but is consistent with other muscle groups, such as those of the digits and inner ear, that are required to execute finely tuned movements. In other motor systems, precision is facilitated by a decrease in the number of muscle fibers controlled by a single nerve (*i.e.*, an increased innervation ratio). As an example, each neuron innervates more than 600 muscle fibers in the cat gastrocnemius muscle (Burke and Tsairis, 1973), whereas the human digit has an innervation ratio of 1 to 10, and the muscles of the inner ear have a 1-to-1 innervation ratio (reviewed in Binder, 1989). The innervation ratio of individual tongue muscles has not been determined, but Sutlive *et al.* (1999, 2000) estimate the rat styloglossus muscle to have a ratio of 1:22 and the genioglossus muscle to have a ratio of 1:20. The ratio for intrinsic tongue muscles is expected to be much closer to that of the digits, because these are the muscles devoted to the more precise movements required for speech and mastication. The work of Mu and Sanders (1999) provides further reinforcement for the large innervation ratio of intrinsic tongue muscles. Using Sihler's stain to examine innervation of the canine tongue muscles by XIIn, they estimated approximately 50 primary branches from the lateral and medial nerve trunks, of which at least 32 project to muscle compartments of the intrinsic tongue muscles.

(3) Tongue muscle contractile properties

Tongue muscle interdigitation, absence of compartmentalization, and the lack of discrete attachment sites have impeded the determination of tongue contractile properties and severely retarded studies of tongue physiology. Recently, Goldberg and his colleagues (Gilliam and Goldberg, 1995; Sutlive *et al.*, 1999, 2000) creatively circumvented some of these problems in their electrophysiologic studies of rat tongue contractile properties. By attaching the tongue to a small strain gauge, Gilliam and Goldberg (1995) were reliably able to measure speed, force, and fatigue properties of retrusive and protrusive movements in response to peripheral stimulation of the hypoglossal whole nerve and its branches and to central stimulation within the hypoglossal nucleus. Their results suggest that the tongue retruders and protruders are primarily composed of fast, fatigue-resistant muscle groups. Sutlive *et al.* (1999, 2000) initiated their investigations of individual muscles by carefully dissecting the styloglossus muscle from its attachments to the whole tongue and the genioglossus from its proximal attachment to the mandible. Using electrophysiologic techniques for studying contractile properties and combining the results with histochemical data, they were able to demonstrate the predominance of fast-fatigue-resistant motor units (> 90%) (Fig. 3). Most recently, Sokoloff (2000) identified the intrinsic tongue motor units as fast-fatigue-resistant and primarily retrusive. These results are consistent with the demands placed upon tongue muscles to move with remarkable speed and precision between the various complex orofacial behaviors.

The functional designation of extrinsic tongue muscles as retruders or protruders distinct from intrinsic muscle influence has been brought into question by Napadow *et al.* (1999), who performed MR image analysis of human tongue movement and concluded that the orthogonal intrinsic muscles were the primary protruders, with no contribution from the genioglossus muscle. They suggest that control of protrusion by core tongue muscles is consistent with protrusive movements by other muscular hydrostats (*e.g.*, the elephant trunk; Kier and Smith, 1985). Although there is probably a contribution to protrusion from intrinsic muscles, the data supporting the genioglossus muscle as a primary protruder during respiration and Sokoloff's (2000) results indicating that intrinsic motor units are retruders are much too

compelling to be ignored (*cf.* Section IV[B1]). Furthermore, the imaging technique used by Napadow *et al.* (1999) would not detect co-activation of intrinsic and genioglossus muscles. Also, there is evidence suggesting that protrusion during movements such as respiration may involve co-activation of retruders with protruders (Fuller *et al.*, 1998).

(B) Oropharyngeal physiology

Complex orofacial behaviors involve the oral cavity, pharynx, and larynx, so we have included a brief summary of oropharyngeal physiology relative to respiration and swallowing to orient the reader and prepare for our discussion of the neural control of complex orofacial movement (*cf.* Section IV). For more detail, the reader is referred to reviews that primarily focus on oropharyngeal physiology, respiration, and/or swallowing (Miller, 1986, 1993; Martin and Sessle, 1993; Sant'Ambrogio *et al.*, 1995; Shaker and Lang, 1997; Plant, 1998; Pierce and Worsnop, 1999).

Although the tissues and neural pathways of oropharyngeal swallowing and upper airway respiration have many common elements, they appear to have unique brainstem circuitry that enables them to co-exist and provide access to the distinctly separate tissues of the esophagus and lower airway. Coordination of 26 muscles and 5 cranial nerves is required to produce an oropharyngeal swallow, whereas the upper airway aspect of respiration requires activation of muscles and nerves involved with the oropharyngeal swallow as well as those of the nasopharynx. The primary goal of oropharyngeal swallowing is to transport a bolus and seal off the nasopharyngeal and laryngeal airways; however, the primary goal of upper airway respiration is to control airway resistance during inspiration, either through contraction or dilation of the pharynx or larynx. Thus, the two processes are physiologically and biomechanically reciprocal events. During inspiration, upper airway resistance must be decreased to allow maximal passage of air through the trachea, hence requiring dilation of the pharyngeal and laryngeal lumens. This is accomplished through contraction of: (1) the genioglossus muscle, (2) the palatal elevator muscles (levator and tensor veli palatini), (3) the palatoglossus and palatopharyngeus muscles, and (4) the posterior cricoarytenoid, which abducts the vocal cords. Transport of a food bolus through the oral cavity and pharynx during swallowing, which generally occurs during the expiratory phase of respiration, requires: (1) retrusion and protrusion of the tongue; (2) contraction of the palatal muscles; (3) adduction of the vocal cords through contraction of the vocalis, the thyroarytenoid, and lateral cricoarytenoid muscles to close the glottic chink; and (4) contraction of the pharyngeal constrictors.

Interaction of these muscles and nerves is, by necessity, highly complex, because their purpose is to move air and food from the external world and make them compatible with our internal world that has precisely controlled temperature, humidity, osmolarity, acidity, and other metabolic requirements. Previous studies of respiration and swallowing focused on control of the larynx, because the larynx must be reciprocally coordinated during respiration and swallowing. Dysfunction in the laryngeal area can result in aspiration and its related sequelae. New evidence, however, suggests that the central gating mechanisms may also require interaction with hypoglossal motoneurons (*cf.* Section IV[B1]), increasing the vulnerability to dysfunction.

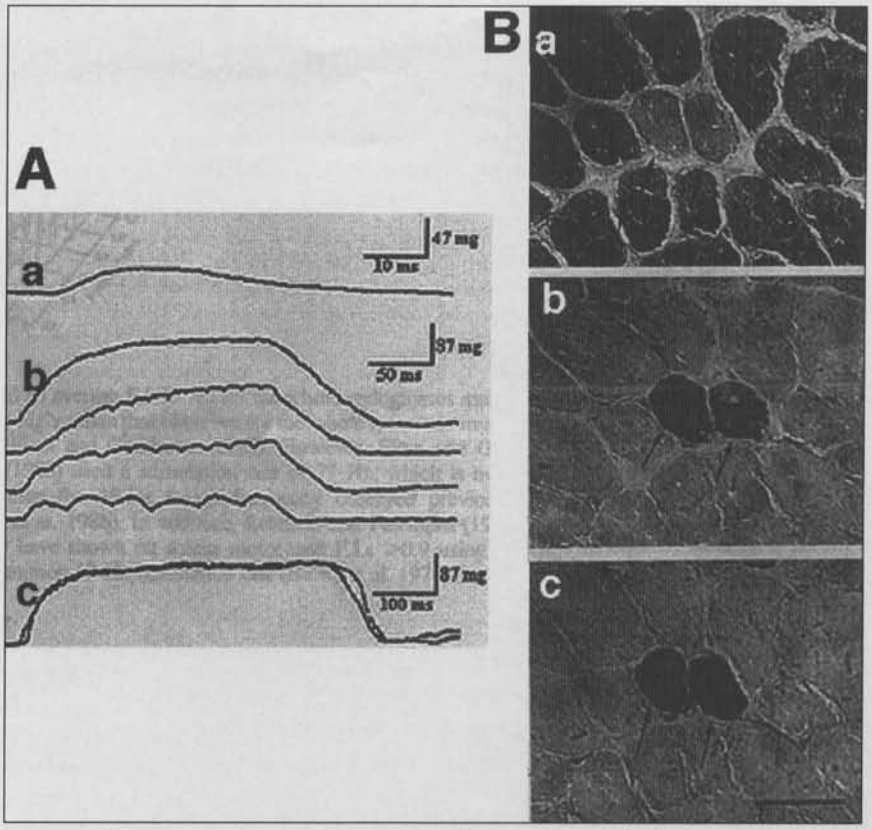

Figure 3. The contractile properties presented in Panel A typify the fast, fatigue resistance of styloglossus motor units. The muscle twitch tension (31.3 mg) and twitch contraction time (11.4 ms) in response to stimulation of a single hypoglossal motoneuron are presented in trace 'a'. The whole muscle twitch contraction time of 12.0 ms is more like the fast rat extensor digitorum longus (13.1 ms) than the slow rat soleus muscle (36.7 ms). The traces in 'b' are responses to tetanic stimulation. Note the lack of sag in the unfused records. Although this response is more consistent with slow motor units, styloglossus motor units are more typical of other fast units. Fusion occurs at 100 Hz, whereas whole styloglossus muscle fusion is at 115 Hz. The fatigue response to 500-ms steps of 90-Hz stimulation for 2 min at maximal isometric tension is presented in 'c'. There is very little decrement in the initial (top trace) and final responses (bottom trace), suggesting that this muscle is fatigue-resistant. These electrophysiologic data are confirmed by the histologic analysis presented in Panel B, which shows stained styloglossus muscle reaction to myofibrillar ATPase following pre-incubation at pH of 9.8 (a), 4.6 (b), and 4.3 (c). The overwhelming majority of muscle fibers were type IIA, which are typical for fast fatigue-resistant motor units. The arrows point to type I muscle fibers. (Modified from Sutlive *et al.*, 1999)

(1) Upper airway respiration

Airway patency is maintained by the palatal muscles, the extrinsic tongue muscles, and the hyoid muscles. These dilators are aided by the pharyngeal constrictors which support the walls of the pharynx and by postural muscles of the head and neck. Innervation of the oral cavity, oropharynx, and nasopharynx relevant to respiration is *via* cranial nerves V, IX, X, and XII (*i.e.*, trigeminal, glossopharyngeal, vagus, and hypoglossal). Receptors of the glossopharyngeal nerve (cranial nerve IX) are thought to mediate the aspiration reflex that clears mucous secretions from the nasopharynx and moves them to the oropharynx to be swallowed or to the larynx to be expelled by coughing (Sant'Ambrogio *et al.*, 1995).

