

**Swallow Safety and Kinematics in Neurological Impairment: A Comparison of
Dysphagia in Parkinson's Disease and Cerebrovascular Accident**

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Chapter 1: Introduction

Line of Investigation and Pre-Dissertation Manuscripts

The overarching goal of my doctoral research is to increase our knowledge of dysphagia associated with laryngeal dysfunction in people with Parkinson's disease (PWPD). The first pre-dissertation research project (manuscript #1, Dumican and Watts, 2020) investigated the frequency and severity of abnormal swallow events and the laryngeal kinematics that predicted the occurrence of those events. The study also sought to determine if PWPD who experienced these abnormal events were able to self-perceive their swallow deficits using a custom questionnaire. We were able to show that airway invasion occurs at a high frequency in Parkinson's disease (PD), laryngeal kinematics (specifically laryngeal vestibule closure reaction time) were the strongest predictor of airway invasion, and that a specific swallow questionnaire could be used to predict occurrences of airway invasion in PWPD.

The concept of utilizing a noninvasive questionnaire as a screening tool for those at risk of dysphagia directly related to the purpose of the second pre-dissertation project (manuscript #2, Dumican and Watts, 2020). That study sought to elucidate the differences in self-perceived swallow function in motor phenotypes of PD. Specifically, the study investigated the frequency of dysphagia symptoms identified by PWPD, and how other measures of communication difficulty (related to speech or voice function) could predict their self-perceived dysphagia symptoms. We were able to show that PWPD reported high frequencies of dysphagia symptoms despite never being screened, assessed, or diagnosed with

dysphagia by any other healthcare professionals. Moreover, more overt symptoms of impairment such as speech or voice difficulty were able to predict dysphagia symptomology in PWPD.

This final study (Manuscript #3, dissertation project) has been designed to build upon the knowledge developed in the previous manuscripts. The goals of this project were to investigate signs of dysphagia across oral, pharyngeal, and esophageal stages of swallowing in PWPD and compare to signs of dysphagia secondary to cerebrovascular accident (CVA). Another major goal of this project was to compare laryngeal kinematics (reaction time, closure duration) during the pharyngeal stage of swallowing in PWPD and those status-post CVA. This project examined a large sample of PWPD to assess the frequency of dysphagia impairments across swallowing stages, which may allow clinicians to develop more accurate clinical hypotheses during clinical assessments. This project also sought to determine which laryngeal kinematic events best predicted laryngeal closure impairment (identified by laryngeal penetration during the pharyngeal stage) with the aim to better inform clinicians of potential clinical targets for swallowing rehabilitation in PWPD.

Problem Statement

Dysphagia (swallow impairment) in PWPD is expected to occur at some point during the disease process, with incidence estimated as high as 95% (Simons, 2018). Dysphagia symptoms in PWPD include deficits in the oral stage (oral residue, tongue pumping), pharyngeal stage (increased residue in the vallecula/pyriform sinuses, increased airway invasion), and/or esophageal stage (decreased upper esophageal sphincter motility) (Andres et al., 2017; Suttrup & Warnecke, 2016). The estimated expenses associated with dysphagia

in a given healthcare episode can increase the cost burden by 40% (Attrill, White, Murray, Hammond, and Doeltgen, 2018) and if aspiration pneumonia occurs secondary to dysphagia, this healthcare episode carries a median cost of \$30,000 per person (Wu, Chen, Wang, & Pinelis, 2017). This is a frequent cost burden and health risk factor for PWPD, as aspiration pneumonia is one of the leading causes of death in this population (Beyer et al., 2001; Suttrup & Warnecke, 2016; Yoritaka et al., 2013).

While symptomatology of dysphagia in PD has been well described, our understanding of the underlying physiological deficits associated with those symptoms are less clear. This is likely due to the heterogeneous presentation of dysphagia in PD across individuals, combined with a lack of consistent evidence for how PD affects the peripheral and cortical structures involved with swallowing (Kwon & Lee, 2019). Additionally, despite the expected occurrence and cost of negative healthcare outcomes related to dysphagia in PWPD, there is a substantial gap in our knowledge of how dysphagia within the different stages of swallowing manifest as impairments in swallow efficiency (pharyngeal residue) or safety (penetration, aspiration) in PWPD, and how laryngeal physiology during swallowing (e.g., laryngeal excursion and closure) are associated with those factors. In fact, our understanding of laryngeal physiology during swallowing in PWPD lags behind that of other neurological causes of dysphagia such as CVA/stroke. The prevalence of dysphagia has been reported as very similar between CVA and PD (up to 80% and 81%, respectively) (Takizawa et al., 2016), yet dysphagia literature describing underlying physiological impairments associated with CVA is far more extensive. This includes interdisciplinary positions on the importance of dysphagia screening post-CVA and the required involvement of Speech Language Pathologists in post-stroke evaluation protocols (De Cock et al., 2020; Martino et al., 2005; Perry et al., 2019) as well as studies

reporting long-term outcomes of patients with stroke-related dysphagia and how dysphagia screening reduces negative outcomes in those populations (Al-Khaled et al., 2016; Sreedharan et al., 2020).

Despite the growing number of individuals diagnosed with PD compared to CVA in the United States alone (930,000 vs. 800,000, respectively) (Marras et al., 2018; Ovbiagele and Nguyen-Huynh, 2011), a growing body of literature is demonstrating that PWPD may be provided with inadequate information regarding dysphagia risk from their primary care professionals, and therefore have a poor understanding of swallowing impairments associated with the disease (Swales et al., 2020) and how to identify symptomology (Salinas et al., 2020). The combination of these factors presents specific problems that the current research proposal aims to address.

Significance

Dysphagia is ubiquitous in PWPD, with an increased risk of pneumonia associated with laryngeal penetration with or without aspiration (Tjaden, 2008). As the population of PWPD will increase to 1.25 million individuals over the next decade (Marras et al., 2018), there is a significant need to better understand the physiology underlying dysphagia in PD so that clinical assessment and treatment planning are better informed (i.e., treatment that targets the etiological physiology of dysphagia). For example, swallow kinematics during the pharyngeal stage of swallowing such as laryngeal vestibule closure reaction (how quickly the airway closes) and duration (how long the airway stays closed for) are considered to be major contributors to airway safety (e.g., preventing laryngeal penetration). Yet our knowledge of

laryngeal kinematics is deficient across many dysphagia etiologies, and particularly so in neurogenic dysphagia such as CVA and PD (Vose and Humbert, 2019).

Research regarding the pharyngeal stage of swallowing in PWPD has evolved from simply considering transit times (how long it takes for the bolus to move through the pharynx and pass below the upper esophageal sphincter) (Ellerston et al., 2016; Ertekin et al., 2002; Lin et al., 2012; Monte et al., 2005; Wang et al., 2017), to more comprehensive assessment of kinematic measures of structures in both the oral and pharyngeal stages. Some studies have sought to distinguish differences between PWPD and healthy controls to elucidate the physiological changes in swallowing as a result of the disease process (Argolo et al., 2015; Baijens et al., 2011; Schiffer & Kendall, 2018). More recent literature has also examined the weight and overall contribution of specific spatiotemporal kinematic events that occur during the pharyngeal stage such as location of the bolus at time of swallow initiation, laryngeal vestibule closure reaction time, and hyolaryngeal excursion in relation to airway safety (penetration and/or aspiration) in PWPD.

Our understanding of dysphagia and the underlying physiological deficits across the disease process of PD remains deficient but has increased in recent years (Ciucci et al., 2013; Gaeckle et al., 2019; Kwon & Lee, 2019; Michou & Hamdy, 2010; Miller et al., 2008; Simons, 2018; Suttrup & Warnecke, 2016). While an increasing number of investigations have examined contrasts in oral and pharyngeal stage impairments in PWPD, the relative heterogeneity of PD as well as the variation in research design and methodology have lacked specificity and methodological rigor, leaving uncertainty if there are consistent, predictable features of dysphagia in PWPD (Ellerston et al., 2016).

This dissertation project primarily aimed to address knowledge gaps existing in the extant literature of dysphagia and PD. By doing so, it may substantially extend our knowledge of how dysphagia presents across a broad sample of PWPD, what the most common and salient characteristics of dysphagia in PD are, and determine how specific kinematics related to laryngeal physiology for airway protection affect swallow safety in PD. Secondly, this project aimed to inform how the presentation of dysphagia in PD compared to that of other neurogenic etiologies of dysphagia, specifically CVA. From a tertiary point, an overarching aim was to document dysphagia frequency and severity in PWPD across the spectrum of the disease. The purpose for doing so was to advance knowledge to inform education, screening, assessment, and therapeutic approaches to dysphagia for PWPD from the time of diagnosis to best preserve swallow function, maintain quality of life standards, and decrease healthcare costs and burden.

Literature Overview

There is a growing body of literature regarding the effects of abnormal spatiotemporal movements of laryngopharyngeal structures during the pharyngeal stage of swallowing in PWPD leading to dysphagia. Much of the earlier literature addressed these changes from a neuromotor based theory perspective, where structures involved with the pharyngeal stage of swallowing are affected by the hallmark motor disturbances of PD (Suttrup & Warnecke, 2016) including bradykinesia, akinesia, and rigidity (Edwards et al., 1992; Leopold & Kagel, 1994; Volonte et al., 2002). However, recent investigations into the consequences of dysphagia in PWPD (i.e., penetration and/or aspiration) and the pathophysiology of these consequences have indicated that sensorimotor related changes in airway protective

mechanisms during the pharyngeal stage of swallowing are also contributing to dysphagia manifestation in PWPD as well. These sensorimotor deficits may serve as the theoretical foundation of impaired swallow function in PD.

In the case of a neurodegenerative disease such as PD, the hallmark neuropathological process is understood to be the death of dopaminergic neurons in the substantia nigra pars compacta (SNpc) of the basal ganglia. This neuronal cell death is precipitated by the formation of neuronal Lewy bodies, collections of misfolded alpha-synuclein proteins in the central nervous system (CNS). It is hypothesized that when dopaminergic neuronal death in the SNpc reaches approximately 80%, the classic motor symptoms of PD including slowed movement (bradykinesia) and muscular rigidity (Sveinbjornsdottir, 2016) reach a perceptible level. Additional motor dysfunction may be associated with bradykinesia or occur separately as part of the disease process including muscle weakness, movement variability (decreased target accuracy), and tremor (Berardelli et al., 2001). The consequence of dopaminergic cell death in subcortical nuclei is an increase in the inhibitory pathway of the basal ganglia including the subthalamic nucleus (STN), globus pallidus internal segment (GPi), and the substantia nigra reticulata (SNr). The combined dopaminergic depletion and over-inhibition of the inhibitory pathway results in insufficient cortical activation to sufficiently disinhibit this system, and suppression of the excitatory thalamocortical projection from the basal ganglia to initiate movement. The resulting inhibitory dominance in basal ganglia circuitry manifests in the typical PD motor complications with prolonged initiation time, slowed movement, and decreased movement amplitude (Bove & Travagli, 2019; Lanciego et al., 2012; Reich & Savitt, 2019).

Recent evidence has identified alpha-synuclein and Lewy body deposits within the peripheral nervous system (PNS), specifically in the axon terminals of cranial nerves innervating skeletal muscles of the larynx and oropharynx in PWPd, but not in individuals without the disease (Mu et al., 2013). The role of alpha-synuclein both in its typical and pathological state is multifactorial. However, whether in the CNS or PNS, its focal location primarily in the terminals of neurons is characterized by the aggregation of abnormally formed deposits and a neurotoxic environment which negatively affects the optimal functioning of neurotransmitters and neurotransmitter release from the presynaptic terminal (Burre, 2015; Villar-Pique et al., 2016). The motor dysfunction caused by these alpha-synuclein Lewy Bodies is a leading theory for the cause of dysphagia in PWPd.

The direction of disease progression through the nervous system has been debated. While both PNS-first and CNS-first pathogenesis hypotheses have been reported, there is also emerging evidence that suggests a bidirectional propagation of the disease (Borghammer & Van Den Berge, 2019). One of the most widely cited theories of PD progression is a PNS-first spread of PD related pathology. This theory suggests that in a large proportion of PWPd the spread of alpha-synuclein and aggregated Lewy bodies moves from the PNS towards the CNS through retrograde transport via the vagus nerve (Braak et al., 2003a; Braak et al., 2003b; Braak et al., 2004; Rietdijk et al., 2017). The direct pathogenic catalyst of PNS-first PD has been disputed including whether a pathogen is ingested, inhaled, or is exposed through some other method (Lionnet et al., 2017). Not all PWPd fit into the PNS-first theory, especially when considering PD subtype such as early onset vs. late onset PD or tremor vs. non-tremor dominant (Dickson, 2018; Jellinger, 2018). Both mouse and human models of PD pathology spread have suggested a predictable occurrence of aggregates in the motor neurons of the

gastrointestinal system, with a caudal spread through the vagus nerve into the dorsal motor nucleus of the vagus nerve (DMV) in the medulla (Greene, 2014; Kim et al., 2019; Ulusoy et al., 2017).

The overall function of the vagus nerve, and by association the DMV, is substantially complex and multifaceted. The vagus nerve and its associated nuclei control gastrointestinal visceral and somatic motor and sensory function, laryngeal and pharyngeal motor function, endocrine and hormonal function, neurotransmitter and cardiovascular regulation, as well as other autonomic function including blood pressure and respiratory rate via projections to all levels of the CNS (Greene, 2014; Mussa & Verberne, 2013).

The close proximity of the DMV to motor nuclei vital for pharyngeal and laryngeal physiology involved in swallowing supports the theory that impaired motor function related to these nuclei may underlie early motor dysfunction, including early emergence of dysphagia, in PWP. Evidence regarding the selectivity of motor neurons, and therefore specific motor nuclei in the dorsal area of the medulla, is inconclusive. Certain research points to sensory nuclei such as the nucleus tractus solitarius (NTS), which is a pivotal synapse point for somatosensory afferents from the oropharynx entering the CNS, may be unaffected (Surmeier & Sulzer, 2013).

While the parasympathetic nerve fibers of the vagus nerve consist of a myriad of branches, connections, and synapse points to different nuclei throughout the medulla and the CNS, PD pathology within the vagus nerve pathways may be less selective than previously thought. Moreover, neuronal loss in the DMV and other vagus associated motor nuclei may be occurring before and/or in conjunction with hallmark neuronal loss in the SNpc (Pelz et al., 2018; Greene, 2014). Neuronal degradation and associated motor output in areas such as

the thalamus, basal ganglia, and motor nuclei in the medulla, as well as pathological evidence in peripheral pathways, support both CNS and PNS involvement in the role of dysphagia in PWPd. The physiological manifestations of dysphagia in PWPd however, is not well understood across the stages of disease degeneration.

Post-mortem studies of PWPd with reported dysphagia indicated that not only were there alpha-synuclein and neuromuscular changes in laryngopharyngeal motor nerves in PWPd (Mu et al., 2013), but there were also alpha-synuclein aggregates in sensory nerve terminals in the pharynx of these patients as well (Mu et al., 2015). This provides pathological evidence that sensory related changes are likely occurring in conjunction with motor related changes. Motor function and sensory input are both critical for safe and efficient swallow function. This includes initiation of the pharyngeal stage of swallowing as well as protective mechanisms related to laryngeal closure and cough in abnormal swallow events to protect the airway and lungs (Ludlow, 2004). Chemo- and mechanoreceptors perceive bolus properties (weight, thickness, temperature, etc.) to program swallow related motor events in the pharyngeal stage of swallowing (Troche et al., 2008). Earlier studies have demonstrated that muscle dysfunction in PD such as rigidity is not linked to or associated with dysphagia (Ali et al., 1994), and the pharmacological approaches typically used to improve motor function in PWPd have shown no definitive improvement in swallow function (Broadfoot et al., 2019; Sapir et al., 2008). This may reveal that a sensory response is pivotal to trigger the rapid onset of swallow musculature (Fregosi and Ludlow; 2013) and that a combination of muscular and sensory function is required for adequate elevation of the larynx, protection of the airway, and propulsion of a bolus safely through the pharyngeal cavity in an optimal temporal manner.

There have been recent advances in our understanding of dysphagia and etiological physiological deficits in PD, even during the non-advanced stages of the disease. (Ciucci et al., 2013; Gaeckle et al., 2019; Kwon & Lee, 2019; Michou & Hamdy, 2010; Miller et al., 2008; Simons, 2018; Suttrup & Warnecke, 2016). A modest body of research has examined the oral stage of the swallow (receiving, masticating, and/or preparing a food or liquid bolus to be swallowed) including tongue strength, lingual control of the bolus, spatiotemporal characteristics, and contributions of the oral stage to swallow impairment (Argolo et al., 2015; Correa-Flores et al., 2012; Fukuoka et al., 2019; Miller, 2017; Minagi et al., 2018; Pitts et al., 2018; Wakasugi et al., 2017). However, inconsistencies in measurements and methodologies leave doubt as to how meaningful oral stage deficits may be for effective swallows and swallowing safety in PWPd.

Another emerging and more comprehensive body of literature has focused on the pharyngeal stage of swallowing and potential physiological manifestations of dysphagia in PWPd. This research has begun to explore the changes and importance of temporal kinematics of structures in the pharyngeal stage of swallowing, including laryngeal vestibule closure reaction and duration time, as they relate to swallow safety (Argolo et al., 2015; Bajens et al., 2011; Schiffer & Kendall, 2018; Andres et al., 2017; Curtis et al., 2019; Curtis et al., 2020, Dumican and Watts, 2020; Kim et al., 2015). However, this body of literature is still relatively new and further investigations are needed into how swallow kinematics impact swallow safety in the pharyngeal stage of swallowing in PD.

As noted previously, symptoms of swallowing impairment in PWPd are often overlooked despite rates of dysphagia similar to other neurogenic etiologies such as stroke. The lack of readily observable or severe manifestation of swallow impairments may cause

clinicians and healthcare professionals to see these deficits as “benign” (Ertekin et al., 2002). It has been shown that PWPD also exhibit a decreased ability to perceive their swallowing deficits, thereby decreasing referrals for assessment (Nienstedt et al., 2019, Pflug et al., 2018). However, recent research has indicated that when asked specifically about their experiences with swallowing, PWPD can perceive the presence of dysphagia (Andres et al., 2017; Dumican and Watts, 2020). Additional research has shown that laryngeal kinematics are the most significant predictors of decreased swallow safety in PD (Curtis et al., 2019; Dumican and Watts, 2020; Gaeckle et al., 2019). Interestingly, laryngeal kinematics related to the pharyngeal stage of swallowing in post-stroke dysphagia have also been observed to be the most significant predictors of decreased swallow safety as well (Lee and Kim, 2001; Wong et al., 2019; Wilsnkoetter et al., 2018; Cabib et al., 2019; Im, 2019; Im et al., 2018; Im et al., 2017; Park et al., 2017; Bingje et al., 2010; Wan et al., 2010, Seo et al., 2016; Vilardell et al., 2017).

Despite these suggested similarities, dysphagia in PD continues to receive less attention in healthcare settings and referrals than other neurogenic etiologies of dysphagia. While previous studies have investigated swallow kinematics broadly across various populations (Choi et al., 2011) their goal was not to differentiate swallowing physiology via kinematic measures between neurogenic populations. Dysphagia etiology (such as neurological condition) may play a relevant role in differentiating the underlying physiological impairments that put airway safety at risk. Unfortunately, most studies often include multiple etiologies as one group, rather than investigating them separately (Molfenter and Steele, 2011). Similarly, while investigations of swallow kinematics in different groups of healthy individuals (young or older adults) have increased (Humbert et al., 2018),

comparisons of how swallow kinematics differ, change, or contribute to airway safety across different neurogenic groups warrants further investigation to better understand how swallow kinematics contribute to airway safety across various neurologically impaired populations.

Research Questions and Hypotheses

The research questions that will be addressed in this proposal are:

1. What (a) signs of dysphagia and (b) associated physiological impairments are most frequent across oral, pharyngeal, and esophageal stages of swallowing in PWPD compared to individuals post CVA when they are referred for an instrumental swallowing assessment using videofluoroscopic swallow study (VFSS)?

Based on the extant literature, we hypothesize that signs and physiological impairments as measured by the Videofluoroscopic Dysphagia Scale (VDS), across swallowing stages will be similarly present in both populations. However, abnormal laryngeal swallow events of penetration and aspiration as measured by the Penetration Aspiration Scale (PAS) (Rosenbeck et al., 1998) will occur more frequently in PWPD due to the ubiquity of laryngeal impairment in this population.

2. For those individuals diagnosed with pharyngeal stage dysphagia and who display abnormal swallow events, as measured by a score of ≥ 3 on the PAS, which laryngeal kinematic measurements are the best predictors of airway invasion?

Based on the available literature, we hypothesize that laryngeal vestibule closure reaction time (LVrt) will be the strongest predictor of abnormal pharyngeal stage swallow events in PWPD, but will be a weaker predictor in those with CVA. While other kinematic measures will be obtained, including laryngeal vestibule closure duration (LVCd), based on previous literature

we do not expect these measures to contribute as strongly to the prediction of abnormal swallow events.

3. Do laryngeal kinematic measures differ between PWPD and individuals with CVA who have been diagnosed with pharyngeal stage dysphagia that includes penetration with or without aspiration?

It is unclear at this time how laryngeal kinematics such as LVCrt will differ between two neurogenic dysphagic groups. While the literature indicates that LVCrt is typically a strong predictor of abnormal swallow events in both populations, how the specific kinematic timings compare between the groups has not been investigated previously.

4. When individuals with CVA are stratified into cortical and subcortical lesion foci, are there differences between these subgroups and PWPD in terms of dysphagia signs and underlying physiological impairments, as measured by the VDS?

This question may be of importance when considering how the potential screening, assessment, and treatment of dysphagia may be affected. If the manifestation of dysphagia in PD appears similar to either CVA subgroup, then this may help guide future research on how to best approach dysphagia assessment in PD. Based on the available literature, it is currently unclear if there will be differences between any of the stroke subgroups and the PD group. While the pathological hallmark of PD involves many subcortical structures, this particular question has not been investigated previously. Moreover, findings from the current dysphagia literature examining cortical vs. subcortical swallow function is mixed, with contradictions regarding the patterns and presentation of dysphagia.

