Proactive Dysphagia Management of Patients with Neurodegenerative Diseases: Early Identification and Intervention

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Patients with neurodegenerative diseases (ND) frequently experience concomitant impairments in pulmonary, cough, and swallow function. These impairments can lead to accelerated morbidity and mortality due to adverse events (e.g. aspiration pneumonia, respiratory failure, malnutrition/dehydration). Historically, exercise-based interventions have been avoided in patients with ND due to fear that they may lead to faster disease progression and increased fatigue, yet, emerging evidence has revealed moderate exercise training in patients with ND may prolong function, life, and quality of life. This has led to the proposal of a paradigm shift from reactive to proactive management of these patients. Therefore, there is high demand for noninvasive, portable methods for continuously monitoring pulmonary and swallow function in patients with ND to proactively implement palliative interventions and mitigate adverse events. Yet, few exist. Gold standard assessments (e.g. spirometry, videofluoroscopy) require in-person clinic visits, which can be challenging for patients with ND to attend due to physical mobility impairments, transportation issues, multifactorial health problems, and compromised immune systems (e.g. COVID-19 pandemic). Therefore, this dissertation examined: 1) The safety, tolerability, and impact of exercise-based interventions on function and quality of life in patients with amyotrophic lateral sclerosis (PALS); and 2) The ability of a novel, non-invasive, sensor-based technology (high-resolution cervical auscultation [HRCA]) to characterize swallow function in patients with ND. To examine Aim 1, the first experiment examined the impact of respiratory interventions on

pulmonary, cough, and surrogates of swallow function in PALS and the second experiment investigated the impact of exercise-based interventions on function and quality of life in PALS via a systematic review. To investigate Aim 2, the third experiment explored HRCA's ability to differentiate between swallows from patients with ND and healthy age-matched adults and the fourth experiment compared temporal and spatial swallow kinematic measures between patients with ND and healthy adults and investigated HRCA's ability to annotate specific swallow kinematic events in patients with ND. Findings revealed: 1) Exercise-based interventions are well-tolerated and may be beneficial for PALS with mild-moderate disease severity, and 2) HRCA has high potential as a noninvasive, accurate method for characterizing swallow function in patients with ND.

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Preface

We made it! In part, I attribute my perseverance, grit, and determination throughout this journey to one of my other passions: competitive long-distance running. There are countless running metaphors that have helped me as I pursued my Ph.D., and I never expected another experience in my life to make running a marathon seem easy. These past five years have changed me, shaped me, and challenged me personally and professionally. While I am proud of reaching this milestone, I am immensely disappointed with the ways the pandemic derailed my initial dissertation plans. Despite the challenges this past year has brought for all, I realize I have much to be grateful for; some of which I will express here. As this stage of my life comes to an end, I am comforted in knowing that this is just the beginning of my next adventure in clinical and research work.

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welcoming me into your exciting world of research, for having confidence in me when I had little, for being a sounding board, and most importantly for making me laugh at times when I wanted to quit or cry. As a role model, you have taught me how to be a resilient and humble clinician scientist. I am grateful for the mentorship of the other members of my dissertation committee. Dr. Sejdić - thank you for the opportunity to assist in establishing a novel field (computational deglutition) by collaborating with you and the members of your lab. I am grateful for your leadership and am even more confident now that I am not meant to be a computer or electrical engineer. Dr. Helou and Dr. Garand- thank you for being role models to me as women in science. Dr. Helou- thank you for encouraging me to think outside the box, for taking time to share your experiences and insight with me, and for providing me opportunities to expand my skill set via training courses and leadership roles within the Communication Science and Disorders (CSD) department. Dr. Garand- thank you for your availability, your positivity, and your passion. You inspire me with your energy, and I am grateful for the opportunities I have had to collaborate with you on research projects. Dr. Lacomis- thank you for your continuous support and mentorship. It has been a privilege to learn from you and the other members of the University of Pittsburgh amyotrophic lateral sclerosis (ALS) clinic. Your generosity and encouragement of my research endeavors over the years has not gone unnoticed. I am grateful for the other faculty members at the University of Pittsburgh who have mentored me and supported me throughout my doctoral studies, including Dr. Shaiman, who served as a member of my plan of study and comprehensive exams committee, and Dr. Perera, who has offered countless, timely statistical consulting.

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to remaining colleagues and friends. To my computer and electrical engineer colleagues (particularly Yassin and Shitong)- thank you for your patience and grace as I asked you endless questions about signal features analyses and machine learning algorithms. To my speech-language pathology colleagues- thank you for allowing me to work beside you clinically. Your hard work and dedication to patient care (especially amidst a pandemic) motivates me. Clinical practice is the inspiration for my research work, and I hope to give back to the profession by establishing pragmatic dysphagia screening, assessment, and treatment methods. Lastly, I am grateful to the patients with dysphagia who were willing to participate in these research studies. Thank you for helping us move the field of communication science and aerodigestive disorders forward.

To my family and friends-thank you for being my support system and my number one cheerleader throughout this journey. Specifically, I am grateful to my parents for encouraging me and for believing that I could reach my goal. Mom-thank you for your thoughtful insight during our weekly phone calls while I simultaneously ran. Dad- I am forever indebted to you for driving Cami, Wifi, and me to Pittsburgh in -30-degree weather when I began the Ph.D. program. These are just two examples of your continuous love and support-words cannot fully express my gratitude. David- thank you for the hours you have spent listening to me practice presentations, for helping me further develop my coding skills, and for never letting me give up on my dreams. Thank you for your steadiness, your patience, your love, and your endless support as I dedicated my waking hours to this endeavor.

1.0 Specific Aims

Patients with ND (including PALS) progressively lose aerodigestive functions (e.g., swallowing and pulmonary) increasing the risk of life-shortening adverse events (e.g. respiratory failure, malnutrition, dehydration, aspiration pneumonia) (Aghaz et al., 2018; Andrews et al., 2018; Ball et al., 2001; Czaplinski et al., 2006; da Costa Franceschini & Mourão, 2015; Easterling & Robbins, 2008; Kühnlein et al., 2008; Onesti et al., 2017; Paris et al., 2013; Takizawa et al., 2016). Historically, exercise training has not been explored in patients with ND due to fear that exercise would lead to faster disease progression or fatigue, especially given that fatigue is one of the most problematic symptoms reported by patients with ND (Newland et al., 2016; Raheja et al., 2016; Siciliano et al., 2018). However, animal and human models have revealed that “moderate” exercise training may be beneficial in patients with ND by resulting in neural and muscular adaptations that are neuroprotective, increasing the efficiency of the body’s systems (thereby reducing fatigue), slowing the progression of disabling impairments, and improving quality of life (de Almeida et al., 2012; Harkawik & Coyle, 2012; Liu et al., 2019; Wert, 2019). In recent years, patients with ND have routinely engaged in ongoing, daily sets of limb-strengthening exercises to exploit their neuroprotective effects on increased neuromuscular efficiency, lower the risk of adverse events (e.g., falls), and to improve quality of life (Casaburi, 1992; de Almeida et al., 2012; Feng et al., 2020; Harkawik & Coyle, 2012; Heyn et al., 2004; Motl & Sandroff, 2015).

Using the limb literature as a framework for moderate exercise training in patients with ND, researchers have explored moderate exercise training to address bulbar disease impairments (i.e. respiratory, swallowing). One specific exercise regimen that targets respiratory musculature, expiratory muscle strength training (EMST), has been explored and shown that EMST may help patients with ND maintain or improve pulmonary, cough, and swallow function (Chiara et al., 2007; Chigira et al., 2018; Ferreira et al., 2016; J. Kim et al., 2009; Plowman, Watts, Tabor-Gray, et al., 2016; Plowman et al., 2019; Reyes et al., 2015, 2018; Robison et al., 2018; Rodríguez et al., 2020; Tabor-Gray, Rosado, et al., 2016; Troche et al., 2010). Progressive resistive EMST and inspiratory muscle strength training (IMST) have led to improvements in pulmonary, cough, and swallow function in patients with various neurological or respiratory diseases, including patients with spinal cord injury, chronic obstructive pulmonary disease, Parkinson's Disease (PD), and multiple sclerosis (MS) (Ferreira et al., 2016; Hegland et al., 2016; Neves et al., 2014; Park et al., 2016; Patchett et al., 2017; S. Pinto et al., 2012; Roth et al., 2010; Troche et al., 2010). Similarly, emerging work examining the impact of EMST in PALS has found that it may lead to improved maximum expiratory pressure (MEP) (a correlate of cough strength), swallowing efficiency, and QOL (Plowman, Watts, Tabor-Gray, et al., 2016; Plowman et al., 2019; Robison et al., 2018; Tabor-Gray, Gaziano, et al., 2016; Tabor-Gray, Rosado, et al., 2016). Lingual strengthening is another potential exercise-based intervention for maintaining swallow function for patients with ND. A case series in PALS found that lingual strengthening led to maintenance of lingual strength and airway protection as well as an improvement in lingual endurance (Robison, 2015). Similarly, a case study of a patient with inclusion body myositis found that lingual pressures and swallow function (i.e. airway protection, efficiency) were maintained over a 5-year time period (Malandraki et al., 2012). While these preliminary results are promising, there is no established standard of care for dysphagia management of patients with ND (although efforts are being made to establish guidelines and to shift care to be proactive rather than reactive) (Pattee et al., 2018; Rogus-Pulia & Plowman, 2020; Troche & Mishra, 2017). Therefore, the Aim 1 experiments (Chapters 3 and 4) explored the safety, tolerability, and impact of exercise-based interventions on function and quality of life in PALS to contribute to the scientific debate regarding the role of exercise in dysphagia management of patients with ND (including PALS). Section 1.1 contains additional information regarding Aim 1.

In addition to determining the safety, tolerability, and impact of exercise-based interventions on function and quality of life for PALS, this dissertation examined the ability of a novel, non-invasive, sensor-based technology (HRCA) to characterize swallow function in patients with ND. There is great interest in portable, noninvasive, inexpensive, and efficient methods for monitoring disease progression for patients with various ND in order to determine the need for further evaluation of pulmonary/swallow function. This would allow earlier identification of patients to benefit from proactive implementation of respiratory and/or swallowing interventions. Currently, a routine clinic visit is best practice to monitor respiratory and swallow function using gold standard assessments (e.g. pulmonary function tests using spirometry, videofluoroscopic swallow studies [VFSSs]), which determines the need for potentially more invasive interventions for patients with ND (e.g., tracheotomy). Yet, attending in-person clinic visits on a regular basis can pose challenges for patients with ND due to patients having physical mobility impairments, transportation issues, multifactorial health problems, and compromised immune systems (e.g. COVID-19 pandemic).

HRCA is a non-invasive, sensor-based technology with great potential to effectively provide real-time feedback about disease progression and swallow function without the need for patients with ND to return to clinic for monitoring. HRCA has demonstrated the ability to detect swallowing safety (Penetration-Aspiration Scale [PAS]), to detect temporal and spatial swallow kinematic events associated with swallowing safety and efficiency (e.g. laryngeal vestibule closure), and to characterize swallows from patients post-stroke with similar accuracy as VFSSs

(Donohue, Mao, et al., 2020; Donohue, Khalifa, et al., 2020b; Dudik, Jestrović, et al., 2015; Dudik, Kurosu, et al., 2015; Dudik, Coyle, et al., 2015; Dudik, Jestrovic, et al., 2015; Dudik et al., 2016, 2018; He et al., 2019; Khalifa et al., 2020, 2021; Kurosu et al., 2019; Lee et al., 2011; Mao et al., 2019, 2021, Sabry et al., 2019, 2020; Sejdić et al., 2013; Zhang et al., 2020). Thus, the Aim 2 experiments (Chapters 5 and 6) explored the ability of HRCA to characterize swallow function in patients with ND. Section 1.2 contains additional information regarding Aim 2.

1.1 Aim 1

The primary goal of Aim 1 was to determine the safety, tolerability, and effects of exercise-based interventions on function and quality of life in PALS (Study 1 in Chapter 3, Study 2 in Chapter 4). Study 1 examined the safety, tolerability, and impact of two respiratory interventions (EMST and respiratory-swallow coordination training [RST]) on pulmonary, cough, and surrogates of swallow function, as well as diaphragm thickness in PALS (Donohue & Coyle, 2020). Study 2 expanded upon Study 1 by investigating exercise-based interventions in PALS through a broader lens. To further investigate the safety, tolerability, and impact of exercise-based interventions on function and quality of life in PALS, a systematic review was performed, and a meta-analysis was attempted including all types of exercise (e.g. aerobic endurance, resistance training, stretching/range of motion, respiratory muscle strength training [RMST]). These two studies provide insight into the role that exercise may have in symptom management and survival of PALS. Further, it allowed for a more integrated understanding of the effect of various exercise regimens on key functional outcome measures related to pulmonary and swallowing function. The combined results from these interrelated studies will contribute to the scientific discussion about a proposed paradigm shift from reactive to proactive management of patients with ND while simultaneously illuminating exercise-based interventions that may be beneficial for prolonging function and quality of life in PALS.

1.2 Aim 2

The primary goal of Aim 2 was to determine the ability of a novel, non-invasive, sensor-based technology (HRCA) to characterize swallow function in patients with ND (Study 3 in Chapter 5, Study 4 in Chapter 6). Study 3 examined HRCA's ability to classify swallows between patients with ND and healthy age-matched adults using logistic regression and decision trees (Donohue, Khalifa, et al., 2020a). Study 4 expanded upon Study 3 by comparing temporal and spatial swallow kinematic measurements between patients with ND and healthy age-matched adults, and investigating HRCA's ability to annotate specific temporal and spatial swallow kinematic events in swallows from patients with ND. The collective findings from these two studies elucidate changes in swallow function that may occur in patients with ND over time, as well as HRCA's potential competence in characterizing swallow function within a broad disease class (i.e. patients with ND). These studies provide preliminary evidence regarding HRCA's potential as a dysphagia screening method for earlier identification of swallowing impairment in patients with ND, and the implementation of pulmonary/swallow interventions to prolong function and enhance quality of life.

2.0 Background and Significance

ND include a heterogenous group of disorders such as Alzheimer's Disease (AD), PD, progressive supranuclear palsy (PSP), multiple system atrophy, Huntington's disease (HD), frontotemporal dementia, and ALS. While ND are grouped together due to some overlapping features, they have variable clinical presentations and underlying pathophysiology (de Pedro-Cuesta et al., 2015; Erkkinen et al., 2018). Based on several systematic reviews and meta-analyses of neurologic conditions worldwide, the prevalence of several ND range from 2.71 per 100,000 (HD) to 4.5 per 100,000 (motor neuron diseases) to 315 per 100,000 (PD) to 4,628 per 100,000 (Dementia, communities 65+) (GBD 2016 Neurology Collaborators, 2019; Pringsheim et al., 2014). While some ND are somewhat rare, it is anticipated there will be an increase in the number of patients with ND in the near future due to an increase in the aging population, leading to an increased burden on the health care system (Arthur et al., 2016; Dorsey et al., 2007; Hebert et al., 2013).

Patients with ND frequently experience weakness, spasticity, rigidity, motor unit deactivation, and atrophy of muscles secondary to motoneuron deterioration (Sandstedt et al., 2018; Sveinbjornsdottir, 2016). In addition to physical mobility impairments, patients with ND frequently have co-occurring impairments in pulmonary, cough, and swallow function (Hegland et al., 2014; Troche, Brandimore, Godoy, et al., 2014; Troche, Brandimore, Okun, et al., 2014; Wang et al., 2017). Prevalence estimates of dysphagia are alarmingly high in patients with ND and are estimated to range up to 80% in PD (Suttrup & Warnecke, 2016), 84-93% in moderate-severe AD (Horner et al., 1994), and greater than 85% in PALS (Ball et al., 2001; Kühnlein et al., 2008; Onesti et al., 2017). Pulmonary and cough function are intimately linked to swallowing because of the coordination between breathing and swallowing to maintain airway protection, the shared anatomy and physiology of the aerodigestive tract, and the shared neural substrates within the brain (Martin-Harris, 2008; Troche, Brandimore, Godoy, et al., 2014). Patients with ND frequently experience pulmonary decline due to obstructive and/or restrictive respiratory patterns (Andrews et al., 2018; Baille et al., 2016; D'Arrigo et al., 2020). For example, in PALS, pulmonary decline is an indicator of ALS disease progression, and thus, used as a predictor of morbidity and survival, and for recommendations of invasive interventions (e.g., mechanical ventilation, gastrostomy) (Andrews et al., 2018; Baumann et al., 2010; D.-G. Kim et al., 2015; Schmidt et al., 2006; Suárez et al., 2002). Furthermore, malnutrition/dehydration, aspiration pneumonia, and respiratory failure (which occur due to impairments in pulmonary, cough, and swallow function) account for mortality in the majority of patients with ND (Brunnström & Englund, 2009; Czaplinski et al., 2006; Karceski, 2018; Kühnlein et al., 2008; Onesti et al., 2017; Pennington et al., 2010).

Management of patients with ND, including dysphagia, is costly and not always accessible for patients (e.g. physical mobility limitations, transportation issues). The total annual U.S. health care cost of PALS reaches more than $1 billion, with an estimated annual cost averaging $64,000 per patient (Larkindale et al., 2014). Similarly, the annual U.S. health care cost of patients with dementia is estimated to be between $157-215 billion with an annual cost of ~$56,000 per patient (Hurd et al., 2013), and the total medical burden of patients with PD was approximately $52 billion in 2017 (Yang et al., 2020). For PALS, the most frequent concurrent diagnoses leading to hospitalization include dehydration/malnutrition (36%), pneumonia (32%), and respiratory failure (25%) (Lechtzin et al., 2001). Likewise, pneumonia/pulmonary infections are reported as a frequent primary reason for hospitalization in patients with PD (M. Braga et al., 2014; Temlett & Thompson, 2006). In addition to this, hospitalizations have been shown to be significantly longer in patients with ND compared to patients with other diagnoses, further contributing to higher costs (Husaini et al., 2015; Lechtzin et al., 2001).

Therefore, there is an urgent need for proactive dysphagia management via implementation of prophylactic exercise-based interventions and early identification of respiratory and swallowing impairments to prevent adverse events/hospitalizations and to prolong function and quality of life. While there is enthusiasm for proactive dysphagia management of patients with ND (Rogus-Pulia & Plowman, 2020), scant research evidence is available to guide the implementation of exercise-based interventions to prolong respiratory and swallow function in patients with ND (Chiara et al., 2007; Chigira et al., 2018; Ferreira et al., 2016; J. Kim et al., 2009; Malandraki et al., 2012; Plowman, Watts, Tabor-Gray, et al., 2016; Plowman et al., 2019; Reyes et al., 2015, 2018; Robison, 2015; Robison et al., 2018; Rodríguez et al., 2020; Tabor-Gray, Gaziano, et al., 2016; Tabor-Gray, Rosado, et al., 2016; Troche et al., 2010; Troche & Mishra, 2017). In addition to this, because access to objective clinical measurements of pulmonary and swallow function with gold standard testing (i.e., spirometry, VFSS) is limited for patients with ND, portable, promising, noninvasive adjunct assessments are under investigation for monitoring disease progression and swallow function (Donohue, Khalifa, et al., 2020b; Donohue, Mao, et al., 2020; Dudik, Coyle, et al., 2015; Dudik et al., 2016, 2018; Dudik, Jestrovic, et al., 2015; Dudik, Jestrovi, et al., 2015; He et al., 2019; Khalifa et al., 2020, 2021; Kurosu et al., 2019; Lee et al., 2011; Mao et al., 2019, 2021, Sabry et al., 2019, 2020; Sejdić et al., 2013; Zhang et al., 2020). Such a tool would contribute valuable diagnostic information to speed identification of patients with ND whose swallowing function poses choking and aspiration risks, and potentially mitigate hospitalizations and prolong life. Therefore, this dissertation study will critically appraise the current research evidence on exercise-based interventions in PALS, provide preliminary evidence regarding the safety, tolerability, and efficacy of RST and EMST+RST in PALS, and demonstrate HRCA's potential in characterizing swallow function in patients with ND for early identification of swallowing impairments and continuous monitoring of disease progression. The long-term goal of this programmatic line of research is to hasten the identification of patients with ND who require further evaluation and who would profit from early deployment of preventative therapeutics.

2.1 Dysphagia Management of Patients with Neurodegenerative Diseases

Prompt identification of individuals with ND with dysphagia and/or dystussia is vital in order to mitigate adverse events that may lead to faster disease progression, reduced physiological reserve, and diminished quality of life (Aghaz et al., 2018; Andrews et al., 2018; Ball et al., 2001; Czaplinski et al., 2006; da Costa Franceschini & Mourão, 2015; Easterling & Robbins, 2008; Kühnlein et al., 2008; Onesti et al., 2017; Paris et al., 2013; Takizawa et al., 2016). As with all patient populations that may experience dysphagia and/or dystussia, clinicians should provide appropriate and individualized assessment and treatment for patients based on the underlying pathophysiology of the disease that is causing impairments in pulmonary, cough, and/or swallow function. In contrast to other patient populations with a high incidence of dysphagia and/or dystussia, there are several key factors unique for dysphagia management of patients with ND. ND are progressive and have variable decline rates and prognosis. Due to the decline in function over time, variable disease progression rates, and fluctuating day-to-day function, it is important for patients with ND to be monitored closely for changes in pulmonary, cough, and swallow function (Audag et al., 2019; Waito et al., 2017). Likewise, instead of treatment goals focusing on rehabilitation of function, they may alternatively focus on maintenance and/or attenuation of the trajectory of functional decline. Goals of care should simultaneously assist patients with ND in safely maintaining their nutrition/hydration and their quality of life. An individualized care plan is of utmost importance given that some patients with ND may choose a proactive, aggressive assessment and treatment approach, while other patients' preferences may align with a palliative treatment style (Rogus-Pulia & Plowman, 2020).

While there are a variety of factors to consider when deploying assessment and treatment techniques in patients with ND, two main dysphagia management approaches have emerged in the research literature to date: 1) the historical, reactive approach and 2) the patient-centered, proactive approach (Rogus-Pulia & Plowman, 2020). This dissertation and the four studies described in this proposal aspired to provide further evidence to support the projected paradigm shift to a proactive dysphagia management approach for patients with ND by 1) investigating the safety, tolerability, and efficacy of employing exercise-based interventions early in ALS disease (Aim 1; Studies 1 and 2), and 2) investigating HRCA's potential as a noninvasive, sensor-based technology that can speed identification of patients with ND with swallowing impairments (Aim 2; Studies 3 and 4).

2.1.1 The Historical, Reactive Dysphagia Management Approach

Due to the progressive nature of ND and fear that proactive, exercise-based interventions may result in faster disease progression and/or fatigue (de Almeida et al., 2012; Harkawik & Coyle, 2012; Newland et al., 2016; Raheja et al., 2016; Siciliano et al., 2018), dysphagia management approaches have historically been reactive and palliative in nature (Rogus-Pulia & Plowman, 2020). Since there is no curative treatment for patients with ND, goals of care have typically focused on symptom management and maximizing quality of life (Alagiakrishnan et al., 2013; Armstrong & Okun, 2020; Dharmadasa et al., 2016; Hobson & McDermott, 2016; Kühnlein et al., 2008). For example, pulmonary and swallow function in PALS is closely monitored to determine the timing of invasive interventions (e.g. mechanical ventilation, gastrostomy) to prevent respiratory failure and allow patients to maintain their nutrition/hydration for increased survival (Baumann et al., 2010; D.-G. Kim et al., 2015; Schmidt et al., 2006; Suárez et al., 2002). Reactive dysphagia management of patients with ND may include counseling patients about early feeding tube placement to maintain nutrition/hydration (i.e. PALS), diet modifications to increase swallowing safety and efficiency (e.g. thickened liquids, soft solids), and compensatory swallowing maneuvers and strategies (e.g. chin tuck, effortful swallow, small bites/sips, etc.) (Kühnlein et al., 2008; Rogus-Pulia & Plowman, 2020). In addition to this, with the reactive dysphagia management approach, patients with ND are typically referred for assessment and treatment after they have symptoms of dysphagia rather than at the time of diagnosis, which may limit the effectiveness of interventions and result in fewer dysphagia management options, especially in cases where disease progression is rapid. In contrast to proactive dysphagia management approaches that strive to preventatively bolster physiological functional reserve and to provide assessment and treatment based on the underlying disease process, reactive dysphagia management approaches are palliative rather than rehabilitative in nature.

2.1.2 The Proactive Dysphagia Management Approach: Early Interventions

Emerging research evidence has led to the proposal of a paradigm shift in dysphagia management of patients with ND from a reactive approach to a proactive approach (Meng et al., 2020; Rogus-Pulia & Plowman, 2020; Tsitkanou et al., 2019). In contrast to a reactive dysphagia management approach, which focuses on implementation of compensations and assessment/treatment of respiratory and swallow function after patients with ND become symptomatic, a proactive dysphagia management approach aims to bolster patients' functional reserve and to deploy prophylactic exercise-based interventions prior to detrimental respiratory and swallowing symptoms manifest (Rogus-Pulia & Plowman, 2020). Maintaining functional reserve is imperative for patients with ND, because functional reserve declines with age, is exacerbated by the presence of ND, and can lead to frailty which is known to increase patients' risk of adverse events and mortality (Bock et al., 2017; Chen et al., 2014; Goldspink, 2005; Murray, 2008).

For example, it is well established in the research literature that a decline in in respiratory, cough, and swallow function occurs over time in elderly people (and even more so in frail elderly people) because of loss of muscle mass and strength (sarcopenia) (Fujishima et al., 2019; Murray, 2008; Namasivayam-MacDonald et al., 2018). These changes in muscle mass and strength start at the age of 40 and occur in increasing percentages every decade after the age of 70 along with changes to the neural innervation of muscles (i.e. loss of cortical neurons, increased response time for sensory input, etc.) (Walston, 2012). Sarcopenia occurs in all muscles throughout the body including the muscles of inspiration and expiration that are important for producing strong, effective coughs, and the muscles that coordinate swallowing, which are responsible for producing safe and efficient swallows (Murray, 2008; Namasivayam-MacDonald et al., 2018). While frailty in elderly adults may contribute to their risk of dysphagia, malnutrition due to dysphagia may also result in an increased risk of overall frailty (Fujishima et al., 2019; Sura et al., 2012).

Kinematic measures of swallow function have been examined in elderly people and have revealed that older adults have longer swallow reaction times, longer pharyngeal delay times, and longer duration of UES opening compared to young adults (Namasivayam-MacDonald et al., 2018). Studies have also shown that elderly adults experience reduced swallowing efficiency (increased residue) and a decline in tongue strength/tongue pressure reserves (Molfenter et al., 2018; Nicosia et al., 2000; Robbins et al., 1995). Commonly reported swallowing impairments in patients with ND include impaired bolus preparation and propulsion, impaired mastication, reduced oral containment, oral residue, impaired tongue movement, impaired pharyngeal timing/coordination, pharyngeal residue, and penetration/aspiration (Waito et al., 2017). When patients with ND encounter swallowing impairments that occur due to the underlying disease process in the setting of swallowing alterations as a result of typical ageing (e.g. presbyphagia), they may experience more problematic deficits and a greater decline in functional reserve. These compounding issues may contribute to an accelerated decline of function and shortened survival.

In the limb literature, exercise-based interventions have frequently been deployed to boost functional reserve, revert age-related changes, and prevent frailty in elderly adults (Chen et al., 2014; Clegg et al., 2012; Theou et al., 2011). Exercise-based interventions have resulted in a variety of benefits in frail elderly people including improved muscular strength, flexibility, functional mobility, balance, ability to perform activities of daily living, and quality of life (Chen et al., 2014; Clegg et al., 2012; Theou et al., 2011). Therefore, using the limb literature as a framework, researchers have investigated implementation of exercise-based interventions to assist in bolstering the physiological functional reserve of the respiratory and swallowing musculature in elderly adults and patients with ND (Azzolino et al., 2019). Researchers have examined the impact of non-load bearing (e.g. Masako maneuver, Shaker) and loadbearing (e.g. EMST, IMST) exercise regimens on respiratory and swallow function in elderly adults and patients with ND. Elderly adults with dysphagia that have undergone non-load bearing swallowing exercise regimens have demonstrated improvements in initiation of the pharyngeal swallow, laryngeal elevation, pharyngeal residue, and airway protection (Balou et al., 2019). Similarly, EMST and IMST have led to improvements in pulmonary, cough, and swallow function and quality of life in elderly adults and patients with ND (Chiara et al., 2007; Chigira et al., 2018; Ferreira et al., 2016; López-Liria et al., 2020; Pitts et al., 2009; Plowman, Watts, Tabor-Gray, et al., 2016; Plowman et al., 2019; Robison et al., 2018; Tabor-Gray, Gaziano, et al., 2016; Tabor-Gray, Rosado, et al., 2016; Troche et al., 2010). Lingual strengthening has also led to maintenance and/or improvements in tongue strength/endurance, quality of life, and maintenance of swallow function (e.g. efficiency, airway protection) in elderly adults and patients with ND with dysphagia (Malandraki et al., 2012; Namasivayam-MacDonald et al., 2017; Robison, 2015; Rogus-Pulia et al., 2016). This promising preliminary research evidence in elderly adults and patients with ND provides support regarding early deployment of exercise-based interventions to preserve functional reserve, maintain quality of life, and enable patients to engage in goals of care discussions early on in the disease process to develop an individualized treatment approach.

Using the proactive dysphagia management approach as a framework for Studies 1 and 2 (Chapters 3 and 4), the following predictions were made about the safety, tolerability, and efficacy of exercise-based interventions in PALS. For Study 1, we hypothesized that: 1) EMST+RST would be safe, well-tolerated, and lead to greater improvements or improved trajectory of decline in all outcome measures than EMST alone or no treatment; and 2) Either treatment (EMST+RST and EMST alone) would lead to greater improvements or attenuated trajectory of decline in all outcome measures than no treatment. For Study 2, we hypothesized that: 1) Exercise-based interventions would be safe, well-tolerated, and lead to improvements in function and quality of life in PALS.

2.1.3 The Proactive Dysphagia Management Approach: Early Identification

In addition to early implementation of exercise-based interventions to preserve respiratory and swallow function for patients with ND, the proactive dysphagia management approach depends on swift identification of patients with dysphagia and/or dystussia to mitigate risk of adverse events (e.g. aspiration pneumonia) and to enable earlier referrals for further evaluation and treatment. For patients with ND, it is recommended that disease progression be monitored via multidisciplinary clinic visits to provide holistic and integrated care, which has demonstrated improved patient satisfaction, prolonged survival, and decreased frequency and length of stay for hospitalizations (Chiò et al., 2006; Howard & Potts, 2019; Kiernan et al., 2011). While objective evaluation tools such as spirometry and VFSSs remain the gold standard for assessing pulmonary and swallow function in patients with ND, they are not always feasible, accessible, or desirable due to time constraints during multidisciplinary clinic visits, clinical site limitations, and individual patient factors (e.g. physical mobility impairments, multifactorial health problems, and difficulty attending in-person appointments due to transportation challenges or having a compromised immune system) (Alagiakrishnan et al., 2013; Audag et al., 2019; Waito et al., 2017). Yet, standardized assessment of swallow function is vital given that there is a high incidence of silent aspiration in patients with ND and some patients may have subclinical signs of dysphagia/dystussia (Alagiakrishnan et al., 2013; Garon et al., 2009; Plowman, Watts, Robison, et al., 2016; Watts et al., 2016). For example, best practice guidelines have been developed for the evaluation of bulbar dysfunction in PALS (Pattee et al., 2018). Recommended elements for swallow screening during clinic visits include 1) patient reported outcome measures (e.g. EAT-10) (Plowman, Tabor-Gray, Robison, et al., 2016), 2) dietary intake (e.g. Neuromuscular Disease Status Scale) (Wada et al., 2015), 3) pulmonary/airway defense capacity (e.g. forced vital capacity [FVC], peak expiratory flow [PEF]) (Plowman, Watts, Robison, et al., 2016), 4) bulbar function (e.g. lingual function using the Iowa Oral Performance Instrument) (Hiraoka et al., 2017), and 5) dysphagia screening (e.g. Yale swallow protocol) (Suiter et al., 2014). Although strides are being made to standardize and improve dysphagia screening for patients with ND, few dysphagia screening tools have been developed specifically for patients with ND and many screening tools lack adequate sensitivity and specificity (O'Horo et al., 2015). In addition to this, dysphagia screening tools rely on subjective human judgment (e.g. identifying patient risk factors, observing a patient drink water) rather than objective measurement of swallowing physiology, which can result in under or over-identification of swallowing impairments.

The current limitations of dysphagia screening methods for patients with ND and the high demand for early identification of detrimental swallowing impairments inspired Studies 3 and 4 (Chapters 5 and 6). With consideration of the proactive dysphagia management approach, the following predictions were made about HRCA's ability to characterize swallow function in patients with ND. For Study 3, we hypothesized that HRCA would accurately classify swallows from patients with ND and age-matched healthy adults to allow for noninvasive, early identification of patients with ND with subclinical signs of dysphagia. For Study 4, we hypothesized that: 1) There would be differences in temporal (bolus passes the mandible, hyoid onset, hyoid maximum, hyoid offset, UES opening, UES closure, LVC, LV re-opening) and spatial (hyoid bone displacement and anterior-posterior UES distension) swallow measurements between patients with ND and age-matched healthy adults; and 2) HRCA would accurately annotate temporal and spatial swallow kinematic events in patients with ND to assist with ongoing monitoring of swallow function and changes that may be associated with disease progression.

2.2 Overall Significance and Innovation

Patients with ND experience progressive, debilitating impairments in pulmonary, cough, and swallow function which impact quality of life and can lead to life-shortening adverse events (Aghaz et al., 2018; Andrews et al., 2018; Ball et al., 2001; Czaplinski et al., 2006; da Costa Franceschini & Mourão, 2015; Easterling & Robbins, 2008; Kühnlein et al., 2008; Onesti et al., 2017; Paris et al., 2013; Takizawa et al., 2016). While there is preliminary evidence that exercise-based interventions may be advantageous to deploy in patients with ND to prolong function, life, and quality of life, it remains a controversial topic within clinical and research settings due to the limited number of high quality research studies that have examined the safety, tolerability, and efficacy of exercise-based interventions in patients with ND (especially in the realm of dysphagia management) (Meng et al., 2020; Robberecht & Philips, 2013; Rogus-Pulia & Plowman, 2020; Tsitkanou et al., 2019). Likewise, while efforts are being made to identify inexpensive, noninvasive, portable tools to speed identification of disease-related functional impairments in pulmonary, cough, and swallow function in patients with ND, VFSSs and spirometry persist as the gold standard assessment tools (Audag et al., 2019; Waito et al., 2017). Therefore, this dissertation is driven by these gaps in the research literature and is inspired by the proposed paradigm shift from reactive to proactive dysphagia management in patients with ND (Rogus-Pulia & Plowman, 2020). These four experiments investigated the following research questions, which are aligned with the specific aims of this dissertation.

Aim 1) Are exercise-based interventions safe and well-tolerated in PALS?

What is the impact of exercise-based interventions on function and quality of life in PALS?

Aim 2) Are there differences in temporal and spatial swallow kinematic measurements between patients with ND and healthy age-matched adults?

Can a novel, non-invasive, sensor-based technology (HRCA) accurately and autonomously characterize swallow function in patients with ND?

To investigate the questions aligned with specific aim 1, Study 1 (Chapter 3) examined the safety, tolerability, and impact of EMST+RST and EMST alone on pulmonary, cough, and swallow function surrogates in PALS, and Study 2 (Chapter 4) examined the safety, tolerability, and impact of a wide variety of exercise-based interventions on function and quality of life in PALS. To explore the questions aligned with specific aim 2, Study 3 (Chapter 5) investigated HRCA's ability to differentiate swallows from patients with ND and age-matched healthy adults, and Study 4 (Chapter 6) investigated differences in temporal and spatial swallow kinematic measurements between patients with ND and healthy age-matched adults, as well as HRCA's ability to annotate specific temporal and spatial swallow kinematic events for swallows from patients with ND by using advanced signal processing and machine learning techniques. Study 1 included a small sample of PALS (N=6), Study 2 was a systematic review that included 24 original research articles (N= 666 PALS/patients with motor neuron disease), and Studies 3 and 4 included the same sample of patients with ND (N=20) and age-matched healthy adults (N= 51). The results of these studies (including the theoretical and clinical implications) are integrated and summarized in the General Discussion and Conclusion chapters (Chapters 7 and 8).

This dissertation research work is innovative in several ways. Study 1 was the first research study to investigate the safety, tolerability, and efficacy of RST in PALS. Study 2 expanded upon previous systematic reviews by examining the safety, tolerability, and impact of a wide variety of exercise-based interventions on function and quality of life in PALS to illuminate whether exercise is beneficial or detrimental for PALS. Study 3 was the first research study to employ HRCA to classify swallows from age-matched healthy adults and a specific underlying disease category that frequently contributes to dysphagia. Similarly, Study 4 was the first study to characterize swallows from a distinct patient population ("patients with ND") by using HRCA combined with machine learning techniques to annotate specific temporal and spatial swallow kinematic events. The combined findings from these studies contribute substantively to clinical and research practice by providing preliminary evidence regarding promising exercise-based interventions and systems for early identification of swallowing impairments in patients with ND.

3.0 Study 1: The safety, tolerability, and impact of respiratory-swallow coordination training and expiratory muscle strength training on pulmonary, cough, and swallow function surrogates in amyotrophic lateral sclerosis

3.1 Introduction

Swallowing difficulty, or dysphagia, negatively impacts quality of life, and is prevalent in PALS with greater than 85% of PALS experiencing dysphagia at some point during the disease course (Ball et al., 2001; Kühnlein et al., 2008; Onesti et al., 2017). Consequences of dysphagia include airway obstruction, malnutrition, dehydration, and aspiration pneumonia (da Costa Franceschini & Mourão, 2015; Desport et al., 1999; Paris et al., 2013), which collectively account for mortality in the majority of PALS (Czaplinski et al., 2006; Kühnlein et al., 2008; Onesti et al., 2017). Respiratory and cough function are strongly tied to swallow function, and pulmonary deterioration alone is a strong indicator of disease progression in PALS due to progressive denervation of the diaphragm and the muscles of the chest wall. There is evidence that attenuated decline rates of slow vital capacity are associated with fewer respiratory-related, life-shortening clinical events in PALS (Andrews et al., 2018). Forced and/or slow vital capacity are indicators of not only muscle strength, but elastic recoil of the lung, patency of the airway, and chest wall anatomy. The threshold for initiating non-invasive positive pressure ventilation (NPPV) in ALS has traditionally been when patients have an FVC<50% predicted, however, NPPV improves quality of life and survival in patients with FVCs <75% predicted (Prell et al., 2016). MEP and peak cough flow (PCF) are pulmonary function tests (PFTs), which are often measured in PALS due to their strong association with the ability to cough. On average, MEPs in healthy people are 96 cm H20 (+/- 36) (Gil Obando et al., 2012), while MEPs in PALS are between 44-53 cm H20 (+/- 22) (D.-G. Kim et al., 2015). MEPs of <70 cm H20 are associated with death or a need for a tracheostomy (Schmidt et al., 2006). PCFs in healthy people range from 240-500 L/min on average (Cardoso et al., 2012) while PCFs in PALS average 213 (+/-193) L/min (Suárez et al., 2002). In order to produce an effective cough, PCFs must be >160L/min (Cardoso et al., 2012). Diaphragm thickness using ultrasound is another method for assessing inspiratory competence (i.e. diaphragm contractility) when PALS with bulbar impairment exhibit reduced ability to produce direct pulmonary function data due to inadequate lip seal (Fantini et al., 2016; S. Pinto et al., 2016). Studies have shown wide ranges of diaphragm thickness in healthy people (Harper et al., 2013; Sarwal et al., 2013), but it is generally agreed upon that a <20% change in diaphragm thickness during one inspiratory and expiratory cycle is associated with paralysis (Sarwal et al., 2013).

Historically, limited treatment options have been explored in PALS due to the rapidly progressing neurodegenerative nature of the disease and fear that exercise training will lead to faster deterioration of function. However, in recent years, both animal and human models have demonstrated promising results indicating that moderate exercise training in PALS may be advantageous by increasing the efficiency of the skeletal muscles exercised, reducing fatigue, slowing the progression of disease-related impairments, and improving quality of life (de Almeida et al., 2012; Harkawik & Coyle, 2012).

