

AIRWAY PROTECTION IN HEALTHY AND DISEASE

By

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To my nieces, I expect one day to be at your dissertation defenses

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LIST OF ABBREVIATIONS

CN IX	Glossopharyngeal cranial nerve
CN X	Vagus cranial nerve
CPD	Compression phase duration, the time from the end of the inspiratory phase to the beginning of the expiratory phase
CVA	Cough volume acceleration, EPPF/EPRT
EEG	Electroencephalography
EMG	Electromyography
ERP	Event related potential
EPRT	Expiratory rise time, the time from the beginning of the expiratory phase to the peak expiratory flow
EPPF	Expiratory phase peak airflow, the peak airflow during the expiratory phase of the cough
GenHy	Geniohyoid
L-Dopa	Levodopa
OOT	Oral Transit Time
P/A Scale	Penetration/ Aspiration Scale
PSEP	Pharyngeal stimulation evoked potential
PTT	Pharyngeal Transit Time
RREP	Respiratory related evoked potential
ROC	Receiver operator curves
S1	First stimulus
S2	Second stimulus
S2/S1	Second stimulus divided into the first stimulus
SD	Standard deviation
SLN	Superior laryngeal nerve

ThAr	Thyroarytenoid
ThPh	Thyropharyngus
TST	Total Swallow Time
VFSE	Videofluorographic examination of swallow

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AIRWAY PROTECTION IN HEALTHY AND DISEASE

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This dissertation represents a collection of works that define a thematic path for describing airway protection in both health and disease. Study 1 defines the effects of Parkinson's disease (PD) impairment on the ability to clear the airway when suffering with swallow dysfunction known as dysphagia. Study 2 defines cough function as a predictor of dysphagia in those with Parkinson's disease which provides outcomes on the discriminative ability of voluntary cough using airflow characteristics to model airway compromise. Studies 3 examines the outcome of an intervention paradigm for improving cough and swallow function in PD in order to disseminate whether these functions respond to remediation. The three studies collectively provide insight into the potential overlapping neural control network involved in airway protection. As a collection of outcomes they lend credence to the development of an animal model which can specifically examine behavioral changes that accompany manipulation of the breathing, cough, swallow interface. Ultimately, study of the neuronal pools involved in motor and control of these subsystems will allow for a better understanding of how each system might be manipulated with pharmacological, medical or behavioral means. Study 4 extends the focus on motor control to that of the sensory system, for its role in providing

feedback in swallow function. Using cortical evoked potentials, this study examined the pharyngeal sensory system in response to airpuff stimulation to determine if PD resulted in diminished response compared to control and whether this diminished response related to dysphagia. Finally, Study 5 moved toward the development of the animal model, and to determine if tracheal stimulation affects the pharyngeal phase of swallow.

CHAPTER 1 INTRODUCTION

Parkinson's Disease

Parkinson's disease (PD) is a neurodegenerative disease with an occurrence rate of 1% for those over 50 years of age and 10% for those over 60 years of age in North America (Shulman, Taback, Bean, & Weiner, 2001; Stern et al., 1993; Young, 1999). Traditionally defined as a nigrostriatal disease affecting just neuronal systems which are processed through the basal ganglia, PD is now believed to affect other anatomical structures such as the hippocampus, hypothalamus, medulla, mesopontine, substance p neurons, etc (Braak et al., 2003; Braak, Rub, Gai, & Del Tredici, 2003).

Traditional evaluation for the diagnosis of PD focuses on the motor symptoms (see description below), however non-motor symptoms such as: neuropsychiatric (McDonald, Richard, & DeLong, 2003; Shulman, et al., 2001; Veazey, Aki, Cook, Lai, & Kunik, 2005), sleeping disturbances (Lees, Blackburn, & Campbell, 1988; Tandberg, Larsen, & Karlsen, 1998), autonomic changes (e.g. hypotension, gastrointestinal issues, etc), (Goldstein, 2006; Sharabi et al., 2006; Shulman, et al., 2001) and alterations to the sensory system have an occurrence rate of up to 88% (Shulman, et al., 2001; Simuni & Sethi, 2008).

Motor symptoms include bradykinesia (slowness of movement), tremor, rigidity, postural abnormalities (Bolser, Poliacek, Jakus, Fuller, & Davenport, 2006;. Fontana, T. Pantaleo, F. Lavorini, F. Benvenuti, & S. Gangemi, 1998; Marsden, 1994a, 1994b), respiratory difficulty (including disrhythmias) (De Keyser & Vincken, 1985; G. A. Fontana, et al., 1998) respiratory muscle weakness (de Bruin, de Bruin, Lees, & Pride, 1993; Fontana, et al., 1998) and laryngeal muscle abnormalities (Fontana, et al., 1998).

Alternatively, sensory symptoms include the presence of general pain (Seiss, Praamstra, Hesse, & Rickards, 2003), sensation of burning in the mouth (Seiss, et al., 2003), loss of sense of smell in 70-100% of patients depending on the study and disease stage (Seiss, et al., 2003), changes in visual function, akathisia (inability to sit still) (Seiss, et al., 2003), increased dependence on visual information due to loss of proprioception (Hore, Meyer-Lohmann, & Brooks, 1977; Seiss, et al., 2003), impaired roughness discrimination (Sathian, Zangaladze, Green, Vitek, & DeLong, 1997; Seiss, et al., 2003), loss of proprioception in the wrist due to impairments in afferent processing induced by tendon vibration (Rickards & Cody, 1997; Seiss, et al., 2003), decreased activation of sensorimotor response to vibratory stimulation of the metacarpal joint of the index finger (Boecker et al., 1999; Seiss, et al., 2003) and a decrease of inhibition of the blink reflex recovery in response to a sensory stimuli (Berardelli, Rothwell, Thompson, & Hallett, 2001; Valls-Sole et al., 1994).

Swallowing

Dysphagia (swallowing disorders) can result from motor or sensory abnormalities (Ertekin, Kiylioglu, Tarlaci, Keskin, & Aydogdu, 2000; Ertekin & Palmer, 2000; Miller, 1982, 2008; Miller et al., 2008; Teismann et al., 2007). Throughout the progression of PD up to 100% of individuals experience some form of dysphagia (Bird, Woodward, Gibson, Phyland, & Fonda, 1994; Monte, da Silva-Junior, Braga-Neto, Nobre e Souza, & de Bruin, 2005). Currently, aspiration pneumonia is the leading cause of death (Fernandez & Lapane, 2002; Schiermeier, Schafer, Schafer, Greulich, & Schlafke, 2001; Shill & Stacy, 1998) and is caused by food, liquid, oral secretions, etc., entering the lungs/lower airway, which is not adequately removed by respiratory reflexes (cough, expiratory reflex, huffing, throat clear, etc.) or action of the ciliary system within the

lungs. Aspiration (bolus falling below the glottis) can be caused by dysphagia during the swallowing of voluntary ingested material or by the lack of swallow initiation (due to unknown changes in the pharynx), which allows material to spill over from the pyriform sinuses or vallecular spaces into the glottal space during rest (Logemann, 1998).

Respiratory reflexes in healthy individuals are initiated by chemoreceptors, mechanoreceptors, or cough receptors located within the laryngeal tissue or tracheal tissue to remove the “unwanted” material. Yet, the evidence that those with PD are silent aspirators, meaning following the penetration or aspiration the patient does not respond with a cough, expiratory reflex, or huffing, etc., puts them at significant swallow safety risk (Addington, Stephens, & Gilliland, 1999; Bolser & Davenport, 2002; Bolser, et al., 2006; Davenport et al., 2007; G. Fontana & Widdicombe, 2004; Fontana & Lavorini, 2006; Lavorini, Fontana, et al., 2007; Lavorini, Pantaleo, et al., 2007; McCool & Leith, 1987).

Phases of Swallow in a Healthy Adult

The phases of swallow are presented for purposes of review. Swallow occurs across three distinct phases referred to as the oral, pharyngeal and esophageal phases. The oral phase can be divided into two stages: oral preparatory and oral. The oral preparatory stage begins with sensory recognition from the visual, proprioceptive, olfactory, etc., systems that indicate that food is approaching and entering the mouth (Logemann, 1998). The second step of the oral preparatory stage includes oral manipulation of the bolus i.e. chewing, and the formation of the bolus on the tongue. This stage is highly dependent upon the bolus size and consistency (Logemann, 1998; Miller, 2008; Miller, et al., 2008). Once the bolus is formed, the movement of the bolus to the back of the mouth is referred to as the oral phase (Logemann, 1998). It begins

with the posterior movement of the tongue and ends when the bolus is moved past the posterior faucial pillars, which initiates the pharyngeal phase of swallowing. Following the pharyngeal phase of swallowing (explained in detail below) the bolus is moved by the esophagus into the stomach. This action of the smooth muscle (peristolic wave) is the final phase of swallowing, known as the esophageal phase (Logemann, 1998).

The Pharyngeal Phase of Swallowing (in Human and Animal Models)

Pattern generation

Originally hypothesized by Meltzer (Meltzer, 1907a, 1907b) the idea of a central pattern generator for the pharyngeal phase of swallowing has been accepted. Since then, the ideas of supramedullary inputs and afferent feedback from the oral and pharyngeal regions have been added to the original model of the central pattern generator for swallowing (Jean, 2001). Jean (2001) described the swallowing central pattern generator location to be in the brainstem, specifically the medulla oblongata. Experiments in animal models (including rabbit, cat, and dog) have confirmed this hypothesis, and additional data on swallow function with the removal of the forebrain, cerebellum and pons resulted in no change in the motor output demonstrating that the neuronal input for the generation of the swallow pattern is contained within the medulla (Jean, 2001). Jean (Jean, 1984; Jean, 2001) discussed a circuit of afferent input coming into the dorsal swallow group in the nucleus tract solatrius (NTS) with interneurons relaying information to the ventral swallow group in the ventrolateral medulla (VLM). The ventral swallow group has interneurons relaying information to the motor nuclei of cranial nerves (CN) V (trigeminal), VII (facial), X (vagus), XII (hypoglossal), the nucleus ambiguus (NA), and C1-C3. However in the awake human the higher level cortical system cannot be ignored as fMRI data has revealed that multiple higher cortical areas

are involved in the voluntary initiation of swallowing, and lesions in these areas result in dysphagia (S. Hamdy, Aziz, Rothwell, Hobson, & Thompson, 1998; S. Hamdy, Mikulis, et al., 1999; S. Hamdy, Rothwell, et al., 1999; Lowell et al., 2008; R. Martin et al., 2007; R. E. Martin, Goodyear, Gati, & Menon, 2001; R. E. Martin et al., 2004; Zald & Pardo, 1999). Jean (2001) described information from supramedullary input coming into the dorsal swallow group in the NTS which was then relayed through the ventral swallow group to the above listed motor nuclei.

Within the brainstem

Lu, Zhang, Neuman, and Bieger (1997) showed that neurons in the NTS receive input from the oral cavity, pharynx and larynx through cranial nerves IX and X and have interneurons which discharge during the pharyngeal phase of swallowing. The reticular formation around the NA has neurons that discharge during the pharyngeal phase of swallowing (Miller, 2008). Regions of the NA have neurons with longitudinal bundling, which Miller (Miller, 2008) suggests as a mechanism for the coordinated motor neuron activation for the muscles activated during the pharyngeal phase of swallowing. Information traveling along the cortical bulbar tract to the NA, etc., is then sent out through cranial nerves IX and X. Cranial nerves IX and X (vagus) exit the medulla laterally to innervate muscles of the pharynx and larynx.

Higher cortical areas controlling the pharyngeal phase of swallowing

Afferent and efferent activity during the pharyngeal phase of swallowing is believed to be lateralized and asymmetrical (Hamdy, Mikulis, et al., 1999; Hamdy, Rothwell, et al., 1999; Miller, et al., 2008; K. Mosier & Bereznaya, 2001; K. Mosier et al., 1999; K. M. Mosier, Liu, Maldjian, Shah, & Modi, 1999) with no distinct relationship to hand or language dominance. Functional MRI of voluntary swallowing in humans

demonstrates activity in cortical areas including: primary motor cortex, supplementary motor cortex, inferior precentral gyrus (which can initiate swallowing with electrical stimulation), primary sensory cortex, cingulate cortex, insula (hypothesized to process afferent information and with lesions results in delay in swallow initiation), basal ganglia (particularly the putamen), thalamus and cerebellum (hypothesized to contribute to the coordination and timing) (Hamdy, Mikulis, et al., 1999; Hamdy, Rothwell, et al., 1999; Lowell, et al., 2008; R. Martin, et al., 2007; R. E. Martin, et al., 2001; R. E. Martin, et al., 2004; Zald & Pardo, 1999). The wide distribution of neuronal areas, which contribute to voluntary swallowing, may help to explain why injuries or lesions to multiple cortical areas result in dysphagia.

Contribution of the basal ganglia to swallow function

Swallowing is a complex pattern of muscle movement, which relies upon peripheral sensory feedback (Jean, 2001; Miller, 1982, 2008). Studies using functional magnetic resonance imaging demonstrate basal ganglia activation during volitional saliva swallowing (Hamdy, Mikulis, et al., 1999; S. Hamdy, Rothwell, et al., 1999; Lowell, et al., 2008; Martin, et al., 2007; Martin, et al., 2001; Martin, et al., 2004). The basal ganglia is a group of deep cortical structures responsible for modulating movement by regulating upper motor neuron activity (Purves, 2004). Classic literature in PD attributes the motor manifestations of the disease to changes in the basal ganglia (Albin, Young, & Penney, 1989; Denny & Behari, 1999; Lees & Stern, 1983; Marsden, 1994a; Y. Stern, Mayeux, Rosen, & Ilson, 1983). Recent hypotheses have added to that model including the basal ganglia's role in integrating sensory information to modulate motor output (Abbruzzese, 2002). The change in basal ganglia function in the early to late stages of PD may be a large factor in the change of swallow patterning.

Anatomy of the pharyngeal wall

The posterior and lateral portions of the pharyngeal wall are made up of encircling striated muscle fibers. Its embryonic division is from splanchnic mesoblast that is found surrounding the foregut (Bosma, 1957). Humans, in contrast with smaller animals, have longitudinal muscle fibers and have the addition of the stylopharyngeus muscle which works to suspend the pharynx for vertical movement which is necessary during the pharyngeal phase of swallowing (Bosma, 1957; Edgeworth, 1916).

Over laying the muscle is mucosa e.g. (Kitagawa, Shingai, Takahashi, & Yamada, 2002). The innervation of the pharyngeal mucosa is complex. Due to this complex innervation it is referred to as the pharyngeal plexus (Kitagawa, et al., 2002). Mu and Sanders (2000a) stained and dissected the afferent innervation in the mucosa of the lateral and posterior pharyngeal walls in a human cadaver and found that the oropharynx is innervated by the IX-ph and X-ph, which are the pharyngeal branches of cranial nerves IX and X, and the laryngopharynx is innervated by the inferior branch of the superior laryngeal nerve. Afferent fiber density, in humans, varied across the pharyngeal complex, with the naso-pharynx having the least dense innervation and the lateral pharyngeal walls having the highest density. The study also demonstrated that within the oral-pharyngeal region there were large variations in the density of the afferent innervations.

The reflexive motor pattern for the pharyngeal phase of swallowing

The pharyngeal phase of swallowing is a “mostly” reflexive patterned behavior (Miller, 2008). There are several actions that take place during this phase. First, the tongue base retracts and then moves superior and posterior, which in turn directs the bolus toward the pharynx. During the tongue movement there is closure of the

velopharyngeal port. Velopharyngeal closure is important because it allows for a build-up of pressure in the pharynx to help propel the bolus toward the esophagus, and the contact of the soft palate with the back pharyngeal wall prevents the bolus from moving into the nasopharynx (Logemann, 1998; Logemann, Rademaker, Pauloski, Ohmae, & Kahrilas, 1998). The pharynx then has two basic movements: there is elevation of the entire pharynx and then a descending activation of various parts of the pharyngeal muscle to act as a peristaltic wave to move the bolus along. As the pharynx is elevated the larynx elevates. The submental muscles contract to move the hyoid bone and larynx superior and anterior into position under the tongue base (See additional information below) (Logemann, 1998). During the movement of the larynx, the vocal folds and aryepiglottic folds adduct preventing material from entering the lower airway. Additionally, the epiglottis folds over the glottal space to act as another layer of protection from material entering the lower airway. The movement of the larynx also pulls open the superior portion of the esophageal sphincter. Following the contraction of the inferior pharyngeal muscle there is a relaxation of the muscles making up the upper esophageal sphincter. The bolus is then passed into the esophagus.

Movement of the hyoid bone during the pharyngeal phase of swallowing

The hyoid bone is a horseshoe shaped bone, situated between the chin and the thyroid cartilage (Kendall & Leonard, 2001; Kim & McCullough, 2008; Paik et al., 2008). The hyoid bone has ten muscular attachments, eight to the superior portion of the bone and three to the inferior portion (Kendall & Leonard, 2001; Kim & McCullough, 2008; Paik, et al., 2008). The superior muscle attachments move the hyoid anterior and superior and the inferior muscle attachments depress the hyoid bone. During the pharyngeal phase of swallowing, movement of the hyoid bone, and the attached

laryngeal complex, moves the larynx superior (Kendall & Leonard, 2001; Kim & McCullough, 2008; Paik, et al., 2008). This superior movement moves the epiglottis in a forward position, which in turn covers the glottal space. The epiglottic positioning, adduction of the vocal folds, and the adduction of the aryepiglottic folds close the airway to material being swallowed (Kendall & Leonard, 2001; Kim & McCullough, 2008; Paik, et al., 2008).

Alterations of swallow pharyngeal movement pattern with variation in stimuli

Varying sensory stimuli can significantly alter the pharyngeal phase of swallowing. Butler, Postma and Fischer (2004) found increased swallow related apnea during the pharyngeal phase of swallowing with increased bolus volume. Kahrilas and Logemann (1993) demonstrated that larger bolus sizes cause an increased duration of laryngeal elevation and longer hyoid excursion. Additionally, a larger bolus volume led to earlier superior movement of the hyoid and larynx, and the upper esophageal sphincter opened earlier (when compared to a smaller bolus volume), (Cook et al., 1989; Teismann, et al., 2007). Ding et al. (2003) demonstrated increased sEMG activity for salty compared with sweet and sour, and decreased activation time for sweet versus sour boluses. Leow, Huckabee, Sharma and Tooley (2007) demonstrated that sour versus sweet taste increased sEMG activation during swallow and also increased the total swallow time. Logemann et al. (1995) found that in a group of participants with dysphagia, a sour liquid-bolus led to a significant decrease in aspiration events. Hamdy et al. (2003) concluded that if a sour bolus was also cold the benefit (decreased aspiration) was no longer seen. Finally, Chee et al (2005) in a group of young adults found that glucose, citrus, and saline decreased “swallowing speed” compared with

water. These findings demonstrate that afferent feedback modifies the motor pattern of the pharyngeal phase.

Swallow pattern with changes in afferent feedback

Using the Aviv model of sensory stimulation (see below), sensory deficits of the pharyngeal and laryngeal mucosa were one of the main predictors of aspiration in post-stroke patients (Aviv, 1997; Aviv, Liu, Parides, Kaplan, & Close, 2000; Aviv et al., 1996; Aviv, Murry, Zschommler, Cohen, & Gartner, 2005; Aviv, Sacco, Mohr, et al., 1997; Aviv, Sacco, Thomson, et al., 1997). The Aviv model uses a mechanical stimulus (air-puff) directed toward the mucosa overlaying the arytenoid complex, and the participant presses a button when the stimulus is “felt,” or in the case of laryngeal sensation the laryngeal adductory reflex is observed via flexible endoscopy. Studies using anesthesia on the pharyngeal and oral mucosa in healthy adults determined that there is an increase in total swallow duration, (Ertekin, et al., 2000; Teismann, et al., 2007), a decrease in voluntary swallow volume/capacity and in young healthy adults the presence of penetration/aspiration in 5 out of the 12 participants in the study. Additionally, those participants who received lidocaine to the pharyngeal mucosa demonstrated decreased bilateral activation of the sensori-motor cortex suggesting that afferent feedback modifies the motor activation of the pharyngeal phase of swallowing and moreover decreasing sensation causing a reduction in swallow safety (Teismann, et al., 2007).

In PD, the most common symptom described by speech-pathologists in swallow evaluations is a “delay” of the pharyngeal phase of swallowing (Leorard, McKenzie, 2006). The afferent modulated control network initiates the pharyngeal phase of swallowing. In person’s with dysphagia a “delay” in the pharyngeal phase has been

described as the bolus reaching the vallecula sinus before the pharyngeal phase was initiated. Delay of the pharyngeal phase of swallowing is also an indicator for increased penetration or aspiration of material making the patient “at-risk.”

Cough

Cough is a mechanism that protects the airway by generating expiratory airflows that create a “scrubbing” action that removes material from the airway (Mahajan, Singh, Murty, & Aitkenhead, 1994; McCool & Leith, 1987; Ross, Gramiak, & Rahn, 1955; Smith Hammond et al., 2001). A disorder of cough is referred to as dystussia. Healthy individuals produce cough with linear airflow velocities as high as three-fourths of the speed of sound, and airflows of 8-10 L/s thus providing the mechanism for airway clearance (Mahajan, et al., 1994; McCool & Leith, 1987; Ross, et al., 1955; Smith Hammond, et al., 2001). To generate high linear airflow velocities during cough, three distinct phases must occur: an inspiratory phase, a compression phase, involving laryngeal closure and an expiratory phase (Mahajan, et al., 1994; McCool & Leith, 1987; Ross, et al., 1955; Smith Hammond, et al., 2001).

The inspiratory phase, initiated by diaphragmatic muscle activity (Bach et al., 2006; Fontana & Lavorini, 2006; Fontana, et al., 1998) posterior crico-arytenoid and the crico-thyroid muscle activation, expands the thoracic cavity, increasing lung volume allowing inspiratory airflow (Bach, et al., 2006; Fontana & Lavorini, 2006; Fontana, et al., 1998). The inspiratory phase lasts approximately 0.65 seconds with the inspiratory volume varying from 50% of tidal volume to approximately 50% of vital capacity (Pryor, 1999; von Leden, 1965; Widdicombe & Chung, 2007; Yanagihara, 1965). A decreased ability to inflate the lungs decreases the potential expiratory airflow for cough (G. A.

Fontana, et al., 1998; Harris & Lawson, 1968), by creating a suboptimal length-tension relationship for expiratory muscle(s) contraction.

Cough effectiveness is dependent on airflow velocity and greater airflow velocities are achieved with the narrowing of the airways and closing of the glottis (via contraction of the thyroarytenoid and interarytenoid muscles). Following the inspiratory phase there is rapid vocal fold adduction and contraction of the expiratory muscles, including all abdominal muscles with a majority of force production from the internal and external oblique muscles (Fontana, et al., 1998; Harris & Lawson, 1968). The closing of the glottis is known as the compression phase and this phase lasts an average of 0.2 seconds (Fontana & Lavorini, 2006; Fontana, et al., 1998; Harris & Lawson, 1968; Ross, et al., 1955). The compression phase creates high interpleural/ intrathoracic pressures due to the isometric contraction of the expiratory muscles. This allows the muscles to maintain the length-tension relationship necessary to generate the high positive pressures. Vocal fold abduction marks the beginning of the expiratory phase. The rapid opening of the glottis, and the explosive release of expiratory air, generates the initial airflow acceleration and high peak flow rates (Fontana & Lavorini, 2006; Fontana, et al., 1998; Harris & Lawson, 1968; Ross, et al., 1955). Additionally, there is contraction of the smooth muscle in the airway, controlled by the vagus nerve, narrowing the bronchi, decreasing the cross-sectional area within the lungs, creating greater force generation during the expiratory phase (Fontana & Lavorini, 2006; Fontana, et al., 1998; Harris & Lawson, 1968; Laviertes, Smeltzer, Cook, Modak, & Smaldone, 1998; McCool & Leith, 1987; Ross, et al., 1955). The entire cough process is

focused on airway clearing, or creating high shearing forces, to remove material from the airway.

