Effects of Deep Brain Stimulation on Swallow Physiology in Patients with Parkinson Disease

by

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A dissertation submitted to the Graduate Faculty in Speech-Language-Hearing Sciences in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York

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This manuscript has been read and accepted for the Graduate Faculty in Speech-Language-Hearing Sciences in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy.

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Abstract

EFFECTS OF DEEP BRAIN STIMULATION ON SWALLOW PHYSIOLOGY IN PATIENTS WITH PARKINSON DISEASE

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The effect of neurosurgical intervention for patients who present with oropharyngeal dysphagia secondary to idiopathic Parkinson Disease is not well understood. Deep brain stimulation of the subthalamic nucleus (DBS-STN) is an effective treatment for the improvement of limb movements, but its effect on speech and swallowing is less predictable. DBS is a reversible therapeutic surgical procedure that uses small electrical pulses to disrupt the brain signals that cause tremor and rigidity. It involves implanting a thin insulated wire (lead) with electrodes into the STN of the brain. To date, the literature that has addressed the effects of DBS-STN on speech has not demonstrated statistically or clinically significant gains. Studies of this nature looking at the effects of DBS-STN on swallow physiology are limited. Most recently, one such study attempted to document positive effects on swallow physiology; however, several methodological questions limited the generalizability of the results reported (i.e., Ciucci, Barkimer-Kraemer & Sherman, 2008). For example, their study protocol

included patients that were off their Parkinson medications for 12 hours, and studied them only one hour after changing the DBS condition (p. 677), from DBS “on” to DBS “off”. The present study, sought to: (1) quantify the temporal and physiological changes in specific aspects of swallow physiology when comparing the DBS “on” to the DBS “off” condition; and (2) to determine benefits/contraindications to DBS placement in patients with oropharyngeal dysphagia. Participants were examined during the DBS “on” condition and subsequently with the equipment turned off for 24 hours so as to complete the DBS “off” condition examination.

It was hypothesized that negative changes in swallow physiology would result during the DBS “on” condition when compared to the DBS “off” condition. Namely, quantifiable changes in bolus flow through the oropharynx to the cervical esophagus would be observed. Six adult participants were included in this preliminary study. No statistically significant differences were found for oropharyngeal swallow efficiency (OPSE), swallow apnea duration (SAD), tongue pressure changes or scores on the United Parkinson’s Disease Rating Scale (UPDRS) when comparing the DBS “on” condition (day #1) to the DBS “off” condition (day #2). Of note, although not statistically significant, was the observation that for bolus consistencies of liquid form (5cc thin liquid and “sips” thin liquid), there was an improvement in OPSE score from day #1 to day #2; whereas for the pudding and cookie consistencies there was a decline in the mean OPSE score. Furthermore, analysis of UPDRS scores attained in the area of speech (question #5) and swallowing (question #7) denoted a non-statistically significant trend towards worsening speech production and swallow function on day #2 (DBS in off condition). Three of the six participants completed tongue pressure measurements and two of these demonstrated an increase in isometric pressure on day #2. Additional participants need be tested in order to gain greater insight into changes in swallow physiology using this particular surgical approach for the treatment of Parkinson Disease.

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This has been a very long, yet enjoyable journey. I have met many new people and learned a great deal. This process has made me realize, more than ever, that the completion of ones studies require passion, focus, intellect and major support from surrounding friends and family.

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Review of the Literature

It has been reported that approximately 70 to 89% of persons with Parkinson Disease (PD) develop speech or voice disorders (Hartelius & Svensson, 1994, p. 16; Logemann, Fisher, Boshes & Blonsky, 1978, p. 50). Furthermore, Hartelius and Svensson suggested that approximately 41% of persons with PD report an "impairment in chewing and swallowing abilities" while others have reported the incidence to be up to 95% (Logemann, Blonsky & Boshes, 1975, p. 69). Neurosurgical interventions for the treatment of advanced PD have been reported to be effective in reducing the severity of parkinsonian signs, especially those motor signs that respond to levodopa (Baron et al., 1996, p. 363; Kumar, Lozano, Montgomery & Lang, 1998, p. 80). These neurosurgical therapies appear to have been driven by the limitation of available pharmacological agents in managing fluctuations in dyskinesias, often stemming from the pharmacological therapies themselves. Interestingly, the effect of these surgical treatments on speech, voice and swallowing mechanisms are not well understood. Most often, it has been assumed that the limb and speech/swallowing motor systems would be affected similarly by neurosurgical interventions. Recent evidence shows a variety of effects on improvement in *speech production* subsequent to several neurosurgical interventions. The literature addressing improvements in *swallow physiology* is extremely limited. One such study exists for one surgical intervention and will be discussed later in this section.

The following review encompasses aspects pertinent to the current study. Upon reviewing relevant neurosurgical interventions, with special emphasis on Deep Brain Stimulator implantation, what is known about its effects on speech motor control and swallow physiology will be reviewed. Lastly, the literature available on the measures utilized for this study will be addressed.

Neurosurgical Interventions

Lang (2000) offers a comprehensive review of the surgical treatments available to persons with PD. He argues that while pharmacological agents undergo rigorous examination before approval for widespread use, surgical interventions do not undergo such scrutiny (p. 1118). Lang also mentions that evidence for most surgical interventions is lacking and in need of well-designed clinical

trials (p. 1119). Difficulties in designing such studies are obvious. Placebo effects, keeping participants blinded to site of intervention, placing participants into surgical and non-surgical intervention groups, and keeping examiners blinded if the participant is unblinded are just a few of the challenges facing researchers. Many have used subjective evaluations of disability, mostly focused on activities of daily living (ADLs). However, these also present many instances of bias on part of the participant and/or the examiner. Another factor to consider is the variability in surgical techniques and overall precision of targets and electrode placement (e.g., creating lesions to the globus pallidus versus lesions to the thalamus; or making decisions regarding location of electrode placement on the thalamus).

The following is a brief summary of the history of neurosurgical interventions, based on Lang's 2000 article. More recent information is included, as appropriate. Furthermore, the issue of microelectrode versus macroelectrode mapping has not been completely resolved, although at this point, most practitioners utilize the former.

Thalamotomy requires surgical ablation of a portion of the thalamus. Targeting the ventral intermediate nucleus has been the area most commonly addressed, and although it reduces tremor, it has had minimal effect on other parkinsonian symptoms. Complications from this intervention have included persistent paresthesias, dystonia, dysarthria, and cognitive changes. The latter two complications have been more frequent following bilateral procedures.

Pallidotomy regained attention in the early 1990s. It involves ablation of a portion of the internal segment of the globus pallidus (GPi). Most of the data reviewing results of this intervention are in the form of case studies. The larger case study series reported inconsistent or "uninterpretable findings" (Iacono, Shima, Lonser, Kuniyoshi, Maeda & Yamada, 1995) based on a sample of 126 participants. One of the major risks with this procedure is the close proximity of the GPi to the optic tract and the internal capsule which may be damaged at the time of lesioning. Benefits of pallidotomy have not been shown to be effective beyond two years.

Subthalamic nucleotomy remains controversial because of fear of its disabling effects if lesion site is inaccurate (e.g., hemiballismus). This area has received increasing interest based on the recognition that the subthalamic nucleus (STN) is overactive in parkinsonism-induced monkeys and that the resulting excitatory drive from this region to the basal ganglia outflow sites accounts for many of the clinical features seen in persons with PD.

Deep brain stimulation, or DBS, is a reversible therapeutic surgical procedure that involves the implantation of a brain pacemaker. The deep brain stimulation system consists of three components: the implanted pulse generator (IPG), the lead, and the extension. The IPG is a battery-powered neurostimulator encased in a titanium housing, which sends electrical pulses to the brain to interfere with neural activity at the target site. The lead is a coiled wire insulated in polyurethane with four platinum iridium electrodes and is placed in one of three areas of the brain. The lead is connected to the IPG by the extension, an insulated wire that runs from the head, behind the ear to the IPG, and is placed subcutaneously below the clavicle or in some cases, the abdomen (Figure 1). The IPG can be calibrated via a remote control by a neurologist, nurse or trained technician to optimize symptom suppression and control side effects. The U.S. Food and Drug Administration (FDA) approved the use of DBS for treatment of Parkinson disease in 2002.

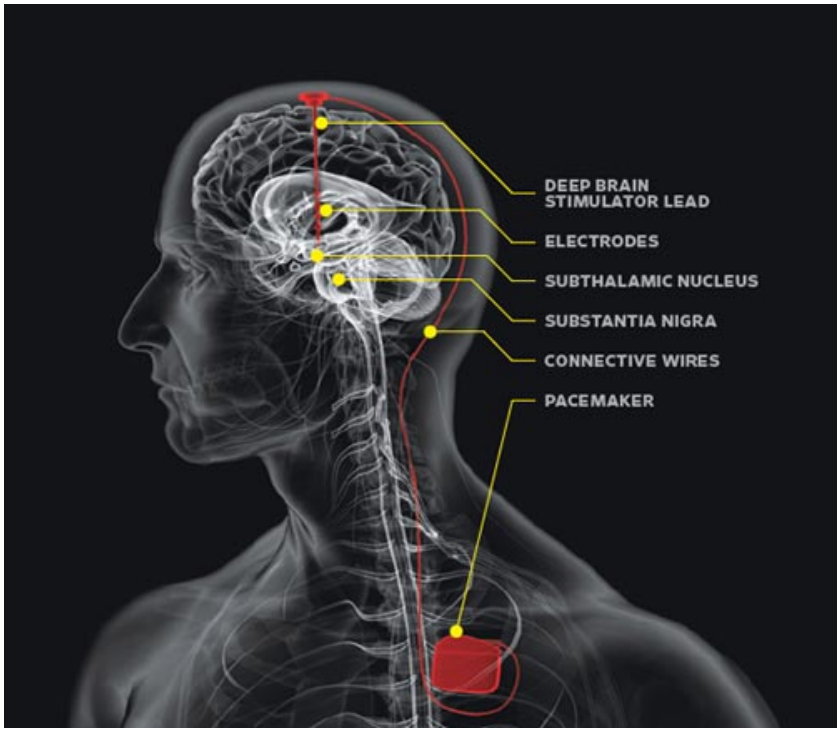

Figure 1. Deep brain stimulation (DBS) system. Reproduced from http://biomed.brown.edu/Courses/BI108/BI108_2008_Groups/group07/Parkinsons.html. Original source unavailable.

Lead placement has been somewhat controversial since its inception. Placement in the globus pallidus, thalamus or subthalamic nucleus (STN) has been studied. Best results for alleviating all motor manifestations of PD have been achieved by DBS of the subthalamic nucleus (DBS-STN). Additionally, STN electrode placement has resulted in a reduction of anti-PD medications and the need for lower voltages for stimulation (resulting in longer battery life). It has been shown to be a safe and effective method for treating idiopathic Parkinson disease, including tremor, rigidity, bradykinesia, on/off fluctuation, oral control, gait/balance difficulties and dyskinesia (as cited in Zonenshayn, Sterio, Kelly, Rezai & Beric, 2004, p. 216). Location of lead placement in the STN has been further studied. Optimal clinical results were reported by Zonenshayn et al. when electrical stimulation was provided to the anterior dorsolateral border of the STN. Most recently, Maks and colleagues (2009, p. 660) confirmed this placement as optimal, in a study addressing the electrical spread of STN stimulation. Both studies reviewed based their conclusions on scores achieved on the United Parkinson's Disease

Rating Scale (UPDRS; Fahn & Elton, 1987) post implantation. The current study included participants with placement in the STN bilaterally, as described above.

A meta-analysis of 22 studies of DBS-STN in Parkinson disease found greater than 50% improvement on the UPDRS and in motor function and activities of daily living, and a 69% reduction in dyskinesias (Kleiner-Fisman, Herzog, Fisman, Tamma, Lyons, & Pahwa, 2006, p. S298). These authors also report that it is estimated that as of 2006 more than 35,000 persons with Parkinson disease had been implanted with DBS-STN worldwide (p. S291).

STN Function

The precise mechanism of action by which DBS alters STN function remains poorly understood. The STN has been regarded as an important modulator of basal ganglia output. Hamani, Saint-Cyr, Fraser, Kaplitt and Lozano (2003) described the role of the STN in the context of movement disorders in a review article. They state that the STN receives its major afferents from the cerebral cortex, thalamus, globus pallidus externus and brainstem, and it projects mainly to both segments of the globus pallidus, substantia nigra, striatium and brainstem (p. 5). It is hypothesized that inhibition of STN function leads to a diminished inhibitory outflow of the internal segment of the globus pallidus onto the motor thalamus (ventrolateral aspect), therefore resulting in an alleviation of motor symptoms. The discussion is further complicated when taking into account differences in high-frequency DBS versus low-frequency DBS and its effects on the specific structures and interactions of the basal ganglia-thalamic-cortical (BG-TH-CTX) system.