Muscles of the larynx are tightly controlled abductors and ad-

ductors that serve as the final bastions of airway protection, admitting perfectly primed air and restricting foreign material from the lungs. Motor and sensory control of the larynx is from the superior laryngeal nerve (SLN). It modulates respiration by detecting upper airway collapse through laryngeal pressure-sensing mechanoreceptors and by initiating reflex mechanisms to ensure preservation of patency (reviewed in Sant'Ambrogio *et al.*, 1995). These reflex mechanisms serve two purposes: (1) to increase activation of upper airway abductor muscles and (2) to decrease inspiratory drive by changing the timing of respiration and decreasing the pressure generated by the thoracic pump muscles. The genioglossus muscle is one of the primary upper airway dilators affected by this reflex (reviewed in Martin *et al.*, 1994; Sant'Ambrogio *et al.*, 1995; Fregosi and Fuller, 1997; Eastwood *et al.*, 1998; Fenik *et al.*, 1998; Pierce and Worsnop, 1999). Laryngeal muscles also have thermo- and chemoreceptors that protect the lower airway from the potentially harmful effects of cold and ensure that secretions entering the lower airway are isosmolar. Additionally, these receptors detect increased levels of CO_2 which have been shown to reduce ventilation and increase genioglossus activity (Sant'Ambrogio *et al.*, 1995).

(2) Oropharyngeal swallowing

Oropharyngeal swallowing afferents include the trigeminal, glossopharyngeal, and vagal nerves (cranial nerves V, IX, and X). Touch and pressure receptors for the trigeminal nerve in the tongue determine the shape, texture, and stereoscopic aspects of the bolus. In fact, it has been suggested that the oral cavity acts as a rheometer during formation of the bolus by sensing and altering the shape and viscosity of food (Coster and Schwartz, 1987). The oropharynx is primarily composed of striated muscle having glossopharyngeal and vagal mechanoreceptors. The overlying mucosa also contains chemoreceptors, thermoreceptors, and free nerve endings. Slowly adapting pressure receptors of the anterior and posterior tonsillar pillars and of the posterior wall of the pharynx are responsible for initiation of the swallowing "reflex". This reflex is more like an automatic behavior than a true reflex and, as such, can be modified by peripheral and central input to the central pattern generator for swallowing (*cf.* Section IV; reviewed in Miller, 1986; Martin and Sessle, 1993).

Swallowing efferents include the trigeminal, facial, glossopharyngeal, vagus, and hypoglossal nerves (cranial nerves V, VII, IX, X, XII) as well as cervical nerves 1 to 3. The muscles involved are those identified above for upper airway respiration. Like respiration, they provide an environment in which the food is not simply propelled through a conduit by gravity but is processed and actively transported in a highly dynamic and plastic manner (Gay *et al.*, 1994; Palmer, 1998). Airway protection from the food bolus occurs at the larynx by adduction of laryngeal muscles, epiglottic tilt, hyoid elevation, and laryngeal elevation that permits passive opening of the upper esophageal sphincter (UES) for food to enter the esophagus. This process is controlled by the SLN. In fact, electrical stimulation of the SLN is the preferred method of producing swallowing in experimental animals (Kessler and Jean, 1985; Car and Amri, 1987; Amri *et al.*, 1991).

(C) Peripheral Interaction of Tongue Movement, Respiration, and Swallowing

The relationship between the neural control of tongue movement and respiration has been well-established (*cf.* Section IV). Less is known of the relationship between tongue movement and swallowing, perhaps because the peripheral structures and innervation have been difficult to isolate from those of respiration. Also, the adductive movements that produce tongue protrusion to ensure airway patency during respiration are less complex than tongue movements for swallowing, which require a combination of retrusion with protrusion.

The relationships between these movements in respiration and swallowing are influenced by several variables, including posture, respiratory-related chemoreception, and bolus consistency. Swallowing occurs during inspiration in most animals and non-human primates but during expiration in the adult human. McFarland *et al.* (1994) found that human swallows were completed earlier in expiration (closer to inspiration) if performed in a position on all four limbs that is more typical of non-human animals. It is likely that posture also affects the modulation of tongue movement during swallowing and respiration.

The modulation of XIIn activity by inspiratory drive has been recognized since the early 1980s (reviewed in Bartlett and St. John, 1988). Bartlett *et al.* (1987) examined this relationship more closely in decerebrate, paralyzed cats by studying peripheral nerve activity during hypercapnia and hypoxia. They found that the XIIn response to changes in ventilatory chemoreception was much greater than phrenic activity and that it occurred earlier during inspiration. Since these early investigations, much attention has been given to the modulation of genioglossus (*i.e.*, protruder) activity by inspiratory drive, particularly with regard to hypoxia (Martin *et al.*, 1994; Hayashi and McCrimmon, 1996; Eastwood *et al.*, 1998; Fenik *et al.*, 1998). Most recently, Fuller *et al.* (1998) demonstrated co-activation of tongue protruders and retruders in response to changes in respiratory chemoreceptor stimulation in the rat which resulted in more tongue retraction than protrusion. They hypothesize that co-activation may improve pharyngeal airway mechanics by stiffening the tongue, albeit at the expense of narrowing the airway. Analysis of these results suggests that we have much to learn about the modulation of tongue activity by respiration and, presumably, by swallowing.

The impact of bolus consistency and mode of delivery on swallowing have been appreciated for many years by researchers and utilized therapeutically by clinicians. Recently, Preiksaitis and Mills (1996) investigated the effects of bolus consistency and presentation on the coordination of respiration and swallowing in healthy adults. They determined that swallow-related apnea, which lasts 1 or 2 sec and occurs during expiration, is maintained over a variety of bolus volumes and consistencies when studied as single-bolus swallows. During more complex eating and drinking that simulates the typical food-intake pattern, however, this apnea is followed by inspiration. They suggest that such a pattern puts the aspiration-prone individual at increased risk.

(III) *Hypoglossal Nucleus Anatomy and Motoneuron Physiology*

(A) Functional Organization of the Hypoglossal Nucleus

(1) Somatotopy within the hypoglossal nucleus

Hypoglossal motoneuron somata are located in the hypoglossal nucleus (NXII), which is positioned in the ventral medulla and caudal pons near the midline. In the rat, this nucleus extends about 2.0 mm rostrocaudally x 1.5 mm mediolaterally from slightly caudal of the obex rostrally to the mid-fourth ventricle. Efforts to determine the precise location of motoneurons within the nucleus have been compromised, because interdigitation of tongue muscles has resulted in most anatomic studies being

plagued by contamination of tracers bleeding into adjacent muscles. Investigators generally agree, however, that the motoneurons are arranged somatotopically (Fig. 4; Odutola, 1976; Uemura-Sumi *et al.*, 1988; Sokoloff and Deacon, 1992; Altschuler *et al.*, 1994; Guo *et al.*, 1996). Motoneurons controlling tongue protrusion are in the ventral part of the nucleus, whereas motoneurons controlling retrusion are in the lateral and dorsolateral parts of the nucleus. Motoneurons controlling the intrinsic tongue muscles (primarily important for speech and mastication) occupy the remainder of the nucleus. The ventral subdivision is in the caudal 2/3 of the nucleus, whereas the dorsal subdivision is in the rostral 2/3 of the nucleus. The two subdivisions overlap in the middle third of the nucleus. About 95% of the neurons in the hypoglossal nucleus are motoneurons, whereas the remaining 5% are interneurons (Viana *et al.*, 1990). The interneurons are primarily restricted to the dorsolateral, lateral, and ventral margins of the nucleus (Aldes, 1990; Altschuler *et al.*, 1994).

(2) Functional organization of the hypoglossal nucleus

There is anatomical evidence of a functional organization to the hypoglossal nucleus and the brainstem networks that modulate them (Dobbins and Feldman, 1995). Neuronal networks controlling tongue retruders are proposed to be primarily in the area of the solitary nucleus of the dorsal brainstem, whereas protruder neurons are primarily in the ventrolateral brainstem near the nucleus ambiguus (*cf.* Section IV|B|). The hypothesis of functional segregation has far-reaching implications for studies of all orofacial behaviors, including tongue movement, but substantiation requires unambiguous identification of motoneurons in the nucleus. This means that confirmation of label in motoneurons must be verified by the demonstration of tracer injection sites localized to the individual tongue muscle being studied. Unfortunately, these data were not available for most previous anatomical studies of the hypoglossal nucleus because of the compartmental and histologic limitations placed on tracer injection into the tongue muscle (*cf.* Section II|A|).

In their study of the hypoglossal complex in the monkey, Sokoloff and Deacon (1992) attempted to address the problem of tracers bleeding between muscles by meticulously relating motoneurons of the nucleus labeled with wheat-germ agglutinin conjugated to horseradish peroxidase (WGA-HRP) to tracer injections in the tongue. Their results were a more accurate confirmation of previous work in cats and rats that demonstrate a dorsal compartment within the nucleus that controls retrusion and a ventral compartment that controls protrusion.

Several investigators have performed labeling studies of tongue protruder motoneurons (particularly the genioglossus) that were controlled by injection-site verification (Brozanski *et al.*, 1989; Sokoloff and Deacon, 1992; Aldes, 1995). Their work is best summarized by Aldes (1995), who studied 72 rat motoneurons labeled with horseradish peroxidase (HRP) applied to the whole nerve or injected into the muscle as a conjugate with cholera toxin (CTHRP). By using the overlapping tracer injection technique of Sokoloff and Deacon (1992), Aldes (1995) identified three subcompartments within the ventral hypoglossal nucleus. Motoneurons of the medial subcompartment (n = 300; D = 22.84 ± 2.33 μm) innervate the verticalis and transversus intrinsic muscles, motoneurons of the lateral compartment (n = 200; D = 27.86 ± 2.8 μm) innervate the genioglossus muscle, and motoneurons of the lateral accessory compartment (outside the main nucleus; n = 100; D = 34.46 ± 2.61 μm) innervate the geniohyoid muscle.

McClung and Goldberg (1999) isolated rat styloglossus and hyoglossus muscles by careful dissection prior to injecting tracer (CTHRP) and thus were able to identify the motoneuron somata in NXII more precisely (Fig. 4). They counted about 100 hyoglossus motoneurons with a mean somata diameter of 29.9 ± 3.3 μm and 50 to 100 styloglossus motoneurons (probably closer to 100; see Sutlive *et al.*, 1999) with a mean somata diameter of 30.6 ± 3.4 μm. The same group of investigators also estimated the genioglossus motoneuron pool to have about 150 motoneurons (Sutlive *et al.*, 2000). Aldes (1995) estimated ventrolateral compartment motoneurons (consistent with genioglossus projection sites) to be 29.49 ± 2.47 μm in diameter and geniohyoid motoneurons in the lateral accessory com-