EMST has been explored in a wide variety of patient populations, including PALS, due to the relationship between respiratory function and swallowing and the necessity of coordinating these two interrelated functions (Martin-Harris, 2008; McFarland et al., 2016). EMST has led to improvements in pulmonary, cough, and swallow function as well as quality of life (Chiara et al., 2007; Ferreira et al., 2016; Hegland et al., 2016; Hutcheson et al., 2018; Laciuga et al., 2014; Neves et al., 2014; Park et al., 2016; Patchett et al., 2017; Plowman et al., 2019; Plowman, Watts, Tabor-Gray, et al., 2016; Reyes et al., 2015; Robison et al., 2018; Roth et al., 2010; Tabor-Gray, Gaziano, et al., 2016; Tabor-Gray, Rosado, et al., 2016; Troche et al., 2010). RST is an emerging treatment that has been effective in improving impaired respiratory-swallow patterns and kinematic swallow events in patients with dysphagia (Brodsky et al., 2010; Gross et al., 2009; Martin-Harris et al., 2015). RST has been explored because there is typically a period of apnea that occurs during swallowing to prevent penetration and/or aspiration. In healthy adults, respiratory patterns during swallowing include post-swallow exhalation, with patterns including exhale-swallow-exhale (67-79% liquid swallows, 87-99% solids) and inhale-swallow-exhale (18-21% liquid swallows) (Hopkins-Rossabi et al., 2019; Matsuo & Palmer, 2009). A recent study in patients with head and neck cancer found that RST led to improvements in not only respiratory-swallow coordination, but also improved measures of swallowing safety including longer duration of airway (laryngeal vestibular) closure, greater bolus propulsion (tongue base retraction), and reduced pharyngeal residue (Martin-Harris et al., 2015). Therefore, there is preliminary research evidence that RST is an alternative treatment to EMST that may result in improvements in pulmonary and swallow function without requiring resistive exercise that may lead to fatigue. However, it remains unknown whether EMST treatment, which targets expiratory pressure and volume as an underlying mechanism supporting airway clearance, may lead to improvements in inspiratory function (as measured by diaphragm thickness). Additionally, it is unknown whether EMST may lead to superior outcomes when combined with RST, which additionally corrects for pathological alterations in the timing of airway closure relative to inspiration and expiration. This combination may provide superior efficacy than EMST alone in mitigating disease-related decline in key parameters of airway protection and pulmonary function.

Therefore, this feasibility study aimed to expand upon previous respiratory intervention studies in PALS by examining the safety, tolerability, and impact of EMST+RST compared to EMST alone and no treatment on pulmonary function, cough function, surrogates of swallow function, and diaphragm thickness, in ordinary clinical settings. We hypothesized that EMST+ RST would be a safe and well-tolerated treatment and that it would lead to greater improvements or improved trajectory of decline in all outcome measures than EMST alone or no treatment. We also hypothesized that either treatment (EMST+RST and EMST alone) would lead to greater improvements or attenuated trajectory of decline in all outcome measures than no treatment.

3.2 Methods

3.2.1 Patients:

Fifteen patients who expressed interest in participating in this research study were screened for participation at the University of Pittsburgh Multidisciplinary ALS Clinic. Six patients were deemed eligible and enrolled in the study. Inclusion criteria for the study included: (1) confirmed diagnosis of ALS by a neurologist, (2) reduced MEP as determined by normative data for age and gender, (3) FVC greater than 60% of predicted values for age, gender, and height, (4) no signs of frontotemporal dementia as determined by a score >10 on the ALS Cognitive Behavioral Screen (ALS-CBS) (Woolley et al., 2010) or a score of ≥27 on the Mini Mental State Examination (Folstein et al., 1975), (5) no tracheostomy or mechanical ventilation, (6) a score of ≥1 on the EAT-10 (Belafsky et al., 2008), and no other concurrent respiratory and/or neurological diagnoses. This study was approved by the institutional review board at the University of Pittsburgh and was conducted in accordance with the Declaration of Helsinki.

3.2.2 Design:

This was a prospective, non-randomized, multiple baseline, delayed intervention, case series feasibility study. After providing written informed consent and undergoing screening procedures for the study, consecutively enrolled patients who were interested in completing one of the respiratory interventions were alternately assigned to one of the two treatments (EMST+RST, N=3) or (EMST, N=2). No patients that were eligible for treatment declined it. However, one patient who was initially assigned to the EMST only treatment was unable to complete the intervention due to health complications unrelated to the study. This patient was followed in the no treatment condition (N=1). All study patients underwent an initial baseline assessment procedure (visit 1), which included measurements of pulmonary and cough function, and surrogates of swallow function as well as diaphragm thickness. Following visit 1, patients underwent a five-week lead-in period in which they did not complete any respiratory interventions in order to establish baselines. Then, patients underwent a repeat of initial baseline assessment procedures (visit 2) to assess for progression of bulbar symptoms. After completion of visit 2, patients assigned to EMST+RST and EMST only began a 5-week treatment period. Following the treatment period, all patients underwent a third assessment procedure, which consisted of the same assessment battery. After the third study visit, patients were given the option to participate in a maintenance phase by continuing only the EMST treatment for another 5 weeks. Patients who were interested in the maintenance period provided informed written consent and continued only EMST treatment for an additional 5 weeks. Following the maintenance period, these patients underwent a fourth baseline procedure using the same assessment battery.

3.2.3 EMST Training Protocol:

EMST was completed using the EMST-150 device (Aspire Products, Gainesville, Florida), which is a one-way, spring-loaded valve with resistance levels ranging from 30-150 cm H2O. Devices were set to a conservative load (50%) of patients' MEP at the time of visit 2 (pre-treatment) using the MicroRPM handheld MEP device (Micro Direct Inc., Lewiston, ME) according to prior studies, which have established this as a well-tolerated and appropriate training load for PALS (Plowman et al., 2019; Plowman, Watts, Tabor-Gray, et al., 2016; Tabor-Gray, Rosado, et al., 2016). To standardize the treatment protocol, the flat-billed mouthpiece for the

EMST-150 device was used for all patients. RST was completed using the Nexus-10 MK II respiratory belt attached to a laptop computer with the Biotrace + software (Mind Media, Netherlands). A speech-language pathologist (SLP) completed training sessions in a private room in patients' homes once per week for the 5-week training period. During each home visit, the SLP completed 3 MEP measurements with patients and adjusted the EMST-150 device to maintain resistance each visit (50% MEP). For training sessions, patients sat in a comfortable upright position in a chair with a nose clip in place in order to prevent nasopharyngeal air leakage (although L005 did not tolerate using the nose plug due to gagging). All patients wore the respiratory belt during EMST in order to quantify changes in inspiratory and expiratory volume and effort during EMST in comparison to tidal breathing. The respiratory belt was placed along the 8th rib laterally in order to quantify thoracic cavity excursion (abdominal wall and rib cage displacement) during breathing. Patients completed 5 sets of 5 repetitions using the EMST-150 device with approximately 15-20 seconds rest between repetitions and approximately one-minute rest between sets for a total of 25 repetitions each training session. Patients were instructed to independently complete one training session per day, 5 days per week, during intervals between home visits, as per the methods reported in other studies in PALS and other diagnoses (Hegland et al., 2016; Hutcheson et al., 2018; Park et al., 2016; Plowman, Watts, Tabor-Gray, et al., 2016; Troche et al., 2010). Patients were given training logs to complete during the week to track exercise completion and report adverse outcomes including fatigue, pain, and shortness of breath. Patients were given pictures of the fatigue rating scale, pain rating scale, and the Modified Borg scale for perceived dyspnea (See Appendix A for treatment logs) and trained in their use. In addition to the training logs, the PI of the study rated overall activity levels of patients as sedentary, light, light-moderate, moderate, moderate-intense, and intense.

3.2.4 RST training protocol:

Following completion of EMST, patients in the RST group received additional training for approximately 15 minutes. During RST, patients were provided with education about swallow apnea, healthy respiratory-swallow patterns, and impaired respiratory-swallow patterns. Patients were taught to identify inhalation, exhalation, and whether they inhaled or exhaled after swallows using the respiratory belt data and visual biofeedback from the laptop display. Patients who exhibited post-swallow inspiration were then trained to modulate their breathing patterns by exhaling after they swallowed thin liquids. Visual and verbal feedback was gradually faded by the SLP across training sessions.

3.2.5 Maintenance training protocol:

Patients who opted-in to the maintenance training period continued EMST at the same resistance level as their final device setting by the SLP during their last home visit. They had weekly phone calls from the SLP to encourage adherence, answer questions, evaluate any subjective reports of adverse outcomes including fatigue, pain, and shortness of breath, and determine continued safety and tolerability of this treatment. Patients continued to complete training logs for five additional weeks.

3.2.6 Outcome Measures:

Patients underwent an evaluation battery that included assessments of pulmonary, cough, and surrogates of swallow function as well as a measurement of diaphragm thickness during visits 1, 2, 3, and 4 for patients who opted-in to the maintenance group (See Figure 1).

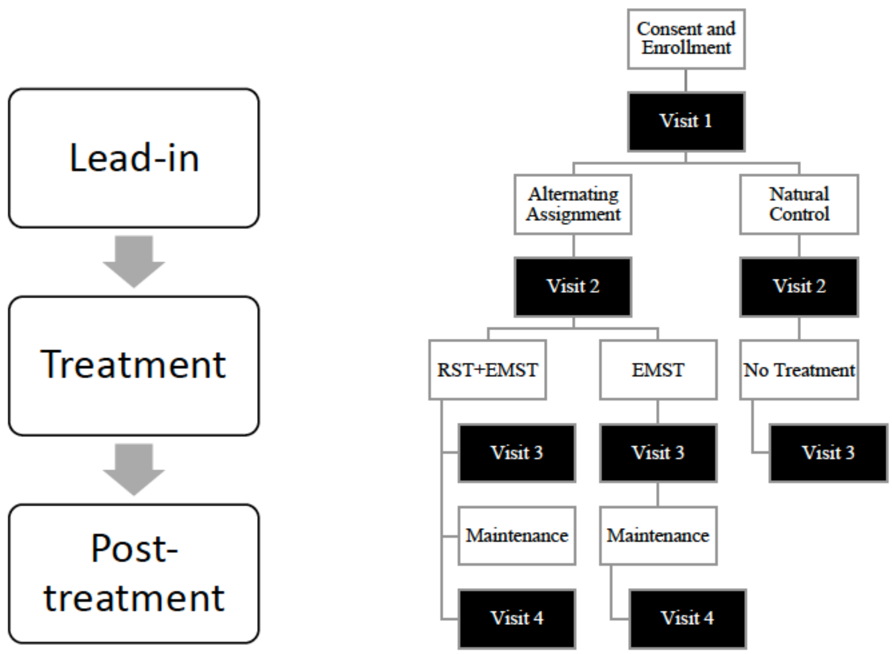

Figure 1: Flowchart of the study design.

3.2.7 Pulmonary and Cough Measures:

PFTs included FVC, forced expiratory volume in one second (FEV1), PCF, and MEP. PFTs were obtained with patients in a comfortable seated position in a chair with a nose clip on, in order to prevent nasopharyngeal air leakage, in line with standard pulmonary function test protocols (Cheung & Cheung, 2015; Moore, 2012). FVC and FEV1 testing was completed using the Spirodoc spirometer and WinspiroPRO computer software (Medical International Research, New Berlin, WI). Patients were instructed to “Take a deep breath, blow out as hard as you can for 5 seconds. When you can’t blow any more air out of your lungs, take a deep breath in again.”(Cheung & Cheung, 2015; Moore, 2012). PCF was completed using a handheld peak flow meter (BV Medical, Barrington, IL) (See Figure 2). Patients were instructed to “Take a deep breath and cough as hard as you can.”(Cheung & Cheung, 2015; Moore, 2012). MEP testing was completed using the MicroRPM handheld MEP device (Micro Direct Inc., Lewiston, ME) (See Figure 3). Patients were instructed to “Take a deep breath and blow out hard against the resistance.”(Cheung & Cheung, 2015; Moore, 2012). For all PFTs, three values were collected from patients and the best values were used for data analysis.

Figure 2: This handheld peak flow meter (BV Medical, Barrington, IL) was used for obtaining PCF measurements.

Figure 3: This MicroRPM handheld MEP device (Micro Direct Inc., Lewiston, ME) was used for obtaining MEP measurements.

3.2.8 Swallowing-Related Measures:

Surrogate swallowing measurements in this study included three patient report questionnaires and a clinical bedside swallow evaluation with a respiratory belt in place. The functional oral intake scale (FOIS) (Crary et al., 2005) was based on patient report. This 7-point ordinal scale has been used as an index to determine how patients with dysphagia maintain their nutrition and hydration. Patients in the study completed the EAT-10, which is a ten-item patient report measure of dysphagia severity that has been shown to differentiate between PALS who have safe and unsafe swallows with a high degree of sensitivity and specificity (Plowman, Tabor-Gray, Robison, et al., 2016). Patients completed the Swallowing Related Quality of Life (SWAL-QOL), which is a questionnaire that measures the impact of dysphagia on swallowing related quality of life (Rinkel et al., 2009; Tabor-Gray, Gaziano, et al., 2016). For the clinical bedside swallow evaluation, patients took three comfortable sips of thin water in a comfortable seated position with the respiratory belt along the 8th rib laterally to assess respiratory-swallow patterns and to observe overt signs of aspiration. This measurement was used as the respiratory-swallow baseline for patients in the RST group.

3.2.9 Ultrasound of the Diaphragm:

Ultrasound of the diaphragm was completed with patients in a comfortable seated upright position using the GE Logic e ultrasound machine (GE Healthcare, Troy, NY). Ultrasound images were obtained in B mode using a high-frequency probe set at 12MHz. An intercostal/axillary approach was used to obtain a clear sagittal view of the diaphragm with visible superior and inferior surfaces, by placing the ultrasound probe between the 7th and 8th or 8th and 9th ribs on the right side of patients. Three measurements of diaphragm thickness were obtained during an inspiratory and expiratory cycle and then averaged for data analysis. The measurements of diaphragm thickness were used to calculate a diaphragm thickening fraction by using the formula (thickness at end inspiration) - (thickness at end expiration/thickness at end expiration) (Sarwal et al., 2013).

3.2.10 Data Analysis:

A trained research assistant completed data entry and analysis. The EAT-10, SWAL-QOL, FOIS, ALS-CBS, PFTs (MEP, FVC, FEV1, PCF), and respiratory exercise logs were initially scored and entered into a database by the PI and were confirmed by the research assistant. To calculate diaphragm thickness, a line was drawn parallel to the peritoneal membrane/edge of the diaphragm to determine the correct angle in each image by using ImageJ image processing software (Schneider et al., 2012). Once the angle of the diaphragm was known, a perpendicular line was drawn to determine the width of the diaphragm at maximum inspiration and maximum expiration (See Figure 4). Following this, the diaphragm thickening fraction was calculated. After training, the research assistant completed measurements of diaphragm thickness and the PI completed measurements of diaphragm thickness that the research assistant was unable to reliably measure. Intraclass correlation coefficients (ICCs) were used to assess inter-rater reliability. The inter-rater reliability between the PI and research assistant for 10% of images was 0.930. The research assistant completed measurements of respiratory-swallow patterns that were obtained during visits 1, 2, 3, and 4, and treatment sessions by analyzing the onset of apnea using the Biotrace + software. The PI analyzed respiratory-swallow patterns that the research assistant was unable to reliably analyze. The inter-rater reliability between the PI and research assistant for 10% of respiratory-swallow patterns was calculated using percent exact agreement and a weighted kappa. Results revealed 89% percent exact agreement and a weighted kappa value of .724 (substantial agreement).

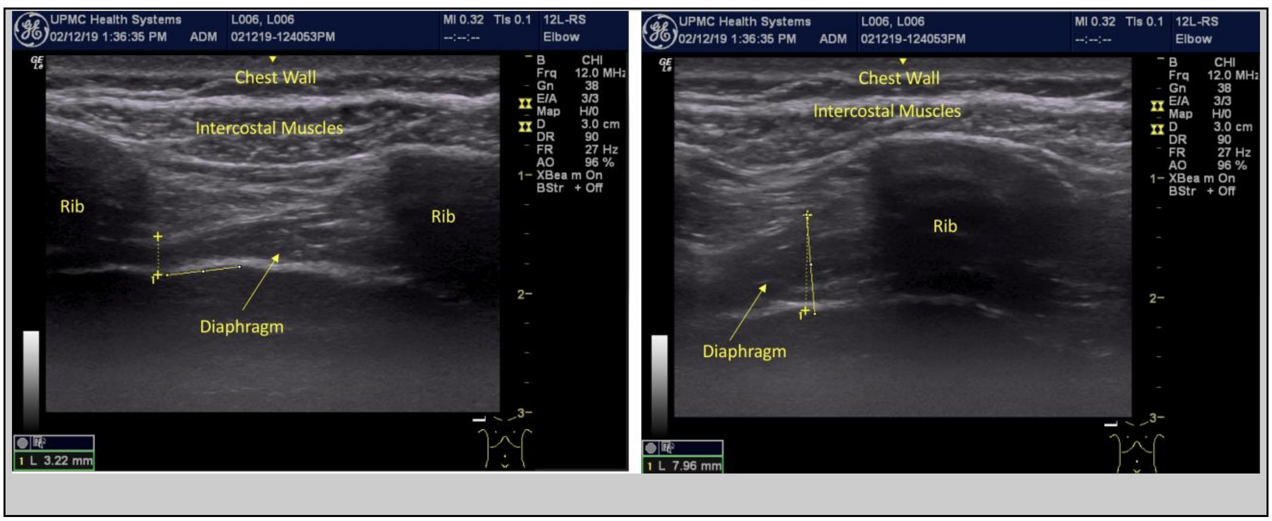

Figure 4: Ultrasonic measurement methods.

3.2.11 Statistical Analysis:

Due to the small sample size from patients who were lost to follow-up and study attrition from patients being deemed ineligible during their first study visit, descriptive statistics were used to describe outcome measures and individual patient performance.

3.3 Results

Fifteen patients expressed interest in the study and underwent initial screening. Of these, four patients were lost to follow-up and did not enter treatment, one patient decided to do EMST clinically instead of as part of the study, one patient had an FVC <60% predicted, two patients had MEP values too low for setting the EMST device to a 50% load, and one patient demonstrated signs of frontotemporal dementia based on the ALS-CBS. Six patients met inclusionary criteria and were enrolled in the study (3 received EMST+RST, 2 received EMST only, 1 received no treatment). Table 1 displays patient demographic information and Table 2 displays outcome measures of all patients across visits.

Table 1: Patient demographics for all patients who completed the study.

Patient	Age	Gender	ALSFRS-R	ALS-CBS	Months Since Diagnosis
RST+EMST					
L002	61	Male	36	13	7
L005	47	Male	33	19	31
L007	76	Female	38	18	5
EMST Only					
L004	58	Male	42	19	34
L006	70	Male	45	NA*	17
Control					
L009	70	Female	41	19	10

Note: ******L006 was enrolled in the study prior to using the ALS-CBS as a cognitive screener. L006 scored 30/30 on the mini mental state examination.

Patients L002, L005, and L007 were in the EMST+ RST group, patients L004, L006, and L009 were in the EMST only group. After enrollment and following the first treatment session, one patient (L009) in the EMST group was no longer able to complete the intervention due to other health complications unrelated to the intervention and was tracked as a “no treatment” case. L004 was unable to come in for a fourth study visit due to being hospitalized for an unrelated event. L009 chose not to have a fourth study visit since the maintenance period was optional. Average adherence for completing EMST across patients during the treatment phase was 97%. During the maintenance phase, adherence for completing EMST was 100% for L002, L005, and L007 and 40% for L006.

3.3.1 Treatment Logs:

There were no adverse events at any time during the study. All patients who completed the treatment and maintenance phases tolerated the procedures and no patients dropped out of the study due to intolerance of the procedures. The maximum fatigue rating for completing EMST was 8/10 by one patient (L006) during the initial study visit after completion of the 5^{th} set of exercise. For all other patients and visits during treatment, fatigue ratings ranged between 0-2 out of 10. During maintenance, fatigue ratings for all patients were 0 out of 10. Perceived dyspnea ratings during treatment ranged between 0.5-1 out of 10 and during maintenance were 0 out of 10. Pain ratings during treatment ranged from 0-1 out of 10 and during maintenance were 0 out of 10 across patients. Negative side effects reported by patients across sessions included mild lightheadedness, mild fatigue, gagging with use of the nose clip, ears popping, and feelings of mildly increased resistance. Positive side effects reported by patients included perceived improvement in breathing, enjoyment from exercising, and improved perception of physical fitness. (See Appendix A for training logs). No patients in this study were rated as sedentary. Patients L005 and L009 were rated as having light-moderate activity levels, patients L002, L006, and L007 were rated as having moderate activity levels, and patient L004 was rated as having an intense activity level.

3.3.2 Pulmonary, Cough, Swallowing-Related, and Ultrasound of the Diaphragm Measures:

Table 2 displays the results for pulmonary, cough, swallowing-related, and ultrasonographic measures of the diaphragm.

3.3.3 Respiratory-Swallow Measures:

The respiratory-swallow (RS) coordination measurements appear in Table 2 and the chest wall excursion measurements inferring inspiratory volume appear in Table 3.

Table 2: Patient outcome measures from Visit 1, 2, 3, and 4 (value, % change).

Patient	Outcome Measure	Visit 1—Baseline	Visit 2—Post lead-in	Visit 3—Post treatment	Visit 4—Post maintenance
EMST+RST					
L002	MEP	108	83 (-23%)	**100 (+20%)**	**85 (-15%)**
	PCF	375	335 (-11%)	**310 (-7%)**	**295 (-5%)**
	FEV1	2.51	2.22 (-12%)	**2.28 (+3%)**	1.9 (-17%)
	FVC	3.36	2.71 (-19%)	**2.73 (+1%)**	**2.41 (-12%)**
	FVC%	74	60 (-19%)	**60 (0%)**	**53 (-12%)**
	FOIS	6	6	**6**	**7**
	EAT-10	2	1	2	**1**
	SWAL-QOL	89.9	81.7	**88.1**	**89.8**
	Diaphragm Thickness	-	0.021	0.011(-48%)	**0.064 (+482%)**
	RS Pattern %	100	33	**67**	**100**
L005	MEP	74	62 (-16%)	**79 (+17%)**	**80 (+1%)**
	PCF	465	450 (-3%)	430 (-4%)	**420 (-2%)**
	FEV1	2.38	2.17 (-9%)	**2.18 (+.5%)**	**2.37 (+9%)**
	FVC	2.82	2.47 (-12%)	**2.59 (+5%)_**	**2.79 (+8%)**
	FVC%	63	55 (-13%)	**58 (+5%)**	**62 (+7%)**
	FOIS	7	7	**7**	**7**
	EAT-10	1	1	**1**	**0**
	SWAL-QOL	90.8	90.6	**91.7**	**92.5**
	Diaphragm Thickness	0.032	0.012(-63%)	**0.015(+25%)**	**0.063(+320%)**
	RS Pattern %	100	33	**100**	**100**
L007	MEP	60	73 (+22%)	68 (-7%)	59 (-13%)
	PCF	185	200 (+8)	-	190 (-5%)
	FEV1	1.64	1.59 (-3%)	1.51 (-5%)	1.31 (-13%)
	FVC	1.98	1.92 (-3%)	1.8 (-6%)	1.58 (-12%)
	FVC%	71	69 (-3%)	64 (-7%)	57 (-11%)
	FOIS	6	6	**7**	**6**
	EAT-10	9	11	9	17
	SWAL-QOL	82.1	75.8	69.6	64.2
	Diaphragm Thickness	0.067	0.041(-39%)	**0.038 (-7%)**	**0.081(+113)**

	RS Pattern %	80	50	**75**	**80**
EMST Only					
L004	MEP	94	93 (-1%)	77 (-17%)	
	PCF	440	435 (-1%)	325 (-25%)	
	FEV1	3.36	2.97 (-12%)	**2.67 (-10%)**	
	FVC	4.59	3.91 (-15%)	**3.51 (-10%)**	
	FVC%	78	67 (-14%)	**60 (-10%)**	
	FOIS	7	7	**7**	
	EAT-10	1	1	**0**	
	SWAL-QOL	97.6	94.9	**95.8**	
	Diaphragm Thickness	0.077	0.035(-55%)	0.02 (-43%)	
	RS Pattern %	100	33	25	
L006	MEP	105	121 (+15%)	**140 (+16%)**	**145 (+4%)**
	PCF	445	380 (-15%)	300 (-21%)	**445 (+48%)**
	FEV1	3.77	3.88 (+3%)	3.84 (-1%)	**3.86 (+1%)**
	FVC	4.53	4.84 (+7%)	4.75 (-2%)	4.73 (-.4%)
	FVC%	102	109 (+7%)	107 (-2%)	**107 (0%)**
	FOIS	7	7	**7**	**7**
	EAT-10	14	15	**15**	**15**
	SWAL-QOL	77.7	75.5	**82**	**83.4**
	Diaphragm Thickness	0.12	0.16 (+33%)	0.067 (-58%)	**0.091(+36%)**
	RS Pattern %	100	67	-	**67**
Control					
L009	MEP	39	38 (-3%)	26 (-32%)	
	PCF	290	255 (-12%)	**230 (-10%)**	
	FEV1	1.77	1.71 (-3%)	1.31 (-23%)	
	FVC	2.05	1.94 (-5%)	1.61 (-17%)	
	FVC%	66	62 (-6%)	52 (-16%)	
	FOIS	7	7	**7**	
	EAT-10	1	1	**0**	
	SWAL-QOL	92.7	93	**94.9**	
	Diaphragm Thickness	0.023	0.026 (+13%)	-	
	RS Pattern %	100	67	**100**	

Note: - = missing data. Patients L004 and L009 did not complete the maintenance period of the study and have a fourth study visit.

Bold= improvement, maintenance, and/or slower decline of outcome measures from visit 2 to visits 3 and 4.

Table 3: Patient % change in inspiratory volume from week 1 to week 5 of therapy as measured by chest wall excursion from the respiratory belt.

Patient	Outcome Measure	ΔWeek 1-Week 5
EMST+RST		
L002	IV for TV	+24%
	IV for EMST	+23%
L005	IV for TV	+10%
	IV for EMST	+12%
L007	IV for TV	+24%
	IV for EMST	+17%
EMST Only		
L004	IV for TV	-14%
	IV for EMST	-13%
L006	IV for TV	+27%
	IV for EMST	+27%

Note: IV=inspiratory volume, TV=tidal volume

3.4 Discussion

This was the first research study to explore RST in PALS. This feasibility study found that EMST+RST and EMST alone were both safe and well-tolerated respiratory interventions in this small case series of PALS. Most patients in both treatment arms maintained or improved in most PFT measures during treatment. While this study had a limited sample size due to patients being lost to follow-up or ineligible to participate, the patients enrolled in the study were able to complete the respiratory interventions with minimal to no adverse side effects. Adherence to EMST was similar in this study as in a recent randomized, double-blinded, control study in PALS (Plowman et al., 2019). Expanding upon this prior work, we used treatment logs to assist with adherence and gain qualitative information about safety and tolerability of these respiratory interventions.

EMST+RST and EMST alone led to varying levels of improvement, maintenance, and/or slower decline rates in pulmonary and cough measurements when compared to no respiratory intervention (no treatment patient), though the sample was very small. The patient that received no intervention (L009) demonstrated consistent decline in all pulmonary measurements, while patients receiving both respiratory interventions demonstrated slower decline rates, and in some cases, improvement in pulmonary function measurements (N=4). These findings align with other respiratory intervention studies in patients with early stage ALS, which have shown that EMST is a safe and well-tolerated intervention, which can lead to improvements in pulmonary, cough, and swallow function. However, in contrast to other studies that have found consistent improvements in MEP (25-29%) (Plowman et al., 2019; Plowman, Watts, Tabor-Gray, et al., 2016; Robison et al., 2018; Tabor-Gray, Rosado, et al., 2016), we found variability in outcome measures (including MEP) across patients receiving both respiratory interventions. The variability in pulmonary outcome measures in our study likely represents the heterogenous nature and progression of ALS. Overall activity level and intensity may also be a factor. L004's activity level was rated as intense and was the only patient receiving one of the respiratory interventions who steadily declined over time in pulmonary function, cough, diaphragm thickness, and chest wall excursion. The small sample size may also have affected these results, however further research work is needed in order to determine the types and characteristics of PALS that are most appropriate for EMST treatment.

Similar to other studies examining the impact of EMST in PALS, the majority of patients receiving the respiratory interventions had stable or improved scores on the FOIS, EAT-10, and SWAL-QOL following the intervention and/or maintenance period (N=4) (Plowman et al., 2019). However, it's important to note that the relatively stable surrogate measures of swallowing function in most patients may not align with actual physiologic decline and may reflect some adaptation and accommodation to swallowing impairments during disease progression. While this study did not include an instrumental swallow evaluation, the primary outcome measures of this study were pulmonary function measures rather than the surrogates of swallow function. Other studies have examined the impact of EMST on swallowing physiology using videofluoroscopy and found that it leads to improvements or maintenance of swallow function in patients with ND, although there is a need for further research in this area (Mancopes et al., 2020; Plowman et al., 2019; Plowman, Watts, Tabor-Gray, et al., 2016).

Similar to other studies that have found a relationship between pulmonary function measurements and thickness of the diaphragm in PALS (Fantini et al., 2016; S. Pinto et al., 2016), patients in this study demonstrated impaired pulmonary function measurements and diaphragm thickness. Interestingly, patients receiving the respiratory interventions demonstrated improvements in diaphragm thickening fractions following the intervention and/or maintenance period of the study (N=4). The improvements in diaphragm thickening fractions were greater than the expected variance that typically occurs between measurements of the diaphragm (<10%) (S. Pinto et al., 2016). This, along with the findings that all patients demonstrated increases in inspiratory tidal volume and inspiratory volume prior to completion of an EMST repetition from week one to week five of therapy, provides preliminary support that EMST may be beneficial to both inspiratory and expiratory function. In addition to this, patients that received the RST+EMST intervention improved or maintained healthy breathing patterns during swallowing while patients that received the EMST only intervention had declines, which may demonstrate the potential efficacy of this treatment. However, in order to confirm the efficacy of RST, this intervention should be explored in a randomized controlled trial in a larger group of PALS.

The astonishing percentage of patients either unable to participate in the study or who did not meet eligibility criteria due to other factors should be underscored. The goal was to enroll 18 PALS for the study with 6 patients in the EMST+RST, EMST only, and natural control groups respectively. Fifteen patients expressed interest in enrolling in the study at clinic and underwent initial screening. Of these, four patients were lost to follow-up, one patient decided to do EMST clinically instead of as part of the study, one patient had an FVC <60% predicted, two patients had MEP values too low for setting the device to a 50% load, and one patient demonstrated signs of frontotemporal dementia based on the ALS-CBS. Serial pulmonary function measures during disease progression are commonly used to assess the trajectory of declining pulmonary function and to predict optimal timing of invasive interventions such as tracheostomy or gastrostomy should patients choose to pursue them (Andrews et al., 2018; Conde et al., 2018). Further research is needed to identify optimal timing for initiation of prophylactic pulmonary interventions to determine if they can mitigate (i.e. postpone, prevent) predicted dependence on these and other interventions for prolonging life and quality of life. Although the patient in the no-treatment condition exhibited worse trajectory than those in the treatment groups, the results from this small sample remain inconclusive.

3.5 Limitations

While this feasibility study provides preliminary evidence that EMST combined with RST may be efficacious and a feasible, safe, and well-tolerated intervention to mitigate declining function in a small case series of PALS, this study has several limitations. This study consisted of a small sample of PALS, which did not allow for sufficient study power to complete robust statistical analysis. Having limited patients that opted into the no treatment condition and using alternating assignment for the patients receiving treatment instead of randomization is another limitation. While randomization would have been a scientifically more rigorous method of assignment, due to ethical concerns, the investigators did not deem randomizing patients into a no-treatment condition as appropriate because this would require withholding an intervention (EMST) that has demonstrated preliminary efficacy without adverse outcomes in PALS. Although unintentional, patients that received EMST only had higher ALSFRS-R scores than patients that received EMST+RST, which indicates a greater degree of functional impairment for patients receiving EMST+RST that may have impacted treatment effects and the study outcome measures. In the future, it may be beneficial to balance treatments based on ALSFRS-R scores. Likewise, patients L006 and L007 had higher EAT-10 scores, indicating greater swallowing impairment at baseline compared to other patients in the study, which may have impacted treatment effects. Several patients that were screened to participate in this study were ineligible due to having MEP values too low to use the EMST-150 device (30-150 cm H20) set at 50% load. While outside the scope of this study, the use of a lower resistance EMST device with a range of 5-20cm H20 (Philips Threshold PEP Trainer; Philips Respironics, Cedar Grove, New Jersey) has been explored in PALS (Plowman et al., 2019). Implementation of this device clinically or for research purposes may allow more patients to be appropriate candidates for this intervention.

In addition to this, the PI and patients in the study were not blinded to study conditions, which can lead to judgment bias though most of the dependent variables in the study were instrumental and not subject to human measurement error. While this study explored the impact of EMST+RST and EMST alone on the EAT-10, SWAL-QOL, and FOIS, these are merely surrogates of swallow function and do not provide information about the impact of these interventions on swallowing physiology. The intervention period of this study was relatively short (5 weeks) and may not have been sufficient to result in clinically significant changes in expiratory muscle function. More recent studies in PALS have used a period of 8 weeks or longer for intervention (Plowman et al., 2019; Robison et al., 2018; Tabor-Gray, Rosado, et al., 2016). While peripheral measures of expiratory muscle function were obtained (PFTs), only muscle fibers of inspiration (ultrasound of the diaphragm) were measured in this study to determine if EMST led to improvements in inspiration as well as improvements in expiratory pressure and volume. Likewise, the exact resistance level of EMST devices for maximizing benefits while minimizing fatigue and adverse outcomes for PALS is unknown. RST has not previously been explored in PALS, and as a result, the best training paradigm for training healthy swallow patterns in PALS (inhale-exhale or exhale-exhale) is unknown. However, RST has been implemented in patients with head and neck cancer, and a similar training paradigm may be investigated in PALS (Martin-Harris et al., 2015). While the respiratory belt that was used in this study was easily transportable to patients' homes, it did not allow for measurements of airflow, so only measurements of abdomen and rib cage displacement could be used as indirect measures of ventilatory function for data analysis. Patients completed training logs with variable levels of adherence, which resulted in limited amounts of qualitative data related to treatment tolerability and fatigue. Despite these limitations, this small study mirrored ordinary clinical management routines which strengthens the external validity of the methods.

3.6 Future Directions

Future investigations should explore the impact of RST and EMST+RST in PALS by conducting large, randomized, double-blinded studies. In order to support larger treatment studies in this heterogenous, constantly evolving, and challenging patient population, collaboration and standardization of treatment protocols across multiple ALS clinic sites may be necessary. This will be challenging given the natural history of ALS and the differences in long-term goals for patients with degenerative and unrelenting diseases. EMST device load and treatment intensity and dosage (including maintenance) for EMST+RST should also be explored in order to balance the need to maximize benefits and minimize fatigue and adverse outcomes while also mitigating functional decline. Future studies should include a videofluoroscopic evaluation of swallowing to examine the impact of EMST+RST on swallowing physiology in PALS. Determining optimal ways to track patient adherence and adverse outcomes should also be explored. For example, creating an electronic method to track exercise completion and side effects would provide more instantaneous feedback for the clinician to monitor patient safety and adherence.

4.0 Study 2: Exercise in patients with amyotrophic lateral sclerosis: A failed meta-analysis

4.1 Introduction

ALS is a neuromuscular disease that results in degeneration of upper and lower motor neurons leading to spastic and flaccid paralysis of the limb, trunk, respiratory, and bulbar musculature. Motor declines drastically impede patients' ability to complete functional activities of daily living and impact quality of life (Hardiman, 2001; Wijesekera & Leigh, 2009). Disease progression in PALS is rapid, with an average life expectancy of 2 to 5 years following diagnosis (Ball et al., 2001). Life expectancy is frequently shorter for patients with bulbar onset (typically manifested by dysphagia [swallowing problem] and dysarthria [slurred speech]), comprising approximately one-third of cases (Brown & Al-Chalabi, 2017; da Costa Franceschini & Mourão, 2015; Kühnlein et al., 2008; Paris et al., 2013). The remaining two-thirds of cases will have initial symptom onset in the limbs. Although the most common motor neuron disease (MND), ALS is rare, with a prevalence of 5 cases per 100,000 people each year in the United States (Mehta et al., 2018).

While there is no cure for ALS at this time, recent studies have shown treatment may slow loss of function and improve quality of life, particularly when provided as part of an interdisciplinary approach to patient management (neurology, nursing, nutrition, speech pathology, social work, pulmonology and respiratory care, occupational and physical therapy) (Kiernan et al., 2011). There are currently four drugs approved by the Food and Drug Administration, with two (riluzole and edaravone) targeted to increase survival – albeit minimally (Brown & Al-Chalabi, 2017). Effective therapies for ALS are postulated to inhibit excessive motor neuron activity, decrease oxidative stress, and delay respiratory decline – the latter being the major cause of mortality (Andrews et al., 2018; Czaplinski et al., 2006; Kühnlein et al., 2008; Onesti et al., 2017). Until a cure is found, clinical care continues to involve early interventions promoting improved symptom management (Kühnlein et al., 2008).

Because of the limitations of current drug treatments, recent studies have examined the impact of exercise in PALS. Exercise can result in a variety of neuromuscular benefits including cross-education, increased motor unit activation and synchronization, as well as increased skeletal muscle fiber hypertrophy, protein synthesis, and capillary density, which may lead to more optimal functioning of the neuromuscular system (de Almeida et al., 2012; Harkawik & Coyle, 2012). Historically, exercise has been avoided in PALS due to baseline fatigue, muscle atrophy and weakness from disuse and denervation, and fear that it may lead to faster muscle degeneration (de Almeida et al., 2012; Francis et al., 1999). While there is preliminary evidence that moderate exercise training may be beneficial in symptom management and survival in PALS, strenuous exercise in animal models has been shown to lead to faster deterioration (Kirkinezos et al., 2003; Mahoney et al., 2004). Due to the lack of consensus in the literature, the topic of exercise in PALS remains controversial among clinicians and researchers, with some researchers proposing a paradigm shift to a proactive approach rather than a reactive one (Robberecht & Philips, 2013; Rogus-Pulia & Plowman, 2020; Tsitkanou et al., 2019). Therefore, we conducted a systematic review of the literature that expanded upon previous reviews of the literature (Meng et al., 2020; Tsitkanou et al., 2019) to evaluate outcome measures related to function and quality of life following exercise in PALS to determine whether exercise in PALS may be beneficial or detrimental.

4.2 Methods

4.2.1 Protocol

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-2009) guidelines were followed for reporting.

4.2.2 Search Strategy

Studies were identified and extracted according to PRISMA guidelines. A single author conducted a search in four electronic databases (CINAHL, Scopus, PubMed, and Cochrane Library) from time of database inception until December 2019. Search terminology included: *ALS* OR *amyotrophic lateral sclerosis* OR *motor neuron disease* OR *Lou Gehrig's disease* AND *exercise* OR *remedial exercise* OR *exercise therapy* OR *strength* OR *resistance training* OR *range of motion*. Additionally, a manual search was conducted that included full-text original research articles.

4.2.3 Eligibility Criteria

Articles were included based on the following inclusionary criteria: 1) original full-text article; 2) exercise-based intervention study; 3) published in English; 4) intervention subjects were patients with a diagnosis of ALS/MND. Duplicate results were removed prior to screening.

4.2.4 Study Selection

Articles were independently screened by a single author based on title, abstract, and full text. As needed, a second author was consulted for consensus on article eligibility.

4.2.5 Quality Assessment

Two authors independently judged level of evidence and study quality of each eligible article. Level of evidence was assigned based on *The Oxford Centre for Evidence-based Medicine Levels of Evidence* (Phillips et al., 2009). Study quality was evaluated using the *QualSyst* (Kmet et al., 2004), which consists of 14 items. For each *QualSyst* item, a score of 2 was assigned if the criteria were completely met, 1 if the criteria were partially met, and 0 criteria were not met. "Not applicable" was assigned to items not appropriate for judgment. Scores were totaled and a cumulative score was calculated in the form of a percentage. Overall study quality was determined based on the following: ≥80% indicated strong quality, 60% to 79% indicated good quality, 50% to 59% indicated average quality, and <50% indicated poor quality.

4.2.6 Data Extraction

Findings were imported into Microsoft Excel for independent review. Following data extraction, studies were categorized into similar exercise regimens (combined treatment (Bello-Haas et al., 2007; A. C. Braga et al., 2018a; Clawson et al., 2018; Drory et al., 2001; Kato, Hashida, Kobayashi, et al., 2018; Kitano et al., 2018; Lunetta et al., 2016; Merico et al., 2018; Pegoraro et al., 2019; Zucchi et al., 2019), resistance exercise (Bohannon, 1983; Jensen et al., 2017; Kato, Hashida, & Konaka, 2018), aerobic endurance (A. C. Braga et al., 2018b; A. C. Pinto et al., 1999; Sanjak et al., 2010; Sivaramakrishnan & Madhavan, 2019), and RMST approaches) (Cheah et al., 2009; S. Pinto et al., 2012; S. Pinto & de Carvalho, 2013; Plowman et al., 2019; Plowman, Watts, Tabor-Gray, et al., 2016; Robison et al., 2018; Tabor-Gray, Rosado, et al., 2016). However, due to limited data for studies that explored RMST (EMST, IMST)(Cheah et al., 2009; S. Pinto et al., 2012; S. Pinto & de Carvalho, 2013; Plowman et al., 2019; Plowman, Watts, Tabor-Gray, et al., 2016; Robison et al., 2018; Tabor-Gray, Rosado, et al., 2016) and aerobic endurance exercise regimens (A. C. Braga et al., 2018b; A. C. Pinto et al., 1999; Sanjak et al., 2010; Sivaramakrishnan & Madhavan, 2019), and heterogeneity observed in outcome measures and treatment protocols for studies that explored combined exercise regimens (Bello-Haas et al., 2007; A. C. Braga et al., 2018a; Clawson et al., 2018; Drory et al., 2001; Kato, Hashida, Kobayashi, et al., 2018; Kitano et al., 2018; Lunetta et al., 2016; Merico et al., 2018; Pegoraro et al., 2019; Zucchi et al., 2019), a meta-analysis was not feasible.