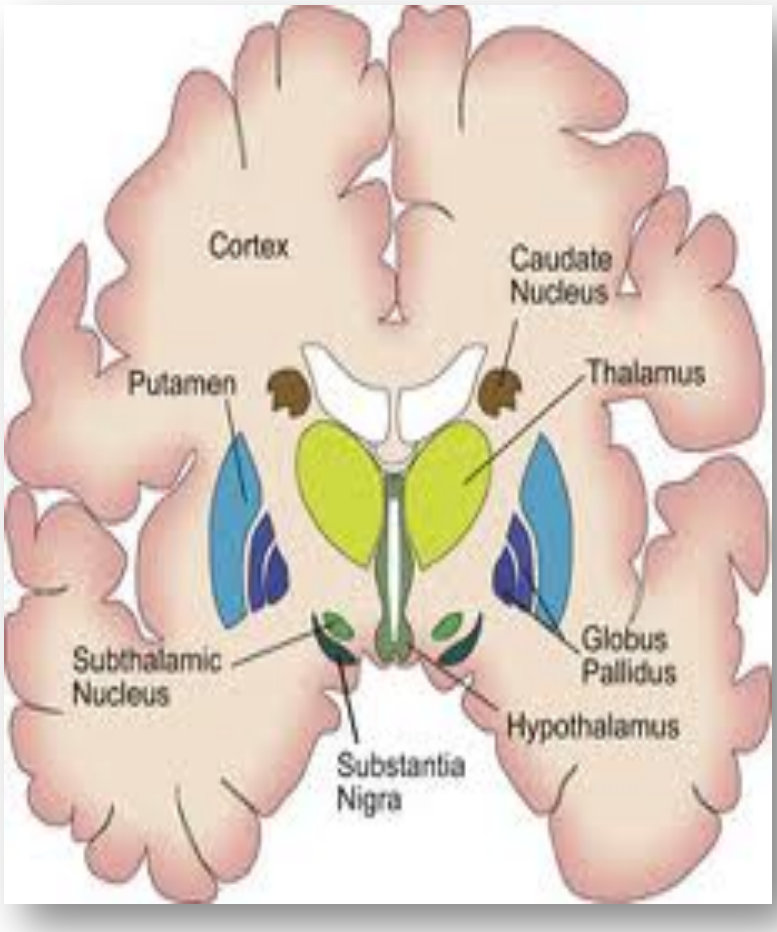

Figure 2. Basal ganglia system. From http://www.dana.org/news/brainwork/detail.aspx?id=6028. Image credit: Ellen Davey. Reprinted with permission.

The subthalamic nucleus (STN) is known to be a "tight" nucleus, and is composed of glutamatergic neurons. These are known to be spontaneous firing neurons that are also capable of firing at very high frequencies.

Based on a comprehensive review article by Montgomery, Jr. and Gale, (2007, p. 390), the central themes in attempting to understand the pathophysiological mechanisms involved in DBS stimulation of the STN include: (1) whether DBS inhibits or excites the stimulated target; (2) whether the therapeutic DBS mechanisms of action are local or attributable to the basal ganglia-thalamic-cortical (BG-TH-CTX) system; and (3) whether the effects follow from responses to a single pulse or a

collective of pulses. Most recently, Montgomery, Jr. (2008) has proposed a theory based on oscillators. Of concern has been the belief that pathophysiological mechanisms are specific to structures rather than generated by systems. In looking at oscillators, he has proposed the "systems oscillators theory." This theory re-interprets the traditional conceptualization of the BG-TH-CTX system from a sequential hierarchical organization to sets of multiple nested, loosely coupled, dynamic, non-linear, reentrant, polysynaptic oscillators (Montgomery, Jr., 2007b, p. 458). Traditional models have presented one-dimensional push-pull dynamics, which in this model are replaced with richer sets based on interactions between oscillators including: resonance, beat interactions, and synchronizations and de-synchronizations. Additionally, in this model not all neurons discharge with each cycle of the oscillator. He argues that with each cycle there are sufficient numbers of neurons discharging so as to continue the oscillations (p. 460). Further, multiple action potentials may be transmitted simultaneously through any connection thereby increasing the range of oscillator frequencies inherent in the neuronal activities. Consequently, the activity of individual neurons may represent multiple frequencies.

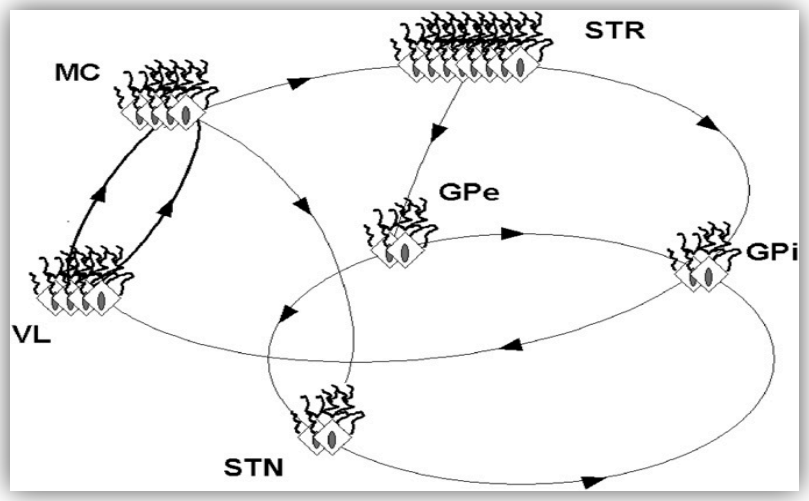

Figure 3. Systems Oscillators Theory. STR = striatum; GPe = globus pallidus external segment; GPi = globus pallidus inernal segment; VL = ventrolateral thalamus; MC or mCTX = motor cortex; STN = subthalamic nucleus. From, "Basal ganglia physiology and pathophysiology: A reappraisal." by E.B. Montogmery, 2007, *Parkinsonism and Related Disorders, 13*, p. 459. Used with permission from the publisher.

This figure represents the BG-TH-CTX system as proposed in the “systems oscillators theory” (Montgomery, Jr., 2007b, p. 459). Each oscillator is composed of nodes and connections between nodes. Nodes represent subsets of neurons within the anatomical nuclei. In the model, a single oscillator (loop) involves multiple structures and a structure may contain multiple oscillators. The number of nodes contained in the oscillator determines the fundamental frequency of any specific oscillator. There are many more loops than shown in Figure 3, such as those connecting the centromedianus and the parafascicular nuclei of the thalamus, the subtantia nigra pars compacta and reticulata, and the pedunculopontine nucleus. The theory further states that there are side loops, and that of “the BG-TH-CTX system through the BG act to modulate the amplitude of oscillations within the VL-mCTX (ventrolateral thalamus to motor cortex) circuit, thereby controlling the amplitude of bulbar and spinal neuronal activity and consequently, electromyographic (EMG) activity. The modulation of the amplitude of oscillations within the VL-mCTX circuit produces the precise orchestration of muscle forces necessary for normal movement.” (Montgomery, Jr., 2007b, p. 460). Following this line of thinking and applying it to swallow physiology, one could propose that DBS may stimulate the oscillating pattern from the STN to the globus pallidus interna, which in turn affects the VL-mCTX oscillator. Difficulty recruiting motor units has been implied in Parkinson Disease, so this would have to depend on resonance amplification of the oscillators, so as to result in a change at the level of the mCTX. This, in turn, would impact specific motor responses related to swallow physiology (specifics yet unclear) at the cortical level. This line of thinking may correspond to the increased force generation in the lips and tongue reported by Gentil, Garcia-Ruiz, Pollack and Benabid (1999) when DBS acts in resonance to amplify the oscillations of the VL-mCTX circuit (p. 332). Additional speculation is offered in the Study Objectives section of this manuscript (p. 17).

Speech Production and DBS-STN

Although after DBS-STN general motor function and dyskinesias improve in persons with Parkinson disease, motor speech abilities often do not respond or respond negatively (D’Alatri et al., 2008, p. 370; Pinto et al., 2004a, p. 553) to the implant and stimulation. Reports of new or worsened dysarthria vary widely. Researchers report ranges from 5% worsening to 61% worsening (Guehl et

al., 2006, p. 969; Krack et al., 2003, p. 1932). Specific speech symptoms associated with DBS-STN include reduced intelligibility (Rousseaux et al., 2004, p. 332), difficulty with speech initiation (Moretti et al., 2003, p. 251), and greater impairment in prosody, articulation and intelligibility (Santens, De Letter, Van Borsel, De Reuck & Caemaert, 2003, p. 256). These authors also found that speech declined or remained unchanged when assessed during on-medication cycles at follow-up sessions one year or more after implantation (p. 256). Most recently, Tripoliti et al., (2011, p. 83) found an average deterioration in speech intelligibility of 14.2% while off-medication and 16.9% while on-medication for a sample of 31 persons with DBS-STN and PD. These authors also reported that speech intelligibility deteriorated one year after DBS-STN in 78% of patients in contrast with the marked 50.7% improvement in parkinsonian motor symptoms (p. 84). Furthermore, Narayana et al. (2009, p. 156) reported on a case study where speech production was perceptually inferior and acoustically less contrastive during left STN stimulation compared to no stimulation. Their case provided some evidence of functional asymmetries affecting speech production, as well as the possible deterioration of production if unintended activation of the dorsal premotor cortex ensued.

A review of the literature suggests that speech performance studies have several limitations. In some studies, speech outcomes were reported based on results from the UPDRS. It should be noted that this scale only includes one item for speech improvement (item 18) and is a perceptual rating. Several studies did not report on medication cycle (on versus off). This is significant as per the impact on each person's daily communication activities. Differences in selection of quantitative measures (e.g., fundamental frequency, sound pressure level, voice onset time) to be assessed also limit clinical generalization. Furthermore, small sample sizes further limit generalizability.

Swallow function and DBS-STN

Swallowing disorders in persons with Parkinson disease encompass deficits in all phases of the swallow (Logemann, 1988, p. 218). Reduced lingual motility has resulted in longer oral transit times, difficulty in bolus formation, and hesitancy in the initiation of the swallow (Logemann, Fisher, Boshes & Blonsky, 1978, p. 56; Silbiger, Pikielney & Donner, 1967, p. 448). Pharyngeal phase

disorders reported include delayed pharyngeal response and decreased pharyngeal contraction (Stroudley & Walsh, 1991, p. 892). Most recently, improvements for the oral phase of swallowing have been noted post Lee Silverman Voice Treatment (LSVT), except for the cookie condition (i.e., where the bolus to be swallowed consists of ¼ of a Lorna Doone cookie impregnated with barium) (Sharkawi et al., 2002, p.33).

Only one research study has been published thus far exploring the role of DBS-STN on swallowing disorders in persons with Parkinson disease (Ciucci, Barkimer-Kraemer & Sherman, 2007). This study compared "on" and "off" conditions for DBS and found significant improvements in a 'pharyngeal total composite score' during the "on" condition (p. 681). No improvements were noted for components of their "oral total composite score;" namely, hyoid bone excursion or oral stage measures. It should be noted that participants in the study were first evaluated with the DBS in "on" condition; then the DBS was turned off for one hour and the participant completed the swallow study protocol once again. Of concern is the fact that the DBS was only turned off for one hour prior to re-studying each participant. This raises the question of how long a time period is necessary for proper "flushing" of neuronal activity from the DBS stimulator, before movements can be studied without its influence. To date, no data exists to answer this question. Of further note is the use of oral and pharyngeal total composite scores which have not been previously reported in the literature, and whose reliability has not been demonstrated yet. The authors defined the scores as qualitative measures translated into quantitative scores using a 0 – 4 scale (p. 678). Oral stage parameters included: number of swallows per bolus, number of festinated tongue movements, range of tongue movement, oral residue, and premature loss of bolus to the pharynx. Pharyngeal stage parameters included: decreased velar elevation, decreased posterior wall displacement, laryngeal penetration, aspiration, vallecular residue, pyriform sinus residue, and upper esophageal sphincter dysfunction. These parameters were not further defined in the article.

The following is a review of the measures employed in this study. As available, data on studies with participants with Parkinson disease are reported. Minimal data specific to persons with Parkinson disease is currently available, hence increasing the need for this study.

Oropharyngeal swallow efficiency (OPSE)

"The OPSE score was developed as a single global measure to reflect all aspects of oropharyngeal dysphagia during videofluoroscopy: oropharyngeal transit times and the observed or measured percentage of bolus swallowed into the esophagus minus an estimate of the percentage aspirated, thus reflecting the efficiency of the swallow" (Logemann et al., 2005, p. 226; Rademaker, Pauloski, Logemann & Shanahan, 1994, p. 323). Rademaker et al., 1994, p. 320, observed that normal participants swallow all of the bolus with only a 2 to 4% residue in the oropharynx. Additionally, Rademaker et al. reported normal volunteers in their study scored an average OPSE of 79 for all consistencies, and 85, 72 and 61 respectively for each of a liquid, paste and cookie bolus (p. 323).

The subjectivity of some of the measures used for calculating the OPSE have been criticized. Namely, the perceptual judgments involved in calculating percent residue. Logemann et al., 2005 reported a comparison of videofluoroscopy with scintigraphy in efforts to better quantify and compare percentages of residue in the oral cavity or pharynx. The results from this study showed that percent residue from videofluoroscopy can be useful and representative when obtained by a well-trained clinician (p. 229). However, the level of training necessary for examiners has yet to be investigated.

The previously described Sharkawi et al. (2002) study used the OPSE measure to assess changes in swallow efficiency in persons with PD pre and post LSVT training. As reported (no numerical data provided, p. 34), improvements were noted for the oral phase of swallowing. In 2005, Sueli-Monte and colleagues reported on results from 27 participants with PD. They reported OPSE scores in the 40-60 range. It should be noted that this data was obtained from a table in the published document, and was not discussed in the narrative section of the results (fig. 3, p. 460).