Cough Pattern Generation

Cough pattern generation is located in the medulla, however in awake humans there is higher cortical area involvement as well. Reflexive cough is stimulated by rapidly adapting receptors and C-Fibers in the larynx and trachea mucosa (especially the area of the carina), which terminate on second order neurons in the nucleus tract solitarius, then project to pontine and medullary respiratory groups as well as recruited neurons in other areas of the brainstem (Pantaleo, Bongianini, & Mutolo, 2002). A more recent hypothesis by Bolser, et al (2006) is that neurons which produce the rhythm generation for eupnea reconfigure to produce the rhythm generation for cough. The network was termed a “holoarchial system,” in which each control area is a holon, and acts as a control element. Holons are subservient to lower subsystems or holons, and can be controlled by higher level holons. Portions of neurons that controls Cough and swallow are examples of such holons, in which a behavior is expressed in a orderly fashion and shared neurons are used with the expression of both behaviors (Bolser, et al., 2006).

Cortical Control of Cough

Davenport, Sapienza, and Bolser (2002) and Davenport, et al (2007), demonstrated that cough, in response to a sensory stimulus, has two components, the first being the sensation of the stimulus (or Urge-to-Cough) and the second being the motor cough action. Of importance was the observation that with every cough response, individuals first have an Urge-to-Cough before the motor event. This consistent pattern, observed across all the participants in the above mentioned studies,

supports the hypothesis (Davenport, Bolser, et al., 2007; Davenport, Sapienza, Bolser, 2002) that in conscious humans there is a cognitive component to reflexive cough behavior.

Dystussia and Parkinson's disease

Using abdominal muscle electromyogram (EMG) activity, (Ebihara et al., 2003; Fontana, et al., 1998) found that the peak EMG amplitude of both reflexive and voluntary cough in PD were significantly decreased compared to age-matched controls. These decreases in peak amplitude may be due in part to the presence of bradykinesia affecting the abdominal muscles ability to perform ballistic contractions (Hallett, 1993) or due to chestwall rigidity, poor vocal fold valving (Zang, Jiang & Rahn, 2005) and/or the presence of restrictive or obstructive lung disease. Additionally, Ebihara, et al. (2003) found decreases in cough reflex sensitivity, in response to a citric acid challenge with advanced stages of PD, suggesting that the progression of the disease may not only compromise the intensity of the cough but impair the reflex sensitivity creating an even higher potential level of aspiration risk.

CHAPTER 2 VOLUNTARY COUGH PRODUCTION AND SWALLOW DYSFUNCTION IN PARKINSON'S DISEASE

Introduction

Symptoms¹ of PD may include bradykinesia (slowness of movement), resting tremor, rigidity, postural abnormalities (Fontana, et al., 1998; Marsden, 1994b), respiratory difficulty (including disrhythmias), (De Keyser & Vincken, 1985;. Fontana, et al., 1998), respiratory muscle weakness (de Bruin, et al., 1993; Fontana, et al., 1998), and/or laryngeal muscle abnormalities (Fontana, et al., 1998). Dysphagia (swallowing dysfunction) can occur from the early stages of PD and aspiration pneumonia is reported as the leading cause of death in PD patients (Ebihara, et al., 2003; Nakashima et al., 1997). Dominant symptoms of dysphagia include: decreased oral transit time, poor bolus formation, a delay in the triggering of the pharyngeal phase of the swallow, prolonged opening of the upper esophageal sphincter, and residue in the vallecular and piriform sinuses (Miller, Noble, Jones, & Burn, 2006; Potulska, Friedman, Krolicki, & Sychala, 2003). Robbins, Logemann and Kirshner (Robbins, Logemann, & Kirshner, 1986) proposed that many individuals with PD present as “silent aspirators” with little awareness of their dysphagia symptoms and little or no cough response to aspiration.

Voluntary cough is a mechanism of airway clearance and its relationship to aspiration has been highlighted by Smith, Hammond, Goldstein, Zajac, Gray, Davenport and Bolser (Smith Hammond, et al., 2001). They demonstrated that patients who experienced stroke and severely aspirate had a more impaired voluntary cough compared to non-aspirators who experienced a stroke. Cough protects the airway by

¹ Reprinted with permission from Pitts, Bolser, Rosenbek, Troche, and Sapienza, 2009. Voluntary cough production and swallow dysfunction in Parkinson's disease (page 297-301) Dysphagia (23).

generating expiratory airflows that create a “scrubbing” action, removing material from the airway (Bolser & Davenport, 2002; Fontana & Lavorini, 2006; Smith Hammond, et al., 2001). To generate high linear airflow velocities during voluntary cough, three distinct phases are needed: an inspiratory phase (involving chest wall and laryngeal inspiratory muscles), a compression phase (involving laryngeal closure and abdominal expiratory muscles), and an expiratory phase (involving chest wall and abdominal expiratory muscles). The inspiratory phase, initiated by diaphragmatic muscle activity (Fontana & Lavorini, 2006; Tomori & Widdicombe, 1969) and posterior cricoarytenoid and cricothyroid muscle activation (Fontana & Lavorini, 2006), allows for thoracic cavity expansion and inspiratory airflow (Macklem, 1973). Because of chestwall rigidity, those with PD may have a decreased ability to inflate the lungs, decreasing the potential to generate expiratory airflow for cough (Bach, 1993). Decreases in cough reflex sensitivity, in response to a citric acid challenge with advanced stages of PD, suggest that the progression of the disease may not only compromise the intensity of the cough but impair the reflex sensitivity contributing to an even higher potential level of aspiration risk (Ebihara, et al., 2003). While it is recognized that a voluntary cough maneuver is distinct from a reflexive cough, recent research suggests that a cough elicited by sensory stimulation is not entirely reflexive in an awake human. Davenport, Sapienza, and Bolser (2002) & Davenport, et al (2007), demonstrated that cough, in response to a sensory stimulus, has two components, the first being the sensation of the stimulus (or Urge-to-Cough) and the second being the motor cough action. Of importance was the observation that with every cough response, individuals first have an Urge-to-Cough before the motor event. This consistent pattern, observed across all the participants in

the above mentioned studies, supports the hypothesis (Davenport, et al., 2007; Davenport, Sapienza, Bolser, 2002) that in conscious humans there is a cognitive component to reflexive cough behavior.

To date, no study has examined the voluntary cough produced by persons with PD as it relates to the degree of penetration/aspiration defined from videofluorographic examination. It was hypothesized that the voluntary cough airflow patterns in those with PD with known penetration/aspiration would be significantly more impaired than those with no evidence of penetration/aspiration. It was further predicted that an increased duration of the inspiratory and expiratory phases of cough and the laryngeal compression time would exist as well as decreased peak expiratory flows and decreased cough volume acceleration in the group with penetration/aspiration into the larynx. Additionally, it was predicted that the level of penetration/aspiration would positively relate to the voluntary cough flow parameters.

Methods

Group 1 included 10 male participants with PD (average age 67.6) who showed no visual evidence of penetration/aspiration into the laryngeal vestibule during a thin, 30 cc, sequential swallow task. Group 2 included 10 male participants with PD (average age years 72.9) who had, at a minimum penetrated into the laryngeal vestibule during a sequential swallow task of a 30 cc, thin liquid. A qualified speech language pathologist based judgment of degree of penetration/aspiration from the videofluorographic examination of the sequential swallow task. The judge had over 20 years experience in dysphagia. Scores indicating the level of penetration/aspiration were made using the Penetration/Aspiration Scale (22). All of the videofluorographic exams were obtained using the Digital Swallow Station (Model 7200; Kay Elemetrics).

A certified movement disorders neurologist affiliated with the University of Florida Movement Disorders Center made the diagnosis of PD. All participants were staged at Hoehn and Yahr II and III (with one participant in the Group 1 at stage IV) (see Table 2-1). All participants were able to follow 3-4 step directions and none had a history of heart and pulmonary disease, stroke, tobacco use within the last five years and cognitive deficits, including a diagnosis of dementia as determined from a neuropsychological battery of tests. Review of the participants' medical chart revealed that all were on standard medications for treatment of the PD, and none were taking any prescriptive drugs that may have had potential influence on cough production, such as codeine. All videofluorographic examinations and cough productions were sampled in a medication "on" phase. Medication "on" was defined as 60 minutes after the ingestion of the participants' medications. The Institutional Review Board at the University of Florida approved the study (IRB 154-2003).

Voluntary cough measures. Airflow produced during voluntary cough production was sampled using an oral pneumotachograph (MLT 1000, ADInstruments, Inc), connected to a spirometer (ML141, ADInstruments, Inc.). A nose clip occluded nasal airflow (Figure 2-1). The airflow signal was measured and digitized at 1 KHz and displayed using Chart, version 5 for Windows.

The production of voluntary cough for each participant followed a minimum of three cycles of tidal volume breathing. Participants were instructed to take a deep breath and cough hard into the pneumotachograph tube. The investigator visually ensured the lip seal around the pneumotachograph tube during the cough trials, and a

nose clip was used to ensure no air leak. Three voluntary cough trials were produced. All three trials were analyzed for the purpose of this study.

The following measures were made from the cough flow waveform (see Figure 2-1) Inspiratory phase duration (IPD) was defined as the onset of inspiration following tidal volume breathing to the end of inspiration prior to the compression phase (C to D) of cough (A to C). Inspiratory peak flow (IPPF), was defined as the peak inspiratory flow during the inspiratory phase preceding the cough (B). Compression phase duration (CPD) was defined as the time from the end of the inspiratory phase to the beginning of the expiratory phase (C to D). Expiratory rise time (EPRT) was defined as time from the beginning of the expiratory phase to the peak expiratory flow (D to E). Expiratory peak airflow (EP) was defined as the peak airflow during the expiratory phase of the cough (E). Cough volume acceleration (CVA) was defined as the expiratory peak flow/ expiratory phase rise time.

Means and standard deviations were calculated from the three trials of the cough productions. Intra-measurer reliability was calculated on 50% of the dataset for the assessment of penetration/aspiration and 20% of the dataset for the measures of the voluntary cough parameters. Group differences for each of the cough parameters were tested using a one-way Analysis of Variance with a between subject factor of group (1 vs. 2). Spearman rho correlations were used to determine if the penetration/aspiration scale scores were related to the dependent variables extracted from the voluntary cough productions. Significance was set at $p = 0.05$ for all statistical testing

Results

Intra-measurer reliability for the penetration/aspiration scores and the measurements made from the cough flow signals were measured using Intraclass

Correlation Coefficients. The ratings were significant for reliability for the penetration/aspiration scores ($F= 4.400$; $p=.001$) and the measurements from the cough flow signals ($F= 1297.772$; $p<.000$).

Group differences were evident for particular parameters of the cough waveform. Means and standard deviations are in Table 2-2. Group 2 produced longer CPD ($F=35.872$; $p<.001$), slower EPRT ($F=35.223$; $p<.001$), decreased EPPF ($F= 43.559$; $p<.001$), and decreased CVA ($F= 63.651$; $p<.001$). No significant group differences were found for IPD ($F= 2.329$; $p = .132$) or IPPF ($F= 3.073$; $p = .085$). Figure 2-1 demonstrates the distinction in cough airflow patterns for the two groups. Results of the Spearman correlations showed modest but significant relationships between IPPF ($r= -.470$), CPD ($r =.593$), EPRT ($r = .744$), EPPF ($r= -.669$), and CVA ($r = -.808$) relative to the penetration/aspiration scores.

Discussion

In patient groups, reduced peak flows during voluntary cough are considered to be indicative of increased risk of respiratory complications (Addington, et al., 1999; Ebihara, et al., 2003; Smith Hammond, et al., 2001). The results from this study indicated that those with PD, with known swallow dysfunction as defined by degree of penetration/aspiration during a sequential swallow, have impaired voluntary cough. This was evidenced by significant differences in measures of cough parameters made from an airflow signal elicited during voluntary cough. Significant group differences existed for CPD, EPRT, EP, and CVA. Moreover, there were modest correlations between penetration and aspiration scores and voluntary cough airflow parameters, suggesting, that the ability to cough voluntarily is related to the degree of airway protection.

The penetration/aspiration group produced significantly longer CPD and EPRT; the IPD was also increased, although not significantly. A longer CPD and ERPT indicate a general slowing down of the cough related events, diminishing the final ballistic action of the cough. Reduced EP in the penetrator/aspirator group represented this. Group 2's significantly weaker EP reduces the production of "shearing forces" decreasing the ability to adequately clear material from the airway creating greater risk for penetration and/or aspiration. Bach (2006) found in healthy male subjects that expiratory peak airflow during a maximal voluntary cough ranged from 8.3 liters/sec to 11.6 liters/sec. When compared to the results from the present study, six out of 10 of the participants in Group 1 fell within this range, but within Group 2 none of the participants fell within the range. The longer CPD found for Group 2 could have been compensatory for reduced motor drive to the expiratory muscles necessary to aid the build up of subglottal pressure for the cough maneuver. This is speculative, but could be verified by the additional measure of abdominal EMG. It is known that subcortical lesions, like that in PD, could be interrupting the cortical pathways necessary to facilitate a coordinated cough response (23). Braak et al. (2003) found lesions beginning in PD stage I, in the dorsal motor group (within the medulla oblongata) controlling the glossopharyngeal and vagus nerve which allow for the activation of swallowing and the laryngeal activation for cough. The locations of lesions on sites that control both swallow and a portion of cough may be a factor dictating changes to both the swallow and cough function in PD.

Continued studies of voluntary cough and reflexive cough in PD may be helpful in elucidating further the neural control mechanisms of cough and swallow as well as their

relationship. For now, this current study suggests that alterations in voluntary cough may be an indicator of risk for penetration/aspiration, particularly in patient populations with known swallow dysfunction. The utility of voluntary cough as a screening tool for penetration and-or aspiration has interesting potential, but further supposition is limited by the small sample size of this study.

Summary

Dysphagia is a symptom of many neurological conditions, (i.e. stroke, traumatic brain injury, motor neuron disease, pseudobulbar palsy, multiple sclerosis, etc.) (Buchholz, 1994). This study suggests that for some with PD, the ability to produce an effective voluntary cough is impaired. This study revealed differences in cough airflow parameters between those with PD who had videofluorographic evidence of penetration/aspiration and those with PD who did not demonstrate penetration/aspiration.

Table 2-1. Participant demographics. N = 10 in each group. Group 1 consisted of individuals judged to have no videofluorographic evidence of penetration/aspiration and Group 2 consisted of individuals judged to have videofluorographic evidence of penetration/aspiration. [Reprinted with permission from Pitts, Bolser, Rosenbek, Troche, and Sapienza, 2009. Voluntary cough production and swallow dysfunction in Parkinson's disease (page 298, Table 1) Dysphagia (23)]

Participant	Group	Sex	Age	H & Y	PA
1	1	M	58	3	1
2	1	M	68	3	1
3	1	M	61	2	1
4	1	M	49	2.5	1
5	1	M	76	4	1
6	1	M	73	2.5	1
7	1	M	64	2.5	1
8	1	M	72	2.5	1
9	1	M	77	2	1
10	1	M	78	2.5	1
11	2	M	72	3	5
12	2	M	77	2.5	5
13	2	M	72	3	3
14	2	M	74	3	5
15	2	M	78	2.5	8
16	2	M	70	3	3
17	2	M	77	3	2
18	2	M	82	3	7
19	2	M	67	3	3
20	2	M	60	3	5

H & Y is Hoehn Yahr Score
PA is Penetration Aspiration Score

Table 2-2. Means and standard deviations across the three trials for each participant.
 [Reprinted with permission from Pitts, Bolser, Rosenbek, Troche, and Sapienza, 2009. Voluntary cough production and swallow dysfunction in Parkinson's disease (page 300, Table 2) Dysphagia (23)]

Part	IPD	IPPF	EP	EPRT	CPD	CVA
1	.936(.035)	3.071(.641)	9.371(.893)	.249(.893)	.162(.068)	38.110(3.537)
2	.851(.221)	6.761(.389)	10.551(.475)	.165(.019)	.120(.013)	35.685(4.957)
3	.852(.028)	5.483(.347)	11.331(.726)	.325(.062)	.278(.062)	35.685(7.405)
4	1.233(.155)	4.977(.512)	7.920(.306)	.323(.033)	.269(.068)	24.759(3.252)
5	1.176(.078)	2.240(.181)	5.420(.338)	.257(.098)	.217(.094)	23.357(9.337)
6	.841(.072)	4.616(.199)	7.436(.309)	.150(.020)	.111(.030)	50.259(9.277)
7	1.257(.026)	3.195(.087)	9.146(1.813)	.273(.065)	.212(.055)	33.978(5.354)
8	.913(.311)	4.343(.435)	8.015(.286)	.141(.019)	.088(.019)	57.732(9.888)
9	.459(.046)	7.754(.615)	9.227(.367)	.121(.020)	.084(.020)	77.315(11.545)
10	.520(.014)	1.360(6.344)	10.961(.679)	.145(.013)	.096(.021)	75.531(1.892)
11	.906(.145)	4.297(.633)	6.663(1.892)	.557(.366)	.516(.357)	16.570(10.563)
12	1.377(.613)	3.129(1.284)	5.975(.127)	.518(.140)	.372(.122)	12.068(2.933)
13	.929(.111)	4.989(.088)	6.609(.807)	.319(.135)	.262(.126)	22.730(7.725)
14	1.338(.354)	3.029(.692)	4.967(1.463)	.370(.140)	.316(.137)	13.873(2.027)
15	.574(.076)	3.741(.848)	6.381(1.912)	.275(.068)	.245(.068)	24.851(9.756)
16	1.532(.069)	1.806(.176)	6.358(1.610)	.414(.028)	.362(.017)	15.250(3.097)
17	.697(.062)	4.968(.226)	4.720(.081)	.576(.081)	.528(.079)	8.162(1.011)
18	.993(.134)	3.077(.078)	6.000(.236)	.319(.065)	.272(.072)	19.397(4.166)
19	.899(.134)	2.898(.726)	6.594(1.868)	.379(.061)	.358(.057)	16.954(6.163)
20	1.067(.035)	2.900(1.024)	7.470(.559)	.399(.167)	.335(.165)	20.337(5.803)

-Mean (Standard Deviation)
 -Group 1 (participants 1-10)
 -Group 2 (participants 11-20)

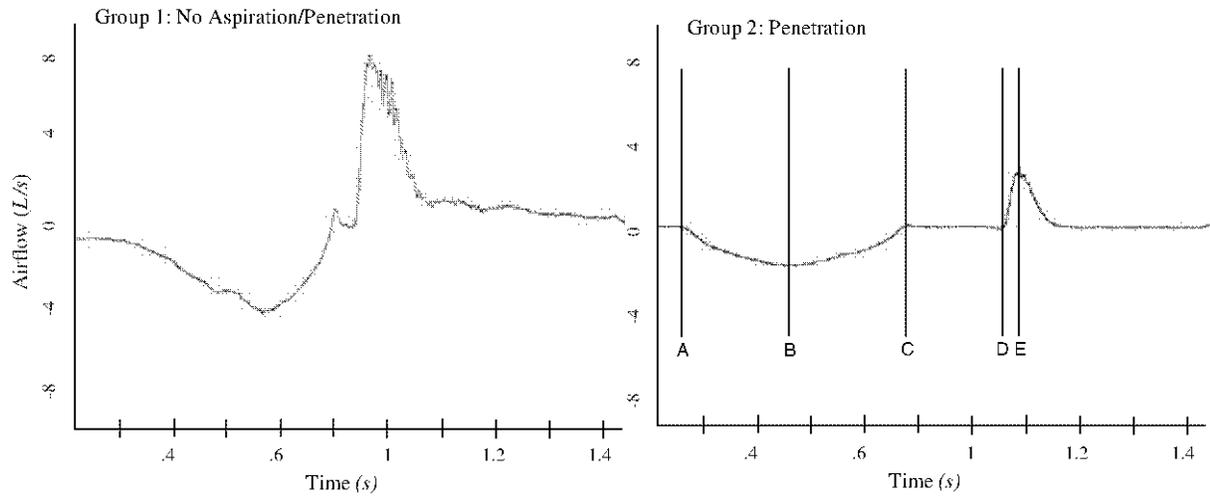


Figure 2-1. Examples of airflow waveforms during a voluntary cough task from Group 1 (no penetration/aspiration) and Group 2 (presence of penetration/aspiration). The vertical lines within the Group 2 waveform denote the phases of the cough waveform: A to C inspiratory phase, C to D compression phase, D to E expiratory rise time. [Reprinted with permission from Pitts, Bolser, Rosenbek, Troche, and Sapienza, 2009. Voluntary cough production and swallow dysfunction in Parkinson's disease (page 299, Figure 1) *Dysphagia* (23)]

CHAPTER 3 UTILIZING VOLUNTARY COUGH TO DETECT PENETRATION AND ASPIRATION DURING SWALLOWING IN PARKINSON'S DISEASE

Introduction

Parkinson's disease (PD) is a nigrostriatal disease (Braak, Del Tredici, et al., 2003; Braak, Rub, et al., 2003) which also affects other neural structures such as the hippocampus, hypothalamus, medulla, mesopontine, substance p neurons, etc (Boecker, et al., 1999; Braak, Del Tredici, et al., 2003; Braak, Rub, et al., 2003). Symptoms associated with PD may include bradykinesia (slowness of movement), tremor, rigidity, postural abnormalities (Fontana, Pantaleo, Lavorini, Benvenuti, & Gangemi, 1998; Marsden, 1994a, 1994b), respiratory muscle weakness and disrhythmias (de Bruin, et al., 1993; De Keyser & Vincken, 1985; Fontana, et al., 1998), and laryngeal muscle defects (Fontana, et al., 1998; Guindi, Bannister, Gibson, & Payne, 1981). Dysphagia, which is characterized in part by a discoordination between respiration and the pharyngeal phase of swallowing, has been considered a strong indicator for aspiration pneumonia risk (Ali et al., 1996; Coates & Bakheit, 1997; Miller, et al., 2008). Currently, aspiration pneumonia is cited as the leading cause of death in PD; moreover, nearly all persons with PD will experience some difficulty with feeding and swallowing (Ebihara, et al., 2003; Nakashima, et al., 1997).

Cough is an airway protective mechanism creating a "scrubbing" action by generating high expiratory airflows to remove unwanted material from the airway (Bolser & Davenport, 2002; Fontana & Lavorini, 2006; Smith Hammond, et al., 2001). To generate high linear airflows during cough, there is a need for three distinct phases: an inspiratory phase (involving chest wall and laryngeal inspiratory muscles), a compression phase (involving laryngeal closure and abdominal expiratory muscles),

and an expiratory phase (involving chest wall and abdominal expiratory muscles). Additionally, during the expiratory phase, the time it takes to achieve the maximum expiration is important because the acceleration of the air during this phase is related to the ability of the cough to remove material from the airway (Bolser & Davenport, 2002; Fontana & Lavorini, 2006; Smith Hammond, et al., 2001).

