

A framework for understanding shared substrates of airway protection

Michelle Shevon TROCHE¹, Alexandra Essman BRANDIMORE¹, Juliana GODOY², Karen Wheeler HEGLAND¹

1- Department of Speech, Language, and Hearing Sciences, University of Florida, Gainesville, FL, USA.

2- Bauru School of Dentistry, University of São Paulo, Bauru, SP, Brazil.

Corresponding address: Michelle S. Troche - PO Box 117420 - Gainesville, FL 32611 - Phone: 352-273-3731 - Fax: 352-846-0243 - michi81@p.php.ufl.edu

Submitted: March 24, 2014 - **Modification:** May 1, 2014 - **Accepted:** May 6, 2014

ABSTRACT

Deficits of airway protection can have deleterious effects to health and quality of life. Effective airway protection requires a continuum of behaviors including swallowing and cough. Swallowing prevents material from entering the airway and coughing ejects endogenous material from the airway. There is significant overlap between the control mechanisms for swallowing and cough. In this review we will present the existing literature to support a novel framework for understanding shared substrates of airway protection. This framework was originally adapted from Eccles' model of cough²⁸ (2009) by Hegland, et al.⁴² (2012). It will serve to provide a basis from which to develop future studies and test specific hypotheses that advance our field and ultimately improve outcomes for people with airway protective deficits.

Keywords: Airway management. Cough. Swallowing. Dysphagia. Neural pathways. Review. Background

BACKGROUND

Deficits of airway protection can lead to significant deterioration of health and quality of life. Of particular concern is the associated risk of aspiration or ingestion of foreign particles into the airway, a potential cause of aspiration pneumonia resulting in high morbidity and mortality^{58,59}. Studies suggest that 40% of adults aged 60 years and older have disordered swallowing, or dysphagia^{26,32}. Additionally, pneumonia is the 5th leading cause of death in persons 65 years or older and the 3rd leading cause of death in persons 85 years and older⁵⁷. In fact, aspiration pneumonia is often the leading cause of death in persons with neurodegenerative diseases, including Parkinson's disease (PD)^{33,39,46,95,98}. Each year, according to the Agency for Health Care Policy and Research (AHCPR), over 60,000 Americans die from complications associated with swallowing dysfunction, most commonly aspiration pneumonia. Despite the staggering statistics, there is an incomplete understanding of the mechanisms underlying dysfunctional airway protection, its assessment, and management.

Airway protection is functionally complex and includes a continuum of behaviors with cough and swallowing at either end of that continuum (Figure 1). More specifically, effective swallowing prevents material from entering the airway and effective coughing ejects the aspirate material when airway compromise occurs. Both cough and swallowing consist of highly coordinated sequences of structural movements, and both require reconfiguration of the ventilatory breathing pattern. There is considerable overlap in the sensory and motor control and execution of the two behaviors, including peripheral and central nervous system components. In fact, there is an emerging literature identifying concurrent swallowing and cough deficits in people with neurogenic disorders with particular interest in whether cough can predict swallowing dysfunction^{83,86,100}. The purpose of this manuscript is to present a framework for understanding the shared mechanisms of cough and swallowing in humans. This framework was originally adapted from Eccles'²⁸ (2009) model of cough by Hegland, et al.⁴² (2012). We now propose further adaptation of the model to include both swallowing and cough overlaid into one framework.

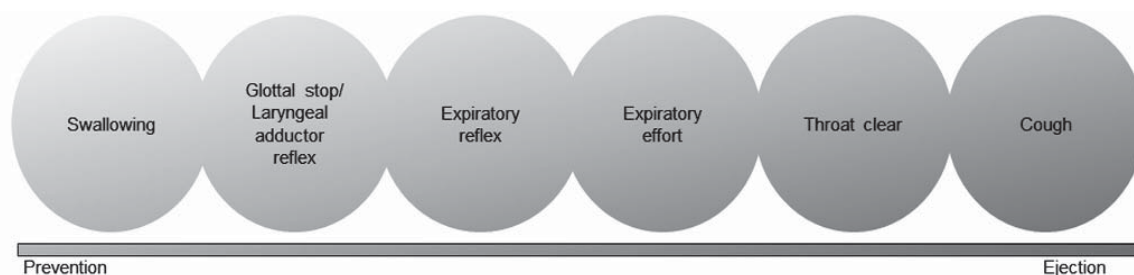


Figure 1- Continuum of airway protective behaviors

PROPOSED FRAMEWORK OF AIRWAY PROTECTION

Cough and swallowing are sensorimotor behaviors which share neuroanatomical substrates. The proposed framework presented in Figure 2 illustrates these shared mechanisms. We now present a general overview of the framework for airway protection. To begin, cough and swallowing share afferents (a) that are essential to the initiation and modification of the behaviors. This afferent (a) information is then sent to the sensory nuclei (b) located in the brainstem. There, the behavioral control assembly (BCA) (c) will receive the afferent information and exert control over the swallowing and cough central pattern generators (CPGs) (d & e) in order to generate the appropriate airway protective behavior. Information fed into the motor nuclei (f) is then sent to the efferent (g) nerves, ultimately resulting in the execution of the behavior.

For humans in the conscious state, higher level processing is involved. Information from the brainstem sensory nuclei (b) travels through ascending pathways to the cortex via the thalamus, allowing for somatosensation (h) of the stimulus. Preceding the motor output there is an urge to act (i) on the stimulus. The magnitude of the perceived urge-to-act will be based on discriminative and affective processing. Ultimately, volitional control (j) (i.e., suppression or up-regulation) of the behavior is dependent upon the perceived magnitude of the stimulus as well as extrinsic factors, for example, suppressing a cough in a quiet testing environment.

Additionally, both cough and swallowing can be initiated through volitional control (k), or on command. This neural information then travels through descending pathways to the brainstem and then through efferents (g) to the periphery. The following paragraphs provide support for the proposed framework. Figure 3 presents a brief overview of the proposed framework and provides a representative sample of literature supporting each framework domain.

AFFERENTS

Peripheral sensory input is essential for the

initiation and modification of the motor act for both behaviors. Swallowing motor output is modified by variations in bolus characteristics including volume, viscosity, taste, and temperature. These characteristics impact various biomechanical parameters of the swallow and include: 1) duration of upper esophageal sphincter (UES) opening^{10,38,47,50}, 2) duration of swallow apnea^{9,44,45}, 3) timing of pharyngeal phase initiation and laryngeal closure^{16,18,49}, 4) lung volume at swallow initiation^{112,113}, 5) oropharyngeal pressure^{10,47,82}, 6) amplitude and duration of muscle activation^{17,104}, and 7) total oropharyngeal swallow duration^{16,47,63,104}. Similarly, cough motor output is modified by type of irritant (i.e., capsaicin, citric acid, fog, bradykinin, etc.)^{60,81}, irritant concentration^{13,20,25,110}, volume and duration of irritant presentation¹⁰⁵, nasal afferent stimulation^{87,116}, and lung volume at cough initiation⁹⁹. These characteristics then result in modifications to cough inspiratory flow rate^{3,4}, number of coughs produced^{22,25,60,74,81,105,110}, self-reported urge to cough^{21,22}, amplitude and duration of expiratory muscle activation during cough^{34,110}, and cough expiratory airflow parameters^{43,60,110}.