Swallow apnea duration

Cessation of respiration, or swallow apnea, is a well known phenomenon that occurs during normal swallowing (Hiss, Strauss, Treole, Stuart & Boutilier, 2003, p. 293; Hiss, Strauss, Treole, Stuart & Boutilier, 2004, p. 573). Hiss, Treole and Stuart (2001, p. 134) reported that expiration was the most frequently interrupted respiratory phase with an occurrence of 62% in normals. Instrumentally, swallow apnea is depicted as a respiratory trace waveform that represents the entire respiratory cycle during the swallow (e.g., inspiration, expiration, apnea). Research studies in this area with populations that present with dysphagia is only just beginning. It is clear that swallow apnea does change in persons with disordered swallowing. In neurological populations, Selley, Flack, Ellis and Brooks (1989) did some of the original work in this area, and found that persons with neurological disease presented different swallow apnea patterns when compared to healthy individuals (p. 175). In older persons with dysphagia, a shorter swallow apnea duration (SAD) was associated with penetration and aspiration (Nilsson, Ekberg, Bulow & Hindfelt, 1997, p. 505). In persons with cerebral palsy, swallow apnea was demonstrated to have greater variability and duration when compared to controls (Rempel & Moussavi, 2005, p. 110). Butler (2007) reported results on a population post CVA. She found that individuals who aspirated presented with longer SAD than individuals who did not aspirate and that in general, SAD for individuals post CVA was longer than that of healthy older adults. With this population, she also found differences in respiratory phase relationships; namely, individuals post CVA who aspirated demonstrated a greater frequency of inspiration-apnea-inspiration than individuals who did not aspirate and healthy older adults (p. 221). Further review of her data revealed that persons post CVA averaged a SAD of 1.53 seconds for a 5ml thin liquid bolus if they did not aspirate, and 2.22 seconds if they did aspirate (table 2, p. 219). Other bolus volumes tested included 10ml, 15ml and 20ml.

The present study was designed to address the duration of the apneic period (i.e., SAD), rather than where in the cycle apnea occurs, or respiratory phase relationships. This data was recorded, however, and may be analyzed at a future date. It is known that SAD is longer with

increases in bolus volume (Hiss et al., 2001, p. 131). Delayed onset of SA predisposes the patient to a misdirected swallow (i.e., laryngeal penetration and/or aspiration). To date, no studies have addressed swallow apnea or respiratory phase relationships in persons with PD or persons with PD status post DBS-STN implantation.

Tongue pressures

Tongue strength has been demonstrated to play a major role in the oral stage of swallow, including influencing oral transit times. It is for this reason that tongue strength was measured in the present study. Lazarus et al. (2000, p. 1018) correlated tongue strength with ability to clear the bolus from the oral cavity (i.e., oral residue). The impact of tongue strengthening exercises on maximal tongue strength (maximal isometric pressure generation) and overall changes in muscle bulk is an area that has received great attention over the past decade. Most of the literature to date has used the Iowa Oral Pressure Instrument (IOPI) for measures of strength and for the purpose of exercise training (Lazarus, Logemann, Huang & Rademaker, 2003; Robbins, Gangnon, Theis, Kays & Hind, 2005).

The present study sought to address differences in isolated maximal isometric tongue pressures (Pmax = strength) for persons with PD status post DBS-STN implantation while the stimulator was on and then when it was off.

Additionally, swallow pressures generated during swallowing have been further studied (Robbins et al., 2005) in the context of the effects of lingual exercises. This encompasses the placement of tongue bulbs in the oral cavity (along the hard palate) during swallow trials. It was decided early in the design stage, that for this study and with this population, the presence of bulbs along the hard palate during swallows might alter other measures of swallow physiology.

No literature currently exists comparing changes in rigidity and/or bradykinesia, to changes in overall tongue function. This would be relevant to the present study, as per the protocol followed, since participants did not change their medication regimen during the study period.

Penetration/Aspiration

Aspiration and aspiration risk have long received attention in studies addressing the swallow physiology of persons with PD. Explanations for the incidence of aspiration in this clinical population remain unclear. Leopold and Kagel (1997, p. 12) found aspiration in 23 of their 71 (32%) participants with PD, and supraglottic penetration in 18 of 71 (25%). They reported that of the 23 who aspirated, 20 did so before the swallow, and three after the swallow. It should be noted that the specific amounts for each consistency presented during videofluoroscopy are not well reported in this study. Of note, thin liquids were administered “from regulated straw and cup sips to continuous drinking of unregulated amounts.” Similar incomplete information was provided for puree and solid boluses “introduced in teaspoon amounts” (p. 12).

One year later, Nagaya and colleagues (1998, p. 97) reported on a sample of 16 participants with PD. They found aspiration in nine of 16 study participants (56%) based on 5ml liquid swallow trials. Most frequent findings in this group were piecemeal deglutition and vallecular residue after the swallow. Of note was their finding that stage transition duration (STD) changes did not correlate with aspiration events (p. 99). Interestingly, in 2007, Kim and McCullough reported positive correlation between increased STD measures and incidence of aspiration in a population post CVA (p. 303). In their study, liquid boluses consisted of 5ml and 10ml trials.

Sueli-Monte (2005) published data on the swallow physiology of 27 persons with PD. Their protocol included 10ml swallows of thin liquid. Participants were instructed to swallow the entire bolus at once (p. 458). They reported two of 27 participants with positive aspiration (p. 459).

In order to quantitatively describe aspiration or penetration events, Rosenbek, Robbins, Roecker, Coyle and Wood (1996) described the development of an eight point scale. The measure is based on observations conducted during a videofluoroscopic examination. Scores on the scale are determined by the depth to which the material passes into the airway and by whether or not material entering the airway is expelled. Intra and interjudge reliabilities of the scale have been assessed and found to be very high. The scale's ordinality has also been established (McCullough, Rosenbek, Robbins, Coyle & Wood, 1998). Utilizing a large sample divided into three groups (15 patients with multiple strokes, 16 patients with head/neck cancer and 98 normal participants), Robbins et al., (1999, p. 232) concluded that the P-A Scale, when used in conjunction with videofluorscopy, "provides a quantitative method to express the occurrence of swallowing-related airway invasion." For the reasons described above, this measure was also a part of the protocol for the present study.

Unified Parkinson's Disease Rating Scale

The Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn & Elton, 1987) is a composite of various previous scales and its use in the United States has largely supplanted other scales. Because of the marked variability between scales and differences in weighting signs and symptoms, a committee chaired by Fahn was created in 1984 to develop a standardized scale. This resulted in the UPDRS. As a consequence of its current widespread use, it has been validated for inter and intrarater reliability, as well as correlated with medical markers of the disease (Metman et al., 2004, p. 1082).

The UPDRS is a composite scale, consisting of six sections. Unless otherwise indicated, all items are rated from zero (normal) to four (severely affected); each item is defined by a short sentence.

Part I of the UPDRS consists of four items, assessing mentation, behavior and mood. Although helpful as a general screen, these items are inadequate to estimate the severity of dementia or depression, which may occur in a person with Parkinson disease. Other instruments should be used for the assessment of dementia and/or depression in this population.

Part II consists of 13 items which describe the ability to perform a number of activities of daily living, including speech, swallowing, bathing, dressing, using utensils, as well as ratings of any difficulty walking, tremor, and sensory symptoms. Although useful, three limitations in this section should be kept in mind. First, the ratings for speech and for swallowing are on the same four-point scale, which does not allow for much differentiation. Second, patient perceptions may differ considerably and it is not unusual to observe large discrepancies between subjective ratings and how the scale relates to objective measures of disease severity. Lastly, functional performance may change during “on” and “off” medication periods. As patients commonly perform certain daily activities during certain times or only during “on” periods, rating functional performance only during “on” or “off” periods may be artificial and difficult for patients to accurately answer.

Part III is a 14-item rating of motor signs based largely on items in the Columbia Disability scale (as cited in Fahn et al., 1987). In addition to ratings of tremor and an assessment of facial and generalized bradykinesia, performance on several tasks are used to rate disease severity, including any difficulty noted while repeatedly tapping the index finger against the thumb, clenching and unclenching a fist, rising from a chair, and other tasks. The definitions of difficulties with each task are straightforward, and the scale is reproducible. However, this motor scale does not take into account any interference from dyskinesias or dystonias that may downgrade motor performance in some patients. It also includes a scale for speech (item #18), which has been used in several studies as the only measure of motor speech changes in persons with PD.

Part IV rates complications of therapy. This includes several questions about the duration and the severity of dyskinesias and motor fluctuations, and a three-item section concerning anorexia, sleep disturbance, or orthostatic hypotension. Unlike the previous sections, some items in Part IV are rated as present or absent.

Part V is a modified version of the Hoehn and Yahr staging system (Hoehn & Yahr, 1967), which is an overall disease severity scale. It is divided into unilateral signs (stage I), bilateral signs without a gait or balance disorder (stage II), and bilateral disease with progressively more difficulty

with mobility and balance (stage III–V); half points are allowed between stage I–II and II–III.

Part VI is the Schwab and England ADL Scale, which is a disability scale estimating the degree of dependency in daily activities.

Summary comments

This review of the literature serves to highlight the minimal amount of data available to date on the swallow physiology of persons that have been implanted with the deep brain stimulator (DBS) to alleviate symptoms of Parkinson disease (PD). It also highlights how far we still are from fully understanding the impact of DBS on the functions of the subthalamic nucleus (STN) and its role in effecting changes in speech and/or swallowing motor control. In addition, differing methodologies make studies addressing speech or swallowing competence difficult to compare with each other. For example, while some studies employed four different liquid volumes (e.g., Sharkawi et al., 2002), others only examined one (Sueli-Monte et al., 2005). Another methodological aspect to consider is lack of knowledge on the time needed to flush the system once the stimulator has been turned off.

It is understood that the information available on DBS-STN is limited, and so this review sought to produce literature specific to persons with Parkinson disease and not necessarily implanted with the DBS. Interestingly, data for this population is not available for all the measures addressed in this study. Namely, there is limited comparison data for persons with PD when addressing oropharyngeal swallow efficiency (OPSE), tongue pressures and penetration/aspiration. As of the writing of this manuscript, no data has been published on swallow apnea duration in this population. The current study sought to address several of the limitations noted in the literature.

Study Objectives

The goals of this study were: (1) to quantify the temporal and physiological changes in specific aspects of swallow physiology when comparing the DBS "on" condition to the DBS "off" condition; and (2) to determine benefits/contraindications to DBS placement in patients with oropharyngeal dysphagia. It was anticipated that if enough evidence was found as to changes in swallow physiology, then improved calibration for frequency (rate) intensity (amplitude) and duration (width) of pulses delivered through the stimulator, as well as patient counseling would result.

It was hypothesized that negative changes in swallow physiology would result during the DBS "on" condition when compared to the DBS "off" condition. Namely, quantifiable changes in bolus flow through the oropharynx to the cervical esophagus would be observed. While the mechanism of stimulation to the subthalamic nucleus is not well understood, several studies focusing on speech motor control have identified cortical, subcortical and cerebellar regions of activation during DBS-STN stimulation. While general motor function and dyskinesia in persons with Parkinson disease improve after DBS-STN, motor speech abilities often do not respond or respond negatively (D'Alatri et al., 2008, p. 366). Several pathophysiological mechanisms have been proposed to explain this phenomena; however, great uncertainty as to the specific actions of the basal ganglia-thalamic-cortical (BG-TH-CTX) system remains. Based on these models, an explanation for changes to a variety of oral motor mechanisms involved in bolus flow through the oral and into the pharyngeal stages of swallow may emerge. This investigation attempted to highlight changes in temporal and bolus flow parameters through the oropharynx by examining persons under two distinct DBS-STN conditions (i.e., "on" and "off").

In efforts to better understand expected differences in motor response to bolus flow based on DBS stimulation "on" or "off" one must review what is available to date in the speech motor control literature. At the table are suggestions of the possible existence of separate motor programs for limbs and for speech (Pinto et al., 2004b). Farrell, Theodorus, Ward, Hall and Silburn (2005) hypothesized that the differences in speech response to DBS might relate to different innervation patterns in which

cranial nuclei for laryngeal systems receive bilateral cortical input as opposed to primarily unilateral innervation of the limbs (p. 16). Another interesting observation has been the differential effect of left- and right-sided DBS on speech. Articulatory accuracy and syllable rates have been shown to decrease with active left STN stimulation when compared to presurgical measurements (p. 11). Conversely, as reported in Narayana et al., 2009, p. 156, STN stimulation on the right side resulted in improvement or no change in speech. Thus, one could conclude that motor asymmetry may result in worse speech outcomes when the left basal ganglia is more damaged in persons with Parkinson disease.

To even better understand the complexities of neural activation in this region, one can review what is known about DBS stimulation to the GPi (globus pallidus internal segment). Based on the "focused attention/action selection theory" the GPi inhibits neurons of the VL (ventrolateral thalamus), which in turn, drive the motor cortex. Parkinsonism would then be due to overactivity in the GPi suppressing the VL. GPi inhibition is not really just inhibition. Many VL neurons demonstrate a postinhibitory rebound increased excitability from GPi inhibition; thus, for some VL neurons the net effect of GPi input is delayed excitation. As per Montgomery 2007a, synchronous GPi outputs could result in delayed excitation whereas asynchronous GPi activity could result in general suppression. Moreover, GPi activity likely becomes synchronous with movement generation and in response to DBS emphasizing the role of GPi as delayed excitation rather than inhibition.