Several factors associated with the progression of PD, beyond neurological change alone, may impact overall cough effectiveness. Chest wall rigidity may decrease lung inflation, which in turn affects the inspiratory and expiratory phases of the cough production (Bach, 1993). Vocal fold bowing, a common symptom in PD, may cause incomplete glottal closure affecting the build-up of subglottic pressure, the compression phase, and the peak airflow of the expiratory phase (Ramig, Fox, & Sapir, 2004; Yuceturk, Yilmaz, Egrilmez, & Karaca, 2002; Zarzur, Duprat, Shinzato, & Eckley, 2007).

Evaluation of dystussia (disorder of cough) has become an important part of the traditional swallow evaluation (Carnaby-Mann & Lenius, 2008; Horner, Massey, & Brazer, 1990; Logemann, 1998). Methods of analysis such as the integrated electromyographic (IEMG) recordings of surface abdominal muscles (Fontana, et al., 1998; Fontana & Lavorini, 2006) and airflow (Pitts et al., 2008; Smith Hammond et al., 2009; Smith Hammond, et al., 2001; von Leden, 1965) have been used. Pitts et al (2008) previously examined voluntary cough production from an airflow waveform produced by a cohort of twenty male patients with PD. Results of this study revealed that penetration/aspiration into the airway during swallow were associated with an impaired voluntary cough. Additionally, the study revealed significantly longer

compression phase duration (CPD), reduced expiratory phase rise time (EPRT), decreased expiratory phase peak flow (EPPF), and decreased and cough volume acceleration (CVA) when compared to patients with PD who did not exhibit penetration/aspiration. Unfortunately, due to the small cohort size, other analyses could not be conducted. Based on the results of this study, it was hypothesized that in a larger cohort of persons with PD, portions of the voluntary cough airflow analysis (CPD, EPPF, EPRT, and CVA) may be able to detect the presence of penetration/aspiration.

Methods

Fifty-eight participants with idiopathic dopamine responsive PD were included in the study. A neurologist with specialization in movement disorders (author, MSO), determined the diagnosis of PD utilizing the UK Brain Bank Criteria (Gibb & Lees, 1988), and evaluated the disease stage with the Hoehn & Yahr staging (Hoehn & Yahr, 1967). All participants were Hoehn Yahr II-III; oriented to person, place and time; able to complete three step directions; and scored at minimum a twenty-four on the Mini Mental State Examination (Folstein, Folstein, & McHugh, 1975). The exclusionary criteria included history of stroke, pulmonary disease, history of dementia, or tobacco use within the last five years. A review of medications was performed to verify that no participants were taking medication which interfered with cough production (i.e. codeine or morphine). The study protocol was completed with all participants in the “on” medication condition, and participants reported feeling “on” during the time of the examination. The University of Florida institutional review board approved the study (IRB 154-2003).

Equipment and Procedures

Videofluorographic examination of swallow (VFSE). Participants were seated in an upright position and asked to swallow a three ounce thin liquid (Varibar, E-Z-Em) in a continuous manner. A qualified speech language pathologist with extensive training in evaluating VFSE images (author, JR), measured degree of penetration/ aspiration from the VFSE of the sequential swallow task using the Penetration/ Aspiration Scale (PA scale), (see Table 3-1) (Rosenbek, Robbins, Roecker, Coyle, & Wood, 1996). The PA Scale is a measure developed and used by speech-pathologists for the evaluation of pharyngeal dysphagia (Colodny, 2002; Daggett, Logemann, Rademaker, & Pauloski, 2006; Kelly, Drinnan, & Leslie, 2007; Robbins, Coyle, Rosenbek, Roecker, & Wood, 1999; Rosenbek, et al., 1996; Troche, Sapienza, & Rosenbek, 2008), and has been reported as a reliable measure among clinicians with extensive training (Hind et al., 2009; Kelly, Drinnan, & Leslie, 2007). The PA scale was defined as the highest degree of penetration/aspiration as visually judged during the swallow task. All of the VFSE data were archived using the Digital Swallow Station (Model 7200; Kay Elemetrics).

Voluntary cough airflow measures. Airflow produced during voluntary cough production was sampled using an oral pneumotachograph (MLT 1000, ADInstruments, Inc) connected to a spirometer (ML141, ADInstruments, Inc.). A nose clip was placed on participants to occlude nasal airflow during the cough maneuver. The airflow signal was measured and digitized at one KHz and displayed using Chart, version five for Windows. Each airflow sample was low-pass filtered at one hundred fifty Hz within the Chart software program. The signal was calibrated using a known volume and imported into the recording system. The instructions given to participants during the cough measurement included: 1) relax and breathe into the pneumotachograph tube (held by

the researcher) and; 2), “take a deep breath and cough hard,” was verbally instructed following three tidal volume breaths. Each participant completed three separate voluntary cough trials into the pneumotachograph tube. Means and standard deviations were calculated from the three trials of the voluntary cough utilizing four cough airflow measures. The following measures were derived from the cough flow waveform (see Figure 3-1). Compression phase duration (CPD) was defined as the time from the end of the inspiratory phase to the beginning of the expiratory phase. Expiratory rise time (EPRT) was defined as the time from the beginning of the expiratory phase to the peak expiratory flow. Expiratory phase peak airflow (EPPF) was defined as the peak airflow during the expiratory phase of the cough. Cough volume acceleration (CVA) was defined as $EPPF / EPRT$.

Analysis

Initially, intra-rater reliability and inter-rater reliability was calculated on 100% of the dataset for the assessment of PA scale score and 20% of the dataset for the measures of the voluntary cough. Analysis of the psychometric accuracy of the cough measures in discriminating the various degrees of airway compromise on the PA scale score was computed. Sensitivity, specificity and likelihood ratios and receiver operator curves (ROC) were derived. Analysis grouped the dependent variable into three groups to determine if voluntary cough measures from the airflow signal were sensitive and specific to detect differences between no penetration/aspiration and penetration or aspiration. The three groups based on scores from the 3oz sequential swallow task were: no penetration/aspiration (PA 1), presence of penetration (PA 2-5), presence of aspiration (PA 6-8). To evaluate the ability of the various cough airflow measures to

discriminate across the range of PA groupings, ROC's were constructed with a grouping of PA (1) compared with PA (2-8); and PA (1-5) compared with PA (6-8).

ROC curves, with measures of sensitivity and specificity, determine the validity of the screen test to discriminate the presence and absence of the condition. Sensitivity measures the ability of the test to determine a positive test when the condition is present, and specificity measures the ability of the test to determine a negative test when the condition is not present. The ROC curve is a graph of the sensitivity versus 1-specificity, which allows for the selection of the optional point for detection (Fletcher, Fletcher, & Wagner, 1988).

Results

There were 58 participants with PD (52 males and six females). Thirteen of 58 (22%) were judged to penetrate to the level of the vocal folds. Five participants of the 58 overall participants (8.6%) aspirated during the sequential swallow task.

Receiver Operator Curve (ROC) Analysis

ROC curve analysis of the PA score of one versus PA Scale Score of 2-8 resulted in significant results. All four of the cough airflow dependent variables were significant for the detection of penetration/aspiration (see Table 3-2 and Figure 3-2). The cough variable with the greatest significant was the CPD (AUC=.83; $p < .001$), followed by CVA (AUC= .78; $p < .001$), EPPF (AUC= .69; $p= .004$), and EPRT (AUC=.71; $p= .004$) for the discrimination of penetrators/aspirators. ROC analysis of PA score of 1-5 versus of 6-8 resulted in one significant result. EPPF was significant with an AUC of .88 ($p < .001$) (see Table 3-3 and Figure 3- 3).

Discussion

The primary aim of this project was to determine if objective measures derived from an airflow waveform produced during voluntary cough could accurately detect “at-risk” patients with PD. Features of the cough airflow waveform did indeed relate to penetration/aspiration as judged from VFSE during a three ounce swallow task for this particular sample of participants with PD of moderate severity. To our knowledge this is the first study to evaluate the discriminative ability of voluntary cough airflow characteristics to model airway compromise persons with PD. Further understanding of airway compromise is important because if the theorized relationship between impairment in cough and swallow exists, a patient who is aspirating material is at more risk because it is likely their cough is also impaired. Even with our sample size and low event rates for penetration and aspiration, this pilot data provides valuable insights into the role of cough in examining upper airway competency.

All four of the variables (CPD, EFRT, EPPF, and CVA) were successful at accurately detecting penetration and aspiration on the VFSE. EPPF was also successful at accurately detecting the presence of aspiration above chance level. This variable resulted in a fair discriminative ability, AUC (.88). Even with the small rate of aspiration, five of fifty-eight participants (8.6%), it emerged as significant.

Literature on the neural control systems of cough and swallow suggest that these relationships are not a surprise. Oku (1994) demonstrated that neurons which participate in the pattern generator for swallow also participate in the pattern generator for cough. Additionally Braak, et al (Braak, Del Tredici, et al., 2003) found lesions beginning in the early stages of PD in the dorsal motor group (within the medulla) which control the glossopharyngeal and vagus cranial nerves, allowing for the activation of

swallowing and the laryngeal portion of the cough. The location of the lesions on sites that control cough and swallow may be a strong factor in the change in function. Moreover, work examining those with stroke has demonstrated similar results, with ROC curves comparing PA scale scores of 1-4 versus PA scale scores of 5-8 with EPPF (AUC = .86), EPRT (AUC = .93), and CVA (AUC = .92) as significant (Smith Hammond, et al., 2009).

Unfortunately to date these results cannot be expanded to the bedside evaluation of swallowing where cough is evaluated by sound. McCullough, et al.³⁷ examined the bedside evaluation of swallow in patients with stroke and found that when cough sound was perceptually evaluated by coughs sound the strength of sensitivity was 42% and specificity was 79% for the detection of penetration and/or aspiration on a VFSE, and if assessed by quality of the cough the sensitivity was 26% and specificity was 89% (AUC values were not reported in the article). These results suggest that more specific analysis of cough is needed for it to be useful in detecting penetration/aspiration.

For ease of clinical use our focus has turned to EPPF which has been reported to be a strong indicator of swallow change in PD and stroke. It is the only portion of the cough signal that can be easily measured with hand-held peak-flow device that could theoretically be used at a patient's bedside to collect its measurement. Our current studies are focusing on providing clinicians with normative values in multiple clinical populations, to help ascertain risk at bedside. This research may distinguish EPPF as a robust clinical measure which could easily be added to the bedside evaluation of swallowing.

Conclusions

Aspiration pneumonia is the leading cause of death in persons with PD (Ebihara, et al., 2003; Nakashima, et al., 1997). This pilot project is the first to determine the accuracy of detecting presence of penetration/aspiration judged from VFSE during a three ounce swallow task, from changes in airflow waveform measures collected during voluntary cough in PD. Our results demonstrate that the four cough variables accurately detected healthy swallows versus penetration/aspiration. Additionally, EPPF emerged as a measure that may be useful in determining aspiration risk in multiple patient populations. Future studies should examine larger cohorts of patients with a greater diversity of disease severity and the presence of dysphagia, to determine if the value of EPPF will continue to model airway protection, or if a stronger cough feature will emerge.

Table 3-1. Penetration/Aspiration scale (Rosenbek, et al., 1996)

1	Contrast does not enter the airway	No penetration/ aspiration
2	Contrast enters the airway, remains above the vocal folds	Penetration
3	Contrast remains above the vocal folds with visible residue	Penetration
4	Contrast contacts vocal folds, no residue	Penetration
5	Contrast contacts vocal folds, visible residue	Penetration
6	Contrast passes glottis, no subglottic residue	Aspiration
7	Contrast passes glottis, visible subglottic residue despite patient response	Aspiration
8	Contrast passes glottis, visible subglottic residue no patient response	Aspiration

Table 3-2. Results from receiver operator curves analysis penetration/aspiration scale score of 1 versus penetration/aspiration scale score 2-8

	Compression Phase Duration	Expiratory Phase Rise Time	Expiratory Phase Peak Flow	Cough Volume Acceleration
Optimal cut point	0.21	0.06	7.49	84.53
Sensitivity (95% CI)	95.83 (78.9-99.9)	70.83 (48.9-87.4)	87.50 (67.6-97.3)	54.17 (32.8-74.4)
Specificity (95% CI)	64.71 (46.5-80.3)	73.53 (55.6-87.1)	50.01 (32.4-67.6)	97.06 (84.7-99.9)
Likelihood ratio (95% CI)	2.72 (2.10-3.45)	2.68 (01.9-03.7)	1.75 (01.2-02.5)	18.42 (12.7-26.7)
Area under curve (95% CI)	0.83 (0.72-0.92)	0.71 (0.57-0.82)	0.69 (0.56-0.81)	0.78 (0.65-0.88)
Standard error	0.06	0.07	0.07	0.06
Significance Level	$p<.001$	$p=.003$	$p=.004$	$p<.001$

Significance level set at $p=.05$.
 CI (Confidence Interval)

Table 3-3. Results from receiver operator curves analysis penetration/aspiration scale score of 1-5 versus penetration/aspiration scale score of 6-8

	Compression Phase Duration	Expiratory Phase Rise Time	Expiratory Phase Peak Flow	Cough Volume Acceleration
Optimal cut point	0.25	0.06	5.24	115.19
Sensitivity (95% CI)	57.15 (43.2-70.3)	41.07 (28.1-55.0)	85.71 (73.8-93.6)	60.71 (46.8-73.5)
Specificity (95% CI)	100.0 (15.8-100.)	100.0 (15.8-100.)	100.0 (15.8-100.)	100.0 (15.8-100.)
Likelihood ratio (95% CI)	N/A	N/A	N/A	N/A
Area under curve (95% CI)	0.63 (0.49-0.76)	0.59 (0.46-0.72)	0.88 (0.76-0.95)	0.71 (0.58-0.82)
Standard error	0.22	0.19	0.09	0.16
Significance Level	$p=.54$	$p=.61$	$p<.001$	$p=.17$

Significance level set at $p=.05$.

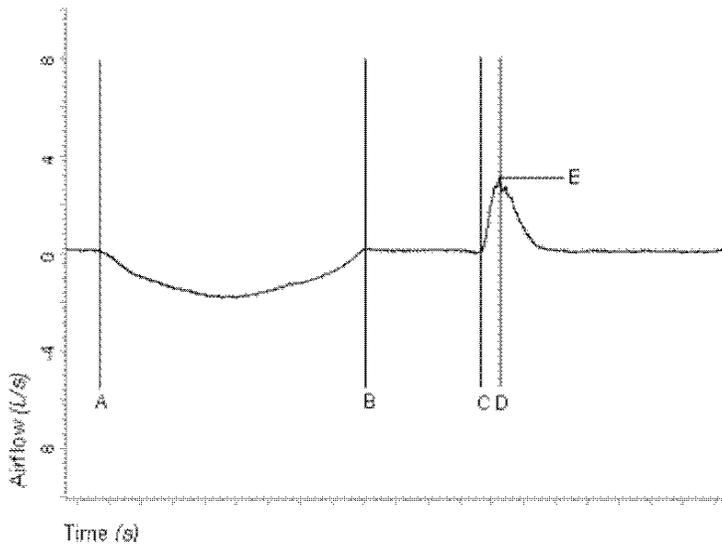


Figure 3-1. Example of airflow waveform produced during a voluntary cough task. The vertical lines denote the phases of the cough waveform: A to C inspiratory phase, C to D compression phase, D to E expiratory rise time

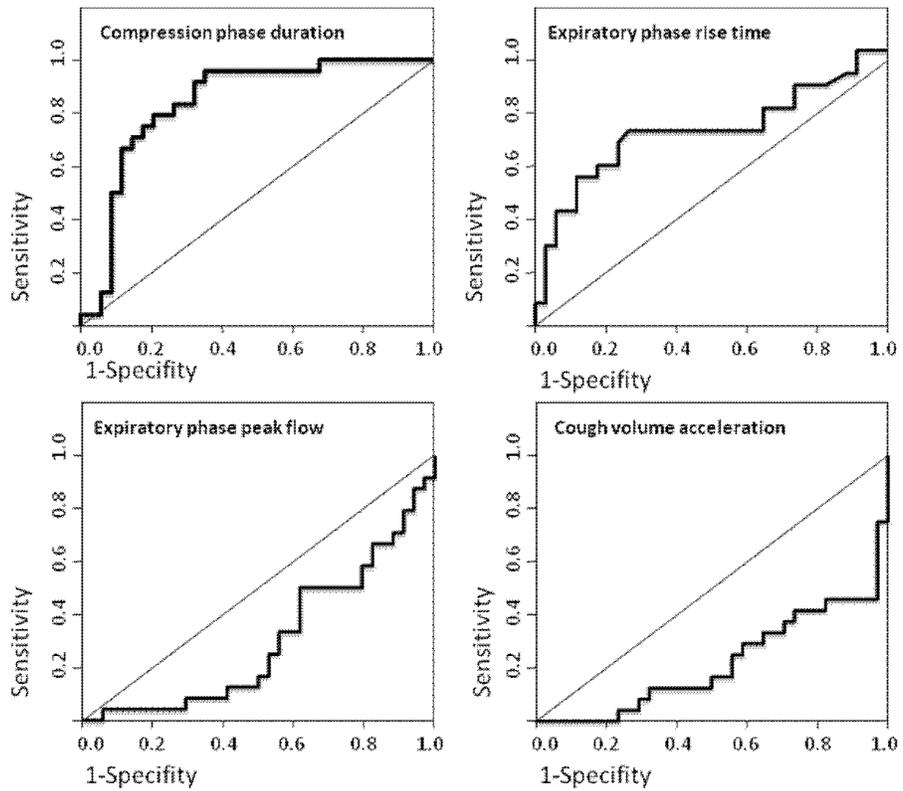


Figure 3-2. ROC analysis for penetration/aspiration scale score of 1 versus PA scale scores of 2-8 (significant cough variables)

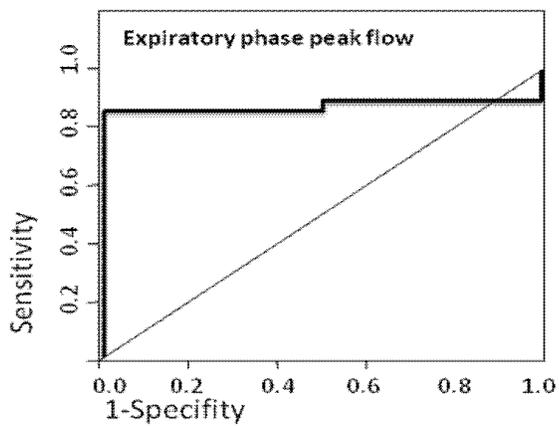


Figure 3-3. ROC analysis for penetration/aspiration scale scores of 1-5 versus PA scale scores 6-8 (significant cough variable)

CHAPTER 4

IMPACT OF EXPIRATORY MUSCLE STRENGTH TRAINING ON VOLUNTARY COUGH AND SWALLOW FUNCTION IN PARKINSON'S DISEASE

Introduction

Cough² is a mechanism of airway clearance that adds to normal ciliary function for the removal of material from the airways (McCool, 2006; McCool & Rosen, 2006).

Comprised of three events, cough production contains an inspiratory effort which is followed by a rapid vocal fold adduction and contraction of the expiratory muscles, including all abdominal muscles with a majority of force production from the internal and external oblique muscles (Ebihara, et al., 2003; G. A. Fontana & Lavorini, 2006; G. A. Fontana, et al., 1998; G. A. Fontana & Widdicombe, 2007; Mahajan, et al., 1994). The dynamic narrowing of the airways and ballistic vocal fold adduction (via contraction of the thyroarytenoid and interarytenoid muscles), allows for the production of high expiratory airflow velocity. The high airflow velocity provides the force to aerosolize material and safely remove it from the lungs (G. A. Fontana & Lavorini, 2006; Macklem, 1973). These events are followed by vocal fold opening to widen the glottis, releasing the high subglottic pressure.

Current treatments that have been promoted to assist airway clearance include: postural drainage (Pryor, 1999; Tucker & Jenkins, 1996); manually assisted cough (Braun, Giovannoni, & O'Connor, 1984; McCool & Rosen, 2006); incentive spirometry (Hall, Tarala, Harris, Tapper, & Christiansen, 1991; Pryor, 1999); percussion and vibration (chest clapping/ shaking) (Bauer, McDougal, & Schoumacher, 1994; Gallon, 1991; Mazzocco, Owens, Kirilloff, & Rogers, 1985; McCool & Rosen, 2006); forced

² Reprinted with permission from Pitts, Bolser, Rosenbek, Troche, Okun and Sapienza, 2009. Impact of expiratory muscle strength training on voluntary cough and swallow function in Parkinson's disease (page 1301-1308) *Chest* (135)5.

expiratory technique also known as huffing (McCool & Rosen, 2006); and active cycle of breathing techniques; (Pryor, 1999; Pryor, Webber, Hodson, & Batten, 1979) etc. Most of these training paradigms include forced expiratory maneuvers. Van Den Eeden, et al. (Van Den Eeden et al., 2003) concluded that this forced expiratory maneuver is an effective component for airway clearance.

In those with PD, it has been reported that aspiration may occur during swallowing, potentially causing pneumonia (Ebihara, et al., 2003; Nakashima, et al., 1997); a leading cause of death in the PD population (Fernandez & Lapane, 2002; Gorell, Johnson, & Rybicki, 1994; Schiermeier, et al., 2001; Shill & Stacy, 1998). Given the high prevalence of morbidity and mortality due to aspiration in PD, treatments focusing on airway protection from aspiration while improving cough effectiveness are ideal.

Fontana et al., (1998) and Ebihara et al., (2003) reported significant decrement in cough function with PD including decreased peak EMG amplitude of abdominal muscles during both reflexive and voluntary cough, and decreases in cough sensitivity necessary for activation of a reflexively induced cough. These changes represent the difficulty that the pulmonary and/or laryngeal systems may have reacting to and eventually removing foreign material from the airway. Furthermore, Pitts et al (2008), demonstrated significant differences in the voluntary induced cough patterns of participants with PD who penetrated/aspirated compared to those with PD who did not. The cough pattern changes also were related significantly to the level of penetration/aspiration during a 30 cc sequential swallow task.

Recently, the authors have examined the use of expiratory muscle strength training (EMST) as a treatment for increasing maximum expiratory pressure generation. Evidence of its benefits following training come from numerous studies including persons with PD (A. Saleem, Sapienza, C., Rosenbek, J., Musson, N., Okun, M., 2005; Saleem, Sapienza, & Okun, 2005; A. F. Saleem, Sapienza, C., Rosenbek, J., Musson, N., Okun, M., 2005; C. Sapienza, 2004), the sedentary elderly (J. Kim & Sapienza, 2005), those with multiple sclerosis (Chiara, Martin, Davenport, & Bolser, 2006; Chiara, Martin, & Sapienza, 2007), instrumentalists (C. M. Sapienza, Davenport, & Martin, 2002), professional voice users (Wingate, Brown, Shrivastav, Davenport, & Sapienza, 2007) and young healthy adults (Baker, Davenport, & Sapienza, 2005).