Chapter 2: Predicting Airway Invasion Using Screening Tools and Laryngeal Kinematics in People with Parkinson's Disease

Introduction

Dysphagia in people with PD (PWPD) is associated with negative healthcare outcomes, decreased quality of life, and pneumonia secondary to aspiration. Aspiration pneumonia is a significant contributor to mortality rate in neurogenically impaired populations, especially in those with PD (Attrill et al., 2018; Lim et al., 2018). Dysphagia is a public health concern, as it significantly increases costs for providers, increases the length of stay for inpatients, and decreases long-term health outcomes (Brodsky et al., 2016). Studies have shown that delayed movement timing of swallow mechanics contributes to increased laryngeal penetration and aspiration in people with PWPD (Argolo et al., 2015; Schiffer and Kendall, 2018). These impairments are likely associated with the sensorimotor manifestations of PD among which include bradykinesia and akinesia (Berardelli, 2001). It stands to reason that hypokinetic movements may impair swallow related muscular function and decrease swallowing safety in PWPD. Movements in PD can be substantially slowed, reduced in amplitude, and/or delayed. In swallowing this hypokinesia has been associated with reduced pharyngeal contraction for food bolus propulsion and delayed timing of laryngeal closure for airway protection (Ellerston et al., 2016).

Airway penetration and/or aspiration are often identified in PWPD, even with no or minimal complaints of swallowing difficulty (Pflug et al., 2018; Tjaden, 2008). The pathophysiological cause of decreased swallow safety in this population is thought to be multifactorial including poor bolus control, decreased esophageal function, and

somatosensory deficits (Kwon and Lee, 2019; Suttrup and Warnecke, 2016). While laryngeal kinematics during swallowing, such as laryngeal vestibule closure reaction and duration times, are likely associated with dysphagia (specifically airway invasion) in PWPD, they have not been investigated until recently. Current evidence has shown that the timing of airway closure was the strongest predictor of airway invasion in non-advanced PD (Curtis et al., 2019). However, further knowledge of laryngeal function during swallowing in PWPD is needed to more fully inform our understanding of laryngeal impairment as the disease progresses and to inform treatment planning for rehabilitation of swallowing function.

There is evidence that the perception of swallowing impairment in PWPD is also impaired throughout the stages of disease progression. For example, while oropharyngeal dysphagia in non-advanced PD (e.g., Hoehn & Yahr stages I – III) may be present, many PWPD are unaware of their swallowing difficulties or their dysphagia symptoms may be self-perceived as “benign” (Ertekin et al., 2002). This leaves the possibility of aspiration and subsequent sequelae as potential risks to health, even in non-advanced stages of the disease (Michou et al., 2013). Dysphagia in non-advanced stages may also be present at rates higher than previously expected. A meta-analysis reported increases in dysphagia diagnosis post instrumental assessment despite there being no overt or subjectively reported dysphagia symptoms at pre-assessment (Kalf et al., 2008). Extant literature also supports the use of standardized measures for detection of swallowing impairment in PWPD in both advanced and non-advanced stages (Manor et al., 2007). The potential lack of self-awareness in the perception of swallowing disturbances combined with increased evidence of penetration and/or aspiration in non-advanced stages supports the need to objectively determine if there

are measures or means to better identify swallowing impairments in PWPD across the continuum of progression.

The purpose of the current pilot study was twofold. The first was to investigate the predictive ability of swallow screening tools for identifying dysphagia in PWPD in non-advanced stages. Our second purpose was to identify how specific laryngeal kinematics predict penetration and/or aspiration occurrence. We hypothesized that scores from a validated swallow questionnaire (Swallow Disturbance Questionnaire, SDQ) (Manor et al., 2007) and a conventional screening method (3 oz water swallow screening test, WSST) would be able to predict the occurrence of penetration and/or aspiration identified by instrumental assessment. We also hypothesized that participants in our sample would exhibit frequent occurrences of abnormal airway invasion as measured by the Penetration Aspiration Scale (PAS). We lastly hypothesized that laryngeal kinematics, specifically laryngeal vestibule closure reaction time (LVrt) and duration time (LVCd), would predict the occurrence of larger (abnormal) PAS scores.

Materials and Methods

This study was approved by a university institutional review board (IRB). 14 individuals diagnosed with PD were recruited to participate. Inclusion criteria consisted of: 1) diagnosis of idiopathic PD by a neurologist, 2) current disease severity in stage I-III based on the original H&Y scale (Goetz et al., 2004) which has been previously staged by the participants' neurologist, 3) no previous diagnosis of dysphagia or treatment for dysphagia by a healthcare professional, 4) no comorbid neurological impairments not associated with PD, and 5) no history of pneumonia or other pulmonary/respiratory illness within the last two

years. Patients were considered to have no prior history of dysphagia if there was no previous documentation of dysphagia evaluation or treatment contained in the patient records obtained in accordance with IRB protocols, which have been previously obtained as part of an ongoing program of research in our lab, as well as verbal confirmation by the subjects. Inclusion criteria also necessitated self-reports of dysphagia-symptoms on a swallowing symptom questionnaire and was completed by the participants during a previous visit to the research laboratory. This questionnaire consisted of several general dysfunctions potentially related to swallow function. The questionnaire asked subjects how frequently they experienced the dysfunction presented, including items such as “Drooling” and “I cough when I eat solid foods”. If the subjects identified experiencing at least one dysfunction, they were considered eligible for inclusion into the present study assuming all other inclusion criteria were met. Participants were required to complete all consenting procedures prior to enrolling in the study. All research activities took place on a university campus and a mobile radiography unit.

Participants completed a self-report questionnaire of their swallow function (SDQ), performed a 3 oz water swallow screen test, and completed a VFSS. Based on previous literature using the SDQ, the optimal score for detecting dysphagia in PD is 11 (Manor et al., 2007). However, this number is nonspecific as individuals may only respond to important items regarding airway safety such as coughing frequently on liquids and solid foods, yet not score above the dysphagia cutoff score. The SDQ was therefore treated as a continuous measure where individuals may report their dysphagia on a continuum of symptoms, rather than needing to meet a cutoff.

For the 3 oz WSST, positive responses (suggestive of dysphagia) included (a) coughing, (b) throat clearing, and (c) wet, gurgling vocal quality were compared to baseline

(e.g., prior to swallowing water). This was aligned with previous literature which utilized variations of the 3 oz WSST (Brotsky et al., 2016). Participants were provided with 3 ounces of room temperature water via cup, as measured by syringe, and were cued to “drink the water as fast and as comfortably as they could on consecutive sips”. Previous research has investigated the application of swallowing speed with a water swallow protocol to detect airway invasion (Miller et al., 2008; Pflug et al., 2019; Sulena et al., 2017), but with inconsistent findings related to the measure of swallow speed during this test. Therefore, while we did not specifically measure swallow speed, the decreased synchrony of the respiratory-swallow pattern in PWP (Miller et al., 2008; Wang et al., 2017) may be used to identify episodes of aspiration causing an active airway response. Any positive sign of airway invasion related to throat clearing, coughing, or wet voicing after drinking were recorded as a “1”, while no signs exhibited were recorded as “0”.

For the VFSS, all participants were asked to consume three thin liquid bolus trials at increasing volumes (10, 15, and 20 mL), three trials of 1 tablespoon (tbsp) of pudding, and three trials of a regular food texture (for which a cookie was used) that were mixed and/or coated with barium (E-Z Paque). For the thin liquid bolus swallows, participants were instructed to place the whole bolus into their mouth, hold, and then swallow when ready. Pudding and regular texture boluses were administered to the participant but swallow timing was not cued, allowing patients to orally prepare the bolus that is typical for their everyday swallow performance.

All VFSS were conducted via a mobile swallowing/dysphagia assessment unit (Diagnostex, LLC, Hurst, TX) on the university campus in order to reduce additional travel burden for the participants. All studies were recorded at 30 frames per second (fps) in

agreement with current literature (Mulheren et al., 2019). All swallow studies were conducted by a trained Speech-Language Pathologist (SLP) who was blind to the conditions and purposes of this particular study. The principle investigator (PI) was present for all VFSS studies to maintain fidelity of the methodology. All swallow studies were recorded on de-identified digital recordings and analyzed at a later date.

Video analysis software Avidemux v. 2.7 was used to gather the kinematic measures of laryngeal movements. Two kinematic timing measures were obtained from the VFSS recordings: laryngeal vestibule closure reaction time (LVrt) and laryngeal vestibule closure duration (LVcd). These measurements have been utilized in previous studies to assess physiological timing events related to airway closure and protection during swallowing (Vose and Humbert, 2018). LVrt was operationally defined as beginning with (a) the initial and consistent anterior-superior burst of the hyoid and ending when (b) the arytenoids contacted the underside of the epiglottis and the maximum extent of laryngeal vestibule obstruction was observed. LVcd was defined as beginning at (a) the moment of maximum obstruction of the laryngeal vestibule was observed and ending when (b) the descent of the arytenoids from the underside of the epiglottis began, as seen by the reemergence of the vestibule. Both kinematic measurements, based on timing of movement, were treated as continuous variables for our analysis. The PAS (Rosenbek et al., 1996) was applied to every swallow recording of each participant. The PAS measured the degree of laryngeal penetration and/or aspiration as judged by the depth of bolus material entering the airway. It has been used in previous literature to measure swallow safety in people with PD (Argolo et al., 2015; Baijens et al., 2011). All timing measurements were performed independently by the 1st author and a second trained assistant so that measures of inter- and intra-measurement reliability could be obtained (Table

1). 30% of swallows were chosen at random and remeasured by the second rater for all kinematic measures.

All statistical analyses were performed in SPSS (v. 24). Descriptive statistics were computed to identify demographic information including H&Y stage, age, LVrt, LVcD, and PAS scores. A standard entry logistic regression was performed to predict the probability of identifying laryngeal impairment as a function of the PAS from a preselected set of predictor variables including: the SDQ, the 3 oz WSST, LVrt, and LVcD. These predictor variables were specifically chosen *a priori* to be included into the analysis based on the projects aims and hypotheses. In order to conduct this analysis, PAS scores were coded to reflect either a “normal” and safe swallow (PAS score of 1 or 2), or “abnormal” (PAS score ≥ 3). This method has been suggested as one of several appropriate approaches with a logistic regression (Steele and Grace-Martin, 2017) and used in recent work (Curtis et al., 2019) to quantify the PAS. Receiver operating characteristics (ROC) analysis was then performed to produce an area under the curve (AUC) for sensitivity and specificity of screening methods (SDQ and 3 oz WSST) for predicting those who are at risk of dysphagia.

Reliability

A 30% randomly assigned remeasure of all kinematic timing measurements (LVrt and LVcD) was performed by a second, trained, independent rater for reliability measurement. A 30% remeasure was also performed by the 1st author to obtain intrarater reliability. Both inter- and intra-rater reliability for all timing measures were classified as excellent based on intraclass correlation coefficients (ICC) obtained. Reliability values are presented in Table 1.

Table 2.1 Interrater and intrarater reliability for LVrt and LVcD

<i>Measurement (type)</i>	<i>ICC</i>	<i>95% CI</i>	<i>Sig. (p-value)</i>
LVrt (Inter)	.93	.88 - .97	< .001
LVCd (Inter)	.94	.91 - .97	< .001
LVrt (Intra)	.97	.94 - .99	< .001
LVCd (Intra)	.98	.97 - .99	< .001

Results

A total of 135 swallows across the 14 participants were included in the analysis and no swallows were excluded. Descriptive statistics of the participant pool are shown in Table 2. A total of 7 males and 7 females with PD participated. Participants had a mean age of 66 years ($SD \pm 9.8$), and a median H&Y stage of 2 ($IQR = 1$) (Table 2). 40% of swallows were considered abnormal (PAS score ≥ 3) and bolus material in 27% of these swallows either reached the level of the vocal folds or entered the trachea (PAS scores 4-8) (Steele and Grace-Martin, 2017). Mean LVrt & LVCd were 0.42 seconds ($SD \pm .22$) and 0.46 seconds ($SD \pm .22$), respectively. There were no occurrences of incomplete laryngeal vestibule closure.

Table 2.2 Descriptive and demographic information

Descriptive Categories	Mean(\pmSD)/# of cases
Age	66 (9.8)
Hoehn and Yahr Stage*	2 (1)

Years post onset	4.77 (1.9)
LVrt	.42 (.22)
LVCd	.46 (.22)
3 oz Water Swallow Screen**	Positive response: n = 1
	Absent response: n = 13
SDQ scores	6.2 (3.9)
PAS scores	1-2: n = 81
	3-8: n = 54

*Expressed as Median(Inter-Quartile Range)

**Expressed in a positive response or absent response

The regression model produced a significant result above the constant model, $\chi^2(4) = 15.99$, $p = .003$, and Hosmer-Lemeshow Test of fit ($\chi^2 = 6.5$, $p = .592$) indicated that our predictive model accurately fit our data. Inspection of our correlation matrix to assess multicollinearity between our predictor variables indicated no R greater than 0.28. This indicated there were high correlations between predictor variables in the model, and we were able to move forward with interpretation of our analysis. Both LVrt ($\beta = 2.18$, $p = .042$, OR = 1.11) and the SDQ ($\beta = .156$, $p = .003$, OR = 1.17) contributed significantly to predicting abnormal swallow function in the sample. This indicated that in terms of screening tools, the SDQ showed a significant ability to predict airway invasion, while the 3 oz WSST ($p > .05$) did not. For kinematic measurements, these results indicated that LVrt was able to

significantly contribute to predicting the occurrence of airway invasion while LVCd ($p > .05$) was not. A full model summary is provided in Table 2.

Table 2.3. Logistic regression model predicting swallow function

Predictors	β	Wald	Sig. (p-value)	Odds Ratio
LVrt	2.18	4.12	.042	1.11
SDQ	.156	8.7	.003	1.17
LVCd	-.53	.37	.55	.11
3 oz WSST	-1.12	2.27	.13	.33

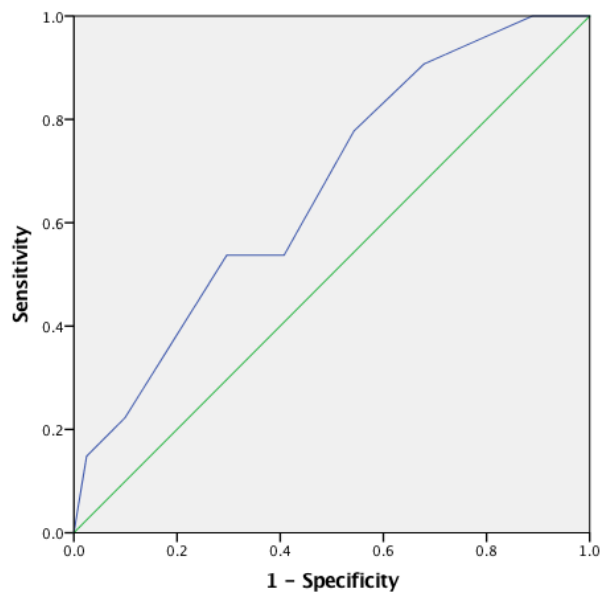


Fig. 2.1 AUC for SDQ

detecting impaired swallow
safety

ROC (Figure 1)

analysis revealed a
significant result and area
under the curve for the
SDQ of .67 ($p < 0.001$,
95% CI = 0.599 – 0.836).

This indicated that the SDQ was robust for identifying true positive states related to

abnormal swallowing. Our ROC analysis for the 3 oz WSST (Figure 2) however, indicated a nonsignificant result ($A = .49$, $p > 0.05$). This suggested that in this particular sample of participants, this water screen methodology was no better than chance at detecting the potential penetration and/or aspiration.

Discussion

Questionnaire Responses and VFSS Findings

Dysphagia in non-advanced stages of PD has been well documented, particularly without any subjective signs or reports of penetration or aspiration (Walker et al., 2011). Evidence has shown that many individuals with PD, regardless of stage, are poor and inconsistent self-reporters of dysphagia symptoms unless sufficiently prompted to intentionally focus on the symptoms (Kalf et al., 2012; Nienstedt et al., 2018). Our study sought to investigate how specific, non-invasive screening methodologies (questionnaire and water screen) detected swallow safety related to laryngeal kinematics and penetration/aspiration in a population of PWPD at non-advanced disease stages.

Our findings showed that for every unit increase in perceptual SDQ scores there is a 17% increase in the odds of experiencing swallow impairment as confirmed with instrumental assessment. A mean SDQ score of 6 in our sample may indicate that while PWPD in early disease stages do not report a critical cutoff score of 11 for the SDQ, swallow impairment characterized by impaired airway safety may be present. Nienstedt et al. (2018) recently reported that when PWPD are provided with questions related to swallow function from typical assessments, they are unreliably and inconsistently reporting their symptoms. Questions utilized in published research have provided limited specificity of dysphagia

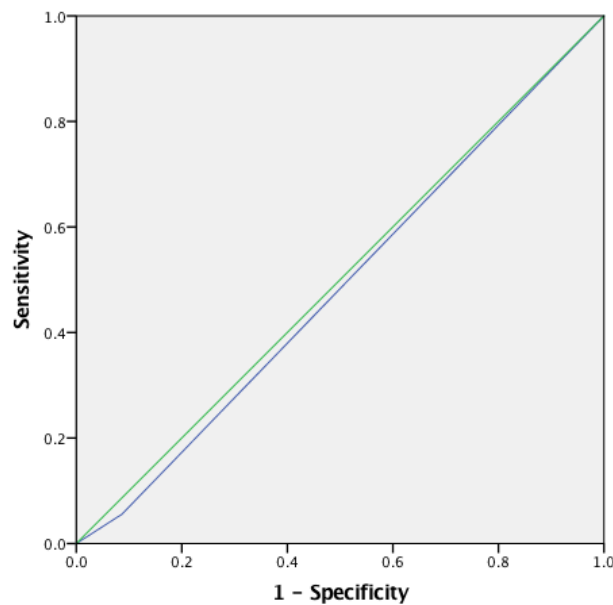
symptomology. Questions that only include “difficulty with pills” and “voluntary diet alterations” (Goetz et al., 2008) or broad queries of experience choking while swallowing (Chaudhuri et al., 2006) may not be sensitive to the range of swallowing symptoms experienced by PWPD. Despite different outcome measures, Andres et al. (2017) reported that when PWPD indicated even a minimal degree of dysphagia when given the SDQ, 94% were measured as exhibiting swallow impairment. Results from our current study indicate a similar trend, that when PWPD are provided with more specific sets of symptoms within a questionnaire such as the SDQ, those who are experiencing dysphagia (as confirmed with instrumental assessment) are more likely to perceive and report the symptoms. This supports the need to include comprehensive methods of dysphagia assessments for PWPD in early disease stages.

Water Swallow Screen and VFSS results

The 3-ounce water swallow test has shown high sensitivity for detecting aspiration events in various neurodegenerative populations, including PWPD (Suiter and Leder, 2007), and is recommended for inclusion in clinical swallow assessments related to PD such as the SCAS-PD (Branco et al., 2019). A broad clinical swallow assessment such as the SCAS-PD is recommended to detect those at risk of aspiration. However, a precursor to a clinical swallow assessment in many settings is the use of a simple water screening, which can be administered by various healthcare professionals including SLP’s and nurses. Warner et al., (2014). There are several variations of the water swallow screen test that may be used, which differ by either volume, consecutive or single sips, or other metrics (Brodsky et al., 2016). Our results indicated that in non-advanced PD, the 3-ounce water swallow screen protocol implemented was not effective at identifying participants with impaired swallow safety. This

supported the supposition that despite the water screen's low-cost and easy administration, the use of a speed-based water swallow screen may not be effective for identifying PWPD in non-advanced stages who are experiencing dysphagia but have not yet been referred for formal diagnostic assessment. Our findings agree with Pflug et al. (2019) that swallow speed ability in a water screen test does not accurately reflect dysphagia or aspiration risk. Different methodologies exploring volume may be more sensitive to detecting aspiration risk in PD (Suttrup and Warnecke, 2016). Further studies with substantially larger participant samples are needed to further investigate this phenomenon in PWPD at non-advanced stages.

Fig. 2.2 AUC for 3 oz WSST detection of impaired swallow safety.



Airway Invasion and Laryngeal Kinematics

Our findings indicated that a large proportion (40%) of swallows in this study were abnormal (PAS score ≥ 3) and of those abnormal swallows, 27% either reached the level of the vocal folds or entered the trachea (PAS scores 4-8). Literature has indicated that PAS

scores of 1 and 2 are within normal limits, and in healthy older adults PAS scores > 2 occur rarely (Humbert et al., 2018). A much higher rate of abnormal swallows even in a smaller sample suggested that changes in laryngeal and airway responses are present in non-advanced stages of PD. An important observation in this study was that penetration and aspiration events occurred multiple times across different swallows in multiple participants. Considering this and the large proportion of swallows that received “abnormal” PAS categorization, these results were likely not due to a single poor performer or isolated events.

Continuing research is needed to more fully understand the contribution of LVrt and LVCd to airway safety during swallowing in PWPD. Our findings showed that LVrt was a significant predictor for more severe penetration and aspiration events (e.g., higher PAS scores). Our OR (1.11) for LVrt indicated a small increase in the odds of an abnormal penetration or aspiration event (11%) with slower LVrt times. It is possible that the low OR is due to sample size as our findings agree with recent work by Curtis et al. (2019). Predictive models have also shown that other kinematic factors including hyolaryngeal movement are useful predictors for decreased airway safety in PWPD (Gaeckle et al., 2019) and warrant further investigation.

The detection of abnormal swallowing and increased airway invasion in the non-advanced stages of PD contributes to the body of knowledge about dysphagia manifestation in this population. The identification of penetration and aspiration of material into the airway during swallowing could have a significant impact on screening approaches, assessment methods, and directions for future therapeutic research in PWPD at non-advanced stages. If dysphagia in PWPD results from a combination of impaired somatosensory responses coupled with slowed kinematic timing, results from our study suggest that these impairments are

occurring at a substantial rate in PWPd at non-advanced stages, and across multiple swallows and bolus textures. Moreover, the current level of screening methodologies (i.e, 3 oz WSST) may not be sensitive enough to detect swallowing changes in this subgroup of PWPd. From a translational perspective, clinically relevant recommendations could include the use of a detailed questionnaire to gather patient perceptions of swallow function as part of a comprehensive swallow assessment. Future directions for research should include investigating other aspects of laryngeal kinematics in non-advanced PD as well as considering volume and consistencies of trials. Replication of this study in healthy, older individuals is also needed to determine if kinematic changes seen in PWPd are due to disease process or aging.