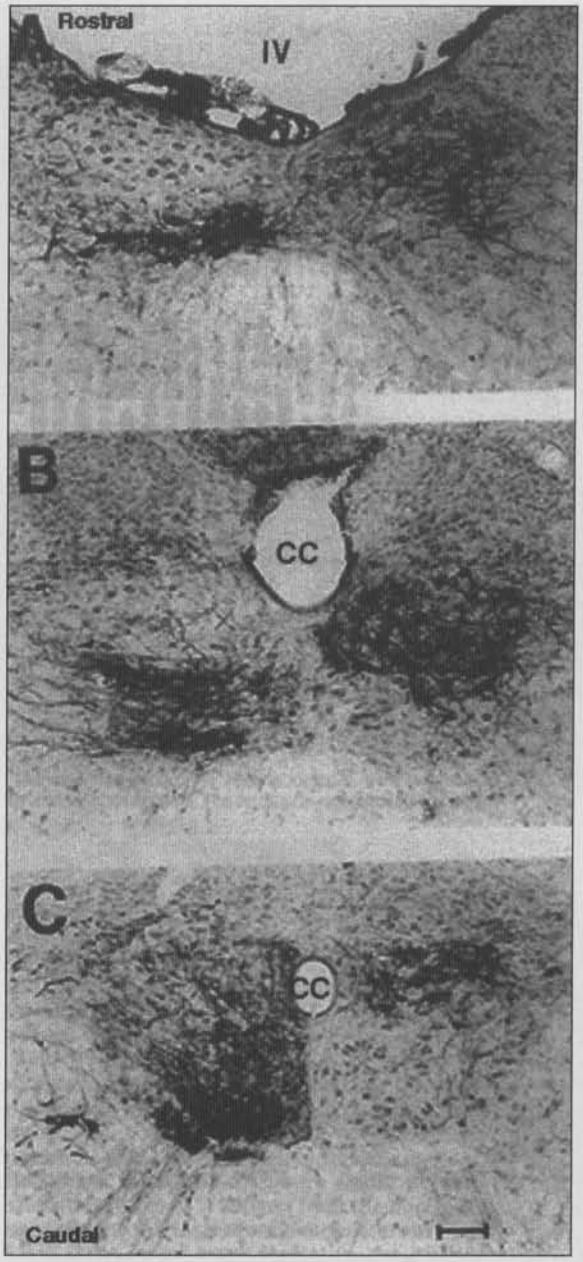

Figure 4. Somatotopy of the hypoglossal nucleus produced by retrograde tracer (cholera toxin conjugated to horseradish peroxidase) applied to the hypoglossal nerve branches. Stain applied to the right lateral branch labels the right dorsal motoneurons, and stain to the left medial branch labels the left ventral motoneurons. The rostrocaudal differences in the distribution of these motoneurons are also evident in this Fig. The lateral branch primarily projects to the rostral 2/3 of the nucleus, whereas the medial branch projects to the medial 2/3 of the nucleus. (Modified from McClung and Goldberg, 1999)

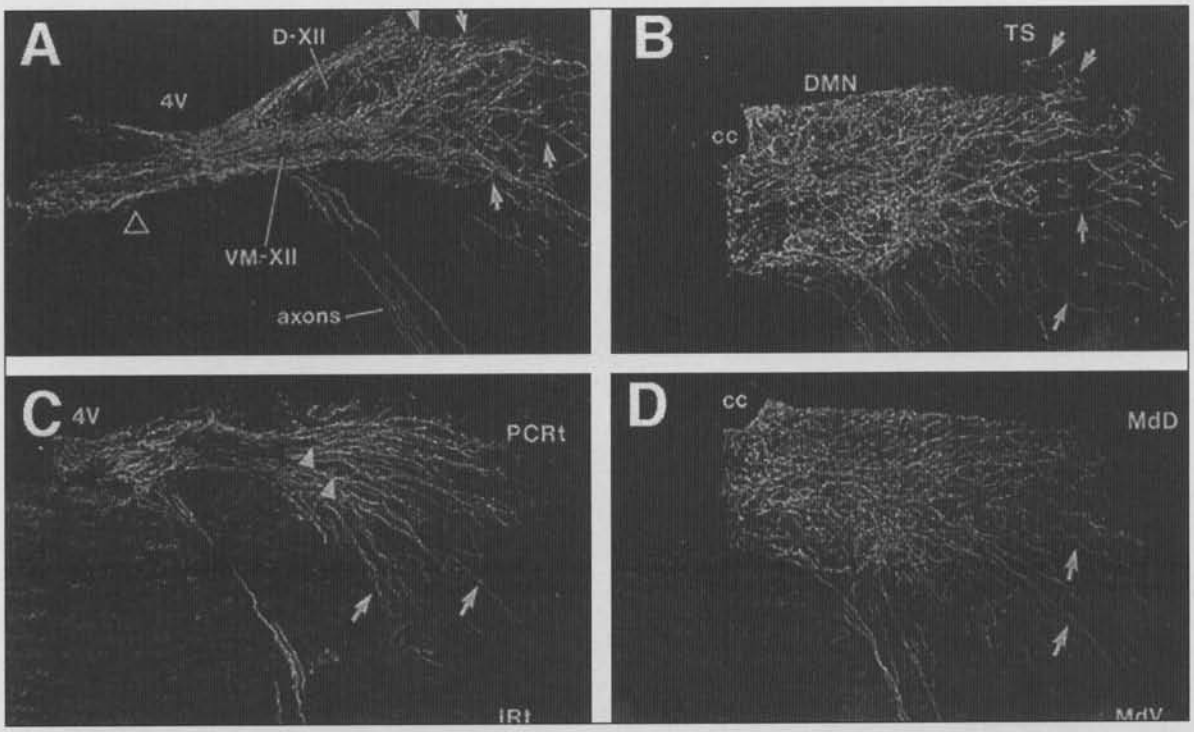

Figure 5. The dendritic architecture of genioglossus (Panels A and B) and styloglossus (Panels C and D) provides anatomic support to the complexity of hypoglossal interactions. Both groups of motoneurons have extensive dendritic processes that project between subnuclei and into the lateral and medial reticular formation. Additionally, they have considerable dendritic 'bundling' that may provide a substrate for coordination between tongue muscles. (Modified from Altschuler *et al.*, 1994)

partment to be 34.46 ± 2.61 μm.

Investigations of brainstem afferents to hypoglossal motoneurons have been aided by studies of the dendritic architecture. Altschuler *et al.* (1994), using CTHRP, performed a careful examination of the architecture of the extrinsic hypoglossal motoneuron dendritic arborization in the rat. Their work confirmed the results of other studies (Aldes, 1990, 1995; Sokoloff and Deacon, 1992) showing that the dendritic projections were oriented in lateral columns along the rostrocaudal axis within and between subnuclei and extended in the mediolateral plane beyond the nucleus to the ipsilateral dorsal motor nucleus of the vagus, adjacent reticular formation, raphe obscurus, and nucleus tractus solitarius, as well as the contralateral hypoglossal nucleus. Their techniques enabled them to compare the dendritic arborization of the extrinsic motoneurons in detail (Fig. 5). They noted that dendritic bundling and axodendritic contacts were characteristic within and between motoneurons and interneurons of each subnucleus and related this to the networking required of neurons involved in complex movements. Dendrites of genioglossus motoneurons also projected to the contralateral ventrolateral hypoglossal nucleus. The dendritic arborization and the extranuclear projections were less extensive for the ventrolateral motoneurons, particularly the geniohyoid motoneurons, which radiated as single processes from the cell body rather than as a dense bundle. These results add further credence to the concept of functional segregation proposed by Dobbins and Feldman (1995), who attempted to identify afferents to the hypoglossal nucleus with pseudorabies virus. Their results suggest the presence of mono- and disynaptic connections between styloglossus motoneurons and the nucleus tractus solitarius (NTS) (*cf.* Section IV[B2]).

Fukunishi *et al.* (1999) extended the work of Altschuler *et al.* (1994) by isolating single XIImns in the ventromedial NXII of the cat using sharp electrodes filled with HRP. Detailed study of the somatodendritic organization of labeled motoneurons revealed 2 types that differed in the location of their somata and in their dendritic arborizaton patterns. Type I neurons innervated tongue protruders. They had a large polygonal somata and dendrites that extended ventrolaterally beyond the nucleus, whereas Type II neurons had small somata and fan-shaped, mirror-image dendritic trees that were confined to NXII. These results are consistent with those described for the rat except for minor differences in the extranuclear projections of Type I neurons. The most interesting aspect of this study was the shape of Type II neurons, which has not been reported for other motoneurons. The significance of these results was not addressed by the investigators but may relate to the need for rapid communication between motoneurons controlling different muscle groups within the tongue.

(B) Hypoglossal motoneuron physiology

In recent years, membrane and discharge properties of hypoglossal motoneurons have received considerable attention by respiratory and motor systems physiologists (Nunez-Abades *et al.*, 1993; Sawczuk *et al.*, 1995a,b, 1997; Viana *et al.*, 1995; Poliakov *et al.* 1997). These investigators have studied hypoglossal motoneurons with the *in vitro* rodent preparations because they offer a more stable environment in which the cell properties can be studied for prolonged periods with combined electrophysiological, pharmacological, and anatomical approaches. Studies of the passive and active intrinsic membrane properties described for hypoglossal motoneurons are summarized by investigator and technique in the Table. Comparisons made with spinal and other cranial motoneurons suggest that hypoglossal motoneuron intrinsic membrane properties are very similar to those of other motoneurons when considerations are made for size, shape, and preparations used. For a complete review of hypoglossal motoneuron passive and active membrane properties and the conductances that are proposed to produce them, the reader is referred to other review articles that provide a more focused and detailed discussion (*e.g.*, Binder *et al.*, 1996; see also Rekling *et al.*, 2000). Two intrinsic properties of hypoglossal motoneurons are relevant to this review: (1) endogenous calcium levels and (2) the character of prolonged repetitive firing.

Spontaneous bursting activity can be recorded from XIIn *in*

vitro. This phenomenon appears to be a response to the intrinsic bursting of pattern generators for complex movements and has been studied primarily with regard to respiration (*cf.* Section IV). The ability of hypoglossal motoneurons to respond rapidly to this modulation, however, has been proposed by Lips and Keller (1998) to be an intrinsic property that may be related to unusually low endogenous calcium concentrations. By combining electrophysiologic measurement of Ca^{++} conductances with measurement of intracellular Ca^{++} concentration using fura-2 fluorescence, they determined that 98% of the Ca^{++} entering the motoneuron was bound by endogenous buffers. Thus, the available Ca^{++} was considerably reduced from that in other cells having the same size and geometry. Lips and Keller (1998) suggest that the "faster Ca^{++} dynamics" may facilitate the rhythmicity required of respiratory neurons but places them at increased risk from systemic disorders such as amyotrophic lateral sclerosis by causing them to be more vulnerable to hypoxia and to Ca^{++}-mediated excitotoxicity.

