Swallowing Physiology and Impairment in Individuals with Amyotrophic Lateral Sclerosis (ALS)

by

Ashley A. Waito

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Rehabilitation Sciences Institute
University of Toronto

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Abstract

Dysphagia, or swallowing impairment, is a common symptom of bulbar disease in Amyotrophic Lateral Sclerosis (ALS). Dysphagia in ALS significantly affects quality of life and places an affected individual at risk of developing chest infections, becoming malnourished, and shortened life expectancy. The purpose of this doctoral thesis is to provide a comprehensive overview of swallowing physiology in ALS and elucidate potential relationships between swallowing physiology and clinical swallowing function.

The first chapter of this thesis provides an introductory overview of normal swallowing, dysphagia, and ALS pathology, highlighting commonly reported swallowing impairments and associated complications in individuals with ALS. Chapter 2 builds on this discussion through a comprehensive review of research literature on dysphagia in ALS. Following scoping review methodology, we identified research trends and areas for further exploration, including a need for further quantitative analysis of swallowing physiology.

Chapter 3 involves a retrospective, cross-sectional study of swallowing physiology in ALS, using quantitative videofluoroscopic analysis. Measures of pharyngeal area at maximum constriction and swallow-related hyoid kinematics were obtained and compared against reference data to test face validity of the measures and identify changes associated with disease pathology. Through this analysis, we identified reductions in maximum pharyngeal constriction and anterior hyoid movement, compared to healthy reference data. Further, we revealed relationships between enlarged maximum pharyngeal constriction areas and measures of swallowing inefficiency.
Expanding on these findings, we completed a comprehensive summary of swallowing physiology and function in ALS, summarized in Chapter 4, comparing additional metrics of swallowing physiology against healthy norms, examining relationships between parameters of swallowing physiology and function (i.e., safety/efficiency), and exploring modulatory effects of liquid thickness. Proposed approaches to future research, incorporating theories of motor control and methodological frameworks, are provided in Chapter 5.
Acknowledgments

I must extend sincerest gratitude to the many wonderful individuals who supported me and this doctoral research. To my Ph.D. supervisor, Dr. Catriona Steele, none of this research could have been accomplished without your knowledge and support. Thank you for your ongoing mentorship throughout this process and for continuing to challenge my critical lens. You introduced me to the field of dysphagia and inspired me to pursue research way back when I was completing my undergraduate degree and I am grateful to have had the opportunity to study under your guidance.

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For the patients who inspired this pursuit.
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List of Abbreviations

ALS  Amyotrophic Lateral Sclerosis

ALSFRS-R  ALS Functional Rating Scale - Revised

ASPEKT  Analysis of Swallowing Physiology: Events, Kinematics, Timing

CASM  Computational Analysis of Swallowing Mechanics

CPG  Central Pattern Generator

LVCdur  Duration of Laryngeal Vestibule Closure

UESOdur  Duration of Upper Esophageal Sphincter Opening

EMG  Electromyography

EMST  Expiratory Muscle Strength Training

FTLD  Frontotemporal Lobar Degeneration

IDDSI  International Dysphagia Diet Standardization Initiative

IOPI  Iowa Oral Performance Instrument

LMN  Lower Motor Neuron

LVA  Laryngeal Vestibule Approximation (between arytenoids/epiglottis)

LVC  Laryngeal Vestibule Closure

LVCrt  Laryngeal Vestibule Closure Reaction Time

MND  Motor Neuron Disease

MPCA_N  Maximum Pharyngeal Constriction Area (normalized)

NA  Nucleus Ambiguus

NTS  Nucleus Tractus Solitarius

NRRS  Normalized Residue Ratio Scale

PAS  Penetration-Aspiration Scale

PBP  Progressive Bulbar Palsy

PEG  Percutaneous Endoscopic Gastrostomy
<table>
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<tr>
<th>Abbreviation</th>
<th>Condition/Procedure</th>
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<tr>
<td><strong>PLS</strong></td>
<td>Primary Lateral Sclerosis</td>
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<tr>
<td><strong>PMA</strong></td>
<td>Progressive Muscular Atrophy</td>
</tr>
<tr>
<td><strong>SLN</strong></td>
<td>Superior Laryngeal Nerve</td>
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<tr>
<td><strong>UES</strong></td>
<td>Upper Esophageal Sphincter</td>
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<tr>
<td><strong>UMN</strong></td>
<td>Upper Motor Neuron</td>
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<tr>
<td><strong>VFSS</strong></td>
<td>Videofluoroscopic Swallowing Study</td>
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Note to the Reader

Indebted to the astute observations of a reviewer on my defense panel, I have come to appreciate that various concepts discussed in this work evolved throughout the course of my learning and development. As a result, subtle changes in the use of terminology create potential for ambiguity. This brief preamble is to acknowledge several sources of ambiguity in the language used throughout the dissertation, and to define/clarify specific terms.

1) **“Impairment”**: Early in this thesis (specifically in Chapter 2: Scoping Review), the use of the word “impairment” was used broadly to define the construct of dysphagia (i.e., “swallowing impairment”), while simultaneously encompassing deviations in swallowing movements/kinematics (e.g., “physiological impairments”, “laryngeal impairments”, etc.) as well as outcomes reflecting swallow safety or efficiency (e.g., “functional [swallow] impairments”). Although the inclusion of structural and kinematic differences aligns with a definition of “impairment” provided by the World Health Organization’s International Classification of Functioning, Disability and Health (ICF) (i.e., “a deviation/loss in body structure or function”\(^1\)), it became evident throughout further work that measurable differences in swallow timing/kinematics may not directly impact the success of the swallow, defined in terms of safety or efficiency. Thus, latter Chapters 3 and 4 define “impairment” more specifically as a challenge to swallow safety or efficiency, and those features which were initially labelled as “physiological impairments” were redefined as “physiological differences/changes”.

2) **“Function”**: For the purpose of this thesis, “swallow function” is defined as the overall performance of the swallow (i.e., measured in this work using metrics of swallow safety and efficiency). This definition stems from a more teleological or “goal-directed” understanding of swallowing behaviour\(^2\) and differs from that cited in the WHO-ICF\(^1\) which aligns more closely with my use of the word “physiology” (see below).

3) **“Physiology”** and **“Pathophysiology”**: As this thesis focuses on swallowing behavior at the musculoskeletal level, the use of the term “physiology” is in reference to the mechanics, movements, sequencing/timing and kinematics of muscles and structures involved during swallowing. Likewise, when discussing *at the level of the swallow*,
“pathophysiology” is defined by the changes in swallow physiology which contribute to impaired safety or efficiency. However, it is acknowledged that this term is also used frequently in the ALS literature, referring to aberrance at the cellular/neuromuscular level contributing to the disease process. For clarity, “pathophysiology of the swallow” was exchanged for “physiological mechanisms of swallowing impairment (i.e., safety/efficiency)”.

4) Muscle “Tone” and “Strength”: Muscle tone and strength are defined as a) resting contraction and resistance to passive stretch and b) force/potential force generated during isotonic or isometric contraction, respectively. In ALS, muscle tone commonly refers to degree of flaccidity and/or spasticity, secondary to upper and lower motor neuron pathology. Of note, “muscle tone” was selected as a theme heading in Chapter 2 to encompass what would be more appropriately defined as muscle “properties” or “features” which may impact the overall performance of a muscle in speech or swallowing (e.g., tone, strength, range of motion).

5) “Sensory Trick”: In Chapter 2, the term “sensory trick” is used to describe strategies or maneuvers that have been shown to have a therapeutic influence on swallow behavior (e.g., manipulation of bolus texture/temperature, thermal-tactile stimulation). This term would be more appropriately labelled as “sensory manipulation” or “therapeutic sensory stimulation” to avoid confusion with “sensory tricks” as defined in dystonia literature.

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Swallowing is a complex motor process, relying on the synergistic coordination of oral, pharyngeal and laryngeal muscles to reconfigure the pharynx from a breathing tube to a pathway for safe bolus transport. On average, humans swallow more than 400 times per day (Rudney & Larson, 1995), paying little conscious attention to the task. However, when swallowing becomes disordered secondary to neurological, anatomical, or psychological factors, the resulting impact on quality of life and risks to a person’s health is significant. Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disorder which often results in physiological changes in swallowing, negatively impacting the safety and efficiency of swallowing (Tabor & Plowman, 2017), as well as quality of life (Tabor, Gaziano, Watts, Robison, & Plowman, 2016). This doctoral thesis will be exploring swallowing in individuals with ALS, to delineate and quantify physiological changes associated with disease pathology and explore preliminary relationships between swallowing physiology and functional impairment. To begin, a brief review of swallowing and ALS pathology is provided.

1.1 Normal Swallowing Physiology

Swallowing physiology is classically divided into three phases: oral, pharyngeal, and esophageal. During the oral phase of swallowing, the tongue prepares and centralizes the bolus, while creating a seal with the soft palate to contain the bolus in the oral cavity. Once the bolus is prepared, the tongue is responsible for propelling the bolus posteriorly towards the oropharynx, while the soft palate elevates to permit bolus escape and seal off the nasopharynx (Hiiemae & Palmer, 1999). Throughout the pharyngeal phase of swallowing, contraction/activity of the pharyngeal and laryngeal muscles is carefully coordinated to maintain airway safety, while the bolus flows through the pharynx and into the upper esophagus. Closure of the laryngeal vestibule, paired with inversion of the epiglottis and adduction of the vocal folds, provides airway protection during the swallow to prevent food and liquids from entering the lungs (Vose & Humbert, 2018). Elevation of the hyolaryngeal complex also aids in moving the airway out of the path of bolus flow, while applying traction to distend a relaxed upper esophageal sphincter (UES) (Cock, Jones, Hammer, Omari, & McCulloch, 2017; Cook et al., 1989; Ishida, Palmer, & Hiiemae, 2002). With the UES distended, the pharyngeal constrictor muscles contract in a rostro-caudal pattern to form a stripping wave (Kahrilas, Logemann, Lin, & Ergun, 1992), which
effectively clears the bolus from the pharynx into the esophagus. In parallel with bolus flow and airway protection, respiratory cycles must be appropriately timed to pause and resume the inhalation-exhalation airflow pattern (Martin-Harris et al., 2005) and esophageal peristalsis must move the bolus further along the gastrointestinal tract (Jean, 2001) to clear a path for the next bolus.

![Diagram](image)

**Figure 1-1.** Schematic sequence of oral and pharyngeal phases of swallowing, followed by post-swell pharyngeal relaxation. The bolus (shown in orange) is propelled towards the pharynx by the tongue and subsequently chased into a relaxed upper esophageal sphincter via mechanisms of pharyngeal constriction.

From a neurophysiological perspective, there is a great deal of overlap between the phases of swallowing, with each phase priming and modulating the output of the next. The oral phase is the only swallowing behaviour considered to be under full volitional control, although supported by rhythmic motor control for chewing and bolus preparation (Lang, 2009); that is, one could voluntarily halt or initiate oral preparatory behaviours at any point in the sequence, prior to the triggering of any pharyngeal phase events. In contrast, once pharyngo-esophageal events are
initiated, the sequence unfolds without an opportunity for volitional interruption. This reflexive and stereotyped portion of the swallowing motor sequence is thought to be primarily controlled by a bilaterally-paired central pattern generator (CPG) located within the medullary region of the brainstem (Ertekin & Aydogdu, 2003a; Jean, 2001; Lang, 2009).

Reflexive triggering of the pharyngeal swallow can occur in response to stimulation of afferent cranial nerve fibers, particularly the internal branch of the superior laryngeal branch (iSLN) of the vagus nerve (Lever et al., 2010; Steele & Miller, 2010). Peripheral afferent fibers carry sensory information from orofacial, pharyngeal and laryngeal regions to the nucleus tractus solitarius (NTS) in the dorso-lateral medulla (Jean, 1984b; Steele & Miller, 2010), which communicates with the nucleus ambiguus (NA) in the ventrolateral medulla responsible for initiating the final motor output for swallowing (Jean, 1984a). Motoneurons in the swallowing CPG are organized myotopically, analogous to the homunculus in the motor cortex, to orchestrate rostrocaudal firing patterns observed in deglutition (Jean, 2001). Concurrent to the pharyngeal swallowing sequence, interconnections between the swallowing and respiratory CPGs direct inhibition of respiration, until the swallow is complete (Barlow, 2009; McFarland & Lund, 1993; Saito, Ezure, Tanaka, & Osawa, 2003).

Although it can operate without top-down cortical involvement, the swallowing CPG in humans receives input and modulation from descending cortical networks involved in volitional swallow behaviours (e.g., oral bolus preparation) (Ertekin & Aydogdu, 2003). Initiation of the pharyngo-esophageal swallowing sequences can result from cortical and subcortical swallowing control, via regions involved in feeding and deglutition behaviours, including the anterior cingulate and insular cortices, ventrolateral sensory and motor areas, orbitofrontal regions, basal ganglia, and structures inherent to the limbic system (Daniels et al., 2002; Daniels & Foundas, 1997; Humbert et al., 2009; Martin, Goodyear, Gati, & Menon, 2001; Suzuki et al., 2003). Damage to these cortical and subcortical regions, or to cranial nerves involved in the sensorimotor swallowing process, can result in serious swallowing impairment.

### 1.2 Swallowing Impairment

Dysphagia, or swallowing impairment, can be defined as breakdown in any phase of swallowing which impacts the safety or efficiency of swallowing. Unsafe swallowing relates to the occurrence of food/liquids entering the airway. Airway invasion of bolus material is also referred
to as penetration or aspiration, according to the depth of bolus airway invasion (i.e., *penetration* = at or above the level of the vocal folds; versus *aspiration* = below the level of the vocal folds) (Robbins, Hamilton, Lof, & Kempster, 1992; Rosenbek, Robbins, Roecker, Coyle, & Wood, 1996), depicted in Figure 1-2. Impaired swallowing safety places an affected individual at risk of developing aspiration pneumonia (i.e., chest infection secondary to aspirated material), choking and premature death (Holas, DePippo, & Reding, 1994; Schmidt, Holas, Halvorson, & Reding, 1994). Inefficient swallowing relates to the effectiveness of bolus transport and may present as bolus residue remaining in the throat post-swallow, the need to swallow multiple times or reliance on compensatory maneuvers to aid bolus clearance (e.g., Dejaeger, Pelemans, Ponette, & Joosten, 1997; Eisenhuber et al., 2002; Hamlet et al., 1994; Hutcheson et al., 2017). Impairments in either safety or efficiency can have serious impact on patient experience during meals (i.e., reduced quality of life) (e.g., Bennett & Steele, 2005; McHorney, Martin-Harris, Robbins, & Rosenbek, 2006) and reduce overall food/liquid intake, placing patients at risk of becoming malnourished and dehydrated (e.g., Carrión et al., 2015; Carrión, Roca, Ortega, Arreola, & Clave, 2013; Foley, Martin, Salter, & Teasell, 2009; Namasivayam & Steele, 2015).

**Figure 1-2.** Schematic diagram depicting aspiration versus penetration, based on depth of airway invasion. Penetration (yellow) refers to material at or above the level of the vocal folds. Aspiration (red) refers to material falling below the vocal folds, even if it eventually recovers to a higher level.
Comprehensive assessment of dysphagia typically involves a clinical examination, to evaluate cranial nerve function and observe a patient’s response to various bolus types (e.g., difficulties with masticating solids, coughing associated with swallowing liquids). When swallowing safety or efficiency are in question, instrumental assessments allow clinicians to view and evaluate swallowing function and bolus flow directly, delineate physiological mechanisms of impairment and trial the effectiveness of compensatory strategies (e.g., postural changes, bolus modification). Videofluoroscopy, for example, is one instrumental assessment method which yields a dynamic radiographic exam for evaluating bolus flow and characterizing swallowing physiology (American Speech-Language-Hearing Association, 2003; Martin-Harris & Jones, 2008; O’Donoghue & Bagnall, 1999).

1.3 Amyotrophic Lateral Sclerosis (ALS)

ALS is a neurodegenerative disorder, characterized by progressive loss of upper (UMN) and lower motor neurons (LMN), resulting in changes to muscle strength and tone (i.e., spasticity, flaccidity) throughout the body. Consequently, patients with ALS experience a range of serious complications affecting mobility, respiration, communication, and functional independence (National Institute of Neurological Disorders and Stroke, 2012). There is no cure for ALS, and few pharmaceutical therapies are currently available to slow the rate of ALS disease progression (Miller et al., 2009; Naganska & Matyja, 2011). The leading cause of death is respiratory compromise, often complicated by recurrent chest infections, including aspiration pneumonia (Corcia et al., 2008).

ALS is a heterogeneous disease; clinical onset, progression rates and the degree of UMN/LMN involvement affecting overall presentation varies across patients (Ravits & La Spada, 2009). Approximately 70% of individuals diagnosed with ALS present with spinal-onset ALS, whereby signs and symptoms are first identified through the corticospinal tract and related peripheral spinal nerves, leading to foot drop, imbalance/impaired mobility, reduced grip strength, or impaired fine motor control. For the remaining cases (~20-30%), initial symptoms are secondary to degeneration of the corticobulbar tracts and cranial nerves, affecting muscles of the face, mouth, tongue, pharynx or larynx, referred to as bulbar-onset ALS (Miller & Britton, 2011; Swinnen & Robberecht, 2014). Despite differences in location of onset, most patients with ALS will eventually experience challenges in both spinal and bulbar systems as the disease
progresses. Still, current descriptions highlight different clinical presentations and prognoses for the two onset types, with shorter life expectancy for individuals diagnosed with bulbar-onset ALS, compared to spinal-onset cases (Daghlas, Lever, & Leary, 2018), likely due to direct relationships with respiration and deglutition (Swinnen & Robberecht, 2014). The degree of LMN/UMN involvement leads to a mixed presentation of flaccid versus spastic muscles, varying between individuals (Chiò et al., 2011; Swinnen & Robberecht, 2014).

The pathophysiology of ALS is highly complex and remains under current investigation. Only ~5-10% of ALS cases are considered familial, while most ALS cases emerge sporadically, without known etiology of the disease (Al-Chalabi et al., 2012; Byrne et al., 2011). Over the past two decades, numerous genetic correlates have been identified in relation to disease mechanisms in ALS and related conditions. The most thoroughly studied genetic correlates involve mutations affecting super oxidative dismutase (SOD1), TAR-DNA binding protein (TARDBP), chromosome 9 (C9orf72), and Fused in Sarcoma (FUS) (Al-Chalabi et al., 2012; Beckerman, 2015; Robberecht & Philips, 2013), with related pathophysiological mechanisms including cytoplasmic aggregation of misfolded FUS and TAR-binding (TDP-43) proteins, and ubiquitin-positive inclusions in astrocytes and motor neurons which contribute to axonal death. Although classically considered a disease that selectively impacts motor neurons, a more contemporary view suggests that ALS is a multi-system disorder. Concomitant changes in cognition and extra-motor processes are common, and ALS has recently been described on a continuum with frontotemporal lobar degeneration (FTLD), based on common co-occurrence and shared pathophysiological mechanisms (Al-Chalabi et al., 2012; Mackenzie, 2007; Strong, 2008; Swinnen & Robberecht, 2014). Recent work has also suggested that changes in sensation may also occur in some patients with ALS (Amin, Harris, Cassel, Grimes, & Heiman-Patterson, 2006; Isaacs et al., 2007; Pelletier, Abou-Zeid, Bartoshuk, & Rudnicki, 2013; Ruoppolo et al., 2016).

1.4 Swallowing in ALS

Oropharyngeal dysphagia (described above) is a serious symptom of bulbar disease in ALS secondary to neuropathological changes in corticobulbar tracts, estimated to affect more than 80% of individuals with ALS (Briani et al., 1998; Ruoppolo et al., 2013), irrespective of onset-type. Overall risk and severity of dysphagia in ALS has been linked to: bulbar-onset, female sex, older age at onset, and duration of bulbar symptomology (Luchesi, Kitamua, & Mourao, 2014;
Strand, Miller, Yorkston, & Hillel, 1996). Reports have shown a strong association between swallowing and quality of life in ALS (Tabor et al., 2016), and associated sequelae (e.g., malnutrition, aspiration) have been directly shown to increase risk of death in ALS. In a recent post-mortem study by Corcia and colleagues (2008), pneumonia was identified as the leading cause of death in patients with ALS (71%), followed by heart failure (10%) and pulmonary embolism (6%).

Dysphagia in individuals with ALS commonly results in challenges to swallowing safety and efficiency (D'Ottaviano, Linhares Filho, Andrade, Alves, & Rocha, 2013; Goeleven, Robberecht, Sonies, Carbonez, & Dejaeger, 2006; Lo Re et al., 2007; Robbins, 1987), and as the disease progresses, individuals with ALS ultimately experience a worsening of swallowing signs and symptoms. Individuals with ALS who are unable to meet their nutritional requirements by oral intake due to severe dysphagia often require surgery to place enteral feeding tubes (e.g., gastrostomy) to maintain nutritional status while bypassing the oropharyngeal mechanism (Mitumoto et al., 2003; Rio et al., 2010).

Reports of dysphagia in ALS have described a variety of changes in swallowing physiology, including:

- Oral impairments – e.g., impaired tongue function, difficulty chewing, incomplete tongue-palate seal, bolus spillage, ineffective oral bolus transport (D'Ottaviano et al., 2013; Leder, Novella, & Patwa, 2004; Li et al., 2009; Nagasaki, Yoshida, Yamashina, Suei, & Tanimoto, 2004);

- Pharyngeal impairments – e.g., delayed triggering of the pharyngeal swallow, prolonged bolus transit times, reduced pharyngeal strength and pressure, cricopharyngeal dysfunction (Ertekin et al., 2000; Higo, Tayama, & Nito, 2004; Li et al., 2009; Murono et al., 2015; Robbins, 1987);

- Laryngeal impairments – e.g., reduced hyolaryngeal excursion, incomplete or delayed airway closure (Lo Re et al., 2007; Murono et al., 2015; Plowman, Tabor, Robison, & Wymer, 2016; Robbins, 1987; Solazzo et al., 2011);
• Respiratory impairments – e.g., atypical respiratory-swallow patterns, reduced cough effectiveness (Aydogdu, Tanriverdi, & Ertekin, 2011; Nozaki et al., 2008; Plowman, Watts, Robison, et al., 2016); and

• Esophageal dysfunction – e.g., reduced esophageal motility, impaired function of the lower esophageal sphincter, gastro-esophageal reflux (Borasio & Miller, 2001; Jesus et al., 2012).

In rodent models of ALS with bulbar impairment (SOD1-G93A), degeneration and vacuolization of the NA and NTS has been reported (Lever et al., 2010). These histological findings were linked to slowed rate of licking and mastication.

Any one of the above changes in isolation can contribute to signs and/or symptoms of dysphagia. However, it is currently unknown which physiological impairments are most closely associated with functional impairments (i.e., safety, efficiency) in individuals with ALS and how external factors such as bolus properties influence the altered swallowing mechanism.

1.5 Thesis Overview

Dysphagia is a devastating symptom of ALS disease pathology, placing the affected individual at risk for serious health consequences, reduced quality of life, and early death (Corcia et al., 2008; Ruoppolo et al., 2013; Strand, Miller, Yorkston, & Hillel, 1996; Tabor, Gaziano, et al., 2016). As swallowing physiology is complex and involves the coordination of multiple subsystems, it is highly susceptible to breakdown in when any one or more subsystems are affected. Therefore, to guide clinical assessment and management of dysphagia in ALS, we must first identify the specific parameters of swallowing physiology which directly contribute to impaired swallowing safety and efficiency. The purpose of this thesis is to describe and characterize swallowing in patients with ALS. Three studies were conducted to identify physiological changes and functional consequences associated with the disease: a literature review to summarize current research on dysphagia in ALS (Chapter 2), followed by two studies characterizing swallowing physiology using videofluoroscopic measures (Chapter 3). Further, we sought to delineate relationships between swallowing physiology and function in ALS and explore modulatory influences of bolus properties on these relationships (Chapter 4). It is hoped that the preliminary work from this study will help guide dysphagia assessment and management in ALS by
highlighting specific parameters and factors for clinical focus, reveal potential biomarkers or outcome measures for clinical trials, and provide proof-of-principle towards potential compensatory strategies or rehabilitative therapy.
Trends in Research Literature Describing Dysphagia in Motor Neuron Disease (MND): A Scoping Review

2.1 Preface

Given the complexity of the swallowing mechanism, paired with the clinical variability in ALS presentation, we were initially interested in gaining a comprehensive understanding of the manifestation of dysphagia in patients with ALS and summarizing existing research on the topic. Thus, the first phase of this dissertation involved a literature review. The goal of the review was to explore the landscape of research on ALS and dysphagia, to reveal existing research themes and knowledge gaps for further inquiry.

We chose to conduct a scoping review, following methodological recommendations outlined by Arksey & O’Malley (2005), Levac, Colquhoun, & O’Brien (2010), and the Joanna Briggs Institute (2015). This study design allowed us to identify and explore themes which exist within the current literature and identify knowledge gaps to guide the remainder of the thesis project.

With kind permission from Springer Publishing, this chapter was cited in full from the following journal article:


References and tables have been re-formatted to APA style and linked to the end of the dissertation. The full article can be found on the publisher’s website at https://doi.org/10.1007/s00455-017-9819-x.
2.2 Abstract

Dysphagia in motor neuron diseases (MNDs) is highly complex, affecting all stages of swallowing and leading to impaired swallowing safety and efficiency. In order to explore the degree to which research is capturing the symptom of dysphagia in MND, we conducted a scoping review of the existing literature. The primary aims of this review were to identify common themes within the literature on dysphagia in MND, explore patterns and trends in research focus, and identify if any imbalances exist between the research themes related to dysphagia description and management.

Methods: A comprehensive search strategy yielded 1690 unique articles for review. Following relevance screening, a total of 157 articles were included in the synthesis. Relevant data and keywords were extracted from each article and grouped into themes. Frequency estimates were calculated for each theme to identify trends across research literature.

Results: Swallowing impairment in MNDs is described in a variety of ways across current research. The most commonly reported theme was Aspiration/Penetration, mentioned in 73.2% of all included articles; a significant imbalance was identified between reports of swallowing safety and efficiency ($p=0.008$). The most frequently reported theme related to dysphagia management was Enteral Nutrition, and very few studies have reported on the efficacy of Rehabilitation/Compensatory recommendations.

Conclusions: It is suggested that researchers and clinicians remain mindful of imbalances and gaps in research and aim to characterize dysphagia in MNDs in a comprehensive manner. Further research investigating discrete, measurable changes in swallowing pathophysiology would be beneficial to delineate the key factors contributing to impaired swallowing safety and efficiency.
2.3 Introduction

Motor neuron disease (MND) represents a class of neurodegenerative disorders characterized by progressive deterioration of motor neurons, leading to weakness, spasticity, and atrophy of the innervated muscles (National Institute of Neurological Disorders and Stroke, 2012). In addition to classic Amyotrophic Lateral Sclerosis (ALS), which affects upper and lower motor neurons of the corticobulbar and spinal tracts, the International Statistical Classification of Diseases and Related Health Problems (ICD-10) recognizes three additional subtypes of MND, based on differing patterns of motor neuron involvement (i.e., upper vs. lower motor neurons), and muscle involvement (i.e., spinal vs. bulbar). These subtypes include progressive bulbar palsy, primary lateral sclerosis, and progressive muscular atrophy (World Health Organization, 2015) (summarized in Table 2-1). Progressive bulbar palsy (PBP) leads to degeneration of upper and lower motor neurons, selectively affecting bulbar musculature, and has a relatively shorter predicted survival. Primary lateral sclerosis (PLS) is diagnosed when only upper motor neurons are affected. In contrast, progressive muscular atrophy (PMA) affects lower motor neurons only, and primarily involves spinal muscle groups. Disease progression is generally slower and longer for individuals with PMA and PLS, compared to classic ALS or PBP. Due to these differences in motor neuron and muscle involvement, there is inherent variability between the subtypes of MND. Still, the diagnoses are not mutually exclusive, as each has the potential to be relabeled as classic ALS if additional pathophysiological signs develop (Al-Chalabi et al., 2016; D’Amico, Pasmantier, Lee, Weimer, & Mitsumoto, 2013; Gordon et al., 2006; Karam, Scelsa, & MacGowan, 2010; Miller & Britton, 2011; Swinnen & Robberecht, 2014).

At this time, there is no cure for MND, and symptomatic management is the primary course of treatment (Barber, 2015; Borasio & Miller, 2001; Houseman, 2008; Valadi, 2015). This highlights the importance for researchers and clinicians to identify and explore mechanisms of impairment early, in order to provide management options in an appropriate and timely manner.
Table 2-1

Subtypes of MND and relevant pathophysiology (adapted from Miller & Britton, 2011).