4.3 Results

The initial search yielded 959 total results, with only 24 meeting inclusionary criteria (Figure 5).

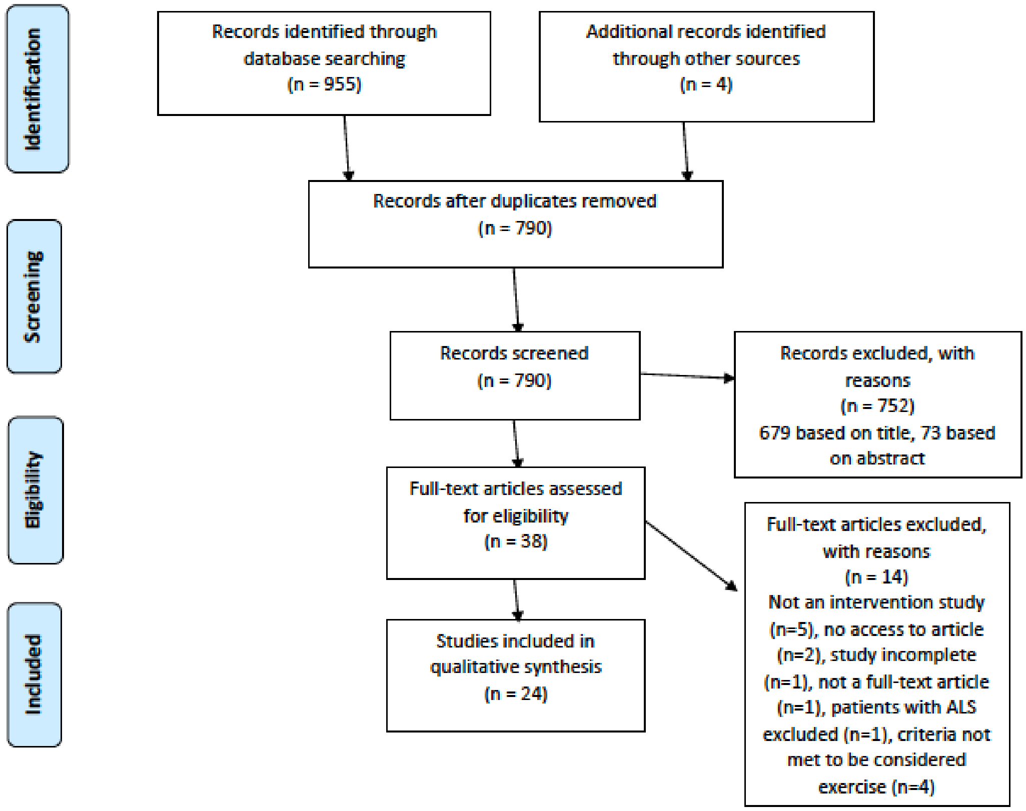

Figure 5: PRISMA flow diagram.

Study Design and Methodological Quality

Of the 24 eligible studies, the majority (37.5%) were randomized controlled trials (RCTs) (Level 1b) (Table 4), followed by cohort (Level 2b) and case series (Level 4) investigations. Most studies were rated as having "strong" quality (87.5%), while the remaining studies were assigned a "good" quality rating (12.5%). Average *QualSyst* scores were 91.55% (±8.09). The most common biases observed in these studies was insufficient description of method of subject selection or source of input variable, inadequate sample size, and inadequate control of confounding variables.

Table 4: Level of evidence and appraisal of quality of studies.

Study	*Level of Evidence*	*KMET Score*	*Quality*
(Bohannon, 1983)	4	12/12 (100%)	Strong
(A. C. Pinto et al., 1999)	2b	20/26 (76.9%)	Good
(Drory et al., 2001)	1b	22/26 (84.6%)	Strong
(Bello-Haas et al., 2007)	1b	24/26 (92.3%)	Strong
(Cheah et al., 2009)	1b	27/28 (96.4%)	Strong
(Sanjak et al., 2010)	2b	20/22 (90.9%)	Strong
(S. Pinto et al., 2012)	1b	24/26 (92.3%)	Strong
(S. Pinto & de Carvalho, 2013)	2b	19/26 (73.1%)	Good
(Tabor-Gray, Rosado, et al., 2016)	4	11/12 (91.7%)	Strong
(Lunetta et al., 2016)	1b	25/26 (96.2%)	Strong
(Plowman, Watts, Tabor-Gray, et al., 2016)	2b	20/22 (90.9%)	Strong
(Jensen et al., 2017)	4	18/20 (90%)	Strong
(Clawson et al., 2018)	1b	24/26 (92.3%)	Strong
(Kato, Hashida, Kobayashi, et al., 2018)	4	12/12 (100%)	Strong
(Kato, Hashida, & Konaka, 2018)	4	18/20 (90%)	Strong
(Robison et al., 2018)	4	12/12 (100%)	Strong
(Kitano et al., 2018)	3b	22/22 (100%)	Strong
(Merico et al., 2018)	1b	25/26 (96.2%)	Strong

(A. C. Braga et al., 2018a)	2b	25/28 (89.3%)	Strong
(A. C. Braga et al., 2018b)	4	18/20 (90%)	Strong
(Zucchi et al., 2019)	1b	26/26 (100%)	Strong
(Plowman et al., 2019)	1b	28/28 (100%)	Strong
(Pegoraro et al., 2019)	2b	16/22 (72.7%)	Good
(Sivaramakrishnan & Madhavan, 2019)	2b	19/22 (86.4%)	Strong

Participant Characteristics

A total of 666 participants (419 males) diagnosed with definite or probable ALS/MND were included across all studies. When symptom onset location was reported, the majority of patients (76.0%; N=450) presented with spinal onset. When reported, baseline ALSFRS-R scores ranged from 32 to 46, suggesting minimal-mild to mild-moderate disease severity (Gordon et al., 2004; Gordon & Cheung, 2006). Complete demographic information can be viewed in Table 5.

Table 5: Demographic information of study participants.

Study	*Sample*	*Sex (M/F)*	*Mean Age ± SD (Years)*	*Onset Location (Spinal/Bulbar)*	*Mean Disease Duration ± SD (Months)*	*Baseline ALSFRS-R*
(Bohannon, 1983)	ALS (N=1)	0/1	56	1/0	22	Not reported
(A. C. Pinto et al., 1999)	ALS/MND (N = 20)	14/6	Treatment: 62±14 Control: 64±16	Not reported	0	Not reported
(Drory et al., 2001)	ALS (N = 25)	14/11	60	22/3	Treatment group: 20.7 Control group: 19.4	27.5
(Bello-Haas et al., 2007)	ALS (N=27)	Not reported	Not reported	Not reported	Not reported	Not reported
(Cheah et al., 2009)	ALS/MND (N = 19)	12/7	Treatment: 54.2±9.8 Control: 53.4±9.5	16/3	Treatment group: 29.8±15.7 Control group: 34.6±33.8	Treatment group: 38.2±6.5 Control group: 38.9±2.7
(Sanjak et al., 2010)	ALS (N = 9)	4/5	62±14.1 (39-77)	Not reported	Not reported	34±5
(S. Pinto et al., 2012)	ALS (N = 26)	18/8	Group 1: 57.14±9.3 Group 2: 56.8±8.7	22/4	Group 1: 11.5±5.3 Group 2: 12.6±6.6	Group 1: 34.39±3.64 Group 2: 33.5±3.8
(S. Pinto & de Carvalho, 2013)	ALS (N = 34)	20/14	Not reported	27/7	Treatment group: 36.99±13.1 Control group: 24.06±11	Treatment group: 34.3±2.4 Control group: 33.8±3.3
(Tabor-Gray, Rosado, et al., 2016)	ALS (N = 1)	1/0	71	1/0	21	32
(Lunetta et al., 2016)	ALS (N = 60)	38/22	Treatment: 61.1±10.1 Control: 60.3±9.9	42/18	Treatment group: 15.2±7.2 Control group: 13.7±6.1	Treatment group: 39.1±4.7 Control group: 38.3±5.1

(Plowman, Watts, Tabor-Gray, et al., 2016)	ALS (N = 25)	14/11	62.2±10.5	15/10	14.5±11.7	32±8.5
(Jensen et al., 2017)	ALS (N=6)	5/1	62.2±8.2	4/2	5 patients: <12 1 patient: 180	39.7±2.4
(Clawson et al., 2018)	ALS (N = 59)	39/20	Stretching group: 57.68±9.72 Resistance group: 63.65±10.55 Endurance group: 57.82±11.88	45/14	Stretching group: 11.08±13.21 Resistance group: 7.25±7.21 Endurance group: 7.30±6.80	Stretching group: 39.67±3.71 Resistance group: 39.17±4.91 Endurance group: 39.55±4.97
(Kato, Hashida, Kobayashi, et al., 2018)	ALS (N = 2)	2/0	Case 1: 60 Case 2: 52	1/1	Case 1: 10, 20 Case 2: 15, 20	Case 1: 42, 33 Case 2: 44, 34
(Kato, Hashida, & Konaka, 2018)	ALS (N= 10)	9/1	61.9±11.7	5/5	30.6±31.3	41±4.6
(Robison et al., 2018)	ALS (N= 1)	1/0	58	0/1	2	46
(Kitano et al., 2018)	ALS (N=105)	72/33	Treatment: 62.8±10.2 Control: 62.7±12.1	70/35	Treatment group: 26.4±18.8 Control group: 18±20.4	Treatment group: 41.1±4.5 Control group: 40.3±4.4
(Merico et al., 2018)	ALS (N= 38)	23/14	Treatment: 61.6±10.6 Control: 59.8±14.7	37/1	Treatment group: 30.2±11.8 Control group: 30.3±6.7	Treatment group: 36.1±4.71 Control group: 34.5±3.6
(A. C. Braga et al., 2018a)	ALS (N = 48)	32/16	Not reported	38/10	Treatment group: 10.8±6.5	Treatment group: 42.92±3.

					Control group: 10.79±7.7	51 Control group: 41.13±4.83
(A. C. Braga et al., 2018b)	ALS (N=10)	7/3	57±9.1	9/1	7.6±4.12	43±2.1
(Zucchi et al., 2019)	ALS (N = 65)	49/16	Not reported	54/11	Treatment group: 15.67±9.74 Control group: 16.64±8.98	Treatment group: 39.84±5.70 Control group: 40.15±5.17
(Plowman et al., 2019)	ALS (N = 48)	29/19	Treatment group: 63.1±10.0 Control group: 60.1±10.3	35/11 2 mixed	Treatment group: 20.9±14.5 Control group: 16.9±6.8	Treatment group: 36.6±6.3 Control group: 37.5±6.1
(Pegoraro et al., 2019)	ALS (N= 18)	11/7	61.1±12.8	Not reported	51.6±12	34.6±4.9
(Sivaramakrishnan & Madhavan, 2019)	ALS (N = 9)	5/4	59.22±12.3	6/3	28.44	33

Exercise Regimen and Treatment Outcomes

Findings from each of the included studies are summarized in Table 6. A total of 10 studies utilized a combination of aerobic endurance, resistance, and stretching/range of motion (Bello-Haas et al., 2007; A. C. Braga et al., 2018a; Clawson et al., 2018; Drory et al., 2001; Kato, Hashida, Kobayashi, et al., 2018; Kitano et al., 2018; Lunetta et al., 2016; Merico et al., 2018; Pegoraro et al., 2019; Zucchi et al., 2019); 3 employed resistance exercise only (Bohannon, 1983; Jensen et al., 2017; Kato, Hashida, & Konaka, 2018); 4 consisted of solely aerobic endurance (A. C. Braga et al., 2018b; A. C. Pinto et al., 1999; Sanjak et al., 2010; Sivaramakrishnan & Madhavan, 2019);

and 7 studies employed RMST (IMST and/or EMST) (Cheah et al., 2009; S. Pinto et al., 2012; S. Pinto & de Carvalho, 2013; Plowman et al., 2019; Plowman, Watts, Tabor-Gray, et al., 2016; Robison et al., 2018; Tabor-Gray, Rosado, et al., 2016). Length of exercise regimens ranged from 2 weeks to 2 years in duration. Overall, no adverse outcomes attributed to participation in the exercise intervention under study were reported. The most commonly reported outcome measures were the ALSFRS-R total score (n = 19), FVC (n = 12), measures of fatigue (n = 9), MEP/maximum inspiratory pressure (MIP) (n = 7), and quality of life scales (n = 8). Although four studies (16.7%) did not demonstrate significant improvements after completion of the exercise intervention, most studies (N=20, 83.3%) reported significant positive changes in their primary outcome measure of interest.

Table 6: Summary of exercise regimens and study outcomes.

Study	*Exercise Arms*	*Dosage*	*Outcome Measures*	*Selected Results*
Combination Exercise Regimens				
(Drory et al., 2001)	Individualized daily exercise program designed by physical therapist (N=14); Control (N=11)	Length of exercise: 15 min Times per day: 2 Length of regimen: 3-12 months	1) Manual muscle strength testing 2) ASH 3) ALSFRS-R 4) FSS 5) Visual analog scale for musculoskeletal pain 6) SF-36	• Decreased spasticity in exercise group at 3 months (p<0.05). • Slower decline in ALSFRS-R scores in exercise group at 3 months (p<0.001). • Increase in subjective pain over time in both groups.
(Lunetta et al., 2016)	Active exercise (N=30): three subgroups: active exercises associated	Length of exercise: 20 min	1) ALSFRS-R 2) Number of deaths or	• ALSFRS-R total scores and motor sub scores were higher for the

	with cycloergometer activity (n=10), active exercises (n=10), passive exercises (n=10) Control exercise programs (N=30): passive and stretching exercises	Days per week: 2 Length of exercise regimen: 6 months	tracheostomies 3) FVC 4) McGill Quality of Life questionnaire 5) Subjective well-being	exercise group (p=0.0298, p=0.0293). • McGill Quality of Life scores improved from baseline to 180 days for the exercise group (p=0.0031). • Improvement in subjective well-being after exercise sessions for exercise group.
(Clawson et al., 2018)	Resistance (N=18): cuff weights for the upper limbs and hip flexion Endurance (N=20): upper and lower limb cycling Stretching/range of motion (N=21): passive upper and lower limb stretching with a partner	Length of exercise regimen: 6 months	1) ALSFRS-R 2) FVC 3) Limb strength 4) Grip strength 5) VO2 max 6) FSS 7) Visual Analog Scale for pain/muscle cramps 8) ASH 9) ALS Quality of Life Scale	• No significant changes in any outcome measures or differences between groups.
(Kato, Hashida, Kobayashi, et al., 2018)	Resistance exercise (N=2): lower limb muscle strengthening exercises	Length of exercise: 30 min Days per week: 5 Length of exercise regimen: 2 weeks	1) KEMS 2) FAC	• KEMS improved by 20% or more during the first hospitalization for both patients; KEMS was maintained for 10 months for case 1. • FAC improved during the first hospitalization for case 2.

(Kitano et al., 2018)	Home based exercise (N=21): muscle stretching and strength training for upper and lower limbs Historical cohort (N=84): exercise under the direction of a physical therapist	Frequency/ reps: determined by a physical therapist Length of exercise regimen: 6 months	1) ALSFRS 2) Muscle strength of quadriceps and deltoid muscles 3) CPF	• Total ALSFRS score and respiratory sub score was higher for the exercise group ($p=0.44$, $p<0.001$).
(Merico et al., 2018)	Specific exercise program (N=23): aerobic workout and isometric contractions Control exercise (N=15): stretching, active mobilization, general muscle reinforcement	Length of exercise regimen: 5 weeks	1) FIM 2) 6MWT 3) MRC Muscle Grading Scale 4) Cardiovascular measures 5) FSS	• Difference in FIM scores after 5 weeks for both groups ($p<0.05$); no difference between groups ($p>0.05$). • Difference in MRC sum score, R biceps muscle strength, oxygen consumption, FSS after 5 weeks for specific exercise group ($p<0.05$). • FIM scores were associated with ventilation during exercise ($r=0.25$, $p<0.01$), resting heart rate ($r=-0.20$, $p=0.01$), R biceps strength ($r=0.24$, $p<0.01$), and the 6MWT ($r=0.23$, $p<0.01$). • FSS scores were associated with oxygen consumption ($r=0.26$, $p<0.01$), resting heart rate ($r=0.29$, $p<0.01$), R biceps strength ($r=-0.21$, $p=0.01$), R tibial strength

				(r=-0.19, p=0.02), the MRC sum score (r=-0.28, p<0.01), and the 6MWT (r=-0.27, p<0.01).
(A. C. Braga et al., 2018a)	Cardiopulmonary exercise training (N=24): standard of care exercises+ aerobic exercise protocol on a treadmill Control exercise: range of motion exercises, limbs relaxation, trunk balance, gait training.	Days per week: 2 Length of exercise regimen: 6 months	1) ALSFRS-R 2) Pulmonary function measures (FVC, nocturnal pulse oximetry, MIP, MEP, phrenic nerve conduction studies) 3) Cardiopulmonary exercise testing variables (oxygen uptake, carbon dioxide output, and minute ventilation)	• Higher FVC predicted at time point one for CPET group (p=0.002). • Higher ALSFRS-R scores at time point two for CPET group (p=0.035). • Spinal ALSFRS-R scores (p<0.001) and the CPET group (p=0.021) were significant predictors of overall ALSFRS-R scores at time point two (R^2=0.51). • Difference in oxygen uptake between groups at time point two (p<0.05).
(Zucchi et al., 2019)	Intensive exercise regimen (N=32): aerobic and endurance resistance exercise training Control exercise regimen (N=33): aerobic and endurance resistance exercise training	Length of exercise: 45 min Days per week: 2-5 Length of exercise regimen: 10 weeks	1) ALSFRS-R 2) Survival time 3) Time to gastrostomy, noninvasive ventilation, or invasive ventilation 4) FVC 5) Quality of life (ALSAQ-40, McGill Quality of	• No differences in any outcome measures between groups. • Increase in FSS scores for the last 12 months for the intensive exercise regimen.

			Life Questionnaire) 6) FSS 7) Depression (Beck Inventory Scale) 8) Caregiver Burden Scale	
(Pegoraro et al., 2019)	Progressive muscular strength training, aerobic endurance exercises (N=18): cycle ergometer, arm-leg ergometry or treadmill, standard rehab (stretching, active mobilization, general reinforcement)	Length of exercise: 60 min Days per week: 7 Length of exercise regimen: 6 weeks	1) FIM 2) FSS 3) Barthel Index 4) ALSFRS-R 5) MiRNAs	• Improvement in FIM, Barthel Index, ALSFRS-R, and FSS scores ($p \leq 0.05$). • In the majority of patients there were lower levels of MiRNAs (miR-1, miR-206, miR-133a, miR-133b) ($p<0.05$).
(Bello-Haas et al., 2007)	Home exercise program (N=13): individualized upper and lower extremity resistance exercise + usual care stretching exercises; Control exercise (N=14): upper and lower extremity stretching 1x/day	Times per day: 1 Length of regimen: 6 months	1) ALSFRS-R 2) FSS 3) SF-36 4) MVIC 5) FVC	• Differences in ALSFRS-R scores between groups at 3 and 6 months ($p=0.05$, $p=0.02$, $p=0.01$). • Difference in physical functioning sub score of SF-36 at 6 months ($p=0.02$). • Slower decline in lower extremity MVIC in the exercise group at 6 months ($p=0.03$).
Resistance Exercise Regimens				
(Bohannon, 1983)	Resistance exercise of upper extremity (N=1):	Number of repetitions: 10	1) Arm/shoulder strength (static force)	• No consistent trends of static muscle force following

	stretching/flexibility of upper extremities	Number of sets: 2 Number of days/week: 6 Length of regimen: 75 days		exercise training- some muscles increased (14 muscle groups), some decreased (4 muscle groups).
(Kato, Hashida, & Konaka, 2018)	Individualized physical therapy exercises (N=10): lower limb muscle strengthening exercises and respiratory, gait, and stair-climbing exercises	Length of exercise regimen: 2-3 weeks	1) KEMS 2) Gait and stair climbing scores on the ALSFRS-R 3) ASH	• KEMS improved for stronger and weaker limbs (p<0.01).
(Jensen et al., 2017)	Resistance training (N=6): upper and lower body resistance exercises	Days per week: 2-3 Sets: 2-3 Reps: 5-12 Length of exercise regimen: 24 weeks (12 weeks lead-in, 12 weeks resistance training)	1) ALSFRS-R 2) 30 second chair rise, timed up and go) 3) Neuromuscular function (strength and power of various muscles) 4) Voluntary muscle activation 5) Muscle fiber morphology	• Decline in ALSFRS-R scores at the same rate or more after training. • Decrease in strength post-training for knee extensor, hand grip, and leg extensor strength (p<0.05). • Percentage of small and large muscle fibers increased post-training (p<0.05).
Aerobic Endurance Exercise Regimens				
(A. C. Pinto et al., 1999)	Treatment (N=8): Endurance-based exercise: Bruce or Naughton ramp treadmill protocol with Bipap STD until anaerobic threshold was reached; Control (N=12)	Length of regimen: 1 year	1) FVC 2) Barthel Index 3) FIM 4) Spinal and Bulbar Norris scores	• Attenuated FVC decline rate for exercise group (p<0.02). • Higher FIM scores for exercise group (p<0.03).

				• Slower decline of spinal Norris scores for exercise group (p<0.02).
(Sanjak et al., 2010)	Supported treadmill ambulation (N=9)	Length of exercise: 30 min (5 minutes exercise/5 minutes rest) Days per week: 3 Length of regimen: 8 weeks	1) ALSFRS-R 2) VC 3) Manual muscle test 4) RPE 5) FSS 6) MVIC 7) 6MWT 8) 25FWT	• Improvement in ALSFRS-R scores, RPE, and 6MWT at 4 and 8 weeks ($p \leq 0.05$).
(Sivaramakrishnan & Madhavan, 2019)	Recumbent stepping (N=9):	Length of exercise: 40 min Days per week: 3 Length of exercise regimen: 4 weeks	1) PSQ 2) ALSFRS-R 3) 10MWT 4) 6MWT 5) Timed up and go test 6) FSS 7) Beck depression inventory 8) SF-12 9) TMS motor-evoked potentials	• No significant differences in any outcome measures 1-month post-treatment. • Only two participants had motor-evoked potentials that could be elicited using TMS. One participant had no change following treatment and one participant had a reduction in motor-evoked potential.
(A. C. Braga et al., 2018b)	Home-based aerobic exercise program (N=10): treadmill protocol, training zone above ventilator threshold 1, below 75% of predicted maximum heart rate, $SpO_2 \geq 93\%$	Length of exercise: 25 min Days per week: 1 Length of exercise regimen: 6 months	1) ALSFRS-R 2) Metabolic equivalents 3) FVC 4) SpO_2	• Decline in ALSFRS-R scores and metabolic equivalents (p=0.008, p=0.015).

	RMST Exercise Regimens			
(Tabor-Gray, Rosado, et al., 2016)	Sham/EMST (N=1): for sham, spring-loaded valve removed from device; for EMST, device set to 50% of MEP	Number of reps: 25 Days per week: 5 Length of exercise regimen: 16 weeks (8 weeks sham, 8 weeks active EMST)	1) MEP 2) Voluntary cough spirometry 3) ALSFRS-R	• MEP: 5cm H_20 decline after sham training; 52cm H_20 increase after active EMST. • Cough inspired volume and median cough total within an epoch increased following sham and active EMST training. • ALSFRS-R scores remained relatively stable from baseline (32), post-sham (29), and post EMST (30).
(Robison et al., 2018)	IMST and EMST (N=1): device set to 30% of MIP/MEP	Reps: 25 each Days per week: 5 Length of exercise regimen: 24 months	1) MIP 2) MEP 3) FVC 4) PEF 5) ALSFRS-R	• MIP: 63cm H_20 increase. • MEP: 89cm H_20 increase. • Stable FVC (104% predicted). • PEF: 324L/min increase. • Two-point decrease in ALSFRS-R score.
(Plowman, Watts, Tabor-Gray, et al., 2016)	EMST (N=25): devices set to 50% of MEP	Sets: 5 Reps: 5 Days per week: 5 Length of exercise regimen: 5 weeks	1) MEP 2) Physiologic measures of swallowing and PAS 3) Voluntary cough spirometry	• Increase in MEP over time ($p<0.03$). • Increase in hyoid displacement ($p<0.02$).
(Plowman et al., 2019)	Active EMST (N=24): devices set to 50% of MEP	Sets: 5 Reps: 5 Days per week: 5	1) MEP 2) VFSS ratings of airway protection and	• Increase in MEP for active EMST group pre to post treatment ($p=0.009$).

	Sham EMST(N=24): devices set to 0% resistance	Length of exercise regimen: 8 weeks	swallowing efficiency (PAS, DIGEST) 3) FOIS 4) EAT-10 5) Voluntary Cough Spirometry 6) FVC 7) ALSFRS-R	• Global swallow function and swallowing efficiency decreased for the sham group (p=0.02).
(Cheah et al., 2009)	IMST (N=9): first week: device 15% of SNIP, second week: device 30% of SNIP, third week: 45% of SNIP, fourth week: 60% of SNIP, and then maintained at 60%; Sham (N=10)	Length of exercise: 10 min Times per day: 3 Days per week: 7 Length of regimen: 12 weeks	1) Respiratory measurements (FVC, vital capacity, lung volumes, MIP, MEP, SNIP) 2) SF-36 3) ALSFRS-R 4) 6MWT 5) Neurophysiological index 6) Grip strength	• MIP, MEP, and SNIP declined for both groups following training withdrawal (p=0.05, p<0.05, p<0.05). • After training withdrawal, both groups had declines in 6MWT and grip strength (p=0.01, p<0.01).
(S. Pinto et al., 2012)	Active IMST (N=13): Device set to 30-40% resistance Delayed intervention (N=13): First 4 months device set to lowest resistance, last 4 months followed IMST protocol	Length of exercise: 10 minutes Times per day: 2 Length of regimen; 4-8 months	1) ALSFRS-R 2) Pulmonary function tests (erect, supine positions) (FVC, MEP, MIP, PEF, SNIP, maximal voluntary ventilation, nocturnal pulse oximetry) 3) Neurophysiological Index 4) Visual analog scale of dyspnea	• Improvement in maximal voluntary ventilation sitting and supine from baseline to time point one for the active IMST group (p=0.017, p=0.042). • Improved visual analog scale of dyspnea between time point one and two for the active IMST group (p<0.001).

			5) Fatigue ratings (FSS, Borg scale) 6) Hamilton Rating Scale for Depression 7) Epworth daytime sleepiness scale 8) FIM 9) European QOL-5D	
(S. Pinto & de Carvalho, 2013)	Early intervention exercise group (N=11); Late intervention exercise group (N=7): IMST with device set to 30-40% of maximum inspiratory pressure; Historical control group (N=16)	Length of exercise: 10 min Times per day: 2 Length of exercise regimen: 8-32 months	1) Survival 2) ALSFRS 3) Respiratory ALSFRS-R 4) FVC 5) Mean phrenic nerve amplitude	• Patients in the early and late intervention groups survived longer ($p<0.001$). • FVC was a prognostic factor for the exercise group ($p<0.05$) and diagnostic delay was a prognostic factor for the control ($p<0.05$). • IMST, gender, and phrenic nerve response amplitude were predictive of mortality ($p<0.05$).

List of Abbreviations (Table 6):

10MWT (10 Minute Walk Test), ALSAQ-40 (ALS Assessment Questionnaire), ALSSQoL-R (ALS Specific Quality of Life-Revised), ASH (Ashworth Spasticity Scale), CPET (cardiopulmonary exercise training), CPF (cough peak flow), MiRNA (micro ribonucleic acid), MMT (manual muscle testing), PSQ (Participant Satisfaction Questionnaire), SF-12 (Short Form-12), SF-36 (Short Form-36), TMS (transcranial magnetic stimulation), VC (vital capacity)

Statistical Analyses Metrics of Study Outcomes

Table 7 summarizes statistical analyses measures that were reported from each of the studies. Across studies, the attrition rate ranged from 0% to 80%. While most studies reported whether exercise regimens resulted in statistically significant differences in outcome measures, few studies reported effect sizes (N=5, 20.8%). Similarly, intention-to-treat (ITT) analyses was reported for three out of nine studies that likely could have reported it (33.3%).

Table 7: Summary of statistical analyses related to study outcomes.

Study	*Power Analysis Performed*	*Attrition*	*ITT analysis*	*Effect sizes*	*Adherence to Treatment*
(Bohannon, 1983)	N/A (case study)	0%	N/A (case study)	Not reported	Not reported
(A. C. Pinto et al., 1999)	No	0%	N/A (cohort study)	Not reported	Not reported
(Drory et al., 2001)	No	3 months: 28% 6 months: 44% 9 months: 68% 12 months: 80% (unable to perform statistical analyses at 9 and 12 months)	Not reported	Not reported	Not reported
(Bello-Haas et al., 2007)	Yes	33%	Yes	Yes (d=0.53)	"Moderate-High"
(Cheah et al., 2009)	No	5%	Yes	Not reported	Experimental: 81.7±28.0%

					Control: 85.2±24.9%
(Sanjak et al., 2010)	No	33%	N/A (cohort study)	Not reported	"Excellent"
(S. Pinto et al., 2012)	No	Study entry: 7.7% 4 months: 15.4% 8 months: 23.1%	Yes	Not reported	"Excellent"
(S. Pinto & de Carvalho, 2013)	Not reported	Not reported	N/A (cohort study)	Not reported	Not reported
(Tabor-Gray, Rosado, et al., 2016)	N/A (case study)	0%	N/A (case study)	Not reported	100%
(Lunetta et al., 2016)	Yes	End of treatment period: 6.7% End of follow-up period: 21.7% (dropout rates and reasons for dropouts did not differ significantly between groups, p=0.141)	Not reported	Not reported	"Good, most patients completed the prescribed exercise sessions"
(Plowman, Watts, Tabor-Gray, et al., 2016)	No	40%	N/A (cohort study)	Not reported	79%
(Jensen et al., 2017)	No	16.7%	N/A (case series)	Not reported	3 participants: 85-95% 2 participants: 50-60%
(Clawson et al., 2018)	Yes	Before 3 months: 18.6% Between 3-6 months: 25.4%	Not reported	Not reported	Stretching/range of motion group: 85% had ≥50% adherence

					Resistance group: 78% had ≥50% adherence Endurance group: 50% had ≥50% adherence
(Kato, Hashida, Kobayashi, et al., 2018)	No	0%	N/A (case study)	Not reported	Not reported
(Kato, Hashida, & Konaka, 2018)	No	0%	N/A (case series)	Not reported	Not reported
(Robison et al., 2018)	No	0%	N/A (case study)	Not reported	100%
(Kitano et al., 2018)	Yes	28.6%	N/A (case control studies)	Yes (d=0.35-0.71)	Exercise completion: 5.9±1.6 times per week
(Merico et al., 2018)	No	17.4%	Not reported	Not reported	Not reported
(A. C. Braga et al., 2018a)	No	0%	N/A (cohort study)	Yes (d=-0.26, 1.99, f^2=1.04)	Not reported
(A. C. Braga et al., 2018b)	No	0%	N/A (case series)	Not reported	"Excellent," average number of sessions: 29
(Zucchi et al., 2019)	Yes	End of treatment: 10.8% One year: 43.1% End of follow-up: 69.2%	Not reported	Not reported	Not reported
(Plowman et al., 2019)	No	4.2%	Not reported	Not reported	95-100%
(Pegoraro et al., 2019)	No	0%	N/A (cohort study)	Not reported	Not reported
(Sivaramakrishnan & Madhavan, 2019)	No	22.2%	N/A (cohort study)	Not reported	100%

4.4 Discussion

This systematic review evaluated the potential risks and benefits of PALS engaging in various exercise regimens. A broad range of exercise regimens were implemented (aerobic endurance, resistance, stretching/range of motion, and RMST [EMST and/or IMST]), with various dosage parameters employed (frequency, repetitions, intensity, and duration). Despite heterogeneity across methodologies, the majority of studies demonstrated that exercise-based interventions were safe, well-tolerated, and may lead to maintenance and/or improvements in function and quality of life for early-stage PALS with mild-moderate functional impairment.

4.4.1 Combination of aerobic endurance, resistance, and stretching/range of motion

Ten studies examined the impact of a combination of types of exercise (e.g. aerobic endurance, resistance, stretching/range of motion) on various outcomes related to muscle health and quality of life (Bello-Haas et al., 2007; A. C. Braga et al., 2018a; Clawson et al., 2018; Drory et al., 2001; Kato, Hashida, Kobayashi, et al., 2018; Kitano et al., 2018; Lunetta et al., 2016; Merico et al., 2018; Pegoraro et al., 2019; Zucchi et al., 2019). The majority of studies (N=6; 60%) employed an RCT design, with sample sizes ranging across all 10 studies from 10-105 participants (Bello-Haas et al., 2007; A. C. Braga et al., 2018a; Clawson et al., 2018; Drory et al., 2001; Kato, Hashida, Kobayashi, et al., 2018; Kitano et al., 2018; Lunetta et al., 2016; Merico et al., 2018; Pegoraro et al., 2019; Zucchi et al., 2019). While all studies reported tolerability of the exercise regimens, attrition over time ranged from 0% to 80% (Bello-Haas et al., 2007; A. C. Braga et al., 2018a; Clawson et al., 2018; Drory et al., 2001; Kato, Hashida, Kobayashi, et al., 2018; Kitano et al., 2018; Lunetta et al., 2016; Merico et al., 2018; Pegoraro et al., 2019; Zucchi et al., 2019). Eight studies found statistically significant improvements and/or attenuated decline in measures of ALS functioning, overall disease progression, and patient reported outcomes (Bello-Haas et al., 2007; A. C. Braga et al., 2018a; Drory et al., 2001; Kato, Hashida, Kobayashi, et al., 2018; Kitano et al., 2018; Lunetta et al., 2016; Merico et al., 2018; Pegoraro et al., 2019). In contrast, two studies did not find any significant differences in outcome measures after exercise completion (Clawson et al., 2018; Zucchi et al., 2019). Furthermore, one study found that an intensive exercise regimen led to an increase in FSS scores, suggesting an increase in overall fatigue severity that may impact patients' function (Zucchi et al., 2019).

4.4.2 Resistance exercise

Three studies investigated the impact of resistance exercise on muscle strength, functional measures (e.g. Functional Ambulation Categories [FAC], 30 second chair rise), neuromuscular function, voluntary muscle activation, and muscle fiber morphology in PALS (Bohannon, 1983; Jensen et al., 2017; Kato, Hashida, & Konaka, 2018). All studies that examined resistance exercise were case studies or case series (N=1, N=2, N=6). The exercise regimens were well-tolerated with no reported adverse outcomes. Only one patient withdrew for reasons unrelated to the exercise program (Jensen et al., 2017). Resistance exercise led to variable outcomes with one study reporting no consistent trends (Bohannon, 1983), one study reporting improvements in muscle strength, and one study reporting mixed results in measures of function and muscle strength (Jensen et al., 2017). While there were no adverse events due to exercise in these case studies, further research is necessary to draw conclusions about the impact of resistance exercise on muscle strength and overall function in PALS. Future studies should implement resistance exercise in PALS in large, randomized, controlled trials to bolster the mixed research evidence to date.

4.4.3 Aerobic endurance

Four studies explored the impact of aerobic endurance on pulmonary function, muscle strength, flexibility, overall functional impairment/disease severity, fatigue, depression, and quality of life in PALS (A. C. Braga et al., 2018b; A. C. Pinto et al., 1999; Sanjak et al., 2010; Sivaramakrishnan & Madhavan, 2019). Three aerobic endurance exercise studies were cohort studies (N=20, N=9, N=9) and one was a case series (N=10) (A. C. Braga et al., 2018b; A. C. Pinto et al., 1999; Sanjak et al., 2010; Sivaramakrishnan & Madhavan, 2019). Aerobic exercise regimens were well-tolerated and the attrition rate ranged from none to 33% across studies (A. C. Braga et al., 2018b; A. C. Pinto et al., 1999; Sanjak et al., 2010; Sivaramakrishnan & Madhavan, 2019). Two studies found statistically significant improvements in several measures of ALS functioning and patient perception (A. C. Pinto et al., 1999; Sanjak et al., 2010), while one study found no statistically significant differences in any outcome measures (Sivaramakrishnan & Madhavan, 2019), and another found a statistically significant decline in several functional measures following the exercise regimen (A. C. Braga et al., 2018b). These mixed findings indicate the importance of replicating these research studies with larger sample sizes of PALS to delineate treatment recommendations for prolonging function and quality of life.

4.4.4 Respiratory Muscle Strength Training

EMST: Four studies examined the impact of EMST on a variety of pulmonary function tests, overall functional impairment/disease severity, patient perception of swallowing impairment, and physiologic measures of swallowing (Plowman et al., 2019; Plowman, Watts, Tabor-Gray, et al., 2016; Robison et al., 2018; Tabor-Gray, Rosado, et al., 2016). Two studies were case studies, one study was a delayed intervention clinical trial (N=25), and one study was a double-blind, randomized, controlled trial (N=48). In all four studies, EMST was safe and well-tolerated with no adverse events related to the intervention (Plowman et al., 2019; Plowman, Watts, Tabor-Gray, et al., 2016; Robison et al., 2018; Tabor-Gray, Rosado, et al., 2016). The attrition rate in the delayed intervention clinical trial was 40% and in the double-blind, randomized, controlled trial was 4.2% (Plowman et al., 2019; Plowman, Watts, Tabor-Gray, et al., 2016). EMST led to improvements in MEP (a correlate of cough function) in all four studies (Plowman et al., 2019; Plowman, Watts, Tabor-Gray, et al., 2016; Robison et al., 2018; Tabor-Gray, Rosado, et al., 2016). The impact of EMST on voluntary cough measurements, FVC, and ALSFRS-R scores was mixed across studies. In addition to this, one study that examined the impact of EMST and IMST found an increase in MIP (Robison et al., 2018). Two studies found that EMST led to positive improvements in swallow function as well (Plowman et al., 2019; Plowman, Watts, Tabor-Gray, et al., 2016). These preliminary studies provide support for the use of EMST in patients with early-stage ALS, however, further research is warranted to examine the impact of EMST over a longer period of time and to determine optimal dosage parameters.

IMST: Four studies investigated the impact of IMST on a variety of pulmonary function tests, overall functional impairment/disease severity, survival, fatigue, depression, and quality of life in PALS (Cheah et al., 2009; S. Pinto et al., 2012; S. Pinto & de Carvalho, 2013; Robison et al., 2018). Of the studies examining IMST, one was a case study, one was a cohort study (N=34), and two were randomized, controlled trials (N=19, N=26) (Cheah et al., 2009; S. Pinto et al., 2012; S. Pinto & de Carvalho, 2013; Robison et al., 2018). Across studies, IMST was well-tolerated and attrition rates ranged from 0 to 23.1% (Cheah et al., 2009; S. Pinto et al., 2012). All four studies found that IMST led to improvements or attenuated declines in various measures of pulmonary function, although not all study results reached significance (Cheah et al., 2009; S. Pinto et al., 2012; S. Pinto & de Carvalho, 2013; Robison et al., 2018). In addition to this, one study found that patients that completed IMST lived significantly longer (S. Pinto & de Carvalho, 2013). Similar to studies examining EMST in PALS, IMST exhibits potential for prolonging pulmonary function and life in PALS. Future studies should investigate IMST with larger sample sizes of PALS and should expand upon the findings from the case study, which examined the benefits of EMST combined with IMST.

4.5 Study Limitations

A primary limitation was including only full-text articles available in English. As such, this may have led to the exclusion of other relevant research studies that have been reported in the grey literature. PALS are challenging to study due to the rapidly progressing nature of the disease. This is exemplified by the high attrition rates and small sample sizes in many research studies examining exercise in PALS. Thus, many research studies included in this review were likely under-powered (majority did not calculate a power analysis), limiting the generalizability of findings. In addition to this, exercise may impact PALS differently due to individual patient factors such as age, body mass index, FVC, spinal vs. bulbar onset, idiopathic vs. genetic ALS, time since diagnosis, psychosocial factors, cognitive function, premorbid health, socioeconomic status, and whether or not they are on medications (Andrews et al., 2018; Chiò et al., 2009; Czaplinski et al., 2006; Gallo et al., 2016; Onesti et al., 2017). While most studies had clear inclusion/exclusion criteria for patients enrolled and reported common patient demographic/clinical information (age, onset type, etc.), few studies reported whether patients had idiopathic vs. genetic ALS and what medications (if any) patients were on. According to the baseline characteristics of PALS included in these research studies, exercise regimens have only been explored in patients with minimal-mild disease severity (>40 ALSFRS-R scores) and mild-moderate disease severity (39-30 ALSFRS-R scores) (Gordon et al., 2004; Gordon & Cheung, 2006). Therefore, the findings from these studies support the implementation of exercise-based interventions in the early stages of ALS disease progression. While most studies reported disease duration and functional measures of ALS, they did not stratify patients to treatment arms based on disease duration or rate of progression, which could lead to bias and profoundly influence findings due to imbalanced groups. The types of exercise as well as the frequency, repetitions, intensity, and duration of exercise regimens varied greatly across studies. Exercise frequency ranged from 2x/week to 3x/day, up to 7 days/week, with repetitions of sets ranging from 20-25, intensity ranging from 30-60% of a patient's maximum value, and treatment duration ranging from 2 weeks to 2 years. Importantly, the small sample sizes, limited data due to lack of study replication, and heterogeneity of treatments and outcome measures explored across studies did not allow for a meta-analysis to be performed and significantly limits the strength of findings to date. Replication of research findings along with further research to determine the optimal types of exercise and the appropriate dosage for exercise training and maintenance for PALS is vital.