Motoneurons involved in such activities as maintaining posture, jaw, and tongue position are capable of sustained repetitive discharge for minutes to hours. Because motoneuron repetitive discharge controls the muscle during movement, adaptation of motoneuron discharge must also have significance during movement and, therefore, has been proposed to be a primary component of central fatigue (reviewed in Sawczuk *et al.*, 1995a). Using the *in vitro* rat brainstem slice preparation, Sawczuk *et al.* (1995b) studied spike-frequency adaptation during hypoglossal moto-

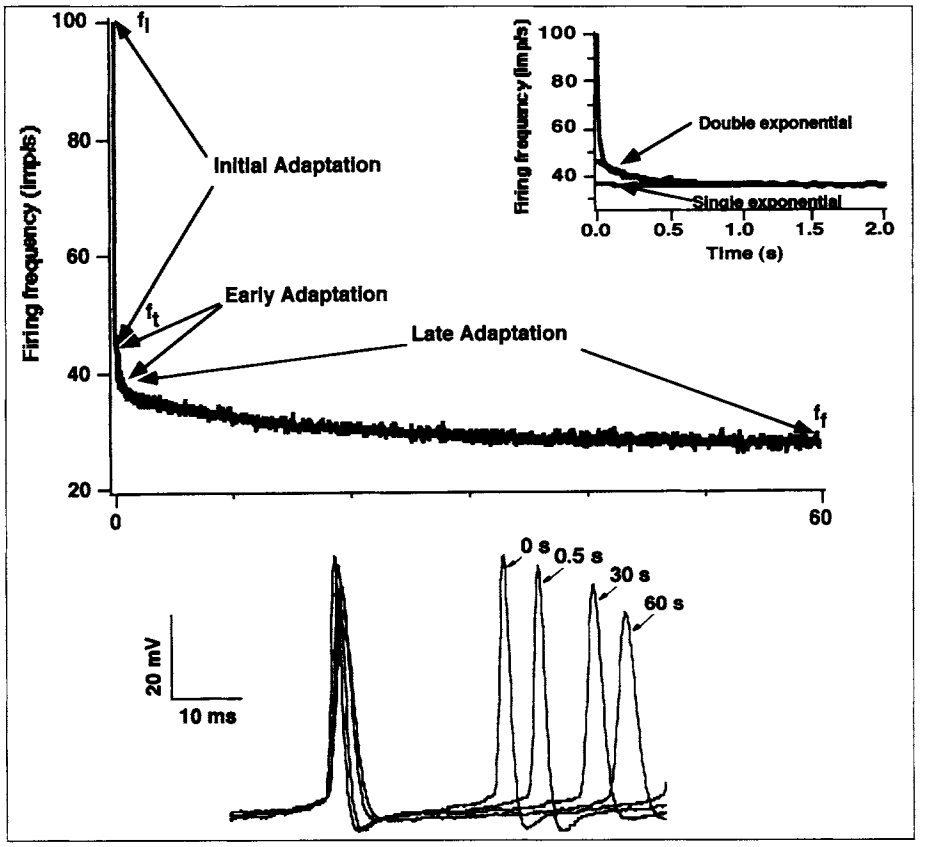

Figure 6. There are 3 phases to spike frequency adaptation in hypoglossal motoneurons: an initial, dramatic linear phase, an early exponential decline with a relatively fast time constant, and a late exponential decline that has a slow time constant. These phases appear to be intrinsic to the motoneuron and dependent on specific membrane properties not yet identified. Clues to the properties involved may be embedded in changes in the shape of the action potential and after-hyperpolarization during discharge which reflect changes in membrane kinetics during channel and pump activity (lower panel). The small decrease in amplitude that occurs during late adaptation may provide some of the fatigue-resistant properties described by Sutlive *et al.* (1999a). (Modified from Sawczuk *et al.*, 1997)

TABLE. Membrane Properties of Hypoglossal Motoneurons

Source	V_m (mV)	I_{Rh} (nA)	R_{nss} (mΩ)	I_o (nA)	τ_m (ms)	f-I Slope (ips*nA^{-1})
Mosfeldt Laursen and Rekling, 1989 Guinea pig brain slice prep. I-cell at 36.5°C	-63.4 ± 5.7	—	—	—	4.1 ± 1.3	—
Haddad *et al.*, 1990 Rat brain slice prep. I-cell at 35-36°C	-80 ± 2	2.1 ± 0.4	14.6 ± 1.4	—	—	—
Nunez-Abades *et al.*, 1993 Rat brain slice prep. I-cell at rm. temp.	-54.7 ± 9.1	0.26 ± 0.16	39.2 ± 11.5	—	6.8 ± 1.7	—
Sawczuk *et al.*, 1995a Rat brain slice prep. I-cell at rm. temp.	-70.3 ± 10.0	0.28 ± 0.18	23.5 ± 12.5	0.38 ± 0.21	7.5 ± 1.9	23.2 ± 8.4

V_m, resting membrane potential; I_{Rh}, rheobase current; R_{nss}, input resistance; I_o, threshold current for repetitive discharge; τ_m, membrane time constant; f-I slope, slope of the frequency-to-current relationship; I-cell, intracellular.

neuron repetitive discharge by injecting a series of long constant-current pulses into the hypoglossal motoneurons. They identified three distinct phases (Fig. 6) to hypoglossal motoneuron adaptation which appear to be produced by different membrane mechanisms (Sawczuk *et al.*, 1995b, 1997). The first phase is a dramatic linear decrease in firing frequency that is complete within 1 to 4 interspike intervals (isi). Following this initial adaptation is an exponential decline in frequency lasting for the duration of firing, which may be several minutes. This decline is an intrinsic, non-varying property of the motoneuron that is described by one of two possible exponential functions, either a single function for late adaptation only or a double function that includes both early and late components to adaptation.

The time-course of hypoglossal spike-frequency adaptation is so consistent over repeated trials that it appears to be *a fingerprint* for intrinsic cell activity (Sawczuk *et al.*, 1995a). Furthermore, this consistency remains even when the discharge is interrupted by the introduction of current pulses of various durations or by extended periods of "white noise". Most importantly, the late phase of adaptation has a small-magnitude change over several minutes (Sawczuk *et al.*, 1995b), suggesting that fatigue resistance is a property of hypoglossal motoneurons. These results support the investigations of Sutlive *et al.* (1999, 2000) that demonstrated fast, fatigue-resistant contractile properties for the styloglossus muscle. They also lend credence to the proposal that fatigue resistance is desirable for tongue function during complex movements such as respiration, swallowing, and speech. Fatigue resistance may be particularly important for facilitating the constant, rapid switching between these movements that must occur during a 24-hour period.

(IV) *Neural Control of Complex Orofacial Movements*

(A) Brainstem control of swallowing and respiration

Earlier in this review, we noted that, although upper airway respiration and oropharyngeal swallowing have peripheral structures in common, it is in the brainstem that they appear to segregate. Unfortunately, details of the circuitry have been difficult to study because of the shared peripheral innervation. Some insight has been gained from neurophysiological investigations of lower airway respiration, esophageal swallowing, and tongue movement. We will review selected aspects of brainstem anatomy and physiology related to swallowing and respiration prior to examining their involvement in the control of tongue movement. For a more complete review of the neural control of swallowing and respiration, the reader is referred to other sources (Miller, 1986, 1993; Sessle and Henry, 1989; Bianchi *et al.*, 1995; Plant, 1998).

(1) Brainstem anatomy relevant to respiration and swallowing

Primary vagal and glossopharyngeal afferents from the oral cavity, pharynx, and larynx enter the brainstem from the various cranial nerve ganglia that house their cell bodies and project to the solitary nucleus (NTS). The brainstem projection of the cervical vagus nerves and the superior laryngeal (SLN) and pharyngeal (PhN) nerves in the rat is confined to the interstitial nucleus of the NTS (Altschuler *et al.*, 1989; Mrini and Jean, 1995; Furusawa *et al.*, 1996; Sawczuk and Covell, 1999), which extends from slightly caudal to the obex in a rostral direction for a distance of approximately 600 to 800 μm. Umezaki *et al.* (1998a) identified neurons that were exclusively swallow-related in the cat interstitial nucleus lateral to the solitary tract. The intermediate nucleus in the mid-NTS is rostral to the interstitial nucleus, receives afferent projections from the glossopharyngeal nerve, and relays sensory information from the palate and pharynx. The ventral and ventrolateral subdivisions of the NTS receive pulmonary afferents (Kalia and Richter, 1985, 1988).

Kawai and Senba (1996) were able to maintain and study the local circuitry of the caudal solitary nucleus in a rat thin-slice preparation. They describe 3 different cell groups: (1) local circuit neurons with axon collaterals restricted to the solitary nucleus but with the main axon leaving the nucleus, (2) presumed interneurons with axons restricted within the solitary nucleus, and (3) projection neurons whose axons leave the nucleus. The projection neurons have a somal surface area > 150 μm^2, whereas both the local circuit neurons and the putative interneurons have smaller cell bodies, < 150 μm^2. Projection neurons have few, if any, axonal collaterals, whereas both local circuit neurons and the putative interneurons have extensive arborization of their axonal collaterals.

Vagal and glossopharyngeal efferents to the oral cavity, pharynx, and larynx have their cell bodies in the nucleus ambiguus (NA). Furusawa *et al.* (1996) have shown that rat SLN efferents are localized to a 1-mm segment of the NA between 1.5 and 2.5 mm rostral to the obex. Bieger and Hopkins (1987) localized the PhN motoneuron pool to the caudal aspect of the semicompact formation of the NA, whereas the SLN motoneuron pool is in the rostral aspect. Altschuler *et al.* (1991) used cholera toxin-HRP to characterize pharyngeal efferent neurons in the NA semicompact formation into 3 shapes: multipolar (20-30 x 25-35 μm), oval (15-20 x 20-25 μm), and fusiform (15 x 30 μm). Their functional significance is not clear.

(2) Central pattern generators

Complex orofacial movements are either tonic, phasic, or episodic motor sequences characterized by rhythmic, patterned, or cyclic activity. These motor sequences appear to be controlled by central pattern generators (cpg) in the brainstem. Cpgs are thought to be small networks of neurons or, perhaps, a single neuron that will produce an oscillatory discharge in response to stimulation and will continue to oscillate even when the stimulation has been removed (reviewed in Feldman and McCrimmon, 1999; see also Stein *et al.*, 1997, and Rekling *et al.*, 2000). There are 5 brainstem cpgs that have been proposed to control orofacial movements for respiration, swallowing, mastication, licking, and rejection. We will limit this discussion to the generators for respiration and swallowing. The reader is encouraged to refer to other recent resources for investigations of the cpgs for mastication (reviewed in Lund *et al.*, 1998), licking (Travers and Jackson, 1992; Brozek *et al.*, 1996; Travers *et al.*, 2000), and rejection (Dinardo and Travers, 1994).

Respiratory central pattern generator

The rhythmic activity of respiration is controlled in the brainstem by at least 2 central pattern generators: (1) the pneumotaxic center in the pons, which includes the nucleus parabrachialis medialis and the Kolliker-Fuse nucleus; and (2) the dorsal and ventral respiratory groups of the dorsomedial medulla, which are associated with the caudal NTS and NA, respectively. The pneumotaxic center may be important for switching between respiratory phases, but its lesion does not abolish respiratory rhythm, which appears to be centered in the NA (Smith *et al.*, 1991). Inspiratory-phase activity is controlled by neurons in the middle and rostral aspects of the NA. Expiration is controlled by neurons of the Botzinger complex in the rostral NA and inspiration by neurons in

the pre-Botzinger complex in the caudal NA. Both rostral groups of NA neurons synapse on motoneurons in the spinal cord (*i.e.*, phrenic and thoracic) that generate contraction of the respiratory muscles. Neurons in the pre-Botzinger complex control rhythmic oscillations in the cranial motoneurons involved in respiration (*i.e.*, the vagus, glossopharyngeal, and hypoglossal; Smith *et al.*, 1991). In fact, the neural control of inspiratory drive appears to include modulation of genioglossus (protruder) motoneurons in the hypoglossal nucleus (Smith *et al.*, 1990, 1991).