There are multiple types of sensory receptors located in the upper and lower airways, the majority of which regulate the rate and depth of the ventilatory/respiratory pattern (e.g.^{11,12,15,89,102,115,116,118}). Of particular relevance for the proposed framework are those receptors and nerves associated with the initiation of cough and swallowing. There are multiple receptor types that participate in the production of reflexive cough^{13,115,117,118}. These include primarily cough receptors, as well as subtypes of c-fibers, trachea-bronchial rapidly adapting receptors (RARs), and intrapulmonary stretch receptors [for complete review see Canning and Chou¹³ (2009)]. Similarly, a constellation of receptor-types participate in initiation of swallowing including mechanoreceptors and chemoreceptors sensitive to pressure, gustatory stimuli, and temperature located throughout the oral, pharyngeal, and laryngeal mucosa [for complete review see Miller⁷⁶ (1986)]. The similarities between the receptors initiating cough and swallowing are highlighted by recent animal research in which water was injected into the

oropharynx in the presence of tracheal mechanical stimulation. This dual stimulation resulted in context-dependent, alternating production of cough and swallowing⁸⁵.

Several cranial nerves (CNs) provide sensory innervation throughout the upper and lower airways. Specifically, CNs V and VII innervate the oral cavity and rostral pharynx, functioning largely to transduce sensory information regarding bolus characteristics that then shape the swallow motor response [for review see Jean³⁰ (2001) and Ertekin, et al.⁵² (2003)]. CNs IX and X are primarily responsible for the initiation of cough and swallowing^{27,37,52,75,76,88,97,102,106}, and will thus be the focus of this discussion.

The glossopharyngeal nerve, CN IX, consists of the pharyngeal and lingual branches. The lingual branch is minimally involved with the elicitation of cough and swallowing, but serves to innervate the posterior tongue, tonsils, vallate papillae, and epiglottis⁷⁸. The pharyngeal branch of CN IX is directly involved in the initiation of cough

and swallowing⁵⁶. This branch of CN IX further subdivides into superior, middle, and inferior branches providing sensory innervation to the oropharynx, lateral pharyngeal wall, and pharyngeal plexus (including the UES and inferior pharyngeal constrictor)⁷⁸. Most essential for the modification of cough and swallowing, is the sensory information transmitted from the posterior third of the tongue and upper pharynx through the general (somatic) sensory component of CN IX. This sensory information then synapses within the contralateral ventral posterior nucleus of the thalamus then ascending to the sensory cortex¹¹⁹.

The vagus nerve contributes to visceral innervation and provides sensory information to the central nervous system about the state of various organ systems. Of relevance for cough and swallowing, the vagus divides into two main branches: the superior laryngeal nerve (SLN) and the recurrent laryngeal nerve (RLN). The internal branch of the SLN (ISLN) is critical for initiating reflexive coughing and swallowing^{36,51,52,102} and

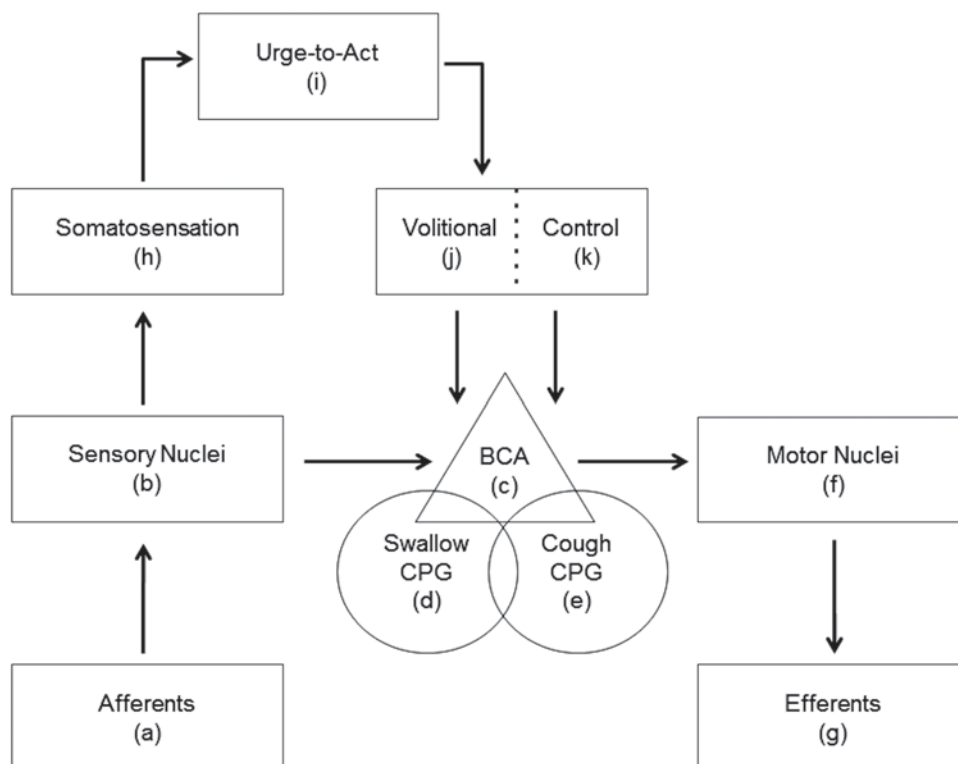


Figure 2- Proposed framework of airway protection. Cough and swallowing share afferents (a) that are essential to the initiation and modification of the behaviors. This afferent (a) information is then sent to the sensory nuclei (b) located in the brainstem. There, the behavioral control assembly (BCA) (c) will receive the afferent information and exert control over the swallowing and cough central pattern generators (CPGs) (d & e) in order to generate the appropriate airway protective behavior. Information fed into the motor nuclei (f) is then sent to the efferent (g) nerves. Information from the brainstem sensory nuclei (b) travels through ascending pathways to the cortex via the thalamus, allowing for somatosensation (h) of the stimulus. Preceding the motor output there is an urge to act (i) on the stimulus. This will enable suppression or up-regulation of the airway protective behavior through volitional control (j). Both cough and swallowing can be initiated through volitional control (k), or on command. This neural information then travels through descending pathways to the brainstem and then through efferents (g) to the periphery

glottal closure^{51,103}. The ISLN innervates and receives afferent input from the laryngeal and pharyngeal mucosa, epiglottis, aryepiglottic folds,

false and true vocal folds, cricoarytenoid joint, anterior wall of the laryngopharynx, and the posterior pharyngeal wall⁷⁸. More specifically, the