4.6 Conclusion

The current systematic review provides support that deliberate, well-designed exercise regimens are safe, well-tolerated, and may prolong function, life, and quality of life in early-stage PALS with mild-moderate functional impairment. Unfortunately, heterogeneity across study methodologies (particularly, dosage differences) precluded aggregation of study findings to determine a more precise treatment effect for each intervention category. Therefore, while results are promising, variability prohibits firm conclusions. Future studies should expand upon these promising preliminary results by conducting large, multi-site, randomized controlled trials that examine the impact of various exercise regimens over a longer period of time to assist in elucidating superior exercise regimens and optimal dosage parameters for exercise training in this vulnerable patient population. Replication studies are strongly encouraged which would allow for aggregation of study data in this rare population.

5.0 Study 3: A preliminary investigation of whether HRCA signals can differentiate between swallows from healthy people and swallows from people with neurodegenerative diseases

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5.1 Introduction

Accurately and non-invasively assessing swallow function is vital within the clinical setting in order to correctly identify patients with dysphagia who are at risk of aspiration and complications that arise secondary to aspiration such as aspiration pneumonia, malnutrition, and dehydration. Current clinical dysphagia screening methods have a high degree of sensitivity and a poor degree of specificity, which results in over-identification of people with dysphagia (Groves-Wright et al., 2010; Suiter et al., 2014; Waito et al., 2011). This is because dysphagia screening protocols rely on subjective human judgment of risk factors and observing patients drink a limited amount of liquid and by their nature, do not measure any aspects of swallow physiology. There is also a risk of false negatives with current dysphagia screening methods due to the asymptomatic nature of silent aspiration. Poor specificity of dysphagia screening methods results in misuse of time and resources with unnecessary, expensive procedures for patients such as undergoing videofluoroscopy, which remains one of the gold standards for assessing swallowing physiology. While VFSSs are useful for characterizing swallow function, for many patients they are not always feasible or available in a time frame that enables rapid diagnostic assessment, leaving clinicians to temporarily manage cases as best they can with available clinical information. Therefore, there is a high demand to increase accessibility to dysphagia assessment for underserved patients for the development of non-invasive methods for accurately screening and assessing swallowing that might also provide insight into underlying swallowing physiology.

HRCA is an emerging method for non-invasively screening several aspects of swallow function that has demonstrated promising preliminary evidence of its effectiveness (Dudik, Coyle, et al., 2015). HRCA combines the use of acoustic signals from a contact microphone, vibratory signals from a tri-axial accelerometer, and signal processing and machine learning techniques to effectively characterize swallow function. Non-invasive neck sensors are placed on the anterior laryngeal framework at the cricoid cartilage to record signals that occur during swallowing. To this date, our database consists of concurrent VFSS and HRCA recordings from 274 patients with suspected dysphagia and 70 community dwelling healthy adults. We are analyzing the data in our database in a systematic way (e.g. one temporal swallow kinematic event at a time, one patient population at a time) to evaluate the potential of HRCA as an effective dysphagia screening method. HRCA signals combined with signal processing and machine learning techniques have demonstrated the ability to automatically detect swallowing events with similar accuracy to trained human judges, and to effectively differentiate between safe and unsafe swallows by approximating

VFSS judgments made using the PAS (Dudik, Coyle, et al., 2015; Dudik et al., 2018; Dudik, Jestrovi, et al., 2015; Dudik, Kurosu, et al., 2015; Jestrović et al., 2013; Movahedi et al., 2017; Robbins et al., 1999; Sejdić et al., 2013; Yu et al., 2019). We are examining the association between HRCA signals and scores of physiological components on the Modified Barium Swallow Impairment Profile (MBSImP) (Martin-Harris et al., 2008) and are finding promising levels of agreement in patients with suspected dysphagia. Results have revealed statistically significant associations between HRCA signals and anterior hyoid bone movement (component #9), pharyngoesophageal segment opening (component #14), and pharyngeal residue (component #16) (Donohue, Khalifa, et al., 2020b; Donohue, Mao, et al., 2020; Sabry et al., 2019). In addition to this, we have found a strong association between HRCA signal features and hyoid bone displacement (He et al., 2019; Rebrion et al., 2019; Zhang et al., 2018, 2020). A recent study examining hyoid bone displacement found that $\geq$50% of the body of the hyoid bone could be accurately tracked on each frame using HRCA signals and machine learning techniques alone in healthy community dwelling adults and patients with suspected dysphagia (Donohue, Mao, et al., 2020; Mao et al., 2019). HRCA signals combined with machine learning techniques have demonstrated effectiveness in detecting other kinematic swallowing events including laryngeal vestibular closure and UES opening with a high degree of accuracy in healthy community dwelling adults and patients with suspected dysphagia (Donohue, Khalifa, et al., 2020b; Khalifa et al., 2021; Mao et al., 2021).

While HRCA has been used to detect penetration and aspiration, clinical ratings of physiological events of swallowing using the MBSImP, and various kinematic events of swallowing, it has not previously been used to characterize swallow function in specific patient populations. Patients with ND often experience progressive dysphagia along with other physical mobility impairments, which greatly impacts their quality of life (Alali et al., 2018; da Costa Franceschini & Mourão, 2015; Leow et al., 2010; Paris et al., 2013; Schwartz, 2018; Tabor-Gray, Gaziano, et al., 2016). Dysphagia in patients with ND is frequently characterized by impaired bolus preparation and propulsion, impaired mastication, reduced oral containment, oral residue, impaired tongue movement, impaired pharyngeal timing/coordination, pharyngeal residue, and penetration/aspiration (Waito et al., 2017). While VFSSs remain the primary method for assessing swallow function in patients with ND, there are limitations to implementing instrumental swallow evaluations in patients with progressive, degenerative diseases (Audag et al., 2019; Waito et al., 2017). Because of their multifactorial health problems, physical mobility impairments, and transportation issues it can be challenging for patients with ND to undergo VFSSs as outpatients at medical facilities. In addition to this, patients with ND are at increased risk of fatigue over the course of a meal and may have fluctuating swallow function day-to-day, which is a challenge to capture during short instrumental swallow evaluations (Audag et al., 2019). Moreover, because of the progressive nature of ND, it is advantageous to monitor swallow function more closely over time in order to predict and mitigate adverse events that may occur secondary to progressing dysphagia such as aspiration pneumonia. Completing frequent instrumental swallow evaluations such as VFSSs or fiberoptic endoscopic evaluation of swallowing (FEES) to monitor swallowing throughout disease progression is costly, burdensome to patients and caregivers, and relatively invasive (e.g. exposure to radiation, uncomfortable) (Audag et al., 2019). Amongst other patient populations, people with ND would benefit from a non-invasive, inexpensive, easily transportable device to infer about swallow function using noninvasive methods such as HRCA because of the high prevalence of dysphagia and the variety of kinematic changes in swallow function that occur throughout disease progression. Therefore, this study investigated the ability of HRCA to broadly differentiate (i.e., screen) between swallows from healthy people and people with ND. We hypothesized that HRCA would accurately differentiate these two classes of swallows by identifying significant differences in vibratory and acoustic signal features between swallows from healthy people and from people within a single class of “people with ND.”

5.2 Methods

5.2.1 Equipment and Procedures

This study was approved by the Institutional Review Board at the University of Pittsburgh and all participants provided informed written consent. Data analysis for this study was conducted on two separate sets of data that were collected at two different timepoints in a similar fashion. The first data set consisted of 170 thin liquid swallows from 20 patients with various ND between the ages of 35-82 with a mean age of 61.25 (10 males). Diagnoses of ND included PD, myasthenia gravis, motoneuron disease, MS, muscular dystrophy (MD), ALS, myotonic dystrophy, and progressive muscle weakness not otherwise specified. All patients underwent VFSSs at the University of Pittsburgh Medical Center Presbyterian hospital due to suspected dysphagia. Patients were imaged in the lateral plane. VFSSs on patients were completed as a part of their clinical care rather than for research purposes alone. For this reason, patients were examined under a variety of bolus volumes and consistencies and asked to perform compensatory maneuvers (i.e. chin tuck) as deemed appropriate based on clinical presentation of dysphagia. See Table 8 for the bolus characteristics for all swallows included in data analysis from the patient data for this study.

Table 8: Bolus characteristics for all swallows included in the neurodegenerative patient data set.

Bolus viscosity and utensil	Number of swallows	Percentage of swallows
Thin by spoon	35	20.59%
Thin by cup	90	52.94%
Thin by straw	45	26.47%
Head position	Number of swallows	Percentage of swallows
Chin down	15	8.82%
Head neutral	155	91.18%
Number of Swallows	Number of swallows	Percentage of swallows
Single	29	17.06%
Sequential	23	13.53%
Multiple	118	69.41%

The second data set consisted of 171 thin liquid swallows from 51 healthy community dwelling adults between the ages of 39-87 with a mean age of 67.21 (22 males). Inclusionary criteria for healthy community dwelling adults included no prior history of swallowing difficulties, neurological disorder, surgery to the head or neck region, or chance of being pregnant based on participant report. For healthy participants, data collection also occurred in the same institution under a separate IRB approval. Participants were imaged in the lateral plane. In contrast to the patients with ND, the healthy community dwelling adults underwent a standardized (i.e., five 3mL boluses by spoon and five unmeasured self-selected "comfortable" cup sips in head neutral position) and short (average fluoro time of 0.66 minutes) VFSS procedure of ten thin liquid boluses administered in random order to minimize radiation exposure. For spoon presentations, the researcher instructed participants to "Hold the liquid in your mouth until I tell you to swallow it." For cup presentations, the researcher instructed participants to "Take a comfortable sip of liquid and swallow it whenever you're ready." See Table 9 for the bolus characteristics for all swallows included in data analysis from the healthy community dwelling adults for this study. For the purposes of this study and to effectively compare between groups, only thin liquid swallows administered by cup and spoon were included for data analysis, because only thin liquid swallows were collected from the healthy community dwelling adults.

Table 9: Bolus characteristics for the swallows included in the healthy community dweller data set.

Bolus viscosity and utensil	Number of swallows	Percentage of swallows
Thin by spoon	78	45.61%
Thin by cup	93	54.39%

Note: Thin by spoon swallows were 3 mL and thin by cup swallows ranged from 3-40 mL.

A standard fluoroscopy system (Ultimax system, Toshiba, Tustin, CA for the patient data collection; and Precision 500D system, GE Healthcare, LLC, Waukesha, WI for the healthy community dwelling adult data collection) set at a continuous pulse rate of 30 PPS was used to obtain swallowing video segments. To capture the raw videos directly from the x-ray apparatus at a rate of 60 or 73 frames per second, we used a frame grabber module (AccuStream Express HD, Foresight Imaging, Chelmsford, MA). Once data collection was complete and prior to conducting kinematic analysis of swallowing, the videos were down sampled from 60 or 73 frames per second to 30 frames per second to get rid of the duplicate frames that were inserted into the videos due to the oversampling in the frame grabber necessary to align with the higher sampling rate of the signals acquisition system. This step produced accurate 30FPS videos for analysis. To obtain HRCA signals during concurrent VFSS, a tri-axial accelerometer (ADXL 327, Analog Devices, Norwood, Massachusetts) and contact microphone were placed on the anterior laryngeal framework at the level of the cricoid cartilage with tape. Prior to placing the non-invasive neck sensors on the anterior neck region of participants, researchers cleaned participants with alcohol pads. To ensure adequate signals were obtained from the sensors, the accelerometer and contact microphone were placed in custom casings to allow for flat contact surfaces with the skin. The accelerometer was placed at midline at the cricoid arch and the contact microphone was placed at the right of midline and inferior to the accelerometer in order to obtain the best x-ray images and signals and so as not to interfere with imaging of the upper airway. For each participant, we aligned the axes of the tri-axial accelerometer (anterior-posterior, superior-inferior, and medial-lateral) with the participant's neck. The exact placement of the non-invasive neck sensors can be viewed in Figure 6 (Dudik, Coyle, et al., 2015; Takahashi et al., 1994).

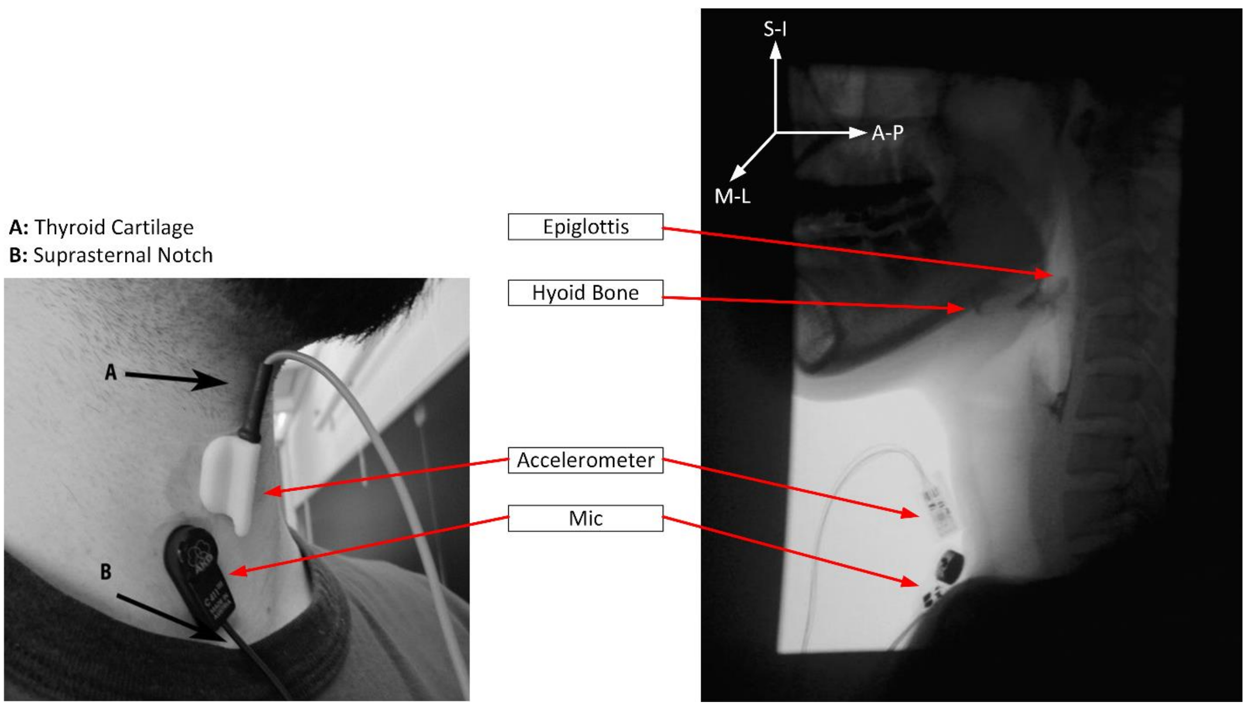

Figure 6: Neck sensor placement during data collection.

The accelerometer was powered by a power supply with a 3V output (model 1504, BK Precision, Yorba Linda, California). Following data collection with the accelerometer, the raw signals were bandpass filtered (model P55, Grass Technologies, Warwick, Rhode Island) from 0.1 to 3000 Hz and amplified ten times. Then, the signal data from each accelerometer axis was entered into a data acquisition device (National Instruments 6210 DAQ) to be recorded at a sampling rate of 20kHz using the Signal Express program within LabView (National Instruments, Austin, Texas). To overcome measurement errors and because multiple kinematic events occur simultaneously during swallowing, the signals were down sampled into 4kHz prior to analysis.

5.2.2 Kinematic swallow analyses

Before performing swallow segmentation, raters were trained and tested in swallow kinematic analyses. Intra and inter-rater reliability was assessed with ICCs (Shrout & Fleiss, 2005) with ICCs greater than 0.99 for both measures. VFSSs were segmented into individual swallows for analyses. The onset of the swallow was defined as the frame in which the bolus head passed the shadow of the ramus of the mandible, and the offset of the swallow was defined as the frame in which the hyoid returned to its lowest position after clearance of the bolus tail through the UES. Ongoing intra-rater reliability during swallow segmentation was completed to control for drift by having raters randomly select one out of ten swallows to re-analyze and compute ICCs. Inter-rater reliability for swallow segmentation was performed on 10% of swallows with ICCs of 0.99 or above for all trained raters. Since the purpose of this study was merely to determine whether there was a difference in HRCA signal features between swallows from healthy people and swallows from patients with ND, no swallow kinematic analyses were performed aside from swallow segmentation.

5.2.3 Pre-Processing and feature extraction from HRCA signals

In order to reduce the multi-source noise associated with the vibratory and acoustic signals of HRCA, each component was filtered to remove the device noise. These filters were designed based on the output of each sensor when no input was present using an auto-regressive model.

Head movement interference was removed using a fourth order splines approximation algorithm (Sejdić et al., 2010, 2012). Any additional noise component that existed was removed using wavelet denoising. This preprocessing procedure has previously demonstrated its effectiveness in many studies that investigated the use of HRCA signals in swallow kinematic analysis (He et al., 2019; Khalifa et al., 2021; Rebrion et al., 2019; Yu et al., 2019). Features that have proven to be significant to swallow kinematics and swallowing disorders based on previous research studies (He et al., 2019; Khalifa et al., 2021; Rebrion et al., 2019; Yu et al., 2019) were then extracted from the HRCA signals in order to determine the association between HRCA signals and the diagnostic class (i.e., neurodegenerative disease) of the patient. A summary of the features used and the definition of each appears in Table 10.

Table 10: Summary of the features extracted from the HRCA signals.

Domain	Feature	Significance
Time Domain		
	Standard deviation	Reflects the signal variance around its mean value.
	Skewness	Describes the asymmetry of amplitude distribution around the mean.
	Kurtosis	Describes the “peakness” of the distribution relative to normal distribution.
Information-Theoretic Domain		
	Lempel-Ziv Complexity	Describes the randomness of the signal.
	Entropy rate	Evaluates the degree of regularity of the signal distribution.
Frequency Domain		
	Peak Frequency (Hz)	Describes the frequency of maximum power.
	Spectral Centroid (Hz)	Evaluates the median of the spectrum of the signal.
	Bandwidth (Hz)	Describes the range of frequencies of the signal.
Time-Frequency Domain	Wavelet Entropy	Evaluates the disorderly behavior for non-stationary signals.

5.2.4 Data Analysis:

We fit a series of linear mixed models to examine the association between 36 different HRCA signal features, swallows from healthy people, and swallows from people with ND. Support vector machine (SVM), Naïve Bayes, logistic regression, and decision tree classifiers, which represent supervised machine learning techniques, were constructed to differentiate between swallows from patients with ND and swallows from healthy subjects based on either the entire set of features extracted from the HRCA signals or a subset that was proven statistically significant based on the results of the linear mixed models or a feature selection method. This yielded three training procedures for the used classifiers, the first procedure was performed through using the entire set of features extracted from HRCA signals (36 features) and the second procedure used only the set of features that was proven significant by the statistical analysis (22 features). The third procedure included training the classifiers after performing a principal component analysis (PCA) on the features which represent a feature selection method that only keeps the statistically independent features. SPSS (IBM, Armonk, NY) was used for fitting the linear models while MATLAB (The MathWorks, Inc., Natick, MA) and R (The R Foundation) were used to build and evaluate the classifiers. The performance of each classifier was evaluated through a leave-one-out procedure. This procedure involves training the classifier with the whole set of swallows from both groups except for one swallow that is selected randomly to test if it is classified correctly and then the process is repeated until all swallows are included as a testing sample at least once. To determine whether the swallow is classified correctly, the labels from VFSS images are used as the "ground truth." The accuracy, sensitivity, and specificity of classification between healthy and neurodegenerative disease swallows were calculated based on the number of correctly classified swallows during the evaluation process with respect to the complete set of swallows from both groups.

5.3 Results

Results from the linear mixed model revealed that 22 HRCA signal features extracted from the microphone and tri-axial accelerometer were statistically significant ($p<0.05$) for predicting whether swallows were from healthy people or from patients with ND (See Table 11).

Table 11: Summary of the statistically significant HRCA signal features associated with differentiating between swallows from healthy people and swallows from patients with ND.

	Microphone	Anterior-posterior	Superior-inferior	Medial-lateral
Standard Deviation	**0.0005***	**<0.0001***	**<0.0001***	**<0.0001***
Skewness	**0.035***	0.8560	0.6066	0.2223
Kurtosis	0.0645	0.2103	**0.0017***	**<0.0001***
Lempel-Ziv	0.1248	0.7192	**<0.0001***	**<0.0001***
Entropy Rate	0.6804	0.2462	**<0.0001***	**0.0004***
Peak Frequency	0.0666	0.4258	0.9209	**<0.0001***
Spectral Centroid	**0.0105***	**0.0031***	**<0.0001***	**<0.0001***
Bandwidth	**0.0105***	**0.0002***	**<0.0001***	**<0.0001***
Wavelet entropy	0.8160	**0.0054***	**<0.0001***	0.4474

Note: *= $p<0.05$

Statistically significant HRCA signal features from microphone signals included: standard deviation, skew, centroid frequency, bandwidth; from accelerometer anterior-posterior axis: standard deviation, centroid frequency, bandwidth, wave entropy: from accelerometer superior-inferior axis: standard deviation, kurtosis, Lempel-ziv, entropy rate, centroid frequency, bandwidth, wave entropy; and from accelerometer medial-lateral axis: standard deviation, kurtosis, Lempel-ziv, entropy rate, centroid frequency, peak frequency, and bandwidth. Figures 7 and 8 show a density plot and a power spectral density plot from the HRCA microphone signals that demonstrate the differences in standard deviation and peak frequency between the swallows from a healthy person and a person with a neurodegenerative disease.

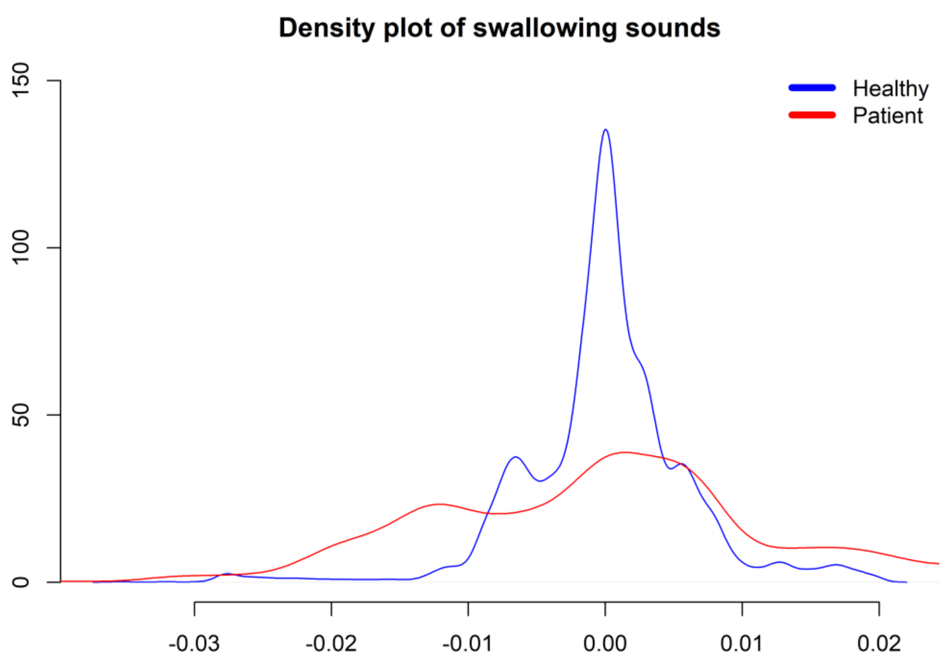

Figure 7: Density plot from the HRCA microphone signals showing the difference in standard deviation between the swallows from a healthy person and a person with a neurodegenerative disease.

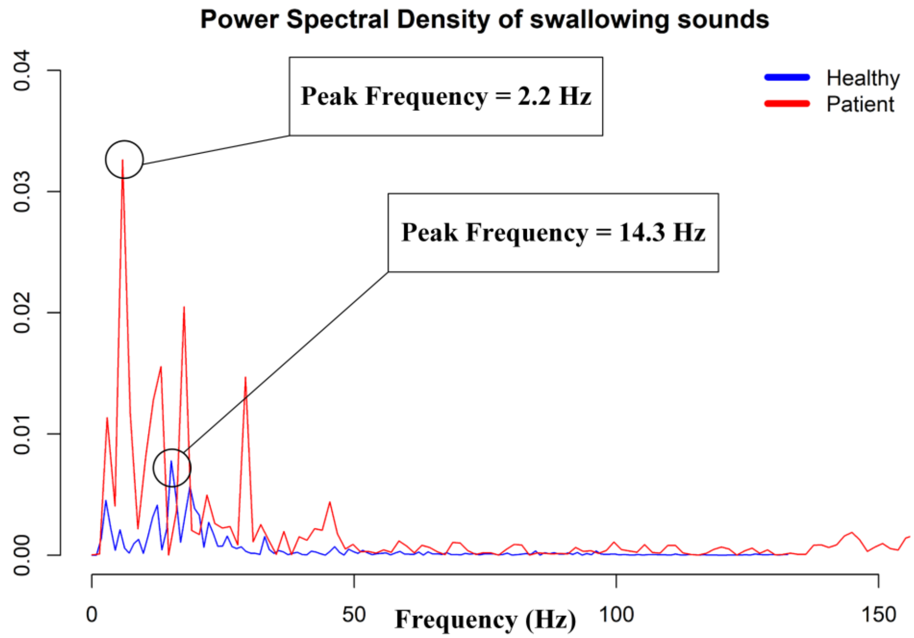

Figure 8: Power spectral density plot from the HRCA microphone signals showing the difference in peak frequency between the swallows from a healthy person and a person with a neurodegenerative disease.

Among the used classifiers, logistic regression and decision trees provided the best performance in comparison to SVM and Naïve Bayes with 99% accuracy, 100% sensitivity, and 99% specificity when using the full set of HRCA signal features (See Table 12).

Table 12: Performance of classifiers used to differentiate between swallows from healthy people and swallows from patients with ND.

Classifier	Entire set of features (36 features)			Subset of features (22 most significant features – Table 7)			Feature selection (PCA)		
	Acc.	Sens.	Spec.	Acc.	Sens.	Spec.	Acc.	Sens.	Spec.
SVM	0.94	0.94	0.94	0.91	0.90	0.92	0.94	0.93	0.95
Naïve Bayes	0.97	1	0.95	0.97	1	0.95	0.95	0.94	0.97
Logistic Regression	0.99	1	0.99	0.99	1	0.99	0.97	0.96	0.99
Decision Trees	0.99	0.99	0.99	0.99	0.99	0.99	0.95	0.93	0.97

Note: Acc.=accuracy, Sens.=sensitivity, Spec.=specificity

5.4 Discussion

This study is the first study to date that has used HRCA to differentiate between healthy swallows and swallows from people in a category of underlying disease that commonly results in dysphagia. Since this is the first study to explore this, it will be important to replicate this study with a larger sample of people with ND and with additional patient populations. We found that HRCA combined with statistical methods and machine learning techniques could differentiate between swallows from healthy people and swallows from people with a variety of ND effectively with a high degree of accuracy. While the results do not characterize the nature of swallowing physiology that differed between the two groups, we accomplished our intended aim of providing a screening-level differentiation between “normal” and “neurodegenerative disease” swallows. While these preliminary results are promising, they do not by any means provide discrete diagnostic/physiologic information, therefore it will be important to expand this work to gain insight into the underlying swallowing physiology that may contribute to statistically significant signal features between these two groups. However, the importance of identifying and differentiating a class of swallows that is distinctly different from "normal" swallows cannot be overstated, given the typical pattern of subclinical signs and symptoms during the early progression of ND, and the fact that many such patients are not identified before clinically important dysphagia ensues. Characterizing the safety and efficiency of swallow function in patients with ND is important but challenging due to the multiple and heterogeneous disease-related factors which contribute to dysphagia, including weakness, spasticity, rigidity, motor unit deactivation, and atrophy of muscles secondary to motoneuron deterioration. Due to the heterogeneity and progressive nature of ND, there is a need for an individualized approach to dysphagia management with close monitoring of swallow function over time to maximize quality of life and to prevent adverse outcomes that can result in faster disease progression. A readily deployable and portable device using HRCA, which can non-invasively monitor and classify swallow function as disordered or not disordered within the variety of clinical settings occupied by these patients, and even in the home would be beneficial toward a goal of early identification and referral for many patients with ND.

Future studies should examine the ability of HRCA to characterize and distinguish swallows from healthy people and swallows from specific ND (e.g., ALS only) as well as other patient populations that have dysphagia, and the ability of HRCA to characterize swallows between various patient populations that have dysphagia (e.g. ALS vs. patients who have had a stroke) to determine whether HRCA may have diagnostic value. In addition to this, future work should refine HRCA methods to further characterize swallow function of specific patient populations to broadly differentiate between safe and unsafe swallows, and as a potential adjunct to dysphagia diagnostics, to quantify a variety of swallowing kinematic measurements such as hyoid bone displacement and predict laryngeal vestibular closure and UES opening (Donohue, Khalifa, et al., 2020b; Donohue, Mao, et al., 2020; Dudik, Coyle, et al., 2015; Dudik et al., 2018; Dudik, Jestrovi, et al., 2015; Dudik, Kurosu, et al., 2015; Jestrović et al., 2013; Khalifa et al., 2021; Kurosu et al., 2019; Mao et al., 2019; Movahedi et al., 2017; Sejdić et al., 2013; Yu et al., 2019). Other areas of potential interest would be examining the ability of HRCA signals to differentiate between dysphagia severity levels in specific patient populations based on swallowing safety and efficiency, as well as improvement or deterioration of swallowing function as a function of disease progression or treatment. The robustness of the machine learning algorithm used in this study should also be improved by including a larger variety of bolus consistencies and swallow conditions in future studies. Expanding upon the current study with this future work will result in more advanced and accurate non-invasive screening, and potentially, characterization of swallowing physiology across a variety of patient populations to more quickly and accurately identify and treat swallowing impairments when imaging instrumentation is temporarily unavailable or undesired by patients, or otherwise not feasible. Given clinician reliance on all available information, the addition of accurate and quantitative, noninvasively-obtained data regarding swallow function will be a valuable adjunct to the screening process, and hopefully in the future to the diagnostic process, in all but the most ideal clinical situations in which all diagnostic methods are available.

5.5 Limitations

The main purpose of this study was to broadly characterize and classify swallows between two groups using HRCA rather than to characterize swallow function based on bolus or swallowing conditions during VFSSs. While we included only single thin liquid swallows for data analysis between the two groups, it is important to note that the data collection methods for patients with ND were consistent with clinical care while the data collection methods for the healthy community dwelling adults were consistent with a standardized research VFSS protocol. Each data collection method has strengths and limitations: methods consistent with clinical care result in improved generalizability and real-world application (external validity) while methods that follow a strict research protocol result in increased internal validity. Another limitation of this study was the heterogenous group of patients with ND. Due to the small sample size of individuals with ND within our database, we included a variety of diseases within this classification category. While the presentation and severity of dysphagia may vary across these diseases, the ability of the machine learning algorithm to differentiate between healthy swallows and swallows from people with a variety of ND with a high degree of accuracy, sensitivity, and specificity demonstrates the robustness of the machine learning algorithm. For this study, we included a relatively large sample of swallows within each group (~170). However, it will be important to test the accuracy of this algorithm on larger data sets that consist of the same, and different bolus textures and volumes, swallows from individual ND (e.g. ALS only), and swallows from other diseases that result in dysphagia.

5.6 Conclusion

This study found that HRCA signal features combined with statistical methods and machine learning techniques could predict whether swallows were from healthy people or from patients with ND with a high degree of accuracy (99%), sensitivity (100%), and specificity (99%).

These results provide preliminary evidence that HRCA may be a beneficial early detection method to further explore in future studies to determine whether it can be used to characterize swallows between different patient populations and to characterize whether noninvasive data collected during swallows exhibit evidence of impairment when imaging is not available or feasible. The ability to differentiate between swallows from different patient populations combined with the ability to noninvasively differentiate between safe and unsafe swallows and predict swallow kinematic events would make HRCA a useful dysphagia screening method with future potential to be a diagnostic adjunct to instrumental swallowing evaluations.

6.0 Study 4: Characterizing swallows from people with neurodegenerative diseases using high-resolution cervical auscultation signals and temporal and spatial swallow kinematic measurements

6.1 Introduction

Patients with ND are frequently diagnosed with dysphagia at some point during the disease course as motor function progressively deteriorates. In fact, prevalence estimates of dysphagia in patients with ND such as dementia, MS, PD, and ALS range from 13-98% (Aghaz et al., 2018; Alagiakrishnan et al., 2013; Easterling & Robbins, 2008; Onesti et al., 2017; Suttrup & Warnecke, 2016). Closely monitoring swallow function throughout the disease course is vital for patients with ND to predict and mitigate adverse outcomes (e.g. malnutrition, dehydration, aspiration pneumonia, respiratory failure) while simultaneously helping patients maintain quality of life via methods of intake that are safe and align with patient preferences and intake requirements (da Costa Franceschini & Mourão, 2015; Paris et al., 2013; Schwartz, 2018; Smith & Ferguson, 2017). While VFSSs and FEES remain the gold standards for swallowing instrumental assessment methods, they are not always feasible or easily accessible, especially for patients with ND who may have physical mobility impairments, multifactorial health problems, and difficulty attending in-person appointments due to transportation challenges or concerns related to having a compromised immune system (e.g. COVID-19 pandemic) (Audag et al., 2019; Waito et al., 2017). Likewise, patients with ND may require frequent re-evaluation of swallow function due to the progressive disease nature, day-to-day variability in swallow function, and the inability to fully capture a patient's swallowing ability during instrumental swallow evaluations due to time constraints (i.e. limited clinician availability, need to minimize radiation exposure) (Audag et al., 2019). In addition to this, while some research studies have characterized some aspects of swallow function in patients with ND, few studies report objective changes in swallowing based on normative reference data, and further, there is a general lack of consensus regarding specific impairments that occur throughout the disease courses of various ND (Waito et al., 2017). Therefore, the ability to monitor swallow function continuously, remotely, non-invasively, and objectively would be an especially useful innovation for patients with ND as well as clinicians and caregivers of patients with ND.

HRCA is a promising, non-invasive, sensor-based dysphagia screening method with potential as an adjunct to VFSSs. HRCA autonomously quantifies several aspects of swallowing physiology via acoustic and vibratory signals that are obtained from a contact microphone and tri-axial accelerometer that are attached to the anterior laryngeal framework during swallowing. Using advanced signal processing and machine learning techniques, HRCA has classified swallows as safe vs. unsafe based on the PAS (Dudik, Coyle, et al., 2015; Dudik et al., 2018; Dudik, Jestrovi, et al., 2015; Dudik, Kurosu, et al., 2015; Jestrović et al., 2013; Robbins et al., 1999; Sejdić et al., 2013; Yu et al., 2019)**,** tracked hyoid bone movement (Donohue, Mao, et al., 2020; Mao et al., 2019), annotated specific temporal swallow kinematic events (e.g. UES opening, UES closure, LVC, LV re-opening) (Donohue, Khalifa, et al., 2020b; Khalifa et al., 2021; Mao et al., 2021), and classified swallows based on MBSImP scores (Martin-Harris et al., 2008) with similar accuracy as human judges (Donohue, Khalifa, et al., 2020b; Donohue, Mao, et al., 2020). Recently, HRCA has demonstrated promise in characterizing swallow function in specific patient populations including patients post-stroke and patients with ND (Donohue, Khalifa, et al., 2020a; Kurosu et al., 2019). A preliminary study found that using HRCA signals as input, logistic regression and decision trees classified swallows between patients with ND and age-matched healthy adults with 99% accuracy, 100% sensitivity, and 99% specificity (Donohue, Khalifa, et al., 2020a), offering a promising and noninvasive system for early detection of significantly atypical swallow physiology in mildly symptomatic patients who may otherwise evade traditional methods of identification. In the present study, we sought to expand upon this prior work, which explored HRCA's capability in classifying (i.e., screening) between swallows from patients with ND and swallows from age-matched healthy adults, with the following aims: 1) Compare temporal and spatial swallow kinematic measures between patients with ND and age-matched healthy adults; and 2) Investigate HRCA's ability to accurately annotate specific swallow kinematic events in patients with ND. We hypothesized there would be differences in temporal (bolus passes the mandible, hyoid onset, hyoid maximum, hyoid offset, UES opening, UES closure, LVC, LV re-opening) and spatial (hyoid bone displacement and UES anterior-posterior distension) swallow measurements between patients with ND and age-matched healthy adults, and that HRCA would accurately annotate temporal and spatial swallow kinematic events in patients with ND.

6.2 Methods

6.2.1 Participants, study procedures, and equipment:

We conducted data analyses on two distinct sets of data collected at two different time points from patients with ND and age-matched healthy community dwelling adults. All enrolled participants provided written informed consent and both studies were approved by the appropriate Institutional Review Board. The data set from patients with ND consisted of 170 thin liquid swallows from 20 patients (age range: 35-82 years, mean age (±SD): 61.25±12.17 years, 10 males). Bolus characteristics from the swallows used for analyses can be viewed in Table 13.

Table 13: Bolus characteristics for all swallows included in the neurodegenerative patient data set.

Bolus condition	Number of swallows (Percentage)
Thin by spoon	35 (20.59%)
Thin by cup	90 (52.94%)
Thin by straw	45 (26.47%)
Head position	Number of swallows (Percentage)
Chin down	15 (8.82%)
Head neutral	155 (91.18%)
Swallow type	Number of swallows (Percentage)
Single	29 (17.06%)
Sequential	23 (13.53%)
Multiple	118 (69.41%)

Patients with ND had a variety of diagnoses including PD, myasthenia gravis, motoneuron disease, MS, muscular dystrophy (MD), ALS, myotonic dystrophy, and progressive muscle weakness not otherwise specified. Patients with ND were referred for VFSSs by their physicians and had volunteered to participate in an ongoing HRCA project and underwent clinician guided VFSSs with concurrent HRCA as a part of their clinical care due to suspected dysphagia rather than a standardized VFSS for research purposes. In contrast, the age-matched, healthy community dwelling adults' data set consisted of 171 thin liquid swallows from 51 adults (age range: 39-87 years, mean age (±SD): 67.21±10.56 years, 22 males). Bolus characteristics for the swallows used for analyses can be viewed in Table 14.

Table 14: Bolus characteristics for the swallows included in the healthy community dweller data set.

Bolus condition	Number of swallows (Percentage)
Thin liquid by spoon	78 (45.61%)
Thin liquid by cup	93 (54.39%)

Note: Thin by spoon swallows were 3 mL and thin by cup swallows ranged from 5-40 mL (mean: 16.87 mL).

Healthy community dwelling adults were enrolled based on self-report of absence of the following exclusionary criteria: history of swallowing difficulties, neurological disorder, surgery to the head or neck region, or chance of being pregnant (if female). Healthy participants underwent standardized VFSSs in the lateral plane with concurrent HRCA to minimize radiation exposure (average fluoroscopy time 0.66 minutes for 10 swalllows). Our standardized VFSS methods are described in detail in previous publications (Donohue, Khalifa, et al., 2020a, 2020b; Donohue, Mao, et al., 2020).

Equipment for both research studies included a standard fluoroscopy system (Ultimax system, Toshiba, Tustin, CA for the ND patient data collection; Precision 500D system, GE Healthcare, LLC, Waukesha, WI for the age-matched healthy adult data collection), a frame grabber module for obtaining video segments (AccuStream Express HD, Foresight Imaging, Chelmsford, MA), a tri-axial accelerometer (ADXL 327, Analog Devices, Norwood, Massachusetts) powered by a power supply with a 3V output (model 1504, BK Precision, Yorba Linda, California), and a contact microphone. VFSSs were conducted at a pulse rate of 30 PPS. VFSS images and HRCA signals were obtained at a higher sampling rate (60-73 frames per second) according to Shannon's sampling theorem and then later down sampled to 30 FPS (Oppenheim et al., 1999). The HRCA sensors (contact microphone and tri-axial accelerometer) were carefully placed on the anterior laryngeal framework with tape in alignment with the participant's neck to obtain the best VFSS images and signals (See Figure 9) (Dudik, Coyle, et al., 2015; Takahashi et al., 1994).