Limitations of the Study

Generalizations of the results from this pilot study should be guarded for a number of reasons. As an initial pilot study, the sample size for this particular project was small. Therefore, translation related to non-significant findings such as the water screening should be interpreted with caution. This small sample only including PWPd at non-advanced stages of the disease (H&Y I-III) which will limit the generalization of the current results to the larger population of PWPd. However, data obtained from this study can be used for future *a priori* power analyses to determine appropriate sample sizes for subsequent investigations.

This study only targeted two kinematic measures of interest (LVrt and LVCd). Future studies in this sample should investigate other kinematic measures to determine spatial and temporal factors which might also be contributing to decreased airway safety. Although normal values related to LVrt and LVCd are available, there were no healthy control

participants for comparison of timing measures or PAS scores to examine changes in swallow safety.

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Chapter 3: Self-Perceptions of Speech, Voice, and Swallowing in Motor Phenotypes of Parkinson's Disease

Introduction

Impairments of speech and swallowing are expected to occur at rates as high as 95% in people with Parkinson's Disease (PWP) across the full time-course of the disease (Pawlukowska et al., 2018; Simons, 2017). It is likely that a combination of sensorimotor and executive function deficits contributes to these impairments. (Dashtipour et al., 2018; Sapir, 2014). The ability of PWP to perceive the presence and severity of these speech and swallowing impairments appears to also be impaired. Multiple studies have shown an inability of PWP to perceive or self-correct speech deficits (Ho et al., 2000; Keyser et al., 2016) and a decreased ability to perceive swallow deficits (Nienstedt et al., 2018).

A limited number of studies have shown that the ability of PWP to perceive changes in speech and/or swallowing is impacted even in the non-advanced stages of disease progression. Available research has shown that communication deficits occur early and are some of the most salient impairments in PWP regardless of disease stage or duration (Miller et al., 2008). In one study more than 40% of PWP identified changes in swallow function, which were shown to be associated with penetration and/or aspiration. This same study also highlighted the concurrence of reported speech and voice impairments with swallow impairment (Schalling et al., 2017).

There is also limited knowledge of how the heterogeneous nature of PD influences the progression and severity of speech and swallowing impairments. For example, it is not clear how different forms of PD motor phenotype (i.e., tremor vs. non-tremor dominant) impact the

manifestation of communication impairments in PWPD, or how motor phenotype affects the ability to perceive those impairments (Broadfoot et al., 2019). Patient based reports of communication deficits from PWPD have shown Non-Tremor Dominant (NTD) PWPD reported greater communication impairment than Tremor Dominant (TD) (Hariz and Forsgren, 2010; Wu et al., 2015). However, physiological evidence of speech and voice function in PWPD as a function of phenotype have shown conflicting results (Burk and Watts, 2018; Miller et al., 2008a).

There is also limited knowledge of how dysphagia manifests in different PD phenotypes or how dysphagia progresses from the time of PD diagnosis (Mohamed et al., 2018). This has led to poor understanding of the degree of swallow impairment experienced by PWPD in non-advanced stages, and if they are able to predict existing swallowing impairments. Dysphagia in non-advanced PD may not be perceived without overt signs or symptoms, while oral-motor and/or speech deficits may be more pronounced (Ciucci et al., 2013) and therefore more readily diagnosed than impaired swallow function. There is an apparent gap in our knowledge associated with the perceptual and physiological characteristics of swallowing impairment related to both non-advanced stages of PD and different PD phenotypes.

The current study sought to answer three questions. The first question asked: How do PWPD perceive speech, voice, and swallowing impairments and how well do their perceptions of speech and voice predict their awareness of swallowing impairments. We hypothesized that PWPD, when provided with a perceptual questionnaire specific to swallowing symptoms, would be able to identify symptoms of swallowing impairment. We then hypothesized that those perceptions would be predicted by similar perceptions in the domains of speech and

voice (communication) function. That is, as the frequency of perceived speech and voice impairment symptoms increases, so would the frequency of perceived swallow impairments. The second question asked if there were differences in speech or swallow impairment perceptions between tremor dominant (TD) and non-tremor dominant (NTD) phenotypes. We hypothesized that NTD would report a greater frequency of symptoms in at least one domain of speech or swallowing. The final question asked how accurately perceptions of speech and swallowing impairment could predict whether an individual with PD was tremor or non-tremor dominant. We hypothesized that the perceptual reports of speech and swallowing impairment would accurately classify PWPD of different phenotypes.

Methodology

38 PWPD were recruited as part of an ongoing program of research. Inclusion criteria consisted of: 1) a diagnosis of idiopathic PD by a neurologist, 2) current disease severity in stage I-III based on Hoehn and Yahr (H&Y) score, and 3) no comorbid neurological impairments associated with conditions other than PD. Information relevant to disease history, stage and progression was collected including gender, age at diagnosis, years post diagnosis, Hoehn and Yahr stage (H&Y), and tremor phenotype. Tremor phenotype determination has been described and performed in previous work from our lab (Burk and Watts, 2018) therefore the PI's assigned participants to either TD or NTD based on a combination of factors including neurologist report, patient history, and patient responses to a motor questionnaire (Appendix A). There is conflicting evidence on the best approach to determining motor-based phenotypes of PD. Some previous communication and swallowing literature have utilized a cutoff score derived solely from motor severity scales such as the Unified Parkinson's Disease

Rating Scale (UPDRS) (Miller et al., 2008b; Mohamed et al., 2018). However, more recent work has suggested this standard of determining motor or tremor phenotyping lends to significant variability and unreliable phenotyping upon reexamination (Qian and Huang, 2019). We therefore chose to use a stratification strategy for tremor phenotype similar to that of Selikhova et al (2009) and has been used previously in the literature (Burk and Watts, 2018). Participants were categorized as TD phenotype if they met the following criteria: (a) a unilateral tremor was the predominant initial sign of the disease, (b) there was a report and clinical confirmation of tremor progression since initial diagnosis, and (c) tremor was a current major sign and impairment associated with PD in relation to other motor signs. Participants were categorized as NTD phenotype if they met the following criteria: (a) There were no reports of tremor at initial onset, (b) there was a report and clinical confirmation of minimal progression of tremor since diagnosis, and (c) tremor was not a current major manifestation or impairment associated with PD. Based on this dichotomous categorization, any participant who did not meet criteria for TD phenotype was assigned to the NTD group. After consenting procedures, participants completed a battery of self-perception assessments and questionnaires. This included the Dysphagia Handicap Index (DHI) (Silbergleit et al., 2012) and the Voice Related Quality of Life (V-RQOL) (Hogikyan and Sethuraman, 1999).

A custom questionnaire for the self-report of speech and voice (communication) and swallow impairment symptoms was also administered (see Appendix A). The goal of the questionnaire was to establish an overall count of communication and swallowing symptoms perceived by the participants. While both the DHI and V-RQOL have subdomains of their questionnaires and different overall scoring techniques (Hogikyan & Sethuraman, 1999; Silbergleit et al., 2012), both utilize an overall severity score. Therefore, rather than have each

item be counted separately in our questionnaire, items related to speech and voice were totaled to determine a communication severity score, and the same was done with all swallowing questions to determine a swallow severity score. The questionnaire asked participants to rate their perceptions of speech, voice, and swallowing symptoms during a typical day, when their impairments from PD would be at their worst. Participants rated each symptom as “Never”, “Occasionally”, “Sometimes”, “Often”, or “Always”. For each item that participants rated as occurring more often than never, 1 point was recorded. Each item was scored 1 as the goal of the questionnaire was not to determine the severity of each item, but to establish a total count of symptoms being perceived in each domain (communication and swallowing). As an example, there are 8 total swallow symptom questions ranging from “Drooling” to “Food or pills gets stuck in throat”. If a participant confirmed they experienced all of these problems at least occasionally, they would be scored 8 on the swallow symptom count. A higher count of symptoms would therefore indicate a higher level of symptom severity being experienced by the participant. This method was applied to all symptom sections of the questionnaire, including swallowing symptoms and communication symptoms. All questionnaires were completed by the participants, independently and one at a time, in the presence of one of the PI’s. When each questionnaire was completed the scores were tallied and recorded by the PI.

Statistical analyses were performed in SPSS (v. 24). Descriptive statistics and frequency tables were computed to identify target demographic information including motor phenotype, age at diagnosis, years post diagnosis, H&Y staging, and scores from questionnaires. A standard multiple linear regression (MLR) was run to determine the ability of self-reported perceptions of speech & voice symptoms and V-RQOL to predict increased frequencies of swallow symptoms on a custom questionnaire. We utilized a standard entry

method with all variables of interest entered into the model, rather than a stepwise regression method, in order to minimize type I error. The DHI was not included into our regression model due to the anticipated likelihood of extreme influence on model results, as the DHI and the swallow symptom perceptions are likely to measure similar symptomology.

A multivariate analysis of variance (MANOVA) was used to determine differences in communication and swallowing symptom frequency counts (speech & voice symptoms, V-RQOL, DHI, and swallow symptoms) reported between TD and NTD phenotypes. Finally, a multivariate binomial logistic regression (LR) was performed to predict group membership of phenotype by the independent variables of speech & voice symptoms, V-RQOL, DHI, and swallow symptoms. We then used the predicted probabilities derived from the logistic regression (PRE_1) in a ROC analysis to evaluate the regression model's ability to discriminate between TD and NTD phenotypes, based on the risk of reporting scores of communication and swallow impairment perception. All α levels for rejecting the null were set to 0.05.

Results

Descriptive statistics including mean, median, and standard deviation, of the participant sample are included in Table 1. All variables and descriptive statistics fell within appropriate skewness (< 2.0) and kurtosis (< 2), therefore indicating a normal distribution in our data to proceed with hypothesis testing. 38 participants ($n = 38$) were included with no participants excluded from final analysis and no missing data points. Participants had a mean age of 66 and mean time post diagnosis of 3.9 years. 24 (63%) participants were classified as NTD, with the remaining 14 (37%) classified as TD. H&Y staging (median & interquartile

range) for TD was 2.5(1) and 3(.75) for NTD. Bivariate analysis using independent samples t-tests indicated no significant differences of demographic information between TD and NTD including age at time of investigation, age at diagnosis, and years post diagnosis. Chi-Square tests similarly displayed no differences in gender distribution or H&Y stages between TD and NTD. Cumulatively, 71% of participants reported a DHI score >7 , and 53% of participants reported a swallow symptom frequency of ≥ 3 symptoms. 71% reported a speech & voice symptom frequency ≥ 3 , and 100% of participants reported a total V-RQOL score of <50 .

Table 3.1 Descriptive Statistics of TD and NTD phenotype PWP

Participant characteristics	Tremor Dominant Mean(\pmSD); Median	Non-Tremor Dominant Mean(\pmSD); Median
Hoehn and Yahr*	2.5(1)	3(.75)
Gender Distribution (% Male/Female)	57%/43%	63%/37%
Age at Diagnosis	64.4(9.7); 66.5	67(7.8); 68
Years Post Diagnosis	3.9(2.5); 3.2	3.8(3.1); 2.9
Age at Time of Investigation	68.3(9.1); 71.3	70.9(6.5); 6.5
Speech & Voice Severity	2.3(1.7); 2	4.6(1.5); 5
Swallow Severity Rating	1.8(1.5); 2	3.3(1.9); 3
DHI	10.8(11.5); 7.5	13.1(9.7); 10
V-RQOL	14.2(5.2); 15	21.3(10); 20

*Expressed as Median(Interquartile Range)

The regression met all necessary assumptions including linearity, tolerance ($>.2$), VIF (<10), & all correlations were well below threshold ($>.7$). Our regression model produced a significant result ($F[35] = 8.13$, $p = .001$), with an adjusted $R^2 = .28$, indicating the variables present in our model were accounting for 28% of the variance in our data. For predicting the perception of swallowing impairment overall, participants' perceptions of speech and voice symptoms were the strongest predictor in the model ($\beta = .43$, $p = .017$, $CI = .08-.77$). V-RQOL did not significantly contribute to predicting perceptions of swallowing impairment. An overall model and coefficient summary are presented in Table 2.

Table 3.2 Linear Regression for Predicting Reported Swallow Symptoms: Model and Coefficient Summary

<i>Perceptual Predictors</i>	β	Std. β	Sig. (p-value)	CI (95%)
<i>Speech and Voice Severity</i>	.43	.42	.017	.08 - .77
<i>Rating</i>				
<i>V-RQOL</i>	.04	.21	.23	-.03 - .12

Our MANOVA met all necessary assumptions including linearity inspection of scatterplots, skewness/kurtosis measures of normality within acceptable ranges (<2 and <7), and Box's Test of Equal Variances $>.001$. There were no outliers excluded from analysis. The overall multivariate model displayed a significant result ($\Lambda = .605$, $F[4, 33] = 5.397$, $p = .002$), indicating the leveraged results of dependent variables in the model displayed a significant effect of phenotype on communication and swallowing symptom reporting in our sample. An analysis of our Tests of Between Subjects Effects indicated that speech and voice symptoms

($F = 18.95$, $p < .001$), swallowing impairment symptoms ($F = 6.48$, $p = .02$), and V-RQOL ($F = 6.01$, $p = .02$) were all significantly worse in the NTD group compared to the TD. There was no effect of phenotype for DHI reporting, despite differences in mean reporting score. A model summary with effect sizes are presented in Table 3.

Table 3.3 Multivariate Analysis of Communication and Swallowing Perceptions Between NTD and TD

<i>Perceptual Variables</i>	<i>F statistic</i>	<i>Sig. (p-value)</i>	<i>Pairwise Difference (NTD-TD)</i>	<i>Effect Size (ω^2)</i>
<i>Speech and Voice Severity Rating</i>	18.95	< .001	-2.30	.07
<i>Swallow Severity Rating</i>	6.48	.02	-1.55	.04
<i>V-RQOL</i>	6.01	.02	-7.08	.02
<i>DHI</i>	.45	.51	-2.34	.006

The LR model revealed a significant result above the constant model ($\chi^2 [4] = 17.6$, $p = .001$), and the Hosmer & Lemeshow Test of model fit ($\chi^2 = 3.21$, $p = .921$) indicated that our predictive model accurately fit the observations within our data. Analysis of the predictor variables contribution to the model showed speech and voice symptoms as the strongest

contributor ($\beta = -.70$, $W = 3.92$, $p = .048$, $OR = .50$). The odds ratio (OR) for speech and voice symptoms ($OR = .50$) indicated that TD phenotype PWP displayed a 50% decrease in the odds of reporting increased speech and voice symptoms. No other predictor variables contributed significantly to the model for predicting phenotype group. Despite the non-significant results, counts of swallow symptoms ($OR = .63$) indicated that TD phenotype displayed a 37% decrease in the odds of reporting increased swallow symptoms. The DHI and V-RQOL did not contribute significantly to predicting group membership ($p > .05$) and provided minimal change in the odds of being classified into either group ($OR = 1.1$ and $.95$, respectively). A comprehensive model summary is provided in Table 4.

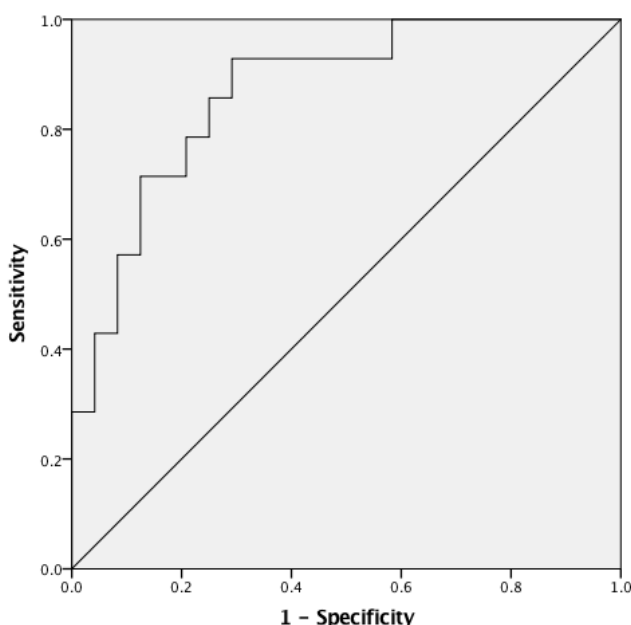
Table 3.4 Logistic Regression Model for Predicting Phenotype Group

<i>Perceptual Classifiers</i>	β	Wald Statistic	Sig. (p-value)	OR(95%CI)
Speech and Voice Severity Rating	-.703	3.9	.04	.50 (.25-.99)
Swallow Severity Rating	-.46	1.6	.20	.63 (.31-1.3)
DHI	.10	2.1	.15	1.1 (.96-1.3)
V-RQOL	-.06	.48	.49	.95 (.81-1.1)

Our subsequent ROC analysis for determining the sensitivity or specificity of the use of questionnaires to predict whether an individual belonged to the TD or NTD phenotype

groups (Figure 1) revealed a significant result and positive area under the curve for the combined predicted probabilities of .87 ($p < .001$, 95% CI = .76 - .98). This suggested that the utilization and scoring of tools used in this study for perceptions of speech & voice symptoms, swallow symptoms, and V-RQOL were robust for discriminating between TD and NTD phenotype in PWPD.

Figure 3.1 AUC Graph for Discriminating Phenotype Membership by Communication and Swallow Impairment Measures



Discussion

Perceptual Reporting of Communication and Swallowing in PWPD

The goals of this study were to investigate perceptions of speech, voice and swallowing in PWPD as well as identify relevant differences in symptomatic perceptions between two motor phenotypes of PWPD. Our results indicated that the sample of PWPD in our study, all of whom were in non-advanced stages, were able to identify speech, voice, and

swallowing symptomology regardless of motor phenotype. Communication and swallowing changes such as those perceived by participants in this study have been documented to negatively affect overall quality of life in PWP (Chu & Tan, 2019; Plowman-Prine et al., 2009). Results from this study are not in agreement with previous reports, which have indicated that PWP demonstrated an impaired ability to consistently perceive and identify communication and swallow impairment. Rationale for that impairment was associated with changes to both central and peripheral sensorimotor feedback loops (Gllivan-Murphy et al., 2019; Hegland et al., 2019). However, we found that a set of questionnaires with questions specific to communication (speech and voice) and swallowing function increased the likelihood that participants would be able to identify impairments

Our theory as to why participants in this study were able to perceive swallowing impairment symptoms is that we provided them with specific questions that allowed for intentional consideration of multiple perceptual factors specific to speech, voice and swallowing. It is possible that using multidimensional perceptual prompts for symptomology increases the participant's odds of identifying communication or swallowing impairment. This would typically be a concern when interpreting regression results. However, our results indicated that all perceptual measures were well below the accepted correlation threshold. This suggested that while our questionnaire battery may be addressing similar constructs, administering them together increases the likelihood of a patient reporting impairment. Similarly, the DHI and V-RQOL have reported good test-retest reliability (.83 and .93, respectively) even in populations with neurological impairment, including PD (Hogikyan and Sutheraman, 1999; Silbergleit et al., 2012). Recent work has also suggested that when provided with specific questions related to swallow function, a questionnaire may be able to

predict impaired swallow function in people with PD (Dumican & Watts, 2020). This supports the notion that while we are asking different communication and swallowing symptom questions, the construct of the questions being asked may be stable enough to include in a battery of perceptual questionnaires to help detect communication or swallow impairment.

The results from our present cohort also indicated that reports of speech and voice impairments may predict the reporting of swallowing impairment. Van Hooren et al. (2016) have previously reported that a decline in voice related quality of life is associated with a decline in swallowing related quality of life, consistent with our findings. Though the questions in their work were different from ours, their use of questionnaires was similar to the one used in this study in administering multiple questionnaires of communication and swallowing was performed to observe differences in perceived impairment between groups. Our results build on this body of literature, indicating that the frequency of speech and voice symptoms reported may be used to predict an increased risk of swallowing impairment in PWPD. These findings may be applicable in clinical settings as diagnosed speech or voice impairment may indicate the need to further assess swallowing function.

Differences in Communication and Swallowing Perceptions by Motor Phenotype

Previous studies have shown that motor phenotype influenced the severity of disease manifestation and differences in disease progression (Aleksovski et al., 2018), in addition to decreased quality of life perception (Herman et al., 2015). Results from this study indicated that PWPD categorized as NTD were likely to report symptoms of impairment more frequently than the TD group. Those categorized as NTD reported significantly more frequent or severe communication and swallowing impairments across all assessments except for the DHI. In terms of classifying people with PD into TD or NTD phenotype based on

communication or swallowing impairment reports, communication impairment severity was the most important contributing factor ($p = .048$, $OR = .50$). Recent physiological outcomes by Tykalová et al. (2020) lend support to these findings, as their results indicated communication impairment was a significant discriminating factor between TD and NTD, and impairment was more severe in NTD subjects. In addition, while non-significant, reports of more severe swallow symptoms were reported substantially less in TD than in NTD ($OR = .63$). This may indicate that while the overall severity of the symptoms themselves may not be perceived as more or less severe, people with PD may report experiencing more symptoms overall. The approach of allowing people with PD to identify specific communication or swallowing symptoms on the basis of the number of symptoms being reported rather than how severe the symptoms are may increase identification of communication or swallowing impairment and therefore, referral for assessment. Although addressing different outcomes, Andres et al. (2017) found that even though PWPD may not meet a pre-specified total cutoff score on a questionnaire to be considered as possibly having dysphagia, they may report multiple symptoms without reporting a high severity of the symptoms. More than 93% of individuals who reported at least some type of dysphagia were confirmed to have impaired swallow safety or efficiency after assessment.

