

Tongue Anatomy and Physiology, the Scientific Basis for a Novel Targeted Neurostimulation System Designed for the Treatment of Obstructive Sleep Apnea

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Introduction: Obstructive sleep apnea (OSA) is a chronic condition that affects millions adults. The effective standard treatment is positive airway pressure (PAP). However, approximately half of the patients that are prescribed PAP are unable or unwilling to comply with this therapy. Untreated OSA ultimately leads to very serious comorbidities. An alternative therapy for this patient population, therefore, is desirable. Hypoglossal nerve (HGN) stimulation is under investigation by multiple groups as a possible alternative therapy for OSA.

Objective: To understand the underlying mechanisms of actions related to HGN stimulation, and the implication of this knowledge for specifying and designing a neurostimulation system for the treatment of OSA.

Results: Loss of lingual and pharyngeal tone within a narrow airway is the primary mechanism for OSA. Posterior and anterior tongues are different in their anatomy and physiology. Muscle fibers in the posterior tongue are predominantly fatigue resistant that are responsible for the long sustained tonic activities required for maintaining the tongue's position and preventing its mass from falling into the retroglossal airway. The human tongue is a muscular hydrostat and hence would benefit from a sophisticated HGN stimulation system that is capable of achieving a concerted spatio-temporal interplay of multiple lingual muscles, including retrusors.

Conclusion: Targeted neurostimulation of the proximal HGN presents as a viable system approach that is far more versatile and physiologic and quite different than prior systems.

Keywords: electrical stimulation, hypoglossal nerve, obstructive sleep apnea, THN sleep therapy, tongue

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INTRODUCTION

Obstructive sleep apnea (OSA) is a common disorder that affects over 6% adults (1) with very serious consequences (comorbidities) (2). It is characterized by repetitive episodes of obstructions of the upper airway, causing decline in blood oxygen, and subsequent arousal from sleep (3). Progressive loss of lingual and pharyngeal tone in the upper airway is the primary cause of OSA (4). Airway blockage is associated with a reduction of lingual muscle tone and is presumably attributed to inadequate neural signals normally provided by the hypoglossal nerve (HGN) (5,6). Positive airway pressure (PAP) therapy is generally regarded as the current standard for mild to severe OSA; however, a substantial proportion of patients are unable or unwilling to adhere to PAP therapy (7). These patients are left with only two alternative treatments, i.e., oral appliance therapy and upper airway surgery, which are not only less effective but also result in severe side effects (8). Consequently, there is a significant need for additional therapeutic alternatives for patients who are noncompliant with PAP therapy.

Neurostimulation has been applied to many neural system dysfunctions often with great success; however, attempts to utilize it for OSA have had mixed results (9–11). Perhaps one reason for the modest results to date was the use of technology developed for

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another application (cardiac pacing) rather than designing a system explicitly for the requirements unique to OSA. The human tongue and its neural supply are different from other organs and hence require a new approach to their treatment. Another reason is that all these attempts have focused upon one single muscle, the largest upper airway protruder muscle, the genioglossus (11). However, not all muscle fibers inside the genioglossus muscle necessarily open the airway. Some genioglossus fibers do in fact lead to tongue depression and subsequent airway occlusion (12). Therefore, neurostimulation systems that stimulate the entire distal branch of the hypoglossal nerve (mainly innervating the genioglossus muscle; GG) lack the ability to select between productive and counter productive fibers (12). As a result, the two antagonistic functional groups of GG fibers work against each other, fail to achieve the maximum response, and set a premature fatigue in the tongue. Lastly, the role of tongue's retruder muscles, in the maintenance of airway patency, has been largely ignored (11).

The primary purpose of this review is to discuss the neurobiology of the human tongue, the basic requirements for hypoglossal nerve stimulation, and the implication of this knowledge in specifying and designing a neurostimulation system for the treatment of OSA. The technology rationale of the aura6000™ System and the scientific arguments supporting targeted neurostimulation of the hypoglossal nerve as applied by the Targeted Hypoglossal Nerve (THN) Sleep Therapy are described.

A TALE OF TWO TONGUES

The human tongue assists in a variety of functions, from speech and mastication to maintenance of the pharyngeal stability. In particular, the anterior tongue plays a prominent role in speaking and mastication, while the posterior tongue performs a critical role in upper airway maintenance. Speaking and mastication require fine motor movement, while upper airway maintenance requires sustained muscle tone. It is not surprising then, that as discussed later, the anterior and posterior portions of the tongue are anatomically and physiologically different. The design of a successful neurostimulation system for OSA must take these differences into accounts.

THE POSTERIOR AND ANTERIOR TONGUES ARE DIFFERENT IN THEIR ANATOMY AND PHYSIOLOGY

The tongue is a unique motor organ that is comprised almost entirely of muscles with very little skeletal support (13). The human tongue consists of eight pairs of skeletal muscles—four extrinsic muscles (attached to bony attachment): the genioglossus, styloglossus, hyoglossus, and palatoglossus, and four intrinsic muscles (without any bony support): the transversalis, verticalis, inferior longitudinalis, and superior longitudinalis [(14); Fig. 1]. Extrinsic muscle fibers originate from external bony attachments and terminate in the tongue, whereas the intrinsic muscles originate and terminate within the tongue mass. Instantaneous whole tongue movements are attributed to former, lingual shape deformation to the latter (14). The extrinsic muscles, palatoglossus, styloglossus, hyoglossus, and genioglossus enter tongue proper from superior, postero-superior, postero-inferior, anterior-inferior directions, respectively (14). The physiologic properties of muscles are reflected in their composition of myosin heavy chain (MHC) isoforms and fiber types (15). Hence, the fiber composition of the tongue is that of a non-homogeneous

organ, varying from muscle to muscle and region to region. Fibers located in the posterior tongue display a highly uniform and parallel organization, whereas fibers in the anterior tongue are progressively non-uniform in orientation (15,16). Continuous arrays of interweaving muscle fibers with varying strengths and orientations coordinate a concerted effort that is required for speech, mastication, feeding, and respiration (17,18).