EMST (EMST 150; Aspire Products; Gainesville, FL) uses a calibrated, one-way, spring-loaded valve to mechanically overload the expiratory muscles. The valve blocks the flow of air until a sufficient expiratory pressure is produced. Once the targeted pressure is produced, the valve opens, and air begins to flow through the device. The physiological load on the targeted muscles can be increased or decreased depending on the device setting. When calibrated to a person's maximum expiratory pressure generation, the load can create a condition which results in peripheral adaptations to the muscle (Adams, Hather, Baldwin, & Dudley, 1993; Lieber, 2002; Powers & Howley, 2004)

By using the device to facilitate the development of greater maximum expiratory pressures following training, the functional ability to develop higher expiratory airflows during cough should result. Preliminary evidence supporting this hypothesis comes from Chiara et al (Chiara, et al., 2006; Chiara, et al., 2007). Compared to other positive

expiratory pressure devices, the EMST device may provide additional benefits (Falk et al., 1984; Pryor, 1999). To achieve the pre-set pressure level and open the valve on the EMST device, the user must produce an isometric muscle contraction. With most other positive expiratory devices, the respiratory load is less, and the manner of the resistance allows the user to simply alter their breathing in a compensatory manner to reach the target. The authors hypothesize that EMST operates by allowing task specific training directed to the “ballistic nature” of voluntary and reflexive cough. This training activity may provide a major advantage in populations like PD, who have difficulty performing high velocity tasks.

It was hypothesized that the voluntary cough airflow pattern in those with PD with known penetration/aspiration would improve significantly pre to post EMST. Specifically, the authors predicted that with training, there would be a decrease in the duration of the inspiratory and compression phases along with the expiratory phase rise time as measured from the cough airflow waveform. Additionally, it was hypothesized that with training, there would be an increase in the peak expiratory flow and cough volume acceleration (a measure relating to the “shearing force” potential). Thirdly it was hypothesized that there would be a significant decrease penetration/ aspiration score, as measured from the videofluorographic examination of the sequential swallow (3 oz) task.

Methods

Ten male participants (60-82 years of age) with PD were included in the study. A neurologist specialized in movement disorders, affiliated with the University of Florida Movement Disorders Center, provided the diagnosis of PD by UK Brain Bank Criteria, and further provided the evaluation disease stage (Hoehn and Yahr, 1967). Mid-stage

PD participants were utilized exclusively Hoehn and Yahr between II and III (see Table 4-1), and these participants had demonstrated videofluorographic evidence of penetration/ aspiration into the laryngeal vestibule during a thin, 30 cc, sequential swallow task. Participants were all oriented to person, place and time, able to follow 2-3 step directions, and scored at least a 24 on the Mini Mental State Examination (M. F. Folstein, S. E. Folstein, & P. R. McHugh, 1975).

All participants reported no history of being treated for pulmonary disease, stroke, tobacco use within the last five years, or a diagnosis of dementia as confirmed by neuropsychological testing. Review of the participants' self-reported medical history at the start of the study determined that all were on standard medications for treatment of PD, and none were taking any medications with a potential influence on cough production, such as codeine. All videofluorographic examinations and voluntary cough productions were sampled in a medication "on" phase. Medication "on" was defined as sixty minutes following the ingestion of the participants' medications. The Institutional Review Board at the University of Florida approved the study IRB# 154-2003.

The participants completed one baseline session, trained with the EMST device (EMST 150; Aspire Products; Gainesville, FL) (see Figure 4-1) for four weeks, and then returned for a post-visit one week following completion of training. During the four week training period, the participants used the device five days per week at home, performing five sets of five breaths through the device for a total of twenty-five breaths per day. The sets were performed sequentially and approximately the same time each training day for four weeks. The trainer was set at 75% of the participant's maximum expiratory

pressure (MEP) (discussed below). The participants were provided with verbal and written instructions for the task.

Videofluorographic examination of swallow (VFSE). Participants were seated in an upright position and asked to swallow a 30 cc, thin bolus (Varibar, E-Z-Em, thin liquid), in a continuous manner. A qualified speech language pathologist, blinded to the experimental condition, measured degree of penetration/ aspiration from the videofluorographic examination of the sequential swallow task using the Penetration/Aspiration Scale (see Table 4-2) (Rosenbek, et al., 1996). The Penetration/Aspiration Scale is a standard measure developed and used by speech-pathologists for the evaluation of pharyngeal dysphagia (Colodny, 2002; Daggett, et al., 2006; A. M. Kelly, et al., 2007; J. Robbins, et al., 1999; Rosenbek, et al., 1996; Troche, et al., 2008). The judge had over twenty years experience in dysphagia. All of the videofluorographic exams were archived using the Digital Swallow Station (Model 7200; Kay Elemetrics).

Maximum expiratory pressure. As an indirect measure of expiratory muscle strength, maximum expiratory pressure (MEP) was determined for each participant. MEP was measured using a pressure manometer (FLUKE 713-30G) coupled to a mouthpiece by a 50 cm, 2 mm inner diameter tubing, with an air-leak achieved with a 14-gauge needle. The participant was asked to stand, a nose clip was used to occlude the nose, and they were then asked to breathe in to total lung capacity and blow hard into the tubing. Three measures of MEP were made until three values were obtained within +5% of one another. The average of the three values was used as the average measure of MEP.

Voluntary Cough Measures. Airflow produced during voluntary cough production was sampled using an oral pneumotachograph (MLT 1000, ADInstruments, Inc), connected to a spirometer (ML141, ADInstruments, Inc.). A nose clip was used to occlude nasal airflow during the cough maneuver. The airflow signal was measured and digitized at 1 KHz and displayed using Chart, version 5 for Windows. Each sample was low-pass filtered at 150 Hz within the Chart software program.

The instruction given to the participants included: 1) Relax and breathe into the pneumotachograph tube (held by the researcher); 2) Following three tidal volume breaths, the participant was asked to breathe deeply and then cough hard; 3) Each participant completed three trials of the voluntary cough. The following measures were made from the cough flow waveform (see Figure 4-2). Inspiratory phase duration (IPD) defined as the onset of inspiration, following tidal volume breathing, to the end of inspiration prior to the compression phase. Compression phase duration (CPD) was defined as the time from the end of the inspiratory phase to the beginning of the expiratory phase. Expiratory rise time (EPRT) was defined as the time from the beginning of the expiratory phase to the peak expiratory flow. Expiratory phase peak airflow (EPPF) was defined as the peak airflow during the expiratory phase of the cough. Cough volume acceleration (CVA) was defined as expiratory peak flow/ expiratory phase rise time.

Means and standard deviations were calculated from the three trials of the cough. Intra-measurer reliability was calculated on 100% of the dataset for the assessment of penetration/aspiration and 20% of the dataset for the measures of the voluntary cough parameters. Pre and post training differences for PA scores, MEP, and the cough

measures were tested using Wilcoxin Signed-Rank test. Significance was set at $p=0.05$ for PA score and MEP but adjusted for the number of comparisons for the cough airflow waveform parameters using the Bonferonni correction procedure because significant relationships existed between the dependent variables ($p= 0.05/5= 0.01$).

Results

Intrameasurer reliability for the penetration/aspiration scores and the measurements made from the cough flow signals was assessed using Intraclass Correlation Coefficients. The ratings were significant for reliability for the penetration/aspiration scores ($\alpha = .56$; $p= 0.001$) and the measurements from the cough flow signals ($\alpha = .70$; $p< 0.001$). Penetration/ aspiration scores pre-post training significantly decreased ($Z= 2.388$; $p= 0.01$) (see Table 4-1). There was a significant increase in MEP ($Z= 2.803$; $p= 0.005$) due to training. The mean MEP before training was 108.2 ± 23.2 and the mean MEP following training was 135.9 ± 37.5 . Pre-post training differences were found for particular parameters of the cough waveform. Means and standard deviations are shown in Table 4-3. There was a reduction (but not significant) in the IPD ($Z= 2.090$; $p= 0.04$). There was a significant reduction in the CPD ($Z= 2.803$; $p= 0.005$), and EPRT ($Z= 2.492$; $p= 0.01$) following the EMST training (see Figure 4-3). Due to the decrease in EPRT, there was a significant increase in Cough VA ($Z= 2.497$; $p= 0.01$) (Figure 4-3 and 4-4). There was no significant training effect for IPPF ($Z= 1.376$; $p= 0.17$) or EPPF ($Z= 0.459$; $p= 0.65$).

Discussion

This study examined the effects of four weeks of EMST on voluntary cough function and the occurrence of penetration/aspiration in a group of persons with PD. The overall effectiveness of the participants' voluntary cough increased, as indicated by

the increase in CVA. CVA relates to the ability of the cough to create shearing forces and remove unwanted material from the airway (Smith Hammond, et al., 2001). Specifically, CPD and EPRT, as measured from the voluntary cough airflow waveform, pre to post training, significantly decreased. The significant decrease in the EPRT led to a significant increase in the CVA. This may be due to the nature of the training task which includes a short duration and isometric contraction of the expiratory muscles to generate the maximum pressure to open the pressure release valve on the device. Specifically, to complete a trial with the EMST device, participants were required to achieve 75% MEP repeatedly on the trainer by producing an expiratory maneuver forcefully. If the task was performed at slower speeds, producing decreased force generation, an inadequate amount of flow would result and the device's valve would not release. The release of the valve with air moving through the trainer is the signal that the trial was successful.

There was no significant increase in EPPF. Rather than simply examining cough magnitude, analysis of the cough pattern provides more information as to the viability of airway clearance, this is so because EPPF is highly dependent on pulmonary function (Ross, et al., 1955) and not entirely on the participant's effort or strength (Loudon & Shaw, 1967). Moreover, a productive cough relies on all three phases to generate the necessary pressures, and acceleration of the gases within the pulmonary system, to achieve shearing forces. Pulmonary function testing revealed that 80% of the participants in this study presented with restrictive lung disease, which is well known in PD (Pal, Sathyaprabha, Tuhina, & Thennarasu, 2007; Sathyaprabha, Kapavarapu, Pall, Thennarasu, & Raju, 2005). A post hoc comparison of pulmonary function pre to post

training revealed no significant training effect on the measures of pulmonary function FEV₁ ($t = -1.115$; $p = 0.29$) or FVC ($t = 1.702$; $p = 0.12$). Thus, potential change in EPPF is limited by the restrictions of the pulmonary system regardless of the participant's effort.

The PA scores, obtained from the videofluorographic examination of participant's 3oz sequential swallow task, significantly decreased. PA scores reflect a clinician's evaluation, of the depth, of material penetrated into the airway, and whether there is a cough or throat clearing response to assist in the removal of the material. See Table 4-2 for a description of the defined criteria used for judging to degree of penetration or aspiration. For example, when penetration/aspiration scores are of a value of 8, this indicates a severe degree of threat to the airway because the material has passed below the level of the vocal folds and was not removed with a reflexive cough. A decrease in the score from pre to post indicates a decrease in the severity of the material entering the laryngeal vestibule or airway and this improvement hypothetically decreases participant risk.

Wheeler, Chiara, and Sapienza (2007) describe the biomechanical events that occur with EMST beyond the exercise of expiratory muscles that could be contributing to reduced PA scores, including increased vertical elevation of the hyoid bone via increased activation of the submental muscles. Vertical elevation of the hyoid bone is important for the pharyngeal phase of swallowing, and lack of coordination or muscle weakness in the submental group results in changes in laryngeal elevation and the opening of the upper esophageal sphincter, all leading to penetration/ aspiration of the bolus into the airway (Kendall & Leonard, 2001; Schultz, Perlman, & VanDaele, 1994;

Wheeler, et al., 2007). It is speculated that the decrease in the PA scores is due in part to a strengthening of the submental muscles that are responsible for elevating the hyoid bone, and thus the larynx which is necessary to close-off the airway during the swallow.

Another possible mechanism for the change in the PA scores post-training is an increase in subglottic air pressure during the swallow. Various studies examining participants with tracheotomy tubes (Dettelbach, Gross, Mahlmann, & Eibling, 1995; Gross, Mahlmann, & Grayhack, 2003; Muz, Mathog, Nelson, & Jones, 1989) demonstrate that closure of the tube during swallow results in a general decrease in the depth of penetration and/or aspiration of the bolus compared to a condition in which the tube was open. The current results demonstrated a significant increase in the MEP pre to post training, and this increase in respiratory pressure generation capacity could have assisted the participants in generating higher subglottal pressures during swallow. However, the amount of pressure needed during a swallow at tidal volume is very low. Diez Gross et al (Gross, Steinhauer, Zajac, & Weessler, 2006) demonstrated (in one healthy participant) that a swallow at tidal volume uses approximately two cm H₂O. A swallow at total lung capacity requires approximately seven to ten cm H₂O. It may be that an increase in the magnitude of MEP does not influence the generation of subglottal pressure needed during swallow in these participants, but induces better coordination in generating subglottal pressure for the swallow task. Strength training, in general, alters the way in which motor units are recruited, the total number of motor units recruited, and the coordination of recruitment. These changes in neural activation are observed clinically not only as improvement in force production, but also in

coordination and precision of movement (Burkhead, Sapienza, & Rosenbek, 2007; Powers & Howley, 2004).

In the future, it would be interesting to determine the relationship between PA scores and timing events such as laryngeal course during swallow and how they relate to changes in voluntary cough pattern with EMST, particularly the relationship between laryngeal closure during swallow and laryngeal compression phase during cough.

Wheeler, et al (2008) demonstrated that those with PD, and who had penetration/aspiration, produced a significantly later maximum laryngeal closure during a single 5 ml swallow. Unfortunately, voluntary cough was not measured in this cohort of participants.

One conclusion from the results could be that the positive effects were due to a practice effect. Early researchers believed that any therapeutic interventions focusing on speech or laryngeal function with PD would fail because of the progressive nature of the disease (Allan, 1970; Sarno, 1968). Sarno (1968) studied over 300 PD participants attempting to develop methods to rehabilitate speech volume, facial mobility, speed of speech, and accuracy of articulation. He was able to demonstrate effects within a treatment session (which lasted 2 hours). However, even with 2 hours a week/ for six weeks, he was unable to establish significant carry-over effects to any of these areas. Later work done by Ramig, et al (1995) into PD demonstrated positive treatment effects when the participants were treated for 50-60 minutes/ 4 times a week, citing significant changes in speech including vocal loudness and articulation. Based on this prior literature, the evaluation time (1 hour then repeated four weeks later) does not meet to

the minimum time threshold to elicit a practice effect. Therefore a larger/longer research protocol would be necessary to achieve this effect.

Conclusions

This study demonstrates clear improvement in cough and swallow, as measured by PA scores, following EMST training, and demonstrates that it is a viable treatment option for PD participants who are at risk for aspiration. Future studies should examine larger cohorts and also a more diverse group of participants, including those in different disease stages, and different gender. Future studies also aim to establish the relationship between PA scores and timing events. These events may include the laryngeal course during a swallow and the relationship to changes in voluntary cough pattern with EMST. We are particularly interested in the relationship between laryngeal closure during swallow and laryngeal compression phase during cough. If findings, from these studies, can be related delaying the morbidity and mortality from aspiration in PD, and to correlate with validated measures of quality of life, the EMST approach may be an appealing approach for participants with PD who exhibit evidence of aspiration.

Table 4-1. Participant demographics and Penetration/Aspiration scores pre-post training. [Reprinted with permission from Pitts, Bolser, Rosenbek, Troche, Okun and Sapienza, 2009. Impact of expiratory muscle strength training on voluntary cough and swallow function in Parkinson's disease (page 1303, Table 1) Chest (135)5]

Participant	Sex	Age	H&Y*	PA*	
				Pre	Post
1	M	72	3	5	3
2	M	77	2.5	5	2
3	M	72	3	3	3
4	M	74	3	5	5
5	M	78	2.5	8	1
6	M	70	3	3	2
7	M	77	3	2	1
8	M	82	3	7	5
9	M	67	3	3	3
10	M	60	3	5	2

*H & Y is Hoehn Yahr Score

*PA is Penetration Aspiration Score

Table 4-2. Penetration/Aspiration scale (Rosenbek, et al., 1996). [Reprinted with permission from Pitts, Bolser, Rosenbek, Troche, Okun and Sapienza, 2009. Impact of expiratory muscle strength training on voluntary cough and swallow function in Parkinson's disease (page 1303, Table 2) Chest (135)5]

Score	Contrast	PA
1	Contrast does not enter the airway	No penetration/aspiration
2	Contrast enters the airway, remains above the vocal folds	Penetration
3	Contrast remains above the vocal folds with visible residue	Penetration
4	Contrast contacts vocal folds, no residue	Penetration
5	Contrast contacts vocal folds, visible residue	Penetration
6	Contrast passes glottis, no subglottic residue	Aspiration
7	Contrast passes glottis, visible subglottic residue despite patient response	Aspiration
8	Contrast passes glottis, visible subglottic residue no patient response	Aspiration

Table 4-3. Means and standard deviations for the voluntary cough measures pre-post training. [Reprinted with permission from Pitts, Bolser, Rosenbek, Troche, Okun and Sapienza, 2009. Impact of expiratory muscle strength training on voluntary cough and swallow function in Parkinson's disease (page 1304, Table 3) Chest (135)5]

Measure	Pre-training Mean (SD)*	Post-training Mean (SD)
IPD	1.02 (0.30)	0.75 (0.27)
CPD	0.32 (0.03)	0.15 (0.01)
EPRT	0.10 (0.04)	0.06 (0.03)
EPPF	6.54 (0.84)	6.77 (1.09)
Cough VA	80.63 (28.3)	165.35 (87.7)

(SD): standard deviation

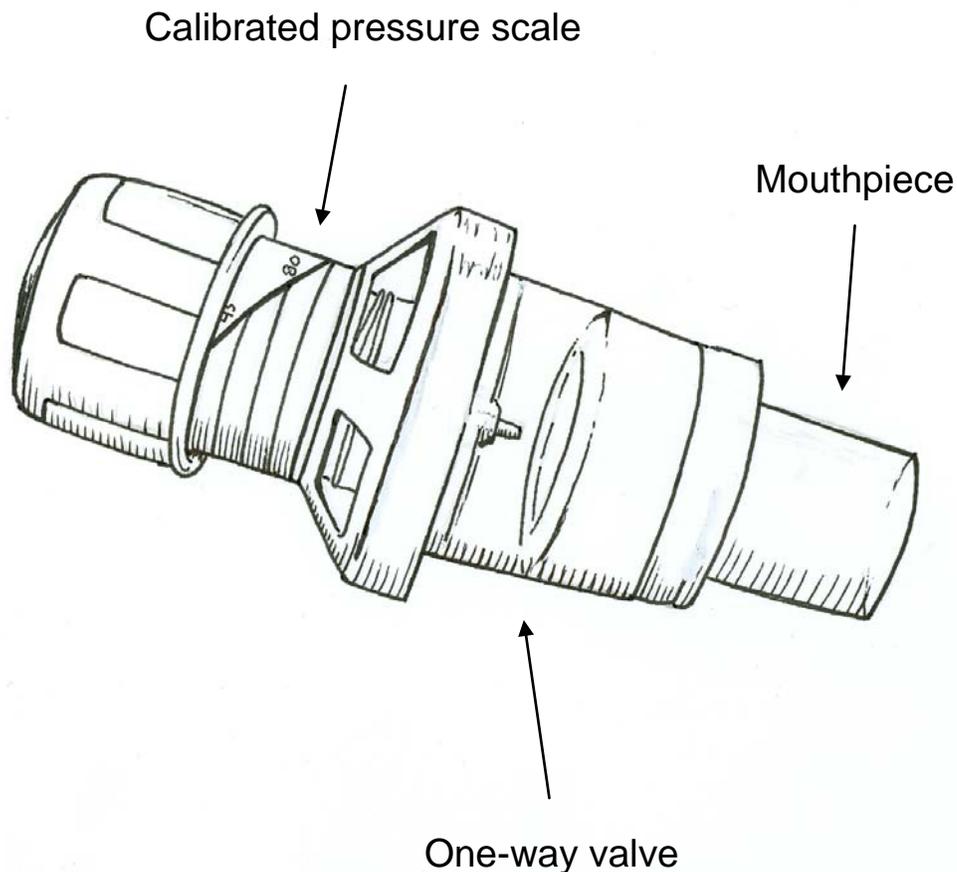


Figure 4-1. Picture of Expiratory Muscle Strength Training Device. [Reprinted with permission from Pitts, Bolser, Rosenbek, Troche, Okun and Sapienza, 2009. Impact of expiratory muscle strength training on voluntary cough and swallow function in Parkinson's disease (page 1303, Figure 1) Chest (135)5]

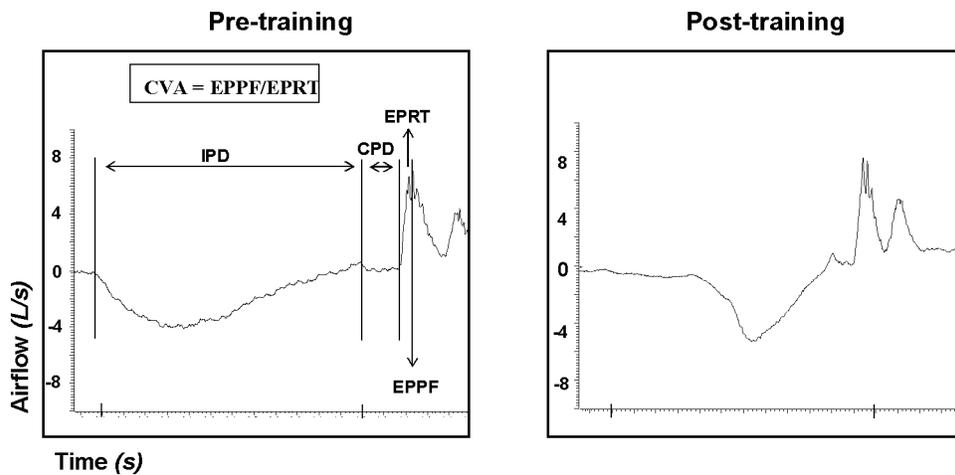


Figure 4-2. Examples of airflow waveforms during a voluntary cough task from Group 1 and Group 2. The vertical lines within the Group 2 waveform denote the phases of the cough waveform as described in the text. [Reprinted with permission from Pitts, Bolser, Rosenbek, Troche, Okun and Sapienza, 2009. Impact of expiratory muscle strength training on voluntary cough and swallow function in Parkinson's disease (page 1304, Figure 2) Chest (135)5]

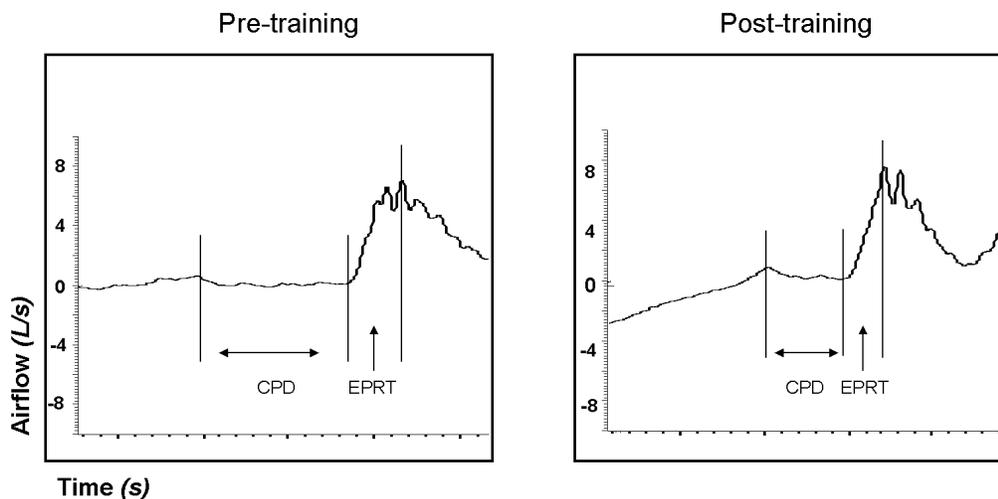


Figure 4-3. Portions of the cough waveform demonstrating differences in inspiratory phase (IP) compression phase duration (CP) and expiratory rise time (EPR) pre to post training. [Reprinted with permission from Pitts, Bolser, Rosenbek, Troche, Okun and Sapienza, 2009. Impact of expiratory muscle strength training on voluntary cough and swallow function in Parkinson's disease (page 1305, Figure 3) Chest (135)5]