Stimulation of the STN has not been studied to the level of detail that GPi has. Therefore, it is difficult to hypothesize expected changes in swallow physiology from its stimulation. Of importance is the relationship between the STN with the VL to mCTX oscillator. Descriptors of motor speech changes vary by study, and are mostly perceptual or based on the UPDRS only. This limits the possibility of making generalizations to the swallow tract physiology. Changes in articulation have been noted (Wang et al., 2006, p. 330), which may result in increased lingual pumping or reduced bolus cohesion during the oral stage of the swallow. Initiation of speech has also been implicated as worsening with DBS-STN (Moretti et al, 2003, p. 252). This may translate into longer oral transit times

during bolus propulsion. Other hypotheses are difficult to consider, as per what little is known about the neuropathology and interactions between the STN and the VL-mCTX system.

Methodology

Participants

All participants were adults diagnosed with idiopathic Parkinson Disease, who underwent bilateral DBS-STN surgery at least 3 months prior to the study, as performed by Dr. Martin Zonenshayn, neurosurgeon at New York Methodist Hospital in Brooklyn, New York. No age or gender restrictions were pre-determined. Participants presented with no history of stroke, head injury, head/neck cancer, nerve palsies, botulinum toxin injection near the larynx, or other neurologic diseases. All participants were kept in a stable medication state throughout the study; namely, they continued to take their medications as prescribed. All participants consented to participate in this study, as approved by the institutional review boards at The Graduate Center, City University of New York, and New York Methodist Hospital.

Demographics

The study sample originally consisted of eight adults that met all inclusion criteria (as described in the Methodology section, page 20) and consented to participate in the study. Namely, adults diagnosed with idiopathic Parkinson Disease, who underwent bilateral DBS-STN surgery at least 3 months prior to the study and presented with no history of stroke, head injury, head/neck cancer, nerve palsies, botulinum toxin injection near larynx, or other neurologic diseases. Two participants were subsequently excluded from the sample, as they showed overt signs of not tolerating the DBS implant in the off condition. Both participants developed moderate to severe non-intention tremors of the extremities within 3 minutes of turning the apparatus off. Given reduced ability

Table 1: Participant demographics.

Partic	**Gender/ Ethnicity**	**Age**	**PD Dx**	**Medication Initiation**	**DBS implanted**	**Months post DBS**	**Time DBS off (hrs)** for Day #2
1 CW	M/Black	59	2004	2004	8/08	12	24.50
2 GB	F/White	73	2003	2003	3/09	05	24.00
3 EV	F/Hisp	47	1974	1986	3/03	77	23.75
4 LPS	F/Black	66	1993	1993	12/07	23	22.00
5 DM	M/Black	53	2000	2000	7/08	16	22.00
6 NJ	F/Indian	61	1994	1994	3/10	14	25.25

to control the tremors independently, the DBS was returned to its on position, given the original calibration, and cessation of symptoms ensued. The remaining six participants completed the study protocol without overt complications. As described in Table 1, the age range for the six participants was 47 to 73 years of age (mean = 59.83 ± 9.21); four were female, and two were male. Time since initial diagnosis of Parkinson Disease averaged 14.66 years ± 11.14, range = five to 35 years. All participants were on PD medications and were kept on their regular dosage and schedule for the study. Time on medications ranged from five to 23 years (mean = 12.66 ± 7.11). In addition, all six participants underwent bilateral DBS implantation to the subthalamic nucleus (STN) within 5 months – 6 years of partaking in this study (mean = 1.91 ± 2.05). The range of time DBS was kept off was 22 – 25.25 hours (mean = 23.58 ± 1.32).

Subjective complaints offered by each participant upon arrival to day #2 of testing, after greater than 22 hours with the DBS in the off condition, included slight increase in tremors and slight increase in bradykinesia (four of six participants, or 66%). Additional complaints included increased rigidity, and reduced balance. Two participants complained of uncontrolled motor responses; one of a mild and short-timed "mouth twisting" episode, and another of "in-toeing" for a short period in the morning. Both of these participants reported prompt resolution of symptoms. Specific to the speech and swallowing mechanisms, complaints included mild change in articulation, reduced vocal intensity and slower rate of PO intake. Each of these symptoms was reported by no more than one participant. No other speech or swallowing related complaints were reported or noted after maintaining the DBS apparatus in the off position for the extended period described above (i.e., >22 hours).

Equipment

The Kay/Pentax Digital Swallow Workstation (DSW) Model 7120 (Kay/Pentax, Lincoln Park, NJ) coupled with the Swallow Signals Lab was utilized for data acquisition and analysis. Concurrent videofluoroscopic images and respiratory data was recorded. Lingual pressure data was collected separately, immediately prior to the instrumental examination (videofluoroscopy). The UPDRS scale was completed immediately preceding the turning of the stimulator "on" or "off."

Videofluoroscopy: The Kay/Pentax DSW was coupled to the monitor in the radiology/fluoroscopy suite. Imaging was acquired at 60 fields (30 frames) per second allowing for measurement resolution of approximately 17ms per field. Each participant was seated in a Halsted videofluoroscopy chair. The X-ray beam was coned to image the oral cavity, pharynx, upper airway and cervical esophagus of each participant in the lateral projection.

Contrast Material. Barium used for the videofluoroscopic (VFSS) studies included VARIBAR Thin Liquid, EZ-HD powder mixed with pudding for semi-solids, and VARIBAR Honey for coating the cookie. All barium products are produced by EZ-EM, Inc. (Westbury, NY). The VARIBAR line of barium products was originally standardized for viscosity and yield stress and designed to match those of actual food consistencies.

Respiratory data: The swallow apnea information was gathered via a 2mm nasal cannula (Hospitak, Farmingdale, NY) identical to that used for delivery of supplemental oxygen. The proximal end of the nasal cannula was placed at the entrance of each nare. The distal end of the nasal cannula tubing was coupled to the analog-to-digital airflow sensor transducer in the Kay/Pentax Swallow Signals Lab. Digital samples were obtained with a sampling frequency of 250 Hz. The system software generated concurrent airflow waveforms as a function of time.

Tongue pressures: A 3-bulb pressure transducer was employed. Each participant placed the anterior bulb immediately posterior to the alveolar ridge and held it in place during recording. The bulbs were 13 mm in diameter, attached via a silica strip and spaced 8 mm apart. The three bulbs rested along the hard palate and were placed in an anterior to posterior alignment. The bulb data was also be coupled to the Kay/Pentax Swallow Signals Lab with a sampling frequency of 250 Hz and displayed in a 0 – 750 mmHg display window. Data for all three bulbs were displayed in one window as a function of time.

Procedures

Each participant underwent two days of testing. On day #1 the participant's DBS remained in the "on" condition. After the instrumental examination (tongue pressure measures and videofluoroscopy with concurrent respiratory tracings) was completed, the United Parkinson's Disease Rating Scale (UPDRS) was administered and the stimulator turned "off" by a board certified neurologist. On day #2, or 18-24 hours after the stimulator was turned to the "off" condition, the participant underwent another set of the same instrumental examinations. At the end of this examination, the same board certified neurologist completed another UPDRS and turned the stimulator to the pre-testing "on" condition. Use of the same experienced rater, in this case a board certified neurologist with specialization in movement disorders, is supported by several studies noting high intra-rater reliability for the UPDRS and excellent test-retest reliability for the scale (Metman et al., 2004, p. 1082; Siderowf et al., 2002, p. 761). All appropriate precautions were taken to ensure patient safety during, and soon after, the changes in DBS stimulator condition.

Videofluorscopic swallowing samples and respiratory tracings were recorded concurrently for each participant. Each participant was seated with the nasal cannula in place. Four bolus conditions were presented: thin liquid barium (5ml and "sips" from cup, three trials each), pudding (3ml, three trials), and Lorna Doone cookie (1/4 bite, two trials). This totaled eleven recorded swallows. The 5 ml liquid boluses were presented in a 30cc medicine cup; "sips" were presented in a half-full 8oz cup; pudding was pre-measured and presented on a spoon; and the bites of cookie were pre-coated with honey thick barium and cut into two halves (participant bit off half, resulting in ¼ cookie portion). Trials were not randomized because of concerns regarding a cumulative effect of residue if thicker boluses were administered before the thinner viscosities. Swallows were not cued, as per previous literature noting the effect of cuing on bolus flow during videofluoroscopic examinations (Daniels, Schroeder, De George, Corey & Rosenbek, 2007, p. 146). Therefore, each participant completed 11 swallows on day #1 and 11 swallows on day #2. Each examination was initiated with the 5ml thin liquid and advanced accordingly. Prior to commencing the videofluoroscopic examination, while seated in the Hausted chair, each participant was tested for tongue pressures. Once the bulbs were

in place, with the most anterior bulb immediately posterior to the alveolar ridge, the participant was instructed to “press as hard as you can.” This was repeated for three trials of 3 sec each. Data from the anterior, middle and posterior bulbs was recorded in real time.

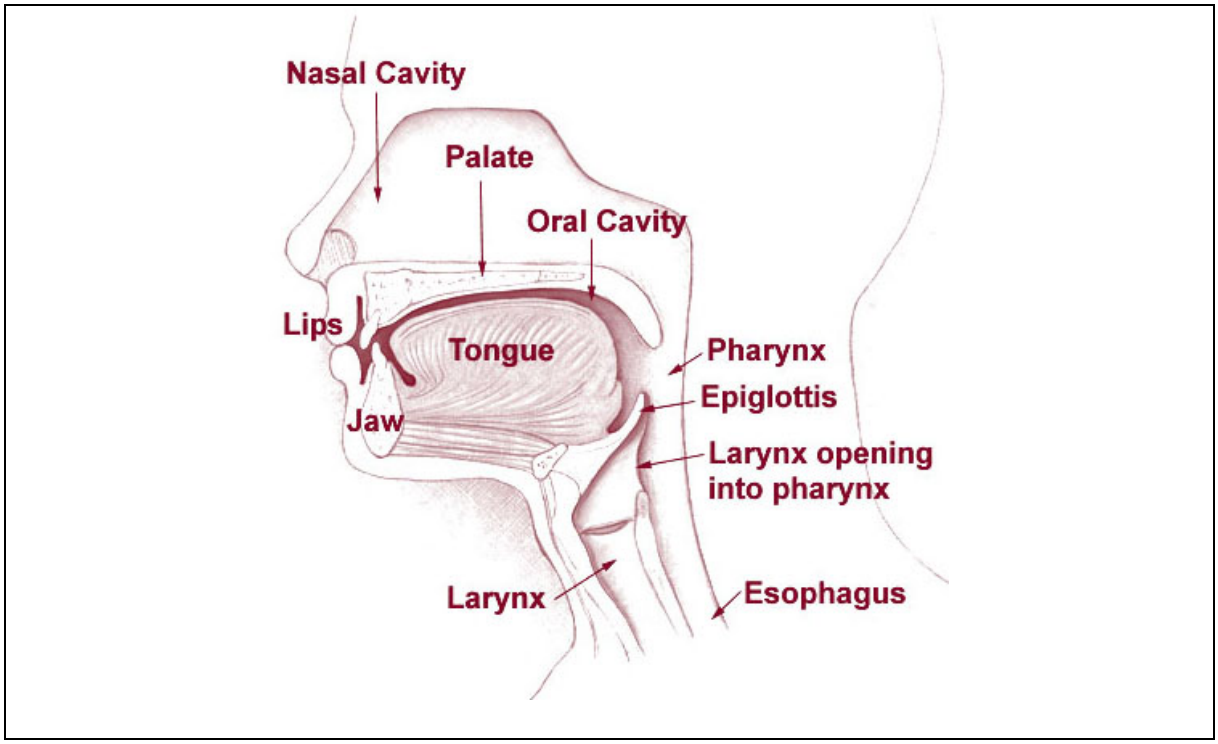

Figure 4: Head/neck schemata. From http://training.seer.cancer.gov/head-neck/anatomy/overview.html. Public domain, United States Federal Government.

Data from the videofluoroscopy (see below), swallow apnea duration and tongue pressures was extracted from the appropriate images and waveforms offline. Figure 4 is provided to serve as an anatomical reference. The following data was extracted:

From videofluoroscopic images:

Oral Pharyngeal Swallow Efficiency (OPSE; Rademaker et al., 1994): Calculation composed of the following measures: (1) Oral transit time (OTT): onset of bolus movement in the oral cavity to time when head of bolus reaches the angle of the ramus of the mandible. OTT was measured in seconds. (2) Stage Transition Duration (STD): bolus passage from oropharynx to hypopharynx. Defined as the end of the oral stage (time when head of barium bolus passes the angle of the ramus

of the mandible) to the beginning of the pharyngeal motor response (time when hyoid begins its anterior/superior excursion). STD was measured in seconds. (3) Pharyngeal transit time (PTT): begins at the time the head of the bolus passes the angle of the ramus of the mandible to the time when tail of bolus passes through the pharyngoesophageal segment region. It is composed of the STD + the PRT (pharyngeal response time: time when the hyoid begins its anterior/superior excursion to when the tail of the bolus passes the PE segment). PRT was measured in seconds. (4) Percent of bolus entering the cervical esophagus (BSWALL). (5) Percent oral residue (ORES). (6) Percent pharyngeal residue (PRES). (7) Percent amount aspirated. (8) Timing of aspiration: before or during the swallow. Calculation:

$$\frac{100 - [\text{oral residue} + \text{phx residue} + \text{amount aspirated before and/or during}]}{[\text{OTT} + \text{PTT}]}$$

From respiratory traces, the swallow apneic duration (SAD) was calculated. Airflow direction was shown as a green trace (expiration), and a red trace (inspiration). The apneic period was defined and measured as a flat, black respiratory trace along the abscissa (Martin-Harris, Michel & Castell, 2005, p. 763) that occurred in conjunction with the swallow as viewed videofluoroscopically. SAD was measured in seconds.