Muscle fibers are classified into one of two main types, MHC Type I and MHC Type II with different MHC composition (15,19). Type I muscle fibers, also referred to as slow twitch muscle fibers (contract slowly), are more efficient at using oxygen to generate adenosine-5'-triphosphate for continuous and extended muscle contractions without fatigue [Table 1; (19)]. Therefore, slow twitch fibers enable sustained or tonic activities. Type II muscle fibers are also referred to as fast twitch muscle fibers, fatigue quickly. Fast twitch fibers are subdivided into Type IIa, Type Iix, and Type IIb fibers [Table 1; (19)]. In general, fast twitch fibers are less efficient in creating energy-rich substrate, and are better suited to generate fast but short-lasting bursts of strength or speed, or phasic activities (19). On the contrary, slow twitch fibers are more adapted to generate slow long-lasting tonic activities such as required for maintaining tongue's position and preventing its mass from falling into the retroglossal airway.

An immuno-histochemical study by Stål P et al. suggests that upto 52% of the MHC fibers in the posterior human tongue (intrinsic muscle) are of Type I [(20); Fig. 2]. The anterior tip, on the contrary, contains only 17% of Type I fibers [with 75% of the Type II fibers in the intrinsic muscles [(20); Fig. 2]. MHC I rich posterior tongue is adapted for slow and long-lasting tonic actions such as those required for maintaining the oropharyngeal stability (to keep the airway open for long durations). In other words, the posterior tongue is inherently evolved to accommodate long sustained actions such as involved in maintaining the retroglossal airway patent, while the anterior tongue is accommodated to short bursts of activities like chewing, speaking, etc. Interestingly, the majority of fibers in the extrinsic muscles are of Type I and the majority in the intrinsic muscles are of Type II (20–23), suggesting the role of extrinsic muscles in initiating and maintaining the bulk movements while intrinsic muscles contributing to its fine-tuning.

FATIGUE RESISTANT PROPERTIES OF THE MAMMALIAN TONGUE: THE POSTERIOR TONGUE MUSCLES ARE MORE FATIGUE RESISTANT THAN THE ANTERIOR TONGUE MUSCLES

While the fatigue resistance properties of cardiac and diaphragmatic muscle have been recognized for some time, it is only recently emphasized in the posterior tongue (24–26). The ability of the muscles to resist fatigue is related to the type and the metabolic properties of muscle fibers. The oxidative capacity of muscle fibers, as measured by the activity of mitochondrial enzyme NADH-TR, is known to be associated with the fatigability of muscle (27). The human tongue muscles, like that of extra-ocular muscles (28), soft palate (29), and human oro-facial muscles (30,31), display higher oxidative capacity as compared to other skeletal muscles, implying that the tongue is one of the fatigue resistant organs [(32) in rats].

Muscle force and sustainability is proportional to the diameter of the fiber with large fibers adapted to strong and long-lasting forces (33). Hence, the thick fibers in the posterior tongue are responsible for coarsely graded activities like those involved in swallowing and

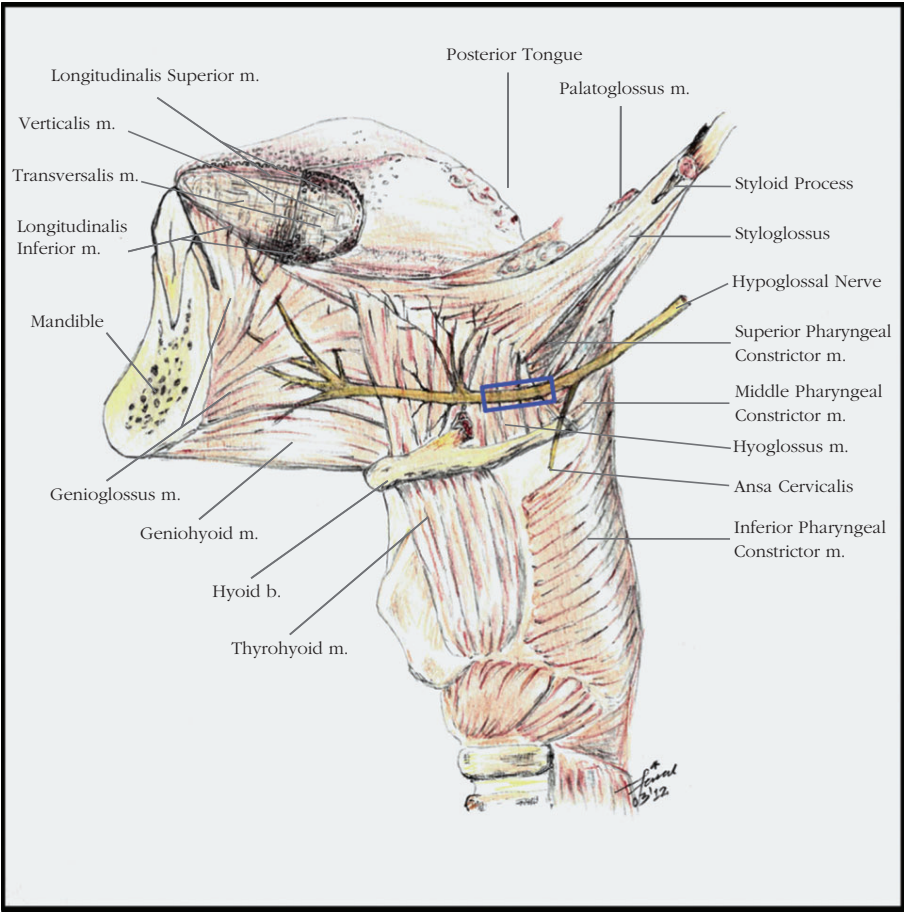


Figure 1. Sketch diagram showing the neuromusculature of the human tongue. HGN under the blue box shows the location of Imthera’s six-contact electrode cuff placement site.