Framework Domain	Cough	Swallow
Afferents (a) Cough and swallowing share afferents that are essential to the initiation and modification of the behaviors.	Barros, et al. ^{3,14} (1990, 1991) Canning, et al. ^{11,13} (2001,2009) Dicipinigitis ²⁵ (2009) Fontana, et al. ³⁴ (1998) Gestreau, et al. ^{36,37} (2000,1996) Jafari, et al. ⁵¹ (2003) Midgren, et al. ⁷⁴ (1992) Pecova, et al. ⁸¹ (2007) Smith, et al. ⁹⁹ (2012) Sant'Ambrogio, et al. ⁸⁹ (1996) Widdicombe, et al. ^{115,117} (2001,1954)	Butler, et al. ¹⁰ (2009) Dantas, et al. ^{17,18} (1990) Doty ^{26,27} (1951,1956) Gestreau, et al. ^{36,37} (2000,1996) Hiss, et al. ^{44,45} (2004,2001) Hoffman, et al. ⁴⁷ (2010) Jean ⁵² (2001) Kitagwa, et al. ⁵⁶ (2009) Miller ^{75,76} (1972,1986) Saito, et al. ⁸⁸ (2003) Shaw & Martino ⁹⁴ (2013) Storey ^{102,103} (1968, 1975)
Sensory and Motor Nuclei (b, f) Afferent information is then sent to the sensory nuclei located in the brainstem. There, the BCA will receive the afferent information and exert control over the CPGs to generate the appropriate airway protective behavior.	Bolser, et al. ^{5,6} (2009,2013) Davenport, et al. ²⁰ (2011) Gestreau, et al. ³⁵⁻³⁷ (1997,2000,1996) Jordan ⁵³ (2001) Jordan & Spyer ⁵⁴ (1986) Pitts, et al. ^{84,85} (2012,2013) Shannon, et al. ⁹⁰⁻⁹² (2000,1996,1998)	Bolser, et al. ⁶ (2013) Broussard, et al. ⁸ (2000) Dick, et al. ²⁴ (1993) Ertekin, et al. ^{29,30} (2011,2003) Gestreau, et al. ^{36,37} (2000,1996) Jean ⁵² (2001) Jordan ⁵³ (2001) Jordan & Spyer ⁵⁴ (1986) Saito, et al. ⁸⁸ (2003)
Somatosensation (h) Information from the brainstem sensory nuclei travels through ascending pathways to the cortex via the thalamus, allowing for somatosensation.	Chan & Davenport ¹⁴ (2008) Farrell, et al. ³¹ (2012) Mazzone, et al. ^{71,72} (2013,2007) Simonyan, et al. ⁹⁶ (2007) Wheeler-Hegland, et al. ¹¹⁴ (2011)	Ertekin, et al. ^{29,30} (2011,2003) Hamdy, et al. ⁴¹ (1999) Lowell, et al. ⁶⁴ (2008) Martin, et al. ⁶⁷ (2001) Mosier, et al. ⁷⁷ (1999) Soros, et al. ¹⁰¹ (2008)
Urge-to-act (i) Preceding the motor output there is an urge to act on the stimulus. The magnitude of the perceived urge-to-act will be based on discriminative and affective processing.	Davenport, et al. ^{19,21,23} (2009,2009,2007) Farrell, et al. ³¹ (2012) Mazzone, et al. ^{71,72} (2013,2007) Van den Bergh, et al. ¹⁰⁹ (2012) Yamanda, et al. ¹²⁰ (2008)	Theurer, et al. ^{106,107} (2005,2009)
Volitional Control (j, k) Volitional control of the behavior is dependent upon the perceived magnitude of the stimulus as well as extrinsic factors. Additionally, both cough and swallowing can be initiated through volitional control or on command.	Farrell, et al. ³¹ (2012) Hegland, et al. ⁴² (2012) Hutchings, et al. ⁴⁸ (1993) Leech, et al. ⁶¹ (2013) Leow, et al. ⁶² (2012) Mazzone, et al. ^{69,71,72} (2011,2013,2007) Simonyan, et al. ⁹⁶ (2007) Widdicombe, et al. ¹¹⁸ (1988)	Augustine ² (1996) Hamdy, et al. ^{41,40} (2001,1999) Malandraki, et al. ^{65,66} (2011,2009) Martin, et al. ^{67,68} (2001,2004) Mosier, et al. ⁷⁷ (1999) O'Rourke, et al. ⁷⁹ (2014) Park, et al. ⁸⁰ (2012) Wheeler-Hegland, et al. ¹¹³ (2009)
Efferent Control (g) Neural information travels through descending pathways to the brainstem and then through efferents to the periphery.	Pitts, et al. ⁸⁴ (2012) (Review)	Shaw & Martino ⁹⁴ (2013) (Review)

*behavior control assembly (BCA); central pattern generator (CPG)

Figure 3- Literature supporting shared substrates of airway protection. The first column presents the proposed framework domain (with corresponding letter from framework Figure 2) and brief overview. The second and third columns present a representative sample of the most relevant literature supporting the framework domains

ISLN is a general (somatic) sensory nerve synapsing contralaterally in the ventral posterior nucleus of the thalamus, ultimately ascending through the internal capsule to the sensory cortex¹¹⁹.

SENSORY AND MOTOR NUCLEI

Multiple research studies have identified a shared network of brainstem respiratory motor neurons that participate in the production of cough and swallow. Based on afferent input, the cough or swallow response is shaped by collections of excitatory and inhibitory interneurons that ultimately produce specific motor neuron discharge patterns for the production of either the cough or swallow. These swallow and cough brainstem neural networks are known as CPGs and serve to initiate complex, standardized motor output^{8,24,37} and regulate the amount, duration, and temporal relationship of muscle activation required for the task⁶. There is strong evidence to support the notion that most, if not all, afferent fibers for both cough and swallowing converge on the nucleus tractus solitarius (NTS). The caudal two thirds of the NTS and the surrounding reticular formation at the level of the obex are functionally organized (rostrocaudally) and are considered the CPG for swallowing^{8,29,30,37,52-54,88}. Stimulation of the NTS and reticular formation results in excitation of neurons within the dorsal swallowing group (DSG)⁵² which is primarily responsible for the initiation of swallow. The CPG for cough has not been as well described, but is thought to include the NTS and the surrounding reticular formation^{35-37,53,54,90}.

Although the CPGs for cough and swallowing are separate entities, recent research indicates they both converge on and reconfigure the respiratory neural network^{5,20}. This results in modification of the ventilatory breathing pattern necessary for the execution of the appropriate airway protective behavior^{6,20,91-93}. Bolser, et al.⁶ (2013) have proposed the concept of BCAs to explain the way in which shared populations of respiratory neurons control the generation of various airway protective behaviors based on afferent stimuli. The BCA ensures production of the appropriate behavior (i.e., cough, swallow, throat clear, expiratory reflex, etc.) by exerting control over the CPGs. Although the precise neural mechanisms by which airway protective behaviors are coordinated is not completely understood, there is evidence from animal models demonstrating shared brainstem substrates and supporting the idea of BCAs. For example, Gestreau, et al.³⁶ (2000) recorded the activity of respiratory laryngeal motor neurons within the brainstem of decerebrate cats during the production of fictive cough and swallowing elicited by direct stimulation of the SLN. Fictive

cough was induced with repetitive SLN stimulation at 2-5 Hz, and fictive swallowing was induced with repetitive SLN stimulation at a higher frequency range of 10-30 Hz. They also found that the majority of laryngeal respiratory motor neurons were activated during stimulation of both cough and swallow. Recent work by Pitts, et al.⁸⁵ (2013) studying aspiration response in a cat model provides further evidence for coordination of swallowing and cough at the brainstem level. The researchers found respiratory phase restriction in the elicitation of the cough and swallowing behaviors in response to aspiration. These differences likely exist, in part, to maximize the effectiveness of the behaviors within the mechanical constraints distinct to each behavior. Therefore, coordination of cough and swallowing, at the brainstem level, may result in elicitation of multiple behaviors for appropriate airway protection.