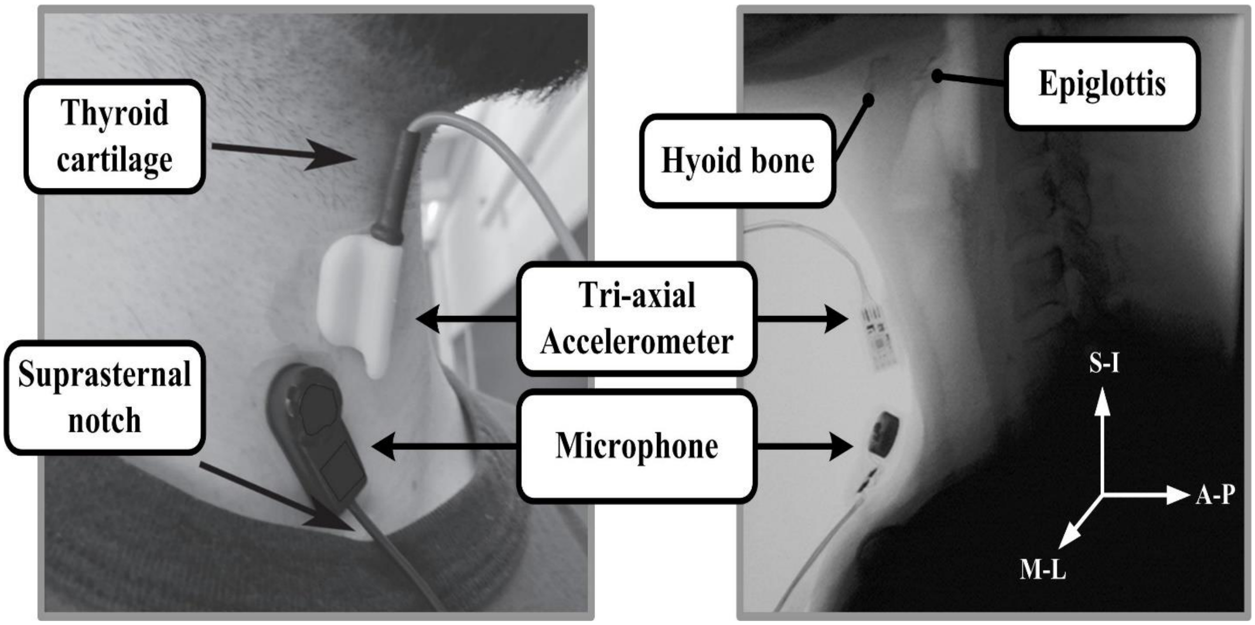

Figure 9: Location of HRCA sensors (contact microphone and tri-axial accelerometer) during data collection.

Following data collection, acoustic and vibratory signals from the contact microphone and tri-axial accelerometer were bandpass-filtered, amplified (model P55, Grass Technologies, Warwick, Rhode Island), digitized via a data acquisition device (National Instruments 6210 DAQ) through the Signal Express program in LabView (National Instruments, Austin, Texas) at a sampling rate of 20kHz.

6.2.2 Temporal and spatial swallow kinematic analyses:

Prior to performing temporal or spatial swallow kinematic measurements and PAS ratings, trained raters underwent inter and intra-rater reliability tests returning ICCs (Shrout & Fleiss,

2005) of at least 0.9 and percent exact agreement of at least 80% respectively. Temporal swallow kinematic measurements included the video frames at which the following events occurred: bolus head passes the mandible, onset of maximal hyoid displacement (recently labeled “hyoid burst” in other studies), hyoid reaches maximum displacement, hyoid return to rest, onset of UES opening, onset of UES closure, onset of LVC, and onset of LV re-opening. The definition of all temporal swallow kinematic measurements can be viewed in Table 15.

Table 15: Definitions of temporal swallow kinematic events.

Swallow kinematic event	Definition
Bolus crosses mandible	The first frame in which the organized bolus head first reaches or crosses the plane of the ramus of the mandible and is associated with oral propulsion.
Onset of hyoid movement	The first movement of hyoid leading to maximal hyolaryngeal excursion.
Maximal hyoid displacement	The first frame in which the hyoid is at its maximally displaced position (superior and anterior) during the pharyngeal phase.
Offset of hyoid movement	The first frame in which the hyoid is clear and in a stable position for at least two frames after descent at the end of the swallow (the bolus will typically have passed through the UES).
Laryngeal vestibular closure	The first frame in which no air or barium contrast is seen in the collapsed laryngeal vestibule.
Laryngeal vestibular re-opening	The first frame in which the laryngeal vestibule reopens.
UES opening	The first frame in which separation of the posterior and anterior walls of the UES has begun.
UES closure	The first frame in which no column of air or barium contrast is seen separating the posterior and anterior walls of the UES.
Swallow reaction time	The time between the bolus crossing the mandible and hyoid onset.
Hyoid onset to UES opening	The time between hyoid onset and UES opening
Duration of UES opening	The time between UES opening and UES closure.
LVC reaction time	The time between hyoid onset and LVC.
LVC duration	The time between LVC and LV re-opening.

Spatial swallow kinematic measurements included distance of hyoid bone displacement and width of anterior-posterior UES distension. The methods used for hyoid frame-by-frame tracking are described in our previous publications (Donohue, Mao, et al., 2020; Mao et al., 2019; Zhang et al., 2020). The methods used for anterior-posterior UES distension were the same as our previous work with the exception of rating 3 frames per swallow instead of 5 frames (Shu, 2019; Shu et al., 2021). This was done to increase the efficiency of data analysis since a paired t-test revealed non-significant differences (p-value=0.363) between 3 and 5 frame measurements of anterior-posterior UES distention. Spatial swallow kinematic measurements were scaled to anatomical scalars (length of C3, length of C2-C4) to control for participant size (Brates et al., 2019; Molfenter & Steele, 2014). Three trained raters completed temporal swallow kinematic measurements with ongoing intra-rater reliability within a 3-frame tolerance (0.1 second) and ICCs of 1.00 for each event by randomly selecting one swallow to re-code every ten swallows. Another trained rater completed inter-rater reliability for temporal swallow kinematic measurements by randomly selecting and re-coding 10% of swallows with ICCs of 1.00. Two trained raters completed spatial swallow kinematic measurements with ongoing intra-rater reliability to minimize and control for judgment drift. Intra-rater reliability for hyoid frame-by-frame tracking was maintained by randomly re-coding 10 swallows out of every 100 swallows with average ICCs of 0.976. Intra-rater reliability for anterior-posterior UES distention was maintained by randomly re-coding 10 swallows out of every 100 swallows with ICCs of at least 0.9. Inter-rater reliability for hyoid frame-by-frame tracking was maintained by randomly re-coding 10 swallows out of every 100 swallows with average ICCs of 0.951. Inter-rater reliability for anterior-posterior UES distention was completed by another trained rater on 10% of swallows that were randomly selected with ICCs of at least 0.9. Two trained raters completed PAS ratings. Intra-rater reliability of at least 80% exact agreement was maintained by randomly recoding 10% of swallows. Another trained rater re-coded 10% of swallows with inter-rater reliability of at least 80% exact agreement.

6.2.3 HRCA signals pre-processing:

Signals from the microphone and the tri-axial accelerometer were down-sampled from an original sampling rate of 20 kHz to 4 kHz to smooth the transient (high frequency) noise components. The baseline output from HRCA sensors was recorded prior to data collection in order to model the device noise and filter it out from HRCA signals during the data collection. To perform the filtration process, the device noise of each sensor and axis of acceleration was modeled using an autoregressive process which was then used to build sensor-specific finite impulse response (FIR) filters that remove such noise from signals. Afterwards, motion artifacts and low-frequency noise was eliminated from all three axes of acceleration using fourth order least-squares spline approximation. Finally, wavelet denoising was performed to enhance the signal quality and reduce the effect of other noise sources. Prior to analyzing the data using the LVC machine learning algorithm with HRCA signals as input, the channel signals were normalized (Goodfellow et al., 2016). Table 16 summarizes and describes the nine HRCA signal features that were extracted from the contact microphone and the three directions of the tri-axial accelerometer (anterior-posterior, superior-inferior, medial-lateral) and were used to develop the machine learning algorithms. These HRCA signal features have effectively been used to differentiate between different types of swallows and for extraction of temporal kinematic swallow events (Donohue, Khalifa, et al., 2020a, 2020b; Dudik, Jestrovic, et al., 2015; Yu et al., 2019).

Table 16: Features extracted from the HRCA signals.

Domain	Signal Feature	Meaning of the HRCA signal feature
Time	Standard deviation	Reflects the signal variance around its mean value.
	Skewness	Describes the asymmetry of amplitude distribution around mean.
	Kurtosis	Describes the “peakness” of the distribution relative to normal distribution.
Information-Theoretic	Lempel-Ziv Complexity	Describes the randomness of the signal.
	Entropy rate	Evaluates the degree of regularity of the signal distribution.
Frequency	Peak Frequency (Hz)	Describes the frequency of maximum power.
	Spectral Centroid (Hz)	Evaluates the median of the spectrum of the signal.
	Bandwidth (Hz)	Describes the range of frequencies of the signal.
Time-Frequency	Wavelet Entropy	Evaluates disorderly behavior for non-stationary signal.

6.2.4 Data analyses:

To compare the temporal and spatial swallow kinematic measurements from the ND patient data set and the age-matched healthy adults, we fit linear mixed models. To examine differences in hyoid bone displacement based on PAS score for the ND swallows, we fit a linear mixed model. We also fit linear mixed models to examine differences in HRCA signal features associated with maximum anterior-posterior UES distention for swallows from patients with ND and age-matched healthy adults when using features from the entire swallow segment and when using features from the UES opening duration swallow segment.

Three different machine learning algorithms using the HRCA signals as input were developed to annotate the following events: UES opening onset, UES closure onset, LVC onset, LV re-opening onset, and hyoid frame-by-frame tracking. We built a convolutional recurrent neural network (CRNN) to determine UES opening and closure. The CRNN had two convolutional layers, two max pooling layers, three recurrent neural network layers, 4 fully connected layers, and used the accelerometer signals as input. This CRNN is described in detail in prior publications (Donohue, Khalifa, et al., 2020b; Khalifa et al., 2021). To train the CRNN, 10-fold cross validation was used on our lab's entire HRCA patient data set omitting the swallows from the patients with ND (N=1505 swallows). After training the CRNN, we tested its performance on the swallows from patients with ND and calculated the accuracy, sensitivity, and specificity of the CRNN for UES opening and closure compared to human measurements (see Figure 10).

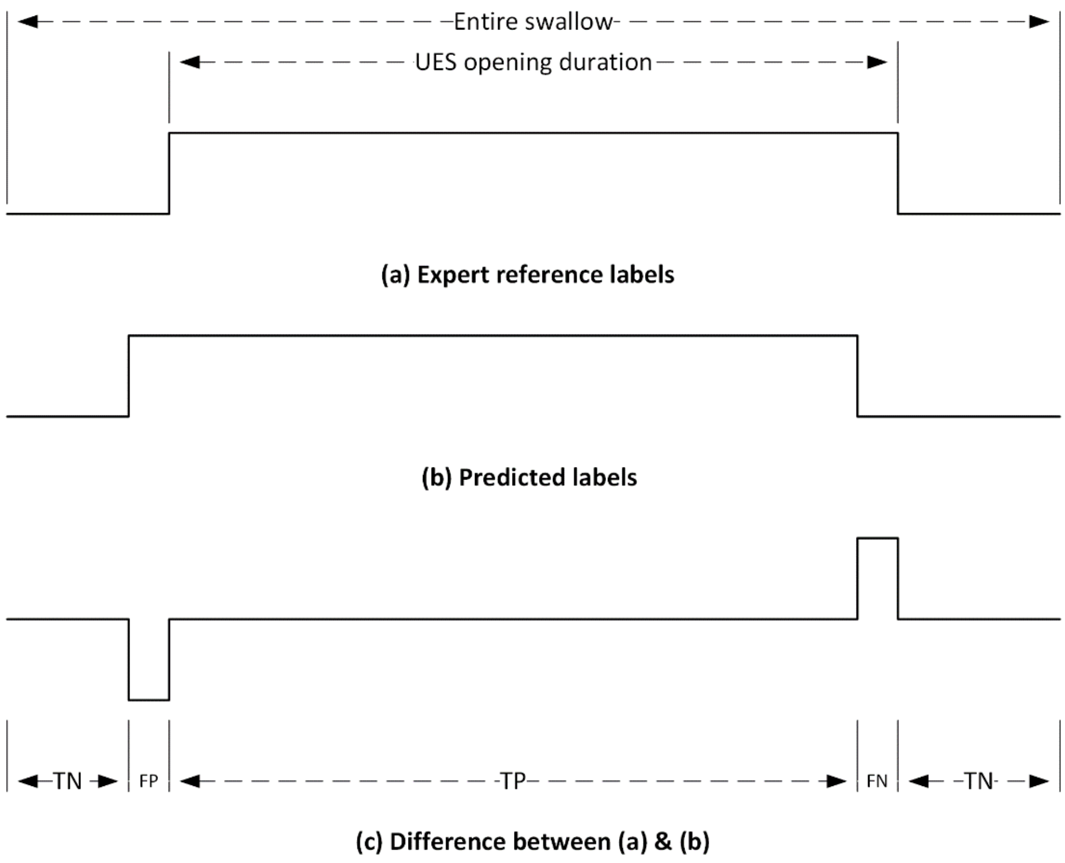

Figure 10: The evaluation procedure for comparing the accuracy of (a) human measurements of UES opening and closure and (b) the CRNN measurements of UES

opening and closure by (c) calculating the difference between human measurements and the CRNN measurements.

We also built a CRNN to determine LVC and LV re-opening. This CRNN was similar to the network described for UES opening and closure with the exceptions that it had two recurrent neural network layers, and 3 fully connected layers for decision making, and is also described in detail in a prior publication (Mao et al., 2021). The CRNN was trained using 10-fold cross validation on our lab's entire patient data set omitting the swallows from the patients with ND (N=885 swallows). After training the CRNN, we tested its performance on the swallows from patients with ND and calculated the accuracy, sensitivity, and specificity of the CRNN for LVC and LV re-opening compared to human measurements (see Figure 11).

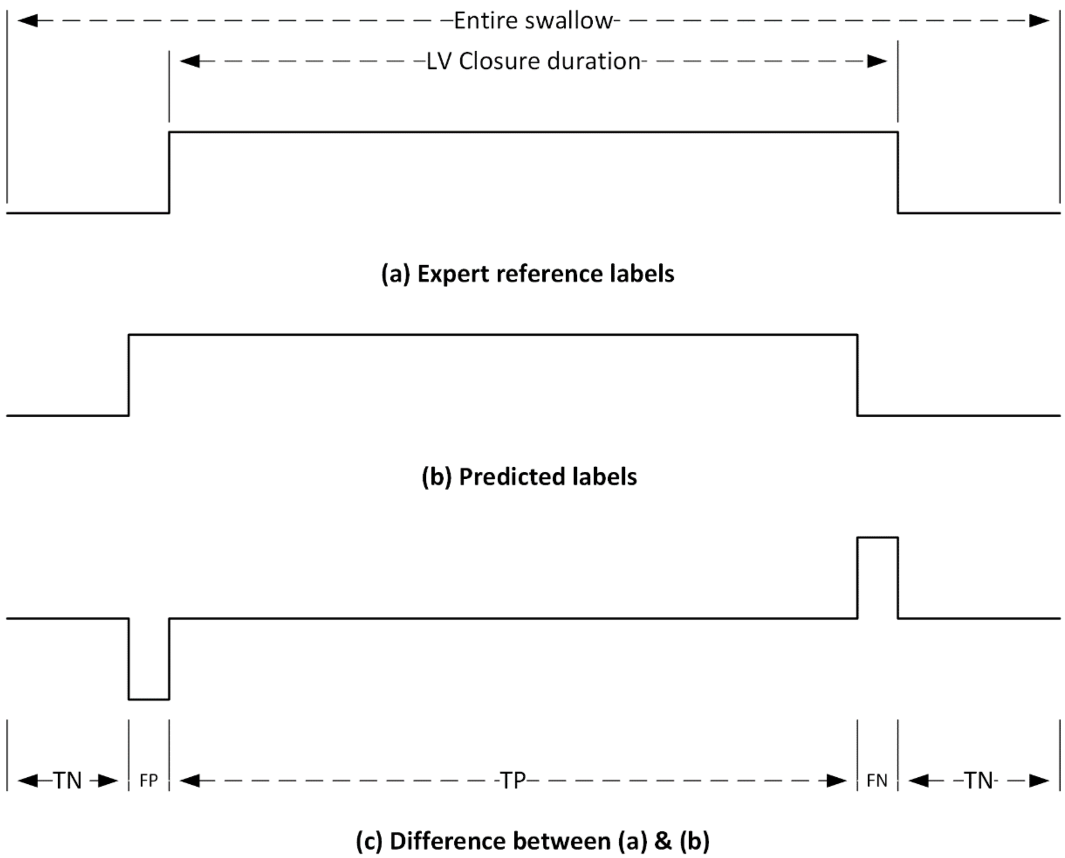

Figure 11: The evaluation procedure for comparing the accuracy of (a) human measurements of LVC and LV re-opening and (b) the CRNN measurements of LVC and LV re-opening by (c) calculating the difference between human measurements and the CRNN measurements.

We built a stacked multi-layer recurrent neural network (SRNN) with tenfold cross validation to predict the location of the body of the hyoid bone on each frame using HRCA signals as input and a bounding box that was 35x35 pixels. The methods that were used for HRCA feature extraction and for generating the bounding box have been described in previous publications (See Figure 12) (He et al., 2019; Mao et al., 2019; Rebrion et al., 2019). The SRNN was trained using 10-fold cross validation on our lab's entire patient data set of hyoid displacement, omitting the swallows from the patients with ND (N=400 swallows). After training the SRNN, we tested its performance on a subset of the swallows from patients with ND (N=88 swallows) and calculated the relative overlapped percentage (ROP) of the bounding boxes for the predicted hyoid bone location based on the CRNN and the ground truth measurement of hyoid bone location based on human judges. ND swallows were excluded from the testing data set because they were part of the original training data set (N=18 swallows) or because the HRCA signals were corrupted (N=64 swallows).

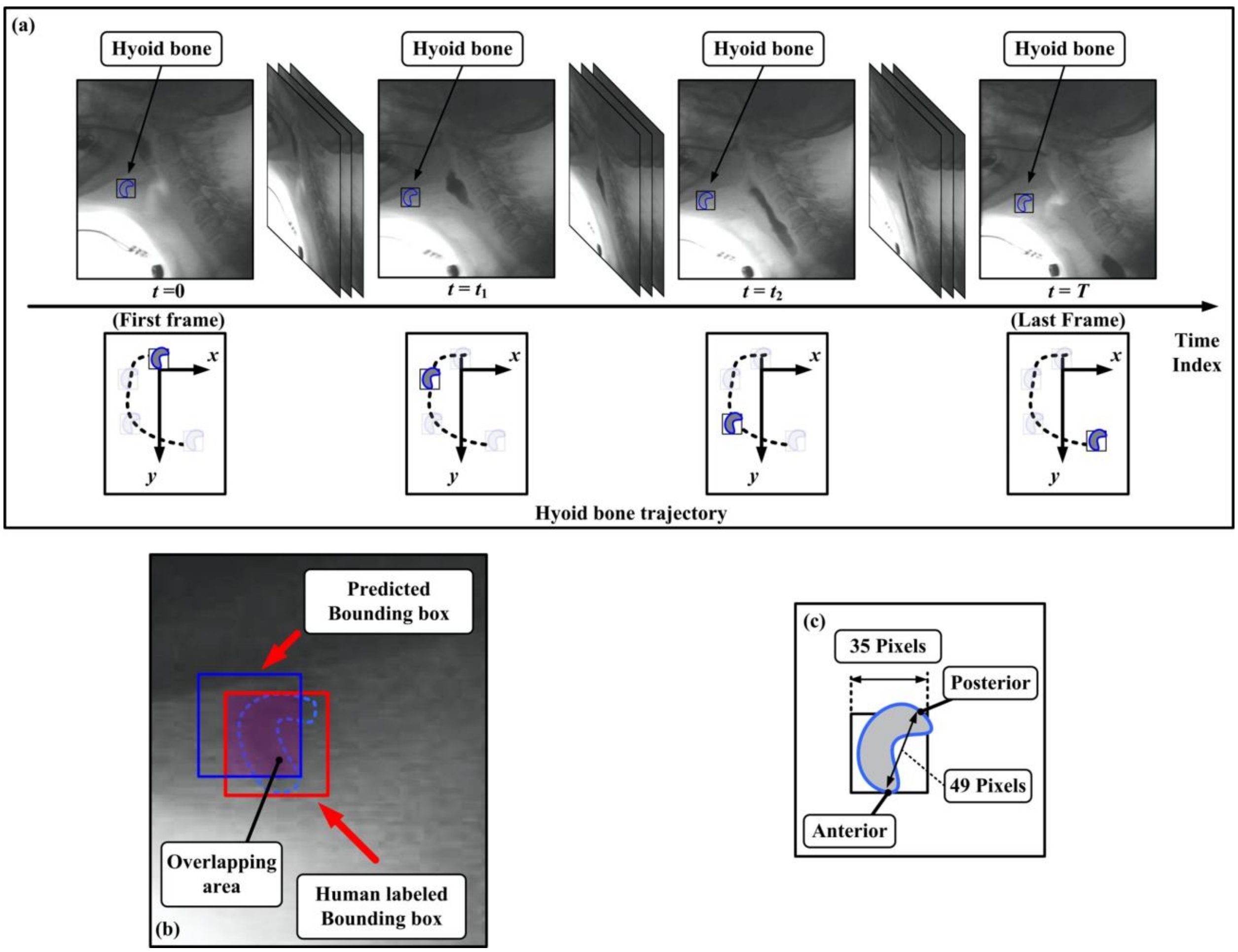

Figure 12: a. The tracking of the body of the hyoid bone on each frame during a swallow, b. the ROP of the human labeled and SRNN predicted bounding boxes, and c. the dimensions of the bounding box.

6.3 Results

6.3.1 Temporal swallow kinematic event results

Results revealed statistically significant differences ($p<0.05$) between swallows from patients with ND and swallows from healthy age-matched adults for hyoid onset to UES opening and duration of UES opening for thin by cup swallows. There were also statistically significant differences ($p<0.05$) between the swallows from patients with ND and the swallows from healthy age-matched adults for swallow reaction time, hyoid onset to UES opening, and LVC duration for thin by spoon swallows. A complete summary of the descriptive statistics for the temporal swallow kinematic measurements and the results of the linear mixed model for the ND patients and the age-matched healthy adults can be viewed in Table 17.

Table 17: Comparison of temporal swallow kinematic measures from the neurodegenerative patient data set and the age-matched healthy community dwelling adult data set after averaging multiple swallows from the same person using a linear mixed model.

	Neurodegenerative patient data set				Age matched healthy community dwelling adult data set				
Temporal measure (thin by cup)	Mean	SD	95% CI Lower bound	95% CI Upper bound	Mean	SD	95% CI Lower bound	95% CI Upper bound	p-value
Swallow reaction time	0.094	0.050	0.069	0.119	0.079	0.071	0.057	0.101	0.3642
Hyoid onset to UES opening	0.243	0.061	0.214	0.273	0.149	0.058	0.131	0.167	**<0.0001***
Duration of UES opening	0.648	0.109	0.596	0.701	0.821	0.100	0.790	0.852	**<0.0001***
LVC reaction time	0.408	0.098	0.361	0.456	0.438	0.115	0.403	0.474	0.2297
LVC Duration	0.384	0.148	0.313	0.456	0.329	0.124	0.291	0.367	0.1134
Temporal measure (thin by spoon)	Mean	SD	Lower bound	Upper bound	Mean	SD	Lower bound	Upper bound	p-value
Swallow reaction time	0.143	0.072	0.094	0.192	0.086	0.117	0.048	0.123	**0.0039***
Hyoid onset to UES opening	0.316	0.072	0.267	0.364	0.203	0.061	0.184	0.223	**<0.0001***

Duration of UES opening	0.652	0.159	0.545	0.759	0.735	0.114	0.699	0.771	0.0544
LVC reaction time	0.430	0.060	0.387	0.472	0.402	0.094	0.372	0.432	0.1454
LVC Duration	0.456	0.148	0.350	0.562	0.336	0.127	0.296	0.378	**0.0026***

Note: Temporal swallow kinematic measures are in seconds.

6.3.2 Spatial swallow kinematic event results

Statistically significant differences ($p<0.05$) were found between the patients with ND and healthy age-matched adults for superior hyoid bone displacement (normalized to C3, C2-C4) for thin by cup swallows and for anterior and superior hyoid bone displacement (normalized to C3, C2-C4) for thin by spoon swallows (See Table 18).

Table 18: Comparison of mean (±SD) overall hyoid displacements in C3 units and C2-C4 units for thin liquid swallows from the neurodegenerative patient data set and the age-matched healthy community dwelling adult data set after averaging multiple swallows from the same person using a linear mixed model.

Displacements (thin by cup)	Neurodegenerative patient data set		Age-matched healthy community dwelling adult data set		p-values	
	Anterior hyoid	Posterior hyoid	Anterior hyoid	Posterior hyoid	Anterior hyoid	Posterior hyoid
Anterior Displacement in C3 units	1.18±0.36	1.10±0.30	1.18±0.27	1.08±0.23	0.8386	0.9496
Superior Displacement in C3 units	1.58±0.49	1.40±0.43	1.40±0.31	1.21±0.29	0.1175	0.0442*
Anterior Displacement in C2-C4 units	0.46±0.19	0.42±0.16	0.42±0.10	0.39±0.08	0.3911	0.3001
Superior Displacement in C2-C4 units	0.61±0.24	0.54±0.21	0.50±0.10	0.43±0.10	0.0136*	<0.0038*
Displacements (thin by spoon)	Neurodegenerative patient data set		Age-matched healthy community dwelling adult data set			
	Anterior hyoid	Posterior hyoid	Anterior hyoid	Posterior hyoid		
Anterior Displacement in C3 units	1.01±0.20	0.88±0.21	1.18±0.27	1.11±0.28	0.0465*	0.0113*
Superior Displacement in C3 units	1.46±0.55	1.35±0.50	1.32±0.27	1.11±0.19	0.3166	0.0373*
Anterior Displacement in C2-C4 units	0.38±0.07	0.33±0.08	0.43±0.10	0.40±0.10	0.1377	0.0283*
Superior Displacement in C2-C4 units	0.54±0.20	0.50±0.18	0.48±0.09	0.40±0.07	0.1767	0.0145*

There were also statistically significant differences ($p<0.05$) in superior hyoid bone displacement (normalized to C3, C2-C4) for thin by cup swallows when comparing swallows with PAS scores of <3 vs. PAS scores of ≥3 (See Table 19).

Table 19: Comparison of mean overall hyoid displacements in C3 units and C2-C4 units for thin liquid swallows from the neurodegenerative patient data set based on penetration-aspiration scale scores after averaging multiple swallows from the same person using a linear mixed model.

Displacements (thin by cup)	Neurodegenerative patient data set		
	PAS 1-2	PAS 3-8	p-value
Anterior Displacement in C3 units of the anterior hyoid	1.12±0.20	1.31±0.62	0.2227
Anterior Displacement in C3 units of the posterior hyoid	1.05±0.23	1.15±0.45	0.6672
Superior Displacement in C3 units of the anterior hyoid	1.54±0.43	1.66±0.74	0.0045*
Superior Displacement in C3 units of the posterior hyoid	1.38±0.40	1.44±0.63	0.0091*
Anterior Displacement in C2-C4 units of the anterior hyoid	0.42±0.08	0.52±0.35	0.0523
Anterior Displacement in C2-C4 units of the posterior hyoid	0.40±0.09	0.45±0.26	0.9823
Superior Displacement in C2-C4 units of the anterior hyoid	0.58±0.16	0.66±0.41	0.0009*
Superior Displacement in C2-C4 units of the posterior hyoid	0.52±0.15	0.57±0.35	0.0038*
Displacements (thin by spoon)	Neurodegenerative patient data set		
	PAS 1-2	PAS 3-8	p-value
Anterior Displacement in C3 units of the anterior hyoid	0.98±0.31	1.09±0.29	0.7749
Anterior Displacement in C3 units of the posterior hyoid	0.85±0.32	1.04±0.32	0.5634

Superior Displacement in C3 units of the anterior hyoid	1.52±0.62	1.49±0.49	0.5740
Superior Displacement in C3 units of the posterior hyoid	1.41±0.58	1.36±0.40	0.5564
Anterior Displacement in C2-C4 units of the anterior hyoid	0.37±0.11	0.42±0.14	0.6428
Anterior Displacement in C2-C4 units of the posterior hyoid	0.31±0.11	0.40±0.16	0.5179
Superior Displacement in C2-C4 units of the anterior hyoid	0.56±0.22	0.55±0.16	0.5039
Superior Displacement in C2-C4 units of the posterior hyoid	0.52±0.21	0.51±0.14	0.5510

When examining differences in anterior-posterior UES distention between the two groups of swallows, there was a statistically significant difference ($p<0.05$) in anterior-posterior UES distention (normalized to C3) for thin by spoon swallows only (See Table 20).

Table 20: Comparison of anterior-posterior UES distention maximum width from the neurodegenerative patient data set and the age-matched healthy community dwelling adult data set after averaging multiple swallows from the same person using a linear mixed model.

	ND patient data set		Healthy adult data set		
Anterior-posterior UES distention (thin by cup)	Mean	SD	Mean	SD	p-value
Maximum width in pixels	47.53	13.20	41.01	10.16	0.0378*
Maximum width normalized to C3 length	0.90	0.29	0.95	0.26	0.5353
Maximum width normalized to C2-C4 length	0.34	0.11	0.34	0.09	0.9067
Anterior-posterior UES distention (thin by spoon)	Mean	SD	Mean	SD	p-value
Maximum width in pixels	35.04	6.59	34.56	7.30	0.8453
Maximum width normalized to C3 length	0.67	0.10	0.81	0.21	0.0124*

Maximum width normalized to C2-C4 length	0.26	0.05	0.29	0.07	0.0970

In addition to this, there were two statistically significant differences ($p<0.05$) in HRCA signal features for thin by cup swallows and 11 statistically significant differences ($p<0.05$) in HRCA signal features for thin by spoon swallows associated with maximum anterior-posterior UES distention (normalized to C2-C4) for differentiating swallows from patients with ND and age-matched healthy adults when using features from the entire swallow segment (See Table 21).

Table 21: Summary of the differences in HRCA signal features associated with maximum anterior-posterior UES distention (normalized to C2-C4 length) for swallows from patients with neurodegenerative diseases and age-matched healthy adults when using features from the entire swallow segment.

	Microphone	Anterior-posterior	Superior-inferior	Medial-lateral
Standard Deviation	NS	NS	NS	NS
Skewness	NS	NS	NS	NS
Kurtosis	NS	NS **(0.0258*)**	NS	NS **(0.0084)**
Lempel-Ziv	NS	**0.0195*** **(0.0061*)**	NS **(0.0045*)**	NS
Entropy Rate	NS	NS	NS	NS
Peak Frequency	NS	NS	NS	NS
Spectral Centroid	NS	NS **(0.0234*)**	NS **(0.0286*)**	NS **(0.0152*)**
Bandwidth	NS	**0.0275*** **(0.0027*)**	NS **(0.0078*)**	NS **(0.0188)**
Wavelet entropy	NS	NS **(0.0381*)**	NS	NS

Note: NS= not significant, *= $p<0.05$, thin by cup swallows (thin by spoon swallows)

There were also two statistically significant differences (p<0.05) in HRCA signal features for thin by cup swallows and 10 statistically significant differences (p<0.05) in HRCA signal features for thin by spoon swallows associated with maximum anterior-posterior UES distention (normalized to C2-C4) for differentiating swallows from patients with ND and age-matched healthy adults when using features from the UES opening duration swallow segment (See Table 22).

Table 22: Summary of the differences in HRCA signal features associated with maximum anterior-posterior UES distention (normalized to C2-C4 length) for swallows from patients with neurodegenerative diseases and age-matched healthy adults when using features from the UES opening duration swallow segment.

	Microphone	Anterior-posterior	Superior-inferior	Medial-lateral
Standard Deviation	NS	NS	NS	NS
Skewness	NS	NS	NS	NS
Kurtosis	NS	NS **(0.0487*)**	NS **(0.0047*)**	NS
Lempel-Ziv	NS	**0.0281*** **(0.0128*)**	NS **(0.0031*)**	NS
Entropy Rate	NS	0.2413 **(0.0215*)**	NS	NS **(0.0269*)**
Peak Frequency	NS	NS	NS	NS
Spectral Centroid	NS	NS	NS **(0.0285*)**	NS **(0.0401*)**
Bandwidth	NS	NS	**0.0418*** **(0.0105*)**	NS
Wavelet entropy	NS	NS	NS	NS **(0.0188*)**

Note: NS= not significant, *= p<0.05, thin by cup swallows (thin by spoon swallows)

6.3.3 Machine learning algorithm results

Across the patients with ND data set, the CRNN for UES opening and closure performed with 88.78% accuracy, 91.28% sensitivity, and 86.83% specificity. When comparing the CRNN's accuracy to human measurements, the CRNN annotated UES opening within a 3-frame tolerance (0.1 second) for 66.25% of swallows and UES closure for 85.0% of swallows (See Figures 13 and 14).

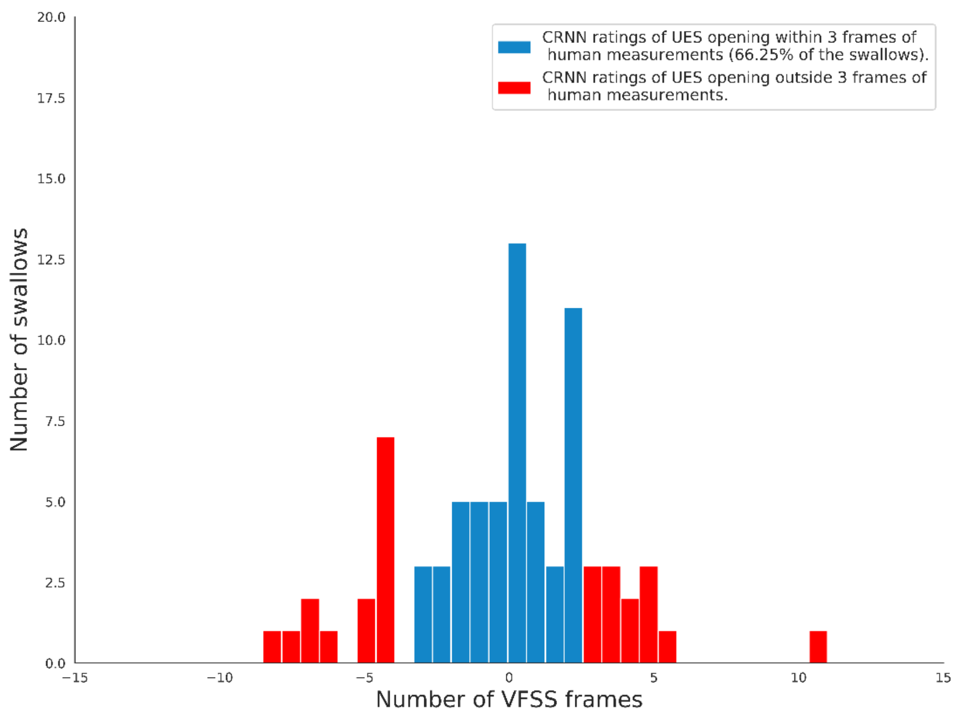

Figure 13: Accuracy of the CRNN for detecting UES opening within a 3-frame (0.1 second tolerance) compared to human measurements of UES opening for the neurodegenerative patient data set.

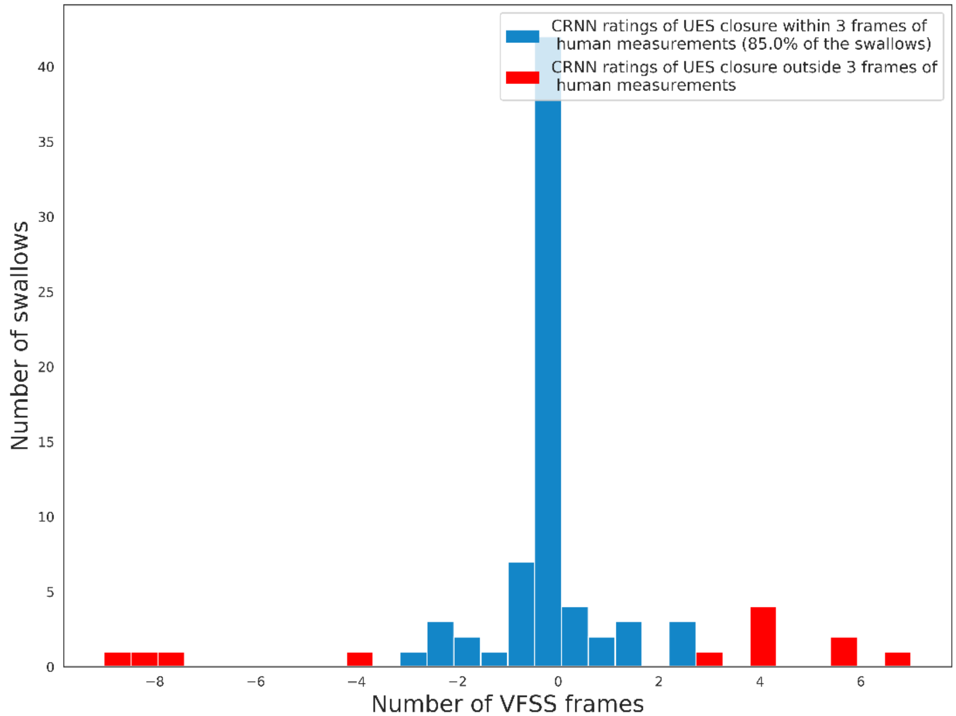

Figure 14: Accuracy of the CRNN for detecting UES closure within a 3-frame (0.1 second tolerance) compared to human measurements of UES closure for the neurodegenerative patient data set.

Across the patients with ND data set, the CRNN for LVC and LV re-opening performed with 81.03% accuracy, 81.39% sensitivity, and 85.43% specificity. When comparing the CRNN's accuracy to human measurements, the CRNN annotated LVC within a 3-frame tolerance (0.1 second) for 68.18% of swallows and LV re-opening for 70.45% of swallows (See Figures 15 and 16).

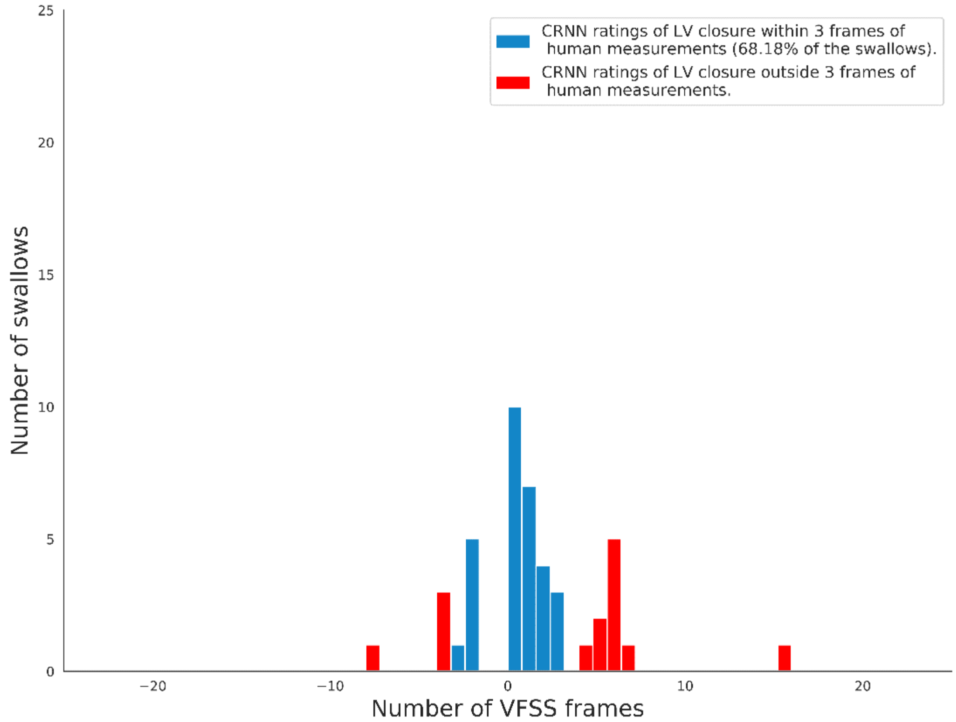

Figure 15: Accuracy of the CRNN for detecting LVC within a 3-frame (0.1 second tolerance) compared to human measurements of LVC for the neurodegenerative patient data set.