Table 1. Muscle Fiber Types and Their Properties [data taken from (19)].				
Characteristic	Type I Fibers		Type II Fibers	
		Type IIa fibers	Type IIx fibers	Type IIb fibers
Contraction time	Slow	Moderately fast	Fast	Very fast
Fatigue resistance	High	Fairly high	Intermediate	Low
Activity	Aerobic	Long-term Anaerobic	Short-term Anaerobic	Short-term Anaerobic
Sustainability	Hours	<30 min	<5 min	<1 min
Power produced	Low	Medium	High	Very high
Mitochondrial density	High	High	Medium	Low
Capillary density	High	Intermediate	Low	Low
Oxidative capacity	High	High	Intermediate	Low
Glycolytic capacity	Low	High	High	High
Major storage fuel	Triglycerides	Creatine Phosphate, Glycogen	Creatine Phosphate, Glycogen	Creatine Phosphate, Glycogen

long-lasting activities like that required for keeping the airway patent (20). Correspondingly, the thin fibers of the anterior tongue are responsible for fine, swift movements like those desired for speech and mastication. Consistent with the role of slow twitch fibers, the posterior third of the human tongue also has an unusually high capillary density of fatigue resistant muscle fibers (34). More recently, muscular twitch tension studies in rats have suggested that styloglossus and genioglossus muscles (whole muscle as well as motor units) are fatigue resistant (26,35). Not surprisingly,

from the ontogenic point of view, tongue muscles share common evolutionary group of fatigue-resistant muscles, like masticatory and oro-facial muscles, originated from branchial arches, while fatigue-prone muscles like those of the extremities are evolved from somites (36,37), suggesting a fatigue-resistant nature of the tongue muscles.

The high oxidative capacity, larger fiber diameter, and prominence of Type I fiber etc. agrees with the observation that mammalian tongues are not easily fatigued [endurance task study in

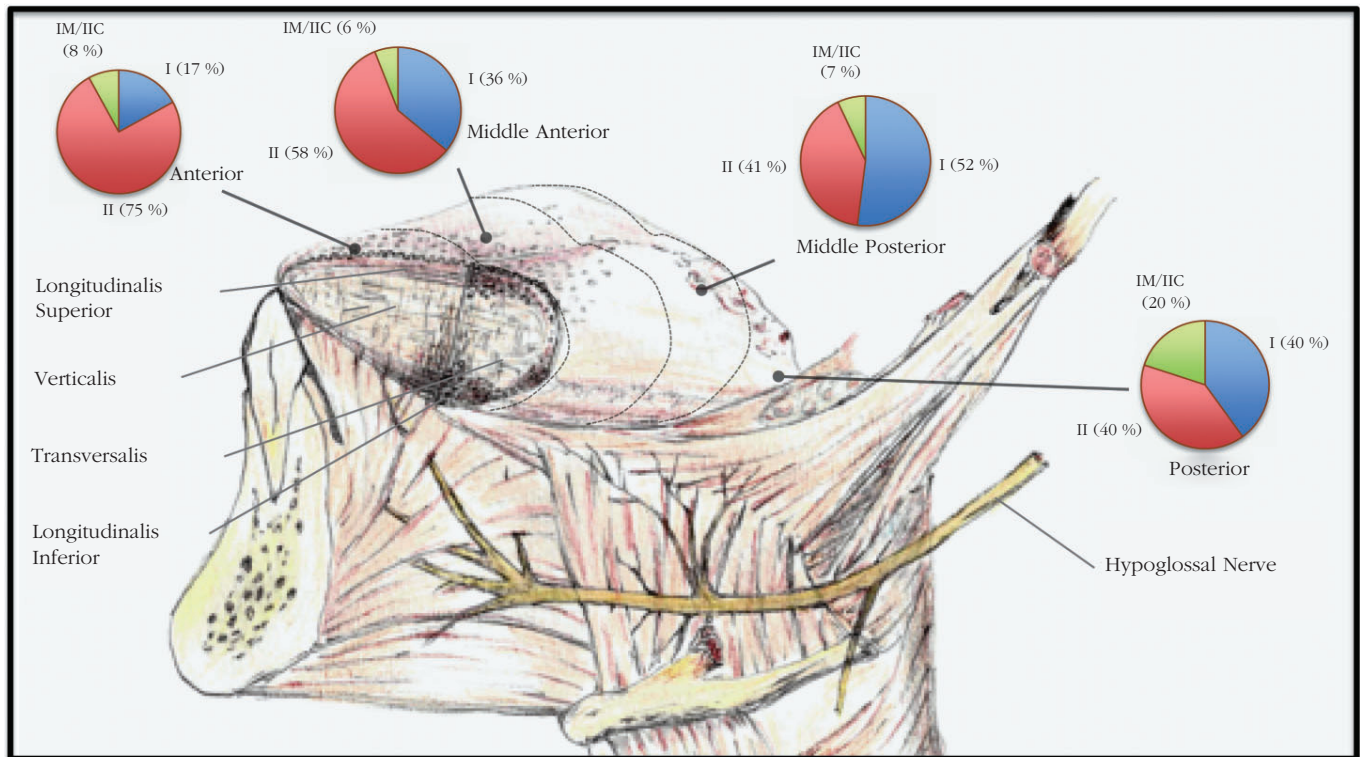


Figure 2. Pie chart showing the distribution of fiber types in various locations of the human tongue skeletal muscles. Only 17% of the total fibers in the anterior tip of the tongue are of fatigue resistant Type I in contrast to the mid-posterior and posterior sections of the tongue where it constitutes 52% and 40%, respectively. The reverse is true with the distribution of Type II fibers.

humans (38), in rats (39)]. The implications for neurostimulation are clear—stimulate the larger Type I rich muscle fibers of the rear tongue to reduce the chance of muscle fatigue.

THE HUMAN HYPOGLOSSAL NERVE IS HISTOLOGICALLY MONOFASCICULAR IN THE PROXIMAL SUBMANDIBULAR REGION: IMPLICATIONS ON THE DESIGN OF THE STIMULATION ELECTRODE

The human HGN, or XII cranial nerve, is the primary motor nerve that innervates seven of the eight muscles of the hemi-tongue. The palatoglossus, an extrinsic tongue muscle, is innervated by the vagus (X cranial) nerve. Nerve axons forming the HGN exit the hypoglossal nucleus as a row of small fascicles (inferior to the fourth ventricle in the medulla) ventrally between the inferior olive and the pyramid via the hypoglossal canal in the skull (40). Upon emerging from the hypoglossal foramen, the HGN gives off a small meningeal branch and picks up a branch from the anterior ramus of C1, spirals behind the vagus nerve, and passes between the internal carotid artery and internal jugular vein inferior to the posterior belly of the digastric muscle, to the submandibular region into the tongue [(40); Fig. 1].