SOMATOSENSATION

Researchers no longer conceptualize the cough and swallowing behaviors as purely brainstem-mediated and recognize that the cortex plays a critical role in the regulation and modification of swallowing and coughing^{6,28,30,42,48,52,69-73,76,96,108}. This is evidenced, for example, by peripheral afferent projections that do not terminate solely in the brainstem, but instead continue to ascend toward the thalamus and then ultimately to cortical regions^{29,30,52,55,96,114}. It is hypothesized that the thalamus integrates all afferent information from the periphery and includes or excludes the sensory input which is relayed to the cortex based on the relevancy and redundancy of the afferent signal. This thalamic integration and filtering of sensory input is defined as sensory gating. Various functional magnetic resonance imaging (fMRI) studies have identified that several regions of the thalamus are active during pharyngeal air puff stimulation¹⁰¹, coughing⁹⁶, and swallowing^{41,64,67,77}, providing further evidence for sensory gating. A recent study by Wheeler-Hegland, et al.¹¹⁴ (2011) identified that repetitive, paired-pulse air puffs to the oropharynx did not result in the typical gating, or attenuation of the sensory signal relayed to the cortex which is observed in other sensory modalities^{1,14}. For auditory and somatosensory repetitive stimuli the cortical response to the redundant stimulus is half that of the initial novel stimulus. This is the mechanism by which the cortex is protected from a bombardment of sensory information. However, for pharyngeal stimuli it is likely not advantageous to gate out information as it may lead to lack of appropriate and timely response in the form of a cough or swallow. Thus, this difference in sensory gating for oropharyngeal stimulation was hypothesized to

relate to the consistent detection and processing of oropharyngeal stimuli necessary in order to maintain airway protection via appropriate cough or swallow response to a given stimulus¹¹⁴.

URGE-TO-ACT

Behavioral reflexes can be modified or shaped to the extent that they can be perceived. In fact, the first component of the cognitive motivational system is initiation of a biological urge which allows for a cascade of neural events resulting in conscious modulation of motor behaviors⁷. Therefore, the urge itself is *essential* for the conscious modulation of the behavioral reflex. These urges, in this case, respiratory sensations, are complex and involve discriminative and affective processing^{71,109}. Discriminative processing involves the assessment of what is sensed including the spatial, temporal, and intensity characteristics of the stimuli⁷¹. Affective processing involves the evaluation of the emotional salience and experience of the stimulus^{19,109}. Research into the role of these two types of processing on the perception of airway stimuli is ongoing.

By definition, the urge-to-cough (UTC) is a respiratory sensation related to a cough stimulus preceding the motor behavior. The UTC has a log-log linear relationship with increasing concentration of a cough-inducing stimulus^{19,21,23}. That is, subjective ratings of UTC increase with increased stimulus intensity. Additionally, as UTC increases so do the associated number of coughs produced^{21,120}.

The UTC seems to be an important construct in understanding airway protective deficits. Yamanda, et al.¹²⁰ (2008) found higher cough reflex thresholds in response to citric acid inhalation in patients with a history of aspiration pneumonia as compared to age-matched elderly controls. Interestingly, although UTC scores at cough thresholds were no different between groups, UTCs were significantly lower for patients with aspiration pneumonia at half the concentration which elicited cough thresholds. This highlights a blunted UTC at subthreshold levels of citric acid for patients with a history of aspiration pneumonia.

Although not studied specifically, we can infer that there is also an urge-to-swallow. Theurer, et al.^{106,107} (2005, 2009) evaluated the effects of air-pulse stimulation on swallowing outcomes in healthy adults. The researchers found that air puff-pulse stimulation to the oropharynx resulted in an 'irrepressible urge-to-swallow' as reported by the participants¹⁰⁶. This resulted in an increased swallowing frequency^{106,107}. More recently, our laboratory studied the pharyngeal swallowing of people with PD and dysphagia under dual task conditions. Results revealed that some participants

experienced cognitive-motor interference with reduced swallowing safety in dual task conditions¹⁰⁸. This supports the idea that the "reflexive" phase of swallowing is influenced by top-down mechanisms, possibly through the cognitive perception of the urge-to-swallow.

VOLITIONAL CONTROL

As stated by Bradley, a behavioral response to stimuli can be cortically modulated if perceived⁷, and this is true for both swallowing and cough. The modulation of swallowing is routinely used in the rehabilitation of dysphagia^{79,80,111}. Treatment paradigms such as the supraglottic swallow, effortful swallow, and Mendelsohn maneuver require that volitional control is exerted over motor output, changing some physiological aspects of the resulting swallow. Similarly, volitional control can modulate the cough motor output^{42,48,62,116}. Anecdotally, when an urge-to-cough is detected in an environment such as a concert hall or testing room, one may try not to cough, or cough softer so as to not disturb others¹¹⁶. This reflects cortical suppression and modulation of the brainstem-controlled cough motor output.

Hutchings, et al.⁴⁸ (1993) were the first to demonstrate this empirically with their study of cough suppression in healthy adults. They showed that cough induced by inhalation of capsaicin could be readily suppressed when participants were given the instruction to not cough during the trial. Hegland, Bolser and Davenport⁴² (2012) studied the ability to modulate the cough response to supra-threshold levels of inhaled capsaicin. In this study, 18 adult participants were able to modify their cough response at a stimulus intensity level where it was not possible to suppress the cough response⁴². This study points to the ability of the cortex to exert modulatory control over brainstem centers. Thus, while both cough and swallowing can be initiated reflexively, each can be modified cortically in healthy, awake humans. Additionally, both behaviors can be initiated on command, or "cortically", without the presence of a sensory stimulus.

Functional MRI studies have identified overlapping regions of cortical activation associated with coughing and swallowing. Both reflex and voluntary cough activate large distributed cortical networks. More specifically, Mazzone, et al.⁷¹ (2013) have defined the network of neural substrates associated with UTC in a three tiered model including sensory, cognitive, and motor components. The "sensory" module of UTC encodes ascending peripheral information related to stimuli discrimination (intensity and perception) and spatial discrimination (localization). Stimuli discrimination activated the

primary somatosensory cortex (S1) and anterior insula. Spatial discrimination activated the posterior parietal cortex and dorsolateral prefrontal cortex. The “cognitive” module serves to shape the affective response to airway irritation and was found to activate the orbitofrontal cortex, cingulate cortex and other limbic regions. These same regions are activated with other visceral sensory experiences (i.e., pain, dyspnea) suggesting a potential core network of cortical activation that controls interoceptive processing. The “motor” module interprets the sensory experience of UTC and modifies the behavioral output of voluntary and reflex cough. Recent work by Farrell, et al.³¹ (2012) has identified dissociable patterns of neural response for high and low concentrations of capsaicin. More specifically, they identified that premotor regions and the cerebellum were activated at only high concentrations of capsaicin, whereas prefrontal and parietal regions were activated independent of capsaicin concentration. Interestingly, activation of somatosensory, associative, and limbic cortices correlated with UTC ratings^{71,72}. This data support the idea that the UTC involves distinct affective and discriminative processing which then results in volitional modulation of the cough^{31,61,69-72}.