The combined use of these perceptual assessments was also able to discriminate the risk of increased communication and swallowing impairment based on participant perception between the two tremor phenotypes of PD in this study. These findings may have direct clinical implications. The NTD motor phenotype in PWPD has been associated with more rapid and more severe disease progression, faster deterioration of both motor and non-motor domains, and decreased quality of life outlook compared to the TD phenotype (Heeden et al.,

2016). Therefore, the ability to use inexpensive and quick assessment methods such as questionnaires to identify who may be at increased risk of communication and swallow impairment may be beneficial in developing a therapeutic prognosis.

There is still mixed evidence in the PD literature about the validity of using a TD vs. NTD classification scheme to predict long-term outcomes due to the heterogenous nature of the disease (Erro et al., 2019). Despite the multifactorial and heterogenous nature of PD, the benefits of classifying motor phenotype in a noninvasive and cost-efficient manner for targeted treatments and anticipating symptom progression may still be beneficial (Fereshtehnejad & Postuma, 2017) to healthcare providers that serve PWPD. The results from our study indicate that the use of a battery of perceptual assessments related to speech, voice and swallowing may discriminate motor phenotypes in PD successfully in those at non-advanced stages. This presents an efficient, cost effective, and noninvasive approach to phenotyping PWPD for clinical considerations. Future research regarding perceptions of impairment related to communication and swallowing should focus on corroborating physiological distinctions between motor phenotypes with perceptual measures to determine the level of actual physiological impairment, rather than only perception.

Limitations

There are several limitations of the present study which warrant caution when considering generalization of findings. A major aim of the study was to identify self-reported perceptual levels of impairment by PWPD. Therefore, no physiological data was included to confirm the presence of swallowing, speech, or voice impairments at the time of data collection. This is important to note as subjects may have perceived subtle or sub-clinical fluctuations in communication or swallow function and therefore would not be diagnosed on clinical

examination by a speech-language pathologist. Additionally, the custom questionnaire used within this study has not been validated or tested for reliability, and construct validity has not been assessed to date. Therefore, isolated conclusions from the results of the custom questionnaire should be used cautiously. While our results indicate that a battery of testing may help identify communication and/or swallow impairment and possibly discriminate between tremor phenotypes, the use of this custom questionnaire as a clinical tool requires substantially more examination as a standalone assessment. The group sample sizes and demographics of the total cohort were only 24 (NTD) and 14 (TD). It is possible that the uneven sample sizes favored NTD, who reported more severe impairment perceptions. A larger sample may reveal similar severity trends in perceptual measures in TD phenotypes, which future research will need to address. Similarly, this sample used in this study was a small cohort (38) from a specific geographical area, which may not be representative of the larger population of PWPD globally.

There was also no control group included in the conduction of this study. Therefore, while the participants in this study report increased communication and swallow impairments we are unable to conclude if these impairments are different from healthy older adults of a similar age. However, normative data from healthy controls for the V-RQOL indicate that scores even as low as 80 indicate a good perception of their voice quality. Our results for both groups indicate significant deviations from this threshold. The DHI indicates controls are expected to have a mean total score of approximately 2. Similar to V-RQOL, our results indicate a substantial deviation from what is expected in control subjects. However, in order to draw more precise conclusions from this information, future directions of this research should be to include control subjects to observe differences. In addition, the PI's were not

blinded to the assignment of participants to either TD or NTD groups. While not a goal of this study to determine the clinical utility of how participants were assigned to phenotype, this introduces an inherent level of bias into the study design. This may have influenced or introduced an increased level of error in group stratification, and should therefore be interpreted with great caution when considering differences between phenotype.

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Chapter 4: Swallow Safety and Kinematics in Neurological Impairment: A Comparison of Dysphagia in Parkinson's Disease and Cerebrovascular Accident

Introduction

Dysphagia (swallow impairment) in People with Parkinson's Disease (PWPd) is expected to occur at some point during the disease process, with incidence as high as 95% by some estimates (Simons, 2018). Dysphagia symptoms in PWPd include abnormalities in the oral stage (oral residue, tongue pumping), pharyngeal stage (increased residue in the vallecula/pyriform sinuses, increased airway invasion), and/or esophageal stage (decreased upper esophageal sphincter motility) (Andres et al., 2017; Suttrup & Warnecke, 2016). While symptomatology of dysphagia in Parkinson's disease (PD) has been well described, our understanding of the underlying physiological deficits associated with symptoms are less clear. This is likely due to the heterogeneous presentation of dysphagia in PD across individuals, combined with a lack of consistent evidence for how PD affects the peripheral and cortical structures involved with swallowing (Kwon & Lee, 2019). There is a substantial gap in our knowledge of how swallowing safety and efficiency in PWPd manifests within the different stages of swallowing. This knowledge gap exists despite the expected occurrence and cost of negative healthcare outcomes related to dysphagia in PWPd, including aspiration pneumonia and death (Beyer et al., 2001; Suttrup & Warnecke, 2016; Yoritaka et al., 2013). Moreover, our understanding of the association between laryngeal physiology during swallowing (e.g., laryngeal closure timing, duration, and response to penetrated or aspirated material) and swallowing safety and efficiency in PWPd is lacking.

Our understanding of laryngeal physiology during swallowing in PWPB lags behind that of other neurological causes of dysphagia, including cerebrovascular accident (CVA; stroke). Research into the role of laryngeal function as a physiological predictor of swallow safety in PWPB has explored temporal kinematics of structures in the pharyngeal stage of swallowing, including laryngeal vestibule closure reaction and duration time (Argolo et al., 2015; Andres et al., 2017; Curtis et al., 2019; Curtis et al., 2020, Dumican and Watts, 2020). However, this body of literature is still relatively new and further investigations into swallow kinematics impact on swallow safety in the pharyngeal stage of swallowing in PD are strongly needed. This is particularly true as the prevalence of dysphagia has been reported as similar between other neurogenic etiologies of dysphagia, such as CVA, and PD (Takizawa et al., 2016). Importantly, laryngeal kinematics related to the pharyngeal stage of swallowing in post-stroke dysphagia have been observed to be the most significant predictors of decreased swallow safety (Lee and Kim, 2001; Wong et al., 2019; Wilsenkoetter et al., 2018; Cabib et al., 2019; Im, 2019; Im et al., 2018; Im et al., 2017; Park et al., 2017; Bingje et al., 2010; Wan et al., 2010, Seo et al., 2016; Vilardell et al., 2017). Whether this is also true of PWPB is not yet clear.

Beyond physiological factors, there are also discrepancies in how swallowing function is screened for, monitored, and assessed across these two neurological etiologies of dysphagia. As an example, there are a multitude of interdisciplinary positions on the importance of dysphagia screening post-CVA and the required involvement of Speech-Language Pathologists in post-stroke evaluation protocols (De Cock et al., 2020; Martino et al., 2005; Perry et al., 2019). Additionally, existing studies report long-term outcomes of patients with

stroke-related dysphagia and how dysphagia screening reduces negative outcomes post-CVA (Al-Khaled et al., 2016; Sreedharan et al., 2020).

Despite the growing number of individuals diagnosed with PD compared to CVA in the United States (Marras et al., 2018; Ovbiagele and Nguyen-Huynh, 2011), similar guidelines or protocols are not widely available in regards to dysphagia in PWP. It is possible that PWP may be provided with inadequate information regarding dysphagia risk from their primary care professionals. As a result, PWP may have a poor understanding of swallowing impairments associated with the disease (Swales et al., 2020) and how to identify symptomology (Salinas et al., 2020). There is a critical need to examine how dysphagia presents across a broad population of PWP, as well as in comparison to other neurogenic etiologies of dysphagia. Knowledge gained from these studies may expand our understanding of how dysphagia presents in PD across the duration of the disease, what the most common and salient characteristics of dysphagia in PD are, and determine how specific kinematics related to laryngeal physiology for airway protection affect swallow safety in PD. Secondly, it may inform how dysphagia presents in one major neurological disorder compared to another. By examining the severity and consequences (such as aspiration) of dysphagia across neurologically impaired populations, new knowledge created through research could be used to facilitate understanding and advocacy about dysphagia in PD for various healthcare professionals and clinicians.

In order to achieve these aims, the current project will address four primary research questions. The first research question asked which signs of dysphagia and associated physiological impairments are most frequent across oral, pharyngeal, and esophageal stages of swallowing in PWP compared to individuals post CVA when they are referred for an

instrumental swallowing assessment using videofluoroscopic swallow study (VFSS). It was hypothesized that frequencies of signs and physiological impairments, as measured by the Videofluoroscopic Dysphagia Scale (VDS) and physician records, will be similar in both populations. It was also hypothesized that abnormal swallow events of penetration and aspiration as measured by the Penetration Aspiration Scale (PAS) (Rosenbeck et al., 1998) will occur more frequently in PWPD due to the ubiquity of sensorimotor dysfunction related to the larynx and upper airway in this population.

The second research question asked which laryngeal kinematic measurements are the best predictors of airway invasion, in individuals diagnosed with neurological impairment and pharyngeal stage dysphagia and who display abnormal swallow events, as measured by a score of ≥ 3 on the PAS. Based on the available literature it was hypothesized that out of the possible kinematic measures of interest (LVCrt and LVCd) laryngeal vestibule closure reaction time (LVCrt) will be the strongest kinematic predictor of abnormal swallow events in those diagnosed with pharyngeal stage dysphagia.

The third research question asked if laryngeal kinematic measures would differ between PWPD and individuals with CVA who have been diagnosed with pharyngeal stage dysphagia. It is unclear at this time how laryngeal kinematics such as LVCrt will differ between two neurogenic dysphagic groups. While the literature indicates that LVCrt is typically a strong predictor of abnormal swallow events in both populations, how the specific kinematic timings compare between the groups has not been investigated previously.

The final research question asked if there would be differences in dysphagia presentation and physiological impairments between PWPD and CVA, when the CVA group was stratified into cortical and subcortical lesion groups? The significance of this question is

associated with the subcortical nature of PD pathology, and has not been investigated previously. Findings from the current dysphagia literature examining cortical vs. subcortical swallow function is mixed, with contradictions regarding the patterns and presentation of dysphagia. Knowledge gained from this question may help guide future research on how to best approach dysphagia assessment in PD.

Methodology

Study Sample

This study was approved by the Texas Christian University (TCU) institutional review board (IRB). The study design was a cross-sectional, observational investigation consisting of VFSS evaluations that were conducted on a clinical sample of the populations of interest (CVA and PD) between January 1st, 2020 and December 31st, 2020. Existing video recordings of instrumental (VFSS) swallow assessments of patients who were previously undiagnosed with dysphagia and referred for VFSS were used with permission from Diagnostex, LLC (Hurst, TX). Patients were referred from and assessed at various healthcare locations throughout the greater Dallas-Fort Worth metroplex (DFW), with all VFSS evaluations taking place in the same mobile radiology unit using the same equipment. An underlying goal within the sample was to reach a comparable distribution of male and female participants, although this was dependent on the actual distribution of male and female patients with exams available within the video database.

A summary flowchart of record reviews, exclusion, and final inclusion numbers can be found in Appendix B. Patients and corresponding VFSS were required to meet the following specific inclusion criteria: 1) Patients in the stroke group were diagnosed with a

CVA within six months of their VFSS and must have had no other underlying neurological impairment according to the medical record; 2) Patients in the PD group were diagnosed with PD prior to their VFSS and with no other underlying neurological impairment unrelated to PD according to the medical record; 3) Patients must have been diagnosed with dysphagia subsequent to the VFSS assessment, as indicated in the examination report, to allow for adequate comparison of dysphagia presentation; 4) Patients that were diagnosed with pharyngeal stage dysphagia must have exhibited abnormal swallow events measured by a score of ≥ 3 on the PAS, indicating some degree of airway safety compromise; 5) Patients must not have undergone targeted dysphagia therapy prior to the VFSS according to medical records; 6) VFSS examination videos must have had minimal movement and motion artifacts for adequate data extraction; and 7) Video quality was clear enough to visualize the upper airway from the arytenoids to the epiglottis to allow for measurement of laryngeal kinematic data and identify the bolus consistency and volume being administered by the clinician.

Procedures and Instrumentation

All VFSS were conducted on a mobile swallowing/dysphagia assessment unit (Diagnostex, LLC). All studies were recorded at 30 frames per second (fps) in agreement with current literature (Mulheren et al., 2019) and conducted by a trained and certified Speech-Language Pathologist (SLP) who was blind to the conditions and purposes of this particular study. These studies were either existing studies that were previously conducted or in the process of being conducted during the project period. All patients were asked to consume bolus trials at varying volumes mixed with a radiographic barium solution (E-Z Paque 96% w/w or 60% w/v) for visualization on VFSS. Multiple swallowing trials of thin liquid (barium)

at varying volumes (tablespoon, cup [single and/or consecutive sips], or via straw), multiple trials of thickened liquids at nectar consistency (tablespoon, cup, or via straw) (IDDSI level 2: mildly thick range), and multiple trials of thick liquids at honey consistency (IDDSI level 3: moderately thick range) using SimplyThick EasyMix were completed by each patient. Patients were also asked to consume pudding boluses (tablespoon; approximate IDDSI level 4), thin puree boluses (room temperature applesauce unlikely to meet fork drip test; approximate IDDSI level 3), mixed consistency boluses (one tablespoon of fruit), and regular consistency boluses (a single cookie). All solid or semi-solid food consistencies were coated with a barium sulfate solution (E-Z Paste 60% w/w) for visualization on VFSS. Videos were de-identified prior to any data collection.

Data Collection

Demographic and diagnostic information was obtained from the patient records. Extracted data included: neurological diagnosis (stroke, or PD) stroke/lesion location (as cortical or subcortical), dysphagia diagnosis (oral, pharyngeal, esophageal, a combination of two such as oropharyngeal, or all three as oropharyngoesophageal), clinician reported signs and physiological impairments, and time elapsed from onset of neurological diagnosis to VFSS, total disease duration, age, and gender.

Video analysis software Avidemux v. 2.7 was used for video playback of VFSS as well as frame-by-frame analysis for kinematic measures and determination of PAS scores. Two kinematic timing measures were obtained from the VFSS recordings: laryngeal vestibule closure reaction time (LVCrt) and laryngeal vestibule closure duration (LVCd). These measures have been utilized in previous studies to assess physiological timing events related

to airway closure and protection during swallowing in these populations elsewhere (Curtis et al., 2019; Im et al., 2017; Park et al., 2017) as well as from our lab (Dumican and Watts, 2020). LVCrt was operationally defined as beginning with (a) the initial and consistent anterior-superior burst of the hyoid and ending when (b) the arytenoids contact the underside of the epiglottis with the maximum extent of observed laryngeal vestibule obstruction. LVCd was defined as beginning at (a) the moment of maximum observed obstruction of the laryngeal vestibule and ending when (b) the descent of the arytenoids from the underside of the epiglottis began, as seen by the reemergence of the vestibule.

Visual-perceptual analysis was applied to every swallow recording of each participant to determine the PAS. The PAS measured the degree of laryngeal penetration and/or aspiration as judged by the depth of bolus material entering the airway. The scale can be found in Appendix C. It has been used in previous literature to measure swallow safety in people with PD (PWPD) (Argolo et al., 2015; Baijens et al., 2011; Dumican and Watts, 2020). After obtaining all PAS scores, data was transformed into a separate dichotomous variable to reflect either a “normal” and safe swallow (PAS score of 1 or 2) or “abnormal” (PAS score 3-8). This method has been suggested as one of several appropriate approaches with this particular study design (Steele and Grace-Martin, 2017) and used in recent work (Curtis et al., 2019; Dumican and Watts, 2020) to quantify the PAS for statistical hypothesis testing.

The VDS was scored and calculated for each recording of every patient. The VDS was used to assign quantifiable severity scores for various signs and physiological characteristics of dysphagia across oral and pharyngeal swallow stages. The signs that can be identified and scored with the VDS can be found in Appendix D. The VDS consists of 14 total items, with 7 separate items designed to assess overall severity of the oral stage of swallowing and 7

separate items to assess overall severity in the pharyngeal stage of swallowing. A patient's VDS score was calculated by adding each item to produce a total score with a maximum of 100, with higher numbers indicating more severe dysphagia. The nature of the VDS also allowed for subcategory (i.e., oral vs. pharyngeal dysphagia) analysis between groups. This has been performed previously (Park et al., 2012) by separating the oral components and pharyngeal components of the VDS based on the physiology of each stage. The oral stage components can be totaled out of a maximum 40 points and pharyngeal stage components out of a maximum of 60 points. The scale has been used and validated in CVA dysphagia research previously (Han et al., 2007), has shown translatability across dysphagia etiologies (Kim et al., 2014), and has been used in recent literature when examining CVA lesion location and dysphagia presentation (Mo et al., 2018).

All kinematic measures, PAS scores, and VDS scores were performed independently by the PI. Recently, there have been concerns regarding reliability in a large proportion of the existing methods for evaluating VFSS, including widely used scoring systems such as the Modified Barium Swallow Impairment Profile (MBSImp) as well as free and open access scales such as the VDS (Kim et al., 2012; Swan et al., 2019). Due to these concerns, a pre-evaluation training protocol was implemented with the PI and second, trained rater to ensure sufficient reliability for using the VDS. Consensus on the necessary time to, or amount of, VFSS content mastery regarding evaluation has been unclear. Training protocols for identifying specific aspects of VFSS range from 2 full length days to 20 minutes for identifying aspiration (Hind et al., 2009), 22 total hours for the MBSImp (Martin-Harris et al., 2008), and no apparent training for the VDS (Kim et al., 2012). These studies have also varied widely on the amount of VFSS videos that were included within the training. Thus, 15% of

all swallows were re-measured by both the PI and a second, trained assistant in order to obtain intra- and interrater reliability for the dependent variables. Three previously recorded swallow studies (9 swallows per study) not associated with the current study protocol or data collection were used for training purposes. While a different overall purpose of their study, Kelly et al. (2007) used a similar number of swallows to obtain reliability measures. The two raters individually scored the three videos for the training. The initial training session was followed by a follow-up meeting to review scores and definitions, then re-evaluation of each video together to reach a consensus. Final training protocol scores were evaluated via intraclass correlation coefficients (ICC) to determine if absolute agreement ratings reached an 80% threshold, which has been used as a way to resolve VFSS rater scoring disagreements (Martin-Harris et al., 2008).

Data Screening

Due to the individual and heterogeneous needs of patients at the time of their VFSS assessment, patients did not consume all bolus consistencies and volumes equally. Therefore, data screening was conducted to determine which consistencies and volumes all patients were able to consume and tolerate during the VFSS, and only data from patients receiving the same bolus types were included in the final analyses. All bolus consistencies and volumes (see Methodology – *Procedures and Instrumentation*) across every patient were identified and recorded. Initial data screening indicated that all patients participated in at least one trial of thin liquid by teaspoon, nectar liquid by teaspoon and cup, and pudding thick consistency by teaspoon. There were no significant between-group differences in the number of patients recorded while swallowing either bolus volume or consistency (all $p > 0.05$). As such,

kinematic and PAS scores derived from only those textures and volumes were included in the final analysis.

Data Analysis

Power Analysis

In order to obtain a sufficient sample size of recordings (where one VFSS recording corresponds to one participant), a priori power analysis was been performed. A priori power analysis was conducted using G*power 3.1 (Faul et al., 2007). For research question #2 utilizing a logistic regression involving one dichotomous DV (abnormal swallow event vs. normal swallow event delineated by PAS score) and two continuous IV (LVrt and LVCd) (set to: z test; Logistic regression). Utilizing inputs for a two tailed test, α set to 0.05, power set to 0.8, the anticipation of a normally distributed sample based on the number of swallows that will be analyzed, and null/alternative hypothesis probability values of 36/64 based on previous literature (Dumican and Watts, 2020) with a smaller sample size used, the output suggests to obtain an estimated Odds ratio (OR) of 3.16 will require a total sample size of 57.

Based on power analysis results from question 1, large effect sizes were chosen as the desired effect size parameters for questions 3 and 4. Though conventions on what values equate to “large” effects of ORs vary (Chen et al., 2010; Berben et al., 2012), ORs corresponding to greater than 3 are generally seen as practically meaningful and large effects (Ferguson, 2009). Our output indicated an OR of 3.16 with a sample of 57. Therefore, a similarly large effect size corresponding to the models and questions in 3 & 4 was chosen.

A priori power analysis was conducted to determine sufficient sample size to achieve a large effect ($f^2 \geq .35$) (Cohen, 1988) within the framework of research questions 3 and 4 (set

to: F test; MANOVA: omnibus). For question #3, assuming the presence of 1 IV (2 levels) and 3 DV (VDS scores, LVrt, and LVCd), with alpha (α) set to 0.05, power ($1 - \beta$) set to 0.8, and a desired effect size of .35, output parameters indicate a necessary total sample size of 36 to achieve the desired power and effect size. For research question #4, to determine an equal effect size of $f^2 \geq .35$, assuming a re-stratification of the main IV into 3 levels and 3 DV with equal parameters for alpha and power, the output indicated a necessary total sample size of 24 to achieve the desired power and effect size. Based on the power analyses conducted, the largest required sample size estimation of 57 was used as the minimum sample included in this study. This sample size was chosen in order to protect subsequent analyses from being underpowered, while maintaining adequate power for all other hypothesis testing.

Statistical Analysis

All statistical analyses were performed in SPSS (v. 24). Descriptive statistics were computed for demographic information including mean and standard deviation of relevant demographic information. Frequencies and percentages of gender, neurological diagnosis, lesion foci, dysphagia diagnosis, VDS scores, and PAS scores were computed for all patients. Independent t-tests were conducted on demographic and key variables to determine if any differences were present between CVA and PD groups. Intraclass Correlation Coefficient (ICC) values were computed to determine the interrater reliability for VDS scoring in an initial training protocol, as well as interrater and intrarater reliability for subsequent kinematic (LVCrt and LVCd), swallow safety (PAS), and VDS oral and pharyngeal sub-scores.

For research question 1 related to differences in patterns and presentation of dysphagia in CVA and PD, chi-square tests were performed to examine differences in distributions of

dysphagia diagnosis and PAS scores between CVA and PD groups. Current recommended statistical treatment of the PAS remains contested (Borders and Brates, 2020; Steel and Grace-Martin, 2017). In the current study, the PAS scale was examined through frequency distributions and investigating distribution differences between groups. This allowed the scale to be examined in its intended ordinal nature, on a measurement scale of 1-8, rather than treated as a continuous variable in a linear model. The PAS may also be described by the various score ranges when examining frequencies of airway invasion. As an example, PAS scores of 1-2 are often defined as “normal”, PAS scores of 3-5 correspond to events of penetration, and scores of 6-8 correspond to events of aspiration. When exploring the differences in airway invasion characteristics between groups, some comparisons were made based on these score ranges.