Typically, peripheral nerve fibers are spatially organized into bundles surrounded by a membrane of connective tissue (perineurium) and are known as fascicles. Each fascicle often bundles a specific group of fibers innervating a particular target, thereby maintaining the structural (somatotopic) and functional (modality)

integrity of nerve supply (41). Fascicles can branch, split, rejoin, disappear, and reappear along the course of peripheral nerves, at the same time maintaining the spatial segregation of the fibers for the most part of the nerve trunk (42). At the level of the hyoid bone (the proximal third and mid portions), the human HGN is normally unfasciculated, becoming polyfascicular only in its distal third where it branches [(40,43); Fig. 3]. Moreover, unlike other mammals, distribution of the lateral and medial nerve branches in humans is not well defined. The lateral branch includes multiple small branches supplying independently the styloglossus, hyoglossus, and inferior longitudinalis muscles, whereas the medial branch innervates the genioglossus, superior longitudinalis, transversalis, and verticalis muscles [(44); Fig. 1]. While the HGN in the sub-mandibular region is unfasciculated, it is most likely organized such that groups of nerve fibers run to unique sets of muscles within the tongue and the nerve is not homogenous. Hence, the HGN neurostimulation system must account for the unique anatomy and physiology of the nerve and its differential innervations of lingual muscles.

Intra-fascicular stimulation using intraneural electrodes can provide highly specific control over the target structures. However, the implantation of the intraneural electrodes is not only highly invasive but require frequent replacements, severely limiting its use (45). In contrast, epineural electrodes, Flat Interface Nerve Electrodes (FINE), have a long life and much simpler implantation procedures. Fine electrodes are limited in that they not only require the nerve to be fascicular but also can lead to nerve compression resulting in nerve reshaping, axonal injury and demyelination (46). Single-contact cuff electrodes, though less damaging, lack the ability to selectively target nerve fibers. Hence, multi-contact, self-sizing cuff electrodes—when paired with a controlled spatio-temporal pattern

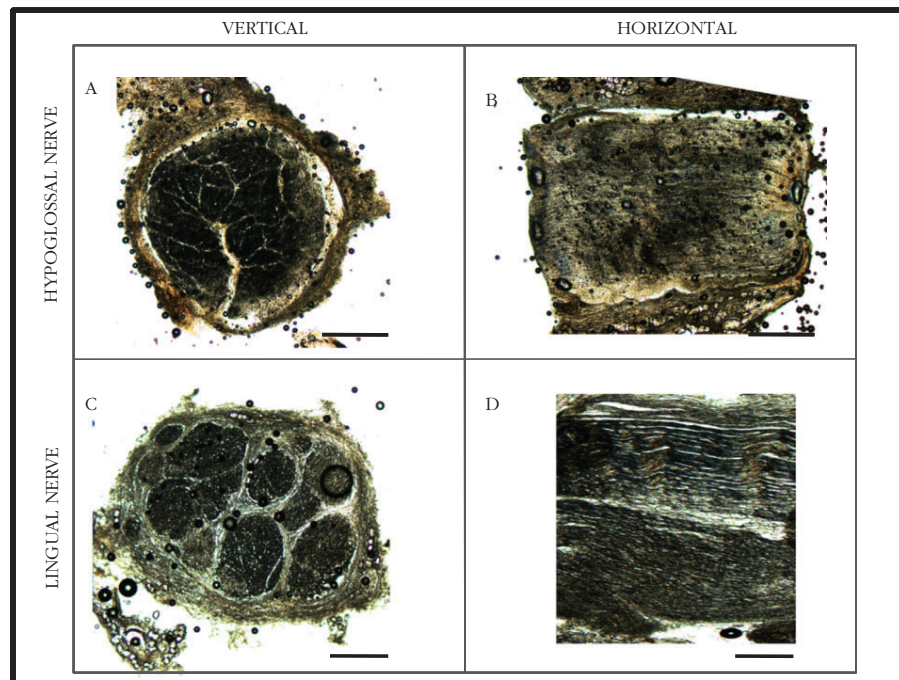


Figure 3. Photomicrograph of Human Hypoglossal nerve sectioned at the level of proximal third ("A": vertical; "B": horizontal) show the monofascicular nature of the nerve. Lower panel shows the histologic fascicles in the distal lingual nerve of the same subject. Scale bar = 1 mm.

of applied current, can achieve the selectivity without compressing the nerve or penetrating the fascicle epineurium or disturbing nerve fibers within, an ideal candidate for the HGN stimulation system. Such multi-contact cuff electrodes can be easily used for both fascicular and nonfascicular nerves without fear of permanent nerve compression and the associated damage.

MUSCULAR HYDROSTAT MODEL EFFECTS TONGUE MOTIONS

The human tongue is unique in the sense that some of its muscles are attached to only one static support (mandible or styloid process, e.g., the genioglossus or styloglossus), or to a floating support (hyoid bone, e.g., the hyoglossus), while other muscles are not attached to any bone and instead are attached to each other (e.g., intrinsic muscles and the free ends of the extrinsic muscles). The implication is that because the muscles cannot contract to a bony support, as in the arm or leg, the muscles of a hydrostat pull upon the hydrostat, work at many points to affect a net productive movement. Previous studies have used the muscular-hydrostat theory to explain the mechanism by which these various muscle groups effect lingual movements (13).

The hydrostat theory posits that the mammalian tongue is a cylindrical structure with a constant volume that adjusts its shape and size by co-activating many of its muscular components. Isovolumetric deformation of the tongue by synergistic multidirectional contraction of orthogonally aligned non-compressible muscle fibers determines the overall shape (47). Because the posterior tongue merges with the musculature of the pharynx (48,49), the geniohyoid (50–52), the hyoid bone (inferiorly—hyolingual complex) and the cranial base (superiorly), the contractile pattern of the posterior tongue is different from that of the anterior free end of the tongue.