<table>
<thead>
<tr>
<th>Motor Neuron Involvement</th>
<th>PMA</th>
<th>PLS</th>
<th>PBP</th>
<th>ALS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper Motor Neuron (UMN)</td>
<td>−</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Lower Motor Neuron (LMN)</td>
<td>++</td>
<td>−</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Spinal</td>
<td>++</td>
<td>++</td>
<td>−</td>
<td>++</td>
</tr>
<tr>
<td>Bulbar</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

Dysphagia (i.e., swallowing impairment), is one of the most common and devastating symptoms affecting individuals with MND, particularly when bulbar muscles are involved (Miller & Britton, 2011), as in PBP, PLS and ALS. Dysphagia is a serious medical complication that places an affected individual at risk for dehydration, malnutrition, and pneumonia secondary to aspiration (i.e., material entering the airway below the level of the vocal folds). Estimates of dysphagia prevalence in patients with ALS, for example, range from 60-86% (Kuhnlein et al., 2008; G. Ruoppolo et al., 2013), with additional sources suggesting that almost all patients with ALS will eventually develop dysphagia to some degree (Briani et al., 1998; Robbins, 1987). Although prevalence rates of dysphagia among other subtypes of MND are not as clearly defined, swallowing problems have been identified in all four subtypes (Briani et al., 1998; Leighton, Burton, Lund, & Cochrane, 1994; Szacka, 2016; Watanabe, Iino, Honda, Sano, & Hara, 1997). In a study by Leighton et al. (1994), swallowing problems were identified in 89% of included participants with PBP, 45% of participants with PMA, and 29% of participants with classic ALS. Signs and symptoms of dysphagia in patients with MND may include loss of food and liquids out of the mouth, premature entry of liquids into the pharynx prior to swallowing, difficulty clearing bolus material from the oral cavity and pharynx during swallowing (i.e., post-swallow residue), frequent episodes of coughing/choking on food or liquids, and esophageal dysmotility (Miller & Britton, 2011). As the disease progresses, individuals with MND ultimately experience a worsening of symptoms, affecting quality of life and placing increased
demands on the healthcare system to evaluate and manage symptoms appropriately. When dysphagia is paired with respiratory impairment, the risk of developing aspiration pneumonia increases significantly; for patients with ALS, broncho- and aspiration pneumonia are leading causes of death (Corcia et al., 2008).

Although research investigating the presentation of dysphagia across the MNDs has provided insight into its prevalence and clinical presentation, there is an ongoing need for additional research to delineate the key physiological mechanisms contributing to functional swallowing impairment, and determine appropriate rationales to recommend or refine existing management strategies. Further, given the variability of dysphagia within and between MND types, and as it evolves throughout disease progression, it is important for research to capture and investigate the full range of swallowing challenges experienced by individuals with MND, and delineate the factors that affect presentation of dysphagia between the four MND subtypes.

We conducted a scoping review in order to summarize the profile of existing research on dysphagia across the subtypes of MND, and to identify gaps in the existing literature. We followed current guidelines for scoping review methodology (Arksey & O'Malley, 2005; Colquhoun et al., 2014; Levac et al., 2010; Pham et al., 2014) to address the following research questions:

1. How does the current research literature describe swallowing physiology and dysphagia in MND?
2. How is swallowing physiology and function in individuals with MND being measured and reported?
3. What recommendations are currently being made for the management of dysphagia in MND?

We kept the search strategy broad to include all four subtypes of MND, due to differences in terminology between different geographical regions (e.g., “Motor Neurone Disease” commonly used synonymously with ALS in Europe), fluidity between subtypes (e.g., PBP typically progresses to classic ALS with onset of spinal muscle involvement), and shared pathophysiology of motor neuron cell death captured under ICD-10 Code 12.2.
2.4 Methods

2.4.1 Search Strategy

We conducted an initial literature search in October 2015, and updated the search on February 7th, 2017. Forty-seven terms related to dysphagia and MND were translated across six databases (Medline, EMBASE, CINAHL, SpeechBite, CENTRAL, Pubmed) by a qualified research librarian. The entire search strategy can be found in Appendix A. Retrieved citations were imported into EndNote X5® software for removal of duplicates, data management and storage. Overall, the search yielded a total of 1691 unique articles for relevance screening.

2.4.2 Relevance Screening

During initial inclusion screening, titles and abstracts were copied into a Microsoft Excel spreadsheet, labelled by EndNote® record number. Title and abstract screening was completed by two independent raters using a shared relevance screening form, with 20% duplication for interrater comparison. At this stage, raters were blinded to the publishing journal and author names to minimize bias related to recognition of familiar authors’ names.

Following title and abstract screening, full-text articles were reviewed by the first author for final inclusion in the planned qualitative synthesis. Articles were excluded if they: (1) reported on a population that was not a subtype of MND, under ICD-10 code G12.2; (2) failed to describe swallowing, dysphagia, or dysphagia management; (3) were not a peer-reviewed journal article; or (4) were not available in English.

2.4.3 Data Extraction & Synthesis

Thematic analysis was completed in two steps: theme identification and tabulation. To identify themes within the dataset, key words and findings were extracted from each included article and summarized in a Microsoft Excel spreadsheet, separating distinctive keywords and phrases using consistent notation (e.g., “Individuals with MND experience coughing during meals, frequent episodes of aspiration, and may require nutritional support via PEG tube” → EXTRACTED → [aspiration; coughing during meals; PEG]). The resulting data were filtered to identify unique keywords, which were then manually grouped into related themes and sub-themes. The resulting themes were reviewed iteratively by both raters for feedback and clarification, until consensus was reached.
Theme headings were used to create a form to count the occurrence of each theme within each article. This step was necessary to calculate the frequency with which each theme occurred across the entire set of included articles, and to control for cases where the same theme was noted more than once in the same article, using slightly different terminology (e.g., [aspiration]+[choking] occurring in the same article would be counted once in the “Aspiration/Penetration” theme). Tabulation was completed by two independent raters, with 20% duplication for interrater comparison. Field codes were used during tabulation to delineate original research findings, either obtained from clinical observations (i.e., clinical findings: [CF]) or instrumental assessment (i.e., instrumental findings: [IF]), for later comparison against themes that were identified as coming from secondary sources (i.e., review: [R]). Following tabulation, proportions were calculated for themes and sub-themes within Excel.
2.5 Results

Following relevance review, a total of 157 full-text articles were included in the qualitative analysis for theme identification and appraisal of research trends.

2.5.1 Interrater Agreement Statistics

Percent agreement was calculated for article inclusion/exclusion decisions during title and abstract screening and for the tabulation of theme occurrence during review. Interrater agreement during initial title and abstract relevance screening was 87%; articles in disagreement were automatically included in detailed full-text review. Overall, substantial agreement was achieved during theme tabulation, calculated using the Kappa statistic (Viera & Garrett, 2005) (summarized in Table 2-2).

Table 2-2

Agreement statistics for theme tabulation. Qualitative agreement based on Kappa statistic (Viera & Garrett, 2005).

<table>
<thead>
<tr>
<th>Theme</th>
<th>% Agree</th>
<th>Kappa</th>
<th>Agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL THEMES (TOTAL)</td>
<td>87.23</td>
<td>0.646</td>
<td>Substantial</td>
</tr>
<tr>
<td>Penetration/Aspiration</td>
<td>89.29</td>
<td>0.512</td>
<td>Moderate</td>
</tr>
<tr>
<td>Oral Phase</td>
<td>89.29</td>
<td>0.781</td>
<td>Substantial</td>
</tr>
<tr>
<td>Pharyngeal Phase</td>
<td>78.57</td>
<td>0.543</td>
<td>Moderate</td>
</tr>
<tr>
<td>Laryngeal/Respiration</td>
<td>78.57</td>
<td>0.475</td>
<td>Moderate</td>
</tr>
<tr>
<td>Esophageal Phase</td>
<td>85.71</td>
<td>0.291</td>
<td>Fair</td>
</tr>
<tr>
<td>Dysphagia Consequences</td>
<td>92.86</td>
<td>0.837</td>
<td>Substantial</td>
</tr>
<tr>
<td>Functional Ability</td>
<td>92.86</td>
<td>0.850</td>
<td>Substantial</td>
</tr>
<tr>
<td>Altered Muscle Tone</td>
<td>82.14</td>
<td>0.620</td>
<td>Substantial</td>
</tr>
</tbody>
</table>

2.5.2 Descriptive Statistics

The majority of articles originated from the United States (32.5%) and United Kingdom (21.7%) (see Table 3). The search yielded a greater number of original, non-review articles (78.3%), than secondary source review articles (21.7%). The most commonly discussed type of MND was ALS (69.4%). See Table 2-3 for a full summary of the included articles, and countries of origin. A list of all included articles can be found in Appendix A.
Table 2-3

Summary of article characteristics, all studies (N=157).

<table>
<thead>
<tr>
<th>Location/Origin</th>
<th>Raw Number</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>51</td>
<td>32.5%</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>34</td>
<td>21.7%</td>
</tr>
<tr>
<td>Italy</td>
<td>15</td>
<td>9.6%</td>
</tr>
<tr>
<td>Japan</td>
<td>14</td>
<td>8.9%</td>
</tr>
<tr>
<td>Australia</td>
<td>7</td>
<td>4.5%</td>
</tr>
<tr>
<td>France</td>
<td>6</td>
<td>3.8%</td>
</tr>
<tr>
<td>Brazil</td>
<td>6</td>
<td>3.8%</td>
</tr>
<tr>
<td>Turkey</td>
<td>5</td>
<td>3.2%</td>
</tr>
<tr>
<td>Canada</td>
<td>4</td>
<td>2.5%</td>
</tr>
<tr>
<td>Germany</td>
<td>3</td>
<td>1.9%</td>
</tr>
<tr>
<td>Korea</td>
<td>2</td>
<td>1.3%</td>
</tr>
<tr>
<td>Spain</td>
<td>2</td>
<td>1.3%</td>
</tr>
<tr>
<td>Poland</td>
<td>2</td>
<td>1.3%</td>
</tr>
<tr>
<td>Portugal</td>
<td>2</td>
<td>1.3%</td>
</tr>
<tr>
<td>Belgium</td>
<td>1</td>
<td>0.6%</td>
</tr>
<tr>
<td>China</td>
<td>1</td>
<td>0.6%</td>
</tr>
<tr>
<td>Netherlands</td>
<td>1</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Article Type</th>
<th>Raw Number</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review</td>
<td>34</td>
<td>21.7%</td>
</tr>
<tr>
<td>Non-Review</td>
<td>123</td>
<td>78.3%</td>
</tr>
<tr>
<td>-Observational</td>
<td>112</td>
<td>71.3%</td>
</tr>
<tr>
<td>-Experimental</td>
<td>8</td>
<td>5.1%</td>
</tr>
<tr>
<td>-Animal</td>
<td>3</td>
<td>1.9%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MND-Type</th>
<th>Raw Number</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALS</td>
<td>111</td>
<td>69.4%</td>
</tr>
<tr>
<td>MND (unspecified/mixed)</td>
<td>39</td>
<td>24.8%</td>
</tr>
<tr>
<td>PBP</td>
<td>4</td>
<td>2.5%</td>
</tr>
<tr>
<td>SOD1 (animal model)</td>
<td>3</td>
<td>1.9%</td>
</tr>
<tr>
<td>PLS</td>
<td>2</td>
<td>1.3%</td>
</tr>
</tbody>
</table>

2.5.3 Themes – Dysphagia Description

Descriptions of dysphagia varied widely across research articles. All primary themes are shown in Figure 2-2, in order of frequency. The following primary themes were identified at least 30% of the articles reviewed (N=157): Aspiration/Penetration (73.2%), Consequences of Dysphagia (66.2%) (e.g., prolonged mealtimes, aspiration pneumonia), Changes in Muscle Tone contributing to dysphagia (58.6%) (e.g., tongue weakness, hyper-/hyporeflexia), Oral Phase
Difficulties (55.4%), Pharyngeal Phase Difficulties (55.4%), measures of Functional Swallowing Ability (36.3%) (e.g., diet tolerance, reduced swallowing capacity), and issues with Secretion Management (35.7%) (e.g., sialorrhea, thick secretions). Other themes that emerged less frequently (i.e., in <30% of all 157 articles) included: Laryngeal/Respiratory Function in relation to dysphagia (27.4%), changes in Sensory Function (12.1%), Esophageal Difficulties (10.2%), and Cortical/Histological findings related to swallowing or dysphagia in individuals with MND (5.7%). Of note, there was significant overlap between themes, as more than one theme was often discussed in the same article.

**Figure 2-2.** Primary themes in dysphagia description in MND, across all articles (N = 157).

### 2.5.4 Swallow Physiology and Function in MND

Sub-themes related to swallowing physiology and function were identified within the Oral and Pharyngeal Phase Impairment themes. The most commonly noted concern within the oral phase was impaired bolus preparation and bolus propulsion, reported in 27.4% (i.e., 43/157) of all included articles. Additional oral phase sub-themes included: Impaired Chewing, Poor Oral
Containment (anteriorly or posteriorly), Oral Residue, Impaired Tongue Movement during the swallow, and Changes in Oral Timing/Coordination. By contrast, Impaired Pharyngeal Timing/Coordination (e.g., delayed swallow onset) was most commonly discussed in reference to Pharyngeal Phase Difficulties, occurring in 29.3% of all included articles (i.e., 46/157). Keywords related to Aspiration/Penetration were grouped independently from specific phases of swallowing, as it was not always clear when a reported event occurred (i.e., before, during, or after the swallow), and the proportion of articles discussing this theme greatly outnumbered all other themes.

2.5.5 Instrumental Assessment

Of all original research articles (i.e., n=123; excluding secondary source review articles), 71 articles (57.7%) used instrumental assessment to support their descriptions of dysphagia, summarized in Table 2-4. The majority of studies used a form of radiographic imaging (39.8%) or endoscopy (14.6%), and although 64.8% of studies (i.e., 46/71) used only one tool, 38.0% (i.e., 27/71) of studies with instrumental assessment methods used two or more tools simultaneously (most commonly, videofluoroscopy + manometry (n=8); videofluoroscopy + endoscopy (n=2); videofluoroscopy + manometry + endoscopy (n=3)). In terms of analysis, observations from instrumental assessment were most often descriptive in nature (e.g., “reduced hyolaryngeal elevation”), rather than reporting quantitative measurements of physiology and function. Instrumental assessment tools were used more frequently in original research articles which specifically reported findings related to Aspiration/Penetration (62.5%; i.e., 35/56), Oral Phase Difficulties (66.0%; i.e., 35/53) or Pharyngeal Phase Difficulties (91.7%; i.e., 44/48).

2.5.6 Safety vs. Efficiency

Figure 2-3 shows a trend in research reporting on swallowing safety and swallowing efficiency. Although a rising trend is seen across both themes over time, a significant discrepancy exists between the proportion of articles reporting Post-Swallow Residue (29.9%) compared to those reporting Aspiration/Penetration (73.2%) (Pearson χ²=6.961, p=0.008).
Table 2-4

Summary of tools and analyses used in studies with instrumental assessment (n=71).

<table>
<thead>
<tr>
<th>Instrumentation Type</th>
<th>Raw Number of Articles</th>
<th>Proportion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiographic</td>
<td>50</td>
<td>70.4%</td>
</tr>
<tr>
<td>Endoscopy</td>
<td>10</td>
<td>25.4%</td>
</tr>
<tr>
<td>Manometry</td>
<td>11</td>
<td>15.5%</td>
</tr>
<tr>
<td>EMG</td>
<td>8</td>
<td>11.3%</td>
</tr>
<tr>
<td>Other</td>
<td>17</td>
<td>21.1%</td>
</tr>
</tbody>
</table>

Simultaneous Tools

<table>
<thead>
<tr>
<th>Instrumentation Type</th>
<th>Raw Number of Articles</th>
<th>Proportion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>One</td>
<td>46</td>
<td>64.8%</td>
</tr>
<tr>
<td>Two</td>
<td>21</td>
<td>28.2%</td>
</tr>
<tr>
<td>Three</td>
<td>4</td>
<td>5.6%</td>
</tr>
<tr>
<td>Four</td>
<td>1</td>
<td>4.2%</td>
</tr>
</tbody>
</table>

Instrumentation Analysis

<table>
<thead>
<tr>
<th>Instrumentation Type</th>
<th>Raw Number of Articles</th>
<th>Proportion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Descriptive</td>
<td>34</td>
<td>47.9%</td>
</tr>
<tr>
<td>Quantitative</td>
<td>15</td>
<td>19.7%</td>
</tr>
<tr>
<td>Combination</td>
<td>17</td>
<td>23.9%</td>
</tr>
<tr>
<td>Not Presented</td>
<td>5</td>
<td>7.0%</td>
</tr>
</tbody>
</table>

Figure 2-3. Trends in reporting swallowing safety versus swallow efficiency.
2.5.7 Management Options

Over 100 unique keywords were identified related to dysphagia management in MND, across 117/157 articles. When grouped thematically, the most commonly discussed management recommendation was *Enteral Nutrition*, occurring in 63.1% of all articles (i.e., 99/157). Remaining management themes included: *Dietary and Texture Modification* (40.8%), *Rehabilitation/Compensatory Strategies* (37.6%), treatment options for *Cricopharyngeal Dysfunction* (14.0%), treatment to aid *Secretion Management* (10.8%), *Surgical Treatment* (excluding cricopharyngeal myotomy) (8.9%), and “Other” options which did not group within a common theme (e.g., pharmaceutical, prosthetic) (7.6%). Across decades, steady rising trends are seen for *Enteral Nutrition*, *Dietary and Texture Modification*, and *Rehabilitation/Compensatory Strategies*, while *Surgical Treatment* and treatments for *Cricopharyngeal Dysfunction* or *Secretion Management* have remained relatively stable (i.e., <10 articles per decade, shown in Figure 2-4). Notably, 48.7% of recommendations (i.e., 57/117) were based on secondary source review (i.e., coded [R]), and 47.0% of recommendations (i.e., 55/117) were based on clinical observation or patient report (i.e., coded [CF]). Only 5 articles reported using instrumental assessment to evaluate a recommended treatment approach (i.e., coded [IF]).

![Themes Related to Dysphagia Management, by Decade](image-url)

*Figure 2-4.* Primary themes in dysphagia management in MND, across all articles (N = 157), by decade.
2.6 Discussion

The aim of this scoping review was to summarize the existing research literature in terms of how dysphagia in MND is described, and how it has been studied to date. Our results point to various strengths and limitations in the existing knowledge base, which can be used to guide future research and provide suggestions to clinicians working with individuals with MND.

Question 1: How does the existing research describe swallowing physiology and dysphagia in MND?

Although there are common physiological characteristics, the individual presentation and clinical impact of dysphagia in MND is highly variable. It is encouraging that the description of dysphagia across existing research is comparably variable and reaches beyond the physiological changes seen in swallowing. While we identified many common themes that describe dysphagia in MND in terms of its clinical presentation (e.g., Aspiration/Penetration, Oral Phase Difficulties, Pharyngeal Phase Difficulties), we also identified descriptors related to the physiological changes contributing to swallowing impairment (e.g., Changes in Muscle Tone), and personal/health-related Consequences of Dysphagia (e.g., reduced quality of life, chest infections, malnutrition). The relationships between swallowing function, disease severity, and secondary health consequences are important to consider when gaining the full clinical picture of ALS and related MNDs. In addition to the physiological health risks associated with dysphagia, swallowing impairments in individuals with ALS are also associated with fatigue and prolonged eating duration, contributing to overall reduced swallow-related quality of life (Tabor, Gaziano, Watts, Robison, Plowman, 2016). Figure 2-5 is a schematic illustration of several possible relationships between swallowing function and related themes, which are extrinsically related to swallowing physiology and function. As we were unable to explore these relationships in detail within the context of this scoping review, future research and systematic review exploring the various relationships between swallowing function and each extrinsic theme these themes will be of great value.
As aforementioned, the research articles included in our thematic analysis include reports on all four MND subtypes, with ALS representing much of our data. When we explored the research reporting themes for classic ALS independently from non-ALS subtypes of MND, or unspecified/aggregated MND data, the descriptive themes did not change significantly. Still, it is important to note that the subtypes are known to differ in terms of disease progression, prognosis and overall impact on functional independence. Further, the clinical presentation and progression of swallowing impairment and dysphagia in MND is heterogeneous – even between subtypes of classic ALS, grouped by onset-type (i.e., bulbar- vs. spinal-onset). Several factors reported to influence or predict the severity and rate of progression of dysphagia in MND (particularly ALS), include: age at disease onset (i.e., older individuals often progress faster, require non-oral feeding sooner) (Atsuta et al., 2009; Luchesi, Kitamua, et al., 2014; Nakamori, 2016), sex (i.e.,
females often present with bulbar symptoms earlier, and possibly greater severity) (Lever et al., 2010; Luchesi, Kitamura, et al., 2014; Strand et al., 1996), and symptom onset (i.e., bulbar-onset ALS and PBP show faster rate of decline, different clinical presentation) (Luchesi, Kitamura, & Mourao, 2014; Nakamori, 2016; Robbins, 1987; Ruoppolo et al., 2013; Strand et al., 1996). Disease duration and the length of time since onset of bulbar symptoms have also been reported as prognostic indicators of function and severity (Higo et al., 2004; Nakamori, 2016).

With respect to non-ALS subtypes of MND, few studies reported only on PBP (n=4) or PLS (n=2), and no studies reported only on swallowing in PMA. To that end, we do not have enough information to provide comprehensive presentations of dysphagia and swallowing physiology, by MND subtype. Still, some common features of dysphagia have been noted for specific subtypes; individuals with PBP (n=5 studies) are reported to have issues with chewing and oral bolus preparation, attributed to orofacial weakness, and may require multiple swallows to clear a single bolus. Further, individuals with PBP may present with a weak cough, bowing of the vocal folds, orofacial pain or changes in sensation, as well as oropharyngeal retention and prolonged esophageal transit (Baker, 1997; Cerero Lapiedra, Moreno Lopez, & Esparza Gomez, 2002; Smith, Sands, Goldberg, Massey, & Gay, 1967; Talacko & Reade, 1990). Common features that have been noted for individuals with PLS (n=3 studies) include: choking, impaired tongue movements, nasal regurgitation, and increased esophageal transit time (Beal & Richardson, 1981; Watanabe et al., 1997).

A recent report by Szacka and colleagues (2016) is the only study we identified which reported independent results for each MND subtype. In this study, results from scintigraphy showed that patients with classic ALS and PBP demonstrated oropharyngeal retention and prolonged esophageal transit, while individuals with PLS and PMA presented only with prolonged esophageal transit (Szacka, 2016). Upon further exploration of UMN versus LMN involvement in the participant sample, the authors were able to infer that LMN damage appeared to have the greatest influence on esophageal transit. Future studies may consider characterizing participant samples in a similar manner, by reporting by subtype and providing estimates of UMN/LMN and spinal/bulbar involvement to explore additional variables related to swallowing function in MND.
Question 2: How is swallowing physiology and function in individuals with MND being measured and reported?

Instrumental assessments provide the most comprehensive evaluation of swallowing physiology through visualization of the swallowing sequence, and/or measurement of swallowing function. Although 91.8% of studies describing Pharyngeal Phase Difficulties based their data on instrumental assessment, reports of Oral Phase Difficulties and Aspiration/Penetration were more likely to be based on clinical signs and patient-reported symptoms; instrumental assessments were cited as the source of these observations 65.5% and 62.1% of the time, respectively. As recent findings have identified that aspiration may be silent in individuals with MND (e.g., Briani et al., 1998; Goeleven et al., 2006; Lo Re et al., 2007; Noh, Park, Park, Moon, & Jung, 2010), this challenges the sensitivity and specificity of clinical observation and patient report, and highlights the importance of conducting instrumental assessment of swallowing with these individuals. In the clinical context, considerations regarding patient goals and priorities, rate of disease progression, and risks associated with repeat radiation exposure (i.e., videofluoroscopy) will help guide the use of instrumental assessment.

Instrumental assessment of swallowing has provided insight regarding the pathophysiology of swallowing in MNDs. Observations from radiographic imaging and endoscopy include delayed swallow onset (Leder et al., 2004; Li et al., 2009; Lo Re et al., 2007; Noh et al., 2010; Paris et al., 2013; Robbins, 1987), the occurrence of penetration/aspiration (Amin et al., 2006; Bevan & Griffiths, 1989; Bosma & Brodie, 1969; Briani et al., 1998; D'Ottaviano et al., 2013; Fattori et al., 2006; Higo et al., 2004; Kawai et al., 2003; Leder et al., 2004; Leighton et al., 1994; Li et al., 2009; Lo Re et al., 2007; Luchesi, Kitamura, et al., 2014; Morimoto et al., 2013; Murono et al., 2015; Noh et al., 2010; Nozaki et al., 2008; Paris et al., 2013; Restivo et al., 2013; Robbins, 1987; Rubin, Griffin, Hogikyan, & Feldman, 2012; Ruoppolo et al., 2013; Scott & Heughan, 1993; Silverstein & Faegenburg, 1965; Solazzo et al., 2011; Takasaki, Umeki, Enatsu, Kumagami, & Takahashi, 2010; Teismann et al., 2011; Watts & Vanryckeghem, 2001; Wright & Jordan, 1997) and post-swallow residue (Bosma & Brodie, 1969; Briani et al., 1998; D'Ottaviano et al., 2013; Higo et al., 2004; Kiuchi, Sasaki, Arai, & Suzuki, 1969; Leder et al., 2004; Lo Re et al., 2007; Morimoto et al., 2013; Murono et al., 2015; Noh et al., 2010; Paris et al., 2013; J. Robbins, 1987; Scott & Heughan, 1993; Silverstein & Faegenburg, 1965; Takasaki et al., 2010; Teismann et al., 2011; Watts & Vanryckeghem, 2001; Wright & Jordan, 1997). Additional
reports from VFSS indicate reduced hyolaryngeal movement (Higo et al., 2004; Li et al., 2009; Murono et al., 2015; Robbins, 1987; Solazzo et al., 2011; Wada et al., 2015) and incomplete laryngeal closure (Lo Re et al., 2007; Solazzo et al., 2011). Still, the majority of studies reporting swallowing physiology/function present observations in descriptive terms, limiting our ability to compare results across studies or measure discrete degrees of change. For example, hyolaryngeal excursion is often reported as “reduced” (e.g., Higo et al., 2004; Solazzo et al., 2011; Teismann et al., 2011), however, when measured in reference to a scalar or anatomical marker, the results are more variable (e.g., Kawai et al., 2003; Plowman, Watts, Tabor et al., 2016). Quantification of swallowing physiology has largely been limited to studies using manometry (e.g., Goeleven et al., 2006; Solazzo et al., 2014; Takasaki et al., 2010) and EMG (e.g., Aydogdu et al., 2011; Ertekin et al., 2000). Manometry studies have yielded measures of reduced pharyngeal pressure during swallowing, and variable cricopharyngeal tonicity (Briani et al., 1998; Goeleven et al., 2006; Higo, Tayama, Watanabe, & Nitou, 2002; MacDougall, Wilson, Pryde, & Grant, 1995; Noh et al., 2010; Omari et al., 2014; Solazzo et al., 2011). Recordings taken from EMG have identified longer swallow durations (Aydogdu et al., 2011; Ertekin et al., 2000; Ertekin et al., 1998), variability in cricopharyngeal pause duration (Ertekin et al., 2000; Ertekin et al., 1998), and discoordination between the timing of laryngeal excursion and cricopharyngeal relaxation (Ertekin et al., 1998). Additional tools used as part of a swallowing assessment, including spirometry/airflow measures, tongue pressure measurement, and sonography, have identified (respectively): irregularities in voluntary cough airflow and respiratory-swallow coordination (Aydogdu et al., 2011; Erdem, 2016; Plowman, Watts, Robison, et al., 2016; Plowman, Watts, Tabor, et al., 2016), reduced swallow pressures and maximum isometric tongue strength (Easterling, Antinoja, Cashin, & Barkhaus, 2013; Kikutani, Tamura, & Nishiwaki, 2006; Morimoto et al., 2013; Umemoto, 2016), and reduced tongue thickness and reduced/disorganized tongue movement during swallowing (Nakamori, 2016; Tamburrini et al., 2010; Umemoto, 2016). Taken together, research to-date has generated a great deal of information regarding the physiological and functional differences of swallowing that may be observed in individuals with MND. An appropriate next-step is to identify relationships between swallowing physiology and function; knowledge regarding these relationships remains limited as few studies have sought to isolate the key physiological mechanisms contributing to functional impairment. Associations have been identified between reduced tongue thickness, tongue strength, and the presence of oral residue; further, predictive associations have been identified between measures of voluntary
cough airflow and risk of aspiration (Plowman, Watts, Robison, et al., 2016). Reasonable relationships have also been postulated between pharyngeal pressure and the accumulation of post-swallow residue (e.g., Goeleven et al., 2006), as well as premature spill of liquids or hyolaryngeal elevation and risk of penetration/aspiration (e.g., Lo Re et al., 2007); however, direct correlations and associated estimates of relative risk have yet to be established. Further exploration of the key physiological mechanisms contributing to functional swallowing impairments will provide outcome measures for clinical trials, serve as markers to identify relative risk of functional impairment, and provide proof of principle for targeted swallowing management options.

Impairments in swallowing safety and efficiency have been recognized in individuals with MND since the 1960s; in fact, three of the four earliest articles included in this review reported radiologically-confirmed impairments in both swallowing safety and efficiency (Bosma & Brodie, 1969; Kiuchi et al., 1969; Silverstein & Faegenburg, 1965). However, over time, research has placed a greater emphasis on swallowing safety than swallowing efficiency: almost three-quarters (73.6%) of research articles identify Aspiration/Penetration as a concern in individuals with MND, while just under a third (30.2%) discuss Post-Swallow Residue; (27.7% discuss both). We hypothesize that this discrepancy is stable across the field of dysphagia, due to known risks associated with aspiration, including aspiration pneumonia. Still, this finding highlights an imbalance in research focus that has the potential to minimize the occurrence and clinical importance of post-swallow residue. In non-MND populations, post-swallow residue has been linked with malnutrition (Carrión et al., 2015; Oliveira et al., 2017; Rofes et al., 2011), which poses an inevitable concern faced by individuals with ALS and related MNDs. Further, some reports from instrumental assessment show that the occurrence of post-swallow residue is more frequent than aspiration (Morimoto et al., 2013; Paris et al., 2013; Silverstein & Faegenburg, 1965; Takasaki et al., 2010; Teismann et al., 2011; Wright & Jordan, 1997) in patients with ALS, and may even present an independent risk factor for later aspiration events (Goeleven et al., 2006; Lo Re et al., 2007; Solazzo et al., 2014). In a recent study by Fattori and colleagues (2016), post-swallow residue was found to be significantly associated with clinical stage of ALS, measured by the Amyotrophic Lateral Sclerosis Functioning Rating Scale (ALSFRS-R) (Cedarbaum et al., 1999), regardless of onset-type. Taken together, these reports
suggest that more research is needed to investigate the factors which lead to the accumulation of post-swallow residue, and the impact it has on individuals with ALS and related MNDs.