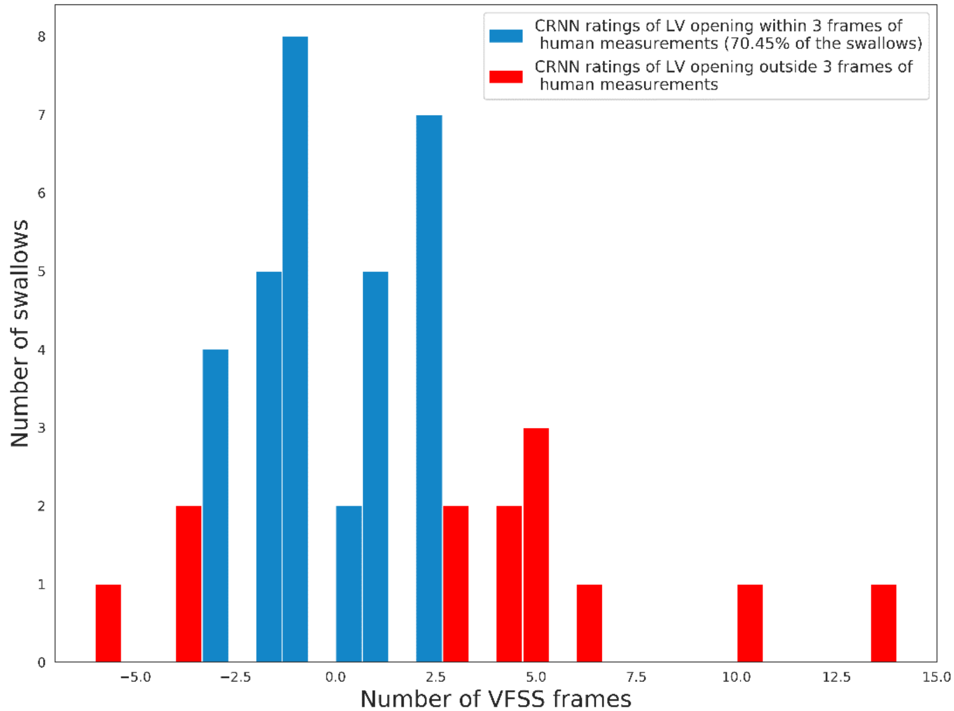

Figure 16: Accuracy of the CRNN for detecting LV re-opening within a 3-frame (0.1 second tolerance) compared to human measurements of LV re-opening for the neurodegenerative patient data set.

When examining the accuracy of the SRNN for hyoid frame-by-frame tracking for the patients with ND data set, the average ROP was 44.6% (±18.5%) when comparing the performance of the SRNN to human ratings (See Figure 17).

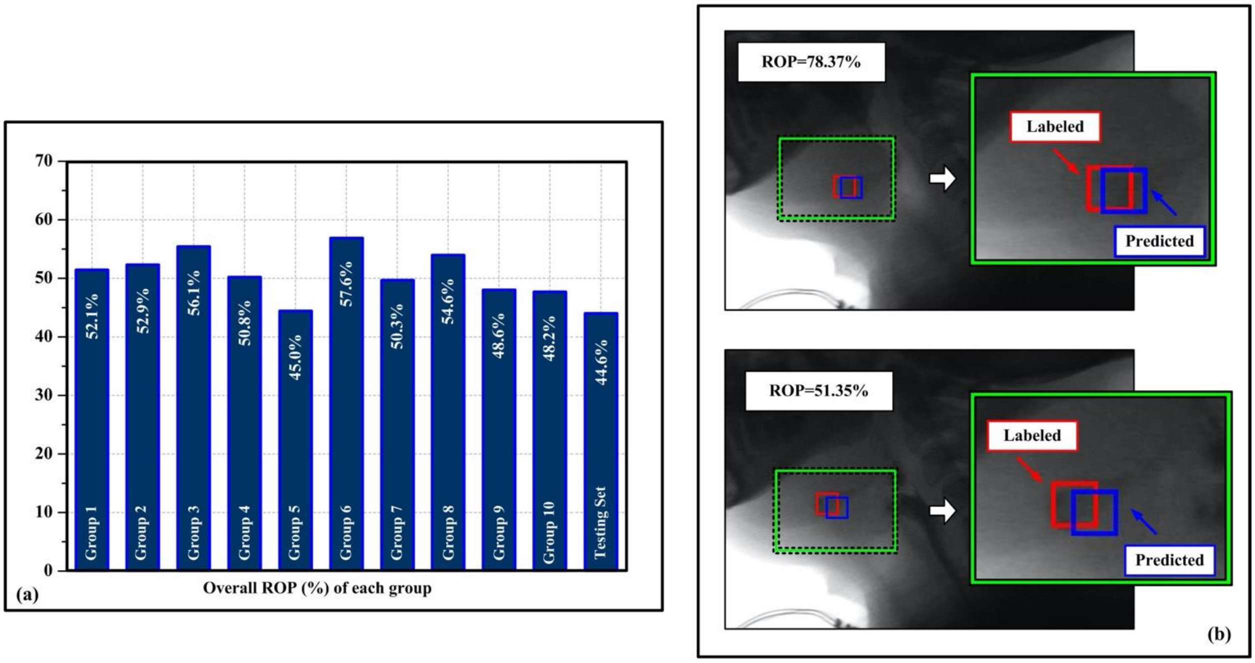

Figure 17: a. ROP of the human labeled and SRNN predicted bounding boxes across the ten groups of training data and the testing data set (the ND swallows) b. two examples of the ROP of the human labeled and SRNN predicted bounding boxes.

6.4 Discussion

This study expanded upon previous preliminary findings that HRCA can accurately differentiate between swallows from the categories “patients with ND” and “age-matched healthy adults” (Donohue, Khalifa, et al., 2020a) by illuminating differences in temporal and spatial kinematic swallow measurements between these two groups, revealing differences in HRCA signal features associated with anterior-posterior UES distention between these two groups, and demonstrating HRCA’s ability to accurately and more efficiently than human judgment, annotate specific temporal swallow kinematic events (UES opening, UES closure, LVC, LV re-opening) and spatial kinematic events (hyoid frame-by-frame tracking) in swallows from patients with ND.

While we hypothesized that there would be differences in temporal and spatial swallow kinematic measurements between the swallows from patients with ND and healthy age-matched adults, there were several unexpected findings. For example, patients with ND had greater superior hyoid bone displacement than the age-matched healthy adults for thin by cup and thin by spoon swallows. Interestingly, when comparing the ND swallows with PAS scores of <3 to the ND swallows with PAS scores ≥3, the swallows with PAS scores ≥3 also had greater superior hyoid bone displacement than the swallows with PAS scores <3 for thin by cup swallows, indicating a potential compensatory adaptation in the patients with ND.

It's important to highlight the accuracy and efficiency of the machine learning algorithms that were implemented in this study. When comparing the efficiency of the CRNN for UES opening and closure to human judges, the CRNN can analyze 150 swallows in approximately 42 seconds. This would take a human judge approximately 2 minutes to code UES opening and closure per swallow for 150 swallows for a total of 5 hours. While a clinician may not make this many measurements of UES opening and closure at once, an average VFSS may contain 20 swallows and would take 40 minutes for a clinician to code in order to fully evaluate UES opening. Availability of rapid measurement of such discrete data from a VFSS examination may provide clinicians with more objective summaries of overall function as opposed to many traditional metrics such as widest or narrowest opening over the course of an examination. These findings contribute substantively to the limited body of research characterizing swallow function in patients with ND by providing objective, quantitative temporal and spatial measurements of swallowing compared to normative reference values from age-matched healthy adults (Waito et al., 2017, 2020). Likewise, despite the limited number of swallows from patients with ND (N=170), the machine learning algorithms achieved remarkably high accuracy for annotating temporal kinematic events within a 3-frame (0.1 second) human error tolerance level (66-85% of swallows) which has been cited as acceptable (Lof & Robbins, 1990; Molfenter & Steele, 2013; Robbins et al., 1992). Likewise, the ROP of the machine learning algorithm and human ratings for tracking hyoid bone displacement was similar to previous studies (~50%, range of 45-57.6%) despite the small number of swallows available for analysis (N=88) (Donohue, Mao, et al., 2020; Mao et al., 2019). This is especially impressive given how small of a structure the hyoid bone is (Loth et al., 2015; Ramagalla et al., 2014) and when considering that the ROP between human raters for hyoid frame-by-frame tracking is only ~79% (Donohue, Mao, et al., 2020; Mao et al., 2019). The marginally reduced accuracy of the SRNN for hyoid tracking for the ND data set may have resulted from the ND swallows having characteristics that were not sufficiently represented in the swallows that were used during the training data set. The accuracy of the algorithms with a relatively small data set may underscore the ubiquity of kinematic swallowing impairments occurring in people with various NDs. The ability to monitor swallow function in patients with ND using a noninvasive, portable device that provides continuous, discrete information about swallowing physiology would be a useful and cutting-edge dysphagia early-identification and monitoring system for dysphagia management of patients with ND and other patient populations.

The value of early identification of swallowing impairments in patients with ND cannot be underscored. HRCA's ability to classify between swallows from patients with ND and swallows from healthy adults provides preliminary evidence regarding its potential in determining dysphagia screening cutoffs to assist in identifying patients that would benefit from instrumental swallow evaluations and/or implementation of therapeutic interventions that may prolong function and quality of life (Plowman et al., 2019; Plowman, Watts, Tabor-Gray, et al., 2016; Robison et al., 2018; Tabor-Gray, Gaziano, et al., 2016; Tabor-Gray, Rosado, et al., 2016; Troche et al., 2010). While the results from this preliminary study are promising, future studies should expand upon this work by investigating HRCA's ability to differentiate and characterize swallows in specific diagnostic categories of ND (e.g. ALS, PD, etc.), to differentiate between various patient populations (e.g. ND vs. patients post-stroke vs. patients post lung transplant), and to characterize swallows across bolus conditions (e.g. viscosity, volume, etc.). In addition to this, it would be advantageous to track changes in temporal and spatial swallow kinematic measurements in patients with ND longitudinally to determine changes associated with disease progression and severity, and to determine whether HRCA can detect subtle changes in swallow function that occur over time. For example, similar to pulmonary function tests, which are frequently used to determine disease progression over time in patients with ND, HRCA may have potential in measuring disease progression and severity related to dysphagia in patients with ND over time. Likewise, future studies should determine HRCA's utility in dysphagia treatment in addition to its capability as a dysphagia screening and diagnostic adjunct to VFSSs. For example, it would be beneficial to determine HRCA's ability to monitor swallow function in patients with ND over the course of a meal to denote decompensation leading to necessary changes in meal duration and frequency, or to provide real-time biofeedback during dysphagia treatment sessions while patients performed compensatory maneuvers (e.g. effortful swallow, Mendelsohn maneuver). Although the machine learning algorithms performed with exceptional accuracy, it will be important to replicate this research study by including a larger number of swallows with variable bolus conditions and patient characteristics to further improve the robustness of the CRNNs and SRNN.

6.5 Limitations

While we attempted to control for confounding variables in this study (e.g. only using thin liquid by cup and 3mL spoon swallows for analyses), we would like to acknowledge that we used different methods of data collection for the swallows from the patients with ND and the swallows from the age-matched healthy adults. The patients with ND underwent VFSSs as a part of their clinical care, while the age-matched healthy adults underwent standardized VFSSs to minimize radiation exposure. In addition to this, only thin liquid swallows were used for analyses in this study because the standardized VFSS protocol for the age-matched healthy adults only included thin liquid boluses. Future studies should compare temporal and spatial swallow kinematic measurements in patients with ND vs. age-matched healthy adults across a variety of bolus conditions (e.g. viscosity, volume, etc.) and should explore the ability of the machine learning algorithms to characterize temporal and spatial swallow kinematic events across bolus conditions. We also investigated a broad, heterogenous class of patients with ND due to the limited number of patients with specific NDs within our swallowing database to ensure that we included enough swallows for analyses (N=170). That said, our aim was to determine whether classification between a broad category of "people with ND that commonly cause dysphagia" and healthy swallows, was feasible with HRCA. Future studies should further characterize swallow function and the accuracy of these machine learning algorithms in ND based on individual disease diagnosis (e.g. ALS, PD, etc.). Likewise, it will be important to replicate this work using a larger number of swallows from patients that are at different stages of disease progression and with varying degrees of dysphagia severity.

6.6 Conclusion

This study found several differences in temporal and spatial swallow kinematic measurements between patients with ND and age-matched healthy adults, highlighting important changes that occur throughout the progressive courses of these conditions. Additionally, this study found differences in HRCA signal features associated with anterior-posterior UES distention between groups and that using HRCA signals as input to several machine learning algorithms could accurately annotate UES opening and closure (88.78% accuracy, 91.28% sensitivity, and 86.83% specificity), LVC and LV re-opening (81.03% accuracy, 81.39% sensitivity, and 85.43% specificity), and hyoid bone displacement (ROP=44.6%) in swallows from patients with ND. This provides further evidence regarding HRCA's utility in characterizing swallow function in specific patient populations for dysphagia screening and assessment purposes. These preliminary results suggest that HRCA has considerable future potential as an ongoing dysphagia monitoring system that can provide noninvasive, real-time feedback regarding swallow function to mitigate adverse events in patients with dysphagia.

7.0 General Discussion

Patients with ND frequently present with co-occurring impairments in pulmonary, cough, and swallow function due to the shared anatomy and physiology of the aerodigestive tract, shared neural substrates, and the necessity of coordinating these seemingly simple and yet highly complex behaviors (Hegland et al., 2012; Martin-Harris, 2008; Troche, Brandimore, Godoy, et al., 2014). Impairments in pulmonary and cough function can lead to reduced quality of life, increased medical expenses (Larkindale et al., 2014; Lechtzin et al., 2001), and increased risk of respiratory-related clinical events and mortality (Andrews et al., 2018; Cvejic et al., 2011; Steele & Cichero, 2014). While it is known that most patients with ND will experience dysphagia and dystussia (Aghaz et al., 2018; Alagiakrishnan et al., 2013; Easterling & Robbins, 2008; Onesti et al., 2017; Suttrup & Warnecke, 2016), there are limited methods available for noninvasive early identification and monitoring of pulmonary and swallow function to prevent subsequent adverse events and to determine appropriate candidates for ameliorative respiratory and swallow interventions (Audag et al., 2019; Waito et al., 2017). Likewise, there is emerging but finite literature to support the implementation of exercise-based interventions (including RMST) in patients with ND (particularly PALS) (Harkawik & Coyle, 2012; Meng et al., 2020; Plowman et al., 2019; Plowman, Watts, Tabor-Gray, et al., 2016; Robison et al., 2018; Rogus-Pulia & Plowman, 2020; Tabor-Gray, Rosado, et al., 2016; Tsitkanou et al., 2019).

The research evidence to date suggests that the key to dysphagia management for patients with ND (including PALS) is early identification and early intervention with the proposal of a paradigm shift toward proactive rather than reactive care of patients with ND in order to bolster patients' physiological functional reserve (Clegg et al., 2012; Murray, 2008; Rogus-Pulia &

Plowman, 2020; Theou et al., 2011; Troche & Mishra, 2017). Aim one of this dissertation study examined the impact of exercise-based interventions on function and quality of life in PALS by 1) Investigating the impact of respiratory interventions (EMST and RST) on pulmonary, cough, and surrogates of swallow function via a prospective pre-post case series of PALS (Study 1) (Donohue & Coyle, 2020); and 2) Investigating the impact of a variety of exercise-based interventions on function and quality of life in PALS via a systematic review (Study 2). Aim two of this dissertation study explored HRCA's ability to characterize swallow function in patients with ND by 1) Determining HRCA's ability to classify swallows from patients with ND and healthy age-matched adults (Study 3) (Donohue, Khalifa, et al., 2020a); and 2) Comparing temporal and spatial swallow kinematic measures between patients with ND and healthy age-matched adults, and HRCA's ability to annotate specific temporal and spatial swallow kinematic events in patients with ND (Study 4).

In summary, the results of these studies contribute substantively to the current evidence base for dysphagia management of patients with ND. Study 1 revealed that RST and EMST are safe and well-tolerated respiratory interventions for clinicians to implement in PALS (Donohue & Coyle, 2020). Similar to prior studies examining the impact of EMST in PALS, this small case series found that the majority of PALS that underwent EMST+RST or EMST alone (N=4) demonstrated improvements, maintenance, or slower decline rates in measurements of pulmonary, cough, and surrogates of swallow function, and diaphragm thickness compared to no treatment (Donohue & Coyle, 2020; Plowman et al., 2019; Plowman, Watts, Tabor-Gray, et al., 2016; Robison et al., 2018; Tabor-Gray, Rosado, et al., 2016). Additionally, this was the first study to implement RST in PALS and demonstrate its efficacy as evidenced by PALS who underwent RST+EMST improving or maintaining healthy respiratory-swallow patterns compared to PALS who underwent EMST only and experienced a decline in healthy respiratory-swallow patterns. Study 2 found that a broad range of exercise regimens (aerobic endurance, resistance, stretching/range of motion, and RMST) with variable dosage parameters (frequency, repetitions, intensity, and duration) were safe and well-tolerated in PALS. The majority of studies found that exercise led to maintenance and/or improvements in function and quality of life in PALS with mild-moderate functional impairment. While the heterogeneity of exercise regimens impeded the ability to determine the most effective type of exercise or the optimal dosage parameters for PALS, the current evidence base indicates that engaging in moderate exercise training is beneficial rather than detrimental for PALS. Study 3 provided preliminary evidence regarding HRCA's ability to classify swallows from a specific patient population (e.g. patients with ND) for dysphagia screening purposes (Donohue, Khalifa, et al., 2020a). Using HRCA signal features as input, logistic regression and decision trees classified swallows between patients with ND and age-matched healthy adults with 99% accuracy, 100% sensitivity, and 99% specificity. Expanding upon this experiment, Study 4 discovered statistically significant differences ($p<0.05$) between the swallows from patients with ND and swallows from healthy age-matched adults for several temporal and spatial swallow kinematic measurements for thin by cup and thin by spoon swallows. In addition to this, Study 4 found that machine learning algorithms with HRCA signal features as input predicted the position of the body of the hyoid bone on each frame with a ROP of 44.6% and detected UES opening, UES closure, LVC, and LV re-opening for 66.25%, 85%, 68.18%, and 70.45% of swallows from patients with ND within a 3-frame (0.1 second) human error tolerance. This study provided additional evidence that HRCA can effectively characterize swallow function in a broad class of patients with ND and demonstrates HRCA's future potential in characterizing swallow function in other patient populations.

When combining the data and findings from these studies, they provide evidence that exercise regimens may be advantageous for patients with ND. In line with proactive dysphagia management approaches of patients with ND, implementing exercise-based interventions early may assist in bolstering the physiological functional reserve of patients to prolong life, function, and quality of life (Clegg et al., 2012; Murray, 2008; Rogus-Pulia & Plowman, 2020; Theou et al., 2011; Troche & Mishra, 2017). Study 1 illuminates the potential for prolonging pulmonary, cough, and swallow function in PALS by employing progressive resistive respiratory exercises (EMST) and/or RST (Donohue & Coyle, 2020). Likewise, studies examining RMST (EMST, IMST) in Study 2 found that EMST led to improvements in MEP (a correlate of cough function), hyoid displacement, and global swallow function and efficiency (Plowman et al., 2019; Plowman, Watts, Tabor-Gray, et al., 2016; Robison et al., 2018; Tabor-Gray, Rosado, et al., 2016), while IMST led to improvements or attenuated decline of pulmonary function, and longer survival time in one study (Cheah et al., 2009; S. Pinto et al., 2012; S. Pinto & de Carvalho, 2013; Robison et al., 2018). In addition to these findings, Studies 3 and 4 provide preliminary evidence to support the use of HRCA as a dysphagia screening method and potential adjunct to VFSSs. The ability to noninvasively detect whether a patient with ND has a functional, “healthy” swallow or an “impaired” swallow would be a useful adjunct to current dysphagia screening methods that are deployed within clinical settings at multidisciplinary ALS clinics and could allow for earlier detection of overall disease progression and functional impairments (Study 3) (Donohue, Khalifa, et al., 2020a). Likewise, Study 4 provided insight into temporal and spatial swallow kinematic changes that are present for patients with ND and HRCA’s ability to autonomously, efficiently, and accurately detect specific temporal and spatial swallow kinematic events in patients with ND. These findings may assist clinicians with early identification of patients with ND that would benefit from undergoing instrumental swallow evaluations, engaging in respiratory/dysphagia interventions, and counseling regarding goals of care. Furthermore, with additional verification and miniaturization of the HRCA system, caregivers and patients with ND may be able to use HRCA as a remote, continuous monitoring system in between clinic visits.

7.1 Theoretical and Clinical Implications

In line with the recently proposed paradigm shift for dysphagia management of patients with ND, this dissertation research supports a proactive approach for dysphagia management via implementation of exercise regimens and demonstrates HRCA's potential as an early identification method so that patients with ND can maintain respiratory and swallow function for as long as possible to maximize their quality of life and engage in decision-making regarding their goals of care (Rogus-Pulia & Plowman, 2020). Study 1 revealed that progressive, resistive EMST (in isolation and combined with RST) is safe, well-tolerated, and efficacious for prolonging pulmonary, cough, and surrogates of swallow function in PALS (Donohue & Coyle, 2020). EMST is a respiratory intervention that is easy for clinicians to deploy and has led to improvements in pulmonary, cough, and swallow function in a variety of patient populations including patients with ND (Hegland et al., 2016; Hutcheson et al., 2018; Park et al., 2016; Pitts et al., 2009; Plowman et al., 2019; Plowman, Watts, Tabor-Gray, et al., 2016; Reyes et al., 2015; Robison et al., 2018; Tabor-Gray, Rosado, et al., 2016; Troche et al., 2010). In addition to this, Study 1 provided preliminary support that RST may be an advantageous alternative and/or adjuvant intervention for maintaining safe swallow function in PALS (Donohue & Coyle, 2020). While future research is needed to replicate the findings from this preliminary work and to identify the best training regimen for RST in PALS, RST is another potential treatment for clinicians to implement in patients with ND who demonstrate maladaptive respiratory-swallow patterns. In fact, another recent study found that RST led to increased frequency of healthy respiratory-swallow patterns and improvements in swallowing safety, efficiency, and quality of life in a case study of a patient with PD (Curtis et al., 2020). These findings combined with emerging work that has demonstrated the ability of computer software to automatically detect swallow onset (91% accuracy) and lung volume at swallow onset (94% accuracy for swallows accurately detected) (Hopkins-Rossabi et al., 2020) provides support regarding the efficacy of RST and the practical capability of clinicians accurately implementing RST within clinical settings.

Similarly, Study 2 elucidated that a wide variety of exercise regimens (aerobic endurance, resistance, stretching/range of motion, and RMST) may be beneficial for prolonging function and quality of life in PALS. Of the exercise regimens studies, EMST and IMST have the greatest potential for assisting PALS in maintaining pulmonary and swallow function (Cheah et al., 2009; S. Pinto et al., 2012; S. Pinto & de Carvalho, 2013; Plowman et al., 2019; Plowman, Watts, Tabor-Gray, et al., 2016; Robison et al., 2018; Tabor-Gray, Rosado, et al., 2016). However, based on the findings from Study 2, there is promising support for clinicians to implement other load bearing and non-load bearing resistance training to maintain swallow function in patients with ND (e.g. Shaker exercise, lingual strengthening) (Burkhead et al., 2007; Malandraki et al., 2012; Robbins et al., 2005; Robison, 2015; Shaker et al., 2002). For example, a case series that implemented 8 weeks of lingual strengthening in two PALS found improved lingual endurance and maintenance of lingual strength and airway protection over a 4-month period (Robison, 2015). Similarly, another case study that implemented 8 weeks of lingual strengthening 3 times and a maintenance period 2 times in a patient with inclusion body myositis over a five year period found that posterior tongue lingual pressure and swallow function was maintained (i.e. airway protection, efficiency) (Malandraki et al., 2012). These findings provide preliminary support regarding the implementation of additional resistance exercises in patients with ND to maintain respiratory and swallow function, but replication with larger samples of patients is necessary to confirm this exciting work. Another inference based on the findings from Study 2 is that any exercise regimen may be beneficial for PALS by helping them maintain muscular strength and endurance to bolster their functional reserve and minimize their frailty (Chen et al., 2014; Clegg et al., 2012; Pandya & Patani, 2019; Theou et al., 2011). It is possible that the type of exercise that PALS undergo has less importance. PALS may maintain function and quality of life by consistently performing any type of exercise regimen, but further research is needed to draw firm conclusions. Nevertheless, maintaining and/or improving functional reserve is important for PALS given that dysphagia that co-occurs with generalized deconditioning and frailty is known to be associated with increased mortality (Bock et al., 2017; Fujishima et al., 2019; Murray, 2008).

The findings from Studies 1 and 2 provide support for Aim 1 of this study, which was to examine the impact of exercise-based interventions on function and quality of life in PALS. In alignment with Aim 2 of this study (to explore HRCA's ability to characterize swallow function in patients with ND) and expanding upon the results of Studies 1 and 2, Study 3 revealed HRCA's ability to accurately and autonomously classify swallows from patients with ND and swallows from age-matched healthy adults (Donohue, Khalifa, et al., 2020a). This preliminary evidence regarding HRCA's ability to noninvasively classify swallows between broad classes ("patients with ND" and "healthy community dwelling adults") demonstrates HRCA's future potential to differentiate swallows between specific patient populations (e.g. PALS and other NDs) and from varying dysphagia severity levels (e.g. mild, moderate, severe). These findings combined with other research studies that have established HRCA's ability to detect safe vs. unsafe swallows based on the PAS (Dudik, Coyle, et al., 2015; Dudik et al., 2016, 2018; Dudik, Jestrovi, et al., 2015; Dudik, Kurosu, et al., 2015; Jestrović et al., 2013; Sejdić et al., 2013; Yu et al., 2019), to accurately track hyoid bone movement (Donohue, Mao, et al., 2020; Mao et al., 2019; Zhang et al., 2020), and to annotate temporal kinematic events (e.g. UES opening, UES closure, LVC, LV re-opening) (Donohue, Khalifa, et al., 2020b; Khalifa et al., 2021; Mao et al., 2021; Sabry et al., 2020) indicate HRCA's promise as a noninvasive, portable, and accurate dysphagia screening method and diagnostic adjunct to VFSSs. With further refinement of the machine learning algorithms along with miniaturization of the HRCA system, HRCA would be a useful tool for clinicians to implement within clinical settings with time constraints and limited (or no) access to instrumental swallow evaluations. For example, HRCA may assist clinicians in early identification of PALS with high risk of swallowing impairment during multidisciplinary team visits by providing objective data in an efficient manner. This would be particularly advantageous given that clinicians within this setting are constrained to brief time windows to screen patients using tools that rely on over signs/symptoms rather than swallowing physiology (e.g. patient questionnaires, 3 oz water test, etc.) (Belafsky et al., 2008; Suiter & Leder, 2008). In addition to this, there is potential for HRCA to be used as a remote continuous monitoring system of swallow function in the future for patients with ND. This would allow clinicians to closely monitor patients' swallow function in between routine clinic visits to mitigate risk of adverse events related to dysphagia and would be especially convenient for patients with ND with mobility impairments, transportation issues, and/or compromised immune systems (e.g. COVID-19) (Audag et al., 2019; Waito et al., 2017).

Study 4 further contributed to these encouraging findings by illuminating differences in temporal and spatial swallow kinematic measurements between swallows from patients with ND and swallows from age-matched healthy adults, as well as highlighting HRCA's competency in annotating specific temporal and spatial swallow kinematic events in a small sample of swallows from patients with ND. Determining differences in swallowing physiology between age-matched healthy adults and patients with ND may assist clinicians in determining detrimental changes in swallow function associated with their patient's specific underlying disease process (and disease progression). Characterizing swallow function in specific patient populations is useful for differential diagnosis and for establishing dysphagia treatment based on the underlying disease mechanism. While quantitative measurements of swallowing physiology are useful for determining cutoffs for normal vs. disordered swallowing (Steele et al., 2019), few clinicians are trained, have the appropriate software, and/or the time to perform temporal and spatial swallow kinematic measurements on VFSS images on a regular basis (Vose et al., 2018). HRCA's ability to classify swallows from patients with ND (Donohue, Khalifa, et al., 2020a) and swallows from age-matched healthy adults combined with HRCA's capability in identifying specific temporal and spatial swallow kinematic events in patients with ND accurately, autonomously, and efficiently, provides preliminary evidence regarding its potential in accurately establishing cutoffs for dysphagia screening to determine whether patients with ND require further assessment and treatment.

Collectively these findings 1) promote implementation of exercise-based regimens in PALS with mild-moderate disease severity to prolong pulmonary function, swallowing, and quality of life (Cheah et al., 2009; Donohue & Coyle, 2020; Malandraki et al., 2012; Meng et al., 2020; S. Pinto et al., 2012; S. Pinto & de Carvalho, 2013; Plowman et al., 2019; Plowman, Watts, Tabor-Gray, et al., 2016; Robison, 2015; Robison et al., 2018; Tabor-Gray, Rosado, et al., 2016; Tsitkanou et al., 2019); and 2) exhibit HRCA's utility and potential as a noninvasive dysphagia screening method and diagnostic adjunct to VFSSs within clinical settings for patients with ND when instrumental swallow evaluations are not possible or desired (Donohue, Khalifa, et al., 2020a, 2020b; Donohue, Mao, et al., 2020; Khalifa et al., 2021; Kurosu et al., 2019; Mao et al., 2019, 2021; Sabry et al., 2020).

7.2 Limitations

While careful consideration was given to the study designs and data analyses of the research studies included in this dissertation, there are several key limitations to acknowledge. Patients with ND (including PALS) are challenging to conduct research on due to the progressive nature of the underlying disease processes, and because patients with ND frequently have physical mobility impairments, multifactorial health problems, and transportation issues (Audag et al., 2019; Waito et al., 2017). As such, the sample size across studies was small (Study 1, N=6; Study 2, N=27.75 [Average sample per study]); Studies 3 and 4, N=20) (Donohue, Khalifa, et al., 2020a; Donohue & Coyle, 2020), restricted the ability to perform robust statistical analyses in some cases, and limited the generalizability of study findings. For example, for Study 1, 15 PALS underwent initial study screening, but only six enrolled and completed the study (Donohue & Coyle, 2020). Likewise, the majority of studies included in the systematic review (Study 2) did not conduct a power analysis and were likely underpowered. In addition to this, the attrition rate across studies included in the systematic review was astonishingly high with some studies reporting attrition as high as 80%. While Studies 3 and 4 included a relatively small number of swallows (N=170) from

20 patients with ND, the machine learning algorithms achieved remarkable accuracy in classifying swallows and annotating specific temporal and spatial swallow kinematic events. However, the accuracy of the machine learning algorithms would likely improve with a larger sample size and with the inclusion of more variable swallows (e.g. bolus conditions, presentation of dysphagia severity, etc.)

Another limitation of this work is the heterogeneity of patients included within the study samples. For example, in Study 1, PALS varied in age (41-76 years old), months since diagnosis (5-34 months), baseline ALSFRS-R scores (33-45), and baseline EAT-10 scores (1-14), which may have impacted post-treatment outcome measures (Donohue & Coyle, 2020). Similarly, while most studies in the systematic review had strict inclusion/exclusion criteria and reported disease duration and functional measures of ALS (e.g. ALSFRS-R), PALS were not stratified to treatment arms based on disease duration or rate of progression. Furthermore, many studies did not report individual patient factors that may have impacted treatment outcomes such as body mass index, whether patients had sporadic vs. familial ALS, psychosocial factors, cognitive function, premorbid health, socioeconomic status, and whether or not they were on medications. Studies 3 and 4 included a broad, heterogenous class of patients with ND due to the limited number of patients with ND within our swallowing database to ascertain that we had enough swallows for analyses (N=170). Diagnoses included PD, myasthenia gravis, motoneuron disease, MS, MD, ALS, myotonic dystrophy, and progressive muscle weakness not otherwise specified. Due to the diverse range of underlying diseases included in Studies 3 and 4, it limits the generalizability of study findings to an individual ND diagnosis (e.g. ALS, PD, etc.).

In addition to the heterogeneity of patients included in these studies, the assessment and treatment methods implemented across studies were variable in some regards. Currently, there is no established “standard of care” exercise regimen for PALS. Because of this, a 5-week training period with an optional maintenance period using EMST devices set to 50% resistance, and an RST training paradigm reflective of clinical practice was used in Study 1. Some studies have used an 8-week training period or longer for EMST, and device load has ranged from 30-50% of a patient’s MEP (Plowman et al., 2019; Robison et al., 2018; Tabor-Gray, Rosado, et al., 2016). However, the optimal training dosage to maximize benefits and minimize risks remains unknown for PALS. Likewise, this was the first study to implement RST in PALS, and therefore the optimal training paradigm for RST for PALS is not yet defined. In alignment with this heterogeneity, findings from the systematic review (Study 2) revealed that the types of exercise and the dosage of the exercise regimens (e.g. frequency, repetitions, intensity, and duration) varied greatly across studies. The outcome measures used to measure treatment efficacy across studies also varied substantially, precluding the ability to perform a meta-analysis or draw firm conclusions about the benefits of specific exercise regimens in PALS. While efforts were made to limit variability and potential confounding variables for Studies 3 and 4 (e.g. only using thin liquid by cup and spoon swallows for analyses), it’s important to note that data collection methods varied between patients with ND and the healthy age-matched adults (Donohue, Khalifa, et al., 2020a). The patients with ND underwent VFSSs as a part of clinical care rather than for research purposes alone. As such, the number of boluses, the bolus viscosity and volume, and the utensil used for bolus presentation varied based on the clinical presentation of dysphagia that the clinician observed during the examination. In contrast, the age-matched healthy adults underwent a standardized VFSS procedure consisting of only thin liquid command swallows by spoon and self-selected cup sips to minimize radiation exposure. While we acknowledge these methodological differences may have limited study findings, the robustness and accuracy of machine learning algorithms improve with greater chaos. Thus, the heterogeneity of Studies 3 and 4 may have been a strength rather than a limitation for performing machine learning on this data set.

7.3 Future Directions

The results of these four studies validate the paradigm shift from reactive to proactive dysphagia management in patients with ND by demonstrating 1) that a variety of exercise regimens are safe, well-tolerated, and potentially beneficial in prolonging function and quality of life in PALS with mild-moderate disease severity and; 2) that HRCA has potential as a non-invasive, early-detection and dysphagia monitoring system for patients with ND (Rogus-Pulia & Plowman, 2020). The findings from these research studies inspire a sense of curiosity for future research work to be conducted in this area. While RST and EMST+RST were safe, well-tolerated, and efficacious interventions in a small case series of PALS (Study 1) (Donohue & Coyle, 2020), future research studies should examine the impact of RST and EMST+RST on pulmonary, cough, and swallow function in a larger cohort of PALS (with randomization and blinding if possible). For treatment trials examining RST and EMST+RST, it may be beneficial to conduct treatment trials at multiple ALS clinic sites to ensure that a large enough sample size is obtained and to allow for stratification of patients based on disease duration and/or rate of disease progression to minimize bias and balance treatment groups. Further research is needed to identify the most favorable exercise regimen and dosage parameters for PALS with mild-moderate functional impairment. Although most studies have found that exercise is safe, well-tolerated, and potentially advantageous for maintaining function and quality of life in PALS with mild-moderate disease severity (Study 2), additional high-quality research studies (large, multi-site, randomized controlled trials) are needed to illuminate the most beneficial type of exercise and training prescription for PALS. Likewise, replication of exercise studies in PALS would be particularly useful to confirm that prior results are valid/reliable, to assess generalizability of exercise regimens across study samples and clinical settings, and to combine study results via a meta-analysis to determine the strength of study findings.

Another potential area of intervention research in patients with ND (including PALS) is the exploration of remote monitoring tools for tracking patient adherence and safety, tolerability, and efficacy of interventions via telehealth modalities (Antonini et al., 2018; Haulman et al., 2020; Helleman, Kruitwagen, et al., 2020; Helleman, Van Eenennaam, et al., 2020; Pulley et al., 2019; Williams et al., 2019). Telehealth may improve the efficiency of services provided and decrease caregiver burden for patients with ND. Synchronous and asynchronous telehealth visits have been used as a platform for things such as multidisciplinary ALS clinic visits and remote monitoring of disease progression (Antonini et al., 2018; Haulman et al., 2020; Helleman, Kruitwagen, et al., 2020; Helleman, Van Eenennaam, et al., 2020; Pulley et al., 2019; Williams et al., 2019), but no studies to date have implemented pulmonary/swallowing interventions (e.g. EMST) via telehealth in patients with ND despite the potential of their feasibility and efficacy (Cox et al., 2018; Hansen et al., 2017; Selzler et al., 2018). While there are some barriers to providing telehealth services (e.g. technology, medical licensure, billing) (Helleman, Kruitwagen, et al., 2020), studies have found that visits lead to positive responses and health outcomes for PALS and caregivers (Helleman, Kruitwagen, et al., 2020; Helleman, Van Eenennaam, et al., 2020). In fact, multiple dysphagia researchers have suggested the implementation of telehealth for dysphagia management in recent years to improve patient access to services and to implement proactive care to mitigate adverse events (e.g. aspiration pneumonia) to prevent patient hospitalizations and subsequent health care costs (Ciucci et al., 2016; Coyle, 2012; Malandraki & Kantarcigil, 2017).

Telehealth and remote monitoring are other promising applications of HRCA in the future when the machine learning algorithms we have developed are finalized and the HRCA system is miniaturized. The ability to remotely and noninvasively monitor disease progression, changes in swallow function, and/or fatigue over the course of a meal using HRCA would be a novel and useful tool for clinicians and caregivers of patients with ND (Baylow & Goldfarb, 2014; Hiramatsu et al., 2015; Kays et al., 2011). While Studies 3 and 4 highlighted HRCA's ability to broadly classify and characterize swallows between a group of patients with ND and age-matched healthy adults (Donohue, Khalifa, et al., 2020a), future research studies should examine HRCA's ability to classify and characterize swallows between different patient populations with dysphagia (e.g. ALS, PD, patients post-stroke) and dysphagia severity levels (e.g. mild, moderate, severe). Furthermore, future research work should examine HRCA's ability to detect changes in swallow function (e.g. temporal and spatial swallow kinematic measurements) due to disease progression or post-treatment to determine treatment efficacy. Although the machine learning algorithms deployed in Studies 3 and 4 achieved remarkable accuracy despite the small sample size, it will be important to replicate these preliminary studies with a larger number of swallows with a variety of bolus, swallowing, and patient conditions to improve the generalizability of findings to clinical settings. Moreover, as the accuracy of HRCA improves, HRCA may have potential as a dysphagia diagnostic and biofeedback instrument in addition to being an accurate and efficient dysphagia screening method.

8.0 Conclusion

This dissertation research work provides evidence in support of proactive dysphagia management of patients with ND via early identification of swallowing impairments and early implementation of interventions to maintain pulmonary, cough, and swallow function, and quality of life. While preliminary in nature, findings from Study 1 established that RST and RST+EMST are safe, well-tolerated, and potentially efficacious treatments for early-stage PALS with minimal-mild or mild-moderate functional impairment (Donohue & Coyle, 2020). Similarly, the results from the systematic review (Study 2) revealed that a broad of range of exercise regimens with varying dosage were safe and well-tolerated in PALS, and that the majority of exercise-based interventions led to maintenance and/or improvement of function and quality of life for PALS with mild-moderate disease severity. These results contribute to a growing body of literature that supports implementation of exercise-based interventions in patients with ND (including PALS) (Malandraki et al., 2012; Plowman et al., 2019; Plowman, Watts, Tabor-Gray, et al., 2016; Robison, 2015; Robison et al., 2018; Rogus-Pulia & Plowman, 2020; Tabor-Gray, Rosado, et al., 2016; Troche et al., 2010).

The findings from Studies 3 and 4 further contribute by characterizing swallows from patients with ND and by illuminating HRCA's potential as an accurate, efficient, and noninvasive dysphagia screening method with future potential as a diagnostic, biofeedback, and remote monitoring system for patients with ND (Donohue, Khalifa, et al., 2020a). The results of Study 3 demonstrated HRCA's promise as a highly accurate dysphagia screening tool by classifying swallows from patients with ND and age-matched healthy adults with unmatched accuracy (99%), sensitivity (100%), and specificity (99%). Study 4 revealed that there are differences in swallowing (e.g. temporal and spatial swallow kinematic measurements) between patients with ND and age-matched healthy adults and that HRCA can accurately annotate specific temporal and spatial swallow kinematic events in patients with ND (UES opening and closure [88.78% accuracy, 91.28% sensitivity, and 86.83% specificity], LVC and LV re-opening [81.03% accuracy, 81.39% sensitivity, and 85.43% specificity], and hyoid bone displacement [ROP=44.6%]), which may assist clinicians in diagnosis of disease-related swallowing impairments. However, future research is necessary to determine the sequence and timing of changes in swallowing safety and efficiency that occur throughout the progression of various ND. The preliminary evidence from these studies provides support regarding the forthcoming ability to monitor changes in swallow function and disease progression remotely in between clinic visits using HRCA, which will assist clinicians in early detection of swallowing impairments to reduce adverse outcomes (e.g. aspiration pneumonia) and to identify patients who would benefit from instrumental swallow evaluations, exercise-based interventions to prolong function and boost physiological functional reserve, and counseling to determine goals of care.

Appendix A Study 1

Table 23: Breathing Exercise Log.

This log is meant to be filled out each day that you complete the breathing exercises for this research study. Below are some scales that can be used to rate how you feel during and after completion of the breathing exercises. Please add any additional notes or comments as needed to the log.

Date	Time	Time to do exercises	Fatigue (0-10)	Pain (0-10)	Borg Scale (0-10)	Negative side effects	Positive side effects	Notes, comments

Appendix B Study 2

8.1 Letter to the Editor Regarding: “Effects of exercise in patients with amyotrophic lateral sclerosis: A systematic review and meta-analysis”

The majority of this dissertation chapter has been previously published. This is a non-final version of an article published in final form in the *American Journal of Physical Medicine and Rehabilitation.* It is reprinted with permission from the *American Journal of Physical Medicine and Rehabilitation* (Donohue, Carnaby, et al., 2020). Donohue, C., Carnaby, G., Colquhoun, R. J., Lacomis, D., & Garand, K. L. (2020). Letter to the editor regarding: “Effects of exercise in patients with amyotrophic lateral sclerosis: A systematic review and meta-analysis”. *American Journal of Physical Medicine & Rehabilitation*. https://doi.org/10.1097/PHM.0000000000001656

To the Editor:

Implementing an exercise regimen in PALS remains a controversial topic. Historically, exercise recommendations have been avoided in PALS from fear that muscles are more susceptible to fatigue, which may result in faster disease progression and adverse events. While there is growing evidence in animal and human models that moderate exercise training may be advantageous in patients with early stage ALS, the current knowledge base is limited.