Swallowing central pattern generator

Details of the swallowing central pattern generator were not revealed until the 1970s, when Andre Jean (reviewed in Jean, 1984a) described 2 brainstem areas in sheep, one ventral and one dorsal, that control swallowing, much like the same areas that control respiration. The firing patterns of these areas are not altered by removal of feedback from the periphery or from the cortex. SLN afferent fibers synapse on neurons of the interstitial subdivision of the NTS in the dorsal brainstem, the site of initiation of the swallowing rhythm and the dorsal aspect of the central pattern generator for swallowing (Mrini and Jean, 1995). The ventral aspect of the generator, which includes the rostral NA and its local reticular formation, is thought to be more important for modifying than for initiating the swallow, because it requires inputs from the ipsilateral solitary neurons prior to execution of a swallow. This arrangement of the swallowing central pattern generator is different from the arrangement of the respiratory central pattern generator described above, in which the solitary nucleus neurons are modifiers, and the nucleus ambiguus neurons control the rhythm.

Neuropharmacology of central pattern generators

Since central pattern generators are typically oscillatory neural networks, much can be learned from understanding the neuropharmacology of the neurons involved in the network. Unfortunately, the studies performed have not been selective enough to determine the functional aspects of the respiratory and swallowing generators themselves. Respiratory rhythm generation from the pre-Botzinger complex of the nucleus ambiguus in the ventrolateral medulla has been studied by *in vitro* slice and *en bloc* preparations (reviewed in Rekling *et al.*, 2000). This rhythm appears to be dependent on endogenously released excitatory amino acids acting at non-NMDA (N-methyl-D-aspartate) receptors (Funk *et al.*, 1993). Other studies of the respiratory rhythm have also shown that serotonin and noradrenaline are involved. Serotonin tends to increase rhythm frequency, whereas noradrenaline decreases the frequency (Al-Zubaidy *et al.*, 1996). These results are consistent with those from *in vivo* studies of fluctuations in serotonin and noradrenaline during waking and sleeping states which seem to correlate with the fluctuations in respiratory rhythm and modulate inspiratory drive to genioglossus (hypoglossal protruder) motoneurons (*cf.* Section IV[B1]).

Tell and Jean (1993) examined the membrane physiology of caudal solitary nucleus neurons using an *in vitro* rat brainstem slice preparation. Addition of NMDA to a non-firing neuron with a resting membrane potential of -55 mV causes the neuron to fire repetitively. When negative current is introduced during this NMDA-induced discharge and the membrane potential is hyperpolarized, the cell changes its firing pattern from a constant firing frequency to oscillatory or bursting behavior. Katakura *et al.* (1995) also demonstrated NMDA-dependent rhythmic activity different from respiration in the XIIn of a neonatal rat brainstem-spinal cord preparation which they propose to be involved in a feeding behavior such as suckling.

(3) Communication between neurons controlling respiration and swallowing

The rapid switching among complex orofacial behaviors suggests that the neurons controlling these behaviors must communicate at the brainstem level. This switching persists even when the descending and ascending inputs are removed (Dick *et al.*, 1993; Zheng *et al.*, 1997; Umezaki *et al.*, 1998b). Although synaptic potentials have been demonstrated between neurons controlling orofacial behaviors, the circuitry has been difficult to identify (Grelot *et al.*, 1992; Travers and Jackson, 1992; Dinardo and Travers, 1994; Oku *et al.*, 1994; McFarland and Lund, 1995; Nakamura and Katakura, 1995; Kogo *et al.*, 1996; Zoungrana *et al.*, 1997). Part of the problem has been isolating the neurons that are exclusive to a single function, in spite of the evidence suggesting a functional segregation (Dobbins and Feldman, 1995; Umezaki *et al.*, 1998a,b,c). This motivated some investigators to examine other possible mechanisms for switching among movements.

Shiba *et al.* (1999) investigated functional characteristics of 82 cat laryngeal motoneurons in the caudal NA by recording intracellular activity during fictive vocalization and upper airway defensive reflexes during swallowing, coughing, and sneezing. They identified 55 expiratory and 27 inspiratory motoneurons that also responded to one or more of the fictive movements with excitation or inhibition. Shiba *et al.* (1999) contend that different functions requiring laryngeal muscle activation are rapidly facilitated by a reorganization of shared neural networks in the ventral brainstem rather than by the utilization of separate pathways. Because laryngeal motor control is critical to protection of the airway, the reorganization hypothesis proposed by Shiba *et al.* (1999) is quite plausible but probably works in parallel with functional segregation, particularly for non-laryngeal circuitry. These results are supported by the work of Oku *et al.* (1994), who describe 5 activation patterns for respiratory neurons in the ventral respiratory group and the Botzinger complex, some of which share their networks with those involved in functions such as coughing and swallowing.

(B) Hypoglossal activity modulation by brainstem neurons

There is considerable evidence indicating that the activity of hypoglossal motoneurons controlling tongue protrusion is modulated by a generator-produced respiratory rhythm initiated by phrenic nerve, SLN, or pre-Botzinger complex stimulation (Sica *et al.*, 1984; Mitra *et al.*, 1986; Withington-Wray *et al.*, 1988; Watchko *et al.*, 1989; Smith *et al.*, 1990, 1991; Jiang *et al.*, 1991; Funk *et al.*, 1993; Martin *et al.*, 1994; Ono *et al.*, 1994; Hayashi and McCrimmon, 1996; Dreshaj *et al.*, 1998; Eastwood *et al.*, 1998; Fenik *et al.*, 1998; Ramirez *et al.*, 1998; Umezaki *et al.*, 1998a,b,c). Although studies of hypoglossal motoneuron activity suggest entrainment to the rhythms of other orofacial central pattern generators (Travers and Jackson, 1992; Nakamura and Katakura, 1995; Dinardo and Travers, 1994), the details of the neural circuitries involved and the hypoglossal motoneuron types activated have not been identified, possibly because the exact nature of the central pattern generators for these movements has not been determined (*cf.* Section IV[B2]). Nor have details of the interaction between hypoglossal motoneurons and neurons controlling other non-rhythmic orofacial behaviors been determined.

There has, however, been a significant contribution to our

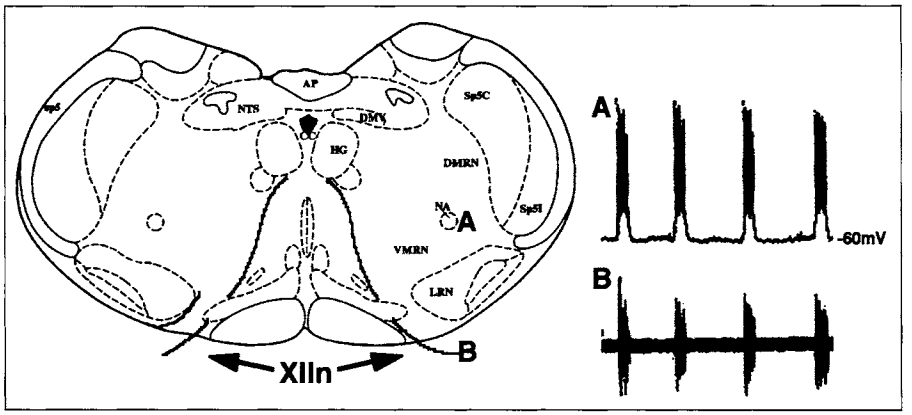

Figure 7. Rhythmic discharge suggestive of inspiratory drive has been recorded at "A" of a 500-μm slice of caudal rat brainstem. This rhythmic activity is also reflected in spontaneous hypoglossal discharge recorded from the nerve rootlets at "B". Additionally, single protruder motoneurons in the ventral hypoglossal nucleus (not shown) are modulated by neurons in the pre-Botzinger complex that produce this respiratory rhythm. (Adapted from Smith *et al.*, 1991)

understanding of the hypoglossal response to afferents from the work of Takata (1993), who measured post-synaptic potentials (psp's) in cat protruder and retruder motoneurons activated by lingual nerve stimulation. Using *in vivo* intracellular recording techniques, he found different activation patterns from each motoneuron type. Protruders responded with either an inhibitory post-synaptic potential (ipsp) alone (40% of 250 protruder motoneurons), an ipsp-ipsp sequence (30%) having a short strychnine (glycine antagonist)-sensitive ipsp and a long picrotoxin-sensitive ipsp, or an excitatory psp (epsp)-ipsp sequence (30%). Retruders responded with either an epsp alone (7% of 200 motoneurons), an epsp-ipsp sequence (68%), or an ipsp-ipsp sequence with the same sensitivities to strychnine and picrotoxin as protruders (25%). The ipsp-ipsp sequence was produced by bilateral afferents for protruders, but the strychnine-sensitive ipsp was unilateral and the picrotoxin-sensitive ipsp was contralateral for retruders. Takata (1993) did not investigate the epsp pharmacologically. Although these results are not directly related to swallowing or respiratory afferents, they lend further support to the segregation of retruder and protruder motoneurons.

(1) Modulation of hypoglossal motoneuron activity by respiratory neurons

The relationship between extrinsic tongue muscles and airway patency has been recognized for many years (reviewed in Lowe, 1981), as has the modulation of hypoglossal activity by inspiratory drive (reviewed in Bartlett and St. John, 1988; Withington-Wray *et al.*, 1988), but the interdependent nature of this relationship was not revealed until recently. Identification of the neural circuitry and transmitters required for coupling between hypoglossal motoneuron activity and rhythmic oscillations of the respiratory central pattern generator has required the use of *in vitro* preparations (Smith *et al.*, 1990, 1991; Funk *et al.*, 1994) and has been instrumental in isolating the neurons responsible for respiratory rhythm. By progressively reducing the brainstem-spinal cord *en bloc* preparation to the dimensions of a thick slice (*i.e.*, 500 μm) containing the necessary neural circuitry for generating respiratory rhythm, Smith *et al.* (1990, 1991) were able to isolate inspiratory rhythmic activity to the pre-Botzinger complex of the caudal NA (Fig. 7). This area also included the hypoglossal nucleus and nerve fragments that were used to monitor spontaneous rhythm generation. These studies clearly demonstrated the modulation of hypoglossal motoneuron discharge by inspiratory drive and have catalyzed a surge of research activity that has unequivocally changed our understanding of the relationship of the neural control of tongue movement to respiration and, perhaps, to other orofacial behaviors.

In vitro techniques have been most valuable in examining the pharmacologic nature of the circuitry (reviewed in Rekling *et al.*, 2000). Several neurotransmitters have been proposed to be involved in modulation of hypoglossal motoneurons by inspiratory drive (*i.e.*, genioglossus motoneurons). The primary neurotransmitter activating genioglossus motoneurons from projection neurons of the pre-Botzinger complex is glutamate, which acts at AMPA/kainate receptors (Funk *et al.*, 1993). The activation appears to be mediated by adenosine triphosphate (ATP), which is also excitatory and is proposed to act at P2 hypoglossal motoneuron receptors (reviewed in Funk *et al.*, 1997). The functional significance of the purinergic mediation is not known.