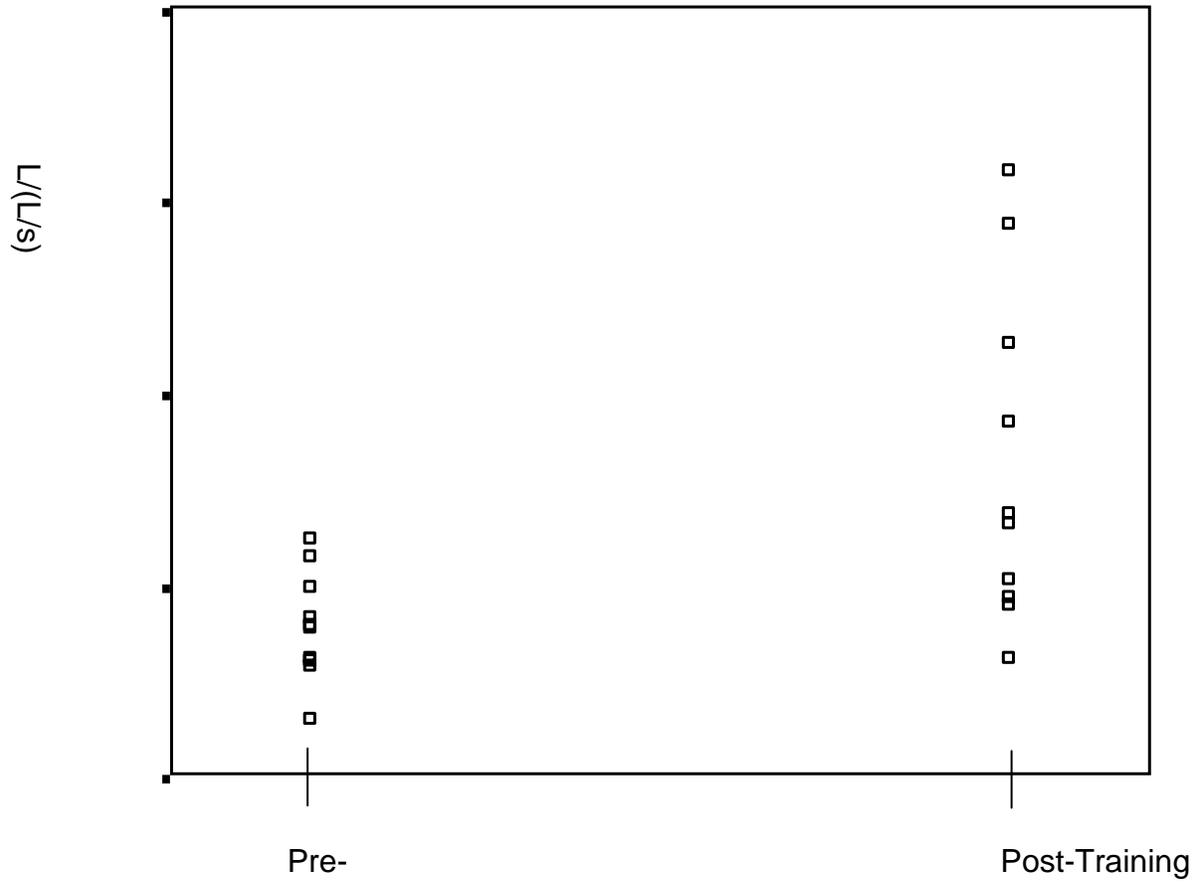


Figure 4-4. Cough volume acceleration (Cough VA) pre to post training. [Reprinted with permission from Pitts, Bolser, Rosenbek, Troche, Okun and Sapienza, 2009. Impact of expiratory muscle strength training on voluntary cough and swallow function in Parkinson's disease (page 1305, Figure 4) Chest (135)5]

CHAPTER 5 SWALLOWING DURING TRACHEAL STIMULATION IN THE CAT

Introduction

Swallowing in humans is a complex coordinated behavior dependent upon afferent feedback for its initiation and modulation. Touch, pressure, and liquid on the tongue, faucial pillars, soft palate, uvula, epiglottis, pharyngeal wall, and junction of the pharynx/esophagus can induce a swallow (Miller, 1982; Miller & Scheeington, 1916; Pommerenke, 1928; Storey, 1968).

The pharyngeal phase of swallowing is a “mostly” reflexive, patterned behavior (Miller, 2008). There are several actions that take place during this phase. First, the tongue base retracts and then moves superior and posterior, which in turn directs the bolus toward the pharynx. During the tongue movement there is closure of the velopharyngeal port. Velopharyngeal closure is important because it allows for a build-up of pressure in the pharynx to help propel the bolus toward the esophagus, and the contact of the soft palate with the back pharyngeal wall prevents the bolus from moving into the nasopharynx (Logemann, 1998; Logemann, Rademaker, Pauloski, Ohmae, & Kahrilas, 1998). The pharyngeal wall also contracts and its medial movement contacts the soft palate. The two basic actions of the pharynx are elevation of the entire pharynx and then a descending activation of the superior, middle, and inferior pharyngeal constrictors to set off a peristaltic wave to move the bolus along. As the pharynx is elevated, the larynx elevates. The submental muscles (mylohyoid, geniohyoid, and anterior belly of the digastric) contract to move the hyoid bone and larynx superior and anterior into a position under the tongue base (Logemann, 1998). During laryngeal movement, the vocal folds and aryepiglottic folds adduct preventing material from

entering the lower airway. Additionally, the epiglottis folds over the glottis to act as another layer of protection from material entering the glottal airway (Miller, 2008; Miller, 1982). Movement of the larynx also pulls open the superior portion of the esophageal sphincter. Following the contraction of the inferior pharyngeal muscle, the upper esophageal sphincter relaxes. The bolus is then passed into the esophagus (Miller, 2008; Miller, 1982).

The hyoid bone is a horseshoe shaped bone, situated between the chin and the thyroid cartilage (Kendall & Leonard, 2001; Y. Kim & McCullough, 2008; Paik, et al., 2008). The hyoid bone has ten muscular attachments, eight to the superior portion of the bone (middle pharyngeal constrictor, hyoglossus, digastric, stylohyoid, geniohyoid, mylohyoid and the genioglossus) and three to the inferior portion (thyrohyoid, omohyoid, and the sternohyoid) (Kendall & Leonard, 2001; Y. Kim & McCullough, 2008; Paik, et al., 2008). The superior muscle attachments move the hyoid anterior and superior and the inferior muscle attachments depress the hyoid bone. During the pharyngeal phase of swallowing, movement of the hyoid bone, and the attached laryngeal complex, moves the larynx superior (Kendall & R. Leonard, 2001; Y. Kim & McCullough, 2008; Paik, et al., 2008). This superior movement moves the epiglottis in a forward position, which in turn covers the glottal space. The epiglottic positioning, adduction of the vocal folds, and the adduction of the aryepiglottic folds close the airway to material being swallowed (Kendall & Leonard, 2001; Kim & McCullough, 2008; Paik, et al., 2008).

Studies of human swallowing demonstrate that peripheral feedback can modulate swallowing. For example, increased swallow related apnea during the pharyngeal phase of swallowing is associated with increased bolus volume Butler, Postma &

Fischer (2004). Furthermore, Kahrilas and Logemann (1993) demonstrated that an increased duration of laryngeal elevation and longer hyoid excursion occur when presented with a larger bolus size. Additionally, a larger bolus volume led to earlier superior movement of the hyoid and larynx, and the upper esophageal sphincter opened earlier (when compared to a smaller bolus volume) (Cook et al., 1989; Teismann et al., 2007). Ding et al. (2003) demonstrated increased sphincter electromyography (EMG) activity for salty compared with sweet and sour tastes, and decreased activation time for sweet versus sour bolus types. Sour versus sweet taste also was related to increased EMG activation during swallow and also increased the total swallow time (Leow, Huckabee, Sharma and Tooley, 2007). Logemann et al. (1995) found that those with dysphagia produced a significant decrease in aspiration events when swallowing a sour liquid-bolus. Hamdy et al. (2003) discovered that if the sour bolus was cold, the benefit (decreased aspiration) no longer occurred. In a group of young adults, Chee et al (2005) found that glucose, citrus, and saline decreased total swallow duration compared with water.

Results from animal studies are varied with a majority showing no changes, and with regard to swallow modulation. Doty and Bosma (1956) and Thexton, Crompton and German (2007) demonstrated consistency in EMG amplitude and duration measures from the hyoglossus, stylohyoid, mylohyoid, middle pharyngeal constrictor, styloglossus, medial pterygoid, palatopharyngus, omohyoid, anterior digastric, thyrohyoid, inferior pharyngeal constrictor, geniohyoid, cricothyroid, sternothyroid, sternohyoid, and the cricopharyngeus, between swallows elicited by water, mechanical stimulation, and superior laryngeal nerve (SLN) stimulation, in species including the pig,

cat, dog and rhesus monkey. A study by Patterson (1999), in an opossum model, is the only study that demonstrated significant differences in the EMG activation during swallowing. Comparing unilateral and bilateral SLN stimulation to pharyngeal stroking, the mylohyoid EMG burst had significantly greater amplitudes and significantly longer burst duration with pharyngeal stroking. Studies altering other conditions in the pharynx, larynx, and respiratory system (i.e CO₂ levels, O₂ levels) have not been performed.

However, changes occur in the respiratory system which affect swallowing (i.e. chronic obstructive pulmonary disease), and diseases like Parkinson's disease have high incidences of aspiration which would be a stimulus to the trachea during subsequent swallows (Buchholz, 1994; Daniels et al., 2006; Ertekin, Aydogdu, Tarlaci, Turman, & Kiylioglu, 2000; Horner & Massey, 1988; Miller, Noble, Jones, & Burn, 2006; Plowman-Prine et al., 2009; Potulska, Friedman, Krolicki, & Sychala, 2003; Robbins, Levine, Maser, Rosenbek, & Kempster, 1993). If the aspiration event is not followed by a cough or significant expiration effort (expiratory reflex, or huff) the patient is said to have silent aspiration (Bushman, Dobmeyer, Leeker, & Perlmutter, 1989; Horner & Massey, 1988). The swallow pattern, which led to the aspiration event, and the presence or absence of the reflexive cough following aspiration, has been studied extensively (Aviv et al., 1997; Aviv et al., 2002; Buchholz, 1994; Clave et al., 2008; DePippo, Holas, & Reding, 1992; Donzelli, Brady, Wesling, & Craney, 2003; Ertekin & Palmer, 2000; Miller, 2008; Miller, et al., 2006; Pitts, Bolser, Rosenbek, Troche, & Sapienza, 2008; Pommerenke, 1928; Potulska, et al., 2003; Robbins, Logemann, & Kirshner, 1986; Smith Hammond et al., 2001). However, the presence of material in the

airway may impact more than just the triggering of a reflexive cough. A mechanical and chemical stimulus to the trachea can also elicit expiration reflex, increased mucous secretions, and/or alterations contractions of the smooth muscle lining the airway (Belvisi & Bolser, 2002; Bolser & Davenport, 2007; Bolser, DeGennaro, O'Reilly, Hey, & Chapman, 1995; Vovk et al., 2007). We hypothesized that afferent feedback from the lower airways during swallowing could lower the swallow number; more specifically, with the tracheal stimulus, an increased number of swallows will be elicited.

The first aim of the project was to define swallow number, in the cat, by giving an injection of water into the oropharynx and recording the number of behaviors elicited. Swallow number was defined as the number of swallows elicited by a set stimulus. The second aim was to define the EMG activity patterns during swallowing, from the geniohyoid, thyropharyngeus, cricopharyngeus, and thyroarytenoid, in order to determine the effects of tracheal stimulation on swallowing. It was hypothesized that swallow number, in the cat, would be decreased by swallow stimuli that occurred during mechanical stimulation of the intra- and extrathoracic trachea. Secondly, it was hypothesized that mechanical stimulation of the trachea, which induces cough in an anesthetized cat, would also modulate swallow by increasing the EMG amplitude or duration of EMG activity in pharyngeal and laryngeal muscles.

Methods

Experiments were performed on five spontaneously breathing adult male cats. The animals were initially anesthetized with sodium pentobarbital (35-40 mg/kg i. v.), and supplementary doses were administered as needed (1-3 mg/kg i.v.). A dose of atropine (0.1-0.2 mg/kg, i. v.) was given at the beginning of the experiment to reduce secretions. The femoral artery and vein were cannulated. The neck musculature was

dissected and the trachea cannulated. An esophageal balloon was placed to measure pressure in the midthoracic esophagus. Arterial blood pressure and end tidal CO₂ were continuously monitored and were maintained using air mixtures with enriched oxygen (25-60%) to maintain PO₂ values above 100 mm Hg. Body temperature was monitored and maintained at 37.5 ± 0.5 °C using a heating lamp and pad.

Electromyograms (EMG) were recorded using bipolar insulated fine wire electrodes. Four muscles were chosen to evaluate the pharyngeal phase of swallowing: geniohyoid, thyropharyngeus, thyroarytenoid and the cricopharyngeus. The mylohyoid muscle was removed and electrodes were placed in the medial body of the geniohyoid muscle. The thyroarytenoid electrodes were inserted through the cricothyroid window into the anterior portion of the vocal folds. Rotation of the larynx and pharynx counterclockwise, revealed the superior laryngeal nerve, which facilitated placement of the thyropharyngeus muscle electrodes. These electrodes were placed caudal to the SLN and inferior to the larynx. To place the electrodes within the cricopharyngeus muscle the larynx and pharynx were rotated counterclockwise to reveal the posterior aspect of the larynx, and the electrodes were placed cranial to the esophagus (see figure 2). The positions of all electrodes were confirmed by visual inspection, and EMG activity patterns during a swallow trial, infusion of a 3cc water bolus into the oropharynx. See figure 1 for EMG pattern. To detect the presence and/or absence of cough the pattern of cough was defined as a burst of activity in the parasternal EMG, followed by (and partially overlapping) a burst in the thyroarytenoid and rectus abdominis, along with a negative to positive change in esophageal pressure (see figure 1). The protocol

was approved by the University of Florida Intuitional Animal care and Use Committee (No 8663-2004).

Stimuli

To initiate swallowing a one-inch long, thin polyethylene catheter (diameter 5.5-1.0 mm), attached to a 6cc syringe was placed into the oropharynx. Three ounces of water were injected via the syringe. Mechanical stimulation of the trachea was conducted using a thin polyethylene catheter (diameter 0.5 – 1.0 mm). The following protocol was performed (see Figure 1):

Condition 1: Infusion of Water Bolus

- Swallow trial, (infusion of 3cc water into oropharynx),
- One minute interstimulus interval,
- Swallow trial,
- One minute interstimulus interval,

Condition 2: Injection of Water Bolus with Tracheal Stimulation

- 20 seconds tracheal stimulation, swallow stimulus intitated 5 seconds after onset of mechanical stimulation of the trachea,
- One minute interstimulus interval,
- 20 seconds tracheal stimulation, swallow stimulus intitated 5 seconds after onset of mechanical stimulation of the trachea,
- One minute interstimulus interval, and
- Repeat conditions 1 and 2 three times.

Analysis

A swallow occurrence was defined as EMG burst in the geniohyoid, thyropharyngeus, and thyroarytenoid, with a corresponding suppression of the cricopharyngeus (see figure 1). This definition is consistent with other reports (German, Crompton, & Thexton, 2009; Thexton, Crompton, & German, 2007; Thexton, Crompton,

Owerkowicz, & German, 2009). Swallow occurrences were counted in both conditions, and averaged for each animal. EMG duration was measured for each muscle during each swallow occurrence for each condition, and averaged for each animal. EMG amplitude was measured for each muscle during each swallow occurrence for each condition. The EMG amplitudes were expressed as a percentage of the strongest swallow, as measured by esophageal pressure, during the first swallow stimulus. The amplitudes were averaged for each condition, for each animal. A one-way analysis of variance was conducted comparing the dependent variables for condition 1 versus condition 2. Data were expressed as mean +/- SD.

Results

Swallows were consistently elicited in both conditions, for each of the animals (Figure 1). Figure 1 shows the occurrence of swallows as noted by the arrows, and presence of cough as noted by the presence of a star. Note the large ballistic-like increases in thyropharyngeus, geniohyoid, and thyroarytenoid EMGs, corresponding to a quiescent period in the cricopharyngeus EMGs (lasting 0.3-.05 seconds) with a burst following during swallowing. This EMGs patterning also corresponded with a negative spike in the esophageal pressure record. These patterns were not present during breathing or coughing. During breathing the thyropharyngeus was phasic with expiration; no notable change in activity was present in the geniohyoid, thyroarytenoid, or the cricopharyngeus. The cricopharyngeus had baseline activity that appeared to increase with the tracheal stimulation (see figure 1), however there was no notable change in activity during respiration. During cough there was no notable change in the activity of the thyropharyngeus or geniohyoid. Using the previously mentioned definition

of a swallow a significant difference ($p \leq 0.01$) occurred for the number of swallows elicited condition one with 1.4 (± 0.8) and condition two with 2.5 (± 1.5).

The average EMG duration, in seconds, for condition one was as follows: geniohyoid 0.43(0.16), thyroarytenoid 0.57(0.16), thyropharyngeus 0.55(0.25), and cricopharyngeus 0.41 (0.06). The average EMG duration, in seconds, for condition two was as follows: geniohyoid 0.44(0.16), thyroarytenoid 0.55(0.25), thyropharyngeus 0.41(0.15), and cricopharyngeus 0.39 (0.08). No significant differences were seen for EMG duration comparing condition one to condition two. During condition one, the average amplitude for each muscle was as follows: geniohyoid 0.78(0.35), thyroarytenoid 1.01 (0.05), thyropharyngeus 0.99 (0.07), and cricopharyngeus 1.18 (0.64). During condition two, the average amplitude for each muscle was as follows: geniohyoid 1.03(0.68), thyroarytenoid 1.02 (0.09), thyropharyngeus 1.17 (0.07), and cricopharyngeus 1.59 (0.38). A significant difference was seen for the thyropharyngus ($p \leq 0.01$) (see table 1).

Discussion

This study is the first to examine the effects of mechanical stimulation of tracheal afferents during water infusion, on subsequent swallows, in an anesthetized cat. By investigating swallow, during mechanical stimulation of the trachea, this study was able to determine if the swallow number could be modified.

This study had two major aims. The first aim was to determine if the swallow number could be altered with tracheal stimulation. The effect on the number of swallows may be due to a change in the swallow activation thresholds. Jean (2001 & 1984) discussed afferent feedback as a primary modulator of the swallow pattern generator. More specifically that the discharge of the central pattern generator can be increased by

peripheral input, such as, afferent response to the size of the bolus or distention of the pharynx (Jean, 2001). This effect has not been previously demonstrated by stimulation of the trachea. The mechanical stimulation of the trachea activates afferent receptors (c-fibers and RAR) with axons in the recurrent laryngeal nerve, which innervate the tracheal mucosa (Kalia & Mesulam, 1980). Jean (1984) stated that the central pattern generator was affected by pharyngeal and esophageal receptors, and our results suggest that tracheal afferents have also had this effect.

The second aim was to determine if the EMG activity pattern would differ significantly when swallowing was elicited during tracheal stimulation. This study found a significantly greater number of swallows elicited and a significant increase in the amplitude of the thyropharyngeus EMG during the tracheal stimulation with water infusion. No significant differences were found for the duration measures (EMG activation time) for any of the muscles or significant differences in amplitude for the cricopharyngeus, geniohyoid or thyroarytenoid. In three of the animals it did appear that all the muscles had significantly greater amplitude; however variability in the other two animals made the differences non-significant.

The EMG amplitude of the thyropharyngeus was significantly greater in the swallow trials with tracheal stimulation as compared with water infusion alone. The thyropharyngeus is part of the inferior pharyngeal constrictor, originating from the midline posterior aponeurosis and inserts on the thyroid cartilage (Kuna, 2000). The inferior pharyngeal constrictor makes up the pharyngeal wall, controlling the size of the pyriform sinus.

The thyropharyngeus was active during expiration, but no notable activity change in activity during cough. It is theorized that because the thyropharyngeus controls the piriform sinus (Miller, 1982; Thexton, et al., 2007), it is advantageous for the system to keep the piriform sinus dilated during the cough to act as a holding place for material that has been removed from the lungs, which is removed by the subsequent swallow. The increase the thyropharyngeus activity may be due in part to the consistency of material being ejected from the trachea. Raut et al (2001) demonstrated increased pharyngeal pressure and increased pharyngeal clearing contractions with increased viscosity of swallowed material in humans. Additional work in the cat model would be needed to further test this hypothesis.

Future Studies

Future studies are envisioned to systematically test swallow change with other respiratory stimuli, such as progressive hyperoxic hypercapnia, and isocapnic hypoxia, in the cat model. There is evidence that the pharyngeal muscles are modified by these stimuli during breathing, but the effect on swallowing has yet been determined. Additionally, investigation of the effects of the bolus injection on subsequent coughs is also of interest. The previous studies in the document, with Parkinson's disease suggest that there is a relationship between cough and swallow, and it would be interesting to see if the relationship continued to cough and swallow stimulated together, in an animal model.

Table 5-1. Mean, standard deviation for EMG amplitude in the two conditions

Muscle	Condition	amplitude*	<i>p</i> value
Geniohyoid	1	0.78 (0.35)	<i>p</i> = 0.48
	2	1.03 (0.68)	
Thyroarytenoid	1	1.01 (0.05)	<i>p</i> = 0.23
	2	1.02 (0.09)	
Thyropharyngeus	1	0.99 (0.07)	<i>p</i> ≤ 0.01
	2	1.17 (0.07)	
Cricopharyngeus	1	1.18 (0.64)	<i>p</i> = 0.25
	2	1.59 (0.38)	

Condition 1 was water stimulus alone. Condition 2 was water stimulus with tracheal stimulus.

*Note: mean(standard deviation)

Table 5-2. Mean, standard deviation for EMG duration in the two conditions

Muscle	Condition	duration*	<i>p</i> value
Geniohyoid	1	0.43 (0.16)	<i>p</i> = 0.93
	2	0.44 (0.17)	
Thyroarytenoid	1	0.57(0.22)	<i>p</i> = 0.89
	2	0.55(0.25)	
Thyropharyngeus	1	0.55(0.25)	<i>p</i> = 0.79
	2	0.58(0.15)	
Cricopharyngeus	1	0.41(0.06)	<i>p</i> = 0.65
	2	0.39(0.08)	

Condition 1 was water stimulus alone. Condition 2 was water stimulus with tracheal stimulus.