Question 3: What recommendations are being made for dysphagia management?

Across the literature, the most common recommendation for dysphagia management in patients with MND is enteral nutrition. As MNDs are progressive with no known cure, enteral nutrition is a key management option to reduce the risk of secondary consequences resulting from dysphagia and maintain optimal health status. Enteral nutrition has been shown improve or maintain to nutritional status (Chio, Finocchiaro, Meineri, Bottacchi, & Schiffer, 1999), weight gain (Desport et al., 2000; Mazzini et al., 1995; Mitsumoto et al., 2003), and prolong survival (Katzberg & Benatar, 2011; Langmore, Kasarskis, Manca, & Olney, 2006) provided that respiratory status is adequate (Chio et al., 2004; Kasarskis et al., 1999). Current recommendations indicate that prophylactic introduction of an enteral nutrition method (e.g., PEG-tube) is preferred, in order to supplement nutrition early and ensure that respiratory capacity is adequate (e.g., FVC>50%) at the time of surgery (Benstead, 2016; Nunes, 2016). Still, enteral feeding does not directly treat the disordered swallow, but rather provides nutritional supplementation in the absence of a safe or efficient swallow. Research on direct management strategies to improve or mitigate swallowing function has been much more limited.

With respect to direct swallowing strategies, a number of techniques have been suggested, including (but not limited to): compensatory maneuvers (e.g., supra-glottic swallow, Mendelsohn maneuver, chin tuck, head turn, head flexion) (Benditt, 2002; Borasio & Miller, 2001; Bosma & Brodie, 1969; Esuro, 2012; Greenwood, 2013; Heffernan et al., 2004; Hillel & Miller, 1989; Houseman, 2008; Johnson et al., 2012; Kuhnlein et al., 2008; Lo Re et al., 2007; Luchesi, Kitamura, & Mourao, 2013; Palovcak, Mancinelli, Elman, & McCluskey, 2007; Solazzo et al., 2011; Solazzo et al., 2014; Spataro, Ficano, Piccoli, & La Bella, 2011; Tamburrini et al., 2010; Watts & Vanryckegehem, 2001; Wijesekera & Leigh, 2009; Wilson, Bruce-Lockhart, & Johnson, 1990); behavioural strategies (e.g., reduced bolus size, taking multiple swallows, avoiding distractions during meals) (Esuro, 2012; Heffernan et al., 2004; Hillel & Miller, 1989; Houseman, 2008; Kuhnlein et al., 2008; Leder et al., 2004; Luchesi et al., 2013; Palovcak et al., 2007; Procaccini & Nemergut, 2008; A. Scott & Heughan, 1993; Watts & Vanryckegehem, 2001; Wilson et al., 1990); sensory tricks (e.g., vibration, thermal stimulation, increase sensory aspects
of bolus) (Escuro, 2012; Hillel & Miller, 1989; Kuhnlein et al., 2008; Palovcak et al., 2007; Scott & Heughan, 1993; Scott & Austin, 1994; Wilson et al., 1990); and dietary modifications (e.g., mechanically altered food, thickened liquids, soft diet, liquidize food) (Benditt, 2002; Borasio & Miller, 2001; Bosma & Brodie, 1969; Corcia & Meiningher, 2008; Elman et al., 2007; Escuro, 2012; Greenwood, 2013; Heffernan et al., 2004; Hillel & Miller, 1989; Houseman, 2008; Jesus et al., 2012; Johnson et al., 2012; Kidney, Alexander, Corr, O'Toole, & Hardiman, 2004; Kosseifi, Abdel Nour, Roy, Byrd, & Alwani, 2010; Kuhnlein et al., 2008; Leder et al., 2004; Lo Re et al., 2007; Luchesi et al., 2013; Nakamori, 2016; Nozaki et al., 2008; Palovcak et al., 2007; Perry, Anderson, Lean, & Cotton, 2002; Procaccini & Nemergut, 2008; Ruoppolo et al., 2013; Scott & Heughan, 1993; Scott & Austin, 1994; Silani, Kasarskis, & Yanagisawa, 1998; Solazzo et al., 2014; Spataro et al., 2011; Stavroulakis et al., 2014; Stavroulakis, Walsh, Shaw, McDermott, & Progas, 2013; Tamburrini et al., 2010; Watts & Vanryckeghem, 2001; Wijesekera & Leigh, 2009; Wilson et al., 1990). Still, almost half (48%) of these recommendations were provided as secondary source review (e.g., Escuro, 2012; Heffernan et al., 2004; Hillel & Miller, 1989; Houseman, 2008; Kuhnlein et al., 2008; Palovcak et al., 2007), which may include general techniques that have not been specifically evaluated for individuals with MND. Of the studies presenting original research findings to support their recommendations, many studies did not describe their efficacy (Dworkin & Hartman, 1979; Jesus et al., 2012; Leder et al., 2004; Luchesi et al., 2013; Scott & Heughan, 1993; Strand et al., 1996), or concluded that swallowing function improved based solely on patient report (Hansen et al., 2014). Only four studies used instrumental assessment to confirm the effectiveness of a prescribed diet texture modification or compensatory strategy to prevent aspiration (Lo Re et al., 2007; Rubin et al., 2012; Solazzo et al., 2011; Watts & Vanryckegehem, 2001). Watts & Vanryckegehem (2001) reported that chin-tuck posture and thickened liquids were effective strategies to prevent aspiration in a single case example. Rubin et al. (2013) presented a case report of a woman with ALS and reported that taking small sips was effective to stop aspiration; however, a head turn was ineffective. Lo Re et al. (2007) evaluated the efficacy of head position (i.e., extension vs. flexion) in a group of ALS patients and reported benefit of anterior head flexion to reduce aspiration/penetration during the swallow. In the most comprehensive study to date, Solazzo et al. (2011) used VFSS used to evaluate the effectiveness of three compensatory postures: chin-tuck, head rotation, and hyperextended head (n=81). Their results suggested that each strategy was effective at eliminating aspiration in very specific contexts; however, not all strategies were effective with all
participants. To that end, the authors advise the use of instrumental assessment to identify appropriate management strategies for individuals with MND.

Recently, more active interventions aimed at improving/maintaining swallowing function in individuals with ALS have been explored, particularly aimed at targeting early stages of the disease. Although active rehabilitation has historically been cautioned for individuals with ALS and related MNDs (e.g., Luchesi et al., 2013; Walshe, 2014), a review by Plowman (2015) concluded that mild forms of exercise may have a positive effect on maintaining motor function in patients with ALS; still, it was advised that more research would be needed to fully understand the role of exercise and its influence on bulbar function. In a recent study by Plowman, Watts, Tabor and colleagues (2016), expiratory muscle strength training led to measurable improvements in maximum expiratory pressure and hyoid displacement, in patients with ALS; however, clinically significant changes in penetration-aspiration severity or measures of voluntary cough were not observed. Tongue strengthening has also been piloted as a potential rehabilitative option, which showed increases in tongue strength and endurance in both included participants (n=2), compared to lead in baseline measures; however, no improvements were seen with respect to swallowing safety (Robison, 2015). Although in preliminary stages, this evolving research is hopeful to expand our understanding of ALS and related MNDs, and identify potential therapeutic targets to maintain swallowing function, for as long as possible.

2.6.1 Unexpected findings

MNDs have classically been considered to selectively impair motor neurons. This has provided a rationale for using sensory tricks in dysphagia management – on the assumption that these strategies exploit unimpaired mechanisms to compensate for impaired motor function (e.g., (Luchesi et al., 2013; Strand et al., 1996). However, we were surprised to find that 7 articles (i.e., 4.5% of all reviewed articles) reported observing silent aspiration (Briani et al., 1998; Goeleven, Robberecht, Sonies, Carbonez, & Dejaeger, 2006; Lo Re et al., 2007; Noh et al., 2010; Ruoppolo et al., 2013; Solazzo et al., 2011; Wright & Jordan, 1997), and an additional subset of articles reported sensory changes such as reduced laryngeal sensitivity, changes in taste, and odynophagia (Amin et al., 2006; Jesus et al., 2012; Luchesi, Kitamura, et al., 2014; Mayberry & Atkinson, 1986; Talacko & Reade, 1990). These observations support a more contemporary view of MND as a multi-system disorder (Isaacs et al., 2007). As sensory impairment at the level of
the larynx has been shown to place stroke patients at greater risk of aspirating thin liquids, irrespective of motor function (Aviv et al., 1997; Setzen et al., 2003), the confirmed presence of sensory dysfunction in MND would have important implications for our understanding of the underlying pathophysiology of dysphagia in this population.

### 2.6.2 Limitations

Several limitations must be taken into account when interpreting our findings. First, only English articles were included in this dataset, excluding research in other languages. Further, the purpose of this study was to gain insight into the profile of existing research on swallowing function in MND, by tabulating the frequency of reported themes. Given this objective, the quality of experimental studies in our database quality was not specifically appraised. Systematic reviews including quality appraisal of research describing swallowing pathophysiology and treatment outcomes will be needed in the future to support conclusions regarding dysphagia and its management in MND.

For the purpose of this review, we opted to include all four MND subtypes, rather than focusing specifically on classic ALS, in order to be inclusive and avoid biasing the data based on regional differences in labelling and reporting of MNDs. Still, this creates a limitation due to known differences in clinical presentation and prognosis between the subtypes. When we explored the proportion of themes between clearly defined classic ALS, against mixed reports (i.e., aggregate MND data) or ambiguous/unspecified MND-type, the results remained stable. Still, the variability between subtypes, as well as variability between cases of bulbar- and spinal-onset ALS, could not be captured in this review. In future research, it may be beneficial to extend beyond a classification of subtype/onset-type, and include estimates of the degree to which bulbar/spinal pathways and UMN/LMNs are affected within the participant sample; this level of detail would allow us to delineate how swallowing physiology and related issues are affected by the idiosyncrasies of each subtype, and between bulbar- and spinal-onsets of ALS.

We also acknowledge that while we aimed to keep this review relatively broad in order to capture overall themes and trends of existing research, we kept a narrow-focus on swallowing physiology and function in our definition of “dysphagia.” It is important to note that there are many related areas of study that significantly interact with swallowing, such as nutrition and respiratory status, that were not explored in exhaustive detail. This constraint has the potential to
present a limited perspective on the overall clinical management of ALS and related MNDs, for which a multi-disciplinary approach has been well-supported (e.g., Corcia & Meininger, 2008; Rodriguez de Rivera et al., 2011). More specifically, the occurrence and management recommendations targeting aspiration pneumonia were not extracted in our literature search, omitting a discussion regarding functional airway clearance, and the roles of assisted-cough strategies, manual insufflation/exsufflation, and non-invasive positive pressure ventilation (for examples, see Sancho et al. (2004, 2007); Miller et al. (2009); Britton et al. (2014)). These closely-related areas of study reach beyond the scope of this review, highlighting the need for future study and systematic review of these very important clinical issues.

2.6.3 Clinical & Research Implications

Our findings highlight the breadth and variability of studies describing dysphagia in MNDs, capturing the complexity of the problem, while identifying existing imbalances in research focus. Such imbalances are important to consider, as they may leave researchers and clinicians with disproportionate concerns and create the potential to overlook important details. Given the breadth found in research descriptions of dysphagia in MND, it is important that clinicians and researchers working with this population approach patients without assumptions and conduct comprehensive oral motor and swallowing examinations to determine how the individual is affected and identify mechanisms contributing to swallowing impairment. To that end, it is equally important that management practices are chosen to target specific observed impairments, and that efficacy is tested using instrumental evaluation. Future research should continue to investigate the pathophysiology of impairments in swallowing safety and efficiency in MND, in addition to considering the factors that influence secondary consequences including changes in participation and quality of life.
Retrospective Analysis of Swallowing Kinematics in ALS, using Quantitative Methods

3.1 Preface

The scoping review in Chapter 1 highlighted several knowledge gaps within the existing literature, including a dominant focus on swallowing safety (i.e., penetration/aspiration) and a reliance on clinical observations and subjective descriptions of dysphagia in ALS/MND. Few studies have used objective measures to quantify ALS-related changes in swallowing physiology, making it difficult to compare results across research studies and to determine at what point physiological changes contribute to or predict functional impairments in swallowing safety and efficiency. Further, it is currently unknown whether existing measures used in quantitative videofluoroscopic analysis are able to detect statistically and clinically significant differences between individuals with ALS and healthy reference values.

For Study 2, we sought to explore the validity of existing metrics used in videofluoroscopic measurement for evaluating swallowing physiology in ALS. To do this, we conducted a retrospective quantitative analysis of videofluoroscopic swallow studies from 26 patients with ALS, focusing on two physiological parameters features commonly reported as aberrant in the literature on ALS: pharyngeal constriction and hyoid kinematics. We aimed to determine whether available measures used to quantify these parameters could detect differences between ALS swallows and existing healthy reference data, and whether any differences were associated with available metrics of disease progression.

With kind permission from John Wiley & Sons Ltd, Part 1 exploring maximum pharyngeal constriction in ALS was cited in full from the following journal article:


The full article can be found on the publisher’s website at: https://doi.org/10.1111/nmo.13450. All tables and references have been re-formatted to APA style and linked to the end of the dissertation.
Part 2 exploring hyoid kinematics was reviewed and accepted for poster presentation at the 26th Annual Dysphagia Research Society Meeting, held in Baltimore, Maryland (March 14-17, 2018). A copy of the research poster can be found in Appendix B.
3.2 Part 1: Reduced Pharyngeal Constriction is Associated with Impaired Swallowing Efficiency in Amyotrophic Lateral Sclerosis (ALS)

3.2.1 Abstract

**Background:** Swallowing inefficiency is a prevalent but understudied problem in individuals with Amyotrophic Lateral Sclerosis (ALS). Although reduced pharyngeal constriction has been identified as a mechanism contributing to swallowing inefficiency following stroke, this relationship has not been empirically tested in the ALS population. This study sought to characterize profiles of swallowing efficiency in a sample of ALS patients and investigate relationships between pharyngeal constriction and swallowing efficiency.

**Methods:** Twenty-six adults with ALS underwent videofluoroscopic swallowing studies, involving 3mL-thin, 20mL-thin, and 3mL-pudding boluses. Full-length recordings were segmented into bolus clips and randomized for analysis. We recorded the total number of swallows per bolus and obtained normalized pixel-based measures of pharyngeal constriction area and post-swallow residue in the vallecular and pyriform sinuses. Linear mixed models with Spearman’s correlations were used to determine relationships between pharyngeal constriction and swallowing efficiency, with added factors of bolus volume and thickness.

**Key Results:** Individuals with ALS demonstrated reduced pharyngeal constriction and increased vallecular and pyriform sinus residue, compared to norms. Reduced pharyngeal constriction had a significant effect on the presence of vallecular and pyriform sinus residue, as well as the number of swallows per bolus. Increased bolus thickness was associated with increased vallecular residue, while increased bolus volume was associated with reduced pharyngeal constriction. Results were significant at p<0.05.

**Conclusions & Inferences:** Our results suggest that reduced pharyngeal constriction is a significant physiological parameter related to swallow inefficiency in ALS. Future work is needed to corroborate these preliminary results and investigate factors to mitigate such impairments.
3.2.2 Background

Dysphagia, or swallowing impairment, is a serious consequence of bulbar disease in Amyotrophic Lateral Sclerosis (ALS) and manifests with functional impairments in both swallowing safety and efficiency (Ruoppolo et al., 2013; Tabor & Plowman, 2017; Waito, Valenzano, Peladeau-Pigeon, & Steele, 2017). Swallowing inefficiency (i.e., the presence of post-swallow pharyngeal residue and/or the need to take multiple swallows per bolus) is particularly challenging for individuals with ALS, leading to prolonged mealtimes, mealtime fatigue, and reduced quality of life (Paris et al., 2013; Tabor et al., 2016). Still, it remains unclear which physiological mechanisms contribute to impaired swallowing efficiency in this complex patient population. Further, in individuals with ALS, post-swallow pharyngeal residue has been identified as an independent risk for subsequent aspiration events (Goeleven et al., 2006; Lo Re et al., 2007; Solazzo et al., 2011) and is linked to the development of malnutrition (Carrión et al., 2015; Oliveira et al., 2017; Rofes et al., 2011) that is noted to increase the risk of death by 7.7 times (Desport et al., 1999). Despite these concerns, the majority of ALS dysphagia research has focused on studying swallowing safety with only 29.9% of published literature on dysphagia in ALS addressing problems with swallowing efficiency (Waito et al., 2017). In order to identify treatments with the potential to improve swallowing efficiency, it is first important to identify the pathophysiological mechanisms behind inefficiency.

Potential mechanisms of impaired swallowing efficiency in ALS can be posited based on findings from manometry data in ALS that document decreased pharyngeal pressures, reduced base of tongue contact to the posterior pharyngeal wall, and overall reduced pharyngeal motility during swallowing (Goeleven et al., 2006; Higo et al., 2004; Higo et al., 2002; Kawai et al., 2003; Murono et al., 2015; Solazzo et al., 2014). Higo et al. (2002) explored pharyngeal pressure generation profiles in patients with ALS, grouping patients by disease duration and onset type (i.e., bulbar vs. spinal/“classic”). The authors identified differences in pharyngeal pressure generation during swallowing for patients with a bulbar-onset, within 6 months following the onset of symptoms. Similarly, Tomik et al. identified reduced base of tongue pressure and prolonged bolus transit times in patients with bulbar ALS (Desport et al., 1999). Using combined manometry and videofluoroscopy, Goeleven and colleagues (2006) reported converging evidence of low tongue driving force and reduced pharyngeal contraction amplitudes during swallowing, and noted co-occurrence of these impairments and the presence of post-swallow
pharyngeal residue. Therefore, physiological impairments in pharyngeal pressure generation have been postulated as mechanisms contributing to swallow inefficiency, thus leading to post-swallow residue in patients with ALS.

Reduced pharyngeal strength and constriction have been implicated as factors contributing to the presence of pharyngeal residue in other clinical populations of individuals with dysphagia (Dejaeger et al., 1997; Kahrilas et al., 1992; Kendall & Leonard, 2001; Palmer, Tanaka, & Siebens, 1988; Swinnen & Robberecht, 2014). Research quantifying pharyngeal area during swallowing, using 2-dimensional (2-D) lateral videofluoroscopy in individuals with dysphagia following stroke, identified associations between larger (i.e., less constricted) measures of pharyngeal area at the point of maximum constriction and the amount of post-swallow residue (Stokely, Peladeau-Pigeon, Leigh, Molfenter, & Steele, 2015). Despite the inherent limitations of using a 2-D measurement to make inferences about 3-dimensional (3-D) anatomical regions, the validity of this analysis method is supported by previous work. Strong correlations have been identified between fluoroscopic measurement of pharyngeal constriction area and concurrent manometric readings of pharyngeal swallowing pressures (Leonard, Belafsky, & Rees, 2006; Leonard, Rees, Belafsky, & Allen, 2011). Further, 2-D measures of pharyngeal residue area on lateral videofluoroscopic images have been shown to have a high correlation with 3-D measures of pharyngeal residue volume on computed tomography (Langmore & Lehman, 1994). On this basis, it is likely that a similar relationship can be expected between lateral measures of pharyngeal area and actual pharyngeal volume.

3.2.3 Aims and Hypotheses

The objectives of the current study were twofold. First, we sought to quantify and characterize various metrics of swallowing efficiency and pharyngeal constriction profiles in a sample of individuals with ALS and explore whether bolus properties (i.e., volume, thickness) modulated measures of pharyngeal constriction and/or swallow efficiency. Second, we aimed to determine whether impaired pharyngeal constriction (i.e., larger unobliterated pharyngeal area during swallowing) is associated with impaired swallowing efficiency in ALS. Based on existing manofluorographic and manometric studies with patients who have ALS, we hypothesized that measures of pharyngeal area during swallowing would show larger unobliterated pharyngeal area at maximum constriction (i.e., less constriction) compared to healthy normative data, correlating
with disease severity and presence of bulbar symptoms. Further, we hypothesized that larger or thicker boluses may evoke larger pharyngeal constriction areas (i.e., reflecting less constriction) compared to smaller/thinner boluses (Leonard, Kendall, McKenzie, Gonçalves, & Walker, 2000), due to increased bolus weight and/or an inability for the swallowing mechanism to adapt to such bolus properties.

In terms of residue, we hypothesized that larger and thicker boluses would be associated with increased post-swallow residue and number of swallows required to clear the bolus (Barata, De Carvalho, Carrara-De Angelis, De Faria, & Kowalski, 2013; Hind et al., 2012) and finally, that the amount of post-swallow residue and the number of swallows needed per bolus would be greater (i.e., less efficient) for individuals with larger pharyngeal constriction area (i.e., less constricted) (Steele et al., 2018a; Stokely et al., 2015).

3.2.4 Methods

3.2.4.1 Data Collection and Processing

This study involved retrospective analysis of videofluoroscopic swallow studies (VFSS) collected from 26 adults (14 male) with a confirmed diagnosis of ALS (definite or probable), based on revised El-Escorial criteria. Eight participants in this analysis presented with bulbar-onset ALS, 17 with spinal-onset ALS, and 1 had a mixed-onset ALS profile. The mean age of participants was 63 years (range: 30-75 years), and average symptom duration was 24 months (range: 1-54 months). ALS Functional Rating Scale-Revised (ALSFRS-R) scores were available for a subset of the sample (n=21), with a mean ALSFRS-R total score of 32.7 (range: 16-45) and a mean ALSFRS-R bulbar sub-score of 8.8 (range: 2-12).

Each participant swallowed pre-measured volumes of thin liquid (3mL, 20mL), and pudding-thick liquid (3mL), using 40% weight-to-volume concentration barium preparations (VARIBAR® barium sulfate, Bracco Diagnostics Inc., Monroe Township, NJ). VFSS were recorded on a KayPENTAX Digital Swallowing Workstation at 30 frames per second. Using MatLab (The MathWorks, Inc., Natick, MA), the full-length recordings were segmented into bolus-level clips, stripped of audio and patient identifiers using screen scrubbers, and randomized for blinded rating. All collected and analyzed data were approved by the governing academic institutional review boards.
3.2.4.2 Videofluoroscopic Rating

Four speech-language pathologists experienced in videofluoroscopic analysis completed blinded ratings of each bolus-level clip using ImageJ software (National Institutes of Health, Bethesda, MD), following a standard protocol. This protocol follows a two-step process: 1) identification of events (frames) and the total number of swallows, and 2) pixel-based tracing of pharyngeal area and residue.

Identification of Events

Frame-by-frame review of each bolus trial was conducted to count the total number of swallows per bolus and select frames utilized to measure pharyngeal constriction (i.e., Maximum Pharyngeal Constriction Frame, defined as the frame showing the least amount of bolus flow and/or airspace in the pharynx) and post-swallow residue (i.e., Swallow Rest Frame, defined as the frame when the pyriform sinuses are at their lowest position after the swallow, relative to the cervical spine). To obtain estimates of inter-rater reliability for Maximum Pharyngeal Constriction Frame identification, 30% of clips (n=21) in this analysis were rated in duplicate. For Swallow Rest Frame identification, we calculated inter-rater reliability based on a larger set of videos rated in duplicate (n=76 bolus clips; 197 swallows in total), which included 19 videos from the current analysis (i.e., 27% of the dataset). Any differences in frame selection which exceeded >5 frames were reviewed and resolved through consensus with a third rater. For cases where the difference between two raters was ≤5 frames, the later frame between the two was selected as the final tracing frame. Once agreement was achieved on frame selection, pixel-based measures of pharyngeal constriction area and post-swallow residue were taken.

Pixel-Based Tracing

Pharyngeal area was traced (in pixels) at the previously identified Maximum Pharyngeal Constriction Frame, following the procedure outlined by Stokely et al.(Stokely et al., 2015) The total number of pixels measured from the unobliterated pharyngeal space was divided by the squared length of an anatomical scalar (i.e., cervical spine: C2-4) (Molfenter & Steele, 2014b) and multiplied by a factor of 100 to yield a normalized measure of pharyngeal constriction area (MPCA_N) in %C2-4 units. The Normalized Residue Ratio Scale (Pearson, Molfenter, Smith, & Steele, 2013) (NRRS) was used to quantify the amount of residue remaining in the valleculae (NRRSv) and pyriform sinuses (NRRSp) at Swallow Rest Frame. Duplicate ratings were
completed for 30% of MPCA\textsubscript{N}, and NRRS\textsubscript{v} and NRRS\textsubscript{p} to calculate inter-rater reliability. Example pixel tracings are shown in Figure 3-1.

![Figure 3-1](image)

*Figure 3-1.* Example pixel-based measures of pharyngeal constriction (left) and post-swallow residue (right), with cervical C2-C4 scalar.

For each bolus trial, we recorded the total number of swallows as well as MPCA\textsubscript{N}, NRRS\textsubscript{v} and NRRS\textsubscript{p} following the first swallow. All ratings were completed for 3mL thin, 20mL thin, and 3mL pudding bolus trials, yielding up to 78 bolus trials. However, \(n=7\) bolus trials were not available or excluded for the following tasks: 1mL thin (\(n=1\)), 20mL thin (\(n=5\)), 3mL pudding (\(n=1\)), adjusting the total \(n=71\) bolus trials for analysis.

### 3.2.4.3 Statistical Analysis

To characterize pharyngeal constriction and swallow efficiency in this sample, we calculated the group mean and 95% confidence intervals (CI) for MPCA\textsubscript{N}, NRRS\textsubscript{v} and NRRS\textsubscript{p}, and average number of swallows for each bolus task. NRRS\textsubscript{v} and NRRS\textsubscript{p} scores were compared against published thresholds (Molfenter & Steele, 2013) to calculate the proportion of the sample with clinically significant residue. MPCA\textsubscript{N} values obtained for the 3mL thin task were compared against normative reference data (based on a 5mL thin liquid barium task) (Stokely et al., 2015) using independent samples \(t\)-tests. Spearman’s correlations were used to illustrate associations between metrics of disease severity (i.e., months since initial symptom, ALSFRS-R total and bulbar sub-scores) and average MPCA\textsubscript{N} NRRS\textsubscript{v} and NRRS\textsubscript{p} values.
To explore associations between pharyngeal area and the total number of swallows per bolus, we tested mean differences in $\text{MPCA}_N$ using Mann-Whitney $U$ tests for each bolus type, comparing trials with only 1-2 swallows to trials with 3 or more swallows. To investigate relationships between pharyngeal constriction and post-swell swallow residue, we ran linear mixed models between $\text{MPCA}_N$ and pharyngeal residue at each anatomical site (NRRSv, NRRSp), with an added factor of bolus type (i.e., 3mL thin, 20mL thin, 3mL pudding). The direction and magnitude of significant associations were illustrated using Spearman’s correlations. All statistical analyses were completed using IBM SPSS Statistics version 24, with statistical significance set at $p<0.05$. A Bonferroni correction was applied for repeated (3) Mann-Whitney $U$ tests (i.e., $p<0.05/3=0.016$).

3.2.5 Results

3.2.5.1 Inter-rater reliability

For frame selection, we calculated the proportion of videos rated in duplicate which exceeded the a priori agreement threshold (>5 frames). For the frame of maximum pharyngeal constriction, all ratings fell within the 5-frame threshold; therefore, none of the videos required secondary review through consensus for Maximum Pharyngeal Constriction Frame selection. For Swallow Rest Frame, 27% of all $n=197$ swallows rated in duplicate exceeded the a priori agreement threshold, requiring resolution through consensus.

Inter-rater reliability for pixel-based measures was evaluated using Intraclass Correlation Coefficients (two-way fixed, consistency). The ICCs for pixel-based videofluoroscopy measures were good-to-excellent for $\text{MPCA}_N$ (0.843, 95%CI: 0.613-0.936), NRRSv (0.914, 95%CI: 0.801-0.963) and NRRSp (0.928, 95%CI: 0.832-0.929).

3.2.5.2 Swallowing Efficiency and Pharyngeal Constriction Profiles

Descriptive statistics for all obtained measures are summarized in Table 3-1. Fifteen participants (i.e., 58% of the sample) presented with significant vallecular residue (NRRSv >0.09) and 35% displayed significant pyriform sinus residue (NRRSp >0.2) on at least one bolus trial. A previous report characterizing pharyngeal residue using NRRS measures identified these cut-off levels (i.e., NRRSv>0.09 and NRRSp>0.2) as being clinically meaningful, due to an increased risk of
aspiration on subsequent swallows (Molfenter & Steele, 2013). The median number of swallows per bolus was 2 (range: 1-6).

Table 3-1

Mean and 95% confidence intervals (CI) for measures of pharyngeal constriction and swallowing efficiency.