From tongue pressures (using a three bulb array on a silica strip): Peak pressure from all three bulbs for each of three trials was obtained.

The Penetration/Aspiration scale was completed offline, based on the videofluoroscopic data recorded. A score of 1 indicates no airway invasion (i.e., no penetration or aspiration). Scores of 2-5 indicate laryngeal penetration using depth and clearance to determine the specific score. Scores 6-8 indicate aspiration using response and clearance to determine the specific score.

Another measure employed, as administered by a board certified neurologist, Dr. Miran Salgado, was the Unified Parkinson's Disease Rating Scale (UPDRS), which is a rating scale used to

follow the longitudinal course of Parkinson disease. As mentioned earlier in this manuscript, the UPDRS was completed immediately prior to changing the condition of the DBS.

For this study, the independent variables included the protocol employed for the VFSS and the DBS "on" and "off" conditions. Dependent variables included all the measures obtained (as noted above).

Statistical analysis

A mean OPSE (oropharyngeal swallow efficiency) score was generated for each bolus viscosity: 5cc thin liquid, "sip" thin liquid, 3ml pudding and ¼ cookie. These means were compared for the "on" and "off" conditions. The difference in scores was analyzed utilizing non-parametric statistics (i.e., less than 0, greater than 0). Non-parametric statistics were suggested for this analysis as there are no assumptions on the probability distribution. Non-parametric analyses make fewer assumptions, hence are more robust. On the negative flip side is the fact that non-parametric tests have less power.

Testing of the difference within participants and between conditions (DBS on or off) was completed using the Signed Rank Test. This is similar to the one-sample t-test for paired observations. The condition of independence of observation is important in applying the Wilcoxon Signed Rank Test, and hence its choice for analysis.

Swallow apnea duration (SAD) measures by bolus viscosity for each condition (on/off) was analyzed using non-parametric approaches to assess the difference by situation. The Spearman Rank Order Correlation Coefficient was employed.

Tongue pressures to oral transit times by condition (liquids, pudding, cookie). This comparison/relationship was to be analyzed utilizing the Spearman Rank Order Correlation Coefficient (in the case of non-parametrics). However, due to equipment difficulties, complete tongue

pressure measurements were obtained on three of the six participants; therefore, descriptive analysis is presented.

UPDRS scores for each condition (on/off). As above, non-parametrics were utilized to assess the difference by situation. Analysis was completed using the Wilcoxon Signed Rank Test as described above.

All analyses were completed using SAS software, version 9.1 (SAS, 2003).

Reliability

Interjudge and intrajudge reliability was calculated on 10% of the temporal and residue measures by an experienced clinician and the principal investigator. Samples were randomly chosen from both days of testing (e.g., day #1, DBS in the on condition; day #2, DBS in the off condition). Raters were blinded as to participant and on or off condition. Interrater reliabilities yielded an interclass correlation coefficient (ICC) of 0.95 for oral transit time (OTT), 0.97 for stage transition duration (STD), 0.18 for pharyngeal response time (PRT), 0.66 for percent oral residue (ORES) and 0.63 for percent pharyngeal residue (PRES). Overall, ICC for intrarater reliability was moderate to strong (mean = .67 $\pm$ .32). Intrarater reliabilities yielded an interclass correlation coefficient (ICC) of 0.95 for oral transit time (OTT), 0.97 for stage transition duration (STD), 0.38 for pharyngeal response time (PRT), 0.79 for percent oral residue (ORES) and 1.0 for percent pharyngeal residue (PRES). Overall, ICC for interrater reliability was strong (mean = .81 $\pm$ .25). Confidence intervals were not calculated as the overall sample size was judged to be too small. Results denote a strong to almost perfect agreement for measures of OTT, STD, ORES and PRES. Fair to poor agreement was obtained for PRT.

Results

Oropharyngeal Swallow Efficiency (OPSE)

Results for oropharyngeal swallow efficiency by participant and by bolus consistency is presented in Table 2a. As described in the Methodology section, this score was developed as "a single global measure to reflect all aspects of oropharyngeal dysphagia during videofluoroscopy: oropharyngeal transit times and the observed or measured percentage of bolus swallowed into the esophagus minus an estimate of the percentage aspirated, thus reflecting the efficiency of the swallow" (Logemann et al., 2005, p. 226; Rademaker, Pauloski, Logemann & Shanahan, 1994, p. 315). Twenty two swallow trials per participant were analyzed (11 on each day of the study); totaling 132 swallows analyzed. Signed rank test comparisons by bolus viscosity are presented in Table 2b and revealed non-significant (all p values were > .05) relationships for each bolus viscosity when comparing day #1 (DBS in on condition) to day #2 (DBS in off condition). Of note, although not statistically significant, is the observation that for bolus viscosities of liquid form (5cc thin liquid and "sips" thin liquid), there was an improvement in OPSE score from day #1 to day #2; whereas for the pudding and cookie consistencies there was a decline in the mean OPSE score.

Table 2a: OPSE data by participant.

OPSE	Viscosity	Day 1		Day 2		Diff (D2-D1)
		Mean	SD	Mean	SD	
Partic 01	5cc Liquid	27.153	6.000	23.204	6.762	-3.949
	Sips Liquid	31.205	7.318	31.477	18.045	0.271
	Pudding	12.044	4.588	14.274	4.091	2.229
	Cookie	6.635	0.129	6.223	0.372	-0.412
Partic 02	5cc Liquid	26.234	17.310	33.811	17.844	7.577
	Sips Liquid	22.640	2.682	30.411	7.350	7.770
	Pudding	18.209	9.585	11.467	3.353	-6.742
	Cookie	5.672	1.489	6.015	1.111	0.342
Partic 03	5cc Liquid	28.175	6.849	35.360	14.138	7.185
	Sips Liquid	35.274	7.060	36.946	4.908	1.671
	Pudding	15.751	4.304	29.137	2.383	13.386
	Cookie	7.536	0.349	10.162	0.232	2.626
Partic 04	5cc Liquid	63.482	3.197	45.129	11.490	-18.352
	Sips Liquid	33.694	3.240	23.90	13.691	-9.792
	Pudding	20.552	7.899	4.907	1.404	-15.645
	Cookie	7.092	2.882	3.894	1.701	-3.198
Partic 05	5cc Liquid	71.547	32.243	51.760	16.532	-19.786
	Sips Liquid	60.886	13.293	43.11	10.273	-17.771
	Pudding	18.735	1.838	17.648	3.218	-1.087
	Cookie	6.800	0.354	5.982	1.336	-0.818
Partic 06	5cc Liquid	41.652	7.095	47.548	7.319	5.895
	Sips Liquid	50.889	7.332	43.169	4.295	-7.720
	Pudding	18.548	3.279	49.069	21.774	30.521
	Cookie	4.039	1.946	7.413	0.436	3.374

Table 2b: OPSE comparisons by bolus viscosity: Wilcoxon Signed Rank Test for mean difference between on (Day 1) and off (Day 2).

OPSE	Viscosity	Day 1		Day 2		Diff (D2-D1)	P value
		Mean	SD	Mean	SD		
	5cc Liquid	39.47	10.60	43.04	19.94	3.57	0.522
	Sips Liquid	34.84	7.65	39.10	14.08	4.28	0.309
	Pudding	21.08	15.88	17.31	3.00	-3.78	0.593
	Cookie	6.62	2.08	6.30	1.27	-0.32	0.758

Additional analysis was conducted for components of the OPSE (Tables 3a and 4a). Namely, oral transit times (OTT) and pharyngeal transit times (PTT). The latter was calculated by combining scores from stage transition duration (STD) and pharyngeal response time (PRT). Group means by bolus viscosity were also compared by condition (day #1 to day #2; Tables 3b and 4b) and did not reveal significant relationships. Again, in analyzing OTT and PTT results, all p values were >.05. However, further review of Tables 3b and 4b reveal that OTT changes were greater than changes in PTT across all bolus consistencies (3.08, mean = .77 versus 1.01, mean = .25 respectively) for day #1 compared to day #2.

Table 3a: OTT data by participant.

OTT	Viscosity	Day 1		Day 2		**Diff (D2-D1)**
		Mean	**SD**	**Mean**	**SD**	
Partic 01	5cc Liquid	2.656	1.368	1.533	0.285	-1.123
	Sips Liquid	1.733	0.923	1.548	1.122	-0.184
	Pudding	4.056	1.648	3.389	0.050	-0.666
	Cookie	6.168	1.036	5.117	2.006	-1.050
Partic 02	5cc Liquid	3.010	3.398	2.299	1.376	-0.711
	Sips Liquid	2.298	0.219	1.066	0.154	-1.231
	Pudding	4.266	2.811	4.012	0.644	-0.253
	Cookie	8.120	2.614	11.450	2.379	3.330
Partic 03	5cc Liquid	2.582	0.494	2.099	1.472	-0.482
	Sips Liquid	1.822	0.334	1.510	0.565	-0.311
	Pudding	4.432	1.508	1.644	0.537	-2.787
	Cookie	10.701	1.175	5.218	0.637	-5.483
Partic 04	5cc Liquid	0.667	0.066	1.433	0.433	0.765
	Sips Liquid	1.869	0.140	4.802	4.419	2.933
	Pudding	2.122	1.507	15.105	4.938	12.982
	Cookie	9.287	0.071	22.351	10.252	13.064
Partic 05	5cc Liquid	0.500	0.152	1.044	0.556	0.544
	Sips Liquid	0.289	0.068	1.256	0.605	0.967
	Pudding	2.922	0.366	3.178	0.221	0.256
	Cookie	10.019	2.332	11.902	2.306	1.883
Partic 06	5cc Liquid	1.321	0.397	0.667	0.172	-0.653
	Sips Liquid	0.978	0.270	0.856	0.331	-0.122
	Pudding	1.621	0.222	1.435	1.387	-0.186
	Cookie	17.986	9.264	11.634	0.188	-6.351

Table 3b: OTT comparisons by bolus viscosity: Wilcoxon Signed Rank Test for mean difference between on (Day 1) and off (Day 2).

OTT	Viscosity	Day 1		Day 2		Diff (D2-D1)	P value
		Mean	SD	Mean	SD		
	5cc Liquid	1.51	0.62	1.79	1.10	0.28	0.410
	Sips Liquid	1.84	1.47	1.50	0.73	-0.34	0.588
	Pudding	4.79	5.15	3.24	1.19	-1.56	0.532
	Cookie	11.28	6.29	10.38	4.00	-0.90	0.769

Table 4a: PTT data by participant.

PTT	Viscosity	Day 1		Day 2		Diff (D2-D1)
		Mean	SD	Mean	SD	
Partic 01	5cc Liquid	1.036	0.500	2.801	1.998	1.765
	Sips Liquid	1.421	0.382	1.989	0.659	0.568
	Pudding	3.977	0.784	2.657	1.548	-1.320
	Cookie	8.303	1.319	9.601	2.546	1.298
Partic 02	5cc Liquid	1.801	1.210	1.137	0.426	-0.664
	Sips Liquid	1.666	0.239	2.011	0.933	0.344
	Pudding	1.276	0.299	3.511	1.870	2.235
	Cookie	7.400	1.461	4.617	0.589	-2.783
Partic 03	5cc Liquid	1.044	0.437	1.180	0.236	0.135
	Sips Liquid	0.734	0.060	1.109	0.422	0.375
	Pudding	1.135	0.365	1.045	0.515	-0.090
	Cookie	1.917	0.590	4.282	0.210	2.364
Partic 04	5cc Liquid	0.777	0.070	0.711	0.050	-0.066
	Sips Liquid	0.814	0.118	0.566	0.058	-0.247
	Pudding	1.910	1.182	2.944	1.034	1.033
	Cookie	4.817	5.161	4.619	1.533	-0.198
Partic 05	5cc Liquid	1.089	0.068	0.823	0.214	-0.266
	Sips Liquid	1.220	0.461	0.833	0.165	-0.387
	Pudding	1.555	0.331	1.922	0.648	0.367
	Cookie	3.968	1.603	3.165	1.651	-0.803
Partic 06	5cc Liquid	0.833	0.088	0.800	0.177	-0.033
	Sips Liquid	0.809	0.071	1.045	0.185	0.235
	Pudding	2.600	1.767	0.888	0.168	-1.712
	Cookie	4.418	1.529	0.849	0.068	-3.569

Table 4b: PTT comparisons by bolus viscosity: Wilcoxon Signed Rank Test for mean difference between on (Day 1) and off (Day 2).