Swallowing also involves a large cortical network [see Malandraki, et al.⁶⁵ (2011) for comprehensive review]^{40,41,65-68}. The cortical areas involved in swallowing have been implicated in sensorimotor integration, motor planning, and execution of the swallow (e.g., inferior frontal gyrus, SMA, sensorimotor cortex, supplementary sensory area, premotor cortex, antereolateral and posterior parietal cortex). The insular cortex, also activated during cough, is considered essential to sensory-motor integration between primary cortical and subcortical sites^{2,77}. Additionally, the involvement of the subcortical control circuits and structures including the thalamus, basal ganglia, and cerebellum cannot be ignored in the downstream production of swallowing and cough^{41,65-68,77,96}.

EFFERENTS

Cough and swallowing require coordinated, but distinct patterned movements of the oral, velopharyngeal, pharyngeal, laryngeal, and respiratory muscles. Therefore, cough and swallowing share many similar nerves and muscles for their execution. In brief, cough and swallowing require the activation of various cranial nerves including the trigeminal, facial, vagus, and hypoglossal nerves, in addition to a multitude of spinal nerves innervating various respiratory muscles. A complete review of all the muscles and nerves involved in cough and swallowing is beyond the scope of this paper. Pitts, et al.⁸⁴ (2012) and

Shaw and Martino⁹⁴ (2013) provide comprehensive reviews of this material.

CONCLUSIONS

Deficits of airway protection, specifically dysphagia and dystussia, result in significant social, financial, and health burden. A comprehensive understanding of the mechanisms underlying these disorders is necessary for the development of effective treatments of airway protective deficits which have generalizable and maintainable outcomes. This framework was developed based on the current state of the art and the currently available literature, and is a working model in many regards. As more information becomes available, the proposed framework will likely need to be revised. In fact, the goal in developing this framework is to promote study into the mechanisms underlying airway protection, thus leading to necessary advancements and revisions to our current understanding of cough and swallowing. For example, considering the overlapping nature of these functions might help us better understand the functional organization of cough and swallowing. To this point, the concurrent study of afferent and brainstem-mediated mechanisms of cough and swallowing has garnered most research interest. These studies are certainly necessary, but in order to translate these findings to the human experience and clinical populations there must be more study into the impact of somatosensation, the urge to act, and volitional control on the production of airway protective behaviors, particularly in disordered populations. Without this critical information, it will be very difficult to develop effective treatments for airway protective dysfunction, specifically in neurologically impaired populations. It can be hypothesized that approaching aspiration as a pervasive deficit in airway protection (i.e., cough and swallowing dysfunction) will result in the development of more specific and robust treatment modalities. Therefore, this framework will serve to provide a basis from which to develop future studies and test specific hypotheses that advance our field and ultimately improve outcomes for people with airway protective deficits.

ACKNOWLEDGEMENTS

Dr. Troche reports no disclosures or conflicts of interest related to this work. Dr. Troche’s research is supported in part by a National Institutes of Health (NIH) [National Center for Advancing Translational Sciences (NCATS)] Clinical and Translational Science Awards (CTSA) through the University of Florida (UL1TR000064 and KL2TR000065).

Ms. Brandimore reports no disclosures related

to this study. Ms. Brandimore's work is supported in part by a pre-doctoral fellowship through the Department of Veterans Affairs.

Ms. Godoy reports no disclosures related to this study. Ms. Godoy's work is supported in part by the Coordination Personnel for the Improvement of Higher Education Personnel (CAPES), an agency under the Ministry of Education of Brazil.

Dr. Hegland reports no disclosures related to this study. Dr. Hegland's work is supported in part by the American Heart Association and BAE defense systems.