Although rare, ALS is the most common motor neuron disease in adults characterized by degeneration of upper and lower motor neuron pathways that results in rapid degeneration with no cure. While several drugs are approved for managing PALS, increases in survival time are minimal. As such, there has been an enthusiastic interest in exploring the impact of exercise on function, survival time, and quality of life in PALS. Because of the lack of consensus regarding exercise in PALS, we eagerly read the article Lijiao et al. “Effects of Exercise in Patients with Amyotrophic Lateral Sclerosis: A Systematic Review and Meta-Analysis,” which analyzed aggregated results from randomized controlled trials (RCTs) to evaluate the safety and efficacy of exercise in PALS (Meng et al., 2020).

In this review, the authors included seven RCTs (N=322) out of 2161 possible studies, which compared various exercise regimens in PALS to standard of care or no exercise (Meng et al., 2020). Due to the heterogeneity of treatment durations, the authors combined studies post hoc into short- (0-3 months), medium- (6 months), and long-term (10-12 months) (Meng et al., 2020). Further, because a variety of outcome measures were used across studies, the authors used a standardized mean difference to measure the pooled effect (Meng et al., 2020). The authors concluded that exercise led to improvements in functional ability in PALS (in the long-term) (Meng et al., 2020). They found no differences in muscle strength, quality of life, fatigue, or adverse events between study groups (Meng et al., 2020).

While we acknowledge the authors efforts to illuminate the effects of exercise on function, survival, and quality of life in PALS, there are several methodological weaknesses that raise concerns regarding study findings. The authors rightfully acknowledge the multiple limitations contributing to potential biases, including small sample sizes, high attrition rates limiting follow-up data available, and heterogeneity related to exercise regimen (type, dosage, duration) and reported outcome measures. The authors examined heterogeneity between studies using a Chi-square test (P=0.10) and arbitrarily considered the I^2 statistic >50% to indicate substantial heterogeneity. While we appreciate the authors attempt to account for heterogeneity, several decisions within the design of this analysis generate concern. Firstly, despite considerable clinical and methodological heterogeneity across studies (e.g. different population characteristics, interventions, and procedures), the authors chose to utilize random or fixed effects models determined solely from statistical review. This action is contrary to published recommendations for meta-analytic analysis (Borenstein et al., 2017). In this regard, the I^2 statistics provided may not be appropriate nor informative given the small number of studies utilized in some comparisons (n=2) and the aggregation of study data that included different exercise regimens and outcome measures. Because of these limitations, it is unlikely that the reported statistical measures here (e.g. SMD, Cochran's Q, Tau and I^2) are a true reflection of the effects of exercise in PALS. Moreover, the predominant use of fixed effects models throughout the paper (irrespective of reported heterogeneity in analyses) appears contradictory. Additionally, the authors assert that endurance/aerobic exercise was the most effective type of exercise in PALS, but this was determined with only two studies in 55 PALS demonstrating small-moderate effect sizes.

Some will argue that a meta-analysis should only include RCTs, because RCTs minimize biases and the chance of confounding (Shrier et al., 2007). However, the inclusion of non-RCTs may benefit clinical decision-making when attributing causal inferences. Therefore, excluding observational studies a priori may inappropriately limit the empirical evidence included given that meta-analyses of observational studies may produce similar estimates of effect as meta-analyses of RCTs (Shrier et al., 2007). RCTs are not always feasible or appropriate to conduct in PALS, and the heterogeneity of the disease process warrants an individualized treatment approach. In addition to this, some of the RCTs included in this meta-analysis compared treatment groups to "usual care" (e.g. range of motion/stretching exercise groups), which are not true control groups. While we agree with the authors that there is preliminary evidence that exercise may be advantageous, there are many unknowns regarding optimal exercise regimens. For example, research studies have only examined exercise regimens in PALS that exhibit mild-moderate functional impairment, with the vast majority of patients enrolled in previous studies having spinal onset type.

There is a substantial need for further high-quality research studies that examine the effects of exercise in PALS to replicate and bolster the findings to date. Although preliminary evidence suggests that exercise is safe, well-tolerated, and potentially efficacious in prolonging function and life in patients with early stage ALS, critical questions remain unanswered. Future research studies should be conducted to elucidate the most appropriate patients to engage in exercise and to determine optimal exercise regimens, treatment dosage, and treatment duration for PALS. Although the publication "Effects of Exercise in Patients with Amyotrophic Lateral Sclerosis: A Systematic Review and Meta-Analysis" suggests benefit from the use of exercise in PALS, we find the conclusions over-reaching and may mislead clinicians and researchers regarding the current evidence base that exercise is safe and beneficial in PALS despite the limited research evidence to date. The potential impacts of possible false positive conclusions to both patient/caregiver emotional burden and potential physiologic decline needs to be weighed in light of stronger research data.

Bibliography

Aghaz, A., Alidad, A., Hemmati, E., Jadidi, H., & Ghelichi, L. (2018). Prevalence of dysphagia in multiple sclerosis and its related factors: Systematic review and meta-analysis. *Iranian Journal of Neurology*, *17*(4), 180–188. https://doi.org/10.18502/ijnl.v17i4.592

Alagiakrishnan, K., Bhanji, R. A., & Kurian, M. (2013). Evaluation and management of oropharyngeal dysphagia in different types of dementia: a systematic review. *Archives of Gerontology and Geriatrics*, *56*(1), 1–9. https://doi.org/10.1016/j.archger.2012.04.011

Alali, D., Ballard, K., & Bogaardt, H. (2018). The frequency of dysphagia and its impact on adults with multiple sclerosis based on patient-reported questionnaires. *Multiple Sclerosis and Related Disorders*, *25*, 227–231. https://doi.org/10.1016/j.msard.2018.08.003

Andrews, J. A., Meng, L., Kulke, S. F., Rudnicki, S. A., Wolff, A. A., Bozik, M. E., Malik, F. I., & Shefner, J. M. (2018). Association between decline in slow vital capacity and respiratory insufficiency, use of assisted ventilation, tracheostomy, or death in patients with amyotrophic lateral sclerosis. *JAMA Neurology*, *75*(1), 58–64. https://doi.org/10.1001/jamaneurol.2017.3339

Antonini, A., Gentile, G., Giglio, M., Marcante, A., Gage, H., Touray, M. M. L., Fotiadis, D. I., Gatsios, D., Konitsiotis, S., Timotijevic, L., Egan, B., Hodgkins, C., Biundo, R., Pellicano, C., & PD_Manager consortium. (2018). Acceptability to patients, carers and clinicians of an mHealth platform for the management of Parkinson's disease (PD_Manager): study protocol for a pilot randomised controlled trial. *Trials*, *19*(1), 492. https://doi.org/10.1186/s13063-018-2767-4

Armstrong, M. J., & Okun, M. S. (2020). Diagnosis and treatment of parkinson disease: A review. *The Journal of the American Medical Association*, *323*(6), 548–560. https://doi.org/10.1001/jama.2019.22360

Arthur, K. C., Calvo, A., Price, T. R., Geiger, J. T., Chiò, A., & Traynor, B. J. (2016). Projected increase in amyotrophic lateral sclerosis from 2015 to 2040. *Nature Communications*, *7*, 12408. https://doi.org/10.1038/ncomms12408

Audag, N., Goubau, C., Toussaint, M., & Reychler, G. (2019). Screening and evaluation tools of dysphagia in adults with neuromuscular diseases: a systematic review. *Therapeutic Advances in Chronic Disease*, *10*, 2040622318821622. https://doi.org/10.1177/2040622318821622

Azzolino, D., Damanti, S., Bertagnoli, L., Lucchi, T., & Cesari, M. (2019). Sarcopenia and swallowing disorders in older people. *Aging Clinical and Experimental Research*, *31*(6), 799–805. https://doi.org/10.1007/s40520-019-01128-3

Baille, G., De Jesus, A. M., Perez, T., Devos, D., Dujardin, K., Charley, C. M., Defebvre, L., & Moreau, C. (2016). Ventilatory dysfunction in parkinson's disease. *Journal of Parkinson's Disease*, *6*(3), 463–471. https://doi.org/10.3233/JPD-160804

Ball, L. J., Willis, A., Beukelman, D. R., & Pattee, G. L. (2001). A protocol for identification of early bulbar signs in amyotrophic lateral sclerosis. *Journal of the Neurological Sciences*, *191*(1–2), 43–53. https://doi.org/10.1016/s0022-510x(01)00623-2

Balou, M., Herzberg, E. G., Kamelhar, D., & Molfenter, S. M. (2019). An intensive swallowing exercise protocol for improving swallowing physiology in older adults with radiographically confirmed dysphagia. *Clinical Interventions in Aging*, *14*, 283–288. https://doi.org/10.2147/CIA.S194723

Baumann, F., Henderson, R. D., Morrison, S. C., Brown, M., Hutchinson, N., Douglas, J. A., Robinson, P. J., & McCombe, P. A. (2010). Use of respiratory function tests to predict survival in amyotrophic lateral sclerosis. *Amyotrophic Lateral Sclerosis*, *11*(1–2), 194–202. https://doi.org/10.3109/17482960902991773

Baylow, H., & Goldfarb, R. (2014). Swallowing effect and suspected neuromuscular fatigue in adults with acute stroke: A videofluorographic analysis. *JMSLP*.

Belafsky, P. C., Mouadeb, D. A., Rees, C. J., Pryor, J. C., Postma, G. N., Allen, J., & Leonard, R. J. (2008). Validity and reliability of the Eating Assessment Tool (EAT-10). *The Annals of Otology, Rhinology, and Laryngology*, *117*(12), 919–924. https://doi.org/10.1177/000348940811701210

Bello-Haas, V. D., Florence, J. M., Kloos, A. D., Scheirbecker, J., Lopate, G., Hayes, S. M., Pioro, E. P., & Mitsumoto, H. (2007). A randomized controlled trial of resistance exercise in individuals with ALS. *Neurology*, *68*(23), 2003–2007. https://doi.org/10.1212/01.wnl.0000264418.92308.a4

Bock, J. M., Varadarajan, V., Brawley, M. C., & Blumin, J. H. (2017). Evaluation of the natural history of patients who aspirate. *The Laryngoscope*, *127 Suppl 8*, S1–S10. https://doi.org/10.1002/lary.26854

Bohannon, R. W. (1983). Results of resistance exercise on a patient with amyotrophic lateral sclerosis. A case report. *Physical Therapy*, *63*(6), 965–968. https://doi.org/10.1093/ptj/63.6.965

Borenstein, M., Higgins, J. P. T., Hedges, L. V., & Rothstein, H. R. (2017). Basics of meta-analysis: I2 is not an absolute measure of heterogeneity. *Research Synthesis Methods*, *8*(1), 5–18. https://doi.org/10.1002/jrsm.1230

Braga, A. C., Pinto, A., Pinto, S., & de Carvalho, M. (2018a). The role of moderate aerobic exercise as determined by cardiopulmonary exercise testing in ALS. *Neurology Research International*, *2018*, 8218697. https://doi.org/10.1155/2018/8218697

Braga, A. C., Pinto, A., Pinto, S., & de Carvalho, M. (2018b). Tele-monitoring of a home-based exercise program in amyotrophic lateral sclerosis: a feasibility study. *European Journal of Physical and Rehabilitation Medicine*, *54*(3), 501–503. https://doi.org/10.23736/S1973-9087.18.05129-8

Braga, M., Pederzoli, M., Antonini, A., Beretta, F., & Crespi, V. (2014). Reasons for hospitalization in Parkinson's disease: a case-control study. *Parkinsonism & Related Disorders*, *20*(5), 488–92; discussion 488. https://doi.org/10.1016/j.parkreldis.2014.01.022

Brates, D., Steele, C. M., & Molfenter, S. M. (2019). Measuring hyoid excursion across the life span: anatomical scaling to control for variation. *Journal of Speech, Language, and Hearing Research, 63*(1), 125–134. https://doi.org/10.1044/2019_JSLHR-19-00007

Brodsky, M. B., McFarland, D. H., Dozier, T. S., Blair, J., Ayers, C., Michel, Y., Gillespie, M. B., Day, T. A., & Martin-Harris, B. (2010). Respiratory-swallow phase patterns and their relationship to swallowing impairment in patients treated for oropharyngeal cancer. *Head & Neck*, *32*(4), 481–489. https://doi.org/10.1002/hed.21209

Brown, R. H., & Al-Chalabi, A. (2017). Amyotrophic Lateral Sclerosis. *The New England Journal of Medicine*, *377*(2), 162–172. https://doi.org/10.1056/NEJMra1603471

Brunnström, H. R., & Englund, E. M. (2009). Cause of death in patients with dementia disorders. *European Journal of Neurology*, *16*(4), 488–492. https://doi.org/10.1111/j.1468-1331.2008.02503.x

Burkhead, L. M., Sapienza, C. M., & Rosenbek, J. C. (2007). Strength-training exercise in dysphagia rehabilitation: principles, procedures, and directions for future research. *Dysphagia*, *22*(3), 251–265. https://doi.org/10.1007/s00455-006-9074-z

Cardoso, F. E., de Abreu, L. C., Raimundo, R. D., Faustino, N. A., Araújo, S. F., Valenti, V. E., Sato, M. A., Martins, S. R., & Torquato, J. A. (2012). Evaluation of peak cough flow in Brazilian healthy adults. *International Archives of Medicine*, *5*(1), 25. https://doi.org/10.1186/1755-7682-5-25

Casaburi, R. (1992). Principles of exercise training. *Chest*, *101*(5 Suppl), 263S–267S.

Cheah, B. C., Boland, R. A., Brodaty, N. E., Zoing, M. C., Jeffery, S. E., McKenzie, D. K., & Kiernan, M. C. (2009). INSPIRATIonAL--INSPIRAtory muscle training in amyotrophic lateral sclerosis. *Amyotrophic Lateral Sclerosis*, *10*(5–6), 384–392. https://doi.org/10.3109/17482960903082218

Chen, X., Mao, G., & Leng, S. X. (2014). Frailty syndrome: an overview. *Clinical Interventions in Aging*, *9*, 433–441. https://doi.org/10.2147/CIA.S45300

Cheung, H. J., & Cheung, L. (2015). Coaching patients during pulmonary function testing: A practical guide. *Canadian Journal of Respiratory Therapy : CJRT = Revue Canadienne de La Thérapie Respiratoire : RCTR*, *51*(3), 65–68.

Chiara, T., Martin, D., & Sapienza, C. (2007). Expiratory muscle strength training: speech production outcomes in patients with multiple sclerosis. *Neurorehabilitation and Neural Repair*, *21*(3), 239–249. https://doi.org/10.1177/1545968306294737

Chigira, Y., Miyazaki, I., Izumi, M., & Oda, T. (2018). Effects of expiratory muscle training on the frail elderly's respiratory function. *Journal of Physical Therapy Science*, *30*(2), 286–288. https://doi.org/10.1589/jpts.30.286

Chiò, A., Bottacchi, E., Buffa, C., Mutani, R., Mora, G., & PARALS. (2006). Positive effects of tertiary centres for amyotrophic lateral sclerosis on outcome and use of hospital facilities. *Journal of Neurology, Neurosurgery, and Psychiatry*, *77*(8), 948–950. https://doi.org/10.1136/jnnp.2005.083402

Chiò, A., Logroscino, G., Hardiman, O., Swingler, R., Mitchell, D., Beghi, E., Traynor, B. G., & Eurals Consortium. (2009). Prognostic factors in ALS: A critical review. *Amyotrophic Lateral Sclerosis*, *10*(5–6), 310–323. https://doi.org/10.3109/17482960802566824

Ciucci, M., Jones, C. A., Malandraki, G. A., & Hutcheson, K. A. (2016). Dysphagia practice in 2035: beyond fluorography, thickener, and electrical stimulation. *Seminars in Speech and Language*, *37*(3), 201–218. https://doi.org/10.1055/s-0036-1584155

Clawson, L. L., Cudkowicz, M., Krivickas, L., Brooks, B. R., Sanjak, M., Allred, P., Atassi, N., Swartz, A., Steinhorn, G., Uchil, A., Riley, K. M., Yu, H., Schoenfeld, D. A., Maragakis, N. J., & neals consortium. (2018). A randomized controlled trial of resistance and endurance exercise in amyotrophic lateral sclerosis. *Amyotrophic Lateral Sclerosis & Frontotemporal Degeneration*, *19*(3–4), 250–258. https://doi.org/10.1080/21678421.2017.1404108

Clegg, A. P., Barber, S. E., Young, J. B., Forster, A., & Iliffe, S. J. (2012). Do home-based exercise interventions improve outcomes for frail older people? Findings from a systematic review. *Reviews in Clinical Gerontology*, *22*(1), 68–78. https://doi.org/10.1017/S0959259811000165

Conde, B., Martins, N., Rodrigues, I., Pimenta, A. C., & Winck, J. C. (2018). Functional and endoscopic indicators for percutaneous endoscopic gastrostomy (PEG) in amyotrophic lateral sclerosis patients. *Journal of Clinical Medicine*, *7*(10). https://doi.org/10.3390/jcm7100352

Cox, N. S., McDonald, C. F., Alison, J. A., Mahal, A., Wootton, R., Hill, C. J., Bondarenko, J., Macdonald, H., O'Halloran, P., Zanaboni, P., Clarke, K., Rennick, D., Borgelt, K., Burge, A. T., Lahham, A., Wageck, B., Crute, H., Czupryn, P., Nichols, A., & Holland, A. E. (2018). Telerehabilitation versus traditional centre-based pulmonary rehabilitation for people with chronic respiratory disease: protocol for a randomised controlled trial. *BMC Pulmonary Medicine*, *18*(1), 71. https://doi.org/10.1186/s12890-018-0646-0

Coyle, J. (2012). Tele-Dysphagia management: an opportunity for prevention, cost-savings and advanced training. *International Journal of Telerehabilitation*, *4*(1), 37–40. https://doi.org/10.5195/IJT.2012.6093

Crary, M. A., Mann, G. D. C., & Groher, M. E. (2005). Initial psychometric assessment of a functional oral intake scale for dysphagia in stroke patients. *Archives of Physical Medicine and Rehabilitation*, *86*(8), 1516–1520. https://doi.org/10.1016/j.apmr.2004.11.049

Curtis, J. A., Dakin, A. E., & Troche, M. S. (2020). Respiratory-Swallow Coordination Training and Voluntary Cough Skill Training: A Single-Subject Treatment Study in a Person With Parkinson's Disease. *Journal of Speech, Language, and Hearing Research*, *63*(2), 472–486. https://doi.org/10.1044/2019_JSLHR-19-00207

Cvejic, L., Harding, R., Churchward, T., Turton, A., Finlay, P., Massey, D., Bardin, P. G., & Guy, P. (2011). Laryngeal penetration and aspiration in individuals with stable COPD. *Respirology*, *16*(2), 269–275. https://doi.org/10.1111/j.1440-1843.2010.01875.x

Czaplinski, A., Yen, A. A., Simpson, E. P., & Appel, S. H. (2006). Predictability of disease progression in amyotrophic lateral sclerosis. *Muscle & Nerve*, *34*(6), 702–708. https://doi.org/10.1002/mus.20658

da Costa Franceschini, A., & Mourão, L. F. (2015). Dysarthria and dysphagia in Amyotrophic Lateral Sclerosis with spinal onset: a study of quality of life related to swallowing. *NeuroRehabilitation*, *36*(1), 127–134. https://doi.org/10.3233/NRE-141200

D'Arrigo, A., Floro, S., Bartesaghi, F., Casellato, C., Sferrazza Papa, G. F., Centanni, S., Priori, A., & Bocci, T. (2020). Respiratory dysfunction in Parkinson's disease: a narrative review. *ERJ Open Research*, *6*(4). https://doi.org/10.1183/23120541.00165-2020

de Almeida, J. P. L., Silvestre, R., Pinto, A. C., & de Carvalho, M. (2012). Exercise and amyotrophic lateral sclerosis. *Neurological Sciences*, *33*(1), 9–15. https://doi.org/10.1007/s10072-011-0921-9

de Pedro-Cuesta, J., Rábano, A., Martínez-Martín, P., Ruiz-Tovar, M., Alcalde-Cabero, E., Almazán-Isla, J., Avellanal, F., & Calero, M. (2015). Comparative incidence of conformational, neurodegenerative disorders. *Plos One*, *10*(9), e0137342. https://doi.org/10.1371/journal.pone.0137342

Desport, J. C., Preux, P. M., Truong, T. C., Vallat, J. M., Sautereau, D., & Couratier, P. (1999). Nutritional status is a prognostic factor for survival in ALS patients. *Neurology*, *53*(5), 1059–1063. https://doi.org/10.1212/wnl.53.5.1059

Dharmadasa, T., Matamala, J. M., & Kiernan, M. C. (2016). Treatment approaches in motor neurone disease. *Current Opinion in Neurology*, *29*(5), 581–591. https://doi.org/10.1097/WCO.0000000000000369

Donohue, C., Carnaby, G., Colquhoun, R. J., Lacomis, D., & Garand, K. L. (2020). Letter to the Editor Regarding: "Effects of exercise in patients with amyotrophic lateral sclerosis: A systematic review and meta-analysis". *American Journal of Physical Medicine & Rehabilitation*. https://doi.org/10.1097/PHM.0000000000001656

Donohue, C., & Coyle, J. L. (2020). The safety, tolerability, and impact of respiratory–swallow coordination training and expiratory muscle strength training on pulmonary, cough, and swallow function surrogates in amyotrophic lateral sclerosis. *Perspectives of the ASHA Special Interest Groups*, 1–13. https://doi.org/10.1044/2020_PERSP-20-00030

Donohue, C., Khalifa, Y., Perera, S., Sejdić, E., & Coyle, J. L. (2020a). A Preliminary Investigation of Whether HRCA Signals Can Differentiate Between Swallows from Healthy People and Swallows from People with Neurodegenerative Diseases. *Dysphagia*. https://doi.org/10.1007/s00455-020-10177-0

Donohue, C., Khalifa, Y., Perera, S., Sejdić, E., & Coyle, J. L. (2020b). How closely do machine ratings of duration of UES opening during videofluoroscopy approximate clinician ratings using temporal kinematic analyses and the mbsimp? *Dysphagia*. https://doi.org/10.1007/s00455-020-10191-2

Donohue, C., Mao, S., Sejdić, E., & Coyle, J. L. (2020). Tracking hyoid bone displacement during swallowing without videofluoroscopy using machine learning of vibratory signals. *Dysphagia*. https://doi.org/10.1007/s00455-020-10124-z

Dorsey, E. R., Constantinescu, R., Thompson, J. P., Biglan, K. M., Holloway, R. G., Kieburtz, K., Marshall, F. J., Ravina, B. M., Schifitto, G., Siderowf, A., & Tanner, C. M. (2007). Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. *Neurology*, *68*(5), 384–386. https://doi.org/10.1212/01.wnl.0000247740.47667.03

Drory, V. E., Goltsman, E., Reznik, J. G., Mosek, A., & Korczyn, A. D. (2001). The value of muscle exercise in patients with amyotrophic lateral sclerosis. *Journal of the Neurological Sciences*, *191*(1–2), 133–137. https://doi.org/10.1016/s0022-510x(01)00610-4

Dudik, J. M., Coyle, J. L., El-Jaroudi, A., Mao, Z.-H., Sun, M., & Sejdić, E. (2018). Deep learning for classification of normal swallows in adults. *Neurocomputing*, *285*, 1–9. https://doi.org/10.1016/j.neucom.2017.12.059

Dudik, J. M., Coyle, J. L., & Sejdić, E. (2015). Dysphagia Screening: Contributions of Cervical Auscultation Signals and Modern Signal-Processing Techniques. *IEEE Transactions on Human-Machine Systems*, *45*(4), 465–477. https://doi.org/10.1109/THMS.2015.2408615

Dudik, J. M., Jestrovi, I., Luan, B., Coyle, J. L., & Sejdi, E. (2015). *Open Access A comparative analysis of swallowing accelerometry and sounds during saliva swallows*. 1–15.

Dudik, J. M., Jestrović, I., Luan, B., Coyle, J. L., & Sejdić, E. (2015). A comparative analysis of swallowing accelerometry and sounds during saliva swallows. *Biomedical Engineering Online*, *14*, 3. https://doi.org/10.1186/1475-925X-14-3

Dudik, J. M., Jestrovic, I., Luan, B., Coyle, J. L., & Sejdic, E. (2015). Characteristics of Dry Chin-Tuck Swallowing Vibrations and Sounds. *IEEE Transactions on Biomedical Engineering*, *62*(10), 2456–2464. https://doi.org/10.1109/TBME.2015.2431999

Dudik, J. M., Kurosu, A., Coyle, J. L., & Sejdić, E. (2015). A comparative analysis of DBSCAN, K-means, and quadratic variation algorithms for automatic identification of swallows from swallowing accelerometry signals. *Computers in Biology and Medicine*, *59*, 10–18. https://doi.org/10.1016/j.compbiomed.2015.01.007

Dudik, J. M., Kurosu, A., Coyle, J. L., & Sejdić, E. (2016). A statistical analysis of cervical auscultation signals from adults with unsafe airway protection. *Journal of Neuroengineering and Rehabilitation*, *13*, 7. https://doi.org/10.1186/s12984-015-0110-9

Easterling, C. S., & Robbins, E. (2008). Dementia and dysphagia. *Geriatric Nursing (New York, N.Y.)*, *29*(4), 275–285. https://doi.org/10.1016/j.gerinurse.2007.10.015

Erkkinen, M. G., Kim, M.-O., & Geschwind, M. D. (2018). Clinical neurology and epidemiology of the major neurodegenerative diseases. *Cold Spring Harbor Perspectives in Biology*, *10*(4). https://doi.org/10.1101/cshperspect.a033118

Fantini, R., Mandrioli, J., Zona, S., Antenora, F., Iattoni, A., Monelli, M., Fini, N., Tonelli, R., Clini, E., & Marchioni, A. (2016). Ultrasound assessment of diaphragmatic function in patients with amyotrophic lateral sclerosis. *Respirology*, *21*(5), 932–938. https://doi.org/10.1111/resp.12759

Feng, Y.-S., Yang, S.-D., Tan, Z.-X., Wang, M.-M., Xing, Y., Dong, F., & Zhang, F. (2020). The benefits and mechanisms of exercise training for Parkinson's disease. *Life Sciences*, *245*, 117345. https://doi.org/10.1016/j.lfs.2020.117345

Ferreira, G. D., Costa, A. C. C., Plentz, R. D. M., Coronel, C. C., & Sbruzzi, G. (2016). Respiratory training improved ventilatory function and respiratory muscle strength in patients with multiple sclerosis and lateral amyotrophic sclerosis: systematic review and meta-analysis. *Physiotherapy*, *102*(3), 221–228. https://doi.org/10.1016/j.physio.2016.01.002

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, *12*(3), 189–198. https://doi.org/10.1016/0022-3956(75)90026-6

Francis, K., Bach, J. R., & DeLisa, J. A. (1999). Evaluation and rehabilitation of patients with adult motor neuron disease. *Archives of Physical Medicine and Rehabilitation*, *80*(8), 951–963. https://doi.org/10.1016/s0003-9993(99)90089-8

Fujishima, I., Fujiu-Kurachi, M., Arai, H., Hyodo, M., Kagaya, H., Maeda, K., Mori, T., Nishioka, S., Oshima, F., Ogawa, S., Ueda, K., Umezaki, T., Wakabayashi, H., Yamawaki, M., & Yoshimura, Y. (2019). Sarcopenia and dysphagia: Position paper by four professional organizations. *Geriatrics & Gerontology International*, *19*(2), 91–97. https://doi.org/10.1111/ggi.13591

Gallo, V., Vanacore, N., Bueno-de-Mesquita, H. B., Vermeulen, R., Brayne, C., Pearce, N., Wark, P. A., Ward, H. A., Ferrari, P., Jenab, M., Andersen, P. M., Wennberg, P., Wareham, N., Katzke, V., Kaaks, R., Weiderpass, E., Peeters, P. H., Mattiello, A., Pala, V., … Vineis, P. (2016). Physical activity and risk of Amyotrophic Lateral Sclerosis in a prospective cohort study. *European Journal of Epidemiology*, *31*(3), 255–266. https://doi.org/10.1007/s10654-016-0119-9

Garon, B. R., Sierzant, T., & Ormiston, C. (2009). Silent aspiration: results of 2,000 video fluoroscopic evaluations. *The Journal of Neuroscience Nursing : Journal of the American Association of Neuroscience Nurses*, *41*(4), 178–85; quiz 186.

GBD 2016 Neurology Collaborators. (2019). Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurology*, *18*(5), 459–480. https://doi.org/10.1016/S1474-4422(18)30499-X

Gil Obando, L. M., López López, A., & Avila, C. L. (2012). Normal values of the maximal respiratory pressures in healthy people older than 20 years old in the City of Manizales - Colombia. *Colombia Medica (Cali, Colombia)*, *43*(2), 119–125.

Goldspink, D. F. (2005). Ageing and activity: their effects on the functional reserve capacities of the heart and vascular smooth and skeletal muscles. *Ergonomics*, *48*(11–14), 1334–1351. https://doi.org/10.1080/00140130500101247

Goodfellow, I., Bengio, Y., Courville, A., & Bengio, Y. (2016). *Deep learning. vol. 1*.

Gordon, P. H., & Cheung, Y. K. (2006). Progression rate of ALSFRS-R at time of diagnosis predicts survival time in ALS. *Neurology*, *67*(7), 1314–5; author reply 1314. https://doi.org/10.1212/01.wnl.0000243812.25517.87

Gordon, P. H., Miller, R. G., & Moore, D. H. (2004). ALSFRS-R. *Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders : Official Publication of the World Federation of Neurology, Research Group on Motor Neuron Diseases*, *5 Suppl 1*, 90–93. https://doi.org/10.1080/17434470410019906

Gross, R. D., Atwood, C. W., Ross, S. B., Olszewski, J. W., & Eichhorn, K. A. (2009). The coordination of breathing and swallowing in chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine*, *179*(7), 559–565. https://doi.org/10.1164/rccm.200807-1139OC

Groves-Wright, K. J., Boyce, S., & Kelchner, L. (2010). Perception of wet vocal quality in identifying penetration/aspiration during swallowing. *Journal of Speech, Language, and Hearing Research*, *53*(3), 620–632. https://doi.org/10.1044/1092-4388(2009/08-0246)

Hansen, H., Bieler, T., Beyer, N., Godtfredsen, N., Kallemose, T., & Frølich, A. (2017). COPD online-rehabilitation versus conventional COPD rehabilitation - rationale and design for a multicenter randomized controlled trial study protocol (CORe trial). *BMC Pulmonary Medicine*, *17*(1), 140. https://doi.org/10.1186/s12890-017-0488-1

Hardiman, O. (2001). Amyotrophic Lateral Sclerosis. In John Wiley & Sons, Ltd (Ed.), *Encyclopedia of life sciences*. John Wiley & Sons, Ltd. https://doi.org/10.1002/9780470015902.a0000014.pub2

Harkawik, R., & Coyle, J. L. (2012). Exercise for better ALS management? *BMJ Leader*, *17*(11). https://doi.org/10.1044/leader.FTR5.17112012.np

Harper, C. J., Shahgholi, L., Cieslak, K., Hellyer, N. J., Strommen, J. A., & Boon, A. J. (2013). Variability in diaphragm motion during normal breathing, assessed with B-mode ultrasound. *The Journal of Orthopaedic and Sports Physical Therapy*, *43*(12), 927–931. https://doi.org/10.2519/jospt.2013.4931

Haulman, A., Geronimo, A., Chahwala, A., & Simmons, Z. (2020). The use of telehealth to enhance care in ALS and other neuromuscular disorders. *Muscle & Nerve*, *61*(6), 682–691. https://doi.org/10.1002/mus.26838

He, Q., Perera, S., Khalifa, Y., Zhang, Z., Mahoney, A. S., Sabry, A., Donohue, C., Coyle, J. L., & Sejdic, E. (2019). The association of high resolution cervical auscultation signal features with hyoid bone displacement during swallowing. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, *27*(9), 1810–1816. https://doi.org/10.1109/TNSRE.2019.2935302

Hebert, L. E., Weuve, J., Scherr, P. A., & Evans, D. A. (2013). Alzheimer disease in the United States (2010-2050) estimated using the 2010 census. *Neurology*, *80*(19), 1778–1783. https://doi.org/10.1212/WNL.0b013e31828726f5

Hegland, K. W., Bolser, D. C., & Davenport, P. W. (2012). Volitional control of reflex cough. *Journal of Applied Physiology: Respiratory, Environmental and Exercise Physiology*, *113*(1), 39–46. https://doi.org/10.1152/japplphysiol.01299.2011

Hegland, K. W., Davenport, P. W., Brandimore, A. E., Singletary, F. F., & Troche, M. S. (2016). Rehabilitation of swallowing and cough functions following stroke: an expiratory muscle strength training trial. *Archives of Physical Medicine and Rehabilitation*, *97*(8), 1345–1351. https://doi.org/10.1016/j.apmr.2016.03.027

Hegland, K. W., Okun, M. S., & Troche, M. S. (2014). Sequential voluntary cough and aspiration or aspiration risk in Parkinson's disease. *Lung*, *192*(4), 601–608. https://doi.org/10.1007/s00408-014-9584-7

Helleman, J., Kruitwagen, E. T., van den Berg, L. H., Visser-Meily, J. M. A., & Beelen, A. (2020). The current use of telehealth in ALS care and the barriers to and facilitators of implementation: a systematic review. *Amyotrophic Lateral Sclerosis & Frontotemporal Degeneration*, *21*(3–4), 167–182. https://doi.org/10.1080/21678421.2019.1706581

Helleman, J., Van Eenennaam, R., Kruitwagen, E. T., Kruithof, W. J., Slappendel, M. J., Van Den Berg, L. H., Visser-Meily, J. M. A., & Beelen, A. (2020). Telehealth as part of specialized ALS care: feasibility and user experiences with "ALS home-monitoring and coaching". *Amyotrophic Lateral Sclerosis & Frontotemporal Degeneration*, *21*(3–4), 183–192. https://doi.org/10.1080/21678421.2020.1718712

Heyn, P., Abreu, B. C., & Ottenbacher, K. J. (2004). The effects of exercise training on elderly persons with cognitive impairment and dementia: a meta-analysis. *Archives of Physical*

Medicine and Rehabilitation, *85*(10), 1694–1704. https://doi.org/10.1016/j.apmr.2004.03.019

Hiramatsu, T., Kataoka, H., Osaki, M., & Hagino, H. (2015). Effect of aging on oral and swallowing function after meal consumption. *Clinical Interventions in Aging*, *10*, 229–235. https://doi.org/10.2147/CIA.S75211

Hiraoka, A., Yoshikawa, M., Nakamori, M., Hosomi, N., Nagasaki, T., Mori, T., Oda, M., Maruyama, H., Yoshida, M., Izumi, Y., Matsumoto, M., & Tsuga, K. (2017). Maximum Tongue Pressure is Associated with Swallowing Dysfunction in ALS Patients. *Dysphagia*, *32*(4), 542–547. https://doi.org/10.1007/s00455-017-9797-z

Hobson, E. V., & McDermott, C. J. (2016). Supportive and symptomatic management of amyotrophic lateral sclerosis. *Nature Reviews. Neurology*, *12*(9), 526–538. https://doi.org/10.1038/nrneurol.2016.111

Hopkins-Rossabi, T., Curtis, P., Temenak, M., Miller, C., & Martin-Harris, B. (2019). Respiratory phase and lung volume patterns during swallowing in healthy adults: A systematic review and meta-analysis. *Journal of Speech, Language, and Hearing Research*, *62*(4), 868–882. https://doi.org/10.1044/2018_JSLHR-S-18-0323

Hopkins-Rossabi, T., Rowe, M., McGrattan, K., Rossabi, S., & Martin-Harris, B. (2020). Respiratory-swallow training methods: Accuracy of automated detection of swallow onset, respiratory phase, lung volume at swallow onset, and real-time performance feedback tested in healthy adults. *American Journal of Speech-Language Pathology / American Speech-Language-Hearing Association*, *29*(2S), 1012–1021. https://doi.org/10.1044/2020_AJSLP-19-00201

Horner, J., Alberts, M. J., Dawson, D. V., & Cook, G. M. (1994). Swallowing in Alzheimer's disease. *Alzheimer Disease and Associated Disorders*, *8*(3), 177–189.

Howard, I., & Potts, A. (2019). Interprofessional care for neuromuscular disease. *Current Treatment Options in Neurology*, *21*(8), 35. https://doi.org/10.1007/s11940-019-0576-z

Hurd, M. D., Martorell, P., Delavande, A., Mullen, K. J., & Langa, K. M. (2013). Monetary costs of dementia in the United States. *The New England Journal of Medicine*, *368*(14), 1326–1334. https://doi.org/10.1056/NEJMsa1204629

Husaini, B., Gudlavalleti, A. S., Cain, V., Levine, R., & Moonis, M. (2015). Risk factors and hospitalization costs of dementia patients: examining race and gender variations. *Indian Journal of Community Medicine : Official Publication of Indian Association of Preventive & Social Medicine*, *40*(4), 258–263. https://doi.org/10.4103/0970-0218.164396

Hutcheson, K. A., Barrow, M. P., Plowman, E. K., Lai, S. Y., Fuller, C. D., Barringer, D. A., Eapen, G., Wang, Y., Hubbard, R., Jimenez, S. K., Little, L. G., & Lewin, J. S. (2018). Expiratory muscle strength training for radiation-associated aspiration after head and neck cancer: A case series. *The Laryngoscope*, *128*(5), 1044–1051. https://doi.org/10.1002/lary.26845

Jensen, L., Djurtoft, J. B., Bech, R. D., Nielsen, J. L., Jørgensen, L. H., Schrøder, H. D., Frandsen, U., Aagaard, P., & Hvid, L. G. (2017). Influence of resistance training on neuromuscular function and physical capacity in ALS patients. *Journal of Neurodegenerative Diseases*, *2017*, 1436519. https://doi.org/10.1155/2017/1436519

Jestrović, I., Dudik, J. M., Luan, B., Coyle, J. L., & Sejdić, E. (2013). Baseline characteristics of cervical auscultation signals during various head maneuvers. *Computers in Biology and Medicine*, *43*(12), 2014–2020. https://doi.org/10.1016/j.compbiomed.2013.10.005

Karceski, S. (2018). Parkinson disease and mortality: Understanding how the two are connected. *Neurology*, *91*(22), e2106–e2108. https://doi.org/10.1212/WNL.0000000000006565

Kato, N., Hashida, G., Kobayashi, M., & Konaka, K. (2018). Physical therapy improves lower limb muscle strength but not function in individuals with amyotrophic lateral sclerosis: A case series study. *Annals of Physical and Rehabilitation Medicine*, *61*(2), 108–110. https://doi.org/10.1016/j.rehab.2017.09.007

Kato, N., Hashida, G., & Konaka, K. (2018). Effect of muscle strengthening exercise and time since onset in patients with amyotrophic lateral sclerosis: A 2-patient case series study. *Medicine*, *97*(25), e11145. https://doi.org/10.1097/MD.0000000000011145

Kays, S. A., Hind, J. A., Gangnon, R. E., & Robbins, J. (2011). Effects of dining on tongue endurance and swallowing-related outcomes. *Journal of Speech Language and Hearing Research*, *53*(4), 898–907.

Khalifa, Y., Coyle, J. L., & Sejdić, E. (2020). Non-invasive identification of swallows via deep learning in high resolution cervical auscultation recordings. *Scientific Reports*, *10*(1), 8704. https://doi.org/10.1038/s41598-020-65492-1

Khalifa, Y., Donohue, C., Coyle, J. L., & Sejdic, E. (2021). Upper esophageal sphincter opening segmentation with convolutional recurrent neural networks in high resolution cervical auscultation. *IEEE Journal of Biomedical and Health Informatics*, *25*(2), 493–503. https://doi.org/10.1109/JBHI.2020.3000057

Kiernan, M. C., Vucic, S., Cheah, B. C., Turner, M. R., Eisen, A., Hardiman, O., Burrell, J. R., & Zoing, M. C. (2011). Amyotrophic lateral sclerosis. *The Lancet*, *377*(9769), 942–955. https://doi.org/10.1016/S0140-6736(10)61156-7

Kim, D.-G., Hong, Y.-H., Shin, J.-Y., Lee, K.-W., Park, K. S., Seong, S.-Y., & Sung, J.-J. (2015). Pattern of respiratory deterioration in sporadic amyotrophic lateral sclerosis according to onset lesion by using respiratory function tests. *Experimental Neurobiology*, *24*(4), 351–357. https://doi.org/10.5607/en.2015.24.4.351

Kim, J., Davenport, P., & Sapienza, C. (2009). Effect of expiratory muscle strength training on elderly cough function. *Archives of Gerontology and Geriatrics*, *48*(3), 361–366. https://doi.org/10.1016/j.archger.2008.03.006

Kirkinezos, I. G., Hernandez, D., Bradley, W. G., & Moraes, C. T. (2003). Regular exercise is beneficial to a mouse model of amyotrophic lateral sclerosis. *Annals of Neurology*, *53*(6), 804–807. https://doi.org/10.1002/ana.10597

Kitano, K., Asakawa, T., Kamide, N., Yorimoto, K., Yoneda, M., Kikuchi, Y., Sawada, M., & Komori, T. (2018). Effectiveness of home-based exercises without supervision by physical therapists for patients with early-stage amyotrophic lateral sclerosis: A pilot study. *Archives of Physical Medicine and Rehabilitation*, *99*(10), 2114–2117. https://doi.org/10.1016/j.apmr.2018.02.015

Kmet, L. M., Lee, R. C., & Cook, L. S. (2004). Standard quality assessment criteria for evaluating primary research papers from a variety of fields: Alberta Heritage Foundation for Medical Research. *Retreived from Http://Www. Ihe. ca/Documents/HTA*.