PTT	Viscosity	Day 1		Day 2		Diff (D2-D1)	P value
		Mean	SD	Mean	SD		
	5cc Liquid	1.24	0.79	1.10	0.37	-0.15	0.689
	Sips Liquid	1.26	0.60	1.11	0.38	-0.15	0.382
	Pudding	2.16	1.06	2.08	1.07	-0.09	0.892
	Cookie	4.52	2.87	5.14	2.35	0.62	0.539

Bolus flow measures were also analyzed further, as these are the numerator component of the formula for calculating the OPSE (Tables 5a, 6a and 7a, respectively). Analyses included percentage of bolus to cervical esophagus (BSWALL), oral residue (ORES) and pharyngeal residue (PRES). Group means by bolus consistency were also compared by condition (day #1 to day #2; Tables 5b, 6b and 7b) and did not reveal significant relationships. Again, in analyzing BSWALL, ORES and PRES results, all p values were >.05. Further review of Tables 6b and 7b reveal that changes in oral residue (ORES) were greater than changes in pharyngeal residue (PRES) across all bolus consistencies (5.74, mean = 1.43 versus -4.82, mean = -1.20 respectively) for day #1 compared to day #2. Gross analysis of this data may suggest that on day #2, or with DBS off for > 18 hours, group means show more oral residue and less pharyngeal residue in comparison to day #1, or in the DBS on condition.

Table 5a: BSWALL data by participant (percentage of bolus to the cervical esophagus).

BSWALL	Viscosity	Day 1		Day 2		Diff (D2-D1)
		Mean	SD	Mean	SD	
Partic 01	5cc Liquid	96.333	2.886	92.666	4.618	-3.667
	Sips Liquid	95.000	1.732	91.000	1.732	-4.000
	Pudding	89.666	2.886	82.666	9.291	-7.000
	Cookie	96.000	0.000	91.500	2.121	-4.500
Partic 02	5cc Liquid	94.333	4.041	99.333	1.154	5.000
	Sips Liquid	89.333	5.131	89.333	1.154	0.000
	Pudding	84.333	8.144	82.666	6.806	-1.667
	Cookie	85.000	0.000	95.000	0.000	10.000
Partic 03	5cc Liquid	99.000	1.414	100.000	0.000	1.000
	Sips Liquid	89.000	9.643	95.666	2.081	6.666
	Pudding	83.333	2.886	78.333	5.773	-5.000
	Cookie	95.000	0.000	96.500	2.121	1.500
Partic 04	5cc Liquid	91.666	2.886	93.333	2.886	1.667
	Sips Liquid	90.000	0.000	88.333	2.886	-1.667
	Pudding	71.666	2.886	83.000	1.732	11.334
	Cookie	92.500	3.535	95.000	0.000	2.500
Partic 05	5cc Liquid	93.333	7.637	88.333	2.886	-5.000
	Sips Liquid	88.333	2.886	86.666	2.886	-1.667
	Pudding	83.333	5.773	88.333	2.886	5.000
	Cookie	95.000	0.000	87.500	3.535	-7.500
Partic 06	5cc Liquid	88.333	7.637	68.333	5.773	-20.000
	Sips Liquid	90.000	5.000	81.666	2.886	-8.334
	Pudding	75.000	15.000	93.333	2.886	18.333
	Cookie	80.000	0.000	92.500	3.535	12.500

Table 5b: BSWALL comparisons by bolus viscosity: Wilcoxon Signed Rank Test for mean difference between on (Day 1) and off (Day 2).

BSWALL	Viscosity	Day 1		Day 2		Diff (D2-D1)	P value
		Mean	SD	Mean	SD		
	5cc Liquid	90.33	11.64	93.83	3.70	3.50	0.378
	Sips Liquid	88.78	4.65	90.28	2.40	1.50	0.490
	Pudding	84.72	5.28	81.22	6.63	-3.50	0.427
	Cookie	93.00	3.26	90.58	6.56	-2.42	0.483

Table 6a: ORES data by participant (percentage oral residue).

ORES	Viscosity	Day 1		Day 2		Diff (D2-D1)
		Mean	SD	Mean	SD	
Partic 01	5cc Liquid	3.000	1.732	3.333	2.886	0.333
	Sips Liquid	3.000	1.732	4.000	1.732	1.000
	Pudding	2.000	0.000	5.666	4.041	3.666
	Cookie	2.000	0.000	5.000	0.000	3.000
Partic 02	5cc Liquid	5.666	4.041	0.666	1.154	-5.000
	Sips Liquid	8.333	2.886	4.000	1.732	-4.333
	Pudding	9.000	9.643	7.333	6.806	-1.667
	Cookie	7.500	3.535	0.000	0.000	-7.500
Partic 03	5cc Liquid	1.000	1.414	0.000	0.000	-1.000
	Sips Liquid	9.000	9.643	3.333	1.527	-5.667
	Pudding	16.666	2.886	21.666	5.773	5.000
	Cookie	5.000	0.000	3.500	2.121	-1.500
Partic 04	5cc Liquid	8.333	2.886	5.000	0.000	-3.333
	Sips Liquid	10.000	0.000	6.666	2.886	-3.334
	Pudding	18.333	2.886	10.000	0.000	-8.333
	Cookie	7.500	3.535	5.000	0.000	-2.500
Partic 05	5cc Liquid	5.000	5.000	11.666	2.886	6.666
	Sips Liquid	11.666	2.886	13.333	2.886	1.667
	Pudding	15.000	5.000	11.666	2.886	-3.334
	Cookie	5.000	0.000	12.500	3.535	7.500
Partic 06	5cc Liquid	11.666	7.637	23.333	2.886	11.667
	Sips Liquid	10.000	5.000	13.333	2.886	3.333
	Pudding	25.000	15.000	6.666	2.886	-18.334
	Cookie	20.000	0.000	7.500	3.535	-12.500

Table 6b: ORES comparisons by bolus viscosity: Wilcoxon Signed Rank Test for mean difference between on (Day 1) and off (Day 2).

ORES	Viscosity	Day 1		Day 2		Diff (D2-D1)	P value
		Mean	SD	Mean	SD		
	5cc Liquid	7.33	8.88	5.78	3.80	-1.56	0.576
	Sips Liquid	7.44	4.70	8.67	3.00	1.22	0.453
	Pudding	10.50	5.91	14.33	7.95	3.83	0.324
	Cookie	5.58	4.19	7.83	6.30	2.25	0.475

Table 7a: PRES data by participant (percentage pharyngeal residue).

PRES	Viscosity	Day 1		Day 2		Diff (D2-D1)
		Mean	SD	Mean	SD	
Partic 01	5cc Liquid	0.666	1.154	4.000	1.732	3.334
	Sips Liquid	2.000	0.000	5.000	0.000	3.000
	Pudding	8.333	2.886	11.666	5.773	3.333
	Cookie	2.000	0.000	3.500	2.121	1.500
Partic 02	5cc Liquid	0.000	0.000	0.000	0.000	0.000
	Sips Liquid	2.333	2.516	6.666	2.886	4.333
	Pudding	6.666	2.886	10.000	0.000	3.334
	Cookie	7.500	3.535	5.000	0.000	-2.500
Partic 03	5cc Liquid	0.000	0.000	0.000	0.000	0.000
	Sips Liquid	2.000	0.000	1.000	1.732	-1.000
	Pudding	0.000	0.000	0.000	0.000	0.000
	Cookie	0.000	0.000	0.000	0.000	0.000
Partic 04	5cc Liquid	0.000	0.000	1.666	2.886	1.666
	Sips Liquid	0.000	0.000	5.000	0.000	5.000
	Pudding	10.000	0.000	7.000	1.732	-3.000
	Cookie	0.000	0.000	0.000	0.000	0.000
Partic 05	5cc Liquid	1.666	2.886	0.000	0.000	-1.666
	Sips Liquid	0.000	0.000	0.000	0.000	0.000
	Pudding	1.666	2.886	0.000	0.000	-1.666
	Cookie	0.000	0.000	0.000	0.000	0.000
Partic 06	5cc Liquid	0.000	0.000	8.333	2.886	8.333
	Sips Liquid	0.000	0.000	5.000	0.000	5.000
	Pudding	0.000	0.000	0.000	0.000	0.000
	Cookie	0.000	0.000	0.000	0.000	0.000

Table 7b: PRES comparisons by bolus viscosity: Wilcoxon Signed Rank Test for mean difference between on (Day 1) and off (Day 2).

PRES	Viscosity	Day 1		Day 2		Diff (D2-D1)	P value
		Mean	SD	Mean	SD		
	5cc Liquid	2.33	3.33	.39	.68	-1.94	0.238
	Sips Liquid	3.78	2.64	1.06	1.16	-2.72	0.051
	Pudding	4.78	5.44	4.44	4.43	-.33	0.764
	Cookie	1.42	2.25	1.58	3.01	.17	0.764

Swallow Apnea Duration (SAD)

Relationships by bolus viscosity for day #1 (DBS in on condition) compared to day #2 (DBS in off condition) were not found, as per Spearman Correlation Coefficient testing. Again, p values were > .05. Measurement of the swallow apnea duration (SAD) proved challenging, as per intermittent episodes of expiratory deflections noted on the waveform during the apneic period. Recent literature has attempted to explain such phenomena (Brodsky et al., 2011) and so correlation with the physiologic components of the swallow, via videofluoroscopic images, was utilized in determining the extent of the apneic period for each swallow included. Of note, and not included in this analysis, was the observation of several brief apneic periods during the oral preparatory stage as denoted by deflections on the respiratory trace.

Table 8a: SAD scores by participant and viscosity.

SAD	Viscosity	Day 1		Day 2		**Diff (D2-D1)**
		Mean	**SD**	**Mean**	**SD**	
Partic 01	5cc Liquid	1.131	0.230	NA		
	Sips Liquid	2.171	1.382	NA		
	Pudding	1.928	0.669	NA		
	Cookie	1.153	0.168	NA		
Partic 02	5cc Liquid	2.269	0.630	NA		
	Sips Liquid	1.470	0.154	NA		
	Pudding	1.678	0.814	NA		
	Cookie	1.720	0.886	NA		
Partic 03	5cc Liquid	1.190	0.190	2.444	0.264	1.253
	Sips Liquid	1.840	0.650	2.475	0.502	0.635
	Pudding	1.498	0.225	1.524	0.159	0.026
	Cookie	1.008	0.074	1.153	0.093	0.145
Partic 04	5cc Liquid	2.184	0.895	1.929	0.138	-0.255
	Sips Liquid	1.952	1.185	1.933	0.720	-0.019
	Pudding	1.857	1.094	1.400	0.568	-0.457
	Cookie	1.455	0.407	0.976	0.030	-0.478
Partic 05	5cc Liquid	1.144	0.202	1.173	0.365	0.029
	Sips Liquid	1.647	0.609	1.061	0.170	-0.586
	Pudding	1.175	0.084	1.326	0.342	0.151
	Cookie	1.206	0.205	1.356	0.424	0.150
Partic 06	5cc Liquid	2.014	0.555	1.350	0.276	-0.664
	Sips Liquid	1.158	0.015	1.016	0.100	-0.141
	Pudding	2.581	0.232	1.210	0.119	-1.370
	Cookie	1.669	0.380	0.995	0.168	-0.674

Table 8b: SAD comparisons for temporal measures by bolus viscosity: Spearman correlation coefficient*

SAD	Viscosity	OPSE		OTT		PTT	
		SpCC*	P value	SpCC*	P value	SpCC*	P value
Day 1	5cc Liquid	-0.028	0.957	0.200	0.704	0.028	0.957
	Sips Liquid	-0.314	0.544	0.142	0.787	0.085	0.871
	Pudding	-0.314	0.544	-0.542	0.265	0.771	0.072
	Cookie	-0.885	0.018*	-0.028	0.957	0.371	0.468
Day 2	5cc Liquid	0.200	0.800	-0.200	0.800	0.200	0.800
	Sips Liquid	-0.800	0.200	0.800	0.200	0.200	0.800
	Pudding	-0.400	0.600	0.400	0.600	0.400	0.600
	Cookie	0.400	0.600	-0.400	0.600	-0.400	0.600

- significant finding

A p <.05 was identified for the cookie bolus on day 1 when correlation with OPSE was conducted (p=.0188, Table 8b). This finding was difficult to interpret, as per the small data set overall.

Penetration/Aspiration (P/A)

Every participant scored a 1 on the Penetration/Aspiration Scale for each of 22 bolus trials during day #1 and day #2. This denotes no material entered the airway, namely, no penetration or aspiration was observed for any material swallowed under any condition. Therefore, no difference was noted for potential bolus entry into the upper airway by condition (DBS on or DBS off).

United Parkinson Disease Rating Scale (UPDRS)

The Signed Rank Test was also utilized to analyze data from the UPDRS scores for day #1 compared to day #2. Results were non-significant, with a p = 0.6875 (p>.05), as seen in Table 9b. Further observation of individual scores, as noted in Table 9a, denotes a trend towards a worsening of scores with the DBS in the off condition (day #2). The reader is reminded that this observation was not statistically significant, and that the UPDRS is a measure of global motor function, encompassing the entire body.

Table 9a: UPDRS scores by participant. Maximum score: 176 total.