In other words the tongue hydrostat is not homogeneous and the hydrostatic mechanism working in the rear of the tongue is perhaps different from its front.

Extrinsic and intrinsic muscles closely merge to optimize the speed and the flexibility of the tongue (47). No single tongue motion is a result of one muscle. Not very surprisingly, it is reported that the protrusion of the tongue results not simply by action of the genioglossus alone but also, by the combined activities of the intrinsic verticalis and transversus muscles and the extrinsic genioglossus muscle (53). Also reported is that the simultaneous but bidirectional contraction of intercrossing vertical and horizontal intrinsic fibers forms the core of the tongue and leads to tongue's protrusion in the anterior-posterior axis, which is opposed by the retraction produced by unidirectional contraction of longitudinal muscles (54). This complex myoarchitecture of interdigitating muscle fibers contribute to tongue's limitless numbers of deformations (47). Hence, extrinsic muscles impart large-scale deformation of the tongue and the intrinsic muscles help in the fine-tuning of the final shape. Similarly, retrusive movements involve the coactivation of styloglossus and hyoglossus muscles along with superior and inferior longitudinalis muscles (47,53). It has been shown that the coactivation of antagonistic muscle groups prevents the occlusive effect of the retractor, thereby improving pharyngeal patency (55–57). Like the tongue, it is proposed that pharynx also works as muscular hydrostat (58). The pharyngeal luminal shape and patency are therefore also controlled, in part, by a complex interplay of the muscles of the pharyngeal wall. Hence, the position of the posterior tongue is most relevant to the maintenance of oropharyngeal patency while anterior tongue is more involved in non-respiratory activities. This has direct and critical implications for the targets of neurostimulation in the treatment of OSA.

This anatomical configuration of the hydrostat suggests that the efficacy of any neurostimulation system that is based on the

premise that stimulating the genioglossus muscle will *pull* the anterior tongue anteriorly and that it will also simultaneously *pull* the posterior tongue anteriorly will be low. Therefore, an effective neurostimulation approach for the successful opening of the retroglossal airway requires a sophisticated system that is capable of achieving a complex concerted spatio-temporal interplay of multiple lingual muscles, including retrusors and the non-tongue muscles (geniohyoid and other pharyngeal muscles).

CO-STIMULATION OF AGONIST AND ANTAGONIST MUSCLES IN OPTIMAL PROPORTIONS IMPROVES THE AIRWAY PATENCY

Extrinsic tongue muscles change the position of the tongue, whereas the intrinsic tongue muscles alter its shape (59,60). Among the extrinsics the genioglossus muscle is considered to be the tongue protruder while styloglossus and hyoglossus muscles are considered retrusors. Geniohyoid, a non-lingual muscle, innervated by HGN, provides the muscular floor for the tongue, also affects the tongue by altering the position of the hyoid complex (51,52,61). However, its precise function is unknown. More recent data suggest that the airway opening or closing effect is a complex interplay of the two groups of muscles, i.e., agonists and antagonists (55–57,62). In addition, these two counteracting groups of muscles when working together (and against each other) not only control the tongue's position but also its tone or stiffness. Tone increases the tongue's inertia, prevents its falling into the retroglossal airway, and improves pharyngeal patency by preventing the occlusive effect of the retractor muscles (55–57). Fuller et al. (56) showed that the muscles that protrude and retract the tongue are coactivated during the respiratory drive and that inspiration is always associated with tongue retraction force. Yoo et al. (62), reported in the canine, that the decrease in the resistance on the pharyngeal airflow increased more during coactivation than during genioglossus muscle stimulation alone and also noted that the diminution effect on the pharyngeal resistance was more enhanced during coactivation than during genioglossus muscle stimulation alone.

Eisele et al. (9) showed that co-activating the tongue muscles by whole XII nerve stimulation (i.e., co-stimulation of both protruder and retruder muscles), in spite of an apparent retraction of the anterior tongue, resulted in a net increase in inspiratory flow (assisted by the oro-pharyngeal stability) in awake and anesthetized human subjects. In the same study, it was noted that electrical stimulation of the main trunk of the XII nerve lead to the protrusion and the ipsilateral deviation of the front of the tongue, while stimulating the genioglossus branch lead to the retrusion and the contralateral deviation. Likewise, Fregosi (63) reported that the stimulation of the genioglossus muscle alone dilates the airway, but does not change the pharyngeal stiffness.

TONGUE STIMULATION STIFFENS PHARYNGEAL WALL AND IMPROVES AIRWAY PATENCY—MECHANICAL DRAG VIA THE SUPERIOR PHARYNGEAL CONSTRICTOR AND THE PALATOGLOSSUS MUSCLES

Reduced muscle tone and increased compliance is the major cause of the pharyngeal collapse in patients with obstructive sleep

apnea (64,65). The anterior wall of the oropharynx (roughly one-third) is formed by the posterior surface of the tongue. The pliant hypo-pharyngeal wall is anchored not only by its own muscles, i.e., the overlapping superior and middle pharyngeal constrictor muscles, but also by lingual muscles. Niimi et al. (48,49) demonstrated that tongue muscles interact anatomically and physiologically with the superior pharyngeal constrictor muscles at the inferior posterior human tongue (Fig. 4C). Superior pharyngeal constrictor muscle fibers enter the tongue base and connect with large diameter fibers of the transversalis in the front, and to the cervical vertebrae (66) in the rear, forming a muscular ring (48). Therefore, the stability of the oro-pharynx is not only dependent on the stiffness of the constrictor muscles but also in part on the stiffness of the posterior lingual muscles, notably some of them are known tongue retractors (63,67). Experiments have shown that the selective electrical stimulation of the hypoglossal nerve improves the pharyngeal patency in addition to the dilation of the airway (beagles (68), rats (69)). Additionally, mechanical stiffening in the velopharynx, as a result of the lingual drag, is mediated via the palatoglossal arch [(70,71); Fig. 4B]. Hence, it is also likely that any movement of the tongue muscles (Fig. 4A) that stretches or stiffens, irrespective of it coming from a protruder, or a retruder, or combination, imparts indirect drag to the superior pharyngeal constrictor muscles of the oro-pharyngeal wall or the palatoglossal fold of the soft palate, making the wall of pharynx less compliant to collapse (particularly during low-pressure events, i.e. the inspirations). This stiffness, in turn, also increases the tongue's inertia (stability), and thus prevents its collapse into the retroglossal airway (57). The geniohyoid, a non-lingual muscle innervated by HGN, associated with respiration (72), is known to displace the tongue by altering the position of the hyoid complex. However, the nature of its effect has been implicated both in favor and against the improvement of the compliance (51,52,61).