*Note: mean(standard deviation)

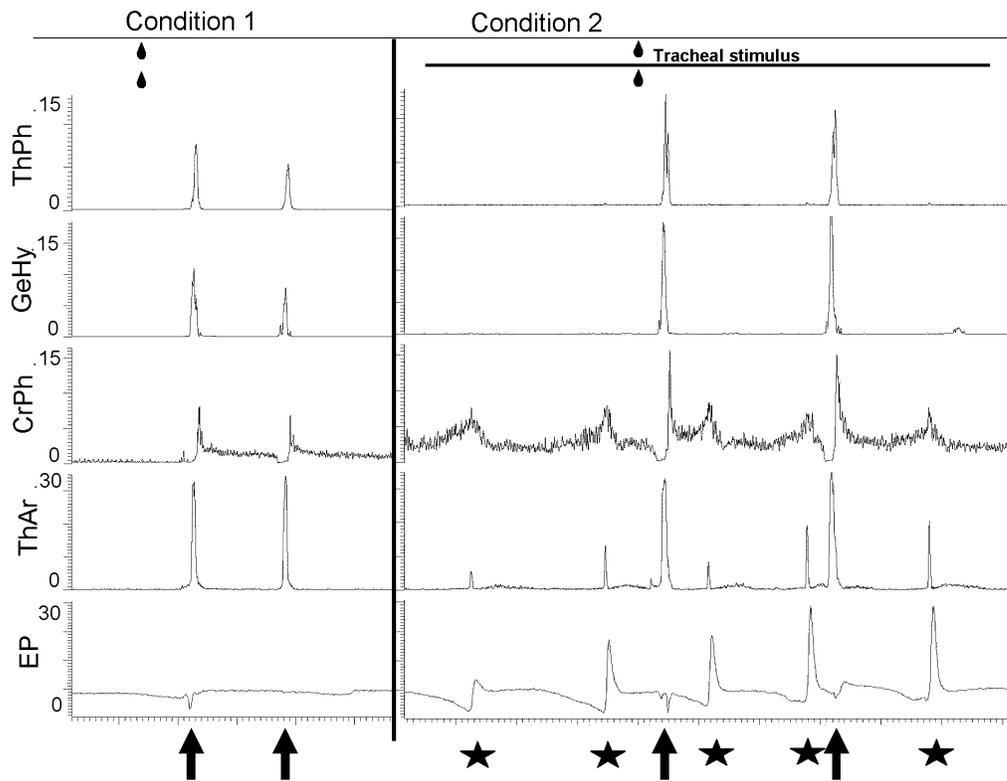


Figure 5-1. Examples of swallowing during condition 1 and condition 2. Water placement in the pharynx is represented by the water droplets (💧). A swallow is represented by an arrow, and a cough is represented by a star. (Note: the thyroarytenoid is active during cough and swallow)

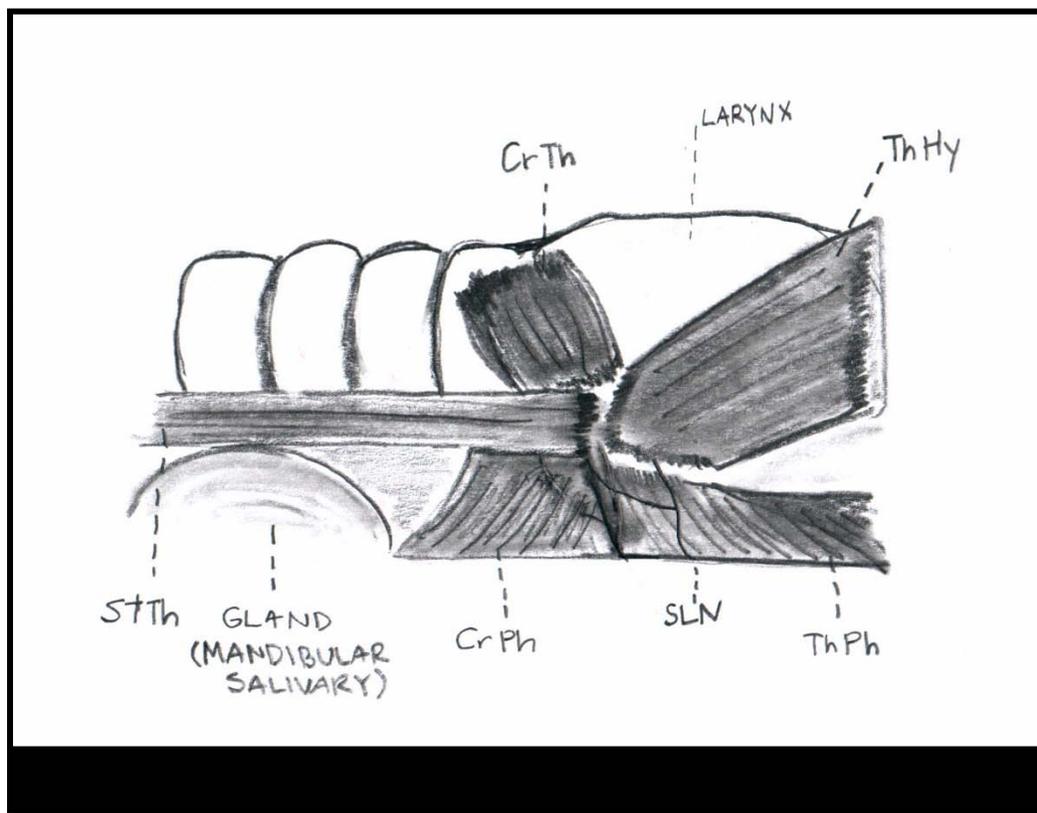


Figure 5-2. Anatomical landmarks used for EMG placement of the cricopharyngeus (CrPh) and the thyropharyngeus (ThPh) EMG electrodes. Landmarks included: sternothyroid (StTh), superior laryngeal nerve (SLN), thyrohyoid (ThHy), larynx, and cricothyroid (CrTh).

CHAPTER 6 PHARYNGEAL SENSORY EVOKED POTENTIALS IN HEALTHY AND PARKINSON'S DISEASE

Introduction

Evoked potentials are the nervous system's electrophysiologic response to sensory stimuli (Colon, 1990; Nunez & Srinivasan, 2006). They are used to record neural activity on the scalp surface in response to stimulation of afferent fibers that have projections to specific cortical areas. Evoked potentials are a method that can be used to objectively determine if differences in afferent pathway from the pharynx to the cortex exist in those with PD.

Event related Electroencephalography

Event related EEG electroencephalography recordings are used to analyze specific stimuli related to changes in the ongoing EEG activity. The assumption is that the event related potential (ERP) is time-locked to the stimulus presentation, and this synchronization is used to average multiple presentations together in order to produce a high signal to noise ratio. The resulting averaged waveform is then used for analysis (Pfurtscheller & Lopes da Silva, 1999). For every doubling of the stimulus events (i.e., 4, 8, 16, etc), the background non-stimulus related EEG is reduced by fifty percent. Thus, for small ERP changes a large number of trials must be presented to generate an adequate signal to noise ratio (i.e. 256 stimuli) (Nunez & Srinivasan, 2006).

A variety of stimuli will elicit an event related response. Generally, any stimulus that can be localized by a research participant will create an ERP with multiple modality specific stimulations (Ashraf, Davarpanah, Yazdani, Mirshams, & Esfahani, 2008; Babiloni et al., 1999; Babiloni et al., 2009; Davenport, Chan, Zhang, & Chou, 2007). There is some evidence that even those stimuli that cannot be specifically localized will

elicit an ERP as well (Nunez & Srinivasan, 2006). This includes, but is not limited to, mechanical stimuli such as air puffs or touch, auditory stimuli such as ear clicks, or electrical stimuli such as direct nerve stimulation. In addition, respiratory-related ERPs have been studied using an inspiratory occlusion paradigm that increases the breathing effort (brief occlusions are applied on the inspiratory phase of respiration) and this results in consistent ERP responses (Davenport, et al., 2007; Davenport, Colrain, & Hill, 1996b; Davenport, Cruz, Stecenko, & Kifle, 2000).

Dipoles

The “cap” (see figure 1 and 2) containing a variable amount of electrodes is able to record charge on the scalp from dipoles within the cortex. A model explaining dipoles in the cortex is based on current dipoles as opposed to an electric dipole model (Nunez and Shrinivasan, 2006; Williamson and Kaufman, 1990). In the current dipole model a group of afferent fibers are stimulated by an excitatory stimulus and the synapses on the dendritic trees respond by permitting positive ions to enter through the membrane channels moving toward the soma. There is a focal/local increase in charge concentration, which creates an electric field moving toward the soma. Williamson and Kaufman (1990) explain that the summation of the current that is created in the dendritic tree multiplied by its length equals the current dipole of an individual neuron. The summation of all the individual current dipoles gives a net current dipole. For studies examining the somatosensory system the somas would be located in layer VI (internal granular layer) (Colon, 1990). The negative net current dipole creates a movement of positive charge from the layers superior to layer IV, which creates a hyper positive field on the cortical surface that is then recorded by the electrode as being the P1 or the first positive peak seen following the stimulus (see figure 3). Depending on the area

stimulated the time-frame for the creation of the P1 can vary significantly e.g. (Nunez, Srinivasan, 2006). The afferent information is then processed horizontally. This movement of the electric charge changes to characteristics of the current dipole, especially if it moves deeper due to a sulcus or fissure. The changes in the current dipole creates a relative negative charge in the same area of the cortex and is called the N1 which is the first negative peak seen (excluding the negative peak seen in the frontal cortex called Nf). Note that the negative scalp potentials may or may not be negative when compared to other surface locations (Nunez, Srinivasan, R., 2006).

Sensory Gating

The thalamus is a subcortical structure, responsible for controlling the flow of sensory information to the cortex for processing (McCormick & Bal, 1994; Gaudrean and Gagnon, 2005). During sleep, rhythmic burst firing inhibits the vast majority of sensory information from reaching the cortex, but during wakefulness single spike activity allows the thalamus to have finer control (McCormick & Bal, 1994; McCormick, 1992). Projections from the thalamus are processed in layer IV of the somatosensory cortex, and layer IV of the somatosensory cortex also has extensive projection to the thalamus. This establishes a feedforward and feedback system, creating a cortical-thalamic loop to prevent the cortex from being flooded by redundant sensory information (McCormick & Bal, 1994; McCormick, 1992). The thalamus then acts as a gate, allowing the primary stimulus to reach the cortex and inhibiting subsequent or redundant information.

In a paired stimulus paradigm, with two identical stimuli delivered 500 ms apart, gating is determined by comparing the second waveform to the first. Sensory gating is examined by comparing the amplitude of the second stimulus in relation to the first

stimulus (S2/S1). Sensory gating has been demonstrated with the paired stimulus paradigm with mechanical stimuli, auditory stimuli, and visual stimuli (Arnfred, Eder, Hemmingsen, Glenthøj, & Chen, 2001; Chan & Davenport, 2008; Kinsley, Olincy, & Freedman, 2001). It was first reported by Adler et al. (1982), using visual stimuli and interstimulus durations of 500- ms, 1- second, and 2- second durations. At the 500- ms duration the amplitude of the P50 was reduced by 90% and for the 2sec duration it was reduced by 30-50%. Chan and Davenport (2008) demonstrated gating of the P50 and N100 peaks, with interstimuli durations of 500 ms, for the respiratory related evoked potentials (RREP) and stimulus of the buccal surface, in healthy young adults.

In other sensory modalities gating ratios are usually associated with disease, such as schizophrenia (Cadenhead, Light, Greyer & Braff, 2000). Kinsley et al (2005) demonstrated a reduction in the auditory evoked potential in relation to age. Sensory gating is modulated by changes in psychological states, attention, diseases, and/or the aging process (Arnfred, et al., 2001; Chan & Davenport, 2008; Kinsley, et al., 2001), however it is unknown whether repeated stimulation of the pharynx elicits a gated response, and whether disease affects this process.

Studies Examining Oropharyngeal Region

Various studies have examined evoked potentials from the oral and pharyngeal region using various stimuli. Fujii et al. (1994) published a study examining evoked potential of the faucial pillars innervated by the glossopharyngeal nerve in 30 young healthy subjects. A plastic rod attached to a mechanical stimulator was used to present eight taps per second to the faucial pillar, and a 16 electrode array was used to record the evoked potentials. Event related potentials P1, N1, P2, N2 and P3 were reported with mean latencies of 11, 16, 22, 27, and 34 respectively. Hummel, Haenel and Hull

(2002) reported event related potentials in response to an airpuff stimulus to the nasopharynx. A N1 was reported with a latency of 289ms and a P2 at approximately 530ms. The latency of the two reported EP are significantly longer than what is traditionally reported for N1 (at approximately 100ms) (Chan and Davenport, 2008; Pratt, Amlie, & Starr, 1979; Pratt, Starr, Amlie, & Politoske, 1979) and P2. Additionally, Mu and Sanders (2000a) studied the afferent densities in the mucosa of the pharynx and hypopharynx in humans and indicated almost no identifiable innervations to the hypopharyngeal mucosa. The conclusions of the evoked potentials coming from afferent activity from only the hypopharynx is circumspect based on the anatomy of the afferent fibers in the mucosa of the hypopharynx, and the reported latency times for the evoked potential peaks.

Maloney, et al (2000) recorded evoked potentials from the lingual nerve and palatine nerve coursing through the hard palate. Electrical stimuli were used with 4.7 stimuli given every second along with 500 to 2000 stimuli to generate the evoked potentials. The investigators stated that the evoked potentials observed resembled potentials that were generated from electrically stimulating the trigeminal nerve (Findler, 1982). Their N1 occurred at approximately 12-13ms and P1 occurred at approximately 16-18ms. The evoked potentials were only recorded from C5' and C6' with the contralateral side used as the reference electrode.

Davenport and Chan (2008) examined evoked potentials from airpuff stimulus to the buccal surface of the cheeks (MEP) in twenty young healthy subjects. A mean MEP P50 was recorded at approximately 63ms and a N100 was recorded at approximately 85ms. Additionally a paired stimulus paradigm was used, with an inter-stimulus

duration of 500ms and significant amplitude reductions for the second stimulus were found, demonstrating sensory gating of the mechanical stimulus to the mouth.

These studies demonstrate that sensory stimuli in the oral and pharyngeal regions result in cortical activation. However, the evoked potentials from a mechanical stimulus to the oropharyngeal wall have not been characterized, nor has the effects of a paired stimulus paradigm been described. This region is of particular interest because of its involvement in the initiation and modification of the pharyngeal phase of swallowing.

Studies Examining Parkinson's Disease

Conflicting results in regards to changes in somatosensory processing of afferent information using CEP in PD have emerged. Rossini, et al (1989) examined evoked potentials following median nerve stimulation, in 43 PD participants. They found a depressed or absent frontal P20-N30-P40 complex in 72.1% of participants. They then administered a bolus of apomorphine chloride, which is used as a test in order to predict the patient's responsiveness to L-Dopa (the gold standard treatment for PD). Following the administration of the apomorphine chloride 90% of the participants with the depressed or absent frontal P20-N30-P40 complex found a significant amplitude within remained during the medication affect time period. Mauguiere, Broussolle and Isnard (1993) using 8 electrode sites over the anterior frontal lobe and the posterior parietal lobe to determine EP's in response to median nerve stimulation found a depression of the N30 waveform in only one of seven individuals with PD. Additionally, Huttunen, and Teravainen (1993) examined PD patients with unilateral symptoms. The EP's were recorded in response to median nerve stimulation in both limbs. The results found no significant differences from control subjects in the primarily affected arm or the alternative arm.

Degardin, et al (2009) examined beta rhythm movement-related synchronization which is related to motor cortex deactivation and sensory afferent processing. EEG was recorded using a 128 electrode cap with the reference on the right mastoid. An accelerometer was attached to the index finger for movement recording. In individuals with PD the peak of the beta synchronization magnitude was significantly lower following active and passive movements, and electrical median nerve stimulation. These results were confirmed from previous studies by Pfurtscheller, et al. (1998; 1998), which also found the post-movement beta potentials to be reduced in PD patients compared to age-matched controls. Examining longer latency potentials in a study by Iijima et al (2000) detected latencies in the P300 with an auditory paradigm, which was significantly correlated with cognitive change in PD.

The morphological characteristics of the ERP response to mechanosensory stimulation in this region are not known. Additionally, the effects of PD on the processing of afferent information from the oropharyngeal wall is not known. The goal of this project was to identify the component peaks and morphological characteristics of the early ERP response to air puff stimuli applied to the posterior oropharyngeal wall. It was hypothesized that the waveforms would include early positive and negative component peaks in bilateral primary somatosensory (parietal) and frontal regions, respectively, with latencies similar to those previously reported for the RREP (Chan & Davenport, 2008). As well, it was hypothesized the waveforms would include mid-latency positive and negative peaks (P2 and N2), similar in latency to those reported for the nasopharyngeal region (Hummel et al., 2002).

Application to Swallow Research

The pharyngeal phase of swallow is initiated from sensory input from the mouth, pharynx and larynx, (Ashraf, et al., 2008; Casale et al., 2008; Dell'Aringa, Sena, Teixeira, Dell'Aringa, & Nardi, 2008; Nishiyama, 2008) and peripheral afferent information is available throughout the pharyngeal phase from the mouth, pharynx, and larynx (Jean, 2001; Miller, 2008; Miller, 1982). Pommerenke (1928) found the oropharyngeal wall and the faucial pillars to be the most consistent locations for the elicitation of swallowing in young adults.

Dysphagia (swallowing dysfunction) can occur from the early stages of PD and aspiration pneumonia is reported as the leading cause of death in PD patients (Ebihara, et al., 2003; Nakashima, et al., 1997). Dominant symptoms of dysphagia include: decreased oral transit time, poor bolus formation, a delay in the triggering of the pharyngeal phase of the swallow, prolonged opening of the upper esophageal sphincter, and residue in the vallecular and piriform sinuses (Miller, et al., 2006; Potulska, et al., 2003). Robbins, Logemann and Kirshner (1986) proposed that many individuals with PD present as “silent aspirators” with little awareness of their dysphagia symptoms and little or no cough response to aspiration.

To date, no study has examined sensory changes in the pharynx in PD, in which no motor response (i.e reflex) was used. No study has examined sensory gating in PD. Additionally, no study has examined event related potentials with relationships with swallowing.

Specific Aims and Hypothesis

The first aim of this project was to determine if evoked potentials (P1, N1, P2, and N2) could be recorded in response to an airpuff stimulus to the pharyngeal wall (PSEP)

in young healthy individuals, older healthy adults, and persons with Parkinson's disease, and if the amplitude and/or latency of the peaks are affected by age or Parkinson's disease. (1a) It was hypothesized that a series of positive and negative peaks (P1, N1, P2, and N2) would be identified in each group. (1b) It was also hypothesized the amplitude all four peaks would be decreased in the older healthy adults and further decreased in the participants with Parkinson's disease.

The second aim of the project was to determine if sensory gating occurred in response to a paired stimuli on the pharyngeal wall. (2a) It was hypothesized that like other somatosensory modalities sensory gating would occur in the young healthy individuals. (2b) It was also hypothesized that the gating ratio would be negatively affected by age and PD; specifically the less gating would occur in the PD group when compared to the older healthy adults group and young healthy adults group.

A third aim of the project was to determine if the relationships exist between the measures of swallow safety and the amplitude and latency of the PESP peaks in the PD and older healthy control group. It was hypothesized that a negative relationship would exist between the PA score and the amplitude of the PSEP peaks, and a positive relationship would exist between the PA score and the PSEP peaks.

Methods

Participants

Forty-five participants were recruited for this study. Twenty-five were young healthy adults (20.5 +/- 3.3 years old), seven were older healthy adults (72.2 +/- 6.9 years old), and thirteen participants diagnosed with idiopathic Parkinson's disease (PD) (67.2 +/- 8.9 years old). All participants reported no history of head or neck cancer, neurologic disease (other than idiopathic PD for the PD group), chronic respiratory

disease, history of smoking within the last ten years, or dysphagia. Participants were asked to refrain from caffeine intake for at least twelve hours prior to the study. The participants with PD had a diagnosis of dopamine responsive PD, from a neurologist at the University of Florida Movement Disorders Center, and were asked to be in the “on” phase of their medication cycle.

Mechanical Event Related Potentials

Each participant was screened for tolerance of the mouth piece (see figure 4) and the flexible endoscope placement (see figure 2). The participant was tested in a sound insulated room. Participants were studied seated, at rest, with the back, neck and head comfortably supported at a ninety-degree angle. An electrode cap (NeuroScan, Inc.) with integral tin electrodes was used to record scalp EEG activity (see figure 2). The cap electrode locations were based on the International 10-20 system with 32 electrodes positioned over the scalp. The cap was placed on the participant’s head (using measurements from the nasion to ion, and ear to ear), positioned and secured with a chin strap. Scalp and electrode contact was made by the application of electro-conducting paste administered through the center opening in the electrode. The electrode gel was placed in syringes with blunt tip needles. This allows for placement of the gel through the small holes in the cap and slight abrasion of the skin to help lower the impedance levels, by removing dead skin cells and increasing blood flow. See figure 1 for evoked potential set-up. The impedance levels for each electrode was checked and maintained around 5 Kohms. The electrode cap was connected to an electroencephalograph system (SynAmps, Compumedics, Inc). The EEG activity was filtered, amplified and stored on computer disk.

A certified as clinically competent speech-language pathologist administered the airpuff protocol. A flexible-endoscopy scope, with a sterile plastic-sheath that allows for the air-puff to be administered, was used (see figure 1 and 4). For the oropharyngeal air puff trial, the participant was asked breathe deeply through a mouthpiece (this tended to lower the gag response of the subjects and open the posterior oral cavity). The flexible scope was placed as close to the oral-pharyngeal wall as possible, without it touching. When the second investigator triggered a solenoid valve, air under positive pressure was delivered through the tubing onto the participant's pharyngeal surface. Two airpuffs were delivered with an inter-stimulus duration of 500ms. The pressure was regulated at approximately 20-30 cm H₂O. The pressure varied depending on the pressure the participant reported relative comfort, without triggering a cough, swallow or gag. Each air puff was delivered for approximately 150-200ms. A 750ms EEG and pressure sample epoch was recorded from the onset of the air-puff pressure. A total of 256 EEG epochs of air puff synchronized data was used for analysis. To ensure limited muscle contraction of the face and neck the participants were intermittently asked to relax and not bite down on the mouthpiece. Additionally, to reduce Alpha –rhythms the participants were asked to keep their eyes open and watch a movie.

Swallowing Evaluation Procedures

The videofluoroscopic examination of swallow (VFSE) was completed at the Malcom Randall VAMC, Gainesville, FL. Participants were seated upright and the images of the examination were recorded in the lateral view. A properly collimated Phillips Radiographic/ Fluoroscopic unit was utilized, and it provides a 63-kV, 1.2-m-A output for full field of the view mode. The videofluoroscopic evaluation was recorded

using the Kay Elemetrics Swallow Station (Kay Elemetrics, Lincoln Park, NJ) with a digital scan converted and was recorded at a setting of 30 frames per second.

The participants were handed the cup and told to swallow continuously until the liquid in the cup is gone. Two tasks were presented in random order: 1) two, 3oz thin sequential swallows; 2) ten 5ml single swallows. Figure 6 demonstrates the recording field during the swallow evaluation.