For research question 2 related to which kinematics would predict airway invasion, a binary logistic regression was used to determine how LVCrt and LVCd predicted normal vs. abnormal swallow events for all swallows measured. Whether a swallow as normal compared to abnormal was defined by the PAS score for a given swallow. A PAS score of 1 or 2 was defined as normal and scored as a “0” and PAS scores 3-8 were defined as abnormal and scored as a “1”. These recoded scores became the binary outcome variable for the logistic regression. Current literature also suggests that timing measures related to pharyngeal movements in various populations, as well as penetration and/or aspiration, may be influenced by bolus properties (Lee et al., 2013; Nascimento et al., 2015; Steele et al., 2019; Steele et al., 2016; Troche et al., 2008). Therefore, bolus characteristics (i.e., volume and consistency) were explored with separate univariate ANOVAs in initial bivariate analyses to determine the potential need to include them as variables of interest in the regression model.

For research question 3 related to kinematic differences between CVA and PD, a multivariate analysis of covariance (MANCOVA) was used to examine the differences of laryngeal kinematic timings (LVCrt and LVCd) between all CVA and PD subjects, controlling for both bolus volume and consistency, due to similar concerns raised in research question 2. Regarding research question 4, bivariate analyses indicated re-stratification of CVA into cortical and subcortical subgroups was unwarranted. Re-stratified groups presented with substantial differences in size and independent t-tests displayed no significant differences between these re-stratified groups. Therefore, a MANOVA was used to assess differences in VDS scores for: 1. oral sub-scores and 2. pharyngeal sub-scores between CVA and PD groups. All α levels for detecting significance were set to 0.05 and effect sizes were computed *post hoc*.

Results

Descriptive Statistics

A total of 110 (60 PD and 50 CVA) individual patients with VFSS exams were included in the final analysis. A full report of descriptive statistics is available in Table 4.1. Within the CVA cohort, 37 were categorized as cortical lesion location while 13 were categorized as subcortical according to the patient records. In addition, 18 CVA patients were classified as having a right hemispheric stroke, 20 as having left hemispheric stroke, and 1 bilateral hemispheric stroke. 11 patients were classified as unknown hemispheric location due to insufficient medical record information but did report a confirmed cortical location stroke. In terms of CVA type, 17 were identified as having an Ischemic stroke, and 6 as having a Hemorrhagic stroke. Overall, the distribution of gender across all patients was 53% male to

47% female. Within the CVA cohort, a 56% female to 44% male breakdown was observed. Within the PD cohort, a distribution of 62% male to 38% female was observed. Chi-square analysis indicated no significant differences between groups in terms of gender ($p > 0.05$). The mean and standard deviation for age of the CVA cohort was $76.24(\pm 12.58)$ years, and for PD was $78.67(\pm 8.08)$ years. Independent t-tests displayed no significant differences between groups for age ($p > 0.05$). The mean time elapsed from CVA diagnosis to dysphagia evaluation was $1.92(\pm 1.6)$ months. The mean disease duration length for PWPd was $4.59(\pm 4.80)$ years. Average LVCrt and LVCd in seconds for CVA were $.21(\pm .09)$ and $.55(\pm .20)$, and for PD was $.24(\pm .24)$ & $.50(\pm .20)$, respectively. In regards to kinematic timing measures for normal swallow events compared to abnormal, normal LVCrt measures were slower in abnormal events with an average of $.22(\pm .09)$ compared to $.23(\pm .09)$. LVCd were similarly longer in abnormal events with an average of $.56(\pm .25)$ compared to $.51(\pm .17)$.

Across all examination videos, a total of 844 swallows were measured and included in the final analysis with PAS scores obtained from every swallow. Across all patients, 68% of swallows were categorized as normal (PAS scores of 1 or 2) and the remaining 32% defined as abnormal (PAS scores ≥ 3). All patients included in the final analysis were diagnosed with oropharyngeal dysphagia (100%). 4 patients in the CVA cohort who were originally diagnosed with oral dysphagia only were excluded from the final analysis as they showed no measurable impairments based on the outcome measures being used in this study. In assessing the frequency of Esophageal dysphagia diagnoses 7 patients were diagnosed with Esophageal dysphagia at time of assessment (14% of patients) in the CVA cohort, compared to 31 (52%) in the PD cohort.

Table 4.1 Descriptive statistics for patient demographics

Disease Group		
Total Demographics	CVA	PD
Gender between groups (Male/Female%)	53/47 ($p > 0.05$)	
Gender within groups (Male/Female%)	56/44	62/38
Age (mean \pm SD)	76.24 (12.58) years	78.67 (8.08) years ($p > 0.05$)
Time from diagnosis (mean \pm SD)	1.92 (1.6) months	4.59 (4.8) years
Oropharyngeal dysphagia diagnosis	100%	100%
Esophageal dysphagia diagnosis	14%	52%
LVCrt	.21 (\pm .09)	.24 (\pm .24)
LVCd	.55 (\pm .20)	.50 (\pm .20)
CVA Lesion Descriptives		
Location*	Cortical	Subcortical
	37	13
	Right Hemisphere	Left Hemisphere
	18	20
Type	Ischemic	Hemorrhagic

	17	6
PAS and Laryngeal	Normal (PAS 1 or 2) vs. Abnormal (PAS \geq 3)	
Kinematics		
PAS (%)	68%	32%
LVCrt (mean \pm SD)	.22(\pm .09)	.23(\pm .09)
LVCd (mean \pm SD)	51(\pm .17)	.56(\pm .25)

*11 patients had no hemispheric location but had confirmed cortical level stroke; 1 patient had bilateral hemispheric stroke

Separate independent t-tests and chi-square analyses indicated no effect of hemispheric location on dysphagia related outcomes or severity, including occurrence of penetration or aspiration ($p>0.05$). Therefore, no further analysis was conducted on these subgroups. Separate independent t-tests and chi-square analyses for CVA type (Ischemic vs. Hemorrhagic) showed no effect of CVA type on dysphagia related outcomes, including occurrences of penetration or aspiration ($p>0.05$). Therefore, no further analysis was conducted on these subgroups.

Distribution of PAS scores and Dysphagia Presentation

The first research question asked what the most frequent signs and physiological impairments are in PD compared to CVA, based on all components scored in the VDS. It was hypothesized that signs and physiological impairments, as measured by item severity scores on the VDS would manifest similarly in both populations. It was also hypothesized that abnormal swallow events of penetration (PAS scores 3-5) and aspiration (PAS scores 6-8) as measured by the Penetration Aspiration Scale (PAS) (Rosenbeck et al., 1998) would occur

more frequently in PWPD. Chi-square analysis revealed no significant differences in the distribution of PAS scores between groups ($\chi^2 = 9.19$, $p=.163$). 69.9% of swallows in CVA patients and 67.2% of swallows in PD patients were considered normal (PAS score 1-2). The distribution of aspiration events was similar with 36 (10%) events and 38 (7.9%). A summary of the distributions of PAS scores per group can be found in Table 4.2. Despite the nonsignificant chi-square, large discrepancies were observed between groups in frequencies of a PAS score of 3, with 58 (16% of swallows) occurrences in the CVA group compared to 105 (22%) for PWPD.

Table 4.2 Distribution of Penetration and Aspiration Events by Group & Consistency

	PAS Levels		
	N(%)		
	Normal (1-2)	Abnormal (3-8)	Aspiration events (6-8)
<i>Diagnosis Status</i>			
PD	67.2%	32.8%	7.9%
CVA	69.9%	30.1%	10%
<i>Consistencies</i>			
Thin	53%	47%	13%
Nectar	66%	34%	9%
Pudding	86%	14%	3.6%
<i>Volume</i>			

Teaspoon	72.3%	27.7%	9%
Cup	59.5%	40.5%	8.8%

Chi-square analyses of dysphagia presentation between CVA and PD based on individual VDS items revealed significant differences in the distribution of scores for several items. Oral transit times ($\chi^2 = 5.28, p = 0.02$) showed a significant association of higher scores (prolonged oral transit timings) with the CVA group. Higher (worse) vallecular residue scores ($\chi^2 = 9.17, p = 0.03$), and reduced laryngeal elevation ($\chi^2 = 7.19, p = 0.007$) both displayed significant associations with the PD group. Though apraxia scores ($\chi^2 = 9.18, p = 0.057$) and tongue-to-palate contact scores ($\chi^2 = 3.70, p = 0.054$) were nonsignificant statistically, both of these sub-scale components indicated a trend towards worse scores for the CVA group. For apraxia scores, 70% of the PD group scored normal in this category while only 52% in the CVA group scored normal. 34% of the CVA group were scored with mild apraxia alone, while 30% of the remaining PD group in total fell into any of the possible apraxia categories (mild, moderate, severe). VDS items that were significantly different in their distribution across groups are presented in table 4.3.

Table 4.3 Distribution of Significant VDS Item Scores Between Groups

VDS Item Scores				
	Oral Transit Times			
	<u>Normal</u>	<u>Abnormal</u> (≥ 1.5 s)	Chi-square	Significance
	(≤ 1.5 s)		(χ^2)	(p -value)
Diagnosis				0.022

CVA	19	38%	31	62%	$\chi^2 = 5.28$					
PD	36	60%	24	40%						
	Reduced Laryngeal Elevation									
	<u>Normal</u>	<u>Reduced</u>			Chi-square (χ^2)		Significance (p-value)			
					$\chi^2 = 7.19$		0.007			
CVA	36	72%	14	28%						
PD	28	46.7%	32	53.3%						
	Vallecular Residue									
	<u>Normal</u>		<u>Mild</u>		<u>Moderate</u>		<u>Severe</u>		Chi-square (χ^2)	Significance (p-value)
	CVA	9	18%	23	46%	9	18%	9	18%	$\chi^2 = 9.17$
PD	2	3.3%	29	48.3%	21	35%	8	13.3%		

Laryngeal Kinematics and Bolus Characteristics on Penetration or Aspiration

The corresponding research question asked which laryngeal kinematic measurements are the best predictors of airway invasion in neurological dysphagia (PWPD and CVA). It was hypothesized that out of the possible kinematic measures of interest, LVCrt would be the strongest kinematic predictor of abnormal swallow events in those diagnosed with pharyngeal stage dysphagia. Due to concerns in the literature regarding bolus characteristics effects on both kinematic timings as well as on airway invasion, separate chi-square analyses were performed to determine the potential utility of either bolus consistency or bolus volume in the

logistic regression model. Chi-square analysis for distribution of PAS scores by consistency displayed a significant result ($\chi^2 = 96.49, p < 0.001$). For consistencies, pudding boluses were categorized with normal swallow events for 86% of those swallows, while nectar (66%) and thin (53%) showed decreasing instances of normal swallow classification respectively. In terms of aspiration events ($PAS \geq 6$), thin liquids were classified as aspiration on 13% of trials for that consistency while nectar (9%) and pudding (3.6%) accounted for far less aspiration related events. Chi-square test for distribution of PAS scores by volume also displayed a significant result ($\chi^2 = 47.99, p < 0.001$). Out of 844 swallows, teaspoon volume accounted for 548 (65%) and cup volume accounted for 296 (35%), indicating that teaspoon sized boluses were administered significantly more often than cup sized. A full report of PAS scores by bolus consistency and volume can be found in table 4.1.

All cup volume boluses were associated with nectar thick consistencies. Despite the thicker consistency of nectar, teaspoon boluses which included both thin and pudding consistencies displayed lower rates of abnormal swallow events with 72.3% of swallows categorized as normal while cup volumes of nectar consistencies displayed normal swallow events 59.5% of the time. Chi-square results also displayed no significant differences (all $p > 0.05$) in the distribution of volume or consistency across diagnosis, indicating that volume and consistency effects on PAS scores were likely not isolated to one disease condition. Due to the apparent contribution of bolus characteristics overall to abnormal swallow events, it was considered appropriate to include them as variables in the logistic regression model.

A binary logistic regression was used to determine which laryngeal kinematics were best able to predict whether a patient would have a normal or abnormal swallow event. The binary outcome variable consisted of previously applied PAS scores recoded into either a

normal (PAS scores of 1 or 2) or abnormal (PAS ≥ 3) state. Kinematic predictor variables included LVCrt and LVCd, as well as volume (teaspoon and cup) and consistency (thin, nectar, pudding) of bolus as non-kinematic variables. Though previous chi-square results for PAS frequency distribution between CVA and PD were nonsignificant, diagnosis as a predictor variable was included in the model to determine if it contributed more to a complete model. A forward-entry regression approach was used to define the most parsimonious set of predictor variables and accurate model fit based on the Wald statistic for the variable's contribution to a significant model. It has been suggested that using the Wald statistic as a criterion for variable selection may be more appropriate with a larger n of observations (Agresti, 2007). We believe that the n of this sample ($n=844$) is appropriate for choosing this method rather than the Likelihood-ratio.

The regression model produced a significant result over the constant ($\chi^2 [4] = 95.8$, $p < 0.001$) and a goodness-of-fit result ($\chi^2 [8] = 15.22$, $p = 0.055$) indicated our regression model accurately fit our data. The Nagelkerke $R^2 = .15$, indicated our model was accounting for 15% of the variance in the data. Overall, our model displayed a correct predictive rate of swallow event 72% of the time. Examination of the correlation matrix indicated no variables correlated higher than $R=0.41$ suggesting there were no strong correlations between variables in the model, and therefore we were able to move forward with interpretation of the model. An overall model summary can be found in Table 4.3. Both Bolus volume ($W = 1.14$, $p = 0.285$) and Diagnosis ($W = 0.039$, $p = 0.843$) were excluded as variables from the final model after failing to contribute significantly in any step of the model produced. The final model (step 3) included LVCrt, LVCd, and Consistency as significant contributors as evidenced by the Wald tests.

Bolus consistency was significant for both categories (nectar and pudding) compared to the reference (thin). Nectar consistencies ($\beta = -0.66$, $W = 14.16$, $p < 0.001$, OR = .52) and pudding consistencies ($\beta = -1.86$, $W = 62.61$, $p < 0.001$, OR = .16) results both indicated substantially decreased odds of abnormal swallow events. Nectar and pudding consistency results suggested a 48% and 84% reduction in the odds of a swallow being classified as abnormal over thin consistencies. In terms of laryngeal kinematics, as LVCrt times became longer (i.e., slower reaction), patients are almost 24 times more likely to have swallows classified as abnormal events rather than normal ($\beta = 3.18$, $W = 11.40$, $p = 0.002$, OR = 23.96). As LVCd times became longer, patients were 5 times as likely to have swallows that were classified as abnormal rather than normal ($\beta = 1.62$, $W = 13.38$, $p < 0.001$, OR = 5.06).

Table 4.4 Regression Summary for Predicting Abnormal Swallow Events

Predictors	β	Wald	Sig. (p-value)	Odds Ratio	95%CI
LVCrt	3.18	11.40	0.002	23.96	3.80 – 51.45
LVCd	1.62	13.38	< 0.001	5.06	2.12 – 12.07
Nectar Consistency	-0.66	14.16	< 0.001	0.52	0.37 – 0.73
Pudding Consistency	-1.86	62.61	< 0.001	0.16	0.10 – 0.25

Laryngeal Kinematic Differences Between CVA and PD

Separate univariate ANOVAs were significant for both consistency ($p = 0.028$) and volume ($p = 0.011$) effects on laryngeal kinematic timings. These variables were then

considered as relevant covariates to move forward in MANOVA hypothesis testing when laryngeal kinematics were included in the model. Age or gender had no significant effect on kinematic, dysphagia, or swallow event related outcomes (all $p > 0.05$) and were therefore not carried forward as covariates of interest into MANOVA models.

A one-way MANCOVA testing for the effect of group membership (PD vs. CVA) on kinematic differences (LVCrt and LVCd) was conducted with both volume and consistency serving as covariates in the model. These categorical variables were dummy coded to fit inclusion as covariates in the model (Howell, 2010). Visual inspection of scatterplots indicated relative normality and Box's M ($M=1.03$, $p=.79$) indicated no concerns for heteroscedasticity. An omnibus multivariate analysis indicated a significant effect of group on kinematic timings (*Hotellings Trace*; $T=.058$, $F[2]=24.20$, $p < 0.001$). Inspection of between-subjects effects indicated significant results for both LVCrt ($F[4]=14.7$, $p < 0.001$) and LVCd ($F[4]=8.64$, $p < 0.001$) when controlling for bolus consistency and volume. Associated R^2 statistics for LVCrt ($R^2=.07$) and LVCd ($R^2=.04$) indicated that our model was accounting for 7% and 4% of the variance in the data, respectively. Inspection of pairwise comparisons showed that LVCrt was significantly longer (i.e. slower) in PWP than in CVA. Additionally, LVCd was significantly shorter in PWP than in CVA. Corresponding effect sizes for kinematic measures indicate the main effect of diagnosis on LVCrt resulted in a medium effect (partial $\eta^2=.07$) while the main effect of diagnosis on LVCd resulted in a small effect (partial $\eta^2=.04$).

Differences in Oral and Pharyngeal VDS scores between CVA and PD

Separate independent t-tests to test for initial differences in LVCrt, LVCd, and all VDS scores (oral total scores, pharyngeal total scores, and overall VDS scores) between cortical

and subcortical CVA subgroups revealed no significant differences in means between these groups on any DVs (all $p > 0.05$). A lack of substantial differences in the means of these samples in respect to these DVs indicates the inclusion of these DVs into our MANOVA model was not warranted. A one-way MANOVA testing for the effects of group membership (PWPD and CVA) for dysphagia severity based on VDS components (oral total scores and pharyngeal total scores) was conducted. VDS total scores were linearly dependent on the two other VDS variables (total scores are a function of oral and pharyngeal scores combined). As such, total VDS score as a variable was omitted from the final analysis. A separate univariate ANOVA confirmed no significant differences between groups for total VDS scores prior to conducting the final MANOVA ($p = .29$). Visual inspection of scatterplots indicated relative normality and Box's M ($M = 1.85$, $p = .61$) indicated no concerns for heteroscedasticity. An omnibus multivariate analysis indicated a significant effect of group (PWPD and CVA) on VDS scores ($T = .098$, $F[2] = 5.26$, $p = .007$). The omnibus associated R^2 statistics for the model ($R^2 = 0.09$) indicated the combined effect of the variables in the model accounted for 9% of variance in the data. Between-subjects effects indicated a significant effect for VDS oral ($F[1] = 7.6$, $p = .007$) and VDS pharyngeal ($F[1] = 4.47$, $p = .037$) scores. Associated R^2 statistics for VDS oral scores ($R^2 = .07$) and VDS pharyngeal ($R^2 = .04$) indicated the variables in our model accounted for 7% and 4% of the variance in the data, respectively. Inspection of pairwise-comparisons showed that the CVA group scored significantly higher (worse) in VDS oral components while the PD group scored significantly higher (worse) in the VDS pharyngeal components. In terms of estimating the size of the effect of these results, main effects of diagnosis on VDS oral scores and VDS pharyngeal scores resulted in medium &

small effects based on partial eta squared (partial $\eta^2 = .07$ and $.04$). A summary of group differences for kinematics and VDS scores can be found in table 4.4.

Table 4.5 Kinematic and VDS score differences between CVA and PD

Kinematic variables	F statistic	Sig. (p-value)	Pairwise Difference (PD – CVA)	Effect size (Cohen's <i>d</i>)
LVCrt	14.17	< 0.001	- 0.40	0.52
LVCd	8.64	< 0.001	0.06	0.27
VDS variables				
VDS oral scores	7.60	0.007	2.26	0.52
VDS pharyngeal scores	4.47	0.037	- 4.62	0.41

Reliability

Intra- and Interrater Reliability

Total VDS scoring interrater reliability was excellent (ICC= .94, $p = 0.02$), indicating that the overall scoring of dysphagia severity can be reproduced even if subcomponents of the scorings may vary when agreements on definitions and scorings are reached prior to administration. Similarly, intrarater reliability for total VDS scoring was excellent (ICC= .96, $p = 0.005$). Interrater reliability regarding kinematic measures indicated excellent reliability for both LVCrt (ICC= .94, $p < 0.001$) and LVCd (ICC= .95, $p < 0.001$). Intrarater reliability was similarly excellent for both LVCrt and LVCd (ICC= .94, $p < 0.001$). For PAS scores,

interrater (ICC= .97, $p < 0.001$) and intrarater (ICC= .95, $p < 0.001$) values both indicated excellent reliability for judging events of penetration and/or aspiration. A final summary of both intra- and interrater reliability can be found in table 4.5.

Table 4.5 Interrater and Intrarater Reliability

Initial Training Protocol Interrater Reliability			
Measurement	ICC Value	<i>P</i>-Value	95% CI
Oral	.99	0.008	0.88 - 1
Pharyngeal	.99	0.006	0.91-1
Total	.99	0.003	0.93-1
Initial Training Protocol Intrarater Reliability			
Oral	.99	0.008	0.70 - 1
Pharyngeal	.99	0.006	0.78 - 1
Total	.99	0.003	0.90 - 1
Overall Interrater Reliability			
VDS	.99	0.021	0.13 – 0.99
LVCrt	.94	< 0.001	0.88 – 0.97
LVCd	.95	< 0.001	0.91 – 0.97
PAS	.97	< 0.001	0.94 – 0.98
Overall Intrarater Reliability			
VDS	.96	0.005	0.57 – 0.99

LVCrt	.94	< 0.001	0.88 – 0.97
LVCd	.94	< 0.001	0.89 – 0.97
PAS	.95	< 0.001	0.91 – 0.98

Discussion

Dysphagia Presentation in PD compared to CVA

A major goal of this study was to compare signs and physiological impairments of dysphagia in PWPD compared to those diagnosed with CVA. Our study indicated that PWPD were more likely to exhibit frequent signs and impairments related to both the pharyngeal and esophageal stages of swallowing, based on analysis of dysphagia diagnosis, VDS item severity distribution differences, and comparisons in pharyngeal stage severity between groups. CVA patients however, displayed more frequent and severe impairments related to the oral stage of swallowing. Although overall dysphagia severity was similar between groups, our results indicated that impairments in specific stages of swallowing may contribute more to the overall dysphagia severity than impairments in other stages.