<table>
<thead>
<tr>
<th></th>
<th>3mL thin</th>
<th></th>
<th>20mL thin</th>
<th></th>
<th>3mL pudding</th>
<th></th>
<th>ALL</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>95%CI</td>
<td>Mean</td>
<td>95%CI</td>
<td>Mean</td>
<td>95%CI</td>
<td>Mean</td>
<td>95%CI</td>
</tr>
<tr>
<td>MPCA_N</td>
<td>8.78</td>
<td>5.22-12.34</td>
<td>13.36*</td>
<td>7.79-18.94</td>
<td>7.95</td>
<td>3.77-12.12</td>
<td>9.81</td>
<td>7.36-12.26</td>
</tr>
<tr>
<td>NRRS_v</td>
<td>0.16</td>
<td>0.07-0.25</td>
<td>0.34</td>
<td>0.13-0.66</td>
<td>0.29*</td>
<td>0.11-0.48</td>
<td>0.25</td>
<td>0.15-0.35</td>
</tr>
<tr>
<td>NRRS_p</td>
<td>0.16</td>
<td>0.03-0.30</td>
<td>0.28</td>
<td>0.00-0.57</td>
<td>0.12</td>
<td>0.01-0.23</td>
<td>0.17</td>
<td>0.08-0.26</td>
</tr>
<tr>
<td># of swallows</td>
<td>1.88</td>
<td>1.52-2.24</td>
<td>2.86</td>
<td>2.11-3.61</td>
<td>1.92</td>
<td>1.48-2.36</td>
<td>2.18</td>
<td>1.88-2.49</td>
</tr>
</tbody>
</table>

MPCA_N = Maximum Pharyngeal Constriction Area (normalized to squared length of C2-4), displayed in %C2-4² units; NRRS_v = Normalized Residue Ratio Scale (Vallecular Space); NRRS_p = Normalized Residue Ratio Scale (Pyriform Sinuses).

*Pairwise comparisons revealed statistically significant difference (p<0.05), compared to 3mL thin task.

When we compared MPCA_N for the 3mL thin task against normative reference data (5mL thin) (Stokely et al., 2015), we identified significantly larger pharyngeal area (i.e., less constriction) in patients with ALS, with a large effect size (t=4.03, p<0.001, Cohen’s d=1.141). When stratified by bulbar- versus spinal-onset cases, we identified that individuals with spinal-onset showed smaller pharyngeal constriction areas (i.e., greater constriction) compared to bulbar cases, however this was not statistically significant (p=0.054). MPCA_N in spinal-onset cases remained above the upper 95% CI obtained from normative data (i.e., >2.2% C2-4²) (Stokely et al., 2015). Group comparisons of MPCA_N are illustrated in Figure 2.

Spearman’s correlations revealed statistically significant relationships between lower (worse) ALSFRS-R bulbar subscores and higher (less constricted) mean MPCA_N (r_s= -0.766, p<0.001), NRRS_v (r_s= -0.650, p=0.001), NRRS_p (r_s= -0.513, p=0.017) and number of swallows (r_s= -0.526, p=0.014). No significant relationships were identified with respect to symptom duration or with ALSFRS-R total score. Linear mixed models exploring bolus factors (volume, thickness) on pharyngeal constriction and residue revealed a main effect of bolus volume on MPCA_N
(F=10.729, df=1,18.505, p=0.004) and a main effect of thickness on NRRSv (F=4.304, df=1,22.387, p=0.05). Pairwise comparisons illustrated larger pharyngeal constriction area (i.e., less constriction) with the larger 20mL thin liquid task, and greater vallecular residue with the pudding-thick bolus.

Figure 3-2. 95% confidence intervals comparing normalized pharyngeal constriction area in a) patients with ALS (3mL thin) vs. healthy normative reference data (5mL thin), and b) spinal- vs. bulbar-onset ALS cases (3mL thin only).
3.2.5.3 Exploration of Relationship between Pharyngeal Constriction and Swallow Efficiency

Results of the Mann-Whitney $U$ tests revealed that 3mL thin bolus trials with fewer than 3 swallows per bolus had smaller MPCA$_N$ values (mean rank = 8.75) than trials with 3 or more swallows (mean rank = 20.00), shown in Figure 3; this difference was statistically significant ($U=4.00, z=-3.674, p<0.001$). A similar result was found for the 20mL thin task (mean rank $<3$ swallows = 7.22; mean rank $\geq 3$ swallows = 12.50); however, once we applied a Bonferroni correction for running multiple tests, this difference did not reach statistical significance ($U=20.00, z=-2.041, p=0.041$). The relationship between MPCA$_N$ and number of swallows was not statistically significant for the 3mL pudding task ($U=27.00, z=-1.342, p=0.180$).

Figure 3. Box-and-whisker plots showing increased pharyngeal area at maximum constriction and increased number of swallows per bolus (i.e., $\geq 3$ swallows for a single bolus), for 3mL thin task.

Linear mixed models exploring the influence of pharyngeal constriction on vallecular residue, with a repeated factor of bolus type, revealed main effects of MPCA$_N$ ($F=92.600, df=1,29.594, p<0.001$) and task ($F=4.340, df=2,31.881, p=0.022$). Increased vallecular residue was seen with
larger pharyngeal constriction areas (i.e., less constriction) and with 3mL pudding compared to 3mL and 20mL thin tasks. Similarly, in terms of pyriform sinus residue, a main effect of MPCA\textsubscript{N} was identified on NRRSp ($F=66.878$, $df=1,33.085$, $p<0.001$), showing increased residue with larger (worse) pharyngeal constriction areas. Significant interaction effects between MPCA\textsubscript{N} and bolus type were identified for both NRRS\textsubscript{v} ($F=12.669$, $df=2,32.499$, $p<0.001$) and NRRSp ($F=6.139$, $df=2,31.664$, $p=0.006$), reflecting differences in the magnitude of the association between pharyngeal constriction and residue, related to bolus type (i.e., 3mL thin, 20mL thin, 3mL pudding). Therefore, we ran post-hoc Spearman’s rank correlations stratified by bolus task.

Spearman’s correlations revealed moderate-to-strong associations between MPCA\textsubscript{N} and NRRS\textsubscript{v}, by task (3mL thin: $r_s=0.821$, $p<0.001$; 20mL thin: $r_s=0.921$, $p<0.001$; 3mL pudding: $r_s=0.631$, $p=0.001$). Similar associations were observed between MPCA\textsubscript{N} and NRRSp (3mL thin: $r_s=0.773$, $p<0.001$; 20mL thin: $r_s=0.852$, $p<0.001$; 3mL pudding: $r_s=0.552$, $p=0.006$). These associations are illustrated in Figure 3-4.

![Figure 3-4](image)

*Figure 3-4.* Associations between normalized pharyngeal constriction area and a) vallecular residue (NRRS\textsubscript{v}), and b) pyriform sinus residue (NRRSp).

### 3.2.6 Discussion

Swallowing inefficiency is often the first clinical sign and patient report of dysphagia in individuals with ALS (Murono et al., 2015). Still, our understanding of the mechanisms contributing to swallow inefficiency is limited given the lack of focus in this area (Waito et al., 2017). Extending from previous reports of poor pharyngeal constriction contributing to post-
swallow residue in post-stroke patients (Stokely et al., 2015), our study aimed to profile pharyngeal constriction during swallowing in patients with ALS and explore relationships between maximum pharyngeal constriction, disease metrics and bolus flow. Our results demonstrate that measures of pharyngeal constriction area in patients with ALS are markedly larger (i.e., reduced constriction) compared to published data from healthy adults (Stokely et al., 2015). These data support previous descriptions of swallowing inefficiency from videofluoroscopy (Murono et al., 2015), as well as studies using manometry that have demonstrated reduced pharyngeal swallowing pressures in individuals with ALS (Goeleven et al., 2006; Higo et al., 2002; Kawai et al., 2003; Solazzo et al., 2014; Tomik et al., 2017). Our data suggest that the degree to which pharyngeal constriction is reduced is more pronounced in bulbar-onset ALS patients compared to spinal-onset, and is associated with ALSFRS-R bulbar sub-scores. Although not as severe as bulbar onset ALS patients, we also identified reduced pharyngeal constriction in individuals with spinal-onset ALS. This later finding is in agreement with reports by Murono et al. who identified reductions in pharyngeal constriction in patients with ALS irrespective of the overt presence of other bulbar signs or symptomology (Murono et al., 2015). Interestingly, a study by Higo et al. (2004) failed to find differences in pharyngeal pressures during swallowing between spinal (“classic”) onset patients and healthy controls. These differences may reflect the inherent heterogeneity of ALS, differences in study samples and disease duration in spinal onset cases, and methodologic differences in instrumental assessment technique and outcome metrics (i.e., measuring pharyngeal pressure via manometry versus constriction via videofluoroscopy).

In this cohort of ALS patients, 58% of swallows demonstrated inefficiency post-swallow at the vallecular anatomical site compared to inefficiency in the pyriform sinus anatomical site on 35% of swallows. Interestingly, upon further inspection of the data, all (100%) of trials with pyriform sinus residue also demonstrated residue in the vallecular anatomical site with no swallows demonstrating residue only at the pyriform sinus site. This finding aligns with a proposed hypothesis of a rostrocaudal pattern of ALS bulbar disease progression, wherein oral and oropharyngeal impairments precede hypopharyngeal impairments (Plowman, Tabor, et al., 2016). Atypical tongue function is commonly reported as the earliest clinical sign of bulbar involvement, (e.g., Langmore & Lehman, 1994; Shellikeri et al., 2016) and instrumental assessments of the pharyngeal stage of swallowing have identified differential impairments
between the oro- and hypopharyngeal regions (Goeleven et al., 2006; Higo et al., 2004; Higo et al., 2002). Still, many of these findings – including those from the current study – are based on cross-sectional studies with small samples and require confirmation by future prospective longitudinal studies to determine the evolution and development of swallowing impairment throughout the ALS disease progression.

Our results illustrate a strong relationship between pharyngeal constriction area and the accumulation of post-swallow residue, such that larger unobliterated pharyngeal areas during the swallow coincide with greater post-swallow residue. This finding was true for both vallecular and pyriform sinus residue, across all bolus types. The pudding-thick bolus also led to greater post-swallow residue in the vallecular space. Thicker boluses have been implicated as a potential risk factor for post-swallow residue, as they require greater driving force through the pharynx (Barata et al., 2013; Hind et al., 2012; Steele et al., 2014; Turner et al., 2013). Still, as thicker liquids flow more slowly and are shown to reduce aspiration in many populations, (e.g., Barata et al., 2013; Bingjie, Tong, Xinting, Jianmin, & Guijun, 2010; Rofes, Arreola, Mukherjee, Swanson, & Clave, 2014; Troche, Sapienza, & Rosenbek, 2008) the prescription of thickened liquids to individuals with ALS who aspirate may still be clinically justified. More work exploring additional liquid viscosities and textural features (e.g., cohesiveness, stickiness) is necessary to determine which bolus types are optimal for patients with ALS who have impaired bolus clearance, in terms of both safety and efficiency.

In this study of individuals with ALS, we identified an inverse relationship between bolus volume on measures of pharyngeal constriction area (i.e., less constriction with 20mL thin, compared to 3mL thin boluses), while no differences in MPCAN were observed when comparing 3mL thin and 3mL pudding-thick boluses. Although Leonard et al. (2000) identified a similar effect of bolus volume on pharyngeal constriction area in healthy individuals, this was only true when comparing 1mL vs. 20mL thin boluses (i.e., 3mL vs. 20mL were not statistically different). It is possible that the influence of bolus volume on pharyngeal constriction area in ALS may be exacerbated by reduced strength/control of the pharyngeal musculature due to ALS neuropathology (e.g., atrophy/wasting from lower motor neuron degeneration; spasticity related to upper motor neuron degeneration) such that the motor plan and/or pharyngeal muscles are unable to accommodate to larger bolus volumes. Current understanding of the role of bolus volume and thickness on pharyngeal constriction and pharyngeal pressures in healthy
swallowing is inconsistent, as some studies identify higher pharyngeal pressures with increasingly larger or thicker boluses, (e.g., (Butler et al., 2009; Omari, Dejaeger, Tack, Van Beckevoort, & Rommel, 2013; Poudreux & Kahrilas, 1995) while other studies show the opposite effect (Leonard et al., 2000; Shiba, Nakazawa, Ono, & Umezaki, 2007) or no differences based on bolus properties (e.g., Gumbley, Huckabee, Doeltgen, Witte, & Moran, 2008; Kahrilas et al., 1992; Lin et al., 2014; Perlman, Schultz, & VanDaele, 1993). Although further research is needed to elucidate these physiological patterns, the presence of unexpected variability and/or the absence of known bolus effects in the ALS population may indicate loss of flexibility in swallowing function, which is imperative to accommodate to the range of stimuli we encounter when eating and drinking.

3.2.6.1 Limitations

There are several limitations to this study. First, it is possible that the degrees of association we have illustrated are inflated due to small sample size and a limited range of disease severity. Future studies with larger sample size and/or additional observations per participant are needed to fully explore these correlations. Further, for the purpose of this preliminary study, we stratified by ALS onset-type when exploring differences in pharyngeal constriction. This poses an important limitation, as many patients with spinal-onset ALS also experience a decline in bulbar function (Green et al., 2013; Higo et al., 2004); this was true to a varying degree for at least 11/17 of the spinal-onset patients included in this study, based on available ALSFRS-R bulbar sub-scores. Unfortunately, due to the retrospective nature of this analysis, further details describing the bulbar involvement in this sample are limited. In an effort to normalize the degree of bulbar involvement across both onset-types, future work investigating swallowing physiology in ALS may consider using the duration of bulbar symptoms (Higo et al., 2004) or articulatory/speaking rates (Green et al., 2013) to characterize the study sample in greater detail.

Previous work has described piecemeal swallowing as a common behaviour in patients with ALS (e.g., Ertekin et al., 2000; Goeleven et al., 2006; Kawai et al., 2003; Tabor & Plowman, 2017). Ertekin and colleagues, and others, have reported on the clinical utility of repeated swallows to detect the presence of dysphagia (e.g., dysphagia limit: the volume of liquid <20mL which evokes repeated swallows) (Aydogdu et al., 2015; Aydogdu et al., 2011; Ertekin et al., 2000; Ertekin et al., 1998). In the current study, we frequently observed repeated swallows per bolus,
even for small 1mL and 3mL volumes. In 55% of all bolus trials, repeated swallows were piecemeal swallows (i.e., the bolus was divided into smaller volumes in the oral cavity, and each division was swallowed separately). As our results indicated an influence of bolus volume on measures of pharyngeal area and bolus volume effects have also been reported on other kinematic variables (e.g., hyolaryngeal movement), published elsewhere, (e.g., Lazarus et al., 1993; Nagy, Molfenter, Peladeau-Pigeon, Stokely, & Steele, 2014; Nascimento, Cassiani, Santos, & Dantas, 2015) an important consideration and potential limitation may exist when it comes to the amount swallowed during each piecemeal swallow. It would be difficult to account for variability related to the volume of bolus swallowed when it is piecemealed into smaller (unknown) amounts. By reporting results following only the first swallow per bolus, we aimed to minimize the influence of variability seen in later swallows, with presumably smaller bolus volumes. Further, the proportion of boluses which required piecemeal or multiple swallows was not significantly different by task, leading us to infer that piecemeal swallowing did not influence the overall findings we reported.

For this study, we maintained a narrow focus to explore the specific role of pharyngeal constriction on swallowing efficiency. This decision was made based on previous descriptive links described in ALS dysphagia research, (e.g., Goeleven et al., 2006) and findings from other clinical populations (Stokely et al., 2015). Such a discrete focus does pose some inherent limitations. First, we focused exclusively on the pharyngeal phase of swallowing, without regard to the oral or esophageal phases. Future work may consider exploring the interaction between the various phases of swallowing, in addition to the discrete features within each individual phase of swallowing. Similarly, we concentrated upon one physiological feature (i.e., pharyngeal constriction) and reported on a limited selection of bolus consistencies (thin, pudding) and volumes (3mL, 20mL) which may impact swallowing efficiency. Future work will be needed to incorporate additional physiological mechanisms into the model (e.g., UES function, epiglottic deflection, tongue strength), and include a broader representation of the textures that patients encounter at mealtimes.

3.2.6.2 Future Research

Although this analysis points to pharyngeal constriction as a key mechanism contributing to the accumulation of post-swallow residue and to overall swallow inefficiency in ALS, it does not
present a perfect correlation, suggesting that other parameters are also involved and further research is needed. Additional factors that may be involved include function of the upper esophageal sphincter (i.e., timeliness and degree of relaxation, maximum distension) and bolus properties such as cohesiveness or stickiness. Further, the metric of pharyngeal constriction area in this paper does not capture the true strength of the pharyngeal musculature nor the patterning of pharyngeal contractions. It is possible that either reductions in pharyngeal strength or changes in the rostral-caudal pharyngeal stripping wave may affect the association identified in the current paper. Future research using combined manometry and fluoroscopy may help us further understand the role of the timing patterns, sequence, and strength of pharyngeal musculature as they relate to swallowing inefficiency in ALS.

3.2.7 Conclusions

Swallowing inefficiency is a common concern for individuals with ALS. Results from this preliminary work indicate that impaired pharyngeal constriction is one mechanism associated with impaired swallowing efficiency in ALS, across selected bolus volumes and consistencies. These data support the assumption that reduced pharyngeal constriction contributes to the presence of post-swallow residue and is a key parameter in the pathophysiology of dysphagia in ALS. Future work is needed to explore these relationships in greater detail, across a wider range of bolus textures, considering additional physiological mechanisms which may also affect swallowing efficiency. Longitudinal research studies will also be beneficial to elucidate how these observations change throughout ALS disease progression.
3.3 Part 2: Hyoid Kinematics in Patients with Amyotrophic Lateral Sclerosis (ALS): A Pilot Analysis

3.3.1 Introduction

Anterior-superior excursion of the hyolaryngeal complex is a predictable and well-documented component of the pharyngeal swallow. The onset of rapid anterior-superior swallow-related hyoid movement (or the hyoid “burst”) is commonly considered to indicate the onset of the pharyngeal/reflexive stages of swallowing (Robbins, Hamilton, Lof, & Kempster, 1992), and as such, has been frequently used as a reference time point for calculating various swallowing durations and latencies, such as Stage Transition Duration/Swallow Reaction Time (Daniels, Schroeder, DeGeorge, Corey, & Rosenbek, 2007) and Laryngeal Vestibule Closure Reaction Time (Guedes et al., 2017). Traditionally, hyoid movement has been associated with other physiological events of the swallow; anterior movement of the hyoid is thought to contribute to UES opening by applying traction to a relaxed cricopharyngeus (Jacob, Kahrilas, Logemann, Shah, & Ha, 1989), while superior hyoid movement and hyoid movement speed is thought to assist airway protection (Logemann et al., 1992; Nagy et al., 2014).

The characteristic movement of the hyoid results from contraction of suprahyoid and longitudinal pharyngeal muscles (Pearson, Langmore, Yu, & Zumwalt, 2012; Pearson, Langmore, & Zumwalt, 2011). As such, hyoid movement serves as an anatomical surrogate to infer function of suprahyoid muscles and to investigate modulatory factors acting upon these muscles, and the swallowing mechanism. Various parameters, including hyoid movement velocity and maximum excursion of the hyoid have been shown to vary as a function of bolus volume and consistency in healthy adults (Bakiroo, Carnaby, & Crary, 2015; Chi-Fishman & Sonies, 2002; Molfenter & Steele, 2014b; Nagy et al., 2014; Nagy, Molfenter, Peladeau-Pigeon, Stokely, & Steele, 2015).

Our current understanding of hyoid speed and range of motion in ALS is largely limited to descriptive accounts (e.g., “reduced hyolaryngeal movement”) (Waito et al., 2017). To our knowledge, only two previous studies have quantified hyoid kinematics in ALS (Garand, Schwertner, Chen, & Pearson, 2018; Plowman, Watts, Tabor, et al., 2016). Plowman and colleagues reported measures of hyoid displacement (i.e., the distance traveled between rest and peak hyoid position) in patients with ALS before and after expiratory muscle strength training
(EMST). The authors reported baseline hyoid displacement to be >90mm (based on 95%CI) and found an increase in hyoid displacement following EMST (mean increase of 57mm, 95%CI = 7-106mm). Still, measures of hyoid displacement have been found to be highly variable between studies and individuals (Molfenter & Steele, 2011), particularly when measures are not anatomically normalized to account for differences in participant height (Molfenter & Steele, 2014b).

Using computational analysis of swallowing mechanics (CASM), Garand and colleagues (2018) identified various differences in hyoid kinematics in a sample (n=15) of individuals with MND, including 10 diagnosed with ALS, compared to age- and sex-matched healthy controls. In this study, individuals with MND displayed greater hyolaryngeal excursion compared to healthy controls, which was interpreted as potential compensation for reductions in tongue base retraction and pharyngeal shortening. Still, the data extracted by CASM is presented in gestalt configuration differences between two physiological states, rather than defining raw hyoid positions/trajectories. Peak hyoid position, speed/velocity of hyoid movement, and modulation of hyoid kinematics by bolus factors has not yet been explored in patients with ALS.

The purpose of this study was to (1) characterize raw hyoid kinematics (speed and range of movement) in a sample of individuals with ALS, using anatomically-normalized measures, and (2) explore differences in hyoid movement related to bolus properties. Compared to published norms, we hypothesized that overall hyoid movement speeds and distances would be reduced in patients with ALS, but that hyoid kinematics would vary predictably by bolus properties.

3.3.2 Methods

This analysis was based on the same dataset described previously in Part 1. All details regarding data collection (i.e., participants, recording equipment) and data processing (i.e., segmentation, randomization) remain unchanged. However, in addition to the bolus trials presented in Part 1, we also measured hyoid kinematics for 1mL thin barium trials (VARIBAR® barium sulfate, Bracco Diagnostics Inc., Monroe Township, NJ).

Blinded raters marked the anterior-inferior corners of the hyoid bone, C2, and C4 frame-by-frame throughout the first swallow of each bolus, from 5 frames preceding the onset of hyoid burst until 10 frames after the beginning of continuous hyoid descent from peak position. Once
tracking was completed, hyoid position from each frame was expressed in a coordinate system in relation to the C2-4 angle (y-axis); the x-axis was defined perpendicular to the y-axis, intersecting at the level of C4 (origin). The position of the hyoid from the origin was anatomically normalized using the length of C2-4 (Molfenter & Steele, 2014b), and multiplied by 100 to obtain values in % C2-4 units. Measures of hyoid speed and range of movement were extracted in anterior (X), superior (Y) and antero-superior (XY) planes using an automated program in MatLab (The MathWorks, Inc., Natick, MA). Example tracking positions and output data is shown in Figure 3-5.

**Figure 3-5.** a) Example position markers for hyoid tracking, for six consecutive frames. b) Hyoid trajectory output data (smoothed), illustrating hyoid position (from C4-origin) throughout the swallow (% C2-4 units). Starting hyoid position for each task indicated by “x” marker; terminal position indicated by triangle marker.
Peak hyoid positions and average velocity/speed of movement were compared against published norms, using unpaired two-tailed $t$-tests. Mixed model repeated measures ANOVAs were performed to explore effects of bolus volume (1mL vs. 3mL vs. 20mL) and consistency (3mL thin vs. 3mL pudding-thick) on hyoid kinematics, with an additional factor of ALS-onset type (bulbar vs. spinal). One participant with “mixed” onset ALS was excluded from this analysis (final $n=25$). A Bonferroni correction was applied when interpreting significance of $t$-tests and ANOVAs to adjust for multiple (6) tests performed in each analysis (i.e., 2 kinematic parameters [maximum position, velocity/speed] × 3 planes of movement [anterior, superior, anterosuperior]; adjusted $p<0.008$). Post-hoc Sidak tests and Cohen’s $d$ effect sizes were calculated to determine the source and magnitude of any statistically significant differences.

### 3.3.3 Results

Hyoid kinematics (speed, peak position) obtained from this analysis are summarized in Table 3-2. Compared to reference data (Molfenter & Steele, 2014a; Nagy et al., 2014, 2015), we identified lower maximum hyoid position in the anterior ($t=-3.43$, $p<0.001$, $d=0.76$) and anterosuperior planes ($t=-2.23$, $p<0.001$, $d=0.49$), with medium and small effect sizes, respectively. In terms of average hyoid speed/velocity, we identified lower anterior hyoid velocity ($t=-5.29$, $p<0.001$, $d=1.05$) and anterosuperior hyoid speed ($t=-4.95$, $p<0.001$, $d=0.94$), with large effect sizes. No statistically significant differences in maximum superior position or average superior hyoid velocity were identified. Comparisons to published reference data are displayed as modified forest plots in Figure 3-6.
Table 3-2

Swallow-related hyoid kinematics (mean, 95% confidence interval) measured in n=25 individuals with ALS.

<table>
<thead>
<tr>
<th>Axis</th>
<th>Peak Position from C4 (% C2-4 units)</th>
<th>Average Velocity/Speed (% C2-4 units, per second)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior (x)</td>
<td>121 (117-125)</td>
<td>52 (48-57)</td>
</tr>
<tr>
<td>Superior (y)</td>
<td>97 (93-101)</td>
<td>76 (68-84)</td>
</tr>
<tr>
<td>Anterosuperior (xy)</td>
<td>154 (150-158)</td>
<td>69 (63-74)</td>
</tr>
</tbody>
</table>

Figure 3-6. 95% confidence intervals for hyoid position and average speed/velocity of hyoid movement, compared to published reference values.

Explorations of hyoid kinematics by bolus properties and onset-type revealed a main effect of bolus volume on average superior velocity ($F=6.022$, $df=2,36.916$, $p=0.005$). Pairwise comparisons (illustrated in Figure 3-7) revealed that 20mL thin boluses evoked faster hyoid movement compared to 1mL thin boluses ($p_{adj}=0.005$, $d=0.81$). No statistically significant
differences in peak hyoid position were identified in relation to onset-type or bolus characteristics. In contrast to reports from healthy individuals (Nagy et al., 2015), hyoid kinematics in this cohort of individuals with ALS did not vary by liquid thickness.

We did identify several trends in the data which approached statistical significance ($p=0.05$) but exceeded our corrected $p$-value. We have chosen to list these findings briefly below, as further investigation with appropriate statistical power and targeted research questions may be warranted:

- Trend towards increased anterosuperior speed, with larger volumes ($p=0.014$)
- Trend towards lower average anterior velocity in bulbar-onset ALS, compared to spinal-onset ALS ($p=0.042$)
- Trend towards increased peak anterosuperior position, with larger volumes ($p=0.052$).

![Figure 3-7. Main effect of bolus volume on average superior hyoid velocity.](image)

3.3.4 Discussion

The purpose of this analysis was to quantify hyoid kinematics in a cross-sectional sample of patients with ALS, compare raw measures to published norms, and explore within-subject variability based on bolus thickness and volume. Our results suggest that speed and range of
hyoid movement along the anterior axis is reduced in patients with ALS, compared to established reference data from healthy individuals. Based on anatomical relationships and directional properties of the suprahyoid muscles, we believe this difference may reflect reduced power from muscle fibres of the small geniohyoid muscle, reported to be largely responsible for anterior hyoid movement (Pearson & Zumwalt, 2014; Pearson, et al., 2011). These inferences highlight areas for further study.

Despite significant differences noted along the anterior axis, no differences in superior hyoid position or velocity were identified. Sparing of movement in this axis may be explained by the redundant involvement of multiple, larger muscles (e.g., mylohyoid, stylohyoid) and potential support from larger pharyngeal muscles which apply longitudinal traction inferiorly upon the thyroid cartilage (i.e., palatopharyngeus, salpingopharyngeus, and stylopharyngeus). Still, given the progressive nature of ALS, it is conceivable that hyoid kinematics along the superior axis may eventually become reduced at later stages in the disease process.

In terms of bolus modulation, our analysis revealed an effect of bolus volume on hyoid movement velocity, along the superior axis. These findings are comparable to previous reports in healthy adults (Bakiroo, Carnaby, & Crary, 2015; Nagy et al., 2014). However, no differences were identified in terms of liquid consistency (thickness); a previous report by Nagy et al. (2015) identified small effects of bolus consistency impacting hyoid kinematics along the anterior axis, such that nectar-thick liquids evoked faster anterior hyoid velocity, compared to measures from thin liquid trials. Although further work is needed to understand hyoid kinematics by bolus thickness in healthy individuals, our findings suggest that there may be qualitative changes with respect to motor accommodation in patients with ALS. Given the reductions in speed/movement distance observed along the anterior axis, one explanation is that the loss of motor neurons (and associated spasticity/atrophy) contributes to inflexibility in the motor output, whereby spontaneous adaptation to bolus thickness is not possible.

It is important to recognize that this analysis is based on a heterogeneous cohort of individuals with ALS. Given the retrospective nature of this analysis, we lack detailed information regarding global bulbar function (e.g., lingual strength) and the degree of UMN/LMN involvement in the participant sample, which could have allowed for participant stratification and deeper interpretation of results.
3.3.5 Conclusions

Individuals with ALS display significant reductions in speed and range of hyoid movement, particularly along the anterior axis. Our results suggest that superior hyoid movement during swallowing may be spared in early stages of ALS. Bolus volume, but not consistency, modulates hyoid movement in patients with ALS. Compared to previous data with healthy individuals, our results suggest possible differences in motor accommodation of hyoid movement in individuals with ALS. Further work is needed to explore the clinical implications of these results, and whether reductions in hyoid movement speed/peak position are associated with functional impairments of safety or efficiency.
Comprehensive Characterization of Swallowing Physiology and Function in Patients with ALS

4.1 Preface

In Chapter 3, normalized measures of pharyngeal area at maximum constriction and swallow-related hyoid kinematics were found to differ between patients with ALS and published reference data from healthy individuals. This finding aligned with expectations based on descriptive accounts of swallowing physiology in ALS, supporting the face validity of these measures for detecting differences in swallowing physiology associated with ALS disease pathology. Still, the previous analysis was limited to only two physiological features of a highly dynamic pharyngeal swallow, with few associations made to swallowing function. Thus, for the current study, we chose to characterize swallowing physiology more broadly in a cohort of individuals diagnosed with ALS and explore additional relationships between swallowing physiology and function.