Measurements Related to Swallow Safety

Penetration/Aspiration score

The 10, 5ml, swallows and the two, 3oz, swallow tasks were judged for swallow safety using the Penetration/ Aspiration scale (Rosenbek, et al., 1996). Each swallow was evaluated individually. Specifically to measure whether or not material entered the airway, and if this did occur, whether or not it was expelled.

Swallow timing

The ten, 5ml, swallows were used for swallow timing measures, to evaluate swallow safety. The Kay Elemetrics Swallow Station, which was used to record the VFSE examination, was also used to assess swallow timing measures. Frame by frame portions of the swallow were tagged and calculated for timing. The first tag was the onset of the oral phase of swallowing, specifically the point in which the tongue tip begins to curl upwards moving the bolus posteriorly (OOP). The second was the beginning of the pharyngeal phase, specifically when the head of the bolus passes the ramus of the mandible (OPP). The third tag was the end of the pharyngeal phase, specifically when the tail of the bolus passes through the upper esophageal sphincter (UES). Using these three points, three measures were calculated: the oral transit time,

the pharyngeal transit time and the total swallow duration (Kendall, 2002; Kendall & Leonard, 2001; Kendall, Leonard, & McKenzie, 2003; Troche, et al., 2008).

Data Analysis

Analysis of the EPs were completed and blinded for participant group. The EEG activity was filtered, amplified and led into an on-line signal processing computer system (Neuroscan, Compumedics, Inc). The averaged CEP for each trial was tested by the computer for a significant change in positive and negative voltage (relative to the standard deviation of be identified. The onset-to-peak latency, peak-to-peak latency and amplitude of each component were determined for each individual participant. Multiple electrode analysis was performed to solve for individual peak dipole source. A “hot-spot” electrode was determined for each peak, for each participant (see figure 5). Using the waveform and two-dimensional map, the electrode with the highest amplitude corresponding to its location on the map was chosen as the hotspot. This hotspot was used for the amplitude and latency measures for the stimulus one and stimulus two measures for that specific peak. The latency and amplitude measures for stimulus one and stimulus two were recorded, along with the location of the hotspot electrode. The results were then analyzed for each group and between group descriptive statistics.

For determination of the presence of dysphagia in the PD group. The PA scores were averaged for the 5ml and 3oz task for each participant. Wilcoxin signed rank tests were used to determine differences in the participants with Parkinson’s disease versus the older healthy adults. Paired sample t-tests were used to determine if differences existed in the oral transit time, pharyngeal transit time, and total swallow time to compare the older healthy adults and the participants with Parkinson’s disease. Significance level was set a $p=.05$.

Results

Pharyngeal Stimulation Evoked Potentials (PSEP)

The pharyngeal mechanical stimulus to the pharynx (airpuff) resulted in four evoked potential peaks (PSEP) (see figure 7). The first positive peak (PSEP P1) occurred at a mean latency of 58.44 +/- 10.96 (SD) ms for the young healthy participants, 71.2 +/- 19.01 for the older healthy participants, and 61.08 +/- 16.2 for the participants with PD. This was followed by the a negative peak (PSEP N1) which occurred at a mean latency of 90.56 +/- 19.14 (SD) ms for the young healthy participants, 100.57 +/- 24.99 for the older healthy participants, and 93.23 +/- 17.0 for the participants with PD. A second positive peak (PSEP P2) occurred at 122.56 +/- 22.43 (SD) ms for the young healthy participants, 152.71 +/- 39.22 for the older healthy participants, and 122.85 +/- 16.75 for the participants with PD. A second negative peak (PSEP N2) occurred at 165.00 +/- 29.19 (SD) ms for the young healthy participants, 211.33 +/- 41.28 for the older healthy participants, and 159.76 +/- 20.34 for the participants with PD. For all means and standard deviation see Table 1.

Hot-Spot

Each peak was taken at the hot-spot location (see Figure 6). For PSEP P1 all participants had hot-spot locations in electrodes located posterior to the central line. For the young healthy participants ten had a left lateralized peak, at electrode P4 or C4'; eleven had a right lateralized peak, at electrode P3 or C3'; and four had the hotspot located at a midline electrode Cz, Pz, or Cz'. For PSEP N1 17/25 of the young healthy participants, 6/7 of the older healthy adults, and 11/13 of the participants with PD had hot-spot positions at midline electrodes (FCz, Fz, Cz or Cz'). Six of the remaining young healthy participants were lateralized to the left, and two to the right. The three

remaining participants from the older healthy group and the participants with PD all lateralized to the right. For PSEP P2 the young healthy participants had nine individuals with pre-central hot-spot positions, five individuals with central hot-spot positions, and eleven individuals with post-central hotspot positions; the older healthy adults group had three individuals with pre-central hotspot positions and four individuals with central hot-spot positions; the participants with PD had five individuals with pre-central positions, five individuals with central positions, and three individuals with post-central positions. For PSEP N2 the young healthy participants six had pre-central positions, five with central positions, and fourteen with post-central positions; the older healthy adults had five individuals with pre-central positions and the PSEP N2 peak was not seen in the other two participants; the participants with PD had six individuals with a pre-central position, three with a central position, three with a post-central position, and in three individuals the N2 peak was not seen.

Sensory Gating

To determine if sensory gating occurred with the mechanical stimulus to the pharynx, two stimuli were delivered 500ms apart. The amplitude of the second stimulus is divided into the first stimulus which gives a ratio (see Figure 10). For PSEP P1 the young healthy adults had a mean gating ratio of 1.03, the older healthy adult had a mean gating ratio of 1.37, and the participants with PD had a mean gating ratio of 0.75. For PSEP N1 the young healthy adults had a mean gating ratio of 1.35, the older healthy adult had a mean gating ratio of 0.54, and the participants with PD had a mean gating ratio of 0.74. For PSEP P2 the young healthy adults had a mean gating ratio of 1.09, the older healthy adult had a mean gating ratio of 0.33, and the participants with PD had a mean gating ratio of 0.35. For PSEP N2 the young healthy adults had a mean

gating ratio of 0.98, the older healthy adult had a mean gating ratio of 1.15, and the participants with PD had a mean gating ratio of 0.26.

Swallow

Penetration/Aspiration scores

None of the subjects reported having dysphagia. A subset of the healthy control participants (n=5) and the participants with PD (n=5) underwent videofluorographic analysis of swallow. The penetration/aspiration scale (PA scale) scores for the ten 5ml and two 3oz were averaged for each participant (see Table 2). Using Wilcoxon signed rank test revealed that the PA scores for the two groups were not significantly for the 5ml task ($Z=-.95$, $p=0.34$) and the 3oz task ($Z=-1.841$, $p=0.16$).

Swallow timing

Oral transit time, pharyngeal transit time, and total swallow time were calculated for each of the 5ml swallow tasks, and averaged across each participant (see Table 2 for means and SD). Paired samples t-tests were completed to assess if differences existed between the healthy older adults and the participants with Parkinson's disease. No significant differences were found comparing the older healthy adults with the participants with Parkinson's disease for oral transit time ($t=.71$, $df=8$, $p=.13$), pharyngeal transit time ($t=-1.61$, $df=8$, $p=.18$), or total swallow time ($t=-.01$, $df=8$, $p=.08$).

Discussion

This current study was designed to determine if somatosensory evoked potentials could be recorded in response to a mechanical stimulus (airpuff) to the oropharyngeal wall. The results support the hypothesis that event related evoked potentials (P1, N1, P2, and N2) can be recorded in response to an airpuff stimulus on the oropharyngeal

wall (PSEP). These results also support the hypothesis that pharyngeal sensory evoked potentials (PSEP) differ from other sensory modalities in the gating response.

Afferents

The oropharyngeal wall has a dense collection of afferents with 5-10 terminals/cm²; it is proposed that the airpuff stimuli activates mechanoreceptors (Mu & Sanders, 2000b). The pharyngeal wall is innervated by fibers from the glossopharyngeal cranial nerve (CN IX) and the pharyngeal branch of the vagus (CN X) (Mu & Sanders, 2000b; Reichert, 1934). Purves, et al (2004) and Wilson-Pauwel, Akesson and Stewart (1988) explain the projections of the glossopharyngeal and vagus afferent tracts as follows. The glossopharyngeal afferent fibers ascend to the cell bodies in the superior or inferior glossopharyngeal ganglia. The secondary neuron crosses the midline in the medulla and ends in the contralateral ventral posterior nucleus of the thalamus. The tertiary neuron ascends, through the internal capsule, to the primary somatosensory cortex (Purves et al., 2004; Wilson-Pauwels, Akesson, & Stewart, 1988). The pharyngeal branch of the vagus afferent nerve fibers unites with the external laryngeal branch, traveling up and combining with the rest of the vagus nerve reaching the inferior vagal ganglion. It then descends in the spinal trigeminal tract, to synapse in its nucleus. The secondary axons then project to the contralateral ventral posterior nucleus of the thalamus. The tertiary neuron, then ascend through the internal capsule, to the primary somatosensory cortex (Purves, et al., 2004; Wilson-Pauwels, et al., 1988).

Recent studies utilizing imaging techniques provide new information. Vagal nerve stimulation has become a tool for the treatment of seizures and depression (Chae, et al, 2003). Using positron emission tomography (PET), vagal stimulation produced increased blood flow to the brainstem, thalamus, hypothalamus, hippocampus, and

temporal cortex (Henry et al, 1998; Henry, 2000). Additionally, Chae, et al (2002) found increased activity in the cerebellum, and the temporal and parietal lobes. It is likely that the afferents affected in the present study were predominately the glossopharyngeal nerve fibers were projected to the cortex, via the thalamus.

Pharyngeal Stimulus Event Related Potentials (PSEP) and Source Localization

The P1 was the first positive peak in response to the airpuff stimulus, and was present in all participants. It is indicative of the arrival the afferent stimulus at the cortex (P. W. Davenport, et al., 1996b; Desmedt, Huy, & Bourguet, 1983; P. Nunez, Srinivasan, R., 2006). Davenport, et al. (1996a) hypothesized that the P1 reflects change in cortical activity from a dipole within the somatosensory cortex, similar to the RREP P1 and the SEP P50 from mechanical stimulation to the hand and leg (Chan & Davenport, in press; Desmedt, et al., 1983). It also suggests cortical awareness of the pharyngeal stimuli, which is not dependent upon the participants attending to the stimuli (P. W. Davenport, Friedman, Thompson, & Franzen, 1986; S. J. Williamson & Kaufman, 1990).

The average latency for the PSEP P1 was 58.44 in the young healthy participants, which is a similar latency to the respiratory related evoked potential (RREP) reported in Chan and Davenport (2008) which was 63 ms for young healthy adults; the P1 at 63ms from an airpuff stimulation to the buccal surface (Chan and Davenport, 2008); and Gow and colleagues (2004) which reported the P1 at 80ms following electrical stimulation to the pharynx. The elicitation of the P1 following the airpuff stimulus to the pharynx is evidence that the stimulus exceeded the detection threshold, and the somatosensory cortex was activated (Chou & Davenport, 2007; Davenport, Chan, et al., 2007).

The source localization for each peak was also of interest. Using the hotspot method, the electrode with the largest amplitude corresponding to the positive or negative peak was used for analysis. The hotspot locations, though a gross measure of source localization, does provide limited information in regards to the source of the dipole. The hotspot locations for the PSEP P1 were all from posterior central or lateral placements. This is similar to the RREP P1. von Leupoldt (2010) reported the RREP P1 cortical source was the centro-parietal region.

N1 was the first negative peak following the stimulus, and was present in all subjects. N1 is indicative of further cortical processing of the sensory stimuli (Davenport, Chan, et al., 2007; Nunez, Srinivasan, R., 2006). It is primarily an exogenous component peak, meaning that it can be elicited by a stimulus whether or not it is attended to by the participant (Crowley & Colrain, 2004; Rosburg, Boutros, & Ford, 2008). Similar other sensory modalities the PSEP N1 for the young adults occurred at approximately 90.56ms. Chan and Davenport (2008) reported the RREP N1 peak at approximately 109 ms in healthy young adults, and a N1 for the buccal stimulation at 85ms. Additionally, because of the similar latency the PSEP N1 could also be compared to the somatosensory N100, occurring at 96ms elicited from a mechanical stimulus to the hand (Pratt, Amlie, et al., 1979; Pratt, Starr, et al., 1979).

The RREP N1 can be affected by changes in the magnitude of the stimulus if participants attend to the stimuli; as opposed to an experimental paradigm in which participants ignore the stimuli (Davenport, Chan, et al., 2007). The pharyngeal airpuff elicited various sensations including urge to swallow, cough and gag. Due to the placement of the scope, and the sensations reported, it would be difficult to confirm if

the subjects were able ignore the stimulus throughout experiment. Wheeler, et al. (2010) examined urge-to-cough, in response to the same pharyngeal airpuff stimulation as was used in this project, in young adults, and found that 68% of airpuff trials elicited an urge-to-cough response. The presence of the N1, following the mechanical stimulus, to the pharynx, may be indicative of cognitive processing which the participants attending to the stimulus could affect.

The PSEP N1 hotspot was consistently located at the electrode Cz. This is similar to other sensory modalities. The RREP N1 is maximal over the vertex of the central somatosensory region, when reference to the joined ear lobes was used (Webster & Colrain, 2000a, 2000b). Additionally, evoked potentials in response to an auditory stimulus also report a vertex negativity at approximately 130ms (Rushby & Barry, 2009). These results demonstrate that the PSEP N1 is similar to N1 vertex peaks recorded from other sensory stimuli.

The P2 peak is evidence of further cortical processing, and was present in all subjects. P2, similar to the N1, is considered to be an exogenous response (Crowley & Colrain, 2004). Until recently the P2 has been viewed as part of the N1 component peak (Crowley & Colrain, 2004). However, Crowley and Colrain (2004) advocate that the P2 is independent; because the RREP P2 has an independent response to the rise time of the respiratory occlusions (Revelette & Davenport, 1990). There are similarities between the N1 and P2 though, including the non-response of P2 to the magnitude of the stimulus load in which the participants do not attend to the stimuli (Crowley & Colrain, 2004; Webster & Colrain, 2000a). Additionally, P2 is affected by participant attending the stimulus (Crowley & Colrain, 2004; Webster & Colrain, 2000b).

The PSEP P2 peak occurred at approximately 122ms, Revelette and Davenport (1990) reported RREP P2 peaks from 131-151ms, and von Leupoldt (2010) reported RREP P2 peaks from 160-230. Due to the time differences in the P2 peak it is not known if the PSEP reflects similar processing as the RREP P2, but with the limited information on the cortical processing on the pharyngeal stimulus it is difficult to speculate if they are different.

The hotspot locations for the PSEP P2 were heterogeneous. The distribution ranged from the frontal, central, and posterior positions. Verdindt et al (1994) hypothesized the auditory evoked P2 has input from two sources: a dipole in the supra-temporal region and a dipole in the temporo-parietal region. If the cortical processing of the auditory evoked P2 is similar to that of the PSEP, this hypothesis may explain the heterogeneity observed. If the amplitude of the two cortical generators were variable, this would affect the location of the chosen hotspot.

The N2 peak is indicative of further processing (Folstein & Van Petten, 2008; Rushby & Barry, 2009). It is influenced by cognitive control, specifically control of motor responses to the stimuli and strategic monitoring (Folstein & Van Petten, 2008; Rushby & Barry, 2009). The PSEP N2 peak was not present in all subjects this has been noted in other event-related potential studies i.e. Ritter (1979) who stated that in cases where a strong P2 is elicited it could obscure the N2. The latency of the PSEP N2 was 165ms in the young healthy participants. Revelette and Davenport (1990) demonstrate the RREP N2 in figure two and three, but do not comment on the average N2 across all subjects. It appears that the RREP N2, in the subjects shown, is after 200ms, which is a longer latency than the PSEP N2.

Parkinson's Disease and PSEP

Studies examining event related potentials and Parkinson's disease (PD) have reported varied results. In the current study the latency and amplitude measures from the PSEP P1, N1, P2, and N2 in the PD group were not different than the young healthy participants or the age matched controls. Evoked potentials are used as diagnostic indicators of PD, even in early stages of the disease (Chiappa and Ropper, 1982; Cracco et al, 1982; Mauguiere and Desmedt, 1991). The N30/P40 evoked potentials, recorded from the frontal cortex, following median nerve stimulation, are closely associated with muscle tone and movement execution in PD (Cheron & Borenstein, 1980; Rossini, et al, 1994). The changes in the N30/P40 also resolve following a bolus administration of synthetic dopamine (Rossini, et al, 1994). Rossini, et al, (1994) hypothesized that the changes in processing of afferent information from stimulation of this corticospinal pathway were valuable indicators of PD. However, the effect was not seen in the present study with a mechanical stimulus to an oropharyngeal wall, which is controlled within the corticobulbar system.

Severity of motor involvement, in PD, within the corticospinal and corticobulbar systems, also does not correlate. Ali, et al (1996) found no relationship between limb and lingual tremour or limb rigidity and pharyngeal dismobility. Furthermore, while Levadopa (L-Dopa) is the gold standard for the treatment of PD, it is not an efficacious treatment option for dysphagia (swallow disorders) (Born, et al, 1996; Hunter, et al, 1997).

Sensory Gating

The second major aim of this project was to determine if sensory gating occurred with a paired airpuff stimulus paradigm. Sensory gating is a process by which redundant

sensory information is inhibited from reaching the cortex (McCormick & Bal, 1994). In other sensory modalities large stimulus two amplitudes divided by stimulus one amplitudes ($S2/S1$) ratios are usually associated with disease, such as schizophrenia (Cadenhead, Light, Geyer, & Braff, 2000). The results are the first to demonstrate a somatosensory modality which does not exhibit a significant gated response in healthy adults. These results support a hypothesis that an airpuff stimulus can be delivered to the pharyngeal wall in a paired pulse paradigm, with a 500ms interstimulus duration, and elicit similar PSEP event related potentials for both. An interstimulus duration of 500ms because the greatest gated response is demonstrated with other somatosensory modalities (Arnfred, et al., 2001; Chan & Davenport, 2008; Kinsley, et al., 2001).

The PSEP P1, gating ratio ($S2/S1$), for the young healthy subjects was 1.03. In comparison, Chan and Davenport (2008) reported RREP P1 gating ratios of 0.55-0.56; gating ratios from airpuff stimulation to the buccal surface of 0.51-0.55; and a gating ratio from mechanical stimulation to the hand of 0.55. The N100 peak (analogous to the P1) in response to an auditory stimuli, was suggested by Fruhstorfer, et.al (1970) to be a key measure of sensory adaptation; and has been used at the gating peak in the RREP paradigm (Chan & Davenport, 2008). Chan and Davenport (2008) reported RREP N1 gating ratios of 0.47; gating ratios from airpuff stimulation to the buccal surface of 0.54; and a gating ratio, from mechanical stimulation to the hand, of 0.55. The PSEP N1, gating ratio for the young healthy subjects was 1.35. Additionally, the P2 and N2 gating ratios were similar to the P1 and N1, with values of 1.09 and 0.98 respectively.

The gating ratios for the PSEP in the young healthy adults suggest that the processing of the mechanical stimulation to the pharyngeal wall is different than other somatosensory modalities. Chan and Davenport (2008) hypothesized an increased gating ratio for the RREP P1 and N1 may be an indicator of respiratory-related anxiety disease, this would make gating of redundant respiration sensation advantageous. The oropharyngeal wall has a different function in airway protection, functioning as a primary location for the initiation and modification of swallowing (Pommerenke, 1928; Miller, 1982; Miller, 2008) The total swallow duration in healthy males, during a sequential swallow task, is 800ms (Chi-Fishman & Sonies, 2000). It is likely that the next bolus has entered the pharynx within the first 500ms, and for safety, the swallow system must be able to respond appropriately to the next bolus. For airway protection, it may be advantageous for the gate to remain open and all incoming stimuli be processed.

Parkinson's Disease and Sensory Gating

No previous studies have examined the effect of Parkinson's disease (PD) on sensory gating. In contrast to the young healthy adults, the older adults and those with PD demonstrated gating. This response is not likely associated with the presence of dysphagia. None of the older healthy adults or the participants with PD reported dysphagia, and the videofluorographic swallow evaluation (VFSE), on a subset of the participants, revealed no significant differences for PA score on the 5ml or 3oz tasks. Additionally the PA scores, within the sequential swallow task, were analogous to other studies in the healthy elderly population (Murguia, Corey and Daniels, 2009; Tsushima, et al, 2009). However, the gating trends suggested that the participants with PD gating the stimulus more than the healthy older adults and the young healthy adults. This trend may have several explanations. First, this method is able to identify disorders in

sensory processing associated with PD and aging before they can be functionally measured with the VFSE. Theoretically, sensory modalities may decline at different rates than motor modalities in response to ageing and Parkinson's disease. A vast majority of studies examining sensation in areas innervated by the cortico-bular system use reflex responses (i.e swallowing, laryngeal adductor response and cough) (Hammer and Barlow, 2010; Hammer, 2009), however if both the sensory and motor modalities are affected at different rates, it would be impossible to tease apart the two separate system within a reflexive task paradigm. The results of this study provide evidence for that hypothesis.

Secondly, the increased gating may be a result of increased processing time of the cortical-thalamic loop associated with age and PD. There is no information to suggest that sensory information from the pharynx is not is not further processed from the layer IV of the somatosensory cortex back to the thalamus. It may be that the processing time is shorter and healthy young adults would show a gated response if the stimuli were presented with shorter inter-stimuli latencies.

Conclusions

In conclusion, the pharyngeal stimuli elicited event related potentials (P1, N1, P2, and N2). These results demonstrated that the airpuff stimulus on the pharyngeal wall was great enough to activate the cortex. The response was consistent with age and with disease. The elicited peaks were similar to event related potentials documents in response to other somatosensory and auditory stimuli.

Sensory gating, in response to a paired stimulus paradigm, was not present in the young healthy adults. Greater gating responses were present within the older healthy adults group and the participants with PD. The gating response within the PD tended to

be larger than the older healthy adults. This response did not necessarily coincide with presence of dysphagia.

Future Studies

Several future studies are envisioned. First to examine persons with PD who are experiencing dysphagia, to determine if dysphagia affects the PSEP peaks and to determine if the gating response would be different in those with dysphagia. Secondly, if the PSEP peaks were affected by dysphagia, if the effect could be mediated by expiratory muscle strength training (EMST), which has been shown to improve penetration/aspiration in PD (Chapter 3). Thirdly, to examine PD participants who are off all medications, to determine if participants in a “non-medicated” state would have differences in the amplitude and/or latency of the PSEP peaks, and whether the medication affects sensory gating.