Recent literature investigating dysphagia in PWPD has highlighted the importance of pharyngeal stage swallow function in maintaining swallow safety. The most common underlying impairments contributing to pharyngeal dysphagia in PWPD appear to be related to the movements of the larynx and upper airway (Curtis et al., 2019; Dumican and Watts, 2020; Gaeckle et al., 2019). Importantly, this study, as well as Curtis et al., and Gaeckle et al. have all indicated that various components of the pharyngeal stage contribute more to decreased swallow safety than various components of the oral stage (both kinematic and other

ratings of impairment such as lip closure). This study was able to show that pharyngeal stage signs and physiological impairments underlying dysphagia, including vallecular residue and hyolaryngeal excursion, were significantly associated in PWPD. This was particularly evident when comparing pharyngeal stage impairments in PWPD to those with CVA.

Pharyngeal stage impairments were still present in our CVA group, which agrees with previous literature using the VDS to investigate dysphagia presentation in similar populations (Han et al., 2016). Patients within the CVA group displayed impairments across the range of potential VDS items, including residue and laryngeal excursion. However, more severe scores were associated with swallows by PWPD rather than those with CVA. This is supported by both the presentation of scores in the pharyngeal stage VDS components, as well as in our multivariate model indicating more severe pharyngeal stage VDS scores in PWPD than CVA. Conversely, patients with CVA exhibited more severe oral stage impairment than patients with PD. In terms of post-CVA dysphagia presentation this appears to agree with the present literature, particularly when examining the most common treatment approaches to post-CVA dysphagia.

Many rehabilitative programs targeting dysphagia in post-CVA dysphagia target oral stage mechanisms in attempts to improve overall dysphagia severity (Kim et al., 2017; Konaka et al., 2010; Park et al., 2019; Steele et al., 2016). This is likely due to the heterogenous nature of CVA lesions and the subsequent variability in their dysphagia presentation and severity (Fernandez-Pombo et al., 2019; Mo et al., 2019). Similarly, although not an apparent goal of their study, Daniels et al. (2017) appeared to show that oral stage related impairment tended to be worse than pharyngeal related impairment in their sample. Previous work by Suntrup et al. (2015) also showed hemispheric and lesion size variables influenced whether oral or

pharyngeal stage impairment would be present. Moon et al., (2017) also addressed that oral stage impairment was prevalent across post-CVA patients regardless of lesion location.

This likely explains why fluctuations in the overall presentation of dysphagia within our study were associated with pharyngeal impairment as well. Our results, while nonsignificant, indicated similar trends in terms of hemispheric location. Additionally, those diagnosed with subcortical stroke tended to score worse in oral, pharyngeal, and total dysphagia severity domains. Results of the current study provide rationale and supports previous literature promoting oral stage treatment paradigms for dysphagia in the CVA population. An important aspect to also consider is the specificity in the treatment approach being selected. In the treatment studies outlined above, the treatment approaches selected tended to improve only oral stage deficits and select aspects of pharyngeal stage swallow impairment (such as residue). However, swallow safety metrics, such as the PAS, were often unimproved. Future research should continue to address how specific deficits can be influenced by specific, targeted treatment approaches.

There is growing evidence that oral stage impairment is not as useful an indicator of dysphagia for PWPD, however. Previous research investigating oral stage impairment in PD, such as tongue pressure or oral transit times, has been based on the supposition that oral stage impairment is the most prevalent issue related to dysphagia in PWPD (Minagi et al., 2018; Wakasugi et al., 2017). However, our study supports an alternative argument. Specifically, our sample of PD patients displayed more frequent and more severe pharyngeal stage related impairment. Our ability to compare this presentation to another etiology of dysphagia such as CVA provides more evidence that, although oral stage impairment does present in PD, it is most likely not the strongest or most reliable contributor to overall dysphagia severity. Our

findings also support those of Nienstedt et al. (2017) who were able to show that deficits in the oral stage do not necessarily cause further issues in the pharyngeal stage such as residue management or decreased swallow safety.

Our study was also able to examine the frequency at which PWPD in our sample were diagnosed with esophageal stage related impairment compared to patients with CVA. It is well established that gastrointestinal (GI) related issues in PWPD are some of the earliest non-motor symptoms reported, they occur throughout the disease, and do so in nearly all PWPD (Mukherjee et al., 2016; Pellegrini et al., 2015; Ramprasad et al., 2018). Esophageal phase related dysphagia is not an uncommon finding in post-CVA patients and can in fact occur independently from other oropharyngeal stage impairments (Silva et al., 2008). Our study indicates that despite the expectation that esophageal dysphagia occurs with CVA, PWPD tend to present with significantly higher frequencies of esophageal impairment.

Though multiple theories of PD manifestation and progression through the nervous system exist, a well-known and supported theory relates to that of “gut first” spread of PD pathology. This theory suggests that GI related pathogenesis of PD pathology propagates to and throughout the CNS via the vagus nerve (Dogra et al., 2021). This vagus nerve propagation is an important potential aspect of why pharyngeal and/or laryngeal related swallow impairment are common manifestations of dysphagia in PD, especially in the context of frequent esophageal dysphagia and GI symptomology. It is well understood that the vagus nerve provides various aspects of motor and sensory innervation to the larynx and pharynx, amongst other sensory and parasympathetic functions (Greene, 2014; Mussa & Verberne, 2013). Both mouse and human models of PD pathology spread have suggested a predictable occurrence of aggregates in the motor neurons of the gastrointestinal system, with a caudal

spread through the vagus nerve into the dorsal motor nucleus of the vagus nerve (DMV) in the medulla (Greene, 2014; Kim et al., 2019; Ulusoy et al., 2017). This expected propagation of the disease supports our findings, particularly in that esophageal and pharyngeal stage dysphagia were more common and severe in PWPD. Moreover, by examining both the pharyngeal and esophageal related presentations of dysphagia in our sample of PWPD, we were able to support the supposition that the spread of PD pathology and symptomology may reach the pharynx and/or larynx as a sequential step in the propagation process. This may give clinicians and researchers additional evidence and information on how dysphagia in PD may manifest or progress, and what the most relevant sources of impairment will be to inform clinical targets. Additionally, the literature also supports the notion that esophageal dysfunction may present with or relate to other pharyngeal impairment related to dysphagia (Kendall et al., 2016). Future research should examine this relationship more closely, including longitudinal cohorts to track potential progression of dysphagia in PD.

An unexpected finding in our study was the lack of separation in terms of PAS scores between the CVA and PD groups. While we originally hypothesized PWPD would have higher rates of penetration with or without aspiration, this was not the case. Patients in the CVA group presented with findings of aspiration 10% of the time and overall abnormal rates of swallow safety in terms of the PAS in 30% of swallows, in line with previous literature exploring swallow safety outcomes in post-CVA patients (Falsetti et al., 2009; Nakamori et al., 2020). PWPD displayed similar outcomes, with 8% categorized as silent aspiration and 33% of swallows categorized as abnormal PAS scores. Although the data did not confirm our hypothesis in regards to PAS scores in PWPD, the rates of patients who did show PAS scores associated with aspiration (PAS 6-8) support findings in the existing literature (Pflug et al.,

2018), with greater than 30% of PWPD having an aspiration related event. Moreover, when considering that normal PAS scores of 1 and 2 should account for greater than 95% of swallows (Humbert et al., 2018; Steele et al., 2019), our study was able to show that both CVA and PD groups displayed substantially worse swallow safety metrics compared to normative data. Particularly for PWPD, our study contributes significantly to a growing body of literature showing that PWPD are exhibiting abnormal swallow events regardless of disease duration, severity, or reports of dysphagia. Our study also supports the need for greater advocacy and screening for dysphagia in PD. The sample of PWPD utilized in this study was a community-based sample that had never previously been referred, assessed, or treated for dysphagia. Future research should be aimed at improving advocacy and screening efforts, as well as screening methodologies, to improve referral for dysphagia assessment in PWPD.

Considerations regarding the use of the VDS to quantify dysphagia presentation and severity across our samples are also important. Although the VDS has been used in multiple studies and shown relative clinical validity, issues regarding its reliability across raters have been noted (Kim et al., 2012). However, the use of a pre-reliability protocol was able to significantly improve the overall reliability of the VDS in our study. Results indicated excellent reliability both within the pre-reliability protocol as well as in our interrater reliability measures. Other concerns have also been raised regarding the accuracy of visuoperceptual scales for judging the extent of residue on VFSS with adequate precision (Steele et al., 2020a). Even though their report indicated that these scales have good interrater reliability and validity, Steele and colleagues provide a well-founded argument for the need to utilize pixel-based measures, particularly when quantifying vallecular or pyriform residue (such as the %C2-C4² measure). The use of the VDS in our study was based upon the ease of

access to the scale as well as the ease in which many of the parameters (such as swallow reaction time or vallecular/pyriform residue) can be applied from a visuoperceptual perspective. We were able to show that a free scale to quantify dysphagia may be used and may produce reliable scores between raters. However, it is suggested that adequate training prior to the use of the VDS, or any type of scale to quantify dysphagia, be performed. Future research related to this study should investigate the use of pixel-based measures to corroborate our findings in disordered and clinical populations.

Predictors of Abnormal Swallowing and Differences Between CVA & PD

Another goal of this study was to determine what factors, such as laryngeal kinematics or bolus properties, could best predict penetration and aspiration. We also sought to examine how laryngeal kinematics differ between the groups (PD vs. CVA) in our study. The largest contributors to whether a patient would have abnormal swallow events included bolus consistency, LVCrt, and LVCd. In terms of bolus consistency, patients were more likely to aspirate on thin liquids than thicker liquids, and were at the lowest risk of penetration or aspiration when consuming pudding thick consistencies. These findings are in line with the general consensus for how individuals may respond to thicker liquids (Steele et al., 2019), as well as maximizing swallow safety in the clinical management of reducing events of penetration and/or aspiration (Bolivar-Prados et al., 2019; Newman et al., 2016; Steele et al., 2015). Although not a significant contributor in our model for predicting abnormal swallow events, we also found significantly higher rates of abnormal swallow events for larger boluses compared to smaller, also in agreement with existing literature regarding clinical populations (Leder et al., 2010; Miles et al., 2018).

In regards to laryngeal kinematics, both closure reaction (LVCrt) and closure duration (LVCd) timings of the laryngeal vestibule were able to predict whether patients would display abnormal swallow events of penetration or aspiration. While closure reaction times predicting penetration or aspiration supports our hypothesis and the current literature in both CVA and PD (Curtis et al., 2019; Dumican and Watts 2020, Lee and Kim, 2001; Wong et al., 2019; Wilsenkoetter et al., 2018; Cabib et al., 2019; Im, 2019; Im et al., 2018; Im et al., 2017; Park et al., 2017; Bingje et al., 2010; Wan et al., 2010, Seo et al., 2016; Vilardell et al., 2017), similar results were not expected in regards to closure duration times. The literature suggests that closure duration times of the laryngeal vestibule are not often considered contributors to instances of dysphagia or abnormal events of penetration or aspiration in PD (Curtis et al., 2019; Dumican and Watts, 2020). In CVA however, this evidence is mixed (Power et al., 2007; Power et al., 2009).

These discrepancies could be related to several factors. Our study looked at the overall contributors to abnormal swallow events including all groups. This was done to assess what factors might be most important in neurogenic populations that commonly experience dysphagia. It is therefore a possibility that longer LVCd timings are associated with abnormal swallow events because CVA patients had longer LVCd times, and are therefore weighing heavily on our regression for predicting abnormal swallow events. Future analysis may provide a better understanding if this data were to be reexamined with separate regression models to determine different contributors to swallow events in each population. It may also be an important consideration that, with limited other kinematic variables of interest for this particular study, LVCd may be taking on inflated importance in this population. Future studies

should also investigate other important kinematic and swallow variables of interest particularly in this population.

A secondary factor may be that only one population was experiencing slower closure duration times. In our analysis of how laryngeal kinematics differ between CVA and PD, we were able to show that patients with CVA have significantly longer closure duration times. These longer duration times were significantly associated with those who displayed penetration or aspiration. The potential cause of longer duration associated with those who are more likely to penetrate or aspirate is unclear. For CVA patients, these longer times predicting abnormal swallow events may be tied to the laryngeal expiration reflex (Ludlow, 2015). The laryngeal expiration reflex involves a forced expiratory effort with a closed glottis, followed by glottic opening, to prevent the aspiration of material. Importantly, it operates fundamentally and mechanistically differently from coughing (Tatar et al., 2008). CVA patients may be attempting to close the laryngeal vestibule longer and in turn build pressure in the glottis to prevent aspirating material further, potentially even in the absence of a functional true cough. Even though these longer times may be more associated with patients who penetrate or aspirate, this may not be a negative physiological attribute but instead suggest that these patients have an intact laryngeal expiration reflex.

Evidence from this study examining closure duration times in PWPD may add additional support that the laryngeal expiration reflex is occurring in patients with CVA but not as functionally in PD. Our results indicated that although the overall instances of abnormal swallow events were not different between our groups, there were significant differences in the distribution of PAS sub-scores. PAS scores of 3, when material enters the laryngeal vestibule and remains without being ejected, occurred significantly more frequently in PWPD

than in CVA. Our findings that CVA patients had longer closure duration times and scored a PAS of 3 significantly less frequently than PD patients may be tied to either an ineffective laryngeal expiration reflex or an inability to modulate or respond with compensatory mechanisms to clear this material. More research and further analysis may be necessary to explore how LVCd timing measures correspond with different PAS levels in both populations as well to examine if there are differences between those who scored a PAS of 3 vs. a score of 4.

Existing literature has explored LVCrt and LVCd timings across aspirators, non-aspirators, and controls as subgroups in CVA (Park et al., 2010). Findings indicated significant differences between healthy controls and aspirators in terms of LVCd, suggesting that patients who have shorter LVCd times are more likely to aspirate. Our findings in comparing two neurogenic etiologies of dysphagia however, indicated that there may be gradients and differences in terms of the underlying physiology associated with or causing airway invasion. As an example, even though our CVA group displayed longer LVCd than our PD group, this does not indicate that either group had normal timing measures. When referencing older healthy adults, LVCd should occur for approximately 500 milliseconds (ms) (.50 seconds; Humbert et al., 2018) but for even a shorter duration in younger healthy adults at a range of approximately 430 ms (.43 seconds; Steele et al., 2019). Evidence from our study indicating that longer LVCd times are more associated with penetration or aspiration events are, therefore, not unsurprising. With mean LVCd timings of .56 (CVA) and .51 (PD) both samples have timings that could be considered outside the norms of healthy adults.

It may also be important to recognize that longer swallow apnea durations have been reported during larger bolus sizes, and that subsequent longer durations of airway closure may

occur (Martin-Harris, 2006). In our study, individual cup sized boluses were administered as a part of the clinical VFSS protocol and encompassed over one third of boluses delivered. Our results indicated that larger bolus sizes also had a significant association with decreased swallow safety. It is therefore possible that patients in either group are unable to effectively manage their swallow-respiratory pattern during larger bolus sizes. Even though bolus volume was not a significant predictor in our model, and is not considered to affect LVCd in healthy individuals (Steele et al., 2019) it should be considered in terms of physiological responses of laryngeal kinematics in disordered populations. Further research is recommended to continue to examine how bolus properties affect kinematic and timing measures, particularly in disordered populations. Moreover, this dysregulation of swallow-respiratory function may be implicated as a potential therapeutic target. However, substantially more research is needed. Therefore, even though longer LVCd timings predicted abnormal swallow events for these groups, it does not mean that longer LVCd timings in comparison to healthy individuals would. This is an important distinction to make given the scope of this study.

It may be more important to consider that increased LVCd timings are a good indicator that patients with CVA are penetrating and aspirating yet still have an underlying airway protective mechanism that is functioning. In cases with shorter LVCd timings in CVA patients, it may be an indicator that this reflex or the sensorimotor responses associated with this mechanism are impaired. For PD patients, the fact that LVCd timings were significantly shorter than those with CVA does not necessarily make it an unimportant indicator. With higher frequencies of PAS scores of 3 in our sample, it may be a useful indicator that PWPD may have been unable to create sufficient closure pressure to eject material from the airway or do so with longer LVCd times, unlike patients with CVA. Longer LVCd timings associated

with penetration and aspiration events may also indicate patients are attempting to close their airway for longer durations when ingesting larger bolus sizes, but it was ineffective. Future researchers and clinicians may be able to use this as an underlying physiological cause of higher PAS scores and decreased swallow safety for treatment targets in PWPD. More research is also needed in examining how LVCd times may differ with each corresponding PAS score (penetration vs aspiration), as well as investigating the underlying physiology related to laryngeal sensory responses in each population.

Finally, as we were able to examine further in our study, closure reaction times of PWPD are significantly associated with increased rates of penetration and/or aspiration. This finding was in line with the current literature from our lab as well as other sources. This provides a substantial amount of evidence to the importance of the closure reaction time of the larynx in this particular population. Future studies should continue to examine these closure reaction times to further our understanding, but should also begin to apply specific targeted treatment approaches in an effort to improve kinematic timings and swallow safety. This should be done in an effort to maintain and improve quality of life in PD in relation to swallow function. Importantly, our study was also able to show there are many other areas of dysphagia in PD that require more extensive work. While we only explored laryngeal kinematics for the purposes of this study, it is likely that other kinematics such as hyolaryngeal movements, as well as other physiological aspects of the pharyngeal stage of the swallow including bolus clearance and residue, need more in-depth investigations. Importantly, recent literature suggests that other factors in PD including bolus clearance and pharyngeal area (Curtis et al., 2020), as well as pharyngeal residue (Steele et al., 2020b) likely contribute to airway invasion as well. It is therefore recommended that future research investigate other

laryngopharyngeal components of the swallow to examine the underlying physiology related to decreased swallow safety, particularly in PD. Moreover, this future research should help lend support to providing the evidence needed to further investigate specific targeted treatment approaches to improve overall swallow safety and function in neurogenic causes of dysphagia.

Limitations and Future Research Recommendations

This study was not without limitations and as such, caution should be used when interpreting these results. This study was conducted without direct comparisons to healthy, normative data. While normative data was used and referenced post-hoc in an effort to set these results in an appropriate context, overall interpretation and meaning of these results is skewed toward use in these clinical populations. Future studies should examine the meaning of these results by utilizing healthy controls as direct comparisons. The two groups used in this study were also two separate, neurological etiologies of dysphagia. While this is a novel approach in comparing dysphagia presentation between two etiologies, it should also be interpreted and used cautiously. While multiple etiologies are typically used in studies looking at scale or questionnaire development or validation, it is rarely done in this type of comparison study design. These results therefore, while interesting, should be assessed cautiously. Future research in this program should focus on separating these two groups data and performing separate analyses to elucidate a deeper understanding of dysphagia in each. As an example, our regression was performed in order to answer an intentionally broad question regarding the importance of LVCrt in neurogenic dysphagia. While an important question, many more questions still persist regarding how important it might be in each group separately, which we were unable to answer in the current model given the lack of separation in penetration and

aspiration events. Future research and analysis should be done to investigate the underlying importance in each group.

The two groups included in this study were also clinically based samples. While this has its advantages (i.e., those who could potentially not participate due to lack of transport or ambulation were not selected out of the study), it also has several drawbacks. The data used was dependent on what was made available via the medical record and the VFSS conducted. Therefore, some data may have been incomplete or other important data sources may have been unaccounted for (i.e., potential other underlying conditions). Despite every effort being taken to exclude patients with any level of concern of confounding variables, it is likely that conditions or circumstances were not always accurately reported by the patient or medical professionals. This also lends to a substantial lack of control over the environment and protocols being implemented in the VFSS that were used. Even though this was a primary analysis of the VFSS obtained, they had been and were continuously being collected in real world, clinical settings. Systematic inclusion and exclusion of bolus types, properties, and methods (i.e., unassisted) were used in an effort to standardize the patient sample as much as possible. However, being a clinically based analysis of VFSS, decision making based on the clinician's judgment and the patient's safety impacted the order of boluses delivered and how the VFSS was conducted. While this is a novel approach that provides useful, real world data that clinicians and researchers may use, it is also a limitation that requires caution when interpreting the overall results of the study. Future research and design should utilize more tightly controlled environments and methods to ensure adequate replication of these results. While our results do align with and support much of the existing literature, future research should seek to confirm these findings.

The use of the Videofluoroscopic Dysphagia Scale (VDS) as a tool to quantify dysphagia presentation across swallow stages should be considered a limitation of this study. While pre-evaluation methods were put in place to improve the reliability of the scale for this study, and the overall reliability for this particular study was good, concerns over certain subscale components in the oral stage warrant caution when interpreting these results. As an example, this is especially evident when considering the inclusion of apraxia as a quantifiable sign of dysphagia in the scale. Apraxia related to swallowing, or any other body part, relies on the exclusion of sensory related deficits being present (Daniels, 2000). Due to the existing nature of this data, we were unable to gather information related to each patient's sensory function in detail. Therefore, the lack of available information regarding sensory function and its potential contribution to dysphagia in this sample should be considered a significant limitation.

Quantification of dysphagia during VFSS in general continues to lack sufficient evidence of reliability in the literature available (Swan et al., 2019). Additionally, recent literature suggests a shift to pixel-based measures of dysphagia presentation rather than visuoperceptual ratings (Steele et al., 2020a) provides more accurate severity ratings. These suppositions in the literature therefore include the VDS used in this study, as well as other widely used quantification tools such as the MBSImp, which both primarily rely on visuoperceptual ratings of dysphagia presentation. However, based on the needs of this particular study, a tool that provides both breadth (oral and pharyngeal swallow stages) and depth (multiple subcomponents of each stage) that was also readily accessible and no cost, was a primary reason for choosing this scale. Importantly, the VDS was also chosen based on its potential availability to clinicians for future use. While this study was able to show that the

VDS may be used with good overall reliability when a training session(s) is used, there is no recommendation regarding the VDS in the literature to do so. This is a significant limitation in this study as well as the overall literature as there is no clear training or learning protocol to become proficient at scoring the VDS, or VFSS in general. Therefore, it is strongly recommended that some type of consensus pre-evaluation learning protocol take place prior to implementing any type of VFSS quantification method, especially the VDS, whether for clinical or research use.