UPDRS	Day 1		Day 2		Diff (D2-D1)
	Score	%	Score	%	
Partic 01	56.50	32	76.50	43	20.00
Partic 02	21.00	11	37.50	21	16.50
Partic 03	34.50	19	85.00	48	50.50
Partic 04	14.00	7	57.50	32	43.50
Partic 05	35.50	20	77.50	44	42.00
Partic 06	56.00	31	77.00	43	21.00

Table 9b: UPDRS comparison: Wilcoxon Signed Rank Test for mean difference between on (Day 1) and off (Day 2).

UPDRS	Day 1		Day 2		Diff (D2-D1)	P value
	Mean	SD	Mean	SD		
	36.25	10.09	68.50	17.50	32.25	0.698

In efforts to further assess changes within the UPDRS scores, specific descriptive analysis of scores attained in the area of speech (question #5) and swallowing (question #7) were reviewed. Table 9c shows a non-statistically significant trend towards worsening speech production on day #2 (DBS in off condition). Scores varied by no more than 1 point on the scale. Table 9d shows a similar trend for swallowing; however, it is noted that Participant #03 worsened from a score of .5 to a 2 on day #2, denoting an increase in difficulty swallowing as measured by episodes of choking (per the UPDRS scale).

Table 9c: UPDRS Question #5 – Speech*

UPDRS #5	Day 1	Day 2	Diff (D2-D1)
Speech			
Partic 01	2	2.5	.5
Partic 02	1	1	0
Partic 03	2	3	1
Partic 04	1	2	1
Partic 05	2	2	0
Partic 06	2	3	1
Mean	1.66	2.25	.59

Scale: 0 = normal; 1 = mildly affected. No difficulty being understood; 2 = moderately affected. Sometimes asked to repeat statements; 3 = severely affected. Frequently asked to repeat statements; 4 = unintelligible most of the time.
*Same results as for Question #18 – Speech.

Table 9d: UPDRS Question #7 – Swallowing

UPDRS #7	Day 1	Day 2	Diff (D2-D1)
Swallowing			
Partic 01	2	3	1
Partic 02	0	0	0
Partic 03	.5	2	1.5
Partic 04	1	1	0
Partic 05	0	0	0
Partic 06	2	3	1
Mean	0.91	1.5	.59

Scale: 0 = normal; 1 = rare choking; 2 = occasional choking; 3 = requires soft food; 4 = requires NG tube or gastrostomy feeding

Tongue pressures

As noted earlier in this manuscript, only descriptive analysis was possible for individual tongue pressures, secondary to equipment difficulties. A total of three participants completed this portion of the testing protocol, as noted in Table 10. Measures were captured in millimeters of mercury (mmHg) as per use of the Kay/Pentax Digital Swallow Workstation Swallow Signals Lab, and converted to kilopascals (kPa) for ease of comparison to other research conducted with the Iowa Oral Pressure Instrument (IOPI). As Table 10 illustrates, two participants showed a gain in tongue pressure on day #2 (DBS in off condition) of a mean 6.31 kPa (or 47.33 mmHg). One participant showed a loss in mean tongue pressure (9.02 kPa, or 67.66 mmHg). These mean scores were calculated using the greatest value of three trials, after calculating a composite score of anterior, middle and posterior tongue pressure measurements for each trial.

Table 10: Tongue pressure data (captured in mmHg, converted to kPa).

Tongue	Day 1		Day 2		Diff (D2-D1)
	Mean A+M+P*	**SD**	**Mean A+M+P***	**SD**	
Partic 01	NA		NA		
Partic 02	NA		NA		
Partic 03	NA		NA		
Partic 04	13.24	2.37	4.22	0.76	-9.02
Partic 05	7.46	0.53	18.57	7.82	11.11
Partic 06	7.37	2.54	8.89	5.69	1.52
Mean	9.35		10.56		

* Mean A+M+P = calculation of the average of anterior, middle and posterior tongue pressure measurements. Calculation noted in table represents that of the greatest value of three trials.

Discussion

The direct relationship between deep brain stimulation of the subthalamic nucleus (DBS-STN) and swallow physiology remains poorly understood. Neuromuscular changes resulting from stimulation to the subthalamic nucleus and its impact on bolus flow through the oropharynx require further investigation. While the effectiveness of this surgical procedure on motor symptoms has been documented (Zibetti et al., 2007, p. 223), only one published study currently exists denoting its impact on the physiology of the oropharyngeal swallow (Ciucci et al., 2007). The current study was designed to identify such an effect on bolus flow through the oropharynx. The methodology employed in this study allowed the investigator to assess oropharyngeal swallow efficiency, and its multiple components, as well as swallow apnea, penetration/aspiration, tongue pressures and scores on the United Parkinson's Disease Rating Scale (UPDRS). In addition, the study protocol included a turned-off period of 18-24 hours for the stimulator. This was hypothesized to allow for proper "flushing" of neuronal activity from the DBS stimulator, and thus permit for the study of movements without its influence. Additionally, as of the completion of this study, no published data exist for time needed for proper neuronal flushing of DBS stimulation. Based on a very small sample, this preliminary study did not demonstrate a significant effect of DBS-STN on specific parameters of swallow physiology.

Oropharyngeal Swallow Efficiency

To date, only two studies have investigated oropharyngeal swallow efficiency (OPSE) in persons with Parkinson Disease (Sharkawi et al., 2002; Sueli-Monte et al., 2005). Sharkawi and colleagues reported an "improvement" in the oral stage of the swallow pre- and post the Lee Silverman Voice Treatment (LSVT), but provided no specific data to support their claim (p. 34). Sueli-Monte et al., 2005, found an OPSE ranging from 40 - 60 in their 27 study participants with Parkinson Disease (PD). Their bolus consistencies, as reported, were 10 ml of thin liquid barium and a "piece of bread coated in barium (approximately 8.0 cm)" (p. 458). The OPSE score was derived from a table in the published article (Table 2, p. 461), as the data was not cited in the narrative portion of the publication. In 1994, the landmark study that introduced this measure (Radmaker et al., 1994) reported an OPSE score of 79 for normal participants (N=8) across all bolus consistencies. A

composite score of 85 was reported for liquids, as obtained by combining all liquid bolus consistencies and volumes studied (i.e., 1, 3, 5, 10 ml). The present study, generated an OPSE of 39.47 for day #1 and 43.04 for day #2 given a 5 ml liquid bolus. While not statistically significant, the results may be indicative of a trend for better oropharyngeal efficiency with the DBS-STN off. If one compared these results to those of the normal participants in the Radmaker study, there is a large difference, of over 45 points, in efficiency post DBS-STN implantation. However, results from this study may be more in line with the findings of a 40-60 point OPSE for liquids found by Sueli-Monte and colleagues. Furthermore, the OPSE score for cookie (1/4 Lorna Doone cookie coated with barium) was approximately 6.5 for both days in this study (6.62 and 6.30 respectively), and 61 for normal participants in the Rademaker study. Of note, although not statistically significant, is the observation that in this study for bolus consistencies of liquid form (5cc thin liquid and “sips” thin liquid), there was an improvement in OPSE score from day #1 to day #2 (3.57 and 4.28 respectively; Table 2b, p. 29); whereas for the pudding and cookie consistencies there was a decline in the mean OPSE score (-3.78 and -0.32 respectively; Table 2b, p. 29). As previously mentioned in the Review of the Literature section of this manuscript, p. 01, several studies have documented specific physiological changes in the oropharyngeal swallow of persons with PD. Namely, reduced lingual motility that has resulted in longer oral transit times, difficulty in bolus formation, and hesitancy in the initiation of the swallow (Logemann, Fisher, Boshes & Blonsky, 1978, p. 56; Silbiger, Pikielney & Donner, 1967, p. 448), as well as pharyngeal phase disorders including delayed pharyngeal response and decreased pharyngeal contraction (Stroudley & Walsh, 1991, p. 891).

This lead this investigator to attempt to explain the changes in OPSE scores described above by further analyzing the oral transit time (OTT) and pharyngeal transit time (PTT) data, as these are the temporal components of the OPSE formula. Interestingly, minimal change in OTT was noted for liquids (both 5cc and sips liquid, Table 3b, p. 31); yet a very slight improvement on day #2 (DBS off) was noted for the pudding and cookie consistencies (-1.56 and -0.90 respectively; Table 3b, p. 31). Mean pharyngeal transit time (PTT) differences between day #1 and day #2 were all judged to be minimal and thus not accountable in any major way for the changes in overall OPSE.

As this conclusion was based on temporal measures only, further analysis of percent of bolus swallowed (BSWALL), percent oral residue (ORES) and percent pharyngeal residue (PRES) was also undertaken. As with the temporal measures, these bolus flow data are a component of the formula utilized to calculate the OPSE score. Percent bolus aspirated was not included in the additional analysis, as there was no aspiration observed for any of the participants under any bolus condition for either day. These additional analyses (Tables 5b, p. 33; 6b, p. 34; and 7b, p. 35) were also non-significant, as all p values were >.05. Further review of Tables 6b and 7b reveal that changes in oral residue (ORES) were greater than changes in pharyngeal residue (PRES) across all bolus consistencies (5.74, mean = 1.43 versus -4.82, mean = -1.20 respectively) for day #1 compared to day #2.

Interesting observations, however, were gleaned from the data, albeit not statistically significant. First is the observation that for bolus consistencies of liquid form (5cc thin liquid and “sips” thin liquid), there was an improvement in OPSE score from day #1 to day #2; whereas for the pudding and cookie consistencies there was a decline in the mean OPSE score. Secondly, it was also noted that OTT changes were greater than changes in PTT across all bolus consistencies (3.08, mean = .77 versus 1.01, mean = .25 respectively) for day #1 compared to day #2 (Tables 3b and 4b). Thirdly, descriptive analysis of bolus flow data may suggest that on day #2, or with DBS off for > 18 hours, group means showed more oral residue (ORES) and less pharyngeal residue (PRES) in comparison to day #1, or in the DBS on condition (Tables 5b, p. 33; 6b, p. 34; and 7b, p. 35).

In summary, oropharyngeal swallow efficiency (OPSE) measures did not reveal significant relationships when compared by condition (day 1: DBS on versus day 2: DBS off) or by bolus viscosity. Further analysis included review of individual components of the OPSE measure, namely, oral transit times (OTT), pharyngeal transit times (PTT), percentage of bolus to the cervical esophagus (BSWALL), oral residue (ORES) and pharyngeal residue (PRES). These descriptive findings may be sustained if given a larger sample.

Swallow Apnea Duration

The coordination of swallowing with respiratory airway protection has been well investigated in normal and in several clinical populations (Brodsky et al., 2011; Brodsky et al., 2010; Butler et al., 2007; Diez Gross et al., 2008; Dozier et al., 2006; Hiss et al., 2004; Hiss et al., 2003; Martin-Harris et al., 2005; and Perlman et al., 2005). Swallow apnea (respiratory cessation to accommodate swallowing) occurs most often during the expiratory phase of respiration, as noted by Martin-Harris and colleagues in 2005 (p. 766), where their normal participants demonstrated a predominantly expiratory/expiratory respiratory pattern for a 5-ml cup drinking task. Additional review of the data obtained from this study reveals that all participants produced their swallowing apneic period during the expiratory phase of respiration for all bolus consistencies presented. Of note, however, were intermittent episodes of expiratory deflections noted during the apneic period for several participants. While not within the scope of this study, these events were reviewed, as to their possible influence in calculating the total swallow apnea duration (SAD). Namely, concern arose over including these deflections as part of the apneic period, or measuring the apneic period only up to the time of deflection. A subsequent review of the literature specific to this issue revealed that concern over these deflections during the inspiratory and/or expiratory phases of respiration in the context of swallow apnea is not new, as several investigators have attempted to explain this phenomena (S. Butler, personal communication, June 2011). Most recently, Brodsky et al., 2011, has described these events as “non-respiratory flow events.” In his article, Brodsky describes non-respiratory inward flow events, termed SNIFs (swallowing non-inspiratory flow). While not within the scope of this study, it should be noted that deflections observed during the apneic period for all participants in this study took place during the expiratory phase. As mentioned by Brodsky, 2011, and Butler, 2011, these deflections may be related to a partial vacuum established by the offset of pharyngeal contraction. The reader is reminded that the nasal cannula, where the airflow is being measured, is located at the anterior nasal cavity, hence distant from the larynx, where the airflow is actually interrupted during swallow apnea. This allows for the suggested explanation provided by Brodsky and colleagues and Butler.

Results for this study revealed an average swallow apnea duration (SAD) of 1.65 sec for 5 ml liquid boluses on day #1 and 1.72 sec on day #2 (Table 8a, p. 45). Butler et al., 2007, reported an average SAD of 1.53 secs for a similar bolus volume and viscosity for participants post stroke who did not aspirate. In looking at data obtained from a sample of normal participants, Hiss et al., 2001, found SAD ranges of .79 to 1.05 secs for 10 ml liquid volumes in middle-aged and older participants.

Nilsson et al., 1997, p. 505, in studying older participants with dysphagia, stated that a shorter SAD resulted in increased risk for penetration/aspiration. Given this sample population, reduced SAD duration as noted in three of six participants, did not result in increased risk for airway invasion, as per videofluoroscopic analysis.