Serotonin has also been widely implicated in the respiratory modulation of hypoglossal motoneurons at the respiratory rhythm generator in the caudal NA and at genioglossus motoneurons innervated by caudal medullary raphe neurons (Aldes *et al.*, 1989; Morin *et al.*, 1992; Li *et al.*, 1993; Manaker and Tischler, 1993). Serotonin modulation of genioglossus activity has been the focus of studies investigating changes in inspiratory drive during sleep, and the disruption of this modulation has been postulated to contribute to sleep apnea and Sudden Infant Death Syndrome (Kubin *et al.*, 1996; Radulovacki *et al.*, 1998). In the *in vitro* neonatal rat slice preparation, serotonin increases respiratory rhythm discharge and XIIn discharge (Morin *et al.*, 1992). However, the effect of serotonin on hypoglossal motoneurons has been the source of some controversy, because it acts on a variety of receptors producing either excitation or inhibition (Monteau *et al.*, 1990; Berger *et al.*, 1992; Morin *et al.*, 1992). There is some suggestion that this differential activation is related to a combination of receptor subtype and developmental stage. In general, activation of serotonin 5-HT_2 post-synaptic receptors produces an inward, depolarizing current in hypoglossal motoneurons (Berger *et al.*, 1992; Al-Zubaidy *et al.*, 1996; Okabe and Kubin, 1996), whereas the inhibitory effect of serotonin has been isolated to pre-synaptic 5-HT_{1B} receptors in adults (Okabe and Kubin, 1996; Singer and Berger, 1996) and post-synaptic 5-HT_{1A} receptors in neonates. The neonatal 5-HT receptors appear to mediate the inhibition of N- and P/Q-type currents producing a decrease in the amplitude of the apamin-sensitive mid-portion of the after-hyperpolarization that follows the action potential, an effect not found in adults (Bayliss *et al.*, 1997). Okabe *et al.* (1997) detected mRNA for 5-HT receptors in the hypoglossal nucleus, which included the 5-HT receptors, 1B, 2A, 2B, and, in lesser amounts, 3 and 7. The functional significance of these results has not yet been determined.

Other hypoglossal neuromediators implicated in sleep-related respiratory disorders such as sleep apnea are the peptide, thyrotropin-releasing hormone (TRH) from the caudal medullary raphe neurons (Manaker and Tischler, 1993), and the transmitter, norepinephrine (NE) from the locus subcoeruleus (Aldes, 1990). TRH increases the excitability of hypoglossal motoneurons by decreas-

ing the resting K^+ conductance through a G-protein-mediated mechanism and increasing an inward current (Rekling, 1992; Bayliss *et al.*, 1992, 1994, 1997). Bayliss *et al.* (1992) suggest that because both genioglossus motoneurons and raphe neurons are less active during sleep, they increase the possibility of airway collapse and obstruction. Norepinephrine is excitatory to hypoglossal motoneurons (Parkis *et al.*, 1995) but decreases respiratory rhythm (Al-Zubaidy *et al.*, 1996) and is tonically released during waking states. The decrease in this tonic release during sleep has suggested to some investigators that the removal of excitatory drive to genioglossus motoneurons could decrease protrusive tongue activity and lead to airway block. Funk *et al.* (1994) studied the development of TRH and NE potentiation of mice hypoglossal motoneuron discharge. They found that NE potentiation is maximum approximately 2 weeks earlier than TRH potentiation, which is maximum by post-natal day 21 in rats (Bayliss *et al.*, 1994). The advantage to differential development of these neuromodulators has not yet been determined but has potential for elucidating the underlying mechanisms of such disorders as Sudden Infant Death Syndrome.

(2) Interaction of hypoglossal motoneurons with swallowing neurons

Clinical and behavioral investigators have traditionally considered tongue movement to begin the swallow and to constitute the only voluntary phase of the swallow (reviewed in Logemann, 1983). Classically, the swallow is believed to proceed sequentially with the pharyngeal phase initiated at the completion of the oral phase. This concept implies that the neural regulation of the transition from the voluntary to involuntary (pharyngeal) phases of swallowing at the level of the brainstem begins with signals from hypoglossal motoneurons. Recent imaging and electromyographic studies (Gay *et al.*, 1994; Mosier, 1997) demonstrate that the temporal, kinematic, and electromyographic parameters of oral, pharyngeal, and laryngeal events during swallowing are not sequential but consist of concurrent overlapping events, and that all parts of the swallow are modifiable. Analysis of these data suggests that although hypoglossal motoneurons may receive signals (ascending or descending) that cause them to initiate bolus formation and transport, they may also become entrained to a swallowing rhythm that was initiated by ascending or, perhaps more notably, by descending signals received by the swallowing generator itself.

Although all tongue muscles help form and transport the bolus, the tongue muscle group most likely to be activated first by swallowing rhythm initiators in the solitary nucleus are retruder muscles. The somatotopy of NXII places the hypoglossal retruder motoneurons closest to NTS neurons in the dorsolateral brainstem which may facilitate this activation. Conversely, the protruder muscle group must be activated to allow the bolus to pass into the pharynx immediately following movements, such as laryngeal closure and epiglottic tilt, that protect the airway. The protruder motoneurons are located in the ventral brainstem closer to the ventral NA swallowing motoneurons and the respiratory central pattern generator. The work of Dobbins and Feldman (1995), who studied hypoglossal afferents with the pseudorabies virus, suggests a differential innervation of retruder and protruder motoneurons. They found that rat retruder motoneurons receive their primary innervation from pre-motoneurons in the dorsolateral medulla, and that protruder motoneurons are primarily innervated by the medullary pre-motoneurons ventrolateral to NXII. Some motoneurons are commonly innervated by pre-motoneurons in the medial reticular formation. These results motivated Dobbins and Feldman (1995) to propose that the brainstem is functionally segregated with regard to modulation of hypoglossal activity.

Tomomune and Takata (1988) performed intracellular recordings from hypoglossal protruder (genioglossus) and retruder (styloglossus) motoneurons of the anesthetized cat during swallowing produced by repetitive stimulation of the SLN and by water placed on the dorsum of the tongue. They describe excitation of styloglossus motoneurons and an excitation-suppression sequence of genioglossus motoneurons during the oropharyngeal swallow which is coupled to rhythmic stimulation of the SLN. These intracellular recordings were correlated with EMG activity of the styloglossus and genioglossus muscles. The suppression phase of genioglossus motoneuron activity correlated with styloglossus muscle activation. Tomomune and Takata did not investigate the origin of these signals but hypothesized that they were from the swallowing central pattern generator. Sumi's investigation (1969) of rhythmic activity of hypoglossal neurons in response to cortically induced swallowing and chewing in rabbits also indicated a differential response pattern from the retruder and protruder motoneurons for swallowing that was not produced for chewing.

This anatomy and physiology suggest that both retruder and protruder hypoglossal motoneurons are modulated by the swallowing rhythm, and that the pattern of control includes modulation of retruder motoneurons by NTS neurons and modulation of protruder motoneurons by the NA neurons, which is also the site of respiratory rhythm generation. The difficult task has been to isolate the brainstem circuits for swallowing so that they are accessible for investigation. The results of Dobbins and Feldman (1995) suggest that the pathways between neurons of the solitary tract and retruder motoneurons are either disynaptic or monosynaptic. Altschuler *et al.* (1994) showed that some retruder motoneurons have dendrites that extend into the solitary nucleus and adjacent reticular formation, suggesting that monosynaptic input from NTS neurons could occur in the hypoglossal nucleus or adjacent reticular formation by NTS projection neurons or in the solitary nucleus by local-circuit NTS neurons (Kawai and Senba, 1996; *cf.* Sections III[A], IV[A1]). Although Altschuler *et al.* (1994) also found protruder dendrites in the NTS area, they were significantly fewer.

Sawczuk *et al.* (2000; Fig. 8) have initiated studies examining the activation of motoneurons in the dorsolateral hypoglossal nucleus (*i.e.*, putative retruder motoneurons) by stimulation of NTS neurons in the rat brainstem slice preparation. XIImns responded to NTS stimulation with short-latency epsps and, in some motoneurons, ipsps that follow high-frequency stimulation, suggesting that the projection pathway is monosynaptic. Stimulation of other ventral areas of the brainstem slice previously shown to be respiratory projection sites produced combinations of polysynaptic psps. The excitatory component of the NTS projection appears to be mediated by glutamate, because it is blocked by the non-NMDA antagonist, DNQX, whereas the inhibitory component appears to be glycine-mediated, because it is blocked by strychnine. These results provide further support for the functional segregation hypothesis proposed by Dobbins and Feldman (1995).

(3) Switching functions and modulation of hypoglossal activity

The tongue moves with remarkable speed and precision between complex movements such as respiration and swallowing. The mechanisms are not known but have been the source of considerable research energy and frustration. One likely scenario is that

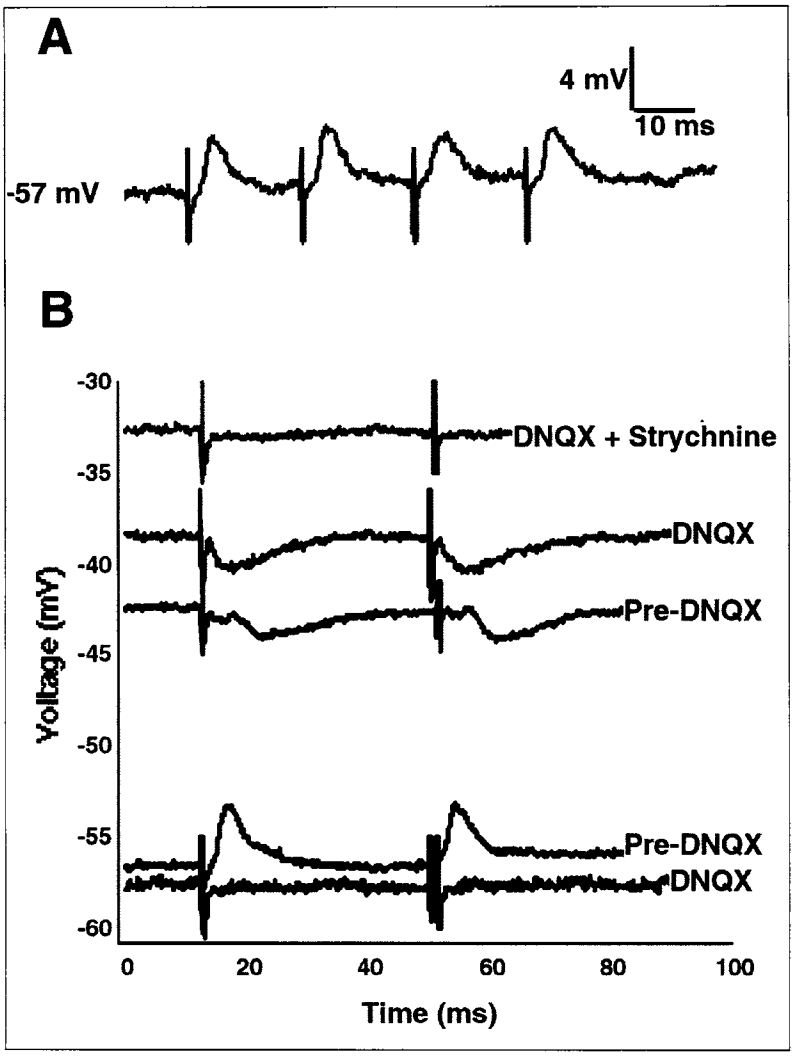

Figure 8. Stimulation of the solitary tract in the rat brainstem slice preparation produced short-latency epsps in this hypoglossal motoneuron that followed high-frequency stimulation of 50 to 100 Hz (Panel A). When the membrane potential was depolarized, a short-latency ipsp was unmasked (middle trace, Panel B). Bath application of DNQX eliminated the epsps (lower trace, Panel B), suggesting that the excitatory neurotransmitter, glutamate, is acting at non-NMDA receptors. Bath application of strychnine eliminated the ipsps (upper trace, Panel B), suggesting that the inhibitory neurotransmitter is glycine. (Adapted from Sawczuk *et al.*, 2000)