Despite reliability concerns the VDS has been used in the dysphagia literature and evidence from this study suggests, when implemented appropriately, can be an adequate method for rating overall dysphagia severity. However, substantially more research is needed to determine if this training protocol is sufficient or could be improved, if training protocols could be used to improve the reliability of the VDS and its components, and how these visuoperceptual ratings compare to pixel-based measures. Therefore, interpretations of the evidence presented in this study regarding the VDS should remain guarded until more research is conducted. Based on the use of the VDS being considered a limitation, future research including this program of research should focus on utilizing pixel-based measures to compare the level of dysphagia severity in these samples. Additional research may examine how pixel-based and visuoperceptual ratings correlate in these samples, and potentially investigate how the use of one scale such as the VDS may compare to the use of another such as the MBSImp.

Finally, many questions arose throughout the data collection, analysis, and interpretation stages of this study. While methodologically we chose our questions *a priori* to remain consistent in our statistical and interpretation approach, many post-hoc questions and potential findings remain unanswered. Therefore, while methodological rigor was of the

utmost importance and something we chose to maintain, a significant limitation of this study was that we remained bound by the questions, and the subsequent answers, that were posed. Future research should aim to examine many other questions that arose during this project, including other hyolaryngeal kinematics, bolus clearance, and other dysphagia presentation related questions in this data. For other researchers and clinicians, a focus on other meaningful kinematics and pharyngeal stage swallow physiology is recommended particularly in PD to further investigate meaningful underlying causes of dysphagia in this population.

Chapter 5: Discussion

The program of research addressed throughout chapters 2, 3, and 4 outline a framework of screening methods, physiological causes, and potential future therapeutic targets to focus on when treating specific neurogenic causes of dysphagia. This research is particularly relevant for dysphagia in PD. The connection between dysphagia assessment, identification of the most salient contributors to dysphagia, and determination of how physiological and kinematic factors inform a potential treatment indicate a comprehensive and cohesive line of research. The studies included in these chapters have examined dysphagia to better understand its implications in neurological and neurodegenerative etiologies through a clinical lens. Importantly, this has been accomplished throughout multiple stages of identifying and quantifying dysphagia to better improve clinical and physiological knowledge. Additionally, these studies have highlighted the limitations of our current knowledge as well as the directions of potential future studies to address those gaps.

Screening and Identification of Dysphagia in PD for Improving Assessment and Advocacy

Chapter 2 (Dumican and Watts, 2020) served as an initial study that examined screening, physiological impairment, and future directions related to dysphagia treatment in PD. Findings from this study suggested that current, common physiological methods of screening for dysphagia may not be applied appropriately when used in PD. These results agree with emerging evidence. Physiological ways of testing an individual's deglutition system by administering food, liquid, or both appear to lack sensitivity for detecting dysphagia when airway safety is at risk (Dumican and Watts, 2020; Frank et al., 2020, Pflug

et al., 2019). The lack of ability for bolus related screening protocols to identify PWPD at risk for dysphagia has required examining other methods for that purpose. This initial study supported the use of a noninvasive questionnaire designed for PWPD to identify those at risk of dysphagia, particularly decreased airway safety (penetration with or without aspiration). The use of a questionnaire in our sample was able to significantly predict whether an individual would go on to display penetration with or without aspiration across a variety of bolus types. These findings support those in the literature when specific, targeted questionnaires are used to detect dysphagia in PWPD (Andres et al., 2017; Simons et al., 2014).

The utility of questionnaires in the PD population has often been questioned due to a common theory of PWPD are unable to accurately self-report symptomology related to swallowing (Buhmann et al., 2018; Kalf et al., 2012; Pflug et al., 2018; Schlickewei et al., 2020). Chapter 3 sought to expand upon the results reported in Chapter 2. . Rather than relying on one questionnaire to determine the need to screen and assess for dysphagia, the second study was designed to examine how a multitude of other clinical factors may predict dysphagia. Several factors including perceived speech and voice severity were used to predict if patients who experienced worsening speech and voice impairment would also report increased swallowing related impairment. The results from this study fit into the broader scope of the literature by confirming that PWPD may experience decreases in quality of life related to aspects of both communication and swallowing simultaneously (Dumican and Watts, 2020b; Van Hooren et al., 2016). Moreover, declines in speech and voice function may predict when patients will report parallel declines in swallowing function. When taken together, Chapters 2-4 indicate that regardless of the severity or

duration of PD early screening and assessment of potential dysphagia in PWPD is warranted. All evidence collected throughout these manuscripts indicate that neither H&Y, time since diagnosis, or overall disease duration predict whether an individual with PD will exhibit dysphagia related symptoms (Dumican and Watts, 2020a & 2020b, Dumican and Watts, 2021 [*unpublished*]). This provides additional evidence regarding potential timing and onset of dysphagia in PD, in that it is likely dysphagia is occurring during early stages of the disease yet is potentially undetected.

Several factors need to be considered in how to improve this detection from a clinical perspective. Namely, how to best screen for dysphagia in PD but also in how to promote awareness in other clinicians involved with caring for PWPD. The data presented throughout these studies display abnormal swallow related events, such as penetration and/or aspiration, are occurring across multiple bolus volumes and consistencies during the early stages of the disease (Dumican and Watts, 2020a & 2020b, Dumican and Watts, 2021 [*unpublished*]). These data also supply evidence that at least two different screening questionnaires may be considered for adequate screening of decreased swallow function in PD, including the SDQ (Dumican and Watts, 2020a) and the DHI (Dumican and Watts, 2020b). Therefore, it may be suitable to recommend a more comprehensive and detailed approach to formally screening PWPD for dysphagia. Future research should include moving beyond water or speed related tests of consuming a bolus in isolation (Dumican and Watts, 2020a; Pflug et al., 2018b), and continuing to investigate cost-effective, noninvasive methods of screening for dysphagia which go beyond singular questions (Buhmann et al., 2018; Chaudhuri et al., 2006; Goetz et al., 2008; Schlickewei et al., 2020) in order to get a comprehensive view of patient experiences (Branco et al., 2019; Dumican and Watts, 2020a,

Dumican and Watts, 2020b, Simons et al., 2014). The more evidence and information that is elucidated from ongoing investigations, the more likely it is that clinicians from interdisciplinary fields (primary care, specialists, nursing, physical therapy, speech-language pathology) may understand the importance of screening early and appropriately for dysphagia in PWP. There continues to be a disconnect between clinicians and healthcare professionals and information PWP are provided. Inadequate screening or information provided to those with PD likely impact how they see (or do not see) swallow impairment and what symptomology looks like (Salinas et al., 2020; Swales et al., 2020). A shift from viewing PWP as having poor self-perception of swallow deficits with the questions being asked of them to understanding they may not know what the questions we are asking them mean, is sorely needed.

Gaps still remain in our understanding of how to screen and identify the risk for dysphagia or decreased swallow safety in PWP. This is largely due to either the ineffectiveness or decreased reliability in many of the assessment tools used, as previously discussed. Therefore, there should also be a closer examination of other physiological testing related to dysphagia risk. Overall, the data presented throughout Chapters 2-4 indicate a salient characteristic of laryngeal dysfunction related to swallowing from sensory, motor, and perceptual perspectives (Dumican and Watts, 2020a & 2020b, Dumican and Watts, 2021 [*unpublished*]). There is currently insufficient evidence on how to best screen for these deficits, particularly from a sensorimotor perspective. Emerging evidence indicates that portable cough reflex testing utilizing capsaicin may be an effective tool in this population (Curtis and Troche, 2020). It is recommended that future studies in this research program continue to examine how to best assess these systems, particularly in the context of

physiological testing related to cough function. Previous research has indicated that decreased cough sensitivity and cough reflex responses are blunted in PWPD (Troche et al., 2014; Wheeler-Hegland et al., 2014). Therefore, increased knowledge and application of feasible, cost-effective, and portable methods of cough assessment would be beneficial to both PWPD as well as the clinicians who treat this population.

Contributors to Airway Invasion

From a physiological perspective, evidence from studies in Chapters 2-4 indicated that laryngeal function during swallowing related to kinematic movements (LVCrt and LVCd) should be considered important factors related to airway invasion (penetration with or without aspiration) of bolus material in PWPD (Dumican and Watts, 2020a; Dumican and Watts, 2021 [*unpublished*]). Even in instances where physiological data on swallow function was not obtained, participants still reported laryngeal related deficits concerning their voice (Dumican and Watts, 2020b). Existing literature has linked decreased vocal function with changes to hyolaryngeal mechanics when swallowing (Venkataraman et al., 2020). Therefore, there appears to be a linkage of laryngeal impairment impacting voice and swallowing in PWPD. The importance of laryngeal kinematics in relation to swallowing and airway protection, particularly in PWPD, is an emerging body of literature. While previous research has only looked at laryngeal kinematics in isolation (i.e., not in the context of predicting or being related to airway invasion) (Ellerston et al., 2016) more recent studies have indicated that laryngeal kinematics such as LVCrt and LVCd are important predictors when PWPD will have penetration with or without aspiration when swallowing (Curtis et al., 2019, Dumican and Watts, 2020a; Dumican and Watts, 2021 [*unpublished*]).

While many studies have taken a comprehensive approach to assessment (i.e., multiple kinematic timings and sequences, quantifying residue or bolus constriction), few have systematically studied both quantification and administration of multiple bolus volumes and consistencies. The approach in the final study of Chapter 4 aimed to expand upon Chapter 2 by providing a more complete picture of swallowing mechanics in PWPD. In this last study, a visuoperceptual scale to quantify dysphagia severity was used (VDS). Across a clinical sample of PWPD, the results revealed two of the most common and severe signs of dysphagia in PWPD were vallecular residue and reduced laryngeal elevation (Dumican and Watts, 2021 [*unpublished*]). Perhaps most importantly, current literature indicates that the accumulation of vallecular residue is more related to pharyngeal mechanics rather than tongue-based mechanics (i.e., tongue base retraction) (Stokely et al., 2015). Additionally, reduced hyolaryngeal movement is significantly associated with pharyngeal (vallecular and pyriform) residue and is therefore likely a driving force behind bolus clearance (Steele et al., 2010). When taken together with existing literature, the collective evidence from Chapters 2-4 suggest that the underlying mechanical cause of dysphagia in PWPD is associated with the pharyngeal stage of swallowing. Moreover, it is also likely that within the pharyngeal stage hyolaryngeal mechanical changes as measured via LVCrt, LVCd, in addition to other laryngeal kinematics such as hyoid displacement, are the largest contributing factors to dysphagia in this population (Dumican and Watts, 2020a, Dumican and Watts, 2020b, Dumican and Watts, 2021 [*unpublished*]).

Examining swallow function and dysphagia presentation in PD against another etiology of dysphagia like CVA was an important and novel step in elucidating the most prominent physiological signs of dysphagia in either group. Comparing VDS scores and

sub-scores between PWPD and CVA revealed the largest potential contributing factors to dysphagia and decreased swallow safety in those etiologies. While dysphagia in CVA and PD presented with similar rates of airway invasion along with LVCrt and LVCd measures outside the range of normal (Humbert et al., 2018; Steele et al., 2019), the most prominent contributors to dysphagia presentation were significantly different in people with CVA compared to PD. In contrasting the findings from these studies in Chapters 2-4, results regarding CVA related dysphagia presentation indicate complex, multi-faceted causes and relationships. These results indicated that the most prominent findings were related to oral stage impairments in CVA patients, though other abnormal findings including reduced laryngeal elevation, vallecular/pyriform residue, and penetration with or without aspiration were also common occurrences.

In the context of the current literature, the findings reported in Chapter 4 support the current levels of evidence. It appears to be more likely both in human and animal models that oral stage physiological impairment is more likely to be impaired and is, therefore, more common in CVA related dysphagia (Cullins and Connor, 2019; Umay et al., 2019). However, it is understood that a multitude of factors involving stroke can influence how dysphagia presents including cortical location, hemispheric location, cortical vs. subcortical, as well as the size and type of the lesion. Therefore, it is not surprising that other factors significantly contribute to dysphagia presentation, especially airway invasion, in post-CVA dysphagia. This can include hyolaryngeal movement, tongue base retraction, and bolus properties, all of which contribute to factors related to airway protection such as epiglottic retroflexion (Choi et al., 2020).

In regards to laryngeal kinematics typically considered important for airway protection, our results were unable to determine if slower LVCrt or LVCd times predict airway invasion in PD over CVA. This could be because longer LVCrt times predicted airway invasion regardless of disease state and that penetration with or without aspiration occurred at similar rates between the groups. In terms of LVCd, this could also be due to both groups consuming cup sized boluses that led to higher rates of airway invasion than smaller boluses, as larger boluses tend to result in longer apnea and closure durations (Martin-Harris, 2006). This could also be attributed to a laryngeal expiration reflex in those with CVA that could be dysfunctional in those with PD (Dumican and Watts, 2021 [*unpublished*]); Ludlow, 2015).

Chapters 2-4 provide evidence that longer LVCrt timing is characteristic of PWPD while significantly longer LVCd timing is characteristic of people with CVA. Healthy LVCrt kinematics across different bolus consistencies show that thin liquid boluses may result in LVCrt measures as high as 202 ms (Steele et al., 2019). In this context, our results indicated that LVCrt in CVA patients would fall very close to this upper bound of normal, whereas LVCrt in PWPD would fall outside of this normal range (Dumican and Watts, 2020a, Dumican and Watts, 2021 [*unpublished*]). LVCd in healthy older individuals can occur close to .600 ms for thin liquid (Humbert et al., 2018). In this context, our results indicate that both PD and CVA LVCd timings could be considered at the upper bound of normal in comparison to healthy older adults (Dumican and Watts, 2020a, Dumican and Watts, 2021 [*unpublished*]), which are also expected to be longer than healthy younger adults, in agreement with the literature (Humbert et al., 2018; Steele et al., 2019).

Evidence from the current studies along with existing literature support a view that longer LVCrt kinematic timings in PWPD are likely more important for airway protection than in those with CVA. This may be especially true when considering findings from Chapter 4. Those results indicated more prominent oral stage impairment in CVA yet similar penetration or aspiration rates, not simply LVCrt or LVCd (Choi et al., 2020). Additionally, although longer LVCd timings were associated with increased airway invasion events, the nature as to why is unclear. Previously suggested theories have included bolus properties or laryngeal reflexes. It may simply be due to the fact that longer LVCd timings were associated with the CVA group, and coupled with similar airway invasion rates as PD, this naturally influenced the predictive ability of longer LVCd times. Subsequent analysis may be required to further elucidate this cause.

It is also a possibility that bolus properties (either volume or consistency) played a substantial role in LVCd's predictive role for airway invasion in these disordered groups. If patients penetrated or aspirated on thicker consistencies at larger volumes, and longer LVCd times may be expected with these properties (Martin-Harris, 2006) then these longer duration times are likely to weigh heavily if someone experiences airway invasion. This may be particularly true given nearly half of abnormal swallow events occurred on larger and thicker bolus types. Though studies have indicated bolus size or consistency do not increase LVCd times, many of these have been conducted either in healthy younger individuals or with bolus sizes as low as 1 milliliter (Newman et al., 2016; Steele et al., 2019). The evidence presented in these studies show that, in populations with dysphagia, increased thickness of boluses reduces penetration and aspiration risk, but introducing increased bolus

size may not. It is recommended that further analysis be conducted to investigate the role that these characteristics played in laryngeal kinematics.

Taken together, evidence from the studies in Chapters 2-4 indicated that bolus properties (volume and consistency) played critical roles in the occurrence of airway invasion and patient perceptions of dysphagia. In regards to bolus properties, patients with neurogenic etiologies of dysphagia have increased risks of airway invasion regardless of volume or consistency, and may report difficulties swallowing various consistencies ((Dumican and Watts, 2020a, Dumican and Watts, 2020b; Dumican and Watts, 2021 [*unpublished*])). However, our results do provide substantially more information to the literature for introducing thickened consistency boluses, at smaller volumes, for improving swallow safety as a diet-modification approach to managing dysphagia. There remains a need for substantially more research to better understand how texture and volume modified diets affect specific aspects of swallowing mechanics. This is particularly true in conditions frequently associated with dysphagia, and especially in the populations considered in this dissertation. Future studies from this program of research will further examine the influence of volume and consistency on laryngeal kinematics and airway safety, as well as how those factors contribute to or alter swallow physiology. Moreover, the collective results from the studies included throughout Chapters 2-4 provide evidence for predictive pharyngeal stage dysphagia changes and characteristics to anticipate, and subsequently target, in PWD. This adds substantially to the body of knowledge regarding how dysphagia may present in PD, when it may present, screening tools that may be used, and specific physiological events (i.e., LVCrt, LVCd, and hyolaryngeal movement) that clinicians may be able to effectively target with therapeutic approaches.

Future Directions

Studies reported in Chapters 2-4 have been discussed in terms of their contributions to the field, the gaps that this knowledge fills, and potential next steps for researchers and clinicians to consider. A final major consideration of this program of research is to consider how the largest predictors and contributors to decreased swallow safety in PD may be targeted for treatment. Overall, dysphagia treatments lack high levels of scientific evidence across healthcare settings and populations (Duncan et al., 2020; Easterling et al., 2017) and lack clear guidance on how to best prescribe the dosage of swallow rehabilitation (Krekeler et al., 2021). In regards to PD, our understanding of treatment methodology, application, and outcomes remains weak. The earliest reviews actually showed no scientific evidence supporting behavioral based therapy for dysphagia in PD due to the lack of interventional studies (Deane et al., 2001). The literature has progressed regarding specific therapeutic approaches to improving dysphagia and swallow function in PWPd including expiratory muscle strength training (EMST) and neuromuscular electrical stimulation (NMES) (Baijens & Speyer, 2009; Ciucci et al., 2013; van Hooren et al., 2014; Sapir et al., 2008; Tjaden, 2008). However, sample size, study design, and methodological rigor of published studies limited the clinical relevance and development of evidence-based practice. More recent reviews have supported increased confidence in some treatment approaches including EMST and Lee-Silverman Voice Training (LSVT). It has also been demonstrated that pharmaceutical (such as levodopa [L-Dopa]) and surgical (deep brain stimulation [DBS]) approaches typically used for treating motor symptoms in PD are largely ineffective and may even negatively impact swallow function in PWPd (Broadfoot et al., 2019; Michou & Hamdy, 2010; Simons, 2018; Suttrup & Warnecke, 2016). Importantly, LSVT treatment evidence has tended to highlight improvements from

baseline without substantial evidence of airway safety (Miles et al., 2017) or has utilized LSVT alongside vocal fold augmentation using questionnaire data rather than physiological swallow outcomes (i.e., penetration or aspiration) (Howell et al., 2019). Even with the growing literature on treatment outcomes and broader knowledge of what may be ineffective, the evidence-based literature is limited.

Regarding the effectiveness of EMST, outside of two double blinded and controlled studies (Claus et al., 2021; Troche et al., 2010), and one detraining study regarding long term outcomes (Troche et al., 2014), successful study outcomes were based on limited assessment and evidence of airway safety (Pitts et al., 2009) in PWP. Moreover, the concept of EMST targeting expiratory muscles as the source of improved swallow function is largely unfounded as the most successful studies (Claus et al., 2021; Troche et al., 2010, 2014) displayed improved swallow function due to hyolaryngeal complex movement, not necessarily improved expiratory muscle strength. Moreover, Claus et al., (2021) found no improvement in airway invasion. Therefore, the appropriate use and positive outcome measures of specific treatments for dysphagia in PD remains limited. When considering the evidence presented from the studies in Chapters 2-4 indicates laryngeal function as a potential foundational contributor to dysphagia in PD, NMES may be a potential treatment approach.

NMES as a therapeutic modality to target improved neuromuscular function has been suggested for use in rehabilitative settings for decades (Lake, 1994; Ward & Shkuratova, 2002; Sheffler & Chae, 2007). Ongoing research has lent to understanding its underlying neuromuscular mechanisms (Doucet et al., 2012), its ability to improve deficits related to motor performance (Maddocks et al., 2013), and its contribution to therapeutic programs for rehabilitation and progressive diseases affecting optimal muscle function (Jones et al., 2016).

Given the exposure speech-pathologists have to this modality in rehabilitative settings, dysphagia literature exploring NMES as a therapeutic technique has grown exponentially across a multitude of etiologies including stroke, traumatic brain injury (TBI), head and neck cancer (H&NC), and neurodegenerative diseases including PD (Carnaby-Mann & Crary, 2007; Chen et al., 2016; Ding & Ma; 2016; Tan et al., 2013). Despite the potential for positive outcomes, the relative heterogeneity of dysphagia etiology, study design, methodology including electrode placement, time and intensity of stimulation, and outcome measures leave a mixed level evidence for NMES as an applicable and effective treatment modality for dysphagia. However, an understanding of its potential use in PWPD experiencing pharyngeal stage dysphagia, particularly within a neuromotor driven theory of decreased muscular function of the larynx and pharynx during swallowing, may be possible.

There is a limited amount of evidence regarding the use of NMES for dysphagia in PWPD, and the evidence that is available is mixed due to questionable methodology regarding electrode placement (Baijens et al., 2012), the frequency (cycles per second; Hz) of stimulation used (Heijnen et al., 2012); and a limited sample size with mixed results regarding overall dysphagia improvement (Park et al., 2018). These studies also highlight the lack of understanding of the application of NMES in treatment. Generally, NMES is meant to be utilized as a modality that generates muscular contractions, facilitates muscular movement, and is intended to do so in conjunction with muscular contractions (Doucet et al., 2012).