This cross-sectional study is divided into three parts, all which share a common methodology for data collection and analysis. Part 1 provides a detailed overview of swallowing function and physiology in the cohort, while Part 2 explores the role of liquid thickness on swallowing function and physiology. Finally, in Part 3, preliminary analyses were performed to determine associations between metrics of swallowing physiology and function, illuminating apparent physiological parameters associated with functional impairment, which will guide future research.

This work is part of a larger research collaboration between the Swallowing Rehabilitation Research Laboratory (Toronto Rehabilitation Institute – University Health Network, Toronto, ON) and the Swallowing Systems Core (University of Florida, Gainesville, FL). Funding for this project and analysis is supported by the National Institute of Deafness & Other Communication Disorders (5R01DC011020), as well as doctoral funding from the University of Toronto and Toronto Rehabilitation Institute - University Health Network.
4.2 Introduction

Swallowing is a complex motor process, carefully controlled to allow the flow of food and liquids through the pharynx, while protecting the airway from entry of foreign material. Dysphagia (i.e., swallowing impairment) is a serious symptom associated with bulbar dysfunction in patients with Amyotrophic Lateral Sclerosis (ALS), leading to impaired swallowing safety (e.g., aspiration) and efficiency (e.g., post-swallow residue). Although swallowing impairment in individuals with ALS and related motor neuron diseases has been documented and studied for more than five decades, there are gaps within the existing research literature. Research to-date has focused narrowly upon the occurrence of aspiration in patients with ALS and related motor neuron diseases (Waito et al., 2017), and relatively little attention has been paid to the mechanisms contributing to swallowing impairment – particularly with respect to impaired swallow efficiency. Further, as most studies have characterized swallowing in ALS descriptively, it remains unclear which objective measures are able to detect differences associated with ALS pathology.

Preliminary investigations of swallowing physiology in ALS using quantitative measurement tools have revealed differences in maximum pharyngeal constriction and swallow-related hyoid kinematics, compared to healthy reference data (Waito, Tabor-Gray, Steele, & Plowman, 2018). Measurable increases in pharyngeal area at maximum constriction (i.e., reduced constriction) were found to be significantly associated with the presence of post-swallow residue and correlated well with patient-reported bulbar function using the ALSFRS-R. Further, measures of hyoid movement throughout the swallow have illustrated fine detail with respect to changes associated with ALS, such that reduced range and speed of hyoid movement is particularly pronounced along the anterior and anterosuperior axes, while superior hyoid movement appears largely spared (Waito, Peladeau-Pigeon, Steele, Tabor, & Plowman, 2018).

Still, as swallowing is a highly dynamic process, there are additional mechanisms which demand further exploration. Abnormal physiology associated with airway protection, such as the differences in the degree and timing of laryngeal vestibule closure (LVC), have been described in patients with ALS (Briani et al., 1998; Lo Re et al., 2007; Murono et al., 2015; Robbins, 1987; Solazzo et al., 2011), and have been implicated in non-ALS populations as factors contributing to unsafe swallowing (Guedes et al., 2017; Nascimento et al., 2018; Steele, Chak, et al., 2015).
Further, reductions in the degree and duration of UES opening have been implicated as a risk factor associated with impaired swallow safety and efficiency (Chiò et al., 2011; D’Amico et al., 2013; Molfenter & Steele, 2014a). Although impaired UES function has been considered a point of debate in the ALS literature, there is evidence to suggest that a subset of individuals with ALS may present with reduced UES opening or heightened UES tonicity (Briani et al., 1998; Ertekin et al., 2000; Ertekin et al., 1998; Higo et al., 2002; Omari et al., 2014; Solazzo et al., 2011). To build on what is currently known about dysphagia in ALS, the first aim of this study is to characterize swallowing physiology in a cohort of patients with ALS and to determine associations between physiological mechanisms and metrics of swallowing safety and efficiency.

In addition to changes associated with disease pathology, physiological mechanisms of swallowing are known to vary according to bolus properties, including liquid thickness (Steele, Alsanei, et al., 2015). In a review by Steele, Alsanei and colleagues (2015), increased bolus thickness was reported to influence overall swallow duration, bolus transit times, duration of UES opening, and tongue-palate pressures. Thickened liquids are commonly recommended to patients with dysphagia to reduce the risk of aspiration (Garcia, Chambers, & Molander, 2005; Oliveira et al., 2017; Robbins et al., 2002), as they flow more slowly through the pharynx and allow additional time to achieve airway protection. Still, as thicker liquids also require greater driving force for effective propulsion from the mouth through the pharynx to the esophagus, it has been suggested that they may also pose a greater risk for post-swallow residue (Hind et al., 2012; Oliveira et al., 2017), particularly in individuals with pharyngeal weakness. This is important to consider, as impaired swallowing efficiency has been indicated as a risk factor for malnutrition (Carrión et al., 2013; Miller et al., 2009; Rofes et al., 2011) and research has suggested that the presence of post-swallow pharyngeal residue poses an independent risk factor for subsequent aspiration events in individuals with ALS (Goeleven et al., 2006; Lo Re et al., 2007; Solazzo et al., 2011). Although thickened fluids are commonly discussed as a management option for dysphagia in individuals with ALS (Benditt, 2002; Houseman, 2008; Johnson et al., 2012; Kosseifi et al., 2010; Kuhnlein et al., 2008; Leder et al., 2004; Scott & Heughan, 1993; Stavroulakis et al., 2014), more research is needed to support the assumed benefit of thickened liquids, while considering potential risk of post-swallow residue related to the use of thickened liquids in individuals with ALS. Thus, as a second aim of this study, we sought to explore the
role of thickened liquids on parameters of swallowing physiology, safety and efficiency in patients with ALS.

4.3 Aim & Hypotheses

4.3.1 Aims

The first aim of this study was to characterize swallowing physiology and function in a cross-sectional sample of individuals with ALS, using quantitative videofluoroscopic analysis. The goal of this analysis was to summarize the occurrence of unsafe and inefficient swallowing and identify physiological metrics that may reveal differences between ALS swallowing and healthy reference data. Twelve physiological parameters were selected for analysis based on previous descriptive accounts that indicate change as part of ALS pathology (e.g., Ertekin et al., 2000; Higo et al., 2004; Lo Re et al., 2007; Murono et al., 2015; Robbins, 1987; Solazzo et al., 2011) as well as associations with swallowing function seen in other clinical populations (e.g., Kendall, Leonard, & McKenzie, 2004; Macrae, Anderson, & Humbert, 2014; Molfenter, Cliffe Polacco, & Steele, 2011; Molfenter & Steele, 2014a; Stokely et al., 2015; Waito, Steele, Peladeau-Pigeon, Genge, & Argov, 2018). Selected parameters were grouped in terms of their functional role during the swallow, such that measures associated with airway protection (i.e., timing, degree and duration of laryngeal vestibule closure) were grouped as “laryngeal” parameters, while measures associated with bolus clearance (e.g., degree and duration of UES opening, pharyngeal constriction) were grouped as “pharyngeal” parameters. Parameters associated with speed and range of hyoid movement were also included in this study; however, because the hyoid bone communicates dynamically with muscles involved in oral, laryngeal, pharyngeal, and respiratory gestures, measures of hyoid kinematics were grouped separately (i.e., “hyoid kinematics”).

As a second aim, we sought to explore the role of liquid thickness on swallowing function and physiology, guided by the following research questions:

1. Are thickened liquids less likely to be penetrated/aspirated compared to thin liquids?

2. Do spoon-thick liquids lead to greater post-swallow residue than thinner (sippable) liquids?

3. Are parameters of swallowing physiology modulated by liquid thickness?
We hypothesized that increased bolus thickness would reduce the presence or severity of penetration/aspiration prior to or during the swallow, and that different levels of liquid thicknesses would modulate parameters of swallowing, based on differing sensory feedback delivered to the swallowing CPG. However, we also anticipated that increases in liquid thickness would lead to measurable increases in post-swallow residue, highlighting a need to determine an optimal liquid thickness for managing dysphagia in individuals with ALS.

Finally, our third aim was to determine which physiological parameters are associated with impaired swallow safety (i.e., penetration-aspiration) or efficiency (i.e., post-swallow residue). We hypothesized that swallowing safety would be largely associated with laryngeal parameters (i.e., airway protection mechanisms) (e.g., Vose & Humbert, 2018), and that swallowing efficiency would be associated with pharyngeal parameters (i.e., bolus flow and propulsion mechanisms) (e.g., Stokely et al., 2015). Despite hyolaryngeal anatomical connections and reported associations between the timing of airway closure and peak hyoid velocity (e.g., Nagy et al., 2014), most studies have failed to identify a consistent link between hyoid kinematics and swallow safely and efficiently (e.g., Kraaijenga et al., 2017; Molfenter & Steele, 2014a; Seo, Oh, & Han, 2016), except when severely disturbed (i.e., anatomically referenced measures falling below first quartile; Steele, Bailey, et al., 2011). Thus, for the current study, we expected to find reductions in hyoid movement velocity/speed and range of motion consistent with the data presented in Chapter 3; however, we did not anticipate finding any direct associations between hyoid movement and swallowing safety or efficiency.

### 4.4 Methods

Data collection for this study was completed in collaboration with the Swallowing Systems Core at the University of Florida, under the supervision of Dr. Emily Plowman. This protocol was reviewed and approved by the University of Florida Institutional Review Board (IRB) and University Health Network Research Ethics Board (REB). Data transfer and sharing agreements were also approved by both institutions.

#### 4.4.1 Participants

Twenty adults (10 female) over the age of 18 years with a confirmed diagnosis of ALS (i.e., Revised El-Escorial criteria) were recruited from the University of Florida ALS Clinic. Nine
participants reported bulbar-onset ALS, while \( n=10 \) reported spinal-onset ALS and \( n=1 \) reported a mixed bulbar/spinal-onset presentation. It is worth noting that the proportion between bulbar vs. spinal-onset ALS cases in this study exceed expected population prevalence rates (approximately 3:7) (Swinnen & Robberecht, 2014); this is likely due to the recruitment strategy and focus towards individuals with bulbar disease who may present with physiological differences in swallowing. Bulbar symptomology was reported by 8/10 participants in the study who initially presented with spinal-onset ALS.

Mean age of participants was 62 (range: 47-78) and the average time since onset of bulbar symptoms ranged from 0-63 months (\( M=18.71, SD = 17.43 \)); two participants did not report bulbar symptoms at the time of assessment. Participant demographics are summarized in Table 4-1.

Table 4-1

Summary of participant demographics and baseline measures.

<table>
<thead>
<tr>
<th>Demographics</th>
<th>( n )</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>20</td>
<td>62</td>
<td>(47-78)</td>
</tr>
<tr>
<td>Bulbar-onset</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spinal-onset</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed-onset</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ALSFRS-R Scores</th>
<th>( n )</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (/48)</td>
<td>20</td>
<td>36.5</td>
<td>(23-44)</td>
</tr>
<tr>
<td>Bulbar (/12)</td>
<td>20</td>
<td>9</td>
<td>(3-12)</td>
</tr>
<tr>
<td>Swallowing (/4)</td>
<td>20</td>
<td>3</td>
<td>(1-4)</td>
</tr>
<tr>
<td>Respiration (/12)</td>
<td>20</td>
<td>11</td>
<td>(4-12)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease Duration</th>
<th>( n )</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months since diagnosis</td>
<td>19</td>
<td>16.53</td>
<td>15.6</td>
</tr>
<tr>
<td>Months since initial symptom</td>
<td>19</td>
<td>36.37</td>
<td>26.68</td>
</tr>
<tr>
<td>Months since first bulbar symptom</td>
<td>19</td>
<td>16.74</td>
<td>17.46</td>
</tr>
</tbody>
</table>
Exclusionary criteria included a medical history of cancer, surgery or radiation in the head and neck region, which may impose structural and neurological differences in the region of interest; any clinical history of dysphagia or neuromuscular disorder unrelated to ALS, which may impose physiological differences that are not directly resulting from ALS pathology; presence of severe cognitive impairment that would impair the participant’s ability to follow necessary instructions during the assessment procedures; and/or significant respiratory compromise (e.g., reliance on mechanical ventilation, diaphragmatic pacer, or forced vital capacity below 65%) which may have elevated risks to the participant.

4.4.2 Data Collection

Following informed consent, a selection of demographic information was recorded or obtained from chart review, including: year of birth, sex, diagnosis date (month, year), ALS onset type (i.e., bulbar, spinal, mixed), and time since onset of initial and bulbar-specific symptoms. To obtain functional severity scores, each participant completed the patient-reported *ALS Functional Rating Scale – Revised (ALSFRS-R)*.

Each participant underwent a videofluoroscopy (i.e., swallowing x-ray), conducted by a speech-language pathologist and a radiology technician, at the Swallow Systems Core laboratory at the University of Florida (Gainesville, Florida). Each participant swallowed up to 15 liquid boluses, ranging in thickness from thin to extremely thick, according to the International Dysphagia Diet Standardization Initiative (IDDSI) Framework (Cichero et al., 2017), shown in Figure 4-1. All liquids were mixed following standardized recipes (Barbon & Steele, 2018) to a 20% weight-to-volume concentration of barium contrast and thickened with a xanthan gum-based thickener (see Appendix C). Boluses were presented from thinnest (IDDSI Level 0) to thickest (IDDSI Level 4) and each participant was given 3 trials of each consistency.

Participants were instructed to take comfortable sips of all sippable liquids (IDDSI Levels 0-2) and a comfortably sized spoonful using a teaspoon for IDDSI Levels 3 and 4. Each cup was weighed before and after the videofluoroscopy to obtain measures of sip weight, which served as a covariate in various statistical analyses as a surrogate measure for sip volume.
Figure 4-1. Framework characterizing food and liquid consistencies, as defined by the International Dysphagia Diet Standardization Initiative (IDDSI).

For patient safety, we followed a series of bail-out criteria: 1) if aspiration or penetration leaving residue in the laryngeal vestibule was observed on two trials of the same stimulus, the remaining trial of that stimulus was omitted and the examiner moved on to the next (thicker) IDDSI level; 2) if aspiration or penetration leaving residue in the laryngeal vestibule was observed on 3 occasions overall, or if severe levels of pharyngeal residue were observed (i.e., either the valleculae or pyriform sinuses were judged to be 75% full or more with risk of overflowing) and persisted despite cued compensatory maneuvers, the protocol was terminated and the patient was provided with standard management care. The attending speech-language pathologist was permitted to use compensatory maneuvers to manage instances of aspiration or residue, as deemed clinically necessary (e.g., cue for multiple swallows, head turn chin down, etc.); any trialed compensatory maneuvers were recorded on the Clinical Reporting Form (Appendix D). The attending clinician was also permitted to terminate the protocol prematurely if he or she deemed the patient to be at significant risk for adverse events.
Videofluoroscopies were performed using continuous fluoroscopy and recorded on a TIMS-DICOM capturing at 30 frames per second. Through quality assurance testing, we identified synchronization challenges between the fluoroscopy system (C-Arm) and TIMS-Dicom recording equipment, which led to the manifestation of replicate images in the recorded output, yielding fewer than 30 unique images per second. Although this technical glitch could not be avoided based on the existing equipment specifications, additional testing of the fluoroscopy capture settings using an analog metronome and a “constant velocity car” (i.e., small, battery-operated toy car traveling at constant velocity) confirmed that replicate frames in the captured image sequence represent a true point in time and were therefore included in our duration/interval calculations (see Figure 4-2). Still, this synchronization issue represents a limitation in this work. To minimize impact, kinematic measures such as hyoid movement velocity were all calculated as average movement over time (frames) to avoid misrepresentation of a kinematic artifact on a single frame change (e.g., twice the movement preceding or following a replicate frame; static movement between two identical frames). Further, any videos with greater than 25% frame duplication (i.e., fewer than 22.5 unique images per second) were excluded from timing/kinematic analysis.

Figure 4-2. Position markings of constant velocity car in a video with 7% replication (left) and 25% replication (right); frames with the same (duplicate) image are shown in orange, while unique-image frames are shown in blue. Significant difference in position from a replicate frame to the next available unique frame is indicative of time being maintained, despite loss of a unique image.
4.4.3 Videofluoroscopy Ratings

At the Swallowing Rehabilitation Research Laboratory at the Toronto Rehabilitation Institute – University Health Network, a procedure referred to as the Analysis of Swallowing Physiology: Events, Kinematics & Timing (ASPEKT) method has been established to guide frame-by-frame analysis of videofluoroscopic swallowing studies (Waito, Peladeau-Pigeon, et al., 2018; Steele et al., under review). The ASPEKT method outlines workflow necessary to capture physiological and functional components of the swallow, including several established scales (e.g., Eisenhuber et al., 2002; Pearson et al., 2013; Rosenbek et al., 1996), and events commonly identified to calculate timing intervals (reviewed in Molfenter & Steele, 2012; Namasivayam-MacDonald, Barbon, & Steele, 2018). Completion of the full protocol yields a comprehensive summary of swallowing impairment (e.g., penetration/aspiration, post-swallow residue), timing intervals between swallow events (e.g., bolus transit times, physiological response times), and quantification of swallow kinematics through pixel-based measurements (e.g., maximum pharyngeal constriction, UES distension, hyoid kinematics). As many of these measures are interval in nature, they allow the investigator to measure differences in function and physiology with a level of precision that exceeds subjective binary or ordinal ratings of swallow function. A flow chart of the protocol is shown in Figure 4-3.

Previous investigations applying this and similar measurement procedures have identified associations between various parameters of swallowing physiology and impaired swallowing safety (penetration-aspiration) or efficiency (post-swallow residue, repeated swallows) in individuals following stroke (Molfenter & Steele, 2013, 2014a; Steele, Chak, et al., 2015; Stokely et al., 2015) and oculopharyngeal muscular dystrophy (Waito, Steele, et al., 2018). For this study, the full ASPEKT method was completed to characterize swallowing function and physiology in a sample of individuals with ALS.
Figure 4-3. Flow-chart overview of the ASPEKT Method, used by the Swallowing Rehabilitation Research Laboratory for characterizing swallowing physiology and function.

The standard operating procedures used for rating, with detailed instructions and operational definitions, can be found in Appendix E. For the purpose of this study, we focused on several parameters derived by the ASPEKT method:

1. Swallowing safety, using the Penetration-Aspiration Scale (Rosenbek et al., 1996);

2. Swallowing efficiency using anatomically normalized measures of post-swallow pharyngeal residue, including the Normalized Residue Ratio Scale (Pearson et al., 2013), and recording the total number of swallow events (including swallow attempts);

3. Event detection required for calculating the following intervals and durations:

   a. Laryngeal Vestibule Closure Reaction Time (LVCrt): the time interval between the onset of hyoid burst (4d) and the frame of complete (or maximally
approximated) laryngeal vestibule closure (4e); (Guedes et al., 2017; Vose & Humbert, 2018)

b. Laryngeal Vestibule Closure Duration (LVCdur): the time between complete (or maximally approximated) laryngeal vestibule closure (4e) and the first frame depicting offset/release of laryngeal vestibule closure (4i); (notated as “dLVC” in Guedes et al., 2017; “LCD” in Molfenter & Steele, 2012; Molfenter & Steele, 2013)

c. Duration of UES opening (UESOdur): the time between initial opening of the UES (4f) and the frame showing UES closure (4j); (Kahrilas, Logemann, Krugler, & Flanagan, 1991; Kern et al., 1999; notated as “UESopen” in Leonard, Kendall, & McKenzie, 2004)

4. Event detection required for rating degree of movement or taking a pixel-based measure:

   a. Frame of Maximum Laryngeal Vestibule Approximation (4e; LVA): for estimating the degree of airway closure as complete or incomplete;

   b. Frame of Maximum UES Distension (4g): for subsequent measurement of UES width (below);

   c. Frame of Maximum Pharyngeal Constriction (4h): for subsequent measurement of pharyngeal area (below);

   d. Frame of Swallow Rest (4l): for measurement of post-swallow residue.

5. Pixel-based measurement of swallowing physiology, normalized to an anatomical scalar (i.e., length from C2-4 vertebrae):

   a. UES Width (7a): measure of the narrowest point along the UES (i.e., point where there is highest resistance to bolus flow), at the frame of maximum UES distension; (Leonard et al., 2004)

   b. Maximum Pharyngeal Constriction Area (7b): measure of unobliterated pharyngeal area at maximum constriction of the pharynx, during the swallow;
(notated as “PAm\textsuperscript{ax}” in Kendall & Leonard, 2001; “MP\textsubscript{CA}\text{\textsubscript{N}}” in Stokely et al., 2015; Waito, Steele et al., 2018; Waito, Tabor-Gray, et al, 2018)

c. Hyoid Tracking (6a) to extract measures of peak hyoid position (6b) and movement velocity/speed (6c); (Molfenter & Steele, 2014b; Nagy et al., 2014, 2015)

Further discussion and interpretation of individual parameters used in this analysis will be described, below, along with the associated analyses.

Blinded ratings were completed by trained and experienced raters, with 100% duplication (i.e., 2 raters) for evaluations of swallowing safety and event frame selection, 70% duplication for pixel-based measures of efficiency and pharyngeal area, and 25% duplication for hyoid tracker kinematics. Thresholds for agreement between two raters were defined for each parameter; ratings which exceeded the agreement threshold were sent for review through consensus with a third rater. For PAS ratings, any difference along the scale was flagged for review. Frame selections exceeding an a priori threshold of >5 frames were reviewed through consensus and differences between two raters which did not exceed the 5 frame threshold were resolved by selecting either the earlier or later frame between the two, defined by the parameter of interest. Thresholds and selection of final ratings between two raters is summarized in the rating SOP (Appendix E). For pixel-based measures, an initial subset of the data was used to determine thresholds of tracing agreement. Difference scores between raters were reviewed for each parameter and the interquartile range (IQR) was calculated. The calculated outlier cut-off (i.e., 1.5 x IQR) was set as the agreement threshold for each parameter. Scores for which the difference between two raters did not exceed the defined threshold were resolved by choosing either the larger or smaller value between two raters, defined by the parameter of interest.
Table 4-2.

Median and IQR for differences between two raters, by parameter. Thresholds of rating agreement for pixel-based measures were calculated based on outlier cut-offs defined by the differences between two raters.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n (swallows)</th>
<th>Median Difference</th>
<th>IQR</th>
<th>Agreement Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum Pharyngeal Constriction Area in C2-4² units</td>
<td>397</td>
<td>0.0105</td>
<td>0.0188</td>
<td>&gt;0.0517</td>
</tr>
<tr>
<td>UES Width in C2-4 units</td>
<td>280</td>
<td>0.0219</td>
<td>0.0364</td>
<td>&gt;0.1012</td>
</tr>
<tr>
<td>Total Pharyngeal Residue in C2-4² units</td>
<td>281</td>
<td>0.0116</td>
<td>0.0179</td>
<td>&gt;0.0500</td>
</tr>
<tr>
<td>Normalized Residue Ratio Scale – Valleculae (NRRSv)</td>
<td>269</td>
<td>0.0260</td>
<td>0.0549</td>
<td>&gt;0.1475</td>
</tr>
<tr>
<td>Normalized Residue Ratio Scale – Pyriform Sinus (NRRSp)</td>
<td>181</td>
<td>0.0154</td>
<td>0.0325</td>
<td>&gt;0.0878</td>
</tr>
</tbody>
</table>

4.4.4 Statistical Analysis

For Part 1 and Part 2, we characterized parameters of swallowing physiology, safety, and efficiency using measures of central tendency and range/variance, as appropriate based on the level of data. Influence of liquid thickness on parameters of swallowing function and physiology was tested using a series of parametric and nonparametric statistical analyses exploring within-group differences by IDDSI Level (5); as each statistical test was selected based on the type and level of data, each test is described independently for each analysis. Finally, associations between swallowing physiology and function (Part 3) were appraised using binary logit and linear Generalized Estimating Equations. Specific rules, assumptions and a priori questions are described for each analysis.
4.5 Results

4.5.1 Inter-rater reliability

Inter-rater reliability was calculated based on values obtained prior to consensus resolution, and results are summarized in Table 4-3. Agreement is also expressed as a percent of videos exceeding the \textit{a priori} thresholds for agreement. Overall results suggested excellent agreement for frame selection and good-to-excellent agreement for continuous pixel-based videofluoroscopy measures (Koo & Li, 2016). However, we acknowledge that agreement measured by the Kappa statistic for binary and nominal ratings of LVC and PAS were “poor” and “moderate”, respectively. Of note, the Kappa statistic becomes less reliable when one or more cells within the data table are “rare” occurrences (Viera & Garrett, 2005); as will be described in greater detail below, the gross majority of cases in the current dataset clustered within a single cell for PAS (1) and LVC (“complete”), with rarer instances of unsafe swallowing or incomplete LVC. To qualify inter-rater agreement of these parameters further, percent agreement was calculated for LVC and PAS (76\% and 82\%, respectively); as per protocol, any discrepancies were reviewed through consensus.

4.5.2 Part 1a: Characterization of Swallowing Function

\textit{Swallowing Safety}

Swallowing safety was characterized using the Penetration-Aspiration Scale (PAS) (Rosenbek et al., 1996). PAS scores fall on an 8-point rating scale to indicate the presence, depth and response to airway invasion of bolus material, including whether or not the material is ejected. A PAS score of 1 indicates no material has entered the laryngeal vestibule, while a PAS score of 2 indicates that bolus material entered the laryngeal vestibule and was immediately ejected. A score of either 1 or 2 is considered to be “safe”, as no bolus material remains in the airway to pose a health risk. Further, scores of 1 and 2 have been observed in healthy individuals (Daggett, Logemann, Rademaker, & Pauloski, 2006; Robbins, Coyle, Rosenbek, Roecker, & Wood, 1999). In contrast, a PAS score of 3 or higher indicates that material enters the airway and is not ejected, leaving residue of foreign material in the airway, and/or reaches a depth which is considered to be “unsafe”. For example, a PAS score of 3 indicates that material enters the airway and is not ejected but remains above the level of the vocal folds. PAS scores of 4-5 indicate that material reached the level of the vocal folds, with and without ejection from the airway, respectively.
Table 4-3

*Inter-rater agreement statistics for PAS scores, frame selection, and pixel-based measurements.*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Level of Data</th>
<th>Agreement Statistic</th>
<th>Value (95%CI)</th>
<th>Interpretation</th>
<th>% Requiring Consensus Resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAS</td>
<td>Nominal</td>
<td>Kappa</td>
<td>0.515; 82% in agreement</td>
<td>Moderate</td>
<td>18</td>
</tr>
<tr>
<td>LVC (+/-)</td>
<td>Binary</td>
<td>Kappa</td>
<td>0.198; 76% in agreement</td>
<td>Poor</td>
<td>24</td>
</tr>
<tr>
<td>Hyoid Burst Frame</td>
<td>Continuous</td>
<td>ICC</td>
<td>(0.966-0.977)</td>
<td>Excellent</td>
<td>8</td>
</tr>
<tr>
<td>LVA Frame</td>
<td>Continuous</td>
<td>ICC</td>
<td>(0.979-0.986)</td>
<td>Excellent</td>
<td>13</td>
</tr>
<tr>
<td>LVC Offset Frame</td>
<td>Continuous</td>
<td>ICC</td>
<td>(0.978-0.985)</td>
<td>Excellent</td>
<td>2</td>
</tr>
<tr>
<td>Maximum Pharyngeal Constriction Frame</td>
<td>Continuous</td>
<td>ICC</td>
<td>(0.976-0.984)</td>
<td>Excellent</td>
<td>3</td>
</tr>
<tr>
<td>UES Opening Frame</td>
<td>Continuous</td>
<td>ICC</td>
<td>(0.980-0.987)</td>
<td>Excellent</td>
<td>3</td>
</tr>
<tr>
<td>Max. UES Distension Frame</td>
<td>Continuous</td>
<td>ICC</td>
<td>(0.998-0.999)</td>
<td>Excellent</td>
<td>3</td>
</tr>
<tr>
<td>UES Closure Frame</td>
<td>Continuous</td>
<td>ICC</td>
<td>(0.976-0.983)</td>
<td>Excellent</td>
<td>9</td>
</tr>
<tr>
<td>Swallow Rest Frame</td>
<td>Continuous</td>
<td>ICC</td>
<td>(0.959-0.972)</td>
<td>Excellent</td>
<td>18</td>
</tr>
<tr>
<td>UES width</td>
<td>Continuous</td>
<td>ICC</td>
<td>(0.783-0.863)</td>
<td>Good</td>
<td>7</td>
</tr>
<tr>
<td>Maximum Pharyngeal Constriction Area</td>
<td>Continuous</td>
<td>ICC</td>
<td>0.903 (0.877-0.932)</td>
<td>Good-to-Excellent</td>
<td>2</td>
</tr>
<tr>
<td>NRRSv</td>
<td>Continuous</td>
<td>ICC</td>
<td>0.906 (0.879-0.927)</td>
<td>Good-to-Excellent</td>
<td>2</td>
</tr>
</tbody>
</table>
Table 4-3 (continued)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Level of Data</th>
<th>Agreement Statistic</th>
<th>Value (95% CI)</th>
<th>Interpretation&lt;sup&gt;c&lt;/sup&gt;</th>
<th>% Requiring Consensus Resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRRSp</td>
<td>Continuous</td>
<td>ICC&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.880 (0.848-0.905)</td>
<td>Good-to-Excellent</td>
<td>1</td>
</tr>
<tr>
<td>Total Residue (%C2-4&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>Continuous</td>
<td>ICC&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.885 (0.848-0.912)</td>
<td>Good-to-Excellent</td>
<td>3</td>
</tr>
<tr>
<td>Hyoid_xmax</td>
<td>Continuous</td>
<td>ICC&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.962 (0.943-0.974)</td>
<td>Excellent</td>
<td>N/A</td>
</tr>
<tr>
<td>Hyoid_ymax</td>
<td>Continuous</td>
<td>ICC&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.964 (0.944-0.976)</td>
<td>Excellent</td>
<td>N/A</td>
</tr>
<tr>
<td>Hyoid_xymax</td>
<td>Continuous</td>
<td>ICC&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.962 (0.944-0.975)</td>
<td>Excellent</td>
<td>N/A</td>
</tr>
<tr>
<td>Hyoid_xvel</td>
<td>Continuous</td>
<td>ICC&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.822 (0.721-0.884)</td>
<td>Good</td>
<td>N/A</td>
</tr>
<tr>
<td>Hyoid_yvel</td>
<td>Continuous</td>
<td>ICC&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.792 (0.686-0.862)</td>
<td>Moderate-to-Good</td>
<td>N/A</td>
</tr>
<tr>
<td>Hyoid_xyvel</td>
<td>Continuous</td>
<td>ICC&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.898 (0.832-0.936)</td>
<td>Good-to-Excellent</td>
<td>N/A</td>
</tr>
</tbody>
</table>

<sup>a</sup>ICC model = two-way random, absolute agreement; <sup>b</sup>n=2 “impossible” values identified and removed from ICC calculations;  
<sup>c</sup>Qualitative interpretation of agreement statistics from following references: Viera and Garrett (2005), Koo and Li (2016).
Finally, scores 6-8 indicate that material enters the airway and passes below the level of the vocal folds (i.e., aspiration), and differ based on attempts and success of ejection; a level 6 indicates that material is ejected back into the laryngeal vestibule (or higher), level 7 indicates that an individual made an attempt to eject (but was unsuccessful), and level 8 indicates that the individual did not make any attempt to eject the aspirated material (i.e., “silent aspiration”).