the central pattern generators of one movement suppress those of the other (McFarland and Lund, 1995; Ono *et al.*, 1998a,b). This proposal would operate equally well whether the neurons are functionally segregated, activated by shared pathways (Dobbins and Feldman, 1995), or activated by networks that re-organize (Shiba *et al.*, 1999). Ono *et al.* (1998a) have described several inspiratory reticular pre-motoneurons in the cat that project only to hypoglossal motoneurons or project to both pharyngeal and hypoglossal motoneurons. Their activation patterns suggest that the majority (76%) of single-projection neurons "switched" between inspiration and fictive ingestion, whereas none of the dual-projection neurons displayed this property. The mechanism for this switching behavior was not addressed. These neurons tended to be positioned either ventrolaterally to the NTS or dorsomedially to the NA, although more of those near the NTS projected to both the hypoglossal and phrenic motoneurons (Ono *et al.*, 1994). They suggest that the dual innervation provides a means of synchronizing synergistic muscles during respiration. Their results support the investigations of Amri *et al.* (1990), who describe swallowing interneurons in the ventral medulla that project to motoneurons in both NXII and the trigeminal motor nucleus. In an unrelated study, Ono *et al.* (1998b) studied pre-motoneurons adjacent to the ventrolateral hypoglossal nucleus that were swallow-related and inhibitory to putative genioglossus motoneurons, and that appeared to suppress genioglossus muscle activity during swallowing. Sawczuk *et al.* (2000) stimulated the same group of pre-motoneurons in the ventrolateral rat brainstem slice preparation that Ono *et al.* (1998b) studied in the cat. They recorded from putative retruder motoneurons in the dorsolateral NXII and studied primarily epsps, although some psps also had an inhibitory component. This dual innervation lends further support to the arguments of Ono *et al.* (1998a,b).

(C) Cortical control

While the contributions from neuroanatomical, pharmacological, and electrophysiological studies of brainstem networks have significantly furthered our understanding of the neural control of tongue movement, the control of tongue movement at a central level remains largely unknown. Primarily, the technical limitations of studying cortical networks in awake, behaving animals or humans have hampered progress in this branch of tongue research. Nevertheless, several recent advances in techniques for studying cortical processes have provided new insights into the central representation of tongue movement. For example, the role of the primary motor cortex (M1) in control of tongue movements has been investigated, most extensively by Sessle and colleagues (Murray *et al.*, 1991; Murray and Sessle, 1992a,b,c; Martin *et al.*, 1997). These studies used intracortical microstimulation (ICMS) and recording techniques to examine the tongue area of the primate M1 during tongue protrusion tasks as well as during swallowing behaviors. The primate tongue M1 occupies a relatively large field at the inferolateral portion of the precentral gyrus. Recordings of single neurons during a tongue protrusion task and during a swallowing task showed significant changes in the firing rate associated with each task. Most notable, however, was the observation that the firing rate was differentially modulated, depending on whether the monkey performed the tongue protrusion task or the swallowing task (Fig. 9).

One consideration is that the differential modulation of these cortical neurons in the tongue M1 may reflect spatially segregated neuronal populations within this cortical area. However, Martin and her colleagues (1997) found that the neurons that responded preferentially to tongue protrusion tasks or to swallowing tasks were distributed throughout the tongue M1, and moreover, there was no spatial segregation between these neuronal populations (Fig. 10).

Despite a lack of evidence for spatial segregation among the neurons of the tongue M1, it should be emphasized that specific neuronal populations within tongue M1 respond differentially to different tasks involving the tongue. Thus, the primate tongue M1, while lacking a discrete functional homunculus, nevertheless contains multiple "distinct efferent zones" that generate

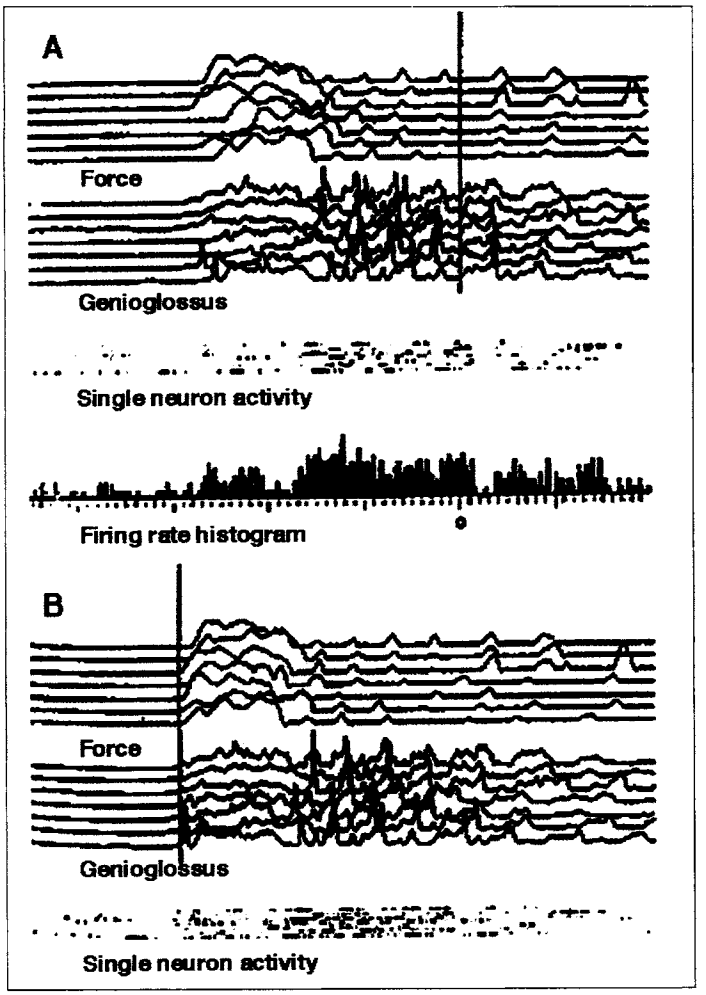

Figure 9. Recordings taken from a single neuron in primate tongue M1 during swallowing tasks (A) and tongue protrusion tasks (B). The top two traces in each panel show the EMG recording of genioglossus muscle (GG) activity recorded during the task and force output by the GG. Neuronal firing rates increase significantly preceding swallow onset (Panel A; swallow onset = vertical bar) and moderately during the tongue protrusion tasks (Panel B). (Modified from Martin *et al.*, 1997)

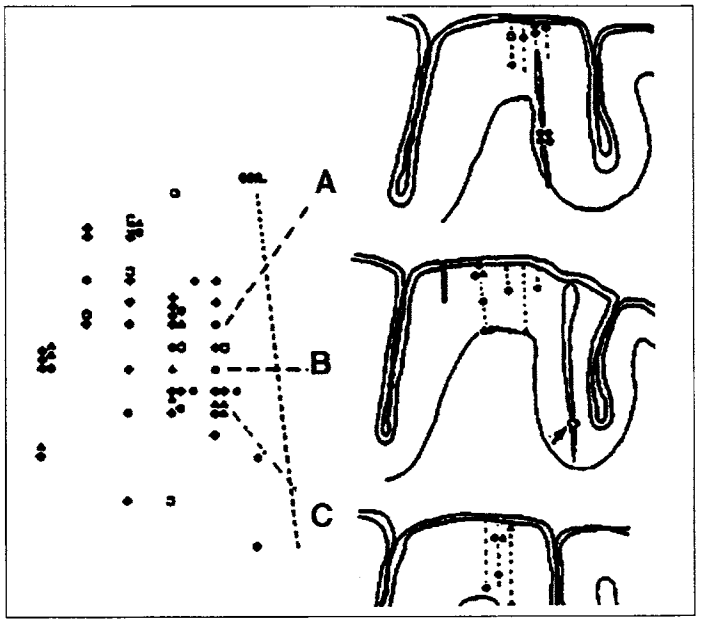

Figure 10. Spatial distribution of neurons in primate tongue M1 that demonstrate significant alterations in firing rate to swallowing or tongue protrusion tasks (either singularly to the task or to both tasks). Cen. = central sulcus. Black triangles = "Swallow-related"; black circles = "Task-related"; black diamonds = "Swallow-related and task-related"; unfilled squares = "Swallow-unrelated and task-unrelated". Camera lucida drawings of parasagittal histologic sections on the right of the Fig. show microelectrode penetrations in the pre- and post-central gyrus. The three drawings correspond to the locations shown in A, B, and C. This Fig. illustrates the heterogeneous distribution of task-related and non-task-related neurons in the primate tongue M1. (Adapted from Martin *et al.*, 1997)

basic tongue movements (Martin *et al.*, 1997). Differential modulation of these efferent zones would facilitate the complex multidimensional movements required for such tasks as swallowing, speech, and mastication.

The question remains, however, as to what cortical substrates are involved in controlling the modulation of these efferent zones within M1. Another question that arises is the degree of similarity between the organization of the tongue M1 in the primate and in the human. Urasaki *et al.* (1994) examined the evoked sensory and motor responses of the tongue to stimulation of the primary motor, sensory, and temporal cortices by chronic subdural electrodes in patients undergoing mapping prior to surgical resection of epileptogenic foci. The evoked motor and sensory responses were localized to a wide area covering the pre-central and post-central gyri in both patient groups, those with and those without brain parenchymal lesions (neoplasms, cysts, and cortical dysplasia). Although this approach provides a gross map of tongue function in behaving humans, these findings must be interpreted with caution, since the underlying cortical changes associated with chronic epiletiform activity (even in the absence of an identifiable parenchymal lesion) may alter the normal representation of sensorimotor function.

Recent advances in imaging technology, however, permit the visualization of cortical activity in awake, behaving humans, circumventing the problems associated with focal grid electrode measurements, and moreover, permit greater spatial resolution than conventional electroencephalography (EEG). To that end, Mosier (1998) utilized fast MRI techniques (Functional Magnetic Resonance Imaging, or fMRI) to image activity in the brain of awake, normal human subjects while they performed tongue movement tasks as well as swallowing tasks. These studies showed that, similar to the primate M1, tongue movement in humans resulted in large areas of activation at the inferolateral portion of the precentral gyrus. In addition, tongue movement tasks resulted in activation of the primary somatosensory cortex, supplementary motor area (SMA), temporal cortex, Broca's area, the posterior parietal cortex (Brodmann's areas 5 and 7), insular cortex, the pulvinar, the corpus callosum, cerebellum, and the hypoglossal nucleus (Fig. 11; Komisaruk *et al.*, 1998; Mosier, 1998; Mosier *et al.*, 1999). Clearly, then, control of tongue movements requires not only the cortical circuits of the primary motor cortex, but also the integration of sensory input and motor processing areas of the cortex, as well as subcortical sites and the expected hypoglossal nucleus.