A $p < .05$ was identified for the cookie bolus on day 1 when correlation with OPSE was conducted ($p = .0188$, Table 8b, p. 37). This finding was difficult to interpret, as per the small data set overall. While the overall sample size for this study was six participants, only four participants completed the SAD measures for both conditions (day 1 and day 2), as per previously noted equipment problems. Of further interest is the observation that in looking at this correlation, the number trends toward the negative, or smaller OPSE. A physiological explanation for this, in the context of swallow apnea for a cookie swallow, could not be ascertained.

Penetration/Aspiration

Although no penetration or aspiration was observed for any of the bolus consistencies presented in this study, previous literature has reported variable incidence of penetration and/or aspiration for participants with PD. Of note are Leopold & Kagan, 1997, p. 12, who given a sample of 71 participants with PD, reported an incidence of aspiration on videofluoroscopy of 32%. Additionally, Nagaya et al., 1998, p. 97, reported an incidence of 52% aspiration in her sample of 16 participants with PD. By contrast, Sueli-Monte et al., 2005, p. 459, found only 7% incidence of aspiration on videofluoroscopy for her sample of 27 persons with PD.

Negative findings for penetration or aspiration in this study may be in line with the minimal changes noted in PTT between day #1 and day #2. Namely, participants did not aspirate under either condition for any bolus viscosity presented. This denotes good airway protection. The physiologic process for protecting the airway during the swallow is known to be a component of the pharyngeal stage of the swallow (Kim et al. 2005, p. 290; Logemann, 1998, p. 218). Given no significant changes in PTT for any of the bolus viscosities presented, would suggest good bolus flow through the pharynx with accompanying good airway protection. The reverse would not be true, as PTT is influenced by several other pharyngeal stage components, in addition to airway protection.

United Parkinson's Disease Rating Scale

The maximum score on the United Parkinson's Disease Rating Scale (UPDRS) is 176, denoting severe impairment secondary to PD. All participants in this study showed an increase in score from day #1 to day #2 (Table 6a, p 34), denoting worsening symptomatology, as expected on this global measure. This was also noted for question #5, speech, and question #7, swallowing (Tables 9c, p. 38, and 9d, p. 39, respectively). These increases in score for the UPDRS, a global measure, support the benefit received from the DBS-STN, as on day #2 each participant had endured an 18-24 hour period of no stimulation (off condition).

Interestingly, subjective complaints on day #2 included slight increases in tremor of the extremities, reduced equilibrium, increased bradykinesia, increased stiffness, increased rigidity and slight increase in weakness. These subjective complaints support the worsening scores for the scale. Of note were three participants (03, 04, 05) who worsened by larger margins with DBS off. All presented with specific subjective complaints: increased stiffness, greater bradykinesia, reduced equilibrium. These subjective complaints support the change in score for the scale. It is also interesting to note that Sueli-Monte found no correlation between OPSE, OTT or PTT with the UPDRS sections II (ADLs) and/or III (ability to perform motor skills) in her study of 27 persons with PD. UPDRS total scores were not reported in her study.

In contrast, it should be noted that while the worsening scores on day #2 support the use of the DBS-STN, the support for changes in swallow physiology remain unclear. Additionally, all six participants reported no swallowing disorder or complaint prior to DBS-STN implantation; yet, four of the six (66%) participants did report symptoms of dysphagia post implantation. Symptomatology included intermittent choking for liquids (reported by three participants) and food "stuck in throat" (reported by one participant). Again, no conclusion can be reached, as per limited sample.

Tongue pressures

As per previously reported equipment problems, data from only three participants was obtained. Isometric tongue pressure data for these participants showed an increase in two and a decrease in one for day #2 (DBS in the off condition). The mean tongue pressures for day #1 was 9.35 kPa, or 70.13 mmHg, with a range of 7.37 to 13.24 kPa; and 10.56 kPa, or 79.21 mmHg, with a range of 4.22 to 18.57 kPa for day #2. The average measure for 8 healthy elders studied by Robbins, et al., 2005, p. 1486, was 41 kPa. Stierwalt and Youmans, 2007, p. 151, reported a mean of 59.78 kPa in a sample of 200 normals, with a range of 28 to 94 kPa. In a sample of 31 young participants aged 20-29, Lazarus et al., 2003, p. 201, reported a mean tongue pressure of 64.4 kPa. As noted earlier in this manuscript, measures for isometric tongue pressures on all studies mentioned were taken with the Iowa Oral Pressure Instrument (IOPI), whereas measures in this study were gathered from the three-bulb tongue array coupled with the Swallow Signals Lab of the Kay/Pentax Digital Swallow Workstation. The instrument used to obtain the tongue pressure measures may well be a significant factor. The choice made for this study was related to the availability of the equipment. The main overt difference between the two instruments is that the Kay/Pentax instrumentation includes a three-bulb array, measuring anterior, middle and posterior tongue isometric pressures, whereas the IOPI is a one-bulb measurement tool, which measures the isometric pressure wherever the bulb is placed along the body of the tongue. In addition, the equivalence of measures between the two instruments is also unclear. The IOPI is calibrated in kilopascals (kPa) and the three-bulb array from Kay/Pentax utilizes millimeters of mercury (mmHg). While two conversion websites were employed in efforts to increase accuracy of the conversion for this study, reliability is yet to be determined. In

addition, the IOPI generates one pressure measurement, as it involves only one bulb; whereas the Kay/Pentax three-bulb array generates three pressure measurements (anterior, middle, posterior), and so in efforts to obtain one score for comparison, an average was calculated for each trial. This averaging is similar to that performed by Robbins et al. (2005, p. 1485) for swallow pressures calculation, where the three-bulb array was also utilized. It should also be noted that assessing swallow pressures while the tongue bulbs are positioned on the hard palate was not included in this study design as per concerns regarding orosensory input, as well as a possible increase in oral residue post swallow trials.

As previously mentioned, the isometric tongue pressures obtained in this study range from 7.37 kPa to 13.24 kPa for day #1, or DBS "on" condition; and from 4.22 kPa to 18.57 kPa for day #2, or DBS "off" condition. This data is not consistent with that reported for other participant groups and discussed earlier in this section. In specifically addressing persons with PD, Solomon et al., 1995, reported that "participants with generally less severe PD were found to have lower-than-normal tongue and hand strength, but not endurance." (p. 23). However, in a subsequent study (2000), she reported that her findings at the time did differ from those of her 1995 study. Consequently, she combined the data from the two studies to conclude that "when the data from the two studies were combined, statistical analysis revealed differences between groups for strength and endurance of the tongue but not the hand. On average, tongue strength was 8.3 kPa lower … for PD than for control participants." (p. 262). Moreover, in 2009, Huckenberry presented data from her study entitled, "The effects of oral-motor exercise on tongue strength, oral-motor agility, speech intelligibility, and dysarthria in individuals with Parkinson's disease" at the annual meeting of the American Speech-Language-Hearing Association. She reported on four participants with PD who completed her study protocol. Of note was that all measures of isometric tongue strength were in the low range, as in the current study. Namely, her data showed individual participant measurements of 9, 9, 13 and 19 kPa respectively at the beginning of the study; and measurements of 11, 16, 17 and 24 kPa at the completion of the study (slides 16-27). While her participants were not implanted with a DBS, the overall etiology of Parkinson disease may be considered a common factor, and thus this data may

support the results reported in the previous section of this manuscript (table 10, p. 40). This data, however, remains inconsistent with Solomon's findings in 2000, based on a sample of 16 persons with PD. Further review of Solomon's findings revealed that the mean isometric tongue strength reported was 48.1 kPa, SD 9.7, with a range of 27 to 62 kPa. Given the small sample reported by Huckenberry for persons with PD and the small sample reported in this study for persons with PD and implanted with the DBS-STN, no meaningful conclusions are possible.

Further discussion on the data presented in this study highlights that the increase in isometric pressures for isolated tongue movements on day #2 may be related to a reduction in inhibitory control of the underlying neuromuscular system involved in generating overall tongue pressures. This may be in line with the suggestion that subthalamic nucleus stimulation may inhibit the output of the globus pallidus interna (GPi) to the thalamus. This, in turn, may result in disinhibition of specific tongue muscle fibers. However, the increase in isometric tongue pressures observed does not correlate with the observation of greater oral residue (ORES) for liquid consistencies reported earlier (p. 41) in this manuscript, which suggests a reduction in swallowing efficiency. Additionally, other tongue behaviors are not accounted for when measuring isometric pressures. Namely, the effects of lingual pumping, lingual festination, bradykinesia or rigidity on overall bolus propulsion through the oral cavity. No conclusion can be reached, as the data being discussed is descriptive and based on a small sample.

Comment of reliability

As previously noted (p. 26) interrater reliability was moderate to strong, and intrarater reliability was strong for temporal and residue measures. Interclass correlation coefficient (ICC) results showed a strong to almost perfect agreement for measures of OTT, STD, ORES and PRES. However, fair to poor agreement was obtained for PRT. Further exploration for the low interrater and intrarater agreements on PRT revealed probable judgment discrepancies for bolus tail passage through the PE segment. This was evident on three swallow trials. Additionally, the perfect intrarater reliability for PRES measures was likely due to the small number of participants and reduced number of swallow trials to reanalyze.

General commentary

The STN has been regarded as an important modulator of basal ganglia output. Best results for alleviating most, if not all, motor manifestations of PD have been achieved by DBS of the subthalamic nucleus (DBS-STN) resulting in a reduction of anti-PD medications and the need for lower voltages for stimulation (resulting in longer battery life). It has been shown to be a safe and effective method for treating idiopathic Parkinson disease, including tremor, rigidity, bradykinesia, on/off fluctuation, oral control, gait/balance difficulties and dyskinesia (as cited in Zonenshayn et al., 2004, p. 216). Understanding why and how stimulation to the STN produces such results remains unclear. Namely, the specific neural correlates of how electrical stimulation to the STN influences the basal ganglia and its functions remains unexplained. While several theories have been proposed to investigate the impact of such stimulation to the region, none has been substantially proven to date. The STN is considered a tight nucleus composed of glutamatergic excitatory neurons, with some GABA interneurons. Afferent input is believed to be received from the cerebral cortex, thalamus, globus pallidus externus (GPe) and brainstem (specifically, dopaminergic neurons from the substantia nigra), and it projects mainly to both segments of the globus pallidus, substantia nigra, striatium and brainstem. It is hypothesized that inhibition of STN function leads to a diminished inhibitory outflow of the internal segment of the globus pallidus onto the motor thalamus (ventrolateral aspect), therefore resulting in an alleviation of motor symptoms. Interestingly, approximately 82% of the efferent fibers leaving the dorsal region of the STN travel to the GPi (Hamani, Saint-Cyr, Fraser, Kaplitt & Lozano, 2003, p. 6). This inhibitory pattern, via the ventrolateral aspect of the thalamus subsequently impacts stimulation to the cerebral cortex, as per various models discussing its effects on the specific structures and interactions of the basal ganglia-thalamic-cortical (BG-TH-CTX) system.

While results of this study did not show statistically significant findings for differences by condition, probably secondary to the small sample employed, the variability of physiological responses warrant further exploration. The suggestion that the participants achieved improved OPSE scores for liquids with the stimulator off (day #2) needs further exploration, particularly since the data are not as clear cut for other viscosities. In addition, changes in OTT were descriptively greater that

changes in PTT (p. 30). It may be that DBS enhances motoric functions, but is a detriment to efficient swallowing, although the observation that none of the participants showed any aspiration either with the stimulator on or off, is an encouraging positive sign in favor of DBS-STN. In addition, changes in isometric tongue pressures in some participants and differences in oral stage physiology by bolus viscosity in others support the need for further investigating the influence of DBS-STN on swallow physiology. Further understanding the specific role of thalamic output to the cerebral cortex will also enhance study in this area, as per recent interest in cerebral representation of swallow (Daniels & Foundas, 1997; Malandraki et al., 2010; Martin et al., 2007; Martin et al., 2001; Steele & Miller, 2010; Suzuki et al., 2003).

Results from this study, while descriptive in nature, serve to emphasize the great variability among study participants. While no strong correlation was found between any of the temporal swallow measures and the UPDRS scores, it is very possible that in studying a population with more advanced PD, the overall trends noted could differ. Also interesting was the observation that increased tongue strength did not result in a more efficient tongue, per the increased oral residue noted for semi-solids and solids in this study population. This greatly differs from reports with “normals” and persons post stroke. Moreover, this study has added preliminary data to the ongoing discussion of differences in swallow physiology between persons with PD without DBS-STN and persons with PD status post implantation of the DBS-STN. The methodology employed has allowed for initial observation of results in several areas of interest; namely, oropharyngeal swallow efficiency, isometric tongue pressures, swallow apnea and penetration/aspiration.

The addition of more participants to this study protocol will serve to further enhance the findings to date and lead to a better understanding of the specific influence of DBS-STN on swallow physiology in persons with Parkinson Disease. The future for this area of research appears to be bright, as we focus on more specific aspects of swallow physiology and try to better understand the neurological correlates of DBS-STN in PD. In addition, the increasingly creative use of pharmacological agents shows promise for a reduction in parkinsonian symptoms when paired with

neurosurgery. And lastly, improvements in neuroimaging, specifically fMRI, may help us on this road to better answer questions about brain function and overall swallow representation at the subcortical level.

Appendix 1

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