TONIC STIMULATION STRENGTHENS THE LINGUAL AND THE PHARYNGEAL MUSCLES

Neuromuscular electrical stimulation of the skeletal muscle has been long used for increasing muscle strength, mass, and functional performance in sports and regenerative medicine (73,74). Changes reported include changes in the myofibrillar proteins expression—fatigue prone-to-fatigue resistance phenotype shift that results in a strengthening of the cytoskeleton; in energy production—a glycolytic-to-oxidative shift in the metabolic profile; in antioxidant mediated defense—an increased intracellular defense against harmful oxygen species (75); and in fiber size—small diameter-to-large diameter fibers shift with higher contractile tensions (76). Tonic electrical stimulation (90 days) of the tibial nerve induced a MHC IIb to IIa shift in the skeletal muscles of [rats (77)]. Likewise, rat superficial masseter muscle exhibited a significant increase in the Type I fibers at the cost of Type II fibers or became more active physically when subjected to the treatment of protrusive appliance (tonic physical stimulation) for the period of two weeks (78).

Similarly the transition of MHC isoform in the mammalian tongue, undifferentiated at birth (79), which occurs postnatally, is both dynamic and adaptive to constantly changing conditions including the tongue activity (80). Short-term electrical stimulation alters tongue muscles fiber types in rabbits—a 13% increase in Type I MHC content (fatigue resistant) and 13% decrease in Type II MHC (fatigue prone) occurred in the genioglossus muscle (81). Kinirons et al. (82), showed that MHC IIa (more fatigue resistant) increases while MHC IIb (less fatigue resistant) decreases (Styloglossus muscles) with the

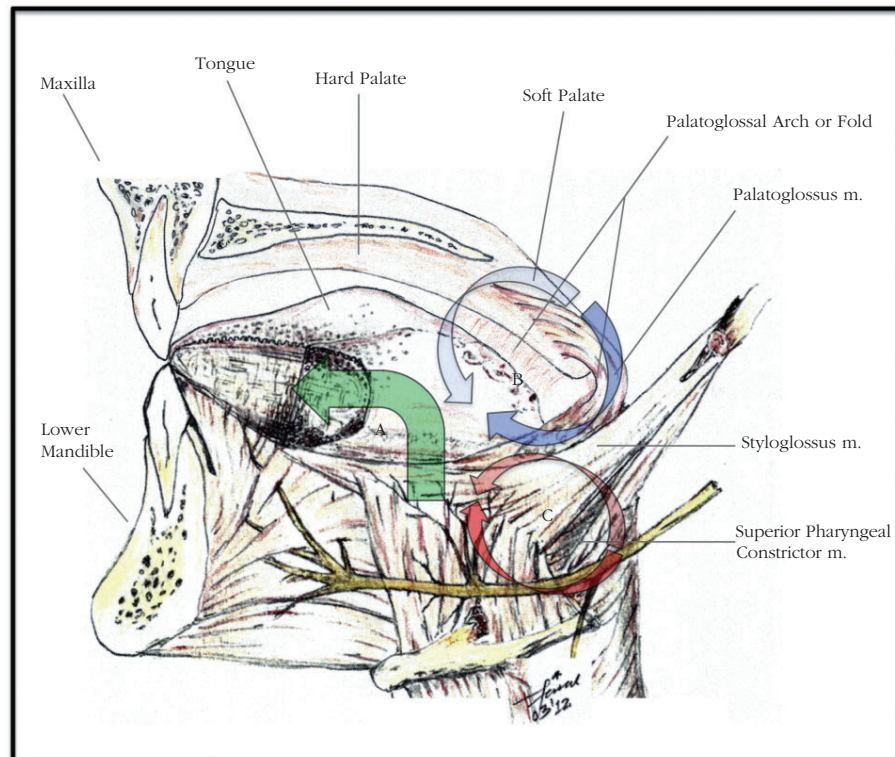


Figure 4. Diagram showing the anatomical and functional relationship between the tongue base and the superior pharyngeal constrictor muscle at the level of the human hypopharynx (C), and the palatoglossal folds at the level of velopharynx (B). Protrusive movements in the tongue (A) impart forward mechanical drag to the superior pharyngeal constrictor muscles of the oro-pharyngeal wall (C) or the palatoglossal fold of the soft palate (B), making the patent wall of the pharynx more stiff and less compliant to collapse. Arrows point toward the direction of mechanical drags.

tongue activity in rats. Neural loss or neural changes leads to a shift from MHC IIb to MHC IIa phenotypes in the genioglossus muscle of rabbits; and vice versa in mice [3–12%; (83,84)] and OSA patients (85). Guimarães et al. (86), reported a significant reduction in OSA severity as a result of short regimens of oro-pharyngeal exercises (three months for 30 min/daily).

ROLE OF THE CYCLIC TONIC ELECTRICAL STIMULATION IN FATIGUE MITIGATION

The application of a current pulse to a peripheral nerve bundle such as the HGN, causing depolarization of the nerve membranes and action potentials, occurring first in axons that lie closest to the activating electrode contact (87). An action potential, whether caused by normal neural activity or by external electrical stimulation appears to the end organ to be indistinguishable by origin (88). The amplitude of current and duration of application at the cathodal contact of a stimulator determines the quantity of fibers excited (89). As stimulation current is increased or phase duration is increased more and more fibers are activated. When nerves are stimulated through a neurostimulator, the fibers that will be activated are determined by their fixed positional relationship to the electrode contact. If activated at a high enough rate for a long enough period of time, muscle fatigue will occur and the therapeutic effect of the stimulation is lost. Thus, the artificial activation of nerve fibers and their end organs is determinate and unchanging, unlike normal, brain-mediated activation in which the brain chooses which fibers to activate and when to recruit others (90,91).