Kühnlein, P., Gdynia, H.-J., Sperfeld, A.-D., Lindner-Pfleghar, B., Ludolph, A. C., Prosiegel, M., & Riecker, A. (2008). Diagnosis and treatment of bulbar symptoms in amyotrophic lateral sclerosis. *Nature Clinical Practice. Neurology*, *4*(7), 366–374. https://doi.org/10.1038/ncpneuro0853

Kurosu, A., Coyle, J. L., Dudik, J. M., & Sejdic, E. (2019). Detection of Swallow Kinematic Events From Acoustic High-Resolution Cervical Auscultation Signals in Patients With Stroke. *Archives of Physical Medicine and Rehabilitation*, *100*(3), 501–508. https://doi.org/10.1016/j.apmr.2018.05.038

Laciuga, H., Rosenbek, J. C., Davenport, P. W., & Sapienza, C. M. (2014). *training : Narrative review*. *51*(4), 535–546.

Larkindale, J., Yang, W., Hogan, P. F., Simon, C. J., Zhang, Y., Jain, A., Habeeb-Louks, E. M., Kennedy, A., & Cwik, V. A. (2014). Cost of illness for neuromuscular diseases in the United States. *Muscle & Nerve*, *49*(3), 431–438. https://doi.org/10.1002/mus.23942

Lechtzin, N., Wiener, C. M., Clawson, L., & Chaudhry, V. (2001). Hospitalization in amyotrophic Causes , costs , and outcomes. *Neurology*, 753–757.

Lee, J., Steele, C. M., & Chau, T. (2011). Classification of healthy and abnormal swallows based on accelerometry and nasal airflow signals. *Artificial Intelligence in Medicine*, *52*(1), 17–25. https://doi.org/10.1016/j.artmed.2011.03.002

Leow, L. P., Huckabee, M.-L., Anderson, T., & Beckert, L. (2010). The impact of dysphagia on quality of life in ageing and Parkinson's disease as measured by the swallowing quality of life (SWAL-QOL) questionnaire. *Dysphagia*, *25*(3), 216–220. https://doi.org/10.1007/s00455-009-9245-9

Liu, Y., Yan, T., Chu, J. M.-T., Chen, Y., Dunnett, S., Ho, Y.-S., Wong, G. T.-C., & Chang, R. C.-C. (2019). The beneficial effects of physical exercise in the brain and related pathophysiological mechanisms in neurodegenerative diseases. *Laboratory Investigation*, *99*(7), 943–957. https://doi.org/10.1038/s41374-019-0232-y

Lof, G. L., & Robbins, J. (1990). Test-retest variability in normal swallowing. *Dysphagia*, *4*(4), 236–242. https://doi.org/10.1007/BF02407271

López-Liria, R., Parra-Egeda, J., Vega-Ramírez, F. A., Aguilar-Parra, J. M., Trigueros-Ramos, R., Morales-Gázquez, M. J., & Rocamora-Pérez, P. (2020). Treatment of dysphagia in parkinson's disease: A systematic review. *International Journal of Environmental Research and Public Health*, *17*(11). https://doi.org/10.3390/ijerph17114104

Loth, A., Corny, J., Santini, L., Dahan, L., Dessi, P., Adalian, P., & Fakhry, N. (2015). Analysis of hyoid-larynx complex using 3D geometric morphometrics. *Dysphagia*, *30*(3), 357–364. https://doi.org/10.1007/s00455-015-9609-2

Lunetta, C., Lizio, A., Sansone, V. A., Cellotto, N. M., Maestri, E., Bettinelli, M., Gatti, V., Melazzini, M. G., Meola, G., & Corbo, M. (2016). Strictly monitored exercise programs reduce motor deterioration in ALS: preliminary results of a randomized controlled trial. *Journal of Neurology*, *263*(1), 52–60. https://doi.org/10.1007/s00415-015-7924-z

Mahoney, D. J., Rodriguez, C., Devries, M., Yasuda, N., & Tarnopolsky, M. A. (2004). Effects of high-intensity endurance exercise training in the G93A mouse model of amyotrophic lateral sclerosis. *Muscle & Nerve*, *29*(5), 656–662. https://doi.org/10.1002/mus.20004

Malandraki, G. A., & Kantarcigil, C. (2017). Telehealth for dysphagia rehabilitation: the present and the future. *Perspectives of the ASHA Special Interest Groups*, *2*(18), 42–48. https://doi.org/10.1044/persp2.SIG18.42

Malandraki, G. A., Kaufman, A., Hind, J., Ennis, S., Gangnon, R., Waclawik, A., & Robbins, J. (2012). The effects of lingual intervention in a patient with inclusion body myositis and Sjögren's syndrome: a longitudinal case study. *Archives of Physical Medicine and Rehabilitation*, *93*(8), 1469–1475. https://doi.org/10.1016/j.apmr.2012.02.010

Mancopes, R., Smaoui, S., & Steele, C. (2020). Effects of expiratory muscle strength training on videofluoroscopic measures of swallowing: A systematic review. *AJSLP*, 1–22.

Mao, S., Sabry, A., Khalifa, Y., Coyle, J. L., & Sejdic, E. (2021). Estimation of laryngeal closure duration during swallowing without invasive X-rays. *Future Generations Computer Systems : FGCS*, *115*, 610–618. https://doi.org/10.1016/j.future.2020.09.040

Mao, S., Zhang, Z., Khalifa, Y., Donohue, C., Coyle, J. L., & Sejdic, E. (2019). Neck sensor-supported hyoid bone movement tracking during swallowing. *Royal Society Open Science*, *6*(7), 181982. https://doi.org/10.1098/rsos.181982

Martin-Harris, B. (2008). Clinical implications of respiratory-swallowing interactions. *Current Opinion in Otolaryngology & Head and Neck Surgery*, *16*(3), 194–199. https://doi.org/10.1097/MOO.0b013e3282febd4b

Martin-Harris, B., Brodsky, M. B., Michel, Y., Castell, D. O., Schleicher, M., Sandidge, J., Maxwell, R., & Blair, J. (2008). MBS measurement tool for swallow impairment--

MBSImp: establishing a standard. *Dysphagia*, *23*(4), 392–405. https://doi.org/10.1007/s00455-008-9185-9

Martin-Harris, B., McFarland, D., Hill, E. G., Strange, C. B., Focht, K. L., Wan, Z., Blair, J., & McGrattan, K. (2015). Respiratory-swallow training in patients with head and neck cancer. *Archives of Physical Medicine and Rehabilitation*, *96*(5), 885–893. https://doi.org/10.1016/j.apmr.2014.11.022

Matsuo, K., & Palmer, J. B. (2009). Coordination of mastication, swallowing and breathing. *The Japanese Dental Science Review*, *45*(1), 31–40. https://doi.org/10.1016/j.jdsr.2009.03.004

McFarland, D. H., Martin-Harris, B., Fortin, A. J., Humphries, K., Hill, E., & Armeson, K. (2016). Respiratory-swallowing coordination in normal subjects: Lung volume at swallowing initiation. *Respiratory Physiology & Neurobiology*, *234*, 89–96. https://doi.org/10.1016/j.resp.2016.09.004

Mehta, P., Kaye, W., Raymond, J., Punjani, R., Larson, T., Cohen, J., Muravov, O., & Horton, K. (2018). Prevalence of Amyotrophic Lateral Sclerosis - United States, 2015. *MMWR. Morbidity and Mortality Weekly Report*, *67*(46), 1285–1289. https://doi.org/10.15585/mmwr.mm6746a1

Meng, L., Li, X., Li, C., Tsang, R. C. C., Chen, Y., Ge, Y., & Gao, Q. (2020). Effects of exercise in patients with amyotrophic lateral sclerosis: A systematic review and meta-analysis. *American Journal of Physical Medicine & Rehabilitation*, *99*(9), 801–810. https://doi.org/10.1097/PHM.0000000000001419

Merico, A., Cavinato, M., Gregorio, C., Lacatena, A., Gioia, E., Piccione, F., & Angelini, C. (2018). Effects of combined endurance and resistance training in Amyotrophic Lateral Sclerosis: A pilot, randomized, controlled study. *European Journal of Translational Myology*, *28*(1), 7278. https://doi.org/10.4081/ejtm.2018.7278

Molfenter, S. M., Brates, D., Herzberg, E., Noorani, M., & Lazarus, C. (2018). The swallowing profile of healthy aging adults: comparing noninvasive swallow tests to videofluoroscopic measures of safety and efficiency. *Journal of Speech, Language, and Hearing Research*, *61*(7), 1603–1612. https://doi.org/10.1044/2018_JSLHR-S-17-0471

Molfenter, S. M., & Steele, C. M. (2013). Variation in temporal measures of swallowing: sex and volume effects. *Dysphagia*, *28*(2), 226–233. https://doi.org/10.1007/s00455-012-9437-6

Molfenter, S. M., & Steele, C. M. (2014). Use of an anatomical scalar to control for sex-based size differences in measures of hyoid excursion during swallowing. *Journal of Speech, Language, and Hearing Research*, *57*(3), 768–778. https://doi.org/10.1044/2014_JSLHR-S-13-0152

Moore, V. C. (2012). Spirometry: step by step. *Breathe*, *8*(3), 232–240. https://doi.org/10.1183/20734735.0021711

Motl, R. W., & Sandroff, B. M. (2015). Benefits of exercise training in multiple sclerosis. *Current Neurology and Neuroscience Reports, 15*(9), 62. https://doi.org/10.1007/s11910-015-0585-6

Movahedi, F., Kurosu, A., Coyle, J. L., Perera, S., & Sejdić, E. (2017). A comparison between swallowing sounds and vibrations in patients with dysphagia. *Computer Methods and Programs in Biomedicine, 144*, 179–187. https://doi.org/10.1016/j.cmpb.2017.03.009

Murray, J. (2008). Frailty, functional reserve, and sarcopenia in the geriatric dysphagic patient. *Perspectives on Swallowing and Swallowing Disorders (Dysphagia), 17*(1), 3–11. https://doi.org/10.1044/sasd17.1.3

Namasivayam-MacDonald, A. M., Barbon, C. E. A., & Steele, C. M. (2018). A review of swallow timing in the elderly. *Physiology & Behavior*, *184*, 12–26. https://doi.org/10.1016/j.physbeh.2017.10.023

Namasivayam-MacDonald, A. M., Burnett, L., Nagy, A., Waito, A. A., & Steele, C. M. (2017). Effects of tongue strength training on mealtime function in long-term care. *American Journal of Speech-Language Pathology / American Speech-Language-Hearing Association*, *26*(4), 1213–1224. https://doi.org/10.1044/2017_AJSLP-16-0186

Neves, L. F., Reis, M. H., Plentz, R. D. M., Matte, D. L., Coronel, C. C., & Sbruzzi, G. (2014). Expiratory and expiratory plus inspiratory muscle training improves respiratory muscle strength in subjects with COPD: systematic review. *Respiratory Care, 59*(9), 1381–1388. https://doi.org/10.4187/respcare.02793

Newland, P., Starkweather, A., & Sorenson, M. (2016). Central fatigue in multiple sclerosis: a review of the literature. *The Journal of Spinal Cord Medicine*, *39*(4), 386–399. https://doi.org/10.1080/10790268.2016.1168587

Nicosia, M. A., Hind, J. A., Roecker, E. B., Carnes, M., Doyle, J., Dengel, G. A., & Robbins, J. (2000). Age effects on the temporal evolution of isometric and swallowing pressure. *The Journals of Gerontology*. *Series A, Biological Sciences and Medical Sciences*, *55*(11), M634-40.

O'Horo, J. C., Rogus-Pulia, N., Garcia-Arguello, L., Robbins, J., & Safdar, N. (2015). Bedside diagnosis of dysphagia: a systematic review. *Journal of Hospital Medicine (Online), 10*(4), 256–265. https://doi.org/10.1002/jhm.2313

Onesti, E., Schettino, I., Gori, M. C., Frasca, V., Ceccanti, M., Cambieri, C., Ruoppolo, G., & Inghilleri, M. (2017). Dysphagia in amyotrophic lateral sclerosis: impact on patient behavior, diet adaptation, and riluzole management. *Frontiers in Neurology, 8*, 94. https://doi.org/10.3389/fneur.2017.00094

Oppenheim, A. V., Schafer, R. W., & Buck, J. R. (1999). *Discrete-time signal processing* (2nd ed.). Prentice Hall Inc.

Pandya, V. A., & Patani, R. (2019). Decoding the relationship between ageing and amyotrophic lateral sclerosis: a cellular perspective. *Brain: A Journal of Neurology*. https://doi.org/10.1093/brain/awz360

Paris, G., Martinaud, O., Petit, A., Cuvelier, A., Hannequin, D., Roppeneck, P., & Verin, E. (2013). Oropharyngeal dysphagia in amyotrophic lateral sclerosis alters quality of life. *Journal of Oral Rehabilitation*, *40*(3), 199–204. https://doi.org/10.1111/joor.12019

Park, J. S., Oh, D. H., Chang, M. Y., & Kim, K. M. (2016). Effects of expiratory muscle strength training on oropharyngeal dysphagia in subacute stroke patients: a randomised controlled trial. *Journal of Oral Rehabilitation*, *43*(5), 364–372. https://doi.org/10.1111/joor.12382

Patchett, K. K., Hausenblas, H. A., & Christine, M. (2017). Expiratory muscle strength training for dysphagia in chronic obstructive pulmonary disease: A meta-analysis and systematic review. *Journal of Preventive Medicine & Healthcare*, *1*(3).

Pattee, G. L., Plowman, E. K., Brooks, B. R., Berry, J. D., Atassi, N., Chapin, J. L., Garand, K., Yunusova, Y., Mcilduff, C. E., Young, E., Costello, J. M., Macklin, E. A., Locatelli, E. R., Silani, V., Heitzman, D., Wymer, J., Goutman, S. A., Gelinas, D. F., Smith, R., … Green, J. (2018). Best practices protocol for the evaluation of bulbar dysfunction: Summary recommendations from the NEALS bulbar subcommittee symposium. *Amyotrophic Lateral Sclerosis & Frontotemporal Degeneration*, *19*(3–4), 311–312. https://doi.org/10.1080/21678421.2017.1404109

Pegoraro, V., Merico, A., & Angelini, C. (2019). Myomirnas dysregulation in ALS rehabilitation. *Brain Sciences*, *9*(1), 8. https://doi.org/10.3390/brainsci9010008

Pennington, S., Snell, K., Lee, M., & Walker, R. (2010). The cause of death in idiopathic Parkinson's disease. *Parkinsonism & Related Disorders*, *16*(7), 434–437. https://doi.org/10.1016/j.parkreldis.2010.04.010

Phillips, B., Ball, C., Sackett, D., Badenoch, D., & Straus, S. (2009). *Oxford Centre for Evidence-based Medicine Levels of Evidence Oxford: Oxford Centre for Evidence-Based Medicine; 2009 [updated 2009; cited 2016 21 ….*

Pinto, A. C., Alves, M., Nogueira, A., Evangelista, T., Carvalho, J., Coelho, A., de Carvalho, M., & Sales-Luís, M. L. (1999). Can amyotrophic lateral sclerosis patients with respiratory insufficiency exercise? *Journal of the Neurological Sciences*, *169*(1–2), 69–75. https://doi.org/10.1016/s0022-510x(99)00218-x

Pinto, S., Alves, P., Pimentel, B., Swash, M., & de Carvalho, M. (2016). Ultrasound for assessment of diaphragm in ALS. *Clinical Neurophysiology*, *127*(1), 892–897. https://doi.org/10.1016/j.clinph.2015.03.024

Pinto, S., & de Carvalho, M. (2013). Can inspiratory muscle training increase survival in early-affected amyotrophic lateral sclerosis patients? *Amyotrophic Lateral Sclerosis & Frontotemporal Degeneration*, *14*(2), 124–126. https://doi.org/10.3109/17482968.2012.726227

Pinto, S., Swash, M., & de Carvalho, M. (2012). Respiratory exercise in amyotrophic lateral sclerosis. *Amyotrophic Lateral Sclerosis*, *13*(1), 33–43. https://doi.org/10.3109/17482968.2011.626052

Pitts, T., Bolser, D., Rosenbek, J., Troche, M. S., Okun, M. S., & Sapienza, C. (2009). Impact of expiratory muscle strength training on voluntary cough and swallow function in Parkinson disease. *Chest*, *135*(5), 1301–1308. https://doi.org/10.1378/chest.08-1389

Plowman, E. K., Tabor-Gray, L., Robison, R., Gaziano, J., Dion, C., Watts, S. A., Vu, T., & Gooch, C. (2016). Discriminant ability of the Eating Assessment Tool-10 to detect aspiration in individuals with amyotrophic lateral sclerosis. *Neurogastroenterology and Motility*, *28*(1), 85–90. https://doi.org/10.1111/nmo.12700

Plowman, E. K., Tabor-Gray, L., Rosado, K. M., Vasilopoulos, T., Robison, R., Chapin, J. L., Gaziano, J., Vu, T., & Gooch, C. (2019). Impact of expiratory strength training in amyotrophic lateral sclerosis: Results of a randomized, sham-controlled trial. *Muscle & Nerve*, *59*(1), 40–46. https://doi.org/10.1002/mus.26292

Plowman, E. K., Watts, S. A., Robison, R., Tabor-Gray, L., Dion, C., Gaziano, J., Vu, T., & Gooch, C. (2016). Voluntary cough airflow differentiates safe versus unsafe swallowing in amyotrophic lateral sclerosis. *Dysphagia*, *31*(3), 383–390. https://doi.org/10.1007/s00455-015-9687-1

Plowman, E. K., Watts, S. A., Tabor-Gray, L., Robison, R., Gaziano, J., Domer, A. S., Richter, J., Vu, T., & Gooch, C. (2016). Impact of expiratory strength training in amyotrophic lateral sclerosis. *Muscle & Nerve*, *54*(1), 48–53. https://doi.org/10.1002/mus.24990

Prell, T., Ringer, T. M., Wullenkord, K., Garrison, P., Gunkel, A., Stubendorff, B., Witte, O. W., & Grosskreutz, J. (2016). Assessment of pulmonary function in amyotrophic lateral sclerosis: when can polygraphy help evaluate the need for non-invasive ventilation? *Journal of Neurology, Neurosurgery, and Psychiatry*, *87*(9), 1022–1026. https://doi.org/10.1136/jnnp-2015-312185

Pringsheim, T., Fiest, K., & Jette, N. (2014). The international incidence and prevalence of neurologic conditions: how common are they? *Neurology*, *83*(18), 1661–1664. https://doi.org/10.1212/WNL.0000000000000929

Pulley, M. T., Brittain, R., Hodges, W., Frazier, C., Miller, L., Matyjasik-Liggett, M., Maurer, S., Peters, M., Solomon, K., & Berger, A. R. (2019). Multidisciplinary amyotrophic lateral sclerosis telemedicine care: The store and forward method. *Muscle & Nerve*, *59*(1), 34–39. https://doi.org/10.1002/mus.26170

Raheja, D., Stephens, H. E., Lehman, E., Walsh, S., Yang, C., & Simmons, Z. (2016). Patient-reported problematic symptoms in an ALS treatment trial. *Amyotrophic Lateral Sclerosis & Frontotemporal Degeneration*, *17*(3–4), 198–205. https://doi.org/10.3109/21678421.2015.1131831

Ramagalla, A. R., Sadanandam, P., & Rajasree, T. K. (2014). Age related metric changes in the hyoid bone. *IOSR Journal of Dental and Medical Sciences*, *13*(7), 54–56. https://doi.org/10.9790/0853-13765456

Rebrion, C., Zhang, Z., Khalifa, Y., Ramadan, M., Kurosu, A., Coyle, J. L., Perera, S., & Sejdic, E. (2019). High-resolution cervical auscultation signal features reflect vertical and horizontal displacements of the hyoid bone during swallowing. *IEEE Journal of Translational Engineering in Health and Medicine*, *7*, 1800109. https://doi.org/10.1109/JTEHM.2018.2881468

Reyes, A., Castillo, A., Castillo, J., & Cornejo, I. (2018). The effects of respiratory muscle training on peak cough flow in patients with Parkinson's disease: a randomized controlled study. *Clinical Rehabilitation*, *32*(10), 1317–1327. https://doi.org/10.1177/0269215518774832

Reyes, A., Cruickshank, T., Nosaka, K., & Ziman, M. (2015). Respiratory muscle training on pulmonary and swallowing function in patients with Huntington's disease: a pilot randomised controlled trial. *Clinical Rehabilitation*, *29*(10), 961–973. https://doi.org/10.1177/0269215514564087

Rinkel, R. N., Verdonck-de Leeuw, I. M., Langendijk, J. A., van Reij, E. J., Aaronson, N. K., & Leemans, C. R. (2009). The psychometric and clinical validity of the SWAL-QOL questionnaire in evaluating swallowing problems experienced by patients with oral and oropharyngeal cancer. *Oral Oncology*, *45*(8), e67-71. https://doi.org/10.1016/j.oraloncology.2009.03.003

Robberecht, W., & Philips, T. (2013). The changing scene of amyotrophic lateral sclerosis. *Nature Reviews. Neuroscience*, *14*(4), 248–264. https://doi.org/10.1038/nrn3430

Robbins, J., Coyle, J., Rosenbek, J., Roecker, E., & Wood, J. (1999). Differentiation of normal and abnormal airway protection during swallowing using the penetration-aspiration scale. *Dysphagia*, *14*(4), 228–232. https://doi.org/10.1007/PL00009610

Robbins, J., Gangnon, R. E., Theis, S. M., Kays, S. A., Hewitt, A. L., & Hind, J. A. (2005). The effects of lingual exercise on swallowing in older adults. *Journal of the American Geriatrics Society*, *53*(9), 1483–1489. https://doi.org/10.1111/j.1532-5415.2005.53467.x

Robbins, J., Hamilton, J. W., Lof, G. L., & Kempster, G. B. (1992). Oropharyngeal swallowing in normal adults of different ages. *Gastroenterology*, *103*(3), 823–829.

Robbins, J., Levine, R., Wood, J., Roecker, E. B., & Luschei, E. (1995). Age effects on lingual pressure generation as a risk factor for dysphagia. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *50*(5), M257-62. https://doi.org/10.1093/gerona/50a.5.m257

Robison, R. (2015). The impact of lingual resistance training in two individuals with amyotrophic lateral sclerosis: a case series. *University of South Florida Scholar Commons [Master's Thesis]*.

Robison, R., Tabor-Gray, L., Wymer, J. P., & Plowman, E. K. (2018). Combined respiratory training in an individual with C9orf72 amyotrophic lateral sclerosis. *Annals of Clinical and Translational Neurology*, *5*(9), 1134–1138. https://doi.org/10.1002/acn3.623

Rodríguez, M. Á., Crespo, I., Del Valle, M., & Olmedillas, H. (2020). Should respiratory muscle training be part of the treatment of Parkinson's disease? A systematic review of randomized controlled trials. *Clinical Rehabilitation*, *34*(4), 429–437. https://doi.org/10.1177/0269215519896054

Rogus-Pulia, N. M., & Plowman, E. K. (2020). Shifting tides toward a proactive patient-centered approach in dysphagia management of neurodegenerative disease. *American Journal of Speech-Language Pathology / American Speech-Language-Hearing Association*, *29*(2S), 1094–1109. https://doi.org/10.1044/2020_AJSLP-19-00136

Rogus-Pulia, N. M., Rusche, N., Hind, J. A., Zielinski, J., Gangnon, R., Safdar, N., & Robbins, J. (2016). Effects of device-facilitated isometric progressive resistance oropharyngeal therapy on swallowing and health-related outcomes in older adults with dysphagia. *Journal of the American Geriatrics Society*, *64*(2), 417–424. https://doi.org/10.1111/jgs.13933

Roth, E. J., Stenson, K. W., Powley, S., Oken, J., Primack, S., Nussbaum, S. B., & Berkowitz, M. (2010). Expiratory muscle training in spinal cord injury: a randomized controlled trial. *Archives of Physical Medicine and Rehabilitation*, *91*(6), 857–861. https://doi.org/10.1016/j.apmr.2010.02.012

Sabry, A., Mahoney, A. S., Mao, S., Khalifa, Y., Sejdić, E., & Coyle, J. L. (2020). Automatic estimation of laryngeal vestibule closure duration using high-resolution cervical auscultation signals. *Perspectives of the ASHA Special Interest Groups*, *5*(6), 1647–1656. https://doi.org/10.1044/2020_PERSP-20-00073

Sabry, A., Mahoney, A. S., Perera, S., Sejdić, E., & Coyle, J. L. (2019, July 3). *Are HRCA signal features associated with clinical ratings of pharyngeal residue using the MBSImP* [Poster Presentation]. Dysphagia Research Society Annual Meeting, San Diego, CA, United States.

Sandstedt, P., Littorin, S., Johansson, S., Gottberg, K., Ytterberg, C., & Kierkegaard, M. (2018). Disability and contextual factors in patients with amyotrophic lateral sclerosis - A three-year observational study. *Journal of Neuromuscular Diseases*, *5*(4), 439–449. https://doi.org/10.3233/JND-180322

Sanjak, M., Bravver, E., Bockenek, W. L., Norton, H. J., & Brooks, B. R. (2010). Supported treadmill ambulation for amyotrophic lateral sclerosis: a pilot study. *Archives of Physical Medicine and Rehabilitation*, *91*(12), 1920–1929. https://doi.org/10.1016/j.apmr.2010.08.009

Sarwal, A., Walker, F. O., & Cartwright, M. S. (2013). Neuromuscular ultrasound for evaluation of the diaphragm. *Muscle & Nerve*, *47*(3), 319–329. https://doi.org/10.1002/mus.23671

Schmidt, E. P., Drachman, D. B., Wiener, C. M., Clawson, L., Kimball, R., & Lechtzin, N. (2006). Pulmonary predictors of survival in amyotrophic lateral sclerosis: use in clinical trial design. *Muscle & Nerve*, *33*(1), 127–132. https://doi.org/10.1002/mus.20450

Schneider, C. A., Rasband, W. S., & Eliceiri, K. W. (2012). NIH Image to ImageJ: 25 years of image analysis. *Nature Methods*, *9*(7), 671–675. https://doi.org/10.1038/nmeth.2089

Schwartz, D. B. (2018). Enteral nutrition and dementia integrating ethics. *Nutrition in Clinical Practice*, *33*(3), 377–387. https://doi.org/10.1002/ncp.10085

Sejdić, E., Steele, C. M., & Chau, T. (2010). The effects of head movement on dual-axis cervical accelerometry signals. *BMC Research Notes*, *3*, 269. https://doi.org/10.1186/1756-0500-3-269

Sejdić, E., Steele, C. M., & Chau, T. (2012). A method for removal of low frequency components associated with head movements from dual-axis swallowing accelerometry signals. *Plos One*, *7*(3), e33464. https://doi.org/10.1371/journal.pone.0033464

Sejdić, E., Steele, C. M., & Chau, T. (2013). Classification of penetration--aspiration versus healthy swallows using dual-axis swallowing accelerometry signals in dysphagic subjects. *IEEE Transactions on Bio-Medical Engineering*, *60*(7), 1859–1866. https://doi.org/10.1109/TBME.2013.2243730

Selzler, A. M., Wald, J., Sedeno, M., Jourdain, T., Janaudis-Ferreira, T., Goldstein, R., Bourbeau, J., & Stickland, M. K. (2018). Telehealth pulmonary rehabilitation: A review of the literature and an example of a nationwide initiative to improve the accessibility of pulmonary rehabilitation. *Chronic Respiratory Disease*, *15*(1), 41–47. https://doi.org/10.1177/1479972317724570

Shaker, R., Easterling, C., Kern, M., Nitschke, T., Massey, B., Daniels, S., Grande, B., Kazandjian, M., & Dikeman, K. (2002). Rehabilitation of swallowing by exercise in tube-fed patients with pharyngeal dysphagia secondary to abnormal UES opening. *Gastroenterology*, *122*(5), 1314–1321. https://doi.org/10.1053/gast.2002.32999

Shrier, I., Boivin, J.-F., Steele, R. J., Platt, R. W., Furlan, A., Kakuma, R., Brophy, J., & Rossignol, M. (2007). Should meta-analyses of interventions include observational studies in addition to randomized controlled trials? A critical examination of underlying principles. *American Journal of Epidemiology*, *166*(10), 1203–1209. https://doi.org/10.1093/aje/kwm189

Shrout, P. E., & Fleiss, J. L. (2005). Intraclass correlations: Uses in assessing rater reliability. *Psychological Bulletin*, *86*(2), 420.

Shu, K. (2019). Association between diameter of upper esophageal sphincter maximal opening and high-resolution cervical auscultation signal features. *University of Pittsburgh [Master's Thesis]*.

Shu, K., Coyle, J. L., Perera, S., & Khalifa, Y. (2021). Anterior-posterior distension of maximal upper esophageal sphincter opening is correlated with high-resolution cervical auscultation signal features. *Physiological*.

Siciliano, M., Trojano, L., Santangelo, G., De Micco, R., Tedeschi, G., & Tessitore, A. (2018). Fatigue in Parkinson's disease: A systematic review and meta-analysis. *Movement Disorders*, *33*(11), 1712–1723. https://doi.org/10.1002/mds.27461

Sivaramakrishnan, A., & Madhavan, S. (2019). Recumbent stepping aerobic exercise in amyotrophic lateral sclerosis: a pilot study. *Neurological Sciences*, *40*(5), 971–978. https://doi.org/10.1007/s10072-019-03736-3

Smith, L., & Ferguson, R. (2017). Artificial nutrition and hydration in people with late-stage dementia. *Home Healthcare Now*, *35*(6), 321–325. https://doi.org/10.1097/NHH.0000000000000550

Steele, C. M., & Cichero, J. A. Y. (2014). Physiological factors related to aspiration risk: a systematic review. *Dysphagia*, *29*(3), 295–304. https://doi.org/10.1007/s00455-014-9516-y

Steele, C. M., Peladeau-Pigeon, M., Barbon, C. A. E., Guida, B. T., Namasivayam-MacDonald, A. M., Nascimento, W. V., Smaoui, S., Tapson, M. S., Valenzano, T. J., Waito, A. A., & Wolkin, T. S. (2019). Reference values for healthy swallowing across the range from thin to extremely thick liquids. *Journal of Speech, Language, and Hearing Research*, *62*(5), 1338–1363. https://doi.org/10.1044/2019_JSLHR-S-18-0448

Suárez, A. A., Pessolano, F. A., Monteiro, S. G., Ferreyra, G., Capria, M. E., Mesa, L., Dubrovsky, A., & De Vito, E. L. (2002). Peak flow and peak cough flow in the evaluation of expiratory muscle weakness and bulbar impairment in patients with neuromuscular disease. *American Journal of Physical Medicine & Rehabilitation*, *81*(7), 506–511. https://doi.org/10.1097/00002060-200207000-00007

Suiter, D. M., & Leder, S. B. (2008). Clinical utility of the 3-ounce water swallow test. *Dysphagia*, *23*(3), 244–250. https://doi.org/10.1007/s00455-007-9127-y

Suiter, D. M., Sloggy, J., & Leder, S. B. (2014). Validation of the Yale Swallow Protocol: a prospective double-blinded videofluoroscopic study. *Dysphagia*, *29*(2), 199–203. https://doi.org/10.1007/s00455-013-9488-3

Sura, L., Madhavan, A., Carnaby, G., & Crary, M. A. (2012). Dysphagia in the elderly: management and nutritional considerations. *Clinical Interventions in Aging*, *7*, 287–298. https://doi.org/10.2147/CIA.S23404

Suttrup, I., & Warnecke, T. (2016). Dysphagia in parkinson's disease. *Dysphagia*, *31*(1), 24–32. https://doi.org/10.1007/s00455-015-9671-9

Sveinbjornsdottir, S. (2016). The clinical symptoms of Parkinson's disease. *Journal of Neurochemistry*, *139 Suppl 1*, 318–324. https://doi.org/10.1111/jnc.13691

Tabor-Gray, L., Gaziano, J., Watts, S., Robison, R., & Plowman, E. K. (2016). Defining swallowing-related quality of life profiles in individuals with amyotrophic lateral sclerosis. *Dysphagia*, *31*(3), 376–382. https://doi.org/10.1007/s00455-015-9686-2

Tabor-Gray, L., Rosado, K. M., Robison, R., Hegland, K. W., Humbert, I. A., & Plowman, E. K. (2016). Respiratory training in an individual with amyotrophic lateral sclerosis. *Annals of Clinical and Translational Neurology*, *3*(10), 819–823. https://doi.org/10.1002/acn3.342

Takahashi, K., Groher, M. E., & Michi, K. (1994). Methodology for detecting swallowing sounds. *Dysphagia*, *9*(1), 54–62. https://doi.org/10.1007/BF00262760

Takizawa, C., Gemmell, E., Kenworthy, J., & Speyer, R. (2016). A systematic review of the prevalence of oropharyngeal dysphagia in stroke, parkinson's disease, alzheimer's disease, head injury, and pneumonia. *Dysphagia*, *31*(3), 434–441. https://doi.org/10.1007/s00455-016-9695-9

Temlett, J. A., & Thompson, P. D. (2006). Reasons for admission to hospital for Parkinson's disease. *Internal Medicine Journal*, *36*(8), 524–526. https://doi.org/10.1111/j.1445-5994.2006.01123.x

Theou, O., Stathokostas, L., Roland, K. P., Jakobi, J. M., Patterson, C., Vandervoort, A. A., & Jones, G. R. (2011). The effectiveness of exercise interventions for the management of frailty: a systematic review. *Journal of Aging Research*, *2011*, 569194. https://doi.org/10.4061/2011/569194

Troche, M. S., Brandimore, A. E., Godoy, J., & Hegland, K. W. (2014). A framework for understanding shared substrates of airway protection. *Journal of Applied Oral Science : Revista FOB*, *22*(4), 251–260. https://doi.org/10.1590/1678-775720140132

Troche, M. S., Brandimore, A. E., Okun, M. S., Davenport, P. W., & Hegland, K. W. (2014). Decreased cough sensitivity and aspiration in Parkinson disease. *Chest*, *146*(5), 1294–1299. https://doi.org/10.1378/chest.14-0066

Troche, M. S., & Mishra, A. (2017). Swallowing exercises in patients with neurodegenerative disease: what is the current evidence? *Perspectives of the ASHA Special Interest Groups*, *2*(13), 13–20. https://doi.org/10.1044/persp2.SIG13.13

Troche, M. S., Okun, M. S., Rosenbek, J. C., Musson, N., Fernandez, H. H., Rodriguez, R., Romrell, J., Pitts, T., Wheeler-Hegland, K. M., & Sapienza, C. M. (2010). Aspiration and swallowing in Parkinson disease and rehabilitation with EMST: a randomized trial. *Neurology*, *75*(21), 1912–1919. https://doi.org/10.1212/WNL.0b013e3181fef115

Tsitkanou, S., Della Gatta, P., Foletta, V., & Russell, A. (2019). The role of exercise as a non-pharmacological therapeutic approach for amyotrophic lateral sclerosis: Beneficial or detrimental? *Frontiers in Neurology*, *10*, 783. https://doi.org/10.3389/fneur.2019.00783

Vose, A. K., Kesneck, S., Sunday, K., Plowman, E., & Humbert, I. (2018). A survey of clinician decision making when identifying swallowing impairments and determining treatment.

Journal of Speech, Language, and Hearing Research, *61*(11), 2735–2756. https://doi.org/10.1044/2018_JSLHR-S-17-0212

Wada, A., Kawakami, M., Liu, M., Otaka, E., Nishimura, A., Liu, F., & Otsuka, T. (2015). Development of a new scale for dysphagia in patients with progressive neuromuscular diseases: the Neuromuscular Disease Swallowing Status Scale (NdSSS). *Journal of Neurology*, *262*(10), 2225–2231. https://doi.org/10.1007/s00415-015-7836-y

Waito, A. A., Bailey, G. L., Molfenter, S. M., Zoratto, D. C., & Steele, C. M. (2011). Voice-quality abnormalities as a sign of dysphagia: validation against acoustic and videofluoroscopic data. *Dysphagia*, *26*(2), 125–134. https://doi.org/10.1007/s00455-010-9282-4

Waito, A. A., Plowman, E. K., Barbon, C. E. A., Peladeau-Pigeon, M., Tabor-Gray, L., Magennis, K., Robison, R., & Steele, C. M. (2020). A cross-sectional, quantitative videofluoroscopic analysis of swallowing physiology and function in individuals with amyotrophic lateral sclerosis. *Journal of Speech, Language, and Hearing Research*, *63*(4), 948–962. https://doi.org/10.1044/2020_JSLHR-19-00051

Waito, A. A., Valenzano, T. J., Peladeau-Pigeon, M., & Steele, C. M. (2017). Trends in research literature describing dysphagia in motor neuron diseases (MND): A scoping review. *Dysphagia*, *32*(6), 734–747. https://doi.org/10.1007/s00455-017-9819-x

Walston, J. D. (2012). Sarcopenia in older adults. *Current Opinion in Rheumatology*, *24*(6), 623–627. https://doi.org/10.1097/BOR.0b013e328358d59b

Wang, C.-M., Shieh, W.-Y., Weng, Y.-H., Hsu, Y.-H., & Wu, Y.-R. (2017). Non-invasive assessment determine the swallowing and respiration dysfunction in early Parkinson's disease. *Parkinsonism & Related Disorders*, *42*, 22–27. https://doi.org/10.1016/j.parkreldis.2017.05.024

Watts, S. A., Tabor-Gray, L., & Plowman, E. K. (2016). To cough or not to cough? examining the potential utility of cough testing in the clinical evaluation of swallowing. *Current Physical Medicine and Rehabilitation Reports*, *4*(4), 262–276. https://doi.org/10.1007/s40141-016-0134-5

Wert, L. (2019). Exercise and its role in treating neurodegenerative diseases: a scientific review. *Exercise & Sports Nutrition Reviews*.

Wijesekera, L. C., & Leigh, P. N. (2009). Amyotrophic lateral sclerosis. *Orphanet Journal of Rare Diseases*, *4*, 3. https://doi.org/10.1186/1750-1172-4-3

Williams, K. N., Perkhounkova, Y., Shaw, C. A., Hein, M., Vidoni, E. D., & Coleman, C. K. (2019). Supporting family caregivers with technology for dementia home care: A randomized controlled trial. *Innovation in Aging*, *3*(3). https://doi.org/10.1093/geroni/igz037

Woolley, S. C., York, M. K., Moore, D. H., Strutt, A. M., Murphy, J., Schulz, P. E., & Katz, J. S. (2010). Detecting frontotemporal dysfunction in ALS: utility of the ALS Cognitive

Behavioral Screen (ALS-CBS). *Amyotrophic Lateral Sclerosis*, *11*(3), 303–311. https://doi.org/10.3109/17482961003727954

Yang, W., Hamilton, J. L., Kopil, C., Beck, J. C., Tanner, C. M., Albin, R. L., Ray Dorsey, E., Dahodwala, N., Cintina, I., Hogan, P., & Thompson, T. (2020). Current and projected future economic burden of Parkinson's disease in the U.S. *Npj Parkinson's Disease*, *6*, 15. https://doi.org/10.1038/s41531-020-0117-1

Yu, C., Khalifa, Y., & Sejdic, E. (2019). Silent aspiration detection in high resolution cervical auscultations. *2019 IEEE EMBS International Conference on Biomedical & Health Informatics (BHI)*, 1–4. https://doi.org/10.1109/BHI.2019.8834576

Zhang, Z., Coyle, J. L., & Sejdić, E. (2018). Automatic hyoid bone detection in fluoroscopic images using deep learning. *Scientific Reports*, *8*(1), 12310. https://doi.org/10.1038/s41598-018-30182-6

Zhang, Z., Perera, S., Donohue, C., Kurosu, A., Mahoney, A. S., Coyle, J. L., & Sejdić, E. (2020). The prediction of risk of penetration-aspiration via hyoid bones displacement features. *Dysphagia*, *35*(1), 66–72. https://doi.org/10.1007/s00455-019-10000-5

Zucchi, E., Vinceti, M., Malagoli, C., Fini, N., Gessani, A., Fasano, A., Rizzi, R., Sette, E., Cavazza, S., Fiocchi, A., Buja, S., Faccioli, T., Storani, S., & Mandrioli, J. (2019). High-frequency motor rehabilitation in amyotrophic lateral sclerosis: a randomized clinical trial. *Annals of Clinical and Translational Neurology*, *6*(5), 893–901. https://doi.org/10.1002/acn3.765