Therefore, the utilization of NMES to facilitate muscular contractions of antagonist muscles without muscular weakness appears inappropriate. This has been previously attempted with NMES in PWPD. The study utilized placements of NMES electrodes above the hyoid bone, below the hyoid, and both simultaneously (Baijens et al., 2012). Moreover,

skeletal muscle unit firing rates during voluntary contractions tend to occur anywhere between a frequency of 10-50 Hz (Doucet et al., 2012; Asmussen et al., 2018). Therefore, higher frequencies in the range of 70-80 Hz (or more) of pulsed electrical current appears to be well above the threshold necessary to induce a muscular contraction and are inappropriate (Heijnen et al., 2012). These factors indicate that NMES in dysphagia treatment should be implemented at the typical firing rate of skeletal motor units and be used in a facilitative fashion to induce muscular contractions. In the context of pharyngeal stage dysphagia in PD that has been outlined in this discussion, considering decreased muscular contractions and elevation of the hyolaryngeal complex for optimal airway protection and pharyngeal constriction, NMES applied to the suprahyoid musculature with an optimal frequency of pulsed current in conjunction with active exercise during NMES (i.e., swallowing) may serve as a potential treatment modality. In terms of suprahyoid structure and function, in depth muscular analysis based on fiber bundle types and concentration indicates that, when functioning together, muscles including the geniohyoid, mylohyoid, and anterior belly of the digastric are designed to move the hyolaryngeal complex superiorly and anteriorly, quickly and timely (Shaw et al., 2017). Evidence presented from the studies highlighted in this discussion have implicated overall hyolaryngeal complex function, including its timing and spatial movements, in dysphagia in PD.

Therefore, in theory, NMES may be applied to induce contractions of the suprahyoid muscle grouping superiorly and anteriorly, thereby facilitating elevation and excursion of the hyolaryngeal complex. Perhaps most importantly however, is that the intention behind this approach should be the concept of retraining the neuromuscular function of this (or any) skeletal muscle group, in a progressive therapy program over time, with increasing frequency

and intensity of therapy as tolerated (Maffiuletti, 2010). The principle and end result of this approach should be to create stronger and faster muscular contractions over time (Maffiuletti, 2010).

A consideration is the use of NMES not only as facilitative modality for improved hyolaryngeal elevation but also to provide a source of perturbation to improve laryngeal vestibule kinematic parameters. The most comprehensive works investigating the concept of perturbation in hyolaryngeal kinematics indicated that NMES found no significant differences in hyolaryngeal movement or laryngeal vestibule closure timings before or after NMES (Arslan et al., 2018; Humbert et al., 2015). While important works, concerns have remained regarding a lack of stimulation frequency reported, and the use of continuous stimulation as well as multiple levels of stimulation intensities, along with inappropriate electrode placement (Humbert et al., 2015).

In contrast, other studies utilizing a similar paradigm with submental placement reported improvements in laryngeal vestibule timing measures post-NMES application in healthy individuals (Watts & Dumican, 2018). Despite a lack of appropriate methodologically designed NMES investigations, current evidence does support the potential of NMES applied as a rehabilitation tool when the appropriate physiological impairment is identified. In the case of PWPD with dysphagia, an appropriate impairment may be decreased hyolaryngeal movement from inefficient muscular contractions. Therefore, NMES may be a useful therapeutic adjunct to improve this hyolaryngeal elevation, thereby facilitating anterior-superior movement of the hyolaryngeal complex, and/or provide a perturbation to the laryngeal vestibule requiring the individual to practice overcoming the resistance of NMES to laryngeal closure throughout the course of treatment. The results presented in this dissertation

have highlighted the evidence regarding decreased hyolaryngeal complex function, including laryngeal vestibule kinematic parameters. Given these results, previous treatment approaches that have been used to target hyolaryngeal function, including both EMST and NMES, should be explored further. Extensions of this program of research, as well as recommendations to future clinicians and researchers, are to establish specific and appropriate parameters and outcome measures (such as airway invasion, hyolaryngeal movement, LVCrt, and/or LVCd) to target with these therapeutic approaches. Due to the lack of current scientific knowledge and translation from the literature to practice regarding this area, targeting these specific breakdowns, particularly in a population such as PD, may add substantially to the knowledge base on dysphagia treatment. Moreover, it is likely to improve long term quality of life, maintain or improve swallow function, and potentially prevent long term health consequences associated with PD.

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patients with Parkinson's disease: prevalence and risks. *Parkinsonism & related disorders*, 19(8), 725–731. <https://doi.org/10.1016/j.parkreldis.2013.04.001>

Appendices

A. Speech, Voice, and Swallow Questionnaire

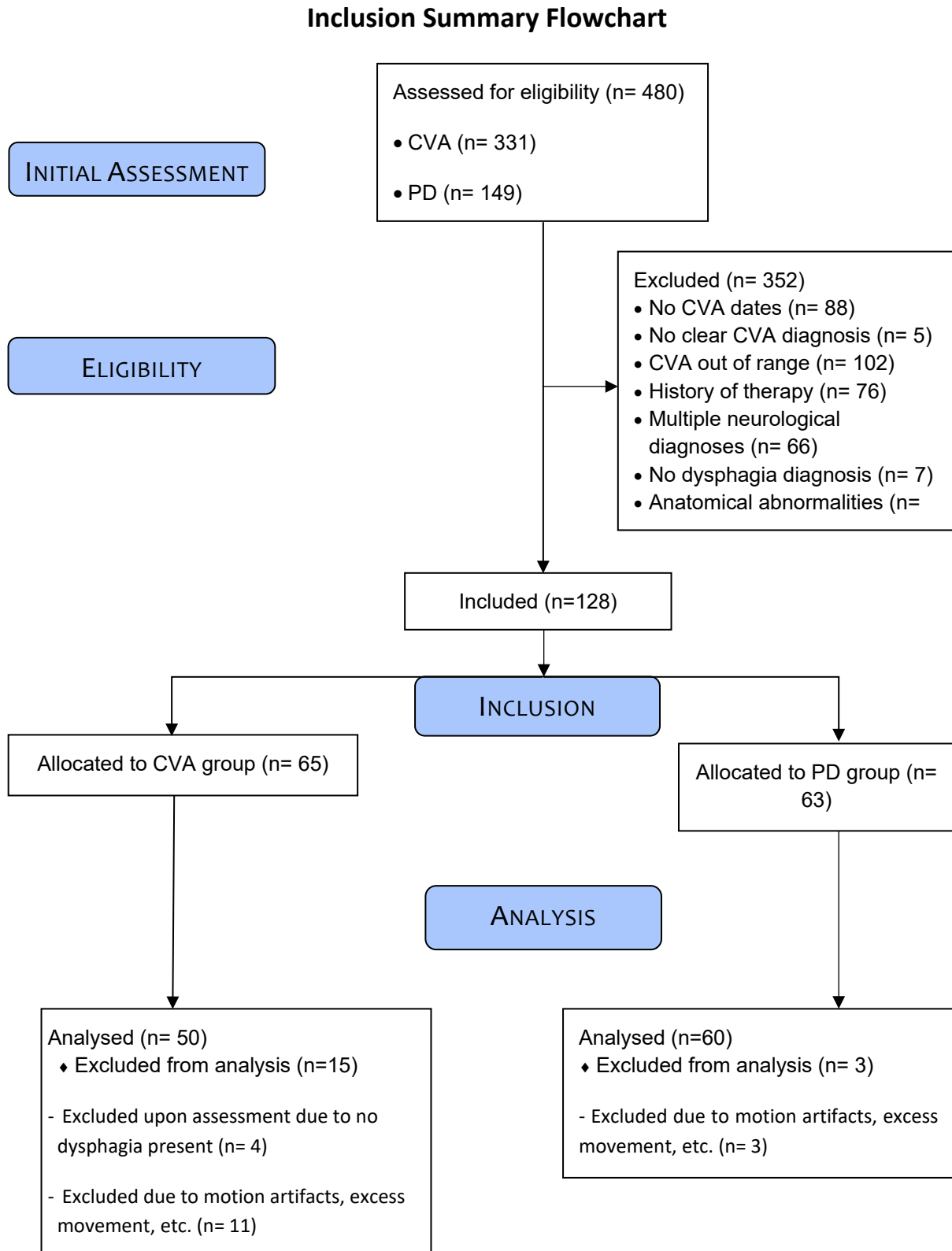
Parkinson's Speech, Voice, Swallowing, and Motor Questionnaire

Answer the following based on what you experience during a typical day when your symptoms are at their worst

Do you experience any of the following?

Problem	Never	Occasionally	Sometimes	Often	Always
Speaking volume is low					
Voice sounds hoarse					
Pitch does not vary when speaking					
Articulation is slurred or mumbled					
Speech rate is too fast					
Speech rate is too slow					
Air comes out of nose when speaking					
Drizzling					
Food falls out of mouth when eating					
Food gets stuck in cheeks when eating					
Clear throat frequently when drinking					
Clear throat frequently when eating					
Cough frequently when drinking					
Cough frequently when eating					
Food or pills gets stuck in throat					
Tremor in hand					
Tremor in arm					
Tremor in foot					
Tremor in leg					
Tremor in head or neck					
Tremor in face or tongue					
Movements are slow					
Muscles are stiff					
Balance problems					
Falling over					
Difficulty getting up from chair					
Posture is slumped when standing					
Shuffling feet when walking					

B. Inclusion Summary Flowchart



C. Penetration Aspiration Scale

1. Material does not enter the airway
 2. Material enters the airway, remains above the vocal folds, and is ejected from the airway
 3. Material enters the airway, remains above the vocal folds, and is not ejected from the airway
 4. Material enters the airway, contacts the vocal folds, and is ejected from the airway
 5. Material enters the airway, contacts the vocal folds, and is not ejected from the airway
 6. Material enters the airway, passes below the vocal folds and is ejected into the larynx or out of the airway
 7. Material enters the airway, passes below the vocal folds, and is not ejected from the trachea despite effort
 8. Material enters the airway, passes below the vocal folds, and no effort is made to eject
-

D. Videofluoroscopic Dysphagia Scale

Parameter	Findings		Parameter	Findings	
Lip Closure	Intact	0	Triggering of pharyngeal swallow	Normal	0
	Inadequate	2		Delayed	4.5
	None	4			
Bolus formation	Intact	0	Vallecular residue	None	0
	Inadequate	3		<10%	2
	None	6		10–50%	4
				>50%	6
Mastication	Intact	0	Laryngeal elevation	Normal	0
	Inadequate	4		Impaired	9
	None	8			
Apraxia	None	0	Pyriform sinus residue	None	0
	Mild	1.5		<10%	4.5
	Moderate	3		10–50%	9
	Severe	4.5		>50%	13.5
Tongue to palate contact	Intact	0	Coating on the pharyngeal wall	No	0
	Inadequate	5		Yes	9
	None	10			
Premature bolus loss	None	0	Pharyngeal transit time	<1.0 s	0
	<10%	1.5		>1.0 s	6
	10–50%	3			
	>50%	4.5			
Oral transit time	<1.5 s	0	Aspiration	None	0
	>1.5 s	3		Penetration	6
				Aspiration	12

Curriculum Vitae

Matthew Dumican, M.S., CCC-SLP

Doctoral Candidate

Davies School of Communication Sciences and Disorders
 Harris College of Nursing and Health Sciences
 Texas Christian University
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 508-212-3480

EDUCATION

Texas Christian University

PhD: Speech Language Pathology

Fort Worth, TX
 Expected May 2021

Texas Christian University

Master of Science: Speech Language Pathology

Fort Worth, TX
 May 2017

Sacred Heart University

Bachelor of Science: Health Sciences
 Minor: Speech Language Pathology

Fairfield, CT
 May 2015

ACTIVE LINES OF RESEARCH

Swallow Safety and Kinematics in Neurological Impairment and Dysphagia: An Epidemiological Study

- This research line is investigating how swallow function differs between individuals with Parkinson's Disease and those with other neurogenic etiologies of dysphagia.
- Seeks to identify trends in dysphagia diagnosis, kinematics, and other variables related to swallow safety across individuals with Parkinson's Disease, as well as in comparison to, other populations.

Perceptual and Physiological Manifestations of Dysphagia in People with Parkinson's Disease

- This project is investigating various aspects of swallowing in people with Parkinson's Disease, particularly as it relates to motor and somatosensory function of the larynx and upper airway.

- Seeks to identify how individuals with Parkinson's Disease are identifying the severity of their dysphagia and how it is manifesting early in the disease process.
- *This work has received support through the Texas Speech and Hearing Foundation (TSHF)*

The Effects of Neuromuscular Electrical Stimulation on Laryngeal Kinematics and Swallow Safety

- This project is retrospectively examining post-treatment changes in various hyolaryngeal kinematics and timing measures as well as swallow safety, in dysphagic patients who received NMES.
- This project also examines the viability and clinical application of using videofluoroscopic review software to measure laryngeal timing and kinematics to evaluate swallow performance.

PUBLICATIONS

Dumican, M.J. & Watts, C.R. (2020) Self-Perceptions of Speech, Voice, and Swallowing in Motor Phenotypes of Parkinson's Disease. *Parkinsonism and Related Disorders*, *In Press*. <https://doi.org/10.1016/j.prdoa.2020.100074>

Dumican M.J., & Watts, C.R. (2020) Predicting Airway Invasion Using Screening Tools and Laryngeal Kinematics in People with Parkinson's Disease. *Journal of Parkinson's Disease*, 10(3) 1153-60.

Watts, C. R., & **Dumican, M. J.** (2018). The effect of transcutaneous neuromuscular electrical stimulation on laryngeal vestibule closure timing in swallowing. *BMC Ear, Nose and Throat Disorders*, 18(1), 1–7. <https://doi.org/10.1186/s12901-018-0054-3>

PRESENTATIONS AND ABSTRACTS

Watts, C.R., Thijs, Z., **Dumican, M.**, (2021) The Effect of Vocal Intensity Mode on Acoustic and Aerodynamic Measures in People with Parkinson's Disease. Voice Foundation Annual Symposium, Virtual Conference. *Accepted*.

Watts, C.R., Thijs, Z., **Dumican, M.J.** (2020) The Effect of Vocal Intensity Mode on Voice Production in People with Parkinson's Disease. Annual Convention of the American Speech-Language-Hearing Association, San Diego, CA. *Accepted* (Convention Cancelled).

Dumican, M.J., & Watts, C.R. (2020) Laryngeal Kinematics During Swallowing in Parkinson's Disease. *Dysphagia Research Society Annual Meeting*, Online.

Dumican, M.J., & Watts, C.R. (2019) Hyolaryngeal Muscular Activation in Response to a Resistive Respiratory Device. *Dysphagia Research Society Annual Meeting*, San Diego, CA., March 8th, 2019.

OTHER RESEARCH AND LABORATORY EXPERIENCE

Research Assistant – Texas Christian University

Laryngeal Function Lab (Dr. Christopher Watts)

1. Effect of Vocal Intensity Mode on Acoustic and Aerodynamic Measurements in People with Parkinson's Disease

This project investigates the effect of vocal intensity mode at differing levels on acoustic and aerodynamic parameters during sustained vowels and connected speech in PD to examine phonation stimulus and intensity mode effect on measurements as well as clinical interpretation of therapeutic outcomes.

2. Acoustic and Aerodynamic Profiles in Motor Subtypes of Parkinson's Disease

This project investigated acoustic and aerodynamic measures of laryngeal function in speakers with PD stratified into motor phenotypes (tremor and non-tremor dominant), age of onset, and time post-onset.

3. Behavior Assessment Battery-Voice of Speakers with Spasmodic Dysphonia.

This project investigated the affective, behavioral and cognitive sequelae associated with SD. Data collection utilizes administration of a standardized assessment originally designed for stutterers – the Behavior Assessment Battery.

EXTERNAL FUNDING

TSH Foundation Elizabeth Wiig Research Award: \$1,500

February 2020-

Present

Project: Perceptual and Physiological Manifestations of Dysphagia in People with Parkinson's Disease

Role: Co-Principle Investigator (with mentor)

Texas Christian University

Goal: To investigate the manifestations of dysphagia particularly in early-stage PD and perceptual correlates experienced by people with PD.

ASHFoundation New Century Doctoral Student Scholarship

Not Funded

Project: Perceptual and Physiological Manifestations of Dysphagia in People with Parkinson's Disease

INTERNAL FUNDING

Graduate Research Travel Award, Harris College of Nursing and Health Sciences; Office of Graduate Studies: \$1,400

2020

Graduate Research Travel Award, Harris College of Nursing and Health Sciences; Office of Graduate Studies: \$1,400

2019

TEACHING EXPERIENCE

Instructor of record, Texas Christian University

Fall 2019 – Spring 2021

Course: COSD 40353 - Neurological Substrates of Communication and Swallowing

Responsibilities: Develop and deliver semester long course (3 hours/week) to a cohort of 30 diverse senior undergraduates in person, online, and in hybrid modality. This included independent development and delivery of all lectures both in person and online, clinical application activities, research and evidence base assignments, quizzes, and exams.

Course: COSD 20333 - Phonetics

Responsibilities: Develop and deliver semester long (3 hours/week) hybrid course (class based with transition to remote learning) to a small cohort of diverse undergraduates of varying majors. This included independent development and delivery of all lectures, in class activities, homework, and exams. Course adapted to function as both in person and online with both synchronous and asynchronous components.

Graduate Teaching Assistant, Texas Christian University

Spring 2019

Course: COSD 6043 – Dysphagia

Responsibilities: Assist in development and delivery of group based, clinical application activities and exam questions. Provide lecture and learning support to instructor as necessary. Deliver multiple lectures independently to a graduate level course – 20 students.

TEACHING QUALIFICATIONS/CONTINUING EDUCATION

Hybrid Course Design and Delivery eFaculty certified, Fall 2020

Learning Management System continuing education: instruction for building and maintaining online learning system courses (D2L), Fall 2020

UNIVERSITY SERVICE

Harris College Graduate Student Cabinet

- Serve as a departmental graduate student representative to the Dean
- Identify graduate level academic and administrative resources requiring review and revision
- Develop and initiate processes of improvement for increasing graduate student quality of life and program success

Doctoral Student Senator

- Service on multiple committees including the Graduate Student Policy and Finance committees.
- Develop and introduce policies and proposals to improve graduate student body resources, increase graduate student campus footprint and involvement, and represent graduate students in sectors of need and improvement.
- Identify, target, and source revenue sources for successful fundraising to maintain and drive funding increases for graduate student events, resources, and overall financial needs.

Global Outlook Institute Ambassador – Diversity, Equity, and Inclusion

- Facilitated deeper knowledge of current issues and barriers related to diversity, equity, and inclusion in higher education from both a national and international perspective
- Convened with experts and stakeholders to discuss diversity, equity, and inclusion in a hierarchical and integrative view from and institutional-to-individual level.
- Developed action plans on how to identify and address academic and individual biases and aspects related to diversity, equity, and inclusion both from an administrative and instructional standpoint.

TEAMWORK EXPERIENCE

Interdisciplinary Education Symposiums:

- Participated in several multidisciplinary educational events encompassing lecture, case studies, professional education tasks, and team-centered & evidenced based practice problem solving roundtables.
- This involved interdisciplinary teams of medical & allied health professionals and administrators representing multiple university programs to improve communicative efficacy across disciplines and professions.

International Professional Events:

- Observed and documented professional, labor, and cultural differences in Speech-Language Pathology across Ireland, Scotland, and England.
- Developed a global perspective and differentiated the major discrepancies in healthcare delivery for Speech and Language Therapists between the United States and abroad.
- Facilitated active roundtables to discover clinical, administrative, and deliverance approach differences with foreign professionals on implementation of Speech Pathology and patient services for improved outcomes in the United States.

PROFESSIONAL MEMBERSHIPS

American Speech-Language-Hearing Association (ASHA)

Dysphagia Research Society (DRS)

CERTIFICATION/LICENSURE

Certificate of Clinical Competency (CCC) in Speech Pathology. Valid Through: 12/2021

State of Texas Licensed Speech Language Pathologist: TDLR Valid Through: 5/2022

CLINICAL EXPERIENCE

Weatherford Rehabilitation Hospital

Weatherford, TX

Speech Language Pathologist

July 2018 - November 2019

Harbor Lakes Nursing and Rehabilitation

Granbury, TX

Lead Speech Language Pathologist

July 2017-August 2018

Harris Arlington Memorial Hospital

Arlington, TX

Speech Pathology Intern

June 2016-August 2016

CLINICAL COMPETENCIES

Ampcare Trained & Certified

Fiberoptic Endoscopic Evaluation of Swallowing (FEES)

Videofluoroscopic Swallow Study experienced (VFSS)

Modified Barium Swallow Impairment Profile (MBSImp) trained

Rigid stroboscopy for vocal fold function assessment

Abstract

Dysphagia (swallow impairment) in PWPD is expected to occur at some point during the disease process, with incidence estimated as high as 95%. Dysphagia symptoms in PWPD include deficits in the oral stage (oral residue, tongue pumping), pharyngeal stage (increased residue in the vallecula/pyriform sinuses, increased airway invasion), and/or esophageal stage (decreased upper esophageal sphincter motility). Growing evidence from the literature has indicated swallow kinematics during the pharyngeal stage of swallowing such as laryngeal vestibule closure reaction (how quickly the airway closes) and duration (how long the airway stays closed for) are considered to be major contributors to airway safety (e.g., preventing laryngeal penetration) in this population.

The comprehensive body of work presented in this dissertation was designed primarily to increase our knowledge of dysphagia associated with laryngeal dysfunction in people with Parkinson's disease (PWPD). This work was able to show evidence of dysfunctional airway protection as a ubiquitous trait in PWPD, with high rates of airway invasion and abnormally slow measures of laryngeal kinematics. Additionally, these results expand upon the current state of evidence regarding the ability of PWPD to perceive swallow impairment, and how dysphagia may commonly present in PD compared to other causes of dysphagia.

The findings in this dissertation provide a framework of future investigation both within this program of research as well as for other clinicians and researchers. Recommendations based on these results include examining other swallow kinematics in the pharyngeal stage of importance, comparing visuoperceptual and pixel-based examinations of swallowing, and targeting laryngeal function as it relates to swallowing in therapeutic interventions. Results regarding bolus characteristics and their effects as a dysphagia

management strategy for swallow safety indicate that thicker bolus consistencies reduce airway invasion rates. However, increasing volume mitigates and may even reduce, this improved safety. Recommendations in line with these findings include the effectiveness of thickened liquid use as a strategy for reducing airway invasion in neurogenic etiologies of dysphagia, but utilizing caution when introducing larger volumes of liquid regardless of consistency.