Traditionally, PAS scores have been handled as a continuous or ordinal measure, such that each level on the scale is considered “more unsafe” than the preceding (e.g., Langmore et al., 2016; Pearson et al., 2016; Troche et al., 2010). Still, recent perspectives have suggested it may be more appropriately interpreted as a nominal/categorical scale and have proposed an alternate framework for grouping the various levels of the scale based on location of bolus material post-swallow and physiological response (i.e., PAS 1, 2, 4 – no material in airway post-swallow; PAS 3, 5, 6 – bolus residue remaining in laryngeal vestibule, but final location rests above the vocal folds; PAS 7 – remaining material located below the vocal folds, with response/attempt to eject; PAS 8 – remaining material located below the vocal folds, no attempt to eject) (Steele & Grace-Martin, 2017). For this study, PAS scores were treated as nominal data to describe the depth and response to airway invasion.

In this study sample, 13/20 participants had at least one bolus trial that was rated as “unsafe” (i.e., PAS ≥3) on the initial swallow, with a total of 45 bolus trials (i.e., 17% of all trials) deemed to be unsafe. Approximately half of these (n=25) were judged to be “trace” amounts of bolus invasion, while the remaining 20 cases were judged to have “more than trace” amounts of bolus invasion. The distribution of PAS scores at the bolus level is depicted in Figure 4-4. No PAS scores of 4 or 7 were observed in this sample.

In terms of the timing of airway invasion, 43/45 instances of unsafe swallowing occurred before laryngeal vestibule closure (or its closest approximation) was achieved, while the remaining 2 instances occurred after the moment of maximal airway protection. This suggests a distinctly higher occurrence of aspiration before or during the swallow than aspiration occurring after the swallow; however, as this study only explored results from the first swallow per bolus trial, these patterns cannot necessarily generalize to higher order swallows, which may have additional factors influencing swallowing safety (e.g., presence of post-swallow residue).
Based on the distribution of PAS scores, we did not have enough statistical power to explore mechanisms at each level or proposed functional categories of the PAS scale. We were also unable to compare occurrences of penetration (PAS 3-5) versus aspiration (PAS 6-8), due to few cases of true aspiration. Thus, for the remainder of the analyses we grouped PAS scores into binary categories of “safe” (i.e., PAS<3) and “unsafe” (i.e., PAS≥3).

**Figure 4-4.** Distribution of PAS scores at the bolus-level, swallow 1 only (n=269; n=1 missing data). Frequency count (raw) displayed above each column.

**Swallowing Efficiency**

Swallowing efficiency was measured in several ways. First, the total number of swallowing events was tallied, per bolus, to indicate how many swallows plus swallow attempts were initiated in effort to clear a given bolus. Pixel-based measures of pharyngeal residue and available space (i.e., “housing area”) were taken separately for the valleculae and pyriform sinuses; these measures were used to calculate the Normalized Residue Ratio Scale (NRRS) (Pearson, Molfenter, Smith & Steele, 2013) within each anatomical location:

\[
NRRS = \left( \frac{\text{residue area}}{\text{housing area}} \right) \times 10 \times \left( \frac{\text{residue area}}{C^2 - 4 \text{ length}^2} \right)
\]
Previous work has identified clinical thresholds using the NRNS at which post-swallow residue places an individual at greater risk for aspiration on a subsequent swallow (Molfenter & Steele, 2013): NRNSv > 0.09; NRNSp > 0.2.

Finally, pharyngeal residue located outside the vallecular and pyriform sinuses (“extra residue”) was measured and added to vallecular and pyriform residues to obtain a measure of total pharyngeal residue, in reference to the squared area of the anatomical scalar:

\[
Total\ Residue = \sumallresidue \times 100
\]

Figure 4-5. Measurement of post-swallow pharyngeal residue. A) Original image. B) Example tracings for calculating the Normalized Residue Ratio Scale (calculated separately for valleculae, pyriform sinuses). C) Example tracing of total residue (yellow) expressed as a percentage of the squared anatomical scalar (%C^2-4^2).
For statistical analysis, we focused primarily on total pharyngeal residue (%C2-42) and the maximum number of swallow events, per bolus. NRRS scores were used descriptively to characterize location of post-swallow residue.

In healthy individuals, total pharyngeal residue has measured less than 1% C2-42 (Steele et al., 2018b). In this study, only 3/20 participants presented with less than 1% C2-42 residue on all trials, while 5 others displayed between 1-2% C2-42 residue amounts on at least one trial. The remaining 12 participants had post-swallow pharyngeal residue which measured more than 2% of the C2-42 reference area on at least one trial (median = 2.42% C2-42, range: 0-23.93). At the bolus-level, 42% of trials had total residue measures above 1% C2-42. Two participants presented as consistent outliers, with post-swallow residue measuring greater than 10% C2-42 on all trials.

Based on previously described clinical thresholds using the NRRS, 7/20 participants in the current dataset displayed above-threshold vallecular residue after the first swallow (i.e., NRRSv >0.09; median = 0.036; range: 0-0.787) while only 1/20 participants displayed above-threshold pyriform sinus residue (i.e., NRRSp >0.20; median = 0.006; range: 0-0.655). Nine participants required 3 or more swallow events on at least one bolus trial (median = 2; range: 1-10) (Molfenter et al., 2011).

4.5.3 Part 1b: Characterization of Swallowing Physiology

Swallowing physiology was characterized based on timing intervals between key physiological events and pixel-based measures of swallowing movements. Parameters of interest are summarized below, grouped by proposed subsystem (i.e., Pharyngeal, Laryngeal, Hyoid) to align with research hypotheses and aims.

Ten bolus clips were excluded from analysis of swallowing physiology due to high numbers of replicate frames (i.e., >25% frames duplicated). Further, bolus clips from n=1 participant were excluded due to a loose-fitting coaxial cable which led to the presence of visual artifacts, asynchronous recording and split frames.

Swallowing physiology was initially characterized based on the thin liquid trial with the best physiological performance for each parameter, by participant. These results are summarized in
Table 4-4. Median and minimum/maximum values are provided, as most parameters were positively skewed or influenced by outliers.

Table 4-4

*Swallowing physiology and kinematics based on the trial (thin barium) with best physiological performance.*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit of Measure</th>
<th>n</th>
<th>Defining “Best”</th>
<th>Median (min;max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVCrt</td>
<td>ms</td>
<td>19</td>
<td>Fastest</td>
<td>266.67 (-633.33;533.33)</td>
</tr>
<tr>
<td>LVCdur</td>
<td>ms</td>
<td>17</td>
<td>Longest</td>
<td>566.67 (266.67;1433.33)</td>
</tr>
<tr>
<td>UESOdur</td>
<td>ms</td>
<td>19</td>
<td>Longest</td>
<td>633.33 (466.67;900.00)</td>
</tr>
<tr>
<td>UES Width</td>
<td>%C2-4</td>
<td>19</td>
<td>Widest</td>
<td>18.04 (5.54;29.43)</td>
</tr>
<tr>
<td>Pharyngeal Constriction Area</td>
<td>%C2-4²</td>
<td>19</td>
<td>Smallest</td>
<td>1.12 (0.00;42.99)</td>
</tr>
<tr>
<td>Hyoid_xmax</td>
<td>%C2-4</td>
<td>19</td>
<td>Farthest</td>
<td>131.90 (102.60;188.90)</td>
</tr>
<tr>
<td>Hyoid_ymax</td>
<td>%C2-4</td>
<td>19</td>
<td>Farthest</td>
<td>101.30 (48.50;168.90)</td>
</tr>
<tr>
<td>Hyoid_xymax</td>
<td>%C2-4</td>
<td>19</td>
<td>Farthest</td>
<td>164.97 (125.45;219.76)</td>
</tr>
<tr>
<td>Hyoid_xvel</td>
<td>%C2-4</td>
<td>19</td>
<td>Fastest</td>
<td>55.57 (10.12;89.93)</td>
</tr>
<tr>
<td>Hyoid_yvel</td>
<td>%C2-4</td>
<td>19</td>
<td>Fastest</td>
<td>102.34 (55.95;213.68)</td>
</tr>
<tr>
<td>Hyoid_xyspeed</td>
<td>%C2-4</td>
<td>19</td>
<td>Fastest</td>
<td>79.15 (42.82;175.82)</td>
</tr>
</tbody>
</table>

*Laryngeal Parameters*

Airway protection was characterized in terms of the *degree, timing, and duration* of laryngeal vestibule closure (LVC). The *degree* of LVC was evaluated at the frame depicting the closest approximation between the arytenoids and laryngeal surface of the epiglottis (i.e., referred to as: maximum laryngeal vestibule approximation (LVA) frame. If full contact between the arytenoids and laryngeal surface of the epiglottis was achieved, leaving no visible airspace in the laryngeal vestibule, LVC was scored as “complete”. If full contact was not achieved, or if there was a
single point of contact with visible space remaining in the laryngeal vestibule, LVC was scored as “incomplete”.

In this study sample, 9/20 individuals presented with incomplete LVC on at least one trial of thin liquid. However, only 2 of these individuals presented with incomplete LVC on all trials of thin, while the remaining 7 were inconsistently able to achieve complete LVC. At the bolus-level (thin only, \( n=56 \)), 13 trials were scored as having incomplete LVC (i.e., 23% of all thin trials).

The timing of LVC was captured by LVCrt, a measure of the interval between onset of hyoid burst and LVA frame, including individuals who did not achieve complete LVC. In the current study, 2 individuals presented with negative LVCrt values, such that these participants achieved complete LVC prior to onset of hyoid burst. As such, central tendency for this parameter is reported based on the median and range, and those extreme values were not included in any further analyses. Previous reports from healthy individuals have shown that LVCrt should be less than 220ms (based on a 5mL barium bolus) (Guedes et al., 2017). Eleven participants displayed prolonged LVCrt on their “best” thin liquid trial, and a total of \( n=43 \) thin boluses (77%) in this study displayed LVCrt >220ms.

The duration of LVC (LVCdur) was calculated based on the number of frames between initial closure of the airway (LVA frame), until initial release of the arytenoids from the laryngeal surface of the epiglottis (offset LVC frame). This measure could not be calculated for two participants; one did not achieve complete LVC on any trial (i.e., no rateable onset), while the other swallowed sequentially and maintained airway closure throughout the second swallow (i.e., no rateable offset, within swallow 1). Of the remaining participants, average LVCdur was recorded at 649.02ms. Existing data from healthy individuals has reported a 95% confidence interval for LVCdur, ranging from 280-570ms (based on a 5mL barium bolus) (Guedes et al., 2017; Sasegbon & Hamdy, 2017). Only two participants presented with short LVCdur (i.e., \( n=5 \) boluses, 9% of thin trials). In contrast, 8 participants presented with LVCdur that was longer than the reported upper confidence interval for healthy individuals (\( n=18 \) boluses, 35% of thin liquids trials).
Pharyngeal Parameters

Evaluation of pharyngeal mechanisms included measures of the degree and duration of UES opening as well as the degree of pharyngeal constriction during the swallow. Width of UES opening was measured at the frame of maximum UES distension and expressed as a percentage of the C2-4 anatomical scalar:

\[
\text{Normalized UES width} = \frac{\text{Width of UES}}{\text{Length of C2 - 4}} \times 100
\]

Normalized UES width has not yet been reported for healthy comparison; previous studies have reported UES width in reference to an external scalar (e.g., coin) and reported in millimeters (Kendall & Leonard, 2002; Leonard et al., 2004; Leonard et al., 2000). A recent exploration of swallowing physiology in patients with oculopharyngeal muscular dystrophy recorded an average UES width of 15.8% C2-4 (95% CI: 14.2 to 17.5) (Waito, Steele, et al., 2018). In comparison, this cohort of patients with ALS displayed marginally wider UES width, with a mean of 17.8% C2-4 (95% CI: 14.1-21.5). Still, this comparison must be interpreted with caution as the OPMD data were based on small 3mL thin barium trials (vs. “comfortable sips” in the current study), and differences in UES function may be expected between these two clinical populations.

Duration of UES opening (UESOdur) was calculated as the number of frames between the first frame showing passage of air or bolus through the UES until the first frame showing a point of closure along the UES segment. In this study, average UESOdur was recorded at 638.60ms (95% CI: 584.18-693.02) for thin liquid trials. Previous reports of UESOdur in healthy adults have reported a range of 562-648ms, based on a 10mL barium bolus (Kern et al., 1999). In the current dataset, 5 individuals presented with short UESOdur (i.e., 38% of all thin bolus trials), while 8 individuals presented with prolonged UESOdur (i.e., 29% of all bolus trials; equivalent to the number of trials falling below the expected reference range). As duration of UES opening has been reported to increase with larger bolus volumes, influence of sip size (weight) will be explored further in a subsequent analysis.

Pharyngeal area at maximum constriction was previously described and identified as a mechanism associated with swallowing efficiency in Study 2. In this study, maximum
pharyngeal constriction areas ranged from 0 to 44% C2-4², with a mean area of 4% C2-4². Seven individuals presented with consistently enlarged maximum pharyngeal constriction areas (i.e., >2.2% C2-4², even on “best” trial), while 9/20 participants consistently fell within the normal range. Of all thin liquid trials, 26 trials (i.e., 46%) displayed above-normal maximum pharyngeal constriction areas >2.2% C2-4². Two participants presented as consistent outliers, with maximum pharyngeal constriction areas measuring above 15% C2-4² on all trials. These cases were excluded from further analysis.

**Hyoid Parameters**

Measurement of hyoid kinematics followed the same methodology as described in Chapter 3, Part 2. The position of the hyoid was tracked frame-by-frame in reference to C2-4 vertebrae, with C4 serving as the origin. Using MatLab (The MathWorks, Inc., Natick, MA), average hyoid peak position and velocity/speed of movement were extracted along three axes of movement: anterior (x), superior (y), and anterosuperior (xy). Hyoid position could not be marked for one bolus trial due to improper patient positioning, adjusting the total number of thin bolus trials to n=55.

Existing reference data for anatomically referenced hyoid movement in healthy individuals were used for comparison (Molfenter & Steele, 2014b; Nagy et al., 2015):

- Peak Position: Anterior (x) <132% C2-4; Superior (y) <84% C2-4; Anterosuperior (xy) <160% C2-4;

- Velocity/Speed: Anterior (x) <75% C2-4/s; Superior (y) <56% C2-4/s; Anterosuperior (xy) <102% C2-4/s.

Along the anterior (x) axis, 12 participants displayed below-reference anterior hyoid position on at least one trial (56% of thin bolus trials) and 18 participants measured below-reference anterior hyoid velocity (86% of thin bolus trials). Comparably, 10 participants displayed reduced movement along the anterosuperior (xy) axis (44% of all thin bolus trials), and 17 individuals displayed below-reference anterosuperior hyoid speed (89% of thin trials). In contrast, only 5 participants displayed below average superior position or velocity (26% and 15% of thin bolus trials, respectively). Interestingly, a small proportion of individuals displayed above-reference
values for maximum anterior \((n=5)\), anterosuperior \((n=7)\) or superior \((n=8)\) position; several individuals also displayed above-reference superior velocity \((n=5)\) or anterosuperior speed \((n=1)\). The source of these variations requires further investigation.

4.5.4 Part 2: Role of Liquid Thickness on Swallowing Behaviour

To test the influence of bolus thickness on swallowing safety, we ran a Cochran Q test (Cochran, 1950; Laerd Statistics, 2017) with a repeated independent variable of IDDSI level (5 levels), against swallowing safety (2 levels). Our a priori research question was whether the proportion of participants with PAS\(\geq 3\) on thin liquids differed from the proportion of participants with PAS\(\geq 3\) on each of the thicker consistencies. Data were expressed at the participant level, such that if a participant were rated as having PAS\(\geq 3\) on the first swallow of at least one bolus trial of a given liquid thickness, they were scored “unsafe” for that IDDSI level. Only those participants who had at least one trial of each thickness were included in the analysis \((n=17)\). Results of the Cochran Q test indicated that the proportion of participants with unsafe swallows differed, based on IDDSI level \((\chi^2(4) = 10.720, p = 0.03)\). Pairwise comparisons using Dunn’s test (Dunn, 1964) with a Bonferroni correction to adjust for multiple (4) comparisons revealed that the proportion of unsafe swallowing was higher for thin liquids (IDDSI Level 0) compared to extremely thick liquids (IDDSI Level 4), \(p = 0.002\). No other comparisons reached statistical significance.

Due to skewness in the residue data, nonparametric Friedman tests were used to determine if swallowing efficiency (% C2-4\(^2\) residue; number of swallow events) varied according to bolus thickness. Data were expressed at the participant-level based on the trial with the greatest amount of post-swallow residue, per IDDSI level. As with safety data, only those participants who had at least one trial of each thickness were included in the analysis \((n=17)\). Median values of total residue (% C2-4\(^2\)) and number of swallow events are presented in Table 4-5. Results indicated that bolus thickness did not influence the total amount of post-swallow residue \((\chi^2(4) = 1.908, p = 0.753)\) nor maximum number of swallow events \((\chi^2(4) = 7.200, p = 0.126)\).

Post-hoc inspection of the data revealed that vallecular residue (NRRSv) demonstrated a rising trend with increased liquid thickness, while pyriform sinus residue (NRRSp) showed a non-linear trend, such that the thinnest and thickest bolus types had less residue compared to mildly thick. These observations were reviewed further with Friedman tests; however, results were not statistically significant \((p>0.05)\).
Table 4-5

Median (min:max) values of post-swallow residue (% C2-4², NRRSv, NRRSp) and number of swallowing events, by IDDSI level. Based solely on cases with at least one trial of each liquid level (n=17).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Thin (0)</th>
<th>Slightly Thick (1)</th>
<th>Mildly Thick (2)</th>
<th>Moderately Thick (3)</th>
<th>Extremely Thick (4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Swallow Events</td>
<td>1 (1;5)</td>
<td>1 (1;10)</td>
<td>1 (1;6)</td>
<td>1 (1;6)</td>
<td>2 (1;6)</td>
</tr>
<tr>
<td>Total Residue (% C2-4²)</td>
<td>0.90</td>
<td>1.09</td>
<td>1.22</td>
<td>1.62</td>
<td>0.97</td>
</tr>
<tr>
<td></td>
<td>(0.00;10.31)</td>
<td>(0.00;10.99)</td>
<td>(0.00;12.37)</td>
<td>(0.00;12.75)</td>
<td>(0.00;13.67)</td>
</tr>
<tr>
<td>Vallecular Residue (NRRSv)</td>
<td>0.000</td>
<td>0.002</td>
<td>0.001</td>
<td>0.005</td>
<td>0.011</td>
</tr>
<tr>
<td></td>
<td>(0.00;0.25)</td>
<td>(0.00;0.38)</td>
<td>(0.00;0.46)</td>
<td>(0.00;0.59)</td>
<td>(0.00;0.74)</td>
</tr>
<tr>
<td>Pyriform Sinus Residue (NRRSp)</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.002</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>(0.00;0.06)</td>
<td>(0.00;0.08)</td>
<td>(0.00;0.12)</td>
<td>(0.00;0.08)</td>
<td>(0.00;0.004)</td>
</tr>
</tbody>
</table>

To determine the influence of bolus thickness on various parameters of swallowing physiology, we ran separate linear mixed models, with a repeated factor of IDDSI level. Further, as bolus volume effects have been previously indicated as modulating swallowing physiology, we included sip weight (g) as a continuous covariate. Consistent with previous analyses, this exploration included only those participants with at least one trial of each thickness (n=16).

For this analysis, we opted not to perform a Bonferroni correction to account for multiple comparisons, as our study is limited in power due to a small sample size, which inherently elevates the risk of committing a type II error (Daniel & Cross, 2013; Krzywinski & Altman, 2013; Smith, 2018), and our research questions remain exploratory (Armstrong, 2014; Bender & Lange, 2001; Ranstam, 2016; Streiner & Norman, 2011). Further, this analysis was used to determine which factors/covariates would be included in any subsequent research questions; thus, the possibility of overcorrecting in this case could give rise to the omission of a potentially important covariate and misrepresenting the final interpretation. For these reasons, it was deemed important to remain inclusive to any results which were statistically significant at p<0.05. Still, these results should be interpreted with caution and future research may use this exploratory data to perform power calculations to guide further study of such parameters.

Results of this analysis did not find an effect of IDDSI level on any of the included physiological parameters. However, a main effect of sip weight (g) was identified on LVCrt (F=4.758,
\( df=1.63.252, p=0.033 \) and UES width \( (F=7.972, df=1.67.490, p=0.006) \), such that larger sips evoked marginally faster LVCrt \( (r=-0.235, p=0.039) \) and wider UES width \( (r=0.491, p<0.001) \); therefore, sip weight will be included as a covariate for these parameters in subsequent analyses. No interaction effects were identified between IDDSI level and sip weight. Results are summarized in Table 4-6.

Table 4-6

Summary of statistical results from linear mixed models, exploring the roles of liquid thickness (IDDSI Level) and sip weight (g) on parameters of swallowing physiology.

<table>
<thead>
<tr>
<th>Physiological Parameter</th>
<th>Factor: IDDSI level (5)</th>
<th>Covariate: Sip weight (g)</th>
<th>Interaction: IDDSI*sip weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVCrt</td>
<td>n.s. ( (p=0.439) )</td>
<td>Sig. ( (p=0.033) )</td>
<td>n.s. ( (p=0.093) )</td>
</tr>
<tr>
<td>LVCdur</td>
<td>n.s. ( (p=0.996) )</td>
<td>n.s. ( (p=0.226) )</td>
<td>n.s. ( (p=0.994) )</td>
</tr>
<tr>
<td>UESOdur</td>
<td>n.s. ( (p=0.293) )</td>
<td>n.s. ( (p=0.406) )</td>
<td>n.s. ( (p=0.121) )</td>
</tr>
<tr>
<td>Hyoid_xmax</td>
<td>n.s. ( (p=0.819) )</td>
<td>n.s. ( (p=0.396) )</td>
<td>n.s. ( (p=0.698) )</td>
</tr>
<tr>
<td>Hyoid_ymax</td>
<td>n.s. ( (p=0.531) )</td>
<td>n.s. ( (p=0.318) )</td>
<td>n.s. ( (p=0.775) )</td>
</tr>
<tr>
<td>Hyoid_xymax</td>
<td>n.s. ( (p=0.466) )</td>
<td>n.s. ( (p=0.340) )</td>
<td>n.s. ( (p=0.362) )</td>
</tr>
<tr>
<td>Hyoid_xvel</td>
<td>n.s. ( (p=0.229) )</td>
<td>n.s. ( (p=0.619) )</td>
<td>n.s. ( (p=0.108) )</td>
</tr>
<tr>
<td>Hyoid_yvel</td>
<td>n.s. ( (p=0.179) )</td>
<td>n.s. ( (p=0.253) )</td>
<td>n.s. ( (p=0.266) )</td>
</tr>
<tr>
<td>Hyoid_xyspeed</td>
<td>n.s. ( (p=0.660) )</td>
<td>n.s. ( (p=0.174) )</td>
<td>n.s. ( (p=0.508) )</td>
</tr>
<tr>
<td>UES width</td>
<td>n.s. ( (p=0.771) )</td>
<td>Sig. ( (p=0.006) )</td>
<td>n.s. ( (p=0.911) )</td>
</tr>
<tr>
<td>MPCA( N )</td>
<td>n.s. ( (p=0.302) )</td>
<td>n.s. ( (p=0.110) )</td>
<td>n.s. ( (p=0.368) )</td>
</tr>
</tbody>
</table>

We were surprised that sip weight had no influence on maximum pharyngeal constriction area or hyoid velocity/speed, as bolus volume effects were seen in Chapter 3. One possible explanation
is that this study is underpowered for identifying this phenomenon, as sip volume was not systematically controlled.

4.5.5 Part 3: Associations between Physiology and Function

The final step in this analysis was to explore the associations between parameters of swallowing physiology and metrics of swallowing safety and efficiency. The analysis involved separate Generalized Estimating Equations (GEE) with a repeated factor of trial number, exploring laryngeal, pharyngeal, and hyoid parameters against PAS (binary) and total pharyngeal residue (%C2-42). Each group of parameters was run separately to test the a priori hypothesized associations between laryngeal parameters and swallowing safety, pharyngeal parameters and swallowing efficiency, and no predicted association between hyoid movement and safety/efficiency. Parameters were clustered as follows:

- **Laryngeal Parameters:** LVC (complete vs. incomplete), LVCdur, LVCrt, LVCrt*SipWeight
- **Pharyngeal Parameters:** Maximum pharyngeal constriction area, UESOdur, UES width, UES width*SipWeight
- **Hyoid Parameters:** xmax, ymax, xymax, xvel, yvel, xyspeed

Videos which had been excluded from kinematic analysis, due to high frequency of frame replication or poor image acquisition, remained excluded from this analysis. Extreme outliers (i.e., LVCrt<0ms, maximum pharyngeal constriction area >15% C2-42) were treated as missing data points to mitigate excess influence on the dependent variables, while maintaining other mechanisms associated with that bolus trial.

*Mechanisms Associated with Penetration-Aspiration*

Explorations focused on mechanisms of swallowing safety included trials with the worst PAS score on swallow one, and the associated timing/kinematic measures from that same trial. If two trials of the same consistency were scored the same in terms of function, we recorded the first occurrence with no missing data points.
We limited the analysis to only include sippable liquids (i.e., IDDSI level 0-2) thin, slightly, and mildly-thick liquid trials. As these IDDSI levels did not differ significantly in terms of PAS occurrence in Part 1, we did not include IDDSI level as an independent factor in the model. However, sip weight was included as an interaction factor with UES width and LVCrt, as sip weight was shown to modulate these physiological parameters in Part 2.

The GEE models for PAS mechanisms followed a binary logit design, with PAS as the dependent variable and the various physiological mechanisms included as independent variables. The first model exploring laryngeal mechanisms on PAS revealed main effects of LVC ($\chi^2(1) = 7.436, p=0.006$) and LVCrt ($\chi^2(1) = 13.889, p<0.001$), such that unsafe swallows were more likely to have incomplete LVC and prolonged LVCrt. Further, a significant interaction effect between LVCrt*SipWeight was identified ($\chi^2(1) = 4.301, p=0.038$), suggesting variation in the relationship between LVCrt and PAS, based on sip weight/volume. Finally, the third model exploring hyoid kinematics revealed a main effect of hyoid_yvel ($\chi^2(1) = 5.696, p = 0.017$), such that unsafe swallows had marginally faster hyoid velocities along the superior axis. No pharyngeal parameters were found to be associated with swallowing safety status. We graphed the influence of each continuous factor using boxplots, stratified by Safe and Unsafe status, shown in Figure 4-6.
Figure 4-6. Box-and-whisker plots depicting differences in a) LVCrt (pooled), b) LVCrt (stratified by sip weight), and c) superior hyoid velocity, based on swallow safety (safe=green vs. unsafe=red).

Mechanisms associated with Post-Swallow Residue

Following a similar convention as conducted with swallowing safety, explorations focused on mechanisms of post-swallow residue included trials with the largest total residue score (% C2-4^2) score on swallow one, and the associated timing/kinematic measures from that same trial. If two trials of the same consistency were scored the same in terms of function, we recorded the first occurrence with no missing data points.

This analysis included trials from all 5 IDDSI levels, as IDDSI level was not found to have an influence on the amount of total post-swallow residue. As with the previous analysis of
swallowing safety, sip weight was included as an independent covariate and as an interaction factor with UES width and LVCrt.