REFERENCES

- 1- Arnfred SM, Eder DN, Hemmingsen RP, Glenthøj BY, Chen AC. Gating of the vertex somatosensory and auditory evoked potential P50 and the correlation to skin conductance orienting response in healthy men. *Psychiatry Res.* 2001;101(3):221-35.
- 2- Augustine JR. Circuitry and functional aspects of the insular lobe in primates including humans. *Brain Res Brain Res Rev.* 1996;22(3):229-44.
- 3- Barros MJ, Zammattio SJ, Rees PJ. Importance of inspiratory flow rate in the cough response to citric acid inhalation in normal subjects. *Clinical Sci (Lond).* 1990;78(5):521-5.
- 4- Barros MJ, Zammattio SL, Rees PJ. Effect of changes in inspiratory flow rate on cough responses to inhaled capsaicin. *Clinical Sci (Lond).* 1991;81(4):539-42.
- 5- Bolser DC, Davenport PW. Codeine and cough: an ineffective gold standard. *Curr Opin Allergy Clin Immunol.* 2007;7(1):32-6.
- 6- Bolser DC, Gestreau C, Morris KF, Davenport PW, Pitts TE. Central neural circuits for coordination of swallowing, breathing, and coughing: predictions from computational modeling and simulation. *Otolaryngol Clin North Am.* 2013;46(6):957-64.
- 7- Bradley MM. Emotion and motivation. In: Cacioppo JT, Tassinary LG, Bernston GG, editors. *Handbook of psychophysiology.* 2nd ed. New York: Cambridge University Press; 2000. p. 602-42.
- 8- Broussard DL, Altschuler SM. Central integration of swallow and airway-protective reflexes. *Am J Med.* 2000;108 Suppl 4a:62S-67S.
- 9- Butler SG, Postma GN, Fischer E. Effects of viscosity, taste, and bolus volume on swallowing apnea duration of normal adults. *Otolaryngol Head Neck Surg.* 2004;131(6):860-3.
- 10- Butler SG, Stuart A, Castell D, Russell GB, Koch K, Kemp S. Effects of age, gender, bolus condition, viscosity, and volume on pharyngeal and upper esophageal sphincter pressure and temporal measurements during swallowing. *J Speech Lang Hear Res.* 2009;52(1):240-53.
- 11- Canning BJ. Role of nerves in asthmatic inflammation and potential influence of gastroesophageal reflux disease. *Am J Med.* 2001;111 Suppl 8A:13S-17S.
- 12- Canning BJ. Neurokinin3 receptor regulation of the airways. *Vascul Pharmacol.* 2006;45(4):227-34.
- 13- Canning BJ, Chou YL. Cough sensors. I. Physiological and pharmacological properties of the afferent nerves regulating cough. *Handb Exp Pharmacol.* 2009;(187):23-47.
- 14- Chan PY, Davenport PW. Respiratory-related evoked potential measures of respiratory sensory gating. *J Appl Physiol (1985).* 2008;105(4):1106-13.
- 15- Chee C, Arshad S, Singh S, Mistry S, Hamdy S. The influence of chemical gustatory stimuli and oral anaesthesia on healthy human pharyngeal swallowing. *Chem Senses.* 2005;30(5):393-400.
- 16- Cook IJ, Dodds WJ, Dantas RO, Kern MK, Massey BT, Shaker R, et al. Timing of videofluoroscopic, manometric events, and bolus transit during the oral and pharyngeal phases of swallowing. *Dysphagia.* 1989;4(1):8-15.
- 17- Dantas RO, Dodds WJ. Effect of bolus volume and consistency on swallow-induced submental and infrahyoid electromyographic activity. *Braz J Med Biol Res.* 1990;23(1):37-44.
- 18- Dantas RO, Kern MK, Massey BT, Dodds WJ, Kahrilas PJ, Brasseur JG, et al. Effect of swallowed bolus variables on oral and pharyngeal phases of swallowing. *Am J Physiol.* 1990;258(5 Pt 1):G675-81.
- 19- Davenport PW. Clinical cough I: the urge-to-cough: a respiratory sensation. *Handb Exp Pharmacol.* 2009(187):263-76.
- 20- Davenport PW, Bolser DC, Morris KF. Swallow remodeling of respiratory neural networks. *Head Neck.* 2011;33:S8-13.
- 21- Davenport PW, Bolser DC, Vickroy T, Berry RB, Martin AD, Hey JA, et al. The effect of codeine on the Urge-to-Cough response to inhaled capsaicin. *Pulm Pharmacol Ther.* 2007;20(4):338-46.
- 22- Davenport P, Sapienza C, Bolser D. Psychophysical assessment of the Urge-to-Cough. *Eur Respir J.* 2002;12(85):249-53.
- 23- Davenport PW, Vovk A, Duke RK, Bolser DC, Robertson E. The urge-to-cough and cough motor response modulation by the central effects of nicotine. *Pulm Pharmacol Ther.* 2009;22(2):82-9.
- 24- Dick TE, Oku Y, Romaniuk JR, Chorniack NS. Interaction between central pattern generators for breathing and swallowing in the cat. *J Physiol.* 1993;465:715-30.
- 25- Dicipinigaitis PV. Clinical cough III: measuring the cough response in the laboratory. *Handb Exp Pharmacol.* 2009;(187):297-310.
- 26- Doggett DL, Turkelson CM, Coates V. Recent developments in diagnosis and intervention for aspiration and dysphagia in stroke and other neuromuscular disorders. *Curr Atheroscler Rep.* 2002;4(4):311-8.
- 27- Doty RW. Influence of stimulus pattern on reflex deglutition. *Am J Physiol.* 1951;166(1):142-58.
- 28- Eccles R. Central mechanisms IV: conscious control of cough and the placebo effect. *Handb Exp Pharmacol.* 2009(187):241-62.
- 29- Ertekin C. Voluntary versus spontaneous swallowing in man. *Dysphagia.* 2011;26(2):183-92.
- 30- Ertekin C, Aydogdu I. Neurophysiology of swallowing. *Clin Neurophysiol.* 2003;114(12):2226-44.
- 31- Farrell MJ, Cole LJ, Chiapoco D, Egan GF, Mazzone SB. Neural correlates coding stimulus level and perception of capsaicin-evoked urge-to-cough in humans. *Neuroimage.* 2012;61(4):1324-35.
- 32- Feinberg MJ, Knebl J, Tully J, Segall L. Aspiration and the elderly. *Dysphagia.* 1990;5(2):61-71.
- 33- Fernandez HH, Lapane KL. Predictors of mortality among nursing home residents with a diagnosis of Parkinson's disease. *Med Sci Monit.* 2002;8(4):CR241-6.
- 34- Fontana GA, Pantaleo T, Lavorini F, Benvenuti F, Gangemi S. Defective motor control of coughing in Parkinson's disease. *Am J Respir Crit Care Med.* 1998;158(2):458-64.
- 35- Gestreau C, Bianchi AL, Grélot L. Differential brainstem Fos-like immunoreactivity after laryngeal-induced coughing and its reduction by codeine. *J Neurosci.* 1997;17(23):9340-52.
- 36- Gestreau C, Grélot L, Bianchi AL. Activity of respiratory laryngeal motoneurons during fictive coughing and swallowing. *Exp Brain Res.* 2000;130(1):27-34.
- 37- Gestreau C, Milano S, Bianchi AL, Grélot L. Activity of dorsal respiratory group inspiratory neurons during laryngeal-induced fictive coughing and swallowing in decerebrate cats. *Exp Brain Res.* 1996;108(2):247-56.
- 38- Ghosh SK, Pandolfino JE, Zhang Q, Jarosz A, Kahrilas PJ. Deglutitive upper esophageal sphincter relaxation: a study of 75 volunteer subjects using solid-state high-resolution manometry. *Am J Physiol Gastrointest Liver Physiol.* 2006;291(3):G525-31.
- 39- Gorell JM, Peterson EL, Rybicki BA, Johnson CC. Multiple risk factors for Parkinson's disease. *J Neurol Sci.* 2004;217(2):169-74.
- 40- Hamdy S, Aziz Q, Thompson DG, Rothwell JC. Physiology and pathophysiology of the swallowing area of human motor cortex. *Neural plasticity.* 2001;8(1-2):91-7. Epub 2001/09/04.
- 41- Hamdy S, Mikulis DJ, Crawley A, Xue S, Lau H, Henry S, et al. Cortical activation during human volitional swallowing: an event-related fMRI study. *Am J Physiol.* 1999;277(1 Pt 1):G219-25.