In electrical stimulation, the only method available to avoid muscle fatigue is to give the muscle an opportunity to rest and recover from its bout of operation before resuming activity. Single-channel electrical stimulation systems, without the ability to target stimulation, must allow the target muscle to rest periodically or the therapeutic effect cannot be maintained. In contrast, multi-channel electrical stimulation systems with a cuff electrode positioned on the unfasciculated proximal HGN trunk may use targeted stimulation to stimulate different muscle groups at different times. In a typical THN application (92), two to four distinct muscle groups (stimulated via two or more active contacts) are stimulated resulting in a 50% to 25% duty cycle for each muscle. This allows one muscle group to recover while another muscle group is stimulated—more closely mimicking what the brain does.

IMPLICATIONS OF HYPOGLOSSAL NERVE STIMULATION FOR THE TREATMENT OF OSA

Attempts to stimulate lingual muscles with intramuscular electrodes to increase tone (93–95) or to stimulate the HGN (9,10,96–101) have produced variable results. In particular, attempts to stimulate the entire HGN lacked selectivity in stimulating those portion(s) of the HGN that would reliably enlarge the airway. Previous neurostimulation efforts have activated the entire HGN (*en masse*), or its distal branch necessitating a synchronized system to avoid the problems associated with electrical stimulation induced muscle fatigue, wherein the HGN activation is synchronized to the respiratory cycle (9,10,96–102). Such efforts required respiration sensing

and control methods to deliver well-timed stimulation in order to achieve a minimally useful clinical result, i.e., opening of the airway. Moreover, some OSA neurostimulation therapies to date utilize stimulation with a constant voltage (98); meaning there was no direct control of the amount of the current delivered to the nerve. Since all portions of the HGN or branches were activated due to the single channel cuff electrode design, both desirable and undesirable tongue movements (e.g., retraction; 12) were generated and without any fine control, particularly of the retractor muscles (11).

The development and success of a neurostimulation approach to activate the tongue and open the airway requires a multi-channel stimulating electrode and comprehensive knowledge of

the precise effects of different forms of electrical activation on the HGN neuromuscular system. Any activation of the system must account for the differential innervations of lingual muscles by branches of the HGN, and the fact that some lingual muscles function to open the airway, while others do not. Individual lingual muscles have different attachments and therefore, some protrude the tongue, some flatten it within the oral cavity, and some pull it back toward the airway (18). The different muscles and their innervating HGN branches are represented centrally by a differential topographic arrangement of motor neurons in the hypoglossal nucleus in the medulla (91). Correspondingly, the HGN is heterogeneous, containing axons that differ in their central origin and in their muscular targets.