The GEE models for mechanisms of post-swallow residue followed a linear design, with total residue (% C2-4^2) as the dependent variable, and the physiological mechanisms of interest included as independent variables. Of all parameters included in the various analyses, MPCA_N was the only parameter identified as having a significant association with total pharyngeal residue (\(\chi^2(1) = 8.439, p < 0.004\)).

Post-hoc modelling of the relationship between maximum pharyngeal constriction area and post-swallow residue is shown in Figure 4-7. A Spearman’s rho test revealed a strong positive association between maximum pharyngeal constriction area and total pharyngeal residue (\(r_s(76)=0.604, p<0.001\)).

![Figure 4-7. Relationship between post-swallow residue and maximum pharyngeal constriction area, extreme cases removed (n=78, bolus-level).](image)
4.6 Discussion

In this study, swallowing function (i.e., safety and efficiency) and physiology were characterized using a standard protocol with naturalistic bolus trials (i.e., uncued, “comfortable” sip size). Focusing on the first swallow per bolus, we summarized patterns of swallowing safety and efficiency in a cohort of individuals with ALS, and identified measurable differences in swallowing physiology, compared to reference data from healthy adults.

We identified a low occurrence of unsafe swallowing in this cohort of individuals with ALS. More than 80% of bolus trials were scored “safe” (i.e., PAS<3) on the first swallow, while the remaining 17% were “unsafe” (i.e., PAS≥3). This is likely reflective of the severity of the study cohort; many of the patients recruited for this study had been recently diagnosed with ALS and presented with early signs of bulbar dysfunction. Still, more than half of the study sample (13/20) presented with at least one trial with a PAS score of 3 or more, highlighting the fact that unsafe swallowing may not be a consistent feature of every swallow (Hedstrom et al., 2017; Steele, Nagy, et al., 2015), even in individuals with bulbar compromise associated with ALS.

When we examined swallowing safety across the different liquid thicknesses, we identified a reduced occurrence of unsafe swallowing with extremely thick liquids (IDDSI level 4), compared to thin liquids (IDDSI level 0). This finding offers continued support to the recommendation of thick liquids to reduce the risk of penetration-aspiration. Still, it is important to highlight that this relationship was only seen between the thinnest and thickest liquid levels and is based on few observations of unsafe swallowing in the study sample. Further, these results are limited to swallowing safety on the first swallow only, with a common pattern of unsafe events occurring before the moment of airway closure. It will be important for future research to evaluate swallowing safety on higher order swallows (e.g., piecemeal, clearing swallows), to determine if the timing of bolus entry remains unchanged and to investigate potential relationships between unsafe swallowing and post-swallow residue. Such an exploration has been previously done in a neurogenic population, revealing levels of post-swallow residue which increased the risk of unsafe swallowing (Molfenter & Steele, 2013).

In terms of swallowing efficiency, 12 participants presented with total pharyngeal residue >2% the normalized reference area (i.e., C2-4^2), on at least one bolus trial, and 9 participants required 3 or more swallows per bolus (Ertekin, Aydogdu, & Yuceyar, 1996; Molfenter et al., 2011).
Swallowing efficiency has been reported as one of the earliest functional changes associated with ALS, often exceeding concerns related to airway safety (Morimoto et al., 2013; Paris et al., 2013; Silverstein & Faegenburg, 1965; Takasaki et al., 2010; Teismann et al., 2011; Wright & Jordan, 1997). In this study, the proportion of individuals with unsafe swallowing was found to be comparable to those displaying inefficiency; however, inefficiency was found to be much more consistent within individuals, as evidenced by a higher proportion of bolus trials displaying inefficiency (i.e., 42% of all trials). Comparable to findings reported in Chapter 3 (Waito, Tabor-Gray, et al., 2018), a higher proportion of individuals in this study displayed clinically significant vallecular residue than pyriform sinus residue, providing continued support towards a hypothesis of rostrocaudal progression of dysfunction through the pharyngeal swallowing mechanism (Plowman, Tabor, et al., 2016). Still, longitudinal studies characterizing swallowing physiology and function in ALS remain imperative to understand whether a predictable pattern of post-swallow residue truly exists.

We had initially hypothesized an association between swallowing efficiency and liquid thickness, such that thicker liquids would result in greater post-swallow residue and/or a greater number of swallows per bolus; however, our results failed to support either of these relationships. Further, previously identified relationships between liquid consistency and vallecular residue (Waito, Tabor-Gray, et al., 2018) were not replicated in the current study. It is possible that the stimuli used for this study were not sufficiently challenging to reveal such relationships and that liquid thickness may not be the only bolus property associated with patterns of post-swallow residue. Anecdotally, several participants subjectively reported the spoon-thick liquids (i.e., moderately, extremely thick) to be “easier to swallow”. When prompted further, one participant expressed that the thicker liquid was easier because it “stayed together” while they swallowed, suggesting a potential benefit of bolus cohesion. Future studies should consider exploring additional textures along the IDDSI continuum and contrasting between thickener types (e.g., xanthan-gum vs. starch), to determine if other bolus properties influence swallowing efficiency. Until we have a greater understanding of the bolus properties associated with swallowing efficiency, clinicians are encouraged to continue prescribing texture-modifications tailored to individual patient presentation.

In this study, we observed comparable differences in maximum pharyngeal constriction and hyoid movement, as previously reported (Waito, Peladeau-Pigeon, et al., 2018; Waito, Tabor-
Gray, et al., 2018). However, these changes were noted in a smaller proportion of the current sample, likely reflecting differences in ALS severity between the study cohorts. In addition to these metrics, we also explored measures of airway protection and UES function. Our results point to changes in the timing and completeness of airway protection – both of which appear to be associated with unsafe swallowing, comparable to previous reports from ALS (Plowman, Tabor, et al., 2016) and other clinical populations (e.g., Kahrilas, Lin, Rademaker, & Logemann, 1997; Park, Kim, Ko, & McCullough, 2010). Post-hoc inspection of the data revealed that all cases with incomplete LVC in this study also displayed prolonged LVCrt, suggesting that the timing of airway closure (LVCrt) may be an earlier physiological change, followed by impairments in the completeness of the airway closure. Again, these inferences will require further exploration through longitudinal study designs.

Based on the neuropathology of ALS, one might hypothesize that measurable changes in physiology would be one-sided, such that all observed changes would indicate slowing, reduced range of motion, and impaired overall function. However, duration of LVC was only found to be reduced in 2 participants, and interestingly, measured longer than reference values in 8 participants. Similarly, duration of UES opening was found to be prolonged in 8 participants of the sample, an observation that also been reported in patients with OPMD (Waito, Steele, et al., 2018) or cricopharyngeal bar (Leonard et al., 2004). These observations are intriguing because they suggest the possibility of physiological compensation, such that unaffected physiological components of the pharyngeal swallow may display altered behaviours that offset the negative contributions of other parameters. Support for such a phenomenon in patients with ALS has also been seen in measures of speech articulation; patients with ALS who display reduced tongue movement often present with compensatory increases in jaw movement to maintain overall intelligibility (Yunusova et al., 2010). Further research exploring the relationships between physiological parameters, including longitudinal timing and co-occurrence of such changes, will help delineate patterns of progression.

Explorations between physiological parameters of swallowing and swallowing function yielded some interesting results. For swallowing efficiency, pharyngeal area at maximum constriction remained the sole parameter associated with the presence of post-swallow residue, comparable to what has been previously identified. Although pharyngeal constriction was estimated using a single gestalt measure, taken when the pharynx was maximally constricted, multiple components
are involved in constriction of the pharynx throughout the swallow, including pharyngeal shortening from long pharyngeal muscles, approximation between the base of tongue and posterior pharyngeal wall, and lateral movement from pharyngeal constrictor muscles (Leonard et al., 2011; Palmer, Tanaka, & Ensrud, 2000). It is possible that one or more of these sub-components represents a primary contributor(s) to enlarged maximum pharyngeal constriction areas in ALS. Previous studies using combined videofluoroscopy and manometry have illustrated differential changes in swallow-related pharyngeal pressure when comparing the oro- and hypopharyngeal regions (Goeleven et al., 2006; Higo et al., 2002), suggesting early involvement of the base of tongue. Future studies may wish to consider exploring estimates of base-of-tongue retraction and pharyngeal shortening (e.g., via elevation of the laryngeal air column) to determine if these sub-components of pharyngeal constriction play distinct roles with respect to swallowing efficiency in ALS.

In contrast, three physiological parameters explored in this study were associated with unsafe swallowing: LVCrt, LVC, and superior hyoid velocity (y-vel). Although parameters of airway closure (e.g., LVC, LVCrt) have the most direct relationship to unsafe swallowing (Vose & Humbert, 2018), additional associations with hyoid kinematics suggest that other concomitant changes in swallowing physiology may co-occur with an increased risk of penetration-aspiration in ALS. It is possible that other physiological subsystems not directly explored in this analysis (e.g., tongue strength, patterns of respiration) may also be associated with unsafe swallowing, requiring further study.

We were surprised to identify superior hyoid velocity as a feature associated with swallowing safety, particularly as no significant group differences in superior velocity were identified in this or previous analyses. Further, one might expect that slower hyoid movements would be most likely to influence swallowing safety, however the association identified in the current study suggested that unsafe swallowing was associated with marginally faster superior hyoid velocity. Further exploration of this finding is needed to delineate the source of the association. It is possible that these events are simply co-occurring, as this study is not designed or sufficiently powered to discern causative relationships. It is also possible that the effect is associated with an unexplored interaction between hyoid velocity and baseline resting position, as a lower resting position of the hyoid (e.g., related to loss of suprahyoid muscle tone) (Bosma & Brodie, 1969;
Ertekin et al., 2000; Fattori et al., 2006) may evoke faster superior hyoid velocities to maintain the target movement despite a change in resting position.

For this study, we contrasted laryngeal and pharyngeal mechanisms as differential sources of functional impairment. The use of a subsystem approach has been strongly supported for evaluating ALS bulbar function for speech (Green et al., 2013), as such an approach allows researchers and clinicians to isolate individual components of an otherwise complex and dynamic mechanism, and contrast subtle differences occurring between and within each system: respiratory, phonatory, resonatory, and articulatory. As swallowing presents a similar challenge with respect to its complexity, and the involvement of multiple components acting synergistically to perform the final behaviour, a similar subsystem paradigm may be appropriate for characterizing swallowing function. Although there is overlap between subsystems for speech and those involved in swallowing, due to shared anatomical features and cross-system coordination, motor control for speech and swallowing remain highly distinct from one another. Thus, it would be necessary to reframe the subsystems to align closely with swallowing mechanics and identify unique metrics which are able to detect meaningful differences associated with swallowing (e.g., early markers of change, associations with function). From the current study, we suggest inclusion of parameters of airway protection and pharyngeal constriction, based on their presumed associations with safety and efficiency. Still, the inclusion of additional metrics remains encouraged to continue exploring patterns of physiological change with disease progression and illuminate potential patterns of physiological compensation.

4.6.1 Limitations

There are several limitations to this research design and analysis. As has been mentioned previously, this study focused on the first swallow per bolus trial to characterize swallow physiology and function. As such, we are unable to generalize the findings to higher-order swallows and variability in bolus volume due to piecemeal swallowing patterns could not be controlled. Further, we limited this analysis to liquid boluses, mixed to 20% w/v barium concentration and thickened with xanthan-gum thickener. It is possible that these liquids may present differently on VFSS than other textures (e.g., semi-solids), thickeners (e.g., starch-based), or barium concentrations (e.g., 40% w/v). Barium concentration has been previously shown to influence parameters of swallowing physiology (Dantas, Dodds, Massey, & Kern,
1989; Fink & Ross, 2009; Stokely, Molfenter, & Steele, 2014). Further, preliminary research has demonstrated that xanthan-gum thickeners may be less likely to lead to residue compared to starch-based thickeners (Vilardell, Rofes, Arreola, Speyer, & Clavé, 2016). It will be important for future work to explore additional factors which influence clinical presentation on VFSS and overall impressions of swallowing function.

It is important to note limitations of frame-by-frame analysis used for calculating timing intervals and estimates of velocity/speed of movement. Based on existing recording settings, time is represented in increments of 1/30 seconds (i.e., 33.33ms, per frame). Although the data in this study have been reported in continuous units (ms), there is an inherent constraint on the level of measurement which may be obtained from each video clip, as continuous time/events which occur between recorded frames cannot be captured. Still, as our parameters are selected based on the presence of an observed event (i.e., a rater cannot rate an event in anticipation of its occurrence), it is likely that any loss of information which occurs between frames would contribute to wider (i.e., more conservative) margins of error, when estimating the time between two events.

For this study, we chose to characterize total pharyngeal residue, referenced to an anatomical scalar (i.e., C2-4 vertebral height); this metric has only recently emerged for characterizing swallowing efficiency (Steele et al., 2018b). Alternative methods for evaluating post-swallow residue typically rely on an estimation of the proportion of the bolus remaining in the pharynx, post-swallow (e.g., Hutcheson et al., 2017; Logemann et al., 2005; Martin-Harris et al., 2008) or estimating the percent of vallecular or pyriform sinus space filled with residue (e.g., Eisenhuber et al., 2002; Kaneoka et al., 2014). These approaches typically rely on visual perception of the amount of bolus remaining in the pharynx and do not necessarily account for patient variability in size as a factor determining residue severity. The NRRS, included as a sub-analysis in this study, is one alternative which scales the amount of residue to the size of the housing (e.g., sinus area) as well as the length of C2-4 account for the individual’s size/height (Pearson et al., 2013); however, NRRS does not permit calculation of residue outside of the vallecular and pyriform sinuses (e.g., base of tongue, posterior pharyngeal wall), commonly seen in individuals with ALS (Briani et al., 1998; Goeleven et al., 2006). Although the metric we used has not yet been widely reported, it allowed us to obtain a global measure of total pharyngeal residue, normalized individually to the “size-of-the-system” (Molfenter & Steele, 2014b). Still, further research is
needed to determine thresholds of clinically significant pharyngeal residue, when anatomically
normalized.

Finally, aligning with the primary focus of this dissertation, this study remained limited to
mechanisms within the pharyngeal phase of swallowing. Further research will be needed to
understand these results in the context of other physiological systems, which precede the
pharyngeal response (e.g., orofacial) and/or remain concurrently involved (e.g., respiration).

4.7 Conclusions

This study provided an overview of swallowing safety, efficiency and physiology, focusing on
liquid barium trials ranging in thickness from thin to extremely thick. We also explored the
influence of liquid thickness on swallowing function and physiology and conducted preliminary
explorations to illuminate potential relationships between swallowing physiology (i.e.,
kinematics, timing) and function (i.e., safety, efficiency).

Compared to thin liquids, we identified a reduced frequency of unsafe swallowing with
extremely-thick liquids. However, liquid thickness did not have an influence on the accumulation
of post-swallow residue. Physiological parameters of swallowing did not vary according to liquid
thickness, but the timing of airway closure and degree of UES opening were found to increase
with larger sip weights.

Impaired swallowing safety appears to be primarily associated with delayed or incomplete
airway closure, while impaired swallowing efficiency is largely associated with reduced
maximum pharyngeal constriction. Although measures of hyoid kinematics were found to differ
from healthy reference data, any association between these changes and swallowing function
requires further examination; changes in hyoid rest position may be an important factor to
consider.

Further research is needed to continue exploring relationships between swallowing physiology
and function in ALS. Longitudinal study designs, in particular, will be imperative to define
patterns of clinical presentation, including potential compensatory relationships between
parameters.
Conclusions

5.1 Thesis Summary

The purpose of this thesis was to characterize swallowing in patients with ALS, as it is described in existing research and through quantitative measurement of physiology using current methodologies. We began this research with a literature review (Chapter 2), to summarize the knowledge foundation and identify research gaps to shape and define subsequent research questions. From this work, we chose to focus remaining efforts on the following knowledge gaps:

1) Lack of quantification when characterizing swallowing physiology and function in ALS research;

2) Limited understanding of the degree of physiological change associated with swallowing in ALS;

3) Emphasis on swallowing safety, with limited attention to swallowing efficiency; and

4) Need for empirical evidence to support presumed associations between swallowing physiology and clinical function.

We began to address these gaps in Chapter 3, by evaluating two commonly reported parameters of swallowing physiology: pharyngeal constriction and hyoid kinematics. This analysis allowed us to quantify the degree of change, frequently described holistically as “reduced” in the literature. Further, this analysis provided support towards the validity of such measures to characterize swallowing physiology in ALS, based on correlations between the measures and existing validated scales of bulbar impairment and the ability for such metrics to illustrate expected differences from healthy reference values.

Following this pilot work, we performed a broader characterization of swallowing physiology and function in Chapter 4. We defined swallowing function in a cohort of individuals with ALS, with an equal focus placed on swallowing safety and efficiency, and quantified various metrics of swallowing physiology. By contrasting each measure to existing data from healthy individuals, we were able to identify which parameters fell outside reference range and illustrate
the degree to which they differed. Reductions in maximum pharyngeal constriction, anterior hyoid velocity, and prolonged LVCt were among the most discernable differences, reflecting theoretically “poorer” physiology. However, we also identified potential group differences related to the duration of LVC and UES opening, as well as increased superior hyoid velocity, reflecting theoretically “better” physiology. Finally, we performed preliminary investigations to relate measureable differences in swallowing physiology to measures of swallowing safety and efficiency, revealing primary associations between airway protection and swallowing safety, as well as pharyngeal constriction and swallowing efficiency.

The investigations within this thesis provide preliminary insight into changes in swallowing associated with ALS and address knowledge gaps identified at the outset. Still, as this work is preliminary and each study was subject to limitations, a great number of research questions remain.

5.1.1 Limitations

Although various limitations were addressed within each chapter, there are a few key theoretical constraints which remained pervasive throughout the thesis and point to areas for future research. First, despite the overlap and known interactions between phases of swallowing (Jean, 2001), we placed primary focus upon discrete physiological aspects of the pharyngeal phase, with little attention paid to the oral and esophageal phases. Nevertheless, evidence of concurrent oral phase dysfunction was noted, descriptively, throughout the rating process (e.g., “disorganized bolus preparation”, “poor oral control”), drawing attention to the need for future research to evaluate oral phase difficulties associated with ALS. Similarly, as respiratory systems interact predictably with swallowing, additional work will be needed to explore swallow-respiratory phase patterns and the role of respiratory capacity on swallowing physiology and function.

In Chapters 3 and 4, we chose to characterize swallowing physiology at the group-level, despite acknowledged heterogeneity within the sample (e.g., mix of onset-types, variable disease durations, UMN/LMN involvement). Although the sample was described in terms of bulbar and respiratory function, these parameters were not included in models of function. More in depth analysis at the participant level, such as a case series research approach, may elucidate individual profiles and dissociative patterns of physiology and function, and expose potential factors to consider for cohort stratification in larger research samples. Finally, as previously acknowledged,
we have drawn conclusions based on a cohort analysis, taken at a single point in time. Given the progressive nature of ALS, longitudinal data will be imperative to define how swallowing physiology changes over time at the patient- and group-level.

5.2 Future Directions

5.2.1 Subsystem Approach to Swallowing

Given the complexity of swallowing physiology and inherent limitations when focusing narrowly on one individual parameter or phase of swallowing, a growing need exists for a larger framework to explore relationships between parameters and phases of swallowing. In Chapter 4, we argued for a subsystem approach to swallowing, comparable to what has been used in bulbar assessment for speech (Green et al., 2013). In order to establish such a paradigm for swallowing, it must be determined which parameters are appropriate to include in each subsystem, based on their ability to serve as markers of change and associations with functional outcomes or impairment. Paired with previous research, results from this project suggest that metrics of airway protection and pharyngeal constriction would be essential components in such a model. Nevertheless, additional metrics require further justification. Building upon the work from this thesis, we hope to continue to elucidate the most-appropriate metrics for inclusion in a subsystem approach to evaluate swallowing in ALS.

5.2.2 Motor Equivalence & Variability

Results from this dissertation highlighted several interesting considerations in terms of motor control. Although several parameters were found to be measurably reduced or delayed in comparison to reference values from healthy individuals, we were surprised to find various parameters which displayed measurable increases in performance. The source of these conflicting observations is currently unclear; however, one possible explanation may relate to motor constancy and equivalence, such that redundancy within and between motor circuits may permit unimpaired mechanisms to compensate for an impaired mechanism to achieve a goal behaviour (e.g., Berkinblit, Feldman & Fukson, 1986). Evidence for this has been seen previously in swallowing research; for example, when individuals perform a Masako or “tongue-hold” maneuver, restricting the involvement of the tongue base during swallowing, the posterior pharyngeal wall has been observed to move further to maintain a functional pharyngeal stripping wave (Fujiu & Logemann, 1996; Hammer, Jones, Mielens, Kim & McCulloch, 2014). It will be
important for future research to explore patterns of change (i.e., increased vs. decreased) to elucidate whether the relationships behave in predictable ways.

In addition to raw differences in the magnitude or timing of swallowing movements, we identified potential differences in motor accommodation in response to varying bolus properties. At this time, the clinical relevance of these findings is unclear; however, these patterns may have prognostic value to detect windows of opportunity for therapeutic intervention or provide evidence of risk/vulnerability. Humans require a baseline degree of motor variability for learning and adapting to environmental perturbations (e.g., Berkinblit, Feldman & Fukson, 1986; Dhawale, Smith & Ölveczky, 2017; Latash, Levin, Scholz & Schöner, 2010); however, having too much motor variability has been implicated in disordered systems (e.g., Hausdorff, 2009). Thus, theories of dynamical motor control propose a balance between system-constraint and flexibility (e.g., Stergiou, Harbourne & Cavanaugh, 2006). We propose that such a paradigm could be applied to swallowing kinematics from videofluoroscopy and encourage the investigation of both raw measures of physiology, as well as within-subject physiological variability, to determine if estimates of motor variability can provide further prognostic information in ALS.

5.3 Conclusions

Three studies were conducted to summarize and characterize parameters of swallowing physiology and function in individuals with ALS. Our results 1) provide support towards the use of quantitative videofluoroscopic analysis methods to measure swallowing physiology in ALS; 2) outline several physiological mechanisms and metrics of swallow timing which differ from healthy swallowing; and 3) illustrate potential relationships between physiological changes and swallowing safety and efficiency. Still, future research is needed to broaden our understanding of the physiological changes associated with ALS pathology, over time, to clarify patterns of change and elucidate their role with respect to swallowing function. Further, novel approaches to characterizing swallowing behaviour, using a subsystem approach and exploring motor variability and accommodation, may reveal new insights into the pathophysiology of dysphagia in ALS.
References


sclerosis. *Journal of Palliative Medicine, 10*(2), 433-457. doi:http://dx.doi.org/10.1089/jpm.2006.9978


110


barium stimuli. Paper presented at the Dysphagia Research Society Annual Meeting and Post-Graduate Course, Chicago, IL.


Appendix A: Scoping Review Supplementary Material

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Database: PubMed

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bulbospinal neuronopath
bulbo spinal neuronopath
bulbospinal atroph
bulbo spinal atroph
bulbar spinal atroph
juvenile muscular atroph
infantile muscular atroph
kugelberg-welander disease
kugelberg-welander syndrom
kugelbergwelander disease
kugelbergwelander syndrom
hereditary motor neuropath
anterior horn cell disease
List of Included Articles, Alphabetically


Appendix B: Research Poster Presented at 26th Annual Dysphagia Research Society Meeting

Hyoid Kinematics in Patients with Amyotrophic Lateral Sclerosis (ALS): A Pilot Analysis

Ashley A. Witto1,2, Melanie Pelletreau-Pigeon1, Catharina M. Steele1,3, Lauren C. Tabor1,2, Emily K. Powellman3

Introduction

Acute decline in the ability to swallow is a common manifestation of ALS, and hyoid movement is among the first to be altered. These changes may be related to the development of dysphagia, and understanding the role of the hyoid in swallowing dysfunction is critical.

1. Swallowing and Respiration Laboratory, University of Toronto, Toronto, Canada.
2. psychiatry and Clinical Neurosciences, University of British Columbia, Vancouver, Canada.
3. Department of Rehabilitation, University of British Columbia, Vancouver, Canada.

Methods

Participants were 20 healthy controls and 20 ALS patients. Videofluoroscopy was used to assess swallowing efficiency and hyoid movement.

Results

Hyoid movement was significantly different between healthy controls and ALS patients. ALS patients demonstrated reduced hyoid movement and increased bolus volume compared to healthy controls.

Conclusions

Hyoid movement is a critical aspect of swallowing in ALS. Further research is needed to determine the role of hyoid movement in swallowing dysfunction and the potential for rehabilitation strategies to improve swallowing in ALS patients.

References

## Appendix C: IDDSI Liquid Mixing Recipes and Instructions

### Barium Liquid Recipes

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<th># of Subjects</th>
<th>IDDSI Level</th>
<th>Thickness</th>
<th>Expected Solution Volume</th>
<th>Mass of Water (g)</th>
<th>ThickenUp ® powder (g)</th>
<th>ThickenUp Clear ® powder (g)</th>
<th>E-Z-Paque powder (g)</th>
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<td>13.5</td>
<td>63</td>
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*Adjusted from Toronto NIH recipes based on flow-test results
Mixing Instructions

NOTE: When you are using the Ohaus PA1502/1602 scale, level the scale by adjusting the back feet until the air bubble is centered in the target.

Prepare the mixer:
1. Place the Bosch mixer on a clean smooth surface.
2. Ensure that the Bosch mixer is unplugged.
3. Confirm that the six-position rotary dial on the right side of the arm is on the “O/Off” position.
4. Press the release button and raise the mixer arm.
5. Attach the beating whisk to the mixer arm.

Measure the water:
6. Place the Bosch mixing bowl on the balance.
7. Press the “tare” button on the balance so the display screen reads 0g.
8. Pour desired liquid into the Bosch mixing bowl (refer to recipe).
9. Remove the Bosch mixing bowl filled with water from the balance and set it aside.

Measure the ThickenUp® OR ThickenUp Clear®:
10. Place the weigh boat on the balance.
11. Press the “tare” button on the balance so the display screen reads 0g.
12. Using a laboratory spoon, add the ThickenUp Clear® or ThickenUp® powder to the weigh boat.
13. Remove the weigh boat filled with thickener from the balance and set it aside.

Measure the E-Z-Paque® barium powder (if applicable):
14. Place a new, clean large weigh boat on the balance.
15. Press the “tare” button on the balance so the display screen reads 0g.
16. Using a clean plastic spoon, add the E-Z-Paque® barium powder to the weigh boat.
17. In order to determine how much barium is needed in the second weigh boat, see recipes below for either barium or non-barium stimuli.
18. Remove the weigh boat with the E-Z-Paque® barium powder from the balance and set it aside.

Mix the water, thickener and E-Z-Paque® barium powder together:
20. Place the Bosch mixing bowl filled with water onto the Bosch mixer stand.
21. Press the release button and push down the mixer arm to lock the bowl into place.
22. Turn the rotary dial to speed setting “1”.
23. Gently pour the E-Z-Paque® barium powder into the Bosch mixing bowl (if applicable).
24. Slowly, over a period of about 30-40 seconds, add the ThickenUp Clear® or ThickenUp® powder to the bowl.
25. Set the timer for 2 minutes.
26. Turn the rotary speed setting to “2” for the first 10 seconds of rotation once the thickener has been added to properly disperse the thickener.
27. After the 10 seconds, turn the rotary speed back to “1”.
28. Allow to mix at level “1” until the timer goes off (1 min 50 sec).
29. Turn the rotary dial on the Bosch mixer to “O/Off” position.
30. Press the release button to lift the mixer arm.
31. Remove the Bosch mixing bowl.
32. Use the whisk from the mixer and mix by hand for 10 seconds slowly (one bowl turn per second).
33. The solution is now prepared.
Appendix D: Forms for Data Collection

Exclusion Criteria Questionnaire

This is a list of conditions that could alter the results of this research study, or impact your eligibility to participate.