- 42- Hegland KW, Bolser DC, Davenport PW. Volitional control of reflex cough. *J Appl Physiol* (1985). 2012;113(1):39-46.
- 43- Hegland KW, Troche MS, Davenport PW. Cough expired volume and airflow rates during sequential induced cough. *Front Physiol*. 2013;4:167.
- 44- Hiss SG, Strauss M, Treole K, Stuart A, Boutilier S. Effects of age, gender, bolus volume, bolus viscosity, and gustation on swallowing apnea onset relative to lingual bolus propulsion onset in normal adults. *J Speech Lang Hear Res*. 2004;47(3):572-83.
- 45- Hiss SG, Treole K, Stuart A. Effects of age, gender, bolus volume, and trial on swallowing apnea duration and swallow/respiratory phase relationships of normal adults. *Dysphagia*. 2001;16(2):128-35.
- 46- Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology*. 1967;17(5):427-42.
- 47- Hoffman MR, Ciucci MR, Mielens JD, Jiang JJ, McCulloch TM. Pharyngeal swallow adaptations to bolus volume measured with high-resolution manometry. *Laryngoscope*. 2010;120(12):2367-73.
- 48- Hutchings HA, Morris S, Eccles R, Jawad MS. Voluntary suppression of cough induced by inhalation of capsaicin in healthy volunteers. *Respir Med*. 1993;87(5):379-82.
- 49- Inamoto Y, Saitoh E, Okada S, Kagaya H, Shibata S, Ota K, et al. The effect of bolus viscosity on laryngeal closure in swallowing: kinematic analysis using 320-row area detector CT. *Dysphagia*. 2013;28(1):33-42.
- 50- Jacob P, Kahrilas PJ, Logemann JA, Shah V, Ha T. Upper esophageal sphincter opening and modulation during swallowing. *Gastroenterology*. 1989;97(6):1469-78.
- 51- Jafari S, Prince RA, Kim DY, Paydarfar D. Sensory regulation of swallowing and airway protection: a role for the internal superior laryngeal nerve in humans. *J Physiol*. 2003;550(Pt 1):287-304.
- 52- Jean A. Brain stem control of swallowing: neuronal network and cellular mechanisms. *Physiol Rev*. 2001;81(2):929-69.
- 53- Jordan D. Central nervous pathways and control of the airways. *Respir Physiol*. 2001;125(1-2):67-81.
- 54- Jordan D, Spyer KM. Brainstem integration of cardiovascular and pulmonary afferent activity. *Prog Brain Res*. 1986;67:295-314.
- 55- Kaji R. Basal ganglia as a sensory gating device for motor control. *J Med Invest*. 2001;48(3-4):142-6.
- 56- Kitagawa J, Nakagawa K, Hasegawa M, Iwakami T, Shingai T, Yamada Y, et al. Facilitation of reflex swallowing from the larynx and pharynx. *J Oral Sci*. 2009;51(2):167-71.
- 57- LaCroix AZ, Lipson S, Miles TP, White L. Prospective study of pneumonia hospitalizations and mortality of U.S. older people: the role of chronic conditions, health behaviors, and nutritional status. *Public Health Rep*. 1989;104(4):350-60.
- 58- Langmore SE, Skarupski KA, Park PS, Fries BE. Predictors of aspiration pneumonia in nursing home residents. *Dysphagia*. 2002;17(4):298-307.
- 59- Langmore SE, Terpenning MS, Schork A, Chen Y, Murray JT, Lopatin D, et al. Predictors of aspiration pneumonia: how important is dysphagia? *Dysphagia*. 1998;13(2):69-81.
- 60- Lavorini F, Pantaleo T, Geri P, Mutolo D, Pistolesi M, Fontana GA. Cough and ventilatory adjustments evoked by aerosolised capsaicin and distilled water (fog) in man. *Respir Physiol Neurobiol*. 2007;156(3):331-9.
- 61- Leech J, Mazzone SB, Farrell MJ. Brain activity associated with placebo suppression of the urge-to-cough in humans. *Am J Respir Crit Care Med*. 2013;188(9):1069-75.
- 62- Leow LP, Beckert L, Anderson T, Huckabee ML. Changes in chemosensitivity and mechanosensitivity in aging and Parkinson's disease. *Dysphagia*. 2012;27(1):106-14.
- 63- Logemann JA, Pauloski BR, Colangelo L, Lazarus C, Fujii M, Kahrilas PJ. Effects of a sour bolus on oropharyngeal swallowing measures in patients with neurogenic dysphagia. *J Speech Hear Res*. 1995;38(3):556-63.
- 64- Lowell SY, Poletto CJ, Knorr-Chung BR, Reynolds RC, Simonyan K, Ludlow CL. Sensory stimulation activates both motor and sensory components of the swallowing system. *Neuroimage*. 2008;42(1):285-95.
- 65- Malandraki GA, Johnson S, Robbins J. Functional MRI of swallowing: from neurophysiology to neuroplasticity. *Head Neck*. 2011;33 Suppl 1:S14-20.
- 66- Malandraki GA, Sutton BP, Perlman AL, Karampinos DC, Conway C. Neural activation of swallowing and swallowing-related tasks in healthy young adults: an attempt to separate the components of deglutition. *Hum Brain Mapp*. 2009;30(10):3209-26.
- 67- Martin RE, Goodyear BG, Gati JS, Menon RS. Cerebral cortical representation of automatic and volitional swallowing in humans. *J Neurophysiol*. 2001;85(2):938-50.
- 68- Martin RE, MacIntosh BJ, Smith RC, Barr AM, Stevens TK, Gati JS, et al. Cerebral areas processing swallowing and tongue movement are overlapping but distinct: a functional magnetic resonance imaging study. *J Neurophysiol*. 2004;92(4):2428-43.
- 69- Mazzone SB, Cole LJ, Ando A, Egan GF, Farrell MJ. Investigation of the neural control of cough and cough suppression in humans using functional brain imaging. *J Neurosci*. 2011;31(8):2948-58.
- 70- Mazzone SB, McGovern AE, Koo K, Farrell MJ. Mapping supramedullary pathways involved in cough using functional brain imaging: comparison with pain. *Pulm Pharmacol Ther*. 2009;22(2):90-6.
- 71- Mazzone SB, McGovern AE, Yang SK, Woo A, Phipps S, Ando A, et al. Sensorimotor circuitry involved in the higher brain control of coughing. *Cough*. 2013;9(1):7.
- 72- Mazzone SB, McLennan L, McGovern AE, Egan GF, Farrell MJ. Representation of capsaicin-evoked urge-to-cough in the human brain using functional magnetic resonance imaging. *Am J Respir Crit Care Med*. 2007;176(4):327-32.
- 73- Mazzone SB, Reynolds SM, Mori N, Kollarik M, Farmer DG, Myers AC, et al. Selective expression of a sodium pump isozyme by cough receptors and evidence for its essential role in regulating cough. *J Neurosci*. 2009;29(43):13662-71.
- 74- Midgren B, Hansson L, Karlsson JA, Simonsson BG, Persson CG. Capsaicin-induced cough in humans. *Am Rev Respir Dis*. 1992;146(2):347-51.
- 75- Miller AJ. Characteristics of the swallowing reflex induced by peripheral nerve and brain stem stimulation. *Exp Neurol*. 1972;34(2):210-22.
- 76- Miller AJ. Neurophysiological basis of swallowing. *Dysphagia*. 1986;1:91-100.
- 77- Mosier K, Patel R, Liu WC, Kalnin A, Maldjian J, Baredes S. Cortical representation of swallowing in normal adults: functional implications. *Laryngoscope*. 1999;109(9):1417-23.
- 78- Mu L, Sanders I. Sensory nerve supply of the human oro- and laryngopharynx: a preliminary study. *Anat Rec*. 2000;258(4):406-20.
- 79- O'Rourke A, Morgan LB, Coss-Adame E, Morrison M, Weinberger P, Postma G. The effect of voluntary pharyngeal swallowing maneuvers on esophageal swallowing physiology. *Dysphagia*. 2014;29(2):262-8.
- 80- Park JW, Kim Y, Oh JC, Lee HJ. Effortful swallowing training combined with electrical stimulation in post-stroke dysphagia: a randomized controlled study. *Dysphagia*. 2012;27(4):521-7.
- 81- Pecova R, Javorkova N, Kudlicka J, Tatar M. Tussigenic agents in the measurement of cough reflex sensitivity. *J Physiol Pharmacol*. 2007;58 Suppl 5(Pt 2):531-8.
- 82- Perlman AL, Schultz JG, VanDaele DJ. Effects of age, gender, bolus volume, and bolus viscosity on oropharyngeal pressure during swallowing. *J Appl Physiol* (1985). 1993;75(1):33-7.
- 83- Pitts T, Bolser D, Rosenbek J, Troche M, Sapienza C. Voluntary cough production and swallow dysfunction in Parkinson's disease. *Dysphagia*. 2008;23(3):297-301.
- 84- Pitts T, Morris K, Lindsey B, Davenport P, Poliacsek I, Bolser D. Co-ordination of cough and swallow *in vivo* and *in silico*. *Exp Physiol*. 2012;97(4):469-73.