Recently, Corfield *et al.* (1999) performed similar Functional Magnetic Resonance Imaging (fMRI) experiments utilizing isometric tongue contraction tasks in awake, behaving humans and reported similar results: activation in the primary motor and somatosensory cortices, the supplementary motor area, insula,

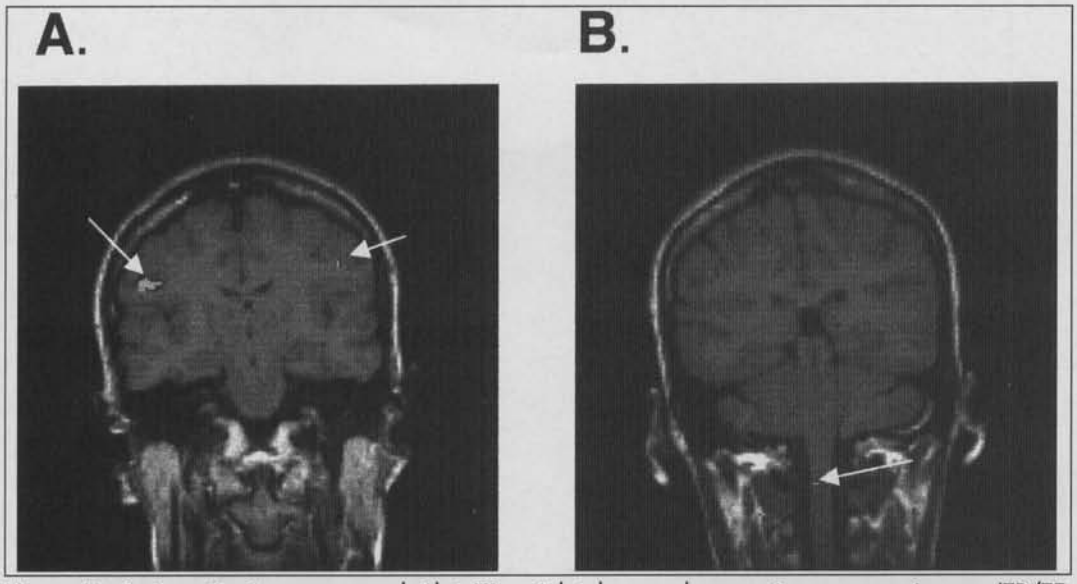

Figure 11. Brain activation maps overlaid to T1-weighted coronal magnetic resonance images (TR/TE; Nex = 450/14; 0.75) in a normal human volunteer. The maps show activation during a tongue-tapping task bilaterally in the primary motor cortex (A; arrow) and in the caudal hypoglossal nucleus (B; arrow). (Adapted from Mosier, 1998).

operculum, cerebellum, and the hypoglossal nucleus.

While the results of these functional imaging studies have provided valuable information on the cortical areas involved with the control of tongue movement, the question as to how these networks are integrated to effect different tongue movements remains unanswered. However, preliminary evidence by Mosier *et al.* (1999) has shown that the temporal parameters of activation across these cortical areas are strongly correlated with the temporal parameters of movement in the middle, back, and base of the tongue, but not significantly correlated with movement of the tongue tip during swallowing tasks. Clinical evidence lends support to these observations, in that patients with surgical removal of the distal two-thirds of the tongue (including the middle, back, and base of tongue) suffer more significant and more prolonged dysphagia, in general, than patients with removal of the tip of the tongue (Hirano *et al.*, 1992; McConnel *et al.*, 1994; Stachler *et al.*, 1994). Thus, central control mechanisms for tongue movement in swallowing may involve different segments of the tongue during the oral or pharyngeal phases that could be expressed through activation of hypoglossal motoneuron networks (*cf.* Section IV|B2|).

Taken together, these studies utilizing fMRI techniques on awake, behaving humans not only shed new light on the cortical control of tongue movements, but also, more importantly, suggest a distributed central organization for the control of tongue movements. It follows that the central role the tongue plays in several of the most complex motor behaviors (swallowing, speech, respiration) would necessitate hierarchical yet plastic control processes at the cortical, subcortical, and brainstem levels.

(V) *Clinical Significance*

Functional deficits of tongue movement have a profound impact on swallowing, speech, and respiration. Functional deficits of tongue movement occur primarily due to pathology involving the central or peripheral nervous system, or to structural alterations of the tongue itself.

(A) Nervous System Conditions or Diseases Affecting Tongue Movement

In the central nervous system, cerebral vascular compromise due to ischemia or infarct is a leading cause of peripheral neuromuscular dysfunction. Cerebral ischemia or infarction involving the cortical bulbar tracts that extend from cortical sites to the pontine nuclei produces prominent orofacial diplegias, including glossodiplegias. Infarction involving sites other than the motor cortex, such as the frontal and temporal operculum, likewise produce orofacial and glossodiplegias. Last, compromise of the vertebral arteries or distal portions of the basilar arteries can affect the hypoglossal nucleus, with the attendant consequence of glossoplegia or glossoparesis (reviewed in Mosier, 1998; Besson *et al.*, 1991; Kim *et al.*, 1994; Gropman *et al.*, 1997).

Secondary to ischemic disease, traumatic brain injuries are the next leading cause of neuronal dysfunction resulting in tongue movement disorders. The specific clinical presentation of tongue movement dysfunction will depend on the site(s) involved: cerebral hemisphere, brainstem, or isolated cranial nerve injuries. Generally, in the acute phases of injury, decreases in the lingual range of motion, strength of the tongue base, and diminished lingual coordination are observed (Morgan and Mackay, 1999).

Other central diseases or conditions that affect tongue movement include Parkinson's Disease, multiple sclerosis, motor neuron disease (amyotrophic lateral sclerosis, or ALS), and progressive supranuclear palsy (PSP). Murdoch *et al.* (1998) studied articulatory performance of adults with multiple sclerosis and found diminished peripheral muscle strength, endurance, and rate of repetitive movement affecting the lingual musculature, yet the lip musculature was unaffected. Lingual tremor, on the other hand, is a unique feature of Parkinson's Disease and is significantly more prevalent in patients with dysphagia (Ali *et al.*, 1996). The clinical presentation of both PSP and ALS will depend on the degree of neuronal degeneration and sites involved, PSP involving centrally mediated tongue pathways, and ALS producing symptoms of upper motor neuron or lower motor neuron disease, or both (Buchholz, 1997). The common element that emerges from these studies is that regardless of central etiology, dysfunction of tongue movement may substantially increase the morbidity and mortality associated with these conditions and diseases. Nevertheless, to what extent dysfunction of tongue movement affects disease co-morbidity and, in particular, the effect of more subtle alterations of tongue movement on co-morbidity is, at present, only minimally understood. Therefore, understanding mechanisms of the central control of tongue movement is a necessary step toward improving the quality of life and survival of these patient populations.

(B) Effects of Structural Alterations on Tongue Movement

Acquired structural alterations of the tongue generally occur either from involvement by neoplastic processes, or secondary to surgical extirpation or medical treatment of these neoplasms. Since alter-

ation due to neoplastic processes is generally a temporary issue, the focus of the remainder of this discussion will address changes in the control of tongue movement following surgical intervention.

Often, surgical intervention to excise a malignant neoplasm of the tongue involves removing not only the tumor tissue but also the surrounding muscles and the supporting neurovascular bundles (Ariyan and Chicarilli, 1990; Kraus, 1996). Once the tumor has been removed, the remaining segments of the tongue (in cases where a partial glossectomy has been performed) must be reconstructed. Reconstruction of the body of the tongue generally takes one of three forms: (1) primary closure of the remaining segments, (2) placement of a non-neurovascularized myocutaneous flap (usually harvested from the pectoralis major muscle), or (3) a neurovascularized fasciocutaneous flap (typically harvested from the radial aspect of the forearm) (Ariyan and Chicarilli, 1990; Panje and Morris, 1990; Sullivan, 1990). Several studies have shown that patients treated with primary closure of a partial glossectomy defect are able to return to normal or near-normal swallowing and speech functions (Mosier, 1997; McConnel *et al.*, 1998). Mosier (1997) demonstrated that the ability of these patients with primary closure to regain tongue function was due to adaptation of the motor system controlling tongue movement. Adaptation was achieved through novel strategies utilizing the remaining tongue segments (Mosier, 1997). Clearly, motor adaptation and learning of a complex structure such as the tongue in the setting of significant structural alteration implicate a plastic central control mechanism (Mosier, 1997).

Reconstruction of tongue body defects by myocutaneous flaps remains a somewhat controversial topic regarding the use of neurovascularized flaps. The introduction of neurovascularized flaps to reconstruct the tongue body was intended to improve the post-operative functional deficits in tongue movement by providing vital tissue with sensory innervation (Schusterman *et al.*, 1991; Urken *et al.*, 1992). Providing sensory re-innervation to the tongue is believed to improve post-operative swallowing, speech, and masticatory function (Schusterman *et al.*, 1991; Urken *et al.*, 1992; Curtis *et al.*, 1997). Nevertheless, clinical studies examining the efficacy of neurovascularized flaps have yielded conflicting and equivocal results (Vaughan *et al.*, 1992; McConnel *et al.*, 1998). The failure of these studies to resolve the question of post-operative tongue function with various flap compositions points to a lack of understanding of the integration of central and peripheral processes controlling tongue movement. Understanding the central organizational relationships between the motor cortex and other cortical, subcortical, and brainstem sites involved with the control of tongue movements is an essential prelude to characterizing functional tongue deficits due to pathology, and to designing rehabilitative strategies that exploit these central control mechanisms.

(VI) *Conclusion*

The tongue is positioned at the anatomic center of multiple complex orofacial behaviors and must respond rapidly with precision and accuracy to barely perceptible stimuli from these behaviors. Research regarding the neural control of these relationships has been confounded by tongue structure and investigators' inability to isolate specific behaviors. It is clear from this review that considerable progress has been made toward an understanding of the neural control of tongue movement, but considerable work remains, particularly with regard to the tongue's ability to respond to rapid switching between orofacial movements such as respiration and swallowing. The surge of research activity in this area over the last decade has provided intellectual and technical tools to help focus our research in the future. From this review, we can identify themes for future consideration:

(1) The tongue is a muscular hydrostat, but the physiology of muscular hydrostats is a mystery, further compounding the already-confusing neurophysiology of the oral environment.
(2) Motor units of the tongue appear to be primarily fast and fatigue-resistant, but we do not know how this property facilitates its primary functions.
(3) Hypoglossal motoneurons are somatotopically arranged in the brainstem nucleus but appear to be functionally segregated as well. Their activity is rhythmically modulated by inspiratory neurons, but they actually appear to participate in the modulatory process. Will this also be true for modulation by other neural networks?
(4) Adaptive mechanisms of neural re-organization and modulation of receptor expression, typically identified with higher CNS function, are also operative in the control of complex brainstem behaviors like respiration and may be a means of switching among movements.
(5) Control of tongue movement and other orofacial behaviors by cortical and subcortical nuclei is an unknown realm filled with possibilities for adaptive changes.

Future studies at the neuromuscular, brainstem, and cortical levels will provide the foundation for a better understanding of the integrated control of these highly complex and essential functions.

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