Please read the list and let us know if any of these apply to you, so that we can be certain that you meet the requirements to participate in the study.

a) Medical or Occupational Conditions:

- People with a prior medical history of stroke
- People with a prior medical history of acquired brain injury
- People with a prior medical history of spinal or spinal cord injury
- People with a prior medical history of cancer or surgery in the head and neck region
- People who have had radiation to the head and neck for cancer
- People who have a prior history of swallowing problems (e.g., from childhood, medical complication)
- People with significant breathing difficulties (e.g., rely on mechanical ventilation)
- People who rely on tube-feeding for all meals and nutrition
- People who have Type I (insulin-dependent) Diabetes
- Women who are pregnant
- People who have allergies to barium, potato starch, corn starch, xanthan gum, milk products, latex or dental glue

b) Medication, Drug and Alcohol Use

- People who are taking sleeping pills or medication that makes them drowsy
# Intake Form

## Demographic Information

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<th>Participant Initials:</th>
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**Sex:**  
M / F  

**Year of Birth:** ______________

## Eligibility

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If excluded, reason: ______________

## Race/Ethnicity Information

**Cultural Heritage:** ______________

**Spanish/Portuguese as L1:** YES / NO

## Participant Health Information

**Primary Diagnosis:** ______________

**Diagnosis Date (mm/yy):** ______________

**Notes (e.g., onset-type):** __________________________________________________________

**Time since initial symptom onset:** _____ months  
**Time since bulbar symptom onset:** _____ months

**Other Medical History:** __________________________________________________________

**Relevant Medications:** __________________________________________________________

**Any previous VFSS:**  
YES / NO  
If so, date of exam: ______________

**VFSS findings:** _________________________________________________________________

## ALS Only

**ALSFRS-R total score:** _______  
**Bulbar sub-score:** _______  
**Swallowing sub-score:** _______

## PD Only

**UPDRS score:** ______________  
**Hoehn and Yahr score:** ______________

**L-dopa:** Y / N  
**Dosage:** ___________  
**Last dose:** ______________

**DBS:** Y / N  
**Location/Notes:** ________________________________
# ALSFRS-R Scale

**ALSFRS-R**  
(ALS Functional Rating Scale)  

**Please circle the number of your answer**

<table>
<thead>
<tr>
<th>1. <strong>Speech</strong></th>
<th>7. <strong>Turning in bed and adjusting bed clothes</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>4 normal speech processes</td>
<td>4 normal</td>
</tr>
<tr>
<td>3 detectable speech disturbance</td>
<td>3 somewhat slow or clumsy, needs no help</td>
</tr>
<tr>
<td>2 inaudible with repeating</td>
<td>2 can turn alone or adjust sheets with great difficulty</td>
</tr>
<tr>
<td>1 speech combined with non-vocal communication</td>
<td>1 can initiate, cannot turn or adjust sheets</td>
</tr>
<tr>
<td>0 loss of useful speech</td>
<td>0 helpless</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. <strong>Salivation</strong></th>
<th>8. <strong>Walking</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>4 normal</td>
<td>4 normal</td>
</tr>
<tr>
<td>3 slight but definite excess of saliva in mouth, may have nighttime drooling</td>
<td>3 early ambulation difficulties</td>
</tr>
<tr>
<td>2 moderately excessive saliva, may have minimal drooling</td>
<td>2 walks with assistance</td>
</tr>
<tr>
<td>1 marked excess of saliva with some drooling</td>
<td>1 non-ambulatory functional movement only</td>
</tr>
<tr>
<td>0 marked drooling, requires constant issue</td>
<td>0 no purposeful leg movement</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. <strong>Swallowing</strong></th>
<th>9. <strong>Climbing Stairs</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>4 normal</td>
<td>4 normal</td>
</tr>
<tr>
<td>3 normal eating habits</td>
<td>3 slow</td>
</tr>
<tr>
<td>2 early eating problems, occasional choking</td>
<td>2 mild unsteadiness or fatigue</td>
</tr>
<tr>
<td>1 dietary consistency changes</td>
<td>1 needs assistance</td>
</tr>
<tr>
<td>0 NPO (exclusively parenteral or enteral feedings)</td>
<td>0 cannot do</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. <strong>Handwriting</strong></th>
<th>R-1. <strong>Dyspnea</strong> (difficult or labored breathing; breathlessness or shortness of breath)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 normal</td>
<td>4 none</td>
</tr>
<tr>
<td>3 slow or sloppy, all words legible</td>
<td>3 occurs when walking</td>
</tr>
<tr>
<td>2 not all words legible</td>
<td>2 occurs with one or more eating, bathing, dressing</td>
</tr>
<tr>
<td>1 able to grip pen, unable to write</td>
<td>1 occurs at rest, either sitting or lying</td>
</tr>
<tr>
<td>0 unable to grip pen</td>
<td>0 significant difficulty, considering mechanical support</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5a. <strong>Cutting food and handling utensils (patients without gastrostomy)</strong></th>
<th>R-2. <strong>Ostheopnea</strong> (difficult or labored breathing that occurs when laying flat and is relieved by elevating the head and chest with two pillows)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 normal</td>
<td>4 normal</td>
</tr>
<tr>
<td>3 somewhat slow and clumsy, needs no help</td>
<td>3 some difficulty sleeping, diff. shortness of breath, does not routinely use more than two pillows</td>
</tr>
<tr>
<td>2 can cut most foods, slow or clumsy, some help needed</td>
<td>2 needs extra pillows to sleep (&gt;2)</td>
</tr>
<tr>
<td>1 foods cut by someone else, can still feed slowly</td>
<td>1 can only sleep sitting up</td>
</tr>
<tr>
<td>0 needs to be fed</td>
<td>0 unable to sleep</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5b. <strong>Cutting food and handling utensils (patients with gastrostomy)</strong></th>
<th>R-3. <strong>Respiratory Insufficiency</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>4 normal</td>
<td>4 none</td>
</tr>
<tr>
<td>3 clumsy, able to perform manipulations</td>
<td>3 intermittent use of BIPAP</td>
</tr>
<tr>
<td>2 some help needed with closures and fasteners</td>
<td>2 continuous use of BIPAP at night</td>
</tr>
<tr>
<td>1 provides minimal assistance to caregiver</td>
<td>1 continuous use of BIPAP day and night</td>
</tr>
<tr>
<td>0 unable to perform any aspect of task</td>
<td>0 invasive mechanical ventilation by intubation/trach</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>8. <strong>Dressing and hygiene</strong></th>
<th><strong>Total Score ____/ 48</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>4 normal</td>
<td></td>
</tr>
<tr>
<td>3 independent self care with effort or decreased efficiency</td>
<td></td>
</tr>
<tr>
<td>2 intermittent assistance or substitute methods</td>
<td></td>
</tr>
<tr>
<td>1 needs attendant for self care</td>
<td></td>
</tr>
<tr>
<td>0 total dependence</td>
<td></td>
</tr>
</tbody>
</table>
# Tongue Strength Measurement

**Participant ID:** __________  **Date:** ____________________

*Before videofluoroscopy:*

<table>
<thead>
<tr>
<th>IOPI Task</th>
<th>Trial 1</th>
<th>Trial 2</th>
<th>Trial 3</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum Anterior Isometric Tongue-Palate Pressure (kPa)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum Posterior Isometric Tongue-Palate Pressure (kPa)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saliva Swallow Tongue Pressure (kPa)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*After videofluoroscopy:*

<table>
<thead>
<tr>
<th>IOPI Task</th>
<th>Trial 1</th>
<th>Trial 2</th>
<th>Trial 3</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum Anterior Isometric Tongue-Palate Pressure (kPa)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum Posterior Isometric Tongue-Palate Pressure (kPa)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saliva Swallow Tongue Pressure (kPa)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**

_______________________________________________________________________

_______________________________________________________________________
**Clinical VFSS Recording Form**

**NIH_Neuro Videofluoroscopy Protocol – Clinical Reporting Form (CRF)**

**Randomization:** A

Positioning Clips: ________________________________  Fluoro time: ____________

<table>
<thead>
<tr>
<th>Trial</th>
<th>Bolus “take a comfortable sip”</th>
<th>Pre-Weight (g)</th>
<th>Post-Weight (g)</th>
<th>Series #</th>
<th>Safe? (PAS&lt;2)</th>
<th>Efficient? (&lt;75%)</th>
<th>Notes (e.g., response, maneuvers trialed, PAS if &gt;2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Thin (20% w/v)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Thin (20% w/v)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Thin (20% w/v)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Slightly (TU)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Slightly (TU)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Slightly (TU)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Slightly (TUC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Slightly (TUC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Slightly (TUC)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>10</td>
<td>Mildly (TUC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Mildly (TUC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Mildly (TUC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Moderately (TU)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Moderately (TU)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Moderately (TU)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Moderately (TUC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Moderately (TUC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Moderately (TUC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Extremely (TUC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Extremely (TUC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>Extremely (TUC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Bailout:**

- **PAS:** 2nd instance of aspiration, move to thicker consistency; 3rd instance aspiration, d/c study.
- **Residue:** >75% space full, trial clearing strategies; if unable to clear >75% full, d/c study.

**Notes:**
Appendix E: ASPEKT Rating Method – Standard Operating Procedures

Round 1 VFSS Rating Steps and Definitions (Lateral View)

Raters will be provided with a Round 1 rating macro, developed in Microsoft Excel by an SRRL Engineer, which will prompt them for specific information (described in sequence below). The macro automatically prompts with 4 pages where up to 3 swallows are rated in detail and any remaining swallows (4+) are grouped together on the final page.

1. **Choose Swallow Type:**
   a. *Single Bolus:* New bolus crosses the ramus of the mandible in just one swallow. This can be followed by a clean-up swallow (where no new material crosses the ramus); however, if new material crosses the ramus on a subsequent swallow, it is considered a piecemeal swallow.
   b. *Piecemeal (either first or subsequent):* If the bolus crosses the ramus of the mandible on multiple swallows, the first and subsequent swallows are all considered “piecemeal”. Note: the amount of material crossing the ramus of the mandible may be very small but still considered a piecemeal swallow.
   c. *Clean-up:* Material being swallowed comes from the pharynx, only – no new material crosses the ramus of the mandible.
   d. *Attempt(s):* Unsuccessful swallow(s) defined as pharyngeal constriction + hyolaryngeal elevation, or obvious volitional elevation of the larynx in effort to initiate a swallow. The UES does not open despite effort.
      i. If there is more than one attempt in a row, they are all grouped together on the same macro page.
   e. *Final event(s):* Selected automatically by the macro when there are more than 3 swallows to capture the remaining swallow events in a group.
   f. *No other events in the video clip:* Selected if there are fewer than 4 events in the swallow to inform the rating macro that there are no remaining swallows or attempts.
2. Rate Penetration/Aspiration (PAS) using the following scale:

   a. 8-Point Penetration-Aspiration Scale

      1 = Material does not enter 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


   b. PAS should only be rated on new material entering the airway for each swallow. In the event that there is residue in the airway from a previous swallow, but no new material is penetrated or aspirated on the current swallow, PAS would be scored as 1.

3. Choose the Penetration-Aspiration Score frame (PAS_frame):

   a. If PAS > 1, record the first frame showing penetration of the material into the laryngeal vestibule (i.e. first frame showing PAS of 2 or higher)

   b. If PAS = 1, PAS_frame is N/A

4. Choose the Bolus at Mandible frame (BPM_frame):

   a. Record the first frame where the leading edge of the bolus touches or crosses the shadow of the ramus of the mandible.

   b. In cases of premature spill, the first entry of bolus material into the pharynx should be counted as the BPM frame.
c. If there is a double mandible shadow, use the lower edge of the more superior ramus as the landmark.

5. **Choose the Bolus Passing Vallecular Pit frame (BPV\_frame):**

   a. Record the first frame where the leading edge of the bolus touches or crosses the vallecular pit (or a line at the level of the vallecular pit).

   b. Optional: It may be helpful to use the angle tool to draw a line at the level of the vallecular pit, for a reference:

      i. Select the Angle tool from the main ImageJ toolbar

      ii. Click on the inferior anterior corner of C4, then the inferior anterior corner of C2, then the posterior aspect of the tongue where the angle is approx. 90 degrees (shown in the ImageJ toolbar)

      iii. Use the arrow keys to move the 90 degree angle up or down, until the line that is perpendicular to the spine is positioned at the pit of the vallecula.

      iv. You may need to adjust the height of the line, with movement of the tongue

6. **Choose the frame containing the first jump of the hyoid (1Hyoid\_frame):**

   a. Record the first anterior-superior ‘jump’ of the hyoid that is associated with a swallow (or swallow attempt).

   b. This is the moment where the hyoid appears to ‘take off’ or ‘burst’; small movements around the starting position that occur prior to this burst should not be counted.

   c. The 1Hyoid frame often has 2 hyoid images on it, because of the speed of the hyoid taking off.

   d. For Final Events or Attempts, 1Hyoid is marked on the first event in the sequence.

7. **Choose the frame containing the first elevation of the larynx (LE\_frame):**

   a. Identify the frame containing the first elevation of the laryngeal air column (LAC; detected anteriorly at the thyroid cartilage) from its rest position, prior to laryngeal vestibule closure.

      i. Note: If the thyroid cartilage is not visible, use the superior tip of the arytenoid cartilage instead.

   b. Start monitoring from the peak laryngeal position associated with the swallow and move backwards frame-by-frame until the point where LAC reverses direction or remains stationary for 5 successive frames. Move forward again to identify the first frame of movement towards peak position.
c. Laryngeal movement associated with jaw opening/closing before the swallow should not be considered part of the LE movement.

8. **Choose the first frame of Maximal Laryngeal Approximation (LVA frame):**
   
a. The first frame where there is maximum approximation of the arytenoids to the laryngeal surface of the epiglottis.

    Complete closure of the laryngeal vestibule (i.e. a seal between epiglottis and arytenoids leaving no visible airspace) may or may not be present.

9. **Indicate completeness of laryngeal vestibule closure (LVC):**
   
a. Mark whether the frame identified as LVA_frame has:
      
      i. Complete closure – no air or contrast in the laryngeal vestibule
      
      ii. Partial closure – narrow column of air or contrast in the laryngeal vestibule OR partial tissue contact between the arytenoids and laryngeal surface of epiglottis with small amount of contrast or airspace visible in part of the vestibule
      
      iii. Incomplete closure – wide column of air or contrast in the laryngeal vestibule


10. **Choose the first frame of UES opening (UES frame):**
   
a. The first frame where the leading edge of the bolus (or in rare cases, air) passes through the upper esophageal sphincter (UES).

   b. The UES is a narrow segment or region that typically lies between C4-C6; the narrowest opening seen between C4-6 during a swallow is usually marked as the location of the sphincter (as per Kendall & Leonard). In the SRRL, our criteria recognize that the UES moves superiorly during the swallow. Therefore, the narrowest portion may be located above C4. The laryngeal air column can be used as a guide to decide where the location of the UES is during pharyngeal shortening.

11. **Choose the frame of maximum UES distension (UESmax_frame)**
   
a. Identify the frame where the distension of the upper esophageal sphincter has the widest width (i.e., widest lumen width and/or bolus column)

12. **Choose the frame of maximum pharyngeal constriction (MPC_frame):**
   
a. Choose the earliest frame of maximum pharyngeal constriction (i.e., least amount of bolus flow and/or airspace in the pharynx)
b. Typically occurs between 1UES and LC_Offset

c. Must choose frame before upper pharynx begins to relax, and before the laryngeal air column begins to open/descend

13. Choose the first frame of UES closure (UESc_frame):

a. Choose the first frame where the UES achieves closure behind the bolus tail. This does not require closure of the entire UES segment, simply closure at any point along the segment

14. Choose the first frame of laryngeal opening (LC_offset_frame)

a. The first frame where there is a visible opening (white space) in the laryngeal vestibule.

b. This requires some separation of the tissues or of the arytenoids from the under surface of the epiglottis. Complete opening is not required. The leaf of the epiglottis may still be in a downward position.

c. If LVC was marked “incomplete”, this variable is N/A “not applicable”

15. Choose the frame of epiglottic return (EpiVert_frame)

a. The first frame depicting the return of the epiglottis to a vertical position. This is usually accompanied by relaxation of the pharynx.

16. Choose swallow rest frame (SwalRest_frame):

a. Select the first frame showing the pyriform sinuses at the lowest position, relative to the spine, within 30 frames (approx. 1 second) of UES closure.

b. The selected frame must occur before any of the following:

   i. End of clip/fluoro

   ii. Hyoid burst of subsequent swallow/clearing swallow

   iii. Non-swallow events (e.g., coughing, talking, UES re-opening)

   iv. No more than 30 frames past UES closure

   c. Note: If UESc cannot be rated (e.g., UES did not open, such as in the case of swallow attempts) the first frame of pharyngeal relaxation will be used as the reference time point for determining swallow rest. To do so:

   i. Identify the first frame of pharyngeal relaxation;

   ii. Select the frame showing the pyriform sinuses at the lowest position, relative to the spine, within 30 frames of pharyngeal relaxation.
d. For Attempts or Final Events, swallow rest is marked on the last event of the sequence

e. Additional notes for Swallow Rest:

- If the pyriform sinus stays in the same lowest position for multiple frames, select the first of the frames where it reaches its lowest location.
- The base of the pyriform sinus will likely arrive at its lowest position after the hyoid has descended.
- If a structure obstructs the view of the pyriform sinus (e.g., it descends behind a raised shoulder), select the frame immediately before it becomes obstructed.
- The pharynx must reach a minimum of 75% dilation in order to be considered “rested”. If the pharynx does not reach 75% dilation, this parameter is considered unrateable.

17. Rate post-swallow residue (Eisenhuber):

a. At swallow rest, rate residue in the vallecular and pyriform sinuses using the following scale:

0 = no residue

1 = ‘mild’ residue (the fluid level of contrast material fills < 25% of the available space of the structure)

2 = ‘moderate’ residue (the fluid level of contrast material fills > 25% and <50% of the available space of the structure)

3 = ‘severe’ residue (the fluid level of contrast material is > than 50% of the available space of the structure)


a. Additional notes for Eisenhuber:

- “Collapsed sinuses” – if the epiglottis collapses tightly to the base of the tongue, or if the pyriform sinuses collapse upon relaxation, Eisenhuber is still rated based on the amount of material in reference to the available space remaining. Therefore, a small amount of residue may be rated as a 2 or 3 if the sinus has reduced significantly in size.
- The following should NOT be measured as post-swallow residue:
i. Additional spill from the mouth after the swallow (i.e., oral residue from a prior bolus or new bolus material crossing the ramus of the mandible)

ii. Regurgitation of material through UES and back into pyriform sinuses

- However, post-swallow residue from the valleculae that is observed to spill further into the pyriform sinuses should be measured.

b. Certain adjustments may be made to the selection of the frame for residue measurement when needed:

- In the case of additional oral spillage or UES regurgitation (noted above), select the frame immediately prior to the additional oral spillage or regurgitation for residue measurement.

- If there is poor visibility of residue on swallow rest frame and the frames prior to swallow rest show incomplete pharyngeal relaxation, then the first frame after swallow rest with adequate visibility may be selected for residue measurement.

- IMPORTANT: Make note of the selected frame number for rating residue in the “Comments” box if it differs from the Swallow Rest frame.

18. Rate overall bolus-level PAS:

a. In some cases, a PAS event may evolve (worsen or resolve) over the course of the bolus clip. To account for this, the macro will prompt for a “Bolus-Level PAS” rating.

b. The macro will present the PAS ratings you initially assigned for each swallow, highlight the WORST score that occurred across all swallows, and prompt “Did this material recover or worsen?”

i. If the worst identified PAS event did not change on subsequent swallows, choose “No”

ii. If the PAS event resolved or worsened after the swallow, click “Yes” and identify the appropriate PAS score at the bolus-level, using the Penetration-Aspiration Scale.
Round 2 VFSS Rating Steps and Definitions (Lateral View)

Raters will be provided with a Round 2 rating macro, developed in Microsoft Excel by an SRRL Engineer, which will prompt them for specific information (described in sequence below). Frame numbers obtained in Round 1 ratings will be provided within the macro to inform the rater when to take measurements.

1. Rate bolus location at swallow onset (BL@SO):
   a. On the frame provided (1Hyoid; obtained in Round 1), determine the location of the bolus according to the following scale:
      
      0 = Bolus head in oral cavity or at posterior angle of ramus (first hyoid excursion)
      
      1 = Bolus head at vallecular pit
      
      2 = Bolus head at posterior laryngeal surface of epiglottis
      
      3 = Bolus head at the level of the pyriform sinuses (i.e., inferior to the arytenoids)
      
      4 = No appreciable initiation at any location


2. Bolus location at laryngeal closure (BL@LVA):
   a. On the frame provided (LVA_frame; obtained in Round 1), determine the location of the bolus according to the following scale:
      
      0 = Bolus head in oral cavity or at posterior angle of ramus (first hyoid excursion)
      
      1 = Bolus head at vallecular pit
      
      2 = Bolus head at posterior laryngeal surface of epiglottis
      
      3 = Bolus head at the level of the pyriform sinuses (i.e., inferior to the arytenoids)
      
      4 = Bolus head in UES
      
      5 = No appreciable initiation at any location

3. **Maximum UES opening (UESmax)**
   
   I. Find the frame of interest in ImageJ (UESmax_frame, obtained in Round 1)
   
   II. Measure C2-C4 length (scalar)
       a. Use the Line tool to measure C2-C4 length
       b. Press Ctrl+M to obtain the measurement – record the Length
   
   III. Measure the **narrowest point** UES Width at frame of maximum distension:
       a. Find the frame of interest in ImageJ (UESmax_frame, obtained in Round 1)
       b. Measure C2-C4 length (scalar)
          a. Use the Line tool to measure C2-C4 length
          b. Press Ctrl+M to obtain the measurement – record the Length
       c. Measure the **narrowest point** within UES at the frame of maximum distension:
          a. Select the Line tool.
          b. Hold the mouse button down and drag the line across the **narrowest point of the bolus/lumen visible on the image below the base of the pyriform sinuses**, extending down not lower than the top of C6, keeping the line perpendicular to the cervical spine.
             • Note: this position will typically appear as the apex of an hourglass shape in the upper esophagus. The height of the laryngeal air column may be used as a guide to identify the position of the UES during pharyngeal shortening.
          c. Press Ctrl+M
          d. Record the Length value from the Results box

4. **Measure maximum pharyngeal constriction (MPC):**

   I. Find the frame of interest in ImageJ (MPC_frame, obtained in Round 1)

   II. Open the ROI Manager

      a. Click on Analyze → Tools → ROI Manager

      b. Make sure the Show All option is checked

   III. Draw the X and Y axes by making a right angle.

      a. Select the *Angle* tool from the main ImageJ toolbar

      b. Click on the inferior anterior corner of C4, then the inferior anterior corner of C2, then the posterior aspect of the tongue where the angle is approx. 90 degrees (shown in the ImageJ toolbar)

      c. In the ROI Manager, click Add

      d. Use the arrow keys to move the right angle up until its vertex is at the superior anterior point of C2. **This is your upper margin.**

   IV. Trace bolus residue and/or any visible air space captured in the pharynx

      a. Select the *Freehand* tool.

      b. Click and hold to trace a contour line around the unconstructed space in the pharynx.

      c. Refer to the following boundaries to capture residue/space:

         - Superiorly: a line perpendicular to the spine connecting the top of C2 vertebra to the tongue base (the line drawn in step III)
         - Posteriorly: the posterior pharyngeal wall
         - Anteriorly: the base of tongue and pharyngeal surface of the epiglottis; connecting the base of the epiglottic petiole to the arytenoid cartilage
         - Inferiorly: Pit of the pyriform sinuses, superior to UES

      d. Press Ctrl+M to obtain the measurement – record the Area

   V. Measure C2-C4 length (scalar)

      a. Use the Line tool to measure C2-C4 length

      b. Press Ctrl+M to obtain the measurement – record the Length

---

1 Note: in the rare event that the velum is captured in the space defined by the upper margin line and the base of tongue, it should be INCLUDED in the pharyngeal space. The upper boundary does not change.
5. **Measure maximum pharyngeal dilation (MPD):**
   
   I. Find the frame of interest in ImageJ (Swallow Rest, obtained in Round 1)
   
   II. Open the ROI Manager
   
   a. Click on Analyze → Tools → ROI Manager
   
   b. Make sure the Show All option is checked
   
   III. Draw the X and Y axes by making a right angle.
   
   a. Select the *Angle* tool from the main ImageJ toolbar
   
   b. Click on the **inferior anterior corner of C4**, then the **inferior anterior corner of C2**, then the **posterior aspect of the tongue** where the angle is approx. 90 degrees (shown in the ImageJ toolbar)
   
   c. In the ROI Manager, click Add
   
   d. Use the arrow keys to move the right angle shape up until the superior corner (the vertex of the right angle) is at the superior anterior point of C2. **This is your upper margin.**
   
   IV. Trace bolus residue and/or any visible air space captured in the pharynx
   
   a. Select the *Freehand* tool.
   
   b. Click and hold to trace a contour line around the unconstricted space in the pharynx.
   
   c. Refer to the following boundaries to capture residue/space:
      
      - **Superiorly**: a line perpendicular to the spine connecting the top of C2 vertebra to the tongue base (the line drawn in step III)
      - **Posteriorly**: the posterior pharyngeal wall
      - **Anteriorly**: the base of tongue and pharyngeal surface of the epiglottis; connecting the base of the epiglottic petiole to the arytenoid cartilage
      - **Inferiorly**: Pit of the pyriform sinuses, superior to UES
   
   d. Press Ctrl+M to obtain the measurement – record the Area
   
   V. **Measure C2-C4 length** (scalar)
   
   a. Use the Line tool to measure C2-C4 length
   
   b. Press Ctrl+M to obtain the measurement – record the Length
6. **Calculate Normalized Residue Ratio Scale (NRRS):**

   I. Find the frame of interest in ImageJ (Swallow Rest, obtained in Round 1)

   II. Draw a scalar reference line from C2 to C4
       a. Select the *Line* tool.
       b. Click on the anterior-inferior edge of C2 vertebra.
       c. Hold the mouse button down and drag the line the anterior inferior edge of C4.
       d. Press Ctrl+M. Record the Length value from the Results box.

   III. Capture the vallecular residue (if any)
       a. Select the Freehand tool.
       b. Click and hold to trace a contour line around the vallecular residue.
       c. Press Ctrl+M. Record the Area value from the Results box (residue).
       d. Select the Oval/Brush Selection tool.
       e. Click and hold to nudge the contour line to include the vallecular housing.
       f. Press Ctrl+M. Record the Area value from the Results box (housing).

   IV. Capture the piriform sinus residue (if any)
       a. Select the Freehand tool.
       b. Click and hold to trace a contour line around the piriform sinus residue.
       c. Press Ctrl+M. Record the Area value from the Results box (residue).
       d. Select the Oval/Brush Selection tool.
       e. Click and hold to nudge the contour line to include the piriform sinus housing.
       f. Press Ctrl+M. Record the Area value from the Results box (housing).

**Additional Criteria:**

- The top of the piriform sinus is defined using a line extending from the tip of the arytenoid shadow to the posterior pharyngeal wall, perpendicular to the vertebral axis.
- If the c-spine vertebrae appear to have two inferior edges (e.g., due to a slightly oblique posture), mark the C2-C4 scalar from the lower lines.
- “Engulfing Sinuses” –if two bilateral sinuses are visible with residue (e.g., due to an oblique position or physical asymmetry), use the Oval/Brush Selection tool to engulf both visible cavities.
- If there are visible osteophytes (or similar) extending the anterior aspect of the cervical vertebrae, C2-C4 scalar measurement should be taken from the true vertebral body.

Following these rating measurements, an SRRL Engineer will process the data to calculate the NRRS values:

\[
NRRS = \left( \frac{\text{Residue Area}}{\text{Housing Area}} \right) \times 10 \times \left( \frac{\text{Residue Area}}{\text{CSpine Scalar}^2} \right)
\]
Agreement Thresholds & Final Reporting

Round 1 Measures:\(^1\):

<table>
<thead>
<tr>
<th>Variable</th>
<th>Discrepancy Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAS</td>
<td>Any differences</td>
</tr>
<tr>
<td>PAS_frame</td>
<td>&gt;5 frames</td>
</tr>
<tr>
<td>BPM</td>
<td>&gt;5 frames</td>
</tr>
<tr>
<td>BPV</td>
<td>&gt;5 frames</td>
</tr>
<tr>
<td>1hyoid</td>
<td>&gt;5 frames</td>
</tr>
<tr>
<td>LE</td>
<td>&gt;5 frames</td>
</tr>
<tr>
<td>LVA_frame</td>
<td>&gt;5 frames</td>
</tr>
<tr>
<td>LVC (complete or incomplete)?</td>
<td>Any differences</td>
</tr>
<tr>
<td>LC_offset</td>
<td>&gt;5 frames</td>
</tr>
<tr>
<td>1UES</td>
<td>&gt;5 frames</td>
</tr>
<tr>
<td>UESmax_frame</td>
<td>&gt;5 frames</td>
</tr>
<tr>
<td>MPC frame</td>
<td>&gt;5 frames</td>
</tr>
<tr>
<td>UESc_frame</td>
<td>&gt;5 frames</td>
</tr>
<tr>
<td>EpiVert</td>
<td>&gt;5 frames</td>
</tr>
<tr>
<td>Swallow Rest</td>
<td>&gt;5 frames</td>
</tr>
<tr>
<td>VRes and PSRes (Eisenhuber)</td>
<td>Any differences</td>
</tr>
</tbody>
</table>

For video pairs where there is a less than 5 frame difference between raters, the following criteria are used for final frame selection and reporting:

- Choose the \textit{earlier frame} for the following variables:
  - PAS_frame
  - BPM
  - BPV
  - 1hyoid
  - LE
  - LVA_frame

- Choose the \textit{later frame} for the following variables:
  - LC_offset
  - MPC
  - UESc
  - 1UES
  - EpiVert
  - UESmax

\(^1\) Agreement definitions of “>5 frames” difference is based on videos captured at 30 frames per second
Round 2 Measures:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Discrepancy Threshold</th>
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</thead>
<tbody>
<tr>
<td>BL@SO</td>
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<tr>
<td>BL@LVA</td>
<td>Any difference</td>
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<tr>
<td>UES width</td>
<td>Project specific</td>
</tr>
<tr>
<td>nMPC</td>
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<tr>
<td>nMPD</td>
<td>Project specific</td>
</tr>
<tr>
<td>NRRSv</td>
<td>Project specific</td>
</tr>
<tr>
<td>NRRSp</td>
<td>Project specific</td>
</tr>
</tbody>
</table>

Final reporting:

For video pairs where the difference between the two raters is below the threshold, the following criteria are used for final number selection and reporting:

- Choose the smallest value for the following variables:
  - nMPD
  - NRRSv
  - NRRSp
  - nMPC

- Choose the largest value for the following variables:
  - UES width

Project specific thresholds:

For each project, an initial subset of the data is used as the basis for determining whether inter-rater agreement in normalized pixel based ratings (i.e., UES width, nMPC, nMPD, NRRSv, and NRRSp) is acceptable. Ratings for this initial subset are performed in duplicate, and difference scores between raters are calculated for the initial duplicate rating set. A 95% confidence interval for rater difference is established where the upper confidence interval boundary serves as a threshold to which difference scores for subsequent duplicate ratings are compared. Difference scores are defined as the absolute values of the difference between the measure of rater 1 and the measure of rater 2.