- 85- Pitts T, Rose MJ, Mortensen AN, Poliacek I, Sapienza CM, Lindsey BG, et al. Coordination of cough and swallow: a meta-behavioral response to aspiration. *Respir Physiol Neurobiol*. 2013;189(3):543-51.
- 86- Pitts T, Troche M, Mann G, Rosenbek J, Okun MS, Sapienza C. Using voluntary cough to detect penetration and aspiration during oropharyngeal swallowing in patients with Parkinson disease. *Chest*. 2010;138(6):1426-31.
- 87- Plevkova J, Brozmanova M, Pecova R, Tatar M. Effects of intranasal capsaicin challenge on cough reflex in healthy human volunteers. *J Physiol Pharmacol*. 2004;55(Suppl 3):101-6.
- 88- Saito Y, Ezure K, Tanaka I, Osawa M. Activity of neurons in ventrolateral respiratory groups during swallowing in decerebrate rats. *Brain Dev*. 2003;25(5):338-45.
- 89- Sant'Ambrogio G, Sant'Ambrogio FB. Role of laryngeal afferents in cough. *Pulm Pharmacol*. 1996;9(5-6):309-14.
- 90- Shannon R, Baekey DM, Morris KF, Li Z, Lindsey BG. Functional connectivity among ventrolateral medullary respiratory neurones and responses during fictive cough in the cat. *J Physiol*. 2000;525(Pt 1):207-24.
- 91- Shannon R, Baekey DM, Morris KF, Lindsey BG. Brainstem respiratory networks and cough. *Pulm Pharmacol*. 1996;9(5-6):343-7.
- 92- Shannon R, Baekey DM, Morris KF, Lindsey BG. Ventrolateral medullary respiratory network and a model of cough motor pattern generation. *J Appl Physiol* (1985). 1998;84(6):2020-35.
- 93- Shannon R, Baekey DM, Morris KF, Nuding SC, Segers LS, Lindsey BG. Production of reflex cough by brainstem respiratory networks. *Pulm Pharmacol Ther*. 2004;17(6):369-76.
- 94- Shaw SM, Martino R. The normal swallow: muscular and neurophysiological control. *Otolaryngol Clin North Am*. 2013;46(6):937-56.
- 95- Shill H, Stacy M. Respiratory function in Parkinson's disease. *Clin Neurosci*. 1998;5(2):131-5.
- 96- Simonyan K, Saad ZS, Loucks TM, Poletto CJ, Ludlow CL. Functional neuroanatomy of human voluntary cough and sniff production. *Neuroimage*. 2007;37(2):401-9.
- 97- Sinclair WJ. Role of the pharyngeal plexus in initiation of swallowing. *Am J Physiol*. 1971;221(5):1260-3.
- 98- Singer RB. Mortality in patients with Parkinson's disease treated with dopa. *J Insur Med*. 1992;24(2):126-7.
- 99- Smith JA, Aliverti A, Quaranta M, McGuinness K, Kelsall A, Earis J, et al. Chest wall dynamics during voluntary and induced cough in healthy volunteers. *J Physiol*. 2012;590(Pt 3):563-74.
- 100- Soros P, Lalone E, Smith R, Stevens T, Theurer J, Menon RS, et al. Functional MRI of oropharyngeal air-pulse stimulation. *Neuroscience*. 2008;153(4):1300-8.
- 101- Smith Hammond CA, Goldstein LB, Horner RD, Ying J, Gray L, Gonzalez-Rothi L, et al. Predicting aspiration in patients with ischemic stroke: comparison of clinical signs and aerodynamic measures of voluntary cough. *Chest*. 2009;135(3):769-77.
- 102- Storey AT. A functional analysis of sensory units innervating epiglottis and larynx. *Exp Neurol*. 1968;20(3):366-83.
- 103- Storey AT, Johnson P. Laryngeal water receptors initiating apnea in the lamb. *Exp Neurol*. 1975;47(1):42-55.
- 104- Taniguchi H, Tsukada T, Ootaki S, Yamada Y, Inoue M. Correspondence between food consistency and suprahyoid muscle activity, tongue pressure, and bolus transit times during the oropharyngeal phase of swallowing. *J Appl Physiol* (1985). 2008;105(3):791-9.
- 105- Ternesten-Hasséus E, Johansson K, Löwhagen O, Millqvist E. Inhalation method determines outcome of capsaicin inhalation in patients with chronic cough due to sensory hyperreactivity. *Pulm Pharmacol Ther*. 2006;19(3):172-8.
- 106- Theurer JA, Bihari F, Barr AM, Martin RE. Oropharyngeal stimulation with air-pulse trains increases swallowing frequency in healthy adults. *Dysphagia*. 2005;20(4):254-60.
- 107- Theurer JA, Czachorowski KA, Martin LP, Martin RE. Effects of oropharyngeal air-pulse stimulation on swallowing in healthy older adults. *Dysphagia*. 2009;24(3):302-13.
- 108- Troche MS, Okun MS, Rosenbek JC, Altmann LJ, Sapienza CM. Attentional resource allocation and swallowing safety in Parkinson's disease: a dual task study. *Parkinsonism Relat Disord*. 2014;20(4):439-43.
- 109- Van den Bergh O, Van Diest I, Dupont L, Davenport PW. On the psychology of cough. *Lung*. 2012;190(1):55-61.
- 110- Vovk A, Bolser DC, Hey JA, Danzig M, Vickroy T, Berry R, et al. Capsaicin exposure elicits complex airway defensive motor patterns in normal humans in a concentration-dependent manner. *Pulm Pharmacol Ther*. 2007;20(4):423-32.
- 111- Wheeler-Hegland K, Ashford J, Frymark T, McCabe D, Mullen R, Musson N, et al. Evidence-based systematic review: oropharyngeal dysphagia behavioral treatments. Part II - impact of dysphagia treatment on normal swallow function. *J Rehabil Res Dev*. 2009;46(2):185-94.
- 112- Wheeler-Hegland K, Huber JE, Pitts T, Davenport PW, Sapienza CM. Lung volume measured during sequential swallowing in healthy young adults. *J Speech Lang Hear Res*. 2011;54(3):777-86.
- 113- Wheeler-Hegland KM, Huber JE, Pitts T, Sapienza CM. Lung volume during swallowing: single bolus swallows in healthy young adults. *J Speech Lang Hear Res*. 2009;52(1):178-87.
- 114- Wheeler-Hegland KM, Pitts T, Davenport PW. Cortical gating of oropharyngeal sensory stimuli. *Front Physiol*. 2011;1:167.
- 115- Widdicombe J. The race to explore the pathway to cough: who won the silver medal? *Am J Respir Crit Care Med*. 2001;164(5):729-30.
- 116- Widdicombe J, Singh V. Physiological and pathophysiological down-regulation of cough. *Respir Physiol Neurobiol*. 2006;150(2-3):105-17.
- 117- Widdicombe JG. Receptors in the trachea and bronchi of the cat. *J Physiol*. 1954;123(1):71-104.
- 118- Widdicombe JG, Tatar M. Upper airway reflex control. *Ann N Y Acad Sci*. 1988;533:252-61.
- 119- Wilson-Pauwels L, Akesson E, Stewart PA. Cranial nerves: anatomy and clinical comments. Ontario: BC Decker Inc; 1988. p.113-137.
- 120- Yamada S, Ebihara S, Ebihara T, Yamasaki M, Asamura T, Asada M, et al. Impaired urge-to-cough in elderly patients with aspiration pneumonia. *Cough*. 2008;4:11.