Figure 6-1. Pharyngeal stimulation evoked potential (PSEP) set-up

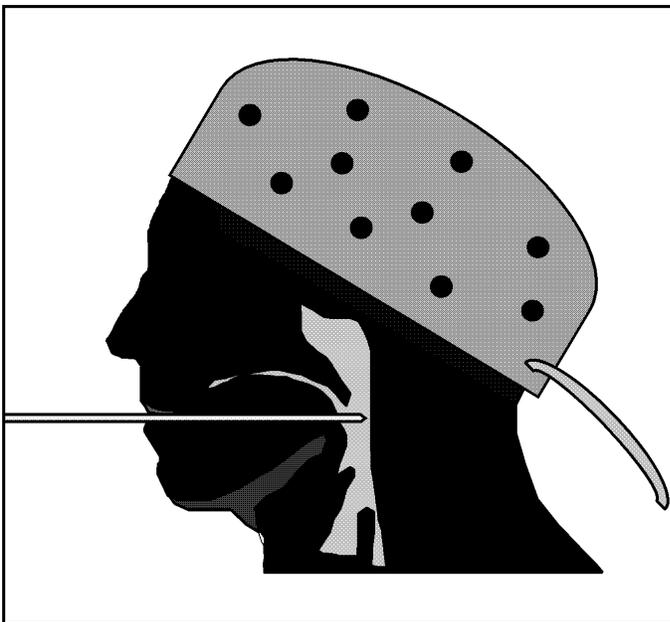


Figure 6-2. Flexible scope placement for the pharyngeal stimulation

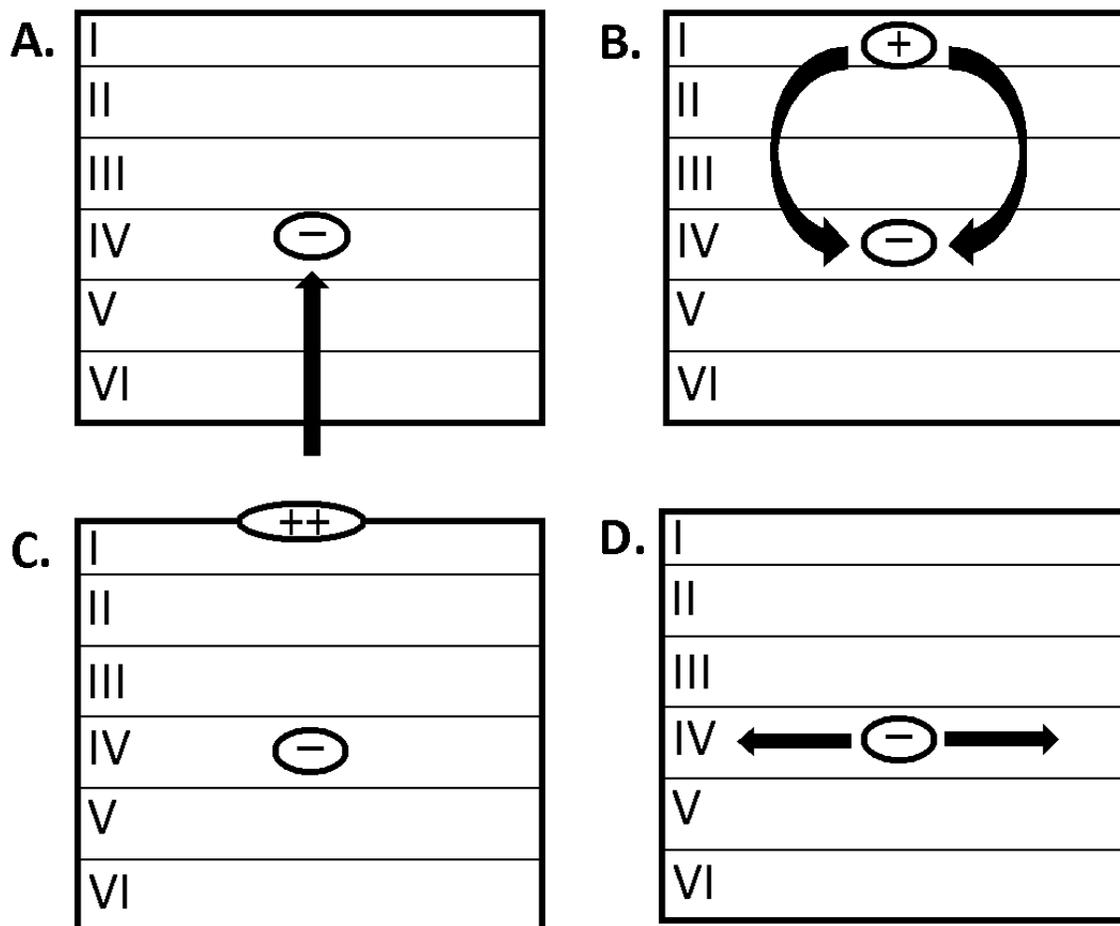


Figure 6-3. Schematic of the dipole within the primary somatosensory cortex. A. Arrival of the stimulus to layer IV of the somatosensory cortex. B. The negative net current dipole creates a movement of positive charge from the layers superior to layer IV, (C) which creates a hyper positive field on the cortical surface that is then recorded by the electrode as being the P1 or the first positive peak seen following the stimulus. D. The stimulus is then processed horizontally through the cortex



Figure 6-4. Mouthpiece

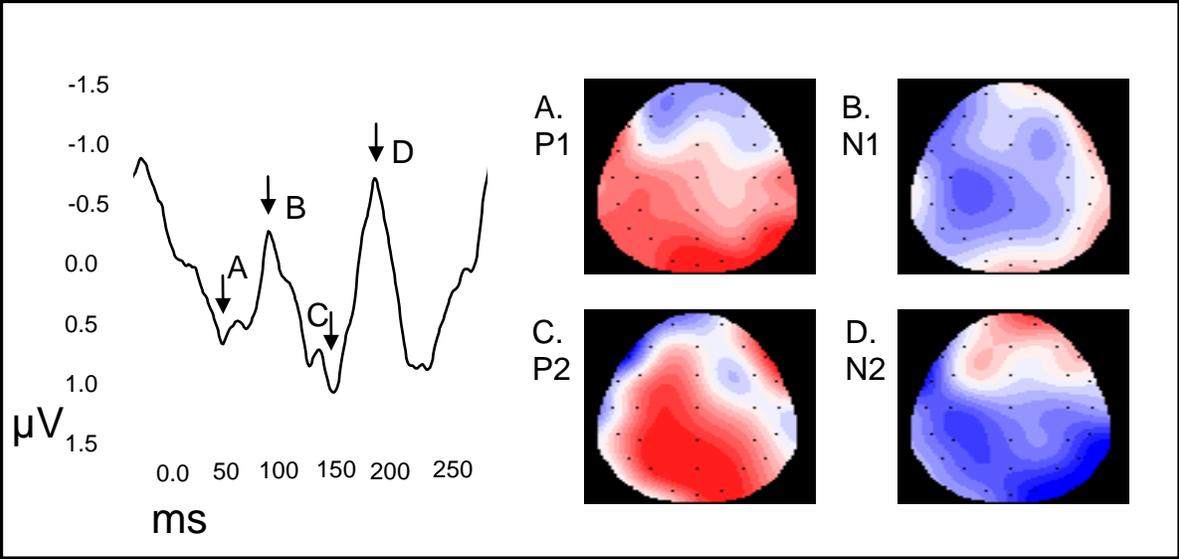


Figure 6-5. Hotspot electrode was determined using the waveform and two-dimensional map. Positive charge is characterized in red, and negative charge is characterized in blue. All PSEP peaks are labeled

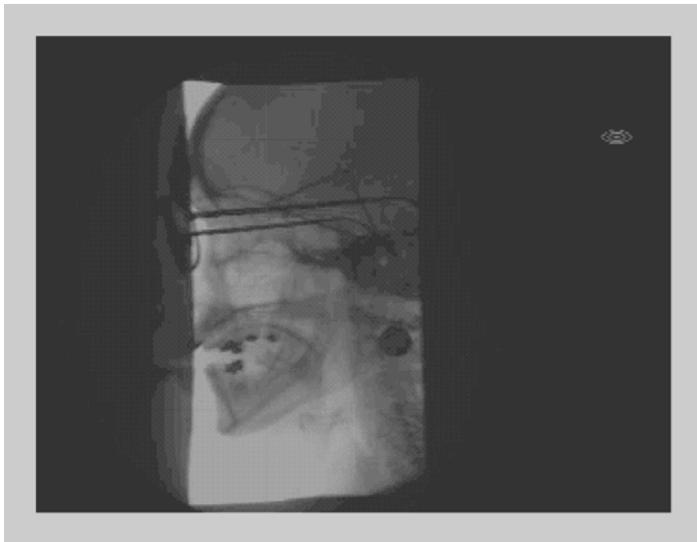


Figure 6-6. Image from a videofluorographic evaluation of swallow

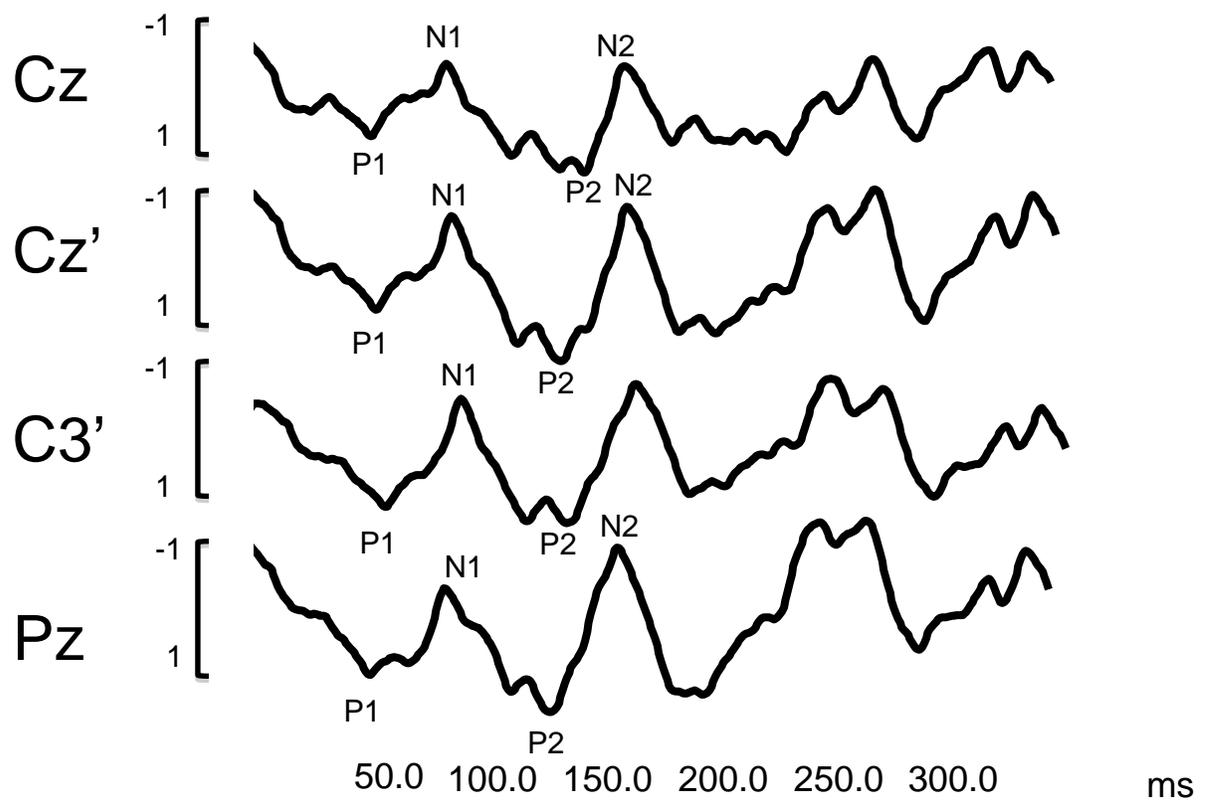


Figure 6-7. Identification of pharyngeal stimulation evoked potentials (PSEP) P1, N1, P2, N2 across four electrode sites

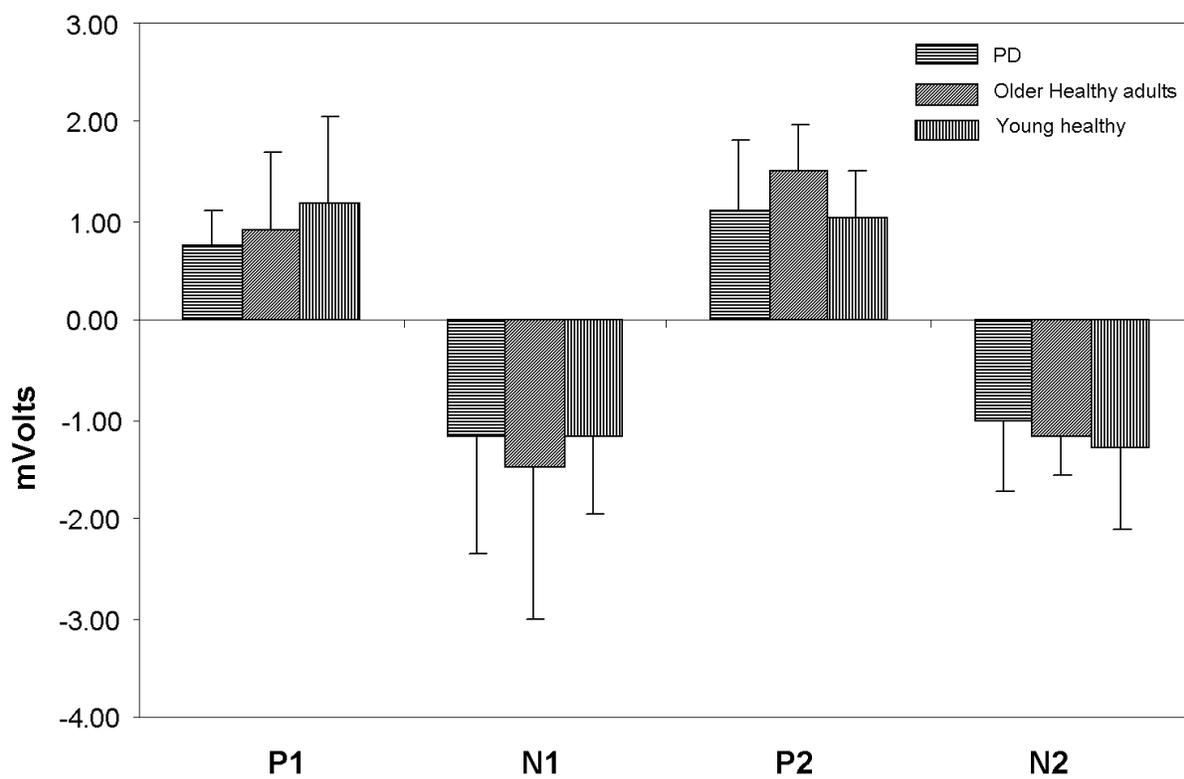


Figure 6-8. Group mean (SD) amplitude, following the first stimulus, of the pharyngeal stimulation evoked potential peaks

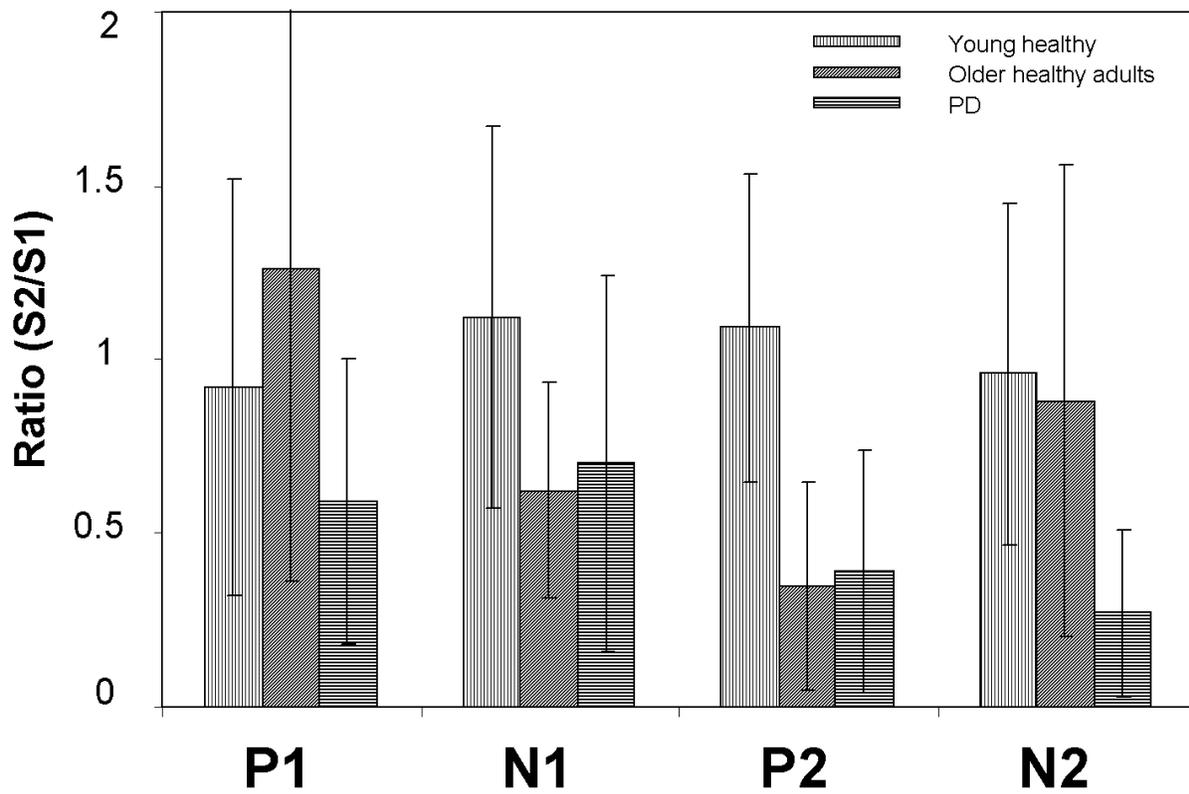


Figure 6-9. Gating ratio for comparison of stimulus two over stimulus one (S2/S1) for all PSEP peaks

Table 6-1. Means and standard deviations (SD) from the pharyngeal stimulus evoked potential (PSEP) peaks (P1, N1, P2, and N2)

	P1		N1		P2		N2	
	mean	SD	mean	SD	mean	SD	mean	SD
S1 Amplitude								
Young Healthy	1.19	0.85	-1.19	0.78	1.05	0.45	-1.30	0.83
Older Healthy	0.91	0.80	-1.49	1.53	1.51	0.48	-1.15	0.42
PD	0.75	0.37	-1.15	1.20	1.12	0.68	-1.03	0.69
S1 Latency								
Young Healthy	58.1	11	89.5	18.5	122	22	166.2	29.21
Older Healthy	71.2	19	107	20.8	137	34	193.2	44.87
PD	61.1	17	93.9	17.6	121	16	160.7	24.16

Table 6-2. Results from videofluorographic analysis of swallow. Oral transit time (OTT), pharyngeal transit time (PTT), total swallow time (TST), averaged penetration/aspiration score (PA) from the 5ml single swallow task, and the 3 oz sequential swallow task. Results expressed as means and standard deviations (SD)

Participant	Group	OTT	SD	PTT	SD	TST	SD	PA 5ml	PA 3oz
1	HC	0.95	0.61	0.82	1.07	1.77	0.84	2	2
2	HC	0.25	0.12	0.42	0.07	0.67	0.09	1.2	1
3	HC	0.35	0.12	0.86	0.15	1.22	0.14	1	3
4	HC	0.76	0.16	0.88	0.11	1.65	0.13	1.8	3
5	HC	1.28	0.81	0.70	0.05	1.98	0.43	1	3
6	PD	0.76	1.60	0.84	0.11	1.59	0.86	1.3	1.5
7	PD	0.48	0.07	1.03	0.16	1.50	0.12	1.5	3
8	PD	0.80	0.48	0.92	0.35	1.72	0.42	3	3
9	PD	0.30	0.15	0.87	0.17	1.18	0.16	2.2	3
10	PD	0.51	0.41	0.80	0.14	1.31	0.28	1.4	3.5

CHAPTER 7 DISCUSSION

There are three major conclusions from this study. First being that there is a relationship between cough and swallow. Chapter 2 is the first study to demonstrate this in Parkinson's disease. The results from this study indicated that those with PD, with known swallow dysfunction as defined by degree of penetration/aspiration during a sequential swallow, have impaired voluntary cough. This was evidenced by significant differences in measures of cough parameters made from an airflow signal elicited during voluntary cough. Significant group differences existed for CPD, EPRT, EP, and CVA. Moreover, there were modest correlations between penetration and aspiration scores and voluntary cough airflow parameters, suggesting, that the ability to cough voluntarily is related to the degree of airway protection.

Chapter 3 added an additional dimension of using voluntary cough as a screening tool for penetration and aspiration during swallowing in PD. This pilot project was the first to determine the accuracy of detecting presence of penetration/aspiration judged from VFSE during a three ounce swallow task, from changes in airflow waveform measures collected during voluntary cough in PD. Our results demonstrate that the four cough variables accurately detected healthy swallows versus penetration/aspiration. Additionally, EPPF emerged as a measure that may be useful in determining aspiration risk in multiple patient populations.

Chapter 5 further added further evidence for the relationship between cough and swallow. The tracheal stimulation, which stimulates cough, modified swallow. This study found a significantly greater number of swallows elicited and a significant increase in the amplitude of the thyropharyngeus EMG during the tracheal stimulation with water

infusion in the cat. This study is the first in a line of studies to further examine how this relationship is modified under various circumstances.

The second major conclusion of this study is that expiratory muscle strength training (EMST) modified the effectiveness of voluntary cough and the safety of swallow in Parkinson's disease (PD). Chapter 4 examined the effects of four weeks of EMST on voluntary cough function and the occurrence of penetration/aspiration in a group of persons with PD. The overall effectiveness of the participants' voluntary cough increased, as indicated by the increase in CVA. CVA relates to the ability of the cough to create shearing forces and remove unwanted material from the airway (Smith Hammond, et al., 2001). Specifically, CPD and EPRT, as measured from the voluntary cough airflow waveform, pre to post training, significantly decreased. The significant decrease in the EPRT led to a significant increase in the CVA. This study demonstrates clear improvement in cough and swallow, as measured by PA scores, following EMST training, and demonstrates that it is a viable treatment option for PD participants who are at risk for aspiration. Future studies should examine larger cohorts and also a more diverse group of participants, including those in different disease stages, and different gender.

The third major conclusions were the differences in the processing of the pharyngeal stimulation in the PD group, in chapter 6. No previous studies have examined the effect of Parkinson's disease (PD) on sensory gating. In contrast to the young healthy adults, the older adults and those with PD demonstrated gating. This response is not likely associated with the presence of dysphagia. None of the older healthy adults or the participants with PD reported dysphagia, and the

videofluorographic swallow evaluation (VFSE), on a subset of the participants, revealed no significant differences for PA score on the 5ml or 3oz tasks. Additionally the PA scores, within the sequential swallow task, were analogous to other studies in the healthy elderly population (Murguia, Corey and Daniels, 2009; Tsushima, et al, 2009). However, the gating trends suggested that the participants with PD gating the stimulus more than the healthy older adults and the young healthy adults. This trend may have several explanations. First, this method is able to identify disorders in sensory processing associated with PD and aging before they can be functionally measured with the VFSE. Theoretically, sensory modalities may decline at different rates than motor modalities in response to ageing and Parkinson's disease. A vast majority of studies examining sensation in areas innervated by the cortico-bulbar system use reflex responses (i.e swallowing, laryngeal adductor response and cough) (Hammer and Barlow, 2010; Hammer, 2009), however if both the sensory and motor modalities are affected at different rates, it would be impossible to tease apart the two separate systems within a reflexive task paradigm. The results of this study provide evidence for that hypothesis.

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--

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BIOGRAPHICAL SKETCH

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