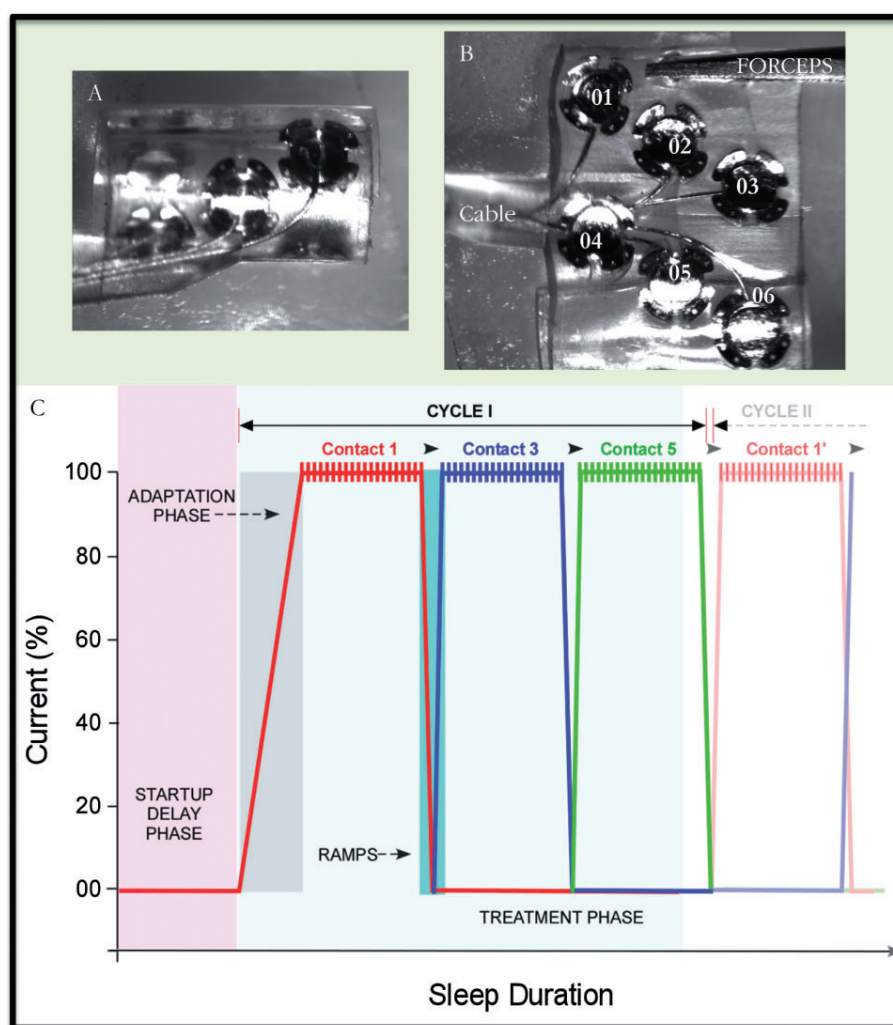


Figure 5. (A,B): Photographs showing the distribution of six contacts in Imthera Medical's hypoglossal nerve cuff electrode (92). Its six contacts are aligned in such a way that they sample the entire circumference of the wrapped nerve in six equal sectors (92). (C) Stimulation Strategy of THN Sleep Therapy (92). The course of events that occurs from the time the patient starts a sleep session through the first group stimulation cycle (with three active contacts) and the beginning of the next is shown. A sleep session starts with a 30–45-min “startup delay phase” allowing the patient to fall asleep. After the delay, the first contact (contact 1) begins to stimulate (“adaptation phase”) using its threshold amplitude, slowly ramping up for the duration of the ramp, until at the conclusion of the ramp and the beginning of the plateau phase (the stimulation current amplitude has reached its target level “treatment phase”). This ramp helps to prevent the patient from being aroused from sleep by the sudden sensation of stimulation at the target level. After the plateau duration is complete for the contact 1, the stimulation begins to ramp back down to threshold levels for the ramp down duration. At the conclusion of the ramp down duration, the first contact is deactivated and the ramp up phase of the second contact is activated. Likewise this process is repeated for all active contacts (Cycle 1) and when all of the active contacts have been stimulated, the cycle repeats again beginning with the first contact (Cycle 2) all through the sleep until the end of the sleep therapy.

TARGETED HYPOGLOSSAL NERVE (THN) SLEEP THERAPY—A NEW APPROACH

An alternative approach to genioglossus-based electrical stimulation would be to selectively activate or target muscle groups that result in restoration of tongue tone and position. It would require simultaneous activation of appropriate muscle groups to obtain a coordinated opening of the oropharyngeal airway. This would be accomplished by activating the proximal HGN in the neck to allow sub-populations to be activated by regional nerve cuff contacts and still activate several motor units belonging to multiple muscle groups. By switching between contacts, different motor units belonging to multiple muscle groups are activated cyclically, mitigating fatigue, and mimicking the natural motor activity of the tongue. This is the method designed to implement THN Sleep Therapy (<http://www.imtheramedical.com>). In the aura6000™ System, stimulation is delivered through a six contact self sizing cuff electrode secured around the hypoglossal nerve at the level of the sub-mandibular gland (Fig. 1). This region of the nerve is afascicular and affects all muscle groups across the entire nerve. By selectively activating some of the six contacts in turn (Fig. 5C), a subset of a broad mix of muscle fibers is activated to gain the desired tone and movement.

An important difference between the aura6000™ System (92) and other HGN systems is the absence of a sensing leads to monitor respiration or thoracic movements (9,10,96–102). These feedback sensors are surgically implanted at various places in the chest. Absence of a sensing lead simplifies the surgical procedure, and improves long-term reliability by eliminating one of the most failure prone parts of a neurostimulator, a lead, as well as eliminating sensing circuitry and detection algorithms and their associated power consumption. In addition, the aura6000™ System has six independent current sources, in effect containing six separate stimulators. Each of the current sources is connected to a single one of the six contacts in the cuff electrode (Fig. 5A,B), so each can activate a single region of the hypoglossal nerve at the implant site. By controlling the duration and amount of current in the delivered pulses the volume of neural activation by electrical stimulation will be constrained to the regions directly facing the cuff contacts. With the contacts spaced circumferentially around the cuff, this effectively divides the hypoglossal nerve into six regions that are activated independently.

Mapping contact activity with desired tongue movement is critical to the success of the system. It is only required that two of the six available contacts result in acceptable tongue response. With a minimum of two contacts active, there is a 50% duty cycle as the system stimulates first one contact, the muscles activated by the second recover before re-activation. If three contacts are acceptable then the duty cycle drops to 33% (as shown in Fig. 5C), if four are found to be useful the duty cycle drops to 25%. With this method, fatigue is mitigated.

SUMMARY

We review the neurobiology of the human tongue and its implications for the specification and design of a novel platform device, an electrical neurostimulation system for the treatment of the OSA.

Recognizing the anatomical design, contractile patterns of the tongue and its neural supply are key to understanding how the tongue functions and what is required to artificially activate it with electrical stimulation. Simple Platform stimulators designed for another physiological system may not work well for this complex organ model. In developing the aura6000™ System, the tongue and

its neural supply were investigated and a stimulation system was developed that meets the demands of the anatomy and physiology of the tongue in the treatment of the OSA. Specifically, the neural interface was designed to comprise of a cuff electrode that can selectively activate regions of the nerve reliably and independently, and be located to take advantage of the neural structures and provide the activation needed for successful movement of the tongue and beneficial therapy to the patient.

This stimulator design is able to avoid fatigue, without the need for additional implanted feedback sensors, by delivering cyclical tonic stimulation via multiple contacts, with a maximum duty cycle of 50% and a minimum of 16.7%. The system targets and can select multiple muscle arrays to provide tone and support to the tongue and pharyngeal wall. Protruder, retruder, extrinsic, and intrinsic muscles are thus activated, irrespective of their role in isolation, to achieve optimal tongue shape and tone for airway patency.

Targeted neurostimulation via a multiple contact cuff electrode implanted on the proximal HGN is a significant technical improvement over earlier approaches.

Authorship Statements

Faisal Zaidi and Paul Meadows wrote the manuscript. Ofer Jacobowitz and Terence Davidson reviewed it. All authors approved the submitted version of the manuscript.

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Obstructive sleep apnea is a prevalent disease with multiple physiologic consequences leading to health impairment and decreased survival. The present treatment, continuous positive airway pressure, is efficient but cumbersome and many patients do not or can not comply with it and are left untreated. New approaches would be welcome. Neurostimulation of the hypoglossal nerve, controlling almost all tongue muscles, represents an interesting possibility being explored nowadays. This manuscript presents the present state of knowledge on tongue anatomy and physiology, upon which a proposal for a neurostimulation device is built.

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Comments not included in the Early View version of this paper.

COMMENTS

This is an interesting and timely review of the anatomy and physiology of the neuro-motor tongue system. It comprehensively reviews the literature and state of knowledge in the field, from both animal and human published studies. The review emphasizes the complexities of tongue muscle function, especially as regards influences on the airway of relevance to causes and treatments of obstructive sleep apnea. It ends with a compelling presentation of “targeted hypoglossal nerve stimulation” as means for treating sleep apnea that has as its rationale the understanding of the system as reviewed in the bulk of the manuscript.

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